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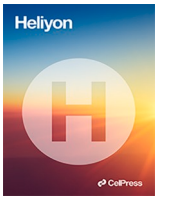

Review article

Therapeutic resistance and optimal drug sequencing in HER2-positive metastatic breast cancer: unmet needs and future perspectives

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A B S T R A C T

In the last couple of decades substantial therapeutic improvements deeply influenced the treatment of HER2-positive metastatic breast cancer. The most impactful advancements were obtained especially in the first-line setting, with the trastuzumab/pertuzumab anti-HER2 double blockade, and in the second line, with the advent of the potent antibody-drug conjugate trastuzumab deruxtecan. Nevertheless, a careful observation of the patterns of early-progression and long-term effects on overall survival of the most novel agents and combinations, highlights the challenges represented by the emergence of therapeutic resistance and optimal drug sequencing. The integration of sequence studies, tumor-related biomarker development/implementation and understanding of primary mechanisms of resistance to novel anti-HER2 agents, will be the way to move forward to effectively tackle these novel unmet needs.

Letter

The advent of anti-HER2-directed monoclonal antibody (mAb) trastuzumab in the early 2000s radically changed the natural history of the HER2-positive(+) breast cancer subtype [1]. Even in the incurable metastatic setting, anti-HER2 agents have provided unprecedented improvements in overall survival (OS) in the last couple of decades, with median OS progressively shifting from the 25.1 months obtained with first-line trastuzumab and chemotherapy, to the 57.1 months observed with first-line taxanes plus trastuzumab and anti-HER2 mAb pertuzumab [2]. While trastuzumab-pertuzumab double-blockade is, up to now, the only therapeutic advancement for the first-line scenario after the advent of trastuzumab, the second and further lines experienced a higher number of changes. First, the tyrosin kinase inhibitor (TKI) lapatinib was introduced in 2006 after showing, in combination with capecitabine, a significant progression-free survival (PFS) improvement over capecitabine monotherapy, in a population pretreated with trastuzumab plus chemotherapy in the first-line scenario [3]. Then in 2012, the antibody-drug conjugate (ADC) trastuzumab-emtansine (T-DM1) rapidly became the novel standard of care in the second-line setting, after improving PFS and OS over lapatinib plus capecitabine in the

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EMILIA trial, from a median of 6.4 to 9.6 months and from 25.1 to 30.9 months, respectively [4]. To note, few patients had previously received pertuzumab and trastuzumab double blockade in this study. Subsequently, the novel ADC trastuzumab-deruxtecan (T-DXd) outplayed second-line T-DM1 in patients pretreated with anti-HER2 double blockade within the DESTINY-Breast03 trial [5], demonstrating an unprecedented median PFS of 28.8 months versus 6.8 months and a median OS not yet reached in the latest update published in 2023 [5]. Later lines also saw the recent introduction of novel agents, especially the TKI tucatinib, which significantly improved OS, in combination with capecitabine and trastuzumab, from a median of 17.4 to 21.9 months in the HER2CLIMB trial [6]. Importantly, this study was conducted in a population pretreated with pertuzumab-based double blockade and T-DM1, including patients with stable or active brain metastases [6]. Nevertheless, this rapidly-evolving therapeutic scenario makes especially challenging to figure out a reasonable therapeutic sequencing capable of balancing between the need to deliver the latest therapeutic improvements to our patients, with the need to select the most appropriate drug on the basis of tumor biology and underlying drug-specific mechanisms of resistance. Actually, some points of discussion arise.

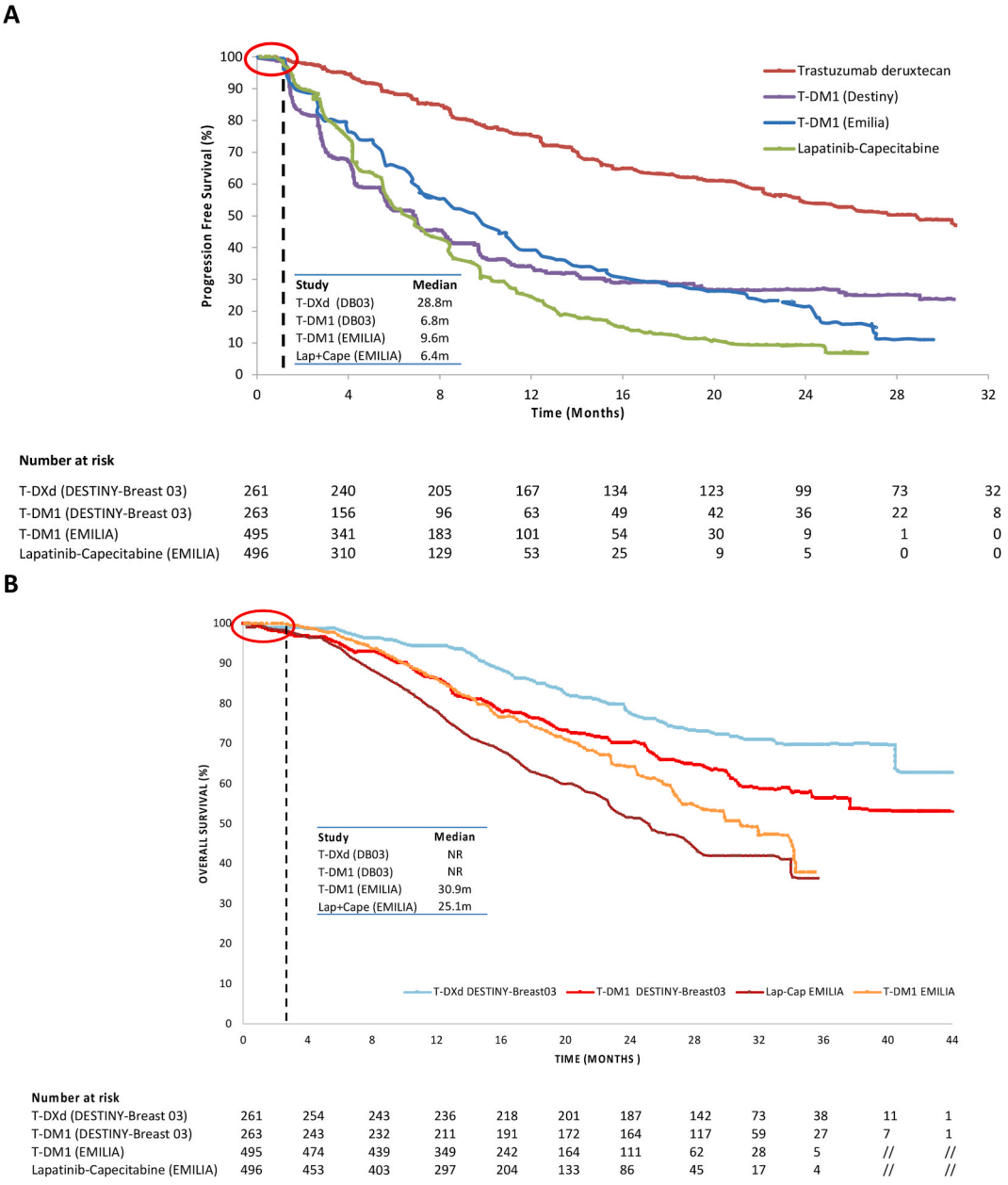

Fig. 1. Digitalized Kaplan Meier curves of PFS and OS of the DESTINY-Breast03 and EMILIA trials

Legend. T-DXd: trastuzumab-deruxtecan; T-DM1: trastuzumab-emtansine; Lap: lapatinib; Cape: capecitabine; DB03: DESTINY-Breast 03; m: months; Destiny: DESTINY-Breast 03; NR: not reached; PFS: progression-free survival; OS: overall survival.

First, a shortening of T-DM1-associated PFS in the DESTINY-Breast03 trial resembling the performance obtained with lapatinib-capecitabine in the EMILIA deserves attention (Fig. 1A). In fact, after retrieving individual patient data (IPD) from digitalized Kaplan-Meier curves [7] and performing an exploratory survival analysis with log-rank test with significance level of $p < 0.05$ to compare the performance of T-DM1 from the DESTINY-Breast03 and lapatinib-capecitabine from the EMILIA, we observed no significant difference in PFS ($p = 0.106$). Differently, T-DM1 from the EMILIA showed significantly worse PFS than T-DM1 in DESTINY-Breast03 ($p = 0.044$) (Fig. 1A). Worth noting, the major baseline difference between the EMILIA and DESTINY-Breast03 populations, is that in the former study, none had received pertuzumab prior to second-line T-DM1 [4,5]. Thus, we can hypothesize double-blockade generates a secondary resistance to anti-HER2 agents, ultimately hampering their performance in the second-line (and likely beyond), at least with regard to capability of later lines to delay tumor progression. In this perspective, the dramatic PFS improvement observed in the DESTINY-Breast03 suggests T-DXd may effectively overcome the possible biological issue of this acquired resistance (Fig. 1A). Nevertheless, median OS with T-DM1 was still not reached in the DESTINY-Breast03, with an OS curve pointing towards better long-term trend compared to the same T-DM1 curve in the EMILIA, but with a strong trend on IPD survival analysis ($p = 0.067$) (Fig. 1B). Although this might seem contradictory, in our opinion, the OS improvement is, at least in part, the consequence of a carry-over effect from first-line double-blockade. Some might argue that this could be also, or exclusively, the consequence of better post-progression treatments, as significant survival improvements from several major novel anti-HER2-directed therapies were observed in real-life HER2+ MBC patients in the last decade [8]. While we cannot exclude this, we should also consider that after the introduction of T-DM1 in the clinical scenario, there were no substantial late-line improvements that might have substantially justified such an OS shift, besides the recent introduction of tucatinib in combination with trastuzumab and capecitabine [6]. However, the HER2CLIMB trial was run almost concomitantly with the DESTINY-Breast03 and the availability of tucatinib in the clinical practice scenario is relatively recent. It is worth noting that ~17 % of the patients progressing to T-DM1 received posterior T-DXd. Hence, this might have had an impact on the OS observed in the control arm of the DESTINY-Breast03 trial. At the same time, ~83 % of patients in the T-DM1 cohort did not receive T-DXd beyond progression to T-DM1, thus it is not possible to rule out the contribution of first-line double blockade on the final OS result of the control arm.

Given all of the above, we wonder what might happen if T-DXd (with or without pertuzumab) would ultimately prove to be superior to standard first-line double-blockade in DESTINY-Breast09 (NCT04784715) in the primary endpoint of PFS, and if it would replace the current first-line. We already know the combination of trastuzumab and pertuzumab is not equally effective when administered in further lines [9], neither pertuzumab rechallenge [10]. Furthermore, first-line chemotherapy is usually stopped at a certain point and trastuzumab-pertuzumab double blockade is continued as maintenance treatment, with no significant safety issues and for prolonged time periods, until disease progression [2,11,12]. We cannot exclude that a proportion of patients might even be cured with the CLEOPATRA first-line scheme. Conversely, T-DXd is a more toxic drug, with ~10 % of patients developing interstitial lung disease (ILD) and several chemotherapy-like adverse events, like hematologic toxicity, alopecia and nausea, among the most frequent [5, 13–15]. These features might represent a non-trivial limitation to its broad use as first-line option in a one-size-fit-all approach. In this perspective, an induction with T-DXd (± pertuzumab), followed by trastuzumab-pertuzumab maintenance could be envisioned as a reasonable upfront therapeutic approach. Moreover, the scientific community should already start to envision research strategies to define the optimal therapeutic sequence granting to most patients the best OS improvement, minimizing toxicity issues. The SONIA trial (NCT03425838) in the context of luminal-like/HER2-negative metastatic breast cancer (MBC) might represent a good practical example of such kind of clinical trials.

Second, in a clinical practice cohort, the detection of low levels of *ERBB2* mRNA was able to identify a subset of pretreated HER2+ MBC patients (~10 %) with no objective response and median PFS of 2.5 months with T-DM1 and a PFS <2 months with lapatinib-trastuzumab double-blockade in the EGF104900 trial [16]. We wonder if this might be related to a downregulation of HER2 associated to previous anti-HER2 therapy and what might be the performance of T-DXd in this setting. In contrast, the combination of high levels of *ERBB2* mRNA and the HER2-enriched molecular subtype can identify HER2+ tumors with high responsiveness to chemo-free HER2-targeted therapies [1]. As also elsewhere observed, DNA alterations in *ERBB2* or in genes associated to the PI3K/Akt/mTOR pathway might play a role in the prediction of benefit from novel pan-HER, PI3K and mTOR inhibitors [1]. Immune-related biomarkers such as tumor-infiltrating lymphocytes, PD-L1 or the IGG signature, among others, might play a role in identifying potential candidate to immunotherapy-based strategies and/or patients in need of more escalated or de-escalated therapeutic approaches, for their prognostic and predictive implications [1,17]. Available evidences highlight the currently unexploited potential of tumor-related biomarkers to refine therapeutic choices. In this perspective, the HER2-PREDICT study (NCT04257162) from the SOLTI Spanish group might help shedding a light on the capability of *ERBB2* mRNA to identify patients with higher likelihood of benefiting from T-DXd, as well as other tissue and blood biomarkers. Other studies on biomarkers of sensitivity/resistance to novel anti-HER2 agents, conducted on tumor tissue and/or blood samples collected in clinical trials, either prospectively planned on purpose or retrospectively analyzed from prospectively-run pivotal trials, would be of outmost importance for future implementations of biomarker-based therapeutic approaches.

Third, a closer look at Fig. 1A allows to detect a minority of patients progressing to second-line treatments within the first 2 months. Despite not having access to individual-patient data, it seems logical to hypothesize that there is a correspondence between these early-progressors and patients experiencing early OS events (Fig. 1B). We could estimate a proportion of ~20 % of early progressors with T-DM1 in the DESTINY-Breast03 and 13 % in the EMILIA, along with ~16 % with lapatinib-capecitabine. These patients might present either with a primary resistance specific to these anti-HER2 agents, or an acquired resistance developed under first-line treatment. It is worth noting that, although small, a subset of ~3 % of patients rapidly progressing to second-line T-DXd was also identified (Fig. 1A). Whether this should be attributable to an intrinsic/primary resistance to the cytotoxic payload, to the linker, or to HER2-related mechanisms of resistance, needs to be urgently defined, since these patients have no alternative effective options following first-line.

To conclude, major therapeutic advances in the first and second-line setting of HER2+ MBC have radically changed the natural history of the disease. However, therapeutic resistance and optimal drug sequencing issues are emerging. We believe the integration of sequence studies, tumor-related biomarker development/implementation and understanding of primary mechanisms of resistance to novel anti-HER2 agents is the way to move forward to effectively tackle these novel unmet needs.

Authors contribution

Daniele Generali and Francesco Schettini conceived the manuscript. Fabiola Giudici digitalized and jointed the Kaplan-Meier curves from the from the DESTINY-Breast 03 and EMILIA randomized phase III trials. Francesco Schettini and Daniele Generali wrote the first manuscript draft. All authors revised and approved the final version of the manuscript.

CRediT authorship contribution statement

Francesco Schettini: Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Fabiola Giudici:** Writing – review & editing, Writing – original draft, Visualization, Formal analysis, Data curation. **Daniele Generali:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Francesco Schettini reports honoraria from Novartis, Gilead and Daiichy-Sankyo for educational events/materials and travel expenses from Novartis, Gilead and Daiichy-Sankyo. Daniele Generali declares personal fees for educational events by Novartis, Lilly, Pfizer, Daiichy-Sankyo, Roche; research funds from Astrazeneca, Novartis and LILT. Fabiola Giudici has nothing to declare.

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