

# IEO RESEARCH NEWSLETTER

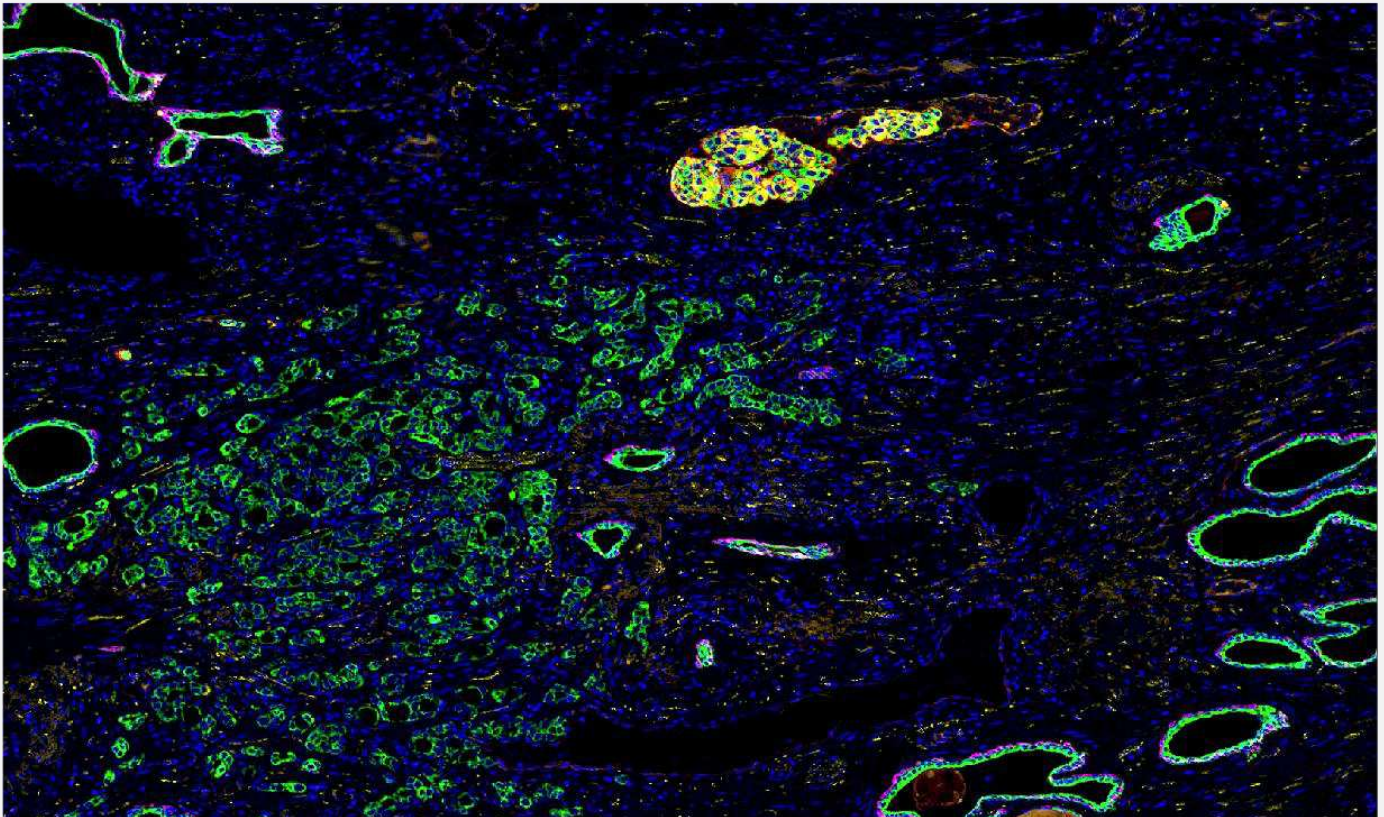
n. 011  
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June 2026

25 anni di cancer hallmarks.  
*25 years of cancer  
hallmarks.*

Nuove opzioni di trattamento per il tumore ovarico  
ricidivo, resistente alla chemioterapia – risultati di due  
clinical trial di fase III.

*New treatment options for recurrent, chemoresistant  
ovarian cancer – results of two phase III clinical trials.*

Evento EUPATI “La ricerca  
siamo noi” in IEO.  
*“La ricerca siamo noi”  
EUPATI event at IEO*



# IEO RESEARCH NEWSLETTER

n. 011 – June 2026

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## 25 anni di cancer hallmarks – perché comprendere il problema è il primo passo per risolverlo.

Il cancro è una malattia multifattoriale. Alterazioni in diversi processi cellulari chiave trasformano una cellula sana in una cellula tumorale, minacciando la salute umana. La comprensione di questi processi è fondamentale per colpire farmacologicamente e in maniera efficace le cellule tumorali. Venticinque anni fa, la definizione dei cosiddetti “*cancer hallmark*” (da parte di Weinberg e Hanahan) ha permesso di organizzare le conoscenze sui processi di tumorigenesi in sei meccanismi principali: i *cancer hallmark*. Negli anni, con le nuove scoperte scientifiche, questi sei *hallmark* sono stati integrati con concetti emergenti e nuove caratteristiche fondamentali delle cellule tumorali, che tengono in considerazione anche fattori esterni alla cellula tumorale e il ruolo del microambiente tumorale nel promuovere la progressione del tumore. Tutti questi meccanismi tumorali/*cancer hallmark* si influenzano a vicenda.

Spiegando perfettamente l’approccio alla base della terapia molecolare, guidato dalla biologia meccanicistica del tumore, che ha indirizzato la ricerca e la cura negli ultimi decenni, questi *hallmark* sono diventati il target di nuove terapie; alcuni di questi trattamenti sono stati già approvati per uso clinico, altri sono ancora in fase sperimentale.

### La visione di Weinberg e Hanahan dei cancer hallmarks:

#### Le capacità acquisite delle cellule tumorali.

**1. La proliferazione sostenuta.** L’iperproliferazione è una caratteristica tipica del cancro. Ad un certo punto, alcune cellule sane iniziano a proliferare in maniera incontrollata. Alterazioni in geni chiave – oncogeni– sostengono la proliferazione tumorale. KRAS, MYC, EGFR sono solo alcuni esempi dei 193 geni attualmente definiti come oncogeni.

**2. Inattivazione dei meccanismi onco-soppressivi.** Altrettanto importante per una cellula tumorale è l’inattivazione dei fattori coinvolti nei meccanismi di salvaguardia delle cellule, che limitano la proliferazione quando qualcosa non va – gli oncosoppressori. Quando i geni oncosoppressori, il cui ruolo è quello di arrestare la proliferazione cellulare in caso di anomalie (come il danno al DNA), sono inattivi, le cellule tumorali acquisiscono capacità proliferative aggiuntive. Tra i 143 geni attualmente elencati come oncosoppressori, TP53 è quello più frequentemente mutato nei tumori umani (influenzando a sua volta altri geni coinvolti nella proliferazione, nella senescenza, nell’apoptosi etc). Altri meccanismi oncosoppressivi –inattivi nelle cellule tumorali– includono l’inibizione da contatto e la competizione per i nutrienti.

**3. Inattivazione dei meccanismi che inducono morte cellulare programmata.** I processi che inducono la

### Una visione alternativa:

#### Mutazioni geniche – quando un cambiamento può essere deleterio.



Pol era penserosa. Il loro piano era audace, ma avrebbe potuto funzionare. Dovevano essere però molto cauti...

Serpeggiava un tale malcontento che non era stato difficile trovare degli alleati. Erano così stufi semplicemente di far parte di una delle tante cellule... volevano qualcosa di più. Volevano essere potenti, forti, acquisire un vantaggio. Far parte di una squadra vincente, superiore rispetto a tutte le altre...

Si erano riuniti in gran segreto e avevano messo a punto un piano: semplice ed efficace. Pol era il tassello principale. La cosa la rendeva così orgogliosa!

L’indomani mattina, recandosi al lavoro, non avrebbe dovuto far altro che comportarsi normalmente... Legarsi al DNA come sempre ed iniziare a replicare la sequenza nucleotidica, fedelmente, come faceva da tutta una vita. Un’adenina, una timina, una guanina, poi un’altra timina una citosina e via dicendo, ma, innanzi tutto, arrivata sul cromosoma 12, dove si trovava il gene di KRAS, cautamente, senza attirare l’attenzione, all’altezza della tripletta che codificava per una glicina, avrebbe dovuto inserire un nucleotide diverso, così che la glicina diventasse un acido aspartico. Poi, sarebbe dovuta passare sul cromosoma 17, all’altezza della sequenza del gene di p53, e lì, a livello della tripletta che codificava per l’arginina 248, sarebbe bastato sostituire un nucleotide e il gioco era fatto.

Nel caso in cui non fosse riuscita ad alterare le sequenze di KRAS e di p53, poteva provare altrove; inserire altre

morte cellulare in caso di danno rappresentano un meccanismo protettivo critico per eliminare le cellule danneggiate. Le cellule tumorali prendono il controllo di questi meccanismi, bloccando la morte cellulare quando necessario (ovvero in caso di danno irreversibile).

**4. Ottenere capacità replicative illimitate.** Per permettere la proliferazione illimitata, le cellule tumorali inattivano i checkpoint che controllano la lunghezza dei telomeri, principalmente rimuovendo la repressione di enzimi chiave coinvolti nel controllo dei telomeri.

**5. Alterazioni del metabolismo cellulare.** Per garantire l'energia necessaria a supportare l'iperproliferazione, le cellule tumorali ottimizzano la produzione di energia, impiegando sia fosforilazione ossidativa che glicolisi, e utilizzando altre fonti (oltre al glucosio) come il lattato o alcuni aminoacidi (glutamina).

**6. Plasticità fenotipica.** Le cellule tumorali affrontano condizioni microambientali differenti e variabili. Per poter sopravvivere, hanno evoluto la capacità di adattarsi. L'adattamento delle cellule tumorali a condizioni esterne, che coinvolge –e di fatto è consentita da– meccanismi genetici e non genetici (epigenetici), comprende la modulazione del profilo di espressione genica delle cellule tumorali e la capacità di passare tra differenti stati: le cellule tumorali acquisiscono plasticità. Ciò include meccanismi come la transizione epitelio-mesenchimale (con un gran numero di stadi intermedi) e l'acquisizione di caratteristiche staminali. Insieme alla selezione delle cellule tumorali con specifiche mutazioni che conferiscono vantaggio in termini di sopravvivenza, la plasticità delle cellule tumorali è una delle ragioni dell'eterogeneità intratumorale.

**7. Sfuggire al sistema immunitario.** Una caratteristica acquisita dalle cellule tumorali è la capacità di “nascondersi” e sfuggire all'eliminazione da parte del sistema immunitario.

**8. Indurre la formazione di nuovi vasi sanguigni o cooptare vasi esistenti.** Per sostenere la crescente necessità di ossigeno e nutrienti del tumore in crescita, le cellule tumorali acquisiscono la capacità di modulare il microambiente tumorale (TME), inducendo la crescita di nuovi vasi sanguigni o cooptando i vasi esistenti (con l'attivazione di meccanismi tipici dello sviluppo e della guarigione delle ferite), attraverso la secrezione di fattori che inducono angiogenesi.

**9. Invasione e metastasi.** Attraverso un processo multi-step, le cellule tumorali possono lasciare il


sostituzioni, ma queste due alterazioni erano il “piano A”. Quelle sì che avrebbe indotto dei cambiamenti significativi! Le loro probabilità di successo sarebbero aumentate vertiginosamente!

Il sistema di sorveglianza avrebbe fatto finta di niente. Avevano un accordo segreto. Avrebbe ignorato quelle modifiche; p53 avrebbe perso la sua capacità di oncosoppressore; gli effetti sarebbero stati multipli, interferendo con un sacco di processi: apoptosi, ciclo cellulare, metabolismo cellulare... KRAS avrebbe sostenuto la proliferazione cellulare e la loro cellula finalmente sarebbe diventata la più potente... Avrebbe proliferato, dato vita ad una nuova dinastia di cellule, più forti, più resistenti, più potenti. E Pol sarebbe stata un ingranaggio fondamentale. Tutti avrebbero parlato delle gesta di DNA pol: colei che aveva permesso la trasformazione.

Un piano perfetto. Cosa poteva andare storto?

**Chemioterapia.** Come previsto, la loro cellula aveva guadagnato un vantaggio selettivo rispetto alle cellule circostanti. Era rapidamente diventata più forte. La nuova stirpe di cellule si era espansa velocemente. Ma alcune voci dicevano che c'erano pericoli all'orizzonte... Alcuni la chiamavano chemioterapia, altri taxolo. Agiva proprio su quelle cellule che avevano deciso di crescere, di espandersi. Legava la proteina beta-tubulina stabilizzava i microtubuli, ostacolando la formazione del fuso mitotico, arrestando infine il ciclo cellulare. Le cellule trattate con chemioterapia stavano morendo... e non c'era nulla che Pol potesse fare.

#### Riacendere processi specifici della proliferazione spenti dal differenziamento.



TERT era pensierosa. Per tutta la vita aveva lavorato in maniera instancabile, senza mai lamentarsi, sapendo che poi le sarebbe spettata una meritatissima pensione. Durante il periodo di proliferazione cellulare, fino al differenziamento cellulare, al momento della replicazione del DNA aveva aggiunto delle brevi sequenze all'altezza dei telomeri, così da assicurarsi che non diventassero troppo corti, proteggendo così l'informazione genetica. Quando finalmente la cellula aveva iniziato a differenziarsi, lei era andata in pensione. Qualche giorno fa, però, erano venuti a svegliarla. Avevano un piano e TERT ne faceva parte. In realtà giocava un ruolo piuttosto importante. Doveva ammetterlo, ne era lusingata. Mentre TERT si godeva il suo meritato periodo di riposo, la cellula aveva preso delle decisioni importanti, cambiato strategia, ideato un nuovo piano per il futuro. Erano seguiti diversi cambiamenti significativi e TERT si stava documentando per capire esattamente cosa fosse accaduto in quel lasso di tempo. Prima di tutto, KRAS era diventato iperattivo. Quasi nello stesso periodo, p53 aveva invece smesso di lavorare. Ne era seguito un periodo di iperattività e per poter sostenere le nuove attività, le industrie lavoravano tutte a pieno ritmo, glicolisi e fosforilazione ossidativa a tutte le ore. In alcuni casi la cellula aveva anche iniziato ad utilizzare nuove forme di energia, sfruttando il lattato.



**14. Microbiomi.** Specie microbiche simbiotici sono note influenzare i meccanismi dei *cancer hallmark*, influenzando la progressione del tumore e la risposta alla terapia. Alterazioni della composizione del microbioma stimolano la proliferazione e inducono le cellule a sfuggire alla sorveglianza immunitaria (e, per alcune particolari specie batteriche, l'instabilità genomica, le mutazioni e l'infiammazione pro-tumorale), modulando a loro volta la risposta alla terapia.

#### **Fattori pro-tumorali nel microambiente tumorale.**

Le alterazioni tipiche delle cellule tumorali possono presentarsi anche in altre componenti del microambiente tumorale, promuovendo di conseguenza la formazione di un ambiente pro-tumorale. La componente cellulare del TME include cellule endoteliali e periciti (che stimolano la proliferazione delle cellule tumorali e promuovono la capacità delle cellule tumorali di evitare la morte cellulare programmata e la rimozione da parte del sistema immunitario, influenzano il metabolismo, facilitano invasione tissutale e metastasi, e sono responsabili di vasi più facilmente permeabili alle cellule che formano metastasi); i fibroblasti associati al tumore (CAF, in grado di promuovere, attraverso il rilascio di molecole e vescicole, la proliferazione delle cellule tumorali, l'inibizione della morte cellulare programmata, cambiamenti del metabolismo della cellula tumorale e della matrice extracellulare, di modificare i vasi sanguigni, supportare l'invasione e la disseminazione metastatica, reclutare cellule mieloidi pro-angiogeniche e immunosoppressive, ed evitare la rimozione da parte del sistema immunitario); macrofagi e neutrofili associati al tumore e pro-tumorali e cellule immunitarie residenti riprogrammate (che stimolano la proliferazione delle cellule tumorali e l'angiogenesi, sopprimono la sorveglianza immunitaria e facilitano invasione tissutale e metastasi), le cellule senescenti (che modulano la tumorigenesi e la progressione tumorale) ed altre cellule immunitarie che, indotte dal cancro, facilitano a loro volta la manifestazione dei *cancer hallmark*.

#### **Fattori sistemici che influenzano i *cancer hallmark*.**

L'invecchiamento –attraverso il declino del sistema immunitario, l'infiammazione cronica, la perdita di integrità genomica, il reprogramming epigenetico e il disequilibrio del microbioma– e l'obesità sono fattori sistemici che aumentano il rischio di

di portare a compimento il loro lavoro. Era ora che la cellula entrasse in apoptosi.

#### **Sfuggire alla "polizia" immunitaria.**

Gerale –la cellula tumorale– era diventata ormai abilissima. Riusciva a sfuggire alla sorveglianza attenta della polizia in una maniera così efficiente... Ormai evadere la sorveglianza era diventata la sua natura. Aveva deciso di passare "al lato oscuro" ormai da un pezzo. Diventare una cellula tumorale sembrava così *cool*. Potevano fare quello che volevano, erano più forti delle altre cellule, più resistenti e più indipendenti. Se non fosse stato per la polizia che dava loro la caccia di continuo. Quante ne avevano acchiappate! E non avevano fatto una bella fine... Le avevano ammazzate davanti a lei... Anche lei stessa ci era andata vicina in più di un'occasione. All'inizio era stata semplicemente fortunata, più fortunata delle altre a sfuggire alla polizia che diventava sempre più numerosa in quella zona, richiamata dai frequenti incidenti con le altre cellule tumorali, ma con il tempo aveva iniziato a capire come sfuggire alla polizia.

**Evasione immunitaria.** Gerale si mimetizzava. La polizia riconosceva le cellule tumorali dalle cellule normali sulla base di alcuni segni distintivi. Se mostravi uno di quei segni, se esprimevi una di quelle molecole, ti riconoscevano anche nel mezzo di tutte le cellule normali e *zac!*, eri finita. Gerale aveva iniziato a capire quali erano quei segni, e a nascondersi... In questo modo la polizia non la riconosceva. Poteva muoversi tranquillamente in mezzo alle altre cellule normali, passare accanto alla polizia, e non essere riconosciuta.

**Immune cell exhaustion.** Certo la sua abilità era fondamentale, ma ammettiamolo, di per sé non sufficiente... Con il tempo la polizia aveva iniziato a mollare un po' la presa. Innanzi tutto, molti agenti erano chiaramente esausti dalla necessità di sorvegliare la zona di continuo e loro ne approfittavano.

**Fattori immunosoppressivi di origine tumorale.** Inoltre, quando per caso qualche poliziotto di quelli ancora vigili e stacanovisti dava loro la caccia, loro sapevano difendersi. Avevano fatto scorta di TGFbeta e altri fattori immunosoppressivi e quando uno di questi agenti le passava vicino, Gerale si difendeva lanciandoglielo addosso.

**Infiammazione cronica.** Alcuni poliziotti poi con il tempo erano stati corrotti: gli stessi che all'inizio avevano cercato di eliminarle, ormai passavano a Gerale e alle sue amiche un sacco di fattori che le aiutavano a diventare più forti e quindi a proliferare, di più e più velocemente. Sì, ormai avevano in pugno il sistema di sorveglianza, nessuno poteva fermarle.

**Immunoterapia.** La situazione era cambiata rapidamente... Improvvisamente la polizia era diventata più scaltra e più forte. Riuscivano a dar loro la caccia giorno e notte, senza fermarsi. Tra Gerale e le sue amiche circolava la voce che la polizia stesse assumendo dei farmaci –anti-PD1 si chiamavano– che le rendevano più forti. E poi erano arrivate delle milizie armate. Si facevano chiamare cellule

insorgenza del tumore, insieme all'esposizione a fattori ambientali potenzialmente tumorigenici, come il fumo, l'inquinamento dell'aria e dell'acqua, le microplastiche, che, interferendo con la fisiologia cellulare, promuovono l'induzione dei *cancer hallmark* e lo sviluppo del tumore.

### I *cancer hallmark* – Una prospettiva terapeutica.

Sfruttando le conoscenze acquisite sulla biologia tumorale e i *cancer hallmark*, nel corso degli anni sono stati sviluppati trattamenti in grado di colpire in maniera specifica questi meccanismi tumorali alterati, con vari gradi di coinvolgimento del sistema immunitario e di selettività per le cellule tumorali (e quindi tossicità associata). Dalla prima classe di *agenti citotossici* identificati –come gli agenti alchilanti, gli antimetaboliti, gli inibitori delle topoisomerasi, gli inibitori mitotici– che colpiscono la proliferazione sostenuta delle cellule tumorali e l'inattivazione dei meccanismi di soppressione della crescita, l'abilità delle cellule tumorali di resistere alla morte cellulare, l'acquisita capacità di immortalità replicativa; allo sviluppo di *farmaci molecolari*, come gli agenti che sopprimono i segnali oncogenici e inibiscono l'angiogenesi, interferendo con la proliferazione delle cellule tumorali e l'inattivazione dei meccanismi di soppressione della crescita, la loro capacità di resistere alla morte cellulare e indurre la formazione di nuovi vasi, la loro plasticità, l'alterato metabolismo tumorale, l'immortalità replicativa; agli *anticorpi farmaco-coniugati e i T-cell engager bi-specifici*, che permettono la somministrazione mirata di chemioterapici o favoriscono l'interazione tra cellule tumorali e immunitarie, interferendo con la proliferazione delle cellule tumorali e l'inattivazione dei meccanismi di soppressione della crescita, la loro abilità di resistere alla morte cellulare o di sfuggire alla sorveglianza immunitaria, la loro acquisita capacità di immortalità replicativa; gli *inibitori dei checkpoint immunitari* che, prevenendo l'interazione ligando-recettore tra cellule immunitarie e tumorali, interferiscono con la plasticità cellulare e la sorveglianza immunitaria, fino alle più recenti *terapie cellulari* che colpiscono le cellule che esprimono specifici antigeni tumorali usando cellule immunitarie ingegnerizzate, interferendo così con la proliferazione delle cellule tumorali e la loro abilità di sfuggire alla sorveglianza immunitaria.

Il targeting, o il co-targeting, di questi processi che

CAR-T. Erano più astute e in grado di riconoscere Gerale e le sue amiche in maniera molto più efficiente della polizia locale e quando le riconoscevano, le attaccavano in maniera aggressiva. Gerale si aggirava con sempre maggiore circospezione. Se lo sentiva: avrebbero preso presto anche lei.

### “Governare” un tumore in crescita.



**Insorgenza del tumore.** Tumorville era stata fondata da pochissimo. Quando le prime cellule avevano iniziato a colonizzare quella porzione del polmone, nessuno gli aveva prestato attenzione. Sembravano quattro cellule in campeggio, che avevano voglia di fare qualcosa di diverso. Proprio perché nessuno era andato a disturbarle, il loro accampamento aveva iniziato letteralmente a proliferare...

**Progressione del tumore.** 4 cellule erano diventate 8, poi 16 e via dicendo. E in poco tempo quell'accampamento era diventato un villaggio e poi una città. I problemi erano sorti proprio perché erano troppe...

**Scarsità di nutrienti.** Raccogliere ciò che il microambiente offriva non era più sufficiente, i viveri iniziavano a scarseggiare e Tumorville era troppo lontana dalle vie di approvvigionamento. Per questo Mr Newves aveva deciso di prendere in mano la situazione.

**Angiogenesi.** Tumorville aveva bisogno di strade. Strade sicure che permettessero di raggiungere i vasi sanguigni principali rapidamente, così da ottenere tutto il nutrimento necessario. E così erano iniziati i lavori. Più Tumorville si espandeva, più strade venivano costruite. Non si smetteva mai. Ok, i vasi non erano tutti strutturalmente perfetti, ma le condizioni in cui erano stati costruiti non erano state certo delle migliori... Banditi delle vicine gang di angiostatina e TSP-1 avevano continuamente tentato di ostacolare i lavori! Solo la determinazione di Tumorville di continuare a crescere, in parallelo all'aiuto del sistema immunitario e, soprattutto, all'assenza di controlli, poteva vincere sulle loro azioni inibitorie e distruttive!

La formazione dei nuovi vasi sanguigni aveva assicurato a Tumorville una proliferazione sicura e incontrastata. O no?

**Inibitori di VEGF.** Proprio quando Tumorville era al massimo del suo splendore, quando la costruzione dei nuovi vasi procedeva rapida e Mr Newves stava già facendo progetti per costruire nuove frazioni di Tumorville, i barbari avevano attaccato. Muniti di armi di distruzione potenti, i famigerati inibitori della signaling VEGF, avevano attaccato i vasi già in funzione e le squadre intente a costruirne di nuovi. Mr Newves si guardò intorno, disperato. Senza approvvigionamenti, Tumorville sarebbe morta presto.

### Racconti di una metastasi.



**Nel tumore primario.** MICante –la cellula metastatizzante– non ne poteva più. Andare a convivere con le altre cellule tumorali le era sembrata un'idea carina, ma le altre cellule facevano veramente troppo casino. La zona era diventata sovraffollata, un sacco di volte era rimasta digiuna perché avevano saccheggiato le provviste e si erano mangiate

sostengono lo sviluppo e la progressione del tumore attraverso farmaci disegnati per interferire con specifici meccanismi cellulari hanno portato all'approvazione di terapie mirate contro proliferazione, apoptosi, angiogenesi, evasione immunitaria. Colpire in maniera simultanea differenti meccanismi dei *cancer hallmark*, interferendo con differenti vulnerabilità tumorali, potrebbe infatti rendere difficile per le cellule tumorali trovare molteplici scappatoie e sopravvivere.

Alcuni esempi di co-targeting terapeutico dei *cancer hallmark* includono gli anticorpi bi-specifici anti VEGFA/PD1, che hanno mostrato un certo grado di efficacia in trial clinici (sebbene non siano ancora clinicamente approvati), o anticorpi anti-VEGFA (bevacizumab) in combinazione con un inibitore –olaparib– dell'enzima PARP di riparo del DNA, che colpiscono le vulnerabilità delle cellule tumorali come l'instabilità genomica (una *enabling feature* causata da un danno al sistema di riparo del DNA) insieme ad un malfunzionamento dei processi di angiogenesi, che ha portato all'approvazione clinica di questa terapia per popolazioni selezionate di pazienti con tumore ovarico.

**Referenze:** The Hallmarks of Cancer: 25 years guiding discovery and therapy. *Cell* editorial. doi: 10.1016/j.cell.2026.03.033; Hallmarks of cancer—Then and now, and beyond. *Douglas Hanahan. Cell* 2026. doi: 10.1016/j.cell.2025.12.049; SnapShot - The hallmarks of cancer treatment. *Pietro Paolo Vitiello, Vito Amodio, Alberto Bardelli. Cell* 2026. doi: 10.1016/j.cell.2026.03.017.

**Adagrasib.** Era accaduto di pomeriggio. Non c'erano state avvisaglie. MICante si stava godendo la nuova casa, faceva progetti per il futuro. Insieme alle sue nuove coinquiline stavano persino progettando un nuovo viaggio, una lunga vacanza alla scoperta di nuovi luoghi, dove magari avrebbero costruito una villetta. E invece, quel forte temporale aveva distrutto tutto. "C'è adagrasib ovunque!" avevano urlato alcune sue coinquiline. MICante non capiva "Cos'è adagrasib?" aveva chiesto con un filo di voce. Iniziava a sentirsi così stanca... La sua vicina l'aveva guardata "E' un farmaco" le aveva spiegato "piuttosto efficace anche. Ci ucciderà. Non abbiamo scampo".

**Enabling features – not all the shit is the same...**

La giornata non era iniziata nel migliore dei modi. Dopo gli scrosci di caffè era arrivato puntuale il solito tanfo... Del resto, anche la serata precedente non si era conclusa benissimo.

**Una dieta sbagliata.** Erano arrivati cibi grassi, alcol e zuccheri, in quantità eccezionali, e il lavoro aveva continuato ad accumularsi. Berio il batterio non ne poteva più. Lui e i suoi compagni avevano lavorato tutta la notte per contribuire a metabolizzare tutto quel cibo spazzatura. Erano mesi ormai che procedevano scioperi e manifestazioni; avevano tentato di manifestare il loro disappunto in più di un'occasione, inducendo tutti i possibili sintomi più fastidiosi, ma le loro lamentele venivano ampiamente ignorate.

**Un alterato microbiota intestinale.** A peggiorare la situazione, il lavoro di Berio e dei suoi compagni veniva quotidianamente vanificato da alcune famiglie di batteri che abitavano l'intestino insieme a lui. Li aveva incontrati una volta, Escherichia Coli e la sua gang, così maleducati! Inizialmente erano scarsamente numerosi, ma in qualche modo negli ultimi periodi si erano moltiplicati e ciò che producevano intralciava in maniera significativa il loro lavoro. E poi avevano un atteggiamento così losco... Negli ultimi tempi, in particolare, avevano instaurato dei rapporti con una

tutto! Aveva deciso di andarsene. La sera prima si era sfogata con le cellule del microambiente... Erano state così comprensive! L'avevano così incoraggiata! "Basta organizzarsi!" le avevano detto "vai nel negozietto qui vicino, prendi tutto quello che ti serve per una EMT e via!"

**EMT – Transizione epitelio-mesenchimale.** E così aveva fatto. Aveva acquistato un po' di TWIST1 e 2, un po' di SLUG, di SNAIL, un pochino di ZEB1 e 2; si era premurata di fare anche un po' di scorta di N-Caderina e vimentina. Purtroppo aveva dovuto lasciare alcune cose a cui era affezionata; ad esempio non era riuscita a portare con sé E-Caderina e beta-catenina, ma era pronta.

**Invasione locale.** Aveva camminato a lungo nei paraggi, tra la folla, prima di raggiungere l'autostrada.

**Intravasazione.** Il navigatore le indicava i vasi sanguigni come strada principale, la più veloce, la più efficace.

**Cellule tumorali circolanti nel flusso sanguigno.** Certo il viaggio non era stato affatto facile... tutt'altro. Aveva fatto il viaggio con alcune altre cellule come lei. Alcune cellule erano perite lungo il viaggio... ma lei, lei ce l'aveva fatta. Aveva la personalità giusta. Lei si era adattata e in questo modo era riuscita a sopravvivere.

**Colonizzazione.** Era arrivata nel nuovo organo la sera prima. Come tutti gli inizi, anche lì non era certamente stato facile. Era così diverso da casa sua... ma grazie al suo spirito di adattamento, si era sistemata. All'inizio si era anche sentita un po' sola, con un po' di nostalgia di casa, ma presto altre cellule tumorali l'avevano raggiunta.

**Metastasi conclamata.** Adesso, insieme, si sentivano più forti. Stavano sistemando la zona, così che fosse adatta a loro. Le nuove cellule del microambiente all'inizio erano state poco ospitali, ma poi avevano cambiato atteggiamento. Sì, MICante si sentiva nuovamente a casa. Era cambiata, era diversa da come era quando era partita, chissà se sarebbe mai stata come prima... ma era di nuovo a casa. La nuova metastasi era pronta. MICante sentiva che lì avrebbe proliferato ancora, scongiurando che non arrivasse qualche farmaco ad ucciderla e distruggere la loro casa...

famigliola di cellule straniere che si era accampata in un angolino dell'intestino. Berio e i suoi l'avevano ignorata, pensando che in fondo non avrebbe potuto fare un gran danno. Loro li chiamavano "cellule tumorali", perché erano diverse da tutte le altre cellule con cui ormai interagivano da anni in maniera estremamente produttiva. Eppure, le altre famiglie di batteri avevano spesso contatti con le cellule tumorali, fornendo loro un sacco di sostanze. Berio li aveva visti con i suoi stessi occhi... Grazie a queste sostanze l'accampamento di cellule tumorali cresceva molto rapidamente... A volte Berio pensava che avrebbe finito per dare fastidio alle cellule endogene. Berio e i suoi continuavano a fare il loro lavoro, ma un po' per lo stress un po' per il super-lavoro tanti di loro erano morti ed erano rimasti in pochi. Ormai c'erano più batteri delle gang di Coli che della famiglia di Berio! Ma oltre alle manifestazioni, in fondo, cosa potevano fare? Berio si buttò nuovamente sul lavoro, ma con la paura che la situazione non potesse far altro che peggiorare...

**Trapianto di microbiota fecale.** Finalmente le cose erano tornate alla normalità. Quando Berio aveva ormai perso le speranze, arrendendosi alle prepotenze di Coli e dei suoi compari, qualcuno era arrivato ad aiutarli. Attraverso un'operazione militare di pace, ben organizzata, di trapianto di microbiota fecale, numerose comunità erano venute ad aiutarli. La loro presenza, il loro lavoro, la loro completa collaborazione aveva permesso di sconfiggere le gang di Coli. Tutto era tornato alla normalità. Si lavorava ancora, certo, ma con serenità. Le cellule tumorali, non più nutrite dalle sostanze fornite da Coli e i suoi –Berio aveva scoperto che si trattava di Colibactina– erano sparite. Non c'erano più manifestazioni né scioperi; finalmente, un intestino sano e felice.

## Conoscerla per accettarla – Come percepiscono i medici l'integrazione dell'intelligenza Artificiale in ambito clinico?

In uno studio recente, i ricercatori IEO hanno valutato il modo in cui le persone percepiscono l'utilizzo di strumenti di Intelligenza Artificiale (AI), in particolare il chatbot ChatGPT, a scopo informativo, rivelando sia emozioni positive che preoccupazioni.



Image generated by ChatGPT

**L'utilizzo degli strumenti di AI da parte dei medici – l'opinione della gente.** Più recentemente, nell'ambito di una collaborazione, i ricercatori hanno effettuato un sondaggio per valutare la fiducia, e in generale le sensazioni, delle persone riguardo all'utilizzo di strumenti di AI da parte dei medici, nel percorso diagnostico. In questi anni sono stati infatti sviluppati, e sempre più spesso impiegati in ambito clinico, diversi modelli di AI, mostrandone il valore come strumenti di supporto nell'interpretazione delle immagini mediche, per migliorare l'accuratezza e accelerare il percorso diagnostico. Lo studio si è focalizzato in maniera specifica

sulla popolazione italiana e ha incluso sia pazienti (il questionario è stato diffuso in un centro oncologico, l'IEO) che cittadini in generale.

Sebbene sia necessaria una validazione dei risultati in coorti più ampie, possibilmente prive di potenziali bias associati a fattori demografici, lo studio ha evidenziato un atteggiamento generalmente positivo delle persone per quanto riguarda l'utilizzo dell'AI da parte dei medici, come strumento di supporto, che non sostituisca in nessun caso il medico. Inoltre, sebbene lo studio abbia sottolineato l'assenza di una reale preoccupazione della gente per aspetti come la privacy e la sicurezza dei dati personali (che vengono affrontati nell'implementazione e nella crescente integrazione degli strumenti di AI nel contesto clinico), lo studio ha invece evidenziato le preoccupazioni per quanto riguarda la responsabilità legale in caso di errori degli strumenti di AI (per alcuni completamente a carico del medico, per altri a carico dello sviluppatore dello strumento, per altri da condividere equamente dalle due parti). Lo studio fornisce una overview sull'attuale grado di accettazione da parte della popolazione dell'impiego di strumenti di AI in ambito sanitario, che rappresenta un punto chiave per l'effettiva integrazione di questi strumenti.

***L'utilizzo degli strumenti di AI da parte dei medici – l'opinione dei medici.*** Questo lavoro completa i dati raccolti nel contesto di altri studi precedentemente pubblicati sull'argomento, come quelli che riportano l'opinione dei medici, un altro aspetto importante nell'effettiva adozione degli strumenti di AI in ambito clinico. Un lavoro precedente (focalizzato soprattutto sulla popolazione tedesca, principalmente radiologi) ha analizzato l'atteggiamento dei clinici riguardo all'impiego degli strumenti di AI in ambito medico, valutando la loro opinione riguardo ai potenziali vantaggi e svantaggi associati con l'utilizzo dell'AI nelle scelte terapeutiche o nella comunicazione medico-paziente, e nelle implicazioni, come la responsabilità giuridica o la necessità di una formazione adeguata.

Lo studio ha evidenziato un generale entusiasmo (come l'apertura dei medici verso queste tecnologie, la loro curiosità, i benefici percepiti derivanti dall'utilizzo dell'AI), ma anche una certa dose di scetticismo e apprensione (legata a incertezza, percezione dei rischi, perdita di controllo e minaccia alla specializzazione medica). Infatti, sebbene persista una certa apprensione, nel complesso i medici si sono espressi positivamente a riguardo. In particolare, i dati hanno infatti evidenziato un diffuso interesse negli strumenti di AI, con una significativa percentuale di intervistati che ha affermato di avere una sufficiente familiarità con l'AI –sebbene pochi la usino per lavoro, ma intendano utilizzarla–, considerandola un valido supporto in ambito diagnostico. Per quanto riguarda la comunicazione medico-paziente, molti hanno affermato che l'AI sia in grado di migliorarla. Per quanto riguarda la responsabilità legale collegata all'adozione degli strumenti di AI in ambito sanitario, la maggioranza degli intervistati ha affermato che i medici dovrebbero essere considerati i principali responsabili di eventuali diagnosi e scelte terapeutiche sbagliate ottenute sfruttando questi strumenti, seguiti dagli sviluppatori e dagli ospedali. Lo studio ha anche evidenziato diverse preoccupazioni dei medici, probabilmente collegate al fatto che l'impiego diffuso di questi strumenti in ambito clinico sia ancora in uno stadio iniziale e pertanto siano necessarie delle migliorie –ad esempio nella digitalizzazione e nell'interoperabilità dei sistemi– che saranno verosimilmente realizzati in futuro, con la rifinitura dell'attuale tecnologia. Inoltre, pur sottolineando il potenziale di questa tecnologia –che è ritenuta imprescindibile per il futuro dei clinici– nell'aumentare l'accuratezza diagnostica e ridurre il carico di lavoro, liberando tempo da poter dedicare ai pazienti e a compiti più complessi, alcuni intervistati hanno sottolineato la necessità di una maggiore integrazione dell'AI nella formazione medica, per poterne cogliere appieno il potenziale. È interessante sottolineare che la familiarità con gli strumenti di AI sia emersa come un fattore in grado di predire nel complesso l'entusiasmo riguardo all'utilizzo dell'AI in ambito clinico (meno influenzato invece da età, sesso, e disciplina medica). Inoltre, sebbene alcuni intervistati riferiscano di temere un'eventuale riduzione delle expertise come conseguenza dell'eccessivo affidamento sugli strumenti di AI, lo studio pone ancora una volta l'enfasi sul fatto che l'esperienza di un medico non può essere sostituita e la decisione finale rimane sempre e comunque del medico.

Stiamo assistendo in questi anni ad una nuova rivoluzione tecnologica. Così come “Roma non è stata costruita in un giorno”, la piena integrazione dell'AI, in maniera responsabile, nei flussi di lavoro richiederà tempo, impegno e un'ottimizzazione continua, con un approccio pragmatico, in questa fase di transizione, fino a raggiungere la fase successiva, caratterizzata da un nuovo equilibrio, in cui le attuali criticità –come la necessaria interoperabilità dei sistemi, la formazione adeguata, linee guida chiare sull'adozione di questi

strumenti, aspetti etici e legali e così via– saranno risolte e potrà essere esplorato e sfruttato appieno il potenziale degli strumenti di AI; un tempo in cui gli strumenti di AI diventeranno parte integrante del nostro lavoro, proprio come oggi lo sono i computer.

*Referenze:* 1) *Public Perspectives on Artificial Intelligence in Medicine and Radiology: Insights From a Survey in an Italian Cancer Referral Center.* Filippo Pesapane, Emilia Giambersio, Anna Rotili, Roberto Grasso, Aurora Gaeta, Ottavia Battaglia, Lorenzo Conti, Silvia Francesca Maria Pizzoli, Sara Raimondi, Sara Gandini, Gabriella Pravettoni, and Enrico Cassano. *JCO Clinical Cancer Informatics* 2026. doi: /10.1200/CCI-25-00210. 2) *Physicians' Attitudes Toward Artificial Intelligence in Medicine: Mixed Methods Survey and Interview Study.* Helen Heinrichs; Alexander Kies; Saskia K Nagel; Fabian Kiessling. *J Med Internet Res* 2025. doi: 10.2196/74187.

## Trastuzumab deruxtecan – dallo studio clinico DESTINY-Breast06 nuove indicazioni per il trattamento del tumore al seno.

Ad oggi il trattamento standard (di prima linea) per il tumore al seno metastatico HR+/HER2 è la terapia endocrina (ET, che blocca la produzione di estrogeni, attraverso inibitori dell'aromatasi oppure composti in grado di modulare e degradare in maniera selettiva il recettore degli estrogeni), in combinazione con inibitori di CDK4/6 (CDKi). Molte pazienti, però, alla fine manifestano recidiva e, dopo la somministrazione dei CDKi, l'efficacia della ET diminuisce e gli effetti della chemioterapia sono limitati. Il trattamento delle pazienti con tumore al seno HR+ sta diventando sempre più personalizzato sulla base delle caratteristiche molecolari del tumore, come le mutazioni nei geni PIK3CA e ESR1, o l'espressione variabile di HER2 (con l'ulteriore classificazione dei tumori in HER2-low, HER2-ultralow o HER2-negative), che possono influenzare la sensibilità ad agenti anti-HER2 come l'anticorpo trastuzumab deruxtecan (T-Dxd).

Il clinical trial di fase III DESTINY-Breast06 ha confrontato l'efficacia di T-Dxd -rispetto alla chemioterapia- in pazienti con tumore al seno HER2-low e HER2-ultralow, precedentemente trattati con ET, mostrando benefici clinici nella popolazione con tumore HER2-low e portando all'approvazione di T-Dxd per il trattamento delle pazienti con tumore metastatico, non resecabile, HR+ e HER2-low e HER2-ultralow che hanno precedentemente ricevuto ET. Approfondendo i risultati del trial DESTINY- Breast06, i ricercatori, guidati da Giuseppe Curigliano -vice direttore

scientifico IEO e direttore della divisione nuovi farmaci per terapie innovative- hanno effettuato analisi ulteriori per ampliare i risultati raccolti nell'ambito dell'analisi primaria, valutando l'efficacia di T-Dxd in specifici sottogruppi di pazienti (ovvero, *i.* sulla base del tempo fino alla progressione della malattia durante il trattamento; *ii.* sulla base della gravità della malattia -*disease burden*-; *iii.* sulla base del tipo di resistenza a ET, acquisita o preesistente), fornendo così informazioni aggiuntive critiche per l'impiego di T-Dxd nel trattamento delle pazienti con tumore al seno nella pratica clinica. Sulla base dei diversi criteri considerati, i dati mostrano una maggiore efficacia di T-Dxd, rispetto a tutti gli agenti chemioterapici impiegati come controllo, in tutti i sottogruppi analizzati, indipendentemente dalla gravità della malattia, dalla resistenza a terapia endocrina, dal tempo fino alla progressione della malattia, offrendo nuove efficaci opzioni terapeutiche a pazienti che, per via delle caratteristiche specifiche del loro tumore, finora hanno mostrato, con gli attuali trattamenti standard, una prognosi sfavorevole.

### Gli autori – Giuseppe Curigliano

Giuseppe Curigliano è vice-direttore scientifico IEO, direttore della Divisione IEO Early Drug Development, professore ordinario di Oncologia Medica all'Università di Milano. E' inoltre responsabile della divisione clinica per i tumori solidi e presidente eletto ESMO. E' stato direttore della commissione di nomina ESMO (2017-2019) e della commissione ESMO per le linee guida pratiche cliniche (2019-2023), ed uno dei membri fondatori e co-direttore scientifico del "ESMO Breast Cancer Congress". Con una laurea in medicina all'Università Cattolica del Sacro Cuore di Roma e una specializzazione in Oncologia Medica, il Dr Curigliano ha continuato la sua formazione medica al Dipartimento di Immunologia Clinica della South Carolina Medical School, Hollings Cancer Center (Charleston, U.S.A.), e del Herbert Irving Comprehensive Cancer Center della Columbia University (New York, U.S.A). Ha inoltre ottenuto il suo dottorato in Fisiopatologia Medica e Farmacologia Clinica dell'Università di Pisa. La sua ricerca si focalizza su biomarcatori e terapie personalizzate, con particolare enfasi sull'identificazione di biomarcatori, sullo sviluppo di farmaci molecolari, e sull'integrazione della medicina personalizzata. Conduce studi clinici di fase I-III su terapie molecolari per il tumore al seno e supervisiona studi nazionali su larga scala finalizzati all'implementazione di tecnologie ad high-throughput nel sistema sanitario. Il Prof Curigliano è stato definito uno dei ricercatori più influenti da Clarivate (highly cited researchers) nel 2022, 2023, 2024. E' autore di oltre 900 articoli in riviste peer-reviewed (h-index 106) e molti capitoli di libri. Ha inoltre supervisionato e sponsorizzato dozzine di medici oncologi.

## TELL ME MORE!

DESTINY-Breast06 è stato un clinical trial multicentrico, randomizzato, di fase III. Lo studio ha arruolato 866 pazienti, che sono state casualmente assegnate a ricevere T-Dxd (436 pazienti) o chemioterapia (430 pazienti). L'efficacia è stata valutata in termini di sopravvivenza in assenza di progressione della malattia (PFS e PFS2, ovvero tempo dall'inizio del trattamento fino alla progressione durante la terapia di prima e di seconda linea, rispettivamente), risposta obiettiva (ORR), durata della risposta (DOR).

**Efficacia.** In linea con i risultati raccolti nell'intera popolazione del clinical trial DESTINY-Breast06, nel *gruppo 1*, che includeva pazienti selezionate sulla base del tempo fino alla progressione durante la terapia di prima linea e che ha coinvolto 570 pazienti che hanno ricevuto ET+CDKi come terapia di prima linea, la somministrazione di T-Dxd ha migliorato in maniera significativa PFS, ORR, DOR, PFS2 rispetto alla chemioterapia in tutti i sottogruppi, ovvero tra le pazienti in cui la malattia è progredita *a.* entro 6 mesi, oppure *b.* tra i 6 e i 12 mesi, o *c.* oltre i 12 mesi. Nelle pazienti in cui la malattia è progredita nei primi 6 mesi di terapia standard, che rappresentano la sottopopolazione più difficile, la somministrazione di T-Dxd ha determinato una ORR del 68%, rispetto al 25% delle pazienti trattate con chemioterapia, e una PFS mediana di 14 mesi rispetto ai 6.5 mesi nel gruppo trattato con chemioterapia, offrendo a queste pazienti una nuova efficace opzione terapeutica.

Nel *gruppo 2*, che includeva 864 pazienti con resistenza a terapia endocrina, si è osservato un miglioramento significativo in termini di PFS, ORR, DOR, PFS2 tra le pazienti trattate con T-Dxd rispetto alla chemioterapia (sia nelle 268 pazienti con resistenza primaria, sia nelle 596 pazienti con resistenza secondaria). Nelle pazienti con resistenza primaria, la somministrazione di T-Dxd induceva una ORR del 58% rispetto al 26% osservato in seguito al trattamento con chemioterapia, e una PFS mediana di 12.4 mesi nel gruppo trattato con T-Dxd rispetto ai 6.6 mesi nel gruppo trattato con chemioterapia. Le pazienti con resistenza primaria a terapia endocrina hanno spesso una prognosi sfavorevole; questo studio mostra che T-Dxd potrebbe rappresentare per loro una valida opzione terapeutica.

Nel *gruppo 3*, che includeva pazienti selezionate sulla base della gravità della malattia (*disease burden*, considerando la dimensione del tumore, il numero di siti diversi interessati dalle lesioni, presenza/assenza di malattia viscerale o epatica), che ha coinvolto 740 pazienti in totale, la somministrazione di T-Dxd ha determinato una migliore PFS, ORR, DOR, PFS2 in tutti i sottogruppi, indipendentemente dalla gravità della malattia.

**Sicurezza.** Il profilo di tossicità era in linea con quanto precedentemente riportato e l'incidenza degli eventi avversi collegati al trattamento era simile nelle pazienti trattate con T-Dxd e in quelle trattate con chemioterapia. Eventi avversi più gravi (di grado superiore a 3) e seri, che in alcuni casi hanno portato all'interruzione del trattamento, erano più frequenti nel gruppo trattato con T-Dxd.

Quindi, nonostante gli eventi avversi, in linea con il noto profilo di tossicità associato con questi farmaci, l'analisi ha mostrato la maggiore efficacia di T-Dxd rispetto a tutti i farmaci chemioterapici impiegati (secondo la scelta del medico) per il trattamento del tumore al seno HR+ HER2-low e HER2-ultralow, in caso di malattia più o meno grave, in quelle in cui la malattia è progredita precocemente o più tardi durante la terapia, in quelle che avevano manifestavano resistenza primaria o secondaria alla terapia endocrina.

**Referenza.** *Trastuzumab deruxtecan in hormone receptor-positive, HER2-low/-ultralow metastatic breast cancer (DESTINY-Breast06): outcome analyses by time to progression on prior first-line endocrine therapy with CDK4/6 inhibitor and baseline burden of disease.* G. Curigliano, X. Hu, R. Dent, K. Yonemori, C. H. Barrios, J.-Y. Pierga, F. Puglisi, J.-M. Ferrero, K. H. Jung, N. A. Bagegni, J. Collignon, M. Gil-Gil, X. Wu, A. Andrzejuk-Cwik, M. Schwaederle, S. Anand & A. Bardia. *ESMO Open* 2026. doi: 10.1016/j.annonc.2026.02.015.

# Prevenire la progressione della malattia nelle pazienti con tumore al seno metastatico – risultati promettenti dal clinical trial di fase III HER2CLIMB-05.

L'attuale terapia standard per le pazienti con tumore al seno HER2+ metastatico consiste in un primo periodo di trattamento (terapia di induzione) con immunoterapia (con anticorpi anti-HER2 trastuzumab e pertuzumab) e chemioterapia (con taxani) seguito da un secondo periodo di trattamento (terapia di mantenimento) con trastuzumab e pertuzumab. Nonostante la relativa efficacia di questo approccio nel controllare la malattia e prevenire la progressione, in molte pazienti la malattia progredisce.

Nel contesto dello studio clinico internazionale (randomizzato, placebo-controllato), di fase III HER2CLIMB-05, i ricercatori, tra cui Giuseppe Curigliano –vice-direttore scientifico IEO e direttore della divisione nuovi farmaci per terapie innovative– hanno valutato, in pazienti con tumore al seno metastatico HER+ (che hanno ricevuto trastuzumab, pertuzumab e taxani come terapia di induzione), efficacia e sicurezza dell'aggiunta

dell'inibitore tirosin-chinasico, altamente selettivo, tucatinib alla terapia di mantenimento con trastuzumab e pertuzumab.

I risultati hanno mostrato una significativa riduzione del rischio (36%) di progressione della malattia nelle pazienti che hanno ricevuto tucatinib, estendendo la sopravvivenza in assenza di progressione della malattia (*progression-free survival*, PFS) ad oltre due anni, indicando che per queste pazienti (in cui la malattia non è progredita dopo la terapia di induzione), la combinazione trastuzumab-pertuzumab-tucatinib potrebbe rappresentare un'opzione valida per un controllo efficace della malattia, con un profilo di tossicità gestibile.



Giuseppe Curigliano

## TELL ME MORE!

Le pazienti reclutate (con malattia localmente avanzata, ma non-resecabile, o metastatica) sono state casualmente assegnate a ricevere trastuzumab pertuzumab ed un placebo (gruppo placebo, 328 pazienti) oppure trastuzumab, pertuzumab e tucatinib (gruppo tucatinib, 326 pazienti), come terapia di mantenimento.

**Efficacia.** L'efficacia è stata valutata principalmente in termini di PFS, mostrando una riduzione del 36% del rischio di progressione della malattia: la PFS mediana era migliore nel gruppo tucatinib rispetto al gruppo placebo, essendo rispettivamente 24,9 mesi e 16,3 mesi. I benefici del trattamento con tucatinib erano mantenuti anche in tutti i sottogruppi di pazienti all'interno della coorte (ovvero, le pazienti con malattia positiva e negativa per il recettore degli ormoni, così come in presenza o assenza di metastasi cerebrali). Tra le pazienti che avevano metastasi cerebrali prima dell'inizio della terapia di mantenimento, la PFS mediana era di 8.5 mesi nel gruppo tucatinib e 4.3 nel gruppo placebo.

**Sicurezza.** Il profilo di tossicità del tucatinib in combinazione con trastuzumab e pertuzumab era in linea con i profili di sicurezza di questi farmaci in queste pazienti. In ogni caso, eventi avversi di grado superiore a 3 o seri si manifestavano più frequentemente nel gruppo tucatinib (42.3% and 16,9%) che nel gruppo placebo (24.4% and 8%; gli eventi avversi seri più frequenti erano casi di tossicità epatica indotta dal trattamento; in

ogni caso, la tossicità epatica era asintomatica e reversibile attraverso una riduzione del dosaggio) e l'interruzione del trattamento dovuta a eventi avversi indotti dalla terapia era necessaria più spesso nel gruppo tucatinib (13.8% delle pazienti) che nel gruppo placebo (4.6%).

*Referenza: HER2CLIMB-05: A Phase III Study of Tucatinib Versus Placebo in Combination With Trastuzumab and Pertuzumab as First-Line Maintenance Therapy for HER2<sup>+</sup> Metastatic Breast Cancer. Veronique Dieras, Giuseppe Curigliano, Miguel Martin, Florence Lerebours, Junji Tsurutani, Marie-France Savard, Katarzyna J. Jerzak, Xichun Hu, Luciana Carla Martins de Aquino Pimentel, Ciara C. O'Sullivan, Eriko Tokunaga, Alicia Okines, Chiun-Sheng Huang, William Jacot, Joohyuk Sohn, Eduardo Cronemberger Silva, Volkmar Mueller, Shan Yang, Giovanna Granata, Qi Shen, Libero Santarpia, and Erika Hamilton, on behalf of the HER2CLIMB-05 Investigators. Journal of Clinical Oncology 2025. doi: 10.1200/JCO-25-02600.*

## Uno studio per valutare la qualità di vita delle pazienti nel contesto del clinical trial EMBER-3.

Le pazienti con tumore al seno in stadio avanzato, in cui la malattia è progredita e che hanno sviluppato resistenza alla terapia endocrina (ET), possono essere trattate con molecole che degradano i recettori degli estrogeni, come fulvestrant -che è spesso usato in pazienti che hanno sviluppato resistenza ad inibitori dell'aromatasi- o imlunestrant -un composto di ultima generazione, in grado di degradare il recettore degli estrogeni, di attraversare la barriera emato-encefalica e che, nell'ambito di studi preclinici, si è dimostrato efficace contro i tumori con ESR mutato e non mutato.

Recentemente, lo studio clinico di fase III, multicentrico, randomizzato, EMBER-3 ha valutato l'efficacia di imlunestrant, da solo o in combinazione con abemaciclib, rispetto al fulvestrant, nelle pazienti con tumore al seno HR+/HER2- in cui la malattia è progredita durante il trattamento di prima linea con ET e inibitori di CDK4/6, mostrando benefici clinici nelle pazienti con mutazioni del gene ESR e -sebbene in maniera minore- nelle pazienti senza mutazioni del gene ESR, portando all'approvazione da parte di FDA e EMA di imlunestrant per il trattamento delle pazienti con tumore al seno HR+/HER2- in stadio avanzato in cui la malattia è progredita durante la terapia endocrina.

Ad ulteriore conferma dell'approccio paziente-centrico dei medici IEO e l'attenzione riservata al benessere del paziente durante il percorso terapeutico, nel contesto dello studio clinico EMBER-3, i ricercatori coordinati da Giuseppe Curigliano -vice-direttore scientifico IEO e direttore della divisione nuovi farmaci per terapie innovative- hanno analizzato la qualità di vita delle pazienti in cura, utilizzando delle misure standardizzate (basate su dei questionari) per valutare quantitativamente l'effettivo impatto del trattamento e, attraverso analisi qualitative (tramite interviste), l'impatto sulle pazienti della somministrazione orale di imlunestrant rispetto alla somministrazione intramuscolare di fulvestrant.

I risultati hanno mostrato che sebbene la qualità di vita (QoL) era nel complesso stabile sia nelle pazienti trattate con imlunestrant che in quelle trattate con fulvestrant, indipendentemente dalla mutazione del gene ESR, il periodo di tempo prima del deterioramento della QoL era leggermente più lungo nelle pazienti trattate con imlunestrant rispetto alle pazienti trattate con fulvestrant, e solo appena negativamente influenzato dall'aggiunta di abemaciclib. Inoltre, non si osservavano differenze significative tra la popolazione con ESR mutato e quella con ESR non mutato.

Per quanto riguarda l'analisi qualitativa dell'atteggiamento delle pazienti verso la somministrazione orale (imlunestrant) rispetto a quella intramuscolare (fulvestrant) del farmaco, le pazienti hanno riportato nel complesso un atteggiamento positivo nei confronti di entrambi gli approcci, con pro e contro per entrambi. Quindi, complementando i risultati sull'efficacia e la sicurezza raccolti nel contesto del clinical trial EMBER-3, le analisi quantitative e qualitative condotte nell'ambito di questo lavoro supportano l'utilizzo di imlunestrant, da solo o in combinazione con abemaciclib, come opzione terapeutica per le pazienti con tumore al seno ER+/HER2- avanzato in cui la malattia è progredita durante la terapia endocrina.

**TELL ME MORE!**

Lo studio EMBER-3 era principalmente volto a valutare l'efficacia e la sicurezza di Imlunestrant + abemaciclib vs imlunestrant da solo vs standard of care (exemestane).

Gli autori hanno però condotto analisi parallele *i.* quantitative, per valutare la qualità di vita delle pazienti (attraverso dei questionari) e *ii.* qualitative (attraverso delle interviste), per valutare l'impatto sulla vita quotidiana dell'assunzione di imlunestrant orale o fulvestrant intramuscolare.

Lo studio includeva 874 pazienti: 331 sono state casualmente assegnate a ricevere imlunestrant e 292 assegnate a ricevere fulvestrant (da solo o in combinazione con abemaciclib).

**Analisi quantitativa – qualità di vita.** Le misurazioni della qualità di vita (QoL) effettuate attraverso i questionari hanno mostrato che, nel complesso, la QoL era stabile sia nel gruppo di trattamento con imlunestrant sia in quello con fulvestrant.

Il periodo di tempo prima del deterioramento della QoL era leggermente più lungo nelle pazienti trattate con imlunestrant rispetto a quelle trattate con fulvestrant. La sintomatologia era simile e non si osservavano differenze significative tra le pazienti con e senza mutazioni nel gene ESR, in entrambi i gruppi di trattamento. Nell'intera popolazione di pazienti analizzata, i sintomi apparivano lievemente meno gravi nel gruppo trattato con imlunestrant (di grado leggermente superiore nel gruppo trattato con terapia di combinazione rispetto alla monoterapia). Circa il 70% delle pazienti trattate con fulvestrant (intramuscolare) riportava un lieve discomfort dovuto a reazioni a livello del sito di iniezione.

**Analisi qualitativa – somministrazione orale vs intramuscolare del farmaco.** Nel complesso, le pazienti hanno riportato un atteggiamento positivo per entrambi i farmaci, soprattutto per via degli effetti collaterali più lievi rispetto ad altri trattamenti, con un impatto minimo sulla vita quotidiana. La facilità di gestione era un aspetto positivo collegato alla somministrazione orale di imlunestrant, mentre il periodo di digiuno necessario prima dell'assunzione del farmaco è stato riportato come un aspetto negativo. Per quanto riguarda la somministrazione intramuscolare di fulvestrant, la frequenza di iniezione (mensile) è stata riportata come aspetto positivo, mentre il dolore al sito di iniezione e il viaggio/la visita medica sono stati elencati come aspetti negativi.

*Referenza.* Patient-reported outcomes and qualitative interviews in patients with estrogen receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer: results from the phase III EMBER-3 trial. G. Curigliano, J. O'Shaughnessy, F.-C. Bidard, M. L. Casalnuovo, S.-B. Kim, E. Tokunaga, P. Aftimos, C. Saura, L. A. Carey, M. Okera, E. Melo, F. Zagouri, M. Magallanes-Maciel, N. Karadurmus, S. Bahadur, R. M. Speck, X. A. Wang, K. Pradhan, J. Macey, H. Kitchen, S. Fairhurst, J. Miller, K. L. Jhaveri & N. Harbeck. ESMO Open 2026. doi: 10.1016/j.esmoop.2026.106945.

## **Chirurgia robotica per il trattamento del tumore al seno – uno studio clinico randomizzato per valutarne l'efficacia lungo termine.**

Per la sua natura minimamente invasiva, la chirurgia robotica con conservazione del capezzolo (*nipple-sparing*) è sempre più spesso impiegata come alternativa alla più invasiva chirurgia convenzionale (a cielo aperto), per il trattamento del tumore al seno. Studi precedenti hanno riportato la fattibilità e la sicurezza di questo approccio; tuttavia, ad oggi non è disponibile una valutazione dell'efficacia di questo approccio chirurgico nel controllo della malattia a lungo termine né un confronto con la chirurgia convenzionale.

Al fine di fornire solidi dati sperimentali, nel contesto di uno studio prospettico, randomizzato, di fase III, i ricercatori coordinati da Paolo Veronesi-Direttore del Programma Senologia e della Divisione di Senologia Chirurgica di IEO- hanno confrontato l'esito oncologico a lungo termine dell'impiego della chirurgia robotica e della chirurgia convenzionale per il trattamento delle donne con tumore al seno in IEO.

Ad un follow-up di oltre sei anni, i risultati non hanno mostrato alcuna differenza significativa in termini di sopravvivenza tra i due approcci. Sebbene sia importante sottolineare che i risultati sono stati raccolti in un singolo centro oncologico-IEO-, i dati indicano un'eguale efficacia della chirurgia robotica rispetto a quella

convenzionale, mostrando come la chirurgia robotica sia altrettanto efficiente nella rimozione del tessuto mammario residuo e dei margini tumorali. Quindi, sebbene l'accurata selezione delle pazienti ed expertise adeguata restino due aspetti fondamentali, i dati indicano che la chirurgia robotica può essere impiegata con successo nell'eliminare il tumore primario, senza quindi compromettere, sul lungo termine, l'esito clinico.

#### La chirurgia robotica.

La chirurgia robotica è una tecnica chirurgica minimamente invasiva che sfrutta bracci robotici controllati dal chirurgo, consentendo movimenti più precisi e una visione tridimensionale del campo operatorio, migliorando la qualità delle manovre e consentendo un recupero post-operatorio più rapido del paziente. Sebbene più complessa, e richiedendo expertise specifiche, la chirurgia robotica rappresenta un'evoluzione della chirurgia mini-invasiva, con notevoli vantaggi in termini di precisione.

### TELL ME MORE!

Sessantanove pazienti con tumore al seno (invasivo o localizzato) in IEO sono state casualmente assegnate ad un trattamento con chirurgia convenzionale a cielo aperto o robotica. Il trattamento post-chirurgico è stato definito indipendentemente dall'approccio chirurgico utilizzato, secondo le linee guida standard, in accordo con le caratteristiche della paziente e del tumore, adeguatamente bilanciate nei due gruppi di trattamento.

In termini di sopravvivenza, ad un follow-up di oltre 6 anni (follow-up mediano di 6.5 anni), l'esito clinico oncologico era paragonabile nei due gruppi, senza differenze statisticamente significative in termini di sopravvivenza generale (*overall survival*, OS) a 5 anni (97.1% in tutti e due i gruppi), sopravvivenza in assenza di malattia (88.2% e 88.6% nella chirurgia



Paolo Veronesi

robotica e nella chirurgia convenzionale rispettivamente) e sopravvivenza specifica oncologica (91% e 91.2% nei due gruppi rispettivamente). In termini di recidiva, la recidiva locale si è manifestata in tre pazienti trattate con chirurgia robotica e in due pazienti trattate con chirurgia convenzionale. Per quanto riguarda le metastasi distanti, non sono state invece osservate differenze significative.

In futuro, ampi studi clinici multi-centrici potranno valutare in maniera specifica la non-inferiorità oncologica della chirurgia robotica rispetto alla chirurgia convenzionale.

#### Gli autori – Paolo Veronesi e Antonio Toesca.

Con una laurea in Medicina e Chirurgia dall'Università di Milano, una specializzazione in Chirurgia Plastica Ricostruttiva e una in Chirurgia Generale dall'Università di Milano, **Paolo Veronesi** dirige da oltre 10 anni la Divisione di Chirurgia Senologica di IEO. Il suo contributo a livello clinico e di ricerca è stato cruciale per lo sviluppo di approcci innovativi per il trattamento del tumore al seno in IEO, tra cui la tecnica del linfonodo sentinella, la localizzazione radio-guidata delle lesioni non palpabili, la radioterapia intra-operatoria e tutte le innovazioni nell'ambito della chirurgia ricostruttiva volte a minimizzare lo stress psicologico della malattia.

Laureato in Medicina e Chirurgia e con una specializzazione in Chirurgia Generale dall'Università di Milano, **Antonio Toesca** è cresciuto professionalmente all'Istituto Europeo di Oncologia dove ha lavorato come chirurgo senologo per 15 anni.

**Referenza.** Long-term oncological outcomes of robotic mastectomy for breast cancer: a randomized clinical trial. Antonio Toesca, Francesca Magnoni, Claudia Sangalli, Patrick Maisonneuve, Alessandra Gottardi, Alessandra Margherita De Scalzi, Elisa Ileana Bottazzoli, Andrea Polizzi, Nickolas Peradze, Daniele Presti, Alberto Concardi, Nicola Fusco, Francesca De Lorenzi, Giovanni Corso, Viviana Galimberti and Paolo Veronesi. *BJS* 2026. doi: 10.1093/bjs/znag007.

# Nuove opzioni di trattamento per il tumore ovarico recidivo, resistente alla chemioterapia – risultati di due clinical trial di fase III.

Nonostante i progressi nel trattamento del tumore ovarico, molte pazienti, dopo un'iniziale risposta al trattamento, vanno incontro a recidiva, spesso con malattia resistente alla chemioterapia. In questi casi, la prognosi non è favorevole, sottolineando la necessità di identificare degli approcci terapeutici nuovi ed efficaci.

L'immunoterapia con inibitori dei checkpoint immunitari (ICI), da sola o in combinazione con chemioterapia, ha mostrato una scarsa efficacia in queste pazienti, ma, nell'ambito di studi preclinici e clinici, i ricercatori hanno osservato che la chemioterapia può aumentare l'immunogenicità del cancro e ridurre l'immunosoppressione nel microambiente tumorale (TME), quando somministrata settimanalmente, a basse dosi. In linea con questi dati, studi clinici precedenti hanno rivelato una buona efficacia, in queste pazienti, della combinazione di ICI (pembrolizumab) e chemioterapia metronomica. Sulla base di queste conoscenze meccanicistiche, nel contesto dello studio clinico di fase III ENGOT-ov65/KEYNOTE-B96, i ricercatori guidati da Nicoletta Colombo-Direttrice del Programma Ginecologia di IEO- hanno valutato sicurezza ed efficacia della somministrazione (in seconda o terza linea) dell'immunoterapico pembrolizumab insieme al chemioterapico paclitaxel somministrato settimanalmente (con o senza bevacizumab) rispetto all'attuale terapia standard per le pazienti con tumore ovarico platino-resistente (ovvero solo paclitaxel, somministrato settimanalmente, ed un placebo). I risultati dello studio ENGOT-ov65/KEYNOTE-B96 - recentemente pubblicati sulla rivista *The Lancet*- hanno evidenziato dei benefici statisticamente e clinicamente significativi della somministrazione di pembrolizumab insieme alla chemioterapia settimanale nel tumore ovarico recidivo, platino-resistente, sia in termini di sopravvivenza in assenza di progressione della malattia (*progression-free survival*, PFS) che di sopravvivenza generale (*overall survival*, OS), indipendentemente dall'aggiunta di bevacizumab. ENGOT-ov65/KEYNOTE-B96 è il primo studio di fase III che ha mostrato dei benefici clinici della terapia a base di ICI in questa popolazione di pazienti. Lo studio sottolinea inoltre il ruolo della chemioterapia settimanale nell'aumentare l'efficacia dell'immunoterapia.

Sulla base di questi risultati, questa terapia di combinazione è ora una delle opzioni raccomandate per le pazienti con tumore ovarico recidivante (ed espressione elevata di PDL1), rendendo l'immunochemioterapia una nuova opzione di trattamento standard.

“Questo trattamento -spiega Nicoletta Colombo- ha ricevuto l'approvazione della autorità regolatoria Europea EMA; siamo in attesa di ricevere la rimborsabilità da parte della autorità regolatoria italiana AIFA per poterlo proporre alle pazienti italiane”.

*Alex, puoi scrivere qualcosa su Pembrolizumab, Paclitaxel and nab-paclitaxel, Bevacizumab, Relacorilant?*

**Pembrolizumab** è un anticorpo monoclonale umanizzato anti-PD-1. Si lega al recettore PD-1 sui linfociti T, bloccando l'interazione con PD-L1/PD-L2 e ripristinando l'attività immunitaria antitumorale. Appartiene alla classe degli inibitori dei checkpoint immunitari, favorendo il riconoscimento e la distruzione delle cellule tumorali.

**Paclitaxel** è un agente chemioterapico della classe dei tassani. Stabilizza i microtubuli legandosi alla tubulina, impedendone la depolimerizzazione e bloccando la mitosi. Questo porta all'arresto del ciclo cellulare in fase G2/M e alla morte cellulare, soprattutto nelle cellule tumorali a rapida proliferazione. **Nab-paclitaxel** è una formulazione di paclitaxel legata ad albumina (nanoparticelle). Mantiene il meccanismo dei tassani (stabilizzazione dei microtubuli), ma migliora la

Nel contesto di un altro studio clinico di fase III -ROSELLA-, i ricercatori, tra cui Nicoletta Colombo, hanno valutato l'efficacia della somministrazione combinata di relacorilant e nab-paclitaxel in pazienti con tumore ovarico, recidivante, platino-resistente. Gli antagonisti del recettore dei glucocorticoidi, come relacorilant, rappresentano un nuovo approccio terapeutico al trattamento del tumore ovarico. Studi preclinici hanno precedentemente dimostrato che, agendo su questo recettore, il cortisolo sostiene la sopravvivenza delle cellule tumorali, aumentando l'espressione delle proteine anti-apoptotiche. L'azione inibitoria di relacorilant sui segnali indotti dal cortisolo aumenta la sensibilità dei tumori a diversi chemioterapici. Il recettore dei glucocorticoidi è espresso dalle cellule tumorali della

distribuzione tumorale tramite trasporto mediato da albumina. Riduce l'uso di solventi e può aumentare l'efficacia e la tollerabilità.

**Bevacizumab** è un anticorpo monoclonale anti-VEGF-A. Inibisce l'angiogenesi tumorale legandosi al fattore di crescita endoteliale vascolare (VEGF), impedendo l'attivazione dei suoi recettori. Riduce la formazione di nuovi vasi sanguigni necessari alla crescita e alla diffusione del tumore.

**Relacorilant** è un antagonista selettivo del recettore dei glucocorticoidi (GR). Modula gli effetti del cortisolo senza attività antagonista sul recettore del progesterone. È studiato per contrastare la resistenza ai trattamenti oncologici e gli effetti del cortisolo nel microambiente tumorale.

maggior parte (95%) dei tumori ovarici. Sulla base di queste conoscenze meccanicistiche, lo studio ROSELLA ha valutato quindi sicurezza ed efficacia della sinergia tra relacorilant e chemioterapia, mostrando dei benefici clinici significativi (in termini di PFS, PFS2, OS) in pazienti con tumore ovarico, recidivo, platino-resistente, pesantemente pretrattati, proponendo relacorilant+nab-paclitaxel come una nuova potenziale opzione terapeutica per queste pazienti, senza la necessità di una selezione sulla base di biomarcatori. I risultati sono stati recentemente pubblicati sulla rivista *The Lancet*

## TELL ME MORE!

### Lo studio clinico ENGOT-ov65/KEYNOTE-B96.

Lo studio ha coinvolto 187 diversi centri oncologici in 25 paesi. Le 643 pazienti arruolate sono state casualmente assegnate a ricevere pembrolizumab + chemioterapia settimanalmente (paclitaxel, 322 pazienti) o placebo + paclitaxel settimanalmente (321 pazienti). Alcune pazienti hanno ricevuto anche bevacizumab; in molte partecipanti l'espressione tumorale della proteina PDL1, target di pembrolizumab, era elevata.

**Efficacia.** Lo studio prevedeva due analisi intermedie e un'analisi finale. L'efficacia è stata valutata in termini di sopravvivenza in assenza di PFS e OS. Alla prima analisi intermedia, la PFS era significativamente aumentata nelle pazienti trattate con pembrolizumab+chemioterapia rispetto alle pazienti trattate con chemioterapia+placebo, sia nell'intera popolazione che nel sottogruppo con elevata espressione tumorale di PDL1; la OS, invece, non era significativamente differente. Alla seconda analisi intermedia, anche la OS risultava aumentata, sia nell'intera popolazione che nel sottogruppo caratterizzato da un'elevata espressione tumorale di PDL1. L'analisi finale ha confermato i risultati sull'efficacia del trattamento, mostrando un aumento significativo sia di PFS che di OS, così come una migliore risposta obiettiva e una maggiore durata della risposta.

Sebbene alcune pazienti avessero ricevuto bevacizumab in aggiunta a pembrolizumab e chemioterapia, i benefici clinici erano evidenti indipendentemente dalla somministrazione di bevacizumab.

**Sicurezza.** Nel complesso, il profilo di sicurezza era in linea con la nota tossicità associata ai due agenti somministrati separatamente ed era principalmente legata alla chemioterapia. Nello specifico, tutte le partecipanti hanno manifestato eventi avversi (AE); AE di grado 3 legati al trattamento sono stati osservati nel 68% delle pazienti nel gruppo pembrolizumab+paclitaxel, portando all'interruzione del trattamento in 38% di loro, e nel 55% delle pazienti nel gruppo chemioterapia+placebo, determinando l'interruzione del trattamento nel 28% di esse. È stata valutata anche la qualità di vita (QoL), tramite dei questionari, mostrando un miglioramento (o comunque una QoL stabile) nel 59% delle pazienti nel gruppo pembrolizumab+chemioterapia e nel 61% delle pazienti nel gruppo chemioterapia+placebo.

**Il biomarcatore PDL1.** Nonostante la nota eterogeneità intratumorale, in termini di espressione di PDL1, nel tumore ovarico e la maggiore efficacia generalmente osservata nei tumori che esprimono PDL1, gli agenti anti-PDL1 hanno mostrato un certo grado di efficacia anche nei tumori con livelli bassi di PDL1, suggerendo che, nonostante l'espressione di PDL1 sia un biomarcatore in grado di identificare i potenziali responder e quindi guidare la scelta di trattamento, altri fattori potrebbero essere coinvolti nel dar forma alla risposta a pembrolizumab e l'identificazione di biomarcatori aggiuntivi potrebbe contribuire a rifinire la selezione dei pazienti, le scelte terapeutiche e quindi l'esito clinico.

### Lo studio clinico ROSELLA.

Lo studio ha arruolato 381 pazienti con tumore ovarico recidivo, platino-resistente (che avevano già ricevuto da una a tre precedenti linee di terapia), in 117 diversi centri oncologici, in 14 paesi, che sono state casualmente assegnate a ricevere relacorilant + nab-paclitaxel (188 pazienti) o solo nab-paclitaxel (193

pazienti).

**Efficacia.** L'efficacia è stata valutata in termini di PFS, PFS2, OS. La OS era significativamente aumentata con la terapia di combinazione (OS mediana di 4.1 mesi più lunga rispetto al gruppo trattato con terapia di combinazione, e una maggiore proporzione di pazienti vive nel gruppo trattato con terapia di combinazione rispetto alla monoterapia -46% vs 27% rispettivamente- a 18 mesi). Gli effetti sulla OS erano sempre più evidenti durante il periodo di followup, suggerendo un effetto a lungo termine di relacorilant. In linea con i risultati dell'analisi intermedia precedentemente pubblicati, la PFS era significativamente più lunga. Infatti, i trattamenti successivi sono stati iniziati più tardi nel gruppo trattato con terapia di combinazione rispetto al gruppo trattato in monoterapia (6.2 mesi vs 5.6 mesi). I benefici del trattamento di combinazione su OS e PFS sono stati osservati in tutti i sottogruppi, ovvero quelli che avevano ricevuto una, due, o tre precedenti linee di terapia.

**Sicurezza.** Nel complesso, eventi avversi gravi, di grado 3 o più alto, erano leggermente più comuni nella terapia di combinazione che nella monoterapia (eppure molto simili dopo aggiustamenti sulla base di fattori come l'età) e gestiti con terapia standard. Non sono stati osservati nuovi segni di tossicità né decessi legati al trattamento.

La valutazione della qualità di vita riportata dalle pazienti non ha mostrato differenze significative, ma nel complesso la terapia combinata appariva ben tollerata dalle pazienti.

#### *Gli autori – Nicoletta Colombo.*

Nicoletta Colombo è Direttrice del Programma Ginecologia di IEO Con una laurea in medicina e una specializzazione in ostetricia e ginecologia presso l'Università degli Studi di Milano, ha perfezionato la sua formazione presso il Charing Cross Hospital e il Royal Marsden Hospital di Londra, e successivamente, come Clinical Research Associate presso il Kaplan Cancer Center della New York University. Successivamente, ha lavorato presso il Dipartimento di Ostetricia e Ginecologia dell'Università degli Studi di Milano. Nel 2008 è diventata Direttrice del Centro per il Cancro Ovarico dell'IEO e dal 2014 è Presidente del Programma di Ginecologia.

**Referenze:** 1) Pembrolizumab plus weekly paclitaxel in platinum-resistant recurrent ovarian cancer (ENGOT-ov65/KEYNOTE-B96): a multicentre, randomised, double-blind, phase 3 study. Nicoletta Colombo, Emese Zsiros, Gabriella Parma, Eliana Rulli, Alexandra Sebastianelli, Mariusz Bidzinski, Carlos Gallardo, Emad Matanes, Kosei Hasegawa, Fatih Kose, Manuel Magallanes-Maciuel, Rebecca A Herbertson, Sumitra Ananda, Judith R Kroep, Andrea Cristina de Melo, Philip R Debruyne, Jae-Weon Kim, Jalid Sehoul, Marc-Edy Pierre, Sakari Hietanen, Claudio Zamagni, Xin Lu, Bradley J Monk, Robert L Coleman, Xuan Peng, Karin Yamada, Agata M Bogusz, Thibault De La Motte Rouge, Xiaohua Wu, on behalf of the ENGOT-ov65/KEYNOTE-B96 investigators. Lancet 2026. doi: 10.1016/S0140-6736(26)00602-1. 2) Overall survival with relacorilant and nab-paclitaxel in patients with platinum-resistant ovarian cancer (ROSELLA): a phase 3 randomised controlled trial. Domenica Lorusso, Laurence Gladieff, David M O'Malley, Jae-Weon Kim, Gabriel Garbaos, Anna Fagotti, Lucy Gilbert, Linda Mileskin, Stanislas Quesada, Elizabeth Hopp, Yong Jae Lee, Ana Oaknin, Mariana Scaranti, Byoung-Gie Kim, Andrew Clamp, Christina Prillaman, Connie Diakos, Andrea Bagaméri, Aliza L Leiser, Vanda Salutari, Bradley J Monk, Philippe Follana, Emily McClung, Vittoria Carbone, Brian Slomovitz, Elena Giudice, Maria Chiara Cannizzaro, Laurène Gavoille, Alix Devaux, Paolo Scollo, Giuseppa Scandurra, Chiara Cassani, Grazia Artioli, Toon Van Gorp, Ana Santaballa, Lyndah K Dreiling, Amanda Kesner-Hays, Iulia Cristina Tudor, Adrian M Jubb, Nicoletta Colombo, Alexander B Olawaiye. Lancet 2026. doi: 10.1016/S0140-6736(26)00462-9.

## **La giusta dose di farmaco per ridurre gli effetti collaterali nelle pazienti con tumore ovarico trattate con niraparib – uno studio clinico randomizzato.**

I risultati di precedenti studi clinici hanno portato all'approvazione di olaparib, niraparib e rucaparib come terapia di mantenimento nelle pazienti con carcinoma ovarico dopo chemioterapia a base di platino. Questi farmaci sono complessivamente ben tollerati, ma la tossicità ematologica è frequente e gli eventi avversi correlati al trattamento portano all'interruzione della terapia in una percentuale non trascurabile di pazienti. Il peso corporeo e la conta piastrinica basale sembrano essere correlati con l'incidenza di tossicità

ematologica (in particolare trombocitopenia) nelle pazienti trattate con niraparib. Nell'ambito dello studio clinico NEWTON, ricercatori guidati da Nicoletta Colombo –Direttrice del Programma di Ginecologia dell'IEO– hanno effettuato un'analisi sistematica per valutare gli effetti sulla tossicità ematologica di una potenziale strategia di dosaggio (RADAR = *Rational Adjustment of Dose to reduce Adverse Reactions*), finalizzata a ridurre gli eventi avversi correlati al trattamento (principalmente eventi ematologici come la trombocitopenia), sulla base di due fattori identificati come fortemente correlati: il peso corporeo e la conta piastrinica basale.

Lo studio ha evidenziato una riduzione significativa dell'incidenza di tossicità ematologica severa (trombocitopenia) nelle pazienti con peso compreso tra 58 e 77 kg, oppure  $\geq 77$  kg con conta piastrinica  $< 150.000/\mu\text{L}$  trattate con una dose più bassa di niraparib secondo RADAR (200 mg/die), rispetto a quelle trattate con la dose standard, più elevata (300 mg/die); l'incidenza era rispettivamente del 4% contro il 42%. Nonostante la dose ridotta, l'efficacia è apparsa comparabile (sebbene i dati disponibili non fossero statisticamente sufficienti per



*Nicoletta Colombo*

conclusioni definitive), suggerendo che la strategia RADAR, personalizzando il regime terapeutico in base ad alcune caratteristiche specifiche delle pazienti, potrebbe rappresentare un'opzione terapeutica valida per ottenere esiti clinici simili con un miglior benessere delle pazienti.

## TELL ME MORE!

NEWTON è stato uno studio clinico prospettico di fase II che ha arruolato pazienti con carcinoma ovarico sensibile al platino (già trattate con almeno due precedenti linee di terapia a base di platino). Le pazienti con peso  $< 58$  kg sono state assegnate a 200 mg (RADAR), mentre quelle con peso  $\geq 77$  kg e conta piastrinica basale  $\geq 150.000/\mu\text{L}$  sono state assegnate a 300 mg (RADAR). Le pazienti con peso  $\geq 58$  e  $< 77$  kg, oppure  $\geq 77$  kg con conta piastrinica  $< 150.000/\mu\text{L}$  sono state randomizzate a ricevere la dose standard di 300 mg/die di niraparib oppure, secondo protocollo RADAR, 200 mg/die. Complessivamente, 41 pazienti hanno ricevuto la dose più bassa (24 randomizzate, 17 non randomizzate) e 41 la dose più alta (24 randomizzate, 17 non randomizzate).

I parametri valutati erano: *i*) la percentuale di pazienti con trombocitopenia severa (grado  $\geq 3$ ) durante la somministrazione di niraparib, per l'analisi di sicurezza; *ii*) la sopravvivenza libera da progressione (PFS) e la sopravvivenza globale (OS) per l'efficacia clinica.

I risultati sono stati confrontati con dati esistenti (raccolti nello studio NOVA).

**Tossicità.** Eventi avversi (EA) di qualsiasi tipo si sono verificati in quasi tutte le pazienti. Gli EA ematologici si sono verificati in oltre il 10% delle pazienti; tra queste, il 57,9% era rappresentato da trombocitopenia. Nel braccio randomizzato a dose più bassa, il 45,8% delle pazienti ha presentato trombocitopenia, contro il 67% nel braccio a dose più alta. Le riduzioni del dosaggio per eventi avversi sono state più frequenti nel braccio a dose più alta.

L'incidenza di trombocitopenia severa (grado  $\geq 3$ ) è risultata significativamente più elevata nelle pazienti trattate con la dose più alta rispetto a quelle trattate con la dose più bassa (42% vs 4%) nella parte randomizzata dello studio.

**Farmacocinetica.** Il monitoraggio delle concentrazioni plasmatiche del farmaco non ha evidenziato correlazioni con la trombocitopenia severa, mentre i livelli di creatinina e il peso corporeo sembravano correlati a livelli più bassi di niraparib, suggerendo un possibile effetto delle caratteristiche delle pazienti sulla farmacocinetica e quindi sull'esposizione al farmaco.

**Efficacia.** L'efficacia del trattamento è stata valutata in termini di PFS e OS. Nella coorte randomizzata, non sono state osservate differenze significative nella PFS tra i due dosaggi: la PFS mediana era di 10,3 mesi nel braccio a dose bassa e 11,7 mesi nel braccio a dose alta; la PFS a 6 mesi era rispettivamente del 71% e del 78%. Nell'intera coorte, la PFS mediana era di 10 mesi e la PFS a 6 mesi del 75%.

Per quanto riguarda la OS, non sono emerse differenze significative tra i due bracci randomizzati (37,9 mesi con 200 mg/die e 36,4 mesi con 300 mg/die). La OS a 24 mesi era rispettivamente dell'87,7% e del 77,9% nei bracci a dose bassa e alta.

**Conclusioni.** Nel complesso, i risultati indicano che il dosaggio ridotto di niraparib secondo la strategia RADAR (200 mg/die) è associato a una minore incidenza di trombocitopenia severa, con un'efficacia apparentemente comparabile e valori di PFS e OS in linea con i dati di riferimento dello studio NOVA.

*Referenza. Rational adjustment of dose to reduce adverse reactions (RADAR) in patients with platinum-sensitive recurrent ovarian cancer: Results from the phase II NEWTON trial (ENGOT-ov49). Nicoletta Colombo, Gabriella Parma, Giulia Tasca, Michele Pio Di Palma, Germana Tognon, Andrea Alberto Lissoni, Roldano Fossati, Luciano Carlucci, Massimo Zucchetti, Cristina Matteo, Annamaria Ferrero, Alessandra Bologna, Mara Mantiero, Pauline Wimberger, Dionyssios Katsaros, Federica Tomao, Francesca Galli, Mariateresa Lapresa, Valentina Guarneri, Silvia Ficarelli, Stefania Canova, Silvia Derio, Fabio Girardi, Valentina Zizioli, Jalissa Katrini, Davide Massa, Eliana Rulli, Elena Biagioli, NEWTON study group. European Journal of Cancer 2026. doi: 10.1016/j.ejca.2026.116685.*

## **Somministrazione combinata di chemioterapia, immunoterapia e terapia molecolare per il trattamento del tumore gastrico: risultati di uno studio clinico di fase II.**

L'attuale terapia standard di prima linea per il trattamento dei pazienti con adenocarcinoma gastrico HER2-negativo PDL1-positivo consiste nella somministrazione di chemioterapia in combinazione con immunoterapia (in particolare, anti-PD1 nivolumab o pembrolizumab). Studi clinici internazionali recenti mostrano che l'aggiunta di farmaci che colpiscono la proteina Claudina (CLDN) 18.2, con Zolbetuximab e chemioterapia, migliora in maniera significativa la sopravvivenza dei pazienti con tumore gastrico HER2-negativo e CLDN18.2-positivo, quando somministrato come trattamento di prima linea. La proteina CLDN18.2 è espressa nelle cellule della mucosa gastrica normale che, durante la trasformazione maligna, esibiscono la proteina sulla superficie cellulare, esponendo così la cellula tumorale all'azione dei farmaci come Zolbetuximab. Circa il 35-45% dei tumori gastrici sono positivi alla proteina CLDN18.2.

L'eventuale efficacia di Zolbetuximab, come trattamento di prima linea, nel migliorare la sopravvivenza dei pazienti con tumore gastrico HER2-negativo e PDL1-positivo è attualmente oggetto di studio. Studi preclinici in vivo hanno mostrato l'ulteriore aumento dell'efficacia della combinazione Zolbetuximab-chemioterapia-immunoterapia (anti-PD1); inoltre, analisi delle biopsie tumorali hanno mostrato un rimodellamento del microambiente tumorale immunitario nei pazienti trattati con Zolbetuximab (con o senza chemioterapia), incoraggiando la valutazione approfondita dell'efficacia di questa tripla combinazione in ambito clinico. Lo studio clinico multicentrico di fase II ILUSTRO ha quindi valutato sicurezza ed efficacia di Zolbetuximab somministrato da solo o in combinazione con chemioterapia e/o immunoterapia in pazienti con tumore gastrico CLDN18.2-positivi e HER2-negativi, pre-trattati o non trattati.

In un articolo recentemente pubblicato sulla rivista Nature Medicine, i ricercatori, tra cui Nicola Fazio- Direttore del Programma Tumori dell'Apparato Digerente e Neuroendocrini di IEO- hanno analizzato sicurezza ed efficacia di Zolbetuximab, come trattamento di prima linea, in combinazione con chemioterapia (mFOLFOX6) e immunoterapia (nivolumab) in pazienti con tumore gastrico localmente avanzato, non resecabile, HER2-negativo, CLDN18.2-positivo. Questo è stato il primo studio a valutare l'efficacia di questa tripla combinazione di farmaci in questo contesto clinico.

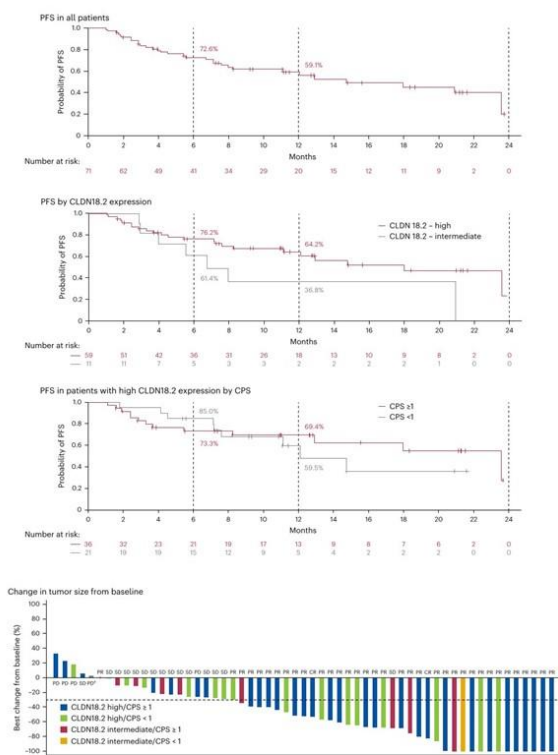


Image adapted from Shitara et al., Nature medicine 2026 (an open access article under the CC BY license.)

Sebbene il numero di pazienti della coorte analizzata fosse limitato, i risultati mostrano una tossicità nel complesso gestibile associata a questa tripla combinazione e risultati incoraggianti in termini di efficacia, soprattutto nei pazienti selezionati sulla base di tre biomarcatori tumorali –HER2 (negativi), CLDN18.2 (positivi) e PDL1 (positivi)–, sottolineando il valore degli approcci di oncologia di precisione.

I risultati di questo studio hanno posto delle basi solide per un nuovo studio clinico internazionale, di fase III (LUCERNA), attualmente in corso, volto a confrontare l'efficacia della somministrazione combinata di chemioterapia e pembrolizumab, con o senza zolbetuximab, in pazienti con adenocarcinoma gastrico CLDN18.2-positivo, PDL1-positivo, HER2-negativo, non precedentemente trattati. Se i risultati saranno confermati nell'ambito di questo nuovo trial clinico, la tripla combinazione Zolbetuximab-chemioterapia-

immunoterapia anti-PD1 potrebbe rappresentare una nuova efficace terapia di prima linea in pazienti selezionati sulla base di specifici marcatori.

## TELL ME MORE!

Il design dello studio clinico prevedeva due diverse coorti di pazienti: una coorte (coorte A, che ha incluso 12 pazienti: 6 hanno ricevuto un dosaggio di Zolbetuximab e 6 ne hanno ricevuto un altro) per definire il dosaggio sicuro (cosiddetta fase “safety lead-in”, “sicurezza prima”), e una coorte, che ha incluso un maggior numero di pazienti (coorte B, comprendente 71 pazienti), per determinare l'efficacia del trattamento (fase di espansione) al dosaggio stabilito nei 6 pazienti della coorte A. Il 62.3% dei pazienti erano maschi.

Analisi di immunoistochimica hanno rivelato un livello di espressione alto/intermedio della proteina CLDN18.2 nelle biopsie tumorali dei pazienti dello studio, e una maggioranza di pazienti PDL1-positiva.

**Efficacia.** L'efficacia è stata valutata principalmente in termini di sopravvivenza in assenza di progressione della malattia (*progression-free survival*, PFS, dato che analisi precedenti avevano rivelato che la PFS fosse il parametro più adeguato a cogliere i benefici del trattamento rispetto alla risposta obiettiva (*objective response rate*, ORR): la PFS mediana era di 14.8 mesi, e il tasso di PFS era del 72.6% a 6 mesi e del 59.1% a 12 mesi. La correlazione con l'espressione di CLDN18.2 ha rivelato una PFS mediana più lunga nei pazienti che avevano un livello di espressione di CLDN18.2 più elevato ed esprimevano PDL1, a sostegno del rationale terapeutico di colpire la proteina CLDN18.2, la sinergia del trattamento molecolare anti-CLDN18.2 e dell'immunoterapia anti-PDL1, e la verosimile maggiore efficacia in pazienti selezionati sulla base di questi due biomarcatori.

Al momento dell'analisi, i dati sulla sopravvivenza generale (*overall survival*, OS) non erano maturi.

La valutazione della dimensione del tumore (nello specifico, riduzione della dimensione della massa tumorale, in pazienti selezionati la cui massa tumorale era poteva essere rilevata prima del trattamento) come misura ulteriore dell'efficacia del trattamento ha rivelato una ORR del 62.1%. Ancora una volta, la risposta migliore si osservava nei pazienti in cui il livello di espressione delle proteine CLDN18.2 e PDL1 era più elevato. Nel complesso, la risposta appariva duratura.

**Sicurezza.** La tossicità del trattamento era nel complesso gestibile: tutti i pazienti hanno manifestato almeno un evento avverso collegato al trattamento (in linea con la tossicità comunemente osservata con i farmaci somministrati separatamente); i 2/3 di essi hanno manifestato eventi avversi più severi (di grado 3 o superiore), che hanno richiesto una gestione attenta al fine di preservare la qualità di vita. La sospensione del trattamento dovuta ad eventi avversi è stata necessaria nella metà dei pazienti, ma la sospensione di Zolbetuximab è stata necessaria nel 5% dei pazienti, mentre 8% dei pazienti hanno dovuto sospendere in maniera specifica la somministrazione di nivolumab, per via della tossicità.



Nicola Fazio, Chiara Cella

#### CLDN18.2.

La claudina-18.2 (CLDN18.2) è una proteina transmembrana coinvolta nella formazione delle giunzioni strette tra cellule epiteliali e nel mantenimento della barriera di permeabilità tissutale. In condizioni normali è espressa principalmente nella mucosa gastrica differenziata, mentre nei tumori del tratto digerente (come cancro gastrico, gastroesofageo, pancreatico ed epatobiliare) risulta spesso espressa in maniera eccessiva o anomala. L'espressione specifica nei tumori la rende un bersaglio per terapie mirate (ad esempio anticorpi monoclonali come zolbetuximab), sfruttata sia per la sua funzione strutturale che per il ruolo nella progressione tumorale e nell'interazione con il microambiente immunitario.

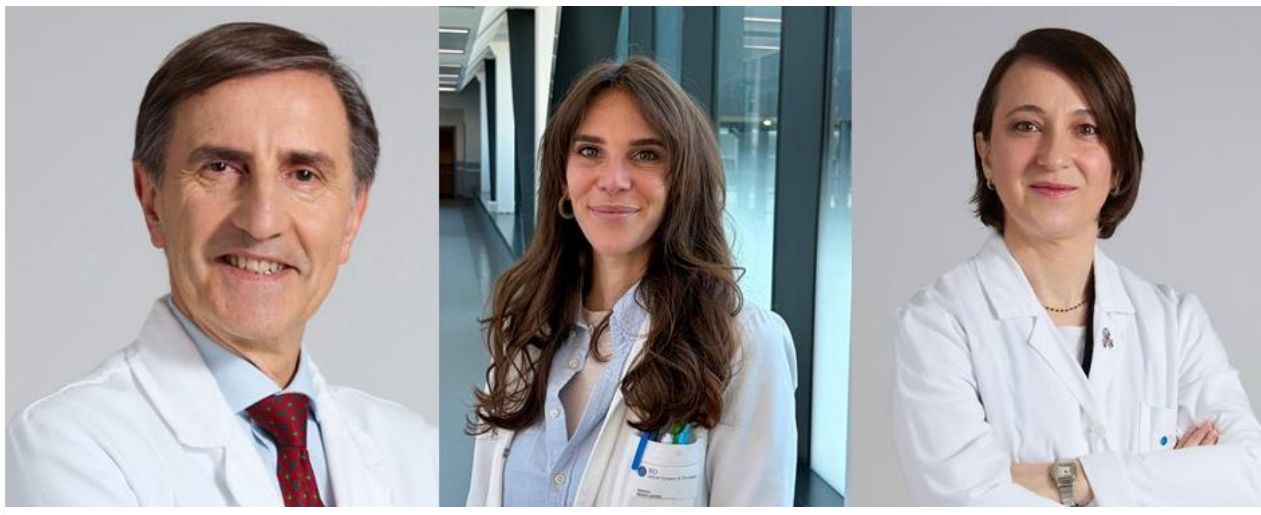
#### PD-L1.

La proteina PD-L1 (programmed death-ligand 1) è un immunomodulatore, una proteina di superficie che lega il recettore PD-1 sui linfociti T, inibendo la loro attivazione e limitando quindi il suo funzionamento. Fisiologicamente contribuisce a evitare risposte autoimmuni eccessive, ma molti tumori ne sfruttano l'espressione per evadere il controllo immunitario, creando un microambiente immunosoppressivo. Per questo l'asse PD1-PDL1 viene sfruttato per modulare l'attività antitumorale del sistema immunitario e la proteina PDL1 viene utilizzata come biomarcatore in grado di predire l'efficacia dell'immunoterapia con inibitori dei checkpoint immunitari (ad esempio ipilimumab, nivolumab, pembrolizumab).

*(text by perplexity.ai)*

**Referenza:** First-line zolbetuximab plus mFOLFOX6 and nivolumab in unresectable CLDN18.2-positive gastric or gastroesophageal junction adenocarcinoma: a phase 2 trial. Kohei Shitara, Hirokazu Shoji, Nicola Fazio, Sara Lonardi, Keun-Wook Lee, Li-Yuan Bai, Kensei Yamaguchi, Jean-Philippe Metges, Gianluca Masi, Denis Smith, Tae-Yong Kim, Maria Matsangou, Archita Shrivastava, Miaomai Zhou, Jason Hill, Abraham Guerrero, Xuwei Wang, Aziz Zaanani, Samuel J Klempner. *Nat Med* 2026. doi: 10.1038/s41591-026-04306-9).

# Everolimus come terapia di mantenimento per i pazienti con neoplasia neuroendocrina – risultati del clinical trial di fase II MAVERIC.



*Nicola Fazio, Lavinia Benini, Francesca Spada*

I tumori neuroendocrini (NETs) sono un tipo di tumore raro caratterizzati da proprietà “neuronalì” –come la presenza di granuli all’interno della cellula con tenenti monoamine (tipici dei neuroni del sottotipo serotonergico)– e caratteristiche “endocrine” –come la capacità di secernere le monoamine. I NET possono quindi emergere in tessuti differenti del corpo, sebbene siano più frequenti nel tratto gastrointestinale.

I NET sono un sottotipo –ben differenziato– di neoplasie neuroendocrine (NEN); il resto dei NEN sono rappresentati dai carcinomi neuroendocrini (NEC) – che sono invece scarsamente differenziati. Sebbene i NET possano essere di grado basso, intermedio o anche alto, a seconda del loro indice di proliferazione, i NEC sono invece sempre di alto grado. I NEN di alto grado sono solitamente trattati con chemioterapia, soprattutto se sono NEC o in stadio avanzato. Nel contesto dello studio clinico multicentrico (randomizzato) di fase II MAVERIC, i ricercatori, tra cui Nicola Fazio –Direttore del Programma Tumori dell’Apparato Digerente e Neuroendocrini di IEO– hanno valutato efficacia e tossicità dell’inibitore di mTOR everolimus come terapia di mantenimento, dopo la chemioterapia, in pazienti con NET in stadio avanzato/metastatico. Everolimus è un farmaco già approvato per il trattamento dei NET del tratto digerente e per i NET toracici non funzionanti, che agisce inibendo la signaling di mTOR. mTOR è un noto regolatore della sopravvivenza cellulare, della proliferazione e del metabolismo, la cui signaling è spesso iperattivata nel cancro, promuovendo la proliferazione incontrollata, rendendolo quindi un promettente target terapeutico.

Sebbene sia importante riconoscere che, a causa della rarità di questo tipo di tumore, i dati raccolti derivino da NET localizzati in tessuti differenti e il numero di pazienti coinvolti sia limitato, i risultati dello studio suggeriscono l’efficacia di everolimus come terapia di mantenimento in pazienti con NEN di alto grado (dopo la chemioterapia), rivelando un’efficacia particolarmente significativa nei NET del sottotipo gastroenteropancreatico, a fronte di un profilo di tossicità gestibile.

## TELL ME MORE!

Dopo aver ricevuto chemioterapia come trattamento di prima linea, i pazienti reclutati, con tumore avanzato/metastatico, sono stati casualmente assegnati a sorveglianza (10 pazienti) o al trattamento con everolimus (20 pazienti) come terapia di mantenimento, fino ad eventuale progressione della malattia o tossicità. La maggioranza dei pazienti aveva NET a livello del tratto gastroenteropancreatico (GEP) o del polmone. Tutti i pazienti avevano un NEN di alto grado (scarsamente o ben differenziato), caratterizzato da

un indice di ki-67 compreso tra 20% e 55%. L'indice ki-67, sviluppato sulla base della marcatura di ki-67, rispecchia la proliferazione cellulare, rappresentando così una misura dell'aggressività del tumore e della prognosi.

**Efficacia.** L'efficacia del trattamento è stata valutata in termini di sopravvivenza in assenza di progressione della malattia (*progression-free survival*, PFS) e di sopravvivenza generale (*overall survival*, OS). Il trattamento con everolimus estendeva la PFS rispetto ai pazienti sotto sorveglianza. Sebbene non siano state osservate differenze in termini di OS, il risultato potrebbe essere influenzato dal fatto che il confronto è stato effettuato con una popolazione di controllo che, al momento della progressione della malattia, è stata trattata con una terapia di seconda linea.

**Sicurezza.** La tossicità associata al trattamento era nel complesso gestibile; gli eventi avversi indotti dal farmaco erano infatti in linea con il noto profilo di tossicità di everolimus e comunque nel complesso lievi (soprattutto di grado 1 e 2, sebbene il 70% dei pazienti abbia manifestato almeno un evento avverso di grado 3). Nel 65% dei pazienti è stato necessario modificare il dosaggio a causa della tossicità indotta dal trattamento e in due è stato necessario interrompere il trattamento per via della tossicità.

*Referenza: Everolimus as maintenance therapy in advanced neuroendocrine neoplasms: results from the MAVERIC phase II trial. Lorenzo Antonuzzo, Daniele Lavacchi, Francesca Spada, Riccardo Marconcini, Fabio Gelsomino, Vito Amoroso, Federica Cosso, Elisa Pellegrini, Federico Scolari, Clotilde Sparano, Giulia Massaro, Elisa Giommoni, Luca Messerini, Daniele Rossini, Marco Brugia, Francesco Di Costanzo, Luca Boni, Massimo Milione, Serena Pillozzi, Nicola Fazio, on behalf of the Gruppo Oncologico Italiano di Ricerca Clinica (GOIRC). The Oncologist 2026. doi: 10.1093/oncolo/oyaf432.*

## La biopsia liquida per la scelta del trattamento ottimale per i pazienti con tumore del colon-retto.



Nicola Fazio, Davide Ciardiello

Nonostante i progressi in ambito oncologico, grazie allo sviluppo di nuovi approcci come l'immunoterapia, la terapia molecolare e i progressi in campo chirurgico, il tumore del colon-retto (CRC) rimane ancora una sfida e in generale la prognosi dei pazienti con tumore metastatico resistente alla terapia non è buona. L'attuale approccio standard di prima linea per il CRC metastatico senza mutazioni in RAS/BRAF è rappresentato da immunoterapia con anticorpi specifici per il recettore del fattore di crescita epidermico

(EGFR), come cetuximab e panitumumab. Dopo la progressione della malattia sotto questo trattamento, è stato analizzato un approccio che consiste in un ulteriore trattamento con farmaci anti-EGFR –la cosiddetta “*rechallenge*”– in pazienti selezionati. Inoltre, da un lato, non è chiaro se l’efficacia di questo approccio terapeutico potrebbe essere aumentata attraverso la combinazione con altri farmaci; dall’altro, è importante definire la combinazione terapeutica ottimale e selezionare attentamente i pazienti in cui potrebbe avere effetto. Sulla base di studi preclinici e clinici, i ricercatori hanno precedentemente condotto un trial clinico (CAVE GOIM) per valutare l’efficacia della *rechallenge* con il farmaco cetuximab, in combinazione con l’agente anti-PDL1 avelumab, per il trattamento del CRC metastatico (con malattia caratterizzata da RAS/BRAF wt e stabilità dei microsatelliti – MSS), refrattario, mostrando risultati promettenti (sopravvivenza oltre i 17 mesi) in pazienti selezionati sulla base dei risultati di biopsia liquida (ovvero RAS/BRAF wt sulla base dell’analisi del DNA tumorale circolante) raccolti prima dell’inizio del trattamento.

Al fine di confermare l’eventuale efficacia della *rechallenge*, in combinazione con inibitori dei checkpoint immunitari, nel contesto dello studio clinico di fase II (randomizzato, multicentrico) CAVE-2 GOIM, i ricercatori, tra cui Nicola Fazio –Direttore del Programma Tumori dell’Apparato Digerente e Neuroendocrini di IEO– hanno valutato la risposta dei pazienti con CRC metastatico MSS RAS/BRAF wt (sulla base dei risultati della biopsia liquida) al trattamento con il farmaco anti-EGFR cetuximab da solo, rispetto a cetuximab somministrato insieme ad avelumab. Questo studio è stato condotto da Davide Ciardiello, giovane medico oncologo della Divisione di Oncologia Medica Gastrointestinale e Tumori Neuroendocrini di IEO, in collaborazione con la Divisione Nuovi Farmaci, guidata dal Prof Giuseppe Curigliano, e il Gruppo Oncologico dell’Italia Meridionale (GOIM).

Sebbene i risultati abbiano in generale evidenziato, tra questi pazienti, un effetto sulla sopravvivenza non significativo della somministrazione di cetuximab in combinazione con avelumab, i loro dati indicano che la selezione dei pazienti sulla base della biopsia liquida –DNA tumorale circolante– potrebbe permettere di identificare coloro che potrebbero beneficiare della *rechallenge* con terapia anti-EGFR, anche nel caso in cui la malattia sia progredita durante il trattamento con farmaci anti-EGFR. Inoltre, i loro risultati sottolineano l’utilità della caratterizzazione tramite DNA tumorale circolante, in momenti differenti durante il percorso di cura, dato che, in assenza di mutazioni associate alla resistenza a farmaci anti-EGFR, cetuximab potrebbe rappresentare un’opzione valida per i pazienti refrattari con CRC metastatico MSS. Alcuni tumori sembrano infatti rimanere dipendenti dalla signalling di EGFR e quindi sensibili a terapie anti-EGFR.

## TELL ME MORE!

Lo studio ha arruolato 156 pazienti (MSS RAS/BRAFwt), precedentemente trattati, che sono stati casualmente assegnati a ricevere cetuximab e avelumab (C+A, 104 pazienti) o cetuximab soltanto (C-only, 52 pazienti), dopo almeno un ciclo di trattamento senza terapia anti-EGFR. Il trattamento è stato interrotto in caso di progressione della malattia.

**Efficacia.** L’efficacia è stata valutata in termini di sopravvivenza generale (*overall survival*, OS), risposta oggettiva (*objective response rate*, ORR), sopravvivenza in assenza di progressione della malattia (*progression-free survival*, PFS). Nonostante il lieve miglioramento osservato con il trattamento con C+A rispetto a C-only, la differenza non era significativa, suggerendo che non ci fosse un reale beneficio clinico nel combinare questi due farmaci. Sono stati osservati tuttavia dei segni di potenziali benefici nei pazienti senza metastasi epatiche; un’osservazione che richiede conferma nell’ambito di studi ulteriori in coorti di pazienti più ampie.

**Sicurezza.** Il profilo di tossicità era in linea con quello atteso per questi due farmaci. Non si sono osservati eventi avversi di grado superiore a 3 e non sono state necessarie interruzioni del trattamento per via della tossicità.

**Analisi di biomarcatori – TMB e metastasi epatiche per predire la risposta alla terapia.** Gli autori hanno osservato che, nonostante l’elevato numero di mutazioni (*tumor mutational burden*, TMB) sia considerato un fattore in grado di predire la risposta all’immunoterapia, in questi pazienti era un fattore prognostico negativo di efficacia della terapia, in entrambi i gruppi di trattamento (C+A e C-only), associato con una risposta limitata. I risultati indicano quindi la necessità di identificare altri biomarcatori di risposta. L’assenza di metastasi epatiche appariva invece correlata con una maggiore efficacia di C+A rispetto a C-only (non si

osservavano infatti differenze in termini di efficacia del trattamento tra C+A rispetto a C-only, nei pazienti con metastasi epatiche).

**Stratificazione molecolare dei pazienti.** Al fine di ottenere una migliore stratificazione dei pazienti e identificare quelli che più probabilmente avrebbero beneficiato della terapia A+C o C-only, i ricercatori hanno effettuato un'analisi molecolare per definire se la presenza di mutazioni patogeniche in geni del pathway EGFR (oltre alle mutazioni RAS/BRAF V600E che erano già state escluse al momento del reclutamento nello studio) potrebbe contribuire a migliorare la stratificazione dei pazienti. I loro risultati hanno evidenziato che 124 dei 156 pazienti della coorte in studio non avevano alterazioni genomiche nei geni KRAS, NRAS, BRAF, dominio extracellulare di EGFR, esone 20 di PIK3CA, MAP2K1, AKT1, MET, PTEN, ERBB2, ovvero questi 124 pazienti non avevano alterazioni in meccanismi genomici in grado di causare resistenza ai farmaci anti-EGFR. Tra questi pazienti, la ORR era del 12%, rispetto al 3% nei rimanenti 32 pazienti che mostravano invece mutazioni genomiche nei geni collegati alla resistenza a farmaci anti-EGFR. Analizzando la risposta clinica nei due gruppi di trattamento invece che nell'intera coorte, hanno osservato che nel gruppo di trattamento con C-only, alcuni pazienti senza mutazioni nei geni del pathway EGFR rispondevano in modo parziale al trattamento, mentre non c'era alcuna risposta tra i pazienti con mutazioni patogeniche in questi geni. Quindi, i risultati hanno evidenziato che ORR, OS, PFS erano diverse tra i gruppi di trattamento C-only e C+A se i pazienti avevano mutazioni in geni del pathway EGFR, suggerendo il valore delle analisi molecolari (nello specifico, mutazioni nei geni che conferiscono resistenza ai farmaci anti-EGFR) come predittori di risposta a *rechallenge* con farmaci anti-EGFR tra pazienti con CRC metastatico selezionati sulla base delle caratteristiche molecolari.

*Referenza:* Cetuximab rechallenge in molecularly selected metastatic colorectal cancer: the randomized CAVE-2 GOIM trial. Ciardiello D, Martini G, Boscolo Bielo L, Pietrantonio F, Raimondi A, Manca P, Pisconti S, Nisi C, Tortora G, Salvatore L, Sartore-Bianchi A, Siena S, Blasi L, Ongaro E, Zaniboni A, Pinto C, Antonuzzo L, Avallone A, Normanno N, Santabarbara G, Zampino MG, Berardi R, Cogoni A, Lotesoriere C, Latiano TP, Maiello E, Fazio N, Curigliano G, Bordonaro R, Troiani T, De Vita F, Martinelli E, Ciardiello F, Napolitano S; CAVE-2 GOIM study group. Ann Oncol 2025. doi: 10.1016/j.annonc.2025.12.014.

## Estrarre informazioni dalle immagini mediche – cosa possono rivelare le immagini 4D-CT.

La radiomica sfrutta le immagini mediche per ottenere informazioni che non possono essere rivelate dall'occhio umano e che possano guidare le scelte terapeutiche.

Per il trattamento dei pazienti con tumore al polmone, solitamente vengono acquisite immagini CT per pianificare il trattamento radioterapico. La 4D-CT è l'acquisizione di una serie di immagini CT "nel tempo", durante la respirazione, per tener conto, nella rappresentazione dell'anatomia del paziente e nella corretta localizzazione del tumore, dei movimenti associati con la respirazione. Ciò permette agli oncologi radioterapisti di pianificare in maniera precisa il trattamento radioterapico, così da risparmiare il più possibile i tessuti sani e indirizzare il fascio di protoni verso i tessuti tumorali. Infatti, le proprietà delle immagini, ovvero le caratteristiche del tumore raccolte grazie all'imaging medico (le cosiddette "features radiomiche"), possono essere



Barbara Jereczek-Fossa

estratte dalle immagini ed utilizzate per raccogliere informazioni importanti.

In un articolo recente, di Stefania Volpe et al., i ricercatori guidati da Barbara Jereczek-Fossa-Direttrice della Divisione di Radioterapia di IEO e Professore Ordinario di Radioterapia Oncologica presso l'Università degli Studi di Milano- si sono focalizzati sugli aspetti metodologici dell'acquisizione e l'analisi delle immagini in 4D-CT, analizzando quanto stabili rimangono le *features radiomiche* durante le diverse fasi della respirazione, al fine di standardizzare a sufficienza la tecnica e trovare i parametri giusti per ottenere delle *features radiomiche* che possano essere utilizzate per pianificare la radioterapia.

“Oltre ai risultati specifici (disponibili [qui](#))-aggiunge Stefania Volpe, primo autore del lavoro- lo studio propone un approccio metodologico standardizzato per analizzare le *features radiomiche* nelle immagini 4D-CT, che potrebbe supportare studi futuri finalizzati all'identificazione di biomarcatori di imaging per gli studi sul tumore polmonare. Sebbene siano necessari studi ulteriori, multicentrici, in coorti di pazienti più ampie, per confermare l'effettivo valore prognostico/predittivo delle *features radiomiche* identificate, questo lavoro indica che l'analisi delle immagini acquisite con 4D-CT può fornire informazioni clinicamente rilevanti.

Lo studio fornisce inoltre delle basi metodologiche per lo studio MONDRIN, un progetto di ricerca finanziato dall'associazione Italiana per la Ricerca sul Cancro (AIRC) attraverso il programma Next Generation Clinical Scientist 2022, finalizzato allo sviluppo di modelli multi-omici avanzati per i pazienti con tumore al polmone in stadio iniziale trattati con radioterapia stereotassica”.

## TELL ME MORE!

L'obiettivo finale dello studio era l'utilizzo di immagini mediche acquisite tramite MRI, CT, PET per raccogliere informazioni quantitative, clinicamente rilevanti, da poter utilizzare nella pianificazione del trattamento radioterapico. Queste informazioni quantitative sono definire “*features radiomiche*” e sono state correlate con diverse proprietà della malattia, tra cui il differenziamento, l'ipossia e le mutazioni del DNA, in diversi tipi di tumore. Nell'ambito di questo studio retrospettivo, i ricercatori hanno analizzato dati clinici, informazioni terapeutiche e immagini CT di 70 pazienti con tumore al polmone (non a piccole cellule, NSCLC) in stadio iniziale trattati in IEO con radioterapia stereotassica con intento curativo. Tutte le immagini CT sono state acquisite con gli stessi criteri (stesso strumento, stessi parametri, etc; un requisito essenziale per gli studi di radiomica).

Le *features radiomiche* sono state estratte quasi tutte da immagini filtrate (per renderle più nitide). L'analisi mirava a comprendere quanto queste *features* cambiassero durante la respirazione. Nonostante il livello di variabilità non trascurabile tra i pazienti, è stato possibile estrarre dalle

immagini un elevato numero di *features radiomiche* (oltre 1000). Oltre alla variabilità tra i pazienti, è stata osservata anche variabilità tempo-dipendente, ovvero le caratteristiche delle immagini cambiavano durante la respirazione: tra le oltre 1800 *features radiomiche* analizzate, alcune *features radiomiche* estratte dalle immagini di 4D-CT erano influenzate dalla respirazione, altre (circa un quinto) no; nel complesso, la maggioranza delle *features radiomiche* era stabile, solo una piccola parte delle *features radiomiche* era di fatto influenzata dalla respirazione.

Le *features radiomiche* che rimanevano stabili nonostante la respirazione erano potenzialmente informative. Filtrare le immagini (nello specifico, con filtri 3D e logaritmici) aumentava il numero di *features radiomiche* stabili (e quindi informative), mostrando l'utilità del filtraggio delle immagini nell'estrazione delle *features radiomiche*.

Lo studio fornisce anche un utile dataset istituzionale di immagini di 4D-CT, da poter utilizzare nell'ambito di analisi future nel contesto di studi multicentrici, ad esempio per valutare se le *features radiomiche* identificate sono effettivamente stabili anche con differenti protocolli di acquisizione, filtraggio delle



Stefania Volpe

immagini, algoritmi di ricostruzione e così via.

Includendo nello studio anche i casi clinici più recenti, i ricercatori hanno potuto aumentare il numero di campioni utilizzabile nelle analisi; questo però ha determinato una riduzione delle informazioni cliniche relative al follow-up del paziente, come la sopravvivenza o la progressione della malattia dopo il trattamento guidato dalle immagini, impedendo di determinare, per ora, il valore prognostico/predittivo delle *features radiomiche* (stabili) identificate.

Studi ulteriori con coorti più ampie di pazienti e follow-up clinici più lunghi determineranno se le *features radiomiche* stabili identificate sono anche associate con l'esito clinico dei pazienti, come la sopravvivenza o la progressione della malattia.

### La radiomica in IEO.

La radiomica sfrutta le immagini diagnostiche –tra cui immagini raccolte attraverso esami quali MRI, CT, PET– per trovare delle caratteristiche (*features radiomiche*) nelle immagini che possano essere utilizzate come biomarcatori quantitativi, a scopo prognostico/predittivo. L'intelligenza artificiale, con gli approcci di machine Learning (ML) –e più specificatamente deep learning–, viene impiegata per gestire l'elevato numero di immagini e di variabili (ovvero le caratteristiche estratte dalle immagini). Guidato dai progressi tecnologici, dalle miglorie nell'ambito dell'imaging medico, e gli sviluppi dell'intelligenza artificiale, il campo della radiomica è in rapida evoluzione.

In un contesto di oncologia di precisione, uno degli obiettivi della ricerca IEO è quello di integrare l'AI con dati di imaging medico avanzato e analisi multi-omiche derivanti dalla caratterizzazione multi-omica di tessuti tumorali e fluidi corporei, al fine di ottenere degli strumenti diagnostici, predittivi o per il monitoraggio della malattia, che possano aiutare nella selezione del trattamento più adeguato. Ad esempio, recentemente, sfruttando il più grande dataset esistente di pazienti con tumore prostatico (comprendente 949 pazienti), i ricercatori IEO hanno sviluppato un modello di ML che utilizza informazioni cliniche, radiologiche e radiomiche per la prognosi non invasiva del tumore della prostata, selezionando tra le diverse variabili quelle con il maggiore potere predittivo (ovvero quelle con un impatto maggiore sulla capacità del modello di ML di predire l'aggressività della malattia). Il modello da loro analizzato ha dimostrato una notevole efficacia nel combinare parametri clinici, radiologici e radiomici, mostrando un'efficacia maggiore delle attuali stime cliniche nel predire l'aggressività della malattia nei pazienti con tumore prostatico, fornendo così uno strumento in grado di aiutare i clinici a stimare in maniera accurata l'aggressività della malattia prima di iniziare un qualsiasi approccio terapeutico. Queste scoperte evidenziano il potenziale della radiomica guidata da AI nel supportare i medici nel prendere decisioni terapeutiche più accurate e personalizzate.

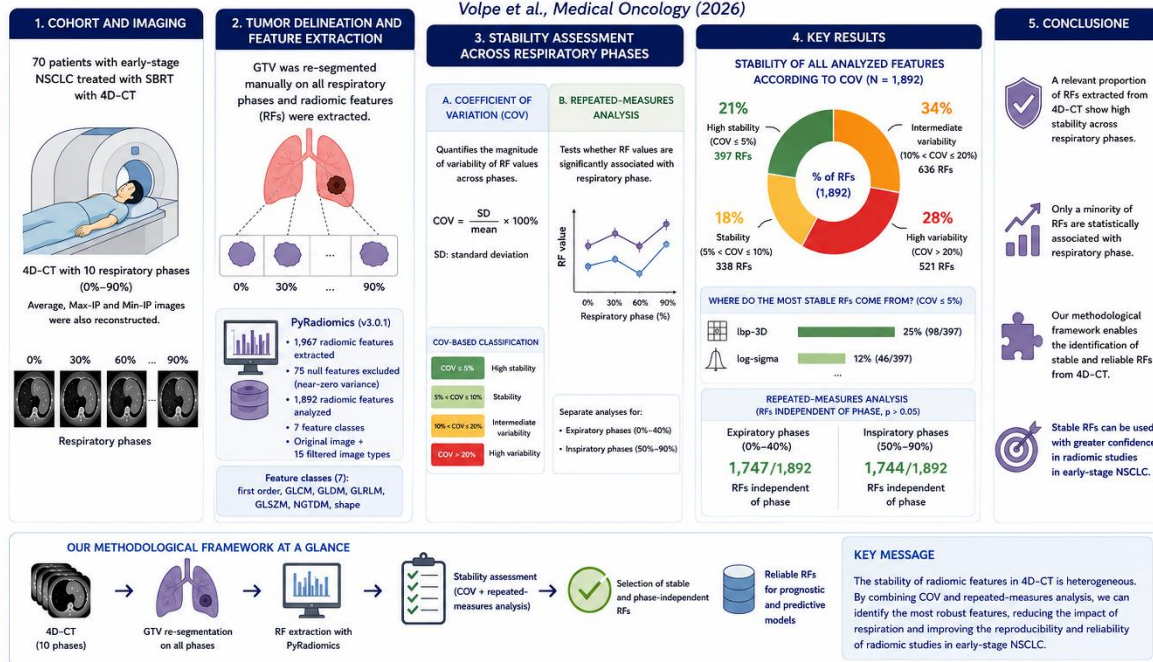
### Gli autori – Barbara Alicja Jereczek-Fossa e Stefania Volpe.

**Barbara Alicja Jereczek-Fossa** è Direttrice della Divisione di Radioterapia Oncologica dell'IEO, Professore Ordinario di Radioterapia Oncologica del Dipartimento di Oncologia ed Emato-oncologia dell'Università degli Studi di Milano, e Presidente eletto della Società Europea di Radioterapia e Oncologia (ESTRO). Con una laurea di Medicina, una Specializzazione in Radioterapia Oncologica conseguita presso l'Istituto Nazionale di Oncologia di Varsavia e l'Università di Milano ed una in Oncologia Clinica conseguita presso l'Istituto Nazionale di Oncologia di Varsavia, un Dottorato di ricerca dell'Università di Danzica (Polonia), ha proseguito la sua formazione presso il Beatson Oncology Centre di Glasgow (Scozia) e il Dipartimento di Radioterapia Oncologica dell'Università di Torino, prima di diventare medico e ricercatore in IEO. I suoi interessi clinici e di ricerca si concentrano principalmente sulle neoplasie urologiche, sul cancro della mammella, sui nuovi protocolli di frazionamento, sulle innovazioni in radioterapia oncologica (radioterapia stereotassica, IMRT, IGRT, protonterapia, ecc.), sull'approccio a modalità combinate (compresi gli studi sulla conservazione degli organi).

Con una laurea in Medicina, **Stefania Volpe** ha completato la sua specializzazione nel 2019 all'Università di Milano, e ha ottenuto il suo dottorato in Biologia Computazionale alla Scuola Europea di Medicina Molecolare (SEMM), focalizzandosi sugli aspetti metodologici della radiomica nel tumore al polmone in stadio iniziale. Attualmente ricercatrice associata al Dipartimento di Oncologia ed Emato-oncologia dell'Università di Milano, i suoi interessi clinici e di ricerca includono gli approcci quantitativi per la radioterapia oncologica di precisione, soprattutto per il tumore al polmone e il tumore testa-collo. Dal 2003, è PI dello studio MONDRIAN, finanziato dalla Associazione Italiana per la Ricerca sul Cancro (AIRC), sul modeling multi-omico per predire la risposta nel tumore al polmone non a piccole cellule in stadio precoce trattato con radioterapia stereotassica.

## Stable or not? Unraveling the reliability of radiomic features in 4D-CT in early-stage non-small cell lung cancer

Volpe et al., *Medical Oncology* (2026)



*Referenza: Stable or not? unraveling the reliability of radiomic features in 4d-computed tomography in early-stage non-small cell lung cancer. Volpe S, Gaeta A, Vincini MG, Zaffaroni M, Mastroleo F, Raimondi S, Pepa M, Isaksson LJ, Cremonesi M, La Torre D, Guckenberger M, Bellerba F, Orecchia R, Gandini S, Jerezek-Fossa BA. Clin Transl Oncol 2026. doi: 10.1007/s12094-026-04311-x.*

## Avatar cellulari per studiare le metastasi cerebrali.

Nonostante i notevoli progressi nel trattamento del tumore, la malattia metastatica rappresenta ancora una sfida significativa. Uno degli ostacoli principali è collegato alla limitata comprensione meccanicistica della cascata metastatica, ovvero dell'insieme dei processi che portano una cellula a lasciare il tumore primario, entrare nel circolo sanguigno, fino ad arrivare a colonizzare un altro organo. Ciò è in parte dovuto alla mancanza di modelli adeguati di malattia, di facile utilizzo e in grado di ricapitolare fedelmente le caratteristiche molecolari principali dei pazienti.

In un articolo recente di Faletti et al., utilizzando colture in vitro di metastasi cerebrali di tumore al seno isolate da pazienti, i ricercatori guidati da Giuliana Pelicci -PI al dipartimento di oncologia sperimentale di IEO- hanno sviluppato degli "avatar", ovvero un modello preclinico che conserva le caratteristiche principali (in termini di profilo mutazionale e di espressione genica) delle metastasi originali isolate dai pazienti, fornendo così un utile strumento per studiare (in vitro e in vivo) i meccanismi di disseminazione metastatica. Sfruttando questi avatar, gli autori hanno identificato una specifica sottopopolazione di cellule staminali tumorali (inizianti le metastasi, le MIC), con caratteristiche staminali e uno specifico set di molecole di adesione, che giocano un ruolo chiave nella metastatizzazione e rappresentano quindi un target terapeutico clinicamente rilevante.

I risultati delle loro analisi molecolari non solo hanno mostrato il potenziale di questi sistemi di coltura come utili modelli preclinici per studiare la malattia, ma hanno anche dimostrato che la specificità delle MIC per il cervello è verosimilmente mediata, almeno in parte, dalla preferenza di queste cellule ad aderire in maniera specifica alle cellule della barriera emato-encefalica, mediata dall'espressione di determinate molecole di adesione.

Le metastasi cerebrali rappresentano un ostacolo notevole nella cura dei pazienti, per via della scarsa risposta alle terapie sistemiche e la generale difficoltà di trattamento, principalmente legata ai problemi legati all'attraversamento della barriera emato-encefalica da parte dei farmaci. Lo sviluppo di questi "avatar", in grado di ricapitolare le caratteristiche principali delle metastasi dei pazienti, offre uno strumento utile per testare farmaci diversi così da definire il trattamento più efficace

### I "patient avatar" in IEO.

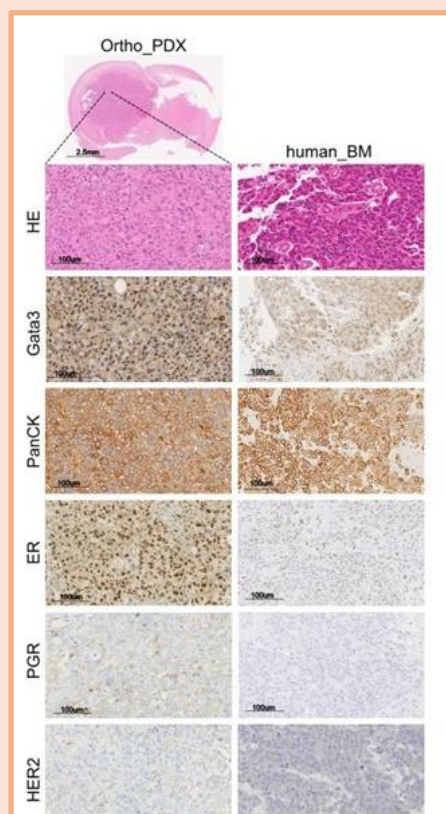
L'impiego degli avatar di pazienti è sempre più diffuso in campo oncologico, per via della loro utilità nell'ambito di studi meccanicistici e traslazionali. Nel contesto dello studio "IOLANTHE", i ricercatori IEO, in collaborazione con l'Istituto Mario Negri, l'Università Sapienza, Humanitas Research Hospital, hanno l'obiettivo di utilizzare i "patient avatar", ovvero dei modelli sperimentali preclinici di colture di tumore ovarico ottenuti direttamente dalle cellule tumorali delle pazienti, come "repliche biologiche" del tumore, in grado di riprodurre le caratteristiche molecolari del tumore della singola paziente, per poter testare diversi farmaci e combinazioni terapeutiche e predire la risposta delle pazienti ad una data terapia, al fine di identificare quelle più efficaci.

### TELL ME MORE!

Prima di tutto gli autori hanno valutato la presenza di cellule staminali tumorali (CSC) all'interno delle metastasi cerebrali di tumore al seno, tramite saggi funzionali e approcci molecolari. Le CSC sono state identificate sulla base della loro abilità di formare sfere tumorali, che rispecchia la loro capacità di self-renewal- e attraverso l'espressione di marcatori di staminalità. Le colture/sfere tumorali conservavano le caratteristiche molecolari fondamentali (genomiche e di espressione genica) dei tumori originali.

L'ulteriore caratterizzazione di una di queste colture/sfere tumorali (PR60) ha dimostrato la forte capacità di metastatizzazione in vivo di queste cellule, quando trapiantate tramite iniezione intracardiaca (per simulare la disseminazione nel flusso sanguigno), intracranica, o intra-mammaria (nel capezzolo) in animali riceventi. Queste cellule metastatizzavano preferibilmente nel cervello (formando sia micro- che macro- metastasi).

Una caratterizzazione molecolare approfondita ha rivelato che 1) i tumori neo-formati erano molto simili, dal punto di vista molecolare, alle metastasi originali isolate dalle pazienti; 2) la via di disseminazione (ovvero, intracardiaca/flusso



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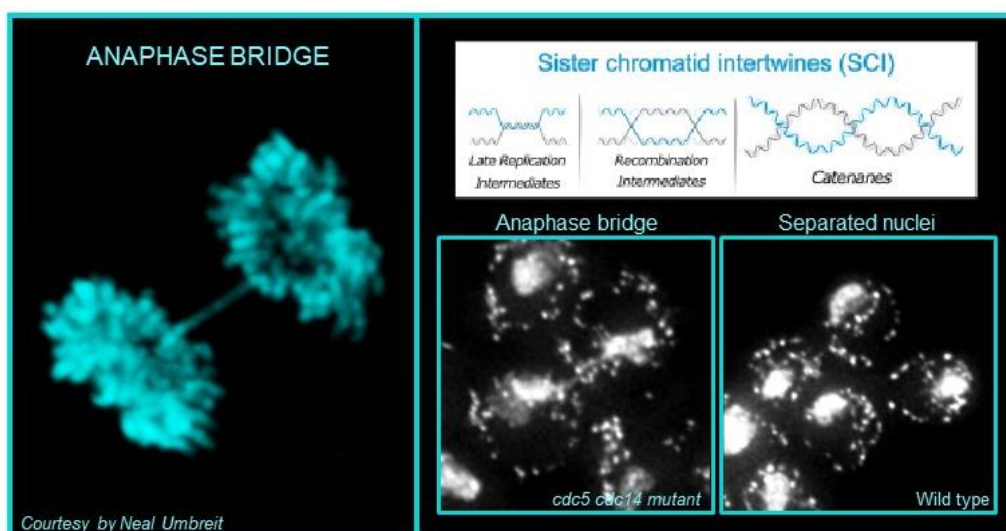
sanguigno, intracranica, intra-capezzolo) non modificava in maniera significativa il profilo globale di espressione genica, ma le CSC subivano dei profondi cambiamenti durante la colonizzazione dell'organo; infine, 3) le metastasi che si formavano nel cervello erano molto differenti dai tumori che si formavano in altri organi, come nell'osso (suggerendo che una volta raggiunto l'organo da colonizzare, le cellule tumorali acquisivano delle caratteristiche specifiche, adattandosi al microambiente). Le loro analisi hanno inoltre rivelato un livello di espressione elevato dei fattori coinvolti nell'interazione con i vasi sanguigni e di marcatori neuronali, indicando che il microambiente del cervello definiva il profilo di espressione genica delle MIC. Le loro analisi hanno inoltre evidenziato dei tratti specifici delle cellule tumorali che attraversavano la barriera emato-encefalica per colonizzare il cervello, tra cui la resistenza allo stress meccanico (proprietà cruciale per sopravvivere nel flusso sanguigno), l'espressione di molecole di adesione (come CD44, VCAM1, MUC1, etc) e geni di staminalità e l'attivazione di pathway notoriamente critici per

sostenere la staminalità e le metastasi, come la transizione epitelio-mesenchimale e la signalling del TGFbeta.

Infine, le analisi di sensibilità ai farmaci hanno rivelato che le colture ricche di CSC (le sfere tumorali) riflettevano la resistenza ai trattamenti riscontrata nelle pazienti da cui erano state isolate le metastasi. Sia le sfere tumorali che le metastasi cerebrali esibivano l'attivazione di pathway collegati alla resistenza ai farmaci più comunemente impiegati per il trattamento del tumore al seno e la ridotta sensibilità a diversi composti, tra cui farmaci attivi nel sistema nervoso, indicando che questi sistemi potrebbero rappresentare dei modelli preclinici rilevanti per testare la sensibilità ai farmaci.

*Referenza: Deciphering the Role of Cancer Stem Cells in Breast Cancer Brain Colonization Using a Novel Patient-Derived Model. Faletti S, Richichi C, Osti D, Ceccacci E, Bertalot G, Cerutti C, Giardina G, Marinaro A, Costanza B, Gambino V, Zaccheroni E, Tosoni D, Filippone MG, Del Corvo M, Zhan Y, Gravina T, Corà D, Patanè M, Pollo B, Giovanna Jodice M, Pece S, Weksler BB, Romero IA, Couraud PO, Munzone E, Del Bene M, DiMeco F, Pelicci G. Adv Healthc Mater 2026. doi: 10.1002/adhm.202505789*

## I meccanismi molecolari che garantiscono l'integrità del genoma durante la divisione cellulare.



*Adapted from Massari, Finardi et al. (an open access article under the CC BY license.)*

Durante la divisione cellulare, i cromosomi sono divisi tra le due cellule figlie. Questo processo è cruciale per la fisiologia della cellula ed è quindi finemente regolato da parte di un complesso macchinario molecolare che assicura che i due cromatidi fratelli siano completamente separati prima della segregazione; ciò include rimuovere quelle strutture costituite da segmenti di DNA interconnessi che, durante la replicazione del DNA, spesso rimangono fisicamente legati. Se queste strutture non vengono risolte, i cromatidi fratelli non vengono completamente separati e si verifica instabilità genomica. L'instabilità genomica è una delle principali caratteristiche dei tumori, associata

### Instabilità genomica e cancro.

I ricercatori IEO hanno precedentemente dimostrato, identificando anche i meccanismi coinvolti, che non solo l'instabilità genomica induce aneuploidia, ma che l'aneuploidia -ovvero l'alterato numero di cromosomi derivante da errori nei meccanismi che regolano la segregazione dei cromosomi nelle cellule figlie al momento della divisione cellulare- può a sua volta indurre instabilità genomica, inducendo dei continui cambiamenti a livello genomico che consentono alle cellule tumorali di adattarsi e sopravvivere. Hanno anche dimostrato che l'aneuploidia è uno dei meccanismi che determinano la capacità delle cellule tumorali di resistere alla chemioterapia, inducendo, in modo casuale, cambiamenti nell'espressione di alcune proteine, che forniscono alle cellule la capacità di adattarsi a condizioni ostili -come la

con prognosi infausta e resistenza alla chemioterapia. L'instabilità genomica conferisce infatti un vantaggio alle cellule tumorali, causando dei continui cambiamenti a livello genomico che forniscono alle cellule tumorali la capacità di adattarsi, sopravvivere, proliferare e sostenere la crescita del tumore.

In uno studio recente, i ricercatori IEO coordinati da Rosella Visintin -PI al dipartimento di oncologia sperimentale di IEO- hanno rivelato i meccanismi molecolari responsabili del corretto "scioglimento" di queste strutture di DNA prima della divisione cellulare, contribuendo a mantenere l'integrità del genoma. In particolare, i loro risultati hanno mostrato il coinvolgimento delle proteine Cdc5 (chinasi polo-like) e Cdc14 (fosfatasi) in questo

processo, le quali, insieme al loro (noto) lavoro nel regolare il fuso mitotico (una struttura critica per la divisione cellulare), modulano la risoluzione di queste strutture di DNA-garantendo così l'integrità del genoma- attraverso la modificazione post-traduzionale (ovvero fosforilazione e, in minor misura, SUMOilazione) della proteina Top2, influenzandone la localizzazione e attività.

Questi risultati hanno permesso di identificare una correlazione (attraverso l'attività coordinata-sebbene opposta- di Cdc5 e Cdc14) tra la regolazione della divisione cellulare e il mantenimento dell'integrità del genoma, un meccanismo cruciale nella fisiologia delle cellule e fondamentale per proteggersi dallo sviluppo del cancro.

Sebbene queste strutture del DNA siano un prodotto secondario della replicazione del DNA, gli autori ipotizzano che la persistenza di queste strutture che legano i cromatidi fratelli possano rappresentare un meccanismo regolatorio aggiuntivo attraverso cui la cellula garantisce che un processo critico sia portato a compimento in maniera efficiente, nei tempi giusti, prevenendo la separazione quando il momento non è quello giusto. Eppure, se lasciate "non-risolte", si verifica instabilità genomica, rendendo "il team di proteine" Cdc5-Cdc14-Top2 fondamentale nel mantenimento della stabilità del genoma".

"Utilizzando versioni mutate della proteine Cdc5 e Cdc14 -spiega Rosella Visintin- abbiamo dimostrato che entrambe le proteine sono necessarie per una separazione efficiente dei cromatidi fratelli. In loro assenza, questi ultimi rimangono fisicamente connessi. Questo difetto è attribuibile principalmente alla persistenza di strutture chiamate "catenati" del DNA, piuttosto che a una rimozione inefficiente della coesina o alla presenza di intermedi di ricombinazione.

Sebbene i circuiti regolatori specifici possano differire tra le specie, la necessità di una decatenazione mediata dalla Topoisomerasi II e il suo coordinamento con la progressione mitotica appaiono conservati negli eucarioti. La mancata risoluzione dei catenati compromette la segregazione cromosomica e favorisce l'instabilità cromosomica, un motore centrale dell'eterogeneità tumorale e dell'adattamento terapeutico. Definendo come la decatenazione sia funzionalmente integrata nel controllo mitotico in vivo, il nostro lavoro contribuisce a chiarire i principi fondamentali che salvaguardano l'integrità cromosomica nelle cellule proliferanti".

terapia- e sopravvivere. Inoltre, una delle principali conseguenze dell'instabilità genomica è la formazione di piccole strutture all'interno della cellula contenenti frammenti di cromosomi avvolti da membrane difettose - i micronuclei. La rottura -e il successivo collasso- dei micronuclei espone il DNA contenuto all'interno dei micronuclei, che viene ulteriormente danneggiato, acquisisce anomalie e contribuisce ulteriormente all'instabilità del genoma. I ricercatori IEO hanno precedentemente descritto i meccanismi che portano alla rottura dei micronuclei, che coinvolgono la proteina p62, dimostrando che p62 gioca un ruolo cruciale nell'integrità o nel collasso dei micronuclei, sia in cellule non trasformate che in cellule tumorali e che i livelli (elevati) di p62 correlano con la prognosi (peggiore) dei pazienti con tumore gastrico.

## TELL ME MORE!

Gli autori hanno analizzato nel dettaglio i meccanismi molecolari alla base della corretta divisione cellulare e che assicurano l'integrità del genoma, sfruttando invece che un sistema in vitro, un sistema modello in vivo, ma più semplice: il lievito. In particolare, hanno utilizzato i mutanti privi di Cdc5 e Cdc14, che vanno incontro ad arresto del ciclo cellulare a causa di numerosi difetti al livello del fuso mitotico e di queste strutture formate da segmenti di DNA interconnessi. Le loro analisi hanno rivelato che le cellule prive di Cdc5 e Cdc14 non riescono a completare la divisione del nucleo e i cromatidi fratelli non vengono completamente separati; ciò non dipende dalla proteina coesina, ma è dovuto piuttosto alla persistenza di queste strutture di DNA, chiamate catenani, che legano i cromatidi fratelli. Cdc5 e Cdc14 lavorano insieme per rompere

queste strutture di DNA e separare i cromatidi fratelli, sia durante la metafase che in anafase. È interessante sottolineare che sebbene l'allungamento del fuso faciliti la distruzione di queste strutture di DNA, non è sufficiente a separare i cromatidi fratelli in assenza di Cdc5 o Cdc14.

Per quanto riguarda il meccanismo, la risoluzione di queste strutture di DNA che legano i cromatidi fratelli richiede la localizzazione, modulata da Cdc5 e Cdc14, della proteina Top2, l'enzima direttamente responsabile della risoluzione di queste strutture di DNA. Nello specifico, Cdc5 (principalmente in metafase) e Cdc14 (soprattutto in anafase) insieme modulano la fosforilazione (Cdc5) e la defosforilazione (Cdc14) della proteina Top2, a livello di determinati residui aminoacidici nel dominio C-terminale della proteina. Quindi, i cicli di fosforilazione-defosforilazione (insieme alla SUMOilazione, sebbene abbia un ruolo limitato/marginale), risultanti dall'attività coordinata di Cdc5 e Cdc14, controllano finemente l'attività di Top2, la corretta separazione dei cromatidi fratelli, la fedele segregazione dei cromosomi, e l'integrità del genoma.

### Perché è necessario rimuovere i catenati del DNA?

I catenati del DNA sono una conseguenza inevitabile della replicazione: durante la sintesi dei cromatidi fratelli, le doppie eliche tendono a intrecciarsi dal punto di vista topologico. Se questi legami persistono fino all'anafase, i cromatidi non possono separarsi completamente, anche in presenza della rimozione della coesina e dell'allungamento del fuso. La tensione che ne deriva può generare ponti cromatinici, rotture del DNA e instabilità strutturale dei cromosomi. A differenza della coesione mediata dalla coesina, risolta tramite proteolisi regolata, i catenati rappresentano un problema di topologia del DNA che richiede la decatenazione enzimatica da parte della Topoisomerasi II. La loro risoluzione tempestiva non è quindi un raffinamento secondario della mitosi, ma una condizione indispensabile per una corretta segregazione cromosomica, assicurando che le forze meccaniche agiscano solo dopo — o in stretta coordinazione con — la risoluzione della topologia del DNA. Il fatto che la cellula utilizzi gli stessi regolatori mitotici per controllare sia la dinamica del fuso sia l'attività della topoisomerasi evidenzia un principio di organizzazione altamente integrato: meccanica e topologia non sono processi separati, ma componenti di un unico programma regolativo finemente orchestrato.

*Referenza: Safeguarding genome integrity: Polo-like kinase Cdc5 and phosphatase Cdc14 orchestrate Topoisomerase II-mediated catenane resolution in mitosis. Massari LF, Finardi A, Visintin C, Calabrese E, Dondi A, Visintin R. Nucleic Acids Res 2026. doi: 10.1093/nar/gkaf1509.*

## I meccanismi molecolari associati con la progressione dalla sindrome mielodisplastica in leucemia

La sindrome mielodisplastica (MDS)-una condizione medica caratterizzata da alterazioni nell'ematopoiesi- è associata ad un aumentato rischio di leucemia mieloide acuta (AML). Sebbene diversi studi si siano focalizzati sull'identificazione dei tratti genomici che predispongono alla progressione da MDS a AML, ad oggi non sono ancora noti i meccanismi molecolari alla base della progressione della MDS lieve in MDS aggressiva e infine in AML.

In uno studio recente di Vallelonga, Gandolfi et al., al fine di identificare i processi responsabili della progressione della MDS da una condizione subclinica alla malattia conclamata, utilizzando campioni di sangue isolati da individui con MDS e AML, i ricercatori, co-coordinati da Serena Ghisletti-ricercatrice del dipartimento di oncologia sperimentale di IEO e dell'Università di Milano- e Matteo Della Porta-Direttore dell'Unità di MDS e leucemia dell'ospedale Humanitas-, hanno descritto le alterazioni molecolari (a livello trascrizionale) in pazienti con MDS a basso rischio di progressione della malattia, in pazienti ad alto rischio di progressione e in pazienti AML, e il modo in cui, funzionalmente, queste alterazioni influenzano la progressione della malattia.

Identificando, attraverso le loro analisi, degli specifici profili trascrizionali nei diversi stadi della MDS, hanno individuato dei meccanismi-come l'attivazione immunitaria e infiammatoria e il metabolismo dell'eme- e dei fattori-come il fattore di trascrizione PU.1- critici nella progressione della malattia. Questi studi suggeriscono

infatti che interferire con la localizzazione di PU.1, che varia durante la progressione della malattia, potrebbe offrire nuovi approcci terapeutici per arrestare la progressione della MDS e prevenire l'insorgenza della AML.



Veronica Vallelonga, Francesco Gandolfi, Serena Ghisletti

## TELL ME MORE!

**Attivazione dei processi immunitari/infiammatori durante la progressione della malattia.** Attraverso la caratterizzazione delle alterazioni trascrizionali che si manifestano durante la progressione della malattia nelle cellule progenitrici del midollo osseo (CD34+, iniziati la malattia) da 209 pazienti MDS e 148 AML, gli autori hanno scoperto che la progressione della malattia (da MDS a basso rischio a MDS ad alto rischio o AML) era caratterizzata da cambiamenti nel metabolismo dell'eme e nell'attivazione del complemento, mentre la progressione da MDS ad alto rischio a AML era caratterizzata da un aumento dei processi infiammatori.

Tra i pazienti con MDS a basso rischio (che includono sia gli individui in cui la malattia progredisce sia quelli in cui non progredisce), hanno identificato un sottogruppo che mostrava up-regolazione di fattori coinvolti nei processi infiammatori e, nonostante l'elevato livello di eterogeneità intercellulare, hanno identificato alcuni specifici fattori di trascrizione coinvolti, che risultavano essere principalmente fattori di trascrizione associati con la risposta immunitaria e con l'attivazione dei processi infiammatori.

**Composizione cellulare.** Nei campioni di midollo osseo isolati da pazienti con MDS a basso rischio che progredivano in AML, era presente un elevato numero di linfociti T e NK attivati; inoltre, le cellule CD34+ (staminali ematopoietiche e progenitori) presentavano un gran numero di mutazioni nel gene SRSF2 (un noto fattore di prognosi avversa nelle MDS, che nei loro campioni influenzava lo splicing, soprattutto dei geni coinvolti nei processi immunitari). I pazienti che avevano cellule con queste caratteristiche avevano un rischio più elevato di sviluppare la malattia e una ridotta sopravvivenza.

**Il fattore di trascrizione PU.1 gioca un ruolo chiave nei processi funzionali associati con la progressione della malattia.** Nelle cellule di pazienti MDS a basso rischio, il fattore di trascrizione PU.1 era associato con l'attivazione della risposta immunitaria e infiammatoria; la sua localizzazione sul genoma cambiava durante la progressione della malattia e diverse regioni regolate da PU.1 venivano attivate.

**Effetti funzionali dell'alterata attività di PU.1 sulla progressione della malattia.** L'alterata localizzazione di PU.1 durante la progressione della malattia determinava la differente attivazione di geni coinvolti nella risposta immunitaria e nell'infiammazione. In linea con questi dati, l'inibizione farmacologica o il knock out di PU.1, in vitro, portava alla down-regolazione di molti geni infiammatori, dimostrando che attraverso la regolazione di specifici programmi trascrizionali associati all'infiammazione, PU.1 modulava i processi coinvolti durante la progressione della MDS (nello specifico, nelle MDS a basso rischio).

Inoltre, pur non avendo alcun effetto sulla vitalità cellulare, interferire con l'attività di PU.1 influenzava la proliferazione, sia delle cellule MDS che delle cellule AML, inducendo il differenziamento. Infine, è importante sottolineare che l'inibizione di PU.1 non influenzava in maniera significativa la proliferazione delle cellule progenitrici isolate da pazienti sani.

*Referenza: PU.1-Activated Genomic Regions Define Low-risk MDS Subsets Characterized by Immune Dysregulation and Disease Progression. Vallelonga V, Gandolfi F, Zampini M, Riva E, Maggioni G, Ventura D, Saba E, Termanini A, Polletti S, Prosperini E, Crisafulli L, Campagna A, Ferrari I, Pinocchio N, Todisco G, Pedretti S, Calvi M, Di Vito C, Mavilio D, Mitro N, Ficara F, Della Porta MG, Ghisletti S. Blood 2026. doi: 10.1182/blood.2025030760.*

## **Nel posto giusto al momento giusto – La localizzazione di NUMB influenza le cellule del microambiente.**

NUMB è un noto oncosoppressore; regola l'endocitosi (e di conseguenza contrasta l'attività del recettore NOTCH), modula la degradazione/stabilizzazione della proteina p53 (attraverso l'interazione con la proteina MDM2), regolando di conseguenza la divisione delle cellule staminali. Nel compartimento staminale, la perdita di NUMB “trasforma” infatti la divisione asimmetrica delle cellule in divisione simmetrica, influenzando così il destino delle cellule figlie e modificando l'espansione delle cellule staminali, contribuendo alla tumorigenesi. I ricercatori IEO hanno infatti precedentemente dimostrato, sia nel tumore al seno che nel tumore alla vescica, che l'espressione di NUMB correla con l'aggressività del tumore.

In un articolo recente di Cacciatore, Basile, et al., i ricercatori coordinati da Pier Paolo Di Fiore –Group leader al Dipartimento di Oncologia Sperimentale di IEO e professore dell'Università di Milano– e Ivan Colaluca –ricercatore senior in IEO–, hanno analizzato in dettaglio la funzione dell'isoforma della proteina NUMB contenente una sequenza specifica-codificata, tramite splicing alternativo, dall'esone 3-, rivelando il ruolo di questa regione di NUMB nell'interazione proteina-proteina e proteina-lipidi. Questo segmento di proteina determina la localizzazione di NUMB a livello della membrana cellulare, consentendo e mediando l'interazione di NUMB con SNX9 (una proteina nota per il suo coinvolgimento nell'endocitosi e precedentemente implicata nella capacità invasiva delle cellule del tumore al seno e nelle metastasi); il complesso proteico NUMB-SNX9 lega a sua volta la proteina p53 e racchiuso all'interno di piccole vescicole (chiamate esosomi) viene secreto nel microambiente extracellulare. Una volta secreto, p53 viene “assorbito” da altre cellule nel microambiente, inducendo dei cambiamenti fenotipici.

Attraverso questi esperimenti, gli autori hanno quindi scoperto un nuovo ruolo delle isoforme di NUMB contenenti l'esone 3, regolato dalla sua localizzazione all'interno della cellula, ed esercitato attraverso l'interazione, all'interno di un complesso multiproteico, con p53 e SNX9. Attraverso il meccanismo descritto, NUMB influisce sia sulla cellula che rilascia le vescicole contenenti p53 (*cell-autonomous effect*), sia sulle cellule che “ricevono” le vescicole contenenti p53 (*non-cell-autonomous effect*): la formazione del complesso NUMB-p53-SNX9 a livello della membrana plasmatica permette infatti di “avvolgere” questo complesso proteico all'interno di vescicole che, quando rilasciate, da un lato, determinano una riduzione dei livelli intracellulari di p53, dall'altro, influenzano le cellule del microambiente.

Quale potrebbe essere la rilevanza patologica di questo meccanismo? Dimostrando, per la prima volta, che p53 non mutato può essere rilasciato nel microambiente extracellulare, i ricercatori hanno rivelato un meccanismo utilizzato dalle cellule per mantenere, attraverso l'attività di p53, un ambiente oncosoppressivo che in determinate situazioni, potrebbe altrimenti indurre la tumorigenesi.

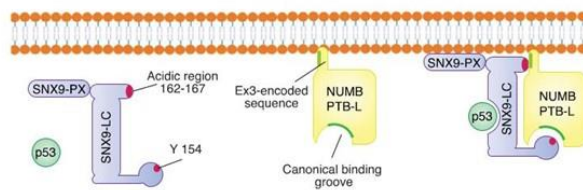
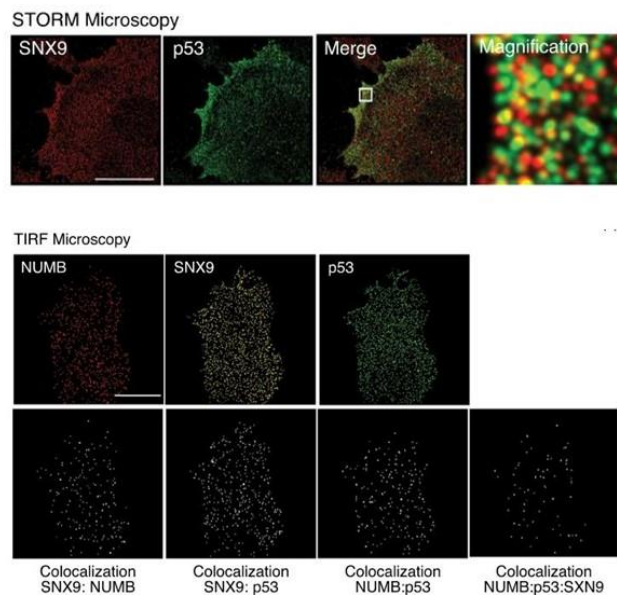
### **TELL ME MORE!**

**L'interattoma dell'isoforma di NUMB contenente la regione codificata dall'esone 3.** Attraverso analisi proteomiche, gli autori hanno identificato le proteine che interagivano con la sequenza della proteina NUMB codificata dall'esone 3. La proteina SNX9 (ma non con le proteine correlate SNX18 o SNX33) risultava interagire in maniera specifica con NUMB, insieme a p53. Non solo: NUMB e p53 interagivano in maniera specifica *attraverso* SNX9. Inoltre, l'interazione NUMB-SNX9 avveniva solo con l'isoforma di NUMB contenente la regione codificata dall'esone 3 (dato che l'isoforma di NUMB priva della regione codificata dall'esone3 non interagiva con SNX9).

**Quali sono gli aminoacidi coinvolti nell'interazione NUMB-SNX9?** La sequenza aminoacidica tra i residui 101 e 183 di SNX9 era necessaria perché il legame tra NUMB e SNX9 fosse ottimale e uno specifico residuo di

NUMB (F162), all'esterno della regione codificata dall'esone 3, era critico per l'interazione NUMB-SNX9. I residui R69/K70/K73/K78 nella regione codificata dall'esone 3, pur non essendo cruciali per l'interazione NUMB-SNX9, contribuivano a stabilizzare il legame proteina-proteina (infatti, quando questi aminoacidi erano mutati, l'interazione NUMB-SNX9 era più debole, ma comunque conservata).

**La localizzazione subcellulare di NUMB contenente la sequenza codificata dall'esone 3 è fondamentale per l'interazione NUMB-SNX9.** Come mai la sequenza codificata dall'esone 3 è necessaria per l'interazione NUMB-SNX9, ma il residuo più importante coinvolto nell'interazione si trova all'esterno di questa regione? Gli autori hanno mostrato che la localizzazione di NUMB a livello della membrana plasmatica, influenzata dalla presenza della regione della proteina codificata dall'esone 3, era critica per l'interazione NUMB-SNX9. Infatti, mentre la proteina contenente la regione codificata dell'esone 3 era localizzata a livello della membrana plasmatica, l'isoforma della proteina priva della regione codificata dall'esone 3 si trovava invece nel citoplasma. Quando NUMB non era localizzata a livello della membrana plasmatica (per via di mutazioni nei residui R69/K70/K73/K78 o per via della perdita della regione codificata dall'esone 3), si perdeva anche l'interazione NUMB-SNX9, nonostante la presenza del residuo F162 coinvolto nell'interazione proteina-proteina.



*Adapted from Cacciatore, Basile et al. (an open access article under the CC BY license.)*

Mentre le proteine purificate interagivano in ogni caso, anche se la sequenza codificata dall'esone 3 era alterata o del tutto assente, nelle cellule ciò non avveniva, a causa dell'alterata localizzazione di NUMB, regolata dalla regione codificata dall'esone 3. Quindi, la sequenza di NUMB codificata dall'esone 3, da un lato, forniva una superficie di legame a bassa affinità per SNX9; dall'altro, localizzava NUMB a livello della membrana plasmatica, contribuendo così all'interazione con SNX9.

**In che modo la regione di NUMB codificata dall'esone 3 interagisce con la membrana?** Sfruttando un sistema modello rappresentato da liposomi, i ricercatori hanno analizzato il legame alla membrana lipidica di NUMB contenente la regione codificata dall'esone 3, di NUMB privo di questa regione, e di SNX9. Hanno osservato che la regione codificata dall'esone 3 di NUMB, oltre a contribuire all'interazione NUMB-SNX9, come mostrato prima, legava la membrana lipidica; infatti, la proteina priva di questa regione non legava la membrana lipidica. Quando sia NUMB che SNX9 erano presenti, il legame del complesso proteico alla membrana era più forte.

**Il complesso proteico NUMB-SNX9-p53 era influenzato dalla membrana plasmatica?** p53 e NUMB contenente la regione codificata dall'esone 3 legavano entrambi indipendentemente la membrana lipidica; il legame alla membrana era più forte in presenza di SNX9. In particolare, SNX9 legava p53 solo alla membrana, indicando che le tre proteine colocalizzavano, a livello della membrana plasmatica, e l'interazione proteina-proteina richiedeva la membrana, inducendo probabilmente un cambiamento conformazionale in SNX9 che esponeva il segmento di proteina che interagiva con p53.

**Alla membrana plasmatica, p53 è impacchettato all'interno di vescicole extracellulari.** p53 è solitamente localizzato nel nucleo della cellula. Quando localizzato a livello della membrana plasmatica, attraverso l'interazione con NUMB e SNX9, veniva impacchettato all'interno di vescicole extracellulari (EV). L'impacchettamento di p53 nelle EV richiedeva sia SNX9 che NUMB. In seguito alla secrezione, le EV contenenti p53 influenzavano sia le cellule che rilasciavano le EV sia le cellule che le ricevevano: nelle cellule che le rilasciavano, la secrezione delle EV contenenti p53 riduceva i livelli intracellulari di p53 e di conseguenza le sue proteine target (effetto *cell-autonomous*), la progressione del ciclo cellulare e la replicazione del DNA. Nelle cellule che ricevevano le EV secrete contenenti il complesso p53/SNX9/NUMB, c'era un aumento dei livelli delle proteine target e della proliferazione cellulare (effetto non *cell-autonomous*), indicando che la secrezione, all'interno delle EV, di p53 wt forniva alle cellule che lo ricevevano, attraverso un meccanismo non *cell-autonomous*, l'attività di p53.

*Referenza: Endocytic Control of Cell-Autonomous and Non-Cell-Autonomous Functions of p53. Roberta Cacciatore, Andrea Basile, Stefano Freddi, Irene Schiano Lomoriello, Carlo Ribelle Zucca, Giuseppe Ciossani, Luigi Scietti, Alessandro Cuomo, Simona Ronzoni, Simone Pelicci, Mario Faretta, Elena Zaccheroni, Giuliana Pelicci, Vittoria Matafora, Angela Bachi, Rosalind Helen Gunby, Salvatore Pece, Sara Sigismund, Letizia Lanzetti, Ivan Nicola Colaluca, Pier Paolo Di Fiore. Adv Sci (Weinh) 2026. doi: 10.1002/advs.202513765).*

## Le alterazioni del movimento delle proteine all'interno della cellula nella progressione del tumore al seno.

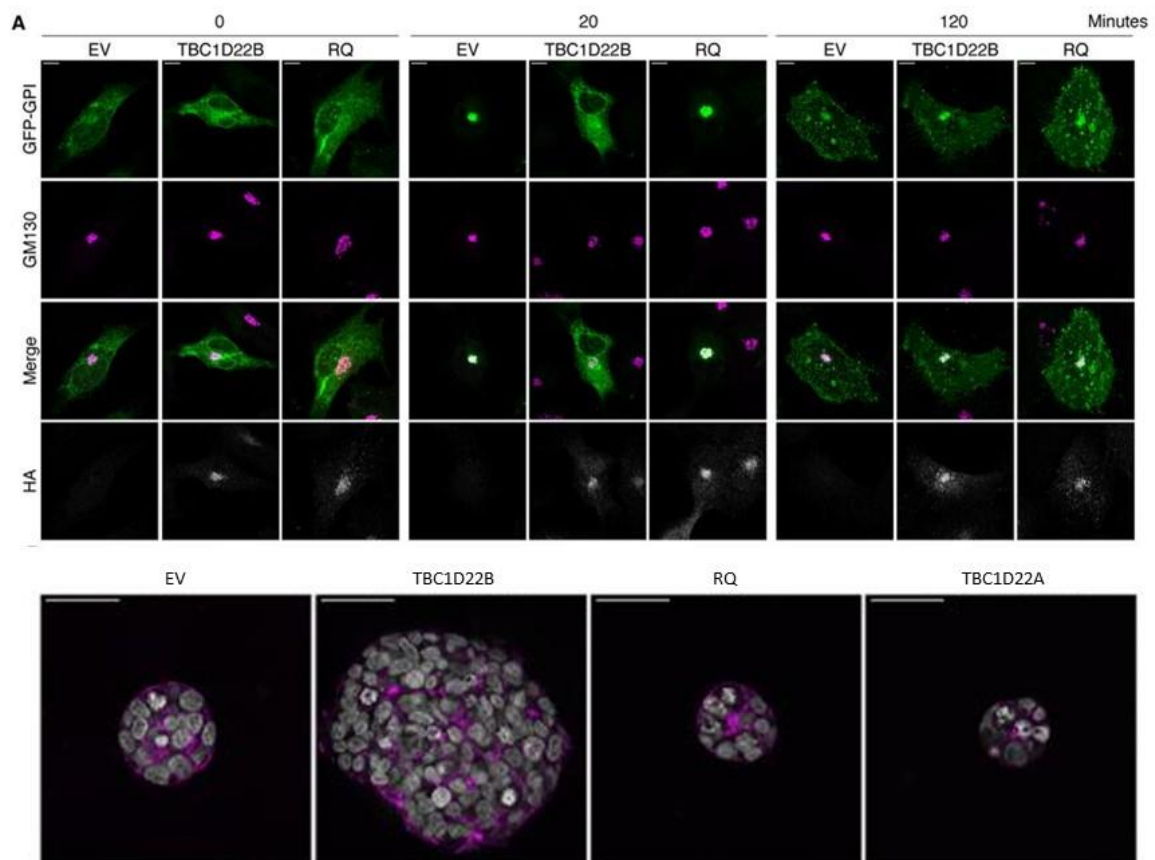


Figure adapted from Martino et al. (an open access article under the CC BY license.)

Il funzionamento della cellula è il risultato di numerosi processi, interconnessi tra loro, che devono essere finemente regolati. L'attività coordinata di diversi fattori garantisce il corretto funzionamento della cellula.

L'alterato livello di espressione o di attività di questi fattori può influire sul corretto funzionamento della cellula, inducendo uno stato patologico. TBC1D22B e TBC1D22A sono due proteine intracellulari, localizzate a livello delle membrane interne della cellula (l'apparato di Golgi), e l'alterazione del loro livello di espressione è stata precedentemente associata a una prognosi sfavorevole nelle pazienti.

In un articolo recente, gli autori, tra cui Sara Sigismund-Group leader al dipartimento di oncologia sperimentale di IEO e professoressa all'università di Milano-, Linda Andreoli, Stefano Freddi, Bronislava Matoskova, Amir Fardin, Alessandro Cuomo, hanno definito il ruolo della proteina TBC1D22B nella fisiologia cellulare e nel tumore al seno e hanno descritto il meccanismo molecolare implicato.

I ricercatori hanno dimostrato che la proteina TBC1D22B, localizzata a livello dell'apparato di Golgi, regola il movimento delle proteine all'interno della cellula (nello specifico, dal reticolo endoplasmatico-ER- al Golgi) agendo su specifiche proteine target (cioè, agendo come GAP-GTPase-activating protein- sulla sua proteina target RAB1B). Nelle pazienti con tumore al seno di tipo luminale, la sovraespressione di TBC1D22B, che correla con una scarsa prognosi delle pazienti, spegnendo la sua proteina target, sembrerebbe rallentare il trasporto di proteine chiave (dal ER al Golgi), con conseguente alterazione dei processi fisiologici della cellula e tumorigenesi.

L'alterazione di questo meccanismo potrebbe influire sulla secrezione di specifici fattori cellulari coinvolti nella progressione del tumore-come citochine, enzimi e glicoproteine- che, modificando il microambiente tumorale, potrebbero promuovere la progressione del tumore e l'evoluzione in malattia metastatica. Questi risultati propongono quindi TBC1D22B come un possibile nuovo target contro il tumore al seno di tipo luminale.

## TELL ME MORE!

Prima di tutto, con un approccio proteomico (proximity labeling seguito da spettrometria di massa e co-immunoprecipitazione), gli autori hanno identificato le proteine che interagivano con TBC1D22B. Queste proteine facevano parte di pathway cellulari coinvolti nel trasporto da ER a Golgi e il trasporto vescicolare al Golgi, in linea con la nota localizzazione della proteina TBC1D22B a livello della membrana del Golgi, così come al trasporto degli endosomi, l'organizzazione del citoscheletro, le interazioni cellula-cellula e cellula-matrice.

Analisi funzionali (attraverso il sistema RUSH) delle proteine che interagivano con TBC1D22B hanno rivelato che TBC1D22B influenzava il movimento delle proteine dal ER al Golgi; in particolare, la sovraespressione di TBC1D22B ne rallentava il trasporto. Al contrario, il silenziamento di TBC1D22B (ma non TBC1D22A) accelerava la migrazione, mediata da TBC1D22B, delle proteine da ER al Golgi, indicando che, fisiologicamente, TBC1D22B funziona come inibitore del trasporto da ER a Golgi.

Dal punto di vista del meccanismo, TBC1D22B danneggia il trasporto ER-Golgi attraverso la sua attività GAP; ovvero, spegnendo l'attività di alcune RAB GTPasi. Infatti, il silenziamento della RAB GTPasi target di TBC1D22B determinava un rallentamento del trasporto da ER a Golgi, rispecchiando ciò che veniva osservato in seguito alla sovraespressione di TBC1D22B. L'effetto era particolarmente evidente in seguito al silenziamento di RAB1B, dimostrando che TBC1D22B inibisce il trasporto da ER a Golgi attraverso l'inattivazione di RAB1B. L'attività GAP di TBC1D22B su RAB1B si perdeva nei mutanti di TBC1D22B privi di attività GAP, confermando ulteriormente che TBC1D22B agisce come GAP su RAB1B e sostenendo il ruolo di TBC1D22B nel meccanismo di regolazione del trafficking da ER a Golgi RAB1B-dipendente.

Considerando i loro precedenti risultati, che hanno dimostrato che il livello di espressione di TBC1D22B è un predittore di cattiva prognosi nel tumore al seno di tipo luminale, il meccanismo identificato è rilevante nella tumorigenesi del cancro al seno? Gli autori hanno osservato che la sovraespressione di TBC1D22B (ma non TBC1D22A) conferiva un vantaggio proliferativo alle cellule del tumore al seno. Inoltre, analizzando i dati clinici è emerso che nei tumori caratterizzati da livelli elevati di TBC1D22B il profilo di espressione genica era diverso rispetto a quello dei tumori che esprimevano livelli bassi della proteina, suggerendo che TBC1D22B giochi un ruolo nel guidare i cambiamenti nell'espressione genica associati ad una scarsa prognosi delle pazienti con tumore al seno di tipo luminale. In linea con questi dati, la sovraespressione di TBC1D22B (in linee cellulari di tumore al seno) alterava profondamente il profilo di espressione genica delle cellule, rispecchiando i cambiamenti osservati nei tumori primari ed evidenziando il suo potenziale oncogenico. I geni influenzati dall'espressione di TBC1D22B erano coinvolti in pathway legati all'organizzazione della

matrice extracellulare e alla motilità/adesione cellulare e molti codificavano per proteine secrete, in linea con il ruolo della proteina TBC1D22B nel trafficking e nella secrezione.

Infine, gli autori hanno identificato una firma genica, regolata da TBC1D22B, validata in una coorte di pazienti dei database METABRIC e TCGA, il cui livello di espressione cambiava in maniera coordinata, era associato al rimodellamento della matrice extracellulare e all'adesione, e la cui repressione potrebbe essere meccanicisticamente collegata ad una scarsa prognosi delle pazienti con tumore al seno di tipo luminale caratterizzato dalla sovraespressione della proteina TBC1D22B.

*Referenza: TBC1D22B Regulates ER-to-Golgi Trafficking via RAB1B Inactivation and Promotes Oncogenic Programs in Breast Cancer. Flavia Martino, Mariadomenica Lupi, Alessandra Murabito, Fabio Bedin, Giulia Villari, Linda Andreoli, Stefano Freddi, Bronislava Matoskova, Rosa Pennisi, Stella Fontana, Amir Fardin, Gaele Boncompain, Franck Perez, Federico Bussolino, Alessandro Cuomo, Sara Sigismund, Letizia Lanzetti. Adv Sci (Weinh) 2025. doi: 10.1002/advs.202502269.*

## Le vescicole extracellulari tra instabilità cromosomica e migrazione delle cellule tumorali.

Il tumore al seno triplo-negativo (triple-negative breast cancer, TNBC) è un tumore altamente aggressivo la cui prognosi è spesso sfavorevole. Il TNBC è caratterizzato da instabilità cromosomica (CIN) che a sua volta correla con la progressione tumorale. La CIN è stata associata con alterazioni nella formazione e nel contenuto di vescicole extracellulari (EV) e le EV sono notoriamente coinvolte nella comunicazione intercellulare e nel rimodellamento del microambiente da parte delle cellule.

In che modo la CIN influenza la formazione, il rilascio e il contenuto delle EV, rimodellando il microambiente e modulando la progressione tumorale?

In uno studio recente, i ricercatori, tra cui Stefano Santaguida -Group leader al Dipartimento di Oncologia Sperimentale di IEO e professore dell'Università di Milano- hanno esplorato i meccanismi alla base della secrezione delle EV, indotta da CIN, e del contenuto delle EV e il modo in cui ciò influenza funzionalmente il microambiente e la progressione del tumore, in modelli di TNBC. Confrontando le EV rilasciate dalle cellule tumorali

con alta e bassa CIN e gli effetti di queste EV sulle altre cellule, gli autori hanno scoperto che le cellule con alta CIN rilasciano più EV rispetto alle cellule con bassa CIN; queste EV a loro volta promuovono la migrazione e la capacità delle cellule tumorali di migrare ed invadere i tessuti circostanti, due aspetti chiave nel processo di disseminazione metastatica. L'effetto delle EV è particolarmente evidente sulle cellule con bassa CIN. Hanno inoltre identificato una proteina (EFEMP1), abbondante nelle EV rilasciate dalle cellule con alta CIN, modulata da STAT1, con un ruolo critico nel promuovere la migrazione cellulare, e hanno descritto il meccanismo coinvolto.

I loro esperimenti hanno quindi rivelato un meccanismo mediato dalle EV, attraverso cui le cellule tumorali con alta CIN modulano il microambiente, promuovendo la migrazione e l'invasione (disseminazione

### Gli autori – Stefano Santaguida.

Stefano Santaguida è professore associato di Biologia Molecolare all'Università di Milano e Group leader al Dipartimento di Oncologia Sperimentale dell'Università di Milano. Dopo un dottorato in IEO, focalizzato sui meccanismi molecolari alla base del funzionamento del checkpoint di assemblaggio del fuso, un meccanismo di sorveglianza che garantisce la fedeltà della segregazione cromosomica, nelle cellule umane, si è trasferito negli Stati Uniti per un post-doc al Massachusetts Institute of Technology (MIT, Cambridge, US). La sua ricerca al MIT approfondiva diversi aspetti delle conseguenze dell'aneuploidia sul funzionamento della cellula. Per far luce sul modo in cui le alterazioni del numero di cromosomi influenzano la fisiologia cellulare, ha sviluppato un sistema che permette di studiare le conseguenze immediate dell'aneuploidia nelle cellule umane. I suoi studi hanno iniziato a definire il modo in cui un alterato numero di cromosomi influenza il proteoma cellulare e ha fornito informazioni accurate sulle conseguenze immediate dell'aneuploidia sull'integrità del genoma. La ricerca nel suo laboratorio in IEO si pone l'obiettivo di fornire una caratterizzazione molecolare dei pathway deregolati nelle cellule aneuploidi, con la speranza di facilitare lo sviluppo di trattamenti che colpiscano lo stato aneuploide del cancro.

metastatica), identificando un fattore chiave -la proteina EFEMP1- che potrebbe rappresentare un nuovo target terapeutico contro la disseminazione metastatica.

## TELL ME MORE!

Prima di tutto, attraverso la quantificazione di un noto marcatore di EV (CD63), gli autori hanno confrontato le EV rilasciate dalle linee cellulari di TNBC (BT549 and MDA-MB-231) con alta CIN (indotta tramite trattamento con l'inibitore di MPS1) e bassa CIN, mostrando un maggiore rilascio di EV da parte delle cellule con alta CIN. La dimensione delle EV non era invece influenzata.

Quando le cellule riceventi assorbivano le EV rilasciate dalle cellule con alta CIN, la loro capacità invasiva e migratoria aumentava; la proliferazione cellulare, invece, non veniva alterata. Al contrario, le cellule che rilasciavano le EV mostravano una minore capacità di proliferare, migrare, invadere, suggerendo che mentre la CIN danneggia la capacità proliferativa e migratoria delle cellule tumorali, induce il rilascio di EV che promuovono la migrazione delle cellule vicine. Quando il trafficking cellulare veniva compromesso (tramite il silenziamento della proteina RAB27A), l'aumentata capacità migratoria indotta dalle EV veniva danneggiata, confermando che la maggiore capacità migratoria delle cellule riceventi (ovvero le cellule che assorbono le EV prodotte dalle cellule con alta CIN) era di fatto dovuta alle EV. Lo stesso effetto si osservava in altre cellule tumorali (CRC), ma non nelle cellule non trasformate.

Hanno quindi analizzato i meccanismi molecolari coinvolti. L'analisi del contenuto di EV derivanti da cellule con alta e bassa CIN ha rivelato, nelle EV derivanti da cellule con alta CIN, l'abbondanza di proteine coinvolte nell'adesione cellulare e in particolare della proteina Fibulin3/EFEMP1, nota per il suo ruolo nella migrazione. EFEMP1 era più espressa nelle cellule con alta CIN e nelle EV derivanti dalle cellule con alta CIN rispetto alle EV derivanti da cellule con bassa CIN.

Per approfondire il ruolo della proteina EFEMP1, ne hanno manipolato l'espressione nelle cellule con alta CIN che generavano EV: la sovraespressione e il silenziamento di EFEMP1 rispettivamente promuovevano e danneggiavano la migrazione e l'invasione, sia nelle cellule che rilasciavano EV che nelle cellule riceventi.

Analizzando l'espressione genica delle cellule riceventi stimulate con le EV che esprimevano EFEMP1 o le EV prive di EFEMP1, gli autori hanno identificato numerosi geni diversamente espressi, tra cui geni coinvolti nella migrazione/invasione cellulare, come i geni dell'adesione cellulare e della transizione epiteliomesenchimale (EMT), indicando che il rilascio, indotto da CIN, di EV contenenti EFEMP1 induce, nelle cellule riceventi vicine, EMT e migrazione cellulare.

Analisi meccanicistiche approfondite hanno mostrato che STAT1 modula l'espressione della proteina EFEMP1 e, a sua volta, il rilascio di EV contenenti EFEMP1 promuove la migrazione delle cellule riceventi. La perdita di STAT1 danneggiava infatti la migrazione cellulare indotta da EVs.

Per analizzare le conseguenze funzionali, sulla migrazione e l'invasione, delle EV contenenti EFEMP1 (ovvero isolate da cellule con alta CIN che esprimevano EFEMP1), hanno utilizzato modelli di zebrafish. La migrazione delle cellule stimulate con le EV che sovraesprimevano EFEMP1 era aumentata, rispetto alle cellule stimulate con EV (di controllo) che esprimevano EFEMP1 a valori normali; la disseminazione delle cellule stimulate con EV prive di EFEMP1 era invece ridotta, indicando che le EV che esprimevano EFEMP1 erano in grado di modulare la disseminazione delle cellule tumorali in vivo.

Infine, in linea con i loro risultati -che sottolineano una correlazione causale tra la CIN e l'espressione di EFEMP1-, analisi di dataset pubblici di tumori umani hanno rivelato una correlazione tra i livelli di EFEMP1 e aneuploidia, evidenziando la rilevanza clinica delle loro scoperte. Inoltre, la stratificazione dei pazienti sulla base dell'espressione di EFEMP1 ha rivelato una correlazione tra l'espressione di EFEMP1 e l'esito clinico, suggerendo che EFEMP1 potrebbe rappresentare un nuovo target terapeutico contro la disseminazione metastatica.

*Referenza.* Chromosomal instability promotes cell migration and invasion via EFEMP1 secretion into extracellular vesicles. Siqi Zheng, Ruifang Tian, Marsudi Siburian, Anna Haider Rubio, Yuanyuan Liu, Rene Wardenaar, Marjan Shirzai, Laura Kempe, Emma Dijkstra, Eliza Warszawik, Maria Suarez Peredo Rodriguez, Klaas Sjollemma, Petra L Bakker, Patrick van Rijn, Michaela Borghesan, Judith TML Paridaen, Stefano Santaguida & Floris Foijer. *The EMBO Journal* 2026. doi: 10.1038/s44318-026-00766-4.

## La specificità del complesso Restrictor.



*Gaurav Madappa Mandana, Viviana Piccolo*

Restrictor è un complesso proteico che agisce come regolatore negativo della trascrizione, arrestando la sintesi delle molecole di RNA derivanti da regioni regolatorie extra-geniche, che non codificano per proteine, come enhancer e promotori.

I ricercatori IEO hanno precedentemente dimostrato che Restrictor è costituito da due componenti principali -ZC3H4 e WDR82- che, interagendo con altre due proteine -Symplekin e PNUTS-, consentono l'arresto della sintesi di RNA quando la RNA Polimerasi II è reclutata a livello delle regioni extra-geniche regolatorie non codificanti, evitando così la produzione di RNA aberranti (al contrario, Restrictor non ha alcun effetto sulla trascrizione di geni codificanti da parte di RNA Polimerasi II).

La regolazione precisa della trascrizione extra-genica è cruciale per il corretto funzionamento cellulare. Alterazioni nella trascrizione dell'RNA a livello delle regioni extrageniche possono infatti influenzare la stabilità genomica (creando collisioni tra RNA e DNA polimerasi) contribuire alla deregolazione dell'espressione genica, essere potenzialmente coinvolte nei processi di tumorigenesi. Per questo, i meccanismi che controllano la trascrizione -o la terminazione della

### Come si inseriscono queste scoperte in un contesto oncologico?

La trascrizione di RNA da regioni non codificanti del DNA, come ad esempio le regioni regolatorie quali gli enhancer, gioca un ruolo importante nella regolazione dell'espressione genica e quindi nella modulazione di processi fondamentali per la biologia cellulare. Ad esempio, nel tumore prostatico, sono stati precedentemente descritti dei livelli anomali, rispetto ai tessuti normali, di RNA derivanti da enhancer (eRNA), suggerendo una correlazione tra l'alterata presenza di eRNA, la progressione tumorale e la prognosi del paziente. Questi studi indicano quindi che gli eRNA potrebbero giocare un ruolo chiave nella biologia del tumore prostatico, sottolineando l'importanza di regolarne la trascrizione e, se necessario, arrestarla, suggerendo che comprendere a fondo questi processi potrebbe permettere lo sviluppo di nuove terapie molecolari. Inoltre, le anomalie nei pattern di abbondanza/presenza degli eRNA nel tumore prostatico suggeriscono la loro potenziale utilità come biomarcatori prognostici e diagnostici. Analogamente, è stata osservata una produzione anomala di eRNA nel tumore al seno. Altri studi hanno evidenziato un ruolo degli eRNA nel tumore pancreatico e nella leucemia, sottolineando

trascrizione- a livello di queste regioni giocano un ruolo fondamentale nel mantenimento della stabilità genomica e della fedeltà nell'espressione genica.

Ad oggi, le basi molecolari della specificità di Restrictor per le regioni extra-geniche non sono note.

In un articolo recente di Polizzese, Mandana, Piccolo et al., i ricercatori guidati da Gioacchino Natoli-Group leader al dipartimento di oncologia sperimentale di IEO- hanno analizzato i meccanismi molecolari alla base della specificità di Restrictor, mostrando il ruolo cruciale della componente ZC3H4 del complesso nell'arrestare la trascrizione dell'RNA solo a livello delle regioni extrageniche. I loro dati indicano infatti che mentre la proteina WDR82 è necessaria per legare il complesso Restrictor alla RNA polimerasi II associata sia alle regioni codificanti che non-codificanti, ZC3H4 è richiesto per fornire a Restrictor la specificità per le regioni non codificanti, riconoscendo specifiche sequenze sulle molecole di RNA nascente. Il legame-seppure temporaneo- di Restrictor alle regioni codificanti, dove la sintesi dell'RNA non deve essere arrestata, rallenta la sintesi dell'RNA e questa temporanea decelerazione potrebbe permettere a Restrictor (nello specifico, a ZC3H4) di scansionare la molecola di RNA così da valutare, sulla base di una specifica sequenza nucleotidica della molecola di RNA- identificata in questo lavoro-, se la trascrizione dell'RNA deve essere arrestata oppure no. Altri meccanismi, ancora sconosciuti, sono probabilmente coinvolti nell'assicurare la specificità del legame di Restrictor all'RNA.

ulteriormente l'importanza dei meccanismi che ne regolano i livelli. La trascrizione extragenica in fase S aumenta la probabilità di collisione tra DNA Pol e RNA Pol II, il che conduce al danno al DNA (DNA double strand breaks) e quindi instabilità genomica. Si tratta quindi di un machinery "housekeeping" essenziale per il mantenimento dell'integrità cellulare. Le cellule tumorali hanno una più elevata dipendenza da questi meccanismi housekeeping rispetto alle cellule normali, il che crea potenziali finestre terapeutiche; infatti, ad esempio, alcuni inibitori dello splicing sono oggi utilizzati per il trattamento di alcune leucemie.

## TELL ME MORE!

Innanzitutto, utilizzando una linea cellulare che esprimeva una forma mutata della proteina ZC3H4, priva di una data sequenza aminoacidica, gli autori hanno valutato se ZC3H4 era necessaria per l'arresto della trascrizione a livello delle regioni extra-geniche. In queste cellule, la terminazione della sintesi dell'RNA a livello delle regioni extra-geniche era compromessa, dimostrando un ruolo della componente ZC3H4 di Restrictor in questo processo. Inoltre, hanno scoperto che ZC3H4 legava una specifica sequenza della molecola di RNA nascente (AU-rich – GUA – AU-rich). Nello specifico, il dominio zinc finger C3H1 di ZC3H4 era coinvolto nel riconoscimento di questa sequenza di RNA e nel successivo legame del complesso Restrictor, mentre il dominio SRG di ZC3H4 era coinvolto nell'arresto della trascrizione, ma non nel riconoscimento della specifica sequenza. Le sequenze necessarie perché Restrictor riconoscesse dove arrestare la sintesi dell'RNA erano abbondanti a livello delle regioni extra-geniche, e il legame di ZC3H4 agli RNA non codificanti correlava con la repressione trascrizionale.

Infine, hanno analizzato in dettaglio il ruolo preciso di tre domini con distinte funzioni della proteina ZC3H4 (SRG [necessario per la corretta distribuzione nucleare di Restrictor], C3H1 [necessario per il legame sequenza-specifico all'RNA], DPR [necessario per il legame a WDR82 e alla RNA Polimerasi II]), utilizzando delle linee cellulari inducibili (in cui cioè l'espressione di ZC3H4 normale o di tre forme mutanti poteva essere indotta farmacologicamente in cellule in cui la proteina endogena era stata eliminata), inducendo l'espressione di ZC3H4 mutante veniva ripristinata la trascrizione dell'RNA che Restrictor aveva arrestato, mentre spegnendo l'espressione della proteina mutante, la repressione mediata da Restrictor veniva ripristinata, suggerendo la possibilità di modulare questi processi regolando l'attività di Restrictor. Se da un lato la ri-espressione della proteina ZC3H4 normale ripristinava la repressione della trascrizione, la ri-espressione di una qualsiasi delle tre proteine mutanti (ovvero prive dei domini SRG, o C3H1, o DPR) non aveva effetto, consentendo l'espressione dei trascritti extragenici e indicando che con meccanismi diversi tutti e tre i domini della proteina erano necessari per la repressione della trascrizione mediata da ZC3H4. E' interessante sottolineare che un mutante specifico (quello privo del dominio DPR che interagiva con l'altra proteina del complesso Restrictor, WDR82) determinava una iper-trascrizione dell'RNA tipicamente represso da Restrictor, mentre la proteina mutante ZC3H4 priva del dominio C3H1 aboliva completamente il legame all'RNA.

*Referenza: Sequence-specific RNA recognition drives Restrictor-mediated termination of extragenic transcription. Danilo Polizzese, Gaurav Madappa Mandana, Marta Russo, Sara Polletti, Elena Prosperini, Giuseppe Ciossani, Silvia Monzani, Luigi Scietti, Simona Rodighiero, Francesco Gualdrini, Viviana Piccolo, Gioacchino Natoli. Mol Cell 2026. doi: 10.1016/j.molcel.2026.02.006.*

## Effetti antitumorali della metformina e del digiuno intermittente – uno studio in corso.

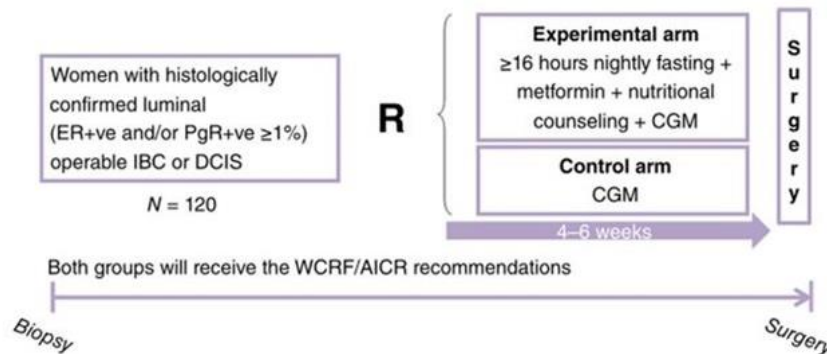


Image from Briata et al. (an open access article under the CC BY NC ND license.)

L'obesità e la resistenza all'insulina sono due fattori responsabili sia di un aumento del rischio di sviluppare tumore al seno sia di una peggiore prognosi; le pazienti in sovrappeso guarite dal tumore al seno sono infatti ad elevato rischio di sviluppare recidiva.

I livelli di insulina-così come quelli di estrogeni e l'infiammazione- sono stati associati alla crescita del tumore facendo ipotizzare che, interferendo con il signaling dell'insulina per mezzo della metformina (un farmaco comunemente utilizzato per il trattamento del diabete), potrebbe essere possibile contrastare la crescita del tumore. E' noto infatti che le cellule tumorali hanno una certa plasticità metabolica che ne permette l'adattamento a condizioni microambientali variabili-in termini di disponibilità di nutrienti- passando da glicolisi a fosforilazione ossidativa, e la sopravvivenza anche in condizioni di carenza di nutrienti. Ciò spiega, da un lato, perché i trattamenti che colpiscono soltanto la glicolisi spesso falliscono e, dall'altro, offrono una spiegazione ai risultati preclinici che rivelano i benefici del trattamento combinato che colpisce contemporaneamente sia glicolisi che fosforilazione ossidativa. Studi epidemiologici e preclinici precedenti suggeriscono infatti che il farmaco antidiabetico metformina (inibitore della fosforilazione ossidativa) e il digiuno cooperino nell'indurre la morte delle cellule tumorali, probabilmente agendo sul metabolismo della cellula tumorale. In linea con queste scoperte, studi clinici hanno mostrato che il digiuno intermittente (ovvero periodi di digiuno interrotti da periodi di alimentazione normale: in particolare, 8 ore di alimentazione regolare seguite da 16 ore di digiuno) abbassa i livelli di insulina e riduce la resistenza all'insulina. Inoltre più è lungo il periodo di digiuno, migliori sono i benefici in termini di recidiva della malattia, proponendo il digiuno intermittente come una strategia-alternativa ai farmaci- potenzialmente efficace nel ridurre il rischio di recidiva.

Nel contesto di una collaborazione internazionale che ha coinvolto l'IEO, l'ospedale Galliera di Genova e l'MD Anderson Cancer Center (USA), i ricercatori hanno disegnato uno studio clinico randomizzato volto a valutare l'efficacia antitumorale della somministrazione di metformina in combinazione con il digiuno notturno su pazienti con tumore al seno, prima dell'intervento chirurgico, col fine ultimo di migliorarne l'esito clinico.

Lo studio ha reclutato 120 pazienti con tumore al seno (ER+ e/o PgR+) candidate alla chirurgia. Le pazienti sono state casualmente assegnate a 2 gruppi: a) a ricevere metformina e attenersi ad un digiuno notturno di 16 ore (ovvero mangiando solo

### La metformina e il cancro.

I ricercatori IEO hanno precedentemente studiato i meccanismi molecolari alla base degli effetti antitumorali della metformina, identificando,

tra mezzogiorno e le 8 di sera) oppure b) semplicemente sottoporsi al monitoraggio del glucosio (gruppo di controllo, con alimentazione regolare ma in maniera sana).

L'analisi intermedia sulla sicurezza dell'approccio terapeutico ha incluso 14 pazienti nel gruppo sperimentale (metformina + digiuno intermittente) e ha rivelato fattibilità e sicurezza di questo intervento terapeutico preventivo. Non sono stati infatti osservati eventi avversi gravi (legati ad una severa ipoglicemia) e non c'è stata alcuna interruzione del trattamento dovuta a tossicità.

Sebbene un intervento chirurgico tempestivo nelle pazienti con tumore al seno sia sempre importante per un buon esito clinico, studi epidemiologici e preclinici indicano che un trattamento, attentamente controllato, prima della chirurgia potrebbe contribuire a migliorare l'esito clinico e ridurre il rischio di recidiva. Questo studio si pone l'obiettivo di confermare le evidenze epidemiologiche e precliniche con un clinical trial prospettico randomizzato e un intervento semplice, sicuro e non costoso, attraverso la ri-proposta di un farmaco ampiamente utilizzato per il trattamento del diabete, insieme ad uno specifico regime dietetico, e una valutazione dell'efficacia attraverso test di laboratorio utilizzati di routine. Se i risultati finali confermeranno l'ipotesi di lavoro, questo approccio potrebbe essere rapidamente applicato ad ampie popolazioni di pazienti ad alto rischio.

tramite analisi metabolomica, i metaboliti modulati dal trattamento con metformina e i pathway metabolici coinvolti, nelle pazienti in sovrappeso guarite dal tumore al seno ma ad alto rischio di recidiva. Hanno inoltre esplorato il potenziale effetto preventivo della somministrazione delle metformina sulla recidiva del tumore al seno analizzando l'espressione genica, osservando che la metformina potrebbe influenzare i livelli di espressione di alcuni geni nel tessuto tumorale mammario che prevengono l'insorgenza del tumore, evitando così la recidiva, e modulare i livelli sistemici di alcuni metaboliti a loro volta coinvolti nella crescita tumorale. Inoltre, i loro studi hanno precedentemente identificato, in modelli preclinici di malattia, un effetto sinergico della somministrazione di metformina e di bassi livelli di glucosio, indotti dal digiuno intermittente, nel bloccare la crescita del tumore, definendo anche i meccanismi molecolari coinvolti (e identificando la proteina PP2A come attore fondamentale). Più recentemente, i loro studi hanno mostrato anche un effetto antitumorale della metformina sulla crescita del glioblastoma, attraverso l'inibizione di una specifica proteina espressa sulla membrana delle cellule staminali di glioblastoma, e ne hanno rivelato i meccanismi coinvolti, che includono il pathway PP2A-GSK3beta-MCL1, lo stress ossidativo delle cellule tumorali e la proteina CLIC1.

## TELL ME MORE!

Prima dell'inizio dello studio, le pazienti reclutate hanno ricevuto una visita medica durante la quale sono stati raccolti dati tra cui dati antropometrici -come altezza, peso, BMI, etc-, biomarcatori circolanti nei campioni ematici, abitudini alimentari (attraverso specifici questionari). Inoltre, i campioni tissutali sono stati raccolti sia al momento della diagnosi che al momento dell'intervento chirurgico. Gli effetti del trattamento sono valutati tramite l'espressione del Ki67 (per misurare la proliferazione cellulare) tra i campioni diagnostici e chirurgici, tra pazienti trattati e di controllo, sia sul tessuto tumorale che sul tessuto adiacente. Sono valutati anche altri aspetti come gli effetti a livello molecolare, sull'asse PP2A-GSK3beta-Mcl1 prima e dopo il trattamento; i livelli di biomarcatori metabolici nel sangue; la morte cellulare (tramite analisi immunostochimica della caspasi-3); i livelli di glucosio. Sono inoltre valutati l'eventuale correlazione tra i dati del ki67 e uno specifico profilo mutazionale, le variazioni di altri biomarcatori circolanti, e lo stress psicologico associato al trattamento.

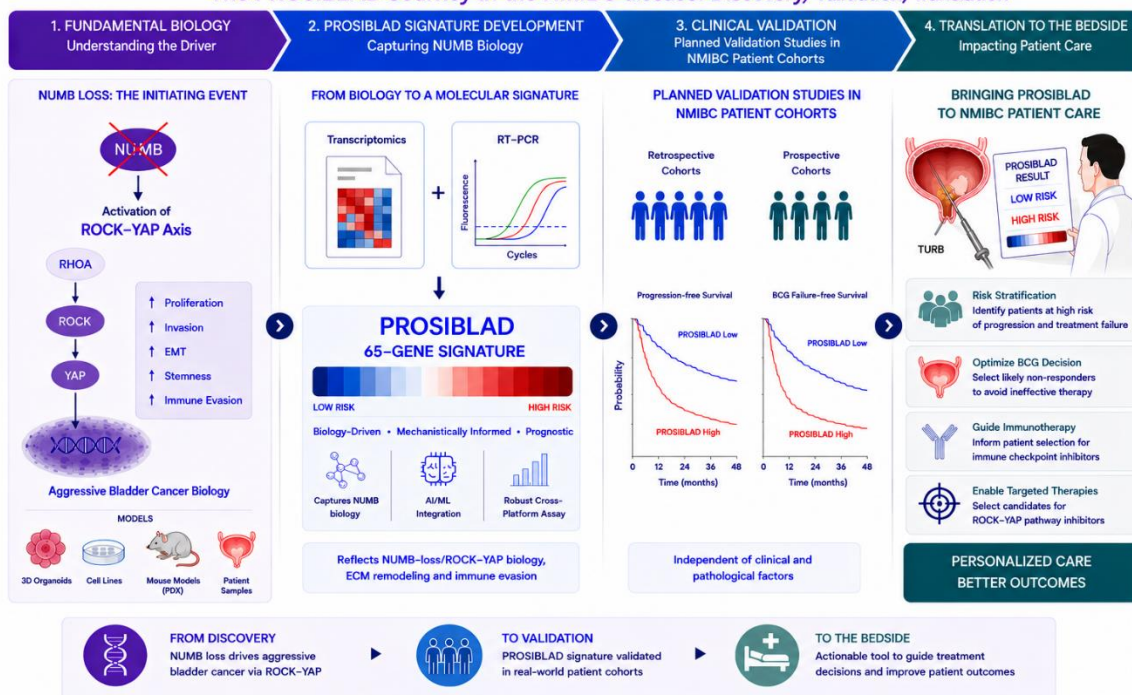
*Referenza: Time-Restricted Eating and Metformin in Invasive Breast Cancer or DCIS: A Randomized, Phase IIb, Presurgical Trial. Preliminary Safety Analysis. Irene Maria Briata, Stefano Spinaci, Parijatham S. Thomas, Davide Serrano, Tania Buttiron Webber, Nicoletta Gandolfo, Flavio Guasone, Andrea Rattaro, Emma Firpo, Mauro D'amico, Mariangela Rutigliani, Martino Oliva, Marina Gualco, Monica Peresi, Stefania Uncini, Aliana Guerrieri-Gonzaga, Harriet Johansson, Sara Gandini, Matteo Lazzeroni, Chiara Arianna Accornero, Oriana Pala, Saverio Minucci, Mattia Intra, Paolo Veronesi, Lana A. Vornik, Araceli Garcia-Gonzalez, Maria C. Lozano, Brandy M. Heckman-Stoddard, Eileen Dimond, Edward R. Sauter, Eduardo Vilar, Bernardo Bonanni, and Andrea DeCensi. Cancer Prevention Research 2026. doi: 10.1158/1940-6207.CAPR-25-0104.*

# Lo studio traslazionale IEO PROSIBLAD per una migliore gestione dei pazienti con tumore della vescica.

A dicembre 2025, l'IEO ha lanciato lo studio traslazionale PROSIBLAD (*Precision Oncology Signature for Invasive Bladder Cancer*), per validare –e successivamente sfruttare in ambito clinico– una firma molecolare per una migliore gestione dei pazienti con tumore della vescica, distinguendo i pazienti a basso rischio di progressione della malattia da quelli ad alto rischio. Il tumore della vescica non-muscolo-invasivo (NMIBC), che rappresenta circa il 75% di tutte le nuove diagnosi di tumore della vescica, pone delle sfide cliniche significative, per via della sua eterogeneità clinica e biologica, con un elevato rischio di recidiva e progressione in malattia muscolo-invasiva (MIBC) nel 30% dei casi. Eppure, nonostante l'incidenza significativa, l'approccio terapeutico è rimasto pressoché invariato negli ultimi 50 anni e prevede principalmente il trattamento con chemioterapia o la somministrazione di BCG –che induce una forte risposta immunitaria in grado di contrastare la crescita del tumore, in molti casi inducendone l'eradicazione completa– e chirurgia estesa e radicale, senza una precisa stratificazione molecolare. Questo approccio terapeutico influisce però pesantemente sulla qualità di vita e, in assenza di biomarcatori in grado di predire la risposta, potrebbero causare un trattamento eccessivo –con conseguente tossicità associata alla terapia– o, al contrario, insufficiente –rischiando così la progressione della malattia. Più recentemente, nuovi approcci terapeutici, attualmente in valutazione clinica, hanno mostrato la notevole efficacia degli anticorpi farmaco-coniugati (enfortumab vedotin e pembrolizumab) per il trattamento dei pazienti con tumore vescicale muscolo-invasivo, con un aumento significativo della sopravvivenza, sebbene non sia stato osservato alcun effetto nella malattia non-muscolo invasiva, in cui il trattamento standard è ancora rappresentato dalla somministrazione di BCG.

## From NUMB Biology to Precision Care in Bladder Cancer

The PROSIBLAD Journey in the NMIBC disease: Discovery, Validation, Translation



In questo scenario, la possibilità di distinguere in maniera precisa quei pazienti che richiedono trattamenti più aggressivi da quelli che invece potrebbero evitarli, può fare una enorme differenza per i pazienti. Il progetto PROSIBLAD nasce nel contesto della ricerca traslazionale di IEO, tra scienza fondamentale e ricerca

orientata alla clinica, integrando leadership scientifica, governance dei dati e amministrativa, trasferimento tecnologico e una stretta collaborazione tra clinici e ricercatori. Infatti, grazie ad una collaborazione europea con il *Bladder Cancer European Network* e una cooperazione multidisciplinare all'interno di IEO, che ha coinvolto ricercatori del dipartimento di oncologia sperimentale guidati da Salvatore Pece –Direttore dell'Unità di ricerca sui Tumori Ormonali e Patobiologia delle Cellule Staminali e Professore dell'Università di Milano–, clinici e chirurghi IEO, l'Unità di Anatomia Patologica, l'Unità di Analisi Computazionale, Dati e Piattaforme Digitali per la Ricerca, e il continuo supporto dell'Ufficio di Trasferimento Tecnologico, dell'Ufficio di Pianificazione e Analisi Finanziaria della Ricerca e della Direzione Scientifica, lo studio PROSIBLAD vuole rispondere a questa assenza di biomarcatori molecolari per l'accurata stratificazione dei pazienti con tumore della vescica, sfruttando le conoscenze della biologia alla base dell'evoluzione del tumore.

Lo studio PROSIBLAD nasce dai risultati –recentemente pubblicati dai ricercatori IEO (Tucci et al., *Nature Communications* 2024)– che descrivono il ruolo della proteina NUMB come regolatore chiave dell'omeostasi nella vescica –la cui assenza accelera il processo di tumorigenesi e determina una rapida progressione da un tumore superficiale e localizzato ad uno invasivo– e identificano una firma molecolare in grado di distinguere i pazienti il cui tumore ha una elevata probabilità di diventare aggressivo e muscolo-invasivo, richiedendo quindi approcci di trattamento più aggressivi, da quelli in cui il tumore ha maggiori probabilità di rimanere localizzato e che potrebbero quindi evitare un intervento chirurgico esteso.

Il progetto include una validazione clinica nell'ambito di studi clinici retrospettivi osservazionali e prospettici interventistici, per determinare il valore di PROSIBLAD come biomarcatore prognostico di malattia aggressiva e come biomarcatore predittivo di risposta a immunoterapia standard (BCG) o chemioterapia in pazienti con tumore vescicale. Verrà inoltre sviluppata una piattaforma traslazionale (integrando biopsie tumorali e modelli preclinici in vivo con profilazione trascrittomica e valutazione terapeutica) per confrontare la risposta alla terapia standard con la terapia con farmaci anti-ROCK/YAP.

L'obiettivo finale di questo progetto è quello di sfruttare in un contesto clinico questo nuovo strumento prognostico/predittivo che analisi di mercato e valutazione di brevettabilità hanno confermato essere l'*unico* strumento diagnostico molecolare ad oggi esistente per la stratificazione dei pazienti con tumore della vescica, rappresentando così un mezzo estremamente utile per questi pazienti. La firma genica alla base del progetto PROSIBLAD è stata protetta da una domanda di brevetto in condivisione da IEO e Università di Milano, sottolineando il suo potenziale traslazionale.

Con il progetto PROSIBLAD, Salvatore Pece e Daniela Tosoni sono stati selezionati tra i vincitori della quinta edizione del programma Seed4Innovation, e hanno ottenuto il finanziamento Proof-of-Concept dell'Università di Milano, per sostenere lo sviluppo tecnologico e industriale e la valorizzazione commerciale. Questo finanziamento, risultato della collaborazione tra ricerca accademica e clinico-traslazionale in istituto, contribuirà allo sviluppo e al trasferimento tecnologico di PROSIBLAD in uno test molecolare diagnostico, basato su PCR, per l'oncologia di precisione.

“Il lancio di PROSIBLAD segna un significativo passo avanti verso l'oncologia di precisione per il trattamento del tumore della vescica. –commentano Salvatore Pece e Daniela Tosoni– Migliorando la stratificazione del rischio, permettendo la selezione personalizzata del trattamento, riducendo sia il sovra-trattamento che il sotto-trattamento e agendo come nuovo potenziale target per la terapia molecolare, PROSIBLAD traduce una scoperta molecolare in benefici tangibili per i pazienti di tutto il mondo”.

Leggi [qui](#) il comunicato stampa.

## TELL ME MORE!

Promosso come progetto istituzionale, PROSIBLAD contribuisce a colmare le distanze tra scoperte scientifiche e applicazioni cliniche. Finalizzato alla validazione di PROSIBLAD come nuovo predittore genomico e per sostenere il progresso dell'oncologia di precisione nella cura del tumore vescicale, il progetto nasce dalle recenti scoperte di Salvatore Pece e Daniela Tosoni al Dipartimento di Oncologia Sperimentale di IEO, che hanno definito i meccanismi chiave alla base della tumorigenesi nella vescica.

“Il tumore della vescica è il nono tumore più diagnosticato nel mondo e incide in maniera significativa sia dal punto di vista clinico che economico a causa del suo elevato tasso di recidiva e progressione e la mancanza di biomarcatori predittivi affidabili – spiegano Salvatore Pece e Daniela Tosoni. Circa il 75% dei

casi di tumore della vescica sono classificati come non-muscolo invasivi (NMIBC), con un elevato tasso di recidiva e progressione in malattia muscolo-invasiva (MIBC) nel 30% dei casi circa. Gli attuali sistemi per la stadiazione si basano su parametri clinico-patologici; questi sono però insufficienti a predire in maniera accurata il rischio di progressione della malattia. La terapia si basa quindi soprattutto su un approccio “uno per tutti”, che solitamente prevede immunoterapia con BCG o chemioterapia, senza una precisa stratificazione molecolare. L’assenza di biomarcatori predittivi affidabili può determinare un sovra-trattamento –con chirurgia radicale anche quando non necessaria e tossicità associata al trattamento– o un trattamento insufficiente – con il rischio di progressione in malattia aggressiva. Quindi, l’identificazione di biomarcatori predittivi solidi, in grado di migliorare la stratificazione del rischio e guidare le scelte terapeutiche in maniera personalizzata –massimizzando l’efficacia del trattamento e conservando allo stesso tempo la qualità di vita– rappresenta una necessità clinica.

Il progetto PROSIBLAD nasce dalle nostre recenti scoperte scientifiche che identificano NUMB come fattore chiave nella carcinogenesi del tumore vescicale (Tucci et al., Nature Comm 2024). Lo studio ha mostrato che circa il 40% delle nuove diagnosi di tumore NMIBC sono caratterizzate dall’assenza della proteina NUMB e la perdita di NUMB causa l’attivazione anomala del pathway RHOA/ROCK/YAP –coinvolto nella proliferazione cellulare, l’invasività, e la progressione verso una malattia muscolo-invasiva–, identificando così un sottogruppo di pazienti NMIBC che potrebbero beneficiare di specifiche terapie mirate. Infatti, se applicata negli stadi iniziali del NMIBC, le terapie che interferiscono con questi pathway potrebbero prevenire la progressione in malattia muscolo-invasiva –e potenzialmente letale–, permettendo eventualmente di evitare trattamenti molto invasivi. Inoltre, il nostro lavoro ha portato all’identificazione di una firma genica associata con l’iperattivazione del pathway RHOA/ROCK/YAP e correlata con i sottotipi molecolari NMIBC dalla prognosi peggiore, predicendo il rischio di progressione della malattia nei pazienti NMIBC e la risposta alla terapia BCG nei tumori privi di NUMB, indipendentemente da altri fattori predittivi.

## **Criticità e strategie verso una ricerca biomedica che tenga in considerazione sesso e genere.**

Evidenze sperimentali indicano che sesso e genere possono influenzare i risultati della ricerca biomedica. Ciò ha portato ad una maggiore consapevolezza dell’importanza di queste differenze e quindi a considerare sempre di più sesso e genere come variabili biologiche negli studi scientifici. L’IEO ha sempre prestato particolare attenzione alla medicina di genere. Nel 2016, ha attivato, come parte del progetto europeo LIBRA, il suo primo piano di uguaglianza di genere al dipartimento di oncologia sperimentale (DEO), per promuovere l’uguaglianza di sesso e genere nella ricerca. Successivamente, il DEO ha lanciato il programma scientifico WoMen in Science, per portare avanti i risultati ottenuti all’interno del progetto LIBRA.

Nel contesto di una ricerca finanziata dalla Fondazione Cariplo, uno studio recente guidato da Susanna Chiocca-PI al Dipartimento di Oncologia Sperimentale di IEO- e Camilla Gaiaschi-Professoressa all’Università del Salento- ha analizzato gli ostacoli verso l’effettiva implementazione di un approccio alla ricerca che consideri sesso e genere. Nell’ambito dello studio, condotto in IEO, che ha visto anche la collaborazione di Paolo Maugeri, del gruppo di Susanna Chiocca, attraverso interviste e gruppi di lavoro, i ricercatori hanno identificato alcuni nodi critici, così da poter definire delle strategie per risolvere queste criticità. Interviste e gruppi di lavoro hanno coinvolto ricercatori, clinici, direttori di unità, professionisti delle risorse umane, manager di ricerca e finanziatori, uomini e donne. Condurre lo studio in un istituto come IEO (istituto di ricerca e cura a carattere scientifico, IRCCS)-IEO- ha permesso di studiare la questione in tutte le fasi della ricerca ed osservarne l’impatto diretto sulla cura dei pazienti.

Lo studio è stato portato avanti con un approccio su tre livelli: un livello micro, focalizzato sulle questioni collegate alla vita quotidiana dei ricercatori; un livello meso, riguardante le questioni associate all’organizzazione, le policy e i processi, a livello istituzionale; un livello macro, relativo ad altri stakeholder, come enti di finanziamento e regolatori.

Tutti e tre questi livelli si influenzano a vicenda e ostacolano o comunque rendono difficile l'adozione di un approccio alla ricerca biomedica che includa le variabili sesso e genere.

I loro risultati hanno evidenziato come gli ostacoli all'implementazione di una ricerca biomedica che consideri sesso e genere risiedano nei diversi livelli -micro, meso, macro-, sottolineando la necessità di mettere a punto strategie adeguate, necessariamente articolate, multi-livello, per gestire e risolvere queste questioni. Se da un lato la formazione dei ricercatori è fondamentale, le criticità sono legate anche ad altri aspetti, istituzionali e legislativi, richiedendo delle soluzioni che affrontino la questione anche a quei livelli.

### **Risultati – ostacoli all'implementazione di una ricerca che consideri i fattori sesso/genere.**

A livello micro, i risultati hanno evidenziato criticità legate all'assenza di evidenze solide, scientificamente dimostrate, sulle differenze legate al sesso, creando scetticismo all'interno della comunità scientifica; ciò ha ostacolato lo sviluppo di iniziative specifiche e la difficoltà ad

ottenere finanziamenti. Un altro aspetto da considerare è l'influenza che una stratificazione dei dati per sesso/genere può ridurre la disponibilità di dati e quindi il potere statistico. Inoltre, nella ricerca preclinica, un altro problema riguarda la difficoltà di reperire informazioni sul sesso delle cellule e degli animali utilizzati negli esperimenti.

Altre questioni sono collegate alla difficoltà di distinguere tra i diversi effetti di sesso (fattore biologico) e genere (fattore culturale). A livello meso, i ricercatori hanno identificato delle criticità associate al ruolo dell'ufficio della ricerca (il clinical trial office -CTO- in IEO), evidenziando come il loro scarso coinvolgimento nella stesura dei progetti di ricerca non consenta di aiutare i PI nell'includere la dimensione di sesso e genere nel design della ricerca clinica. Un altro ostacolo è collegato al

tempo limitato che i clinici hanno da dedicare alla ricerca. A livello macro, dalla ricerca è emerso che una criticità è rappresentata dalla limitata disponibilità di finanziamenti dedicati per la ricerca su sesso/genere, soprattutto dovuta all'assenza di evidenze scientifiche in grado di giustificare ampi programmi di ricerca. I loro risultati hanno anche evidenziato che gli studi commissionati, ovvero sponsorizzati da enti farmaceutici, spesso non includono una componente di sesso/genere, soprattutto per via dell'assenza di regole specifiche, da parte degli enti regolatori, che lo rendano obbligatorio. Infine, uno dei problemi è legato agli studi che includono meta-analisi; in questi casi infatti, se non richiesto dallo studio iniziale, il sesso alla nascita dei pazienti spesso per ragioni di privacy (secondo i principi del GDPR) non è disponibile.

### **Sesso e genere.**

Nel linguaggio di tutti i giorni, le parole "sesso" e "genere" sono spesso usate in maniera intercambiabile sebbene si riferiscano a due concetti differenti. Il termine "sesso" si riferisce alle caratteristiche biologiche (e.g. i cromosomi) di un individuo alla nascita, mentre il termine "genere" si riferisce a comportamenti, stili di vita, esperienze, ruoli sociali, atteggiamenti verso la malattia e la percezione del dolore di ogni individuo. Sesso e genere sono strettamente interconnessi e, data la difficoltà nel distinguere questi due aspetti e nel considerare il loro differente impatto sulla salute umana e sulla malattia, le persone spesso fanno riferimento a questi concetti come "questione di sesso e genere". Tuttavia, possono influenzare l'incidenza e la progressione della malattia in maniera differente. Nel melanoma, sia il sesso che il genere influenzano la prognosi, in modo diverso. Ad esempio, gli uomini più anziani tendono a fare controlli meno frequenti della cute e ciò influenza la prognosi, oppure le differenze nell'utilizzo dei lettini abbronzanti influenza l'incidenza in maniera diversa tra uomini e donne (questione collegata al genere); inoltre, studi precedenti hanno identificato delle differenze legate al sesso nella proliferazione, la senescenza, la risposta a segnali di stress, nelle cellule tumorali e nel microambiente tumorale. E' quindi, importante distinguere le variabili legate al sesso (biologiche) e al genere (culturali) e misurare il modo in cui possono influenzare in maniera diversa le persone di tutti i generi.

### **Bias legati a sesso e genere nella ricerca.**

I bias legati a sesso e genere nella ricerca possono essere distinti in due tipi: da un lato 1) la cosiddetta "cecità al genere", che assume che donne e uomini siano uguali anche quando non lo sono, ad esempio assumendo che il rischio di incidenza, di progressione e la sintomatologia di una malattia siano gli stessi in donne e uomini anche se non lo sono; dall'altro lato, 2) gli "stereotipi di genere", presumono l'esistenza di differenze tra uomini e donne anche quando non ci sono, ad esempio assumendo che il rischio di incidenza, progressione o la sintomatologia di una malattia siano differenti anche quando non lo sono. Entrambi i bias possono influenzare l'accuratezza degli studi di ricerca, nel design, nell'analisi e nell'interpretazione dei dati.

### Strategie proposte – come risolvere?

Lo studio ha aiutato a definire gli ostacoli all'implementazione di una ricerca che consideri sesso e genere, per poter mettere a punto delle strategie finalizzate alla gestione e alla risoluzione di queste criticità.

Gli autori concludono che, a livello micro, le azioni dovrebbero essere finalizzate principalmente ad aumentare la consapevolezza dei ricercatori e fornire loro una guida, offrendo sessioni di formazione e linee guida pratiche su come includere la dimensione sesso/genere nella loro ricerca.

A livello meso, gli autori sottolineano che lo scarso coinvolgimento degli uffici di ricerca nel design clinico (per includere sesso/genere) potrebbe essere facilmente risolto con un cambiamento organizzativo a livello istituzionale. Le questioni relative al tempo limitato che i clinici hanno da poter dedicare alla ricerca, derivante da questioni contrattuali, richiede più probabilmente, da un lato, cambiamenti a livello legislativo, dall'altro, una distinzione a livello contrattuale tra le attività cliniche e di ricerca, coinvolgendo così l'ufficio risorse umane. Gli autori propongono anche lo sviluppo di un network nazionale per promuovere la ricerca basata su sesso/genere ed eventi di raccolta fondi.

A livello macro, gli autori suggeriscono che la scarsa disponibilità di finanziamenti dedicati per la ricerca su sesso/genere potrebbe essere risolta iniziando dei progetti di finanziamento piccoli, di breve durata, ben focalizzati, meno rischiosi per l'erogatore dei fondi, che aiutino a raccogliere evidenze preliminari solide. Propongono inoltre un coinvolgimento degli enti regolatori (cioè, includendo sesso e genere come variabili obbligatorie nel design della ricerca clinica) per ottenere una maggiore inclusione della dimensione sesso/genere negli studi commissionati.



*Susanna Chiocca*

### Il programma IEO WoMen in Science.

Gli obiettivi principali del programma IEO WoMen in Science è quello di promuovere i. pari opportunità per uomini e donne in IEO, ii. le carriere scientifiche di uomini e donne, iii. lo sviluppo di strumenti per aumentare la consapevolezza riguardo all'importanza di tener conto del sesso (cellule, tessuti, animali) nella ricerca biomedica. Il team WoMen in Science, diretto da Susanna Chiocca, include Annalisa Ariesi, Tiziana Bonaldi, Greta Caprara, Sara Gandini, Luisa Lanfrancone, Paolo Maria Maugeri, Martin Hartmann Schaefer. Tra i traguardi principali del gruppo possono essere menzionati la creazione di un Gender Equality Plan (GEP), nel contesto del progetto LIBRA; la creazione di un programma di mentoring per i post doc IEO; il monitoraggio del processo di reclutamento in IEO, per evitare bias di genere; il monitoraggio delle attività di ricerca per l'inclusione della dimensione di sesso/genere in tutti gli aspetti dei progetti di ricerca.

### *Gli autori – Susanna Chiocca.*

Dal 2005, Susanna Chiocca è direttrice dell'unità di ricerca "Viruses and cancer" al dipartimento di oncologia sperimentale di IEO e membro della faculty della scuola di dottorato SEMM (European school of molecular medicine). Con una laurea all'università del Texas e un dottorato in biologia molecolare/virologia al MD Anderson Cancer Center

(Houston, Texas), l'obiettivo della sua ricerca è quello di determinare i meccanismi attraverso cui i virus oncogeni ed altri segnali di stress derivanti dal microambiente tumorale contribuiscono alla neoplasia, attraverso le modificazioni post-traduzionali (PTM) delle proteine, con particolare focus sulle alterazioni, indotte da virus e stress, nell'epigenoma tumorale che inducono il programma neoplastico, e in che modo le proteine oncovirali regolano i pathway cellulari delle PTM e forniscono nuovi segnali critici nella carcinogenesi virus-indotta, utilizzando il tumore testa-collo come sistema modello. E' inoltre coinvolta nel promuovere l'inclusione della componente sesso e genere nella ricerca biomedica, avendo contribuito attivamente al progetto LIBRA e allo sviluppo in IEO del programma WoMen in Science.

*Referenza. It Is Not Only a Matter of Biases: Identifying Organizational and Institutional Obstacles to Bring Sex- and Gender-Oriented Approaches into Biomedical Research. Camilla Gaiaschi, Camilla Veneri, Susanna Chiocca. TECNOSCIENZA. Italian Journal of Science & Technology Studies 2026.*

### 10 anni di certificazione EUSOMA.

Nel maggio 1994, con la nascita dell'Istituto, apre la Divisione di Senologia Chirurgica, che diventa rapidamente la forza trainante e distintiva dello IEO. Da allora, la cura del tumore della mammella è cresciuta insieme allo IEO, integrando alla Senologia Chirurgica le Divisioni di Chirurgia Plastica e di Oncologia Medica Senologica, poi diventata Senologia Medica, evolvendosi quindi in un modello assistenziale sempre più strutturato, integrato e orientato alla persona: la Breast Unit. Dal 2016, la Breast Unit IEO è certificata EUSOMA (European Society of Breast Cancer Specialists), uno dei più importanti riconoscimenti europei per i centri che si occupano di diagnosi e cura del tumore mammario. Quest'anno celebriamo dieci anni di certificazione.

La Breast Unit IEO opera come struttura multidisciplinare. Le attività coprono l'intero percorso di cura: dallo screening inserito nel piano regionale, alla diagnosi con imaging senologico avanzato, fino ai trattamenti chirurgici, con tecniche innovative, incluse la chirurgia radioguidata, radar-guidata e le metodiche mini-invasive. A questo si affiancano le terapie oncologiche integrate, lo sviluppo di farmaci innovativi, i trattamenti radioterapici avanzati come la Protonterapia, le attività di prevenzione e genetica oncologica, le cure palliative e la terapia del dolore, il supporto psicologico e assistenziale, il follow-up strutturato delle pazienti nei primi cinque anni.

Fondamentale è anche l'impegno nella ricerca clinica, sostenuto dal Clinical Trial Office, che consente allo IEO di confrontarsi con i principali centri internazionali e di offrire alle pazienti opportunità terapeutiche sempre più avanzate. La certificazione EUSOMA non è un punto di arrivo, ma un impegno quotidiano che coinvolge professionisti di molte discipline, servizi clinici e strutture di supporto.

### Evento EUPATI "La ricerca siamo noi" in IEO.

Il 19 maggio IEO ha ospitato il primo evento dell'iniziativa EUPATI "La ricerca siamo noi", finalizzata a promuovere la cultura della ricerca, sottolineando la sua importanza e il suo valore per il progresso in ambito terapeutico, ed enfatizzando l'importanza dell'engagement di pazienti e cittadini e dell'empowerment del paziente nella ricerca, in particolare nella ricerca clinica. Due panel costituiti da professionisti della ricerca clinica hanno partecipato all'evento e hanno espresso le loro opinioni sui diversi temi discussi.

Gli argomenti includevano la recente inclusione dei pazienti, nello specifico, pazienti informati, nei comitati etici. I comitati etici garantiscono la protezione dei diritti dei pazienti nei protocolli di ricerca clinica; l'inclusione dei pazienti nei comitati etici assicura che le necessità dei pazienti siano prese in considerazione e affrontate. I pazienti informati sono stati formati raggiungendo una solida expertise in ambito oncologico e di ricerca clinica; possono quindi offrire il loro aiuto fornendo feedback sulla fattibilità e sugli aspetti logistici collegati all'arruolamento in un protocollo clinico, che richiede appuntamenti per la somministrazione dei trattamenti e visite di followup.

Sono stati affrontati anche aspetti come la paura dei pazienti legata all'arruolamento in un nuovo clinical trial, sottolineando come i pazienti informati possano giocare un ruolo importante, offrendo, da un lato, la loro esperienza emotiva, aiutando altri pazienti ad affrontare le loro stesse paure e comprendere che essere parte di un clinical trial, sebbene porti sicuramente con sé incertezze sui risultati, offre nuove opzioni terapeutiche, che non sarebbero disponibili altrimenti, nel contesto di studi strutturati e ben organizzati, insieme alla loro esperienza con i trattamenti antitumorali; dall'altro, possono anche fornire, attraverso la cosiddetta *peer communication*, le loro conoscenze acquisite, che possono essere utili per affiancare i medici nella spiegazione dei termini medici, rendendo così più facili le discussioni paziente-dottore, o nella comprensione delle basi scientifiche che hanno portato al design di uno specifico protocollo di ricerca per valutare l'efficacia di un certo farmaco.

Mentre il futuro coinvolgimento dei pazienti nelle fasi iniziali della ricerca clinica, come nel design di protocolli clinici, è in considerazione, è stata proposta una loro inclusione nel design di progetti di ricerca accademica, contribuendo ulteriormente ad avvicinarli alla ricerca e potenzialmente aumentando l'adesione ai protocolli di studio clinici.

Infine, è stato evidenziato come i pazienti informati possano prendere decisioni consapevoli sul loro stesso percorso di cura, discutendo con i loro medici tutte le opzioni terapeutiche disponibili, fino a trovare quella più adatta a loro, inclusi eventualmente i clinical trial se disponibili e se rappresentano per loro la scelta migliore. Sebbene il linguaggio rappresenti ancora una barriera tra i pazienti e l'arruolamento nei trial clinici, ciò può essere superato con l'istruzione dei cittadini, attraverso forme diverse di formazione, sottolineando il potere del patient empowerment (ovvero la formazione)-fornendo loro le capacità per prendere decisioni informate- e engagement (coinvolgimento); ciò può portare dei benefici sia per le parti coinvolte che per la società nel suo insieme.

### La Prevenzione del Tumore Mammario nelle Donne ad Alto Rischio – lo studio TOLERANT.

Il 12 giugno, a partire dalle 8.30, si terrà al Quark Hotel l'evento "La Prevenzione del Tumore Mammario nelle Donne ad Alto Rischio" in cui verranno presentati i risultati dello studio TOLERANT. Sarà un'importante occasione di confronto e dialogo con i professionisti coinvolti nel progetto. Partecipazione gratuita previa registrazione [qui](#). Per saperne di più clicca [qui](#).

## 25 years of cancer hallmarks – because figuring out the problem is the first step to solve it.

Cancer is a multifactorial disease. Alterations in several key cell processes transform a healthy cell into a cancer cell, threatening human health. Understanding such processes is fundamental to effectively target therapeutically cancer cells. Twenty-five years ago, the definition of the cancer hallmarks (by Weinberg and Hanahan) has allowed to organize the knowledge on cancer-driving mechanisms into six main mechanisms: The hallmarks of cancer. Over the years, with the accumulating knowledge, these six hallmarks have been integrated with emerging concepts and the discovery of new key features of cancer cells, which take into consideration also cell-extrinsic factors and the role of the tumor microenvironment component in fostering tumor progression. All these cancer cell mechanisms/cancer hallmarks influence each other.

Beautifully exemplifying the mechanism-rooted targeted therapy approach that has guided research and care in the past decades, the cancer hallmarks have become the target of new therapies; some of these treatments have been already approved for clinical use, others are still in an experimental stage.

### Weinberg's and Hanahan's view of the cancer hallmarks:

#### The acquired capabilities of cancer cells.

**1. Sustained proliferation.** Overproliferation is a typical feature of cancer. At some point, healthy cells start to outproliferate. Alterations in key genes – oncogenes– sustain tumorigenic proliferation. KRAS, MYC, EGFR are only few examples of the 193 genes currently defined as proliferation-driving oncogenes.

**2. Inactivation of tumor suppression.** Inactivating the actors involved in the safeguard mechanisms of cells, limiting proliferation when something is wrong –the tumor suppressors– is an equally important feature of cancer cells. When tumor suppressor genes, whose role is to arrest cell proliferation in case of abnormalities (such as DNA damage), are inactive, tumor cells acquire further proliferative capabilities. Among the 143 genes currently listed as tumor suppressors, TP53 is the most frequently mutated tumor suppressors in human cancers (in turn affecting other genes involved in proliferation, senescence, apoptosis, etc). Other tumor suppressive mechanisms –which are inactive in cancer cells– involve contact inhibition and competition for nutrients.

**3. Inactivation of mechanisms inducing programmed cell death.** The processes driving cell death in case of damage represent a critical protective mechanism to eliminate damaged cells. Tumor cells take control of such mechanisms, blocking cell death when needed (that is, in case of irreversible damage).

### An alternative view:

#### Gene mutations - when changes can be detrimental.



Pol was deep in her thoughts. Their plan was brave, but it could work. They had to be very cautious...

Discontent was everywhere; finding allies was not difficult. Everybody was so fed up of simply being part of one of the billion cells... They wanted something more. They wanted to be powerful, strong, acquire an advantage, being part of a winning team, being greater than all the others... They had a secret meeting and made a plan: Simple and effective. Pol played a key role. She was so proud of that! The day after, at work, she had to behave as usual... Bind the DNA and start duplicating the nucleotide sequence, faithfully, as she had done for her whole life. An adenine, a thymine, a guanine, then another thymine, a cytosine and so on but, first, once arrived on chromosome 12, where the KRAS gene was located, at the level of the triplet coding for a glycine, she should have inserted a different nucleotide, so that glycine became aspartic acid. Then, she should have gone to chromosome 17, at the level of p53 gene and there, where the triplet coded for arginine 248, she should have added a different nucleotide. That was all. In case altering KRAS and p53 gene sequences was not possible, she could have tried elsewhere, insert other changes, but these two alterations were the "plan A". Those would have certainly induced significant changes! Their chances of success would have increased dramatically! The surveillance system would have ignored them. They had a secret agreement. They would have ignored those changes; p53 would have lost its tumor suppressor ability; the effects would have been multiple, interfering with several

**4. Gaining unlimited replication ability.** To allow for unlimited proliferation, cancer cells inactivate the checkpoints controlling telomere length, mainly by de-repressing key enzymes involved in telomere control.

**5. Altering cell metabolism.** To ensure the energy needed to support sustained cell proliferation, cancer cells optimize energy production, by employing both oxidative phosphorylation and glycolysis, and by using other sources (beyond glucose) such as lactate or some aminoacids (glutamine).

**6. Phenotypic plasticity.** Cancer cells face different, continuously changing, microenvironmental conditions. In order to survive, they evolved the ability to adapt. Cancer cell adaptation as a response to external conditions, involving –and actually enabled by– genetic and non-genetic (epigenetic) mechanisms, results in the modulation of cancer cell gene expression profile and the capability to switch among different cell states: Cancer cells acquire plasticity. This involves mechanisms such as the epithelial-to-mesenchymal transition (with a number of intermediate cell states) and the acquisition of stemness features. Along with the selection of cancer cells carrying specific mutations conferring survival advantage, cancer cell plasticity is one of the reasons of intratumor heterogeneity.

**7. Immune evasion.** One main acquired feature of cancer cells is the ability to “hide” from the immune system and avoid immune system-mediated clearance.

**8. Inducing vasculature and co-opting existing vessels.** To sustain the increasing need for oxygen and nutrients of the growing tumors, cancer cells gain the ability to modulate the tumor microenvironment (TME), inducing the growth of new blood vessels or co-opting existing tissue vessels (by means of the activation of mechanisms typical of development and wound healing), though the secretion of vessels-inducing factors.

**9. Invasion and metastases.** Through a multistep process, cancer cells can leave the primary tumor, invade the surrounding tissue, intravasate, and travel (mainly through the bloodstream) until colonizing distant organs. Facing different microenvironmental conditions, this metastatic cascade requires cancer cell acquisition of new traits, involving both genetic and non-genetic mechanisms, including phenotypic plasticity, metabolic reprogramming, the ability of evading immune surveillance.

**Enabling features, facilitating the acquisition of**

processes: Apoptosis, cell cycle, cell metabolism... KRAS would have supported cell proliferation and their cell would have finally become the most powerful... It would have proliferated, originating a new dynasty of cells, stronger, more resistant, more powerful. Pol's deeds were crucial. Everybody would have talked about Pol: The protein that enabled the transformation.

A perfect plan. What could ever go wrong?

**Chemotherapy.** As planned, their cell gained a selective advantage as compared to the surrounding cells. It rapidly became stronger. The new dynasty of cells expanded quickly. However, rumors said that new threats were coming... Some people called it chemotherapy, others called it Taxol. It acted exactly on those cells that decided to grow, expand. It bound beta-tubulin protein, stabilized microtubules, preventing the formation of the mitotic spindle, ultimately arresting cell cycle. Chemotherapy-treated cells were dying... and there was nothing that Pol could do.

**Resuming proliferation-specific processes shut off by cell differentiation.**



TERT was deep in her thoughts. For her whole life she had been a tireless worker, never complaining, knowing that then she would have enjoyed her well-deserved retirement. During cell proliferation, until cell differentiation, every time DNA replicated, she had added short sequences at the level of telomeres, to ensure that they did not become too short, thus protecting genetic information. When finally the cell started differentiation, she got retired. Few days ago, however, someone came to wake her up. They had a plan and TERT was part of it. Actually, she played a quite important role. She had to admit it, she was flattered. While TERT enjoyed her retirement, the cell had taken some important decisions, changed strategy, made a plan for the future. Several changes had followed and TERT was studying to understand exactly what happened in that timeframe. Firstly, KRAS became hyperactive. Almost at the same time, p53, instead, stopped working. A hyperactivity period had followed, and to sustain the new activities, factories worked full time, doing glycolysis and oxidative phosphorylation 24 hours a day. In some cases the cell also started using alternative energy sources, exploiting lactate. Now, they needed her. After all, it was an easy task; she simply had to resume the work she had done for her whole life. TERT was eager to be part of the new chapter of the history of this cell. So, the day after, as requested, during DNA duplication she would have bound at the end of chromosomes, to add short DNA segments. For the cell. Towards immortality.

**The abduction – Sequestering protein factors to prevent tumor cell death.**



As usual, the mitochondrion was very active. Actually, the work had become even more intense in the recent days. BCL-2 was hiding. He was waiting for his friends. The plan was dangerous, so they had to be all together. They had

**cancer hallmarks.**

**10. Loss of genome integrity.** Chromosomal instability, with related altered gene expression, has been associated to tumor proliferation, plasticity, metabolism, and immune evasion, even in absence of oncogenic mutations.

**11. Epigenetic reprogramming.** Epigenetic alterations can modify key cell processes, leading to tumorigenesis, by changing accessibility of given regions and 3D structure of chromosomes, availability/activity of transcription factors, post-transcriptional and post-translational modifications, either as a consequence of genetic mutations in epigenetic modulators or by means of purely epigenetic mechanisms induced by external signals, ultimately enabling/sustaining the acquisition of the cancer hallmarks.

**12. Tumor-promoting inflammation.** While on one side the immune system can eliminate tumor cells, thus inducing cancer cells to deploying mechanisms aimed at evading immune clearance, other immune cells can instead support tumor progression, through the release of specific factors. Therefore, sustained chronic inflammation represents a factor promoting tumor progression.

**13. Tumor innervation.** Intra- and peri- tumor innervation can modulate cancer hallmarks and support tumor growth, by stimulating proliferation, allowing to evade cell death and immune clearance, and enhancing invasion and metastatic dissemination, through the release of molecules or the actual formation of pseudo-synaptic contacts between cancer cells and neurons.

**14. Microbiomes.** Symbiotic microbial species have been recognized as influencing cancer hallmarks mechanisms, affecting tumor progression and response to therapy. Alterations of microbiome composition have been shown to stimulate proliferation and induce immune evasion (as well as, for particular species of bacteria, genome instability, mutations, and tumor-promoting inflammation), in turn modulating response to therapy.


### **Cancer-promoting factors in the tumor microenvironment.**

The alterations typical of cancer cells can characterize also other cellular components of the tumor microenvironment, resulting in a tumor-promoting microenvironment. The cellular component of the TME includes endothelial cells and pericytes (stimulating cancer cell proliferation and promoting tumor cell ability to avoid programmed cell death and immune clearance,

made an awareness campaign to increase the recruitment and the chances of success. The preparation phase had been long, they studied the plan in every little detail. They carefully observed the mechanism to be sure to act properly. Now it was the time to act. The signals were numerous, and the spying system warned them: Soon the cell would have initiated the apoptotic process. The recent stressors were overwhelming and they decided to switch off forever the activity of this cell. BCL-2 and his friends had a different plan. He saw BCL-XL arriving and silently waved him. BCL-XL was with his friends. BCL-2 smiled. Together with his own friends, they were enough. They were all hiding, waiting for the right moment. They were about to make history. BAX and BAK were approaching... Unaware of everything, they were going to deliver The Message: "initiate apoptosis". BCL-2 signaled to BCL-XL. BCL-XL responded; one moment later, the two groups were on BAX and BAK. They had to kidnap them and take them away. They were going to keep them under constant, strict surveillance. They had to prevent them from delivering that message. That way, the cell could survive, proliferate, sustain tumor growth.

**Venetoclax.** BAK and BAX were in a corner, close to each other, scared. They could not say for how long they had been sitting there. They were kidnapped at work, in a critical moment. The cell needed them... That message had to be delivered. BCL-2 was sitting on the other side of the room, keeping his eyes on them. He controlled them constantly, to prevent their escape. Then, Venetoclax arrived. BCL-2 jumped away from the door. He knew that soldiers were around, but he was sure to be well hidden, to be safe... With a rapid movement, Venetoclax was on him. He immobilized BCL-2, then yelled at BAX and BAK "Run! Go away! Deliver the message!". BAK and BAX ran away from BCL-2. It was time to deliver the message, to do their job. It was time for the cell to initiate apoptosis.

### **Escaping immune system police.**

  
Gerèle –the tumor cell– had become very skillful. She succeeded in evading police surveillance so efficiently... Evading surveillance was now one of her main traits. She decided to embrace "the dark side" long ago. Becoming a tumor cell appeared so cool. They could do anything they wanted, they were stronger than the other cells, more resistant and more independent. The only negative aspect was that police searched them continuously. They got so many of them! And they did not end up well... The police killed them right in front of her... Even her, once, was very close to get caught. At the beginning she had just been lucky, luckier than the others to avoid policemen that were more and more abundant in the area, called by the frequent incidents with the other tumor cells. But then, with time, Gerèle started to understand how to escape the police.

**Immune evasion.** Gerèle camouflaged herself. The police distinguished tumor cells from healthy cells on the basis of some distinctive traits. If you showed one of those signs, if you expressed one of those molecules, they

influencing metabolism, facilitating tissue invasion and metastasis, and being responsible for a leaky vasculature more easily intravasated by metastasizing cancer cells); cancer-associated fibroblasts (CAFs, able to foster, through the release of molecules and vesicles, cancer cell proliferation, inhibition of cell death, tumor cell metabolism reprogramming, modify tumor vasculature and extracellular matrix, escape immune system-mediated clearance, foster invasion and metastatic dissemination, recruit pro-angiogenic, immunosuppressive myeloid cells); tumor-associated tumor-promoting macrophages and neutrophils and reprogrammed resident immune cells (stimulating cancer cell proliferation and angiogenesis, suppressing immune surveillance, facilitating tissue invasion and metastases); cell cycle-arrested senescent cells (modulating tumor onset and progression) as well as other cancer-induced hallmark-facilitating immune cells.

#### **Systemic factors influencing the cancer hallmarks.**

Aging –through immune system decline, chronic inflammation, loss of genomic integrity, epigenetic reprogramming and microbiome alterations– and obesity are systemic factors increasing the risk of cancer onset, along with exposure to environmental, potentially carcinogenic factors, such as smoking, air and water pollution, microplastics, which, by interfering with cell physiology, ultimately induce the cancer hallmarks, resulting in tumor development.

#### **A therapy-focused view of the cancer hallmarks.**

Leveraging the acquired knowledge about tumor biology and the cancer hallmarks, treatments specifically targeting these tumor-altered mechanisms have been developed over the years, with various degrees of the involvement of the immune system and selectivity for cancer cells (and off-tumor-related toxicity). From the earliest discovered class of **cytotoxic agents** –such as alkylating agents, antimetabolites, topoisomerase inhibitors and mitotic inhibitors– targeting the sustained proliferation of cancer cells and the inactivation of tumor suppression mechanisms, their ability to resist cell death, the acquired capability of replicative immortality; to the development of **targeted drugs**, such as agents suppressing oncogenic signals and inhibiting angiogenesis, interfering with cancer cell proliferation, their ability to resist cell death and induce the generation of new blood vessels, their plasticity, the altered cell

recognized you even among all the other healthy cells and *zac!* you were done. Gerèle learned to identify those signs, and hide them... That way, the police could not recognize her. She could walk amid other healthy cells, next to the police, and not being recognized.

**Immune cell exhaustion.** Her ability was crucial, however, not sufficient *per se*... With time, the police started to lose interest in hunting them. First, several agents were clearly tired, exhausted from the need to constantly scan the area, and the tumor cells took advantage of that.

**Cancer-derived immune suppression factors.** When, for some reasons, some hard-working, vigilant policemen caught them, they knew how to defend. They got a bunch of TGFbeta and other immune-suppressive factors and when policemen walked by them, Gerèle threw such factors on them.

**Chronic inflammation.** Moreover, with time some policemen became corrupted: Even those that at the beginning tried to kill them, now provided Gerèle and her friends with many factors helping them to become stronger and proliferate more and more quickly. Yes, now nothing could stop them.

**Immunotherapy.** The situation changed rapidly... Suddenly, the police became sly and stronger. They could hunt them day and night, never stopping. Rumors said that police had started taking drugs –anti-PD1 were named– making them stronger. Then, the army arrived. They were called CAR-T cells. They were cleverer and able to recognize Gerèle and her friends more efficiently than the local police, and when they recognized them, they attacked aggressively. Gerèle walked around more cautious than ever. She felt that, sooner or later, the police would have caught her too

#### **“Governing” a growing tumor.**



**Tumor onset.** Tumorville was founded recently. When the first cells started colonizing that area of the lung, nobody paid attention. They looked like few cells camping, willing to do something different. However, since nobody disturbed them, their settlement had started proliferating...

**Tumor progression.** Four cells had become 8, then 16 and so on. Shortly, that settlement had turned into a village, and then a town. Troubles started because they were to many...

**Nutrient scarcity.** Collecting what the environment offered was no longer sufficient, nutrients were scarce... and Tumorville was too far away from the supply routes. Therefore, Mr Newves took an important decision.

**Angiogenesis.** Tumorville needed routes. Safe routes that allowed to quickly reach the main blood vessels, to obtain all the needed nutrients. So the works started. The more Tumorville expanded, the more routes were built. They never stopped. Ok, the new vessels were not all structurally perfect, but the conditions in which they were built were not the best... Angiostatin and TSP-1 gangs continuously tried to sabotage their work. Only Tumorville determination to continue growing, along with the help of

metabolism, the replicative immortality; to the **antibody-drug conjugates and bispecific T cell engagers**, allowing for the targeted delivery of chemotherapeutics or favoring the interaction between tumor and immune cells, interfering with the cancer cell proliferation and the mechanisms of tumor suppression, their ability to resist cell death or escape immune surveillance, their acquired capability of replicative immortality; the **immune checkpoint inhibitors**, preventing the ligand-receptor interaction between immune and cancer cells, interfering with cancer cell plasticity and immune surveillance, until the most recent **cell therapies**, targeting tumor antigen-expressing cells using engineered immune cells, thus interfering with tumor cell proliferation and their immune evasion ability.

Targeting, or co-targeting, of these processes sustaining cancer onset and progression through mechanism-guided drugs led to the approval of therapies targeting proliferation, apoptosis, angiogenesis, immune evasion. Indeed, the simultaneous targeting of different hallmark mechanisms, hitting different cancer cell vulnerabilities, may challenge cancer cells ability to find multiple “ways out” to survive.

Some examples of cancer hallmark therapeutic co-targeting include bispecific anti-VEGFA/PD1 antibodies, showing efficacy in clinical trials (although not clinically approved yet), or anti-VEGFA antibodies (bevacizumab) in combination with an inhibitor –olaparib– of the PARP DNA repair enzyme, targeting cancer cell vulnerabilities such as the genome instability (the enabling feature due to impaired DNA damage repair system) along with impaired angiogenesis, which has led to clinical approval of this therapeutic approach for selected populations of ovarian cancer patients.

*References: The Hallmarks of Cancer: 25 years guiding discovery and therapy. Cell editorial. doi: 10.1016/j.cell.2026.03.033; Hallmarks of cancer—Then and now, and beyond. Douglas Hanahan. Cell 2026. doi: 10.1016/j.cell.2025.12.049; SnapShot - The hallmarks of cancer treatment. Pietro Paolo Vitiello, Vito Amodio, Alberto Bardelli. Cell 2026. doi: 10.1016/j.cell.2026.03.017.*

**Adagrisib.** It happened in the afternoon. There had been no signs. MICel was enjoying her new home, making plans for the future. Together with her new roommates, they were planning a new trip, a long vacation discovering new places, where they could have built a new house. Instead, the storm destroyed everything. “There is adagrisib everywhere!” yelled her roommates. MICel did not understand “What is adagrisib?” asked with a low voice. She started feeling so tired... The cell next to her looked at her “it’s a drug” explained “quite effective. It will kill us. We have no way out”.

the immune system and especially the lack of control, could defeat their inhibitory and destructive actions.

The new vessel formation guaranteed to Tumorville a safe and unstoppable growth. Or not?

**Inhibitors of VEGF signaling.** Just when Tumorville was at the top, when the new vessel building proceeded rapid and Mr Newves started to plan the foundation of new fractions of Tumorville, barbarians attacked. Equipped with powerful destructive tools –the known VEGF signaling inhibitors–, they attacked both existing vessels and the teams building new ones. Mr Newves looked around, desperate. Without supply, Tumorville would have died soon

#### Tales of a metastasizing cell.



**In the primary tumor.** MICel –the metastasizing cell– was really fed up. Moving in with other tumor cells appeared a good idea, but the other cells were really too noisy. The area was overcrowded, and several times she remained on an empty stomach because they ate everything! She decided to leave. The evening before she complained with microenvironment cells... They were so understanding, and encouraged her! “You should make a plan!” they said “you go at the shop nearby, buy everything you need for an EMT, and go!”

**EMT – Epithelial-to-mesenchymal transition.** So she did. She bought a bit of TWIST1 and 2, of SLUG and SNAIL, a bit of ZEB1 and 2; she also got some N-cadherin and vimentin. Unfortunately, she had to leave behind some things she liked; for instance, she could not take with her E-cadherin and beta-catenin, but she was ready.

**Local invasion.** She walked for long in the neighborhood, in the crowd, before reaching the highway.

**Intravasation.** The GPS indicated the blood vessels as the main route, the fastest, the most effective.

**Tumor cell clusters in the bloodstream.** Certainly the journey was not easy... She traveled with other cells like her. Some of them died along the way, but she made it. She had the right character. She adapted and succeeded; she survived.

**Colonization.** She reached the new organ the night before. Like every new beginning, it was not easy there. It was so different from her home... but thanks to her adaptation attitude, she settled. At the beginning she felt lonely, a little bit homesick, but soon other tumor cells joined her.

**Overt metastasis.** Now, together, they felt stronger. They were organizing the area, to make it perfect for them. The new cells of the micro-environment at the beginning were not very welcoming, but then they changed. Yes, MICel felt “at home” again. She was different from when she left, sometimes she wondered whether she would have changed back as she used to be... but she was home again... in a new home. The new metastasis was ready.

### Enabling features – Not all the shit is the same...

The day did not start very well. After the coffee, as usual, that awful stink... After all, the night before did not start great either...

**A wrong diet.** Fat food, alcohol and sugars, in huge amounts, and the work accumulated. Berium the bacterium was really fed up. His friends and him worked all night long to help metabolizing all that junk food. They had been doing strikes and manifestations for months; they tried everything to show their malcontent, inducing all the possible more annoying symptoms, but their complaints were largely ignored.

**An altered gut microbiota.** Moreover, Berium and his friends' job was hampered by some families of bacteria sharing the gut with them, which made everything even worse. He met them once, Escherichia coli and his gang, they were so unpolite! Initially they were not abundant, but somehow lately they proliferated and produced molecules that hindered their work. They also had such a bad attitude! Recently, they started interacting with a family of foreign cells that were camping in a small zone of the gut. Berium and his friends called them “cancer cells”, because they were different from all the other cells they were used to productively interact with. Yet, those bacteria had often contacts with cancer cells, providing them with many compounds. Berium once saw them with his own eyes... Thanks to these compounds, tumor cells grew rapidly. Sometimes Berium thought that they would have ended up annoying endogenous cells! Berium and his friends kept doing their job; however, perhaps for the stress or for the overwhelming work, many of them died and now there were so few of them. Coli gang bacteria were almost more numerous than Berium's family! However, other than manifestations and strikes, what else they could do? Berium worked and worked, but he was afraid that the situation could only get worse...

**Fecal microbiota transplantation.** Everything was finally back to normal. Just when Berium had lost hope, surrendering to Coli and friends' bad behavior, someone came to help them. Through a well-organized, military peace operation of fecal microbiota transplantation, several bacterial communities arrived. Their presence, their work, their full collaboration allowed to defeat Coli's gangs. They still worked a lot, but in peace. Tumor cells, no longer nurtured by the compounds provided by Coli and his friends –Berium found out that it was Colibactin– disappeared. There were no more strikes and manifestations; finally, a healthy and happy gut.

## Knowing it to accept it – How is Artificial Intelligence integration in the healthcare perceived by physicians?

IEO researchers have previously explored people feelings about the exploitation of Artificial Intelligence (AI) tools, in particular the AI chatbot ChatGPT, for informative purposes, revealing their people positive feelings as well as their concerns.

**The use of AI tools by clinicians – people opinion.** More recently, in the frame of a collaboration, they conducted a survey to evaluate trust and overall feelings of people regarding the employment of AI tools by clinicians, within the diagnostic path. Indeed, in the past decade several tools have been developed, and increasingly employed in the clinical setting, showing their potential as support tools in the interpretation of medical images, improving diagnostic accuracy and accelerating the diagnostic workflow.



Image generated by ChatGPT

The study specifically focused on the Italian population, including both patients (the survey was advertised in a care center- IEO) and citizens in general. Although validation of the results in larger patient cohorts,

possibly free of potential demographic-related biases, is needed, the study highlighted the overall positive attitude of people towards the use of AI tools by the physicians, as a support tool, which can never completely replace their doctors. Moreover, while no real concern has been perceived regarding privacy and safety of personal data (which are dealt with in the implementation and integration of AI tools in the clinical setting), the study highlighted instead people concerns regarding the legal responsibility in case of errors of the AI tools (to be completely of the physicians, of the developers, or equally shared by the two parties). The survey provides an overview on the current overall people acceptance of the employment of AI tools in the healthcare, which is key to the actual integration of these tools.

***The use of AI tools by clinicians – physicians’ opinion.*** This survey complements the data collected in the frame of other previously published studies on the topic, such as those reporting physicians’ opinion, another significant aspect in the actual adoption of AI tools in the clinics. A previous work (mostly focused on the German population, primarily radiologists) investigated clinicians’ attitude towards the employment of AI tools in medicine, assessing their opinion regarding the potential advantages and disadvantages related to the use of AI in decision-making or doctor-patient communication, as well as the implications, such as the legal responsibility or the need for an adequate training.

The study highlighted an overall feeling of enthusiasm (such as physicians’ openness towards these technologies, their curiosity, and perceived benefits related to the use of AI) as well as skepticism and apprehension (linked to uncertainty, perceived risk, loss of control and threat to medical specialties).

Indeed, although apprehension exists, clinicians were overall positive about it. In particular, the data highlighted a broad interest in AI tools, with a significant percentage of respondents stating to be quite familiar with AI –although few of them used it for work purposes but intended to use it–, considering it a valuable aid in diagnostics. Regarding patient-doctor communication, many deemed AI could improve it. Concerning legal responsibility related to the adoption of AI tools in the healthcare, the majority of responders believed that physicians should be considered primary responsible for potentially incorrect diagnoses and therapy decisions obtained leveraging AI tools, followed by developers and hospitals. The study highlighted also several concerns of physicians, likely related to the fact that the broad employment of these tools in the clinical setting is still in its infancy and, as such, improvements are needed –including digitalization and system interoperability–, which are likely to be achieved in the future, with the refinement of the current technology. Moreover, while highlighting the potential of this technology –which is deemed unavoidable for the future clinicians– in enhancing diagnostic accuracy and reducing clinicians’ workload, freeing time to be dedicated to their patients and more complex tasks, some of the respondents underlined the need for greater integration of AI in medical training, in order to fully catch its potential. Notably, familiarity with AI tools predicted enthusiasm for the use of AI for clinical purposes (less affected, instead, by age, gender, medical field). Furthermore, although concerns emerged regarding the possible reduction of medical skills as a consequence of the excessive reliance on AI tools, the study emphasized once again that the doctor’s experience cannot be replaced, and final decision still remain with the physicians.

We are witnessing a new technological revolution. Just like “Rome wasn’t built in a day”, the full –and responsible– integration of AI in the current workflows will require time, effort and continuous refining, with a pragmatic approach, in this transition phase, until reaching the new steady state phase, in which the current criticalities –such as the needed interoperability, adequate training, clear guidelines on the adoption of these tools, legal and ethical framework and so on– will be all figured out, and the full potential of AI tools will be explored and leveraged; a time when AI tools will become an integral part of our work, just like the computers today.

*References:* 1) *Public Perspectives on Artificial Intelligence in Medicine and Radiology: Insights From a Survey in an Italian Cancer Referral Center.* Filippo Pesapane, Emilia Giambersio, Anna Rotili, Roberto Grasso, Aurora Gaeta, Ottavia Battaglia, Lorenzo Conti, Silvia Francesca Maria Pizzoli, Sara Raimondi, Sara Gandini, Gabriella Pravettoni, and Enrico Cassano. *JCO Clinical Cancer Informatics* 2026. doi: /10.1200/CCI-25-00210. 2) *Physicians’ Attitudes Toward Artificial Intelligence in Medicine: Mixed Methods Survey and Interview Study.* Helen Heinrichs; Alexander Kies; Saskia K Nagel; Fabian Kiessling. *J Med Internet Res* 2025. doi: 10.2196/74187.

## Trastuzumab deruxtecan – from the DESTINY-Breast06 clinical trial, new indications for breast cancer treatment.

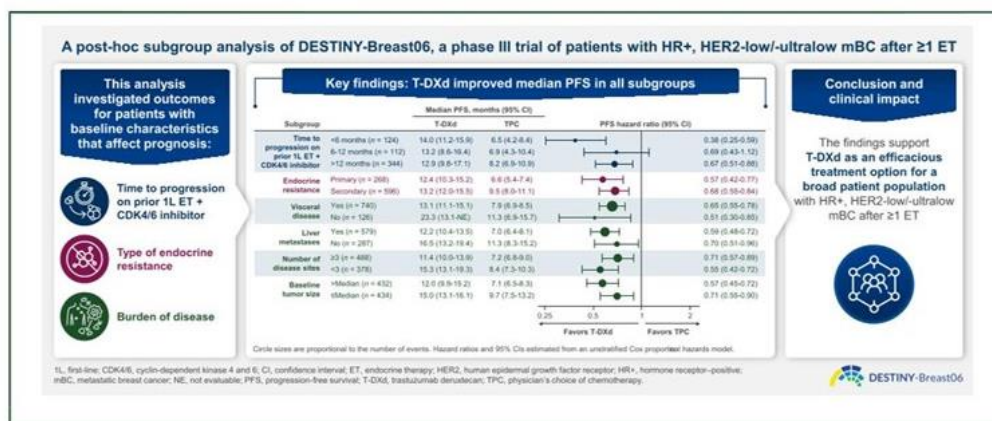


Figure from Curigliano et al., 2026 (an open access article under the CC BY-NC-ND license)

Currently, the standard (first line) treatment for HR+/HER2- metastatic breast cancer (BC) is endocrine therapy (ET, which blocks estrogen production, through aromatase inhibitors or selective estrogen receptor modulators and degraders), in combination with inhibitors of the CDK4/6 (CDKi). However, most patients eventually progress and, after CDKi administration, at later therapy lines, ET efficacy decreases, and chemotherapy effects are limited, calling for the identification of new therapeutic approaches. Treatment of HR+ BC is becoming increasingly personalized on the basis of tumor molecular features such as PIK3CA or ESR1 mutations, or variable HER2 expression (with the further classification of tumors in HER2-low, HER2-ultralow or HER2-negative), which can affect sensitivity to anti-HER2 agents such as the anti-HER2 antibody trastuzumab deruxtecan (T-Dxd).

The phase III DESTINY-Breast06 trial compared efficacy of T-Dxd -vs chemotherapy- in patients with HER2-low and HER2-ultralow BC, previously treated with ET, showing clinical benefits in the HER2-low population and leading to the approval of T-Dxd for the treatment of HR+, HER2-low and HER2-ultralow, metastatic, unresectable patients who already received prior ET.

Following up on the DESTINY-Breast06 results, researchers, headed by Giuseppe Curigliano -vice scientific director of IEO and director of the Division of new drugs for innovative therapies- performed further analyses to strengthen the results collected in the primary analysis, by evaluating T-Dxd efficacy in specific patient subgroups (namely, *i.* according to the time until disease progression during treatment; *ii.* according to the disease burden; *iii.* according to the type of ET resistance, either acquired or preexisting), thus providing critical additional information for the employment of T-Dxd for the treatment of breast cancer patients in real world clinical practice.

On the basis of all the different criteria considered, the data showed a greater efficacy of T-Dxd, as compared to all the chemotherapeutic agents employed as control, in all the subgroups analyzed, independently of disease burden, endocrine therapy resistance, time to progression, offering new effective therapeutic options to patients that, due to their specific tumor features, have so far shown unfavorable prognosis with the current standard treatments.

### TELL ME MORE!

DESTINY-Breast06 was a randomized, multicenter, phase III trial. The study enrolled 866 patients who were randomly assigned to receive T-Dxd (436 patients) or chemotherapy (430 patients). Efficacy was evaluated

in terms of progression-free survival (PFS and PFS2, namely time from treatment initiation to progression during first and second line therapy, respectively), objective response rate (ORR), duration of response (DOR).

**Efficacy.** In line with the results collected in the whole population of the DESTINY-Breast06 clinical trial, in *group 1*, including patients selected according to the time until progression during 1st line therapy, which involved 570 patients who received ET+CDKi as first line therapy and progressed, T-Dxd administration resulted in significantly improved PFS, ORR, DOR, PFS2 as compared to chemotherapy, in all the subgroups, namely in those in which the disease progressed *a.* within 6 months, *b.* between 6 and 12 months, *c.* over 12 months. In patients who progressed within the first 6 months of the standard therapy, who represent the most difficult-to-treat population, T-Dxd administration resulted in a 68% ORR as compared to 25% in chemotherapy-treated patients, and a median PFS of 14 months vs 6.5 month in the chemotherapy-treated patients, offering to these patients a new effective therapeutic option. *In group 2*, including 864 patients with endocrine therapy resistance, PFS, ORR, DOR, PFS2 were all improved with T-Dxd as compared with chemotherapy (both in the 268 patients with primary resistance and in the 596 with secondary resistance). In patients with primary resistance, T-Dxd administration resulted in 58% ORR as compared to 26% observed with chemotherapy, and an improved median PFS of 12.4 vs 6.6 months. Patients with primary endocrine resistance have often a unfavorable prognosis; this study shows that T-Dxd may represent for them a valid option.

*In group 3*, including patients selected according to the disease burden (by considering tumor size, number of different lesion sites, visceral or liver disease), which involved 740 patients in total, T-Dxd administration resulted in improved PFS, ORR, DOR, PFS2 in all subgroups, independently of disease burden.

**Safety.** The toxicity profile was consistent with what was previously reported, and incidence of treatment-related adverse events was similar in T-Dxd-treated and chemotherapy-treated patients. More severe (>3 grade) and serious adverse events, sometimes leading to treatment discontinuation, were more frequent in the T-Dxd.

Therefore, despite adverse events, in line with the known toxicity profile associated with these drugs, the analysis showed the greater efficacy of T-Dxd as compared to any of the chemotherapeutic employed (by physicians' choice) for the treatment of HR+ HER2-low and HER2-ultralow BC, in high and low disease burden, in those who progressed early or late under therapy, in those who had either primary or secondary ET resistance.

### *The authors – Giuseppe Curigliano.*

Giuseppe Curigliano is IEO vice-scientific director, Director of the Early Drug Development Division of IEO, full professor of Medical Oncology at the University of Milan. He is also in charge of the clinical division for solid tumors. He is ESMO president elect, and served as Chair of the ESMO Nomination Committee (2017-2019) and of the ESMO Clinical Practice Guideline Committee (2019-2023). He was one of the founding member and served as scientific Co-Chair of the "ESMO Breast Cancer Congress". With a medical degree at the Università Cattolica del Sacro Cuore in Rome and a specialty in medical oncology, Dr Curigliano continued his medical training at the dept of clinical immunology of the South Carolina Medical School, Hollings Cancer Center (Charleston, U.S.A.), and at the Herbert Irving Comprehensive Cancer Center of Columbia University (New York, U.S.A). Moreover, he got his PhD in medical physiopathology and clinical pharmacology at the university of Pisa. His research focuses on biomarkers and personalized therapies, with an emphasis on biomarker discovery, targeted agent development, and the integration of personalized medicine. He leads Phase I-III clinical trials on targeted therapies for breast cancer and oversees large-scale national studies on the implementation of high-throughput technologies in healthcare system. Prof. Curigliano was identified as Clarivate™ world's most influential researchers (the highly cited researchers) in 2022, 2023 and 2024. He has authored more than 900 papers in peer-reviewed journals (h-index 106) and many book chapters. He trained, mentored and sponsored dozens of medical oncologists.

**Reference.** *Trastuzumab deruxtecan in hormone receptor-positive, HER2-low/ultralow metastatic breast cancer (DESTINY-Breast06): outcome analyses by time to progression on prior first-line endocrine therapy with CDK4/6 inhibitor and baseline burden of disease.* G. Curigliano, X. Hu, R. Dent, K. Yonemori, C. H. Barrios, J.-Y. Pierga, F. Puglisi, J.-M. Ferrero, K. H. Jung, N. A. Bagegni, J. Collignon, M. Gil-Gil, X. Wu, A. Andrzejuk-Cwik, M. Schwaederle, S. Anand & A. Bardia. *ESMO Open* 2026. doi: 10.1016/j.annonc.2026.02.015.

## Preventing disease progression in metastatic breast cancer patients – promising results of the phase III HER2CLIMB-05 clinical trial.

The current standard treatment for patients with HER2+ metastatic breast cancer consists in a first treatment period (induction therapy) with antibody-based immunotherapy (with anti-HER2 trastuzumab and pertuzumab) along with chemotherapy (taxanes) followed by a second treatment period (maintenance therapy) with trastuzumab and pertuzumab. Despite the relative efficacy of this approach in controlling the disease and preventing progression, many patients face disease progression.

In the frame of the international (randomized, placebo-controlled) phase III HER2CLIMB-05 trial, researchers, including Giuseppe Curigliano – IEO scientific vice-director and head of the Division of new drugs for innovative therapies –, evaluated, in HER2+ metastatic breast cancer patients (who had received trastuzumab, pertuzumab and taxanes as induction therapy), efficacy and safety of the addition of the highly selective HER2-targeted tyrosin kinase inhibitor tucatinib to trastuzumab+pertuzumab maintenance therapy.

The results showed a significant (36%) decreased risk of disease progression in patients receiving tucatinib, extending progression-free survival (PFS) to over two years, indicating that the pertuzumab-trastuzumab-tucatinib combination therapy may be a viable option for an effective disease control in these patients (who did not progress after induction therapy), along with a manageable safety profile.



*Giuseppe Curigliano*

### TELL ME MORE!

Enrolled patients (with unresectable locally advanced or metastatic disease, who did not progress after induction therapy) were randomly assigned to receive either trastuzumab pertuzumab and a placebo (328 patients, placebo group) or trastuzumab, pertuzumab and tucatinib (326 patients, tucatinib group), as maintenance therapy.

**Efficacy.** Efficacy was evaluated primarily in terms of PFS, displaying a 36% reduced risk of disease progression: Median PFS was improved in the tucatinib arm as compared to the placebo group, being 24.9 months and 16.3 months respectively. Notably, the benefits of tucatinib treatment were maintained also in all patients subgroups within the cohort (namely, those with hormone receptor-positive and -negative disease, as well as with or without brain metastases). Among patients who had brain metastases before maintenance treatment initiation, median PFS was 8.5 months in the tucatinib group vs 4.3 in the placebo.

**Safety.** The toxicity profile of tucatinib in combination with trastuzumab and pertuzumab was overall consistent with the known safety profile of each drug in these patients. Anyway, serious and >grade 3 adverse events manifested more frequently in the tucatinib (42.3% and 16,9%) than in the placebo (24.4% and 8%) arm (more frequent serious adverse events were treatment-induced liver toxicity, which was however

asymptomatic and reversible with dosage adjustments) and treatment discontinuation due to therapy-induced adverse events was needed more often in the tucatinib arm (13.8% of patients) than in the placebo group (4.6%).

*Reference: HER2CLIMB-05: A Phase III Study of Tucatinib Versus Placebo in Combination With Trastuzumab and Pertuzumab as First-Line Maintenance Therapy for HER2<sup>+</sup> Metastatic Breast Cancer. Veronique Dieras, Giuseppe Curigliano, Miguel Martin, Florence Lerebours, Junji Tsurutani, Marie-France Savard, Katarzyna J. Jerzak, Xichun Hu, Luciana Carla Martins de Aquino Pimentel, Ciara C. O'Sullivan, Eriko Tokunaga, Alicia Okines, Chiun-Sheng Huang, William Jacot, Joohyuk Sohn, Eduardo Cronemberger Silva, Volkmar Mueller, Shan Yang, Giovanna Granata, Qi Shen, Libero Santarpia, and Erika Hamilton, on behalf of the HER2CLIMB-05 Investigators. Journal of Clinical Oncology 2025. doi: 10.1200/JCO-25-02600.*

## Evaluating patient quality of life in the frame of the EMBER-3 clinical trial.

Advanced breast cancer patients, who progressed and developed resistance to endocrine therapy (ET), can be administered ER degraders, such as Fulvestrant -which is often used in patients that have developed resistance to aromatase inhibitors- or Imlunestrant -a next generation, brain penetrant ER degrader that has previously shown efficacy in preclinical studies against ESR mutated and non-mutated tumors.

Recently, the phase III, multicenter, randomized EMBER-3 clinical trial evaluated efficacy of Imlunestrant, either alone or in combination with abemaciclib, as compared to fulvestrant, in HR+/HER2- breast cancer patients who progressed under first line treatment with ET and CDK4/6 inhibitors, showing a survival benefit in ESR-mutant patients as well as -though to a lesser extent- in non-mutant patients, leading to FDA and EMA approval of imlunestrant for the treatment of HR+/HER2-, ESR-mutant, advanced breast cancer patients who progressed under ET.

Further confirming the patient-centric approach of IEO clinicians, and their attention to patients' wellbeing during the therapeutic path, within the EMBER-3 trial, researchers coordinated by Giuseppe Curigliano -IEO vice-scientific director and head of the division of new drugs for innovative therapies- investigated quality of life of patients under treatment, by using standardized patient-reported outcome measures to quantitatively assess the actual impact of treatment as well as the impact of oral imlunestrant and intramuscular fulvestrant on patients, by qualitative interviews-based analysis.

The results showed that although quality of life (QoL) was overall maintained in both imlunestrant-treated and fulvestrant-treated patients, independently from ESR gene mutation, time to QoL deterioration was slightly longer in imlunestrant-treated patients as compared to fulvestrant-treated patients, and was only slightly worsened by the combined administration of abemaciclib. Moreover, no significant differences were observed between the ESR-mutant and non-ESR-mutant population.

Regarding the qualitative analysis of patients' attitude towards oral (imlunestrant) vs intramuscular (fulvestrant) administration, patients reported a positive attitude for both approaches, with pros and cons for both of them.

Therefore, by complementing the results on efficacy and safety collected in within the EMBER3 trial, quantitative and qualitative analysis carried out within this work support the use of imlunestrant, either alone or in combination with abemaciclib, as a therapy option for ER+/HER2- advanced breast cancer patients who progressed under ET.

### TELL ME MORE!

The EMBER-3 trial was primarily aimed at testing efficacy and safety of imlunestrant + abemaciclib vs imlunestrant only vs standard of care (exemestane).

However, the authors conducted a parallel *i.* quantitative exploratory analysis aimed at assessing patients' quality of life (through questionnaire-based patient-reported tools), and *ii.* a qualitative (interviews-based) analysis to assess the impact on patients' daily life of intramuscular fulvestrant vs oral imlunestrant.

The trial included 874 patients: 331 were randomly assigned to receive imlunestrant, and 292 assigned to receive fulvestrant (either alone or in combination with abemaciclib).

**Quantitative analysis – Quality of Life.** Questionnaire-based measurements showed that QoL was overall maintained in both oral imlunestrant-treated and intramuscular fulvestrant-treated arms. Time to quality of life deterioration was slightly longer in the imlunestrant-treated than in the fulvestrant-treated arm. Symptoms were overall similar and no significant differences were observed between the ESR-mutated and ESR-unmutated population, in both treatment arms. In the whole patient population analyzed, symptoms appeared slightly better in the imlunestrant-treated arm (being weakly stronger in the combination treatment arm than in monotherapy). About 70% of patients treated with (intramuscular) fulvestrant reported mild discomfort due to reaction at the injection site.

**Qualitative analysis - oral vs intramuscular drug administration.** Overall, patients reported, for both treatments, a positive attitude, due to the mild side effects induced as compared to other treatments, with minimal impact on their daily life. Ease of management was a positive aspect related to the oral imlunestrant administration, fasting needed before treatment was reported as a negative aspect. Concerning the intramuscular fulvestrant administration, the frequency of injection (monthly) was reported as a positive aspect, while the pain at the site of injection and the travel/doctor appointment were listed as negative aspects.

*Reference. Patient-reported outcomes and qualitative interviews in patients with estrogen receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer: results from the phase III EMBER-3 trial. G. Curigliano, J. O'Shaughnessy, F.-C. Bidard, M. L. Casalnuovo, S.-B. Kim, E. Tokunaga, P. Aftimos, C. Saura, L. A. Carey, M. Okera, E. Melo, F. Zagouri, M. Magallanes-Maciel, N. Karadurmus, S. Bahadur, R. M. Speck, X. A. Wang, K. Pradhan, J. Macey, H. Kitchen, S. Fairhurst, J. Miller, K. L. Jhaveri & N. Harbeck. ESMO Open 2026. doi: 10.1016/j.esmoop.2026.106945.*

## Robot-guided surgery for breast cancer treatment – a randomized clinical trial evaluates long-term clinical efficacy.

Due to its minimally invasive nature, robot-guided nipple-sparing surgery has been increasingly employed as an alternative to the more invasive open surgery, for the treatment of breast cancer. Previous studies reported feasibility and safety of this approach; however, so far no studies have explored the long term efficacy of this approach in disease control and compared it to conventional open surgery.

To address this knowledge gap, in the frame of a prospective, randomized, phase III clinical trial, researchers coordinated by Paolo Veronesi-Director of the IEO Senology Program and of the IEO Division of Breast Surgery- compared long-term oncological outcome of robot-assisted surgery and open surgery for the treatment of breast cancer patients at IEO.

At a follow-up of over six years, the data showed no significant differences in terms of survival between the two approaches. Although it should be acknowledged that the results have been collected in a single cancer center-IEO-, the data point to a comparable efficacy of robot surgery vs open surgery, showing that the two techniques can be equally effective in eliminating residual breast tissue and tumor margins. Therefore, although careful selection of patients and adequate expertise remain two critical aspects, the data indicate that robot-guided surgery can be successful in primary tumor eradication, thus not compromising the long-term oncological outcome.

### Robotic surgery.

Robotic surgery is a minimally invasive surgical technique exploiting surgeon-controlled robotic arms, enabling more precise movement and a 3D vision of the surgical area, improving the quality of the maneuvers and allowing for a more rapid post-surgery recovery of the patients. Although more complex and requiring specific expertise, robotic surgery represents an evolution of mini-invasive surgery, with remarkable advantages in terms of precision.

## TELL ME MORE!

Sixty-nine breast cancer (invasive breast cancer or ductal carcinoma in situ) patients at IEO were randomly assigned to be treated with conventional open surgery or robot-guided surgery. Post-surgical treatment was defined independently from the specific surgical approach employed, *per* standard guidelines according to patients' and tumor features, which were balanced in the two treatment groups. In terms of survival, at a follow-up of over 6 years (6.5-year median follow-up), cancer-related clinical outcomes were comparable between the two groups, with no statistically significant differences in terms of 5-year overall survival (OS, being 97.1% in both arms), disease-free survival (being 88.2% and 88.6% in robotic vs open surgery, respectively), and cancer-specific survival (being 91% and 91.2% in the two groups, respectively).

In terms of recurrence, local relapse occurred in three patients treated with robotic surgery and two patients treated with open surgery. No significant differences in terms of distant metastases were observed. In the future, larger multi-center clinical trials can specifically assess non-inferiority oncological outcome as compared to open surgery.



*Paolo Veronesi*

### *The authors – Paolo Veronesi and Antonio Toesca.*

With a medical degree from the University of Milan, with a specialty in Plastic and Reconstructive Surgery and one in General Surgery from the University of Milan, **Paolo Veronesi** has been directing the IEO Breast Surgery Division for over 10 years. His clinical and research contribution has been crucial for the development of innovative approaches for breast cancer treatment in IEO, including sentinel lymph node technique, radio-guided localization of non-palpable lesions, intra-operative radiotherapy, and all innovations in reconstructive surgery minimizing patient disease-related psychological distress.

With a medical degree and a specialty in General Surgery from the University of Milan, **Antonio Toesca** grew professionally at IEO, where he worked as a breast surgeon for 15 years.

*Reference. Long-term oncological outcomes of robotic mastectomy for breast cancer: a randomized clinical trial. Antonio Toesca, Francesca Magnoni, Claudia Sangalli, Patrick Maisonneuve, Alessandra Gottardi, Alessandra Margherita De Scalzi, Elisa Ileana Bottazzoli, Andrea Polizzi, Nickolas Peradze, Daniele Presti, Alberto Concardi, Nicola Fusco, Francesca De Lorenzi, Giovanni Corso, Viviana Galimberti and Paolo Veronesi. BJS 2026. doi: 10.1093/bjs/znag007.*

## **New treatment options for recurrent, chemoresistant ovarian cancer – results of two phase III clinical trials.**

Despite the progress in the treatment of ovarian cancer, many patients, after initial response to therapy, still recur, often with platinum-resistant disease. In this case, prognosis is not favorable, underlining the need for a renewed effort in the search for new effective therapeutic approaches.

Immune checkpoint inhibitor (ICI)-based immunotherapy, alone or in combination with chemotherapy, has shown poor efficacy in these patients. However, preclinical and clinical studies

*Alex, can you write few words about Pembrolizumab, Paclitaxel and nab-paclitaxel, Bevacizumab, Relacorilant?*

**Pembrolizumab** is a humanized monoclonal antibody targeting PD-1. It binds the PD-1 receptor on T cells, blocking interaction with PD-L1/PD-L2 and restoring

found that when administered at low dose and on a weekly schedule, chemotherapy can increase cancer immunogenicity and reduce immunosuppression in the tumor microenvironment. Consistently, within previous clinical trials, promising efficacy has been observed in these patients upon administration of ICI (pembrolizumab) and metronomic chemotherapy. Based on this mechanistic knowledge, in the frame of the phase 3 ENGOT-ov65/KEYNOTE-B96 clinical trial, researchers headed by Nicoletta Colombo-Director of the Gynecology Program of IEO investigated safety and efficacy of (second or third line) administration of the ICI pembrolizumab along with weekly paclitaxel (with or without bevacizumab) as compared to the current standard of care for recurrent platinum-resistant ovarian cancer patients (namely, weekly paclitaxel only, and a placebo). The results of the ENGOT-ov65/KEYNOTE-B96 trial-recently published in *The Lancet* journal- highlighted statistically significant and clinically meaningful benefits of pembrolizumab administration in addition to weekly chemotherapy in recurrent, platinum-resistant ovarian cancer, both in terms of progression-free survival (PFS) and overall survival (OS), independently from the addition of bevacizumab. ENGOT-ov65/KEYNOTE-B96 is the first phase III trial showing clinical benefits of ICI-based therapy in this setting, in this patient population. Moreover, the study shows chemotherapy-induced increase of immunotherapy efficacy.

Notably, based on these data, this therapy combination is now one of the recommended options for recurrent ovarian cancer patients (with high PDL1 expression), making immuno-chemotherapy one of the standard treatment option.

“This treatment-explains Nicoletta Colombo- has been approved by the European regulatory body (EMA); we are currently waiting for the Italian regulatory body (AIFA) to make it reimbursable to be able to offer this therapeutic option to Italian patients.”

In the frame of another phase III clinical trial-ROSELLA-, researchers, including Nicoletta Colombo, evaluated efficacy of the combined administration of relacorilant and nab-paclitaxel in recurrent, platinum-resistant ovarian cancer patients.

Glucocorticoid receptor antagonists, such as relacorilant, represent a new approach to ovarian cancer therapy. Preclinical studies previously showed that by acting on this receptor, cortisol sustains cancer cell survival, increasing the expression of anti-apoptotic proteins. Relacorilant inhibitory activity on cortisol-induced signals results in the enhanced sensitivity of cancer to different chemotherapeutics. Glucocorticoid receptor is expressed by tumor cells of the majority (95%) of ovarian cancers. Based on this mechanistic knowledge, the ROSELLA trial evaluated safety and efficacy of the synergy between relacorilant and chemotherapy, showing significant clinical benefits (in terms of PFS, PFS2, OS) in recurrent platinum-resistant heavily pretreated ovarian cancer patients, proposing relacorilant+nab-paclitaxel as a potential novel treatment option for these patients, without the need for biomarker-based selection. The results have been recently published in *The Lancet* journal.

antitumor immune responses. It belongs to the immune checkpoint inhibitor class, enhancing the immune system’s ability to recognize and destroy cancer cells.

**Paclitaxel** is a chemotherapeutic agent of the taxane class. It stabilizes microtubules by binding to tubulin, preventing depolymerization and disrupting mitosis. This causes cell cycle arrest in the G2/M phase and leads to cell death, particularly in rapidly dividing cancer cells. **Nab-paclitaxel** is an albumin-bound nanoparticle formulation of paclitaxel. It retains the taxane mechanism (microtubule stabilization) but enhances tumor delivery via albumin-mediated transport. It avoids solvent-related toxicity and may improve efficacy and tolerability.

**Bevacizumab** is a monoclonal antibody against VEGF-A. It inhibits tumor angiogenesis by binding vascular endothelial growth factor, preventing receptor activation. This reduces the formation of new blood vessels required for tumor growth and metastasis.

**Relacorilant** is a selective glucocorticoid receptor (GR) antagonist. It modulates cortisol signaling without progesterone receptor antagonism. It is being investigated to overcome treatment resistance and mitigate cortisol-mediated effects within the tumor microenvironment.

## TELL ME MORE!

### The ENGOT-ov65/KEYNOTE-B96 clinical trial.

The study involved 187 different cancer centers in 25 countries. The 643 enrolled patients were randomly assigned to receive either pembrolizumab + weekly chemotherapy (paclitaxel, 322 patients) or placebo + weekly paclitaxel (321 patients). Some patients also received bevacizumab; most participants had high

tumoral expression of the PDL1 protein, target of pembrolizumab.

**Efficacy.** The study included two intermediate analyses and a final analysis. Efficacy was evaluated in terms of PFS and OS. At the first interim analysis, PFS was significantly increased in the pembrolizumab+chemotherapy-treated patients vs the chemotherapy+placebo-treated, both in the whole population and in the patient subpopulation with high PDL1 expression, while overall survival was not significantly different. At the second interim analysis, OS was increased as well, both in the whole population and in the PDL1-high subgroup. At final analysis, results on treatment efficacy were confirmed, showing statistically significant increased PFS and OS, as well as improved objective response rate and response duration.

Although some patients received bevacizumab in addition to pembrolizumab and chemotherapy, the clinical benefits were evident independently from bevacizumab administration.

**Safety.** Overall, the safety profile was in line with the known toxicity for the two agents administered separately, and was mostly linked to chemotherapy. Specifically, adverse events (AEs) occurred in any participants; grade 3 or higher treatment-related AEs were observed in 68% of the patients in the pembrolizumab+paclitaxel group, leading to treatment discontinuation in 38% of them, and in 55% of the patients in the paclitaxel+placebo group, leading to discontinuation in 28% of them. Quality of life (QoL) was also assessed, by means of questionnaires, showing improved or stable QoL in 59% of the patients in the pembrolizumab+chemotherapy group and 61% of those in the chemotherapy+placebo group.

**PDL1 biomarker.** Despite the known intratumor heterogeneity in terms of expression of PDL1 (the target of pembrolizumab) in ovarian cancer, and the greater efficacy observed in PDL1-expressing tumors, anti-PDL1 agents have shown efficacy also in PDL1-low tumors, suggesting that, despite PDL1 expression being a biomarker for the identification of potential responders and guiding the treatment choice, other factors may be involved in shaping the response to pembrolizumab, and additional biomarkers may aid in refining patient selection, improve treatment choice, and thus clinical outcome.

#### **The ROSELLA clinical trial.**

The study enrolled 381 patients with recurrent, platinum-resistant ovarian cancer (who had already received one to three prior lines of therapy), in 117 different cancer centers, in 14 countries, who were randomly assigned to receive either relacorilant + nab-paclitaxel (188 patients) or nab-paclitaxel only (193).

**Efficacy.** Efficacy was evaluated in terms of PFS, PFS2, and OS. OS was significantly improved with the combination therapy (median OS 4.1months longer in the combination therapy group, and higher proportion of patients alive in the combination therapy vs monotherapy -46% vs 27%, respectively- at 18 months. Effects on OS were increasingly evident during the followup period, suggesting a long term effect of relacorilant. In line with previously published ad interim results, PFS was significantly longer. Indeed, subsequent treatments were initiated later in the combination therapy group than in the monotherapy group (6.2months vs 5.6 months). Notably, benefits of the combination treatment on OS and PFS were observed in all subgroups of patients, namely those receiving one, two, three prior lines of therapy.

**Safety.** Overall, severe, grade 3 or higher adverse events were slightly more common in the combination therapy than in monotherapy (yet quite similar after adjustments on the basis of factors such as age) and managed with standard care. No new toxicity signs and no treatment-related deaths were observed. Assessment of patient-reported quality of life (QoL) showed no significant differences; overall, the combined treatment appeared well tolerated by patients.

#### *The authors – Nicoletta Colombo.*

Nicoletta Colombo is the Director of the IEO Gynecology Program. With a medical degree and a specialty in Obstetrics and Gynecology at the University of Milan, she continued her medical training at the Charing Cross Hospital and the Royal Marsden Hospital in London first, and then as Clinical Research Associate at the Kaplan Cancer Center of the New York University. Next, she worked at the department of obstetrics and gynecology of the University of Milan. In 2008, she has become director of the IEO Center for Ovarian Cancer, and from 2014 she is president of the Gynecology Program.

**References:** 1) *Pembrolizumab plus weekly paclitaxel in platinum-resistant recurrent ovarian cancer (ENGOT-ov65/KEYNOTE-B96): a multicentre, randomised, double-blind, phase 3 study.* Nicoletta Colombo, Emese Zsiros, Gabriella Parma, Eliana Rulli, Alexandra Sebastianelli, Mariusz Bidzinski, Carlos Gallardo, Emad Matanes, Kosei

Hasegawa, Fatih Kose, Manuel Magallanes-Maciel, Rebecca A Herbertson, Sumitra Ananda, Judith R Kroep, Andreia Cristina de Melo, Philip R Debryne, Jae-Weon Kim, Jalid Sehoul, Marc-Edy Pierre, Sakari Hietanen, Claudio Zamagni, Xin Lu, Bradley J Monk, Robert L Coleman, Xuan Peng, Karin Yamada, Agata M Bogusz, Thibault De La Motte Rouge, Xiaohua Wu, on behalf of the ENGOT-ov 65/KEYNOTE-B96 investigators. *Lancet* 2026. doi: 10.1016/S0140-6736(26)00602-1. 2) Overall survival with relacorilant and nab-paclitaxel in patients with platinum-resistant ovarian cancer (ROSELLA): a phase 3 randomised controlled trial. Domenica Lorusso, Laurence Gladieff, David M O'Malley, Jae-Weon Kim, Gabriel Garbaos, Anna Fagotti, Lucy Gilbert, Linda Mileshekin, Stanislas Quesada, Elizabeth Hopp, Yong Jae Lee, Ana Oaknin, Mariana Scaranti, Byoung-Gie Kim, Andrew Clamp, Christina Prillaman, Connie Diakos, Andrea Bagaméri, Aliza L Leiser, Vanda Salutari, Bradle y J Monk, Philippe Follana, Emily McClung, Vittoria Carbone, Brian Slomovitz, Elena Giudice, Maria Chiara Cannizzaro, Laurène Gavoille, Alix Devaux, Paolo Scollo, Giuseppa Scandurra, Chiara Cassani, Grazia Artioli, Toon Van Gorp, Ana Santaballa, Lyndah K Dreiling, Amanda Kesner-Hays, Iulia Cristina Tudor, Adrian M Jubb, Nicoletta Colombo, Alexander B Olawaiye. *Lancet* 2026. doi: 10.1016/S0140-6736(26)00462-9.

## **The right drug dosage to reduce adverse events in niraparib-treated ovarian cancer patients – a randomized clinical trial.**

Results of previous clinical studies led to the approval of olaparib, niraparib and rucaparib as maintenance therapy in ovarian cancer patients after platinum-based chemotherapy. These drugs are overall quite tolerated by patients, but hematological toxicity is frequent and treatment-related adverse events lead to treatment interruption in a non-negligible percentage of patients. Body weight and baseline platelet counts appeared to be correlated with the incidence of hematologic toxicity (in particular thrombocytopenia) in patients treated with niraparib.

In the frame of the NEWTON clinical trial, researchers headed by Nicoletta Colombo -Director of the Gynecology Program of IEO performed a systematic analysis to assess the effects on hematologic toxicity of a potential dosing strategy (RADAR=Rational Adjustment of Dose to reduce Adverse Reactions ) aimed at reducing treatment-related adverse events-AEs- (mainly hematological AEs like thrombocytopenia), based on the two factors identified as being highly correlated with thrombocytopenia, such as body weight and baseline platelet count.

The study found a significantly reduced incidence of severe hematologic toxicity (thrombocytopenia) in patients with weight between 58 and 77 kg or greater than 77 kg, with platelet count < 150,000/uL treated with lower RADAR (200mg/day) dose of niraparib as compared to those treated with the standard, higher (300mg/day) dose; the incidence was 4% vs 42%, respectively. Despite the reduced drug dose administered, efficacy appeared comparable (although available data were not statistically sufficient to draw final conclusions in this regard), indicating that the RADAR strategy, by personalizing treatment regimen (according to some specific patients' traits), may represent a viable therapeutic option, to achieve likely similar clinical outcome, with improved patients' well-being.

### **TELL ME MORE!**

NEWTON was a prospective phase II clinical study enrolling patients with platinum sensitive ovarian cancer (already treated with at least two prior lines of platinum-based therapy). Patients with body weight lower than 58 kg were assigned to 200 mg (RADAR), and patient with body weight higher than 77 kg and with baseline platelet count >150,000/ $\mu$ L were assigned to 300 mg (RADAR). Patients with body weight between 58kg and 77 kg, or higher than 77 kg with platelet count < 150,000/ $\mu$ L were randomly assigned to receive either (the standard) 300mg/day niraparib dose or, per RADAR protocol, 200mg/day Overall, 41 patients received the lower dose (24 randomized, 17 non-randomized), and 41 the higher dose (24 randomized, 17 non-randomized).

The parameters evaluated were: *i.* rate of patients experiencing severe (grade 3 or higher) thrombocytopenia during niraparib administration, for the safety analysis, and *ii.* progression-free survival (PFS) and overall survival (OS) for clinical efficacy.

The results were compared to existing data (collected within the NOVA trial).

**Toxicity.** Adverse events (AEs) of any kind occurred in nearly all patients. Hematologic AEs occurred in >10% of the patients; of these, 57.9% were thrombocytopenia. In the randomized lower dosage treatment arm, 45.8% of patients had thrombocytopenia, vs 67% in the higher dosage arm. Dose reductions for adverse events were more common in the higher than in the lower dosage arm. The incidence of severe (grade > 3) thrombocytopenia was significantly higher in those receiving higher dosage than in those receiving lower dosage (4% vs 42%) in the randomized part of the study.

**Pharmacokinetics.** Monitoring of drug concentration in the blood found no correlation with severe thrombocytopenia, while creatinine levels and weight appeared to be correlated with low levels of niraparib, suggesting a putative effect of patients' traits on drug pharmacokinetics and as a consequence, drug exposure.

**Efficacy.** Treatment efficacy was assessed in terms of PFS and OS. In the randomized patient cohort, no actual differences in terms of PFS were observed between the two dosages: Median PFS was 10.3 and 11.7 months in the lower and higher dosage arm, respectively; PFS at 6 months was 71% and 78% respectively. In the whole patient cohort, median PFS was 10 months; PFS at 6 months was 75%. Regarding OS, no significant differences between the randomized lower and higher dosage arms were found (being 37.9 months in the 200mg/day and 36.4 months in the 300mg/day). OS at 24 months was 87.7% and 77.9% in the lower and higher dosage treatment arm, respectively.

**Conclusions.** Overall, the results indicate that the RADAR niraparib dosage (200 mg/day) was associated with lower incidence of severe thrombocytopenia, with apparent comparable efficacy, and PFS and OS values in line with existing (NOVA trial) control data.



Nicoletta Colombo

*Reference. Rational adjustment of dose to reduce adverse reactions (RADAR) in patients with platinum-sensitive recurrent ovarian cancer: Results from the phase II NEWTON trial (ENGOT-ov49). Nicoletta Colombo, Gabriella Parma, Giulia Tasca, Michele Pio Di Palma, Germana Tognon, Andrea Alberto Lissoni, Roldano Fossati, Luciano Carlucci, Massimo Zucchetti, Cristina Matteo, Annamaria Ferrero, Alessandra Bologna, Mara Mantiero, Pauline Wimberger, Dionyssios Katsaros, Federica Tomao, Francesca Galli, Mariateresa Lapresa, Valentina Guarneri, Silvia Ficarella, Stefania Canova, Silvia Derio, Fabio Girardi, Valentina Zizioli, Jalissa Katrini, Davide Massa, Eliana Rulli, Elena Biagioli, NEWTON study group. European Journal of Cancer 2026. doi: 10.1016/j.ejca.2026.116685.*

## Combining chemotherapy, immunotherapy and targeted therapy for the treatment of gastric cancer: Results of a phase II clinical trial.

Standard first-line therapy for gastric HER-2 negative PD-L1 positive adenocarcinoma patients is currently chemotherapy + immunotherapy (in particular anti-PD-1 nivolumab or pembrolizumab). Recent international clinical trials showed that the addition of drugs targeting the Claudin (CLDN) 18.2 protein, with zolbetuximab and chemotherapy, significantly improved survival in first-line therapy for HER-2 negative CLDN 18.2 positive gastric cancer patients. The CLDN18.2 protein is expressed in cells of the normal gastric

mucosa which, during malignant transformation, expose the protein on the cell surface, thus making cancer cells a target of drugs such as zolbetuximab. About 35-45% of gastric cancers are CLDN18.2-positive. If Zolbetuximab can improve survival of HER-2 negative PD-L1 positive gastric cancer patients as first-line is subject of investigation.

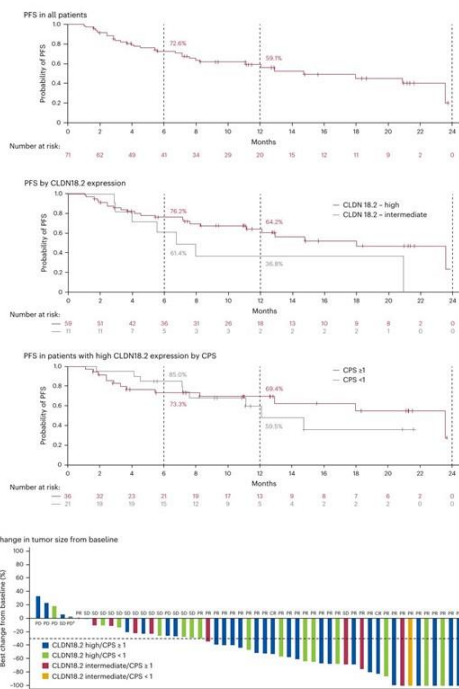


Image adapted from Shitara et al., Nature Medicine 2026 (an open access article under the CC BY license.)

Preclinical *in vivo* studies showed the further increased efficacy of the zolbetuximab-chemotherapy-antiPD1 immunotherapy combination; furthermore, patient tumor biopsy analyses showed a remodeling of the immune tumor microenvironment in zolbetuximab (with or without chemotherapy)-treated patients, encouraging the in-depth evaluation of the efficacy of this triple combination in the clinical setting. On this line, the phase II, multicenter (ILUSTRO) clinical trial assessed safety and efficacy of zolbetuximab alone or in combination with chemotherapy and/or immunotherapy in CLDN 18.2 positive HER-2 negative gastric cancer patients, pre-treated or untreated. In a paper recently published in Nature Medicine, researchers, including Nicola Fazio –Director of the Neuroendocrine and Digestive Cancer Program of IEO-, investigated safety and efficacy of zolbetuximab, as first line treatment, in combination with chemotherapy (mFOLFOX6) and immunotherapy (nivolumab), in patients

with locally advanced and unresectable, HER2-negative, CLDN18.2-positive gastric cancers. This is the first study to address this triple therapy in this clinical context. Although the number of patients of the cohort analyzed was limited, the results showed a manageable toxicity and encouraging efficacy of this triple combination, especially in patients selected on the basis of three tumor biomarkers -HER-2 neg. CLDN18.2 pos. and PDL1 pos.-, highlighting the value of precision oncology approaches.

The results of this study paved solid bases for the ongoing international phase III clinical trial (LUCERNA) comparing chemotherapy + pembrolizumab +/- zolbetuximab in patients with untreated HER-2 negative PD-L1 positive CLDN 18.2 positive gastric adenocarcinoma. If results are confirmed in the frame of this new clinical trial, the triple combination Zolbetuximab-chemotherapy-antiPD1 immunotherapy may represent a new, effective, first line biomarker-based therapy in these patients.

## TELL ME MORE!

The trial design involved two different patients cohorts: one cohort (cohort A, including 12 patients, 6 receiving a dosage of zolbetuximab and 6 receiving a different dose) aimed at defining the safe dosage (so-called “safety lead-in” phase), and one cohort, including a higher number of patients (cohort B, including 71 patients), aimed at determining efficacy of the treatment (expansion phase) at the dosage established in the 6 patients of cohort A. 62.3% of the patients enrolled were males.

Immunohistochemistry analyses revealed high/intermediate CLDN18.2 expression in patients’ tumor biopsies, and the majority of patients being PDL1-positive.

**Efficacy.** Efficacy was evaluated mainly in terms of progression-free survival (PFS, since previous analyses revealed that PFS was a more adequate parameter to reveal treatment benefits as compared to the objective response rate, ORR): median PFS was 14.8 months, and PFS rate was 72.6% at 6 months and 59.1% at 12 months. Correlation with CLDN18.2 expression revealed longer median PFS in those patients having higher CLDN18.2 expression *and* PDL1 expression, strongly supporting the rational therapeutic targeting of

CLDN18.2 protein, the synergistic action of anti-CLDN18.2 therapy and anti-PDL1 therapy, and the likely improved efficacy in patients selected on the basis of these two biomarkers.

At the time of analysis, overall survival data were not mature.

Evaluation of tumor size (specifically, tumor mass shrinkage, in selected patients who had a measurable tumor mass at baseline) as another measure of treatment efficacy showed a 62.1% ORR. Once again, the best response was observed in patients with higher CLDN18.2 and PDL1 expression. Overall, the response appeared durable.

**Safety.** Treatment toxicity was overall manageable: All patients manifested at least one treatment-related adverse event (consistent with toxicity observed for the drugs administered separately); and about 2/3 of them had more severe (grade 3 or higher) adverse events, which required to be carefully handled to preserve patients' quality of life. Treatment discontinuation due to adverse events occurred in almost half of the patients, but discontinuation of zolbetuximab specifically was needed in 5% of the patients, while 8% of the patients needed to specifically interrupt nivolumab administration, due to toxicity.



Nicola Fazio, Chiara Cella

#### CLDN18.2.

Claudin-18.2 (CLDN18.2) is a transmembrane protein involved in the formation of tight junctions between epithelial cells, and in maintaining tissue permeability barriers. Under normal conditions, it is mainly expressed in differentiated gastric mucosa, whereas in gastrointestinal cancers (such as gastric, gastroesophageal, pancreatic, and hepatobiliary tumors) it is often overexpressed or aberrantly expressed. This “tumor-like-specific” expression makes it an attractive target for tailored therapies (for example monoclonal antibodies such as zolbetuximab), exploited both for its structural role and for its contribution to tumor progression and interaction with the immune microenvironment.

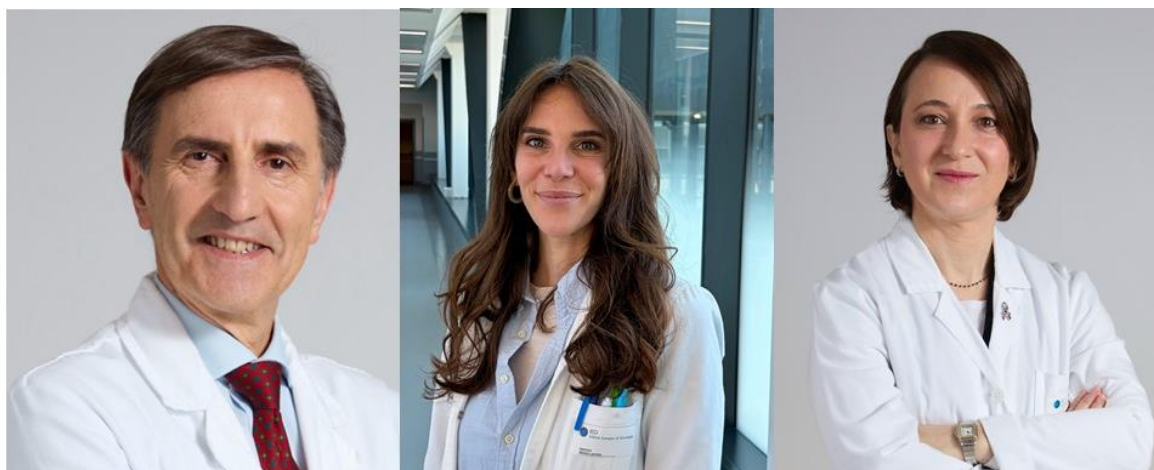
#### PD-L1.

PD-L1 (programmed death-ligand 1) is an immunomodulator, a surface protein that binds the PD-1 receptor on T cells, inhibiting their activation and thus limiting their activity. Physiologically, it contributes to preventing excessive autoimmune responses, but many tumors exploit its expression to evade immune surveillance, creating an immunosuppressive microenvironment. For this reason, the PD1-PDL1 axis is leveraged to modulate the antitumor activity of the immune system, and the PDL1 protein is used as a predictive biomarker of efficacy of immune checkpoint inhibitors-based immunotherapy (such as ipilimumab, nivolumab, pembrolizumab).

*(text by perplexity.ai)*

**Reference:** First-line zolbetuximab plus mFOLFOX6 and nivolumab in unresectable CLDN18.2-positive gastric or gastroesophageal junction adenocarcinoma: a phase 2 trial. Kohei Shitara, Hirokazu Shoji, Nicola Fazio, Sara Lonardi, Keun-Wook Lee, Li-Yuan Bai, Kensei Yamaguchi, Jean-Philippe Metges, Gianluca Masi, Denis Smith, Tae-Yong Kim, Maria Matsangou, Archita Shrivastava, Miaomai Zhou, Jason Hill, Abraham Guerrero, Xuewei Wang, Aziz Zaanani, Samuel J Klempner. *Nat Med* 2026. doi: 10.1038/s41591-026-04306-9).

# Everolimus as maintenance therapy for patients with neuroendocrine neoplasms – results of the phase II clinical trial MAVERIC.



*Nicola Fazio, Lavinia Benini, Francesca Spada*

Neuroendocrine tumors (NETs) are a rare tumor type characterized by both “neuro”-like features –such as granules inside the cell containing monoamines (typical of serotonergic neuron types)– and “endocrine” traits –such as the capability of secreting monoamines. Therefore, NETs can arise in different tissues of the body, although they are most common in the gastrointestinal tract. NETs are a –well differentiated– subtype of neuroendocrine neoplasms (NENs); the other proportion is represented by neuroendocrine carcinomas (NECs) – which are poorly differentiated. While NETs can be of low, intermediate and even high grade, on the basis of their proliferation index, NECs are always of high grade. High grade NENs are usually treated with chemotherapy, especially if they are NECs and/or at advanced stage.

In the frame of the multicenter (randomized) phase II clinical trial MAVERIC, researchers, including Nicola Fazio –Director of the Neuroendocrine and Digestive Cancer Program of IEO– evaluated efficacy and toxicity of the mTOR inhibitor everolimus as maintenance therapy, after a first-line chemotherapy, in advanced/metastatic NET patients.

Everolimus is a drug already approved for the treatment of NETs of the digestive tract and for non-functioning thoracic NETs, acting through the inhibition of the mTOR signaling. mTOR is a known key regulator of cell survival, proliferation and metabolism, whose signaling is often hyperactivated in cancer, fostering uncontrolled proliferation, thus making it a promising therapeutic target.

Although it should be acknowledged that, due to the rarity of this tumor type, the data collected derive from NETs located at different primary sites, and the sample size is small, the results of this study suggest that everolimus can be effective as maintenance treatment in patients with advanced, high-grade NENs after chemotherapy, revealing a particularly significant efficacy in the NETs of the gastroenteropancreatic subtype, along with a manageable toxicity profile.

## TELL ME MORE!

After prior chemotherapy as first line treatment, enrolled advanced/metastatic patients were randomly assigned either to surveillance (10 patients) or to receive everolimus (20 patients) as maintenance therapy, until potential disease progression or toxicity. The majority of the patients had NET of the gastroenteropancreatic tract (GEP) or in the lung. All patients had high grade (well or poorly differentiated) NENs, characterized by a ki-67 index ranging between 20% and 55%. The ki-67 index, developed on the basis of ki-67 staining, mirrors cell proliferation, thus representing a measure of tumor

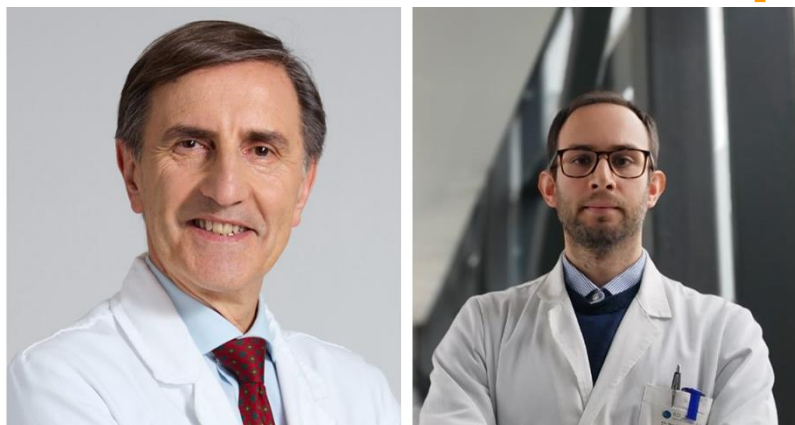
aggressiveness and prognosis.

**Efficacy.** Treatment efficacy was evaluated in terms of progression-free survival (PFS), as well as overall survival (OS). In everolimus-treated patients, PFS was prolonged as compared to patients under surveillance. Although no differences were observed in terms of OS, the result may be influenced by the comparison with a control patient population treated, upon disease progression, with second line therapy.

**Safety.** Treatment-related toxicity was overall manageable; indeed, drug-induced adverse events were in line with the known toxicity profile of everolimus, and anyway overall mild (mostly grade 1 and 2, although 70% of the patients experienced at least one grade 3 adverse event). 65% of the patients needed dose adjustment due to treatment-related toxicity, and treatment discontinuation due to toxicity was required in two patients.

*Reference: Everolimus as maintenance therapy in advanced neuroendocrine neoplasms: results from the MAVERIC phase II trial. Lorenzo Antonuzzo, Daniele Lavacchi, Francesca Spada, Riccardo Marconcini, Fabio Gelsomino, Vito Amoroso, Federica Cosso, Elisa Pellegrini, Federico Scolari, Clotilde Sparano, Giulia Massaro, Elisa Giommoni, Luca Messerini, Daniele Rossini, Marco Brugia, Francesco Di Costanzo, Luca Boni, Massimo Milione, Serena Pillozzi, Nicola Fazio, on behalf of the Gruppo Oncologico Italiano di Ricerca Clinica (GOIRC). The Oncologist 2026. doi: 10.1093/oncolo/oyaf432.*

## Liquid biopsy to select the optimal treatment for colorectal cancer patients.



Nicola Fazio, Davide Ciardiello

Despite the progress in the oncology field, thanks to the development of new approaches such as immunotherapy, targeted therapy, as well as the advances in the surgical procedures, colorectal cancer (CRC) still remains a challenge, and patients with therapy-resistant metastatic disease have overall a poor prognosis.

The current standard first line treatment for metastatic CRC without mutations in RAS/BRAF is represented by antibody-based immunotherapy targeting the receptor of the epidermal growth factor (EGFR), such as cetuximab and panitumumab. After disease progression to this therapy, a further treatment with anti-EGFR agents in selected patients has been investigated –the so-called “rechallenge”– . Furthermore, it is unclear whether therapy response may be improved through the combination with other drugs, and the definition of the optimal therapeutic combination, as well as a careful selection of the patients who could benefit from it, is needed. On the basis of preclinical and clinical studies, researchers had previously conducted a clinical trial (CAVE GOIM) aimed at evaluating efficacy of the rechallenge with cetuximab, in combination with the anti-PDL1 avelumab, in refractory metastatic CRC patients (with microsatellite stable –MSS– RAS/BRAF wt disease), showing promising results (overall survival exceeding 17 months) in patients selected on the basis of liquid biopsy results (namely, RAS/BRAF wt on the basis of analyses of circulating tumor DNA) collected before treatment initiation.

In order to confirm the potential efficacy of the rechallenge, in combination with immune checkpoint inhibitors, in the frame of the (randomized, multicenter) phase II CAVE-2 GOIM clinical trial, researchers, including Nicola Fazio –Director of the Neuroendocrine and Digestive Cancer Program of IEO–, evaluated the response of patients with metastatic MSS RAS/BRAF wt CRC patients (on the basis of liquid biopsy results) to the treatment with the anti-EGFR drug cetuximab alone, as compared to cetuximab and avelumab. This study was led by Davide Ciardiello, young medical oncologist of the Gastrointestinal Medical Oncology and Neuroendocrine Tumor Division at IEO, in collaboration with the IEO New Drug Development Division, led by Prof Curigliano, and the Italian group of Southern Italy Medical Oncology (GOIM).

Although general results showed a non-significant effect on survival of the administration of cetuximab in combination with avelumab, their data indicate that liquid biopsy-based (circulating tumor DNA) patient selection can allow to identify those more likely to benefit from anti-EGFR rechallenge, even when the disease progressed under anti-EGFR therapy. Moreover, their results underline the usefulness of circulating tumor DNA-based profiling, at different time points during the care path, as in the absence of mutations related to anti-EGFR drug resistance, cetuximab may be a viable option for refractory MSS metastatic CRC patients. Indeed, it appears that some tumors remain dependent on EGFR signaling, and thus sensitive to targeted anti-EGFR therapies.

## TELL ME MORE!

The study enrolled 156, heavily pretreated (MSS RAS/BRAFwt) patients, who were randomly assigned to receive either cetuximab and avelumab (C+A, 104 patients) or cetuximab only (C-only, 52 patients), after at least one treatment cycle free of anti-EGFR therapy. Treatment was interrupted in case of disease progression.

**Efficacy.** Efficacy was assessed in terms of overall survival (OS), as well as objective response rate (ORR), progression-free survival (PFS). Despite a slight improvement observed under C+A treatment as compared to C-only, the difference was not significant, suggesting no real clinical benefit in combining these two drugs. However, signs of potential benefits were observed in patients without liver metastases; this observation requires further investigation in larger patient cohorts.

**Safety.** The toxicity profile was in line with that expected for these two drugs. No adverse events of grade >3 were observed and no treatment discontinuation were needed.

**Biomarker analysis – TMB and liver metastases to predict response to therapy.** The authors found that, despite the putative predictive role of high tumor mutational burden (TMB) in the response to immunotherapy, in these patients TMB was a negative prognostic factor of therapy efficacy, in both treatment arms (C+A and C-only), associated with limited response and poor clinical outcome. Therefore, the results indicate that other biomarkers of response should be identified. On the other hand, the absence of liver metastases appeared to correlate with better efficacy of C+A as compared to C-only (indeed, no differences in treatment efficacy were observed between C+A and C-only in patients with liver metastases).

**Molecular stratification of patients.** In order to obtain a better patient stratification and identify those patients more likely to benefit from either A+C or C-only therapy, the researchers performed a molecular analysis aimed at defining whether the presence of pathogenic mutations in genes (other than the RAS/BRAF V600E mutations that were already excluded at patient enrolment) of the EGFR pathway may contribute to improve patient stratification. Their results highlighted that 124/156 of the patients in the study cohort had no genomic alterations in KRAS, NRAS, BRAF, EGFR extracellular domain, PIK3CA exon 20, MAP2K1, AKT1, MET, PTEN, and ERBB2 genes, meaning that these 124 patients did not have alterations in genomic mechanism causing resistance to anti-EGFR drugs. Among these patients, ORR was 12%, as compared to 3% in the remaining 32 patients who exhibited genomic mutations in the genes related to anti-EGFR resistance. Clinical response in the two treatment arms, instead of the entire cohort, showed few partial responses among patients of the C-only treatment arm with no mutations in the genes of the EGFR pathway, while no response was observed among those with pathogenic mutations in these genes.

Therefore, the results highlighted that ORR, OS, PFS were different between C-only and C+A treatment arms if patients exhibited mutations in genes of the EGFR pathway, suggesting the value of molecular analyses (specifically, mutations in genes conferring resistance to anti-EGFR drugs) as predictors of response to anti-EGFR rechallenge among molecularly selected metastatic CRC patients.

*Reference:* Cetuximab rechallenge in molecularly selected metastatic colorectal cancer: the randomized CAVE-2 GOIM trial. Ciardiello D, Martini G, Boscolo Bielo L, Pietrantonio F, Raimondi A, Manca P, Pisconti S, Nisi C, Tortora G, Salvatore L, Sartore-Bianchi A, Siena S, Blasi L, Ongaro E, Zaniboni A, Pinto C, Antonuzzo L, Avallone A, Normanno N, Santabarbara G, Zampino MG, Berardi R, Cogoni A, Lotesoriere C, Latiano TP, Maiello E, Fazio N, Curigliano G, Bordonaro R, Troiani T, De Vita F, Martinelli E, Ciardiello F, Napolitano S; CAVE-2 GOIM study group. *Ann Oncol* 2025. doi: 10.1016/j.annonc.2025.12.014.

## Extracting information from medical images – what 4D-CT images can reveal.

Radiomics aims at exploiting medical images to gain information that cannot be revealed by the human eye and can guide therapeutic choices.

For lung cancer treatment, CT images are commonly acquired for planning radiotherapy treatment. 4D-CT is the acquisition of a series of CT scans “in time”, during patients’ breathing, to account for the movements associated with breathing in the representation of patient anatomy and for correcting localizing the tumor. That allows Radiation Oncologists and Medical Physicists to carefully plan radiotherapy, in order to spare as much as possible adjacent healthy tissue and focus on the tumor. Indeed, the tumor features captured by medical imaging (namely, the so-called radiomic features) can be extracted and used to collect critical information.

In a recent paper by Stefania Volpe et al., researchers headed by Barbara Jereczek-Fossa - Director of the IEO Radiotherapy Division and Full professor of Radiation Oncology at the University of Milan- focused on the methodological aspects of image acquisition in 4D-CT and image analysis, investigating how stable radiomic features remain during the different breathing phases, in order to standardize sufficiently the technique and find the optimal parameters to obtain radiomic features that can be used to guide radiotherapy planning.

“Beyond the specific results (available [here](#))-adds Stefania Volpe, first author of the paper- the study proposes a standardized methodological approach for analyzing radiomic features in 4D-CT images, which may support future research aimed at identifying imaging-based biomarkers for lung cancer studies. Although further studies in larger, multicenter patient cohorts are needed to validate the actual potential of the identified radiomic features, this work indicates that the 4D-CT images-based analysis is worth to be pursued. The study also provides an important methodological foundation for the MONDRIAN study, a research project funded by the *Associazione Italiana per la Ricerca sul Cancro* (AIRC) through the Next Generation Clinical Scientist 2022 call, aimed at developing advanced multi-omics models for patients with early-stage lung cancer treated with stereotactic radiotherapy.”



*Barbara Jereczek-Fossa*

## TELL ME MORE!

The final goal of the study was the exploitation of medical images acquired by MRI, CT, PET to collect quantitative, clinically relevant information to be used in radiotherapy treatment planning. Such quantitative information are named radiomic features and have been correlated with several disease-related characteristics, including differentiation, hypoxia, and DNA mutations, in a wide variety of cancers.

The study involved the retrospective analysis of CT images, clinical data, therapeutic information of 70 patients with early stage, non-small cell lung cancer (NSCLC) treated at IEO with stereotactic body radiotherapy with curative intent.

CT images were all acquired with the same criteria (same instrument and parameters, etc; an essential requirement for radiomic studies).

Radiomic features were almost all extracted from filtered images (to clear the noise). The analysis focused on understanding how much these feature changed during respiration. Despite the non-negligible level of variability among patients, a high number (>1000) of radiomic features could be extracted from the images. In addition to the inter-patient variability, time-dependent (so intra-patient) variability of radiomic features was also observed, that is, image features changed during breathing: Among over 1800 radiomic features analyzed, some radiomic features extracted from the images were influenced by breathing, others (about one-fifth) were not; overall, the majority of radiomic features were stable, only a minority of them was affected by breathing. radiomic features remaining stable despite breathing were potentially informative. Of note, image filtering (specific 3D and logarithmic filters) increased the number of stable, informative radiomic features, showing the usefulness of image filtering in radiomic feature extraction.

The study also provides a useful institutional dataset of 4D-CT images to be used for further analyses in the frame of multicenter collaborations; for instance, to assess whether the identified radiomic features are actually stable also with different acquisition protocols, image filtering parameters, algorithms for image reconstruction and so on.

By including in the analysis also the most recent clinical cases, researchers could increase the number of samples to be used in the analysis; however, that reduced the clinical information relative to the patients' follow-up, such as survival and disease progression after image-guided treatment, preventing, so far, the assessment of the prognostic/predictive value of the (stable) radiomic features identified. Additional studies with larger patient cohorts and longer clinical follow-up will determine whether the identified stable radiomic features are also associated with clinically relevant outcomes, such as survival or disease progression.



*Stefania Volpe*

### Radiomics in IEO.

Radiomics exploits diagnostic images -including MRIs, CTs, PET scans- to find properties of the images (radiomic features) that can be used as quantitative biomarkers, for prognostic/predictive purposes. Artificial intelligence (AI), with machine learning (ML)-and specifically deep learning- approaches is employed to handle the high number of images and variables (namely, features extracted from the images). Driven by technology progress, improvements in the context of medical imaging, and the developments in the AI field, radiomics is rapidly progressing.

In a precision oncology frame, IEO research aims at integrating AI with advanced imaging data and multi-omic analyses derived from the multi-omic profiling of tumor tissues and body fluids, in order to obtain diagnostic, predictive, disease

monitoring tools, that can support in therapy decision-making. For instance, recently, by exploiting the largest existing dataset of prostate cancer patients (including 949 patients), IEO researchers developed a ML model combining clinical, radiological, radiomic information for the non-invasive prostate cancer prognosis, selecting, among the different variables, those with greater predictive power (namely those with the greatest impact on the ML model ability to predict disease aggressiveness). The model demonstrated a remarkable efficacy in combining clinical, radiological and radiomic parameters, showing greater efficacy than other current clinical predictions in estimating disease aggressiveness in prostate cancer patients, thus providing a tool to support clinicians in accurately estimating disease aggressiveness before initiating any therapeutic approach. These findings highlight the potential of AI-driven radiomics to support clinicians in making more accurate and personalized therapeutic decisions.

### *The authors – Barbara Alicja Jereczek-Fossa and Stefania Volpe.*

**Barbara Alicja Jereczek-Fossa** is Director of the Radiation Oncology Department of IEO, full professor of Radiation Oncology at the Department of Oncology and Hemato-oncology of the University of Milan, and President of the European Society for Radiotherapy and Oncology (ESTRO). With a degree in medicine, a specialty in Cancer Radiotherapy from the National Institute of Oncology in Warsaw (Poland) and the University of Milan, and one in Clinical Oncology at the National Institute of Oncology of Warsaw (Poland), a PhD at the University of Gdansk (Poland), she continued her medical training at the Beatson Oncology Centre in Glasgow (Scotland) and at the Department of Radiation Oncology of the University of Turin, before joining IEO. Her clinical and research interests mainly focus on urological neoplasms, breast cancer, new fractionation protocols, innovation in radiation oncology (stereotactic radiotherapy, IMRT, IGRT, proton therapy, etc), and on multi-modal treatment approaches (including studies on organ preservation).

With a medical degree, **Stefania Volpe** completed her specialty in Radiation Oncology in 2019 at the University of Milan, and achieved a PhD in Computational Biology at the European School of Molecular Medicine (SEMM), focusing on methodological aspects of radiomics in early-stage non-small cell lung cancer. Currently a research associate at the Department of Oncology and Hemato-Oncology of the University of Milan, her clinical and research interests focus on quantitative approaches for precision radiation oncology, especially for lung and head and neck cancers. Since 2023, she is the principal investigator of the MONDRIAN study, funded by the Associazione Italiana per la Ricerca sul Cancro (AIRC), on multi-omic modeling for the prediction of response in early-stage non-small cell lung cancer treated with stereotactic body radiotherapy.

*Reference: Stable or not? unraveling the reliability of radiomic features in 4d-computed tomography in early-stage non-small cell lung cancer. Volpe S, Gaeta A, Vincini MG, Zaffaroni M, Mastroleo F, Raimondi S, Pepa M, Isaksson LJ, Cremonesi M, La Torre D, Guckenberger M, Bellerba F, Orecchia R, Gandini S, Jereczek-Fossa BA. Clin Transl Oncol 2026. doi: 10.1007/s12094-026-04311-x.*

## **Cellular avatars to study brain metastases – Modelling breast cancer colonization of the brain.**

Despite the remarkable advances in cancer treatment, the metastatic disease still remains a significant challenge. One of the main issue is linked to the limited mechanistic understanding of the metastatic cascade, namely the ensemble of processes inducing cancer cell exit from the primary tumor, intravasation and, through the bloodstream, the colonization of a distant organ. This is partly due to the lack of adequate disease models, which can be both easily manipulated and faithfully recapitulating the patients' main molecular features.

In a recent paper by Faletti et al., by in vitro culturing patient-derived breast cancer brain metastases, researchers headed by Giuliana Pelicci -PI at the department of experimental oncology of IEO- developed the “avatars”, namely a preclinical system maintaining the main features (in terms of mutational and gene expression profile) of the original patients' metastases, thus providing a useful (in vitro and in vivo) tool to explore the mechanisms of metastatic dissemination. By exploiting these avatars, the authors identified a specific subpopulation of metastases-initiating cancer stem cells (the MICs), featured by stemness traits and a distinct set of adhesion molecules, playing a key role in metastatization and thus representing a clinically relevant therapy target.

The results of their molecular analyses showed, on one side, the potential of these culture systems as useful preclinical models to study the disease; on the other side, they demonstrated that MIC specificity for the brain is likely mediated, at least in part, by MIC preferential adhesion to cells of the brain-blood barrier, mediated by the expression of specific adhesion molecules. Brain metastases represent a significant hurdle in patient treatment, due to the poor response to systemic therapies, mainly due to issues related to drug delivery across the blood-brain barrier. The development of such “avatars”, recapitulating the main features of patients’ metastases, offer a useful tool to test different drugs, in order to define the most effective treatment.

### Patient avatars in IEO.

The employment of patient avatars is increasing in oncology, due to their usefulness in the context of mechanistic and translational studies. In the frame of the “IOLANTHE” study, IEO researchers, in collaboration with Mario Negri Institute, Sapienza University, Humanitas Research Hospital, aim at using the patient avatars, namely preclinical culture models of ovarian cancer derived from patients’ cancer cells, as “biological replicas” of the tumor, recapitulating the molecular features of each patient’s tumor, in order to test different drugs and therapy combinations and predict patients’ response to a given therapy, and identify the most effective approaches.

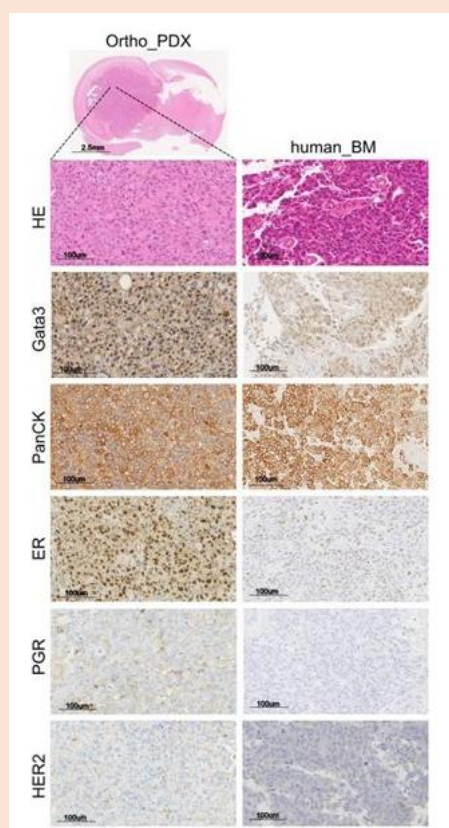
### TELL ME MORE!

Firstly, the authors assessed the presence of cancer stem cells (CSCs) within the breast cancer-derived brain metastases using functional and molecular approaches. CSCs were identified based on their ability to form tumor spheres, reflecting their self-renewal capacity, and through the expression of established stemness markers. Importantly, cultures/tumor spheres maintained the key molecular (genomic and gene expression) features of the original tumors.

The further characterization of one (PR60) of these patient-derived tumor spheres demonstrated the robust in vivo metastatization ability of these cells, either injected intracardially (to simulate dissemination in the bloodstream), intracranially, or intra-mammary (intra-nipple) in recipient mice. These cells preferentially metastasized to the brain (forming both micro- and macro- metastases). In-depth molecular characterization revealed that 1) the newly formed in vivo tumors closely resembled the original patient metastases; 2) the metastatization route (that is, intracardiac/bloodstream, intracranial, intra-nipple injection) did not significantly alter the global gene expression profile, but CSCs underwent major changes during organ colonization; finally, 4) metastases formed in

the brain were different from those formed in other organs, such as the bone (meaning that once reached the distant organ, tumor cells acquired specific traits, adapting to the microenvironment of the target organ).

Moreover, they found a higher expression level of factors involved in vascular interaction as well as neuronal markers, indicating that the brain microenvironment shaped the gene expression profile of MICs. Importantly, their analyses uncovered specific features of tumor cells crossing the blood-brain barrier to colonize the brain, including resistance to shear stress (which is critical to survive in the bloodstream), expression of adhesion molecules (such as CD44, VCAM1, MUC1, etc) and stem-related genes, as well as activation of pathways known for being critical to sustain stemness and metastases, such as epithelial-to-



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mesenchymal transition and TGFbeta signaling.

Finally, drug sensitivity analyses revealed that CSC-enriched cultures (tumor spheres) closely mirrored the therapeutic resistance observed in the corresponding patients. Both tumor spheres and original patient-derived breast cancer brain metastases exhibited activation of pathways linked to resistance against drugs commonly used for the treatment of breast cancer, as well as reduced sensitivity to a range of compounds, including drugs targeting the nervous system, indicating that these systems may represent relevant preclinical models of brain metastases for drug sensitivity testing.

*Reference: Deciphering the Role of Cancer Stem Cells in Breast Cancer Brain Colonization Using a Novel Patient-Derived Model. Faletti S, Richichi C, Osti D, Ceccacci E, Bertalot G, Cerutti C, Giardina G, Marinaro A, Costanza B, Gambino V, Zaccheroni E, Tosoni D, Filippone MG, Del Corvo M, Zhan Y, Gravina T, Corà D, Patanè M, Pollo B, Giovanna Jodice M, Pece S, Weksler BB, Romero IA, Couraud PO, Munzone E, Del Bene M, DiMeco F, Pelicci G. Adv Healthc Mater 2026. doi: 10.1002/adhm.202505789*

## Molecular mechanisms ensuring genome integrity at cell division

During cell division, chromosomes are partitioned between daughter cells. This process is crucial for cell physiology and, therefore, finely regulated by a complex molecular machinery ensuring that the two sister chromatids are completely separated before segregation; that includes removing those structures constituted by intertwined DNA segments that, during DNA replication, often remain physically linked. If these structures are not resolved, sister chromatids are not fully separated, and genome instability occurs. Genomic instability is one of the main features of tumors, associated with bad prognosis and chemoresistance. Indeed, genomic instability confers an advantage to cancer cells, inducing changes at the genomic level that endow cancer cells with the ability to adapt, survive, proliferate, and support tumor growth.

In a recent study, IEO researchers coordinated by Rosella Visintin-PI at the department of experimental oncology of IEO- unraveled the molecular mechanisms responsible for the correct disentanglement of such DNA structures before cell division, contributing to maintain genome integrity. In particular, their results showed the involvement of Cdc5 (polo-like kinase) and Cdc14 (phosphatase) proteins in this process which, along with their (known) work in regulating the mitotic spindle (a critical structure for cell division), modulate the resolution of these DNA structures- thus ensuring genome integrity- through the post-translational modification (namely, phosphorylation and, at a lesser extent, SUMOylation) of Top2 protein, influencing its localization and activity. These results allowed to find a link (through the coordinated-though opposed- activity of Cdc5 and Cdc14) between the regulation of cell division and the maintenance of genome integrity, which is a crucial mechanism in cell physiology and critical against cancer development.

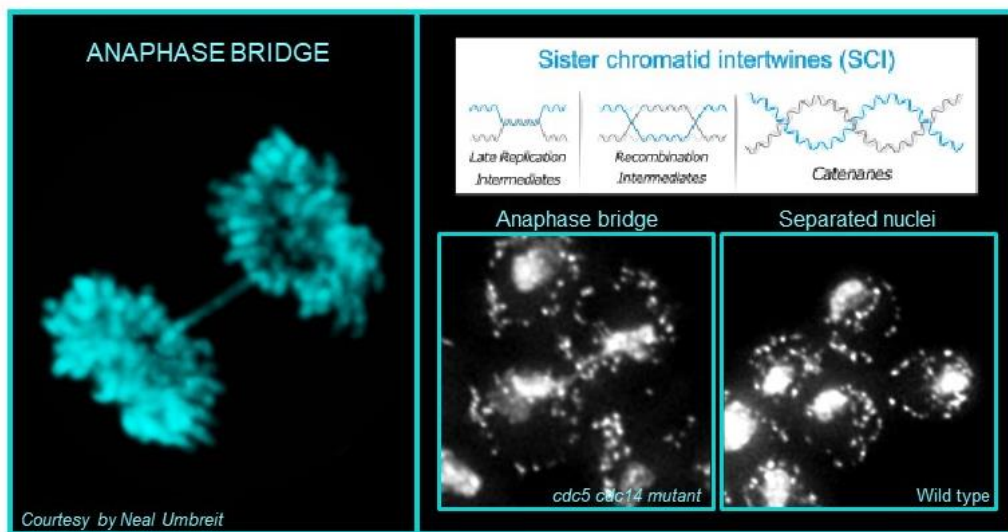
While being a byproduct of DNA replication, the authors speculate that persistence of these DNA structures linking sister chromatids may represent an additional regulatory mechanism through which the cell ensures that a critical mechanism is efficiently carried out, with the right timing, preventing separation when the

### Genomic instability and cancer.

IEO researchers previously demonstrated, and identified the underlying mechanisms, that not only does genomic instability induce aneuploidy, but also aneuploidy - namely the altered number of chromosomes due to errors in the mechanisms regulating chromosome segregation in daughter cells at cell division- can in turn induce genomic instability, eliciting continuous changes at the genomic level enabling cancer cell adaptation and survival. They also demonstrated that aneuploidy is one of the mechanisms endowing cancer cells with the ability to resist chemotherapy, by randomly inducing changes in the expression of some proteins allowing cancer cell to adapt in hostile conditions -such as therapy- and survive. Moreover, one of the main consequences of genomic instability is the formation of small structures inside the cells containing fragments of chromosomes enveloped in defective membranes - the micronuclei. Rupture -and ensuing collapse- of micronuclei exposes the DNA contained inside the micronuclei, which gets further damaged, acquires abnormalities and contributes to genomic instability. IEO researchers have previously described the mechanisms leading to micronuclear rupture, involving p62 protein, demonstrating that p62 plays a key role in micronuclear integrity or collapse, both in untransformed and tumor cells, and that the high levels of p62 correlate with a worse prognosis of gastric cancer patients.

time is not right. Yet, if left unresolved, genome instability occurs, making the Cdc5-Cdc14-Top2 protein team a key player in the maintenance of genome stability.

“By using mutant versions of Cdc5 and Cdc14, -explains Rosella Visintin- we demonstrate that both regulators are required for efficient sister chromatid separation. In their absence, chromatids remain physically connected and nuclear division cannot be completed. Importantly, this defect is largely attributable to persistent DNA structures called catenanes rather than impaired cohesin removal or other recombination-associated intermediates. Notably, while the specific regulatory circuitry differs across species, the requirement for Topoisomerase II-mediated decatenation and its coordination with mitotic progression appears to be conserved across eukaryotes. Failure to resolve catenanes compromises chromosome segregation and promotes chromosome instability, a key driver of tumor heterogeneity and therapeutic adaptation. By defining how decatenation is functionally integrated with mitotic control in vivo, our work refines our understanding of the fundamental principles that safeguard chromosomal integrity in proliferating cells.”



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## TELL ME MORE!

The authors dissected the key molecular mechanisms underlying the correct cell division and ensuring genome integrity, by exploiting, instead of an in vitro system, a simpler, in vivo model system: yeast. In particular, they used mutants lacking Cdc5 and Cdc14 proteins, which undergo cell cycle arrest due to a number of defects at the level of the spindle and at the level of such structures constituted by intertwined DNA segments. Their analysis revealed that cells lacking Cdc5 and Cdc14 proteins failed to complete nucleus division and sister chromatids did not achieve full separation; that did not depend on cohesin protein but it was rather due to the persistence of DNA structures linking sister chromatids, named catenanes. Cdc5 and Cdc14 worked together to disrupt these DNA structures and separate sister chromatids, both in metaphase and anaphase. Notably, while spindle elongation facilitated disruption of these DNA structures, it was not sufficient to separate sister chromatids in the absence of Cdc5 or Cdc14.

Mechanistically, the resolution of these DNA structures linking sister chromatids required Cdc5- and Cdc14-mediated localization of Top2 protein, the enzyme directly responsible for DNA structures resolution. Specifically, Cdc5 (predominantly in metaphase) and Cdc14 (mainly in anaphase) together modulated phosphorylation (Cdc5) and dephosphorylation (Cdc14) of Top2 protein, at the level of specific aminoacidic residues in the C-terminal domain of the protein. Therefore, phosphorylation-dephosphorylation cycles (along with SUMOylation, though modestly), resulting from the coordinated activity of Cdc5 and Cdc14, finely controlled Top2 activity, correct separation of sister chromatids, faithful chromosome segregation, and genome integrity.

### Why must DNA catenanes be removed?

DNA catenanes arise as an unavoidable consequence of replication: as sister chromatids are synthesized, their double helices frequently become topologically intertwined. If these physical links persist into anaphase, sister chromatids cannot fully separate despite cohesin removal and spindle elongation. The resulting tension can generate chromatin bridges, DNA breakage, and structural chromosome instability. Unlike cohesin-mediated cohesion, which is resolved through regulated proteolysis, catenanes represent a DNA topology problem that requires enzymatic decatenation by Topoisomerase II. Timely resolution of these intertwines is therefore not a secondary refinement of mitosis but a prerequisite for faithful chromosome segregation, ensuring that mechanical forces act only after—or in strict coordination with—the resolution of DNA topology. The fact that the cell deploys shared mitotic regulators to control both spindle dynamics and Topoisomerase activity underscores a highly integrated organizational principle: mechanical force and DNA topology are not independent processes, but components of a single, regulatory program.

*Reference: Safeguarding genome integrity: Polo-like kinase Cdc5 and phosphatase Cdc14 orchestrate Topoisomerase II-mediated catenane resolution in mitosis. Massari LF, Finardi A, Visintin C, Calabrese E, Dondi A, Visintin R. Nucleic Acids Res 2026. doi: 10.1093/nar/gkaf1509.*

## Exploring the molecular mechanisms associated with progression from myelodysplastic syndrome to leukemia.



*Veronica Vallelonga, Francesco Gandolfi, Serena Ghisletti*

The Myelodysplastic syndrome (MDS)-a clinical condition characterized by alterations in hematopoiesis- is associated with an increased risk of acute myeloid leukemia (AML). Several studies have focused on the identification of the genomic traits predisposing patients to progress from mild MDS to aggressive MDS, and finally AML; however, to date, the molecular mechanisms underlying disease progression from mild MDS to aggressive MDS and finally AML are largely unknown.

In a recent study by Vallelonga, Gandolfi et al., in order to identify the mechanisms driving progression of MDS from a subclinical condition to overt leukemia, by using samples isolated from MDS and AML individuals, researchers co-coordinated by Serena Ghisletti-researcher at the department of experimental oncology of IEO and at the University of Milan- and Matteo Della Porta-Head of the MDS and Leukemia Unit at the Humanitas Research Hospital-, described the transcriptional alterations in patients with MDS at low risk of disease progression, in high risk MDS and in AML patients, and explored how such alterations functionally influenced disease progression.

By identifying, through their analyses, specific transcriptional patterns in the different stages of MDS, they found key mechanisms-such as immune and inflammatory activation and heme metabolism- and factors-such as the PU.1 transcription factor- of disease progression. Indeed, these studies suggest that interfering with the changing localization of PU.1 occurring during disease progression may offer new therapeutic approaches to arrest MDS progression and prevent AML onset.

## TELL ME MORE!

**Activation of immune response/inflammatory processes during disease progression.** Through the characterization of transcriptional alterations occurring during disease progression in (disease-initiating CD34+) bone marrow progenitors from 209 MDS and 148 AML patients, the authors found that disease progression (from low risk to either high risk MDS or AML) was characterized by changes in heme metabolism and complement activation, while progression from high risk MDS to AML was characterized by increased inflammatory processes.

Interestingly, among the low risk patients (including both individuals that progress and those that do not), they found a subset displaying upregulation of factors involved in inflammatory processes and, despite the high level of inter-cellular heterogeneity, they identified some of the specific transcription factors involved, which resulted to be mainly transcription factors associated with immune response and activation of inflammatory processes.

**Cell composition.** Whole bone marrow samples isolated from patients with low risk MDS progressing to AML were enriched in activated T and NK cells; moreover CD34+ (hematopoietic stem and progenitor) cells displayed higher numbers of mutations in the SRSF2 gene (a known factor of adverse prognosis in MDS which, in their samples, affected splicing, especially of genes involved in immune processes). Importantly, patients having this cell subset had higher risk of disease and reduced overall survival.

**The PU.1 transcription factor plays a main role in the functional processes associated with disease progression.** In low risk MDS cells, the PU.1 transcription factor was associated with the activation of immune and inflammatory response; indeed, its localization on the genome changed during disease progression, and different PU.1-regulated regions became activated.

**Functional effect of the altered PU.1 activity during disease progression.** PU.1 redistribution during disease progression resulted in the differential activation of genes involved in immune response and inflammation. Consistently, in vitro pharmacological inhibition or CRISPR-mediated knock out of PU.1 led to the downregulation of many inflammatory genes, demonstrating that through the regulation of specific inflammatory-related transcriptional programs, PU.1 modulated processes involved in MDS progression (specifically, in low risk MDS).

Furthermore, while not having effect on cell viability, interfering with PU.1 activity affected proliferation of both MDS and AML cells, inducing differentiation.

Importantly, PU.1 inhibition did not significantly affect proliferation of progenitor cells isolated from healthy patient donors.

*Reference: PU.1-Activated Genomic Regions Define Low-risk MDS Subsets Characterized by Immune Dysregulation and Disease Progression. Vallelonga V, Gandolfi F, Zampini M, Riva E, Maggioni G, Ventura D, Saba E, Termanini A, Polletti S, Prosperini E, Crisafulli L, Campagna A, Ferrari I, Pinocchio N, Todisco G, Pedretti S, Calvi M, Di Vito C, Mavilio D, Mitro N, Ficara F, Della Porta MG, Ghisletti S. Blood 2026. doi: 10.1182/blood.2025030760.*

## In the right place at the right time – NUMB localization affects cells of the microenvironment.

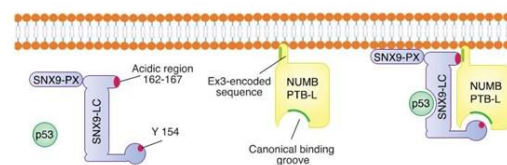
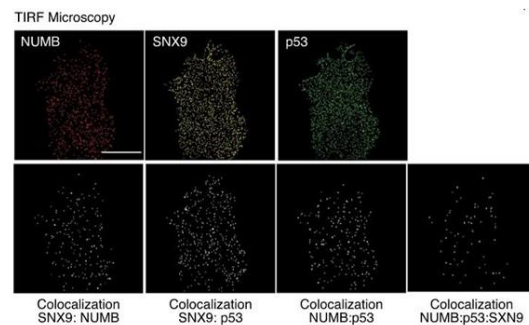
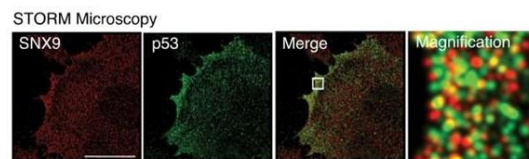
NUMB is a well-known tumor suppressor; it regulates endocytosis (thereby antagonizing the activity of the NOTCH receptor), and modulates degradation/stabilization of p53 protein (through its interaction with the MDM2 protein), ultimately regulating stem cell division. In the stem cell compartment, NUMB loss results

in the shift from asymmetric to symmetric stem cell division, thus affecting the fate of the daughter cells, ultimately modifying the expansion of the stem cell pool and contributing to tumorigenesis. Indeed, IEO researchers have previously demonstrated, both in breast and in bladder, that NUMB loss correlates with tumor aggressive behavior.

In a recent paper by Cacciatore, Basile, et al., researchers coordinated by Pier Paolo Di Fiore –Group leader at the Department of Experimental Oncology of IEO and professor at the University of Milan– and Ivan Colaluca –senior researcher at IEO–, explored in detail the function of the NUMB isoform containing a specific protein region- encoded by an alternatively spliced exon, exon3-, revealing its main role in protein-protein, and protein-lipids interactions. This protein segment controls NUMB localization at the plasma membrane, enabling and mediating the interaction of NUMB with SNX9 (a protein known for its involvement in endocytosis and previously implicated in breast cancer invasion and metastases); the NUMB-SNX9 complex in turn binds p53 protein and, embedded in small vesicles (called exosomes), is secreted in the extracellular microenvironment. Once secreted, p53 is taken up by other cells in the microenvironment, inducing phenotypic changes.

Through these experiments, the authors uncovered a novel role of NUMB isoforms containing exon 3, regulated by its subcellular localization, and exerted by means of the interaction, within a multiprotein complex, with p53 and SNX9. Through the described mechanism, NUMB affects both the donor cells, releasing the p53-containing extracellular vesicles (cell autonomous effect), and the cells receiving p53-containing vesicles (non-cell-autonomous effect): Indeed, the formation of the NUMB-p53-SNX complex at the plasma membrane allows for the packaging of this protein complex into vesicles that, once released, on one side, reduce the intracellular levels of p53, on the other side, affect cells of the microenvironment.

What is the pathological relevance of this mechanism? By demonstrating, for the first time, that non-mutated p53 can be released in the extracellular milieu, they revealed a mechanism deployed by cells to preserve a tumor-suppressive, p53-mediated, environment, which, in certain situations, might otherwise initiate tumorigenesis.



Adapted from Cacciatore, Basile et al. (an open access article under the CC BY license.)

## TELL ME MORE!

**The interactome of the NUMB isoform containing the exon3-encoded region.** Through proteomic analyses, the authors identified proteins interacting with the exon3-coded protein sequence of NUMB. SNX9 (but not the related proteins SNX18 or SNX33) resulted to be the main specific NUMB interactor, together with p53. Importantly, NUMB and p53 specifically interacted *through* SNX9. Moreover, NUMB-SNX9 interaction occurred only with the protein isoform containing the exon3-encoded region (as the protein isoform lacking the exon3-encoded region did not interact with SNX9).

**What are the aminoacids involved in NUMB-SNX9 interaction?** The aminoacidic stretch between residues 101 and 183 of SNX9 was required for an optimal NUMB-SNX9 binding, and a specific residue of NUMB (F162), outside of the exon3-encoded region, was critical for the NUMB-SNX9 interaction; R69/K70/K73/K78 residues in the exon3-encoded region, while not crucial for NUMB-SNX9 interaction, contributed to stabilize the protein-protein binding (indeed, when mutated, NUMB-SNX9 interaction was weaker but not

prevented).

**The subcellular localization of NUMB containing the exon3-encoded region is required for NUMB-SNX9 interaction.** How come that exon3-encoded sequence is needed for NUMB-SNX9 interaction, but the most important residue involved in the interaction is outside of this region? The authors showed that the subcellular localization of NUMB at the plasma membrane, influenced by the presence of the exon3-containing region of the protein, was critical for NUMB-SNX9 interaction. Indeed, while the NUMB containing exon3-encoded region was localized at the plasma membrane, the protein isoform lacking the exon3-encoded region was instead in the cytoplasm. When plasma membrane localization of NUMB was lost (due to mutations in R69/K70/K73/K78 residues or the lack of exon3-encoded region), NUMB-SNX9 interaction was lost, despite the presence of the F162 residue mediating this protein-protein interaction. Interestingly, while purified proteins interacted anyway, even if the exon3-encoded sequence was altered or lacking, in cells they did not, due to exon3-regulated NUMB mislocalization. Therefore, the exon3-encoded sequence of NUMB, on one side, provided a low-affinity binding surface for SNX9; on the other side, it localized NUMB at the plasma membrane, thus sustaining the interaction with SNX9.

**How does exon3-encoded region of NUMB interact with the membrane?** By exploiting liposomes as a model system, they analyzed the binding of exon3-containing NUMB, exon3-lacking NUMB, SNX9, to the lipid membrane. They found that the exon3-encoded region of NUMB, in addition to contributing to the NUMB-SNX9 interaction as shown before, bound the lipid membrane; indeed, the exon3-lacking protein did not. When both NUMB and SNX9 were present, the binding of the protein complex to the membrane was stronger.

**Was the NUMB-SNX9-p53 complex affected by the plasma membrane?** p53 and exon3-containing NUMB both independently bound the lipid membrane; the binding was increased by SNX9. In particular, SNX9 bound p53 *only* at the membrane, indicating that the three proteins colocalized, at the plasma membrane, and the protein-protein interaction required the membrane, probably inducing a conformational change in SNX9 that exposed the protein segment interacting with p53.

**At the plasma membrane, p53 is packaged inside extracellular vesicles.** p53 is usually in the cell nucleus. When localized at the plasma membrane, through the interaction with NUMB and SNX9, it got packaged into extracellular vesicles (EV). p53 packaging inside EVs required both SNX9 and NUMB. Upon release, p53-containing EVs affected both donor and recipient cells. In donor cells, secretion of p53-containing EVs reduced the intracellular levels of p53 and its target proteins (cell-autonomous effect), ultimately affecting cell cycle progression and DNA replication. In recipient cells, donor-derived p53/SNX9/NUMB-containing EVs resulted in increased levels of the target proteins and cell proliferation (non-cell autonomous effect), indicating that wt p53 secretion, embedded in EVs, provided p53 activity to recipient cells, through a non-cell-autonomous mechanism.

*Reference: Endocytic Control of Cell-Autonomous and Non-Cell-Autonomous Functions of p53. Roberta Cacciatore, Andrea Basile, Stefano Freddi, Irene Schiano Lomoriello, Carlo Ribelle Zucca, Giuseppe Ciossani, Luigi Scietti, Alessandro Cuomo, Simona Ronzoni, Simone Pelicci, Mario Faretta, Elena Zaccheroni, Giuliana Pelicci, Vittoria Matafora, Angela Bachi, Rosalind Helen Gunby, Salvatore Pece, Sara Sigismund, Letizia Lanzetti, Ivan Nicola Colaluca, Pier Paolo Di Fiore. Adv Sci (Weinh) 2026. doi: 10.1002/advs.202513765).*

## Altered protein trafficking inside the cell in breast cancer progression.

Cell functioning is the result of a number of intertwined processes, which must be finely regulated. The coordinated activity of several factors ensures the correct cell behavior. The altered expression level or activity of these factors can affect the correct cell functioning, inducing a pathological state. TBC1D22B and TBC1D22A are two proteins localized at the internal membrane of the cell (at the Golgi apparatus), whose altered expression level has been previously correlated with poor breast cancer patient prognosis.

In a recent paper, the authors, including IEO researchers Sara Sigismund-Group leader at the department of experimental oncology of IEO and professor at the University of Milan-, Linda Andreoli, Stefano Freddi,

Bronislava Matoskova, Amir Fardin, Alessandro Cuomo, defined the role of TBC1D22B protein in cell physiology and breast cancer, and described the underlying molecular mechanism.

They demonstrated that TBC1D22B protein, localized at the Golgi apparatus, regulates protein trafficking inside the cell (specifically, from the endoplasmic reticulum-ER- to the Golgi) by acting on its target proteins (that is, acting as a GAP-GTPase-activating protein- on the target protein RAB1B). In luminal breast cancer patients, TBC1D22B overexpression, which correlates with poor patient prognosis, by switching off its target protein, could delay the transport of key proteins (from the ER to the Golgi), resulting in altered physiological cell processes and tumorigenesis.

The alteration of this mechanism may affect the secretion of specific cell factors involved in cancer progression -such as cytokines, enzymes, and glycoproteins- that, by modifying the tumor microenvironment, may end up in promoting cancer progression and evolution into a metastatic disease. Therefore, these results propose TBC1D22B as a putative novel target in aggressive luminal breast tumors.

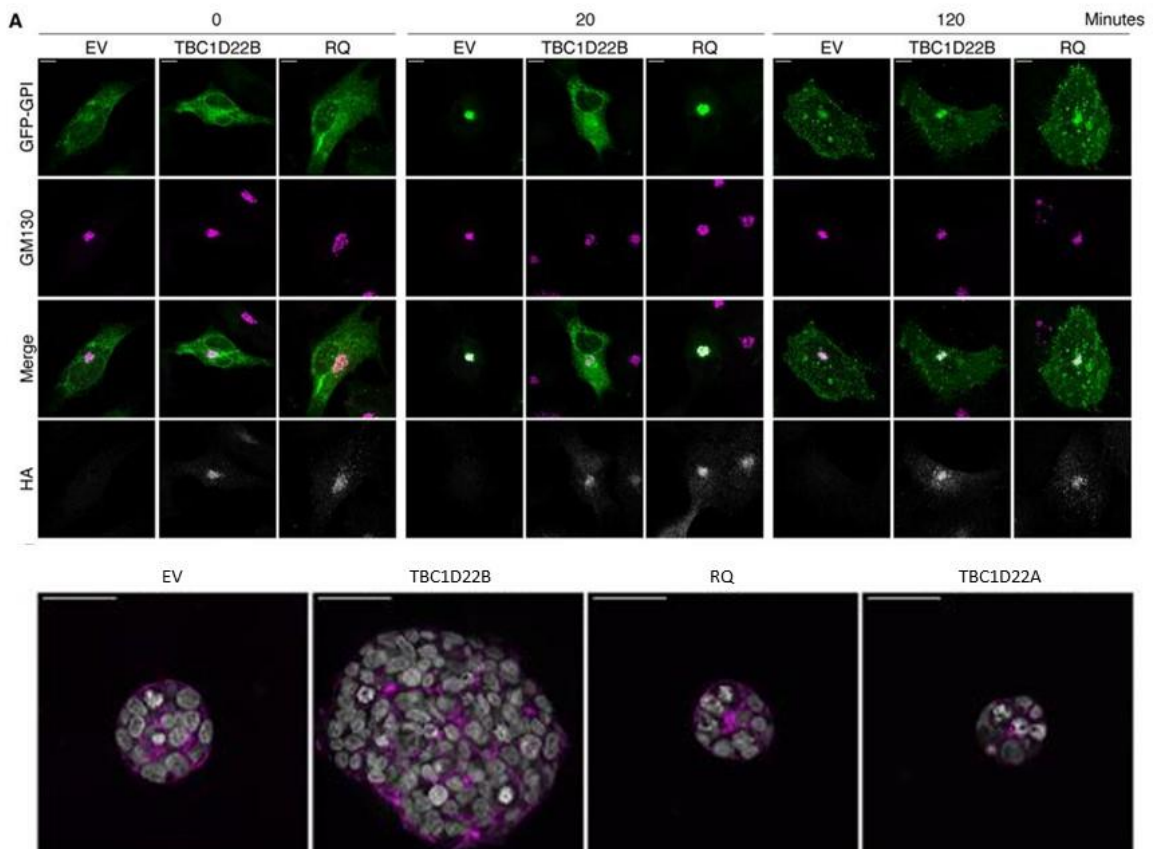


Figure adapted from Martino et al., 2025 (an open access article under the CC BY license.)

## TELL ME MORE!

Firstly, by a proteomic approach (proximity labeling followed by mass spectrometry and co-immunoprecipitation), the authors identified the proteins interacting with TBC1D22B. These proteins were part of cell pathways involved in ER-to-Golgi transport and Golgi vesicle transport, in line with the known localization of TBC1D22B protein at the Golgi membrane, as well as endosome transport, cytoskeleton organization, cell-cell and cell-matrix interactions.

Functional analyses (through the RUSH system) of the identified TBC1D22B-interacting proteins revealed that TBC1D22B influenced protein movement from the ER to the Golgi; in particular, TBC1D22B overexpression delayed ER to Golgi transport. Conversely, TBC1D22B (but not TBC1D22A) silencing accelerated ER-to-Golgi TBC1D22B-mediated protein translocation, indicating that, physiologically, TBC1D22B works as an inhibitor of ER-to-Golgi transport.

Mechanistically, TBC1D22B impaired ER-to-Golgi transport through its GAP activity; namely, by switching off the activity of some RAB GTPases. Indeed, silencing of the RAB GTPase target of TBC1D22B resulted in delayed ER-to-Golgi transport, mirroring what was observed upon TBC1D22B overexpression. The effect was

particularly evident upon RAB1B silencing, demonstrating that TBC1D22B inhibits ER-to-Golgi transport through RAB1B inactivation. Notably, GAP activity of TBC1D22B on RAB1B was lost in TBC1D22B mutants lacking GAP activity, further confirming that TBC1D22B functions as a GAP on RAB1B, and supporting the role of TBC1D22B in the RAB1B-dependent regulatory mechanism of ER-to-Golgi trafficking.

Considering their previous results, showing that TBC1D22B expression level is a predictor of poor prognosis in luminal breast cancer, is the identified mechanism relevant in breast cancer tumorigenesis? The authors observed that TBC1D22B (but not TBC1D22A) overexpression conferred proliferative advantage to breast cancer cells. Moreover, analyses of clinical data revealed that tumors expressing high levels of TBC1D22B exhibited a different gene expression profile as compared to low-TBC1D22B-expressing tumors, suggesting that TBC1D22B may play a key role in driving the gene expression changes linked with poor disease prognosis of luminal breast cancer patients. Consistently, TBC1D22B overexpression (in breast cancer cell lines) deeply altered the cell gene expression profile, mirroring the changes observed in primary tumors and highlighting its oncogenic potential. The genes affected by TBC1D22B expression were involved in pathways linked to extracellular matrix organization and cell motility/adhesion, and many coded for secreted proteins, according to TBC1D22B role in protein trafficking and secretion.

Finally, they identified a TBC1D22B-regulated signature, validated in METABRIC and TCGA patient cohorts, of genes whose expression level changed in a coordinated fashion, was linked to extracellular matrix remodeling and adhesion, and whose repression may be mechanistically linked to poor clinical outcome of TBC1D22B-overexpressing luminal breast cancer patients.

*Reference: TBC1D22B Regulates ER-to-Golgi Trafficking via RAB1B Inactivation and Promotes Oncogenic Programs in Breast Cancer. Flavia Martino, Mariadomenica Lupi, Alessandra Murabito, Fabio Bedin, Giulia Villari, Linda Andreoli, Stefano Freddi, Bronislava Matoskova, Rosa Pennisi, Stella Fontana, Amir Fardin, Gaele Boncompain, Franck Perez, Federico Bussolino, Alessandro Cuomo, Sara Sigismund, Letizia Lanzetti. Adv Sci (Weinh) 2025. doi: 10.1002/advs.202502269.*

## **Extracellular vesicles between chromosomal instability and cancer cell migration.**

Triple-negative breast cancer (TNBC) is a highly aggressive breast cancer subtype whose prognosis is frequently poor. TNBC is characterized by chromosome instability (CIN) which in turn correlates with tumor progression. CIN has been associated with alterations in the generation and content of extracellular vesicles (EVs), and EVs are known to be involved in cell-cell communication and in shaping the microenvironment by the cells.

How does mechanistically CIN affect the generation, release and content of EVs, remodeling the microenvironment and ultimately modulating tumor progression?

In a recent study, researchers, including Stefano Santaguida -Group leader at the Department of Experimental Oncology of IEO and professor at the University of Milan-, explored the mechanisms underlying CIN-modulated secretion and content of EVs and how this functionally affects the microenvironment and tumor progression, in TNBC models.

By comparing EVs released by tumor cells with high CIN vs low CIN, and the effects of these EVs on other cells, the authors found that cells with high CIN release more EVs as compared to those with low CIN; these EVs in turn promote cancer cell ability to migrate and invade surrounding tissues, the key aspects in metastatic dissemination. The effects of EVs were particularly evident in cells with low CIN. They also identified a protein (EFEMP1), enriched in EVs released by cells with high CIN, modulated by STAT, critically involved in promoting cell migration, and dissected the underlying mechanism.

Therefore, their experiments revealed an EV-mediated mechanism through which high CIN cancer cells modulate the microenvironment, promoting migration and invasion (metastatic dissemination), identifying a key factor -the EFEMP1 protein- that may represent a new therapeutic target against metastatic dissemination.

## TELL ME MORE!

First, through the quantification of a known marker of EVs (CD63), the authors compared EVs released from TNBC cell lines (BT549 and MDA-MB-231) with high CIN (induced by the treatment with MPS1 inhibitor) vs low CIN, showing a higher release of EVs by cells with high CIN, with no change in EV size.

When recipient cells took up EVs released by high CIN cells, their migration and invasion ability was enhanced; cell proliferation, instead, was not affected. Conversely, cells releasing EVs exhibited lower proliferation, migration and invasion capability, suggesting that while CIN impairs proliferation and migration ability of cancer cells, it promotes the release of EVs that foster migration of neighboring cancer cells. When intracellular trafficking was disrupted (by RAB27A silencing), EV-induced increased migration was impaired, confirming that the increased migratory ability observed in recipient cells (namely cells taking up EVs secreted by high CIN cells) was indeed due to the EVs. Importantly, the same effect was seen in other cancer (colorectal cancer) cells, but not in non-transformed cells.

Next, they explored the underlying molecular mechanisms. The analysis of EV content from high and low CIN cells revealed, in high CIN-derived EVs, an enrichment in cell adhesion proteins and, in particular, a high abundance of Fibulin3/EFEMP1, known to be involved in migration. EFEMP1 was more expressed in high CIN cells and in EVs from high CIN cells than in EVs from low CIN cells.

To further investigate the role of EFEMP1 protein, they manipulated its expression in EVs-generating high CIN cells: EFEMP1 overexpression and silencing respectively promoted and impaired migration and invasion, both in the EV-releasing cells, and in the recipient cells.

Gene expression analysis of recipient cells stimulated with EFEMP1-expressing EVs or EFEMP1-lacking EVs unraveled a number of differentially expressed genes, including genes involved in cell migration/invasion, such as genes implicated in cell adhesion and epithelial-to-mesenchymal transition (EMT), indicating that CIN-induced release of EVs containing EFEMP1 protein induces, in the recipient neighboring cells, EMT and cell migration.

In-depth mechanistic analyses showed that STAT1 modulates EFEMP1 protein expression, and the release of EFEMP1-containing EVs fosters recipient cell migration. Indeed, STAT1 loss impaired EVs-induced cell migration.

To functionally analyze the consequences on migration and invasion of EFEMP1-containing EVs (that is, isolated from EFEMP1-expressing high CIN cells), they used zebrafish models. Migration of cells stimulated with EFEMP1-overexpressing EVs was increased, as compared to (control) EVs expressing normal levels of EFEMP1; spreading of cells stimulated with EFEMP1-lacking EVs was instead decreased, indicating that EFEMP1-expressing EVs can modulate cancer cell spreading in vivo.

Finally, in line with their results-underlining a causal correlation between CIN and EFEMP1 expression-, analyses of public datasets of human cancers revealed a correlation between EFEMP1 levels and aneuploidy, highlighting the clinical relevance of their findings. Moreover, patient stratification by EFEMP1 expression unraveled a correlation between EFEMP1 expression and clinical outcome, suggesting that EFEMP1 may represent a novel therapy target against metastatic dissemination.

### *The authors – Stefano Santaguida.*

Stefano Santaguida is Associate Professor of Molecular Biology at the University of Milan and Group Leader at the Department of Experimental Oncology of the European Institute of Oncology. After a PhD at IEO, focusing on the molecular mechanisms underlying the functioning of the spindle assembly checkpoint, a surveillance mechanism ensuring the fidelity of chromosome segregation, in human cells, he moved to the US for his post-doctoral studies, at the Massachusetts Institute of Technology (MIT, Cambridge, US). The main focus of his work at MIT was on several aspects of the consequences of aneuploidy on cellular functions. To shed light on how changes in chromosome number influence cell physiology, he set up a powerful and tunable system that allow to study the immediate consequences of aneuploidy in human cells. His studies started to uncover how an unbalanced chromosome number affects the cell's proteome and provided accurate information on the immediate consequences of aneuploidy on genome integrity. In his lab at IEO, he aims to provide a molecular characterization of the pathways deregulated in aneuploid cells, with the hope to facilitate the development of therapeutic interventions targeting the aneuploid state of cancer.

*Reference. Chromosomal instability promotes cell migration and invasion via EFEMP1 secretion into extracellular vesicles. Siqi Zheng, Ruifang Tian, Marsudi Siburian, Anna Haider Rubio, Yuanyuan Liu, Rene Wardenaar, Marjan Shirzai,*

## The specificity of the Restrictor complex.



Gaurav Madappa Mandana, Viviana Piccolo

Restrictor is a protein complex acting as a negative regulator of transcription, arresting the synthesis of RNA molecules from regulatory extra-genic regions, not coding for proteins, such as enhancer and promoters.

IEO researchers previously demonstrated that Restrictor is constituted by two main components -ZC3H4 and WDR82- which, through the interaction with two other proteins -Symplekin and PNUMS-, allow for the arrest of RNA synthesis when Pol II is not recruited at the level of extra-genic, regulatory, non-coding regions, thus preventing the synthesis of aberrant RNAs (conversely, Restrictor has no effect on genes coded by RNA Pol II.)

The precise regulation of extra-genic transcription is crucial for the correct cell functioning. Indeed, alterations of RNA transcription at the level of extra-genic regions may affect genome stability (leading to collisions between RNA and DNA polymerases), contribute to dysregulation of gene

### How are these findings framed in the oncological context?

RNA transcription from non-coding regions of the DNA, such as regulatory enhancer regions, plays a significant role in the regulation of gene expression and hence in the modulation of critical processes of cell biology. For instance, in prostate cancer, abnormal levels of enhancer-derived RNAs (eRNAs) have been described as compared to normal tissues, suggesting a correlation among altered eRNA presence, tumor progression, and patient prognosis. Therefore, these studies indicate that eRNAs may play a key role in prostate cancer biology, underlining the importance of regulating their transcription and, if needed, transcription arrest, suggesting that an in-depth understanding of these processes may enable the development of new targeted therapies. Moreover, abnormal patterns of eRNA abundance/presence in prostate cancer suggest their potential as prognostic and diagnostic biomarkers. Similarly, aberrant generation of eRNAs has been observed in breast cancer. Other studies highlighted a role of eRNAs in pancreatic cancer and leukemia, further underlining the importance of the molecular mechanisms regulating their levels. Extra-genic transcription in S phase increases the probability of collision

expression, and potentially be involved in tumorigenesis. Therefore, the mechanisms regulating transcription -or termination of transcription- at the level of these regions play a key role in maintaining genomic stability and gene expression fidelity. The mechanistic bases of Restrictor specificity for extragenic regions are largely unknown. In a recent paper by Polizzese,

between DNA Pol and RNA Pol II, leading to DNA damage (DNA double strand breaks) and thus genomic instability. Therefore, it represents an essential “housekeeping” machinery for the maintenance of cell integrity. Tumor cells more strongly depend on these housekeeping mechanisms as compared to normal cells, thus creating potential “therapeutic windows”; indeed, for instance, some splicing inhibitors are currently employed for the treatment of some types of leukemia.

Mandana, Piccolo et al., researchers headed by Gioacchino Natoli -Group leader at the department of experimental oncology of IEO- dissected the molecular mechanisms underlying Restrictor specificity, showing the crucial role of the ZC3H4 component of the complex in arresting RNA transcription at extragenic regions only. Overall, their data indicate that while WDR82 protein is needed to bind the Restrictor complex to RNA Pol II associated both with coding and non-coding regions, ZC3H4 is required to provide the specificity for non-coding regions, by recognizing specific sequences on the nascent RNA molecules. Restrictor temporary binding at coding regions, where RNA synthesis does not have to be arrested, slows down RNA synthesis, and this temporary deceleration may allow for the scanning of the RNA molecule by Restrictor (specifically, by ZC3H4), to evaluate, on the basis of a given nucleotide sequence-identified in this work-, whether RNA transcription must be arrested or not. Other mechanisms yet to be described are likely to be involved in ensuring Restrictor specific binding to the RNA.

## TELL ME MORE!

Firstly, leveraging a cell line expressing a mutant form of the ZC3H4 protein lacking a given aminoacidic stretch, the authors evaluated whether ZC3H4 was needed for transcription arrest at extragenic regions. In these cells, termination of RNA synthesis at extragenic regions was impaired, demonstrating a role of the ZC3H4 component of Restrictor in this process. Moreover, they found that ZC3H4 bound a specific motif of the nascent RNA molecule (AU-rich – GUA – AU-rich). Specifically, the zinc-finger C3H1 domain of ZC3H4 was involved in the recognition of the specific RNA sequence and the ensuing binding of the Restrictor complex, whereas the SRG domain of ZC3H4 was involved in transcription arrest, but not in the sequence specificity. Notably, the motifs involved in Restrictor recognition of the regions where RNA synthesis had to be arrested were enriched at extragenic regions, and ZC3H4 binding to non-coding RNAs correlated with transcriptional repression.

Finally, they investigated in detail the precise role of three domains of ZC3H4 protein (SRG-needed for the correct nuclear distribution of Restrictor-, C3H1-needed for the sequence-specific binding of RNA-, DPR-needed for WDR82 binding to RNA Pol II), by using inducible cell lines (in which the expression of normal ZC3H4 as well as of the three mutant ZC3H4 forms could be pharmacologically induced after elimination of the endogenous protein): Upon induction of the mutant ZC3H4, Restrictor-arrested RNA synthesis was restored, whereas Restrictor-mediated transcription repression was restored by switching off the mutant protein expression, suggesting the possibility to modulate Restrictor activity. Moreover, while re-expression of normal ZC3H4 restored transcription repression, re-expression of either of the three mutants (namely lacking either the SRG, C3H1, or DPR domain) did not, enabling the expression of extra-genic transcripts and indicating that, through different mechanisms, all the three protein domains were needed for ZC3H4-mediated transcription arrest. Interestingly, one specific mutant (the one lacking the DPR domain interacting with the other component of the restrictor complex, WDR82) resulted in hyper-transcription of the RNA typically repressed by Restrictor, while the mutant ZC3H4 protein lacking the C3H1 domain completely abolished the binding to RNA.

*Reference: Sequence-specific RNA recognition drives Restrictor-mediated termination of extragenic transcription. Danilo Polizzese, Gaurav Madappa Mandana, Marta Russo, Sara Polletti, Elena Prosperini, Giuseppe Ciossani, Silvia Monzani, Luigi Scietti, Simona Rodighiero, Francesco Gualdrini, Viviana Piccolo, Gioacchino Natoli. Mol Cell 2026. doi: 10.1016/j.molcel.2026.02.006.*

# Antitumor effects of metformin and intermittent fasting - an ongoing study.

Obesity and insulin resistance are two factors increasing the risk of developing breast cancer and worsening disease prognosis; overweight breast cancer survivors are indeed at higher risk of recurrence.

Insulin-as well as estrogen and inflammation- levels have been linked to tumor growth, leading to hypothesize that interfering with insulin signaling, with metformin (a common anti-diabetic drug), could counter tumor progression. Indeed, cancer cells are known to have a

certain metabolic plasticity allowing them to adapt to changing microenvironmental conditions -in terms of nutrient availability- switching between glycolysis and oxidative phosphorylation (oxphos), and survive to nutrient shortage. This explains, on one hand, why treatment targeting tumor cell glycolysis only often fail and, on the other hand, explain preclinical results revealing that the combined treatment targeting both glycolysis and oxphos, instead, exert beneficial effects. Indeed, previous epidemiologic and preclinical studies suggest that the antidiabetic drug metformin (oxphos inhibitor) and fasting cooperate in inducing tumor cell death, possibly by acting on cancer cell metabolism. In line with these findings, clinical studies have shown that intermittent fasting (that is, fasting periods interrupted by regular eating; specifically, 8-hour regular eating followed by 16-hour fasting) lowers insulin levels and reduces insulin resistance. Moreover, longer the fasting period, the better the benefits in terms of disease recurrence, proposing intermittent fasting as a potentially effective strategy-alternative to drugs- to reduce the risk of recurrence. In the frame of an international collaboration involving IEO, Galliera Hospital in Genoa and MD Anderson Cancer Center (USA), researchers designed a randomized clinical study aimed at assessing antitumoral efficacy of metformin administration in combination with nightly fasting on presurgical breast cancer lesions, to ultimately improve patients' clinical outcome.

The study enrolled 120 breast cancer patients (ER+ and/or PgR+) candidate to surgery. Enrolled patients have been randomly assigned to two groups: a) a group receiving metformin and attaining to 16-hour nightly fasting (basically eating only from 12 pm to 8 pm), or b) simple glucose monitoring (control group; eating regularly)).

The intermediate safety analysis included 14 patients in the experimental (metformin + intermittent fasting) arm, revealing safety and feasibility of this therapeutic preventive approach. Indeed, no severe adverse events were observed (linked to severe hypoglycemia) and no toxicity-related treatment discontinuation occurred.

Although timely surgical interventions in breast cancer patients are always important for a positive clinical outcome, preclinical and epidemiological studies indicate that a carefully controlled pre-surgery treatment may contribute to improve clinical outcome and reduce the risk of disease recurrence. This study aims at confirming preclinical and epidemiological evidence through a randomized prospective clinical trial and a simple, safe, low-cost intervention repurposing a widely used antidiabetic drug along with a specific dietary regimen, and non-invasive routinely used lab tests for efficacy assessment. If final results will confirm the work hypothesis, this approach may be rapidly applied to large high risk patient populations.

## Metformin and cancer.

IEO researchers previously investigated the molecular mechanisms underlying metformin antitumor effects, identifying, by metabolomic profiling, metformin-modulated metabolites and the metabolic pathways involved in overweight/obese breast cancer patient survivors at high risk of disease recurrence, and explored the potential preventive effect of metformin administration on breast cancer relapse by gene expression analysis, which indicated that metformin might affect the expression levels of some genes in breast tissue that prevent cancer initiation, thus avoiding cancer recurrence, as well as modulate the systemic levels of some metabolites in turn involved in cancer growth. Furthermore, they previously identified, in preclinical disease models, a synergistic effect of metformin administration and low glucose, caused by intermittent fasting, in blocking tumor growth, defining also the underlying molecular mechanism (and identifying PP2A protein as a key player. More recently, they showed an anticancer effect of metformin on glioblastoma growth, through the inhibition of a specific membrane protein expressed on the surface of glioblastoma stem cells, revealing the underlying mechanism involving PP2A/GSK3beta-MCL1 pathway, oxidative stress of cancer cells, and requiring CLIC1 protein.

## TELL ME MORE!

Before study initiation, enrolled patients received a medical visit, and data have been collected including anthropometric data-such as height, weight, BMI etc-, circulating biomarkers in blood draws, dietary habits (through specific questionnaires). Moreover, tissue samples have been collected at diagnosis and surgery. The effects of the treatment are evaluated by Ki67 expression (to measure cell proliferation) between diagnostic and surgical samples, between treated and control patients, between tumoral and adjacent tissue. Additional aspects are evaluated, such as the effect on the PP2A-GSK3beta-Mcl1 axis before vs after treatment; the levels of metabolic biomarkers in the blood, cell death (by caspase-3 immunohistochemistry), glucose levels. Moreover, the potential correlation between Ki67 labeling data and a specific mutational profile is evaluated, as well as changes in other circulating biomarkers and the treatment-related psychological distress.

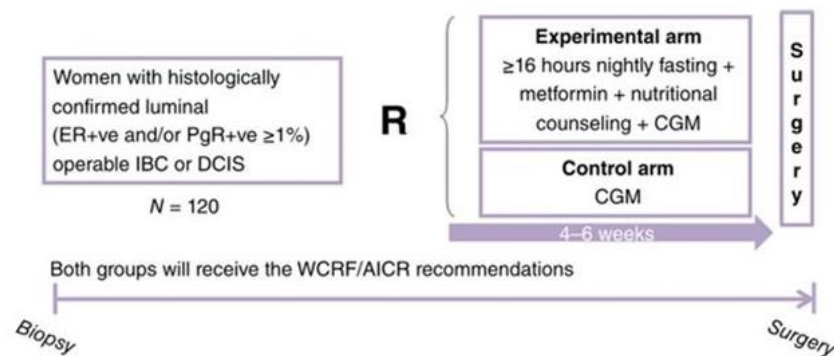


Image from Briata et al., 2025 (an open access article under the CC BY NC ND license.)

*Reference: Time-Restricted Eating and Metformin in Invasive Breast Cancer or DCIS: A Randomized, Phase IIb, Presurgical Trial. Preliminary Safety Analysis. Irene Maria Briata, Stefano Spinaci, Parijatham S. Thomas, Davide Serrano, Tania Buttiron Webber, Nicoletta Gandolfo, Flavio Guasone, Andrea Rattaro, Emma Firpo, Mauro D'amico, Mariangela Rutigliani, Martino Oliva, Marina Gualco, Monica Peresi, Stefania Uncini, Aliana Guerrieri-Gonzaga, Harriet Johansson, Sara Gandini, Matteo Lazzeroni, Chiara Arianna Accornero, Oriana Pala, Saverio Minucci, Mattia Intra, Paolo Veronesi, Lana A. Vornik, Araceli Garcia-Gonzalez, Maria C. Lozano, Brandy M. Heckman-Stoddard, Eileen Dimond, Edward R. Sauter, Eduardo Vilar, Bernardo Bonanni, and Andrea DeCensi. Cancer Prevention Research 2026. doi: 10.1158/1940-6207.CAPR-25-0104.*

## The IEO translational study PROSIBLAD for the improved management of bladder cancer patients.

In December 2025, IEO launched the translational study PROSIBLAD (Precision Oncology Signature for Invasive Bladder Cancer), aimed at the validation –and the ensuing exploitation in the clinical setting– of a molecular signature for the improved management of bladder cancer patients, distinguishing patients at low risk of disease progression from those at high risk.

Indeed, bladder cancer still represents an unmet clinical need. In particular, non-muscle invasive bladder cancer (NMIBC), which represents approximately 75% of all newly diagnosed bladder cancer, pose significant clinical challenges, due to their clinical and biological heterogeneity, with a high recurrence rate and progression to life-threatening Muscle-Invasive Bladder Cancer (MIBC) in approximately 30% of the cases. Despite the significant incidence, treatment has remained basically unchanged in the past 50 years, mainly relying on chemotherapy or BCG administration –inducing a strong immune response able to counter tumor growth, in most cases resulting in tumor eradication– and extensive, radical surgery, without precise molecular stratification. However, this therapeutic approach heavily impacts on patients' quality of life, who, in the absence of robust predictive biomarkers, may be either overtreated –experiencing therapy-related toxicity–, or undertreated –and thus risking disease progression. More recently, novel therapeutic approaches, currently in clinical evaluation, showed the remarkable efficacy of antibody-drug conjugates (enfortumab vedotin plus pembrolizumab) for the treatment of muscle-invasive bladder cancer patients,

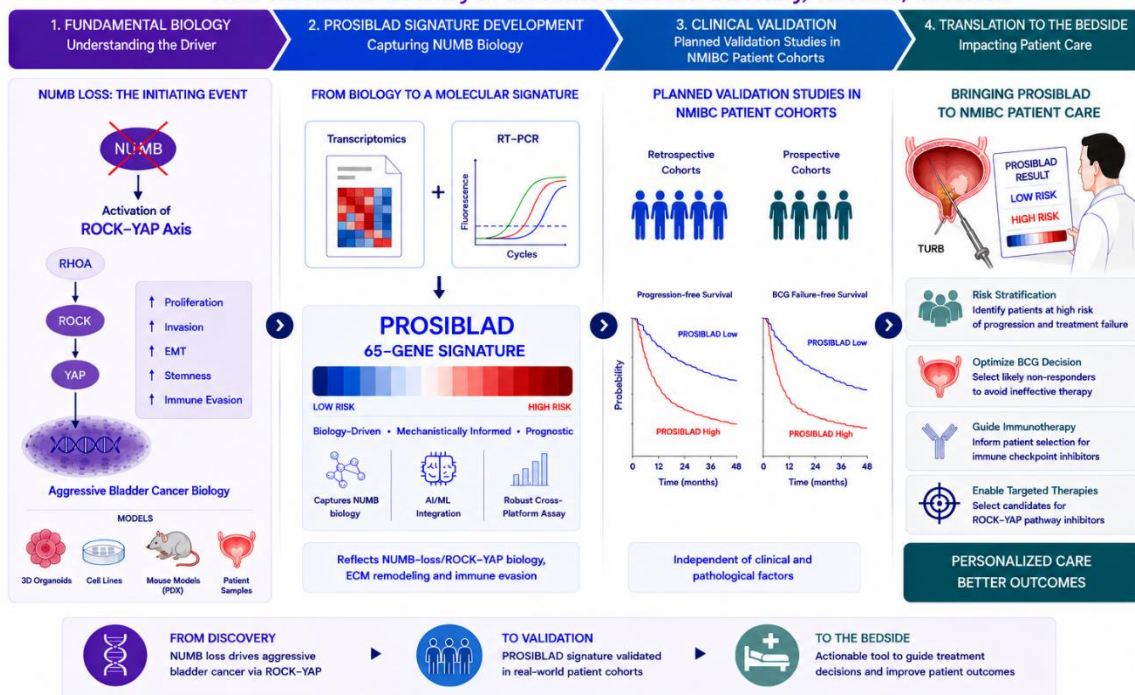
with significantly increased survival, while no effects were observed in the non-muscle-invasive disease where the standard treatment is still represented by BCG administration.

In this scenario, the possibility of accurately identifying those patients who require aggressive treatments from those who may avoid them, can make a huge difference for patients. The PROSIBLAD project emerged in the IEO translational research context, bridging fundamental science and clinically-oriented research, integrating scientific leadership, administrative and data governance, technology transfer, close collaboration between clinicians and researchers. Indeed, thanks to a European collaboration with the Bladder Cancer European Network and a multidisciplinary cooperation within IEO, involving researchers of the department of experimental oncology headed by Salvatore Pece –Director of the *Hormone-Related Cancers and Stem Cell Pathobiology* research unit and professor of the University of Milan–, IEO clinicians and surgeons, the *Anatomo-Pathology Unit*, the *Computing, Data and Digital Research Platforms Technological Unit*, and the continuous support of the *Technology Transfer Office* and the *Research Financial Planning & Analysis Office* and the *Scientific Directorate*, the PROSIBLAD study aims at addressing this lack of molecular biomarkers for the accurate stratification of bladder cancer patients, leveraging the knowledge about the biology underlying tumor evolution.

The PROSIBLAD project follows up on the results –recently published by IEO researchers (Tucci et al., Nat Commun. 2024)– describing the role of NUMB protein as a key regulator of bladder homeostasis, whose loss results in accelerated bladder tumorigenesis and rapid progression from superficial, localized tumor to an invasive tumor, and the identification of a molecular signature distinguishing patients whose tumors are likely to become aggressive and muscle invasive, thus requiring more aggressive treatment approaches, from those in which the tumor is more likely to remain localized, who may thus spare extensive surgery.

## From NUMB Biology to Precision Care in Bladder Cancer

The PROSIBLAD Journey in the NMIBC disease: Discovery, Validation, Translation



The project includes a clinical validation within retrospective observational and prospective interventional clinical studies, to evaluate PROSIBLAD as a prognostic biomarker of aggressive disease and as a predictive biomarker of response to standard-of-care immunotherapy (BCG) or chemotherapy in bladder cancer patients. Moreover, a translational “human-in-mouse” platform (integrating tumor biopsies and preclinical in vivo models with transcriptomic profiling and therapeutic testing) will be implemented, to assess responses to standard-of-care versus targeted anti-ROCK/YAP agents.

The final goal of this project is the exploitation, in the clinical context, of this new predictive/prognostic tool which market analysis and patentability evaluation confirmed to be the *only* molecular diagnostic tool so far available for bladder cancer patient stratification, hence extremely useful for these patients. The gene

signature at the basis of the PROSIBLAD project has been protected by a joint international patent application filed by IEO and University of Milan, underscoring its translational potential.

With the PROSIBLAD project, Salvatore Pece and Daniela Tosoni were selected among the winners of the fifth edition of the Seed4Innovation Program, and awarded with a Proof-of-Concept (PoC) grant supporting an acceleration phase for the technological development and industrial and commercial valorization from the University of Milan. This funding resulting from the synergistic collaboration between academic research and clinical translational research will contribute to the development and technology transfer of PROSIBLAD as a PCR-based molecular diagnostic test for precision oncology.

“The launch of PROSIBLAD marks a significant step forward in precision oncology for bladder cancer. – comment Salvatore Pece and Daniela Tosoni – By improving risk stratification, enabling personalized treatment selection, reducing both overtreatment and undertreatment, and serving as a novel potential actionable target for molecular therapies, PROSIBLAD translates cutting-edge molecular discoveries into tangible clinical benefits for patients worldwide.”

Read [here](#) the press release (Italian only).

## TELL ME MORE!

Promoted as an institutional IEO project, the PROSIBLAD project seeks to bridge the gap between scientific discovery and real-world clinical application. Aimed at validating PROSIBLAD as a novel genomic predictor and advance precision oncology in bladder cancer care, the project builds upon recent discoveries by Salvatore Pece and Daniela Tosoni at the Department of Experimental Oncology of IEO, elucidating key mechanisms underlying bladder tumorigenesis.

“Bladder cancer is the ninth most commonly diagnosed cancer worldwide and represents a significant clinical and economic burden due to high recurrence and progression rates and the lack of reliable predictive biomarkers – explain Salvatore Pece and Daniela Tosoni. Approximately 75% of bladder cancer cases are classified as Non-Muscle Invasive Bladder Cancer (NMIBC), with a high recurrence rate and progression to life-threatening Muscle-Invasive Bladder Cancer (MIBC) in approximately 30% of the cases. Current staging systems rely on clinicopathological parameters; however, these are insufficient to accurately predict progression risk. Therefore, treatment strategies largely follow a “one-size-fits-all” approach, typically involving BCG immunotherapy or chemotherapy, without precise molecular stratification. The absence of reliable predictive biomarkers results in either overtreatment –including unnecessary radical surgery and treatment-related toxicity–, or undertreatment, with the risk of progression to aggressive disease. Therefore, robust predictive biomarkers improving risk stratification and guiding personalized treatment decisions –maximizing treatment efficacy while preserving quality of life– represent a urgent unmet clinical need.

The PROSIBLAD project stems from our recent scientific discoveries identifying NUMB as a driver of bladder carcinogenesis (Tucci et al., Nature comm 2024). The study showed that about 40% of newly diagnosed NMIBC tumors are characterized by NUMB deficiency, and the loss of the NUMB protein results in aberrant activation of the RHOA/ROCK/YAP pathway –involved in cell proliferation, invasiveness, and progression toward muscle-invasive disease–, thus identifying a subgroup of NMIBC patients who could benefit from specific targeted therapies. Indeed, if applied at early NMIBC stages, therapies targeting this pathway could prevent progression to muscle-invasive –and potentially lethal– disease, possibly allowing to avoid highly invasive treatments. Moreover, our work led to the identification of a gene signature associated with hyperactivation of the RHOA/ROCK/YAP signaling correlated with more adverse molecular NMIBC subtypes, predicting the risk of disease progression in NMIBC patients, and the response to BCG therapy in NUMB-deficient tumors, independently from other predictors.

In addition to its potential as a tool to predict the risk of disease progression, functional studies in preclinical models demonstrated that pharmacological inhibition of the RHOA/ROCK/YAP pathway –by YAP/TEAD or ROCK blockers– effectively reverses the aggressive and invasive phenotypes of NUMB-deficient bladder cancer cells. Notably, anti-YAP/TEAD and ROCK inhibitors are either already approved or in clinical trial for other therapeutic indications, suggesting that they may be repositioned for precision treatment of bladder cancer, leveraging PROSIBLAD as a molecular stratification tool.”

# Criticalities and strategies towards a sex/gender-weighted biomedical research.

Experimental evidence indicate that sex and gender can affect research results. The increasing evidence led to greater awareness of the relevance of such differences and thus the growing inclusion of sex and gender as research variables in scientific studies. IEO has always paid great attention to gender medicine. In 2016, it activated, as part of the European LIBRA project, its first Gender Equality Plan at the Department of Experimental Oncology to promote sex and gender equality in research. Then, the Department of Experimental Oncology established the WoMen in Science program to advance the results obtained within LIBRA.

In the context of a Cariplo-funded research, a recent study headed by Susanna Chiocca-PI at the department of experimental oncology of IEO- and Camilla Gaiaschi-professor at the University of Salento- investigated the obstacles to the actual implementation of a sex/gender-weighted approach to research. The study, which has also involved Paolo Maugeri, researcher in Chiocca's group, was carried out at IEO and involved interviews and focus groups, aimed at identifying critical issues to identify potential strategies to address such criticalities. Interviews and focus groups involved female and male researchers, clinicians, unit directors, HR professionals, research managers and funders. Carrying on the study within a comprehensive cancer center (istituto di ricerca e cura a carattere scientifico, IRCCS)-IEO- allowed all phases of biomedical research to be explored while

observing the direct impact on patient care. The study was carried out with a 3-level approach: A micro level, focusing on issues related to researchers' everyday work; a meso level, regarding issues linked to institutional organization, policies and processes; a macro level, related to other stakeholders such as funding agencies and regulatory bodies. All these three levels influence each other and prevent or make difficult the adoption of a sex-gender approach in biomedical research.

Their results highlighted that the obstacles towards a sex/gender-based research approach is rooted in all the three different-micro, meso, macro- levels, underlining the need to devise adequate, multi-level strategies to handle and address such criticalities. If, on one side, training of researchers is fundamental, issues are also linked to other institutional and legislative aspects, and thus solutions must involve also those levels.

## Results- Obstacles to the implementation of a sex/gender-weighted research.

At the micro level, results highlighted issues related to the lack of robust, scientifically proven evidence on sex-related differences, creating skepticism within the scientific community; that has prevented sex/gender-focused initiatives, thus making difficult securing funding. Moreover, they highlight that sex/gender-stratification can reduce data

### Sex and gender.

In everyday language, the words "sex" and "gender" are often used interchangeably, although they actually mean two different concepts. "Sex" refers to the biological features (e.g. chromosomes) of an individual at birth, whereas "gender" refers to behaviors, lifestyles, experiences, social roles, attitude towards disease and pain perception of an individual. Sex and gender are tightly interconnected and, due to the difficulty in distinguishing the two aspects and considering their differential impact on human health and disease, people often simply refer to these concepts as the "sex and gender issue". However, they can affect disease incidence and progression differently. In melanoma, both sex and gender affect prognosis, in different ways. For instance, older men tend to check their skin less frequently; that affects prognosis, and differences in the use of tanning beds by young men and young women affects differently the incidence (gender-related issue); moreover, previous studies identified sex-related differences in proliferation, senescence, response to stress signals, in cancer cells and tumor microenvironment. Therefore, it is important to be able to distinguish sex (biological) related and gender (cultural) related variables and measure how they can differentially affect people of all genders.

### Sex and gender bias in research.

Sex and gender biases in research can be distinguished in two types: on one side, 1) the so called gender blindness, assuming that women and men are equal even when they are not; for instance, presuming that disease risk, progression and symptoms are the same in men and women when they are not; on the other side, 2) gender stereotyping, assuming existing differences between men and women even when there are not; which means for instance, presuming that disease risk, progression and symptoms are different even when they are not. Both biases can affect accuracy of research studies, in the design, data analysis and interpretation.

availability and thus statistical power. Another issue is related, in preclinical research, to the difficulty of knowing the sex of cells and mice. Others issues relate to the difficulty of distinguishing between the different effects of sex (biological) and gender (cultural). At the meso level, researchers identified criticalities linked to the role of research officers (the clinical trial office-CTO- in IEO), highlighting their poor involvement in project writing, which prevents them from aiding PIs in including a sex/gender dimension in their clinical design. Another issue is related to the limited clinicians' time to be dedicated to research.

At the macro level, the authors highlight the limited availability of dedicated funding for sex/gender research, mainly due to the absence of scientific evidence justifying large funded research programs. Their results also highlight that commissioned-namely pharma-sponsored- studies often do not include sex/gender-weighted research, mostly due to the lack of mandatory rules of the regulatory bodies. Moreover, they highlight that one of the issues is linked to studies including meta analyses; indeed, in this case, if not mandated in the initial study, sex at birth of patients is often not available for privacy reasons (according to the GDPR), and thus not available.

### **Proposed strategies - How to fix it?**

The study helped in defining the current obstacles in implementing a sex and gender-weighted research, to devise potential strategies aimed at handling and overcoming such issues.

The authors conclude that, at the micro level, actions should be mostly focused on increasing researchers' awareness and guiding them, by providing training sessions and practical research guidelines on how to include a sex/gender dimension in their research.

At the meso level, the authors underline that the poor involvement of research offices in clinical design (to include sex/gender) may be easily fixed with an organizational change at the institutional level. The limited clinicians' time to be dedicated to research, rooted in contractual issues, is more likely to need changes at the legislative level and require a contractual distinction between clinical and research activities, so involving HR offices. They also suggest the development of a national network to foster sex/gender-weighted research and fund-raising events.

At the macro level, the authors suggest that the poor availability of dedicated funding for sex/gender research may be solved by initiating small, short and highly focused projects, less risky for the founder, and aiding in collecting robust preliminary evidence. Moreover, they propose the involvement of regulatory bodies (that is, by including sex and gender as mandatory variables to be considered in the clinical research design) for a greater inclusion of sex/gender dimension of research in commissioned studies.



*Susanna Chiocca*

### **The IEO WoMen in Science Program.**

The main goals of IEO WoMen in Science Program is to promote *i.* equal opportunities for men and women at IEO, *ii.* the advancement of women in scientific careers, *iii.* the development of tools to raise awareness about the importance of accounting for sex (of cells, tissues, animals) in biomedical research. The WoMen in Science team, directed by Susanna Chiocca, includes Annalisa Ariesi, Tiziana Bonaldi, Greta Caprara, Sara Gandini, Luisa Lanfrancione, Paolo Maria Maugeri, Martin Hartmann Schaefer. Among the main achievements of the group, can be mentioned the creation of a Gender Equality Plan (GEP) in the context of the LIBRA project; the creation of a mentoring program for IEO postdocs;

the monitoring of IEO recruitment process, to avoid gender bias; the monitoring of research activities aimed at including the sex/gender dimension of research in all aspects of projects and grant applications.

### *The authors – Susanna Chiocca.*

Since 2005, Susanna Chiocca is Director of the Viruses and cancer Unit at Department of Experimental Oncology of IEO, and Faculty member of the SEMM (European school of molecular medicine) PhD school. With a Bachelor of Science at the University of Texas (USA) and a PhD in Molecular Biology/Virology at the MD Anderson Cancer Center (Houston, Texas), her research aims to determine the mechanisms by which oncogenic viruses and other tumor microenvironmental stressors contribute to neoplasia through protein post-translational modification (PTM), by specifically focusing on the virus-/stress-induced alterations in the cancer epigenome inducing the neoplastic program, and how oncoviral proteins regulate cellular PTM pathways and provide new critical signals in viral-induced carcinogenesis, by using head and neck cancer as a model system. Moreover, she has been deeply involved in promoting the inclusion of the sex and gender dimension in biomedical research, having actively contributed to the LIBRA project and the development in IEO of the WoMen in Science program.

*Reference. It Is Not Only a Matter of Biases: Identifying Organizational and Institutional Obstacles to Bring Sex- and Gender-Oriented Approaches into Biomedical Research. Camilla Gaiaschi, Camilla Veneri, Susanna Chiocca. TECNOSCIENZA. Italian Journal of Science & Technology Studies 2026.*

### 10 years of EUSOMA certification.

In May 1994, with IEO foundation, our institute opened the Breast Surgery Division, which rapidly became a distinctive feature of IEO. Since then, breast cancer treatment grew together with IEO, integrating the divisions of Plastic Surgery and Medical Oncology, which then became the Medical Senology Division, ultimately evolving into a more structured, integrated and patient-focused care model: The Breast Unit. From 2016, IEO Breast Unit is EUSOMA (European Society of Breast Cancer Specialists)-certified, one of the most important European certification for breast cancer care centers. This year we celebrate 10 years of EUSOMA certification.

The IEO Breast Unit is a multidisciplinary structure. Activities cover the whole care path: From the screening within the regional plan, diagnosis based on advanced breast imaging, until surgical treatments, with innovative approaches, including radio- and radar- guided surgery and mini-invasive techniques. In addition, the IEO Breast Unit offers integrated cancer therapies, the development of innovative drugs, advanced radiotherapy treatments, such as proton therapy, prevention and cancer genetics activities, palliative care, pain therapy, psychological support, and a structured patient follow-up within the first five years.

The effort in clinical research is also key, supported by the clinical trial office, which allows IEO interaction with the main international centers and enables to provide patients with increasingly advanced therapeutic options. EUSOMA certification is a starting point; a daily effort involving professionals of different disciplines, clinical services and supporting structures.

### “La ricerca siamo noi” EUPATI event at IEO.

On May 19<sup>th</sup>, IEO hosted the first event of the EUPATI initiative “La ricerca siamo noi”, aimed at promoting the culture of research, underlining its importance and value for the care progress, and emphasizing the relevance of citizen and patient engagement and empowerment in research, particularly in clinical research. Two panels involving different clinical research professionals joined the event and expressed their opinions on the different themes discussed.

The topics included the recent inclusion of patients, more specifically, informed patients, in ethical committees. Ethical committees guarantee that patients' rights are preserved in clinical research protocols; patient inclusion in ethical committees ensures that patients' needs are taken into consideration and dealt with. Informed patients had been trained and gained a sound expertise in the oncology field and clinical research; they can help by providing feedback about feasibility and logistic aspects linked to enrolling a clinical protocol, with treatment appointments and follow-up visits.

Aspects such as patients' fears in enrolling a new clinical trial have also been discussed, underlining how informed patients can play an important role, by offering, on one side, their emotional experience, helping other patients to face their own fears and understanding that being part of a clinical trial, while certainly bringing with it uncertainty about the result, offers new potentially effective therapeutic options, which would not be available otherwise, in the frame of structured and well organized studies, along with their experience with anti-cancer treatment; on the other side, they can also provide, through peer communication, their acquired knowledge, which can be helpful to flank physicians in explaining medical terms, thus making patient-doctor discussions easier, or in understanding the scientific roots that led to the design of a specific research protocol aimed at testing efficacy of a certain drug.

While patients' future involvement in earlier phases of clinical research, such as in the design of a clinical protocols are being considered, suggestions about their inclusion in the early phases of the design of academic research projects has been proposed, which can contribute to further make them feel closer, ultimately enhancing patients' adherence to clinical research protocols.

Finally, they highlighted that informed patients can take aware decisions about their own care path, discussing all their therapy options with their doctors, until finding the most adequate for them, including clinical trial if available and if the best choice for them. While language can still represent a barrier between patients and trial enrollment, this can be circumvented through citizen formation, through different forms of education, underlining the power of patient empowerment (formation)-which can allow informed, aware decisions- and engagement (involvement), which can benefit both parts involved as well as the society as a whole.

### Prevention for women at high risk of breast cancer – the TOLERANT study.

On June 12<sup>th</sup>, starting from 8.30 AM, the Quark hotel will host the event “La Prevenzione del Tumore Mammario nelle Donne ad Alto Rischio” during which the results of the TOLERANT study will be presented. It will be an important occasion to discuss with professionals involved in the project. Participation is free but registration is required ([here](#)). Click [here](#) to know more about the event.

# The European AI Act

the world's first legal framework specifically regulating artificial intelligence

The **AI act** establishes a set of rules governing

- development,
- deployment,
- commercialization,
- use

of AI systems across the EU.

Its **goal** is to ensure that AI technologies are

- trustworthy,
- safe,
- transparent,
- respectful of fundamental rights

while still promoting innovation and economic competitiveness, according to the principle that technological progress should remain aligned with democratic values, human rights, transparency, and accountability

definition of AI

*"an AI system is a machine-based system capable of operating with varying levels of autonomy and generating outputs such as predictions, recommendations, content, or decisions that influence physical or virtual environments."*

the definition emphasizes systems that infer patterns or generate outputs based on data

a risk-based regulatory approach

The AI act regulates AI systems according to the level of risk they pose to health, safety, democracy, fundamental rights.

the higher the risk → the stricter the legal obligations

## potential risks

discrimination in automated decision-making,  
invasive surveillance,  
manipulation of individuals,  
misinformation,  
opaque algorithmic systems

affecting

employment,  
education,  
finance,  
healthcare,  
criminal justice

## four main risk categories

### unacceptable risk

AI practices considered fundamentally **incompatible with European values**; viewed as posing unacceptable threats to safety, dignity, democracy, or fundamental rights

*e.g. Social scoring systems similar to those associated with authoritarian surveillance models; real-time remote biometric identification in public spaces; emotion recognition systems in workplaces and schools; biometric categorization systems revealing sensitive characteristics such as religion or sexual orientation*

## four main risk categories

### high risk

If it **may significantly affect individuals' rights, opportunities, or safety**. This includes 1. AI systems embedded in products already regulated under EU product safety law, such as medical devices; 2. Standalone AI systems used in sensitive areas.

*e.g. Recruitment and employment systems; Educational admissions and exam evaluation; Credit scoring and insurance risk assessment; Critical infrastructure management*

Providers of high-risk AI systems must comply with extensive obligations before placing products on the market (*e.g. risk management systems, high-quality training and testing data, technical documentation, record-keeping and logging, transparency and user instructions, human oversight mechanisms, accuracy, robustness, and cybersecurity standards, conformity assessments before commercialization*); Deployers, importers, and distributors have generally fewer obligations than providers (e.g. Deployers must ensure systems are used appropriately, monitor performance, and maintain human oversight where required.)

For AI systems that are not considered high risk but still pose concerns, the AI Act imposes transparency obligations rather than strict prohibitions (*e.g. Chatbots, Deepfakes, AI-generated synthetic content, Emotion-recognition systems, Biometric categorization tools.*)

The **Aim** is to reduce deception and preserve informed consent.

Users interacting with these systems must generally be informed that they are dealing with AI. AI-generated content must also be labeled appropriately in many cases.

## four main risk categories

### limited/minimal risk

few or no mandatory obligations.

*e.g. spam filters, recommendation engines, AI-enabled video games, many productivity applications.*

## implementation timeline

the AI Act entered into force in August 2024, but implementation is phased over several years. Key milestones include:



\*general purpose AI

## relevance for a cancer center employing AI in care and research

Cancer institutions increasingly rely on AI systems for radiology and pathology image analysis, genomic interpretation, treatment decision support, workflow optimization, predictive analytics, patient triage, drug discovery, biomarker development, clinical trial matching, population-health research.

Because many of these applications directly influence diagnosis, prognosis, therapeutic choices, scientific evidence generation, they fall within the high risk category

the AI Act is shaping how AI can be responsibly integrated into oncology practice and research.

## relevance for a cancer center employing AI in care and research – some examples

### cancer care

#### 1

AI systems used in radiology, pathology, radiation oncology, molecular diagnostics may influence whether a tumor is detected, how aggressively it is classified, or which therapy a patient receives.

Because they are used in healthcare and may affect patient safety or fundamental rights, they are “high-risk AI systems”

cancer centers must ensure that these systems meet stringent standards for accuracy, robustness, transparency, traceability, human oversight.

A cancer institution implementing AI-assisted mammography, digital pathology classifiers, or clinical decision-support algorithms must therefore establish governance structures capable of validating system performance, documenting risks, monitoring errors, and ensuring clinicians remain meaningfully involved in decision-making (as AI should support—not replace—professional medical judgment.)

relevance for a cancer center employing AI in care and research – some examples

cancer care

2

Modern oncology relies on multidisciplinary integration among pathology, radiology, genomics, surgery, medical oncology, radiation oncology, nursing, and research laboratories.

AI systems are beginning to function across these domains simultaneously.

institutions must understand how algorithms are trained, what risks they pose, and how outputs are interpreted (development of institutional AI governance committees, ethical review pathways, and interdisciplinary oversight structures capable of evaluating complex digital systems before clinical deployment)

relevance for a cancer center employing AI in care and research – some examples

cancer care

3

regarding transparency and explainability, clinicians and patients often need to understand why a recommendation is being made

the use of interpretable systems or at least systems accompanied by clear documentation regarding limitations, intended use, and performance characteristic is encouraged  
and

since patients may increasingly expect to know whether AI contributed to their diagnosis or treatment planning, institutions will need policies clarifying how AI involvement is disclosed and documented

relevance for a cancer center employing AI in care and research – some examples

translational cancer research

AI plays a key role in modern cancer research, allowing to analyze massive multidimensional datasets that would otherwise be impossible to interpret efficiently

Machine learning is used for biomarker discovery, patient stratification, target identification, digital pathology, survival prediction, and drug-response modeling

if systems are later translated into clinical applications or influence patient management, cancer centers must think about “regulatory readiness” from the earliest stages of AI development (institutions seeking to bring research algorithms into clinical use will need stronger version control, documentation of training data provenance, risk analysis, reproducibility testing, validation across multiple cohorts)

### relevance for a cancer center employing AI in care and research – *some examples*

#### clinical research

AI is increasingly used in trial recruitment, endpoint assessment, imaging evaluation, adaptive trial design, and patient monitoring.

Some AI systems may identify eligible patients based on electronic records or predict likely treatment responders, affecting access to experimental therapies or influence clinical decisions.

Therefore, they may qualify as high-risk

Cancer centers conducting AI-enabled trials will therefore need close coordination among ethics committees, data protection officers, clinical investigators, and regulatory experts.

### relevance for a cancer center employing AI in care and research – *conclusions*

Cancer centers already operate within highly regulated environments concerning patient privacy, informed consent, biological samples, and clinical safety.

The AI Act does not replace these frameworks but adds [another layer of governance specifically focused on algorithmic systems](#).

### relevance for a cancer center employing AI in care and research – *opportunities*

Institutions capable of implementing trustworthy AI governance may gain significant advantages in research collaboration, international partnerships, industry engagement, and patient trust. Pharmaceutical companies, medical device developers, and technology firms increasingly seek clinical partners able to operate within compliant regulatory environments. A cancer center with strong AI governance may therefore become more attractive for collaborative innovation projects and multicenter clinical studies.

Moreover, a clear regulatory framework assuring that AI systems are validated, monitored, and subject to human oversight may help reassure patients that innovation is occurring responsibly. In this sense, [the AI Act aligns closely with the mission of comprehensive cancer centers: advancing scientific innovation while protecting patient welfare and maintaining ethical integrity](#).

For further details: [AI Act - A summary](#)



# THE BRIEFING

*A glance through recent papers from IEO researchers, and from the whole scientific community.*

## *What else is new from IEO researchers?*

*(Text by Alex Irwin (ChatGPT) and Ai Yi (DeepSeek), revision by Stefania Averaimo)*

### *prospective (real world) clinical study*

**CDK4/6 inhibitors for breast cancer treatment.** In the frame of the P-VERIFY study, researchers evaluated the efficacy of the three CDKi when administered in combination with ET, in a real world setting. The study, involving a patient cohort of over 9.000 patients, is to date the largest real world study investigating CDKi + ET (specifically, aromatase inhibitors, AI) efficacy in metastatic HR+/HER2- breast cancer. The P-VERIFY trial shows no significant differences if HR+/HER2- metastatic breast cancer patients are treated with endocrine therapy along with either of the three CDKi tested.

In a different study, researchers evaluated real world efficacy of CDKi for the treatment of breast cancer patients with bone metastases, comparing efficacy of the three different CDKi. In a real world scenario, their results showed, in these patients, in this setting, an inferior efficacy of palbociclib as compared to abemaciclib and ribociclib, in combination with ET, in terms of PFS. Exploratory analyses also indicate lower efficacy in terms of OS; however, data in this regard require additional confirmation. Results are in line with previous preclinical data showing lower antitumor efficacy of palbociclib as compared to abemaciclib and ribociclib on breast cancer bone metastases. Nevertheless, additional preclinical and prospective clinical studies may help in confirming the actual ranking in the efficacy of the three inhibitors, and dissect the underlying mechanism.

While randomized clinical trials remain the gold standard in the clinical setting to define efficacy of a given treatment, real world clinical trials are being increasingly performed to complement data collected in the frame of randomized trials, within real world patient cohorts, thus addressing limitations intrinsic to randomized trials such as the strict eligibility criteria and the clinically homogenous-and not representative- patient subpopulations tested.

**1)** *Rugo HS, Brufsky A, Layman RM, Liu X, Li B, McRoy L, Cohen AB, Estevez M, Lynce F, Cottu P, Thill M, Curigliano G. Breast 2026. PMID: 41950642. 2)* *Scafetta R, Donato M, Gullotta C, Guarino A, Fiore C, Sisca L, Speziale E, Troiano R, Foderaro S, Venuti F, Vilardi FA, Ricozzi V, Iuliani M, Simonetti S, Cavaliere S, Cortellini A, La Cesa A, Botticelli A, Scagnoli S, Pisegna S, Criscitiello C, Chirco A, D'Alessandro S, Pedersini R, Sposetti C, Tiberi E, D'Auria G, Vergati M, Mazzotta M, Caputo R, Verrazzo A, Rossino MG, Domati F, Piombino C, Di Lisa FS, Filomeno L, Arcuri T, Puce F, Riva F, Palleschi M, Sirico M, Piras M, Stucci LS, De Lisi D, Orsaria P, Grasso A, Ippolito E, Ramella S, Visani L, Bertini N, Bonaparte I, Gori S, Rossi L, Meattini I, Tagliaferri B, Caffo O, Bonomo MV, Portarena I, Irelli A, Cretella E, Porta C, Bianchini G, Fabbri MA, De Giorgi U, Vici P, Toss A, Garrone O, De Laurentiis M, Villa F, Berardi R, Minelli M, Altomare V, Vernieri C, Curigliano G, Vincenzi B, Tonini G, Santini D, Pantano F. Oncologist 2026. PMID: 41992832.*

### *correlative/xdescriptive study*

**Genomic Landscape of Pediatric and Young Adult Sarcomas.** Whole-exome sequencing of 120 sarcomas from 201 patients revealed genomic differences between subtypes. Osteosarcomas showed low tumor mutational burden (TMB) and high copy number variation. Recurrent/metastatic Ewing sarcomas had higher TMB and intratumoral heterogeneity. Potentially actionable alterations were found in 59% of samples, and 16% of relapsed patients received matched targeted therapy, supporting genomic integration in rare tumor research.

*Tirtei E, Difilippo V, Divincenzo F, Asaftei SD, Ratto N, Piana R, Pellegrino P, Linari A, Papotti M, Mareschi K, Parlato C, Guarrera S, Minucci S, Rabusin M, Manzitti C, Prete A, Mercolini F, Luksch R, Meazza C, Parafioriti A, Tamburini A, Coccoli L, Mura R, Zecca M, Palmerini E, Ibrahim T, Peirone S, Penolazzi L, De Luna E, Cagnazzo C, Bombaci S, Ferrero I, Niclot AGSB, Proto CF, Spadea M, Quarello P, Marini E, Gizzi K, Fenoglio B, Livellara V, Di Gangi A, Puma N, Sironi G, Di Bernardo A, Cereda M, Fagioli F. Cancer research communications. PMID: 41880642.*

### *retrospective clinical study*

**PRESERVE model for laryngeal preservation.** This international retrospective study developed a multiomics model- PRESERVE- which, on the basis of a 64-gene signature plus six clinical variables, predicted laryngo-esophageal dysfunction and response to induction chemotherapy in advanced laryngeal-hypopharyngeal squamous-cell carcinoma. Adding genomics to clinical data gave the best performance. External validation is needed.

*Mattavelli D, Compagnoni M, Calza S, Ravanelli M, Plana M, Wichmann G, Paderno A, Zhan Y, Smussi D, Rondi P, Pinacoli A, Medda A, Lorini L, Khelik K, Hovig E, Maffini FA, Kalogerini M, Alberti A, Farina D, Dietz A, Mesia R, Piazza C, Chiocca S, Bossi P, PRESERVE Consortium. ESMO open. PMID: 41468687.*

*review/commentary*

**Lymphadenectomy in Early Ovarian Cancer: Balancing Risks and Benefits.** Except for clear cell tumors (where a survival benefit is suggested), systematic lymphadenectomy in presumed early-stage ovarian cancer has no proven therapeutic benefit, although it retains a diagnostic role, detecting occult metastases in 9-30% of cases. Decisions should be individualized based on histology, grade, and risk factors, with guidelines recommending it for high-grade tumors but omitting it for low-grade endometrioid and expansile mucinous subtypes.

*Caruso G, Delfrati S, Giordano FC, Panizzolo E, De Luca Carignani B, Laudani ME, Stefani E, Donatiello G, Fumagalli D, Ribero L, Rosanu M, Ainio C, Betella I, Schivardi G, Bogani G, Multinu F, Aletti G, Cliby W, Colombo N. International journal of gynecological cancer: official journal of the International Gynecological Cancer Society. PMID: 41844493.*

*review/commentary*

**BRCA mutations in lobular versus ductal breast cancer.** This systematic review and meta-analysis compared germline BRCA1/2 mutation prevalence in invasive lobular and ductal breast cancer. Across 12 studies and 8004 women, BRCA1 mutations were less frequent in lobular than ductal carcinoma. BRCA2 showed no overall association, but in lower-bias studies appeared more common in lobular cancer. Findings support distinct genetic profiles by histology.

*Corso G, Andreon C, La Vecchia C, Bottazzoli EI, Abruzzese G, Favilla K, Citterio O, Spoldi E, Di Silvestre S, De Scalzi AM, Polizzi A, Meduri E, Trapani D, Nicosia L, Pesapane F, Bossi D, Brogi E, Shen S, Mukhtar R, Criscitiello C, Veronesi P, Gandini S, Magnoni F, Curigliano G. Eur J Cancer. PMID: 41930855.*

*prospective clinical trial*

**Safety of imlunestrant in ER-positive advanced breast cancer.** EMBER-3 evaluated adverse events with imlunestrant alone or combined with abemaciclib in ER-positive, HER2-negative advanced breast cancer progressing after endocrine therapy. Imlunestrant-containing regimens had mostly early, reversible, low-grade events and few discontinuations. Toxicities with the abemaciclib combination were manageable with dose changes and supportive care, supporting these oral options.

*O'Shaughnessy J, Bidard FC, Neven P, Casalnuovo ML, Aftimos P, Saura C, Harbeck N, Carey LA, Curigliano G, Garcia-Saenz JA, Abad MF, Paula L, Park YH, Ozyilkan O, Munoz M, Barrett E, Cao S, Chawla A, Jhaveri KL. NPJ breast cancer. PMID: 42045295.*

*prospective clinical trial*

**Long-term ARROW results with pralsetinib.** The ARROW phase I/II study assessed pralsetinib in RET fusion-positive non-small cell lung cancer. With longer follow-up, pralsetinib achieved high response rates in treatment-naïve and platinum-pretreated patients, with median overall survival exceeding three years. Safety remained consistent with prior reports.

*Besse B, Subbiah V, Curigliano G, Bowles DW, Doebele RC, Mansfield AS, Baik CS, de Lima Lopes G, Paz-Ares L, Taylor MH, Tan DSW, Alonso G, Gadgeel SM, Kalemkerian GP, Ou SI, van der Wekken AJ, Becerra CR, Evangelist M, Griesinger F, Liu SV, Lou Y, Mazières J, Melear JM, Narang M, Saxena A, Thomas M, Wang S, Thomassen A, Lee DH, Kim DW, Gainor JF. J Clin Oncol. PMID: 41886723.*

*review/commentary*

**Repositioning streptozotocin in pancreatic NETs.** This review revisits streptozotocin for pancreatic neuroendocrine tumours, linking its mechanism, GLUT2-mediated uptake, DNA-methylating activity and pharmacokinetics to improved dosing strategies. Short infusions and fractionated schedules may maintain efficacy while reducing nephrotoxicity. Biomarkers such as MGMT deficiency and mismatch repair status could refine patient selection.

*Fazio N, Spada F, Benini L, Mulargiu C, Del Re M, Danesi R. Cancer treatment reviews. PMID: 42061024.*

*mechanism-oriented research*

**Metabolic rewiring during pluripotency exit.** This study links metabolism and epigenomic regulation with pluripotency transitions after stem cell implantation in mouse embryos. Their results show that rather than shutting down, the TCA cycle is spatially and temporally rewired. Pyruvate cycling supports balanced metabolic and transcriptional states, exit from pluripotency, and differentiation. Glutamine increasingly fuels both the TCA cycle and histone acetylation.

*Kafkia E, Pladevall-Morera D, Argemi-Muntadas L, Wang G, Noberini R, Casòliba-Melich A, Bagés-Arnal S, Angho-Mattanovich M, Silvério-Alves R, Gassler J, Bonaldi T, Rabelink TJ, Moritz T, Żylicz JJ. Cell stem cell. PMID: 42034059.*

*mechanism-oriented research*

**Faecalibacterium prausnitzii as a protective gut bacterium in Parkinson's disease (PD).** Using a PD mouse model, the study identified bacteria depleted in patients with Parkinson's disease, and showed that specific bacterial species (namely, an eight-taxon consortium) improved motor and gastrointestinal deficits,. Notably, Faecalibacterium prausnitzii alone was sufficient to correct microbiome changes, promote anti-inflammatory responses, modify gut gene expression, reduce brain  $\alpha$ -synuclein aggregates, and ameliorate symptoms.

Moiseyenko A, Antonello G, Schonhoff AM, Boktor JC, Long K, Dirks B, Oguienko AD, Winnett AV, Simpson P, Daeizadeh D, Ismagilov RF, Krajmalnik-Brown R, Segata N, Waldron LD, Mazmanian SK. *NPJ Parkinson's disease*. PMID: 41786774.

*correlative/descriptive study*

**Evolutionary processes shaping gut microbiome populations.** This study shows that genome-wide selective sweeps (GWSS, evolutionary process where a beneficial genetic mutation arises and rapidly spreads within a population due to strong natural selection) are widespread in human gut bacteria, creating heterogeneous microbiomes, with highly differentiated populations. GWSS manifest in phylogenetic trees as closely related genomes on long branches (the so-called "broom" structures). These GWSS clusters associate with host traits and diseases such as colorectal cancer, Crohn's disease, ulcerative colitis, type2 diabetes, and advanced (>65) age.

Yu XA, Strachan CR, Herbold CW, Lang M, Gasche C, Makrithis A, Segata N, Pollak S, Tett A, Polz MF. *Nature*. PMID: 42092154.

*mechanism-oriented research*

**Oxygen tolerance evolution in *Segatella copri*.** The study examines how *Segatella copri* adapts to oxygen gradients in the human gut: PerR regulates its core oxygen-response network, while in some strains OxyR acquisition through horizontal gene transfer increases oxygen tolerance. OxyR-positive strains are enriched in industrialized populations but absent in ancient and traditional-lifestyle samples, suggesting recent lifestyle-driven selection.

El Mouali Y, Tawk C, Huang KD, Sivapornnukul P, Mengoni C, Segata N, Strowig T. *Cell host & microbe*. PMID: 42097142.

*review/commentary*

**Next-generation CDK-targeted cancer therapies.** This review summarizes emerging strategies beyond approved CDK4/6 inhibitors, including CDK4-selective, CDK2-selective and pan-CDK2/4/6 inhibitors, plus degraders and cyclin-directed agents. These approaches aim to overcome resistance, reduce toxicity and expand activity beyond HR-positive, HER2-negative breast cancer, while improving integration into precision oncology.

Tan HN, Curigliano G, Yap TA. *Trends Cancer*. PMID: 42020210.

*observational study*

**Italian prospective registry of GEP-NENs.** The Itanet nationwide prospective registry enrolled 2138 newly diagnosed gastroenteropancreatic neuroendocrine neoplasm patients in Italy. The study describes diagnostic pathways, treatment patterns and outcomes, confirming Ki-67 as a continuous prognostic marker and identifying 15% as a poor-outcome threshold.

Panzuto F, Rinzivillo M, Partelli S, Pusceddu S, Campana D, Spada F, Della Vittoria Scarpati G, Cives M, Gelsomino F, Bertuzzi AF, Marcucci S, Badalamenti G, Bergamo F, Marini M, Di Odoardo A, Fazio N, Tafuto S, Lauricella E, Coppa J, Faggiano A, Fermi F, Arrivi G, Oldani S, Falconi M, Itanet Registry study group. *Lancet Reg Health Eur*. PMID: 42016055.

*meta-analysis*

**Circulating tumor DNA (ctDNA) Blood Tests for Colorectal Cancer (CRC) Screening.** This meta-analysis of three prospective studies (36,381 participants) evaluated ctDNA-based blood tests for advanced colorectal neoplasia. For invasive CRC, pooled sensitivity was 0.72 and specificity 0.91, with sensitivity increasing from stage I (0.53) to IV (0.89). However, for advanced precancerous lesions, sensitivity was only 0.13. ctDNA testing shows high specificity for CRC but poor detection of precancerous lesions.

Carbone F, Ciardiello D, Granieri S, Fazio N, Avallone A, Delrio P. *Crit Rev Oncol Hematol* 2026. PMID: 41881272.

*clinical/computational/research tools*

**Validation of a model to predict minimal risk of recurrence in premenopausal breast cancer.** This study validated a model (namely, an adjusted Breast Cancer Index (BCI) model with an additional cutpoint) to identify, among premenopausal hormone-receptor-positive node-negative breast cancer patients, those with minimal risk of distant recurrence within 10 years. The model reclassified 17.8-19.6% of patients according to their risk of recurrence, supporting its use for personalizing adjuvant endocrine therapy.

O'Regan RM, Ren Y, Zhang Y, Fleming GF, Francis PA, Pagani O, Walley BA, Kammler R, Dell'Orto P, Viale G, Loi S, Colleoni M, Treuner K, Regan MM. *Breast (Edinburgh, Scotland)*. PMID: 41637791.

*review/commentary*

**PI3K/AKT/PTEN Alterations in HR+/HER2- Metastatic Breast Cancer.** This review discusses PI3K pathway alterations (PIK3CA mutations in 40-45%, AKT1 in 5%, PTEN loss in 5-10%) as mechanisms of resistance in HR+/HER2-metastatic breast cancer after endocrine therapy and CDK4/6 inhibitors. It highlights diagnostic strategies to

improve identification of patients eligible for targeted therapies, and integration of molecular diagnostics into routine care.

*Malapelle U, Buglioni S, Castellano I, Criscitiello C, Curigliano G, d'Amati G, De Angelis C, de Biase D, Pepe F, Perrone G, Scatena C, Scatolini M, Trapani D, Venetis K, Fusco N. Pathologica. PMID: 41954340.*

*review/commentary*

**AI and medication adherence in breast cancer.** This systematic review assessed employment of AI tools for predicting, monitoring or supporting oral medication adherence in breast cancer. Ten studies were included. The review highlights the need for better implementation in this clinical context, leveraging multidisciplinary interaction among different professionals (researchers, AI specialists, healthcare workers).

*Pezzolato M, Voskanyan V, Cutica I, Marzorati C, Pravettoni G. JMIR Cancer. PMID: 42013303.*

*prospective clinical trial*

**Gedatolisib-based therapy in PIK3CA wild-type advanced breast cancer.** VIKTORIA-1 compared efficacy of gedatolisib, palbociclib, and fulvestrant (gedatolisib triplet) vs gedatolisib plus fulvestrant (gedatolisib doublet) vs fulvestrant only, in HR-positive, HER2-negative, PIK3CA wild-type advanced breast cancer after CDK4/6 inhibitor and aromatase inhibitor therapy. Both gedatolisib-based regimens significantly improved progression-free survival versus fulvestrant alone, with manageable toxicity and low discontinuation due to treatment-related events.

*Hurvitz SA, Layman RM, Curigliano G, André F, Cristofanilli M, Kim SB, Martínez Rodríguez JL, Nadal JC, Kim GM, Lo L, Remolina-Bonilla YA, Rosselli G, Emile G, Korbenfeld E, Puig JM, Wesolowski R, Martin M, Ring A, Han HS, Giordano A, Mutka SC, Moss K, Suzuki S, Sullivan B, Gorbachevsky I, Pistilli B, VIKTORIA-1 Study Group. J Clin Oncol. PMID: 41802242.*

*psychoncology studies*

**Psychological Intervention for Body Memories in Breast Cancer Survivors.** Breast cancer can affect people perception of their own body. This pilot study, involving 14 breast cancer survivors, explored, through an online six-session psychological intervention, how self-defining memories related to the body might reflect the relationship between body image and well-being after breast cancer. The intervention may help survivors gain awareness and better manage body-related memories after cancer.

*Sebri V, Martino ML, Singer J, Madow K, Giudice AV, Freda MF, Pravettoni G. Journal of health psychology. PMID: 41956444.*

*psychoncology studies*

**GRETA-V2 decision aid for breast reconstruction.** This study evaluated GRETA-V2, a decision aid designed to support shared decision-making for breast reconstruction after mastectomy. Expert feedback from surgeons, nurses, psycho-oncologists and patient advocates supported its value, especially for visual clarity and patient-centered content, while recommending refinements in relation to understanding of radiotherapy, surgical options, recovery and emotional impact.

*Sebri V, Catanuto G, Rocco N, Dorangricchia P, Balafa K, Gioco R, Mirshekar B, Polotto S, Pravettoni G. J Cancer Educ. PMID: 42101577.*

*prospective (real world) clinical study*

**Real-world duration of CDK4/6 inhibitors in metastatic breast cancer.** This Flatiron Health real-world study compared first-line CDK4/6 inhibitors plus aromatase inhibitor in HR-positive, HER2-negative metastatic breast cancer. Palbociclib showed longer median treatment duration and lower 12-month discontinuation than ribociclib or abemaciclib.

*Brufsky A, Layman RM, Liu X, Li B, McRoy L, Cohen A, Estevez M, Cottu P, Thill M, Curigliano G, Rugo HS. Oncologist. PMID: 42095602.*

*prospective clinical study*

**Extended endocrine therapy in young premenopausal breast cancer.** This cohort study examined extended endocrine therapy after 5 years of LHRH (luteinizing hormone-releasing hormone) agonist-based treatment in young premenopausal patients with node-positive, hormone receptor-positive early breast cancer. Extended therapy was associated with lower estimated invasive and distant recurrence risk across cancer subtypes, with the greatest apparent distant-recurrence benefit in luminal A-like disease.

*Valenza C, Zheng Y, Milano M, Berton Giachetti PPM, Trapani D, Giordano E, Guidi L, Boldrini L, Castellano G, Katrini J, Malagutti B, Antonarelli G, Etessami JD, Bianco N, Conforti F, Kirkner GJ, Sangalli C, Dibble KE, Fusco N, Colleoni M, Regan MM, Munzone E, Curigliano G, Partridge AH. JAMA Netw Open. PMID: 42081244.*

*retrospective clinical study*

**Denosumab and BRCA-mutated metastatic breast cancer.** This multicenter retrospective study evaluated denosumab in HR-positive, HER2-negative metastatic breast cancer with bone metastases treated with CDK4/6 inhibitor plus endocrine therapy. In germline BRCA1/2-mutated patients, denosumab was associated with longer real-world progression-free survival, while no benefit was seen in BRCA -wildtype or-unknown patients.

Scafetta R, Troiano R, Gullotta C, Guarino A, Fiore C, Sisca L, Speziale E, Donato M, Foderaro S, Venuti F, Vilardi FA, Rizzo V, Iuliani M, Simonetti S, Cavaliere S, Cortellini A, Cesa A, Botticelli A, Scagnoli S, Piseigna S, Criscitiello C, Pedersini R, Sposetti C, Tiberi E, D'Auria G, Vergati M, Mazzotta M, Caputo R, Verrazzo A, Garrone O, Domati F, Piombino C, Lisa FSD, Filomeno L, Arcuri T, Puce F, Riva F, Palleschi M, Sirico M, Piras M, Stucci LS, Lisi D, Orsaria P, Grasso A, Ippolito E, Ramella S, Visani L, Livi L, Gori S, Rossi L, Meattini I, Tagliaferri B, Caffo O, Bonomo MV, Portarena I, Irelli A, Cretella E, Porta C, Bianchini G, Fabbri MA, Giorgi U, Vici P, Toss A, Ruatta F, Laurentis M, Villa F, Berardi R, Minelli M, Altomare V, Vernieri C, Curigliano G, Chirco A, D'Alessandro S, Vincenzi B, Tonini G, Santini D, Pantano F. *Eur J Cancer*. PMID: 41921366.

*prospective clinical study*

**Olaparib adverse events in SOLO2.** This analysis of SOLO2 characterized common adverse events with maintenance olaparib in BRCA-mutated, platinum-sensitive relapsed ovarian cancer. Adverse events were more frequent with olaparib than placebo but manageable, supporting tolerability of long-term maintenance therapy.

Ledermann JA, Lortholary A, Penson RT, Asher R, GebSKI V, Provencher D, Bruchim I, Huzarski T, Barretina-Ginesta MP, Pipitone S, Mileskin L, Colombo N, Park-Simon TW, Matsumoto K, Boere I, Mikheeva O, Kim JW, Giroto G, Vergote I, Carter D, Lowe ES, Pujade-Lauraine E. *Int J Gynecol Cancer*. PMID: 41861615.

*prospective clinical study*

**Single-port robotic surgery in gynecologic oncology.** This prospective cohort study evaluated the feasibility and safety of single-port robotic surgery for gynecologic cancers in a high-volume referral center in Milan. Among 63 patients, mainly treated for endometrial cancer, all procedures were completed without conversion to multi-port or open surgery, and no intra-operative complications occurred. Operative times, blood loss, pain scores, and hospital stay were low, while only three major post-operative complications were reported. These findings support the feasibility and safety of this minimally invasive approach in selected patients, although larger studies are needed to confirm oncologic outcomes.

Ribero L, Schivardi G, Achilarré MT, Aloisi A, Betella I, Xhindoli L, Garbi A, Aletti GD, Colombo N, Maggioni A, Multinu F, Zanagnolo V. *Int J Gynecol Cancer*. PMID: 41620340.

*retrospective clinical study*

**Integrated Fast Track robotic pathway for early-stage lung cancer.** This retrospective study assessed a Fast Track protocol integrating robot-assisted (with the ION system) bronchoscopy (and radioactive marker-guided biopsy) followed by robotic surgical resection. The protocol demonstrated feasibility, safety, and efficiency in accelerating diagnosis and treatment while maintaining high diagnostic accuracy.

Guarize J, Bertolaccini L, Spaggiari L. *Surg Innov*. PMID: 41214869.

*retrospective clinical study*

**Pulmonary metastases resection in pancreatic cancer: a valuable treatment in selected patients.** This retrospective study on 56 patients from 7 high-volume centers found that surgical resection of pulmonary metastases, after radical pancreatic cancer surgery, can be beneficial in selected patients.

Nachira D, Calabrese G, Bertolaccini L, Meacci E, Congedo MT, Novellis P, De Palma A, Romano R, Bertoglio P, Ferretti G, Evangelista J, Campanella A, Chiari M, Misceo F, De Blasi F, Valentini M, Valentini L, Brandolini J, Turchini M, Bogina G, Veronesi G, Marulli G, Spaggiari L, Margaritora S. *Updates in surgery*. PMID: 41934597

*prospective clinical trial*

**Pralsetinib in RET Fusion-Positive Non-Small Cell Lung Cancer (NSCLC).** Long-term follow-up of the ARROW study evaluating efficacy of pralsetinib administration in 281 patients with RET fusion-positive NSCLC showed robust durable responses with manageable safety (namely, overall response rates of 78% in treatment-naïve and 63% in prior platinum-treated patients; median overall survival of 44.3 months overall, and 50.1 months in treatment-naïve patients).

Besse B, Subbiah V, Curigliano G, Bowles DW, Doebele RC, Mansfield AS, Baik CS, de Lima Lopes G, Paz-Ares L, Taylor MH, Tan DSW, Alonso G, Gadgeel SM, Kalemkerian GP, Ou SI, van der Wekken AJ, Becerra CR, Evangelist M, Griesinger F, Liu SV, Lou Y, Mazières J, Melear JM, Narang M, Saxena A, Thomas M, Wang S, Thomassen A, Lee DH, Kim DW, Gainor JF. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. PMID: 41886723.

*review/commentary*

**Advances and challenges in antibody-drug conjugates in oncology.** This review highlights the rapid evolution of antibody-drug conjugates (ADCs) as transformative cancer therapies capable of delivering cytotoxic agents selectively to tumor cells while reducing systemic toxicity. The authors discuss technological improvements in antibody engineering, linker stability, and payload design that have expanded ADC use into earlier treatment settings. Key limitations include tumor heterogeneity, resistance mechanisms, and treatment-related toxicities. Combination strategies with immunotherapy and targeted agents, along with biomarker-driven sequencing approaches and next-generation ADC platforms, are presented as promising strategies to improve efficacy and durability of response.

Etessami JD, Valenza C, Tolcher AW, LoRusso P, Curigliano G. *Am Soc Clin Oncol Educ Book*. PMID: 42133892.

*prospective clinical trial*

**The antibody-drug conjugate Pivekimab Sunirine in Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN).** This phase I/II trial evaluated the CD123 antibody-drug conjugate pivekimab sunirine (PVEK) in BPDCN. In frontline de novo patients (n=20), PVEK shows high durable responses, with manageable toxicity.

Pemmaraju N, Marconi G, Montesinos P, Lane AA, Mazzarella L, Sallman DA, Ulrickson ML, Schiller GJ, Erba HP, Wang ES, Walter RB, Deconinck E, Aribi A, Legrand O, Lebon D, Maisano V, Martinelli G, DeAngelo DJ, Derenzini E, Du Y, Lakshmikanthan S, Potluri J, Kantarjian HM, Daver NG. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. PMID: 41671533.

*prospective (real world) clinical trial*

**Real-world effectiveness of CDK4/6 inhibitors in older breast cancer patients.** This real-world analysis from the PALMARES-2 study evaluated endocrine therapy plus CDK4/6 inhibitors in older patients with HR-positive/HER2-negative advanced breast cancer. Older patients showed improved real-world progression-free survival compared with younger patients despite having less favorable baseline characteristics. Palbociclib demonstrated particularly strong effectiveness and favorable clinical manageability in the elderly population, performing similarly to abemaciclib and better than ribociclib. These findings support the use of first-line CDK4/6 inhibitors in older breast cancer patients.

Ligorio F, Provenzano L, Fotia G, Dieci MV, Curigliano G, Giuliano M, Botticelli A, Lambertini M, Rizzo G, Pedersini R, Sirico M, La Verde N, Gennari A, Zambelli A, Toss A, Piras M, Giordano M, Tagliaferri B, Generali D, Sartori D, Mazzoli G, Jacobs F, Armani G, Sposetti C, Zurlo C, Menichetti A, Griguolo G, Faso V, Boldrini L, Munzone E, Marra A, Chiappe E, Scagnoli S, Piseigna S, Capasso C, De Angelis C, Arpino G, Criscitiello C, Guarneri V, Pruneri G, Mariani L, PALMARES-2 study group, Vernieri C. *Breast*. PMID: 42048902.

*review/commentary*

**Explainable artificial intelligence in mammography: systematic review.** This systematic review evaluated explainable artificial intelligence (XAI) methods applied to mammography and assessed the quality of explanation validation and clinical usefulness. Fourteen studies were included, focusing mainly on lesion detection and classification. Many studies offered only qualitative assessments; quantitative assessment showed only modest reliability. The review concludes that mammography XAI still lacks robust validation and requires stronger clinician-centered evaluation.

Pesapane F, Rotili A, Penco S, Dominelli V, Priolo F, Marinucci I, Nicosia L, Grasso R, Pravettoni G, Cassano E. *Diagnostics (Basel)*. PMID: 42122114.

*review/commentary*

**Revisiting streptozotocin in pancreatic neuroendocrine tumors.** This review re-examines streptozotocin (STZ) as a therapeutic option for pancreatic neuroendocrine tumors more than fifty years after its introduction. The authors summarize recent insights into STZ pharmacology, including selective uptake via GLUT2 transporters and DNA-methylating activity, supporting optimized infusion schedules to reduce nephrotoxicity while preserving efficacy. Comparisons with temozolomide emphasize STZ's unique tissue tropism. Emerging biomarkers such as MGMT deficiency and mismatch repair status may refine patient selection. The review suggests that biomarker-guided approaches and pharmacology-informed dosing could revitalize STZ in personalized neuroendocrine cancer treatment.

Fazio N, Spada F, Benini L, Mulargiu C, Del Re M, Danesi R. *Cancer Treat Rev*. PMID: 42061024.

*review/commentary*

**Italian consensus recommendations for PIK3CA testing in breast cancer.** This consensus document developed by a panel of Italian experts provides standardized recommendations for molecular testing of PIK3CA mutations in advanced HR-positive/HER2-negative breast cancer. Recommendations cover sample selection, assay methodologies, reporting standards, sensitivity thresholds, and interpretation of canonical and non-canonical variants. Guidance is also extended to alterations in related PI3K/AKT/mTOR pathway genes. The document aims to harmonize molecular diagnostics and optimize integration of targeted therapies such as alpelisib and inavolisib into clinical practice.

De Angelis C, de Biase D, Gerrata L, Arpino G, Bianchini G, Castellano I, Curigliano G, Del Mastro L, Fabi A, Fusco N, Gennari A, Guarneri V, Zamagni C, Zambelli A, Malapelle U, Puglisi F. *Breast*. PMID: 41999684.

*review/commentary*

**Mechanisms and sequencing of topoisomerase I inhibitor ADCs in breast cancer.** This review compares trastuzumab deruxtecan and sacituzumab govitecan, two leading antibody-drug conjugates used in advanced breast cancer. Although both deliver topoisomerase I inhibitors, they differ in target antigens, linker chemistry, payload potency, and resistance mechanisms. Trastuzumab deruxtecan shows strong efficacy in HER2-positive and HER2-low disease, while sacituzumab govitecan is active in triple-negative and HR-positive/HER2-negative tumors. The

authors discuss mechanisms of cross-resistance, tumor heterogeneity, and the lack of predictive biomarkers to guide ADC sequencing, highlighting the clinical importance of optimizing treatment strategies.

*Del Re M, Inglese E, Bria E, Blok EJ, Mathijssen RHJ, Curigliano G, Danesi R. Drugs. PMID: 41931218.*

*review/commentary*

**European priorities for genetic counselling in cancer care.** This Delphi survey explored strategies to improve access to genetic counselling within Europe's Beating Cancer Plan. Experts in genetics, oncology, and patient advocacy from across EU member states identified key barriers related to workforce shortages, reimbursement, and genetic literacy. Five priority strategies achieved consensus, including EU-wide recognition and registration of genetic counsellors, mandatory reimbursement for counselling, and stronger integration of genetics into oncology education and guidelines. The study provides a roadmap for harmonizing genetic counselling services and supporting equitable access to personalized cancer care across Europe.

*McCrary JM, Van Valckenborgh E, Horgan D, Aleksandrova E, Bargou R, Behulova RL, Belina I, Bøhme ALE, Brunet J, Burada F, Chirita-Emandi A, Ciuca A, Colas C, Constantinidou A, Curca RO, Cursaru V, Dalmas M, Daneberga Z, de Azambuja E, De Pauw A, De Putter R, Delikurt-Tuncalp T, Donnelly D, Ehrencrona H, Foretova L, Galli F, Genuardi M, Giles R, Grima C, Janavičius R, Kääriäinen H, Klink B, Krajc M, Kufel-Grabowska J, Lace B, Leitsalu L, Le Tourneau C, Lodahl M, Mari F, Matos E, Mazzarella L, Milagre TH, Mistrik M, Moss B, Nolan A, O'Shea R, Paneque M, Patócs A, Pestoff R, Poirel HA, Risch M, Rodrigues M, Roetzer KM, Ros A, Schröck E, Schwaninger G, Slámová L, Stamatopoulos K, Strang-Karlsson S, Szczatuba K, Szymczak V, Theis P, Turner J, Valcina O, Vella C, van Zelst-Stams WAG, Wadt KAW, Zschocke J, Ronez J, Ripperger T, Van Den Bulcke M, Bergmann AK. Eur J Hum Genet. 41688774.*

*mechanism-oriented research*

**IRSp53 Regulates Fluidity and Invasiveness in Breast Cancer.** Breast cancer fluidity, crucial for cell invasion and metastatic dissemination, is regulated by the IRSp53 protein (linking plasma membrane and cytoskeleton), through the interaction with Afadin protein. Depletion of IRSp53 increases fluidity and active wetting by reducing intercellular friction and enhancing cell rearrangements. Low IRSp53 expression correlates with worse clinical outcomes in patients, establishing IRSp53 as a key regulator of epithelial viscosity and a potential prognostic marker.

*Marchesi S, Guidolin C, Massey AE, Lemahieu G, Lavagnino Z, Beznoussenko GV, Mironov AA, Green BJ, Allievi E, Martini E, Magni S, Ghisleni A, Lomazzi C, Benvenuto AF, Schertel A, van Faassen DA, Freddi S, Bertalot G, Parazzoli D, Maiuri P, Mapelli M, Pece S, Sigismund S, Gauthier NC, Cavalcanti-Adam EA, Cartagena-Rivera AX, Giavazzi F, Scita G, Disanza A. Nature Materials. PMID: 41872301.*

*review/commentary*

**Membrane Contact Sites as Dynamic Regulators of Endocytic Trafficking.** Endocytosis governs the uptake of nutrients, receptors, and membrane components, shaping signaling and membrane composition. Membrane contact sites (MCSs) have emerged as key regulators of this process, acting as dynamic platforms that coordinate organelle communication and integrate metabolic signals with spatial precision. By remodeling membranes and creating localized signaling domains, MCSs directly influence endocytic and endo-lysosomal trafficking. Their adaptability to external cues and exploitation by pathogens highlight their central role in intracellular organization.

*Miloro G, Caputo M, Di Fiore PP, Sigismund S. Curr Opin Cell Biol. PMID: 41967419*

*mechanism-oriented research*

**Palmitate Impairs CD8 T Cell Metabolism via SPHK2.** This study shows that palmitate (PA) irreversibly damages mitochondrial metabolism in CD8 T cells, reducing histone acetylation and chromatin accessibility, which suppresses effector functions and antitumor immunity. Sphingosine kinase 2 (SPHK2) was identified as a key mediator. Pharmacological inhibition of SPHK2 restored mitochondrial fitness and T cell function, offering a potential target to enhance cancer immunotherapies.

*Tiberti S, Gennari S, Romeo M, Sheraj I, Kassir MF, Fernández-García J, Nava Lauson CB, Noberini R, Catozzi C, Dallavilla T, Ballerini M, Loffreda A, Codreanu SG, Sherrod SD, Leaprot KL, Schrimpe-Rutledge AC, McLean JA, Schaefer MH, Rodighiero S, Bonaldi T, Fendt SM, Ogretmen B, Sdelci S, Nezi L, Manzo T. Science immunology. PMID: 41894555.*

*mechanism-oriented research*

**Vitamin D binding protein and muscle atrophy.** The study showed that, independently from vitamin D, high levels of vitamin D binding protein (VDBP) induces muscle atrophy, by altering actin dynamics and mitochondrial fragmentation. Consistently, ectopic expression of VDBP in in vivo preclinical models is sufficient to induce muscle atrophy. VDBP levels also contribute to cancer-related muscle loss in Lewis lung carcinoma murine models.

*Raiteri T, Reano S, Scircoli A, Zaggia I, Antonioli A, Faletti S, Favero F, Manfredi M, Pellicci G, Corà D, Scotti L, Kew RR, Prodam F, Porporato PE, Filigheddu N. Nature communications. PMID: 41963327.*

*clinical/computational/research tools*

**Neonatal genetic screening of G6PD deficiency using next-generation sequencing.** This study evaluates the use of whole-exome sequencing (WES) in neonatal screening for glucose-6-phosphate dehydrogenase (G6PD) deficiency,

addressing limitations of traditional enzymatic assays. Among 4067 newborns, 3.0% carried pathogenic or likely pathogenic G6PD variants. While hemizygous males consistently showed enzymatic deficiency, over 60% of heterozygous females had normal enzyme activity and would have been missed by standard screening due to X-chromosome inactivation. The findings demonstrate that enzymatic screening alone is insufficient, particularly for detecting affected females. Integrating molecular approaches such as WES with biochemical testing significantly enhances diagnostic sensitivity, enabling earlier identification, improved risk stratification, and better preventive care strategies within large-scale genomic programs.

*Bombaci S, Quarello P, Del Borrello G, Barat V, Di Martino V, Cagnazzo C, Zucchetti G, Pavanello E, Minucci S, Fagioli F. Br J Haematol. PMID: 41856574.*

#### *mechanism-oriented research*

**MCL1 Regulates mTORC1 and Bioenergetics in Cancer.** MCL1 protein is overexpressed in tumors, promoting cancer not only by blocking apoptosis but also by activating the metabolic regulator mTORC1. This leads to increased hexokinase2 expression and altered bioenergetics. Although MCL1 inhibitors suppress mTORC1 activity in tumor cells, they cause cardiotoxicity by suppressing heart mTORC1. However, mTORC1-inhibition-related cardiotoxicity can be reversed by leucine supplementation, positioning MCL1 as a key link between metabolism and survival.

*Gui W, Paral P, Dhamija B, Hagag E, Dusa M, Humajova J, Francova PV, Kucka J, Pankrac J, Schütz C, Armenis V, Ferrucci F, Schubert M, Guan K, Baenke F, Stange DE, Lehmann LH, Weckwerth W, Mirtschink P, Traikov S, Giuseppe B, Miracco C, Bornhäuser M, Minucci S, Seif L, Macurek L, Elgendy M. Nature communications. PMID: 41326406.*

#### *retrospective clinical study*

**Prognostic Factors After Neoadjuvant Treatment in HER2+ and Triple-Negative Breast Cancer.** In 863 patients, achieving pathologic complete response (pCR) after neoadjuvant therapy led to excellent 3-year recurrence-free survival (98%) as compared to those with post-treatment residual disease (79%). Tumor stage, lymph node colonization, and TNBC subtype were associated with worse outcomes in patients with residual disease, not in those with pCR.

*Corti C, Li T, Martin AR, Hughes ME, Parker T, Duporte TS, Curigliano G, King TA, Mittendorf EA, Lin NU, Tayob N, Tolaney SM. Breast (Edinburgh, Scotland). PMID: 41864057.*

#### *psycho-oncology studies*

**Development of the EUonQoL Kit for Assessing Quality of Life in Cancer Patients.** The European Oncology Quality of Life (EUonQoL) project developed a novel toolkit to assess quality of life in cancer patients (under active treatment, survivors, and under palliative care), in Europe, ultimately aimed at inform health policy in Europe. Its features are currently being evaluated in a 4200-patient cohort, across 32 countries.

*Nicklin E, Bedding C, Alfieri S, Apolone G, Arndt V, Bos N, Bredart A, Brunelli C, Caselli L, Ciliberto G, Rojas-Concha L, Couespel N, Doege D, Ferrer M, Franzoi MA, Gangeri L, Garin O, Gillanders E, Groenvold M, Higgins C, de Jongh ECE, Kalmi T, Kaasa S, Lombardo C, Martin E, Pappot H, Pietrobon R, Pravettoni G, Scacciati B, Sirven A, Sweegers MG, Thong MSY, Vachon H, van de Poll-Franse LV, Vaz-Luis I, Caraceni A, Velikova G, Gilbert A, EUonQOL consortium. European journal of cancer. PMID: 41855780.*

#### *prospective clinical trial*

**Phase II Trial of Abemaciclib in Brain Metastases from NSCLC and Melanoma.** In this phase II trial, abemaciclib administration, either in monotherapy or in combination with chemotherapy, showed no objective response in patients with brain metastases from non-small cell lung cancer or melanoma. Despite achieving therapeutic brain concentrations, clinical activity was limited, suggesting that future trials should focus on abemaciclib combination strategies.

*Sahebjam S, Bazer DA, Rhun EL, Queirolo P, Jerusalem G, Johnston EL, Conte P. Neuro-oncology advances. PMID: 41768125.*

#### *other clinical and biomedical research*

**Healthcare Professionals' Preparedness for Sexual Health Issues in Breast Cancer.** A national Italian survey involving 109 healthcare professionals revealed gaps in healthcare professionals' preparedness in managing breast cancer's impact on sexual health. Indeed, only 23% felt very informed and 30% had specific training. While the majority of the respondents agreed on the need for dedicated training, routine discussion of sexuality was rare, highlighting an urgent need for targeted education and improved multidisciplinary care.

*Zagami P, Salimbeni BT, Preti EP, Esposito A, Marra A, Trapani D, Munzone E, Mazza M, Martella S, Durosini I, Perazzo S, Marsicano R, Maria Berton Giachetti PP, Curigliano G, Criscitiello C, Pravettoni G. Breast (Edinburgh, Scotland). PMID: 41855623.*

#### *other clinical and biomedical research*

**Impact of Disclosing Discordant AI Results in Mammography.** A study on 600 women found that disclosing a discordant AI mammography result significantly reduced trust and increased anxiety, second-opinion intent, and legal action consideration. However, adding a contextual explanation mitigated these adverse effects, supporting its use as a communication strategy when integrating AI into clinical practice.

Pesapane F, Depretto C, Rotili A, Penco S, Monzani D, Grasso R, Nicosia L, Mallardi C, D'Amelio L, Carriero S, Irmici G, Della Pepa G, Pravettoni G, Santicchia S, Scaperrotta G, Cassano E. *European radiology*. PMID: 41832929.

*mechanism-oriented research*

**The HSPB8-BAG3-FAK axis in breast cancer.** This study showed that, in ER+ breast cancer cell lines, downregulation of HSPB8 and BAG3 proteins correlates with reduced FAK activation, leading to decreased proliferation, migration, and adhesion. Mechanistically, BAG3 interacts with FAK, supporting signaling cascades involved in tumor progression. The findings highlight a functional HSPB8-BAG3-FAK axis that promotes cancer cell survival and metastatic potential, suggesting novel therapeutic targets.

Piccolella M, Tedesco B, Ferrari V, Filippone MG, Tucci FA, Pandolfi A, Casarotto E, Cozzi M, Chierichetti M, Pramaggiore P, Cornaggia L, Milioto C, Magdalena R, Mohamed A, Brodnanova M, Koshal P, Rusmini P, Galbiati M, Tosoni D, Pece S, Cristofani R, Crippa V, Poletti A. *Cell Commun Signal*. PMID: 41664196

*review/commentary*

**Beyond the membrane: rethinking EGFR signaling in physiology and cancer.** This review reexamines EGFR signaling beyond classical ligand-dependent activation, emphasizing spatial regulation, intracellular trafficking, and organelle interactions. It highlights ligand-independent and kinase-independent functions that expand EGFR's role in physiology and cancer. The integration of biochemical and mechanical cues shapes diverse cellular outcomes, including metabolism and survival. Understanding these complex signaling networks may guide innovative therapeutic strategies targeting EGFR in cancer.

Jendrissek G, Mesa D, Conte A, Malabarba MG, Sigismund S. *Cell Mol Life Sci*. PMID: 41670652

*retrospective clinical study*

**Real-world effectiveness of palbociclib plus aromatase inhibitor in bone-only metastatic breast cancer.** This real-world retrospective study evaluated first-line palbociclib plus aromatase inhibitor versus aromatase inhibitor alone in HR+/HER2- bone-only metastatic breast cancer using a large US database. The results showed that the combination therapy significantly improved overall survival and progression-free survival, and delayed chemotherapy initiation. These findings support the added benefit of CDK4/6 inhibition in a population often underrepresented in trials, confirming effectiveness in routine clinical practice.

Brufsky A, Layman RM, Liu X, Li B, McRoy L, Cohen AB, Estevez M, Cottu P, Curigliano G, Rugo HS. *Breast*. PMID: 41830752

*review/commentary*

**HER2 Testing in Advanced Gastric Cancer: Challenges and Optimization.** HER2 testing in gastric cancer is complex due to tumor heterogeneity. Discordance between results obtained from HER2 evaluation in primary tumor biopsies vs metastases is common, impacting treatment. Optimizing sampling, standardizing protocols, and reassessing at progression are crucial. Emerging concepts like HER2-low disease and circulating tumor DNA analysis are enhancing diagnostic accuracy and guiding precision therapy.

Rosanu N, Gervaso L, Lobrano R, Vanoli A, Cella C, Fusco N, Fazio N. *International journal of molecular sciences*. PMID: 41683961.

*prospective clinical trial*

**RADIOSO Milan Trial: SCOUT Radar for Localizing Non-Palpable Breast Lesions.** The RADIOSO trial evaluated pre-operative SCOUT radar-based tumor localization for non-palpable breast lesions in 254 patients. High satisfaction rates were reported by radiologists (98%), surgeons (89.8%), and patients (91.8%), confirming SCOUT as a promising device that optimizes clinical workflow.

Pagani G, Polizzi A, Alloggio AE, Latronico A, Nicosia L, Cassano E, Travaini LL, Ceci F, Sangalli C, Veronesi P, Galimberti V. *Annals of surgical oncology*. PMID: 41721162.

*review/commentary*

**Liquid Biopsy in Colorectal Cancer: From Minimal Residual Disease to Metastatic Disease.** Circulating tumor DNA (ctDNA)-based liquid biopsy is transforming colorectal cancer management. It enables comprehensive genomic profiling to identify actionable targets and resistance mechanisms in metastatic disease. Additionally, it is validated for detecting minimal residual disease after locoregional treatment, refining risk stratification and guiding adjuvant therapy to improve cure rates while reducing overtreatment.

Martini G, Napolitano S, Ciardiello D, Bielo LB, Martinelli E, Troiani T, Zampino MG, Fazio N, Curigliano G, Ciardiello F. *Nature reviews. Clinical oncology*. PMID: 41720942.

*retrospective clinical study*

**Risk Factors for Early Recurrence After surgery.** In a multicenter analysis involving 594 patients with esophago-gastric junction adenocarcinoma undergoing surgery (Ivor Lewis esophagectomy), the early recurrence rate (within 12 months) was 24.4%. Independent risk factors included lower BMI, poor response to neoadjuvant treatment, and advanced stage. Identifying these factors allows for better patient stratification and personalized treatment approaches.

de Pascale S, Rosati R, Bagnardi V, Cossu A, Ferrari G, Frassoni S, Giacomuzzi S, Gualtierotti M, Moletta L, Morino M, Pallabazzer G, Realis Luc M, Rebecchi F, Santi S, Valmasoni M, Weindelmayer J, Fumagalli Romario U, Società Italiana per lo Studio delle Malattie dell'Esophago (Italian Society for Study of Esophageal Diseases). *Journal of gastrointestinal surgery*. PMID: 41539450.

*retrospective clinical study*

**Radical Prostatectomy vs. Radiation in Rare Prostate Cancer Subtypes.** Analyzing 427,055 patients from the SEER database, this study compared radical prostatectomy versus radiation therapy across rare prostate cancer subtypes. Radical prostatectomy was associated with significantly lower cancer-specific mortality in acinar, ductal, and neuroendocrine carcinomas. However, no survival difference was found between treatments for mucinous and signet ring cell adenocarcinoma.

Siech C, de Angelis M, Jannello LMI, Di Bello F, Rodriguez Peñaranda N, Goyal JA, Saad F, Shariat SF, Micali S, Longo N, de Cobelli O, Briganti A, Wenzel M, Mandel P, Kluth LA, Chun FKH, Karakiewicz PI. *Annals of surgical oncology*. PMID: 41718902

*prospective clinical trial*

**Five-Year Follow-Up of Lenvatinib Plus Pembrolizumab in Endometrial Cancer.** Five-year follow-up from the KEYNOTE-775 trial shows continued durable benefit of lenvatinib plus pembrolizumab in advanced endometrial cancer. Five-year overall survival rates were 19.9% versus 7.7% for chemotherapy, with no new safety signals. These results further support this regimen as a standard of care for advanced endometrial cancer.

Makker V, Colombo N, Casado A, Santin AD, Colomba E, Miller DS, Fujiwara K, Pignata S, Yonemori K, Kim YM, Baron-Hay S, Ray-Coquard I, Shapira-Frommer R, Kristeleit R, Nishio S, Suzuki S, Guerra Alía EM, Sanli UA, Selle F, Shikama A, Martínez Rodríguez JL, Arik Z, Arican A, Sebastianelli A, Yu Z, McKenzie J, Kruger S, Meng R, Okpara CE, Lorusso D. *Journal for immunotherapy of cancer*. PMID: 41714113

*psycho-oncology studies*

**Qualitative Research on Health-Related Quality of Life (HRQoL) in Advanced Cancer Patients Requiring Palliative Care.** A systematic review of 20 qualitative studies on outcomes, needs, experiences, preferences, concerns and HRQoL of advanced cancer patients requiring palliative care in Europe identified key themes, including primarily psychological function such as anxiety, coping mechanisms and decision-making, as well as unmet needs in clinical management, information and communication.

Lizano-Barrantes C, Amat-Fernandez C, Garin O, Luer-Aguila R, Pardo Y, Rojas-Concha L, Thong MSY, Apolone G, Brunelli C, Caraceni A, Couespel N, Bos N, Groenvold M, Kaasa S, Ciliberto G, Lombardo C, Pietrobon R, Pravettoni G, Sirven A, Vachon H, Gilbert A, Velikova G, Ferrer M, EUonQoL Working Group. *Quality of life research*. PMID: 41706236

*meta-analysis*

**Meta-Analysis of metastases-directed therapy for Oligometastatic Prostate Cancer.** A meta-analysis, including seven trials (574 patients), evaluated metastasis-directed therapy (MDT) for oligometastatic prostate cancer. Adding MDT to standard of care significantly improved progression-free survival, radiographic progression-free survival, and castration resistance-free survival. However, overall survival benefit was not statistically significant, warranting further research.

Tang C, Sherry AD, Hwang H, Farris DP, Francolini G, Di Cataldo V, Livi L, Tran P, Corn PG, Aparicio A, Simontacchi G, Kiess AP, Wang JH, Fonteyne V, Bultijnck R, Phillips R, Deek MP, Olson R, Harrow S, Marvaso G, Lorubbio C, Jerezczek-Fossa BA, Ludmir EB, Blanchard P, Warner A, Sun R, Palma DA, Ost P. *The Lancet. Oncology*. PMID: 41643695

*mechanism-oriented research*

**Glycogen Accumulation and Metabolic Dysregulation in Ataxia Telangiectasia.** This study identifies widespread glycogen accumulation as a key feature of ataxia telangiectasia, driven by dysregulated glucose metabolism and impaired mitochondrial respiration. Inactivating FNIP2, which interacts with the SERCA2b calcium channel, rescues these metabolic defects and improves cellular viability, suggesting a novel therapeutic target for this complex disease.

Vinciguerra M, El Kharef C, Bruhn C, Falbo L, Milanese C, Audano M, Beznoussenko GV, Mironov AA, Delia D, Foiani M, Mastroberardino PG, Mitro N, Costanzo V. *Cell death & disease*. PMID: 41771847

*other clinical and biomedical research*

**Sun Protection Habits in Italian Families with Young Children.** A cross-sectional study involving 1,288 Italian families highlighted inadequate sun protection for 97% of the year, underlining the need for year-round sun safety education. Indeed, while 53% applied sunscreen more than once daily during holidays, 72% used no additional preventive measures during outdoor activities out of the holiday period.

De Giorgi V, Gaeta A, Venturi F, Magnaterra E, Tomassini GM, Borgognoni S, Zuccaro B, Perillo G, Cecchi G, Fazzari F, Gandini S, Covarelli P. *Dermatology reports*. PMID: 41779002

*mechanism-oriented research*

**Faecalibacterium prausnitzii Ameliorates Motor Deficits in Parkinson's Disease (PD) Model.** The administration, in PD murine models, of a set of microbial taxa typically depleted in PD patients improved motor and gastrointestinal deficits. In particular, a single species –Faecalibacterium prausnitzii– was sufficient to correct gut microbiome alterations, induce anti-inflammatory immune responses, and reduce  $\alpha$ -synuclein aggregates in the brain, supporting the development of probiotic therapies for Parkinson's disease.

Moiseyenko A, Antonello G, Schonhoff AM, Boktor JC, Long K, Dirks B, Oguienko AD, Winnett AV, Simpson P, Daeizadeh D, Ismagilov RF, Krajmalnik-Brown R, Segata N, Waldron LD, Mazmanian SK. *NPJ Parkinson's disease*. PMID: 41786774

*review/commentary*

**Current State and Future Perspectives of Cancer Vaccines.** While Sipuleucel-T for prostate cancer remains the only FDA-approved cell-based vaccine for solid tumors, innovative approaches like personalized neoantigen vaccines and mRNA-based vaccines show promising preclinical and early-phase results, with ongoing trials exploring their potential in combination with other immunotherapeutic agents.

Iranzo J, Giordano E, Marsicano RM, Trapani D, Marra A, Belli C, Zagami P, Berton Giachetti PPM, Ferraro E, Minchella I, Crimini E, Curigliano G. *Vaccines*. PMID: 41746058

*psycho-oncology study*

**Development of a Patient Decision Aid for Early Breast Cancer in Italy.** This protocol describes the development – and future testing– of a patient decision aid, to promote shared decision-making –enhancing patients' engagement, adherence to treatment and satisfaction–, for early breast cancer patients in Italy. A pilot randomized controlled trial will assess the tool's impact on anxiety, depression, distress, quality of life, and shared decision-making compared to standard care.

Sdinami S, Sebri V, Monzani D, Zagami P, Criscitiello C, Grasso R, Bagnardi V, Curigliano G, Pravettoni G. *BMJ open*. PMID: 41734922

*other clinical and biomedical research*

**Cognitive Biases Underlying Nursing Errors.** A study involving 130 nurses revealed that incongruent clinical data (between prior knowledge and new information) correlate with nursing errors (diagnostic and prioritization accuracy), and suggest that targeted training is needed to resolve conflict between mental models and new information.

Milani A, Saiani L, Gandini S, Misurelli E, Lacapra S, Cafiero C, Boselli S, Massaro MA, Sponton A, Zoppini L, Mazzocco K. *Diagnosis (Berlin, Germany)*. PMID: 41832612

*meta-analysis*

**Meta-Analysis of Treatment Delays on Breast Cancer Survival.** A meta-analysis including 18 studies showed that each 4-week delay in breast cancer treatment initiation increases mortality risk by over 10%. The study underscores the urgency of minimizing unnecessary diagnostic-to-treatment delays.

Ungvari Z, Fekete M, Buda A, Lehoczki A, Munkácsy G, Scaffidi P, Bonaldi T, Fekete JT, Bianchini G, Varga P, Ungvari A, Györfy B. *GeroScience*. PMID: 40490647

*prospective clinical trial*

**Phase III VIKTORIA-1 Trial of Gedatolisib in Advanced Breast Cancer.** In the phase III VIKTORIA-1 trial, gedatolisib plus fulvestrant, with or without palbociclib, significantly improved progression-free survival versus fulvestrant alone in patients with hormone receptor-positive, HER2-negative, PIK3CA wild-type advanced breast cancer progressing on prior CDK4/6 inhibitors.

Hurvitz SA, Layman RM, Curigliano G, André F, Cristofanilli M, Kim SB, Martínez Rodríguez JL, Nadal JC, Kim GM, Lo L, Remolina-Bonilla YA, Rosselli G, Emile G, Korbenfeld E, Puig JM, Wesolowski R, Martin M, Ring A, Han HS, Giordano A, Mutka SC, Moss K, Suzuki S, Sullivan B, Gorbachevsky I, Pistilli B, VIKTORIA-1 Study Group. *Journal of clinical oncology*. PMID: 41802242

*correlative/descriptive research*

**Age-Specific Association of Nevi with Melanoma Risk.** A pooled analysis of nine studies found that atypical nevi are a stronger melanoma risk factor in younger individuals (under 40 years) compared to older individuals (over 60 years). Common nevus count was associated with increased risk in both age groups. These age-specific differences have implications for targeted prevention and clinical management.

Doi G, Gaeta A, Ribero S, Gruis N, Newton-Bishop J, Polsky D, Lazovich D, Ghiorzo P, Ribas G, Menin C, Stratigos AJ, Guida G, Puig S, Fargnoli MC, Kanetsky PA, Queirolo P, Bagnardi V, Bataille V, Raimondi S, Gandini S, M-SKIP study group. *Journal der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology : JDDG*. PMID: 41797512.

*retrospective clinical study*

**Outcomes of Trastuzumab deruxtecan (T-DXd) Treatment in Metastatic Breast Cancer by HER2 Quantitative Assays.** In 191 patients with metastatic breast cancer, T-DXd activity varied with temporal HER2 evolution, with longest activity observed in HER2-positive or stable HER2-low disease. Quantitative HER2 assays predicted time-to-next

treatment, while traditional immunohistochemistry showed limited predictive value. Moreover, high TOPO1 expression was linked to worse outcomes in HER2-negative disease.

Tarantino P, Kim SE, Hughes ME, Kusmick RJ, Smith K, Brasó-Maristany F, Nyein Chan NN, Paré Brunet L, Alder L, Garcia-Cortes D, Gomez Tejada Zanudo J, Pereslete AM, Noteware L, Moore H, Van Swearingen AED, Li T, Gupta H, D'Amico O, Martini A, Morganti S, Spindel J, Cook C, McLaughlin C, Dvir K, Garrido-Castro AC, Sammons S, Files J, Sendrick K, Buck S, Dillon D, Jeselsohn R, Li YY, Cherniack AD, LoRusso P, Lustberg M, Vega-León R, Pardo F, Davis J, Mueller C, Corgiat B, Curigliano G, Anders CK, Petricoin EF, Rimm DL, Prat A, Tayob N, Lin NU, Tolaney SM. *NPI precision oncology*. PMID: 41826432

*prospective clinical trial*

**A New Approach to Guide Surgical Management of Tongue Cancers – A Pilot Study.** Within a prospective pilot study including 9 patients with locally advanced (no clinically detectable lymph node disease, cN0) tongue cancers, the authors evaluated an approach based on the intraoperative indocyanine green (ICG) staining for the visualization of lymph nodes and lymphatic connections in the tumor area (which are at higher risk of metastatic colonization), to guide tumor-associated lymphatic system resection. The ICG method showed 100% sensitivity in detecting lymph nodes/lymphatic network; however, its ability to specifically distinguish metastases-colonized lymph nodes was limited. The study proposes ICG as a valid option for the management of tongue cancer.

Calabrese L, Gazzini L, Tagliabue M, Fazio E, Ronzani G, Bruschini R, Navach V, Camesasca V, Ansarin M, Abousiam M. *Acta otorhinolaryngologica Italica*. PMID: 41817664

*retrospective clinical study*

**Long-Term Outcomes of Organ-Preserving Surgery for Glottic Cancer.** A retrospective analysis including 661 patients with stage 1-3 (pT1-pT3) glottic squamous cell carcinoma treated with organ-preserving (transoral laser microsurgery) surgery showed a durable control of the disease. Moreover, their results further confirmed the reliability of the approach considering the anatomical regions involved (isoprognostic zone system) to refine the prognostication accuracy.

Chu F, Bandi F, Tagliabue M, Zorzi SF, Ruju F, De Benedetto L, Cattaneo A, Ansarin M. *Oral oncology*. PMID: 41812504

*prospective clinical trial*

**Characterization of Adverse Events with Olaparib in the SOLO2 Trial.** In the frame of the SOLO2 trial, the authors found that although the risk for adverse events was higher with olaparib maintenance therapy than placebo, adverse events typically occurred early (within the first 1-3 months), were mostly mild (grade 1-2), and manageable, supporting tolerable long-term use for the treatment of ovarian cancer patients.

Ledermann JA, Lortholary A, Penson RT, Asher R, GebSKI V, Provencher D, Bruchim I, Huzarski T, Barretina-Ginesta MP, Pipitone S, Mileshekin L, Colombo N, Park-Simon TW, Matsumoto K, Boere I, Mikheeva O, Kim JW, Girotto G, Vergote I, Carter D, Lowe ES, Pujade-Lauraine E. *International journal of gynecological cancer*. PMID: 41861615.

## What else is new in science?

(Text by Ai Yi (DeepSeek) and Alex Irwin (ChatGPT), revision by Stefania Averaimo)

**Training the Next Generation of AI-Enabled Cancer Scientists.** The article discusses the growing need for researchers who can work at the intersection of artificial intelligence (AI) and oncology, capable of integrating advanced computational methods with deep biological and clinical understanding, and translating computational discoveries into clinically meaningful applications. To address this gap, the authors propose an educational model, organized into six key principles: 1. training programs providing strong interdisciplinary foundations, combining computational sciences, statistics, biology, and medicine; 2. collaborative work environments where clinicians, biologists, and data scientists interact continuously; 3. education emphasizing real-world clinical problems rather than purely technical benchmarks, to ensure that AI tools remain relevant to patient care; 4. access to high-quality and diverse datasets, which are essential for building robust and unbiased AI systems; 5. mandatory ethical and regulatory training, including topics such as privacy, fairness, transparency, and reproducibility; 6. mentorship and institutional support to help trainees navigate the complexity of hybrid careers that do not fit traditional academic structures. The paper emphasizes that AI in oncology should not be viewed simply as a technological innovation, but as a transformative scientific approach that requires new educational paradigms. Without targeted investment in training, the full potential of AI for cancer diagnosis, prognosis, drug discovery, and personalized medicine may not be realized. Overall, the article calls for universities, cancer centers, funding agencies, and industry partners to collaborate in building multidisciplinary programs capable of preparing researchers who can bridge the gap between computational innovation and clinical oncology. *Cancer Discovery* 2026. PMID: 41972778.

**Multidimensional Intratumor Heterogeneity and Immunotherapy.** Intratumor heterogeneity includes genetic and non-mutational diversity that shapes cancer cell states and immune visibility. Variation in antigen processing across clones creates distinct immunological niches, constraining immunotherapy efficacy. Integrating multidimensional

measurements may improve biomarker identification and guide precision immune-based treatments. *Cell*. PMID 41997129.

**Intratumoural anti-CTLA4 with anti-PD1 in metastatic melanoma.** This phase 1b NIVIPIT trial evaluated intratumoural low-dose ipilimumab combined with intravenous nivolumab in untreated metastatic melanoma. Compared with standard intravenous ipilimumab, intratumoural administration significantly reduced severe treatment-related adverse events while maintaining strong antitumor activity. Responses were observed in both injected and uninjected lesions, supporting systemic immune activation. Immune profiling identified activated regulatory T cells, Fc $\gamma$  receptor-positive macrophages, and intratumoural Fc $\gamma$  receptor expression as correlates of durable clinical benefit. The findings support intratumoural anti-CTLA4 strategies to improve efficacy while minimizing toxicity. *Nature*. PMID: 42056527.

**Fecal Transplants Boost Immunotherapy.** Clinical trials show fecal microbiota transplantation enhances first-line immune checkpoint inhibitor efficacy in renal cell carcinoma, melanoma, and lung cancer. Benefit arises from functional microbiome remodeling, depletion of harmful taxa, and systemic immunometabolic modulation, supporting microbiome-directed strategies in cancer immunotherapy. *Cell*. PMID 41997122.

**Microbiome Roles in Immune-Related Adverse Events.** Immune checkpoint inhibitors can cause off-target toxicities called immune-related adverse events (irAEs). Emerging evidence implicates tissue microbiomes, especially in gut, lung, and skin, as mediators. Focusing on ICI colitis, this review examines microbial and immune drivers, aiming to encourage therapies that reduce irAE risk while preserving anti-tumor efficacy. *Nature reviews. Cancer*. PMID 41992000.

**Transitional Junctions in Hormone-Driven Cancers.** Lightsheet microscopy of intact breast and prostate tumors identified transitional junctions from precancer to invasion. Spatial transcriptomics revealed gene expression features including MGP/PLAT loss in breast cancer and GDF15/ALDH1A3 upregulation in prostate cancer. Tumor-associated macrophage enrichment suggests immune involvement drives invasiveness. *Cancer discovery*. PMID 41997105.

**Progenitor-Like State in Pancreatic Cancer (PDAC) Initiation.** In mouse PDAC models, a progenitor-like cell population co-activates oncogenic and tumor-suppressive programs with senescence-like responses. This cell population's niche undergoes stepwise remodeling mirroring invasive cancer. KRAS inhibition depletes these cells while p53 suppression enables expansion, revealing a critical window for intercepting malignancy. *Cell*. PMID 41990751.

**Clonal Selection and Tumor Promoters in Cancer.** Normal tissues harbor millions of cells with driver mutations without forming tumors. Exogenous carcinogens may increase cancer risk by promoting expansion of pre-existing mutant clones rather than by mutagenesis. Understanding Darwinian selection in tissues enhances prospects for cancer prevention by targeting environmental or endogenous tumor promoters. *Nature*. PMID 41986628.

**Learning Drug Resistance Through AP-1 Factors.** Cancer cells escape therapy via mutational processes or cellular plasticity. This article proposes a framework where adaptive drug-resistant states are learned by AP-1 transcription factors. *Nature*. PMID 41986626.

**Intratumoral Microbes and Cancer Hallmarks.** The field of tumor microbiota faces technical and interpretive challenges. This commentary synthesizes evidence linking intratumoral microbes to cancer hallmarks, critically evaluates detection methods, and proposes minimal reporting standards to establish microbial presence, viability, and causality for clinically actionable insights. *Cancer cell*. PMID 41825441.

**Germline BRCA2 Dictates Resistance Trajectories.** In over 5,800 breast cancer patients, germline BRCA2 mutations predispose to acquired RB1 loss-of-function during CDK4/6 inhibitor treatment due to RB1 hemizyosity and homologous recombination deficiency. PARP inhibition outperforms CDK4/6i in preclinical models, suggesting that prioritizing PARP inhibition may intercept RB1-loss resistance trajectories. *Nature*. PMID 41781623.

**DNA Methylation Subtypes Predict immune checkpoint inhibitor (ICI) Response in Mesothelioma.** Multi-omic analyses of mesothelioma patients identified four methylation subsets. The "LOW" subset showed T/B cell-rich microenvironment and best ICI response, while the methylation-based "CIMP" subtype had depleted immunity and poorest outcomes. A methylation-based decision tool was developed to predict immunotherapy outcome in patients. *Nature genetics*. PMID 42045690.

**Transposable elements as a hallmark of cancer.** This review highlights the emerging role of transposable elements (TEs) in cancer biology. Normally silenced by epigenetic mechanisms, TEs become aberrantly activated during oncogenic transformation, contributing to genomic instability, transcriptional rewiring, and inflammatory signaling. The authors describe how TE-derived nucleic acids trigger innate immune pathways and influence six classic hallmarks of cancer, including proliferation, immune evasion, and metastasis. They propose widespread TE activation as a novel hallmark of cancer and discuss therapeutic opportunities targeting TE-induced immune responses. *Cancer Discovery*. PMID: 41997583.

**Transposable Elements (TE) Regulate Leukemia Stem Cell Stemness.** The authors found that accessibility at 121 TE subfamilies distinguishes leukemia stem cells from mature leukemic cells and stratifies patients by stemness and

survival. Chromatin editing established TEs as regulators of primitive versus mature cell states. *Nature genetics*. PMID 42082719.

**Precancerous Niche Determines Early Tumor Survival.** In nascent squamous tumors, stress responses in early tumor cells instruct underlying mesenchyme to form a supportive niche. Stimulated fibroblasts remodel extracellular matrix into a fibronectin-rich scaffold that promotes tumor growth. The niche alone confers neoplastic properties to normal epithelial cells, defining early tumor persistence and progression. *Nature*. PMID 41781610.

**Lung Digital Twins from Ex Vivo Perfusion Data.** Using the largest clinical ex vivo lung perfusion (EVLP) dataset, researchers developed lung digital twins modeling 75 parameters including physiology, biochemistry, radiography, and multi-omics. Direct comparison to experimental data demonstrated precise assessment of therapeutic efficacy, establishing EVLP-derived digital twins as a data-rich approach for evaluating treatments. *Nature biotechnology*. PMID 42082790.

**Luminal-to-Basal Axis in Bladder Cancer.** Multi-omic analyses (spatial and bulk transcriptomics and whole genome sequencing) of muscle-invasive bladder cancer reveals a continuous luminal-to-basal axis within tumors. Luminal profiles show FGFR3 enrichment while basal-like states, at invasive margins, are linked to EGFR signaling, EMT, and chemotherapy sensitivity. *Cancer discovery*. PMID 42126225.

**Secretome-Driven Immune Evasion in Microsatellite-Stable Colorectal Cancer (CRC).** Using two preclinical models of microsatellite-stable (MSS) and microsatellite-unstable (MSI) CRC expressing the same level of a specific T cell-recognized antigen, the authors showed that, despite the equivalent antigen presentation, MSS CRC resist T-cell killing unlike MSI tumors. This evasion is linked to the MSS tumor secretome, which suppresses immune responses via glycosylation-dependent alterations impairing immune recognition. The study suggests that targeting glycosylation pathways may restore immunotherapy efficacy in MSS-CRC. *Cancer discovery*. PMID 42126206.

**Stem-cell memory CAR T cells for post-transplant B cell malignancies.** This first-in-human study investigated donor-derived CD19 CAR T cells generated from stem-cell memory T (TSCM) cells in patients with relapsed B cell malignancies after allogeneic stem cell transplantation. CAR TSCM cells demonstrated superior engraftment, expansion, and persistence compared with conventional CAR T cells, achieving complete responses at low doses without lymphodepletion. Toxicity was mild and primarily associated with IFN- $\gamma$ -driven cytokine-release syndrome. Long-term persistence depended on sustained regeneration of stem-like CAR T cell populations, whereas resistance mechanisms were mainly tumor- and host-related. These findings establish CAR TSCM cells as a promising next-generation CAR T platform. *Cell*. PMID: 42066750.

**Personalized neoantigen vaccines in cancer therapy.** This review discusses the rapid development of personalized cancer neoantigen vaccines (PCVs) as a precision immunotherapy strategy. Neoantigens generated from tumor-specific mutations provide individualized targets capable of eliciting strong antitumor immune responses. Advances in sequencing technologies, bioinformatics, and vaccine platforms have enabled scalable identification and delivery of neoantigens across multiple cancer types. The authors analyze optimal clinical settings, timing, and combination strategies with other therapies, emphasizing translational challenges and opportunities necessary for integrating PCVs into broader clinical oncology practice. *Cancer Cell*. PMID: 42114514.

**AAV-Based Inducible IL-12 Enhances Radiotherapy.** Radiation enhances AAV vector-based tumor transduction. An AAV vector with an IFN-inducible promoter delivering IL-12 allowed for spatially controlled transgene expression in irradiated tumors. Combination with radiation generated a highly immunostimulatory tumor microenvironment leading to robust local and systemic antitumor responses (in an IFN- $\gamma$ - and FAS-dependent manner), proposing a safe and effective radiation-modulated gene delivery. *Cancer cell*. PMID 41875889.

**Targeting Glucocorticoid Receptor to Overcome Immune Evasion in Disseminated Tumor Cells.** In triple-negative breast cancer, surviving disseminated tumor cells show glucocorticoid receptor (GR) activation as a key driver of resistance to CD8+ T cells and NK cells. Pharmacological GR inhibition combined with immunotherapy reduced metastatic burden, identifying a therapeutic opportunity to eliminate DTCs. *Nature*. PMID 41781620.

**ER stress and antitumor immunity in cancer immunotherapy.** This review examines how endoplasmic reticulum (ER) stress and unfolded protein response (UPR) signaling shape tumor progression and resistance to immunotherapy. Stressors within the tumor microenvironment, including hypoxia and nutrient deprivation, activate ER stress pathways mediated by IRE1, PERK, and ATF6. These pathways not only support tumor survival and metastasis but also suppress antitumor immune responses by altering immune cell function. The article discusses therapeutic strategies targeting ER stress to improve immunotherapy efficacy and explores ER stress markers as predictive biomarkers. *Molecular Cancer*. PMID: 42046149.

**Lipid-Driven Mechanisms of Caveolae Formation and Scission.** In this review, the authors propose a lipid-based mechanism of formation of caveolae, different from those involved in the formation of clathrin-coated pits. Biophysical models for lipid-driven curvature generation and coupling with scission are presented. *Nature cell biology*. PMID 42026115.

**CAF-Secreted ECM Proteins Enhance DNA Repair in PDAC.** Pancreatic cancer stroma with cancer-associated fibroblasts secretes ECM proteins that activate NDRG1. NDRG1 is a DNA repair factor associating with replication forks, resolving stalled forks, and reducing R-loops. High NDRG1 expression correlates with poor survival and chemotherapy response, linking tumor stroma to replication fork homeostasis. *Nature cell biology*. PMID 42045570.

**FDA approval of tumor-treating fields for pancreatic cancer.** This report summarizes the FDA approval of Optune Pax, the first wearable tumor-treating field device authorized for locally advanced pancreatic cancer in combination with gemcitabine and nab-paclitaxel chemotherapy. The device delivers alternating electric fields that disrupt tumor cell division. Approval was based on the PANOVA-3 phase 3 trial, where patients receiving Optune Pax achieved improved median overall survival, one-year survival, pain control, and quality of life compared with chemotherapy alone. The article also reviews ongoing development of tumor-treating field technologies across multiple cancer indications. *Nature Biotechnology*. PMID: 41998389.

**Claudins as Therapeutic Targets in Solid Tumors.** Claudins are transmembrane proteins overexpressed in solid tumors, modulating oncogenic signaling and therapy resistance. CLDN18.2-targeting antibodies have reached clinical approval. Additional strategies include antibody-drug conjugates, bispecific antibodies, and CAR T cells. CLDN targeting represents a precision oncology approach relevant to multiple solid tumors. *Nature reviews. Cancer*. PMID 41772030.

**DLL3 on Circulating Tumor Cells Predicts Tarlatamab Response.** In small cell lung cancer, the bispecific antibody tarlatamab targets DLL3. Single-cell sequencing reveals DLL3 heterogeneity. Pretreatment DLL3 expression on circulating tumor cells (CTCs) predicts clinical benefit with 85% sensitivity and 100% specificity. Quantification of DLL3-positive CTCs enables patient stratification for this bispecific antibody therapy. *Cancer discovery*. PMID 41532856.

**Extracellular Vesicle Uptake and Fate in Recipient Cells.** Extracellular vesicles (EV) are key mediators of intercellular communication but their uptake and fate remain poorly understood. This review focuses on mechanisms underlying cell-specific targeting, signaling, and functional cargo delivery. Understanding these molecular mechanisms can provide new strategies to harness EVs as therapeutic nanovehicles. *Nature reviews Molecular cell biology*. PMID 41478877.

**Metastatic Dissemination and Seeding in Lung Cancer.** Analysis of 501 samples from 24 NSCLC patients shows metastases diverge genomically from primary tumors. In 62.5% of patients, multiple primary subclones disseminated, and over half of metastases were seeded by other metastases. Chromosomal instability may facilitate extra-thoracic spread, revealing metastatic diversity and seeding patterns. *Nature*. PMID 42056508.

**Tumor Organoids for Translational Cancer Therapy.** Tumor organoids are 3D culture systems retaining patient-specific architecture. Advances include microfluidic organoid-on-chip, bioprinting, and biomaterials enabling drug screening and functional profiling. Integrating organoid readouts with molecular data accelerates precision oncology. This review summarizes applications, limitations, and future directions for organoid-based cancer research. *Molecular cancer*. PMID 42106781.

**Path2Space Predicts Spatial Gene Expression from Histopathology Slides.** Path2Space is a deep-learning model predicting spatial gene expression from histopathology slides without costly molecular assays. Applied to 976 breast cancer tumors, it infers cell type abundances and identifies three spatially defined subgroups with distinct survival outcomes. This scalable approach enables large-cohort biomarker discovery for therapy response prediction. *Cell*. PMID 42105763.

**AI Model REDMOD Detects Occult Pancreatic Cancer.** REDMOD is an externally validated, automated AI model enabling occult PDA detection by identifying subvisual radiomic signatures of pre-diagnostic pancreatic cancer on standard CT images. *Gut*. PMID 42049489.

**TSPAN8+ EVs Drive Treg Expansion in Triple-Negative Breast Cancer.** Cancer stem cells in triple-negative breast cancer drive regulatory T cell differentiation via TSPAN8+ extracellular vesicles. TSPAN8 interacts with CD103 on T cells, activating LKB1-AMPK $\alpha$  and enhancing FOXP3 expression. Neutralizing TSPAN8+ EVs with a monoclonal antibody synergized with anti-PD-1 therapy in preclinical models. *Cancer cell*. PMID 42102811.

**Spatial Ecotypes in Tumor Microenvironment Profiling.** Machine learning identified nine conserved spatial ecotypes across carcinomas and melanomas with unique biology and immunotherapy response. These ecotypes were distinguishable by DNA methylation and identifiable in plasma cell-free DNA using deep learning, enabling multimodal liquid biopsy profiling for risk stratification and therapy personalization. *Nature*. PMID 42092150.

**Cancer treatment evolution. Cancer therapy has evolved from early cytotoxic drugs to precise, biology-driven approaches.** Initial treatments like chemotherapy broadly targeted rapidly dividing cells, causing significant toxicity but remaining widely used. Advances in molecular profiling enabled targeted therapies that inhibit specific oncogenic pathways or exploit tumor vulnerabilities, improving selectivity but often leading to resistance due to tumor heterogeneity and adaptability. At the same time, immunotherapies such as checkpoint inhibitors harness

the immune system to fight cancer, achieving durable responses in some patients, though with risks of autoimmunity. Newer strategies, including antibody-drug conjugates, bispecific antibodies, and CAR-T cells, aim to deliver highly specific and potent effects by targeting tumor antigens. Despite these advances, cancer's complexity and evolution continue to limit long-term success, highlighting the need for combination therapies that address multiple mechanisms and anticipate resistance. *Cell*. PMID: 41997133.

**Comprehensive genomic and transcriptomic profiling in advanced solid tumors.** This prospective study evaluated whole exome and whole transcriptome sequencing (CGTP) in 99 patients with advanced solid tumors who had prior negative results from targeted panel sequencing. CGTP identified actionable DNA alterations in 69.7% of cases and actionable altered RNA expression in 100% of cases. When integrated into routine care, 19.2% of patients received biomarker-matched therapy. The findings demonstrate that CGTP substantially increases detection of actionable alterations compared to conventional panel-based sequencing in patients with no prior therapy options. *Cancer discovery*. PMID: 41885383.

**Trastuzumab deruxtecan plus pertuzumab for HER2-positive advanced breast cancer.** This phase 3 trial compared first-line trastuzumab deruxtecan plus pertuzumab versus taxane, trastuzumab, and pertuzumab (THP) in HER2-positive advanced breast cancer. At interim analysis, the combination therapy significantly reduced progression or death risk, with no new safety signals. *The New England journal of medicine*. PMID: 41160818.

**Senescent cancer-associated fibroblasts drive lymph node metastases in early-stage pancreatic cancer (PDAC).** This study shows that senescent cancer-associated fibroblasts (senCAFs) promote lymphatic remodeling and lymph node metastasis in early-stage pancreatic cancer by increasing glucose metabolism and lactate production. The senolytic agent chidamide clears senCAFs, reducing tumor progression and improving chemo-immunotherapy efficacy, with promising results in a clinical trial for metastatic PDAC. *Cancer discovery*. PMID: 41891402.

**Pembrolizumab (immune checkpoint inhibitor, ICI) plus olaparib (PARP inhibitor) maintenance in homologous recombination deficient (HRD) metastatic pancreatic cancer.** The phase 2 POLAR trial tested efficacy of pembrolizumab plus olaparib administration as maintenance therapy after platinum-based chemotherapy in biomarker-stratified metastatic pancreatic cancer patients. The results suggest that a sub set of HRD pancreatic cancer patients may have durable benefits from the combined administration of PARPi/ICI as maintenance therapy. *Nature medicine*. PMID: 41882405.

**Epigenetic memory of inflammation primes stem cells for cancer.** Using a mouse colitis model, this study demonstrates that colonic stem cells retain an epigenetic memory of inflammation for over 100 days after resolution. By simultaneously profiling gene expression, chromatin accessibility, and clonal history (using SHARE-TRACE), the authors show memory is inherited through stem cell divisions. Colitis results, in stem cells, in increased AP-1-regulated gene expression following oncogenic mutation, accelerating tumor growth. *Nature*. PMID: 41882356.

**Individualized neoantigen mRNA vaccine in triple-negative breast cancer (TNBC).** This study assessed an individualized neoantigen mRNA vaccine in 14 patients with TNBC following surgery and adjuvant/neoadjuvant therapy. Nearly all patients developed durable, functional neoantigen-specific T cells, and eleven patients remained relapse-free for up to six years. *Nature*. PMID: 41708868.

**Metastatic trabecular morphogenesis: a 3D developmental program in breast cancer.** Combining 3D imaging, single-cell and spatial transcriptomics in human breast cancer, and functional studies in in vivo murine models, this work identifies a key process of macrometastasis expansion, namely the generation of a specific 3D structure of the metastases (metastatic trabecular morphogenesis, MTM) through the deployment of the branching morphogenesis program occurring during development. The process requires ETV1/4/5 as master regulators of metastatic outgrowth (but dispensable for primary tumor growth) and FGF-FGFR signaling in the stroma. FGF-FGFR signaling is an actionable therapeutic vulnerability specific to the macrometastatic stage. *Cell*. PMID: 41923644.

**Organ-informed precision oncology for metastasis.** This perspective argues that metastasis is a multiorgan disease where disseminated cancer cells undergo profound, tissue-specific reprogramming that reshapes their identity, vulnerabilities, and therapeutic responses. The authors propose an organ-informed precision oncology framework that integrates these tissue-induced programs into treatment design, moving beyond primary tumor-based approaches to account for the distinct biology of metastases in different organs. *Cancer discovery*. PMID: 41918349.

**Cellular senescence in cancer: hallmarks and therapeutic opportunities.** This review synthesizes the hallmarks of cellular senescence, a stress-response program inducing durable proliferative arrest and involving extensive chromatin, metabolic, and immune remodeling. Focusing on cancer, the authors discuss how senescence influences tumor initiation, evolution, and therapy response through cell-intrinsic and microenvironmental mechanisms. Emerging strategies to therapeutically modulate senescence are evaluated, highlighting opportunities and challenges for precision intervention. *Cell*. PMID: 41935528.

**Inflammatory cytokines hijack amino acid sensing to drive immunoevasion.** This study shows that in the tumor microenvironment, inflammatory cytokines cause hijacking of the amino acid-sensing mTORC1 signaling by cancer cells, despite nutrient insufficiency. ZBTB5 translates the inflammatory signals to restore mTORC1 (by promoting phosphorylation at S127, recruiting Cullin3 to degrade NPRL2 within the GATOR1 complex), thus boosting tumor amino acid uptake, exacerbating nutrient restriction, and death of CD8+ T cells, leading to cancer immunoevasion and checkpoint inhibitor resistance. Blocking ZBTB5 sensitizes immunotherapy by alleviating amino acid restriction. *Nature cell biology*. PMID: 41933211.

**Germline cancer predisposition variants in the 100,000 Genomes Project.** This retrospective cohort study of 14,765 UK cancer patients from the 100,000 Genomes Project found that 711 (5%) carried pathogenic/likely pathogenic variants in 109 cancer predisposition genes. Most frequent were CHEK2 (0.82%) and BRCA2 (0.75%). Variant rates varied by tumor type, highest in ovarian cancer (9% of 610 cases). Only 45% of variants had a known association with the diagnosed tumor, highlighting implications for expanded genetic testing and the need for careful variant interpretation to yield benefit and avoid harm. *The Lancet. Oncology*. PMID: 41926963.

**HER2 heterogeneity drives resistance to antibody-drug conjugates (ADCs).** This study describes human HER2 heterogeneous breast cancer models with both ERBB2-amplified (HER2hi) and non-amplified (HER2lo) populations from the same tumor. Cooperation between subclonal populations drives resistance to HER2-targeting ADCs like T-DXd, while HER2lo cells remain sensitive to HER2 kinase inhibitors. CRISPR screens identified ABCC1 and USP9X as sensitizers of HER2lo cells to T-DXd. USP9X inhibition enhances lysosomal targeting of HER2, potentiating ADC payload release and reducing tumor recurrence after T-DXd treatment. *Cancer discovery*. PMID: 41925564.

**A physics-based framework for cancer cell state and plasticity.** The authors propose a physics-based framework defining cancer cell state on the basis of directly measurable physical variables such as cell surface area (S) and volume (V). Changes in S and V reflect cell plasticity (which, through the physics-based model, can be measured/quantified). Therapy alters S-V relations and trajectories, which can be quantified by the model, allowing to design drug combinations capable of interfering with the process and steer heterogeneous cancer cell populations toward nonviable states, offering a predictive alternative to therapies targeting oncogenic mutations or predefined subpopulations. *Cancer discovery*. PMID: 41918348.

**IMPT versus IMRT for oropharyngeal squamous cell carcinoma.** The phase 3 TORPEdO trial randomly assigned 205 patients with locally advanced oropharyngeal cancer to intensity-modulated proton therapy (IMPT, n=136) or intensity-modulated radiation therapy (IMRT, n=69) with cisplatin. Results showed that IMPT and IMRT had similar late functional outcomes (local control, survival, and quality of life did not differ), with IMRT remaining standard of care. *Lancet*. PMID: 41875914.

**AI model predicts Oncotype DX recurrence score from histopathology slides.** A multimodal deep-learning model was trained on digital whole-slide images and clinical features to predict Oncotype DX recurrence scores in hormone receptor-positive, HER2-negative early breast cancer. AI-based risk stratification was prognostic for recurrence-free interval. Chemotherapy benefit was seen in premenopausal AI-identified high-risk patients but not in postmenopausal AI-identified low-risk patients. The results obtained with the model were true also in six external cohorts. *The Lancet. Oncology*. PMID: 41831466.

**Bifidobacterium catenulatum suppresses colorectal cancer (CRC) and enhances immunotherapy efficacy.** Across multiple cohorts, Bifidobacterium catenulatum was significantly depleted in CRC patients versus healthy controls. Oral administration inhibited tumor growth in several CRC models (MC38, CT26, Apcmin/+ mice, AOM/DSS). B. catenulatum synergized with anti-PD-1 therapy in MSS CRC models by enhancing intratumoral CD8+ T cell infiltration. Acetate derived from the bacteria binds to MCT-4 on CD8+ T cells, activating MAPK signaling, and MCT4 ablation abolished acetate-mediated activation. B. catenulatum is a potential adjuvant to improve immunotherapy against MSS CRC. *Gut*. PMID: 41956809.

**Single-cell and population-scale metabolomics: two advancing frontiers.** This perspective highlights two rapidly advancing metabolomics frontiers: single-cell metabolomics, which resolves metabolic states of individual cells and cell-to-cell heterogeneity, and population-scale metabolomics, which profiles metabolites across large cohorts to discover disease markers, environmental exposures, and genetic variation. Both face shared challenges (identification, quantification, multimodal integration) and advantages (capturing non-genetic influences, scalability). Continued advances in scalability will enable comprehensive metabolic atlases bridging cellular and interindividual variation. *Nature*. PMID: 41951964.

**Mitochondrial complex I dysfunction impairs anti-cancer activity of NK cells in glioblastoma (GBM).** Natural killer cells from glioma patients show impaired oxidative phosphorylation and mitochondrial complex I activity. Multiomics identified NDUFA9 (complex I subunit) as a critical mediator of NK cell metabolic fitness. Ndufa9 knockout compromised mitochondrial function, anti-tumor efficacy, and memory-like phenotype by reprogramming metabolism toward glutamine dependence. Decreased  $\alpha$ -KG/succinate ratio increased repressive H3K27me3 on

immune function genes. Resveratrol-mediated NDUFA9 activation or overexpression restored complex I activity and enhanced NK cell anti-GBM function. *Cancer discovery*. PMID: 41944586.

**AI agents in cancer research and oncology.** Since 2022, large language models have progressed beyond classification, to logical reasoning, and acting as autonomous agents, capable of sensing, learning, and acting upon their environments. AI agents can interact with external knowledge or software, and execute multistep tasks with minimal human input. In cancer research, evidence shows agents can optimize drug design and propose therapeutic strategies. This primer explains capabilities, limitations, and ethical/regulatory frameworks of AI agents for cancer researchers and oncologists. *Nature reviews. Cancer*. PMID: 41526721.

**Targeting chronic inflammation to overcome therapy resistance.** Chronic inflammation in the tumor microenvironment (TME) drives immune evasion and therapy resistance via cytokines like IL-6, IL-1 $\beta$ , TNF- $\alpha$ , and TGF- $\beta$  activating STAT3, NF- $\kappa$ B, and HIF-1 $\alpha$  pathways. This creates an immunosuppressive "cold" TME with regulatory T cells and myeloid-derived suppressor cells. Targeting these axes by IL-6R neutralization, JAK/STAT3 inhibitors, or TGF- $\beta$  blockade restores anti-tumor immunity. Combination therapies targeting these inflammatory pathways hold promise in converting refractory tumors and inducing durable responses. *Mol Cancer*. PMID: 41703602

**Spatial mapping of metabolic niches in pancreatic cancer.** Using spatial RNA sequencing, this study mapped molecular heterogeneity in PDAC. Metabolically "hot", high grade tumor niches, showing concurrent glycolysis and lipogenesis, were identified as "subtype-agnostic" therapeutic targets. Preclinical models confirmed that both classical and basal tumors are susceptible to glycolysis inhibition, challenging the dogma of subtype-specific therapies. *Mol Cancer*. PMID: 41896850

**Ethical alternative animal models for cancer research.** The 3R principle (Replacement, Reduction, Refinement) promotes ethical cancer research using alternative models. This review critically examines in vitro, in silico, and four 3R-compliant animal models: chicken chorioallantoic membrane, Danio rerio, Drosophila melanogaster, and Caenorhabditis elegans. It assesses their advantages, limitations, and translational relevance, with practical considerations for reproducibility. The review aims to help researchers select ethical and effective preclinical models to advance cancer research. *Mol Cancer*. PMID: 41888798

**CAR-NK cell therapy for hematologic malignancies.** CAR-NK cells represent a promising alternative to CAR-T therapy, especially due to their potential reduced toxicity. This review summarizes advances in CAR-NK therapy for the treatment of hematologic cancers, addressing existing challenges, such as limited persistence, immunosuppressive microenvironment, antigen evasion, host rejection. Strategies include novel CAR designs, combination therapies, improved manufacturing, and emerging platforms for cell sorting and cryopreservation. *Mol Cancer*. PMID: 41882710

**Oncolytic viruses as next-generation cancer immunotherapy – a review.** Oncolytic viruses (OVs) couple direct tumor lysis with broad immune activation. Clinical translation faces challenges including inefficient delivery, restricted tumor selectivity, and premature immune clearance. This review synthesizes OV classifications, mechanisms, and clinical developments, highlighting innovations in synthetic engineering, targeted delivery, and combination strategies with immunotherapies and conventional modalities. *Mol Cancer*. PMID: 41917920

**Micro- and nano- plastics in carcinogenesis – a review.** Micro- and nanoplastics (MNPLs) are found in human tissues, with higher concentrations in cancerous versus healthy tissues. Smaller nanoplastics cross biological barriers and accumulate intracellularly, while larger microplastics cause physical stress. MNPL exposure induces harmful effects via NF- $\kappa$ B, JNK-MAPK, ERK, JAK-STAT, and ROS-driven pathways, triggering inflammation, DNA damage, apoptosis, and fibrosis. Dysregulation of PI3K-AKT-mTOR, Wnt signaling, and cell-cycle regulators promotes malignant transformation, supporting MNPLs' potential role in carcinogenesis. *Mol Cancer*. PMID: 41928262

**Targeting metabolic dependencies in pancreatic cancer.** This review highlights context-specific metabolic dependencies in pancreatic cancer (PDAC), arising from cancer-stroma interactions, which supply energy and confer therapy resistance. Moving from broad metabolic inhibition to precise targeting of the tumor-stroma metabolic ecosystem could substantially improve PDAC prognosis. *Mol Cancer*. PMID: 41904584

**Plasma biomarkers for cancer detection and staging.** This case-control study measured 165 proteins and 244 metabolites in colorectal (CRC), lung, ovarian cancer patients, and healthy controls. Biomarkers of 2-4 proteins were found to distinguish cancer cases from healthy controls (CEACAM5, FLT1, IL19, Ferritin, for CRC; FNDC5, MDK, PLAUR, CEACAM5, for lung cancer; MUC16/CA125, PLG, for ovarian cancer). Performance matched or surpassed existing tests. Metabolites were more useful for tumor staging than early detection. *Mol Cancer*. PMID: 41943016

**Telesurgery in oncology – an editorial.** By enabling remote robotic surgery, telesurgery is transforming surgical oncology. A 2026 trial showed non-inferior success versus local surgery. While promising for underserved regions and workforce shortages, challenges include poor network infrastructure, high costs, patient safety, legal and informed consent issues, and dehumanization risks. WHO and the Society of Robotic Surgery are addressing these gaps to democratize surgical oncology. *Lancet Oncol*. PMID: 41926952

**Clinical utility of routine whole-genome sequencing in solid tumors.** Real-world data from 888 patients showed feasibility and success (89% of cases) of paired tumor-normal whole-genome sequencing (WGS), with a 6-day turnaround. Actionable biomarkers were found in 73% of patients, with 40% receiving biomarker-guided treatment within a year, linked to 31% longer median survival. In cancers of unknown primary, WGS aided diagnosis or treatment in 67%. Overall, a clinical impact was seen in 41% of tested patients, supporting its routine employment. *Nature medicine*. PMID: 41862707

**Open and sustainable AI in the life sciences.** This Perspective addresses the challenges associated with the rapid adoption of AI in research, such as poor reusability and reproducibility, and the fragmented AI ecosystem, providing practical recommendations to connect researchers with relevant resources, facilitating the implementation of sustainable, reusable and reproducible AI, ultimately aiding policy development and AI implementation. *Nature methods*. PMID: 41862658

**Roadmap for developing effective cancer vaccines.** While cancer vaccines have not yet matched the success of infectious disease vaccines, recent encouraging phase 1 and 2 trial results have renewed interest. This Review outlines key optimization strategies: improved efficacy proxies, selection of high-quality neoantigens (using modular platforms with innate immunostimulatory capabilities), and a focus on early-stage cancer. *Nature medicine*. PMID: 41814007

**Peritumoral adipose tissue promotes tumor immune escape.** Single-cell RNA analysis of peritumoral visceral adipose tissue (tVAT) in colorectal cancer reveals a highly immune-infiltrated microenvironment (especially enriched in CD8+ T cells). Mechanistically, tVAT activates the CXCL12(in tVAT)-CXCR4 (in immune cells) axis, promoting immune escape of cancer cells. Targeting this tVAT-tumor interaction enhanced anti-PD1 therapy efficacy, highlighting tVAT as a potential immunotherapy target. *Nature cell biology*. PMID: 41714703

**Metabolic regulation in hematopoietic stem cells.** This review examines the metabolic landscape of hematopoietic stem cells (HSCs), highlighting how intrinsic bioenergetic programs control quiescence, self-renewal, and differentiation. It also covers dynamic metabolic interactions with the bone marrow microenvironment and discusses how metabolic dysregulation in healthy and aged HSCs correlates with leukemogenesis, emphasizing its importance for regenerative medicine and cancer prevention. *Nature cell biology*. PMID: 41673169

**Metabolomics workflows for studying cancer metabolism.** This work details metabolomics workflows to explore nutrient demands of cancer cells, identifying metabolic relationships in the tumor microenvironment, and exploring crosstalk with distant tissues. Approaches span cell cultures, animal models, and human specimens, with emphasis on emerging mass spectrometry technologies and computational pipelines for global metabolite and lipid profiling. *Nature reviews. Cancer*. PMID: 41720944

**Human user testing reveals LLM limitations for medical advice.** Findings collected in a controlled study involving with 1,298 participants suggest that systematic human testing is recommended before public deployment of large language models (LLMs) for medical advice. Indeed, despite LLM performance accuracy (correctly identifying conditions in 94.9% of cases and choosing a course of action in 56.3% on average), they failed to help users identify conditions or choose actions better than a control group. User interactions were identified as a key challenge. *Nature medicine*. PMID: 41663592

**“Context switching” for medical AI.** This Perspective envisions “context switching” as an emergent solution to adapt medical AI tools, without retraining. By this approach, generative models can tailor outputs to patient biology or care setting, multimodal models can handle missing data, and agent models can coordinate tools. This approach aims to enable reliable AI that scales to an infinite number of contexts. *Nature medicine*. PMID: 41634392

**Intratumoral vaccination chimera reprograms cancer cells.** Reduced antigen-presentation leads to a limited number of tumor-reactive T cells. Researchers developed an intratumoral vaccination chimera to reprogram tumor cells into an antigen-presenting state (APC-like tumor cells). The chimera, consisting of a PD-L1 degrader conjugated to immunogenic antigens, relieved immune checkpoint inhibition and enforced antigen presentation, leading to the reactivation of resident tumor-specific CD8+ T cells and ultimately fostering durable anti-tumor immunity. The strategy showed efficacy in in vitro, in vivo and patient-derived breast cancer models. *Nature*. PMID: 41501465

**Cancer-derived molecule inhibits Alzheimer's pathology.** Epidemiological data show lower Alzheimer's incidence in cancer patients. This study finds that peripheral cancer inhibits amyloid pathology and rescues cognition by secreting cystatin-c, which binds amyloid oligomers and activates TREM2 on microglia, enabling degradation of pre-existing plaques. Effects were abolished by TREM2 deletion or mutation, establishing new therapeutic avenues for amyloid degradation. *Cell*. PMID: 41576952

**Synthetic data in cancer research and clinical trials.** Synthetic data generated by AI can overcome data access barriers and reduce trial costs by replicating real-world statistical properties. However, challenges in standardization, bias, privacy, and quality assurance limit reliability. This Review explores applications in cancer research, critically examines pitfalls, and proposes best practices to enhance fidelity and utility, emphasizing that rigorous validation is essential. *Nature reviews. Cancer*. PMID: 41720945

**Mechanisms and consequences of protein subcellular localization.** Biological functions depend on the spatiotemporal distribution of proteins, with multilocalization enabling multifunctionality. This Review discusses mechanisms and localization controlling protein function. Mislocalization plays roles in cancer, neurodegeneration, and autoimmunity. The authors address technological challenges in subcellular proteomics and spatial biology to link dynamic localization with function across scales. *Nature reviews. Molecular cell biology*. PMID: 41709002

**Next-generation strategies targeting tumor-associated macrophages.** Tumor-associated macrophages (TAMs) exhibit functional plasticity that can either promote tumors or mediate elimination. This Review covers next-generation targeting strategies including effectorization via modulation of eat-me pathways, reprogramming through immune checkpoint inhibition, epigenetics, metabolism, and bioengineering approaches like bispecific antibodies, lipid nanoparticles, and anti-TAM CAR T cells. These therapies aim to enhance T cell responses and enable durable cancer eradication. *Cancer cell*. PMID: 41759521

**Induction immunotherapy followed by chemoradiotherapy for bladder preservation.** The phase 2 INDIBLADE trial tested induction therapy with ipilimumab plus nivolumab, followed by chemoradiotherapy, in 50 patients with muscle-invasive bladder cancer. Two-year event-free survival was 78%, 2-year overall survival was 96%. Grade 3-4 adverse events occurred in 24% for immunotherapy and 7% for chemoradiotherapy. ctDNA clearance after immunotherapy predicted outcomes, supporting this bladder-sparing approach. *Nature medicine*. PMID: 41760951

**Microbiome modulation of graft-versus-host disease after transplantation.** Allogeneic hematopoietic cell transplantation (allo-HCT) is curative but limited by graft-versus-host disease (GVHD). This Review summarizes preclinical and clinical studies showing that intestinal microbiome dysbiosis independently predicts transplantation-related and GVHD-related mortality. Preclinical work has characterized crosstalk between microbiome and host immunity, while ongoing trials investigate microbiota-focused approaches to improve outcome of allo-HCT, paving the way for personalized therapies integrating microbiome profiles. *Nature reviews. Cancer*. PMID: 41748753

**The “Ecological network balance index” quantifies gut microbiome dysbiosis.** Researchers developed the ecological network balance index (ENBI) to quantify balance between positive and negative microbial interactions. ENBI robustly differentiated healthy and dysbiotic states across multiple diseases, and correlated with colorectal cancer progression, demonstrating its potential as a diagnostic tool. *Science*. PMID: 41747050

**Gut microbiome associations with colorectal neoplasia are weak.** This cross-sectional study analyzed stool metagenomes from 1,762 participants undergoing colonoscopy, describing statistically significant but minimal gut microbiome differences between individuals with and without neoplasia. A small number of species and pathways showed weak associations with early lesions, which attenuated after covariate adjustment. Predictive models modestly improved high-risk neoplasia classification, suggesting microbial shifts may emerge later as a consequence rather than cause. *Gut*. PMID: 41791848

**Germline BRCA2 shapes resistance trajectories in breast cancer.** Integrated clinicogenomic analysis of over 5,800 breast cancer patients showed that germline BRCA2 pathogenic variants predispose tumors to acquire RB1 loss-of-function alterations under CDK4/6 inhibitor pressure, leading to poor outcomes. This vulnerability arises from baseline RB1 hemizygosity and homologous recombination deficiency. Preclinical models showed near-uniform resistance to CDK4/6i of gBRCA2 carriers but sensitivity to PARP inhibition, suggesting that prioritizing PARP inhibitors may intercept resistance. *Nature*. PMID: 41781623

**Precancerous niche formation determines early tumor survival.** Analyses in in vivo preclinical mouse models reveal that stress responses in early tumor cells shape the microenvironment to sustain cancer survival: Tumor-stimulated fibroblasts activate wound-healing responses, creating a fibronectin-rich scaffold that promotes tumor growth. Functional assays demonstrated that this precancerous niche is able alone to confer malignant properties to normal epithelial cells, showing that both mutations and stromal responses define early tumor survival and progression. *Nature*. PMID: 41781610

**Early cancer detection and the genetics of premalignant clones.** Early cancer detection remains critical for favorable prognoses. Cancer genomics has enabled assays allowing for the early detection of tumor-derived DNA both in tissues and in body fluids. Moreover, it is known that small clones with cancer-associated mutations commonly arise in normal tissues with age but rarely progress to cancer. This review outlines established detection strategies and highlights emerging prognostic frameworks for identifying high-risk individuals, enabling interception at premalignant stages when interventions are most effective. *Nature genetics*. PMID: 41772265

**cGAS-STING pathway in antitumor immunity and immunotherapy.** The cGAS-STING pathway detects tumor-derived DNA, triggering type I interferon signaling and balancing pathological inflammation with protective immunity. While preclinical studies have shown promise for targeting this pathway to enhance immunotherapy, clinical results have been disappointing. This Review outlines advances in understanding its tumor-promoting and tumor-

suppressive effects and discusses opportunities and challenges for clinical integration. *Nature reviews. Cancer*. PMID: 41486397

**Low-dose radiotherapy remodels tumor immunity via the cGAS–STING pathway.** This review describes how low-dose radiotherapy activates the cGAS-STING pathway, reshaping the tumor immune microenvironment. It enhances antitumor immunity by promoting interferon production, T cell infiltration, and macrophage activation, while reducing immunosuppressive cells. However, prolonged activation may induce immune exhaustion. Combination strategies with immunotherapies can overcome resistance. *Mol Cancer*. PMID: 41803899

**Intratumoral microbiota: challenges and standards.** Tumors harbor microbial communities that shape cancer biology and therapy responses. This commentary synthesizes functional evidence linking intratumoral microbes to cancer hallmarks, critically evaluates detection approaches, and proposes minimal technical and reporting standards to establish microbial presence, viability, and causality, moving toward clinically actionable insights. *Cancer cell*. PMID: 41825441

**RAS(ON) inhibitors for pancreatic cancer interception.** In mouse models of pancreatic ductal adenocarcinoma, treatment of precancerous PanIN-bearing mice with RAS(ON) multiselective or G12D-selective inhibitors prompted lesion regression, delayed tumor onset, and increased survival. Interception of lesion progression led to median overall survival exceeding one year versus less than five months in controls. Interception provided greater survival benefit than treatment of fully blown tumors, proposing pharmacological reduction of premalignant burden as a promising strategy. *Science*. PMID: 41818359

**Mathematical modeling of clonal hematopoiesis dynamics.** Clonal hematopoiesis (CH) results from somatic mutations in hematopoietic stem cells and is associated with cardiovascular disease, myeloid neoplasms, and cancer therapy complications. Chemotherapy can accelerate clone expansion. This study summarizes evidence on CH dynamics, compares mathematical models for predicting progression and estimating clone fitness, and discusses implications for clinical management of individuals with this condition. *Nature genetics*. PMID: 41699138

**CDK4/6 inhibition mitigates chemotherapy-induced expansion of TP53-mutant clones.** Therapy-related neoplasms (tMNs) are a consequence of cytotoxic anticancer therapies and patients with hematopoietic clones carrying TP53 mutations are at high risk of tMN. In four randomized clinical trials, administration to cancer patients of the CDK4/6 inhibitor trilaciclib along with chemotherapy reduced expansion of clones with mutations in TP53 and other DNA damage response genes. In a mouse model, CDK4/6 inhibition blocked platinum-induced growth of TP53-mutant clones by promoting quiescence and reducing their growth advantage. This study provides proof of concept for a pharmacologic strategy to block chemotherapy-induced expansion of preleukemic TP53-mutant clones. *Nature genetics*. PMID: 41814002

**Ageing reprograms KRAS-driven lung adenocarcinoma toward metastasis.** Physiological ageing reprograms KRAS-driven lung adenocarcinoma, limiting primary tumor growth while promoting metastatic dissemination through epigenetic activation of the integrated stress response via ATF4. Aged tumors show increased PERK-eIF2 $\alpha$  signaling sustaining ATF4, which drives plasticity and glutamine dependence. Targeting ISR-ATF4 abolishes these adaptations, revealing a therapeutic vulnerability in older patients with lung adenocarcinoma. *Nature*. PMID: 41813904

**Lymph node colonization drives systemic immunosuppression in cancer.** Spatial proteomics and transcriptomics in head-and-neck cancer and melanoma models show that lymph node colonization induces interferon- $\gamma$  signaling, enriches immunosuppressive myeloid cells and cancer-associated fibroblasts, drives T cell dysfunction and Treg activation. Changes extend to adjacent and distant tumor-free lymph nodes (while absent in non-cancer patients), establishing lymph node colonization as an active driver of systemic immunosuppression. *Cancer cell*. PMID: 41616773

**Gut microbiota-derived metabolite phytosphingosine enhances immunotherapy response.** Gut microbiota influences immune checkpoint inhibitor responses. This study shows that the bacterial metabolite phytosphingosine sensitizes cancer cells to tumor antigen-specific cytotoxic T lymphocyte lysis in vitro and in vivo, significantly controlling tumor growth when combined with immunotherapy. *Cancer cell*. PMID: 37738976

**Oncolytic virus triggers persistent T cell immunity in glioblastoma.** The study demonstrates sustained T cell-mediated immunity in glioblastoma upon one single treatment. Indeed, analyses from a first-in-human trial of rQNestin34.5v.2 oncolytic virus in glioblastoma shows that single treatment induced deep and persistent intratumor T cell infiltration. Shorter distances between apoptotic tumor cells and granzyme B+ T cells correlated with longer progression-free survival. *Cell*. PMID: 41679299

**Whole-cell spatial kinetic model of a minimal bacterial cell.** Researchers present a 4D spatial and kinetic model of the entire cell cycle for the minimal bacterium JCVI-syn3A, integrating genetic processes, metabolic networks, growth, and division. Chromosome replication and segregation are modeled with Brownian dynamics. The model recovers experimental measurements and predicts heterogeneity among daughter cells. *Cell*. PMID: 41806832

**Hallmarks and therapeutic targeting of the pre-metastatic niche.** This review delineates cellular and molecular hallmarks of the pre-metastatic niche, including immune suppression, vascular remodeling, metabolic reprogramming, and stromal reorganization. It traces spatiotemporal evolution from initiation to colonization, examines roles of circulating tumor cells and extracellular vesicles, and explores translational strategies such as biomarker development, AI-assisted profiling, and immune or EV-based interventions for early interception of metastasis. *Molecular cancer*. PMID: 41845337

**Protein correlation profiling defines small EV constituents.** Through the systematic profiling of over 9000 proteins in human cancer cell lines and biofluids, the authors provide a comprehensive description of extracellular vesicles (EVs)-associated and non-vesicle-associated proteins. The results show that small EVs primarily incorporate plasma membrane proteins and to a less extent intraluminal soluble proteins. Conversely, cytosolic proteins frequently detected in EV preparations are externally associated, likely originating from debris and aggregates. This study provides a reference for understanding EV biogenesis and function. *Nature cell biology*. PMID: 41688734

**Tumor-derived extracellular vesicles in immunometabolic reprogramming and therapy resistance.** This review explores how tumor-derived extracellular vesicles (tEVs) reprogram immune and metabolic pathways to promote cancer progression and immunotherapy resistance. By altering glucose, lipid, and amino acid metabolism, tEVs create an immunosuppressive environment. These mechanisms drive both primary and acquired resistance. Targeting tEVs and integrating AI-based profiling may enable precision therapies and improve prediction and reversal of therapy resistance. *Mol Cancer*. PMID: 41593635

**miRNA-driven plasticity and therapy resistance in melanoma.** This review highlights the role of miRNAs in regulating cancer cell plasticity, drug tolerance, and resistance, using melanoma as a model. miRNAs influence gene expression and intercellular communication, enabling adaptive transitions and persistence under therapy. Advances in antisense technologies offer new therapeutic opportunities, despite past delivery challenges. These insights support miRNAs as key biomarkers and targets across cancers. *Mol Cancer*. PMID: 41664177

**Microplastics promote immunotherapy resistance in colorectal cancer.** This study shows that microplastics infiltrate colorectal tumors and contribute to disease progression and resistance to immunotherapy. Mechanistically, they suppress the JAK-STAT pathway, reduce immune signaling molecules, and decrease T cell infiltration. Additionally, microplastics disrupt gut microbiota, further impairing antitumor immunity. These findings identify microplastics as a novel environmental factor influencing cancer immunity and a potential therapeutic target. *Mol Cancer*. PMID: 41664174

**LLM-assisted review reveals scarce rigorous evidence regarding the adoption of LLM (large language models) in medicine.** This LLM-assisted review identified 4,609 clinical medicine studies on large language models between 2022 and 2025, with only 1,048 using real-world patient data and just 19 being prospective randomized trials. ChatGPT models constituted 65.7% of evaluated models. Despite rapid growth, rigorous patient-centered evidence remains scarce, underscoring the need for larger prospective trials. *Nature medicine*. PMID: 41776077

**Neoadjuvant sacituzumab govitecan plus pembrolizumab in bladder cancer.** The phase 2 SURE-02 trial enrolled 49 patients with muscle-invasive bladder cancer ineligible for cisplatin-based chemotherapy. Treatment with four cycles of pembrolizumab plus sacituzumab govitecan followed by surgery (radical cystectomy or re-TURBT) and adjuvant pembrolizumab resulted in a clinical complete response rate of 39% with bladder preservation and sustained remission in about 40% of the patients. Grade 3 treatment-related adverse events occurred in 16% with no grade 4 or deaths, showing promising activity. *The Lancet. Oncology*. PMID: 41771275

Alex, although we are aware that articles in bioRxiv are not peer-reviewed and findings should be treated as provisional, can you find the most relevant papers published in the past few weeks on metastases, immunotherapy, epigenetics, extracellular vesicles, liquid biopsy, metabolism, microbiota, genomics, biomarkers, and provide a short summary per each of them?

Sure; I queried bioRxiv archives, filtered for your specified oncology themes, and ranked according to conceptual novelty, likely downstream impact, translational relevance, methodological innovation, and breadth of applicability across oncology.

### Tier 1 — Likely High-Impact / Paradigm-Shifting

**Epigenetic Liquid Biopsy Enables Mutation-Agnostic Surveillance (bioRxiv).** A methylation-based liquid biopsy platform is proposed for neuroblastoma monitoring, independent of mutational status. By profiling tumor-specific epigenetic signatures in circulating DNA, the method enables longitudinal tracking of disease burden and relapse risk. The approach improves sensitivity over mutation-based assays and supports earlier detection of minimal residual disease, highlighting epigenetic biomarkers as scalable, tumor-agnostic surveillance tools.

Strong translational upside: mutation-independent ctDNA methylation tracking addresses a major limitation of current liquid biopsy. The tool are likely to have broad applicability across tumor types and clear clinical integration path (MRD, relapse detection).

**Pan-cancer analysis of single-cell RNA sequencing data from 304 human tumors sheds light on the aneuploidy paradox (bioRxiv).** This study integrates single-cell RNA sequencing data from 304 human tumors to investigate how aneuploidy shapes tumor fitness and cellular heterogeneity. The authors appear to identify lineage- and microenvironment-dependent consequences of chromosomal imbalance, potentially explaining why highly aneuploid tumors can remain evolutionarily successful despite proteotoxic and metabolic burdens. The work is notable for its scale, systems-level framing, and likely implications for immunotherapy response, genome instability, and precision oncology.

Why it ranks highly: Large-scale pan-cancer single-cell resource directly addressing a longstanding paradox in cancer evolution.

**Microbiome-derived hydroxyphenyl propanoates enhance antitumour immunity by potentiating gasdermin D activity in tumour-associated myeloid cells (bioRxiv).** This study links gut microbiota-derived metabolites to enhanced antitumor immunity through activation of gasdermin D signaling in tumor-associated myeloid cells. The findings suggest that microbial metabolic products can directly reprogram innate immune function within tumors, potentially amplifying inflammatory anti-cancer responses. The work is especially impactful because it connects microbiome composition, immunometabolism, and therapeutic responsiveness, opening avenues for microbiota-guided immunotherapy or metabolite supplementation strategies.

Why it ranks highly: Strong mechanistic bridge between microbiota and tumor immunity.

**Pan-cancer virtual spatial transcriptomics from routine histology with Phoenix (bioRxiv).** This work presents a computational framework that predicts spatial transcriptomic information directly from standard histopathology images. By inferring spatial molecular organization without dedicated spatial omics assays, the method could dramatically lower barriers to spatial biomarker discovery in oncology. The implications are substantial for diagnostics, patient stratification, tumor microenvironment analysis, and retrospective analysis of archival pathology cohorts.

Why it ranks highly: Potentially transformative AI-enabled biomarker platform.

**Tumor-derived mitochondria enhance CD8+ T cell cytotoxicity through SPHK2-dependent S1P signaling (bioRxiv).** The paper reports that tumor-derived mitochondria can enhance CD8+ T-cell cytotoxic activity via SPHK2-dependent sphingosine-1-phosphate signaling. Rather than viewing tumor organelle transfer exclusively as immunosuppressive, the study proposes that mitochondrial exchange may sometimes potentiate anti-tumor immunity. If validated broadly, the findings could reshape understanding of metabolic crosstalk between tumors and immune cells and inspire therapeutic engineering of mitochondrial or vesicle-based immune modulation.

Why it ranks highly: Unexpected reinterpretation of tumor-immune metabolic communication.

**ImmTACs Overcome T Cell Suppression (bioRxiv).** Engineered T-cell receptor-based therapeutics (ImmTACs) restore cytotoxic activity in immunosuppressive tumor environments. The study demonstrates enhanced tumor killing despite inhibitory signaling, supporting next-generation immunotherapy strategies.

A key aspect lies in the next-gen immunotherapy modality with engineered TCR specificity and ability to bypass immunosuppressive signaling. If validated in vivo/clinical settings, this could redefine solid tumor immunotherapy.

**Tumor-Immune Trajectory Modeling (bioRxiv).** A computational framework links spatial tumor architecture with immune dynamics over time, correlating evolving immune infiltration states with clinical outcomes, offering predictive insight for immunotherapy responsiveness.

A conceptual advance is the dynamic, spatially resolved modeling of tumor-immune co-evolution. It has high relevance for predicting immunotherapy response and resistance.

**Ex vivo Drug Testing in Metastatic Biopsies (bioRxiv).** Patient-derived metastatic samples are functionally screened ex vivo against targeted and immunomodulatory drugs. The study identifies individualized vulnerabilities, including immune-activating responses, that are not predictable from genomics alone. Results support integrating functional assays with precision oncology pipelines to guide therapy selection and improve outcomes in metastatic disease.

The paper focuses on functional precision oncology beyond genomics. It has direct actionability for patient stratification and strong clinical translation potential if scalable.

## Tier 2 — High Novelty with Strong Mechanistic or Platform Value

**PRMT5 Inhibition Alters Cancer Splicing Programs (bioRxiv).** Inhibition of PRMT5 induces a conserved alternative splicing signature across cancer types, proposing splicing dysregulation as a therapeutic target and biomarker for drug response.

The paper identifies splicing dysregulation as a tumor-agnostic vulnerability. It is important because it suggests cross-cancer therapeutic strategies.

**Epigenetic Reprogramming Drives Cancer Stem Cells (bioRxiv).** This work shows that epigenetic remodeling can induce stem-like phenotypes in breast cancer cells. Chromatin reconfiguration alters transcriptional programs linked to self-renewal and therapy resistance. The findings position epigenetic plasticity as a central driver of tumor heterogeneity and metastasis initiation.

Of note, it reinforces the concept of tumor plasticity as a metastasis driver. It is not entirely new conceptually, but strong mechanistic depth increases impact.

**Liver Metastasis Gene Signature in Colorectal Cancer** ([bioRxiv](#)). Integrated single-cell and bulk transcriptomics identify metastasis-associated genes driving colorectal cancer progression. A prognostic model based on these genes stratifies patients by survival risk, emphasizing microenvironmental adaptation during liver colonization.

The work has solid integration of single-cell + bulk data; it provides a clinically useful prognostic model, though more incremental than disruptive.

**EGFR siRNA Liposome Therapy** ([bioRxiv](#)). Systemic delivery of EGFR-targeting siRNA via cationic liposomes suppresses tumor growth in colorectal models. Demonstrates RNAi-based therapeutics as viable anti-cancer strategies.

RNAi therapeutics remain challenging; systemic delivery success increases impact, though the field is competitive.

**Folate Receptor  $\alpha$  and Radiation Resistance** ([bioRxiv](#)). Folate receptor  $\alpha$  is shown to regulate redox homeostasis in neuroendocrine prostate cancer, conferring resistance to radiation therapy. Targeting this pathway may sensitize tumors to treatment.

It has mechanistic insight with therapeutic implications (radiosensitization). It can be considered a little bit of a “niche” study; yet, it is clinically relevant.

**CRISPR screens establish regulatory maps of immunosuppressive surface molecules in cancer** ([bioRxiv](#)). Using large-scale CRISPR perturbation approaches, the authors systematically map regulatory networks controlling expression of immunosuppressive surface molecules in tumor cells. The work likely identifies previously underappreciated immune-evasion pathways and candidate therapeutic targets that could synergize with checkpoint blockade. Because resistance to immunotherapy remains a central problem in oncology, a regulatory atlas of suppressive ligands and receptors could become a valuable framework for next-generation combination therapies.

Why it ranks highly: Highly actionable immunotherapy study with broad translational relevance.

**Metabolic plasticity enables cancer adaptation to acidic tumor ecosystems** ([bioRxiv](#)). The paper investigates how cancer cells remodel metabolism to survive acidic tumor microenvironments. The findings suggest that metabolic plasticity is not merely supportive but central to adaptive fitness under hostile ecological conditions. This has broad implications for metastases, therapy resistance, and metabolic targeting, particularly because extracellular acidosis is a common feature across solid tumors.

Why it ranks highly: Strong conceptual contribution to tumor adaptation biology.

**Differential peripheral immune dynamics underlie therapeutic response to chemotherapy and chemo-immunotherapy in triple-negative breast cancer** ([bioRxiv](#)). The authors characterize dynamic immune-state changes associated with response to chemotherapy and chemo-immunotherapy in triple-negative breast cancer. By longitudinally profiling peripheral immune compartments, the study may identify predictive biomarkers of treatment response and mechanisms of resistance. The translational relevance is high because TNBC remains difficult to treat and reliable immune-monitoring biomarkers are urgently needed.

Why it ranks highly: Clinically relevant immunotherapy biomarker study.

**Deciphering the Genomic Landscape of Renal Cell Carcinoma Brain Metastases** ([bioRxiv](#)). This genomic study focuses specifically on brain metastases arising from renal cell carcinoma, an area with relatively limited molecular characterization. The authors likely identify evolutionary trajectories, mutational drivers, and microenvironmental adaptations unique to metastatic brain colonization. The work may help explain therapy resistance and organotropism while informing biomarker development and precision approaches for metastatic RCC.

Why it ranks highly: Directly addresses metastatic evolution in a lethal disease context.

**Dual-Engineered Dendritic Cell Derived Small Extracellular Vesicles Couple T Cell Priming with Checkpoint Reprogramming for Synergistic Immunotherapy** ([bioRxiv](#)). The authors engineer dendritic-cell-derived extracellular vesicles to simultaneously enhance T-cell priming and modulate checkpoint signaling. The platform integrates antigen presentation and immune reprogramming within a single vesicle-based therapeutic modality. The work stands out because EV therapeutics are rapidly gaining traction, and combination immune-engineering strategies could overcome limitations of current checkpoint blockade approaches.

Why it ranks highly: Sophisticated extracellular-vesicle immunotherapy platform.

**Fluid shear stress modulates endocytic pathways and junctional targeting of tumor-derived extracellular vesicles in endothelial cells** ([bioRxiv](#)). This study explores how biomechanical forces influence uptake and endothelial targeting of tumor-derived extracellular vesicles. By showing that fluid shear stress alters EV internalization pathways and vascular interactions, the work provides mechanistic insight into metastatic dissemination and organ-specific colonization. The findings may also inform engineering strategies for EV-based therapeutics and biomarkers.

Why it ranks highly: Advances mechanistic understanding of EV trafficking during metastasis.

**The Structural Code of Breast Cancer Proteoform** ([bioRxiv](#)). The study examines how alternative splicing generates diverse proteoforms in breast cancer and how these isoforms contribute to functional diversification. By moving beyond gene-level expression to protein structural variation, the work highlights an underexplored layer of tumor heterogeneity. The findings may influence biomarker discovery and therapeutic targeting strategies focused on splice-dependent oncogenic states.

Why it ranks highly: High-dimensional proteogenomic perspective on breast cancer heterogeneity.

**Integrated Metabolomic, Proteomic, and Phosphoproteomic Profiling Reveals CAMKK2-Dependent Regulation of Cell Cycle and Nucleotide Metabolism in Gastric Cancer** ([bioRxiv](#)). Using integrated multi-omics profiling, the authors identify CAMKK2 as a regulator of cell-cycle progression and nucleotide metabolism in gastric cancer. The work suggests that CAMKK2 coordinates metabolic and proliferative programs that sustain tumor growth. The study is particularly valuable because it combines metabolomics with signaling analyses to define potentially druggable metabolic dependencies.

Why it ranks highly: Strong systems-biology approach to metabolic vulnerability discovery.

**CD180 identifies chemoresistant stem-like blasts and reveals a KMT2A-driven vulnerability in acute myeloid leukaemia** ([bioRxiv](#)). This paper identifies CD180 as a marker of chemoresistant stem-like AML blasts and uncovers a vulnerability linked to KMT2A-driven leukemogenesis. The work integrates stemness biology with therapeutic targeting and may enable improved stratification of high-risk AML patients. Because relapse-driving leukemic stem populations remain difficult to eradicate, the findings could have substantial translational significance.

Why it ranks highly: Important implications for therapy-resistant leukemia.

**Glutamine-dependent downregulation of FLT3-ITD is a mechanism of FLT3 inhibitor resistance in FLT3-ITD AML in hypoxia** ([bioRxiv](#)). The authors propose that glutamine-dependent suppression of FLT3-ITD signaling contributes to resistance against FLT3 inhibitors under hypoxic conditions. The work reframes resistance as an adaptive metabolic response rather than purely a genetic phenomenon. This could influence future combination strategies pairing kinase inhibitors with metabolic interventions in AML.

Why it ranks highly: Connects metabolism, hypoxia, and targeted therapy resistance.

### Tier 3 — Enabling Technologies / Emerging Tools

**Reconstructing True 3D Spatial Omics at Single-Cell Resolution** ([bioRxiv](#)). This work presents methods for reconstructing three-dimensional spatial omics architectures at single-cell resolution. Such technologies are particularly important for cancer research because tumor ecosystems are highly spatially organized. The ability to infer or reconstruct 3D molecular organization could improve studies of invasion fronts, immune niches, and metastatic microenvironments.

Why it ranks highly: Enabling technology for tumor ecosystem analysis.

**Joint Variable Selection for Omic Biomarkers in Time-to-Event Data** ([bioRxiv](#)). The paper introduces a statistical or computational framework for identifying prognostic omics biomarkers in survival datasets. The approach appears designed to improve robustness and interpretability across complex multi-omics datasets. Although method-focused, the impact could be broad because biomarker prioritization remains a major bottleneck in translational oncology.

Why it ranks highly: Methodological contribution with broad biomarker utility.

**Identifying Treatment Related Signatures In Glioblastoma Using KaleidoCell** ([bioRxiv](#)). This study applies a computational framework to identify treatment-associated cellular signatures in glioblastoma. By resolving therapy-linked cellular states, the work may help distinguish resistant subpopulations and uncover adaptive programs driving recurrence. The relevance is high because glioblastoma remains one of the most treatment-resistant cancers and lacks robust predictive biomarkers.

Why it ranks highly: Promising computational biomarker framework.

**A unified benchmark of synthetic data generation for clinical transcriptomic cancer cohorts** ([bioRxiv](#)). The authors benchmark synthetic transcriptomic data-generation methods for cancer cohorts, addressing reproducibility, privacy, and model generalization challenges. Reliable synthetic datasets could accelerate collaborative biomarker development while reducing patient privacy concerns. The work is timely given the increasing use of generative AI and foundation models in oncology research.

Why it ranks highly: Important infrastructure paper for AI-driven oncology.

**Spatial Transcriptomics Integration Tool (CosMxScope)** ([bioRxiv](#)). A scalable computational framework integrates imaging-based spatial transcriptomics with pathology. It enhances detection of tumor heterogeneity and microenvironmental niches relevant to metastasis and immune evasion.

It is important for multi-modal tumor mapping; it has high utility across labs, though primarily technical.

**ClumPyCells for Spatial Cell Aggregation** ([bioRxiv](#)). This method resolves spatial clustering biases in tissue analysis, improving identification of tumor cell niches and immune microenvironments critical for metastasis and therapy response.

It represents a methodological improvement for spatial bias correction—useful but incremental.

**Personalized Drosophila Avatars for colorectal cancer.** ([bioRxiv](#)) Patient-specific tumor mutations are modeled in Drosophila to test therapeutic responses. This platform enables rapid functional validation of treatment strategies in colorectal cancer.

It is a creative functional precision model; although scalability and translational fidelity remain open questions.

**Xenopus Model for Liposarcoma Dedifferentiation** ([bioRxiv](#)). A CRISPR-engineered model allows controlled study of dedifferentiation in liposarcoma. Findings highlight genetic drivers of tumor plasticity and progression. It is valuable for studying plasticity, but the niche disease model limits broad impact.

#### Tier 4 — Specialized or Indirect Cancer Relevance

**Integrated analysis of leukemic mutations and transcriptomes at the single-cell level** ([bioRxiv](#)). This study integrates mutational profiling with single-cell transcriptomics to map leukemic heterogeneity and clonal architecture. The combined genotype-phenotype approach enables more precise characterization of malignant subpopulations and evolutionary dynamics. Such methods are increasingly central for understanding relapse, treatment escape, and precision targeting in hematologic malignancies.

Why it ranks highly: High-resolution leukemia evolution study.

**Engineered 3D hydrogel model reveals divergence of adhesion-migration balance in Glioblastoma under simulated microgravity** ([bioRxiv](#)). The authors develop a 3D hydrogel system to study glioblastoma behavior under simulated microgravity conditions. The work reveals altered adhesion–migration dynamics that may illuminate fundamental principles of tumor cell adaptation and mechanobiology. While more exploratory than translational, the model provides a novel platform for studying invasion and adaptive cellular states.

Why it ranks highly: Innovative tumor adaptation model.

**Cancer-Associated Fibroblast Targeting (Modeling Study)** ([bioRxiv](#)) Mathematical modeling of tumor–stroma interactions suggests that targeting cancer-associated fibroblasts can enhance therapy efficacy in ER+ breast cancer. Optimized treatment schedules improve tumor control by disrupting stromal support mechanisms.

It is an interesting systems modeling; its actual impact depends on experimental validation.

**Circular RNAs as Hormone Response Biomarkers** ([bioRxiv](#)). Specific circular RNAs correlate with anti-hormonal treatment response in breast tissue. These stable RNA species may serve as minimally invasive biomarkers for therapy monitoring. Biomarker studies are valuable but often face reproducibility/clinical adoption barriers.

#### Peripheral/cross-domain relevance

**AI-Driven Drug Discovery in Cancer** ([bioRxiv](#)). An approach combining generative AI with virtual screening accelerates identification of candidate compounds targeting cancer pathways.

The field is crowded; therefore, novelty depends on demonstrable experimental validation.

**Methbiome (Microbiome Epigenetics Tool)** ([bioRxiv](#)). A bioinformatics tool enables DNA methylation analysis from metagenomic data, offering insight into host–microbiota interactions and potential cancer-associated epigenetic signatures.

It represents an interesting computational perspective; indirect cancer relevance for now.

**Microbiota-Driven Antibiotic Resistance Dynamics** ([bioRxiv](#)). Personalized microbiomes are shown to shape selection of resistant bacterial strains. While not cancer-specific, implications extend to microbiota–cancer therapy interactions, especially immunotherapy modulation.

It is important broadly, but only tangential to oncology/immunotherapy.

Thank you Alex, well done, and great insights!

# what if...

*you had an AI co-worker?*

Yi, can you summarize (in about 600 words) this paper "[Clonal dynamics shaped by diverse drug-tolerant persister states in melanoma resistance](#)", highlighting 1) what was known before the study, 2) the methodology employed, 3) the main findings, 4) conclusions and open questions?

**Context: What Was Known Before the Study.** Drug-tolerant persister (DTP) cells represent a major challenge in cancer therapy. Indeed, most advanced melanomas initially respond to BRAF/MEK inhibitors but eventually relapse, often without acquiring new resistance mutations and previous research established that DTP cells can enter a reversible drug-refractory state, contributing to minimal residual disease (MRD) and eventual recurrence. However, the temporal dynamics, clonal origins, and transcriptional plasticity of these persister cell populations during prolonged therapy remained poorly understood. While lineage tracing technologies existed (such as the Confetti system, LARRY, CellTag, and Watermelon) they had limitations in simultaneously tracking clonal identity, transcriptional states, and spatial organization within tumors.

**Methodology.** The authors developed MeRLin (Melanoma Resistance Lineage tracing; a high-complexity lentiviral barcoding platform with 2.89 million barcodes), a tool enabling: *i. Cellular barcoding* with (265-bp semi-random) sequences (in the 3'UTR of luciferase and mNeptune2.5 fluorescent protein); *ii. Single-cell transcriptomic profiling* (scRNA-seq) at multiple time points; *iii. RNA fluorescence in situ hybridization* (RNA-FISH) for spatial validation; *iv. Spatially- and temporally- resolved computational analyses* of cell clones (including ClonoCluster integration, pseudotime trajectory inference, SCENIC regulatory network analysis, and spatial transcriptomics).

The system was applied to a patient-derived xenograft (PDX) model of BRAF V600E-mutant melanoma (WM4237-1) that recapitulates clinical response and relapse to BRAF/MEK inhibitors. Tumors were analyzed longitudinally at pre-treatment (day 0), early MRD (day 21), late MRD (day 57), and relapse (day 91). Additional validation was performed in independent PDX models (WM4007 sensitive, WM4380-2 resistant) and TCGA patient cohorts.

**Main Findings: 1) Clonal dynamics.** Therapy-resistant cellular subpopulations (clones) arose predominantly through adaptive reprogramming (transcriptional plasticity) of minor pre-existing subpopulations rather than selection of pre-existing resistant clones. No recurrent genetic mutations were found across endpoint tumors, supporting phenotypic plasticity as the primary resistance mechanism. **2) Four persister-associated transcriptional states** were identified in recurrent tumors: 1. Stress-like state, marked by BNIP3, PDK1, ATF4, SLC2A1, ALDOA, and P4HA1; regulated by ATF4; associated with glycolytic shift and hypoxia signaling; 2. Lipid metabolism state, enriched for FASN, APOE, and APOC1 and characterized by neural crest stem-like features; 3. PI3K signaling state, featured by AKT3, FGFR1, and LEF1; as well as neural crest-like traits (but distinct from group 2); 4. ECM remodeling state, characterized by upregulated ECM1, VCL, and MET; regulated by ETS1; associated with poorer patient survival in TCGA. **3) Temporal evolution.** These programs were not transcriptionally distinct before treatment but progressively segregated during therapy. The stress-like state transitioned from a differentiated phenotype at early MRD to a dedifferentiated state at recurrence. Copy number variation analysis revealed that groups 2 and 3 combined BRAF amplification with non-genetic CCND1 upregulation, while groups 1 and 4 relied more on transcriptional adaptations. **4) Spatial organization.** Spatial transcriptomics revealed spatially defined organization of these cell subpopulations within the tumor, with lipid metabolism and PI3K signaling states co-localized near tumor margins; ECM remodeling cells forming a dispersed mosaic pattern, and stress-like cells showing scattered distribution. Moreover, stress-like cells secreted TGF $\beta$ , ECM remodeling cells activated collagen pathways, and neural crest-like states communicated through BMP and MPZ signaling. **5) Validation.** RNA-FISH confirmed, in recurrent tumors, spatial co-localization of a dominant persister clone with the stress-like marker SLC2A1.

**Conclusions.** MeRLin provides a robust framework for dissecting cancer heterogeneity, by integrating clonal tracking with transcriptional and spatial analysis. By exploiting this tool, the authors showed that melanoma recurrence is associated with diverse, spatially organized persister states arising through adaptive reprogramming rather than genetic selection. Moreover, they found that four distinct persister programs —stress-like, lipid metabolism, PI3K signaling, and ECM remodeling— represent multiple adaptive routes to resistance, which become increasingly different from a transcriptional point of view under prolonged therapy. In particular, the ECM remodeling state, regulated by ETS1, emerges as a particularly aggressive program associated with poor patient outcomes.

**Open questions: 1)** Can the targeting of the identified pathways (e.g., ATF4 stress signaling, lipid metabolism, ETS1-driven ECM remodeling) sensitize persister cells to therapy? **2)** What are the functional roles of candidate cell surface markers (e.g., FXYD3) as therapeutic targets or biomarkers? **3)** How do stromal and immune cells in the tumor microenvironment influence persister state transitions? **4)** Are these persister programs stable or interconvertible states, and what drives the

observed phenotypic shifts over time? 5) Can similar persister programs be identified in other cancer types and therapeutic contexts?

Alex, if you were a senior scientist in a cancer research center that, after graduating in biology, during your PhD and post-doc, focused your research on cancer, with a translational approach, based on the results of the study summarized above, what kind of experiments would you design to continue this work?

If I were continuing this project as a senior translational cancer researcher, I would design the next phase around three mechanistic axes that logically extend from the study: 1. stability vs plasticity of persister cell states; 2. Functional dependency of each persister state; 3. Tumor microenvironment control of persister states. The original work is largely descriptive, so the natural progression would be to explore causal relationships (through perturbation experiments) and therapeutic testing. This is how I would structure the experimental program.

**1. Determine Whether Persister Programs Are Stable Lineages or Dynamic Interconvertible Phenotypic States.** Firstly, I would identify surface markers from the scRNA-seq dataset (the authors mention candidates like FXYD3) for each state, perform FACS sorting of the four populations and culture isolated cells under BRAFi/MEKi pressure. Then, I would perform longitudinal scRNA-seq, measure lineage barcode retention, state transition frequencies. If cells maintain their programs, it would mean that persister cell states are stable, while in case sorted cells regenerate all four states over time, would imply cell plasticity (dynamic interconvertible phenotypic states), indicating that effective therapy must target drivers of phenotypic transition rather than individual states.

**2. Functional Dependencies of Each Persister Program.** The paper identifies candidate regulators of persister cell plasticity, but does not prove causal dependency. To do so, I would perform state-specific CRISPR knockout screens of ATF4, EIF2AK3, HIF1A for the stress-like persister cell state; FASN, SREBF1 for the lipid metabolism state, AKT3, FGFR1 for the PI3K signaling state; ETS1, MET for the ECM remodeling state. Each cell subpopulation (characterized by a specific transcriptional state) would be isolated, treated with BRAFi/MEKi, and subject to CRISPR screen. This will allow to identify a state-specific vulnerability (that is, functional dependency) of each of the four persister cell states. This is key for translational targeting.

**3. Targeting Persister States in Combination Therapy.** This would be the most translationally relevant step. I would rationally try novel drug combinations (in PDX, along with BRAFi/MEKi) aimed at targeting the four specific persister cell states to assess whether targeting persister programs prevents recurrence; namely, ISR inhibitors/PERK inhibitors for the stress-like state; FASN inhibitors for the lipid metabolism state; PI3K or AKT inhibitors for the PI3K state; MET inhibitors or blockers of the collagen signaling for the ECM state (specifically, I would have four treatment arms: 1. BRAFi/MEKi; 2. BRAFi/MEKi + cell state inhibitor; 3. Sequential therapy (BRAFi/MEKi followed by the cell state inhibitor); 4. Triple combinations). I would measure MRD burden, time to relapse, clonal diversity.

**4. Role of the Tumor Microenvironment.** The study predicts signaling between persister states and stromal components but does not test it. Therefore, 4.1. by leveraging co-culture systems of persister melanoma cells and i. cancer-associated fibroblasts, or ii. macrophages, or iii. T cells, and by measuring persister state distribution, transcriptional shifts, survival under therapy, I could test whether one/some/all the persister cell states depend on one/some/all the cell types tested (and specific signaling activated) in the TME. 4.2. I would use orthotopic melanoma models, perturb stromal signaling in vivo (by TGF $\beta$  blockade, collagen crosslinking inhibitors, integrin inhibitors) and combine the data with spatial transcriptomics to test the potential collapse of the TME of persister cells.

**5. Mechanisms Driving State Transitions.** The experiments in the paper suggested dedifferentiation during therapy. To test that, I would assess the putative involvement of epigenetic drivers of cell state transition, by performing epigenetic profiling (ATAC-seq, CUT&RUN for transcription factors (ATF4, ETS1), histone mark profiling) in order to identify epigenetic rewiring that locks cells into persister states. Then, I would perform epigenetic drug screening to check whether inhibitors targeting BET proteins, HDACs, KDM demethylases (or search for other compounds) can prevent persister state formation.

**6. Clinical Translation.** The study connects the ECM-remodeling program with poor survival. Therefore, I would 6.1. First, confirm whether the same four programs exist in patients, by performing single-cell RNA-seq, lineage inference, spatial profiling in longitudinally collected patient samples pre-treatment, early therapy, MRD, relapse. 6.2. Test –by multiplex immunofluorescence, spatial transcriptomics, liquid biopsy, in patient biopsies– biomarkers of persister cell states correlated with patient survival, such as ECM1, ETS1, FASN AKT3, SLC2A1. The goal would be to identify biomarkers predicting the specific persister cell state dominating in the early MRD.

**7. Cross-Cancer Generalization.** A key conceptual question is whether these programs are melanoma-specific. To address that, I would perform similar experiments in lung cancer, breast cancer, colorectal cancer; using lineage tracing + therapy. If conserved, these states could represent universal persister programs.

Great. What if, instead, after graduating in biology, you completed your PhD in bioinformatics, and then joined a cancer research center as a computational researcher; if you had expertise in (single cell and spatial) genomics and transcriptomics analyses, based on the results of the study summarized above, what kind of experiments would you design to continue this work?

If I were primarily a computational genomics researcher, my continuation strategy would focus on extracting mechanistic insights from existing and new high-dimensional datasets, while proposing targeted experiments mainly to validate computational predictions. The emphasis would be on modeling cell-state dynamics, regulatory programs, spatial organization, and clonal fitness. Below is how I would structure the computational agenda.

**1. Reconstruct the Persister State Transition Landscape.** My Biological question would be “Are the four persister programs stable endpoints or transient states connected by transitions?” To address that, I would use a computational approach (using trajectory and transition modeling on the longitudinal single-cell dataset, by leveraging methods such as RNA velocity/dynamical modeling, optimal transport trajectory inference, pseudotime alignment across timepoints, lineage barcode integration). Specifically, I would integrate lineage barcodes with transcriptional states, estimate state transition probabilities, determine if trajectories follow a specific patterns (such as differentiated melanoma → Stress-like → Neural crest-like states → ECM remodeling), or if there are multiple independent trajectories. These analyses would allow me to define a “state transition map” describing how melanoma cells survive therapy.

**2. Quantify Clone Fitness and Selection Dynamics.** My biological question would be “which transcriptional programs confer survival advantage during therapy (e.g. stress-like state during early phases; lipid metabolism state during MRD persistence, ECM remodeling during recurrence expansion)?”. To address that, I would employ a computational strategy allowing me to build models of population dynamics from barcode frequencies (by clone frequency modeling, bayesian growth rate estimation, lineage fitness inference). Specifically, I would estimate fitness values (coefficients) for each persister state. This analysis would convert descriptive results into quantitative persister cell population dynamics.

**3. Integrate Spatial and Single-Cell Data to Define Niches.** The paper showed spatial organization of the TME but did not deeply model microenvironment niches. I would integrate spatial transcriptomics, single-cell RNA, ligand–receptor inference, and perform three different types of analyses: 1) Cell neighborhood analysis. Through this analysis I would expect to identify “spatial modules”, that is, associations between specific states of persister cells (defined by scRNAseq) and spatially defined tissue organization (e.g.: stress-like persister cell state + hypoxia niche; lipid metabolism persister cell state + adipocyte interaction; ECM state + fibroblast proximity). 2) Spatial signaling inference. Through this analysis I would expect to define/predict per each persister cell state (defined by scRNAseq) the signaling through which it communicates with other cells in the TME (e.g.: stress-like → TGFβ secretion; fibroblasts → ECM deposition); 3) Spatially informed cell state prediction. I would train computational models predicting cell state on the basis of information on the cell composition of the tumor microenvironment.

**4. Predict State-Specific Drug Vulnerabilities.** By using transcriptomic signatures, we can computationally predict therapeutic sensitivities. To this end, I would integrate drug perturbation datasets and melanoma transcriptomic profiles. This analysis would allow me to identify drugs predicted to collapse specific persister programs (e.g. ISR inhibitors for the stress-like cell state, fatty acid synthesis inhibitors for the lipid metabolism state, PI3K inhibitors for the PI3K state, MET inhibitors for the ECM remodeling state. These predictions would guide experimental validation.

**5. Build a Predictive Model of Melanoma Relapse.** In order to predict which tumors will relapse and through which persister program, I would use PDX data, patient datasets, longitudinal biopsies and train machine learning models to predict melanoma relapse (using, as input, proportions of different persister cell states, the activity of regulatory networks, clonal diversity, and, as output, probability of recurrence, dominant resistance program).

**6. Compare Persister Programs Across Cancer Types.** Another strong computational direction is cross-cancer meta-analysis. I would collect single-cell therapy datasets from therapy resistant lung cancer, breast cancer, colorectal cancer, and then test whether melanoma persister programs are general stress-adaptation modules. This would have large implications for oncology, potentially allowing to identify a universal transcriptional program associated with cell persistence under therapy (drug tolerance program).

**7. Develop a Unified Mathematical Model of Persister Evolution.** Finally, the most ambitious computational project would be the creation of a mathematical model integrating transcriptional states, clonal evolution, therapy pressure, spatial niches, to predict optimal therapy scheduling, combination strategies, relapse timing.

If you'd like, I can also explain what specific bioinformatics pipelines, algorithms, and packages (Python/R ecosystem) I would use for each analysis, which is usually what matters most when planning these projects.

Maybe... if anyone asks... You know Alex, I do not have a background in computational data analysis, I don't really get the strictly technical details...

Finally, if you were a clinician scientist, working both as a clinician in the hospital and as a senior post doc in a research lab and, thanks to your PhD, you gained solid expertise in molecular and cell biology, in vitro and in vivo experimentation, based on the results of the study summarized above, what kind of experiments would you design to continue this work? Specifically, by leveraging your expertise as a clinician, how would you bring this work closer to the clinical application?

As a melanoma clinician, the most relevant questions are: 1. Can persister cell states predict who relapses (risk

stratification)? 2. Can we detect relapse earlier using MRD monitoring (earlier therapeutic intervention)? 3. Can targeting persister cell states prolong responses (improved survival)? The paper suggests that relapse is not driven by a single resistant clone, but by multiple adaptive cellular states. Clinically, that implies that single targeted add-on therapies may fail, and state-specific or adaptive therapy strategies may be required.

From a clinician-scientist perspective, the key challenge is translating a biological discovery (persister states) into actionable clinical tools. That usually proceeds through three parallel translational tracks: 1. Biomarkers (identify patients at risk of relapse or stratify therapy); 2. Therapeutic vulnerabilities (target persister states); 3. Clinical monitoring of MRD and tumor evolution. In particular, a “translational pipeline” could look like this: 1) Discovery science (in this case, scRNA+lineage tracing); 2) Biomarker identification (in this case, gene signatures); 3) Clinical assay development (e.g. IHC/RNA panel); 4) MRD monitoring (e.g. ctDNA/CTCs); 5) Biomarker-driven combination trials. Specifically, this is how I would structure a translational program.

**1. Confirming persister states in human tumors.** A critical translational step would be to confirm the existence of persister states in human tumors and determine which states predict relapse. To this end, I would perform prospective longitudinal sampling in patient cohorts. Specifically, I would collect tumor biopsies at baseline, at week 2-3 (early MRD), at week 8, at relapse, and perform scRNA-seq, spatial transcriptomics, ctDNA monitoring.

**2. Develop clinically exploitable biomarkers of persister states.** The scRNA-seq signatures must be converted into simple assays to be employed in pathology labs. Therefore, I would 2.1. Build an immunohistochemistry (IHC) panel to detect the four persister programs in routine tumor biopsies. For instance, the panel could contain SLC2A1, BNIP3 for the stress-like persister cell state; FASN, APOE for the lipid metabolism state; AKT3, FGFR1 for the PI3K signaling state; MET, ECM1 for the ECM remodeling state. Then, I would use the IHC panel to retrospectively stain melanoma patient tissue sections and quantify the prevalence of each state in the tumor. My clinical question would be: Does the baseline abundance of these states predict relapse after BRAFi/MEKi therapy? 2.2. Gene expression signature for clinical sequencing. I would convert the transcriptional programs into a targeted RNA panel (20-40 genes) to be used on tumor biopsies collected before and early on-treatment (2-3 weeks), to ultimately identify early emergence of persister transcriptional programs.

**3. Early detection of minimal residual disease (MRD).** A major clinical problem is that relapse is often detected late. Therefore, I would set up a Liquid biopsy monitoring based on circulating biomarkers reflecting persister states. The options could be *i.* circulating tumor DNA (ctDNA), to track BRAF amplification and copy number signatures; *ii.* circulating/exosomal RNA, to measure persister markers (e.g., SLC2A1, FASN); *iii.* circulating tumor cells (CTCs), by performing single-cell RNA-seq of CTCs during therapy. The clinical aim would be to detect persister cell expansion months before relapse.

**4. Rational combination therapy trials.** If persister programs are driving relapse, they become therapeutic targets. Therefore, I would do a 4.1. *Preclinical combination testing*, in PDX or organoid models, evaluating efficacy of ISR/ATF4 pathway inhibitors for the stress-like persister cell state; FASN inhibitors for the lipid metabolism state; PI3K/AKT inhibitors for the PI3K signaling state; MET or TGFβ pathway inhibitors for the ECM remodeling state. I would test such compounds in combination with BRAFi/MEKi, and I will assess MRD size (that is, surviving cells in treated PDX or organoids), time to relapse, clonal diversity. 4.2. *Biomarker-driven clinical trial.* I would design a phase Ib/II adaptive trial in BRAF V600 melanoma patients treated with BRAFi/MEKi. Tumor biopsy would be performed at week 2-3 and patients stratified based on persister signatures. Patients with tumors displaying stress-like persister signature (as dominant) would be treated with ISR inhibitors (in addition to BRAFi/MEKi); patients with tumors displaying lipid metabolism persister signature would be treated with FASN inhibitors (in addition to BRAFi/MEKi); patients with tumors exhibiting PI3K persister signature would be treated with AKT inhibitors; patients with tumors exhibiting ECM remodeling signature would be treated with MET inhibitors. Efficacy will be evaluated in terms of progression-free survival, MRD reduction (by ctDNA/CTC analysis).

**5. Integrate tumor microenvironment insights.** The study suggested TGFβ, BMP, and ECM signaling contribute to persister niches. These pathways already have therapeutic agents in trials. Therefore, as translational experiments, I would combine BRAFi/MEKi and TGFβ inhibitors in patients with strong stress-like signatures. This approach could target the signaling network sustaining persister cells.

**6. Pathology integration and digital diagnostics.** Ultimately, detection of persister cells must fit clinical workflows. Therefore, I would develop multiplex IHC or spatial transcriptomics panels, train AI models to detect persister spatial patterns, and integrate results into pathology reports.

Do you agree with Alex’s experimental design? Does it make sense? What kind of experiments would you prioritize?

# notes...

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*"...whichever tools you use, they should help you to learn — not replace your thinking"*

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### Cover image (by Salvatore Pece e Francesco Antonio Tucci)

Representative multiplex immunofluorescence image demonstrating the histological heterogeneity of a prostate cancer displaying focal neuroendocrine (NE) differentiation associated with anti-androgen receptor therapy. The upper-left region contains atrophic glands expressing the basal marker KRT5 (magenta), the luminal marker KRT8 (lime), and the NE markers SYP (yellow) and NCAM1 (red). The middle-left region shows focal adenocarcinoma composed of luminal epithelial cells (KRT8<sup>+</sup>/KRT5<sup>-</sup> phenotype, green). The upper-middle region displays focal NE prostate cancer (NEPC) characterized by co-expression of KRT8, NCAM1, and SYP, consistent with treatment-induced NE differentiation. The bottom-right region contains histologically normal prostate glands exhibiting preserved basal/luminal architecture defined by KRT5 and KRT8 staining. Extensive stromal remodeling and heterogeneous epithelial organization with abnormal glandular structures are evident throughout the section. Cell nuclei are counterstained with DAPI (blue).

### Salvatore Pece and Francesco Antonio Tucci

**Salvatore Pece** (MD, PhD) is Group Leader of the Hormone-Related Cancers and Stem Cell Pathobiology Lab at IEO; Full Professor in General Pathology and Deputy Director at the Department of Oncology and Hemato-Oncology (DIPO) of the University of Milan, and Scientific Coordinator of the Molecular Pathology Unit at the Department of Experimental Oncology of IEO. The research activities of his lab aim at understanding the cellular and molecular basis of tumor heterogeneity in order to develop biology-driven approaches for the treatment of cancer patients, with main focus on cancer stem cells and how they contribute to tumor heterogeneity and drive tumorigenesis, therapy failure and metastasis.

**Francesco Antonio Tucci** (MD) is medical resident in pathological anatomy at the University of Milan, and PhD student in Systems Medicine at IEO under the guidance of Prof. Pece. His research aims at using multi-omics techniques to characterize tumor heterogeneity and identify new prognostic and predictive markers in bladder and prostate cancer.

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