Neoadjuvant therapy for stage II-III triple-negative breast cancer: Current evidence, clinical boundaries and emerging strategies (Review)

BINGCHEN LI[1*], XINCHEN TIAN[2*], QING-QING YU[3] and HONGXIA CUI[3]

[1]Department of Clinical Medicine, Jining Medical University, Jining, Shandong 272000, P.R. China;
[2]Clinical Medical Laboratory Center, Jining No. 1 People's Hospital, Jining, Shandong 272000, P.R. China;
[3]Department of Oncology, Jining No. 1 People's Hospital, Jining, Shandong 272000, P.R. China

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Abstract. Neoadjuvant therapy is the standard therapeutic entry point for the majority of stage II-III triple-negative breast cancer (TNBC) cases. However, a number of practical questions remain unresolved in daily care; specifically, it remains unclear how the balance between treatment intensification and toxicity can be maintained, how heterogeneous trial platforms should be interpreted and how biomarkers can be effectively applied without overextending their clinical role. The present review summarizes the currently available evidence on chemotherapy backbones, selective platinum intensification, perioperative immunotherapy, radiotherapy integration, response-adapted strategies, post-neoadjuvant treatment, circulating tumor (ct)DNA-based residual-risk assessment and emerging antibody-drug conjugates. Anthracycline-taxane chemotherapy remains the reference backbone for stage II-III TNBC, whereas platinum is widely regarded as the selective intensifier in chemotherapy-alone platforms. In addition, carboplatin forms part of the evidence-based backbone of a KEYNOTE-522-like chemoimmunotherapy regimen. Among the immunotherapy strategies available, pembrolizumab-based perioperative treatment has the most convincing evidence in terms of pathological complete response, event-free survival and overall survival. Various biomarkers, such as programmed death-ligand 1, stromal tumor-infiltrating lymphocytes, homologous recombination deficiency, residual cancer burden and ctDNA, can improve biological and prognostic resolution. However, to the best of our knowledge few have been validated as stand-alone treatment selectors. Therefore, future management protocols should remain evidence-based, response-aware and explicit regarding the boundary between established practice and investigational escalation.

Correspondence to: Professor Hongxia Cui or Professor Qing-Qing Yu, Department of Oncology, Jining No. 1 People's Hospital, 269 Mencius Avenue, High-tech Zone, Rencheng, Jining, Shandong 272000, P.R. China
E-mail: chxjnyy@sina.com
E-mail: yuqingqing_lucky@163.com

*Contributed equally

Abbreviations: TNBC, triple-negative breast cancer; pCR, pathological complete response; RCB, residual cancer burden; ctDNA, circulating tumor DNA; ADC, antibody-drug conjugate

Key words: TNBC, neoadjuvant therapy, perioperative immunotherapy, pCR, ctDNA, residual disease

Contents

1. Introduction
2. Core clinical challenges of neoadjuvant therapy for stage II-III TNBC
3. Evidence-based neoadjuvant treatment strategies in TNBC
4. Prognostic and predictive biomarkers in neoadjuvant TNBC
5. Post-neoadjuvant treatment guided by response to neoadjuvant therapy
6. Emerging therapeutic strategies in neoadjuvant and post-neoadjuvant TNBC
7. Conclusion and future perspectives

1. Introduction

Triple-negative breast cancer (TNBC) is a type of breast cancer that is defined by the absence of estrogen receptor, progesterone receptor and HER2 expression, accounting for 12-17% of all breast cancer cases (1-3). In the present review, early-stage TNBC refers to non-metastatic stage II-III disease unless otherwise stated; staging terminology follows the American Joint Committee on Cancer (AJCC) 8th edition TNM staging system (4). TNBC remains one of the most clinically aggressive early-stage breast cancer subtypes. Recurrence tends to occur early, and distant failure refers to distant recurrence or metastatic relapse after initial treatment; biological heterogeneity further complicates treatment planning (2,3).

In stage II-III TNBC, neoadjuvant therapy has become a key therapeutic protocol as its application extends beyond tumor downstaging (4-9). By exposing the intact primary tumor and regional disease to systemic treatment before surgery, neoadjuvant therapy provides an *in vivo* assessment of treatment sensitivity, identifies tumors with resistant biology through residual invasive disease, informs post-neoadjuvant risk assessment, and links preoperative and postoperative management within one treatment sequence. These clinical difficulties, namely heterogeneous response, non-uniform chemotherapy and immunotherapy platforms, different endpoints and variable postoperative strategies, explain why the rapid expansion of perioperative TNBC clinical trials has not made clinical decision-making simpler. Studies built on different chemotherapy backbones, immunotherapy schedules, endpoints and risk populations are frequently discussed together, which encourages recurrent errors. In particular, exploratory signals are treated as if they were practice-defining evidence, whereas postoperative strategies are projected backward into the neoadjuvant setting without sufficient validation. For a clinically useful review, the key task is therefore to distinguish what is established from what is context-dependent and what remains investigational.

The present review is organized around the following main decision points in neoadjuvant TNBC therapy: Core clinical challenges, evidence-based treatment strategies, biomarker interpretation, post-neoadjuvant management, circulating tumor (ct)DNA/minimal residual disease (MRD) and emerging drug development. The aim is to distinguish established standards from context-dependent choices and investigational approaches.

Literature search strategy. The present narrative review was informed by targeted searches of PubMed/MEDLINE (https://pubmed.ncbi.nlm.nih.gov/) and ClinicalTrials.gov (https://clinicaltrials.gov/) from database inception until June 15, 2026. Searches were supplemented by contemporary oncology guidelines, including the ASCO neoadjuvant breast cancer guideline, the ASCO pembrolizumab rapid recommendation update, the CSCO Breast Cancer guidelines and the St. Gallen consensus recommendations, as well as pivotal-trial updates, regulatory documents when needed to reconcile data cut-offs and backward reference-list screening (5,9-11). English-language human study publications were prioritized.

Eligible evidence included randomized trials, prospective interventional studies, mature survival updates, clinically annotated prospective translational studies and major guidelines relevant to stage II-III TNBC. In this context, clinically annotated prospective translational studies were defined as prospective biomarker studies linked to clinical variables, treatment exposure and response or survival outcomes. Retrospective studies were used if they addressed clinically important evidence gaps, including treatment delivery, residual-risk assessment or biomarker interpretation. Case reports, non-clinical studies without a direct clinical decision link, duplicate publications and conference abstracts superseded by full peer-reviewed reports were excluded as primary evidence for the present review.

Evidence was prioritized in the following order: i) Practice-defining randomized evidence and mature survival updates, defined as randomized data with clinically meaningful pCR, EFS, DFS or OS endpoints; ii) boundary-defining randomized negative trials, defined as randomized studies that failed to support a proposed escalation, de-escalation or scheduling strategy and therefore helped define the limits of routine practice; iii) guidelines; iv) prospective translational studies; and v) hypothesis-generating observational evidence. Because the present review was narrative rather than systematic, duplicate screening, PRISMA flow reporting, formal risk-of-bias grading and meta-analytic pooling were not performed.

Full search concepts and database search strings are provided in Tables SI and SII.

2. Core clinical challenges of neoadjuvant therapy for stage II-III TNBC

Neoadjuvant therapy has become a key therapeutic strategy for the management of stage II-III TNBC. However, clinical challenges shape routine practice. First, only a limited number of regimens are supported by mature survival-level evidence, meaning EFS, DFS or OS data with sufficient follow-up, and pathological complete response (pCR) gains do not always concur with durable outcome data (6-8,12-14). Second, treatment benefit is biologically heterogeneous, where apparently similar patients may respond differently due to differences in immune infiltration, DNA-repair capacity, tumor burden and residual disease biology (15-19). Finally, regimen intensification is often easier to justify than to deliver safely, with real-world chemo-immunotherapy cohorts showing frequent dose reductions, delays, discontinuation and clinically meaningful immune-related toxicity (20-23). Furthermore, although biomarkers can be used to refine prognosis, far fewer of these can be used as validated stand-alone treatment determinants.

For the majority of patients with stage II-III TNBC, neoadjuvant systemic therapy is the preferred starting point of perioperative management (4-5,9). Selected patients with smaller primary tumors may also enter a neoadjuvant treatment pathway either when breast conservation is a realistic goal or when recurrence risk appears biologically high, as residual disease after neoadjuvant therapy can guide postoperative escalation. Nevertheless, the clinical objective should not be framed simply as 'achieving pCR'. A superior formulation can be proposed threefold: i) To reduce tumor burden and optimize surgery; ii) to identify tumors that are highly sensitive or clearly resistant to the chosen regimen; and iii) to generate interpretable information for post-neoadjuvant escalation or de-escalation. This threshold-based selection is consistent with the American Society of Clinical Oncology (ASCO) neoadjuvant guidelines, which support neoadjuvant systemic therapy for high-risk TNBC when the finding of residual disease would influence postoperative treatment. However, these guidelines do not recommend routine neoadjuvant therapy for cT1a-bN0 disease (5).

Current standard-of-care pathway. In contemporary practice, the baseline clinical treatment method for the majority of fit patients with stage II-III TNBC is neoadjuvant systemic therapy followed by surgery, radiotherapy according to baseline and post-treatment locoregional risk, and response-guided adjuvant therapy (4-11,24,25). For patients eligible for

immune checkpoint inhibition, the most evidence-supported pathway is a KEYNOTE-522-like regimen; namely, pembrolizumab combined with carboplatin-paclitaxel, followed by anthracycline-cyclophosphamide chemotherapy, surgery and completion of adjuvant pembrolizumab (6-9). Patients with residual invasive disease would then require individualized evaluation for evidence-based post-neoadjuvant options, including capecitabine in appropriate residual-disease populations and olaparib for germline BRCA1/2-mutated high-risk HER2-negative disease (24-26). This baseline is essential, because escalation and de-escalation should be judged against an established treatment pathway, not against an undefined chemotherapy reference.

Baseline evaluation must include pathological confirmation, clinical stage according to AJCC TNM criteria, organ function assessment and biomarker sampling, all of which can affect treatment planning (4-5,9-11,27). In TNBC, regional nodal evaluation warrants more attention than it currently receives in routine practice. This is because the additional ultrasound evaluation of regional nodal basins may upstage the disease, alter surgical planning and change the indication or extent of regional nodal irradiation (27-31). This matters because locoregional treatment should be integrated at baseline rather than only reconsidered after surgery.

Response assessment during treatment should be pragmatic and repetitive. Clinical examination combined with breast ultrasound or MRI remains the central approach, and early imaging response has been associated with pathological response in TNBC (32). However, imaging should not be used to justify automatic completion of a preplanned regimen in the face of unequivocal progression. When progression or persistent inoperability is documented, the priority should then shift to multidisciplinary reassessment, restoration of resectability if possible and preservation of local control. The practical value of interim assessment is therefore not merely prognostic. It is to decide whether the current pathway still makes clinical sense. This point has become more relevant in the current immunotherapy era. Certain patients experience notable shrinkage before the full number of cycles have been completed, whereas others develop toxicity that renders nominal treatment completion unrealistic. The key clinical question in this case is therefore not whether the patient remains 'on study', but whether the balance among tumor control, deliverability and postoperative options remains favorable. In practice, treatment escalation, schedule modification or earlier surgery may all be more rational compared with strict adherence to a preplanned timeline when the biology or tolerance profile has been altered.

From a treatment-design perspective, three baseline questions remain especially important: Whether the patient is considered sufficiently high-risk for recurrence, based on stage II-III disease, nodal positivity, larger tumor burden or other adverse clinical features, to justify platinum and/or perioperative immunotherapy; whether germline BRCA1/2 mutations or other molecular features that will influence post-neoadjuvant therapy are present; and whether the anticipated treatment intensity is realistic in light of marrow reserve, comorbidity and expected treatment adherence. The answers to these questions will typically determine outcome as much as any nominal difference between regimens.

3. Evidence-based neoadjuvant treatment strategies in TNBC

The development of neoadjuvant treatment in TNBC has gradually shifted the more traditional chemotherapy-centered treatment to a more perioperative strategy that integrates response evaluation, post-neoadjuvant escalation and residual-risk stratification. In broad terms, the evidence pathway has moved through the following four stages: i) Establishment of anthracycline-taxane chemotherapy as the standard backbone; ii) selective exploration of platinum intensification in high-recurrence-risk disease; iii) maturation of post-neoadjuvant capecitabine and olaparib strategies; and iv) subsequent consolidation of pembrolizumab-based perioperative immunotherapy. However, previous studies have further extended this framework toward ctDNA-guided risk assessment and antibody-drug conjugate (ADC)-based development. The resulting response-adapted clinical framework is summarized in Fig. 1 (6-8,24-25,33-44).

Standard chemotherapy backbone and selective intensification. Anthracycline-taxane chemotherapy remains the most frequently applied neoadjuvant platform for the treatment of early-stage TNBC, particularly non-metastatic stage II-III disease. This is because it most readily delivers pCR rates and provides the scaffold on which the majority of modern perioperative strategies have been tested (5-8,33-38). Accordingly, the interpretation of platinum, immunotherapy and post-neoadjuvant escalation results cannot be analyzed separately from the backbone treatment on which these data were generated.

The continuing role of dose-dense anthracycline-taxane therapy should also be stated clearly, especially for patients who are not appropriate candidates for immune checkpoint inhibition. KEYNOTE-522 established pembrolizumab-based perioperative therapy as the best-supported regimen for patients with high-recurrence-risk early-stage TNBC, but it did not directly compare its efficacy with dose-dense anthracycline-taxane therapy (6-9,45). Therefore, although a KEYNOTE-522-like perioperative pathway is currently the preferred evidence-supported approach for immune checkpoint inhibitor-eligible high-risk patients, dose-dense anthracycline-taxane chemotherapy remains a reasonable standard option for selected patients with active autoimmune diseases, at a high risk of severe immune-related adverse events, prior organ transplantation or with other contraindications to pembrolizumab.

Platinum is a selective intensification strategy reserved for especially high-recurrence-risk populations, rather than a mandatory addition to all TNBC neoadjuvant regimens. Current randomized and pooled evidence supports higher pCR rates, but the magnitude and consistency of survival benefits remain much less stable compared with the pathological response datapoint itself. In addition, platinum comes at the cost of substantially higher rates of grade ≥3 hematological toxicity in intensified regimens (33-38). For that reason, anthracycline-taxane chemotherapy remains the standard backbone treatment option, whereas platinum is best positioned as a conditional intensifier when baseline recurrence risk, expected benefit, marrow reserve and treatment

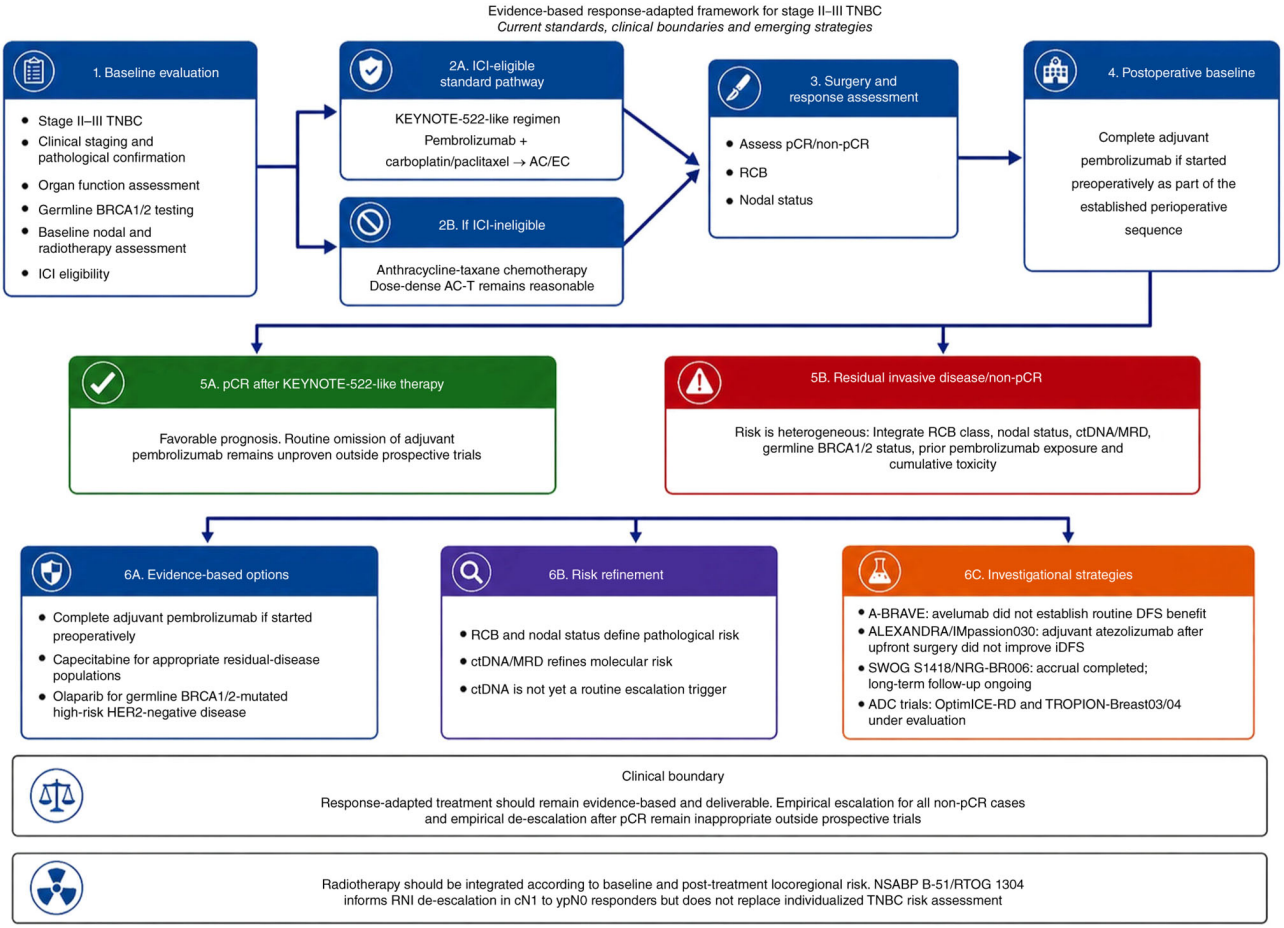

Figure 1. Evidence-based response-adapted framework for stage II-III TNBC. The framework proceeds through six linked decision points: i) Baseline confirmation of non-metastatic stage II-III TNBC and recurrence risk; ii) selection of a chemotherapy-alone or KEYNOTE-522-like chemoimmunotherapy backbone according to eligibility and contraindications; iii) interim response and toxicity assessment to determine whether the selected pathway remains deliverable; iv) surgery and pathological response evaluation using pCR and RCB; v) post-neoadjuvant risk stratification integrating residual burden, nodal status, germline BRCA1/2 status and ctDNA/MRD where available; and vi) response-adapted postoperative treatment, including completion of pembrolizumab, capecitabine, olaparib or trial-based ADC/ctDNA-guided strategies as appropriate. TNBC, triple-negative breast cancer; ICI, immune checkpoint inhibitor; AC, doxorubicin-cyclophosphamide; EC, epirubicin-cyclophosphamide; AC-T, anthracycline-taxane; pCR, pathological complete response; RCB, residual cancer burden; ctDNA, circulating tumor DNA; MRD, minimal residual disease; ADC, antibody-drug conjugate.

deliverability are considered together. This positioning refers specifically to the use of platinum in chemotherapy-alone neoadjuvant platforms. When chemotherapy is used without immunotherapy, platinum is best considered as a selective intensifier, the benefits of which must be weighed against hematological toxicity and treatment completion. By contrast, for patients who are candidates for the KEYNOTE-522 regimen, carboplatin is not an empirical intensification step, but is instead part of the validated chemoimmunotherapy backbone on which the pCR, event-free survival (EFS) and overall survival (OS) data are generated (6-9). Substituting or omitting carboplatin within that pathway should therefore be considered a regimen modification rather than simple de-escalation. Longer-term follow-up from BrighTNess, a randomized phase III trial, further validated this point by EFS: carboplatin, not veliparib, mainly accounted for the observed long-term benefit, whereas adding the PARP inhibitor veliparib to a carboplatin-containing regimen did not improve long-term efficacy (38). This is clinically informative, because it corrects a common overinterpretation that mechanistic appeal does not automatically justify regimen proliferation. In patients with early-stage TNBC, 'more targeted' should not be interpreted as synonymous with 'superior', especially when the incremental component has not improved survival endpoints.

The current anthracycline-free literature is informative but should not be overstated. NeoPACT, a single-arm phase II clinical trial, previously showed that pembrolizumab combined with carboplatin-docetaxel can produce a relatively high pCR rate and encouraging 3-year EFS rate in patients with high-risk TNBC, supporting the feasibility of a non-anthracycline chemoimmunotherapy platform (39). However, this single-arm design lacked a randomized comparator and cannot replace randomized evidence. The Neo-N randomized phase II trial, which evaluated nivolumab timing on a carboplatin-paclitaxel backbone, did not show that a lead-in immunotherapy window was superior to concurrent initiation in terms of pCR (40). WSG-ADAPT-TN, a randomized phase II neoadjuvant de-escalation trial, has contributed invaluable de-escalation framework data. Specifically, short-course anthracycline-free therapy may be reasonable in tumors that show early treatment sensitivity, assessed by early response and pathological response rather than by a pre-treatment test alone, but the key is

biological selection and early response, not empirical subtraction, for all patients; the final analysis supported the prognostic relevance of pCR and molecular markers after de-escalated therapy (41). NeoSTOP reached a similar conclusion from another angle by directly comparing anthracycline-free vs. anthracycline-containing carboplatin-based neoadjuvant chemotherapy in a randomized phase II trial. Anthracycline omission reduced toxicity, but equivalence claims remain limited as the study enrolled 100 patients and follow-up was not powered to establish definitive long-term survival equivalence (46).

In addition, two recent analyses support a cautious interpretation of anthracycline-free strategies. A 2025 meta-analysis of platinum-based anthracycline-free regimens suggested that such approaches are feasible and can generate substantial pCR rates, but heterogeneity is pronounced and survival evidence remains less stable compared with standard anthracycline-taxane regimens (47). Another comparative study of anthracycline-free vs. anthracycline-containing chemoimmunotherapy also reported that efficacy may be similar in certain selected settings, particularly in node-negative disease, but such retrospective or non-standardized comparisons are not sufficient to justify redefining current standard treatment procedures (48). Likewise, differences in dose intensity matter. Dose-dense anthracycline may retain value in patients with higher-burden disease (45), whereas cisplatin-taxane alternatives, such as the HELEN-001 phase II trial, can improve pCR in selected subgroups, including germline BRCA1/2 mutation carriers, without yet establishing a new universal standard (49). A 2024 network meta-analysis also suggested that although intensified regimens may rank higher for pCR in indirect cross-trial comparisons, standard chemotherapy remains one of the most reliable treatments for long-term survival endpoints (13). However, real-world pembrolizumab-based data add a practical warning: Toxicity-related chemotherapy dose reduction or discontinuation can adversely affect the likelihood of pCR, meaning that deliverability is not a peripheral issue in regimen selection (23).

Biologically, the appeal of platinum is high in the patient subtype enriched for DNA repair defects. Clinically, however, the experience of moving PARP inhibitors, such as olaparib, into the neoadjuvant phase is a warning against broad inference. In PARTNER, a randomized clinical trial, adding olaparib to platinum-based neoadjuvant chemotherapy in germline BRCA wild-type TNBC did not improve pCR, EFS or OS (50), meaning that knowledge of a plausible mechanism is not sufficient. Standard chemotherapy remains the core therapeutic scaffold of perioperative TNBC treatment regimen expansion, where platinum is a reasonable intensifier in genuinely high-recurrence-risk disease. However, the use of platinum should be judged together with toxicity, deliverability and the intended postoperative plan. Positioned in this manner, platinum directly addresses the central conundrum between legitimate escalation and avoidable toxicity, while acknowledging that TNBC heterogeneity does not support a universal one-size-fits-all intensified regimen.

Perioperative immunotherapy. Among the recent developments in early-stage TNBC treatment, perioperative immunotherapy has had a notable impact on clinical practice. However, positive studies are not interchangeable: A trial may be positive for pCR without having mature EFS or OS evidence, and studies may differ in checkpoint inhibitor, chemotherapy backbone, timing and risk population. KEYNOTE-522 remains the only perioperative immunotherapy strategy with convincing level I evidence, defined here as randomized phase III evidence, reporting pCR, EFS and OS endpoints (6-8). This hierarchy is also reflected in contemporary guidelines and consensus statements, including ASCO, CSCO and St. Gallen recommendations, which treat pembrolizumab-based chemoimmunotherapy as the most optimally-supported therapeutic option for high-risk stage II-III TNBC (9-11). Representative perioperative immunotherapy trials and pivotal or boundary-defining studies are summarized in Table I, listing study design, population, treatment arms or regimens, primary endpoints, key efficacy findings, survival updates and grade ≥3 adverse-event or treatment-related adverse-event rates.

KEYNOTE-522 remains the reference framework to date, because it delivered the most complete evidence chain. Pembrolizumab added to neoadjuvant chemotherapy and continued after surgery was found to improve pCR and EFS, and the 2024 update reported an OS benefit (6-8). The importance of this sequence of results cannot be overstated. Early-stage TNBC has seen various regimens improve pCR, including platinum intensification and non-pembrolizumab immunotherapy trials, but far fewer have shown conclusive event-driven benefit and fewer still have extended that benefit to OS (6-8,33-38,51-55). For these reasons, KEYNOTE-522 serves as the benchmark against which other prospective perioperative immunotherapy strategies should be compared and then interpreted. This distinction is now reflected in formal guidance. The ASCO rapid recommendation update now specifically endorses pembrolizumab with neoadjuvant chemotherapy followed by adjuvant pembrolizumab for stage II-III or otherwise high-risk early-stage TNBC, rather than extrapolating benefit across all immune checkpoint-inhibitor regimens (9). However, the KEYNOTE-522 data should be interpreted by the publication version and data cut-off. The pCR result of 64.8 vs. 51.2% is derived from the first interim analysis among the first 602 randomized patients, the EFS result reported in 2022 used a later data cut-off and showed 36-month EFS of 84.5 vs. 76.8% [hazard ratio (HR), 0.63; 95% CI, 0.48-0.82], and the 2024 OS update with a March 22, 2024, data cut-off and median follow-up of 75.1 months reported 60-month OS of 86.6 vs. 81.7% (HR, 0.66; 95% CI, 0.50-0.87) (6-8). These figures should therefore serve as complementary updates rather than a single simultaneous analysis, and Table I specifies which update is being cited.

IMpassion031, a randomized phase III clinical trial, reported similar trends but did not provide identical evidence. The original report documented pCR benefits from atezolizumab treatment (51,52). The final 2025 analysis suggested favorable trends in EFS, disease-free survival and OS, while adding informative ctDNA analyses, but wider confidence intervals and postoperative treatment heterogeneity limit interpretation (51).

Negative or neutral trials are equally important for defining the clinical boundaries of perioperative immunotherapy, rather than simply refuting its activity. NeoTRIP, a randomized

Table I. Summary of pivotal and boundary-defining trials in stage II-III TNBC.

Trial	Design/population	Arms/regimen	Primary endpoint	pCR or main efficacy	Survival update	Grade ≥3 toxicity/practical boundary	(Refs.)
KEYNOTE-522[a]	Phase III; 1,174 patients with high-risk stage II-III TNBC	Pembrolizumab + carboplatin-paclitaxel followed by AC/EC, then adjuvant pembrolizumab vs. matched placebo + chemotherapy	pCR and EFS	pCR: 64.8 vs. 51.2% at first interim analysis; 63.0 vs. 55.6% in the FDA regulatory analysis	36-month EFS: 84.5 vs. 76.8% (HR=0.63; 95% CI, 0.48-0.82); 60-month OS: 86.6 vs. 81.7% (HR=0.66; 95% CI, 0.50-0.87)	Grade ≥3 treatment-related AEs: 77.1 vs. 73.3%; establishes the current evidence-supported perioperative pathway, including adjuvant pembrolizumab completion	(6-9,16)
IMpassion031	Phase III; 333 patients with stage II/III TNBC	Atezolizumab + nab-paclitaxel followed by anthracycline-based chemotherapy vs. placebo + chemotherapy; postoperative atezolizumab in the experimental arm	pCR	pCR: 57.6 vs. 41.1% (difference of 16.5%)	Final analysis showed favorable but not definitive time-to-event trends. EFS: HR=0.76 (95% CI, 0.47-1.21); OS: HR=0.56 (95% CI, 0.30-1.04)	Neoadjuvant grade 3-4 treatment-related AEs: ~57 vs. ~53%; supports biological consistency but not the same evidence hierarchy as KEYNOTE-522	(51-52)
NeoTRIP Michelangelo	Randomized phase III; 280 patients with high-risk or locally advanced TNBC	Atezolizumab + carboplatin/nab-paclitaxel vs. carboplatin/nab-paclitaxel before surgery; anthracycline was not part of the preoperative backbone	pCR	pCR: 48.6 vs. 44.4% (absolute difference of 4.2%); odds ratio, 1.18; 95% CI, 0.74-1.89 (P=0.48)	Reported follow-up did not show a clear EFS advantage. 5-year EFS: 70.6 (atezolizumab) vs. 74.9% (without atezolizumab) in later reports	Grade ≥3 drug-related AEs: 77.5 vs. 70.0%; serious AEs: 18 vs. 6%. Defines a boundary for backbone- and setting-specific immune checkpoint inhibitor effects	(53,54)
BrighTNess	Randomized phase III; 634 patients with stage II-III TNBC	Paclitaxel + carboplatin +/- veliparib followed by AC vs. paclitaxel followed by AC	pCR	pCR: 53% with paclitaxel/carboplatin/veliparib, 58% with paclitaxel/carboplatin and 31% with paclitaxel alone. Veliparib added no	4-year EFS favored carboplatin-containing treatment; carboplatin plus veliparib vs. control: HR=0.63 (95% CI, 0.43-0.92). No EFS benefit for veliparib added to	Across treatment, grade 3-4 neutropenia (56%), anemia (29%) and thrombocytopenia (12%); toxicity was higher in carboplatin-containing arms	(38)

Table I. Continued.

Trial	Design/population	Arms/regimen	Primary endpoint	pCR or main efficacy	Survival update	Grade ≥3 toxicity/practical boundary	(Refs.)
				benefit beyond carboplatin	carboplatin		
CALGB 40603 (Alliance)	Randomized phase II; 443 patients with stage II-III TNBC	Weekly paclitaxel followed by dose-dense AC, with or without carboplatin and/or bevacizumab	pCR	Carboplatin increased breast/axillary pCR: 54 vs. 41%	Median follow-up: 7.9 years. Carboplatin: EFS HR=0.94 (95% CI, 0.67-1.32) and OS HR=1.12 (95% CI, 0.77-1.61). Bevacizumab: EFS HR=0.92 (95% CI, 0.66-1.29) and OS HR=0.97 (95% CI, 0.67-1.40)	Carboplatin increased grade 3-4 neutropenia (56 vs. 20%) and thrombocytopenia (22 vs. 4%); CALGB 40603 was not powered for definitive EFS or OS comparison	(35,36)
CREATE-X	Phase III; 910 patients with HER2-negative residual invasive disease after neoadjuvant chemotherapy; prespecified TNBC subgroup	Adjuvant capecitabine vs. no additional chemotherapy	DFS	Not a neoadjuvant pCR trial. Enrolled residual disease	TNBC subgroup DFS: 69.8 vs. 56.1% (HR=0.58; 95% CI, 0.39-0.87); OS: 78.8 vs. 70.3% (HR=0.52; 95% CI, 0.30-0.90)	Hand-foot syndrome occurred in ~75% with capecitabine. Dose interruption or reduction may be required	(24)
OlympiA	Phase III; 1,836 patients with pathogenic germline BRCA1/2 variants and high-risk HER2-negative early breast cancer	1 year of adjuvant olaparib vs. placebo after local therapy and chemotherapy	IDFS	Not a pCR trial. Selection based on germline BRCA1/2 and high-risk features	OS update: HR=0.68 (98.5% CI, 0.47-0.97); 4-year OS: 89.8 vs. 86.4%. IDFS benefit was maintained	Anemia and fatigue were common; standard for eligible germline BRCA-mutated high-risk HER2-negative disease	(25,26)
EA1131	Randomized phase III; 410 of a planned 775 patients with ≥1 cm residual TNBC after neoadjuvant chemotherapy	Adjuvant platinum vs. capecitabine	IDFS/non-inferiority framework	Residual-disease trial, not pCR-based	Basal-subtype 3-year iDFS 42% with platinum vs. 49% with capecitabine; platinum failed the non-inferiority framework and the trial stopped for futility	Grade ≥3 AEs: 25 vs. 15%; argues against empirically replacing capecitabine with postoperative platinum	(86)
NSABP B-51/RTOG 1304	Randomized phase III; initially biopsy-proven cN1 breast cancer converting to ypN0 after	RNI vs. no RNI, according to surgery type	IBCRFI	Not a pCR systemic-therapy trial. Focused on nodal response and	5-year IBCRFI: 92.7 with RNI vs. 91.8% without RNI (HR=0.88; 95% CI, 0.60-1.28)	No unexpected safety issues. Informs RNI de-escalation in ypN0 responders but should be	(31)

Table I. Continued.

Trial	Design/ population	Arms/regimen	Primary endpoint	pCR or main efficacy	Survival update	Grade ≥3 toxicity/practical boundary	(Refs.)
	neoadjuvant chemotherapy			radiotherapy		contextualized for TNBC risk features	
A-BRAVE	Phase III; high-risk early-stage TNBC after standard curative-intent treatment, including residual disease after neoadjuvant chemotherapy or high-risk disease after upfront surgery	1 year of adjuvant avelumab vs. observation	DFS	Post-treatment adjuvant immunotherapy trial	DFS: HR=0.81 (95% CI, 0.61-1.09) in the intention-to-treat population; HR=0.80 (95% CI, 0.58-1.10) in the residual-disease stratum. Descriptive OS signal: HR=0.66 (95% CI, 0.45-0.97)	Does not establish routine adjuvant avelumab. OS remains hypothesis-generating and should not be used to justify routine checkpoint-blockade escalation	(95)
ALEXANDRA/ IMpassion030	Phase III; 2,199 patients with stage II/III TNBC after upfront surgery	Standard adjuvant chemotherapy plus atezolizumab followed by maintenance atezolizumab vs. standard adjuvant chemotherapy alone	Invasive DFS	Not a neoadjuvant pCR trial; evaluated adjuvant-only checkpoint blockade after surgery	Invasive DFS: HR=1.11 (95% CI, 0.87-1.42; P=0.38), showing no benefit from adding atezolizumab to postoperative chemotherapy	Grade 3/4 treatment-related AEs: 54 vs. 44%; supports the boundary that adjuvant-only atezolizumab after upfront surgery should not be routine	(96)
NeoSTAR and ongoing ADC programs	NeoSTAR phase II: 50 patients with localized TNBC; ongoing phase III residual-disease and neoadjuvant ADC trials	SG alone or ADC-based combinations; Dato-DXd +/- durvalumab in TROPION-Breast03/04; SG + pembrolizumab in OptimICE-RD	pCR/ response in NeoSTAR; EFS/ IDFS in ongoing randomized trials	pCR (NeoSTAR): 30% after four cycles of single-agent SG; 64% proceeded directly to surgery after SG alone	NeoSTAR 2-year EFS: 92% overall and 100% among patients with pCR after SG. Randomized perioperative ADC survival data remain preliminary	NeoSTAR grade 3/4 neutropenia: 14%; perioperative ADC regimens remain investigational and must be interpreted by agent and setting	(42-44, 88)

aKEYNOTE-522 pCR, EFS and OS values in Table I are from different publication updates/data cut-offs. The 64.8 vs. 51.2% pCR result is from the first interim analysis, the 63.0 vs. 55.6% pCR result is from the FDA regulatory analysis, and the EFS and OS values reflect later survival updates. AC, doxorubicin-cyclophosphamide; EC, epirubicin-cyclophosphamide; ADC, antibody-drug conjugate; AE, adverse event; CI, confidence interval; EFS, event-free survival; HR, hazard ratio unless used in HR-low/HER2-negative, where HR denotes hormone receptor; OS, overall survival; pCR, pathological complete response; RCB, residual cancer burden; SG, sacituzumab govitecan; TNBC, triple-negative breast cancer.

study of atezolizumab combined with carboplatin-paclitaxel, failed to demonstrate a convincing efficacy advantage on its primary framework when paired with a non-anthracycline carboplatin-paclitaxel backbone (53). This result does not invalidate the survival benefit observed with pembrolizumab in KEYNOTE-522. Instead, it shows that the effect of immune

checkpoint blockade in early-stage TNBC is inseparable from the chemotherapy platform, schedule and risk population in which it is tested. A common clinical mistake is to extrapolate the OS finding of pembrolizumab administered with an anthracycline-taxane platform to unvalidated non-anthracycline regimens within the same drug class; current evidence does not support that shortcut. CamRelief, a randomized clinical trial of camrelizumab plus chemotherapy, likewise supports programmed cell death protein 1-based chemoimmunotherapy, but the survival-level evidence reported remains less complete compared with KEYNOTE-522 (55). Taken together, these studies are important for biological consistency, but they do not erase the hierarchy between exploratory or preliminary benefit parameter findings and a regimen already supported by concrete survival endpoint data.

The question of timing has also not been settled in favor of more complex schedules. Neo-N, a randomized phase II trial, did not support lead-in nivolumab treatment over concurrent administration (40). More aggressive chemotherapy-free or window-only immunotherapy strategies remain hypothesis-generating. Adaptive nivolumab/ipilimumab approaches and short atezolizumab windows suggest that a biologically immune-enriched subset, defined by favorable immune microenvironment features or early immune activation, may respond without the full conventional chemotherapy (56,57). However, toxicity, strict selection criteria and lack of confirmatory randomized outcome data keep these approaches in the research domain at present. In routine care, they should be interpreted as information leveraged for future biomarker development rather than as substitutes for established chemoimmunotherapy.

In addition, endpoint interpretation warrants similar degrees of discipline. A shift in pCR may yield beneficial information in TNBC, but a clinically useful perioperative regimen should also show that it can change the distribution of residual disease, not merely the binary pCR threshold. The residual cancer burden (RCB) analysis of KEYNOTE-522 is therefore particularly informative, because pembrolizumab improved not only RCB-0 but the overall migration toward lower residual disease classes (16). That type of effect is more persuasive compared with isolated pCR gains, especially when later postoperative decisions are increasingly being based on residual burden rather than on a single yes/no pathological definition.

Biomarker enrichment is attractive, but the current data do not support a single universal immunotherapy selector. DetermaIO is an immune-related 27-gene expression signature, tumor-specific MHC-II expression is an immunohistochemical or transcriptomic tumor-cell antigen-presentation marker, and GeparNuevo-derived immune signatures are translational biomarker models derived from a clinical trial dataset; together, these studies suggest that composite immune marker profiles may outperform single markers, such as programmed death-ligand 1 (PD-L1), staining alone (17-18,58-60). However, they remain mainly translational analyses rather than decision-defining tests. Currently, the most defensible position is that perioperative immunotherapy has established clinical activity, meaning improvement in pathological response and survival endpoints in appropriately selected high-risk patients, but treatment selection should remain anchored to conclusive randomized evidence, not to isolated biomarkers (6-9). Contemporary reviews therefore frame the main unresolved questions less as whether checkpoint blockade is active and more as how to select patients appropriately, how to integrate pembrolizumab with other post-neoadjuvant options, such as capecitabine or olaparib, and how to limit the burden of immune-related toxicity and financial hardship (12,14,61). Preserving this evidence hierarchy helps avoid the clinical mistake of treating promising but exploratory biomarker signals as practice-defining evidence, clarifying the present boundary between prognostic enrichment and validated treatment selection.

Radiotherapy integration in the perioperative sequence. Radiotherapy decisions after neoadjuvant therapy remain more nuanced than a simple yes/no discussion based on the yp stage. Current data support a relatively stable principle, whereby benefit from postmastectomy or regional nodal radiotherapy is the most consistent in patients with persistent nodal disease, especially ypN2-3 (28-30). By contrast, omission of regional nodal irradiation is more controversial in ypN0 populations and must be interpreted in combination with initial nodal status, subtype and residual burden (28-31). In TNBC, reducing this decision to a 'ypN0 equals no radiotherapy' rule is likely clinically inappropriate, even in patients who achieved pCR. Locoregional recurrence risk remains dependent on the baseline nodal burden, primary tumor extent and biological behavior of the original disease. Therefore, yp status alone should not be used as a universally simplified standard.

The NSABP B-51/RTOG 1304 randomized clinical trial provided an important reference point for patients who present with biopsy-proven cN1 disease, which then converted to ypN0 after neoadjuvant chemotherapy. In the randomized trial, regional nodal irradiation did not significantly improve the interval free from invasive breast cancer recurrence compared with omission of regional nodal irradiation (5-year rate, 92.7 vs. 91.8%; HR, 0.88; 95% CI, 0.60-1.28) (31). These data support a more evidence-based discussion of regional nodal irradiation de-escalation in ypN0 responders, while still requiring caution in patients with TNBC with high baseline burden, incomplete systemic response or other adverse risk features. These results and the eligibility framework are reported in the primary NSABP B-51/RTOG 1304 publication (31).

However, the more difficult question concerns the timing of radiotherapy relative to postoperative systemic therapy. In residual TNBC, a multi-center Korean retrospective comparative study suggested that concurrent radiotherapy and capecitabine may be associated with superior disease-free and OS compared with sequential treatment, without a major penalty in clinically significant toxicity (62). However, the non-randomized design means this should be treated mainly as a preliminary finding that warrants future validation.

A similarly cautious approach is warranted when radiotherapy is combined with olaparib or pembrolizumab. RADIOPARP, a phase I clinical trial, established feasibility and dose escalation boundaries for concurrent olaparib and radiotherapy by testing dose levels and monitoring acute and 1-year toxicity rather than demonstrating superiority (63,64). Real-world pembrolizumab-radiotherapy reports suggest that concurrent treatment is generally feasible, but these series are

small and are more suitable as safety-oriented implementation data instead of evidence of incremental efficacy (65,66). Modern surgical series also suggest that neoadjuvant chemoimmunotherapy does not necessarily compromise surgical deliverability or cause prohibitive delay to radiotherapy, but these are implementation data rather than efficacy data (67). In a small prospective observational series of residual TNBC, persistent ctDNA positivity before radiotherapy was associated with poor distant control despite local treatment, underscoring that radiotherapy cannot substitute for systemic risk management when molecular residual disease is already present (68).

Axillary management raises a parallel issue. Surgical de-escalation after neoadjuvant therapy is attractive, but for TNBC it cannot be assumed that less axillary surgery necessarily translates into less regional treatment. Ongoing data from modern cohorts suggest that residual nodal disease burden after preoperative therapy continues to matter, where radiotherapy decisions should not simply mirror surgical de-escalation algorithms without conclusive clinicopathological and stage-based information (28-30). The practical conclusion is modest but important: Radiotherapy should be planned as part of the perioperative sequence, but concurrent systemic intensification remains selective and should be interpreted cautiously. In this manner, radiotherapy integration can contribute to local control without blurring the broader boundary between justified multimodality intensification and unsupported combination escalation.

Combined-modality and response-adapted strategies. When chemotherapy, immunotherapy, radiotherapy and postoperative escalation are considered across one treatment course, the key issue is not the number of components added, but whether the sequence remains deliverable and evidence-based. Response-adapted treatment is an attractive concept in TNBC, but it should not mean empirical escalation in response to slow early shrinkage or empirical de-escalation in response to an encouraging interim response. Adjustment should be reasonable only when the evolving response, toxicity profile and evidence of benefit all align. WSG-ADAPT-TN, a randomized phase II clinical trial, suggested that abbreviated anthracycline-free therapy may be appropriate in certain highly sensitive tumors rather than as a routine de-escalation strategy for all patients (41). By the same logic, treatments proven in the post-neoadjuvant residual-disease setting should not be moved upstream without prospective validation. In routine care, combined-modality intensification should remain selective.

4. Prognostic and predictive biomarkers in neoadjuvant TNBC

For clinical interpretation, biomarkers in neoadjuvant TNBC should first be separated by function and then by timing. A prognostic biomarker refines the probability of recurrence or survival outcome, whereas a predictive biomarker identifies a higher likelihood of benefit from a specific intervention (17-19,69-77). This distinction matters because a variety of markers in TNBC have been repeatedly discussed as though prognostic enrichment automatically implies treatment-selection value. In reality, the majority of the currently available markers are instead more beneficial for refining heterogeneity within a given clinical stage than for independently choosing, withholding or replacing a standard regimen. With this boundary in mind, biomarker interpretation is more practical when organized into baseline pretreatment markers, on-treatment dynamic markers and post-treatment residual-risk markers.

Baseline pretreatment biomarkers. The value of biomarkers for early-stage TNBC is not to replace clinical staging, but to resolve heterogeneity within patient groups with apparently similar clinical burden. PD-L1 expression and stromal tumor-infiltrating lymphocytes (TILs) have been found to be associated with higher pCR rates, with more favorable outcomes in some datasets (17-18). Even so, their role in routine practice should not be overstated. The ASCO neoadjuvant guidelines do not support using these markers alone to determine whether established neoadjuvant therapy should be given (5). Despite their prognostic value, PD-L1, TILs, homologous recombination deficiency (HRD) and related baseline markers remain to be fully validated as stand-alone selectors that can safely exclude patients from established perioperative therapies.

An equally cautious interpretation is warranted for HRD. Broad HRD labels do not always predict platinum or PARP inhibitor sensitivity consistently, where more functional readouts may be more informative. In GeparSixto, a randomized clinical trial, low RAD51 foci formation was observed to be a more viable marker compared with conventional HRD labeling for predicting platinum-associated benefit (19). This distinction matters, because TNBC is frequently extrapolated erroneously as if all DNA damage-related biomarkers are clinically interchangeable. In this context, 'conventional HRD markers' refer mainly to germline or somatic BRCA1/2 mutation status and genomic-scar assays based on measures such as loss of heterozygosity, telomeric allelic imbalance and large-scale state transitions (78). RAD51 foci formation is different, because it is a functional readout of homologous recombination activity rather than a static genomic scar (19,79). This distinction may explain why RAD51 performs differently from conventional HRD parameters in predicting platinum sensitivity (19,79).

Phase II clinical trial programs further illustrate why HRD-related signals require clinical context. In I-SPY2, an adaptively randomized phase II platform trial, durvalumab plus olaparib and paclitaxel increased estimated pCR in patients with high-risk HER2-negative disease compared with standard paclitaxel followed by doxorubicin-cyclophosphamide (80). GeparOLA, a randomized phase II trial, compared paclitaxel/olaparib with paclitaxel/carboplatin in HRD-defined HER2-negative disease and reported long-term survival on follow-up after the neoadjuvant comparison (81). These studies support the prospective refinement of functional HRD assessment, but they do not validate a broad range of HRD markers as standalone selectors for routine PARP-based neoadjuvant therapy.

Dynamic biomarkers during treatment. Dynamic biomarkers are more promising compared with static markers for the next stage of treatment personalization. WSG-ADAPT-TN, a randomized phase II neoadjuvant trial, and related analyses

suggest that early changes in stromal TILs, tumor cell density and proliferative markers, such as Ki-67, can improve discrimination beyond baseline measures alone (18,41,82). Early ultrasound tumor-volume reduction after two cycles of anthracycline/taxane-based therapy has likewise shown useful discriminatory value for identifying optimal responders, illustrating that interim assessment can contribute more than simple anatomic restaging when interpreted within the treatment context (32). Similarly, the prognostic value of RCB appears to be more accurate when interpreted together with the baseline clinical stage, as shown in I-SPY2 analyses (83). These observations support a broader shift in how perioperative TNBC should be conceptualized: From a one-time pre-treatment categorization to a trajectory-based model, in which early responses actively influence later decisions. At present, these aforementioned dynamic markers may help interpret evolving sensitivity, but they remain to be fully validated as standalone tools for routine regimen omission, substitution or switching outside the current structured clinical contexts.

Post-treatment residual-risk markers and integrated assessment. Among the post-treatment markers, RCB provides more discriminatory information compared with the simple pCR/non-pCR dichotomy. This is clinically important because postoperative decisions now increasingly depend on the amount of residual disease rather than on the binary absence or presence of residual invasive tumor alone (16,83). Analyses from KEYNOTE-522 and I-SPY2 showed that RCB, when interpreted together with initial staging, can further refine long-term risk assessment beyond pCR alone (16,83). In practical terms, RCB is currently one of the strongest biomarkers for guiding post-neoadjuvant management, although it functions primarily as a prognostic marker rather than a treatment-selective biomarker.

Composite immune and genomic tools remain of clear interest, but their current utility remains in enrichment and risk communication. TNBC-DX is a genomic test, DetermaIO is an immune-related gene-expression signature, tumor-specific MHC-II expression is a tumor antigen-presentation marker, and related integrative models may improve the biological resolution and help identify response-enriched subsets (58-59,84). Mature tertiary lymphoid structures may add another layer of stratification, since higher tertiary lymphoid structure maturity has recently been associated with superior responses to neoadjuvant therapy and more favorable prognosis in TNBC (85). However, they have not replaced established clinical decision frameworks. The most defensible hierarchy at present is therefore to let baseline markers refine the expected sensitivity and let dynamic markers show whether sensitivity is emerging, before allowing post-treatment markers, such as RCB and ctDNA, to redefine residual risk. At present, these integrated tools mainly support residual-risk refinement rather than the independent replacement of established post-neoadjuvant decision frameworks.

ctDNA/MRD and current clinical boundaries in neoadjuvant TNBC. ctDNA is emerging as one of the most informative tools for refining residual risk across the neoadjuvant and post-neoadjuvant continuum in TNBC, but its most notable role is currently prognostic rather than interventional. Current data consistently show that ctDNA positivity after neoadjuvant therapy is associated with residual disease, earlier recurrence and inferior survival outcomes (69-77). This makes ctDNA clinically valuable for risk stratification and for the design of enriched post-neoadjuvant trials. However, it does not yet make ctDNA a validated routine trigger for treatment escalation in unselected practice.

Post-treatment interpretation tends to be most accurate when ctDNA is read together with residual burden rather than in isolation. In residual-disease populations, ctDNA and RCB have been reported to provide complementary prognostic information, including in patients with intermediate-burden disease, where ctDNA separates patients with materially different relapse risks (71,74). In this context, materially different relapse risks means clinically meaningful differences in recurrence probability despite similar pathological residual-burden categories. A post-treatment hotspot-panel study similarly suggested that ctDNA can optimize risk assessment when tissue response alone is insufficient to identify which non-pCR patients remain the most vulnerable to recurrence (75). The practical implication is not that ctDNA can replace pathology, but that it adds another molecular layer to the residual-disease phenotype. Assay sensitivity is therefore not a technical footnote but a clinical boundary. Comparative studies in early-stage TNBC have revealed meaningful differences between molecular residual disease platforms, such that epigenomic approaches may further increase surveillance sensitivity (76-77). These advances may explain why ctDNA-negative results are not automatically equivalent across studies. However, c-TRAK TN, a clinical trial using ctDNA mutation tracking to detect molecular residual disease and trigger intervention, remains the clearest reminder of the present limit. Namely, ctDNA positivity can identify a group at particularly high risk, but intervention triggered at molecular relapse frequently occurs when occult metastatic disease is already present (69). This is a core reason why ctDNA, despite its potent prognostic value, cannot yet be treated as a routine trigger for treatment escalation in standard clinical practice. The major unanswered question is no longer whether ctDNA is prognostic, but when it should trigger intervention, in which patient cohort and if so, with which treatment regimen.

5. Post-neoadjuvant treatment guided by response to neoadjuvant therapy

Postoperative management should follow the extent and biological significance of residual disease rather than a simple non-pCR label. Pathological response remains the key bridge between preoperative treatment sensitivity and adjuvant risk stratification, but residual burden, nodal status, germline BRCA status and prior pembrolizumab exposure can all influence the next step (6-8,16,24-26,61,83,86,87).

Although pCR identifies a group with favorable prognosis, it does not erase all baseline risk. Conversely, residual disease does not define a homogeneous population. The clinically relevant task is therefore not simply to escalate all non-pCR cases, but to determine who remains at sufficiently high risk to justify additional therapy and which therapy has actually yielded benefit (16,24-26,61,83,86,87).

After a KEYNOTE-522-like regimen, pCR has favorable prognostic accuracy but should not currently be used to omit adjuvant pembrolizumab outside prospective trials (6,9,61). Such omission would count as a de-escalation strategy that has not been proven to preserve EFS or OS. For non-pCR disease, the discussion should separate established options from investigational escalation: i) Completion of adjuvant pembrolizumab is viewed as the tested perioperative regimen; ii) capecitabine remains the evidence-based strategy for appropriate residual TNBC populations, particularly after chemotherapy-alone neoadjuvant treatment or when no superior treatment option is available (24,61); iii) olaparib is the evidence-based option for germline BRCA1/2-mutated high-risk HER2-negative disease (25,26); and iv) additional checkpoint blockade, ADCs, ctDNA-triggered therapy or multi-agent escalation should generally remain trial-based (61,88).

For patients with residual invasive disease after neoadjuvant chemotherapy, CREATE-X, a randomized phase III clinical trial, established adjuvant capecitabine as a landmark treatment option, with particularly relevant benefit in the TNBC subgroup compared with no capecitabine (24). For germline BRCA1/2-mutated, high-risk HER2-negative disease, OlympiA, a randomized phase III clinical trial, established adjuvant olaparib as another standard compared with placebo (25). At the prespecified second interim analysis, olaparib improved OS compared with placebo (HR, 0.68; 98.5% CI, 0.47-0.97), with 4-year OS of 89.8 vs. 86.4% (26). By contrast, EA1131, a randomized phase III postoperative trial, did not show platinum to be superior to capecitabine in residual TNBC, instead finding higher toxicity rates (86). Together, these trials define an important boundary, whereby postoperative intensification in residual TNBC should be based on trials that improved clinically meaningful outcomes, not on the linear extension of preoperative platinum sensitivity arguments. The unresolved issue in contemporary practice is therefore not whether escalation matters, but how it should be individualized after prior chemoimmunotherapy. Accounts exist arguing against applying capecitabine, olaparib and adjuvant pembrolizumab completion as interchangeable add-ons. Instead, selection should be based on germline BRCA status, prior pembrolizumab exposure, residual burden and cumulative toxicity (61,87).

The immunotherapy era has not invalidated capecitabine, which deserves stronger emphasis. Previous post-neoadjuvant observational and subtype analyses continue to support the clinical relevance of capecitabine in residual TNBC, even though the magnitude of benefit varies across cohorts and treatment contexts (89-91). For patients with residual invasive disease after neoadjuvant chemotherapy, especially those without germline BRCA1/2 mutations and without access to experimental novel agents in clinical trials, adjuvant capecitabine remains the core evidence-based standard regimen (24,61,89-91). The emergence of pembrolizumab, PARP inhibition and ADCs should therefore not be misread as automatic grounds for marginalizing capecitabine in appropriate residual-disease populations.

Attempts to intensify postoperative immunotherapy beyond established pathways should still be considered investigational. OXEL, a randomized phase II study, suggested immunological modulation, meaning changes in immune activation and immune-cell or tumor immune-marker profiles, with nivolumab plus capecitabine in residual TNBC, but this study was small and not powered for survival practice change (92). MIRINAE, a randomized phase II trial, addressed a clinically important question, namely whether atezolizumab can add benefit to capecitabine in residual TNBC. However, until its results become conclusive it should not be applied to influence routine care (93,94). Likewise, for patients already treated according to a KEYNOTE-522-like perioperative pathway, adjuvant pembrolizumab completion should be viewed as the completion of an integrated strategy rather than as a separate, independently optimized decision (6,7). Recent adjuvant immunotherapy studies have reinforced this boundary. A-BRAVE, a phase III randomized trial, randomized 466 patients with high-risk early-stage TNBC to receive adjuvant avelumab or observation for 12 months after the completion of standard surgery and neoadjuvant or adjuvant chemotherapy. Avelumab did not significantly improve disease-free survival in the intention-to-treat population (HR, 0.81; 95% CI, 0.61-1.09) or in the residual-disease stratum (HR, 0.80; 95% CI, 0.58-1.10), although a descriptive improvement in OS was reported (HR, 0.66; 95% CI, 0.45-0.97) (95). ALEXANDRA/IMpassion030, a randomized phase III trial, likewise showed that adding atezolizumab to postoperative chemotherapy after upfront surgery did not improve invasive disease-free survival (HR, 1.11; 95% CI, 0.87-1.42), supporting the same practical conclusion. Therefore, the effects of additional adjuvant checkpoint blockade outside the established perioperative pembrolizumab pathway remain unresolved and should not be treated as routine care (96). SWOG S1418/NRG-BR006 is a randomized phase III trial of adjuvant pembrolizumab for patients with residual invasive TNBC after neoadjuvant chemotherapy. It opened to accrual in November 2016 and closed to accrual on June 30, 2021. Because complete peer-reviewed final efficacy results are not yet available, it should be cited as an important completed-accrual study under long-term follow-up rather than as evidence supporting routine escalation (97).

The residual-disease setting is also where over-treatment is easiest to justify rhetorically and hardest to justify evidentially. Residual disease certainly marks higher recurrence risk, but not all residual disease carries the same prognosis (16,71,74,83). Small-volume residual disease with low RCB, favorable nodal status and negative postoperative ctDNA is not equivalent to bulky residual burden with persistent ctDNA positivity. The future of post-neoadjuvant management is therefore unlikely to be a single stronger regimen for all non-pCR patients. It is more likely to be a risk-adapted framework in which capecitabine, olaparib, adjuvant pembrolizumab completion and novel agents are positioned according to the quality of residual risk rather than to non-pCR alone.

A practical response-adapted framework should therefore connect the caution against empirical escalation or de-escalation with the later biomarker and post-neoadjuvant treatment discussion, rather than relying on any single marker. pCR supports favorable prognosis but does not prove that adjuvant pembrolizumab can be omitted after a KEYNOTE-522-like regimen (6,9,61). Residual cancer burden and nodal status define the anatomical and pathological risk left after treatment (16,83). ctDNA may refine

molecular residual-risk assessment, but it is not yet a validated standalone trigger for routine escalation (69-77). Germline BRCA1/2 status can identify patients eligible for adjuvant olaparib (25), prior pembrolizumab exposure determines whether the pembrolizumab regimen should be completed or newly introduced and cumulative toxicity determines whether additional treatment is clinically deliverable (61). Response-adapted treatment modification should therefore be based on the convergence of pathological response, molecular residual-risk information, actionable germline status, prior therapy exposure and patient-level tolerability, preferably within prospective trials when de-escalation or novel escalation is being considered.

6. Emerging therapeutic strategies in neoadjuvant and post-neoadjuvant TNBC

ADC development is now one of the most active areas of perioperative treatment research in TNBC, but the field is currently at two different stages depending on the clinical setting. In the neoadjuvant setting, NeoSTAR, a phase II clinical trial, showed that sacituzumab govitecan has clear single-agent activity and can support a response-guided design, with a pCR rate of 30% and encouraging short-term EFS (42). This is an important proof of principle, but not a basis for replacing chemoimmunotherapy in routine care. As such, ADCs should not be treated as a homogeneous drug class. Sacituzumab govitecan is a TROP-2-directed ADC using SN-38 as its topoisomerase I inhibitor payload through a hydrolyzable linker (98). By contrast, datopotamab deruxtecan is also TROP-2-directed, but uses a tetrapeptide-based cleavable linker and a deruxtecan topoisomerase I inhibitor payload (99). Trastuzumab deruxtecan is HER2-directed and is most relevant to HER2-low or HER2-ultralow breast cancer rather than the classic HER2-negative TNBC. Differences in target, linker stability, payload, bystander effect, toxicity profile and clinical setting mean that ADC evidence should be interpreted by agent rather than generalized across the entire class.

The more clinically compelling near-term role for ADCs may be in residual disease. TROPION-Breast03 and OptimICE-RD are randomized phase III post-neoadjuvant residual-disease trials in high-risk populations: TROPION-Breast03 evaluated datopotamab deruxtecan either alone or with durvalumab vs. investigator-selected therapy in patients with residual invasive TNBC after neoadjuvant treatment, whereas OptimICE-RD evaluated sacituzumab govitecan plus pembrolizumab vs. pembrolizumab with or without capecitabine in residual stage II-III TNBC (44,88). These two trials are protocol and trial-design reports, and definitive efficacy findings have not yet been reported; they should therefore be described as ongoing or awaiting efficacy results rather than as positive studies. TROPION-Breast04 has a different position in the treatment sequence, testing neoadjuvant datopotamab deruxtecan plus durvalumab followed by adjuvant durvalumab in treatment-naive early-stage TNBC or hormone receptor-low/HER2-negative breast cancer against a pembrolizumab-chemotherapy standard-of-care arm (43). These are coherent development strategies, but they remain ongoing randomized trials that are awaiting efficacy evidence for routine perioperative ADC use. Here, HR refers to hormone receptor status, not hazard ratio.

7. Conclusion and future perspectives

Current evidence reinforces three practical problems in neoadjuvant TNBC: Heterogeneity in treatment sensitivity; the balance between intensification and toxicity; and the persistent gap between prognostic biomarkers and validated treatment-selection tools. Clinical management should be viewed as a linked sequence of decisions rather than as a list of regimens.

As a result, three conclusions follow. Anthracycline-taxane chemotherapy remains the reference platform, platinum should be treated as a selective intensifier rather than a universal component, and pembrolizumab-based perioperative therapy has the strongest evidence base. Post-neoadjuvant treatment should be risk-adapted, with capecitabine and olaparib anchored to conclusive randomized evidence. In patients receiving a KEYNOTE-522-like regimen, however, carboplatin should be described as part of the validated chemoimmunotherapy backbone rather than as an optional platinum intensifier.

Near-term evidence that requires further verification includes residual-disease ADC programs, such as OptimICE-RD and TROPION-Breast03, in addition to neoadjuvant ADC-immunotherapy strategies, such as TROPION-Breast04. In parallel, A-BRAVE and ALEXANDRA/IMpassion030 help define a negative boundary for empiric adjuvant checkpoint-inhibitor escalation, whereas SWOG S1418/NRG-BR006 has completed accrual and remains an important residual-disease adjuvant pembrolizumab study under long-term follow-up (95-97). These studies are likely to clarify whether the next treatment boundary is defined by additional adjuvant immunotherapy, ADC-based residual-disease treatment, ctDNA/MRD-enriched intervention or safer de-escalation for patients with deep response.

Biomarkers improve risk refinement, particularly RCB and ctDNA, but most function better as prognostic tools instead of as standalone treatment selectors. Progress will depend less on adding agents indiscriminately and more on defining which patients can safely de-escalate, when ctDNA-guided intervention is justified and which residual-disease subsets truly warrant new standards. At present, the most defensible approach remains evidence-based, response-aware, and explicit about the boundary between routine practice and investigation.

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HC and QQY conceived the review topic and supervised manuscript development. BL and XT performed the literature search and evidence appraisal, and drafted the initial manuscript. QQY and HC critically revised the manuscript for important intellectual content. Data authentication is not applicable. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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