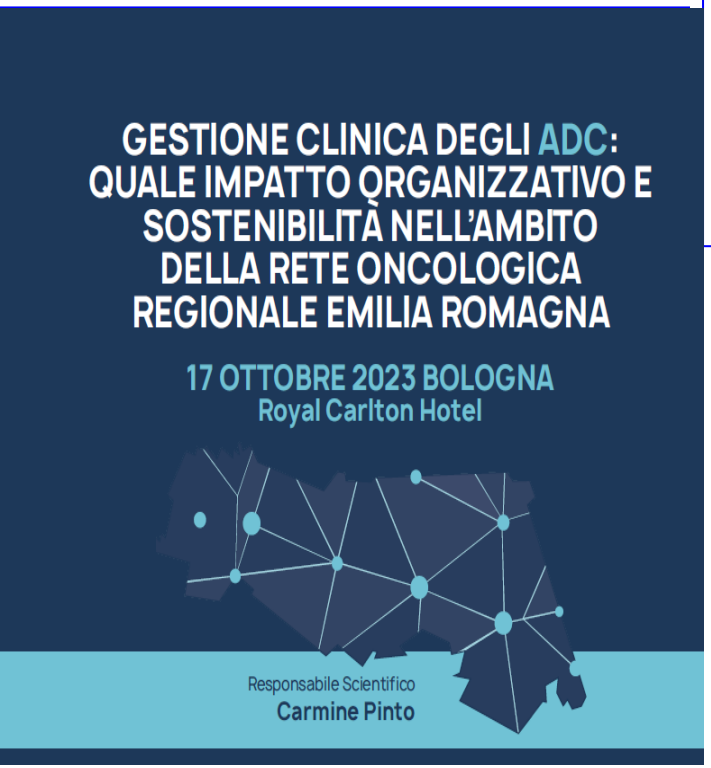
Percorsi Diagnostici



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Nuovi bersagli di ADCs

a) Affinché un ADC sia efficace, un fattore critico è l'antigene bersaglio, che deve essere espresso selettivamente (o sovraespresso) sulla cellula tumorale desiderata

b) Presenza (o la sovraespressione) dell'antigene bersaglio può essere testata come "biomarcatore" per identificare pazienti potenzialmente sensibili.

Signal Transduction and Targeted Therapy www.nature.com/sigtrans

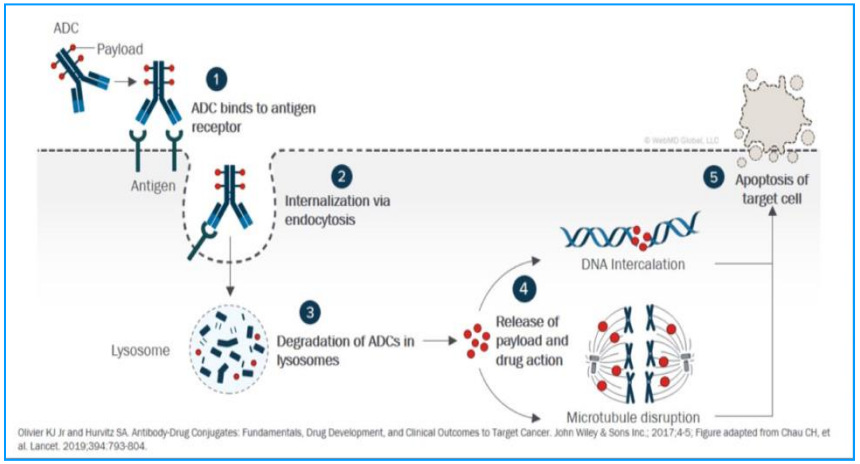
REVIEW ARTICLE OPEN

Antibody drug conjugate: the "biological missile" for targeted cancer therapy

Zhiwen Fu[1,2], Shijun Li[1,2], Sifei Han[3,4], Chen Shi[1,2✉] and Yu Zhang[1,2✉]

Antibody–drug conjugate (ADC) is typically composed of a monoclonal antibody (mAbs) covalently attached to a cytotoxic drug via a chemical linker. It combines both the advantages of highly specific targeting ability and highly potent killing effect to achieve accurate and efficient elimination of cancer cells, which has become one of the hotspots for the research and development of anticancer drugs. Since the first ADC, *Mylotarg*® (gemtuzumab ozogamicin), was approved in 2000 by the US Food and Drug Administration (FDA), there have been 14 ADCs received market approval so far worldwide. Moreover, over 100 ADC candidates have been investigated in clinical stages at present. This kind of new anti-cancer drugs, known as "biological missiles", is leading a new era of targeted cancer therapy. Herein, we conducted a review of the history and general mechanism of action of ADCs, and then briefly discussed the molecular aspects of key components of ADCs and the mechanisms by which these key factors influence the activities of ADCs. Moreover, we also reviewed the approved ADCs and other promising candidates in phase-3 clinical trials and discuss the current challenges and future perspectives for the development of next generations, which provide insights for the research and development of novel cancer therapeutics using ADCs.

Signal Transduction and Targeted Therapy (2022)7:93 ; https://doi.org/10.1038/s41392-022-00947-7



Olivier KJ Jr and Hurvitz SA. Antibody-Drug Conjugates: Fundamentals, Drug Development, and Clinical Outcomes to Target Cancer. John Wiley & Sons Inc.; 2017;4-5; Figure adapted from Chau CH, et al. Lancet. 2019;394:793-804.

Nuovi bersagli di ADCs

a) Affinché un ADC sia efficace, un fattore critico è l'antigene bersaglio, che deve essere espresso selettivamente (o sovraespresso) sulla cellula tumorale desiderata

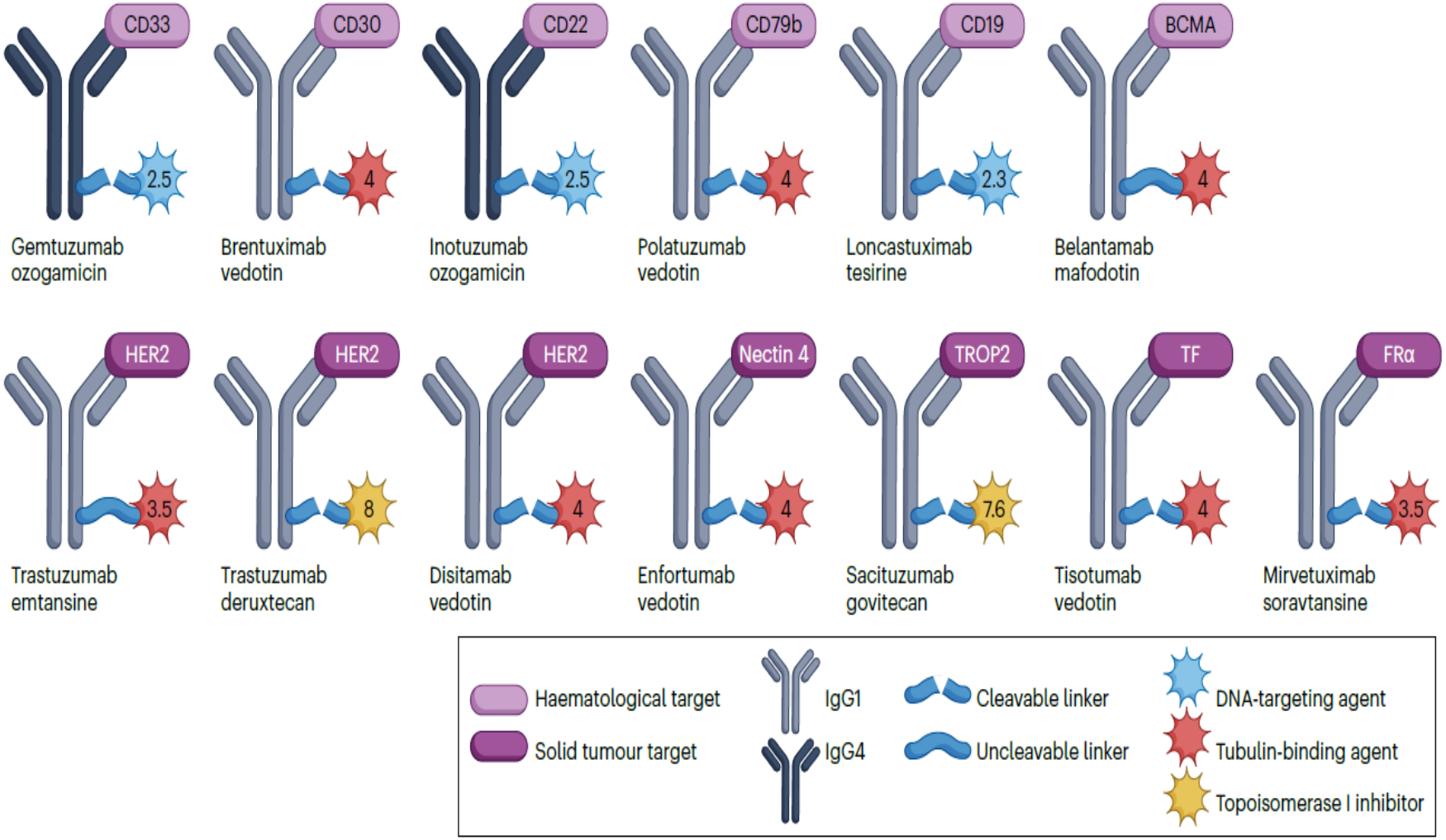
b) Presenza (o la sovraespressione) dell'antigene bersaglio può essere testata come "biomarcatore" per identificare pazienti potenzialmente sensibili

c) Con la disponibilità di molti ADCs (T-DXd,Dato-DXd, Sacituzumab govitecan,TDM1, HER3-DXd…) avremo bisogno di tests in grado di aiutare a dare priorità ad un composto basata sull'espressione del target

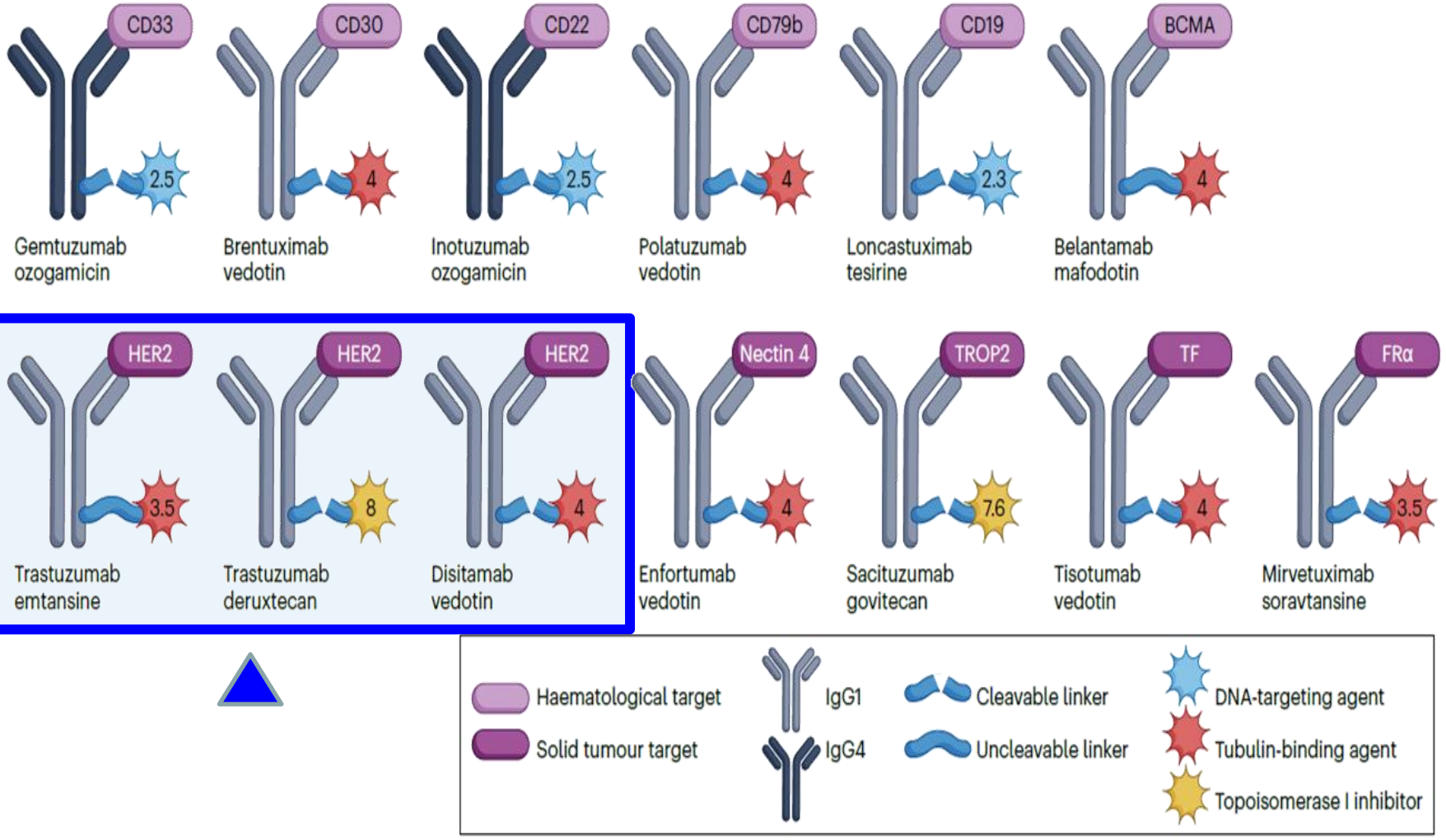
nature reviews drug discovery
https://doi.org/10.1038/s41573-023-00709-2

Review article

Antibody–drug conjugates come of age in oncology



DIS-REGOLAZIONE HER2



DIS-REGOLAZIONE HER2 NEI TUMORI SOLIDI
un gene molte variabili

- Dis-regolazione di HER2 (sovraespressione, amplificazione, mutazione), anche se con prevalenze altamente variabili, presente in quasi tutti i tumori epiteliali … molto rara nei tumori non-epiteliali
- Differenti tipi di mutazione geniche nei diversi tumori
- Correlazioni variabili tra iperespressione proteica ed amplificazione
- IIC : pattern variabili di sovraespressione sulla membrana cellulare… e sistemi di scoring diversi-non armonizzati fra diverse sedi

DI-SREGOLAZIONE HER2 NEI TUMORI SOLIDI
"diver oncogenetico" e Target perTerapia

- Le Terapie mirate anti-HER2 (anticorpi,TKI e ADC) cambiato drasticamente la prognosi dei pz con ca mammella HER2 positivo sia in stadio precoce che avanzato
- Efficaci anche nel trattamento ca gastro-esofagei e colon-retto
- Nuovi approcci terapeutici con farmaci anti-HER2 attualmente testati anche nelle neoplasie ginecologiche, polmonari ed altre sedi
- Test HER2 accurati e "report non ambigui" oggi importanti per identificare i pazienti candidati alle diverse terapie

HER2 e Ca mammella

- 85% ca mammella classificati HER2 negativi
- 60% dimostrerà bassi livelli di espressione di HER2, definiti come IIC HER2 1+ o 2+ non amplificati (Schettini F, et al. NPJ Breast Cancer.2021).

- Questo 60% di pazienti con bassi livelli di espressione di HER2 costituisce un gruppo di crescente interesse nella pratica clinica

- Questo può rappresentare una sfida organizzativa ed interpretativa nella valutazione di HER2

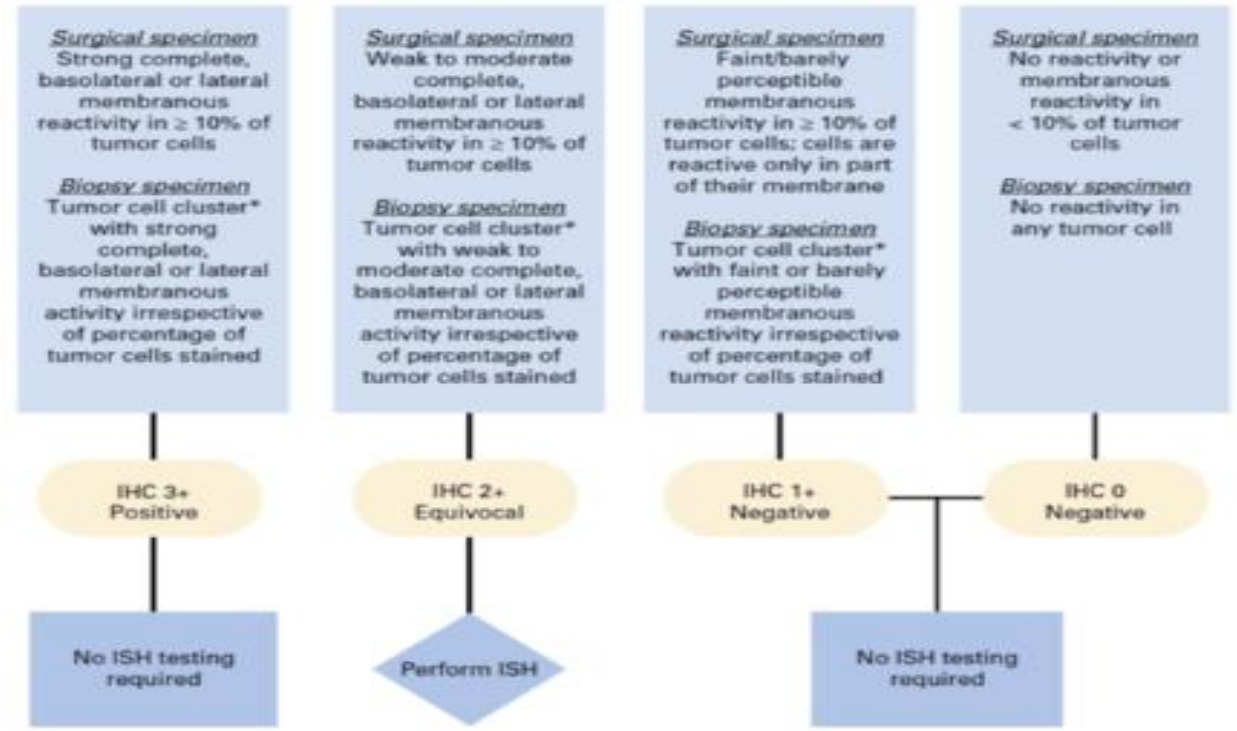
TEST HER2 e LINEE GUIDA

- Le Linee Guida per HER2 esistono solo per i tumori con terapie mirate e approvate (mammella e gastro-esofageo)

- Per altri tipo di tumore sono state adottate le stesse Linee Guida, o più spesso impiegati sistemi di score variabili e non omogenei

- Di conseguenza i dati sulla prevalenza delle alterazioni di HER2 nei diversi tumori sono poco chiari

Linee Guida HER2 e SCORE GASTRO-ESOFAGEO

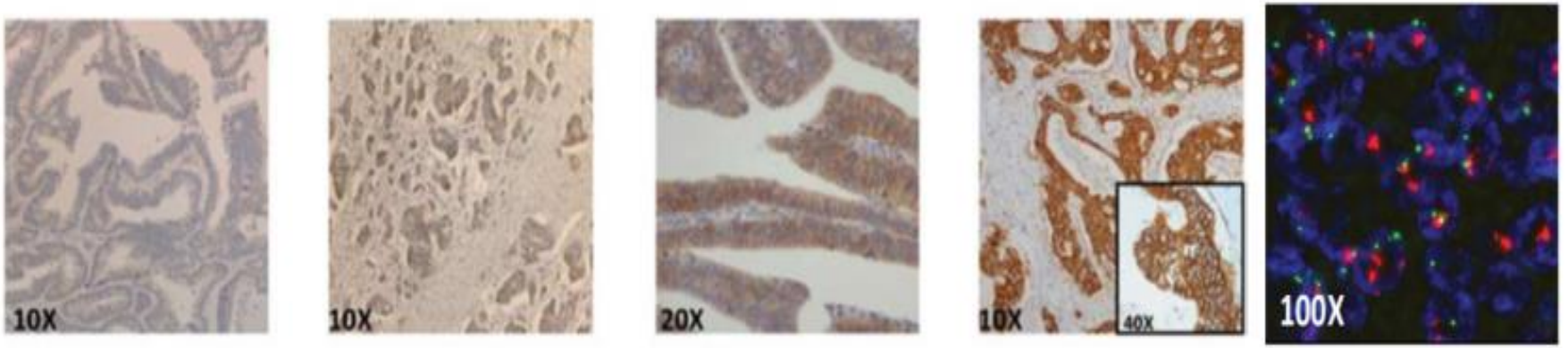


13% to 22%

Bartley AN, et al. *J Clin Oncol*. 2017;35:446-464.

HER2 SCORE COLON-RETTO

0	1+	2+	3+	ISH positivity
Absence of staining	Faint staining (segmental or granular); moderate staining < 50% of cells; intense staining ≤ 10% cells	Moderate complete or basolateral membranous staining in ≥ 50% of cells or intense staining in < 50% of cells	Intense complete or basolateral membranous staining in ≥ 50% of cells	HER2/CEP17 ratio ≥ 2 in ≥ 50% tumor cells



Valtorta E, et al. *Mod Pathol*. 2015;28:1481-1491.

HER2 polmone e altri ADCs

A partire da gennaio 2023 approvato Trastuzumab Deruxtecan-nxki nei NSCLC non resecabile o metastatico precedentemente trattato.

Studi clinici molto attesi esamineranno altri potenziali ADC per il trattamento del NSCLC:

- Datopotamab deruxtecan, target TROP-2;
- Patritumab deruxtecan, target HER3;
- Tusamitamab ravtansine, target CEACAM5.

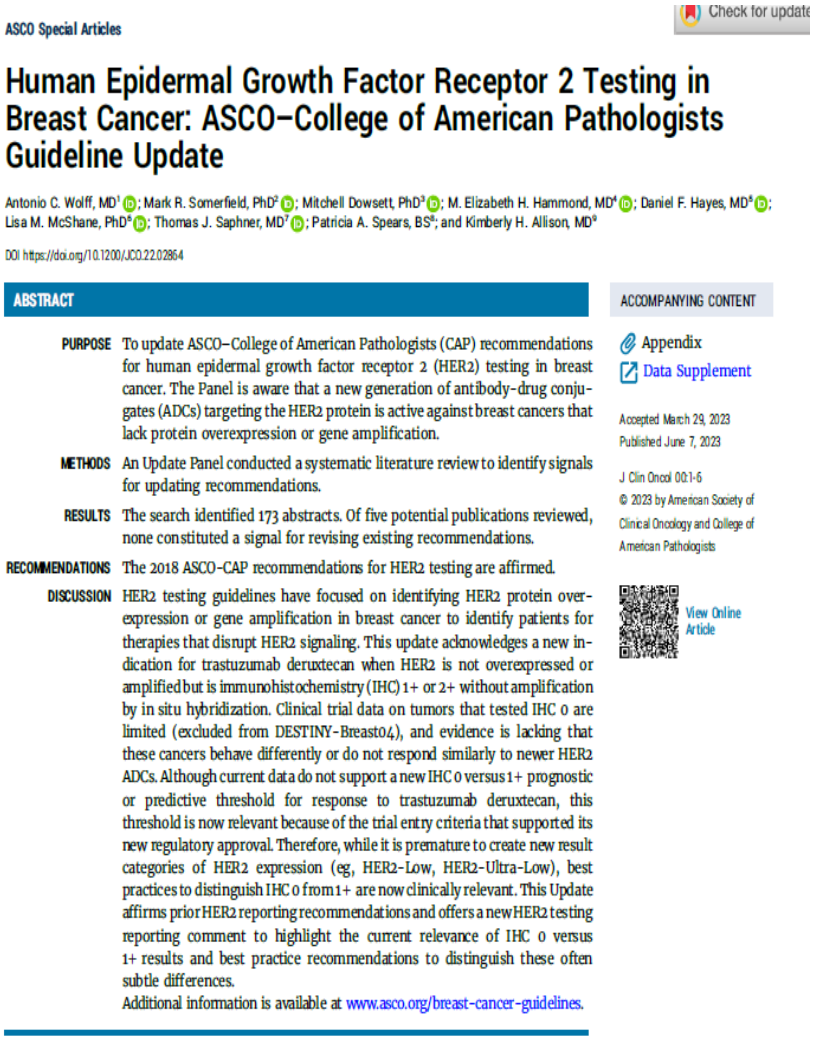
HER2 e ALTRI TUMORI

	Overexpression	Amplification	Mutation
Cervical adenocarcinoma	4%	2% to 17%	5% to 6%
Uterine serous carcinoma	18% to 42%	16% to 42%	1% to 2%
Ovarian carcinoma	3%	1% to 2%	1% to 2%
Urinary bladder	17% to 80%	0% to 25%	10% to 12%
Pancreatic carcinoma	4% to 11%	1% to 2%	1% to 2%
Cholangiocarcinoma	5%	18%	1% to 2%
Head&Neck carcinoma	1% to 2%	2% to 3%	1% to 2%

Connell CM, et al. *ESMO Open*. 2017;2:e000279.

LINEE GUIDA Test HER2 e ca mammella

- LG HER2 2022 rivisitate



ASCO Special Articles

Check for update

Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: ASCO–College of American Pathologists Guideline Update

Antonio C. Wolff, MD[1]; Mark R. Somerfield, PhD[2]; Mitchell Dowsett, PhD[3]; M. Elizabeth H. Hammond, MD[4]; Daniel F. Hayes, MD[5]; Lisa M. McShane, PhD[6]; Thomas J. Saphner, MD[7]; Patricia A. Spears, BS[6]; and Kimberly H. Allison, MD[8]

DOI https://doi.org/10.1200/JCO.22.02864

ABSTRACT

PURPOSE To update ASCO–College of American Pathologists (CAP) recommendations for human epidermal growth factor receptor 2 (HER2) testing in breast cancer. The Panel is aware that a new generation of antibody-drug conjugates (ADCs) targeting the HER2 protein is active against breast cancers that lack protein overexpression or gene amplification.

METHODS An Update Panel conducted a systematic literature review to identify signals for updating recommendations.

RESULTS The search identified 173 abstracts. Of five potential publications reviewed, none constituted a signal for revising existing recommendations.

RECOMMENDATIONS The 2018 ASCO-CAP recommendations for HER2 testing are affirmed.

DISCUSSION HER2 testing guidelines have focused on identifying HER2 protein overexpression or gene amplification in breast cancer to identify patients for therapies that disrupt HER2 signaling. This update acknowledges a new indication for trastuzumab deruxtecan when HER2 is not overexpressed or amplified but is immunohistochemistry (IHC) 1+ or 2+ without amplification by in situ hybridization. Clinical trial data on tumors that tested IHC 0 are limited (excluded from DESTINY-Breast04), and evidence is lacking that these cancers behave differently or do not respond similarly to newer HER2 ADCs. Although current data do not support a new IHC 0 versus 1+ prognostic or predictive threshold for response to trastuzumab deruxtecan, this threshold is now relevant because of the trial entry criteria that supported its new regulatory approval. Therefore, while it is premature to create new result categories of HER2 expression (eg, HER2-Low, HER2-Ultra-Low), best practices to distinguish IHC 0 from 1+ are now clinically relevant. This Update affirms prior HER2 reporting recommendations and offers a new HER2 testing reporting comment to highlight the current relevance of IHC 0 versus 1+ results and best practice recommendations to distinguish these often subtle differences.

Additional information is available at www.asco.org/breast-cancer-guidelines.

ACCOMPANYING CONTENT

Appendix

Data Supplement

Accepted March 29, 2023
Published June 7, 2023

J Clin Oncol 00:1-6

View Online Article

COLLEGE of AMERICAN PATHOLOGISTS

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

LINEE GUIDA Test HER2 e ca mammella

- **2022 LG HER2 rivisitate in linea con dati del DESTINY Trial Breast04.**

Modi et al studio di fase III miglioramento significativo sopravvivenza in pazienti con ca. mammela senza sovraespressione o amplificazione di HER2, ma con risultati immunoistochimici (IHC) 1+ o IHC 2+ non amplificati (ISH), trattati con il ADC Trastuzumab Deruxtecan

- **LG HER2 ASCO/CAP 2007,aggiornate 2013 e 2018.**
- **Aggiornamento raccomandazioni del 2018 restano valide**

FDA approvazione test IIC utilizzato in DESTINY Breast04 (Ventana Anticorpo monoclonale di coniglio PATHWAY anti HER2/neu 4B5 sul BenchMark ULTRAstrument)

LINEE GUIDA Test HER2 e ca mammella

1) La visione dicotomica dello stato di HER2 (positivo o negativo) non più corretta

2) Clinicamente importante distinguere HER2-0 da tutti gli altri gradienti di positività per HER2

3) Importante distinguere accuratamente i tumori con score IIC 1+ da quelli con score 0

4) Tutti i differenti cut-offs necessari per nuove opzioni terapeutiche

5) ISH upfront NON è più algoritmo diagnostico ideale per identificare questo «nuovo gruppo» potenziale target Tp anti HER2

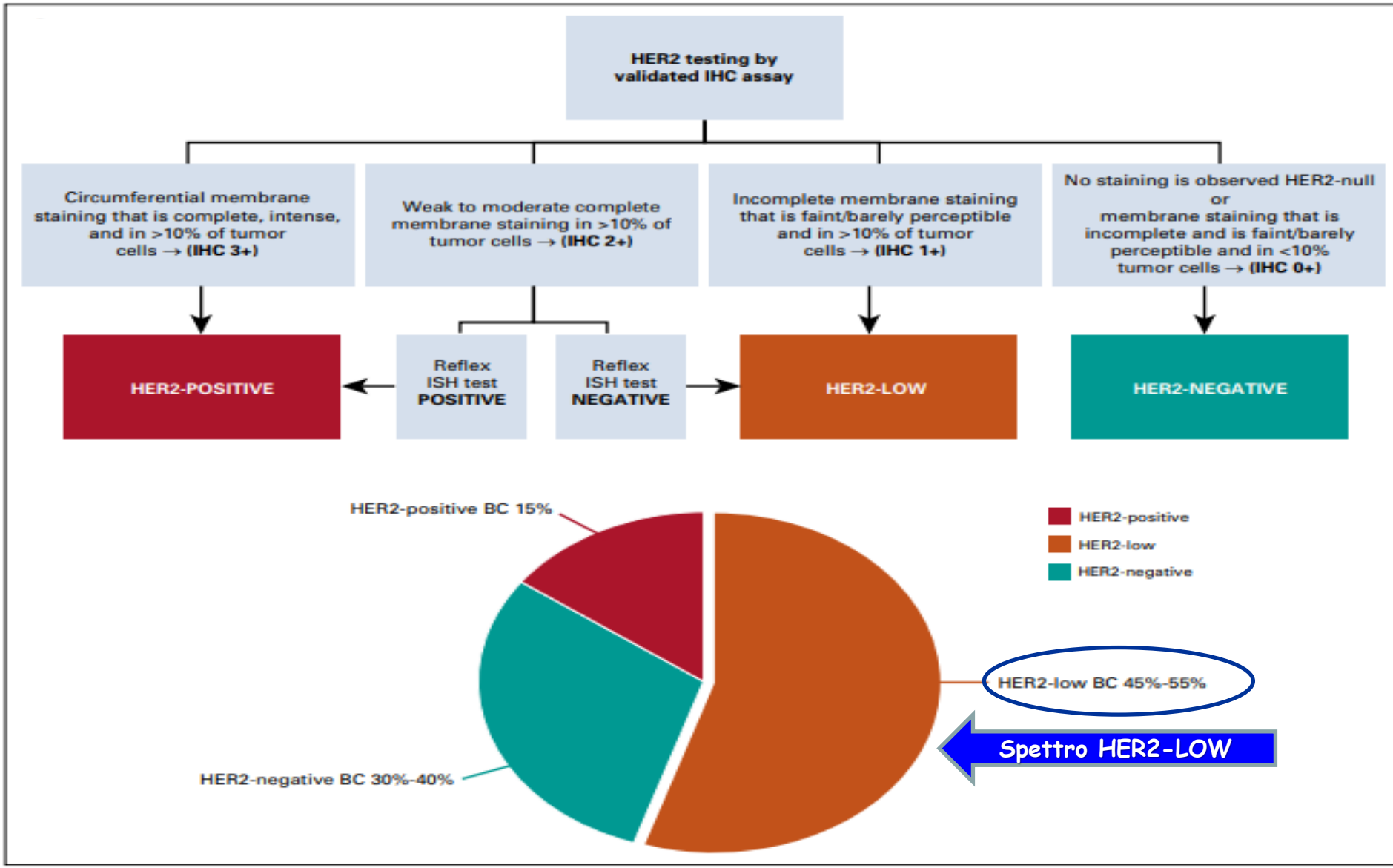
LINEE GUIDA Test HER2 e ca mammella

NO a risultato dicotomico
(positivo-negativo)

↓

HER2 positivo
HER2 negativo
HER2 low

ALGORITMO per definire HER2



Tarantino P, et al. *J Clin Oncol*. 2020;38:1951-1962.

LINEE GUIDA Test HER2 e ca mammella

- LG HER2 2022 rivisitate

ASCO Special Articles

Check for updates

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ACCOMPANYING CONTENT

Appendix

Data Supplement

Accepted March 29, 2023
Published June 7, 2023

J Clin Oncol 00:1-6

View Online Article

Clinical Questions

This clinical practice guideline addresses two overarching clinical questions:

1. What is the optimal testing algorithm for the assessment of HER2 status
2. What strategies can help ensure optimal performance, interpretation, and reporting of established assays?

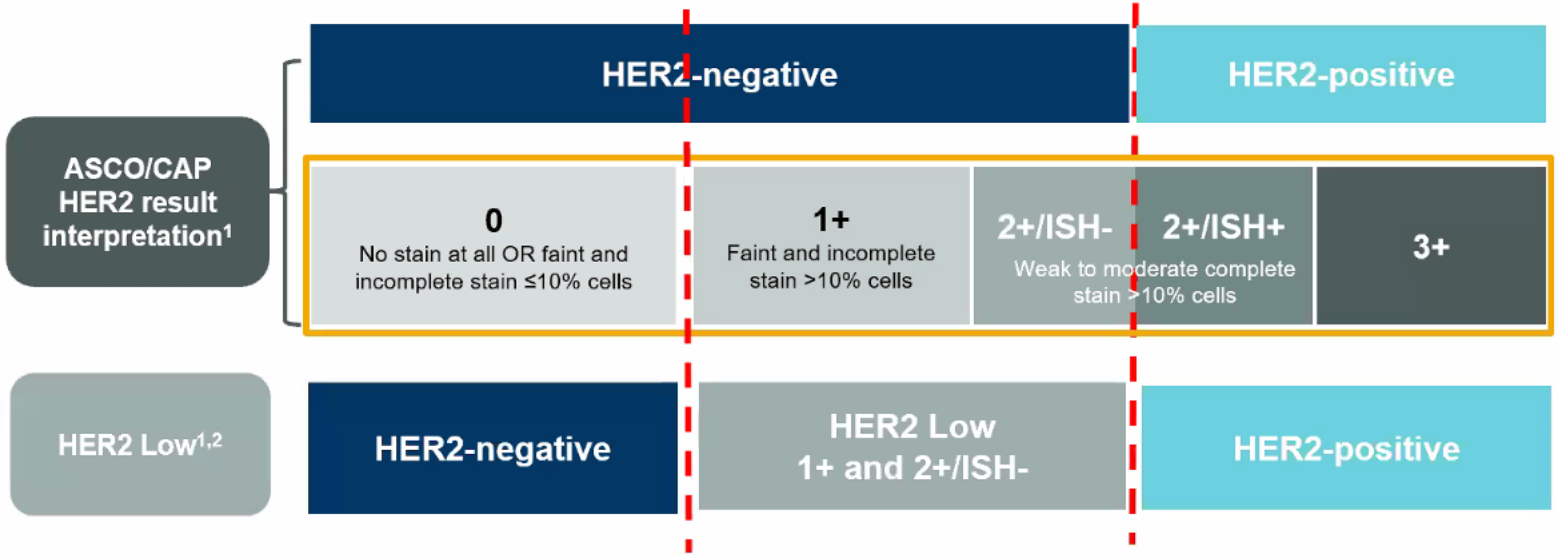
LINEE GUIDA Test HER2 e ca mammella

1. Come lo definisco?
2. Come lo referto?
3. Quale assay?
4. Quando lo valuto e in quale campione?
5. Quale valore re-scoring?
6. QA

1. Come lo definisco??

- **LG HER2 2022 rivisitate**

What might be potential challenges in identifying HER2 Low patients for certain tumour types, if and when clinical utility warrants it?



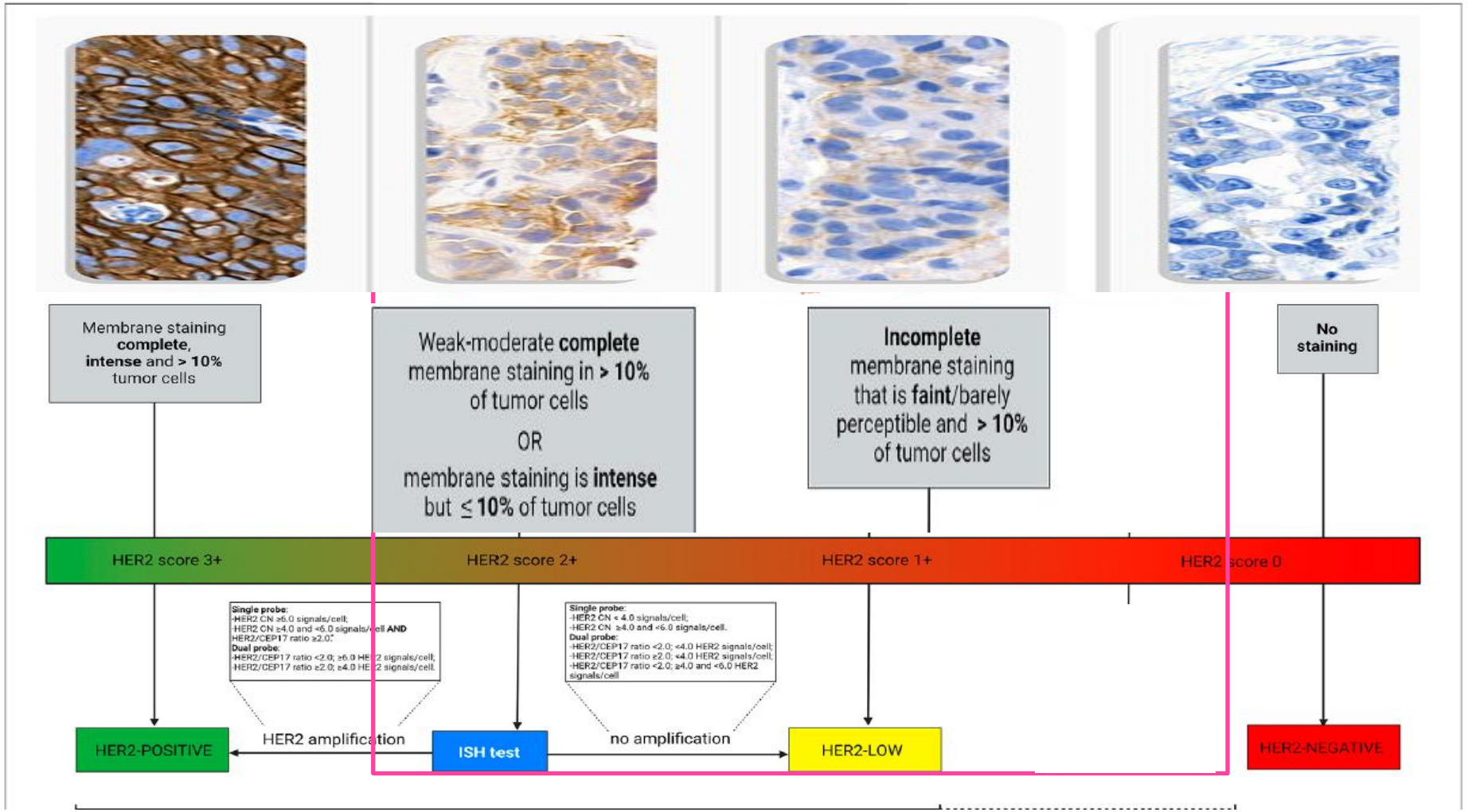
Most published data and ongoing clinical trials define HER2 Low as a HER2 IHC score of 1+ or 2+ with a negative ISH assay[2]

Evidence to date is insufficient for defining HER2 Low breast cancer as an individual subtype[2]

HER2=human epidermal growth factor receptor 2; IHC=immunohistochemistry; ISH=*in situ* hybridisation

1. Wolff AC, et al. *J Clin Oncol*. 2018;36:2105–2122; 2. Tarantino P, et al. *J Clin Onc*. 2020,38(17):1951–1962

1. Come lo definisco??… si espande il concetto di HER2 positività



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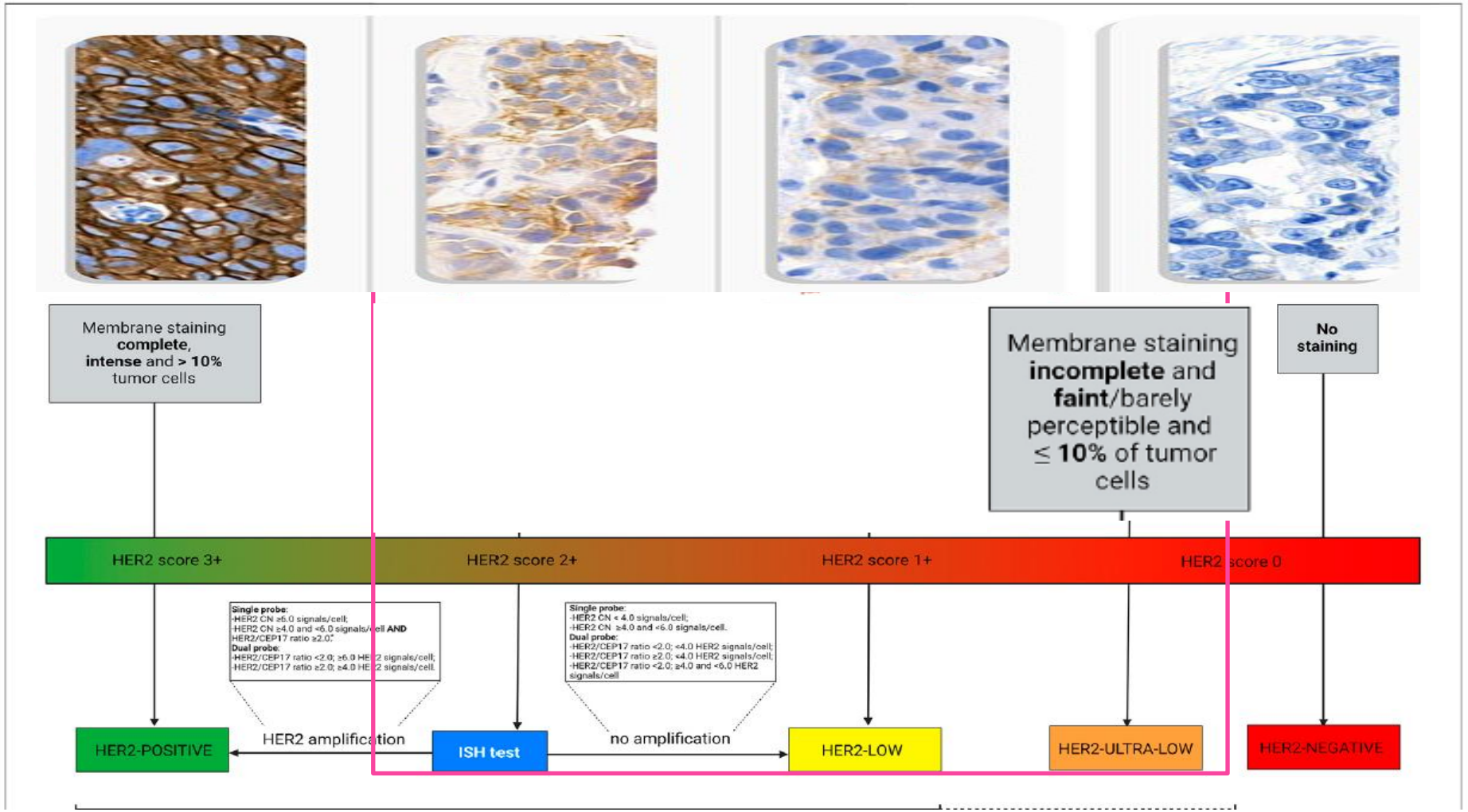

2.Come lo referto??...HER2low?

- LG HER2 2022 rivisitate

While it is premature to change reporting terminology for lower levels of HER2 IHC expression (e.g., "HER2-Low"), pathology labs should include a footnote in their HER2 testing reports (IHC and ISH) with the following recommended comment: *"Patients with breast cancers that are HER2 IHC 3+ or IHC 2+/ISH amplified may be eligible for several therapies that disrupt*

- Trial DESTINY DB-04 escludeva pazienti con HER2 IIC score 0
- In progress: risultati Trial DESTINY DB-06 che potrebbe far luce sui potenziali benefici della terapia con T-DXd anche in pazienti HER2 IIC score 0
- Finché i risultati del DB-06 non vengono resi pubblici, è prematuro modificare le regole consolidate del reporting HER2 con inserimento categoria HER2low

2.Come lo referto??...HER2low?

- **LG HER2 2022 rivisitate**

Utilizzare tutti gli Score scala continua di valutazione

HER20
HER2 1+
HER2 2+/NA
HER2 3+/A

While … xpression (e.g., "… ports (IHC a… …ers that are HE… …disrupt HER2… … 1+ or 2+/ISH… overex… …ein may be pre… … 2+/ISH *not-amplified may be eligible for a treatment that targets non-amplified/non-overexpressed levels of HER2 expression for cytotoxic drug delivery (IHC 0 results do not result in eligibility currently).*"

- HER2 IHC 1+ or 0 results are still both interpreted as "HER2-negative" (HER2 is not overexpressed) using the previously recommended scoring criteria. Importantly, the semi-quantitative IHC score must always be reported as well to ensure patients that meet eligibility criteria for trastuzumab deruxtecan can be identified.
  - Example: HER2-negative for protein over-expression (1+ staining present).

2.Come lo referto?? UltraLOW/negativo

LG HER2 2022 rivisitate

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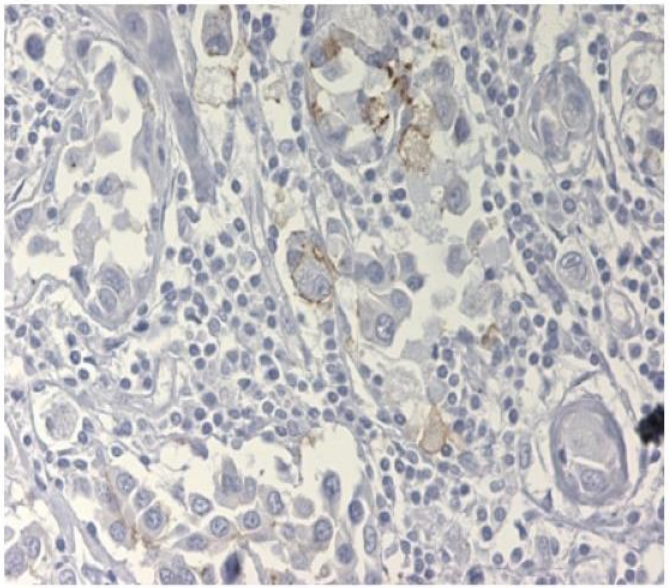
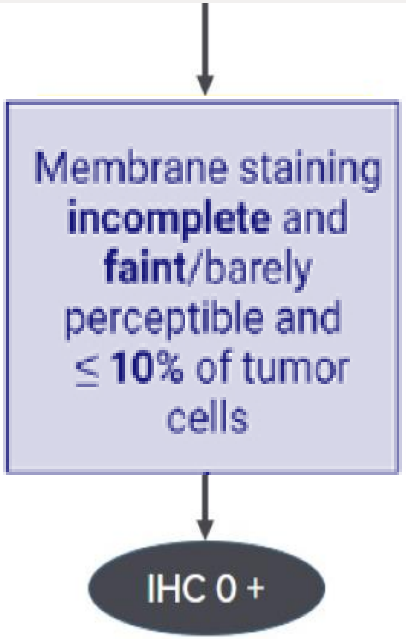
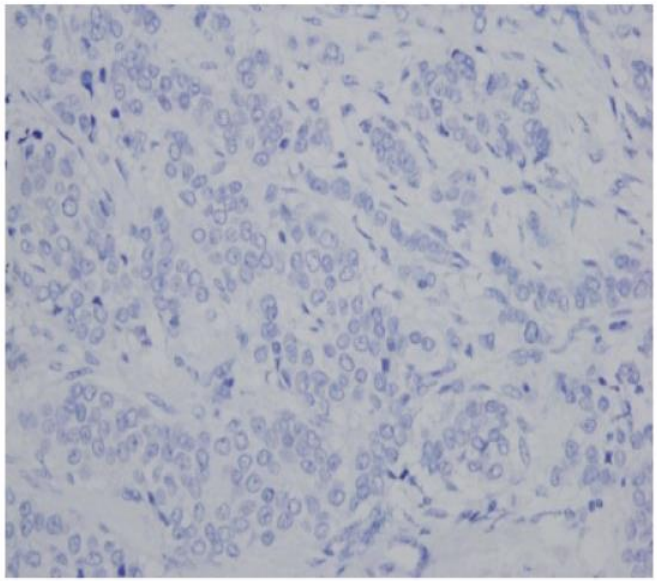


HER2-ultralow: Incomplete and weak membrane staining of 0% to 9% of tumor cells



ASCO®/CAP 2018 definition[a]



HER2 0 (absence of membrane staining)

2.Come lo referto?? UltraLOW/negativo

LG HER2 2022 rivisitate

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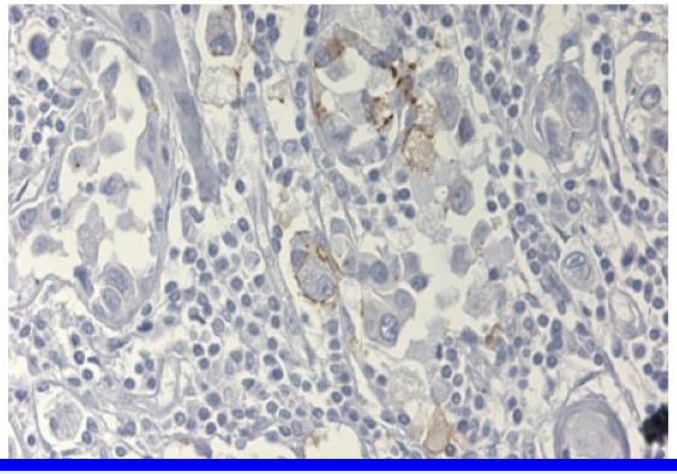
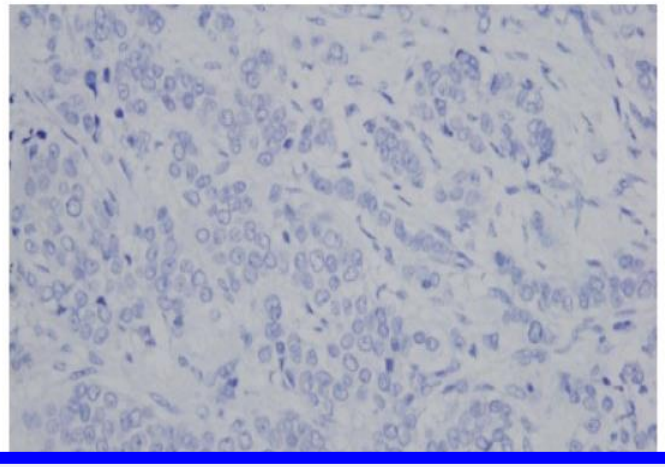


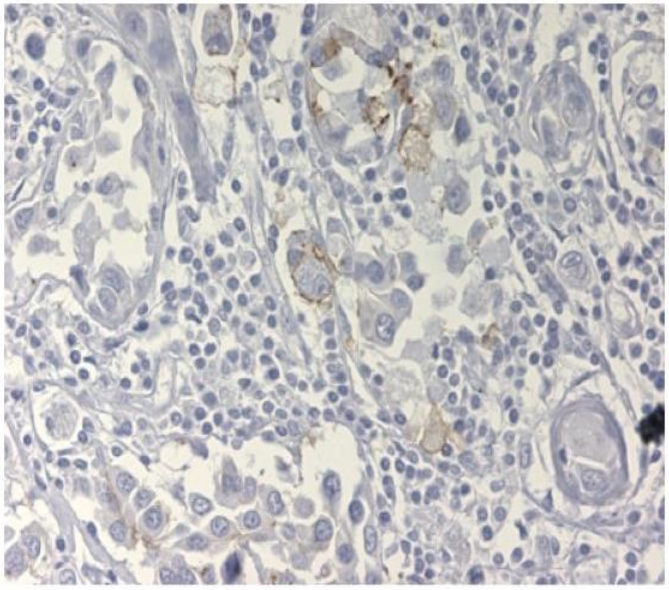
Membrane staining **incomplete** and **faint**/barely perceptible and ≤ **10%** of tumor cells



3. Considering second pathologist review when results are close to the 0 versus 1+ interpretive threshold (>10% of cells with incomplete membrane staining that is faint/barely perceptible).

2.Come lo referto??... Ultra-LOW/negativo

Bose et al.: HER2 "ultra low" mutazioni patogenetiche attivanti di HER2 indipendentemente dallo stato IIC HER2
potrebbero spiegare i risultati positivi in alcuni studi mirati a HER2 nei tumori HER2-negativi



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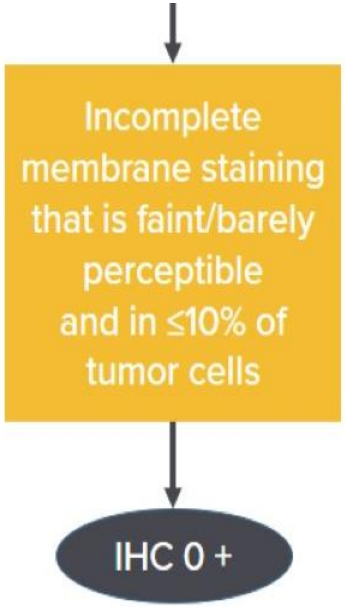


ASCO®/CAP 2018 definition[a]

3.Quale assay?

- Disponibilità di diversi cloni di anticorpi e piattaforme

1. PATHWAY anti-HER-2/neu (4B5), Ventana Medical Systems
2. HercepTest™ pharmDx, DakoCytomation,

- Queste possono avere un impatto significativo sulla riproducibilità dei risultati e complicare identificazione dell'espressione di HER2-low

- Studi di confronto tra HercepTest (policlonale) e 4B5 (monoclonale) hanno mostrato concordanza accettabile tra i due metodi

- Dati più recenti suggeriscono che il test PATHWAY 4B5 può essere più sensibile nella diagnosi di HER2-low.
- Monoclonale HercepTest™ con marchio CE-IVDIl kit Ab pharmDx (per la piattaforma Dako Omnis) a breve disponibile

3.Quale assay?

Virchows Archiv (2022) 481:685–694
https://doi.org/10.1007/s00428-022-03378-5

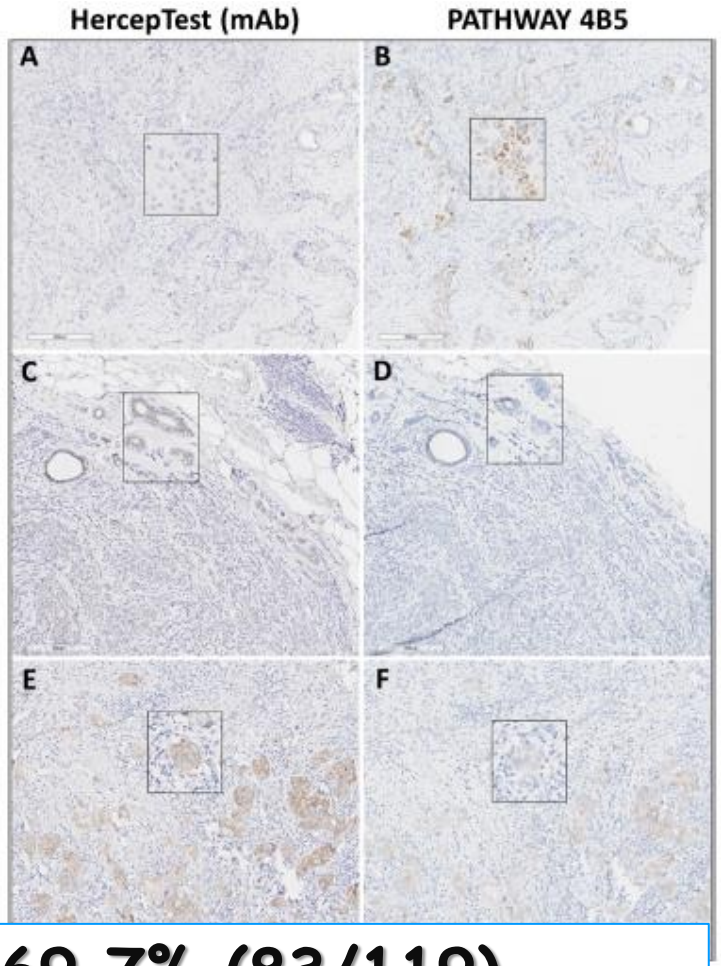
ORIGINAL ARTICLE

Comparison of HercepTest™ mAb pharmDx (Dako Omnis, GE001) with Ventana PATHWAY anti-HER-2/neu (4B5) in breast cancer: correlation with *HER2* amplification and HER2 low status

Josef Rüschoff[1] · Michael Friedrich[1] · Iris Nagelmeier[2] · Matthias Kirchner[2] · Lena M. Andresen[3] · Karin Salomon[3] · Bryce Portier[4] · Simone T. Sredni[4] · Hans Ulrich Schildhaus[1,2] · Bharat Jasani[1] · Marius Grzelinski[1] · Giuseppe Viale[5]

Received: 31 March 2022 / Revised: 30 June 2022 / Accepted: 6 July 2022 / Published online: 16 August 2022

		PATHWAY 4B5				
		0	1+	2+	3+	Total
HercepTest (mAb)	0	35	0	0	0	35
	1+	17	8	0	0	25
	2+	4	12	13	1	30
	3+	0	0	2	27	29
	Total	56	20	15	28	119



Accordo completo Score IIC nel 69,7% (83/119)
Alta concordanza per HER2pos vs HER2neg 98.2%

3.Quale assay?

- Test HER2 attualmente utilizzati progettati principalmente per identificare BC con sovraespressione di HER2, privi di validazione specifica per rilevare la bassa espressione di HER2

- Criticità HER2 test: "score 0"

- Valutazione riproducibilità inter-osservatore per stato HER2-low fonte di preoccupazioni su potenziale misclassificazione

4. Quando lo valuto e in quale campione?

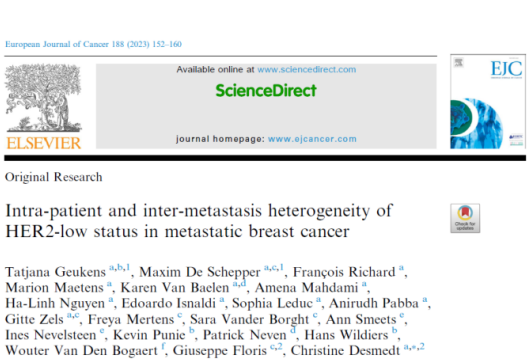
- Possibilità di cambiamento stato HER2-low primitivo vs secondario

- Discordanza HER2 tra primario e metastatico 50-38% dei casi

- Discordanza di più frequente passaggio :
  da HER2 0 a HER2-low (15%)
  da HER2-low a HER2 0 (14%)

4. Quando lo valuto e in quale campione?

Possibilità eterogeneità' spaziale e/o temporale


European Journal of Cancer 188 (2023) 152–160

Available online at www.sciencedirect.com

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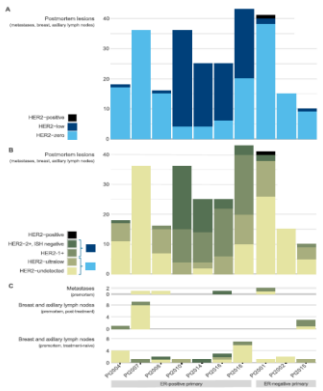
journal homepage: www.ejcancer.com

Original Research

Intra-patient and inter-metastasis heterogeneity of HER2-low status in metastatic breast cancer

Tatjana Geukens [a,b,1], Maxim De Schepper [a,c,1], François Richard [a], Marion Maetens [a], Karen Van Baelen [a,d], Amena Mahdami [a], Ha-Linh Nguyen [a], Edoardo Isnaldi [a], Sophia Leduc [a], Anirudh Pabba [a], Gitte Zels [a,c], Freya Mertens [c], Sara Vander Borght [c], Ann Smeets [e], Ines Nevelsteen [e], Kevin Punie [b], Patrick Neven [d], Hans Wildiers [b], Wouter Van Den Bogaert [f], Giuseppe Floris [c,2], Christine Desmedt [a,*,2]



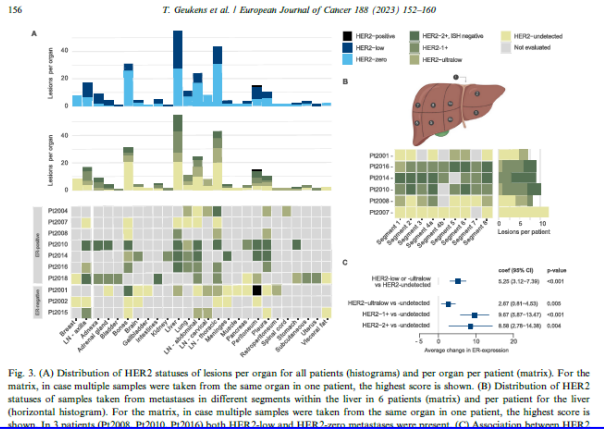


Fig. 3. (A) Distribution of HER2 statuses of lesions per organ for all patients (histograms) and per organ per patient (matrix). For the matrix, in case multiple samples were taken from the same organ in one patient, the highest score is shown. (B) Distribution of HER2 statuses of samples taken from metastases in different segments within the liver in 6 patients (matrix) and per patient for the liver (horizontal histogram). For the matrix, in case multiple samples were taken from the same organ in one patient, the highest score is shown. In 3 patients (Pt2008, Pt2010, Pt2016) both HER2-low and HER2-zero metastases were present. (C) Association between HER2

8/10 pz coesistevano metastasi HER2-low e HER2 score 0, con una percentuale di lesioni HER2-low 5% e 89%.

Importante eterogeneità **inter-metastasi** intra-paziente dello stato HER2-low.

4. Quando lo valuto e in quale campione?

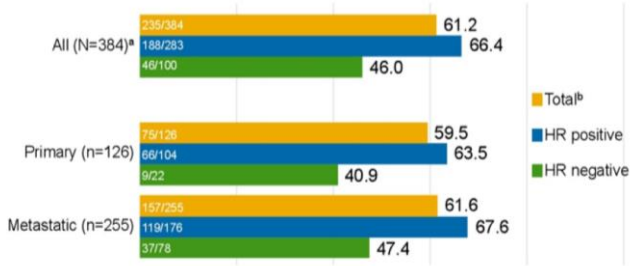
- Considerando instabilità espressione di HER2-low durante progressione malattia, si consiglia di

1. eseguire una biopsia delle lesioni ricorrenti se il tumore primario era HER2 score 0, ove possibile dal punto di vista clinico.
2. se biopsia delle lesioni metastatiche HER2 score 0, è consigliabile tenere in considerazione il risultato iniziale del test HER2 nel tumore primario e/o rivalutarlo se era stato inizialmente diagnosticato come HER2 score 0.

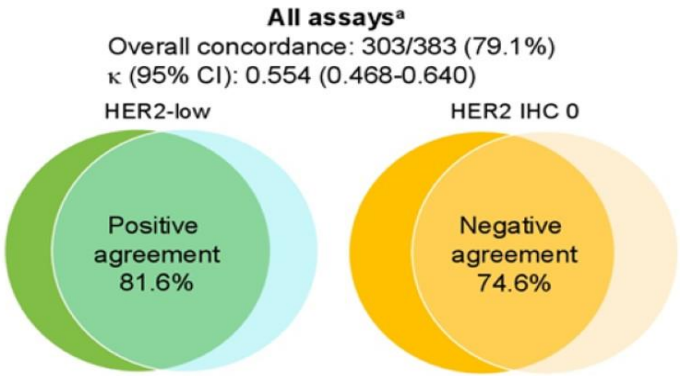
- Idoneità al trattamento T-DXd è concessa a pazienti se almeno un campione di tumore presenta HER2 low, indipendentemente da quando è stato ottenuto il campione

5. Re-scoring tessuto archivio e concordanza

HER2-low prevalenza in RetroBc-HER2L Study



[a]Only patients with available HER2 scores contributed to prevalence calculations. [b]Patients with unknown HR status were included in the total calculations only.
HR, hormone receptor.
Viale G, et al. J Clin Oncol. 2022;40(suppl 17):1087.

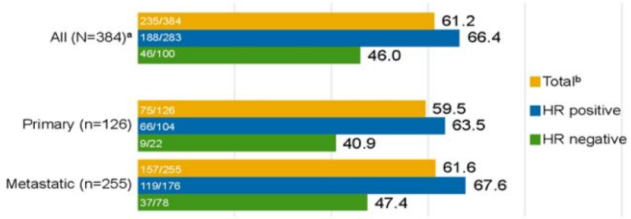


[a]Only patients with historical scores were included.
Viale G, et al. J Clin Oncol. 2022;40(suppl 17):1087.

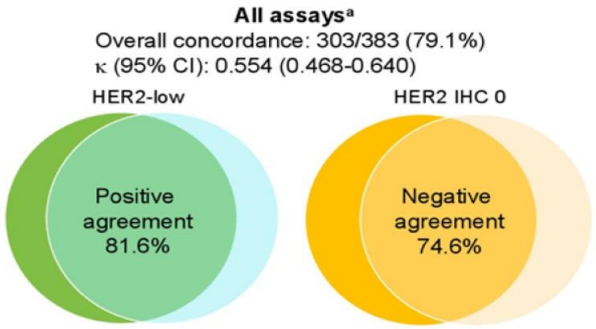
- Studio multicentrico retrospettivo in mBC diagnosticati HER2 0 dal 2014-2017
- Training fra i patologi
- IIC 45B o altri Ab

5. Re-scoring tessuto archivio e concordanza

HER2-low prevalenza in RetroBc-HER2L Study



[a]Only patients with available HER2 scores contributed to prevalence calculations. [b]Patients with unknown HR status were included in the total calculations only.
HR, hormone receptor.



- HER2 test erano re-scored e confrontati con HER2 storico
- Agreement fra score storico e re-score più basso per HER2 0 che per HER2 low
- 30% casi HER2 0 storico erano re-scored HER2-LOW (con tutti gli assay)

6.Quale QA/QC?

ASCO Special Articles

Check for upd

Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: ASCO–College of American Pathologists Guideline Update

Antonio C. Wolff, MD[1]; Mark R. Somerfield, PhD[2]; Mitchell Dowsett, PhD[3]; M. Elizabeth H. Hammond, MD[4]; Daniel F. Hayes, MD[5]; Lisa M. McShane, PhD[6]; Thomas J. Saphner, MD[7]; Patricia A. Spears, BS[8]; and Kimberly H. Allison, MD[9]

DOI https://doi.org/10.1200/JCO.22.02864

ABSTRACT

ACCOMPANYING CONTENT

4. Using controls with a range of protein expression (including 1+) to help ensure the assay has an appropriate limit of detection.
5. Careful attention to preanalytic conditions of breast cancer tissue samples from both primary and metastatic sites.

6.Quale QA/QC?

Tuttavia tutti i dati sottolineano la possibilità che multipli fattori possano condizionare la sensibilità nel rilevamento di bassi livelli di espressione della proteina HER2.

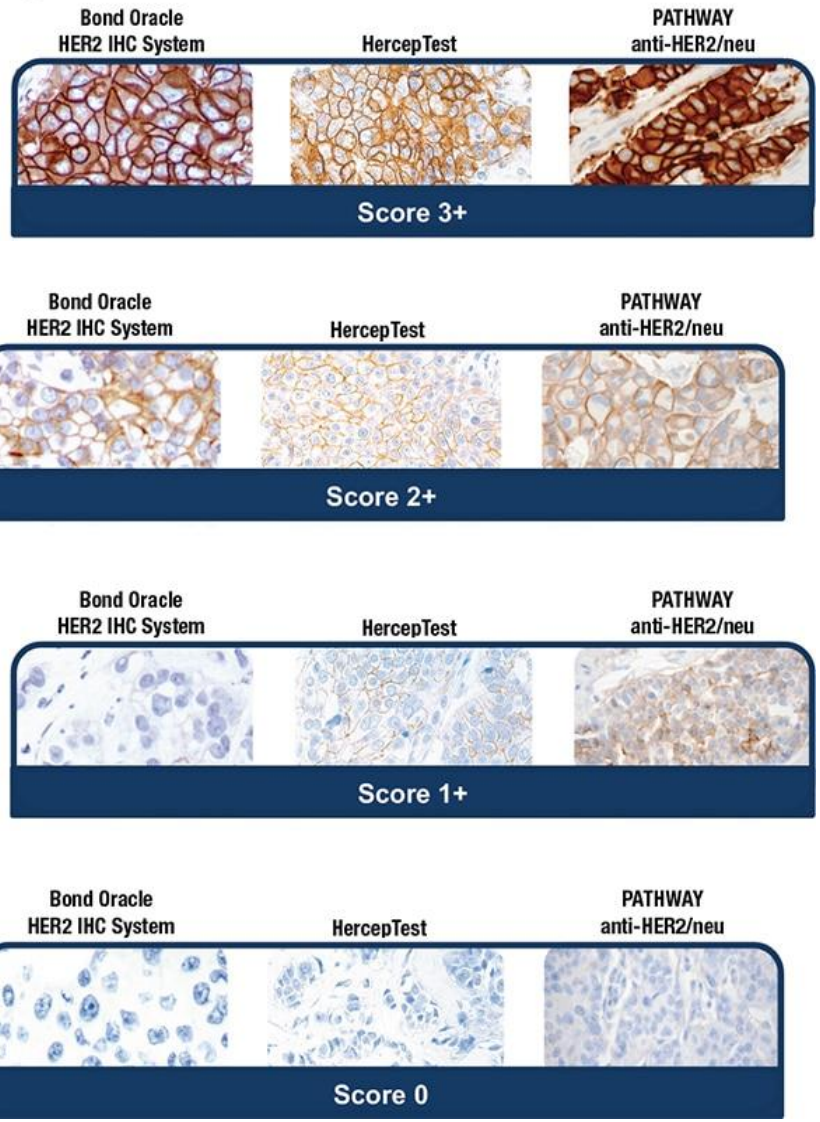
6.Quale QA/QC?

Variabili in gioco ?

- Sede Metastasi
- Numero Metastasi
- Stato HER2 esordio

Materiale Archivio | **Re-score**

Patologo osservatore



6.Quale QA/QC?...studi concordanza

Design of analysis

- CAP surveys (1391-1452 laboratories; 40 ERBB2 cores per laboratory)
- Analytic data from a Yale University study of concordance (18 pathologists)

Results

- CAP surveys: 19% generate results with ≤ 70% concordance for IHC HER2-negative score 0 vs 1+
- Yale University data set: concordance of 26% between 0 and 1+ and 58% between 2+ and 3+

Fernandez AI, et al. JAMA Oncol. 2022;8:1-4.

6.Quale QA/QC?...studi concordanza

The Breast 70 (2023) 82–91

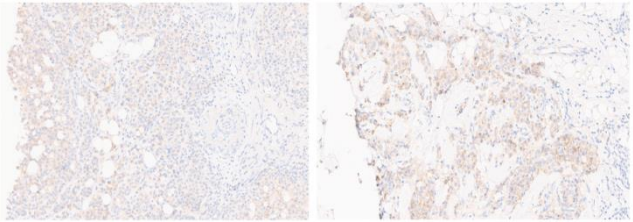
Contents lists available at ScienceDirect

The Breast

journal homepage: www.journals.elsevier.com/the-breast

Concordance of HER2-low scoring in breast carcinoma among expert pathologists in the United Kingdom and the republic of Ireland –on behalf of the UK national coordinating committee for breast pathology

Mohamed Zaakouk [a,b], Cecily Quinn [c,d], Elena Provenzano [e,f], Clinton Boyd [g], Grace Callagy [h], Soha Elsheikh [i,j], Joe Flint [k], Rebecca Millican-Slater [l], Anu Gunavardhan [m], Yasmeen Mir [n], Purnima Makhija [o], Silvana Di Palma [p], Susan Pritchard [q], Bruce Tanchel [r], Emad Rakha [s], Nehal M. Atallah [o,t], Andrew H.S. Lee [e], Sarah Pinder [u], Abeer M. Shaaban [a,v,*]



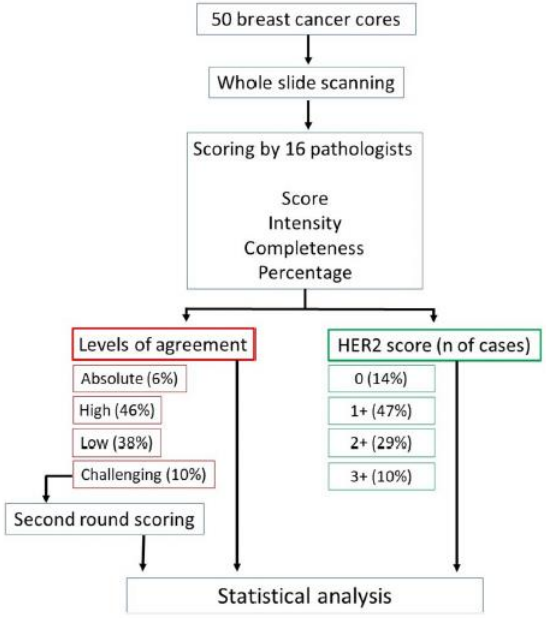


Fig. 1. Flow chart of the study design.

Concordanza scarsa 10% dei casi.
Concordanza assoluta 6% tutti score 3+.
Concordanza maggiore 86% quando score raggruppati 0 vs altri.
Miglioramento kappa concordanza combinando score 1+ e 2+.

HER2-low score minore concordanza tra i patologi esperti.
Mentre maggior parte dei casi classificate in modo riproducibile, piccola percentuale 10% rimane problematica.

6.Quale QA/QC nella RER?

Report di Registrazione

Verbale riunione (I^a parte)
Controllo qualità esterno regionale per la determinazione immunoistochimica dei marcatori predittivi di terapia nel carcinoma mammario e di test molecolari predittivi di terapie oncologiche personalizzate

Tabella 4: Risultati HER2 in IIC

CENTRO	CRITERI	HER2 IIC				
		SEZIONI	Ab (ditta, clone)	SCORE	NOTE	IDONEITA'
ANCONA	ASCO-CAP18	1-3	Bond Max Leica	2+	nel 10% delle cellule	
ASCOLI PICENO	ASCO-CAP19	5-6	Bond Max Leica	1+		
PESARO	ASCO-CAP18	7-8	Ventana Pathway 4B4	2+	nel 12% circa delle cellule	buono
BO AOU	ASCO-CAP18	11-12	Ventana Pathway 4B5	1+	scarse cellule con positività completa di membrana <10%	
IMOLA	ASCO-CAP18	27-28	Ventana Pathway 4B5	1+	nell'80% delle cellule	
BO AUSL	ASCO-CAP18	13-14	Ventana Pathway 4B5	2+	12% di cellule 2+	adeguato
FERRARA	ASCO-CAP18	19-21	Ventana Pathway 4B5	1+		
FORLì	ASCO-CAP18	**23-25**	Ventana Pathway 4B5	1+	le cellule sono marcate soltanto in una parte della membrana (controlli interni negativi)	
CESENA	ASCO-CAP18	17-18	Ventana Pathway 4B5	1+		
RAVENNA	ASCO-CAP18	37-38	Ventana Pathway 4B5	1+		
RIMINI	ASCO-CAP18	43-44	Ventana Pathway 4B5	1+		
MODENA	ASCO-CAP18	29-31	Ventana Pathway 4B5	1+		
PARMA	ASCO-CAP18	/	Ventana Pathway 4B5	2+		
PIACENZA	ASCO-CAP18	33-35	Ventana Pathway 4B5	1+		buono
REGGIO EMILIA	ASCO-CAP18	39-41	Ventana Pathway 4B5	1+		

6.Quale QA/QC nella RER?

Tabella 3: Survey HER2 IIC up-front 2018

		HER2 IIC anno 2018										REFLEX TEST HER2 ISH anno 2018										TOT. POSITIVI	
		score 0		score 1+		score 2+		score 3+		INDETERMINATI		Gruppo 1		Gruppo 2		Gruppo 3		Gruppo 4		Gruppo 5		IHC 3+	
																						IHC 2+ e Gruppo 1/3	
Centro	TOT casi esaminati	n.casi	%	n.casi	%	n.casi	%	n.casi	%	n.casi	%	n.casi	%	n.casi	%	n.casi	%	n.casi	%	n.casi	%	n.casi	%
AN AOU†	924	324	35,1%	240	26,0%	231	25,0%	129	14,0%	0	0,0%	35	13,0%	0	0,0%	3	1,0%	22	8,0%	210	22,7%	129	14,0%
BO AOU	529	227	42,9%	145	27,4%	93	17,6%	64	12,1%	0	0,0%	12	2,3%	0	0,0%	3	0,6%	17	3,2%	61	11,5%	79	14,9%
BO AUSL (Bellaria)	1034	392	37,9%	275	26,6%	279	27,0%	88	8,5%	0	0,0%	62	6,0%	0	0,0%	0	0,0%	0	0,0%	227	22,0%	150	14,5%
Cesena AUSL*	207	86	41,5%	72	34,8%	26	12,6%	23	11,1%	0	0,0%	10	4,8%	0	0,0%	0	0,0%	0	0,0%	0	0,0%	33	15,9%
FE AOU®	451	148	32,8%	200	44,3%	50	11,1%	53	11,8%	0	0,0%	45	10,0%	0	0,0%	0	0,0%	0	0,0%	9	2,0%	62	13,7%
FO AUSL	374	219	58,6%	99	26,5%	34	9,1%	22	5,9%	0	0,0%	NA										35	9,4%
Imola AUSL	133	65	48,9%	39	29,3%	20	15,0%	9	6,8%	0	0,0%	1	0,8%	0	0,0%	1	0,8%	3	2,3%	15	11,3%	11	8,3%
MO AOU•	1099	262	23,8%	525	47,8%	201	18,3%	111	10,1%	0	0,0%	NA										177	16,1%
PC AUSL°	399	243	60,9%	88	22,1%	31	7,8%	36	9,0%	1	0,3%	3	0,8%	0	0,0%	2	0,5%	2	0,5%	19	4,8%	41	10,3%
PR AOU	NA	NA										NA										NA	NA
RA AUSL‡	241	90	37,3%	62	25,7%	44	18,3%	25	10,4%	9	3,7%	4	1,7%	0	0,0%	0	0,0%	0	0,0%	38	15,8%	29	12,1%
RN AUSL¤	331	254	76,7%		0,0%	39	11,8%	38	11,5%	0	0,0%	8	2,4%	0	0,0%	0	0,0%	10	3,0%	21	6,3%	46	13,9%

Tabella 6: Survey HER2 IIC up-front 2019

		HER2 IIC anno 2019										REFLEX TEST HER2 ISH anno 2019												TOT. POSITIVI	
		score 0		score 1+		score 2+		score 3+		INDETERMINATI		Gruppo 1		Gruppo 2		Gruppo 3		Gruppo 4		Gruppo 5		INDETERMINATI		IHC 3+	
																								IHC 2+ e Gruppo 1 o 3	
Centro	TOT casi esaminati	n.casi	%	n.casi	%	n.casi	%	n.casi	%	n.casi	%	n.casi	%	n.casi	%	n.casi	%	n.casi	%	n.casi	%	n.casi	%	n.casi	%
ANCONA	936	340	36,3%	237	25,3%	229	24,5%	130	13,9%	0	0,0%	32	3,4%	0	0,0%	1	0,1%	17	1,8%	179	19,1%	0	0,0%	163	17,4%
PESARO	476	195	41,0%	178	37,4%	48	10,1%	55	11,6%	0	0,0%	16	3,4%	0	0,0%	3	0,6%	6	1,3%	23	4,8%	0	0,0%	74	15,5%
BO AOU	523	249	47,6%	143	27,3%	83	15,9%	48	9,2%	0	0,0%	11	2,1%	0	0,0%	2	0,4%	18	3,4%	47	9,0%	1	0,2%	61	11,7%
BO AUSL (Bellaria)	1162	464	39,9%	319	27,5%	265	22,8%	114	9,8%	0	0,0%	76	6,5%	0	2,0%	2	0,2%	15	1,3%	208	17,9%	0	0,0%	192	16,5%
CESENA	229	84	36,7%	87	38,0%	37	16,2%	21	9,2%	0	0,0%	7	3,1%	2	0,9%	1	0,4%	4	1,7%	23	10,0%	0	0,0%	29	12,7%
FERRARA	456	179	39,3%	193	42,3%	35	7,7%	49	10,7%	0	0,0%	8	1,8%	0	0,0%	0	0,0%	0	0,0%	27	5,9%	0	0,0%	57	12,5%
FORLì	483	264	54,7%	129	26,7%	51	10,6%	39	8,1%	0	0,0%	7	1,4%	2	0,4%	0	0,0%	5	1,0%	36	7,5%	1	0,2%	46	9,5%
IMOLA	125	49	39,2%	48	38,4%	15	12,0%	13	10,4%	0	0,0%	3	2,4%	0	0,0%	0	0,0%	2	1,6%	10	8,0%	0	0,0%	16	12,8%
MODENA	1010	224	22,2%	510	50,5%	176	17,4%	100	9,9%	0	0,0%	51	5,0%	0	0,0%	0	0,0%	1	0,1%	121	12,0%	0	0,0%	151	15,0%
PARMA		NA																							
PIACENZA	370	223	60,3%	80	21,6%	35	9,5%	27	7,3%	0	0,0%	7	1,9%	0	0,0%	2	0,5%	1	0,3%	27	7,3%	0	0,0%	36	9,7%
RAVENNA	425	278			65,4%	112	26,4%	35	8,2%	0	0,0%	8	1,9%	4	0,9%	1	0,2%	11	2,6%	88	20,7%	0	0,0%	44	10,4%
RIMINI	638	221	34,6%	250	39,2%	103	16,1%	64	10,0%	0	0,0%	6	0,9%	1	0,2%	0	0,0%	8	1,3%	88	13,8%	0	0,0%	70	11,0%

Tabella 6: Survey HER2 IIC up-front 2021

Centro	TOT casi	TEST PRIMARIO HER2 IIC										REFLEX TEST HER2 ISH						TOT. POSITIVI	
		score 0	%	score 1+	%	score 2+	%	score 3+	%	INDETERMINATI	%	Gruppo 1 POSITIVO	Gruppo 2 NON NEGATIVO	Gruppo 3 POSITIVO IC0	Gruppo 4 EQUIVOCO	Gruppo 5 NEGATIVO	NON RISPONDENTI DATI	IHC 3+	
		n.casi		n.casi		n.casi		n.casi		n.casi		n.casi	n.casi	n.casi	n.casi	n.casi	n.casi	n.casi	%
ANCONA	777	402	51,7%	154	19,8%	127	16,3%	94	12,1%	0	0,0%	18	0	1	22	86	0	113	14,5%
ASCOLI PICENO	330	86	26,1%	134	40,6%	75	22,7%	31	9,4%	4	1,2%	8	1	0	17	49	0	39	11,8%
PESARO	DATI NON PERVENUTI																		
BO AOU	612	173	28,3%	212	34,6%	179	29,2%	48	7,8%	0	0,0%	16	0	6	22	137	0	70	11,4%
BO AUSL (Bellaria)	1246	473	38,0%	404	32,4%	255	20,5%	114	9,1%	0	0,0%	40	0	4	48	304	0	158	12,7%
CESENA	288	99	34,4%	116	40,3%	38	13,2%	35	12,2%	0	0,0%	4	1	0	3	30	0	39	13,5%
FERRARA	450	181	40,2%	194	43,1%	31	6,9%	44	9,8%	0	0,0%	7	0	0	0	24	0	51	11,3%
FORLì	447	237	53,0%	131	29,3%	38	8,5%	41	9,2%	0	0,0%	11	0	0	3	24	0	52	11,6%
IMOLA	164	78	47,6%	67	40,9%	4	2,4%	15	9,1%	0	0,0%	1	0	0	1	2	0	16	9,8%
MODENA	416	112	26,9%	214	51,4%	61	14,7%	29	7,0%	0	0,0%	56	0	4	3	100	0		0,0%
PARMA	489	221	45,2%	127	26,0%	98	20,0%	43	8,8%	0	0,0%	14	1	4	16	63	0	61	12,5%
PIACENZA	405	214	52,8%	100	24,7%	45	11,1%	37	9,1%	0	0,0%	14	0	1	9	31	0	52	12,8%
RAVENNA	451	126	27,9%	209	46,3%	79	17,5%	37	8,2%	0	0,0%	12	2	0	2	63	0	49	10,9%
RIMINI	429	106	24,7%	213	49,7%	77	17,9%	33	7,7%	0	0,0%	5	4	1	4	63	0	39	9,1%

6.Quale QA/QC nella RER?

Survey HER2 IIC up-front 2021

TOT casi	TEST PRIMARIO HER2 IIC							
	score 0	%	score 1+	%	score 2+	%	score 3+	%
	n.casi		n.casi		n.casi		n.casi	
612	173	28,3%	212	34,6%	179	29,2%	48	7,8%
1246	473	38,0%	404	32,4%	255	20,5%	114	9,1%
288	99	34,4%	116	40,3%	38	13,2%	35	12,2%
450	181	40,2%	194	43,1%	31	6,9%	44	9,8%
447	237	53,0%	131	29,3%	38	8,5%	41	9,2%
164	78	47,6%	67	40,9%	4	2,4%	15	9,1%
416	112	26,9%	214	51,4%	61	14,7%	29	7,0%
489	221	45,2%	127	26,0%	98	20,0%	43	8,8%
405	214	52,8%	100	24,7%	45	11,1%	37	9,1%
451	126	27,9%	209	46,3%	79	17,5%	37	8,2%
429	106	24,7%	213	49,7%	77	17,9%	33	7,7%

TOT. POSITIVI	
IHC 3+	
IHC 2+ e Gruppo 1 o 3	
n.casi	%
70	11,4%
158	12,7%
39	13,5%
51	11,3%
52	11,6%
16	9,8%
	0,0%
61	12,5%
52	12,8%
49	10,9%
39	9,1%

HER2 1+ 1987

HER2 2+ 905

Raccomandazioni generali ASCO/CAP 2020

Standard operating procedures (SOPs) for optimizing HER2-low status assessment

Pre-analytical Phase

Biopsy / surgical excision

-Temperature controlled transferring
-Cold ischemic time <1h

Tissue fixation

-Neutral buffered formalin (6-96 h)

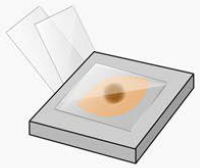
Tissue processing

-Regular laboratory inspections and proficiency testing

Paraffin embedding/microtomy

-5µm-thick sections

-Freshly cut FFPE blocks



Analytical Phase

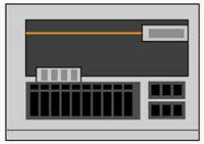
Actual HER2 testing process

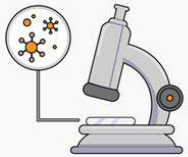
Antibody assay:
-PATHWAY anti-HER-2/neu (4B5)
-HercepTest pharmDx, Dako

Platform:
-Ventana Medical Systems
-Dako Omnis

Tissue controls:
- positive
- negative
- high and low expression

Repeat test if results are equivocal



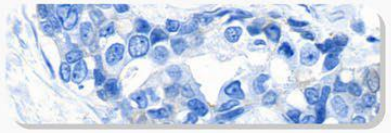
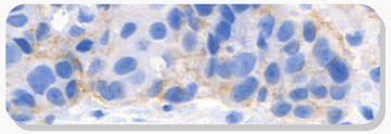
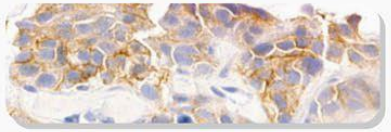
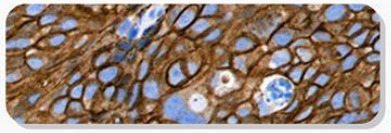


Post-analytical Phase

- Score 0 vs 1+ accuracy
- Reflex ISH for score 2+
- Heterogeneous expression and unusual staining patterns
- Rigorous SOPs, describing the diagnostic workflow from the specimen excision to HER2 report
- Pathologists' training and update
- Archives and clinical report

Raccomandazioni generali ASCO/CAP 2020

Spectrum of HER2 positivity according to ASCO/CAP guidelines

	IHC score	HER2 test intepretation	HER2 status
	0	No staining or incomplete and faint/barely perceptible membrane staning n ≤10% of tumor cells	Negative
	1+	Incomplete and faint/barely perceptible membrane staining in >10% of tumor cells	Low
	2+	Weak-moderate complete membrane staining in >10% of tumor cells OR intense membrane stainingi n ≤10% of tumor cells	NO ISH amplification? YES
	3+	Complete and intense membrane staining in >10% of tumor cells	Positive

Spectrum of HER2 positivity

Raccomandazioni generali ASCO/CAP 2020

Optimized report for HER2 test in HER2-low breast cancer

Cold ischemia time < 1h
fixation 6-72 h
Overfixation may lead to false-negative results

SPECIMEN

Date of collection

DIAGNOSIS

Avoid reporting in DCIS
Beware edge artifacts

HER2 0 challenge:

- distinction between score 0 and score 1+ is now clinically relevant
- intepretation challenges
- heterogeneity
- interobserver reproducibility
- training

HER2 testing by immunohistochemistry:

Assay

IHC Staining platform

Discrepancies in the interpretation of IHC HER2 test results may occur due to different assays and platforms, without proper harmonization

Describe the intensity and pattern of staining:

- weak/moderate/intense membrane staining
- complete/incomplete

Indicate:

- percentage (%) of cells with described pattern and score

RESULT: Positive/Equivocal/Negative (Score #)

Use of internal and external controls is mandatory for each slide run;
There are no normal internal controls.

Follow 2023 ASCO/CAP updates and 2023 ESMO consensus statements

Interpretation:
Score 0, 1+: negative
Score 2+: equivocal (requires ISH)
Score 3+: positive

Reflex in situ hybridization test:

Test type

Number of observers

Number of invasive tumor cells counted

Indicate:

- aneusomy,
- signal heterogeneity
- percentage of cells with amplied HER2 signals

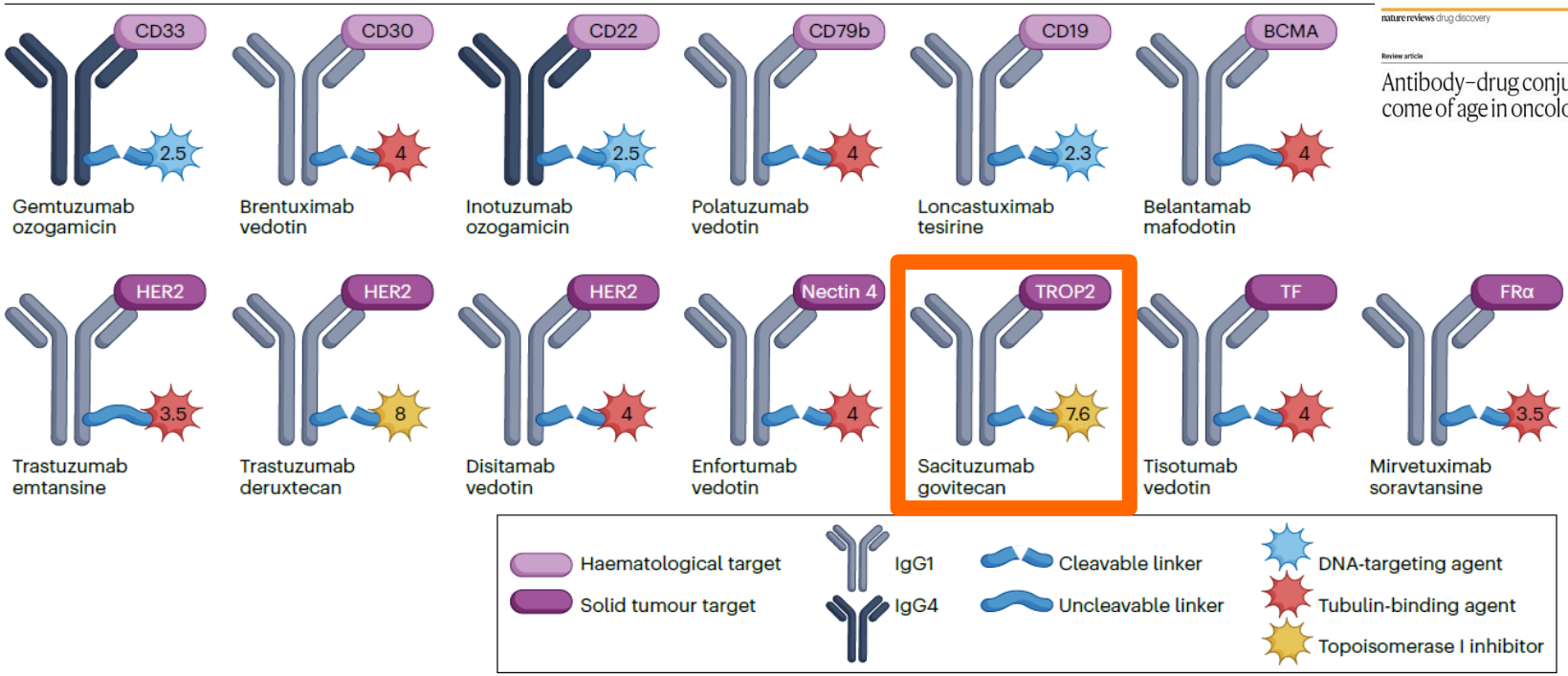
Interpretation issues can be complicated by **spatial and temporal heterogeneity**, which is an independent risk factor for decreased DFS, creating diculties in treatment selection

Average Number of HER2 Signals per Cell: ##
Average Number of CEP17 Signals per Cell: ##
RESULT: HER2 / CEP17 Ratio: ### (Group #) - Positive/Negative (dual-probe)
OR
Average HER2 copy number - Positive/Negative (single-probe)

Identication of invasive carcinoma:

- A pathologist should identify on H&E slide the area of invasive carcinoma to be evaluated
- ISH analysis must be performed on the
- invasive carcinoma
- DCIS may show gene amplication which should be disregarded

Altri bersagli di ADCs



nature reviews drug discovery
Review article
Antibody–drug conjugates come of age in oncology

c) Diverse molecole testate nelle cellule TNBC che soddisfano queste caratteristiche.

Nuovi bersagli di ADCs-Trop-2

- Sacituzumab govitecan (IMMU-132) è il nuovo anticorpo promettente che ha come bersaglio Trop-2, legato all'inibitore della topoisomerasi-I SN-38, il metabolita attivo dell'irinotecan che induce danni al DNA

- Trop-2 è una glicoproteina transmembrana di tipo I, con un ruolo rilevante nella migrazione, proliferazione cellulare, progressione del ciclo cellulare e metastasi

Nuovi bersagli di ADCs-Trop-2

Trop-2 iperespressa in tutti i sottotipi di cancro al seno, tuttavia è più elevata nei TN .
IIC

1. 50% ER
2. 74% HER2+
3. 93% TN

Nuovi bersagli di ADCs-Trop-2

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

Biomarker analyses in the phase III ASCENT study of sacituzumab govitecan versus chemotherapy in patients with metastatic triple-negative breast cancer☆

A. Bardia[1], S. M. Tolaney[2], K. Punie[3], D. Loirat[4], M. Oliveira[5], K. Kalinsky[6,7], A. Zelnak[8], P. Aftimos[9], F. Dalenc[10], S. Sardesai[11], E. Hamilton[12], P. Sharma[13], S. Recalde[14], E. C. Gil[15], T. Traina[16], J. O'Shaughnessy[17], J. Cortes[18], M. Tsai[19], L. Vahdat[20], V. Diéras[21], L. A. Carey[22], H. S. Rugo[23], D. M. Goldenberg[24,25], Q. Hong[24,25], M. Olivo[24,25], L. M. Itri[24,26] & S. A. Hurvitz[27]*

[1]Massachusetts General Hospital, Harvard Medical School, Boston; [2]Medical Oncology, Dana-Farber Cancer Institute, Boston, USA; [3]Department of General Medical Oncology and Multidisciplinary Breast Centre, Leuven Cancer Institute, University Hospitals Leuven, Leuven, Belgium; [4]Medical Oncology Department and D3i, Institut Curie, Paris, France; [5]Hospital Universitari Vall d'Hebron, Barcelona, Spain; [6]Columbia University Irving Medical Center, New York; [7]Winship Cancer Institute, Emory University, Atlanta; [8]Northside Hospital, Atlanta, USA; [9]Institut Jules Bordet — Université Libre de Bruxelles, Brussels, Belgium; [10]Institut Claudius Regaud, Toulouse, France; [11]The Ohio State University Wexner Medical Center, Columbus; [12]Sarah Cannon Research Institute/Tennessee Oncology, Nashville; [13]University of Kansas Medical Center, Westwood, USA; [14]Institut Catala d'Oncologia Hospitalet, Barcelona; [15]Hospital Universitario 12 de Octubre, Madrid, Spain; [16]Memorial Sloan Kettering Cancer Center, New York; [17]Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, USA; [18]International Breast Cancer Center (IBCC), Quiron Group, Madrid & Barcelona, Spain; [19]VPCI Oncology Research, Minneapolis; [20]MSK-Norwalk Hospital Partnership, Norwalk, USA; [21]Centre Eugène Marquis, Rennes, France; [22]University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill; [23]University of California San Francisco Comprehensive Cancer Center, San Francisco; [24]Immunomedics, Inc., Morris Plains; [25]Center for Molecular Medicine and Immunology, Mendham; [26]Department of Clinical Development, Gilead Sciences, Inc., Morris Plains; [27]Department of Medicine, Division of Hematology/Oncology, David Geffen School of Medicine, University of California, Los Angeles, Jonsson Comprehensive Cancer Center, Los Angeles, USA

In the ASCENT study, an exploratory biomarker analysis was performed **using** BRCA1/2 status as well as an H-score. The **H-score** is a score that utilizes an IHC stain for **TROP-2** on tumor tissue and evaluates the intensity and percentage of cells that stain positive

Categorie espressione Trop-2

H-score 0 to <100: Trop-2 low;
H-score 100-200: Trop-2 medium;
H-score >200-300: Trop-2 high

An exploratory analysis was subsequently performed that assessed the potential **clinical utility** of **Trop-2 expression**. ….
Regardless of Trop-2 expression, however, all patients with metastatic TNBC benefited from sacituzumab govitecan in comparison to physician's choice chemotherapy. **Trop-2 expression is not currently recommended to be checked as a biomarker to predict a benefit to sacituzumab govitecan**.

TNBC  &…Terapia

Nuovi bersagli di ADCs-Trop-2

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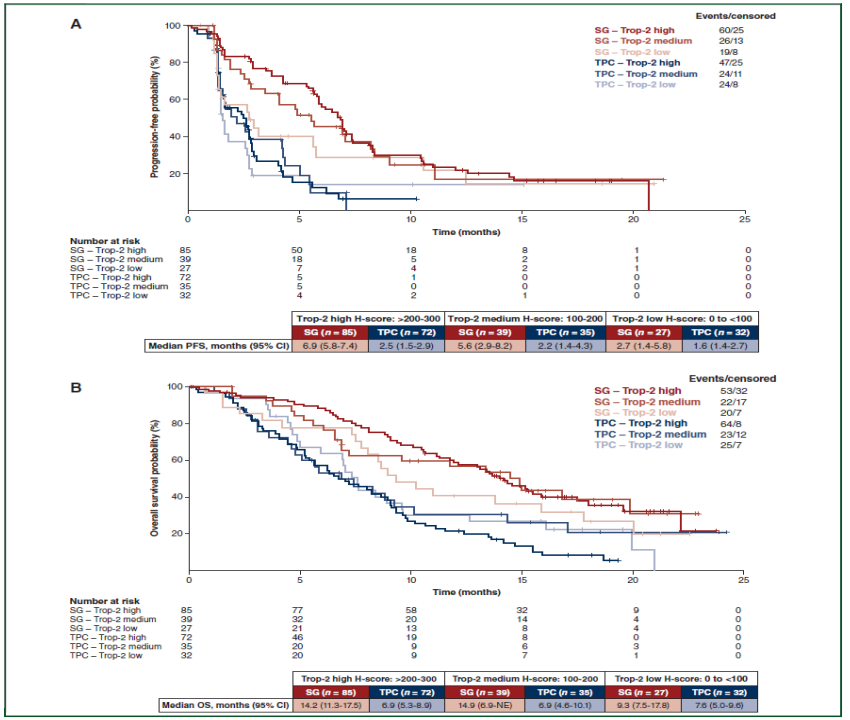
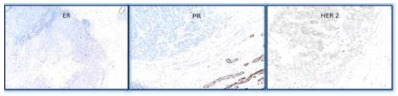
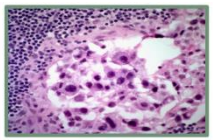


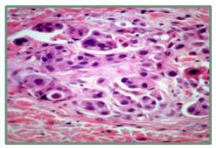
Figure 2. **(A) Progression-free survival by Trop-2 expression. (B) Overall survival by trophoblast cell-surface antigen 2 (Trop-2) expression.**
CI, confidence interval; H-score, histochemical score; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice; Trop-2, trophoblast cell-surface antigen 2.

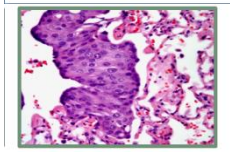
A. Progression-free survival Trop-2 expression
B. Overall survival Trop-2 expression

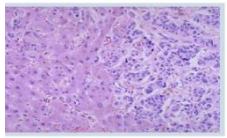
….**Regardless of Trop-2 expression, however, all patients with metastatic TNBC benefited from sacituzumab govitecan** in comparison to physician's choice chemotherapy. **Trop-2 expression is not currently recommended to be checked as a biomarker to predict a benefit to sacituzumab govitecan.**

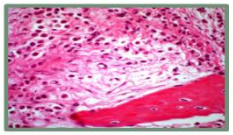
TNBC  &…Terapia


METASTASI LINFONODALE


METASTASI CUTANEA


METASTASI POLMONARE


METASTASI EPATICA


METASTASI OSSEA

IIC ER/PGR/HER2 su metastasi & convertiti in negativi

Cambiamento/Discordanza espressione ER/PgR/HER2

Perdita espressione 25–45%

Eur J Cancer 50,2014
Ann Oncol 24,2013
J Clin ONCOL 30, 2012

Breast Cancer Research and Treatment
https://doi.org/10.1007/s10549-022-06602-7

CLINICAL TRIAL

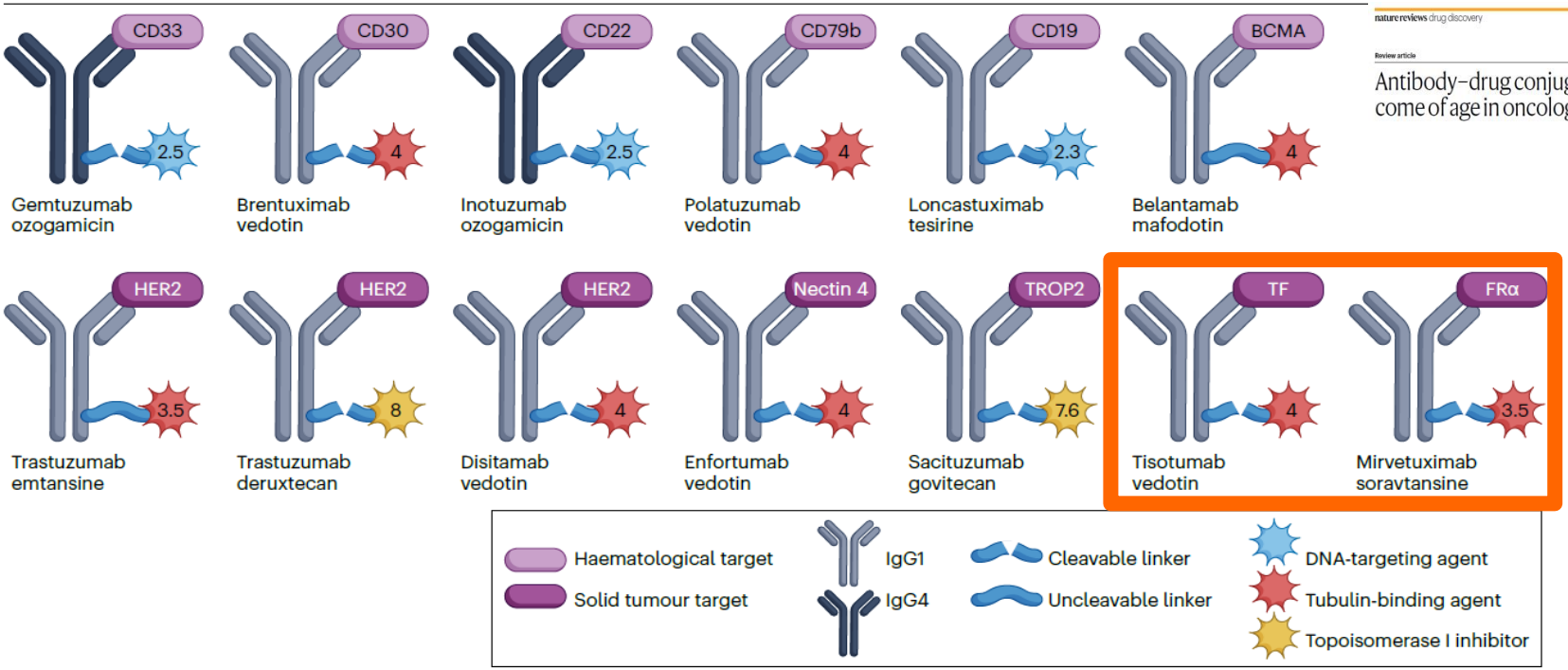
Check for updates

Analysis of patients without and with an initial triple-negative breast cancer diagnosis in the phase 3 randomized ASCENT study of sacituzumab govitecan in metastatic triple-negative breast cancer

Joyce O'Shaughnessy[1] · Adam Brufsky[2] · Hope S. Rugo[3] · Sara M. Tolaney[4] · Kevin Punie[5] · Sagar Sardesai[6] · Erika Hamilton[7] · Delphine Loirat[8] · Tiffany Traina[9] · Roberto Leon-Ferre[10] · Sara A. Hurvitz[11] · Kevin Kalinsky[12,19] · Aditya Bardia[13] · Stephanie Henry[14] · Ingrid Mayer[15] · Yanni Zhu[16] · See Phan[17] · Javier Cortés[18]

Received: 2 December 2021 / Accepted: 6 April 2022

Altri bersagli di ADCs



nature reviews drug discovery
Review article
Check for updates

Antibody–drug conjugates come of age in oncology

Target

Critical Reviews in Oncology / Hematology 190 (2023) 104090

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journal homepage: www.elsevier.com/locate/critrevonc

Next-generation antibody-drug conjugates for breast cancer: Moving beyond HER2 and TROP2

Ilana Schlam [a], Ruth Moges [b], Stefania Morganti [c,d,e,f,g], Sara M. Tolaney [e,d], rantino [c,d,e,f,i,*]

[f] Hematology and Oncology, Tufts Medical Center, Boston, MA, USA
[g] Internal Medicine, Brigham and Women's Hospital, Boston, MA, USA
[h] Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA
[i] cal School, Boston, MA, USA
[*] investor of New Drugs and Early Drug Development, European Institute of Oncology IRCCS, Milan, Italy
[c] Department of Oncology and Onco-Hematology, University of Milan, Milan, Italy
[d] Broad Institute of MIT and Harvard, Cambridge, MA, USA

ADCs in the horizon for the treatment of breast cancer – beyond TROP2 and HER2.

Target	Agent	Trial (Name, phase, identifier)	Trial design	Notes/Available results
Human epidermal growth factor receptor 3 (HER3)	Patritumab deruxtecan (U3 1402, topoisomerase inhibitor, cleavable linker)	Phase 1/2 NCT02980341 (Lambert and Chari, 2014)	Dose escalation, dose expansion trial of patients with metastatic, pretreated HER3-expressing breast cancer	Treatment duration 5.9 months.
		SOLTI 1805 TOT-HER3. Phase 1. NCT04610528 Prat et al., (2022);Pascual et al., (2021)	Single-arm, a window of opportunity trial for patients with untreated HR positive breast cancer	
		VALENTINE, phase 2. NCT05569811	Neoadjuvant chemotherapy or patritumab deruxtecan with or without endocrine therapy for HR positive early breast cancer	
		Phase 2, NCT04699630	Safety and efficacy in patients with advanced breast cancer	
		ICARUS-Breast, Phase 2, NCT04965766	Safety and efficacy in patients with advanced breast cancer	
LIV1	Ladiratuzumab vedotin (SGN-LIV1A, MMAE payload, cleavable linker)	SGNLVA-001. Phase 1. NCT01969643	SGN-LIV1A + /- trastuzumab. Refractory TNBC or HR-positive breast cancer	
		SGNLVA-002/KEYNOTE 721. Phase 1/2 NCT03310957	SGN-LIV1A and pembrolizumab in patients with advanced TNBC	
Carcinoembryonic antigen-related cell adhesion molecule 5 (CECAM5)	Tusamitamab ravstaine (SAR408701, DM4 payload, cleavable linker)	CARMEN-BT01. Phase 2. NCT04659603	SAR408701 for patients with advanced CECAM5 positive breast cancer*	
Mesothelin* *	Anetumab ravtansine (BAY 94–9343, DM4 payload, cleavable linker)	NCT02696642. Phase 1	Basket trial of patients with mesothelin positive advanced malignancies	
	RC88 (tubulin inhibitor)	NCT03102320. Phase 1	Basket trial of patients with mesothelin positive advanced malignancies	
		NCT05508334. Phase 1	Basket trial of patients with advanced malignancies	
		NCT04175847. Phase 1/2	Basket trial of patients with advanced malignancies	
Nectin-4	Enfortumab vedotin (EV-202, MMAE payload and cleavable linker)	NCT04225117. Phase 2	Basket trial of patients with advanced malignancies	
Folate receptor alpha	Mirvetuximab soravtansine (DM4 payload, cleavable linker)	NCT03106077. Phase 2	Mirvetuximab soravtansine for TNBC	
	Farletuzumab ecterbulin (MORab 202, eribulin payload, cleavable linker)	NCT04300556. Phase 1/2	Basket trial of patients with advanced malignancies	
Tissue factor	Tisotumab vedotin (MMAE payload and cleavable linker)	NCT03913741. Phase 1/2	Basket trial of patients with advanced malignancies	
Leucine-rich repeat containing 15 (LRRC15)	ABBV-085 (MMAE payload and cleavable linker)	NCT02565758 Phase 1	Basket trial of patients with advanced malignancies	
A disintegrin and metalloproteinase (ADAM9)	IMGC936 (DM21 payload and a cleavable linker)	NCT04622774 Phase 1	Basket trial of patients with advanced malignancies	Recruiting