Advances in systemic therapies for triple negative breast cancer

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Abstract

Triple negative breast cancer (TNBC) continues to be the subtype of breast cancer with the highest rates of recurrence and mortality. The lack of expression of targetable proteins such as the estrogen receptor and absence of HER2 amplification have made relying on cytotoxic chemotherapy necessary for decades. In the operable setting, efforts to improve outcomes have focused on escalation of systemic therapy and a shift toward preoperative delivery followed by a response adapted approach to postoperative systemic therapy. An improved understanding of tumor biology has resulted in the identification of subsets of patients with specific molecular features, leading to testing and approval of multiple new targeted therapies for this disease. Furthermore, advances in drug development have led to the approval of antibody-drug conjugates that are redefining classification schemes for breast cancer. This review focuses on the modern management of TNBC, with particular focus on recent updates in the treatment of operable disease, and an overview of the most recent promising advances in the therapeutic landscape of metastatic disease. It discusses the practical challenges and unanswered questions resulting from the approval of neoadjuvant immunotherapy and shares an approach in the clinic on topics for which evidence is lacking. In addition, it provides a glimpse into the future, highlighting challenges and opportunities for biomarker based right-sizing of preoperative therapy, refining evaluation of response to preoperative therapy after surgery, early diagnosis and detection of relapse, and areas of needed research for metastatic TNBC.

Introduction

Triple negative breast cancer (TNBC) is defined by absence of the estrogen receptor and progesterone receptor and lack of human epidermal growth factor receptor 2 (HER2) overexpression.[1-3] Compared with hormone receptor positive and HER2 amplified tumors, TNBC is the most aggressive subtype of breast cancer, characterized by higher and earlier rates of recurrence and death in the operable setting (stages I-III)[4] and shorter overall survival in the inoperable (stage IV) setting.[5 6] In keeping with a definition based on absence of molecular markers (estrogen receptor, progesterone receptor, and HER2 amplification) in the tumor rather than features driving tumor growth, TNBC has come to be known as a heterogeneous group of diseases with a poorly understood biology. Because of this, the development of targeted therapies for TNBC has lagged behind the other breast cancer subtypes. Cytotoxic chemotherapy continues to be the backbone of standard of care, with most progress being achieved by the optimization of chemotherapy drug selection, sequencing, dosing, and scheduling schemes.[7] More recently, improvements in our understanding of TNBC biology and an increasing appreciation of the potential of personalized therapy strategies have led to shifting paradigms in both the early and advanced stage settings. As a result, we are entering a true revolution in TNBC, in which researchers and clinicians will move away from thinking about this disease in terms of the three biomarkers it lacks and shift their focus to the "positive" biomarkers that define its biology and that represent potential drug targets.

This review will cover the most clinically impactful evidence supporting the modern management of TNBC, with particular attention to operable breast cancer and to newer therapies that have recently entered or will soon enter the clinical space. In addition, we review common clinical questions that arise in the modern management of TNBC and that lack evidence based answers, sharing our perspectives and approaches to guide practicing clinicians through controversial topics. Importantly,

although we are seeing unprecedented advances in development of drugs for TNBC, the rising cost of and unequal access to these agents worldwide are leading to increasing disparities in clinical outcomes between countries. Where appropriate, we include our viewpoint on alternative management strategies in settings where access to novel therapeutics may be limited.

Sources and selection criteria

We searched PubMed and Medline from 2010 to 2022. We also included one study published before this timeframe, given its notable contribution to the classification of breast cancer subtypes.[7] We evaluated only articles from peer reviewed journals written in English. We used the search terms "triple negative breast cancer" and "basal breast cancer" and the following terms combined with "breast cancer": "PD-L1", "antibody drug conjugates", "immunotherapy", "targeted therapy", "pembrolizumab", "trastuzumab deruxtecan", "BRCA", "PARP inhibitors", "capecitabine", "carboplatin", "cisplatin", "pathologic complete response", "neoadjuvant chemotherapy", "residual cancer burden", "sacituzumab govitecan", "HER2-low", and "minimal residual disease".

For studies evaluating therapeutic agents, we prioritized randomized phase 3 clinical trials but also included earlier phase studies showing promise. For biomarker or clinical outcome studies, we prioritized larger datasets and results from pooled analyses. We also include results of smaller studies from proceedings of key cancer meetings that in our opinion are likely to affect the field over the next decade.

Epidemiology

It was estimated that 287 850 new cases of invasive breast cancer would be diagnosed in the United States in 2022.[8] Of these, TNBC accounted for approximately 15%.[7] Whereas the incidence of breast cancer has increased over the recent years in the US, the incidence of TNBC has declined.[8] TNBC disproportionally affects younger premenopausal women and racial and ethnic minority groups including Black, Latina, and Indian women.[4 8-12] In the operable setting, 30-40% of women with TNBC experience recurrence by five years,[13] and recurrence is even more common (approximately 50%) among patients who do not achieve a pathologic complete response (pCR) after neoadjuvant systemic therapy (NAST).[14] In the metastatic setting, the median overall survival remains shorter than two years, despite the most recent advances in systemic therapy.[5 6]

A shift in focus from "triple negative" to "biomarker positive" TNBC

TNBC can be considered an umbrella term covering diverse and heterogeneous subtypes of breast cancer lacking the biomarkers that either can be effectively targeted in the clinic (estrogen receptor and HER2 amplification) or are prognostic (progesterone receptor). Clinicians have historically managed all patients with TNBC similarly (with cytotoxic chemotherapy), but emerging biomarkers identify subsets of patients who benefit from specific targeted therapies. Furthermore, genomic, transcriptomic, and proteomic analyses of intrinsic features of both tumor cells and non-cancer cells within the tumor microenvironment have led to several classification schemes of TNBC subtypes with very different biological drivers.[15-20] These have allowed a shift from an era in which empiric sequential cytotoxic chemotherapy was the only option for metastatic disease to a modern era in which therapies are selected on the basis of tumor specific biomarkers. In addition, novel targeted agents that have found success in the metastatic setting are quickly moving into the early stage TNBC space as part of neoadjuvant or adjuvant therapy schemes,[21 22] several of which have recently become part of the standard of care.

Intersection between the immune system and TNBC

Immunotherapy has transformed the treatment landscape and prognosis of aggressive malignancies that previously had limited options for systemic therapy. In breast cancer, patients with TNBC have derived the largest benefits from immunotherapy, in keeping with its higher levels of immunogenicity compared with other breast cancer subtypes.[21 23-26] Within TNBC, tumors considered "immune enriched" or "hot"—characterized by high concentrations of tumor infiltrating lymphocytes (TILs)—have better outcomes than "immunologically cold" tumors. Patients with "TIL rich" TNBC have been found to have better survival after adjuvant chemotherapy,[27] higher rates of pCR following NAST,[28] and better survival even in the absence of systemic therapy.[29-32] As such, TILs and other features of immune activation are promising biomarkers for optimization of systemic therapy for TNBC. Beyond simple TIL enumeration, the advent of novel multiplexed platforms is allowing deep and complex analyses of the composition of immune infiltrates and their interactions with the tumor cells.[33-38] In the clinic, expression of programmed death ligand 1 (PD-L1) in the tumor microenvironment identifies patients who benefit from immunotherapy in the metastatic setting (not in the operable setting). However, challenges with this biomarker remain, as multiple assays, methods, and cut-off points to determine "positivity" versus "negativity" exist.[39]

Modern management of operable TNBC

Advances in multidisciplinary care, including surgery, radiation therapy, and systemic therapy have led to improvements in recurrence rates and survival in breast cancer.[40 41] Over the past decade, the management paradigm of TNBC has shifted away from upfront surgery followed by adjuvant systemic therapy to a preference for administering systemic therapy preoperatively, particularly for patients with stage II-III TNBC. The shift to a neoadjuvant strategy has allowed for in vivo evaluation of the sensitivity

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of tumors, which in turn has facilitated acceleration of drug development, de-escalation of breast and axillary surgery (leading to decreased surgical morbidity),[42 43] more accurate prognostication,[44-48] and the opportunity to individualize decisions on postoperative treatment escalation and de-escalation (fig 1).[22 49] Response to NAST has repeatedly been shown to correlate strongly with long term outcomes.[44-48] Patients who achieve pCR enjoy very favorable long term survival, with recurrence and mortality rates of <10%. On the other hand, patients with residual disease after NAST experience higher rates of disease recurrence and death, with the risk increasing as the amount of residual disease increases, as shown with the use of tools such as the residual cancer burden (RCB) index.[48]

Several randomized clinical trials have shown that the risk of recurrence and death among patients with residual disease after NAST can be significantly decreased with additional postoperative systemic therapy.[22 49 50] Given this, patients with residual TNBC are candidates for escalation of postoperative therapy, whereas those who achieve pCR can be spared the toxicities of additional treatments that might not benefit them. With this approach, treatment intensification is more selective and focused on patients at the highest risk for recurrence. However, as many as half of patients with residual disease following NAST never experience recurrence, even in the absence of additional systemic therapy.[14] This highlights the need for better tools to refine estimation of the risk of recurrence among patients with residual disease. Promising biomarkers that may accomplish this include assessment of minimal residual disease (MRD) using cfDNA and assessment of TILs in the residual tumor,[51-53] both of which might complement the RCB index.

Increasing pCR rates as an intermediate goal

For many years, the systemic therapy backbone for operable TNBC has been sequential anthracycline plus cyclophosphamide followed or preceded by a taxane (AC-T). Over the past decade, several treatment optimization strategies have focused on improving pCR rates (as an intermediate surrogate endpoint of improved long term survival outcomes) by incorporating additional chemotherapy or targeted agents into the AC-T backbone. To this end, several studies evaluated the addition of platinums, motivated by preclinical and clinical studies showing that TNBC is especially sensitive to agents that damage DNA.[54 55] Three major studies, GeparSixto,[56] CALGB 40603,[57] and BrighTNess,[58] consistently showed that the addition of carboplatin improved pCR rates, at the expense of higher rates of hematologic toxicities and premature discontinuation of the taxane in the first two studies (table 1). Notably, long term outcomes were improved with the addition of carboplatin in GeparSixto (which used a non-standard chemotherapy backbone lacking cyclophosphamide) but not in CALGB 40603 (which used a standard AC-T backbone). Subsequently, the

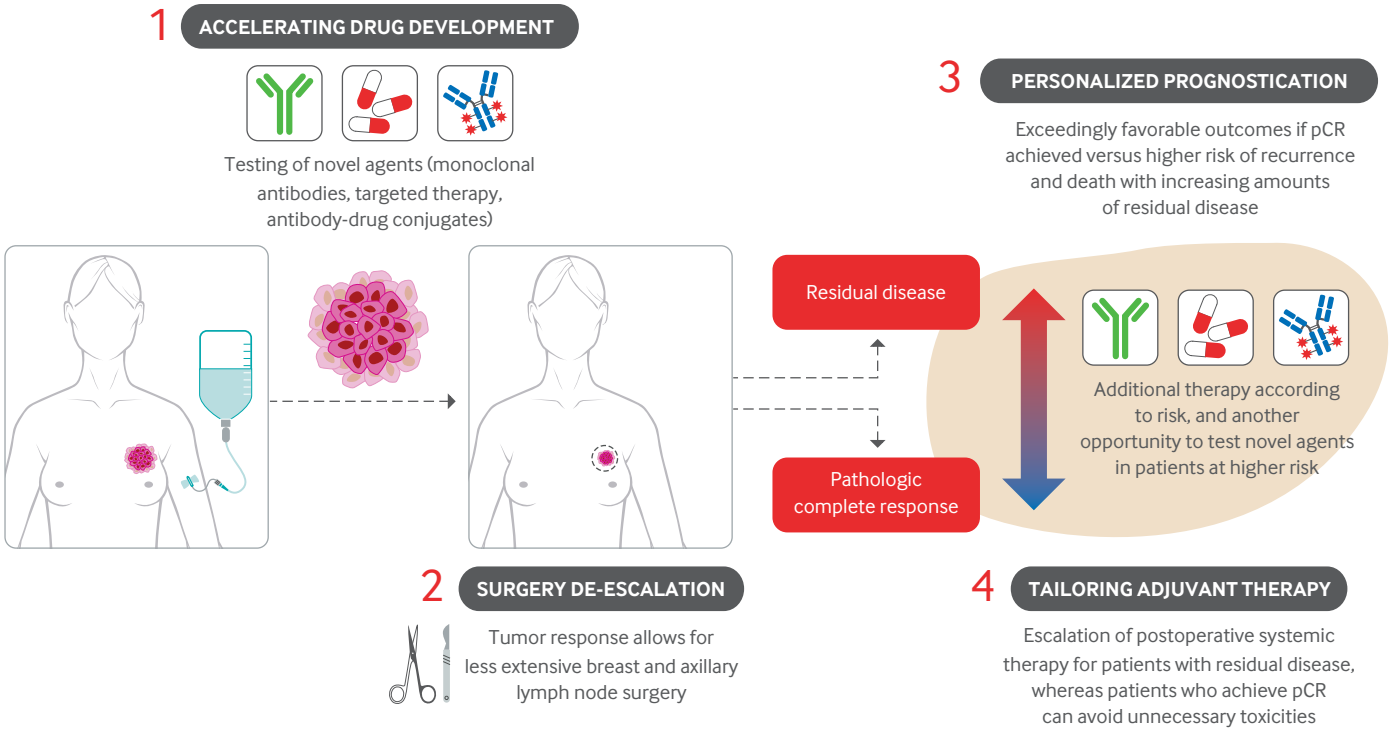

Fig 1 | The neoadjuvant systemic therapy paradigm in breast cancer. The shift to a neoadjuvant systemic therapy paradigm in the management of breast cancer has been leveraged to accelerate drug development and downsize tumor and nodal disease burden allowing for less extensive surgical approaches, personalized recurrence risk prognostication according to residual cancer burden, and tailoring of adjuvant therapy on the basis of response. pCR=pathologic complete response

BrighTNess trial, which incorporated the lessons learnt from both previous studies, broke the tie and showed an improvement in both pCR and event-free survival (EFS) but not overall survival (table 1).[59] Importantly, this study used a standard AC-T backbone and mandated making up for missed taxane doses, improving the rate of taxane delivery compared with the preceding trials. These results motivated clinicians to consider the addition of carboplatin to the AC-T backbone for patients with stage II-III TNBC. However, most of the EFS benefit observed in this study was due to decreased locoregional failures rather than decreased distant metastases.

Building on these improvements in pCR rates, the KEYNOTE-522 trial evaluated the addition of pembrolizumab to a chemotherapy backbone consisting of carboplatin plus paclitaxel followed by an anthracycline and cyclophosphamide.[21 60] A total of 1174 patients with newly diagnosed TNBC with either nodal involvement (N1-N2 were allowed; N3 was not) or tumors measuring at least 2 cm were randomized to receive pembrolizumab plus chemotherapy or placebo plus chemotherapy. After chemotherapy, patients proceeded to surgery and continued pembrolizumab/placebo postoperatively for nine additional cycles (irrespective of response to NAST). The addition of pembrolizumab increased pCR rates (63% (95% confidence interval 59.5% to 66.4%) *v* 56% (50.6% to 60.6%)) and three year EFS by 7% (123 (16%) experiencing an EFS event with pembrolizumab versus 93 (24%) with chemotherapy alone; hazard ratio 0.63 (95% confidence interval 0.48 to 0.82); P<0.001). Unlike the metastatic setting, where the benefit of immunotherapy is limited to patients with PD-L1 positive TNBC,[5] patients in KEYNOTE-522 benefited regardless of PD-L1 status. As such, PD-L1 expression assessment in early stage TNBC offers prognostic value (higher likelihood of achieving pCR regardless of treatment) but cannot be used to selected patients more likely to benefit from immunotherapy. Importantly, whereas patients who achieved pCR had equally favorable outcomes regardless of whether they received pembrolizumab, those with residual disease who received pembrolizumab had improved EFS compared with those who received chemotherapy alone. Whether this benefit can be attributed to the neoadjuvant pembrolizumab portion, to the adjuvant pembrolizumab portion, or to both, remains unknown.

The adoption of neoadjuvant immunotherapy has generated several questions that have no clear evidence based answers but are still encountered by clinicians in daily practice. In the following sections, we review common scenarios and offer our personal perspectives on how to approach them, with the goal of providing practical guidance in the face of absence of evidence. Figure 2 summarizes potential approaches for operable TNBC.

Management of patients who do not achieve pCR after neoadjuvant chemoimmunotherapy

Before KEYNOTE-522, the standard of care for patients with TNBC and residual disease following NAST consisted of additional postoperative systemic therapy. Eight cycles of adjuvant capecitabine led to significant improvements in disease-free survival (DFS; hazard ratio 0.58, 0.39 to 0.87) and overall survival (0.50, 0.30 to 0.90) compared with placebo in the subset of 286 patients with TNBC in the CREATE-X trial.[49] In the subsequent EA1131 trial, adjuvant carboplatin did not improve invasive DFS (hazard ratio 1.06, 0.62 to 1.81) or overall survival (1.13, 0.71 to 1.79) compared with capecitabine among 308 patients with basal TNBC (as defined by the PAM50 50 gene signature),[61] supporting the continued use of capecitabine in this context. Subsequently, one year of adjuvant olaparib improved invasive DFS (hazard ratio 0.58, 99.5% confidence interval 0.41 to 0.82; P<0.001) and overall survival (0.68, 95% confidence interval 0.47 to 0.97; P=0.009) compared with placebo in 1836 patients with germline BRCA (gBRCA) associated breast cancer (including TNBC with residual disease) in the OlympiA trial.[22] However, KEYNOTE-522 started recruitment before the CREATE-X or OlympiA trial results were available. As such, patients with residual disease in KEYNOTE-522 did not receive either capecitabine or olaparib in the adjuvant setting. Rather, patients continued pembrolizumab alone after surgery for an additional nine cycles, regardless of the response observed at the time of surgery.[21] Although EFS improved among patients with residual disease who received pembrolizumab, whether these additional doses of pembrolizumab postoperatively contributed to the observed improvement remains unknown. Furthermore, participants in CREATE-X and OlympiA who had residual disease following NAST had not received pembrolizumab or platinums (only a quarter of patients received platinums in OlympiA and none in CREATE-X). These factors raise

Table 1 | Major studies of addition of carboplatin to anthracycline-taxane based neoadjuvant chemotherapy in triple negative breast cancer (TNBC)

Study	Intervention versus comparison	Pathologic complete response with or without platinum	P value	Survival with or without platinum	Hazard ratio (95%CI: P value)
GeparSixto[56] (n=315 with TNBC)	T+Cb+A+Bev *v* T+A+Bev	53% *v* 43%	0.015	86% *v* 76% (3 year EFS)	0.56 (0.34 to 0.93; P=0.022
CALGB 40603[57] (n=443)	T+Cb ⟶ AC *v* T+Cb+Bev ⟶ AC+Bev *v* T+Bev ⟶ AC+Bev *v* T ⟶ AC	54% *v* 41%	0.003	70% *v* 70% (5 year EFS)	0.94 (0.67 to 1.32; P=0.72)
BrighTNess[58] (n=634)	T+Cb+V ⟶ AC *v* T+Cb ⟶ AC *v* T ⟶ AC	58% *v* 31% (T+Cb ⟶ AC *v* T ⟶ AC)	<0.001	79% *v* 69% (4 year EFS)	0.57 (0.36 to 0.91; P=0.02)

A=anthracycline; Bev= bevacizumab; C=cyclophosphamide; Cb=carboplatin; CI=confidence interval; EFS=event-free survival; T=taxane; V=veliparib.

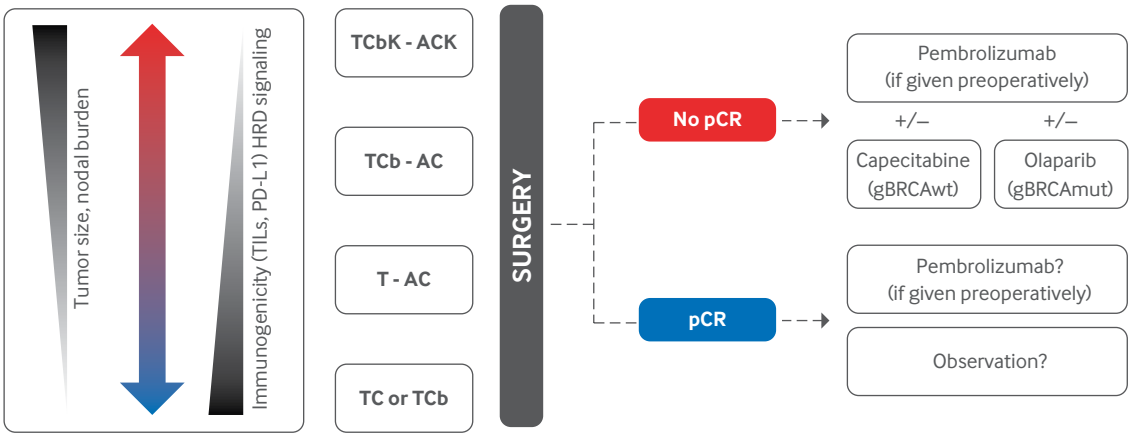

Fig 2 | For patients with operable triple negative breast cancer, several approaches to neoadjuvant systemic therapy can be considered. Selecting the appropriate intensity of treatment for the appropriate patients remains an area of controversy and of active research. Options range from two drug, anthracycline-free regimens to the five drug chemoimmunotherapy regimen established by KEYNOTE-522. Following neoadjuvant therapy, patients with residual disease are offered additional therapy. The need for additional therapy in patients who achieve pathologic complete response (pCR) after chemoimmunotherapy remains controversial. Likewise, the addition of capecitabine or olaparib to pembrolizumab for patients with residual disease has not been prospectively studied. Beyond tumor size and nodal burden, immune biomarkers may have a future role in aiding systemic therapy intensity decisions. A=doxorubicin; C=cyclophosphamide; Cb=carboplatin; gBRCA=germline BRCA; HRD=homologous recombination deficiency; K=pembrolizumab; mut=mutant; PD-L1=programmed cell death ligand 1; T=taxane; TIL=tumor infiltrating lymphocytes; wt=wild type

the concern that residual tumors following both neoadjuvant platinums and immunotherapy may be more resistant than those treated in CREATE-X and OlympiA, possibly leading to a lower degree of benefit from additional capecitabine or olaparib.

Even in the KEYNOTE-522 era, outcomes remain poor for patients with TNBC and residual disease, particularly for those with RCB3, of whom nearly two thirds had recurrence or died within three years.[62] This highlights the need for more effective strategies than simply continuing pembrolizumab as done in the trial. Despite the lack of data supporting or opposing the addition of capecitabine or olaparib to pembrolizumab in this context, the clinician must make a recommendation based on the best available evidence. Until data are available, we discuss the uncertainties with patients in this situation and advocate for adding capecitabine (in the absence of gBRCA mutation) or olaparib (for gBRCA associated breast cancer) to the adjuvant portion of pembrolizumab (fig 2). Several studies have previously shown the safety of these combinations,[63 64] diminishing concerns about potentially causing harm in the absence of efficacy data.

For gBRCA associated breast cancer with residual TNBC following NAST, both capecitabine and olaparib are options supported by phase 3 clinical trials. However, we favor the use of olaparib over capecitabine in this scenario. Although no head-to-head comparisons of olaparib versus capecitabine in this context have been done, several pieces of data inform this recommendation. Firstly, poly(ADP-ribose) polymerase (PARP) inhibitors were superior to physician's choice of chemotherapy (including capecitabine) in the metastatic setting.[65 66] Secondly, the efficacy of capecitabine specifically for gBRCA associated breast cancer with residual disease after NAST in CREATE-X remains unknown. However, data from GEICAM/2003-11_CIBOMA/2004-01[67] and EA1131 suggest that adjuvant capecitabine may benefit mostly TNBC with a non-basal molecular phenotype, whereas it may be less effective in patients with basal tumors (which can be enriched with both germline and somatic BRCA mutations).[61] Similarly, patients with non-BRCA1-like TNBC seemed to derive greater benefit from capecitabine in the FinXX trial.[68] Lastly, from a mechanism of action perspective, PARP inhibitors would have an advantage over capecitabine in the context of gBRCA mutations. Whereas PARP inhibitor exploit the homologous recombination defect characterizing gBRCA associated breast cancer tumors, capecitabine induces errors in DNA base pairs that are repaired through the mismatch repair pathway, a mechanism generally intact in carriers of the gBRCA mutation.

Management of patients who achieve pCR after neoadjuvant chemoimmunotherapy

Patients with TNBC who achieve a pCR after NAST have excellent outcomes (with five year EFS consistently >90%), regardless of the treatment that led to a pCR.[44-47] The KEYNOTE-522 trial solidified this observation, with all patients who achieved pCR having a favorable prognosis, regardless of whether they had received pembrolizumab. However, as discussed previously, the design of KEYNOTE-522 was such that patients randomized to receive neoadjuvant pembrolizumab continued it postoperatively regardless of the response achieved. Given this, questions have emerged about whether continuing pembrolizumab postoperatively offers any additional value to patients who achieve pCR, committing them to an additional seven months of intravenous treatment. Although generally well tolerated, continuing intravenous therapy can be life disrupting and add financial burden, in terms of both

the cost of treatment and time away from work and family.

Although the actual benefit of additional pembrolizumab among patients who achieved pCR cannot be determined from KEYNOTE-522, insights can be gained from other studies of neoadjuvant immunotherapy. In GeparNuevo,[61] which evaluated durvalumab (only before surgery) plus chemotherapy, the three year invasive DFS and the degree of benefit over chemotherapy alone were comparable to what was observed in KEYNOTE-522, despite no additional immunotherapy postoperatively (three year invasive DFS of 85.6% in GeparNUEVO compared with a three year EFS of 84.5% in KEYNOTE-522). These data contribute to the equipoise in the field regarding the need for additional therapy in the setting of pCR, given that many trials have shown that pCR correlates with favorable outcomes without additional systemic therapy.

Until more information is available, we favor following the treatment paradigm of KEYNOTE-522 and recommend continuing pembrolizumab postoperatively for most patients with pCR. However, we discuss with patients that the benefit of the adjuvant portion is uncertain. If returning for nine additional cycles of intravenous treatment represents a significant burden, we discuss the alternatives of administering pembrolizumab every six weeks rather than every three weeks or omitting adjuvant pembrolizumab. The value of adjuvant pembrolizumab in this setting will be evaluated in the upcoming OptimICE-pCR clinical trial (NCT05812807), which will randomize patients with TNBC who achieve pCR after preoperative chemoimmunotherapy to either continue pembrolizumab postoperatively or proceed with observation alone.

When using pembrolizumab neoadjuvantly, should anthracycline plus cyclophosphamide be given every three weeks or dose dense?

After completion of carboplatin plus paclitaxel plus pembrolizumab, patients in KEYNOTE-522 received anthracycline plus cyclophosphamide every three weeks, to align the treatment schedules with that of pembrolizumab. However, before this study, the preference was to administer anthracycline plus cyclophosphamide every two weeks ("dose dense") with growth factor support. A large meta-analysis of nearly 40 000 women participating showed that a dose dense schedule was associated with lower 10 year recurrence rates (28% *v* 31%), breast cancer mortality (19% *v* 21%), and all cause mortality (22% *v* 25%, all P<0.001), both in estrogen receptor positive and estrogen receptor negative breast cancer.[69] However, in this meta-analysis, patients had not received pembrolizumab or platinums, and as such the relative benefit of dose density versus every three week dosing in this context remains unknown. In practice, we adhere to the schedule studied in KEYNOTE-522 but admit that this is a gap in knowledge in the field. If a dose dense anthracycline plus cyclophosphamide schedule is chosen, switching the administration of pembrolizumab to every six weeks, to better align the infusion times and prevent unnecessary extra visits, is reasonable.

Might some patients with TNBC do well with less intensive therapies than with the five drug regimen?

Given the worse prognosis of patients with TNBC compared with other breast cancer subtypes, most efforts to optimize systemic therapy have focused on treatment escalation. Although the incorporation of immunotherapy has undoubtedly improved outcomes, more than half of patients in the control arm of KEYNOTE-522 achieved a pCR with chemotherapy alone.[21] Furthermore, the addition of immunotherapy is associated with toxicities that can be long lasting and, in some cases, life altering. The most common of these noted in KEYNOTE-522 were endocrinopathies, including hypothyroidism or hyperthyroidism (in 14% and 5% of patients randomized to pembrolizumab, respectively), followed by adrenal insufficiency (2%). Other less common, but serious, immune related toxicities observed in trials of immunotherapy across malignancies include pneumonitis, colitis, dermatitis, hepatitis, and myocarditis.[70] How to identify patients with more sensitive tumors (and potential candidates for treatment de-escalation) before choosing a neoadjuvant regimen is a critical gap in our knowledge. Notably, although PD-L1 expression was not predictive of benefit from pembrolizumab, the likelihood of achieving pCR increased with higher levels of PD-L1 expression—even with chemotherapy alone. This suggests that PD-L1 positive tumors are more sensitive not only to immunotherapy but also to chemotherapy and begs the question of whether PD-L1 or other biomarkers of immune activation (for example, TILs) could aid in the identification of patients who may do very well with less intensive systemic therapy. Although counterintuitive, given that these "immunogenic tumors" respond better to chemotherapy than do PD-L1 negative tumors, could these patients be precisely the subset who may be spared the potential long term toxicities of immunotherapy?

In HER2 positive breast cancer, the development of HER2 targeted therapies has allowed clinicians to go from defaulting to five drug regimens containing anthracycline (AC-THP) to rarely using anthracyclines and routinely using single agent taxane plus trastuzumab for stage I disease.[71-73] We anticipate a similar path for TNBC, whereby patients with earlier stages and more favorable biology could be candidates for treatment de-escalation, avoiding the toxicities of multiagent chemotherapy without compromising outcomes.

One of the first datasets to show the potential safety of treatment de-escalation in TNBC was the joint analysis of the ABC clinical trials, evaluating the efficacy of regimens containing anthracycline versus anthracycline-free regimens.[74] Among

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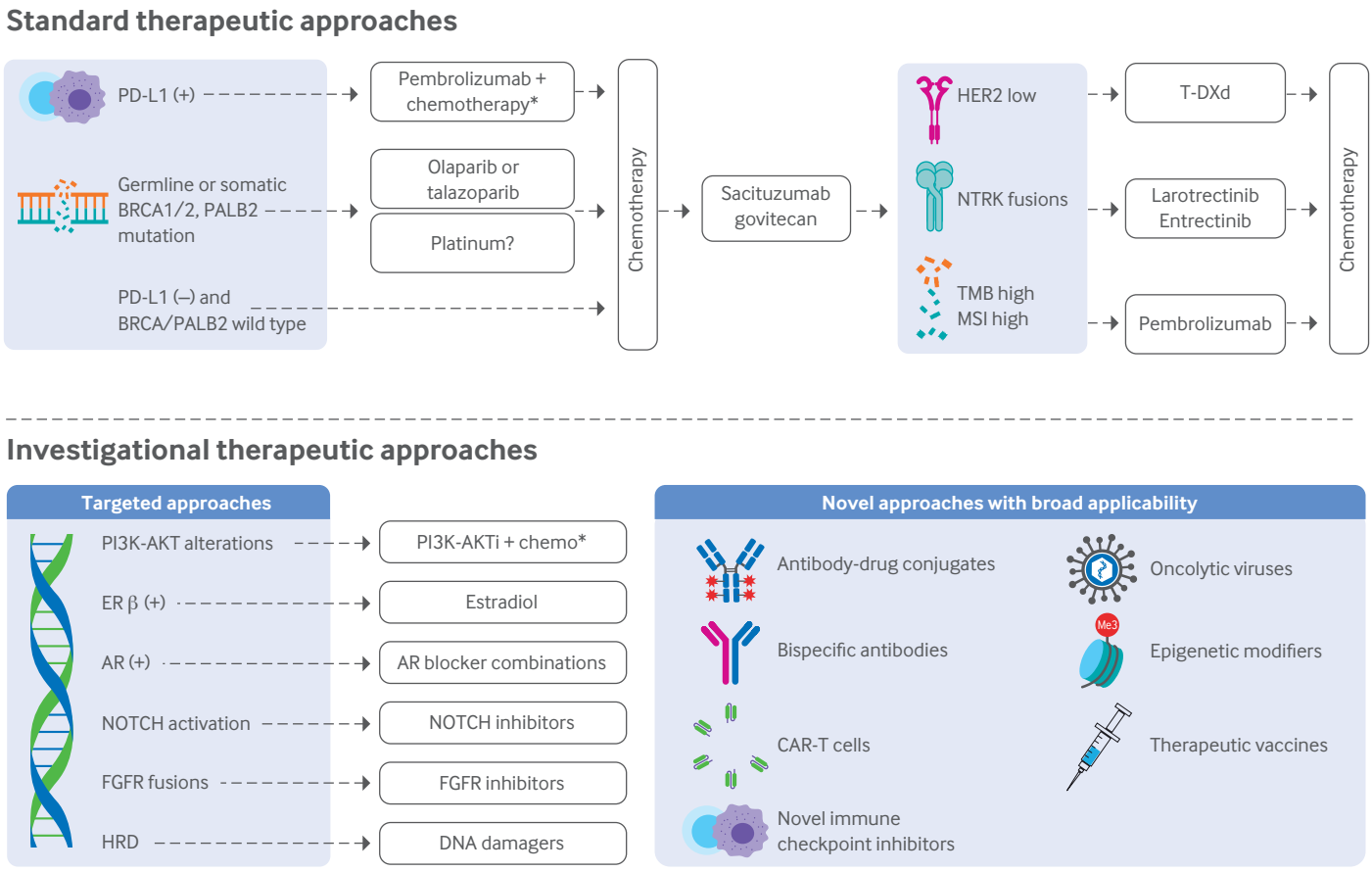

Fig 3 | For patients with metastatic triple negative breast cancer (TNBC), testing for programmed cell death ligand 1 (PD-L1), BRCA, and PALB2 mutation status inform eligibility for immunotherapy and poly(ADP-ribose) polymerase (PARP) inhibitors, respectively. Of note, PARP inhibitors have received regulatory approval only for patients with germline BRCA mutations; however, clinical trial evidence has shown benefit in patients with somatic BRCA mutations and patients with PALB2 mutations. The antibody-drug conjugates sacituzumab govitecan and trastuzumab deruxtecan (for HER2 low tumors) are options for later lines therapy. Small subsets of patients may benefit from other targeted therapies. Otherwise, cytotoxic chemotherapy remains the standard. A wide range of targeted therapies, immune directed approaches, and antibody-drug conjugates are under active investigation. AR=androgen receptor; CAR=chimeric antigen receptor; ER=estrogen receptor; FGFR=fibroblast growth factor receptor; HER2=human epidermal growth factor receptor 2; HRD=homologous recombination deficiency; MSI=microsatellite instability; NTRK=neurotrophic tyrosine receptor kinase; PI3K-AKT=phosphoinositide-3 kinase/Ak strain transforming; TMB=tumor mutation burden. *Taxane or gemcitabine/carboplatin

patients with node negative TNBC, anthracyclines were associated with an absolute improvement in invasive DFS of only 2.5%. This benefit may be offset by the increased risk of cardiotoxicity and secondary leukemias with anthracyclines. In the phase 3 PATTERN trial,[75] adjuvant carboplatin plus paclitaxel showed superior five year DFS (hazard ratio 0.65, 95% confidence interval 0.44 to 0.96; P=0.03) and no differences in five year overall survival (0.71, 0.42 to 1.22; P=0.22) compared with an anthracycline and taxane based regimen. Notably, 74% of the 647 participants had node negative tumors, and slightly more than half had pT1 tumors, suggesting that this may be a reasonable regimen for patients with stage I TNBC. In the neoadjuvant setting, anthracycline-free regimens based on carboplatin and taxanes with and without immunotherapy have achieved pCR rates exceeding 55% in higher risk populations, including a significant number of patients with node positive TNBC.[76 77] On the basis of these data, an upcoming randomized trial (SWOG 2212) will evaluate whether an anthracycline-free chemoimmunotherapy regimen (carboplatin plus taxane plus pembrolizumab) is non-inferior to the KEYNOTE-522 five drug regimen. Importantly, these studies included unselected patients with TNBC. In future studies, patient selection based on biomarkers predictive of more favorable biology (or higher sensitivity to chemotherapy) may allow for the safe evaluation of de-escalation strategies. We review these opportunities later, in the section entitled "Right-sizing systemic therapy."

Considerations for management of operable TNBC in settings with limited access to targeted therapeutics

Although several of the advances reviewed here have led to improvements in pCR rates and EFS, access to immunotherapy and targeted therapeutics is not equitable worldwide. In settings where

immunotherapy is not available, we recommend the standard approach of neoadjuvant anthracycline (delivered dose dense) and taxane based chemotherapy, with consideration for the addition of carboplatin for patients with more advanced stages (particularly for stage III TNBC), following the approach used in the BrighTNess trial.[58] For patients who achieve pCR, no further systemic therapy is recommended. For patients with residual disease, we recommend adjuvant capecitabine. If gBRCA status is known and a mutation is identified, we would still use capecitabine if PARP inhibitors are not available, as which approach might be superior in this population remains unclear. Importantly, whether PARP inhibitors are superior to platinums in the context of gBRCA associated TNBC also remains unknown, and arguments could be made that platinums may be an adequate substitute for PARP inhibitors in settings without access to these agents. However, given the convenience of oral therapies, and in light of the results of the EA1131 trial in which adjuvant carboplatin did not improve clinical outcomes compared with capecitabine among patients with residual TNBC,[61] we would favor the use of capecitabine over platinums in this context.

Modern management of metastatic TNBC

Progress in systemic therapy is allowing clinicians to move from an empiric "pick a chemotherapy drug from a list" approach to a biomarker driven method of drug selection. We anticipate that over the next decade, TNBC will continue to be reclassified into several disease subtypes with distinct profiles that will allow drug development and clinical management to be compartmentalized in a manner that maximizes the likelihood of benefit and limits unnecessary exposure to toxicities. Several novel agents including immunotherapy, targeted therapy, and antibody-drug conjugates have transformed the treatment landscape of metastatic TNBC. That several of these treatments benefit only subsets of patients with TNBC harboring specific biomarkers has also become clear. Figure 3 summarizes current standard approaches for metastatic TNBC and selected emerging therapies under investigation.

PARP inhibitors

Besides immunotherapy, one of the most impactful advances in targeted therapy for metastatic TNBC (and estrogen receptor positive/HER2 negative TNBC) has been the development of PARP inhibitors for patients harboring gBRCA1/2 mutations, which have improved progression-free survival (PFS) and doubled overall response rates compared with standard chemotherapy.[65 66] Although overall survival was not improved in the overall trial populations, a pre-specified subset analysis of the OlympiAD trial suggested that patients treated with olaparib in the first line setting derived an overall survival benefit.[78] These drugs offer a subset of TNBC patients a non-chemotherapy oral treatment option. Smaller studies have shown that carriers of other germline (for example germline PALB2), or somatic mutations in homologous recombination genes may also benefit from these agents.[79 80] However, we note that neither the OlympiAD nor the EMBRACA trial allowed the use of platinums in the standard chemotherapy arms.[65 66] As such, uncertainties remain about how the efficacy of these two classes of agents compare in patients with gBRCA associated breast cancer. Given this, in contexts where PARP inhibitors are not available, we favor early use of platinums for patients with known gBRCA associated metastatic TNBC.[81]

Antibody-drug conjugates

The treatment landscape of metastatic breast cancer is being further redefined by the development of antibody-drug conjugates (ADC).[77 82 83] These drugs link a monoclonal antibody directed against a specific tumor antigen with a cytotoxic payload, allowing more efficient delivery of the cytotoxic drug to the tumor microenvironment. Sacituzumab govitecan, an ADC targeting Trop-2, became the first ADC to show a significant improvement in the overall survival of patients with metastatic TNBC compared with standard chemotherapy.[77] Subsequently, trastuzumab deruxtecan, an ADC targeting HER2, led to a paradigm shift in our thinking of HER2 as a biomarker. Previous HER2 targeted therapy approaches showed antitumor activity only in tumors with HER2 overexpression or amplification,[84] in which HER2 activation triggers downstream signaling pathways that promote tumor growth. By contrast, trastuzumab deruxtecan shows robust antitumor activity not only among breast cancers with traditional HER2 overexpression but also in tumors with lower level of HER2 expression.[77 83] These tumors—previously called HER2 negative, now renamed "HER2 low"—do not rely on HER2 signaling for their growth and do not seem to be a distinct biological entity, but they respond to trastuzumab deruxtecan. The impact of this is significant, considering that up to 50% of tumors previously considered HER2 negative fall under this new category of HER2 low tumors, including many in patients with TNBC.[85] In these tumors, the HER2 protein on the cell surface simply serves as a "docking station" for trastuzumab deruxtecan, allowing entry of the complex into any cells expressing HER2 (even at low levels). Importantly, newer generation ADCs such as trastuzumab deruxtecan are loaded with a membrane permeable cytotoxic payload through a cleavable linker. Both features allow for the payload to be released from the antibody intracellularly and freely diffuse through the cell membranes of neighboring cells that may not express HER2. This so called "bystander effect" is thought to account for the robust activity of these compounds in various settings in which the target antigen may not be homogeneously expressed.

Opportunities in operable TNBC

Right-sizing of systemic therapy

Right-sizing of systemic therapy will be an area of focus for operable TNBC over the next decade. Treatment

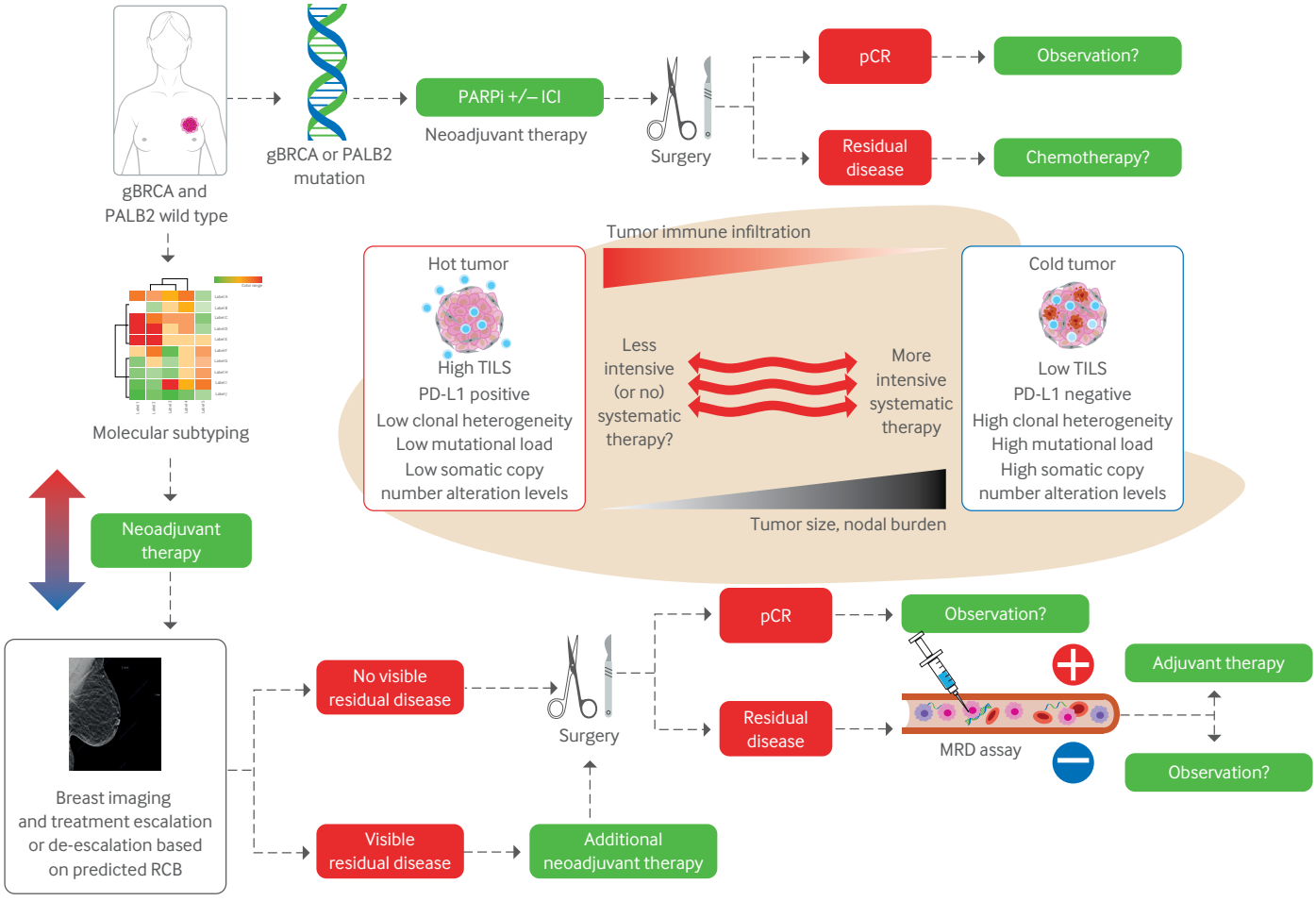

Fig 4 | Potential opportunities to "right-size" systemic therapy in operable triple negative breast cancer (TNBC). In the future, patients with germline BRCA (gBRCA) or PALB2 mutations may be candidates for a neoadjuvant poly(ADP-ribose) polymerase inhibitor (PARPi) rather than cytotoxic chemotherapy. For patients without these alterations, features such as tumor infiltrating lymphocytes (TILs) and other features of immune activation may help in selecting intensity of systemic therapy. Furthermore, after an initial course of neoadjuvant systemic therapy, assessment of response with modern imaging may allow further escalation or de-escalation of systemic therapy before surgery, while evaluation of in vivo response is still possible. For patients who are found to have residual disease at the time of surgery, further refinement of risk stratification with cfDNA technologies may allow selective identification of patients who truly benefit from additional postoperative therapy. ICI=immune checkpoint inhibitor; MRD=minimal residual disease; pCR=pathologic complete response; PD-L1=programmed cell death ligand 1; RCB=residual cancer burden

intensification strategies have undoubtedly improved the outcomes of patients at higher risk of recurrence. Our ability to tailor therapy according to response to NAST has allowed more judicious use of additional adjuvant therapy, reserving it for patients at the highest risk. However, our focus on achieving pCR, while laudable, has shifted the pendulum to near universal intensification of NAST, with most patients with TNBC receiving a five drug regimen (except those with stage I TNBC). Although overall outcomes have improved, we risk overtreatment becoming a real problem, whereby we end up exposing large numbers of patients to toxicities—often long lasting and life altering—to benefit a few patients. To overcome this, research aiming to identify patients with more indolent biology, or with enhanced treatment sensitivity, who may be candidates for less intensive systemic therapy approaches (and, dare we say, no systemic therapy at all), will be critical. We envision a future in which upfront biomarker driven selection of treatment intensity leads to patients with TNBC harboring specific features being matched to less or more intensive treatments before the first dose of drug is administered (fig 4).

One of the most promising treatment de-escalation approaches in operable TNBC includes the use of neoadjuvant PARP inhibitors in patients with gBRCA associated HER2 negative breast cancer. In these patients, PARP inhibitors improved in PFS compared with chemotherapy in the metastatic setting and improved invasive DFS and overall survival in the operable setting.[22 65 66] Several studies have evaluated whether single agent neoadjuvant PARP inhibitor could replace neoadjuvant chemotherapy among patients with gBRCA associated breast cancer. In a small pilot study (n=20) and the subsequent larger (n=61) NEOTALA phase 2 trial,[86 87] approximately half of the patients receiving neoadjuvant single agent talazoparib for six months achieved pCR. These rates are comparable to what

is often achieved with neoadjuvant cytotoxic chemotherapy in all comers with TNBC. Similar results have been seen with single agent niraparib,[88] and an ongoing trial (TBCRC 056; NCT04584255) is evaluating the combination of niraparib and dostarlimab as neoadjuvant treatment for patients with gBRCA or PALB2 mutations. Although this strategy is promising, 16% of patients in NEOTALA experienced disease progression during treatment with single agent PARP inhibitor. As such, this strategy is not ready for routine clinical use. In the context of clinical trials, close monitoring for potential disease progression is needed.

Another emerging group of patients who may be candidates for less intensive systemic therapy approaches includes those with "TIL-rich" TNBC tumors. TILs are highly prognostic among patients with operable TNBC who receive (neo)adjuvant chemotherapy. In a pooled analysis from nine studies (n=2148) including patients with operable TNBC receiving anthracycline based adjuvant chemotherapy, every 10% increase in TILs was associated with a 17% decrease in the risk of distant disease recurrence and mortality.[27] Remarkably, among patients with node negative TNBC with stromal TILs ≥30%, only 3% developed distant recurrence and only 1% had died by three years. In the neoadjuvant setting, in a pooled analysis of six randomized clinical trials (n=3700),[28] higher pre-chemotherapy stromal TILs were significantly associated with increased pCR rates in all breast cancer subtypes. Higher stromal TILs were also associated with improved DFS and overall survival in TNBC. In addition, several studies suggest that quantification of TIL can be leveraged to identify a subset of patients with early stage TNBC who have excellent outcomes even without systemic therapy.[89-91] In a large international pooled analysis including nearly 2000 patients with resected TNBC,[32] patients with stage I TNBC and TILs ≥50% had five year overall survival and distant DFS exceeding 90%. These data suggest that this population of patients may be candidates for de-escalation of chemotherapy, with a low risk of compromising their outcomes. Clinical trials prospectively evaluating de-escalation strategies for systemic therapy in this population are critically needed.

Dynamic monitoring of response to NAST

Equally important to selecting intensity of NAST a priori on the basis of biomarkers is the ability to be nimble and react to observed clinical responses before the patient goes to surgery. After all, the promise of NAST is the ability to assess response in vivo and offer clinicians the opportunity to change course if the response is suboptimal. Dynamic imaging monitoring approaches, such as the magnetic resonance imaging based "predicted RCB" approach being evaluated in the ISPY-2 clinical trial,[92] paired with dynamic cfDNA evaluations, may allow NAST to be de-escalated or escalated more efficiently while it is being administered.[93] For those patients who are predicted not to achieve pCR, early identification (before surgery) may allow the incorporation of novel therapeutic approaches to the neoadjuvant strategy while in vivo response can still be assessed.

Refinement of risk stratification beyond residual cancer burden

Although patients with residual disease are at higher risk of recurrence, many never experience it. As such, refinement of risk stratification strategies beyond what can be currently achieved with the RCB index is needed. Pairing RCB assessment with other biomarkers (for example, MRD evaluation[94] or residual disease TILs[52 53]) may allow the identification of patients who have achieved cure despite not achieving pCR and thus would not benefit from additional systemic therapy. A refined risk stratification tool would permit a better balance in the evaluation of novel agents (for example, ADCs, novel immunotherapeutics, or targeted therapies) in the postoperative setting, focusing on patients at the highest risk and sparing those unlikely to have a recurrence.

Right-sizing of locoregional therapy

The delivery of systemic therapy neoadjuvantly has allowed de-escalation of the extent of breast and axillary surgery for patients with a favorable response, which is in turn associated with decreased surgical morbidity.[42 43] Importantly, in the approximately 60% of patients with TNBC who achieve pCR after NAST, resection of fibrotic tissue without viable residual malignancy presumably results in no therapeutic benefit. In these cases, breast and axillary surgery serves primarily as a diagnostic procedure to accurately identify that a pCR has indeed occurred. Major efforts have been made to develop methods to identify patients who have achieved pCR preoperatively, using a combination of imaging and biopsies guided by imaging.[95-98] This approach has shown false negative rates of ≤5% when applied to TNBC or HER2 positive breast cancer and using multimodality breast imaging, with adequate tissue sampling (at least six tissue cores obtained, with larger gauge needles) and standardized histopathologic processing. Given the promise of these methods, a small prospective phase 2 trial recently suggested that elimination of breast surgery in highly selected patients is feasible.[99] In 31 patients identified as having a pCR by using vacuum assisted core biopsies, surgery was omitted, and standard whole breast radiotherapy was pursued as the sole locoregional therapy. At a median follow-up of 26.4 months, no ipsilateral breast tumor recurrences had occurred. Although longer follow-up and larger prospective studies are needed before this approach can be recommended clinically, true breast conservation may become a reality for a large subset of patients with TNBC and HER2 positive breast cancer in the future if this strategy is successful.

Opportunities in metastatic TNBC

Overcoming resistance to immunotherapy

Despite the progress made in metastatic TNBC, overall survival for patients who progress after the first two lines of systemic therapy remains unacceptably poor. Several novel agents are under active investigation, and some of the most promising are summarized in figure 4. PD-L1-negative TNBC remains an area of critical need. Approaches to turning "cold" into "hot" tumors to allow them to benefit from immunotherapy remain the next frontier. Newer immunotherapy agents targeting different immune checkpoints and immunotherapy combinations are under active investigation. Similarly, strategies to overcome resistance to immunotherapy (and chemotherapy) remain critical, particularly as immunotherapy is now routinely used for most patients with operable TNBC. Many patients presenting with metastatic TNBC today have already been exposed to immunotherapy with taxanes and platinums in the early stage setting. The number of patients in this situation will only increase. Whether re-challenging with the same drugs in the metastatic setting will continue to provide the same degree of benefit observed in KEYNOTE-355 is unknown. KEYNOTE-522 may render KEYNOTE-355 obsolete, highlighting the urgent need for additional novel therapies for these populations.

The rise of the ADCs

Novel ADCs will likely dominate drug development in TNBC and other solid tumors soon. Not only will these drugs transform the therapeutic landscape but they will continue to force us to rethink assay development. In the case of ADCs that target HER2 for HER2 low tumors, more sensitive HER2 assays are of great interest. Further studies may show that all breast cancers might respond to these drugs, regardless of HER2 expression detected by an assay,[100] similarly to what is observed with sacituzumab govitecan, for which Trop2 expression has not been found to predict benefit. In addition to defining who may benefit, proper sequencing of ADCs remains an unanswered question. With multiple options available, understanding whether these agents have overlapping resistance patterns becomes critical. For example, sacituzumab govitecan and trastuzumab deruxtecan target different antigens (Trop 2 and HER2, respectively), but their payloads are similar (both topoisomerase inhibitors). Whether tumors that develop resistance to one ADC will also be resistant to the other is unclear. Work evaluating mechanisms of resistance to sacituzumab govitecan suggests that resistance may emerge both from mutations conferring resistance to the cytotoxic payload (SN38) and from mutations in the target antigen (Trop 2).[101] Preliminary data from novel ADCs such as datopotomab deruxtecan (which targets Trop 2 and delivers deruxtecan) suggest that this ADC is still active after progression on sacituzumab govitecan or trastuzumab deruxtecan, suggesting that mechanisms of resistance may not be completely overlapping. Further research examining this question is needed.

Emerging treatments

Novel ADCs targeting different tumor antigens and delivering different cytotoxic payloads are in various stages of clinical development. Further along in development are the drugs datopotomab deruxtecan (targeting Trop-2 with deruxtecan as the cytotoxic payload) and trastuzumab duocarmazine (targeting HER2 and delivering the alkylator seco-DUBA). Importantly, treating physicians need to be aware that novel ADCs are associated with unique and, in some cases, serious toxicities. Notable adverse events include neutropenia and gastrointestinal toxicities with sacituzumab govitecan,[6] nausea and interstitial lung disease/pneumonitis with trastuzumab deruxtecan and datopotomab deruxtecan,[77 102] and ocular toxicities with trastuzumab duocarmazine.[103]

Guidelines

Guidelines on the management of breast cancer, including TNBC, have been developed by the National Comprehensive Cancer Network (NCCN), the European Society of Medical Oncology (ESMO), and the American Society of Clinical Oncology (ASCO).[104-106] The UK National Institute for Health and Care Excellence has also issued guidelines for breast cancer, but these were updated last in 2018 (planned update in 2023) and are not included here.

For operable breast cancer, all guidelines recommend systemic therapy for most patients with TNBC with the possible exceptions of T1aN0 (but leaving the possibility of offering systemic therapy for younger patients with high grade histology) and those with rare favorable histologic subtypes (for example, adenoid cystic, secretory carcinoma, and rare low grade forms of metaplastic carcinoma). ASCO guidelines recommend upfront surgery for patients with clinically node negative TNBC and tumors ≤1 cm, whereas ESMO uses a tumor size threshold of 2 cm. For patients with stage II-III TNBC, the KEYNOTE-522 regimen is recommended by both NCCN and a rapid recommendation update issued by ASCO in 2022.[104]

For patients with residual disease after NAST, NCCN guidelines recommend adjuvant capecitabine or olaparib (for gBRCA associated breast cancer). Adjuvant pembrolizumab is recommended if given preoperatively (regardless of response). Adjuvant olaparib is also recommended for patients with gBRCA associated breast cancer ≥pT2 or ≥pN1 if treated with upfront surgery (after completion of adjuvant chemotherapy). NCCN acknowledges the lack of data on combining or sequencing adjuvant pembrolizumab, capecitabine, and/or olaparib in the context of residual disease and states that their combined or sequential use may be considered in patients with a high risk of recurrence. The guidelines acknowledge that the inclusion of platinum agents as NAST remains controversial and as such is not recommended for most patients,

except when given as part of the pembrolizumab regimen. Adjuvant platinums are not recommended. For selected patients with TNBC, NCCN endorses the consideration of anthracycline-free regimens including a platinum and a taxane.

For metastatic PD-L1 positive TNBC, NCCN and ESMO recommend pembrolizumab plus chemotherapy (taxane or gemcitabine/carboplatin) as first line therapy (regardless of gBRCA mutation status). ESMO also recommends atezolizumab plus nab-paclitaxel, which is still approved by the European Medicines Agency. In the US, Genentech voluntarily withdrew the atezolizumab indication for TNBC, following the negative results of Impassion131.[107] For metastatic PD-L1 negative TNBC, chemotherapy is recommended for patients without gBRCA mutation, whereas either a PARP inhibitor (olaparib or talazoparib) or a platinum is recommended for patients with gBRCA associated TNBC. In the second line setting, sacituzumab govitecan is recommended by all guidelines. Trastuzumab deruxtecan is considered for patients with HER2 low breast cancer by ASCO and NCCN but not yet by ESMO guidelines. PARP inhibitors are recommended for patients with gBRCA associated TNBC who did not receive it in the first line setting. ESMO recommends eribulin, capecitabine, or vinorelbine for third line setting and beyond; NCCN and ASCO make no specific chemotherapy recommendations.

Conclusions

TNBC remains the most challenging subtype of breast cancer and continues to have inferior outcomes compared with hormone receptor positive and HER2 amplified breast cancer. However, significant progress in understanding its biology and in drug development have paved the way for the incorporation of targeted therapeutics, immune targeting approaches, and ADCs, all of which have transformed the treatment landscape of this disease. In the operable setting, in vivo assessment of preoperative response to therapy has allowed tailoring of postoperative systemic therapy in a manner that has improved the outcomes of patients with resistant disease while avoiding extra toxicity in those with more sensitive tumors. Nevertheless, challenges and opportunities remain, with the next frontiers being right-sizing preoperative therapy, developing more effective postoperative approaches for patients with residual disease, and further developing the treatment armamentarium to improve the outcomes of patients with metastatic disease.

GLOSSARY OF ABBREVIATIONS

- ADC—antibody-drug conjugate
- ASCO—American Society of Clinical Oncology
- DFS—disease-free survival
- EFS—event-free survival
- ESMO—European Society of Medical Oncology
- gBRCA—germline BRCA
- HER2—human epidermal growth factor receptor 2
- MRD—minimal residual disease
- NAST—neoadjuvant systemic therapy
- NCCN—National Comprehensive Cancer Network
- PARP—poly(ADP-ribose) polymerase
- pCR—pathologic complete response
- PD-L1—programmed death ligand 1
- PFS—progression-free survival
- RCB—residual cancer burden
- TIL—tumor infiltrating lymphocyte
- TNBC—triple negative breast cancer

QUESTIONS FOR FUTURE RESEARCH

- Can we detect and effectively treat subclinical relapse of triple negative breast cancer (TNBC) before clinical symptoms arise?
- Can we limit toxicities of systemic therapy by de-intensifying systemic therapy in selected patients with operable TNBC predicted to have favorable biology?
- Can we develop more effective postoperative therapies for patients with residual disease following neoadjuvant systemic therapy?
- Can breast surgery be safely omitted in patients predicted to achieve pathologic complete response after neoadjuvant systemic therapy?
- What are the key mechanisms of resistance to immunotherapy in TNBC, and how can we leverage them to expand the benefit to more patients?
- What is the right sequence of antibody-drug conjugates in metastatic TNBC? Do the resistance mechanisms overlap?
- How should we optimize assay development for metastatic TNBC in the era of antibody-drug conjugates?

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