Hot Topic

Neoadjuvant approach as a platform for treatment personalization: focus on HER2-positive and triple-negative breast cancer

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ABSTRACT

The neoadjuvant setting provides unquestionable clinical benefits for high-risk breast cancer (BC) patients, mainly in terms of expansion of locoregional treatment options and prognostic stratification. Additionally, it is also emerging as a strategical tool in the research field. In the present review, by focusing on HER2-positive and triple-negative subtypes, we examined the role of the neoadjuvant setting as a research platform to facilitate and rationalize the placement of escalation strategies, promote the adoption of biomarker-driven approaches for the investigation of de-escalated treatments, and foster the conduction of comprehensive translational analyses, thus ultimately aiming at pursuing treatment personalization. The solid prognostic role of pathologic complete response after neoadjuvant therapy, and its use as a surrogate endpoint to accelerate the drug approval process were discussed. In this context, available data on escalated treatment strategies capable of enhancing pathologic complete response (pCR) rate or improving prognosis of patients with residual disease (RD) after neoadjuvant treatment, were comprehensively reviewed. We also summarized evidence regarding the possibility of obtaining pCR with de-escalated strategies, with particular emphasis on the role of biomarker-driven approaches for patient selection. Pitfalls of the dichotomy of pCR/RD were also deepened, and data on alternative/complementary biomarkers with a possible clinical relevance in this regard were reviewed.

Introduction

Breast cancer (BC) represents the most frequently diagnosed tumor in women worldwide [1]. Systemic treatments for early-BC (EBC) have been historically administered in the adjuvant setting, however, in the last decades, the strategy of administering systemic therapy before surgery – in the so-called neoadjuvant setting – has been increasingly adopted, in order to expand locoregional treatment option [2], to enable an in-vivo evaluation of treatment sensitivity as well as to provide prognostic information based on the pathologic response at surgery [3]. However, besides these unquestionable clinical advantages, the neoadjuvant setting has also emerged as a strategical tool in the research field. In the present review we discussed the role of the neoadjuvant approach as a platform for personalized cancer therapy, as comprehensively summarized in Fig. 1.

Pathologic complete response as a surrogate for Long-Term outcome

The achievement of pathologic complete response (pCR) after neoadjuvant treatment represents a well-established surrogate for long-term outcome in terms of event-free survival (EFS) and overall survival (OS), especially when defined as the eradication of invasive tumor from both breast and lymph-nodes [3]. Results from the CtNeoBC *meta*-analysis revealed that BC subtype not only influences the likelihood of pCR, with HER2 + and triple-negative (TN)BC being associated with higher pCR rates as compared to hormone-receptor (HR)+/HER2-, but also its prognostic role. In particular, although pCR retained a significant prognostic impact in all BC subtypes, the strength of this association was found to be lower in HR + subgroup [3].

Therefore, based on the assumption that an improvement in pCR with an investigational drug/regimen would reasonably predict, for individual patients, the subsequent improvement in outcome endpoints traditionally used for regular drug approval in EBC, FDA endorsed the
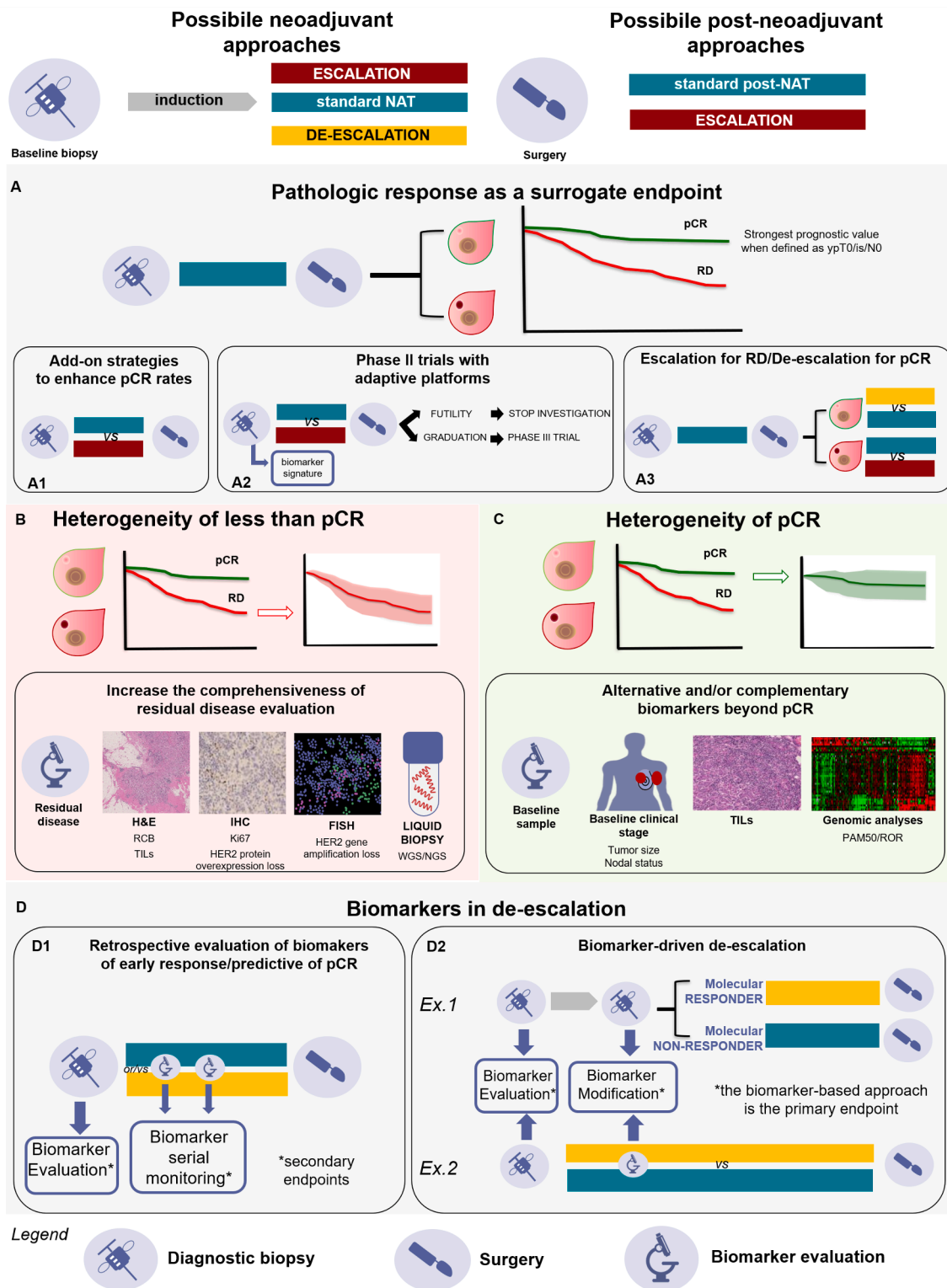
Fig. 1. Neoadjuvant setting as a platform for treatment personalization. A, role of pathologic complete response as a prognostic biomarker and surrogate endpoint for long-term outcome: A1-2–3 represent research strategies relying on pCR as a primary endpoint or pCR/residual as inclusion criteria in the selection of patients for de-escalation/escalation, respectively. B and C depict the heterogeneity of pCR/residual disease: B Biomarkers evaluated on residual disease, suggested as capable of increasing the comprehensiveness of residual disease evaluation; C Baseline biomarkers suggested as capable of providing additional prognostic information beyond pCR. D Biomarker-driven approaches to investigate treatment de-escalation: D1 role of retrospective translational analyses of de-escalation trials, D2 prospective adoption of biomarker-driven approaches in de-escalation trials. Abbreviations: NAT, neoadjuvant treatment; pCR, pathologic complete response; RD, residual disease; H&E, hematoxylin and eosin; RCB, residual cancer burden; TILs, tumor-infiltrating lymphocytes; WGS, whole genome sequencing; NGS, next-generation sequencing; ROR, risk of recurrence.

use of pCR as a surrogate endpoint in neoadjuvant trials with regulatory intent, with the aim of granting accelerated approval to effective investigational treatments, when a substantial improvement is observed, along with a favorable/acceptable safety profile and supportive data from other disease setting (adjuvant/metastatic) (Figure 1.A) [4]. FDA also emphasized that neoadjuvant trials, although harboring the potential of allowing a rapid evaluation of experimental drugs, are intrinsically limited in terms of safety information, and should therefore focus on patients with high-risk features on the basis of conventional clinicopathological features, including HER2 + and TNBC subtypes.

Based on these premises, several trials investigated escalating treatment strategies in HER2 + and TN disease with the goal of improving pCR rates and ultimately enhancing patients' prognosis (Figure 1.A1).

Escalating treatment strategies in TNBC

TNBC, which accounts for 15–20% of all BCs, is recognized as the most biologically aggressive among BC subtypes, being associated with the poorest disease-specific outcomes [5]. However, as already mentioned, it is also associated with the highest likelihood of achieving

pCR after neoadjuvant treatment [1]. This observation, while apparently challenging the role of pCR as a proxy for survival across BC subtypes, actually reflects the so-called triple-negative paradox [6,7]. According to this paradox, TNBC patients retain the highest chance of achieving pCR after neoadjuvant therapy among BC phenotypes, with a positive impact on survival, if so. However, those failing to achieve pCR drive the worst survival rates associated with this BC subtype [6,8]. Based on this assumption, TNBC represents the ideal setting where to investigate treatment strategies aiming at maximizing pCR rates, with the ultimate goal of enhancing prognosis.

The current standard chemotherapy-backbone for the management of TN-EBC is represented by the sequence of taxane (docetaxel/paclitaxel) and anthracycline [2,9], which overall showed to reduce BC-related mortality by, on average, ~33% [10,11]. Despite the lack of direct evidence from phase III trials on the optimal chemotherapy regimens to be administered in the neoadjuvant setting, it is broadly accepted that the chemotherapy regimens considered standard in the adjuvant setting are appropriate also preoperatively [2,11–15]. Regarding the role of nab-paclitaxel in TN-EBC, available evidence is not conclusive, with the phase III GeparSepto trial suggesting a pCR benefit with nab-paclitaxel over paclitaxel in the TNBC subgroup [16], and the

Table 1
Summary of clinical trials testing escalated treatment strategies in TN BC, for which preliminary or final results have been presented and/or published.

Strategy	Trial	Population (n)	Drugs (n per arm)	pCR rates[a] % (95% CI)	p	Ref.
Platinum salts	CALBG 40,603 (phase II 2x2)	Stage II-III TN (4 4 3)	P → ddAC (+/- beva)	41 (35–48)	0.0018	20
			P-Cb → ddAC (+/- beva)	54 (48–61)		
	GeparSixto (phase II)	Stage II-III	P-M (+beva)	36.9 29.4–44.5()	0.005	21
			P-M−Cb (+beva)	53.2 (54.4–60.9)		
	UMIN000003355 (phase II)	Stage II-III HER2- (179; TN cohort, 75)	P → CEF	26.3	0.003	19
			P-Cb-CEF	61.2		
	GEICAM 2006–3 (phase II)*	Basal-like (94)	EC → D	30	NS	24
			EC → D-Cb	30		
	GeparOcto	cT1c-4 TN, HER2 + or high-risk HR+/HER2- (945; TN cohort, 403)	ddE → P → C	48.5	0.584	22
			P-M−Cb	51.7		
PARP-inhibitors (+/-platinum salts)	I-SPY-2	HER2- (116; TN cohort, 102)	P → AC	26 (9–43)	99% probability of veliparib-carboplatin to be superior to control	27
			P-Cb → AC	51 (36–66)		
	Brightness (phase III)	Stage II-III TN (6 3 4)	P-Placebo → AC	31	0.001 (comparison between P-placebo vs P-Cb-V)	28
			P-Cb-V → AC	53		
			P-Cb-Placebo → AC	58		
	GeparOLA (non-comparative phase II)	HER2-negative (106; TN cohort, 77)	P-O → EC	56.0 (43.4–68.0)	NA	29
			P-Cb → EC	59.3 (41.7–75.2)		
Immunotherapy	GeparNuevo (phase II, randomized)	TN (1 7 4)	Durva[b] → Durva-NabP → Durva-EC	53.4 (42.5–61.4) Window cohort: 61.0	1.45 (0.80–2.63), p = 0.224 Window cohort: 2.22 (1.06–4.64), p = 0.035	31
			Durva[b] → Placebo-NabP → Placebo-EC	44.2 (33.5–55.3) Window cohort: 41.4		
	Keynote-522 (phase III)	TN (6 0 2)	Pembro-NabP-Cb → A/E-C-Pembro	64.8 (59.9–69.5)	Estimated treatment difference: 13.6% (5.4–21.8, p > 0.001)	32
			Placebo-NabP-BC → A/E-C-Placebo	51.2 (44.1–58.3)		
	NeoTRIP aPDL1 (phase III)	TN (2 8 0)	Atezo-NabP-Carboplatin	43.5 (35.1–52.2)	1.11 (0.69–1.79), p = 0.66[c]	35
			NabP-Cb	40.8 (32.7–49.4)		
	Impassion 031 (phase III)	TN (3 3 3)	Placebo-NabP → Placebo-AC	41.1	Delta pCR 16.5 (5.9–27.1), p = 0.0044	34
			Atezo-NabP → Atezo-AC	57.6		
	I-SPY-2 (phase II adaptive randomized)	HER2- (205; TN cohort, 21)	Pembro-P → AC	TN: 60 (44–75)	>99.9% predictive probability of being superior to the control arm	32
			P → AC	TN: 22 (13–30)		

Abbreviation: pCR, pathologic complete response; TN, triple-negative; A, doxorubicin; C, cyclophosphamide; dd, dose-dense; M, myocet (non-pegilated liposomial doxorubicin); Cb, carboplatin; V, veliparib; O, Olaparib; Nab-P, nab-paclitaxel.
[a] pCR rates in both breast and axilla in TN population were reported, unless otherwise specified (*pCR in both breast and axilla was a secondary endpoint)
[b] Durvaluamb window phase was stopped after 117 patients recruited
[c] one-sided significance boundary p = 0.0184

subsequent phase III ETNA trial conversely failing to formally establish the superiority of this agent [17].

Several trials investigated the addition of diverse agents to a taxane-anthracycline based chemotherapy backbone as escalation strategies aiming at enhancing pCR rates in TNBC, as detailed in Table 1.

Platinum salts

Several authors investigated the role of DNA-damaging agents, such as platinum salts, in TNBC, Several authors investigated the role of DNA-damaging agents, such as platinum salts, in TNBC which are characterized by the possible presence of deficiencies in DNA-repairing functions, including -but not limited to- those related to the BRCA-associated pathways.

Randomized trials evaluating the addition of carboplatin to anthracycline-taxane combination provided conflicting results. In particular, a pCR advantage with the inclusion of carboplatin in the neoadjuvant chemotherapeutic backbone for TNBC has been reported in the context of several phase II trials [18-20], with also a significant improvement in DFS observed in the GeparSixto trial. Conversely, in the GeparOcto phase III non-inferiority trial, the addition of carboplatin to an anthracycline-taxane-based chemotherapy did not affect pCR rates. However, it should be noted that while carboplatin arm contained non-pegylated liposomal doxorubicin without cyclophosphamide, the carboplatin-free arm included the standard association of epirubicin + cyclophosphamide, thus precluding the possibility of drawing definitive conclusions [21]. In addition, the subsequent survival analysis did not show any difference [22]. Similarly, the in the GAICAM/2006–3 phase II trial, the inclusion of carboplatin in the neoadjuvant management of basal-like BC patients did not affect pCR rates[23].

In order to better elucidate the role of platinum salts for the neoadjuvant management of TNBC, a *meta*-analysis of 9 randomized trials was performed, reporting an absolute 15.1% increase in pCR rates provided by the addition of carboplatin to neoadjuvant chemotherapy as compared to platinum-free regimens. Overall, no survival differences in terms of either EFS or OS have been observed [24].

Despite these results, in the absence of solid data coming from adequately powered phase III trials, and given the large uncertainty regarding the possible impact on survival, carboplatin is currently not unanimously recognized as standard component of the chemotherapy plan for the neoadjuvant management of TNBC and it may be offered only after a careful evaluation of the risk–benefit ratio.

PARP-inhibitors

Beyond platinum salts, a further strategy aiming at targeting deficiencies in DNA repairing functions in TNBC [25] may be represented by the incorporation of Poly-ADP ribose polymerase (PARP)-inhibitor agents to chemotherapy. In the neoadjuvant setting, the addition of PARP-inhibitors (+/-carboplatin), to standard chemotherapy, has been investigated as a possible attempt to enhance pCR rates in TNBC.

In the phase II I-SPY2 trial and the phase III Brightness trial, signals of pCR improvement with the addition of PARP-inhibitor + carboplatin to standard chemotherapy in unselected-TNBC patients were reported [26,27]. Interestingly, HRD(homologous-recombination deficiency)-positive status appeared promising in the identification of responders with PARP-inhibitor + carboplatin. Although the Brightness study was underpowered to detect differences between the two carboplatin-containing arms, pCR rate appeared to be higher (not-significant) in the carboplatin-paclitaxel arm (58%) than the veliparib-carboplatin-paclitaxel arm (53%), suggesting carboplatin as the major determinant in the observed improvement in pCR rates [27]. In this context, if from one hand the Veliparib dose adopted in the Brightness trial was arguably below the maximum tolerated dose thus limiting its PARP-trapping efficiency [28], on the other its concomitant administration, even if only slightly, increased the frequency of paclitaxel dose omission/delay/reduction, thus possibly unbalancing the risk/benefit ratio at the expense of the benefit.

In order to further investigate the relative contribution of either carboplatin or PARP-inhibitors in enhancing pCR rates in patients with germline-BRCA mutations or HRD, the non-comparative phase II GeparOLA study randomized HER2-BC patients to receive taxane-anthracycline-based chemotherapy in association with either carboplatin or the PARP-inhibitor olaparib. Although the study failed to meet its primary endpoint, a not-significant increase in pCR was observed in the Olaparib-containing arm (55.1%) over carboplatin-containing arm (48.6%), especially in the hormone-receptor positive subgroup (pCR rates: 52.6% vs 20.0% respectively) and in younger patients (pCR rates: 576.2% vs 45.5% respectively), thus providing interesting hypothesis-generating insights [107].

Overall considered, the use of PARP-inhibitors as escalated strategy to be combined to an anthracycline-taxane-based chemotherapy, with or without carboplatin in unselected TNBC patient or in those harboring BRCA1/2 deleterious mutations or HRD-positive status, is still to be considered investigational.

Immunotherapy

In the last decade, an increasing interest in the field of immunotherapy fostered the investigation of several immunotherapeutic strategies for the management of BC patients. This led to the approval by FDA of immune checkpoint inhibitors (atezolizumab in March 2019 and pembrolizumab in November 2020) in combination with chemotherapy, as first-line treatment of PD-L1 + TN-metastaticBC (MBC). Because of the strong rationale for immunotherapy in particular in TNBC, several trials tested - and are currently testing - the addition of immunotherapy to a chemotherapy backbone for the neoadjuvant treatment of TNBC patients [29], as detailed in Table 1. In summary, the phase II Gepar-Nuevo and I-SPY2 trials [30,31] and the phase III Keynote-522 and Impassion-031 trials were consistent in suggesting a pCR benefit conferred by the inclusion of immune-checkpoint inhibitors to the chemotherapy backbone for TNBC [32,33], with also (immature) signals of improved EFS [29,30]. In both the Keynote-522 and Impassion-031 trials, the magnitude of pCR benefit deriving from the inclusion of immunotherapy appeared to be greater in patients with heavier disease burden. Conversely, no predictive impact of PD-L1 + status was observed [33]. In contrast, the Neotrip-aPDL1 study, failed to show any pCR benefit with the addition of atezolizumab to carboplatin-taxane-based chemotherapy. It should however be noted that the follow-up for the primary endpoint (EFS) is still ongoing and data on the possible survival advantage with the addition of immunotherapy to neoadjuvant chemotherapy despite the lack of significant pCR delta are awaited [34].

Several possible explanations have so far been suggested for these controversial results, including the omission of anthracycline in the NeoTRIPaPDL1 neoadjuvant treatment backbone, the choice of different immune-checkpoint inhibitors, as well as differences in patients' composition across trials and imbalance in immune infiltration between arms. However, no definitive conclusions can so far be drawn regarding this inconsistency. In addition, it should be noted that no predictive biomarker capable of selecting TNBC patients suitable for the inclusion of immunotherapy in the neoadjuvant setting has so far been identified. In this context, it should be mentioned that the assay platforms and scoring systems adopted to evaluate PD-L1 expression were heterogeneous across clinical trials, thus complicating the generation of conclusive considerations in this regard. Main sources of uncertainty on neoadjuvant immunotherapy in triple-negative breast cancer are summarized in Fig. 2.

Nevertheless, based on the promising results from the Keynote-522 trial and given the unmet clinical need in high-risk TNBC, the combination of neoadjuvant chemotherapy with carboplatin-paclitaxel followed by epirubicin-cyclophosphamide, plus the immune checkpoint inhibitor pembrolizumab is currently being considered for FDA approval in this setting, although there is still uncertainty regarding the actual risk–benefit ratio. It should be noted that the possible clinical benefit
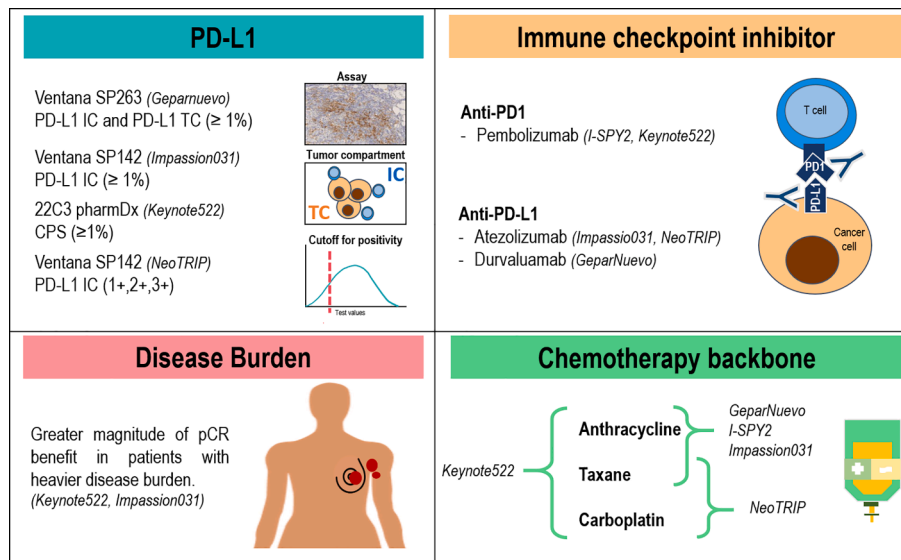
Fig. 2. Main sources of uncertainty on neoadjuvant immunotherapy in triple-negative breast cancer. Abbreviations: TC, tumor cells; IC, immune cells; pCR, pathologic complete response.

deriving from this escalation strategy comes at the cost of increased toxicity, mainly immune-related [35]. Although safety analyses of immunotherapy neoadjuvant trials were overall consistent with those conducted in MBC in terms of a general manageable safety profile, the profound differences between the early and advanced settings in terms of curability intent and relative weight and perception of acceptable toxicities, impose a careful selection of patients potentially suitable for immunotherapy, before its clinical implementation in the curative setting. Indeed, immunotherapy may lead to irreversible adverse events, and, notably, more treatment-related deaths have been reported in the pembrolizumab arm of the Keynote-522 trial [32], thus warning about the imperative need to obtain longer-follow up data, in order to properly establish the long-term safety of this innovative strategy.

Escalating treatment strategies in HER2 + BC

One of the most successful escalating strategy providing a substantial improvement in pCR rates of HER2 + BC patients is represented by the addition of anti-HER2 agents to neoadjuvant chemotherapy. The inclusion of trastuzumab to standard anthracycline-taxane-based chemotherapy was capable of more than doubling pCR rates in 2 pivotal trials [34,37], with also a significant survival impact [36]. Subsequently, increasing efforts were directed to a further improvement in pCR rates in HER2 + BC patients[38], leading to the investigation of several combinations of chemotherapy plus diverse anti-HER2 agents. In particular, the most clinically meaningful benefit in terms of pCR rates has been observed by combining chemotherapy plus HER2 dual blockade, as summarized in Table 2.

In the phase II CHER-Lob trial and phase III NeoALTTO trial, the

Table 2
Summary of clinical trials testing escalated treatment strategies with dual HER2-blockade in HER2 + BC.

Strategy	Trial (design)	Population (n)	Drugs (n per arm)	pCR rates[a] % (95% CI)	p[a]	Predictive biomarkers for de-escalation benefit	Ref
Trastuzumab + Lapatinib	Cher-LOB (II-R)	Stage II-IIIA (1 2 1)	T-H → FEC-H (36) T-L → FEC-L (39) T-HL → FEC-H-L (46)	25 (13.1–36.9) 26.3 (14.5–38.1) 46.7 (34.4–58.9)	0.019[b]	higher TIL levels → higher pCR with escalation	42,50,51
	Neo-ALTTO (III)	Stage II-III (4 5 5)	H → T-H (1 5 4) L → T-L (1 4 9) HL → T-HL (1 5 2)	29.5 (22.4–37.5) 24.7 (18.1–32.3) 51.3 (43.1–59.5)	0.001[b]	-high expression of immune-related gene signatures → higher pCR with escalation-high expression of stroma-related signatures → lower pCR with escalation	41,52
	CALBG-40601 (III)	Stage II-III (3 0 5)	T-H (1 2 0) T-L (67) T-HL (1 1 8)	46 (37–55) 32 (22–45) 56 (47–65)	0.13	NA	45
	NSABP B41 (III)	Stage II-III (5 2 9)	AC → T-H (1 8 1) AC → T-L (1 7 4) AC → T-HL (1 7 4)	49.4 (41.8–56.5) 47.4 (39.8–54.6) 60.2 (52.5–67.1)	0.78	NA	47
Trastuzumab + Pertuzumab	Neosphere (II)[c]	Stage III-III (4 1 7)	D-H (1 0 7) D-HP (1 0 7) D-P (96)	29 (20.6–38.5) 45.8 (36.1–55.7) 24 (15.8–33.7)	0.003*	higher HER2 membrane protein expression → higher pCR with escalation	48,53

Abbreviation: pCR, pathologic complete response; T, paclitaxel; H, trastuzumab; FEC, 5-fluorouracil-epirubicin-cyclophosphamide; L, lapatinib; A, doxorubicin; P, pertuzumab
[a] pCR rates in both breast and axilla in TN population were reported, unless otherwise specified (*pCR rates in breast as the primary endpoint)
[b] dual versus single-HER2 blockade with Trastuzumab
[c] considered only chemotherapy-containing arms

addition of lapatinib to trastuzumab + chemotherapy provided a significant improvement in pCR rates as compared to single-HER2-blockade [39,40]. In addition, although these trials failed to report a significant impact on survival, both the CHER-Lob and NeoALTTO studies were consistent in showing a signal for improved long-term outcome with neoadjuvant dual-HER2-blockade over single HER2-targeting [41,42]. In the phase III CALBG-40601 trial, although the addition of lapatinib to trastuzumab + paclitaxel did not provide a significant improvement in pCR, a significant benefit from dual-HER2 blockade was observed in the HR- subgroup [43]. In addition, in the subsequent survival analysis, dual-HER2 blockade was reported to improve both RFS and OS over trastuzumab + chemotherapy [44]. In the NSABP-B41 trial, a ~ 10% increase of pCR with dual-HER2 targeting was observed over single-HER2 blockade [45].

Comparable deltas in pCR rates between single and dual-HER2 blockade + chemotherapy have been observed by adding pertuzumab to trastuzumab. In the phase II Neosphere trial, higher rate of pCR was reported in patients receiving docetaxel-trastuzumab-pertuzumab as compared to docetaxel-trastuzumab. These results led to pertuzumab FDA and EMA approval as neoadjuvant treatment of patients with high-risk HER2 + EBC [46]. Although also the Neosphere trial failed to formally report a survival advantage with the dual anti-HER2 strategy over single-HER2 blockade, a trend for better outcome has been shown, thus supporting the primary endpoint [47].

Currently, besides classical clinicopathologic features, no predictive biomarker is currently available for the selection of HER2 + BC patients who are more likely to benefit from neoadjuvant dual-HER2 blockade. Despite that, interesting insights in this regard may be captured from biomarker analyses of dual-HER2 blockade trials [47–50], as detailed in Table 2.

Add-on approach: Limitations and alternative/complimentary strategies to speed up drug development in early BC

In its guidance for the use of pCR as an endpoint to support drug accelerated-approval, FDA endorsed the adoption, when designing neoadjuvant trials, of add-on strategies as a possible solution aiming at preventing effective and potentially curative strategies to be withheld in high-risk patients, as well as allowing the isolation of toxicities related to the investigational agent. Although this approach is unquestionably intended to safeguard patients treated in an experimental setting, it inevitably results in complex protocols, with multi-drug regimens, probably leading to overtreatment and, accordingly, to unnecessary toxicity in a not negligible proportion of patients. This may ultimately contribute to increase the social and financial burden, as well as to inevitably slow down the regulatory approval of potentially curative treatments.

For these reasons, several strategical platforms have been put in place aiming at minimizing the number of patients exposed to the risk of overtreatment, speeding-up drug approval for early breast cancer, and ultimately, rationalizing financial and social resources.

Adaptive trials: The I-SPY2 platform

Adaptive trials represent flexible research platforms in which accumulating results in the context of the trial may be used to modify its subsequent course, according to prospectively prespecified and pre-planned rules, without affecting the reliability and validity of the study itself [51] (Figure 1A2). I-SPY2 represents an adaptive platform in which BC patients with high-risk features undergo adaptive randomization to either investigational drugs/regimens added to a standard treatment backbone versus the standard treatment alone, by adopting pCR as the primary endpoint. The goal of the I-SPY2 trial is represented by the identification of effective regimens based on the biomarker signature of the tumor, including – but not limited to – standard biomarkers already approved by FDA (e.g. HR-status, HER2-status). According to the original ISPY2 plan, for each signature, investigational regimens showing a

low Bayesian predictive probability of being superior to the standard treatment will be dropped from the trial for futility reasons, while drugs reaching a sufficient level of predictive probability of success in a confirmatory phase III trial will graduate, ultimately allowing these successful compounds to be tested in smaller and more cost-effective phase III trials, which, probably, would otherwise be larger and more dispersive [52]. The possibility to simultaneously test multiple drugs as well as to provide a large biomarker collection represent innovative features that make the I-SPY2 an appealing platform, currently adopted also in other oncological and non-oncological settings [53]. Interestingly, over 10 years of I-SPY-2 history, while 7 agents have graduated, as many I-SPY2 attempts were stopped due to futility (n = 5) or toxicity (n = 2), thus therefore preventing the unnecessary deployment of further human, economic and social resources in bigger/longer trials.

Residual disease after neoadjuvant treatment as inclusion criteria for post-neoadjuvant trial

The presence of residual disease (RD) after neoadjuvant treatment represents a well-established marker of poor outcome, especially in more biologically aggressive BC subtypes, namely TN and HER2 + . In this context, a more focused approach consisting in targeting a selected population enriched for patients with high-risk features based on the presence of RD, could downsize the resources to be put in place in order to capture a beneficial survival impact of escalated treatment strategies, thus enabling them a more rational positioning from a regulatory point of view(Figure 1A3). Indeed, results from trials testing escalating treatments in patients with RD after standard neoadjuvant treatment, have been recently reported, with practice-changing implications both in TN and HER2 + BC. In detail, the Create-X trial showed a significant improvement in DFS in patients receiving post-neoadjuvant capecitabine in the intention-to-treat (ITT) population. This benefit seemed to be mainly driven by the TN subgroup, where it resulted in a 42% lower risk

Table 3

Ongoing randomized trials enrolling patients with high-risk features (also) on the of the presence of residual disease after neoadjuvant therapy.

Trial reference	Population	Investigational strategy	Post-neoadjuvant treatment arms
NCT02926196 (A-BRAVE)	TN BC: stratum A (adjuvant cohort), stratum B (neoadjuvant cohort)	Immunotherapy	Avelumab vs Observation
NCT02954874 (SWOG-S1418)	TN BC	Immunotherapy	Pembrolizumab vs Observation
NCT02445391 (ECOG-ACRIN EA1131)	TN BC	Chemotherapy	Carboplatin/ Cisplatin vs Capecitabine vs Observation
NCT00494234 (Olympia)	HER2-negative BC with BRCA 1/ 2 deleterious mutations	PARP-inhibitor	Olaparib vs Placebo *
NCT04622319 (DESTINY-Breast05)	HER2-positive	ADC anti-HER2	Trastuzumab-Deruxtecan vs Trastuzumab-Emtansine
NCT04457596 (CompassHER2 RD)	HER2-positive	TKI anti-HER2	Tucatinib + TDM1 vs TDM1
NCT04595565 (SASCIA)	HER2-negative	Anti-TROP2	Sacituzumab-Govitecan vs TPC (capecitabine, carboplatin, cisplatin)

* on February, 17th 2021 a press release announced that the Independent Data Monitoring Committee concluded that the Olympia trial crossed the superiority boundary for the primary endpoint iDFS by observing a statistically significant and clinically relevant survival improvement with Olaparib versus placebo. Results will be presented soon.

of EFS events [54]. One possible limitation of the Create-X trial is represented by the fact that it was conducted in Asia. Indeed, the pharmacokinetic profile of capecitabine may be affected by racial factors, and it is known to differ between Asian and non-Asian patients [55], thus limiting the generalization of Create-X results in a Caucasian population. In the phase III Katherine trial, a significant and clinically meaningful improvement in iDFS rates was observed in patients receiving TDM1 as post-neoadjuvant treatment as compared to standard trastuzumab, with a 50% reduction of the risk if invasive-disease recurrence or death. The benefit of adjuvant TDM1 was consistent across all subgroups, including those defined by HR-status and nodal-status at baseline [56]. Based on these results, on May 2019 FDA approved TDM1 for the adjuvant treatment of HER2 + BC patients failing to obtain pCR after taxane-based + anti-HER2 neoadjuvant treatment.

Based on these compelling results, the approach of using RD after neoadjuvant treatment as a criteria for patients' selection in post-neoadjuvant trials investigating novel drugs or escalated strategies has been recently endorsed by FDA [57]. Indeed, several ongoing trials are currently adopting this approach to select high-risk patients to be enrolled for escalated trials, as shown in Table 3.

Heterogeneity of less than pCR

A growing body of evidence suggest that the mere dichotomization between pCR/non-pCR may be too simplistic, since the presence of RD after neoadjuvant treatment does not necessarily translate into poor outcome. In this context, several biomarkers evaluated on RD proved to retain prognostic and/or predictive value (Figure 1.B).

A more detailed evaluation of RD after neoadjuvant treatment encompassing relevant pathologic characteristics with independent prognostic impact (bi-dimensional measurements of tumor-bed, total tumor cellularity and relative contribution of the invasive components, number/dimension of nodal metastases) into the composite score of residual cancer burden (RCB) was found to be capable of better prognostically stratifying patients beyond the simple distinction between RD vs pCR, in unselected BC patients [58] and each phenotypic BC subsets [59]. In the light of its solid clinical relevance, the evaluation of RCB has been endorsed by the BIG-NABCG recommendations for the standardized pathological characterization of RD after neoadjuvant treatment [60] and subsequently adopted as primary or secondary endpoint in several prospective neoadjuvant trials [61].

Additional efforts have subsequently been made in order to further biologically dissect RD. In this context, the evaluation of the proliferative index Ki67 on RD has been consistently reported to be prognostic in unselected BC patients undergoing neoadjuvant treatment and failing to achieve pCR [62–66]. A further step forward has been represented by the integration of biomarkers reflecting both tumor burden and tumor biology. In particular, it has been reported that the integration of Ki67 with either nodal status or RCB was capable of providing more prognostic information than the residual disease burden alone [65,67,68].

Focusing on HER2 + BC, loss of HER2 protein overexpression or gene amplification has been described in a not negligible proportion of patients undergoing neoadjuvant treatment, ranging from ∼ 30% to ∼ 40% [69,70]. While it remains an unresolved issue whether HER2-loss is mainly driven by chemotherapy or rather HER2-targeted treatment, it has consistently been reported a negative prognostic impact of this phenomenon [69,70]. The role of HER2-loss in affecting prognosis and/or response to anti-HER2 treatment, has been also investigated in the context of the Katherine translational analyses [71], where patients with low HER2-expression on RD experienced poorer iDFS rates as compared to those with high levels of HER2-expression only within the trastuzumab arm, thus generating the hypothesis that low HER2-levels on RD after standard neoadjuvant treatment may reflect a state of resistance to trastuzumab, which could potentially be reverted by the administration in the post-neoadjuvant setting of TDM1. Additionally, in the

CALBG40601 trial of dual-HER2 blockade, PAM50-based HER2-enriched signature on RD was associated with shorter RFS, while a relationship in the opposite direction was reported for an IgG signature [44].

It is currently well acknowledged the solid clinical validity of baseline tumor-infiltrating lymphocytes (TILs) in EBC, especially in TN phenotype, where they reached level-1b evidence as a prognostic biomarker [72] according to the revised determination of Levels of Evidence using elements of tumor biomarker studies, by Simon et al. [73]. Focusing on the neoadjuvant setting, higher levels of TILs have been consistently associated with higher rates of pCR after standard systemic treatments, and improved survival in both TN and HER2 + BC [74]. Their evaluation on treatment-naïve BC samples is currently endorsed by several international guidelines in these BC subtypes [75–77]. Furthermore, based on accumulating preclinical data supporting the association between chemotherapy exposure and lymphocytic attraction into the tumor bed [78,79], the clinical relevance of TILs has been also evaluated by analyzing RD samples, with promising results showing a strong positive prognostic impact of high RD-TILs in TNBC patients failing to achieve pCR after neoadjuvant chemotherapy [80,81].

Preliminary evidence suggests also a possible role of liquid biopsy in optimizing the prognostic stratification of BC patients failing to achieve pCR. In particular, the tracking of somatic mutations in plasma samples (after surgery) was reported to independently correlate with DFS in TNBC patients with RD [82]. In a retrospective study conducted in high-risk BC patients enrolled in the I-SPY2 trial, ctDNA positivity after neoadjuvant therapy (before surgery) proved to retain a negative prognostic impact in unselected BC patients failing to achieve pCR. Interestingly, patients with RD and undetectable ctDNA at the end of neoadjuvant therapy experienced similar survival rates as those achieving pCR [83]. Although affected by suboptimal sensitivity, the adoption of liquid biopsy as a non-invasive tool for the prognostic stratification of patients with RD appears promising and deserves further validation in future studies.

Treatment De-escalation strategies

Another challenging issue is represented by the possibility of obtaining pCR with de-escalated treatments, in order to reduce the toxicity burden without compromising patients' outcome, thus possibly improving the cost-effectiveness ratio.

Omission of anthracyclines

Triple Negative breast cancer

Neoadjuvant chemotherapy including both taxane and anthracycline is currently considered the standard of care in TNBC patients, with the addition of carboplatin emerging as an effective escalated option. In this context, preliminary studies reported pCR rates with anthracycline-free neoadjuvant chemotherapy ranging from 46% to 50% across trials [84,85], which well-compare with that reported in historical controls of anthracycline + taxane as preoperative treatment for TNBC [13,17]. In the NeoCART study, the anthracycline-free arm (carboplatin + paclitaxel) was associated with significantly higher pCR rates as compared to the control arm. Subgroup analysis revealed a larger magnitude of benefit in patients with earlier clinical stage [86]. In the NeoSTOP study, pCR rates were found to be similar between the anthracycline-containing versus anthracycline-free arm, with also similar EFS and OS [87]. As expected, the anthracycline-free arm was associated with higher rates of treatment completions and lower health-related costs. Although preliminary, these findings overall suggest carboplatin-paclitaxel as an effective and promising anthracycline-free option for TNBC patients, especially in those with lower disease burden.

HER2 + breast cancer

The possibility of omitting anthracycline from the neoadjuvant

management of HER2 + BC without impairing pCR rates represents an appealing option. The adjuvant BCIRG006 study suggested a more favorable benefit-risk ratio with the anthracycline-free regimen (docetaxel + carboplatin) as compared to the standard anthracycline-taxane based chemotherapy given the similar efficacy and the lower risk of both short-term and long-term toxicity [88].These findings provided one of the first evidence reassuring on the possibility of safely omitting anthracyclines in HER2 + BC patients with high-risk features, which mirrors the traditional eligibility criteria for the neoadjuvant treatment.

Subsequently, results from the Tryphaena [89] and Train-2 [90] trials conducted in the neoadjuvant setting were consistent in reporting superimposable pCR rates between anthracycline-containing versus anthracycline-free regimens. However, by reasons of statistical limitations, the non-inferiority of this de-escalated approach with respect to anthracycline-containing treatment could not be formally claimed. In addition, both of the abovementioned trials adopted chemotherapy backbones which are not currently considered the standard of care in this setting, thus imposing caution in the interpretation of results. However, the survival analysis of the TRAIN-2 trial was consistent with the primary outcome by reporting the absence of an EFS improvement with anthracyclines added to dual-HER2 targeted-based therapy [91]. Currently, the possibility of using anthracycline-free trastuzumab-based regimens (with or without pertuzumab) is enshrined by several international guidelines for the neoadjuvant management of HER2 + BC patients [2,75].

Omission of chemotherapy in HER2 + BC: Focus on biomarker analyses and biomarker-driven approaches (Figure 1D)

Detailed results from trials investigating chemotherapy-free strategies for the neoadjuvant management of HER2 + BC, are reported in Table 4, with a focus on biomarker analyses.

In particular, growing interest has been directed towards the possibility of (i) delivering dual-HER2 blockade without a chemotherapy backbone or (ii) omitting systemically administered chemotherapy by administering the anti-HER2 antibody-drug conjugate T-DM1. In this context, although available data do not overall support the omission of chemotherapy in unselected HER2 + BC patients receiving neoadjuvant treatment, several biomarker-based approaches – which are listed below - proved to be feasible and capable of allowing the identification of HER2 + BC patients for whom chemotherapy may be safely spared or, conversely, for whom the de-escalated approach would otherwise potentially represent an undertreatment:

- Retrospective translational analysis of samples collected at baseline in the context of prospective trials, aiming at identifying potential predictive biomarkers (HR status [47,92], PIK3CA mutational status [93–95], PAM50 analysis [93], HER2-heterogeneoty [95,96], TILs [94])
- Retrospective evaluation of predictors of early response through pre-planned biomarker serial monitoring (PET/CT scan-based response [97], immune biomarker dynamics [94])(Figure 1D1).
- Biomarker-driven approach adopted as the primary endpoint, aiming at investigating the ability of a biomarker to reliably predict pCR (PAM50 analysis [92], Ki67 drop/invasive tumor cell reduction [98])(Figure 1D2,Example2)
- Adaptive allocation to standard versus de-escalated treatment according to molecular response (ki67 drop [93], PET/CT response [100]) after a short course of induction therapy(Figure 1D2, Example1).

An example of this latter strategy is represented by the Per-Elisa phase II study, where HER2+/HR + BC patients received dual-HER2 blockade in association with either endocrine therapy or taxane-based chemotherapy according to the magnitude of ki67 reduction after a short course of letrozole. The study met its primary endpoint by reaching

the pre-specified threshold for pCR [93], thus providing the proof of principle that Ki67 drop after a short-term course of endocrine therapy may allow to identify triple-positive BC patients with a not negligible likelihood of achieving pCR without chemotherapy (Example1-Figure 1D2).

Overall, promising observations have been made across biomarker analyses conducted in the context of trials investigating diverse de-escalated neoadjuvant strategies, thus providing interesting insights in terms of treatment personalization, as well as prioritization of biomarker investigation in future studies with enrichment designs.

Treatment de-escalation strategies for patients with pCR

The attainment of pCR after neoadjuvant treatment may potentially allow to identify BC patients suitable for de-escalated strategies in the post-neoadjuvant setting, aiming at limiting overtreatment, as shown in Fig. 1. Although preliminary evidence supports the feasibility and acceptability by both patients and clinicians of such approach in HER2 + B[100], in the absence of solid and prospectively-collected evidence, the choice of omitting the remainder post-neoadjuvant standard therapy based on pCR, should not be supported. Interestingly, the phase II CompassHER-pCR study in currently ongoing in this setting (NCT04266249).

Heterogeneity of pCR

In the above-mentioned CTNeoBC *meta*-analysis, among HER2 + and TNBC patients achieving pCR, approximately 15% and 20%, respectively, have experienced a EFS event by the 5th year after randomization [3]. For this reason, based on the assumption that the attainment of pCR after neoadjuvant treatment does not guarantee cure, several authors investigated alternative biomarkers potentially capable of reliably surrogating long-term outcome beyond pCR (Figure 1.C).

Available evidence suggests that standard baseline clinicopathologic features retain a significant prognostic impact even in patients experiencing pCR after neoadjuvant treatment, especially in HER2 + BC. In particular, clinical stage at diagnosis has been suggested to negatively impact on long-term outcome even in patients achieving pCR [101].

The evaluation of immune-related biomarkers on pre-treatment tumor samples was found to provide additional information beyond those provided by traditional clinicopathologic features and pCR, both in TN and HER2 + BC. In particular, it has been consistently reported an association between baseline TILs and prognosis, independently from the achievement of pCR in both TN [102] and HER2+ [75,103] subtypes. Additionally, FOXP3 + TIL density was found to provide added prognostic information beyond clinicopathologic features, pCR and TILs in TNBC[102]. A similar prognostic role of immune-related biomarkers has been captured in the genomic analysis from the CALBG40603 trial, where 52 genomic signatures, 44 of which reflected features of the immune microenvironment were found to be significantly associated with both pCR after neoadjuvant therapy and EFS [44].

Promising data also come from a combined dataset of almost 1000 BCE patients undergoing neoadjuvant chemotherapy with anthracyclines + anti-microtubule agents, where gene expression and clinicopathologic data were evaluated for their predictive and/or prognostic role. Intrinsic subtypes by PAM50-analysis and the integration of Risk-of-Relapse Score based on subtype with proliferation (ROR-P) were found to be independently prognostic, irrespective of the attainment of pCR. In particular HER2-enriched and basal-like subtypes, as well as ROR-P high scores were associated with the most unfavorable DRFS rates [104].

Overall, available evidence highlights that pCR encompasses a wide range of biological and clinical entities. In this context, the identification of baseline biomarkers capable of identifying patients with unfavorable long-term outcome despite the achievement of pCR may refine our ability of prognostic stratification, thus allowing a further step forward

Table 4
Trials investigating de-escalated chemotherapy-free strategies for HER2 + BC, with biomarker analysis.

De-escalated strategy	Study (design)	Population	Treatments	Biomarker-based approach with a predictive intent (biomarker source)				Main findings
				Retrospective evaluation of biomarkers at baseline	Retrospective evaluation of predictors of early response through pre-planned biomarker serial monitoring	Biomarker-driven approach adopted as primary endpoint	Adaptive allocation to standard vs de-escalated treatment according to the response after a short-term therapy	
Dual-HER2 blockade without CT	Neosphere [48] (phase II)	HER + stage II-III	CT-H CT-HP CT-P HP	Baseline HR status (tumor sample)	NA	NA	NA	**pCR rates**[a] **in the chemotherapy-free arm:**-ITT: 16.8%**pCR rates**[a] **in the chemotherapy-free arm by HR status:**-HR+:5.9%-HR-: 27.3%
	PAMELA [92] (phase II, single-arm)	HER2 + stage I-IIIA BC	LH (+/- ET according to HR status)	Baseline HR status (tumor sample)	NA	HER2-enriched subtype by PAM50 analysis (tumor sample)*	NA	**pCR rates**[a]**:**−30%**pCR rates**[a] **by HR status:**-HR+: 18%-HR-: 43%**pCR rates**[a] **by PAM50:**-HER2-E: 41%–non-HER2-E: 10%
	WSG-ADAPT HER2+/HR- [102] (phase II randomized)	HER+/HR- BC	HP CT-HP	NA	NA	Molecular response defined as either ki67 relative reduction from baseline ≥ 30% or < 500 invasive tumor cells at 3-week biopsy (tumor sample)	NA	**pCR rates by treatment:**-control arm: 90.5%-de-escalation: 36.3%**pCR rates by molecular response:**-molecular-responder: 44.7%-molecular NON-responder: 8.3%
	Per-Elisa[93](phase II)	HR+/HER2 + stage II-IIIA BC	ET → HP + ET/CT	Baseline PIK3CA mutational status (tumor sample) and PAM50 intrinsic subtype (tumor sample)	NA	NA	Molecular response defined as Ki67 relative reduction from baseline after 2-weeks of endocrine therapy, by adopting 20% as cutoff (tumor sample)*	**pCR rates by molecular response:**-molecular-responder: 20.5%-molecular NON-responder: 81%**pCR rates by PAM50 in molecular responder:**-HER2-E: 45.5%–non-HER2-E: 13.8%**pCR rates by PAM50 in molecular NON-responder:**-HER2-E: 83.3%–non-HER2-E: 66.7% **pCR rates by PIK3CA in molecular responder:**-PIK3CA mut: 10%-PIK3CA wt: 24.2%
	PHERGain [103] (phase II randomized)	HER2 + stage I-IIIA BC	CT + HP (cohort A) HP +/-ET → HP +/-ET/CT (cohort B)	NA	NA	NA	Response defined as PET/CT SUVmax reduction ≥ 40% from baseline after 2 cycles (PET/CT scan) in cohort B*	**pCR rates by treatment:**-cohort A: 57.7%-cohort B: 35.4%**pCR rates by PET-response (cohort B):**-PET-responder: 37.9%-PET NON-responder: 25.9%
Omission of systemically administered CT	PREDIX [101] (phase II randomized)	HER2 + BC with T ≥ 2 cm or N+	CT-HP TDM1	NA	F-FDG uptake decrease from baseline (PET/CT scan)	NA	NA	**pCR rates by treatment:**-control arm: 47%-de-escalation: 45%**pCR rates by PET-response:**-PET-responder[b]: 22%-PET NON-responder: 19%
	WSG-ADAPT HER2+/HR + [98] (phase II randomized)	HR+/HER2 + BC	TDM1-ET TDM1 H-ET	Baseline PIK3CA mutational status (tumor sample) and TIL levels (tumor sample)	Dynamics of CD8 protein expression predictive for TDM1 benefit (tumor sample)	NA	NA	**pCR rates by treatment:**-TDM1: 40.5%-TDM1 + ET: 45.8%-Trastuzumab + ET: 6.7%**pCR rates by PIK3CA:**-PIK3CA mut: 17.6%-PIK3CA wt: 35.4%**pCR rates by TILs**[c]**:**-high-TILs: 70%**pCR rates by CD8 dynamics:**-CD8 dynamics more

Table 4 (*continued*)

De-escalated strategy	Study (design)	Population	Treatments	Biomarker-based approach with a predictive intent (biomarker source)				Main findings
				Retrospective evaluation of biomarkers at baseline	Retrospective evaluation of predictors of early response through pre-planned biomarker serial monitoring	Biomarker-driven approach adopted as primary endpoint	Adaptive allocation to standard vs de-escalated treatment according to the response after a short-term therapy	
	KRISTINE [99] (phase III)	HER2+Stage II-III	TDM1-P CT-HP	Baseline PIK3CA mutational status (tumor sample) and HER2 levels (tumor sample)	NA	NA	NA	pCR rates by treatment:-control arm: 55.7%-de-escalation: 44.4%pCR rates by PIK3CA:lower pCR with de-escalation in PIK3CA mutpCR rates by HER2 levels:lower pCR with de-escalation in tumors with HER2-low levels
	Dana-Farber [96] (phase II)	HER2+Stage II-III	TDM1-P	Baseline HER2 heterogeneity (tumor sample)	NA	NA	NA	pCR rates by HER2 heterogeneity:-heterogeneous: 0%-NON-heterogeneous: 55%

strongly predictive for de-escalation efficacy than TILs

Abbreviation: BC, breast cancer; CT, chemotherapy; H, trastuzumab; P, pertuzumab; HR, hormone-receptor; ITT, intention-to-treat; L, lapatinib; ET, endocrine therapy; HER2-E, HER2-enriched;

* the biomarker-driven study met the primary endpoint

a pCR in the breast

b PET-responder: ≥45% F-FDG PET SUVmax decrease

c High TILs: >40%

towards treatment personalization.

Conclusions

The administration of systemic treatments in the neoadjuvant setting provides undeniable benefits from the patient perspective, mainly in terms of expansion of locoregional treatment options. Additionally, from a research point of view, the neoadjuvant setting offers the unique opportunity to pursue treatment personalization. The well acknowledged prognostic role of pCR has fostered the investigation of escalated treatment strategies by adopting pCR as surrogate endpoint, allowing a substantial improvement of our ability to completely eradicate the tumor on breast (+/- lymph-nodes) in high-risk BC patients, both in HER2 + and TN subtypes. In order to rationalize the positioning of escalated strategies, novel study platforms focusing on higher risk patients based on the presence of RD after neoadjuvant therapy were adopted for the investigation of escalated treatments, with practice-changing results. Several investigational strategies are currently being investigated in high-risk patients selected by the presence of RD after neoadjuvant therapy, both in HER2 + and TNBC, and results are awaited. In addition, the conduction of adaptive phase II trials allows to rationalize resources by prematurely identifying investigational strategies with a low – or, conversely, high, probability of be successful in subsequent phase III trials.

Additionally, growing interest has been directed towards de-escalation, with the aim of sparing unnecessary toxicities to patients who may achieve pCR with less. In this context, several de-escalated strategies were reported to be associated with promising pCR rates, especially in HER2 + disease, however none of them is currently ready for clinical implementation. Results from translational analyses revealed several biomarkers with a potential clinically relevant role, whose investigation should be prioritized in future de-escalation trials. In addition, biomarker-driven studies for the adaptive selection of patients suitable for neoadjuvant de-escalation are emerging as particularly appealing approaches in this regard.

A final consideration concerns the lack of an established trial-level association between pCR and long-term outcome [1], which challenges the reliability of pCR as a surrogate endpoint in a hypothetical scenario of replacing large adjuvant trials requiring years to generate results with small neoadjuvant trials requiring few months to be completed. The most emblematic example is represented by the investigation of dual-HER2 blockade in the early setting. Indeed, whilst several escalating treatments provided a meaningful improvement in pCR rates in this setting, survival analysis of the same trials [41,42,47], - with the exception of the CALBG 40,601 trial [44], as well as the corresponding adjuvant trials [105,106] generally reported clinically modest differences in survival rates between standard treatment versus the escalated strategy. In this context, the complex multi-arm design of most of these trials may have possibly played a role in diluting the survival deltas observed between single versus dual-HER2 targeting, since all were consistent in reporting a survival trend in the same direction thus suggesting that this lack of survival advantage may reflect a statistical limitation, rather than a real lack of long-term benefit. However, the lack of a formal surrogacy of pCR for survival endpoints still represents an issue. This unfilled gap, along with the intrinsic disparities in the selection of patients for neoadjuvant versus adjuvant trials, currently preclude the possibility to consider as interchangeable the adjuvant and the neoadjuvant platforms.

Declaration of Interest

conception, drafting and revising of the work and have approved the final submitted version.

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