

IEO RESEARCH NEWSLETTER

n. 073 – April 2026

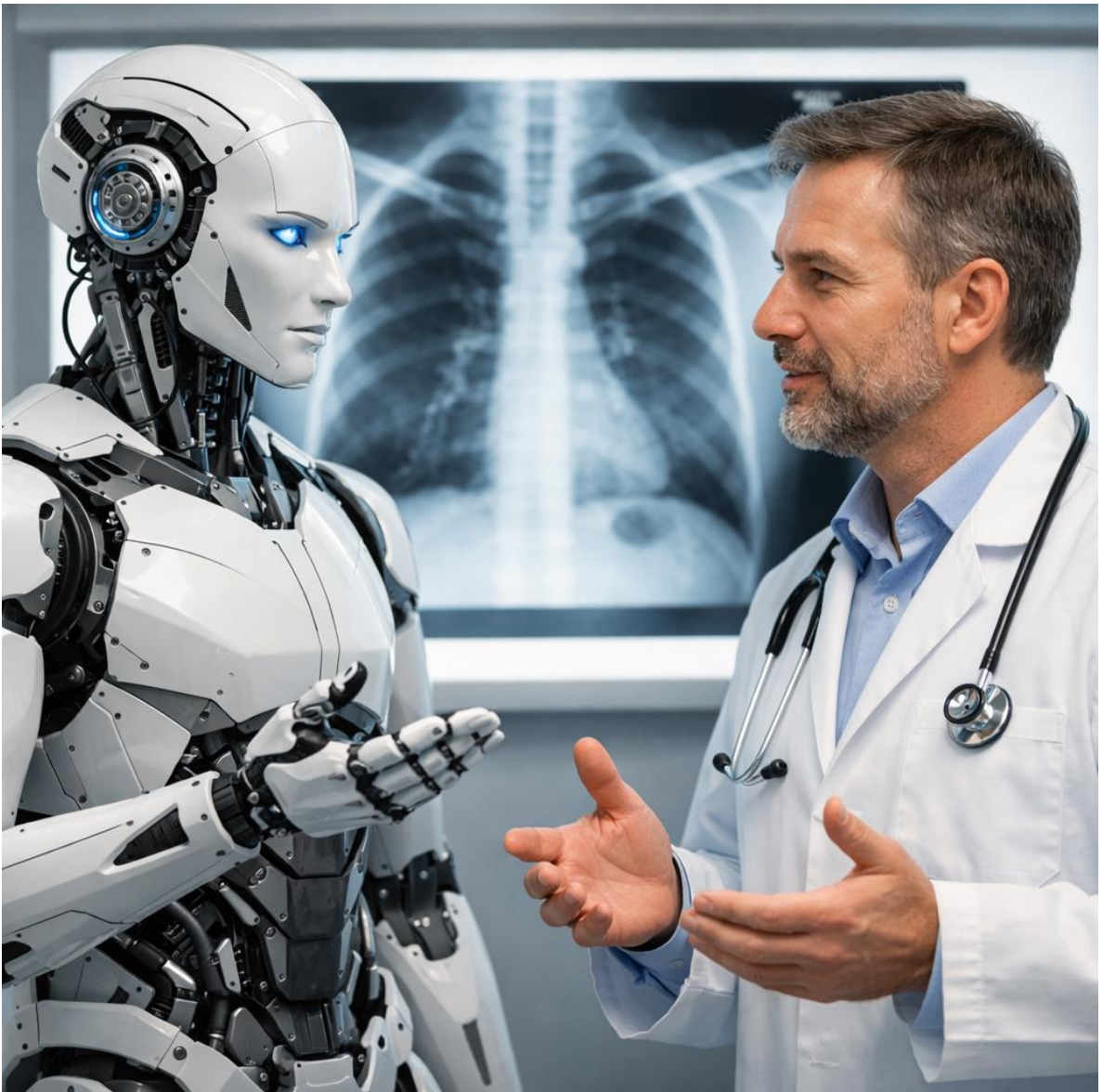


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Conoscerla per accettarla – Come percepiscono i medici l'integrazione dell'intelligenza Artificiale in ambito clinico?

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 (cfr. Newsletter 071).



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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. E' 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).*

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-chinasi, 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 (*Referenza: HER2CLIMB-05: A Phase III Study of Tucatinib Versus Placebo in Combination With Trastuzumab and Pertuzumab as First-Line Maintenance Therapy for HER21 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*).



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.

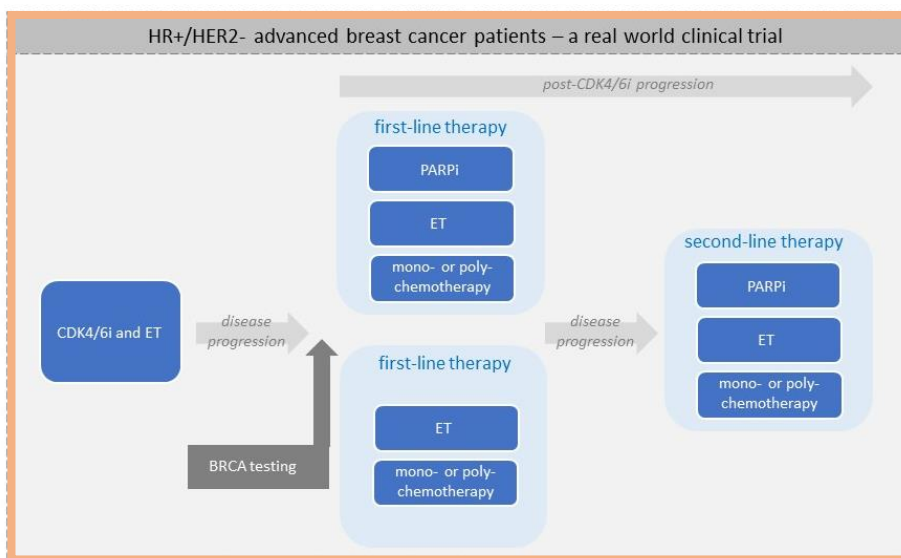
Efficacia. L'efficacia è stata valutata principalmente in termini di PFS, mostrando una riduzione del 36% del rischio di progressione della malattia: la PFS mediana era migliore nel gruppo tucatinib rispetto al gruppo placebo, essendo rispettivamente 24,9 mesi e 16,3 mesi. I benefici del trattamento 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%).

Inibitori di PARP per il trattamento delle pazienti con tumore al seno HR+/HER2- in cui la malattia è progredita: risultati di un real world clinical trial.



Le pazienti con tumore al seno HR+/HER2- in stadio avanzato sono generalmente trattate con inibitori di CDK4/6 (CDK4/6i) e terapia endocrina (ET). Tuttavia, nelle pazienti con mutazioni nella linea germinale, patogene o probabilmente patogene, a livello dei geni BRCA1/2 (mutazioni note per essere associate con un maggiore rischio di malattia), questo approccio terapeutico risulta meno efficace, probabilmente per via dei

meccanismi di resistenza delle cellule tumorali associati alla contemporanea perdita di attività della proteina RB1 nelle pazienti con mutazioni in BRCA2. Studi clinici precedenti di fase III hanno mostrato, nelle pazienti con tumore al seno avanzato HR+/HER2-, i benefici degli inibitori di PARP (PARPi) olaparib e talazoparib, in grado di ridurre in maniera significativa il rischio di progressione della malattia rispetto alla chemioterapia. Tuttavia, ad oggi non è noto se i PARPi siano più efficaci della chemioterapia o della ET nelle pazienti in cui la malattia è progredita dopo il trattamento con CDK4/6i.

Nel contesto di uno studio clinico osservazionale, che ha coinvolto diversi centri di ricerca, i ricercatori, tra cui Giuseppe Curigliano –vice-direttore scientifico IEO e direttore della divisione Nuovi farmaci per terapie innovative– hanno valutato, in un contesto *real world*, l'efficacia degli inibitori di PARP in pazienti con tumore al seno HR+/HER2- in stadio avanzato, con mutazioni (patogene o probabilmente patogene) nei geni BRCA1/2, che avevano ricevuto un precedente trattamento con CDK4/6i.

I risultati dello studio indicano una maggiore efficacia dei PARPi rispetto ad altre opzioni terapeutiche come ET e chemioterapia nelle pazienti in cui la malattia è progredita sotto trattamento con CDK4/6i, soprattutto se

somministrati nelle fasi iniziali (della progressione post-CDK4/6i; ovvero, come trattamento di prima linea piuttosto che come trattamento di seconda linea o successive).

In questo contesto, il test genetico per valutare l'eventuale presenza di mutazioni nei geni BRCA diventa critico, per poter selezionare il miglior approccio di trattamento; ovvero la scelta dei PARPi per le pazienti con mutazioni dei geni BRCA rispetto ad altre opzioni di trattamento più adeguate per la pazienti in cui i geni BRCA non sono mutati.

I meccanismi alla base dell'efficacia di questo trattamento osservata nello studio non sono noti; gli autori evidenziano però che studi preclinici precedenti hanno mostrato una minore capacità di riparare il danno al DNA (*double strand breaks*, DSB) da parte delle cellule tumorali che hanno sviluppato resistenza ai CDK4/6i. E' stata infatti osservata una notevole sensibilità all'inibitore di PARP olaparib da parte delle cellule tumorali con un sistema di riparo delle DSB danneggiato, suggerendo che i CDK4/6i potrebbero sensibilizzare le cellule tumorali a trattamenti successivi con i PARPi (*Referenza: Real-world effectiveness of PARP inhibitors after CDK4/6 inhibitor therapy in BRCA-mutated HR-positive/HER2-negative advanced breast cancer. Emma Zattarin, Antonio Marra, Antonella Palazzo, Gaia Griguolo, Claudio Vernieri, Julian Etessami, Letizia Pontolillo, Giusy Landa, Arianna Daneri, Matteo De Monte, Riccardo Cuoghi Costantini, Elena Tenedini, Ornella Ponzoni, Maria Grazia Razeti, Caterina Sposetti, Elena Barbieri, Martina Manni, Federica Caggia, Laura Cortesi, Giuseppe Curigliano, Emilio Bria, Massimo Dominici, Valentina Guarneri, Matteo Lambertini, Angela Toss. Npj breast cancer 2026. doi: 10.1038/s41523-025-00859-z*).

TELL ME MORE!

Lo studio ha incluso 81 pazienti che hanno ricevuto CDK4/6i (palbociclib, ribociclib, abemaciclib) e ET (inibitori dell'aromatasi o fulvestrant) ed erano portatrici di mutazioni BRCA1/2 nella linea germinale. Tra le pazienti arruolate, quelle in cui la malattia è progredita sono state successivamente trattate con 1) *a.* PARPi, oppure *b.* ET, or *c.* chemioterapia come trattamento di prima linea, o 2) PARPi come trattamento di seconda linea.

Efficacia. 1) le pazienti in cui la malattia è progredita sotto trattamento con CDK4/6i sono state trattate con *a.* **PARPi come terapia di prima linea**, oppure *b.* ET, oppure *c.* chemioterapia. Nelle pazienti trattate con chemioterapia, le metastasi erano più frequenti rispetto a quelle trattate con ET e PARPi. Per quanto riguarda l'analisi della sopravvivenza in assenza di progressione della malattia (*progression-free survival*, PFS), il rischio di progressione era significativamente ridotto con i PARPi: la PFS era significativamente più lunga nelle pazienti trattate con PARPi (11.8 mesi, rispetto a 3.5 mesi in ET, 5.2 e 4.0 mesi con mono- e poli-chemioterapia, rispettivamente). **2)** L'efficacia dei

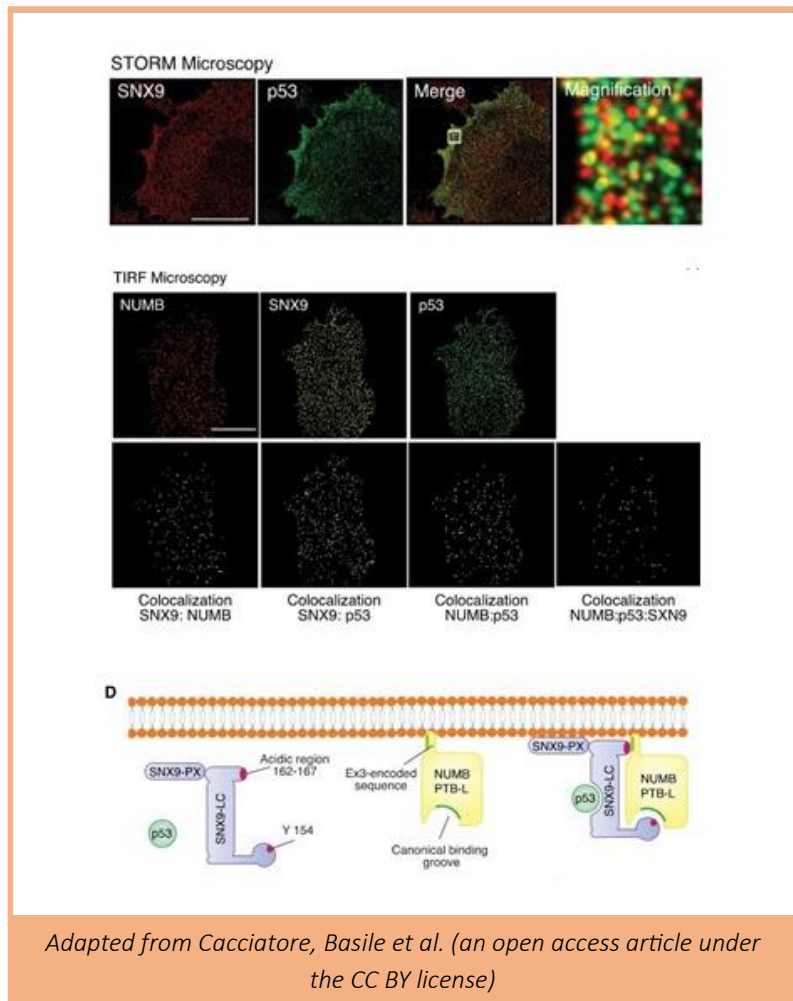
PARPi come trattamento di seconda linea era inferiore, con un rischio di progressione della malattia significativamente più alto. La ridotta efficacia in linee di somministrazione successive era particolarmente evidente per i PARPi rispetto ad altri agenti (chemio e ET) che, invece, mostravano un'efficacia paragonabile ad ogni linea di trattamento.

Mutazioni del gene BRCA ed efficacia del trattamento. Gli autori hanno effettuato un'analisi esplorativa per valutare la potenziale correlazione tra lo stato di BRCA2 (ovvero patogenico o probabilmente patogenico, così come la posizione della mutazione nel gene) e l'efficacia (in termini di PFS) di CDK4/6i e ET o di PARPi. Sebbene i risultati debbano essere considerati alla luce della limitata ampiezza del campione analizzato, non sono state osservate associazioni del tipo di variante di BRCA (patogenica/probabilmente patogenica) e della posizione della mutazione nel gene con la PFS, né per CDK4/6i né per PARPi. In ogni caso, i test genetici per BRCA nella linea germinale rimangono critici per la scelta terapeutica.

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 (cfr. newsletter 034, 065, 059), 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 (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 Sciatti, 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/adv.202513765).

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'esone 3 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. 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.

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

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



Nicola Fazio



Davide Ciardiello

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 (*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*).

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).

“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”

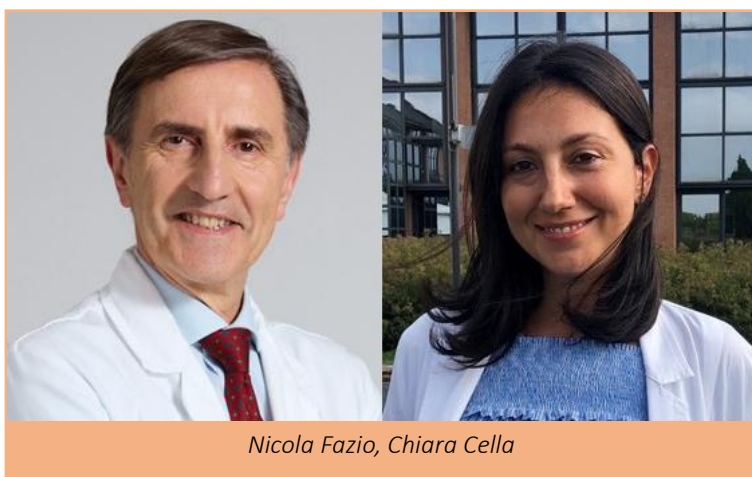
Stratificazione molecolare dei pazienti. Al fine di ottenere una migliore stratificazione dei pazienti e identificare quelli che più probabilmente avrebbero beneficiato della terapia A+C o C-only, i ricercatori hanno

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.

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



Nicola Fazio, Chiara Cella

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.

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 (*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, Xuewei Wang, Aziz Zaanani, Samuel J Klempner. *Nat Med* 2026. doi: 10.1038/s41591-026-04306-9).

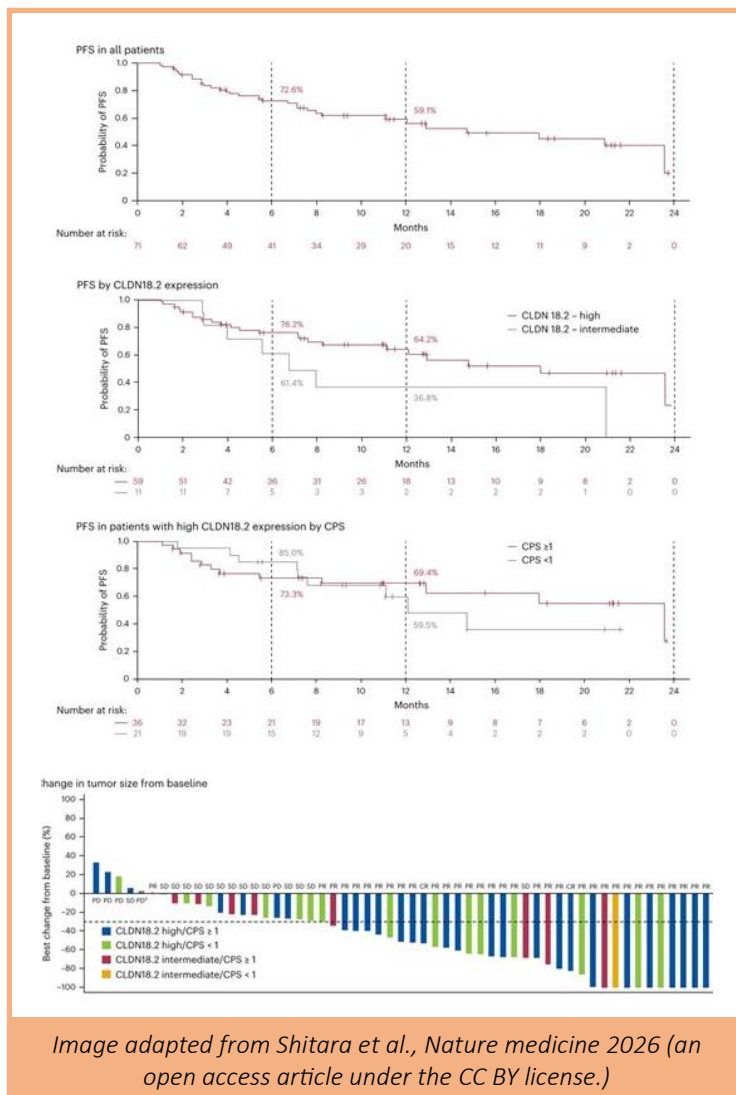


Image adapted from Shitara et al., *Nature medicine* 2026 (an open access article under the CC BY license.)

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 immunistoichimica 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 razionale 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.

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.

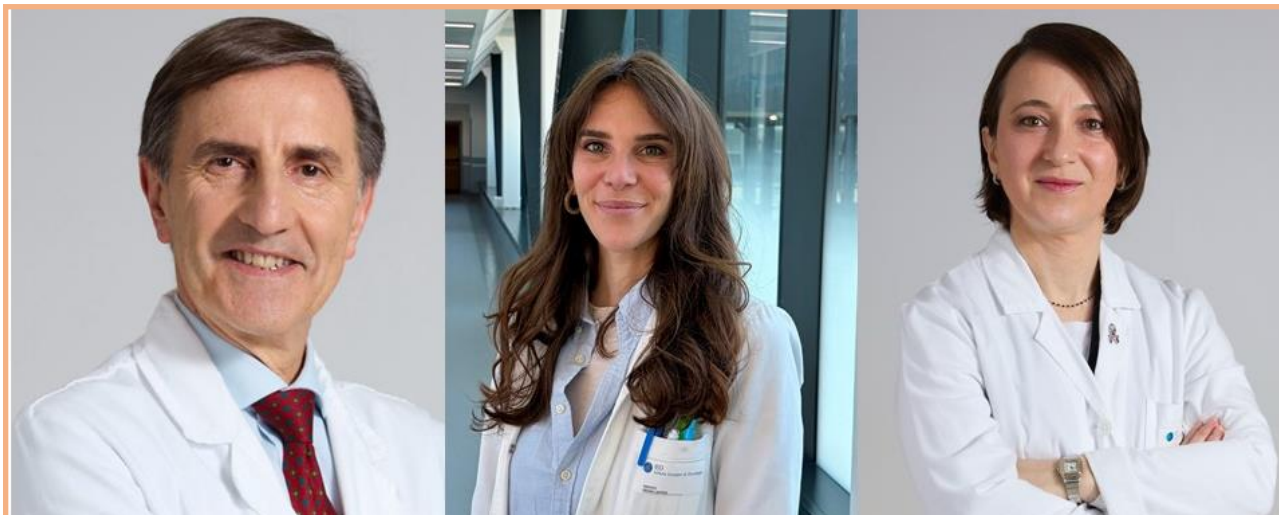
La proteina PD-L1 (programmed death-ligand 1) è un immunomodulatore, una proteina di superficie che lega il recettore PD-1 sui linfociti T, inibendo la loro attivazione e limitando quindi il suo funzionamento. Fisiologicamente contribuisce a evitare risposte autoimmuni eccessive, ma molti tumori ne sfruttano 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)

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

I tumori neuroendocrini (NETs) sono un tipo di tumore raro caratterizzati da proprietà "neuronal" –come la presenza di granuli all'interno della cellula contenenti 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.



Nicola Fazio, Lavinia Benini, Francesca Spada

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 (e.g. Newsletter 070). 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 (*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*).

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 stata necessario interrompere il trattamento per via della tossicità.

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.

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

“l'obiettivo finale di questo progetto è quello di sfruttare in un contesto clinico questo nuovo strumento prognostico/predittivo, 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”

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; Newsletter 059)– 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; cfr. Newsletter 059). 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.

Save the date: 20 anni di chirurgia robotica.



Chirurgia Robotica
2006 • 2026

Un futuro già iniziato

 22 maggio ore 10.00

 Aula Magna

 IEO
Istituto Europeo di Oncologia

MOTORE SANITÀ

Care Colleghe e cari Colleghi, siamo felici di invitarvi a partecipare all’incontro “Ventennale della Chirurgia Robotica IEO – Un futuro già iniziato”, che si terrà presso l’Aula Magna del nostro Istituto il 22 maggio, dalle 10.00 alle 17.00, nell’ambito del programma di Motore Sanità.

Il 2026 è infatti un anno speciale per lo IEO: celebriamo 20 anni di utilizzo continuativo e integrato della chirurgia robotica nella pratica clinica quotidiana di tutte le Divisioni chirurgiche. Quella che inizialmente era una grande innovazione tecnologica — lo IEO è stato il primo centro oncologico italiano a introdurre il robot chirurgico in sala operatoria — è oggi diventata una componente fondamentale del nostro modello organizzativo e assistenziale. Questo anniversario è un’importante occasione per fermarsi e riflettere insieme: la chirurgia robotica rappresenta infatti uno dei pilastri della transizione verso la chirurgia digitale, intesa non come una singola tecnologia, ma come un vero e proprio ecosistema integrato di strumenti e processi. Un’evoluzione che sta trasformando il nostro modo di operare, formare i professionisti e garantire qualità ed equità delle cure. Nei prossimi giorni seguiranno ulteriori dettagli sul programma della giornata, intanto vi invitiamo a segnarvi l’appuntamento in agenda.

Rubrica “Storie Vere”.

Care Colleghe e cari Colleghi, è con piacere che vi presentiamo “Storie Vere”, la nuova rubrica periodica dei magazine IEO e Monzino! Il progetto nasce da un’idea sviluppata da coloro che nell’ambito delle rispettive direzioni sanitarie si occupano della gestione dei rischi. I temi trattati includeranno diversi ambiti, con una attenzione particolare per i percorsi clinici, la gestione dei dati e gli aspetti medico-legali, con l’obiettivo di condividere episodi reali di esposizione al rischio da parte degli operatori e, conseguentemente, dell’ospedale. Periodicamente sarà selezionata una storia significativa, che verrà presentata e commentata in modo sintetico, facendo riferimento al nostro contesto ospedaliero. Auspichiamo che tale iniziativa possa rappresentare una

occasione di riflessione e di apprendimento, per accrescere la sicurezza delle nostre attività quotidiane e la capacità di prevenire situazioni di rischio. Invitiamo pertanto chiunque desideri contribuire con un caso di sua conoscenza di segnalarlo a Luigi O. Molendini, Massimo Monturano e Francesca Pavan. Siamo certi che grazie al contributo di tutti le storie possano essere numerose e interessanti per la nostra comunità!

Storie vere: Il paziente chiede, il medico invia.

Un paziente chiede a un medico la cortesia di inviargli le immagini di un suo esame. Il medico aderisce alla richiesta, nell'intento di favorire il paziente permettendogli di avere per le vie brevi le immagini, ed utilizza allo scopo un comune servizio cloud personale.

A seguito di tale invio, è lo stesso paziente a segnalare il caso agli organi competenti chiedendo e ottenendo un risarcimento danni, e pare che non fosse la prima volta.

In questi casi sono in effetti possibili sanzioni, oltre al riconoscimento di un risarcimento al paziente, nell'ordine di alcune migliaia di euro, per violazione del GDPR (la normativa europea che disciplina la protezione e il trattamento dei dati personali).

Ma se lo chiede il paziente? Questa circostanza non esime dal rispetto delle regole di sicurezza e la buona fede non conta.

Chi paga? Sono esposti a questo rischio sia l'operatore che l'ospedale.

Per questo raccomandiamo di seguire le regole istituzionali per la consegna di documenti clinici ai pazienti e, in caso di esigenze specifiche, di fare riferimento all'archivio clinico.

Hai letto la Rubrica Storie Vere, per conoscere i rischi potenziali e svolgere in modo più sicuro le nostre professioni. Se hai una storia da condividere segnalacela!

A cura di L.O. Molendini, M. Monturano, F. Pavan

Online il CTO Magazine di marzo.



Care Colleghe e Cari Colleghi, È online la quarta edizione del CTO MAGAZINE! La rivista semestrale del Clinical Trial Office IEO torna con un nuovo numero dedicato a chi vuole scoprire da vicino il mondo della Ricerca Clinica, attraverso le voci dei nostri professionisti e dei partner con cui collaboriamo ogni giorno, fra cui Associazioni Pazienti e Pazienti Esperti! Un progetto pensato non solo per informare, ma per condividere idee, visioni e innovazione. Scaricala [qui](#).

IEO COSMETICA: Giornate di Beauty Routine.

INVITO AL BENESSERE



 IEO
COSMETICA

Care Colleghe e Cari Colleghi, la presente per comunicarvi che riprenderanno le giornate di beauty routine organizzate dalla Farmacia IEO alla scoperta di IEO Cosmetica, nell'ambulatorio 5 in RTP (IEO 1) il 26 marzo dalle 10:30 alle 15.

Sarà un'occasione per conoscere da vicino i prodotti della linea e grazie all'esperienza e competenza della Farmacia IEO scoprire i più adatti al vostro tipo di pelle.

L'accesso è libero ma ci si può anche prenotare alla mail info@ieocosmetica.it, le sedute sono gratuite.

Vi aspettiamo!

Save the date: IEO con le Donne 2026!

Care Colleghe e cari Colleghi, siamo felici di annunciarvi che il prossimo 20 maggio 2026 alle ore 10.30, al Teatro Manzoni di Milano, si terrà la diciannovesima edizione di "IEO con le Donne". L'evento è da sempre un momento prezioso di ascolto e dialogo tra i medici del nostro Istituto e le donne che stanno affrontando o hanno affrontato un tumore al seno, un'occasione unica per condividere esperienze, storie e riflessioni.

Potete iscrivervi [qui](#).

Vi aspettiamo numerosi,

Comunicazione IEO

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 (see newsletter 071).



Image generated by ChatGPT

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. 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).

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



Giuseppe Curigliano

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 (*Reference: HER2CLIMB-05: A Phase III Study of Tucatinib Versus Placebo in Combination With Trastuzumab and Pertuzumab as First-Line Maintenance Therapy for HER2+ 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*).

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.

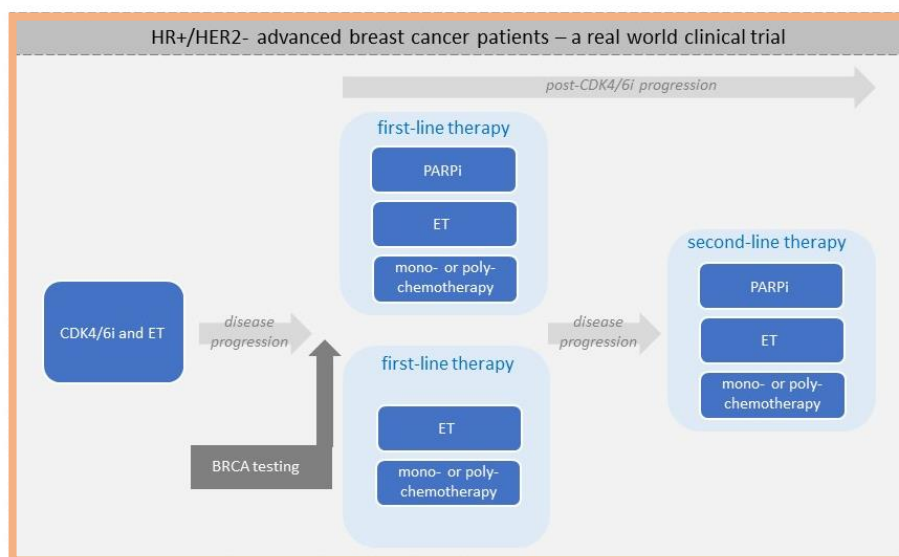
Safety. The toxicity profile of tucatinib in combination with trastuzumab and pertuzumab was overall consistent with the known safety profile of each drug in these patients. Anyway, serious and >grade 3 adverse events manifested more frequently in the tucatinib (42.3% and 16,9%) than in the placebo (24.4% 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%).

PARP inhibitors for the treatment of HR+/HER2- breast cancer patients who progressed after therapy: Results of a real world clinical trial.

HR+/HER2- advanced breast cancer patients are commonly treated with inhibitors of CDK4/6 (CDK4/6i) and endocrine therapy (ET). However, in patients carrying germline, pathogenic or likely pathogenic, BRCA1/2 mutations (which are known to be associated with greater risk of disease), this treatment approach appears less effective, likely because of resistance mechanisms of tumor cells related to the concurrent loss of activity of RB1 protein in BRCA2-mutant patients. Previous phase III clinical studies showed, in HR+/HER2- advanced breast cancer patients, the benefits of the PARP inhibitors (PARPi) olaparib and talazoparib, which significantly reduced the risk of disease progression as compared to chemotherapy. However, to date it is not known whether PARPi would be more effective than chemotherapy or ET in patients who progressed after treatment

with CDK4/6i.



In the frame of an observational clinical study, involving several research centers, researchers including Giuseppe Curigliano –IEO vice-scientific director and head of the Division of new drugs for innovative therapies– evaluated, in a real world setting, the efficacy of PARPi in HR+/HER2- advanced breast cancer patients carrying (pathogenic/likely pathogenic) BRCA mutation who had received prior

treatment with CDK4/6i.

The results indicate a greater efficacy of PARPi as compared to other treatment options such as ET and chemotherapy in patients who progressed under CDK4/6i treatment, especially if administered early after disease progression (that is, as first line rather than second and following therapy lines during post-CDK4/6i progression).

In this frame, gene testing to assess the presence of mutations in BRCA genes becomes critical, to guide the selection of the best treatment approach; that is, the choice of PARPi for BRCA-mutated patients or other more adequate treatment options for non-BRCA-mutated patients.

The mechanistic explanation underlying the observed treatment efficacy is unknown; however, the authors highlight that previous preclinical studies showed a lower ability to repair DSBs of cancer cells that had developed resistance to CDK4/6i. Tumor cells with impaired DSB repair ability were shown to be highly sensitive

to the PARPi olaparib, thus suggesting that CDK4/6i may sensitize tumor cells to subsequent treatment with PARPi (*Reference: Real-world effectiveness of PARP inhibitors after CDK4/6 inhibitor therapy in BRCA-mutated HR-positive/HER2-negative advanced breast cancer. Emma Zattarin, Antonio Marra, Antonella Palazzo, Gaia Griguolo, Claudio Vernieri, Julian Etessami, Letizia Pontolillo, Giusy Landa, Arianna Daneri, Matteo De Monte, Riccardo Cuoghi Costantini, Elena Tenedini, Ornella Ponzoni, Maria Grazia Razeti, Caterina Sposetti, Elena Barbieri, MartinaManni, Federica Caggia, Laura Cortesi, Giuseppe Curigliano, Emilio Bria, Massimo Dominici, Valentina Guarneri, Matteo Lambertini, Angela Toss. Npj breast cancer 2026. doi: 10.1038/s41523-025-00859-z*).

TELL ME MORE!

The study included 81 patients who had received CDK4/6i (palbociclib, ribociclib, abemaciclib) and ET (aromatase inhibitor (AI) or fulvestrant) and carried BRCA1/2 mutations. Among the enrolled patients, those who progressed were administered 1) a. PARPi, or b. ET, or c. chemotherapy as first line therapy, or 2) PARPi as second line therapy.

Efficacy. 1) patients who progressed under CDK4/6i were administered either *a. PARPi as first line therapy*, *b. ET* or *c. chemotherapy*. Analyses of the *metastatic burden* revealed that in patients treated with chemotherapy, metastases were more frequent, as compared to those under ET or PARPi. Regarding the analysis of *progression-free survival*, the risk of disease progression was significantly reduced in PARPi-treated patients: PFS was significantly longer in PARPi-treated patients (11.8 months vs 3.5 in ET and 5.2 and 4.0 with mono- and poly- chemo). 2) Efficacy of **PARPi as second line**

therapy was lower, with significantly higher risk of disease progression. The reduced efficacy in later phases of the care path was particularly evident for PARPi as compared to the other agents (chemo and ET) which, instead, showed comparable efficacy at any treatment line.

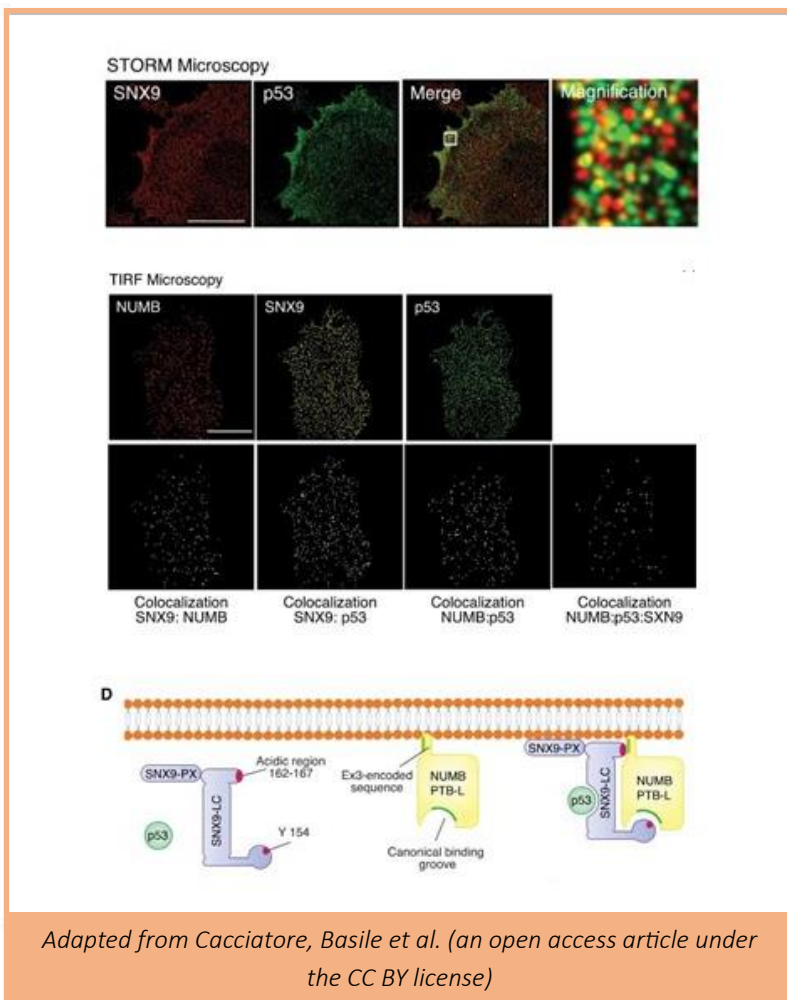
BRCA variants and treatment efficacy. The authors performed an exploratory analysis to assess the potential correlation between BRCA2 status (that is, being either pathogenic or likely pathogenic, as well as the location of the mutation in the gene) and efficacy (in terms of PFS) of CDK4/6i and ET or PARPi. Although results should be considered in light of the limited sample size analyzed, no association were found between BRCA variant (pathogenic/likely pathogenic) type and location in the gene and PFS, neither for CDK4/6i nor for PARPi. Yet, germline BRCA testing remains critical for the treatment decision.

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 (see newsletter 034, 065, 059), 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

“by demonstrating, for the first time, that non-mutated p53 can be released in the extracellular milieu, the authors revealed a mechanism deployed by cells to preserve a tumor-suppressive, p53-mediated, environment, which, in certain situations, might otherwise initiate tumorigenesis”



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 (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 Ciozzani, 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/adv.202513765).

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.

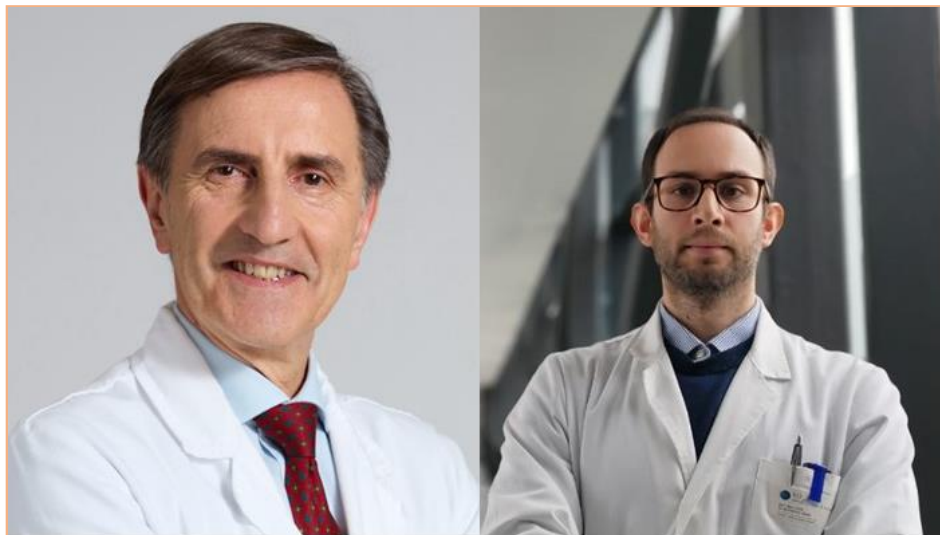
Was the NUMB-SNX9-p53 complex affected by the plasma membrane? p53 and exon3-containing NUMB both independently bound the lipid membrane; the binding was increased by SNX9. In particular, SNX9 bound p53 *only* at the membrane, indicating that the three proteins colocalized, at the plasma membrane, and 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.

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

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.



Nicola Fazio, Davide Ciardiello

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 (*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, Piscanti 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*).

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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

“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”

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.

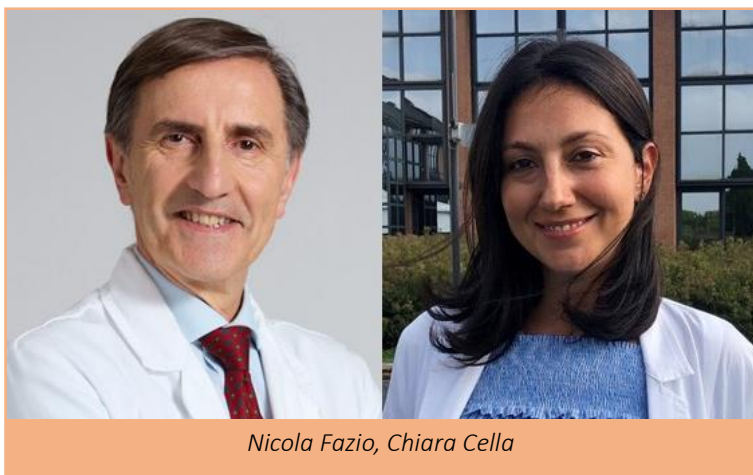
Biomarker analysis – TMB and liver metastases to predict response to therapy. The authors found that, despite the putative predictive role of high tumor mutational burden (TMB) in the response to immunotherapy, in these patients TMB was a negative prognostic factor of therapy efficacy, in both treatment 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.

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



Nicola Fazio, Chiara Cella

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. 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 (*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, Xuwei Wang, Aziz Zaanan, Samuel J Klempner. Nat Med 2026. doi: 10.1038/s41591-026-04306-9*).

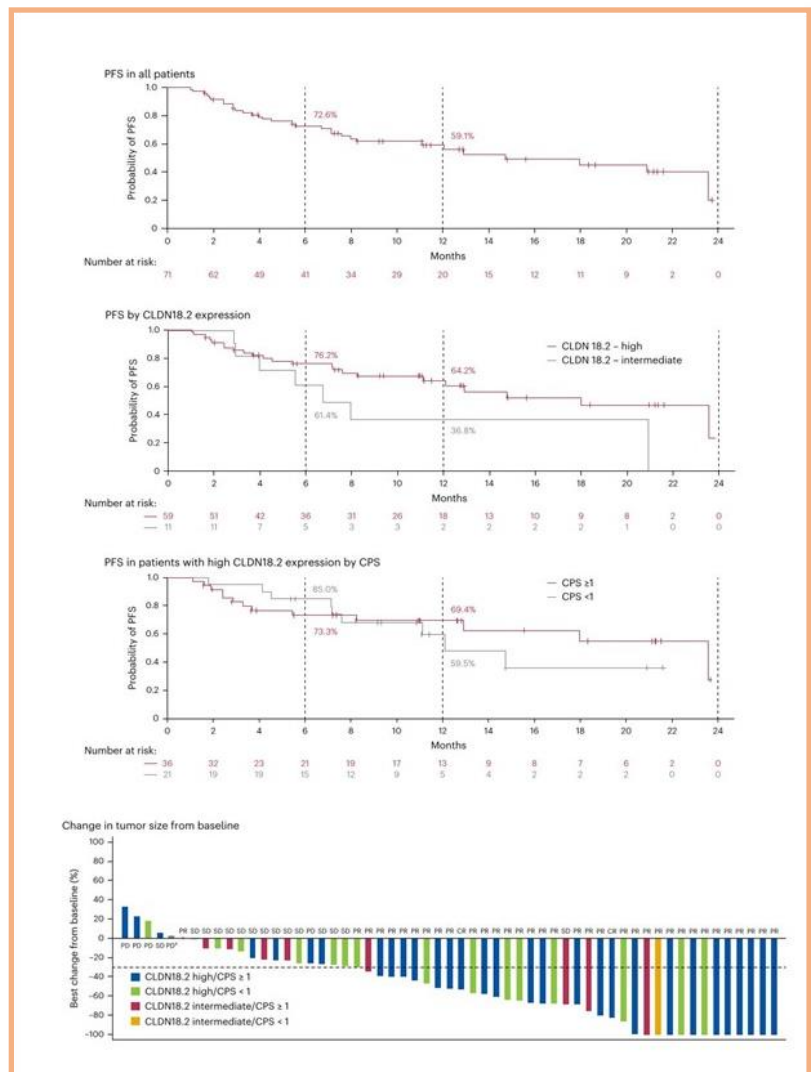


Image adapted from Shitara et al., Nature medicine 2026 (an open access article under the CC BY license.)

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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.

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)

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

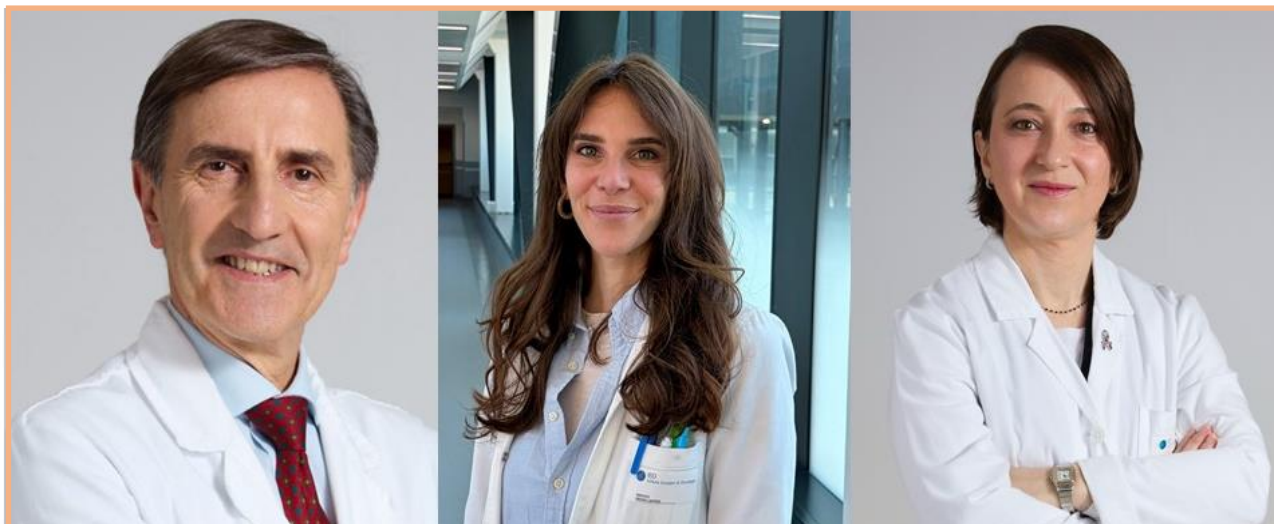
Neuroendocrine tumors (NETs) are a rare tumor type characterized by both "neuro"-like features –such as granules inside the cell containing monoamines (typical of serotonergic neuron types)– and "endocrine" traits –such as the capability of secreting monoamines. Therefore, NETs can arise in different 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 (e.g. see Newsletter 070). mTOR is a known

“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”



Nicola Fazio, Lavinia Benini, Francesca Spada

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 (*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*).

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.

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.

“the final goal of this project is the exploitation, in the clinical context, of this new predictive/prognostic tool, which is the only molecular diagnostic tool so far available for bladder cancer patient stratification, hence extremely useful for these patients”

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, see Newsletter 059)– 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.

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; see newsletter 059). 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.”



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 Ai Yi (DeepSeek) and Alex Irwin (ChatGPT), revision by Stefania Averaimo)

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, Sefc L, Macurek L, Elgandy 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.

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, MilesShkin 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.

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.

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.

Jendrisek 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'Esofago (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, Lorubio C, Jereczek-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 α -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.

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

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, Győrffy 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, Fagnoli MC, Kanetsky PA, Queirolo P, Bagnardi V, Bataille V, Raimondi 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, Kuzmick RJ, Smith K, Brasó-Maristany F, Nyein Chan NN, Paré Brunet L, Alder L, Garcia-Cortes D, Gomez Tejeda Zanutto 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
NPJ 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 (isoprostic 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.

What else is new in science?

(Text by Ai Yi (DeepSeek) and Alex Irwin (ChatGPT), revision by Stefania Averaimo)

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. *The. 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 (New York, N.Y.)*. 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 hemizyosity 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

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

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 (New York, N.Y.).* 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 α 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- γ 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 are 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

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 four weeks on metastases, immunotherapy, epigenetics, extracellular vesicles, liquid biopsy, metabolism, microbiota, genomics, biomarkers, and provide a short summary per each of them?

Sure, below is a curated set of recent (Feb–Mar 2026) bioRxiv cancer-related preprints. I prioritized recency, topic relevance, mechanistic depth.

Epigenetic liquid biopsy in neuroblastoma ([biorxiv.org](https://www.biorxiv.org)). The paper presents a mutation-agnostic liquid biopsy approach exploiting epigenetic signatures to monitor high-risk neuroblastoma. Instead of relying on specific mutations, the method tracks tumor-derived DNA methylation patterns in circulation. It improves early relapse detection and longitudinal disease monitoring, suggesting clinical utility for minimal residual disease assessment and therapy guidance.

Ex vivo drug testing platform ([biorxiv.org](https://www.biorxiv.org)). The authors develop a platform using patient-derived metastatic samples to test drug response ex vivo, using malignant pleural effusions (MPEs) from non-small cell lung cancer (NSCLC) patients and core needle biopsies. The assay is quantitative and reproducible.

EB-driven epigenetic reprogramming in breast cancer ([biorxiv.org](https://www.biorxiv.org)). The paper shows that Epstein–Barr virus infection induces epigenetic remodeling that promotes cancer stem cell phenotypes in breast cancer. Viral-mediated chromatin changes enhance stemness and tumor aggressiveness, suggesting a mechanistic link between infection, epigenetics, and tumor initiation.

KRAS variant-dependent adaptation in pancreatic cancer ([biorxiv.org](https://www.biorxiv.org)). The authors show that baseline cellular states shape how different KRAS mutations reprogram signaling and metabolism. Distinct KRAS variants produce divergent phenotypes depending on pre-existing transcriptional context.

TSC2 nuclear role in PI3K–AKT–mTOR signaling ([biorxiv.org](https://www.biorxiv.org)). The paper identifies a noncanonical function of TSC2 as a transcriptional regulator controlling miRNA expression. This nuclear role modulates PI3K–AKT–mTOR signaling, linking transcriptional control to metabolic and proliferative pathways in cancer.

Flow-sensitive ion channels and tumor signaling ([biorxiv.org](https://doi.org/10.1101/2023.03.15.531811)). The authors describe the mechanotransduction pathway coupling calcium influx, flow-activated K channels, and PI3K/Akt signaling, connecting physical forces in the tumor microenvironment to oncogenic signaling and vascular adaptation.

Chemoradiotherapy reshapes the immune tumor microenvironment ([biorxiv.org](https://doi.org/10.1101/2023.03.15.531812)). The paper shows that adding chemotherapy to radiotherapy differently remodels the immune tumor microenvironment as compared to radiotherapy alone in head and neck cancer. This alters immune landscape and may influence response to checkpoint blockade.

Tumor–host feed-forward loop in chromosomal instability cancers ([biorxiv.org](https://doi.org/10.1101/2023.03.15.531813)). The paper investigates how chromosome instability sustains malignant growth through a non-cell autonomous mechanism. They show that, despite chromosomal heterogeneity, cells display similar transcriptional programs, in turn influencing proliferation and death of cells in the microenvironment.

Niclosamide prodrug targeting HCC pathways ([biorxiv.org](https://doi.org/10.1101/2023.03.15.531814)). The paper introduces a modified compound of the FDA-approved niclosamide with improved bioavailability that inhibits multiple oncogenic pathways in hepatocellular carcinoma, resulting in reduced proliferation, survival, and immune-evasion signaling.

New mouse model for advanced hepatocellular carcinoma ([biorxiv.org](https://doi.org/10.1101/2023.03.15.531815)). The authors present the development of a new patient-derived xenograft model of HCC in mice.

Phenotypic plasticity modeling in breast cancer ([biorxiv.org](https://doi.org/10.1101/2023.03.15.531816)). By modeling cell dynamics and heterogeneous tumor growth, the authors quantified transitions between subpopulations of phenotypically distinct breast cancer cells and changes in spatial reorganization upon therapy, offering insights on how phenotypic plasticity, spatial organization and growth dynamics shape therapy resistance.

ChromSMF multi-omic epigenetic profiling ([biorxiv.org](https://doi.org/10.1101/2023.03.15.531817)). The paper reports the development of a technique integrating DNA methylation, histone marks, and protein-DNA interactions on long DNA molecules, enabling high-resolution mapping of epigenetic heterogeneity in cancer.

Spatial omics exploration framework (KaroSpace) ([biorxiv.org](https://doi.org/10.1101/2023.03.15.531818)). The authors describe the development of a computational tool for analysis of spatial omics data.

Modeling Hepatocellular Carcinoma and its microenvironment on a chip ([biorxiv.org](https://doi.org/10.1101/2023.03.15.531819)). The authors describe the development of a tool for the evaluation of drug-induced responses in the tumor and associated microenvironment, useful for mechanistic preclinical research and the development of new drugs.

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 β , 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 β 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 TGFbeta 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...

11th Annual Meeting *Alleanza Contro il Cancro* (Naples September 10th-12th) – [registration](#) open

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“5th Radiomics: theory and practice” [Course](#) (May 18th → 20th 2026, Paris)

[PhD position](#) International Max Planck Research School for Living Matter

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[PhD Students Meeting](#) 2026 abstract submission deadline april 10th

Feynman — AI Grading & Teaching Assistant [for Professors](#)

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This [AI](#) can improve your peer review — and make it more polite

[perseverance and problem solving](#) – the key for a PhD

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[AI and the PhD student: friend or foe?](#)
“...whichever tools you use, they should help you to learn — not replace your thinking”

[Knock knock, no one's there. Study finds scientists' jokes mostly fall flat](#)
“...scientists have had incredibly interesting lives, and humour comes from the reality of our lived experience. Therefore, you are funny.”

AI raises the productivity bar - [PubMed](#)

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[Hypofractionated nodal radiotherapy in breast cancer: time for an updated standard of care?](#)



QUESTO MESE DIAMO IL BENVENUTO A

THIS MONTH WE WELCOME

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