PROGRAMMA REGIONALE DI SCREENING PER IL TUMORE DELLA MAMMELLA PREVENZIONE SERENA – WORKSHOP 2022

Novità: dalla letteratura scientifica dell'ultimo anno

Grazia Sciancalepore, ASO S. Croce e Carle di Cuneo

12 dicembre 2022

Pietro della Vecchia, 1603, Cà Rezzonico

HER2-LOW

Sottotipi molecolari

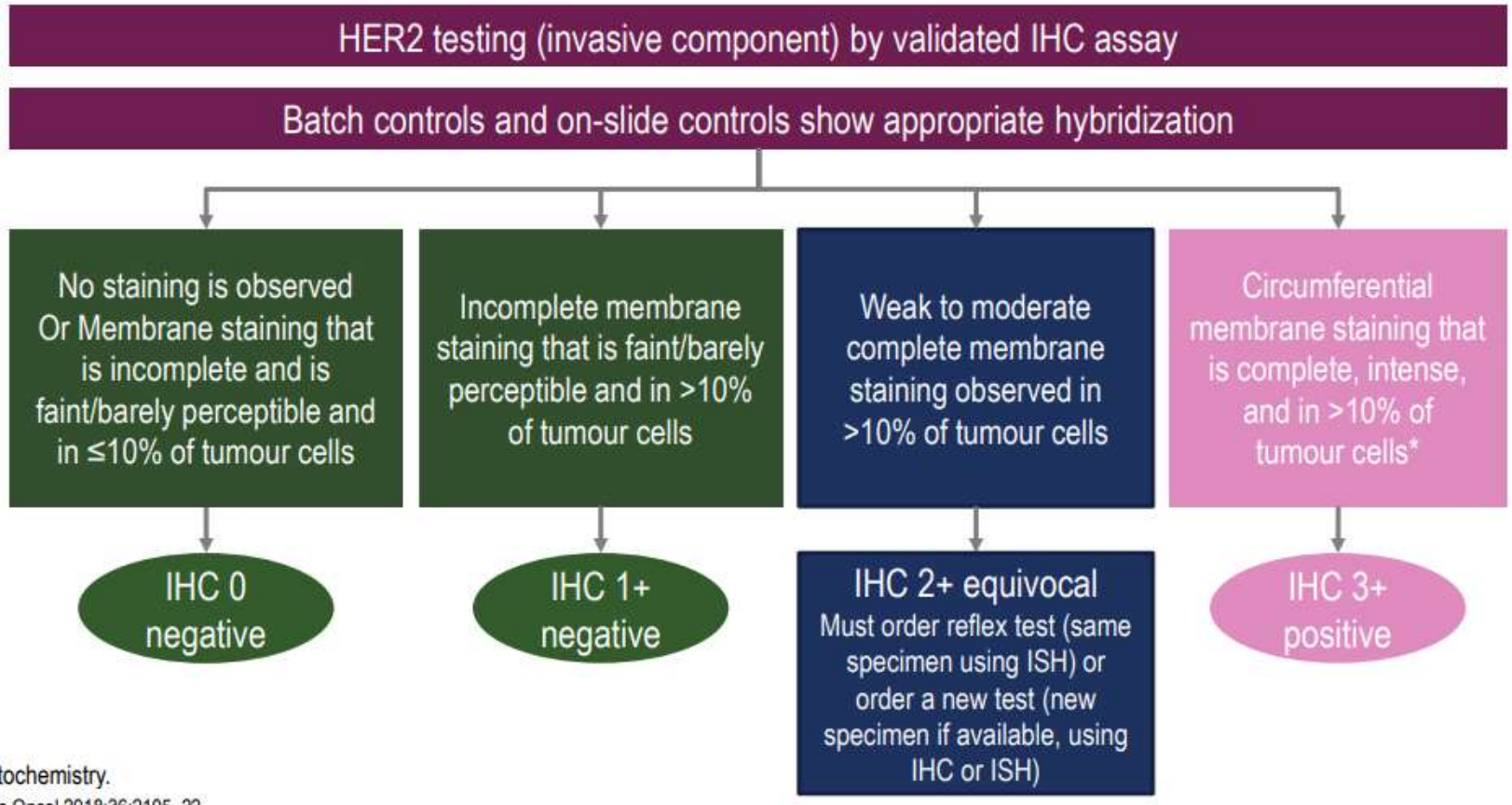
luminal A: neoplasie con espressione dei recettori ormonali, a prognosi favorevole;

luminal B: neoplasie che, pur possedendo l'espressione dei recettori ormonali, hanno un rischio di recidiva elevato, a causa dell'elevato indice proliferativo;

HER2 enriched (human epidermal growth factor receptor 2)": presenza di amplificazione di HER2;

basal like: neoplasie caratterizzate dall'assenza di espressione dei recettori ormonali e di HER2 (Triple Negative).

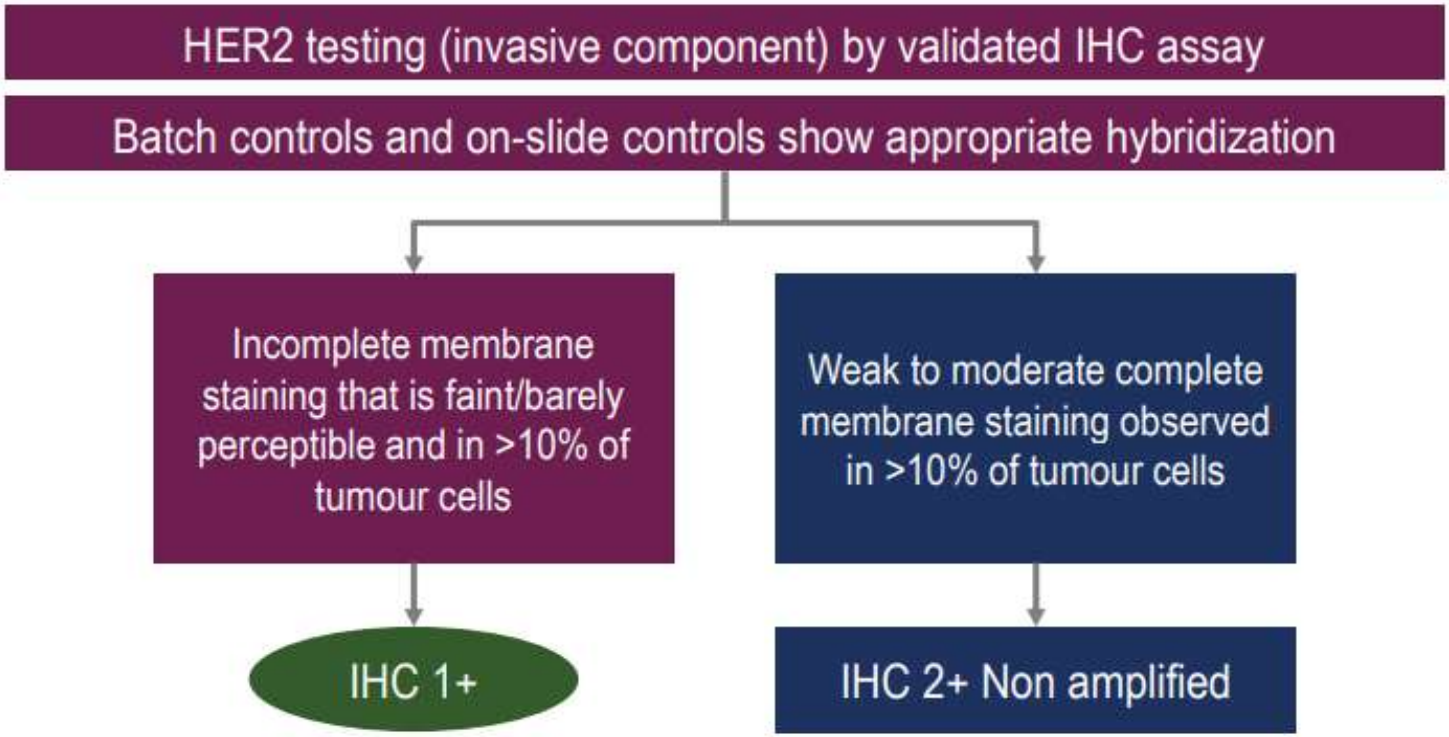
Valutazione immunoistochimica



IHC, immunohistochemistry.

Wolf AC, *et al.* J Clin Oncol 2018;36:2105–22.

HER2-LOW



IHC, immunohistochemistry.

Wolf AC, *et al.* J Clin Oncol 2018;36:2105–22.

Il 5 agosto 2022 FDA ha approvato l'utilizzo di trastuzumab-deruxtecan (T-DXd, Enhertu), per il trattamento delle pazienti con cancro della mammella inoperabile o metastastico, HER2-low, basandosi sui risultati del trial di fase III DESTINY-Breast04.

The NEW ENGLAND JOURNAL of MEDICINE

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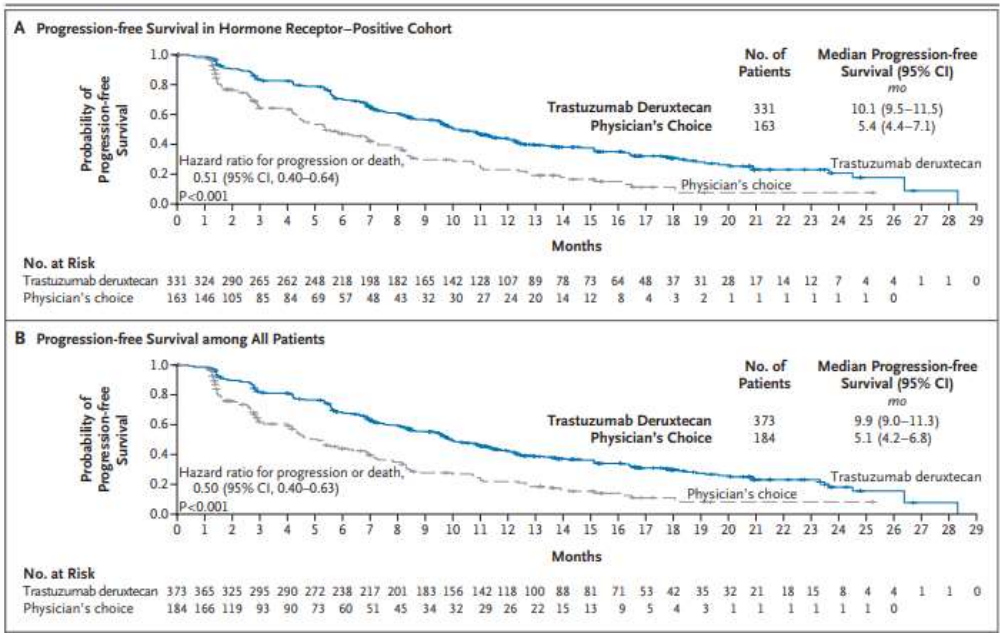
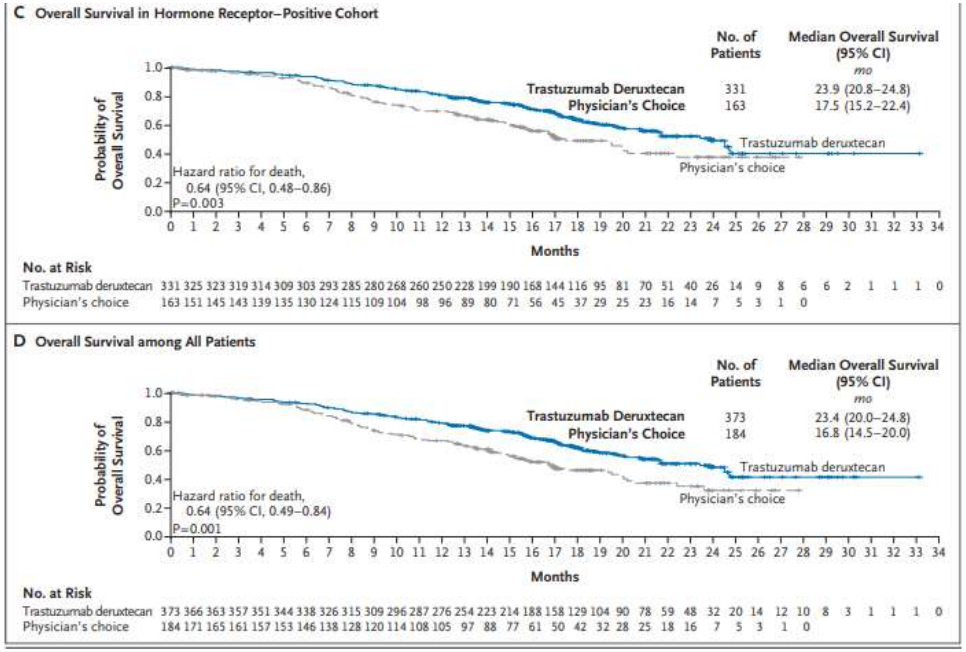
Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer

S. Modi, W. Jacot, T. Yamashita, J. Sohn, M. Vidal, E. Tokunaga, J. Tsurutani, N.T. Ueno, A. Prat, Y.S. Chae, K.S. Lee, N. Niikura, Y.H. Park, B. Xu, X. Wang, M. Gil-Gil, W. Li, J.-Y. Pierga, S.-A. Im, H.C.F. Moore, H.S. Rugo, R. Yerushalmi, F. Zagouri, A. Gombos, S.-B. Kim, Q. Liu, T. Luo, C. Saura, P. Schmid, T. Sun, D. Gambhire, L. Yung, Y. Wang, J. Singh, P. Vitazka, G. Meinhardt, N. Harbeck, and D.A. Cameron, for the DESTINY-Breast04 Trial Investigators*

ABSTRACT

This trial showed **significantly longer progression-free survival and overall survival with trastuzumab deruxtecan** than with the physician's choice of chemotherapy among patients with HER2-low metastatic breast cancer, **regardless of hormone-receptor status**. These results have the potential to improve the treatment outcome for more than half of patients historically categorized as having HER2-negative breast cancer**.**





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HER2-low breast cancers: Current insights and future directions

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ABSTRACT

In light of the significant clinical benefits of novel HER2-targeting antibody-drug conjugates in advanced HER2-low expressing breast cancers in recent phases I and III clinical trials, particularly trastuzumab-deruxtecan (T-Dxd), the new "HER2-low" category in breast cancers (breast cancer with a HER2 IHC score of 1+, or 2+ without gene amplification) has gained increasing attention. In the past year, "HER2-low" breast cancers have been under active investigation by both oncologists and pathologists. In this current review, we update the recent cutting-edge research on HER2-low breast cancers, with a focus on the biology of HER2-low breast cancers, the issues on the identification of HER2-low breast cancers by immunohistochemistry in current practice of pathology, and the future directions in this emerging category in breast cancers.

Current insights on HER2-low breast cancers

Clinicopathologic and molecular features of HER2-low breast cancers

Is HER2-low a distinct clinical/biologic subtype or an emerging new therapeutic subtype of breast cancer?

Research

JAMA Oncology | Original Investigation

Prognostic and Biologic Significance of ERBB2-Low Expression in Early-Stage Breast Cancer

Paolo Tarantino, MD; Qingchun Jin, MPH; Nabihah Tayob, PhD; Rinath M. Jeselsohn, MD; Stuart J. Schnitt, MD; Julie Vincuilla, BS; Tonia Parker, BS; Svitlana Tyekucheva, PhD; Tianyu Li, MS; Nancy U. Lin, MD; Melissa E. Hughes, MSc; Anna C. Weiss, MD; Tari A. King, MD; Elizabeth A. Mittendorf, MD, PhD; Giuseppe Curigliano, MD, PhD; Sara M. Tolaney, MD, MPH

Key Points

Question Is ERBB2 (formerly HER2)–low breast cancer a distinct biologic and prognostic subtype?

Findings In this cohort study of 5235 patients with ERBB2-negative invasive breast cancer, most clinicopathologic differences found between ERBB2-low and ERBB2-0 breast cancers were associated with hormone receptor (HR) expression and ERBB2-low expression had no prognostic significance when adjusting for HR status. ERBB2-low and estrogen receptor (ER) expression were found to be positively associated, with most ER-low–expressing tumors being ERBB2-0 and most ER-high–expressing tumors being ERBB2-low.

Meaning These results did not support the interpretation of ERBB2-low as a distinct biologic subtype of breast cancer.

Important issues on identifying HER2-low breast cancers by IHC in current pathology practice

Inter-observer variation on identifying HER2-low breast cancers by IHC

Examination of Low ERBB2 Protein Expression in Breast Cancer Tissue (JAMA Oncol. 2022;8(4):607-610)*:* Fernandez et al. evaluated the CAP survey data from more than 1400 laboratories around the world and found that **the scoring accuracy for HER2 IHC in the low range (0 and 1+) was poor,** and that 19.0% of cases read by the laboratories generated results with less than or equal to 70.0% concordance for a HER2 IHC score of 0 vs 1+

Inter-antibody variation on identifying HER2-low breast cancers by IHC

FDA-approved HER2 IHC testing kits have been used worldwide in clinical practice for the assessment of patients for whom trastuzumab may be a suitable treatment, including ***PATHWAY HER2 (clone 4B5; Ventana Medical Systems Inc., AZ, USA), HercepTest (Dako Denmark A/S, Denmark) and Oracle HER2 (clone CB11; Leica Biosystems, Germany)***

Currently, it is uncertain whether any differences in the sensitivity of different IHC antibodies used for evaluation of HER2 status creates significant variability between assays and laboratories in this HER2-low range…..

…*Allison and Wolff (*ERBB2-low breast cancer-is it a fact or fiction, and do we have the right assay? JAMA Oncol. 2022;8:610–611) *emphasized the critical issues that remain regarding the fitness of IHC assays for identifying HER2-low breast cancers including: (1) Can a reference standard be set to validate an IHC assay's ability to distinguish between IHC zero and IHC nonzero HER2 staining?; (2) How dependent is HER2 IHC 0 vs 1+ staining on pre-analytic factors, such as cold ischemic time, formalin fixation time, and time since an unstained section is cut from the tissue block?; (3) How much does tissue heterogeneity affect a HER2 IHC score of 0 vs 1+; and (4) How many samples should be used to be certain there is HER2 1+ staining in at least 10% of tumor cells?*

Future directions

Developing quantitative methods in identifying HER2-low breast cancers

Xu K et al. *(Discordance between immunohistochemistry and ERBB2 mRNA to determine HER2 low status for breast cancer. J Mol Diagn. 2022: S1525–S1578 (22)00106-4):* in HER2-negative patients, the range of expression based on RNA abundance suggests that a molecular method defining HER2-low cancers may better serve the treatment decision needs of this group…
Etc….

The biology of HER2-low breast cancers

Although remarkable effort has been made to understand the biology of HER2-low breast cancers, the biological complexity and heterogeneity of HER2-low breast cancers are still far from being understood. In addition, there is no solid evidence to date supporting HER2-low status in breast cancers as an independent prognostic factor and as a distinct biologic/clinical entity. Further studies focusing on clinicopathologic and molecular biomarkers that may possibly affect the response of HER2-low breast cancers to the new ADCs should be considered.

Histopathology

Histopathology 2022, **81**, 770–785. DOI: 10.1111/his.14780

Refining the definition of HER2-low class in invasive breast cancer

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(2022) *Histopathology* **81**, 770–785. https://doi.org/10.1111/his.14780

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(2022) *Histopathology* 81, 770–785. https://doi.org/10.1111/his.14780

Refining the definition of HER2-low class in invasive breast cancer

Background: Emerging evidence indicates that breast cancer (BC) patients whose tumours express HER2 protein without *HER2* gene amplification (HER2-low), can benefit from antibody–drug conjugates (ADC). However, the current definition of HER2-low BC remains incomplete with low rates of concordance. This study aims to refine HER2-low definition with emphasis on distinguishing HER2 score 0 from score 1+ to identify patients who are eligible for ADC.

Methods: A BC cohort ($n = 363$) with HER2 IHC scores 0, 1+ and 2+ (without *HER2* gene amplification) and available *HER2* mRNA was included. HER2 staining intensity, pattern and subcellular localisation were reassessed. Artificial neural network analysis was applied to cluster the cohort and to distinguish HER2 score 0 from 1+. Reproducibility and reliability of the refined criteria were tested.

Results: HER2 IHC score 1+ was refined as membranous staining in invasive cells as either: (1) faint intensity in ≥ 20% of cells regardless the circumferential completeness, (2) weak complete staining in ≤ 10%, (3) weak incomplete staining in > 10% and (4) moderate incomplete staining in ≤ 10%. Based on this, 63% of the HER2-negative cases were reclassified as positive (HER2-low). The refined score showed perfect observer agreement compared to the moderate agreement in the original clinical scores. Similar results were generated when the refined score was applied on the independent BC cohorts. A proposal to refine the definition of other HER2 classes is presented.

Conclusion: This study refined the definition of HER2-low BC based on correlation with *HER2* mRNA and distinguished between HER2 IHC score 1+ and score 0 tumours.

Keywords: ANN, breast cancer, HER2 low, *HER2* mRNA, refining

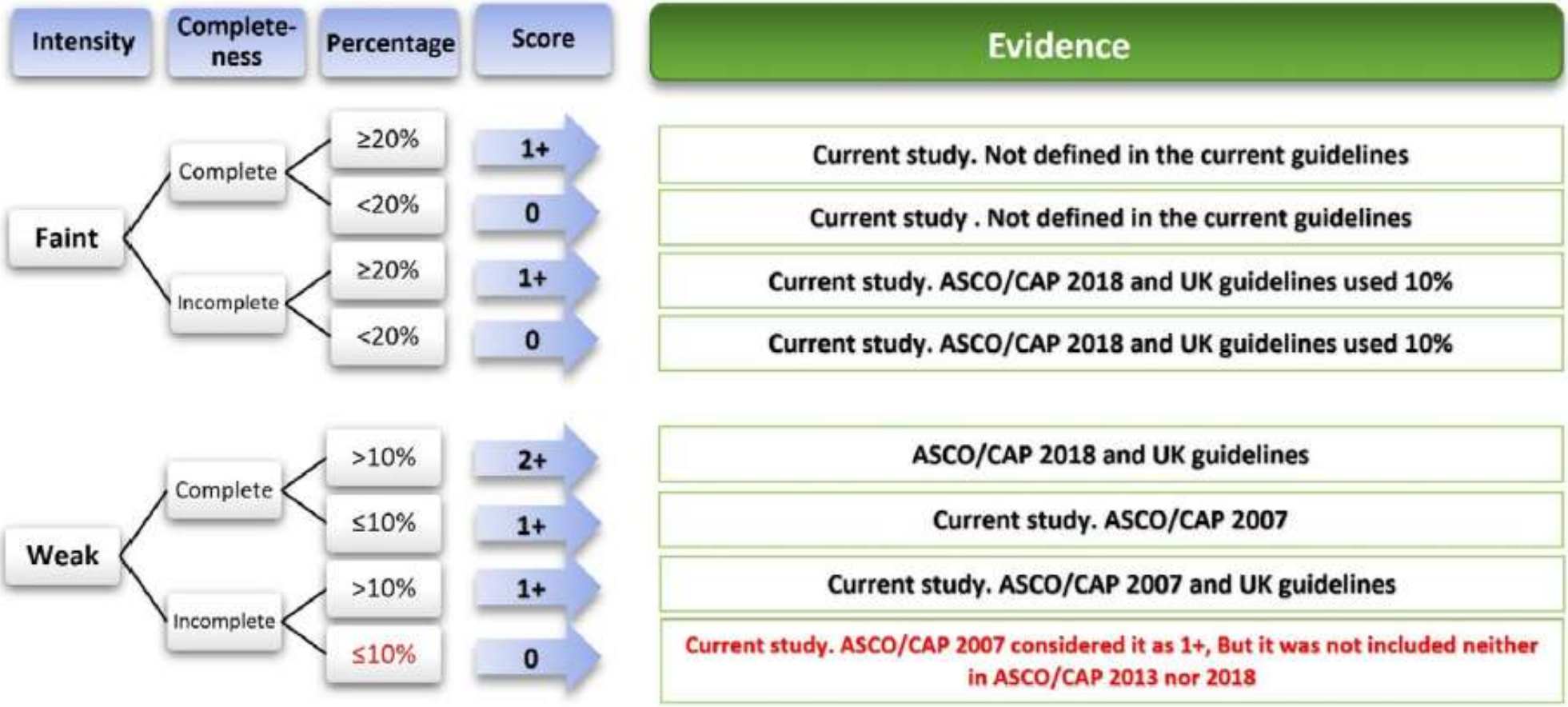
Table 1. Comparison between HER2 score 1+ definition based on the existing guidelines against the refined criteria

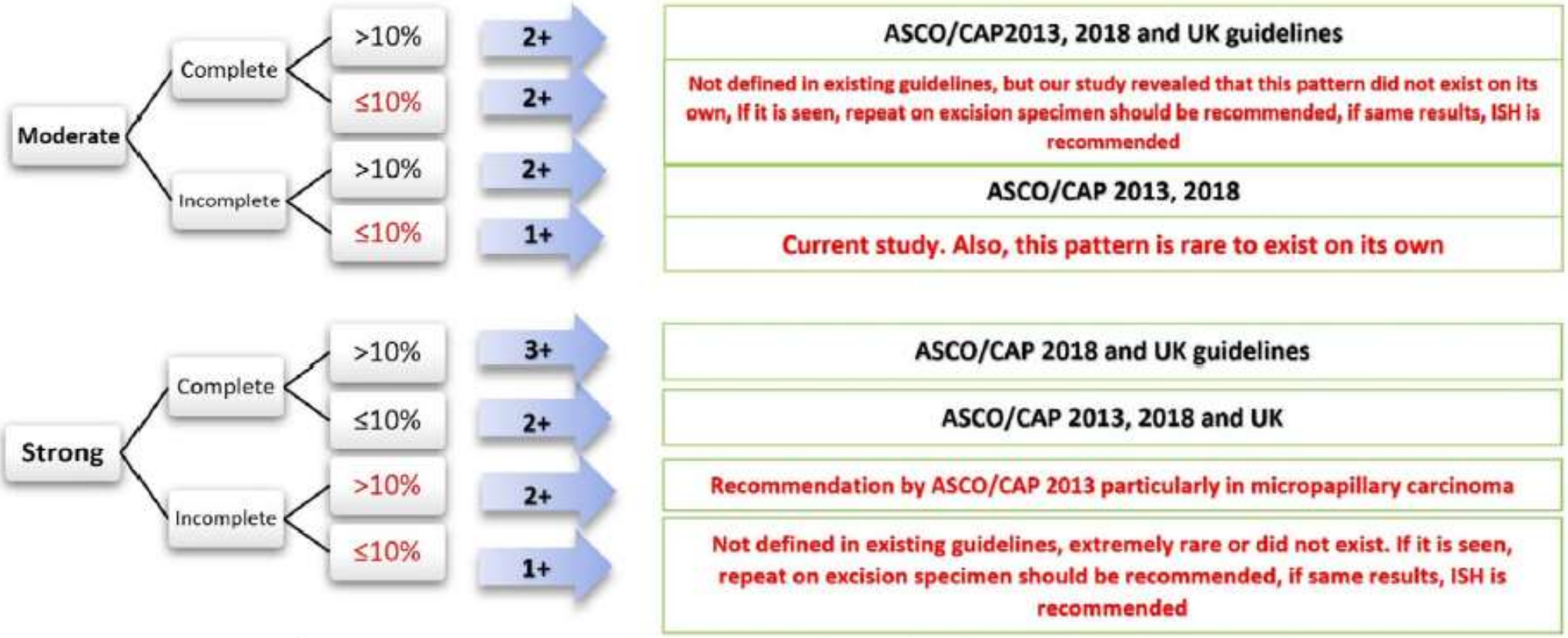
Refined definition	Existing ASCO/CAP and UK guidelines
*Faint complete and/ or faint incomplete in ≥ 20%	Incomplete membrane staining that is faint/barely perceptible and in > 10% of tumour cells
Weak complete ≤ 10%	
Weak incomplete > 10%	
Moderate incomplete < 10%	

ASCO/CAP, American Society of Clinical Oncology /College of American Pathologists; HER2, human epidermal growth factor receptor 2.

*Total faint staining in tumour cells ≥ 20%.

A


Intensity
Complete-ness
Percentage
Score
Evidence
Faint
Complete
≥20%
1+
Current study. Not defined in the current guidelines
<20%
0
Current study . Not defined in the current guidelines
Incomplete
≥20%
1+
Current study. ASCO/CAP 2018 and UK guidelines used 10%
<20%
0
Current study. ASCO/CAP 2018 and UK guidelines used 10%
Weak
Complete
>10%
2+
ASCO/CAP 2018 and UK guidelines
≤10%
1+
Current study. ASCO/CAP 2007
Incomplete
>10%
1+
Current study. ASCO/CAP 2007 and UK guidelines
≤10%
0
Current study. ASCO/CAP 2007 considered it as 1+, But it was not included neither in ASCO/CAP 2013 nor 2018



ASCO/CAP: American Society of Clinical Oncology / College of American Pathologists.

Prospettive

- Necessità di controlli standardizzati validati clinicamente per distinguere tra 0 e 1+.
- Revisione delle attuali linee guida per la refertazione di HER2
- Valutare la possibilità di nuovi test
- Implementare test riproducibili e sensibili per misurare l'espressione di HER2