

Review Article

A Critical Review of the IMpassion031 Trial: Evaluating Peri-operative Atezolizumab in Early-Stage Triple-Negative Breast Cancer

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Abstract: This review critically examines findings from the randomized phase III IMpassion031 trial, which evaluated the integration of peri-operative atezolizumab into standard neoadjuvant chemotherapy for patients with stage II–III triple-negative breast cancer (TNBC). The addition of atezolizumab significantly improved pathologic complete response (pCR) rates, highlighting its potential to enhance early therapeutic outcomes. Although long-term endpoints—including event-free survival (EFS), disease-free survival (DFS), and overall survival (OS)—exhibited favorable trends, they did not achieve statistical significance. Notably, exploratory circulating tumor DNA (ctDNA) analyses emerged as powerful prognostic tools: baseline ctDNA-negativity predicted excellent prognosis, while ctDNA clearance correlated with improved survival outcomes, and persistent ctDNA at surgery signaled high relapse risk. Patient-reported outcomes indicated that treatment burden remained largely unchanged with atezolizumab. Taken together, these findings reinforce the importance of immunotherapy and molecular monitoring in TNBC management. The review synthesizes trial design, therapeutic efficacy, safety profile, ctDNA implications, and patient experience, and explores future directions including ctDNA-guided interventions and the potential refinement of immunotherapy strategies.

Keywords: IMpassion031 trial, peri-operative, atezolizumab, triple-negative breast cancer

1. INTRODUCTION

Triple-negative breast cancer (TNBC) is defined by the absence of estrogen and progesterone receptors and lack of HER2 amplification, accounting for roughly one in five early-stage breast cancers [1]. Its biology is marked by high-grade histology, genomic instability, and a propensity for early relapse, particularly in the first three years after diagnosis. Although anthracycline- and taxane-based chemotherapy remains foundational, a substantial fraction of patients relapses despite modern multimodal therapy, highlighting the need for strategies beyond cytotoxic intensification. Over the past decade, immune checkpoint inhibitors (ICIs) have reshaped paradigms across solid tumors, and TNBC has emerged as the breast cancer subtype with the strongest immunogenic features, including higher stromal tumor-infiltrating lymphocytes (sTILs), increased PD-L1 expression, and a relatively higher tumor mutational burden compared to hormone receptor-positive disease [2]. These attributes provide a biological rationale for combining ICIs with chemotherapy in the neoadjuvant setting to augment pathologic complete response (pCR), deepen eradication of micro metastatic disease, and potentially improve long-term outcomes. Neoadjuvant immunochemotherapy aims to leverage intact tumor antigens to prime and expand anti-tumor T cells in vivo, while chemotherapy induces immunogenic cell death, increases antigen presentation, and depletes immunosuppressive myeloid

populations. Preclinical data suggest that initiating checkpoint blockade before surgery can produce more robust systemic immune memory than adjuvant-only administration, likely due to greater antigenic stimulation within the tumor microenvironment. In TNBC, baseline immune infiltration and dynamic changes during treatment both correlate with response to therapy, supporting a peri-operative strategy. Moreover, the neoadjuvant platform enables early readouts via pCR and embedded translational studies, including circulating tumor DNA (ctDNA) monitoring and serial immune profiling, which can inform patient selection and post-operative management [3].

2. TRIAL DESIGN AND METHODOLOGY

The IMpassion031 trial evaluated peri-operative atezolizumab in combination with standard neoadjuvant chemotherapy for patients with stage II–III TNBC. It employed a randomized, double-blind, placebo-controlled design, with 1:1 allocation to atezolizumab or placebo in combination with weekly nab-paclitaxel followed by dose-dense doxorubicin plus cyclophosphamide, then definitive surgery [4]. Post-operatively, the atezolizumab arm continued maintenance immunotherapy, reflecting a peri-operative strategy intended to consolidate immune-mediated tumor control. Eligibility included previously untreated invasive TNBC with tumors larger than 2 cm, ECOG performance status 0–1, and adequate organ function. The primary endpoint was pCR in breast and nodes; key secondary endpoints included pCR by PD-L1 status, event-free survival (EFS), disease-free survival (DFS), overall survival (OS), and patient-reported outcomes (PROs) [5]. Embedded exploratory analyses evaluated ctDNA at multiple timepoints to assess prognostic and pharmacodynamic relationships. IMpassion031 met its primary endpoint, demonstrating a clinically meaningful improvement in pCR with the addition of atezolizumab to chemotherapy. The pCR benefit was directionally consistent across PD-L1–defined subgroups, supporting the hypothesis that neoadjuvant immunotherapy can expand benefit beyond PD-L1–enriched populations. Early time-to-event analyses showed favorable trends for EFS, DFS, and OS; however, follow-up duration and event counts limited statistical confirmation. A recurring observation across peri-operative immunotherapy studies is that robust pCR gains do not uniformly translate into early survival separation, especially in TNBC cohorts where event accrual and competing adjuvant interventions may dilute early signals. Nevertheless, patient-level correlations between achieving pCR and improved long-term outcomes remain strong, lending credence to pCR as a surrogate for benefit in high-risk TNBC, with the important caveat that trial-level surrogacy is more complex and context dependent [6].

3. COMPARATIVE CONTEXT: POSITIONING AMONG NEOADJUVANT IMMUNOTHERAPY TRIALS

IMpassion031 complements and contrasts with other pivotal neoadjuvant trials. Pembrolizumab-based regimens have shown pCR and event-free survival advantages in early TNBC, leading to regulatory adoption of peri-operative PD-1 blockade with chemotherapy [7]. Trials such as Gepar Nuevo with durvalumab suggested that a short “window” of pre-chemotherapy immunotherapy may augment pCR and potentially impact survival on longer follow-up, reinforcing the biologic premise of priming immunity before cytotoxic therapy. Conversely, alternative regimens such as carboplatin plus nab-paclitaxel with atezolizumab did not improve pCR in certain settings, highlighting the importance of chemotherapy backbone, timing, and immunotherapy pharmacodynamics. The negative results of adjuvant-only atezolizumab in high-risk post-surgical TNBC further emphasize that neoadjuvant exposure to intact tumor antigen may be a critical determinant of benefit in this disease. These mixed outcomes underscore a nuanced landscape in which drug target (PD-1 vs PD-L1), regimen composition, PD-L1 assay selection, and patient selection all shape efficacy. At the patient level, achieving pCR consistently correlates with improved EFS and OS in TNBC, across both chemotherapy and immunotherapy-containing regimen [8]. However, pCR is an imperfect surrogate at the trial level, with meta-analyses showing variable correlation to survival endpoints depending on disease subtype,

regimen, and follow-up. In the immunotherapy era, discordance can be accentuated by the influence of post-neoadjuvant therapies (e.g., capecitabine, PARP inhibitors, continued checkpoint blockade) and evolving standards of care. As such, while pCR remains a valuable endpoint to triage adjuvant risk and guide escalation or de-escalation, definitive validation of long-term benefit requires mature EFS and OS analyses and careful accounting for subsequent therapies. In IMpassion031, favorable but non-significant trends support continued follow-up and harmonized analyses with complementary datasets [9].

4.SAFETY AND PERI-OPERATIVE TOLERABILITY

The addition of atezolizumab produced a safety profile consistent with known toxicities of PD-L1 inhibition layered on chemotherapy. Rates of grade 3–4 treatment-related adverse events were comparable between arms, with a modest increase in serious adverse events in the immunotherapy arm [10]. Immune-related adverse events were generally manageable with established algorithms; the most frequent included thyroid dysfunction, hepatic enzyme elevations, and pneumonitis, typically low grade and responsive to corticosteroids when indicated. Importantly, peri-operative administration did not meaningfully compromise surgical feasibility or timing in the trial framework, an operational consideration critical to adoption [11]. The cumulative tolerability profile supports the feasibility of integrating atezolizumab into a neoadjuvant backbone in appropriately selected patients. PROs add an essential patient-centered dimension to efficacy and safety. In IMpassion031, baseline quality of life metrics was balanced and declined during neoadjuvant therapy in both arms, reflecting the burdens of intensive chemotherapy. Notably, the addition of atezolizumab did not significantly increase treatment burden relative to placebo, and most measures stabilized or returned toward baseline during the adjuvant phase. These data suggest that peri-operative immunotherapy can be deployed without substantial deterioration in patient-reported functioning and well-being beyond the expected chemotherapy effects, supporting its acceptability in routine practice [12].

5.ctDNA DYNAMICS AS A PROGNOSTIC BIOMARKER

One of the defining contributions of IMpassion031 is the integration of serial ctDNA to interrogate prognostic and pharmacodynamic signals. Baseline ctDNA-negative patients comprised a small subgroup with excellent outcomes irrespective of pCR, hinting at a biology of lower tumor burden and lower risk. Among baseline ctDNA-positive patients, high rates of ctDNA clearance by surgery were observed, and clearance correlated with improved survival endpoints. Persistent ctDNA at surgery identified a small but particularly high-risk subset, enriched for non-pCR, with poor outcomes and universal ctDNA positivity at recurrence [13]. These findings reinforce the concept of molecular residual disease (MRD) as an independent prognostic marker that can refine risk beyond pCR status alone, potentially enabling adaptive adjuvant strategies [14]. They are congruent with a broader TNBC literature showing that post-neoadjuvant ctDNA positivity portends markedly higher recurrence risk and shorter survival, and that dynamic changes in ctDNA during treatment have predictive and prognostic relevance. PD-L1 status, while useful, incompletely captures the immunogenic potential of TNBC. sTILs are strongly prognostic and may be predictive of immunotherapy benefit, with higher baseline immune infiltration associated with increased pCR and improved survival. Tumor mutational burden (TMB) is modestly elevated in TNBC relative to other breast cancer subtypes, and exploratory analyses suggest an association between higher TMB and benefit from immunotherapy, though clinical utility is limited by assay variability and overlapping distributions [15]. Immune gene expression signatures capturing interferon gamma signaling, antigen presentation, and T-cell cytotoxicity have also been associated with response to neoadjuvant immunochemotherapy. Composite biomarker models that integrate PD-L1, sTILs, TMB, and gene signatures may ultimately offer superior predictive value than any single marker. The tumor microenvironment's suppressive axes (e.g., TGF- β , adenosine,

myeloid-derived suppressor cells) represent additional levers that can be targeted in rational combinations [16].

6. GERMLINE GENETICS, DNA REPAIR, AND THERAPEUTIC INTERPLAY

Germline BRCA1/2 mutations and homologous recombination deficiency (HRD) are overrepresented in TNBC and carry therapeutic implications. PARP inhibitors improve outcomes in high-risk, early-stage germline BRCA-mutated breast cancer, and platinum agents increase pCR in subsets of TNBC, particularly HRD-enriched tumors [17]. Preclinical and early clinical data suggest immunogenic synergy between DNA damage response targeting and checkpoint blockade via increased neoantigen load and c GAS–STING pathway activation. Rational integration of PARP inhibition with checkpoint blockade in early TNBC is an active area, with careful attention to overlapping toxicities and sequencing. Furthermore, HRD status and genomic scars may refine risk assessment and adjuvant choices for non-pCR patients. The efficacy of peri-operative immunotherapy appears sensitive to the chemotherapy backbone and sequencing. Taxane-anthracycline regimens remain standard in early TNBC, and consistent pCR gains have been seen when PD-1/PD-L1 agents are layered onto taxane followed by anthracycline platforms [18]. The role of platinum requires nuance: while carboplatin increases pCR with chemotherapy alone, its added value on top of immunotherapy may be regimen dependent and contingent on biomarker-defined subsets. Dose density, steroid premedication, and supportive care protocols can also modulate immune responses; avoiding excessive immunosuppression while ensuring safe chemotherapy delivery is a practical consideration. Finally, maintenance immunotherapy post-operatively may consolidate benefit in some settings, but its necessity and duration remain open questions, particularly as negative adjuvant-only studies temper enthusiasm for prolonged exposure absent neoadjuvant priming [19].

7. SPECIAL POPULATIONS AND EQUITY CONSIDERATIONS

Real-world applicability requires attention to patients often underrepresented in trials. Older adults, those with autoimmune comorbidities, and individuals from diverse racial and ethnic backgrounds may have distinct benefit–risk profiles and barriers to access [20]. TNBC disproportionately affects younger women and women of African descent, who also face structural disparities that can exacerbate outcomes. Incorporating PROs, shared decision-making, and supportive resources is critical to equitable implementation [21]. Additionally, PD-L1 testing variability and limited access to advanced assays like tumor-informed ctDNA can widen gaps; standardization and cost-effective pathways are needed for broad adoption. Neoadjuvant immunotherapy raises practical questions for surgery and radiotherapy. The timing of surgery is typically preserved with modern regimens, though vigilance for immune-related toxicities that could delay procedures is warranted. Post-operative radiotherapy planning should account for enhanced immune activation; emerging evidence suggests potential synergy between radiation and immunotherapy via antigen release and adaptive immune priming. Prospective evaluation of optimal sequencing, field design, and toxicity mitigation in the context of peri-operative ICIs is an opportunity to refine multidisciplinary care [22].

8. PATIENT-CENTERED OUTCOMES AND SURVIVORSHIP

Beyond traditional oncologic endpoints, survivorship in TNBC encompasses physical, psychosocial, and financial dimensions. ICIs introduce the possibility of chronic endocrinopathies and rare late immune toxicities that require long-term monitoring and clear patient education. The absence of increased treatment burden in PROs during IMpassion031 is reassuring, yet long-term quality-of-life trajectories and return-to-work metrics remain essential measures for value-based care [23]. Embedding routine PRO assessment and supportive interventions within immunotherapy pathways can improve patient

experience and adherence. The promise of ctDNA lies in transforming static staging into a dynamic risk assessment. Baseline ctDNA may stratify risk before treatment; early on-treatment clearance can serve as a pharmacodynamic marker of chemosensitivity and immunotherapy engagement; post-neoadjuvant persistence may signal residual disease and trigger treatment intensification [24]. Several trial designs are now testing ctDNA-guided strategies, including adjuvant intensification for MRD-positive patients and de-escalation for MRD-negative, pCR achievers. Key challenges include assay standardization, defining clinically actionable thresholds, and demonstrating that ctDNA-directed interventions improve outcomes without undue toxicity. Health system integration will also depend on cost, turnaround time, and equitable access [25].

9.BEYOND PD-1/PD-L1: NEXT-GENERATION IMMUNO-ONCOLOGY IN EARLY TNBC

Combination approaches may further expand benefit. Targets under investigation include LAG-3, TIGIT, and TIM-3, as well as modulators of myeloid inflammation (CSF1R), adenosine signaling (CD73), and TGF- β . Oncolytic viruses, cancer vaccines, and adoptive cellular therapies are being explored as adjuncts to amplify tumor-specific immunity [26]. Antibody–drug conjugates (ADCs) like Sacituzumab govite can have transformed metastatic TNBC care and are entering earlier settings; combinations of ADCs with ICIs could theoretically synergize by providing immunogenic cell death while reinvigorating T-cell responses [27]. As the arsenal expands, adaptive designs and robust translational correlates will be crucial to identify optimal partners, sequences, and biomarkers. As peri-operative immunotherapy becomes more prevalent, understanding cost-effectiveness and implementation barriers is essential. High upfront costs may be offset by reduced recurrence and treatment of metastatic disease, but real-world studies must quantify these trade-offs. ctDNA testing adds another layer of expense and logistics; payer coverage, laboratory capacity, and clinician education will determine scalability. Implementation science frameworks can guide equitable adoption, minimize unwarranted variation, and embed continuous learning into care pathways [28].

10.LIMITATIONS OF THE CURRENT EVIDENCE BASE

Several limitations temper immediate generalization. Follow-up remains insufficient in many neoadjuvant immunotherapy trials to conclusively demonstrate OS benefit, and non-pCR adjuvant strategies confound survival analyses. Heterogeneity in PD-L1 assays and thresholds complicates cross-trial comparisons and clinical decision-making. pCR improvements, while meaningful, do not guarantee survival gains at the trial level, necessitating cautious interpretation. PROs, although encouraging, may not capture longer-term survivorship burdens associated with immune therapy. Finally, most ctDNA analyses remain exploratory; prospective validation and interventional trials are required before routine practice change. IMpassion031 strengthens the rationale for peri-operative immunotherapy in early-stage TNBC, particularly for patients eligible for intensive neoadjuvant chemotherapy. For many, a standard approach now includes checkpoint blockade with taxane–anthracycline backbones, with adjuvant continuation in PD-1–based strategies. For patients without pCR, adjuvant therapy should be individualized based on residual disease burden, germline status, and tolerability, integrating options such as capecitabine and PARP inhibition where indicated. PD-L1 testing can inform expectations but should not solely dictate neoadjuvant immunotherapy use in early TNBC. Incorporating ctDNA into research protocols and, where feasible, into multidisciplinary discussions can enhance risk stratification and trial matching. Shared decision-making remains central to balancing benefits, risks, and patient values.

11.FUTURE DIRECTIONS

Priorities for the next phase include extending follow-up for mature EFS and OS readouts, harmonizing data across peri-operative trials, and refining patient selection through composite biomarkers. Randomized studies testing ctDNA-guided escalation and de-escalation are needed to determine whether molecular response can safely tailor therapy intensity. Comparative effectiveness research should clarify differences between PD-1 and PD-L1 inhibitors, optimal chemotherapy backbones, and the role of platinum in immunochemotherapy regimens. Integrative strategies combining ICIs with PARP inhibitors, ADCs, radiation, or next-generation immunotherapies warrant careful evaluation with robust safety monitoring. Finally, efforts to standardize PD-L1 testing, democratize access to ctDNA assays, and address disparities will be integral to ensuring that advances benefit all patients.

12.Conclusion

IMpassion031 provides a rigorous proof-of-concept that peri-operative atezolizumab can significantly increase pCR in stage II–III TNBC without imposing substantial additional patient-reported burden, and with a safety profile consistent with expectations for checkpoint inhibitors added to chemotherapy. Favorable trends in long-term outcomes and compelling ctDNA dynamics underscore the biologic and clinical promise of neoadjuvant immunotherapy and molecular monitoring in this disease. Set against a broader landscape that includes positive pembrolizumab-based trials and negative adjuvant-only PD-L1 blockade, the totality of evidence highlights two themes: timing matters, and biology matters. The field is now poised to move beyond one-size-fits-all paradigms toward biomarker-enriched, response-adaptive care. Achieving that vision will require longer follow-up, prospective validation of ctDNA-guided strategies, thoughtful combinations, and a commitment to equitable implementation. If realized, these efforts could convert early immunologic gains at the time of surgery into durable survival benefits, reshaping the standard of care for patients with early-stage TNBC.

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