

Severe Adverse Events in Neoadjuvant Therapy of Triple-Negative Breast Cancer: A Systematic Review and Meta-Analysis of Randomized Phase 3 Trials



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PII: S1526-8209(26)00069-8
DOI: <https://doi.org/10.1016/j.clbc.2026.04.016>
Reference: CLBC 2240

To appear in: *Clinical Breast Cancer*

Received date: Oct 14, 2025
Revised date: Mar 6, 2026
Accepted date: Apr 20, 2026

Please cite this article as: Marcelo Antonini , André Mattar , Marcelo Madeira ,
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apy of Triple-Negative Breast Cancer: A Systematic Review and Meta-Analysis of Randomized Phase
3 Trials, *Clinical Breast Cancer* (2026), doi: <https://doi.org/10.1016/j.clbc.2026.04.016>

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Highlights

- **Neoadjuvant therapy in TNBC carries substantial grade ≥ 3 toxicities.**
- **PARP inhibitors significantly increase risk of anemia, neutropenia, and thrombocytopenia.**
- **Immune checkpoint inhibitors add immune-related toxicities but limited hematologic impact.**
- **Platinum-based regimens showed the lowest prevalence of severe adverse events.**
- **Biomarker-driven selection and close monitoring are essential to optimize safety.**

Severe Adverse Events in Neoadjuvant Therapy of Triple-Negative Breast Cancer: A Systematic Review and Meta-Analysis of Randomized Phase 3 Trials

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ABSTRACT

Background: Neoadjuvant therapy (NAT) is standard treatment for triple-negative breast cancer (TNBC) but toxicity is a major concern. This study aimed to assess the incidence and risk of grade ≥ 3 adverse events (AEs) associated with NAT in non-metastatic TNBC.

Methods: We performed a systematic review and meta-analysis registered in PROSPERO (CRD42024562785). Four databases were searched for randomized controlled trials (RCTs) from 2010–2025 reporting grade ≥ 3 AEs in TNBC. Pooled prevalence and risk ratios (RRs) were estimated using random-effects models.

Results: Six RCTs including 3,316 patients were analyzed. Neutropenia was the most common severe AE, with pooled prevalence of 33.5% for ICIs, 23.7% for PARP inhibitors, and 16.0% for platinum regimens. PARP inhibitors significantly increased neutropenia (RR 1.84) and anemia (RR 2.08), while thrombocytopenia risk was also higher (RR 3.56). ICIs were associated with more febrile neutropenia (14.9%) but without significant risk increase. ALT elevation was more frequent with platinum regimens (6.4%). Fatal AEs were rare (<1%).

Conclusions: NAT improves outcomes in TNBC but is associated with substantial severe toxicity. PARP inhibitors carry the greatest hematologic risks, ICIs add immune-related AEs, and platinum regimens showed the lowest AE burden. Biomarker-driven patient selection and vigilant monitoring are essential to optimize safety.

Keywords:

Triple-negative breast cancer; Neoadjuvant chemotherapy; Toxicity; Immune checkpoint inhibitors; PARP inhibitors; Meta-analysis.

1.0 Introduction:

Triple-negative breast cancer (TNBC) is an aggressive subtype of breast carcinoma that predominantly affects younger women and certain racial and ethnic groups, such as African American and Hispanic populations. (1, 2) Defined by the absence of estrogen receptor (ER), progesterone receptor (PR), and HER2 expression, TNBC accounts for approximately 15–20% of all breast cancers (3) and is associated with higher rates of recurrence, early metastasis, and lower overall survival (OS) compared to hormone receptor-positive or HER2-positive subtypes. (4) The lack of targetable receptors renders endocrine and HER2-directed therapies ineffective, making cytotoxic chemotherapy the mainstay of systemic treatment in both early and advanced disease. (4)

Despite the initial responsiveness of TNBC to chemotherapy, its clinical and molecular heterogeneity contributes to variable outcomes. Gene expression profiling has identified several distinct TNBC subtypes—including basal-like, mesenchymal, immunomodulatory, and luminal androgen receptor-positive tumors—each with differing prognoses and therapeutic susceptibilities. (5) This biological complexity highlights the need for individualized, biomarker-driven treatment strategies.

A substantial proportion of TNBC cases—particularly those with basal-like features—harbor germline BRCA1 or BRCA2 pathogenic variants, which confer homologous recombination deficiency and render tumors more susceptible to DNA-damaging agents. (6) This molecular vulnerability provides the rationale for incorporating poly (ADP-ribose) polymerase (PARP) inhibitors, such as olaparib, into systemic treatment strategies. Olaparib induces synthetic lethality by inhibiting DNA repair in BRCA-mutated cells, selectively eliminating tumor cells while minimizing harm to normal tissue. (7) It has demonstrated clinical efficacy in advanced breast cancer and, more recently, showed a significant overall survival benefit in patients with early-stage, high-risk HER2-negative disease carrying germline BRCA mutations, leading to its incorporation into standard adjuvant treatment guidelines. Although the use of PARP inhibitors in the neoadjuvant setting is still under active investigation, emerging evidence suggests that they may enhance pathological response rates in TNBC patients with BRCA mutations, who represent a biologically defined subgroup with increased sensitivity to DNA-damaging agents. (8) Nevertheless, PARP inhibitors are associated with a distinct toxicity profile, particularly Grade ≥ 3 hematologic adverse events such as anemia, neutropenia, and thrombocytopenia. These risks underscore the importance of biomarker-guided treatment selection and close toxicity monitoring when incorporating olaparib into curative-intent regimens for early-stage TNBC. (8, 9)

Neoadjuvant therapy (NAT) has become a standard approach for early-stage TNBC. In addition to facilitating breast-conserving surgery, it provides an opportunity to assess tumor chemosensitivity via pathological complete response (pCR). Achieving pCR is strongly associated with improved disease-free survival (DFS) and OS in TNBC, reinforcing its role as a surrogate endpoint for long-term benefit. (10-12) However, conventional NAT regimens based on anthracyclines and taxanes have limited efficacy in some patients, prompting the investigation of novel agents to improve response rates and survival.

The introduction of immune checkpoint inhibitors (ICIs) represents a major advancement in TNBC management. This subtype is considered more immunogenic than others, due to higher tumor-infiltrating lymphocytes, PD-L1 expression, and mutational burden. (13-16) These features support the rationale for immunotherapy, particularly PD-1/PD-L1 blockade, to potentiate T-cell-mediated antitumor responses.

KEYNOTE-522, a pivotal phase 3 trial, demonstrated that adding pembrolizumab to standard chemotherapy significantly improved pCR and OS early-stage TNBC, irrespective of PD-L1 status.(17) Other trials, including NeoTRIP (18) and studies involving atezolizumab (19) and durvalumab, (20) have further explored the efficacy of ICIs in this setting. These results have led to the integration of ICIs into neoadjuvant treatment guidelines for high-risk TNBC.

However, the use of ICIs introduces new safety considerations. Immune-related adverse events (irAEs) can affect multiple organ systems, including skin, lungs, liver, gastrointestinal tract, and endocrine glands. (21-23) Although most irAEs are manageable with corticosteroids or immunosuppressive therapy, they can be severe, persistent, and occasionally life-threatening, potentially compromising treatment continuity.

While clinical trials have predominantly focused on efficacy endpoints such as pCR and survival, the reporting of irAEs—particularly over long-term follow-up—remains limited. This underreporting poses a challenge in real-world practice, where understanding the full spectrum and incidence of treatment-related toxicities is critical to balancing therapeutic benefit and patient safety.

However, to date, no systematic review has comprehensively quantified the incidence and comparative risk of severe toxicities (Grade ≥ 3 adverse events) across neoadjuvant treatment (NAT) regimens in early-stage TNBC. In light of the expanding use of neoadjuvant immunotherapy and PARP inhibitors and the evolving toxicity landscape, there is a pressing need for robust evaluation of safety outcomes. This review aims to synthesize data from phase III randomized controlled trials published over the last 15 years to characterize and compare Grade ≥ 3 adverse events associated with NAT regimens, including chemotherapy, PARP inhibitors, and immune checkpoint inhibitors. By providing a comprehensive assessment of toxicity risks, this study seeks to inform precision-based treatment planning and support evidence-driven decision-making for patients with early-stage TNBC.

2.0 METHODS

2.1. Study Design and Registration

This systematic review and meta-analysis were conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) (24) guidelines. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42024562785.

2.2. Clinical Question and PICO Framework

This study was guided by the following PICO framework:

- Population: Adult women (≥ 18 years) with newly diagnosed, non-metastatic TNBC;
- Intervention: Neoadjuvant chemotherapy regimens including platinum agents, PARP inhibitors, or immune checkpoint inhibitors (ICIs);
- Comparator: Standard chemotherapy regimens without the investigational agents;
- Outcomes: Incidence of grade 3 or higher adverse events, defined according to the Common Terminology Criteria for Adverse Events, version 5.0 (CTCAE v5.0). (25)

2.3. Eligibility Criteria

Eligible studies enrolled adult women with histologically confirmed, previously untreated, non-metastatic TNBC and reported on grade ≥ 3 adverse events. We included randomized controlled trials published between January 1, 2010, and June 30, 2025. Although our primary focus was on phase 3 trials, phase 2 randomized trials were also eligible if they enrolled a substantial sample size, employed a rigorous randomized controlled design, and reported detailed grade ≥ 3 toxicity outcomes comparable to phase 3 standards. We excluded trials that were single-arm, retrospective, non-randomized, limited to metastatic disease, or lacked toxicity data stratified by severity.

2.4. Data Sources and Search Strategy

A comprehensive search was conducted in MEDLINE (via PubMed), Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL), Google Academic from January 2010 through December 2024. Search terms included combinations of "triple-negative breast cancer", "neoadjuvant chemotherapy", "immune checkpoint inhibitors", "PARP inhibitors", "platinum", and "adverse events". Controlled vocabulary (MeSH/Emtree) and Boolean operators were used. The complete search strategy is presented in Supplementary Appendix A. Reference lists of included articles and relevant reviews were also screened manually.

2.5. Study Selection

Two reviewers independently screened titles and abstracts. Full-text evaluation was conducted for potentially eligible studies. Disagreements were resolved by consensus or arbitration by a third reviewer. The selection process was documented using a PRISMA flow diagram.

2.6. Data Extraction

Two reviewers independently extracted data using a standardized form. Extracted data included trial identifiers (authors, year, journal), sample size, treatment regimens, study duration, inclusion/exclusion criteria, patient characteristics, follow-up, and the incidence of grade ≥ 3 adverse events. Toxicities were classified using CTCAE v5.0.(25) When

absolute numbers were not provided, event counts were estimated from reported percentages and sample sizes.

2.7. Risk of Bias Assessment

The Cochrane Risk of Bias 2.0 (RoB 2) (26) tool was used to assess bias across five domains: randomization, deviations from intended interventions, missing outcome data, measurement of outcomes, and selective reporting. Each study received a global risk of bias judgment (low, some concerns, or high).

2.8. Outcomes and Statistical Analysis

The primary outcome was the incidence of grade ≥ 3 adverse events. Meta-analyses were conducted for toxicities reported in ≥ 3 studies using a random-effects model (DerSimonian and Laird method). For each event, we calculated pooled proportions and risks ratios (RRs) with 95% confidence intervals (CIs). Statistical heterogeneity was evaluated using the I^2 statistic, with values above 50% considered substantial.

Pre-specified subgroup analyses were planned to compare regimens containing platinum agents, PARP inhibitors, and ICIs versus control. Sensitivity analyses included leave-one-out methods and exclusion of studies at high risk of bias. Publication bias will be assessed using funnel plots and Egger's test.

All analyses were conducted using Review Manager (RevMan version 5.4) and R (metafor package, version 4.0 or higher).

3.0 RESULTS

A total of 4,096 records were retrieved through systematic database searches. After removing duplicates and screening titles and abstracts, 22 full-text articles were assessed for eligibility. Of these, ten publications (8, 9, 17-19, 27-31) reporting on six unique RCT met the inclusion criteria and were incorporated into the final analysis. A PRISMA (32) flow diagram outlining the selection process is provided in Figure 1.

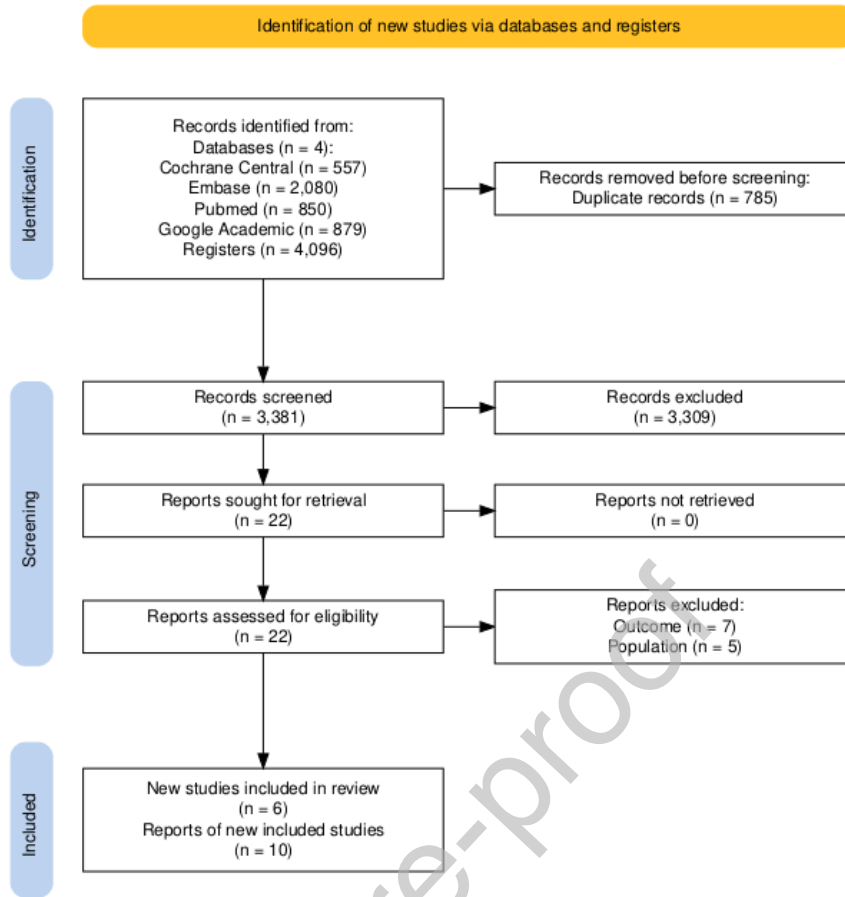


Figure 1 - PRISMA Flow Diagram of Study Selection Process.

3.2 Characteristics of Included Studies

The six included trials were conducted between 2013 and 2024 and collectively enrolled 3,316 women with newly diagnosed, non-metastatic TNBC. (8, 9, 17-19, 27-31) All patients received NAT, either alone or in combination with additional agents such as platinum compounds, PARP inhibitors, or ICIs. Patient eligibility generally required ECOG performance status 0–1, and median age across the trials ranged from 48 to 51 years. Key clinical and methodological features of the studies are summarized in Table 1.

Table 1. Characteristics of the six studies reported by 10 papers

Study name First Author	Publication Year	Period of Inclusion	Sample size	Age, (median [range], in years)	Study arms	Inclusion criteria	Exclusion criteria	Follow-up
BrightNess Loibl et al. (29) Geyer et al. (27)	2018 2022	2014 to 2016	634	50 (IQR 41– 59)	Three groups (2PCV:1PC:1P) 1) paclitaxel plus carboplatin plus veliparib (n=316); 2) paclitaxel plus carboplatin plus veliparib placebo (n=160); 3) paclitaxel plus carboplatin placebo plus veliparib placebo (n=158) *all groups received doxorubicin+ cyclophosphamide	18 years of age or older and had histologically or cytologically confirmed invasive triple-negative breast cancer, clinical stage II–III (T1N1–2 or T2–4N0–2); an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; adequate haematological, renal, and hepatic function; and were deemed candidates for potentially curative surgery by surgeon's assessment at presentation	Patients were ineligible if they had received previous anti- cancer treatment, were receiving ovarian hormonal replacement therapy, had a history of seizure within 1 year before study entry, pre-existing neuropathy, allergy to cremophor-containing medications, any clinically uncontrolled conditions, previous or concurrent cancer, or were pregnant or breastfeeding.	Median= 4.5 years (did not differ by arm)
IMpassion031 Mittendorf et al. (19)	2020	2017 to 2019	333	51 (22–78)	Two groups 1)atezolizumab+ nab- paclitaxel followed by doxorubicin plus cyclophosphamide (n=165) 2)placebo+ nab- paclitaxel followed by doxorubicin plus	Women or men aged 18 years or older; had clinical stage cT2–T4 (tumour size of >2 cm by at least one radiographic or clinical measurement) and cN0–cN3 histologically documented TNBC (by central assessment of negative HER2, oestrogen receptor, and progesterone receptor status according to American Society of	Previous treatment with an anti-CTLA-4, anti-PD-1, or anti- PD-L1 agent for any malignancy; 20.6 months history of ductal or pleomorphic lobular carcinoma in situ unless more than 5 years before the current diagnosis and treated only surgically; bilateral breast cancer; or the patient had undergone incisional or	Median (IQR) Atezo group: 20.6 months (8.7–24.9) Placebo group: 19.8 months (8.1– 24.5)

					cyclophosphamide (n=168)	Clinical Oncology/College of American Pathologists guidelines ^{17,18}); had received no previous systemic therapy for breast cancer and no previous systemic therapy with anthracyclines or taxanes for any malignancy; had an Eastern Cooperative Oncology Group performance score of 0 or 1; and had confirmed centrally assessed evaluation of tumour PD-L1 status as measured by the VENTANA SP142 assay, with PD-L1 positive defined as PD-L1-expressing tumour-infiltrating immune cells covering 1% or more of the tumour area	excisional biopsy, or both, of primary tumour or axillary lymph nodes, or both, or axillary lymph node dissection before initiation of neoadjuvant therapy.	
KEYNOTE-522 Schmid et al. (17, 30, 31)	2020, 2022 and 2024	2017 to 2018	1174	Pembro group 49 (22–80) Placebo group 48 (24–79)	Two groups (2:1) 1) Pembrolizumab (n=784) 2) Placebo (n=390)	At least 18 years of age and had centrally confirmed triple-negative breast cancer in all foci (as defined by the guidelines of the American Society of Clinical Oncology–College of American Pathologists) 17-19; newly diagnosed, previously untreated, nonmetastatic disease (tumor stage T1c, nodal stage N1-2, or tumor stage T2-4, nodal stage N0-2, according to the primary tumor–regional lymph node staging criteria of the American Joint Committee on Cancer, 7th edition), ²⁰ as determined by the investigator in radiologic	Active autoimmune disease for which the patient had received systemic treatment within the previous 2 years, a diagnosis of immunodeficiency or use of immunosuppressive therapy within the previous week, a history of human immunodeficiency virus infection, a history of noninfectious pneumonitis for which the patient had received glucocorticoids, current pneumonitis, active tuberculosis, active hepatitis B virus or hepatitis C virus	Median 15.5 months

						assessment, clinical assessment, or both; an Eastern Cooperative Oncology Group performance-status score ²¹ of 0 or 1 (on a 5-point scale, with higher numbers indicating greater disability); and adequate organ function.	infection, any active infection for which the patient was receiving systemic therapy, and clinically significant cardiovascular disease.	
NeoTRIP Gianni et al. (18)	2022	2016 to 2018	280	50 (24-79)	Two groups (1:1) 1) Atezolizumab + carboplatin + nab-paclitaxel (n=138) 2) Carboplatin + nab-paclitaxel (n=142)	Untreated histologically confirmed unilateral breast cancer with invasive ductal histology not otherwise specified of high proliferation or grade, HER2 negative and estrogen and progesterone receptor negative. Patients had to be aged 18 years or older with an Eastern Cooperative Oncology Group performance status ₁ . The tumour had to be classified as early high risk (T1cN1; T2N1; T3N0) versus locally advanced (T3N1; T4a, b, c; T4d any N; any T and N2-3).	Key exclusion criteria were metastatic disease (stage IV), bilateral breast cancer, other malignancies, inadequate bone marrow or renal function, impaired liver function, impaired cardiac function, uncontrolled hypertension, pregnancy, refusal to use contraception and history of autoimmune disease.	The follow-up of the study in NeoTRIP is ongoing
PARTNER Abraham et al. (8, 9)	2024 and 2025	2016 to 2021	559	49 (23-71)	Two groups (1:1) 1) Carboplatin + paclitaxel + Olaparib (n=287) 2) Carboplatin + paclitaxel (n=272)	Patients aged between 16 and 70 years with histologically confirmed stage T1–4, N0–3 (tumour or axillary lymph node diameter ≥10 mm) invasive breast cancer, confirmed ER-negative and HER2-negative, and Eastern Cooperative Oncology Group performance status 0–1 were eligible. Other key inclusion criteria were patient fitness to receive the trial	Patients were excluded if they had T0 tumour in the absence of axillary node ≥10 mm, apparent distant metastases, prior history of invasive breast cancer in the past 5 years or any previous chemotherapy or targeted agent used for the treatment of cancer in the past 5 years.	Median 38 months

						chemotherapy regimen and availability of slides and paraffin-embedded tissue blocks from the pretreatment biopsy.		
WSG-ADAPT-TN		2013 to 2015	336	50 (26-75)	Two groups (1:1) 1)Nab-paclitaxel + Gemcitabine (182) 2)Nab-paclitaxel + Carboplatin (154)	Women with previously untreated, operable, unilateral, primary invasive noninflammatory early TNBC (ER and PR < 1%, HER2-negative, as defined by current guidelines [37], all by central pathology) were eligible if age 18 years or older with good performance status (0/1) and adequate hematologic, cardiac, renal, and hepatic function	Patients were excluded for grade>2 peripheral polyneuropathy (PNP) or known incorporated hypersensitivity reaction to the therapy compounds. Additional exclusion criteria included prior malignancies with a disease-free interval <10 years, except curatively treated skin basalioma or cervix carcinoma in situ, as well as sequential breast cancer (BC).	12 weeks
Glutz et al. (28)	2018							

3.3 Clinical Overview of Major Trials

To facilitate clinical interpretation of the safety findings, we summarized the major randomized neoadjuvant trials in triple-negative breast cancer together with their key efficacy outcomes and major grade ≥ 3 toxicities (Table 2). This synthesis allows clinicians to interpret toxicity profiles alongside efficacy results reported in pivotal trials and may support individualized treatment decision-making in the neoadjuvant setting.

Table 2. Clinical interpretation of major randomized neoadjuvant trials in triple-negative breast cancer (TNBC), summarizing treatment strategies, key efficacy outcomes, and major grade ≥ 3 toxicities..

Trial	Treatment Strategy	Key Efficacy Findings	Major Grade ≥ 3 Toxicities	Clinical Considerations
KEYNOTE-522	Pembrolizumab + chemotherapy	Significant increase in pCR and improved event-free survival and overall survival	Neutropenia, febrile neutropenia, anemia, ALT elevation, immune-related adverse events	Immunotherapy-based regimens are currently standard for high-risk early TNBC but require monitoring for immune-related toxicities
IMpassion031	Atezolizumab + chemotherapy	Higher pCR rates with addition of immunotherapy	Neutropenia, leukopenia, anemia, hypertension	Demonstrates benefit of immunotherapy in neoadjuvant TNBC, though hematologic toxicity largely reflects chemotherapy backbone
BrightNess	Paclitaxel + carboplatin $\pm$ veliparib	Improved pCR with carboplatin-containing regimens	Neutropenia, anemia, thrombocytopenia	Platinum intensification improves response but increases hematologic toxicity
PARTNER	Carboplatin + paclitaxel + olaparib	Higher pCR particularly in BRCA-mutated patients	Neutropenia, anemia, thrombocytopenia, fatigue	PARP inhibitors may benefit biomarker-selected patients but

				require careful hematologic monitoring
NeoTRIP	Atezolizumab + carboplatin + nab-paclitaxel	No significant improvement in pCR despite immunotherapy	Neutropenia, thrombocytopenia, leukopenia	Highlights variability of immunotherapy benefit depending on chemotherapy backbone
WSG-ADAPT- TN	Nab-paclitaxel + carboplatin vs nab-paclitaxel + gemcitabine	Carboplatin regimen associated with higher pCR	Neutropenia, ALT elevation	Platinum-based regimens improve response but add hematologic toxicity

Legend: This table provides a clinical synthesis of pivotal randomized trials evaluating neoadjuvant therapies in TNBC, including immunotherapy-, platinum-, and PARP inhibitor-based regimens. The summary highlights the balance between treatment efficacy and severe toxicity profiles reported in each study to support clinical interpretation and treatment selection. **Abbreviations:** TNBC, triple-negative breast cancer; pCR, pathological complete response; PARP, poly (ADP-ribose) polymerase; ALT, alanine aminotransferase.

3.4 Hematologic Toxicities

3.4.1 Neutropenia

Neutropenia of grade 3 or 4 was the most frequently reported adverse event across the included trials. The BrighTNess study demonstrated the highest rates, with 57% of patients experiencing neutropenia in the group treated with paclitaxel, carboplatin, and veliparib (PCV), and 53% in the paclitaxel plus carboplatin (PC) arm. In contrast, the group receiving paclitaxel alone exhibited an incidence of less than 5%.^(27, 29) The KEYNOTE-522 trial reported neutropenia in 34.6% of patients treated with pembrolizumab and chemotherapy, compared to 33.2% in the control group.^(17, 30, 31) In NeoTRIP, the neutropenia incidence was 49% in the atezolizumab arm and 54% in the control.⁽¹⁸⁾ The IMpassion031 trial reported relatively lower rates: 23% in the atezolizumab group and 22% in the placebo group.⁽¹⁹⁾ In the, which evaluated olaparib combined with chemotherapy, neutropenia occurred in 44% of patients in the investigational arm and 27.2% in the control arm.^(8, 9) Finally, in the WSG-ADAPT-TN trial, neutropenia was observed in 16.1% of patients receiving gemcitabine and 15.8% in the carboplatin arm.⁽²⁸⁾ Grade 4 neutropenia was reported in several studies. In BrighTNess, it occurred in 13% (PCV) and 11% (PC) ^(16,17); in PARTNER, it was 10.3% in the olaparib group and 8.6% in the control;^(8, 9) in WSG-ADAPT-TN, grade 4 rates

were not separately reported.(28) Grade 4 events were not explicitly documented in KEYNOTE-522, NeoTRIP, or IMpassion031. (18, 19, 30, 31)

The pooled prevalence of Grade ≥ 3 neutropenia was 23.7% (95% CI: 21.6–25.8) in PARP inhibitor regimens (Group A), 33.5% (95% CI: 31.3–35.7) in immunotherapy-based regimens (Group B), and 16.0% (95% CI: 11.9–20.1) in platinum-based regimens (Group C). Between-group differences were statistically significant ($Q_{\text{between}}=71.84$, $p<0.0001$), with high heterogeneity ($I^2=94.9\%$).

In risk ratio meta-analyses, PARP inhibitors were associated with a significantly increased risk compared to placebo (RR=1.84, 95% CI: 1.47–2.30, $p<0.00001$), while immunotherapy regimens showed no significant difference versus controls (RR=1.00, 95% CI: 0.88–1.14, $p=0.94$).

3.4.2 Anemia

Anemia of grade 3 or higher was reported in five of the six studies. In BrighTNess, anemia was observed in 25% of patients in the PCV group and 17% in the PC group.(19, 29) In the PARTNER trial, 24.5% of patients in the olaparib arm developed severe anemia compared to 16% in the control group.(8, 9) In KEYNOTE-522, the anemia rates were 18.2% and 14.9% in the pembrolizumab and control arms, respectively.(17, 30, 31) IMpassion031 reported lower incidence rates, with 9% of patients affected in the atezolizumab group and 7% in the placebo group.(19) WSG-ADAPT-TN reported no grade ≥ 3 anemia in either treatment group.(28) Grade 4 anemia was rare. In BrighTNess and WSG-ADAPT-TN, no grade 4 anemia was reported(27-29). In PARTNER, a single case (0.4%) occurred in the olaparib arm, and none in the control arm.(8, 9) Grade 4 anemia was not reported in KEYNOTE-522 or IMpassion031.(30, 31)

The pooled prevalence of Grade ≥ 3 anemia was 20.6% (95% CI: 18.2–23.0) in Group A and 9.9% (95% CI: 8.6–11.2) in Group B, with no events reported in Group C. Between-group differences were significant ($Q_{\text{between}}=57.77$, $p<0.0001$), with substantial heterogeneity ($I^2=83.4\%$).

Risk analysis showed that PARP inhibitors doubled the risk of anemia compared to placebo (RR=2.08, 95% CI: 1.12–3.84, $p=0.02$), whereas immunotherapy regimens showed no significant increase (RR=1.22, 95% CI: 0.94–1.57, $p=0.13$).

3.4.3 Febrile Neutropenia

Febrile neutropenia was less commonly reported but was documented in four studies. KEYNOTE-522 showed the highest incidence, with 17.7% in the pembrolizumab group and 15.9% in the control arm.(17, 30, 31) IMpassion031 reported febrile neutropenia in 11% of patients receiving atezolizumab and 9% in the placebo group.(19) In the PARTNER trial, the event occurred in 9.3% of patients in both arms.(8, 9) In BrighTNess, febrile neutropenia occurred in fewer than 5% of patients across all treatment groups.(27, 29) Grade 4 febrile neutropenia was infrequently reported. In PARTNER, it occurred in 1.1% of patients receiving olaparib and in 1.9% of those in the control group. (8, 9) No grade 4 febrile neutropenia was explicitly described in BrighTNess, KEYNOTE-522, or IMpassion031.(19, 27, 29-31)

Pooled prevalence was 3.0% (95% CI: 1.9–4.1) in Group A and 14.9% in Group B, with significant between-group differences ($Q_{\text{between}}=113.80$, $p<0.0001$) and high heterogeneity ($I^2=87\%$).

Risk analysis for PARP inhibitors showed no significant increase compared to placebo (RR=1.59, 95% CI: 0.37–6.82, $p=0.53$).

3.4.4 Thrombocytopenia and Leukopenia

Thrombocytopenia of grade 3 or higher was observed with varying frequency across treatment regimens in five of the six trials included. In BrighTNess, the incidence reached 11% in patients treated with paclitaxel, carboplatin, and veliparib (PCV), compared to 6% in those receiving paclitaxel plus carboplatin (PC).^(27, 29) In NeoTRIP, thrombocytopenia was reported in 7% of patients in the atezolizumab arm and 9% in the control arm.⁽¹⁸⁾ The PARTNER trial documented lower rates overall, with 2.5% in the olaparib group and 0.4% in the placebo group.^(8, 9) In the WSG-ADAPT-TN trial, thrombocytopenia occurred in 1.3% of patients treated with gemcitabine, while no events were reported in the carboplatin group.⁽²⁸⁾ Grade 4 thrombocytopenia was uncommon; in BrighTNess, it occurred in 2% of patients in the PCV group and 1% in the PC group, while in PARTNER, it was not reported in the investigational arm and occurred in 0.4% of controls.^(8, 9, 27, 29)

Prevalence of Grade ≥ 3 thrombocytopenia was 2.3% (95% CI: 1.2–3.4) in Group A, 7.9% (95% CI: 4.6–11.2) in Group B, and 1.0% (95% CI: –1.0–3.0) in Group C ($Q_{\text{between}}=12.29$, $p=0.0002$). Heterogeneity was moderate ($I^2=74.1\%$).

In risk analysis, PARP inhibitor regimens significantly increased thrombocytopenia risk compared to placebo (RR=3.56, 95% CI: 1.85–6.85, $p=0.0001$), while immunotherapy regimens showed no significant difference.

Leukopenia was similarly reported across multiple studies, albeit at generally lower frequencies. IMpassion031 documented grade ≥ 3 leukopenia in 9% of patients in the atezolizumab group and in 5% of those receiving placebo.⁽¹⁹⁾ In NeoTRIP, leukopenia occurred in 4% and 5% of patients in the experimental and control groups, respectively.⁽¹⁸⁾ The PARTNER study reported leukopenia in 7.4% of patients across both treatment arms.^(8, 9) Consistent rates were observed in BrighTNess, with 5% incidence in both PCV and PC groups. Grade 4 leukopenia was rare; it occurred in $<1\%$ of PCV patients and 1% in the PC group in BrighTNess, and in 0.7% (olaparib) vs. 2.6% (placebo) in PARTNER.^(8, 9, 27, 29)

The pooled prevalence was 4.0% (95% CI: 2.8–5.2) in Group A, 5.1% (95% CI: 3.3–6.9) in Group B, and 2.0% (95% CI: –3.6–) in Group C ($Q_{\text{between}}=7.15$, $p=0.0037$), with moderate heterogeneity ($I^2=54.2\%$).

Neither PARP inhibitors (RR=1.14, 95% CI: 0.70–1.84, $p=0.60$) nor immunotherapy regimens (RR=1.24, 95% CI: 0.53–2.91, $p=0.62$) showed a significant increase in leukopenia risk.

3.5 Hepatic and Metabolic Toxicities

3.5.1 Elevated Transaminases

Elevations in liver enzymes, particularly alanine aminotransferase (ALT), were observed in a subset of patients across three of the included trials. In KEYNOTE-522, grade ≥ 3 ALT elevation occurred in 5.2% of patients treated with pembrolizumab in combination with chemotherapy, compared to 2.3% in the placebo arm.(17, 30, 31) The IMpassion031 study reported similar rates, with elevations in 5% of patients receiving atezolizumab and 6% in the placebo group.(19) The WSG-ADAPT-TN trial recorded the highest incidence, with 11.7% of patients in the gemcitabine arm experiencing grade ≥ 3 ALT elevation, versus 3.3% in the carboplatin arm.(28) In contrast, elevations in aspartate aminotransferase (AST) were infrequent across studies, with grade ≥ 3 events occurring in fewer than 5% of patients in all arms. Grade 4 ALT elevation was only reported in PARTNER, occurring in 0.4% of patients treated with olaparib and not observed in the control arm.(8, 9) In contrast, elevations in AST were infrequent across studies, with grade ≥ 3 events occurring in fewer than 5% of patients in all arms. Grade 4 AST elevations were not reported.

Prevalence was 2.0% (95% CI: 1.1–3.0) in Group A, 3.8% (95% CI: 2.8–4.8) in Group B, and 6.4% (95% CI: 3.6–9.2) in Group C, with significant between-group differences ($Q_{\text{between}}=12.37$, $p=0.0002$) and moderate heterogeneity ($I^2=70.0\%$). Risk ratios showed no significant difference for PARP inhibitors ($RR=1.07$, 95% CI: 0.36–3.17, $p=0.91$) or immunotherapy regimens ($RR=1.50$, 95% CI: 0.61–3.64, $p=0.38$).

3.5.2 Fatigue and Hypertension

Fatigue of grade ≥ 3 was documented in the PARTNER trial, with an incidence of 9.6% in patients receiving olaparib and 10.4% in the placebo group.(8, 9) In all other included trials, BrighTNess,(29) KEYNOTE-522,(31) IMpassion031,(19) NeoTRIP,(18) and WSG-ADAPT-TN(28) grade ≥ 3 fatigue occurred in fewer than 5% of patients, and no grade 4 fatigue events were reported. Although uncommon, this adverse event remains clinically relevant due to its impact on functional status and treatment adherence, particularly in combination or prolonged systemic therapy.

Hypertension of grade ≥ 3 was explicitly reported in the IMpassion031 trial, with similar frequencies in the atezolizumab (6%) and placebo (7%) arms.(19) In the remaining studies, BrighTNess,(29) KEYNOTE-522,(31) NeoTRIP,(18) PARTNER,(9) and WSG-ADAPT-TN,(28) grade 3 hypertension occurred in fewer than 5% of participants, and no grade 4 events were reported. These findings suggest that severe hypertension was infrequent and generally not exacerbated by the addition of immune checkpoint inhibitors to neoadjuvant chemotherapy regimens.

3.6 Other Serious Events

3.6.1 Sepsis and Septic Shock

Sepsis or septic shock of grade 4 was reported in two studies. In KEYNOTE-522, one patient (0.3%) in each arm developed septic shock (19-21).(17, 30, 31) In the PARTNER trial, the event occurred in 0.4% of patients treated with olaparib and 3.0% in the control arm (23,24).(8, 9)

3.5.2 Pulmonary Embolism and Pneumonitis

Both events were rare and only reported in the KEYNOTE-522 trial.(17, 30, 31) Pulmonary embolism and pneumonitis, both grade 4, occurred in 0.3% of patients in the pembrolizumab arm and were not reported in the control group.

3.7 Safety Outcomes

Fatal adverse events (grade 5) were rare but documented in IMpassion031, with one death in each arm (0.6%),(19) and in KEYNOTE 522, with one treatment-related death per arm (approximately 0.1–0.3%).(17, 19, 30, 31) No toxicity-related deaths were reported in BrighTNess, NeoTRIP, WSG ADAPT TN, or PARTNER. (8, 9, 27, 29)

3.8 Risk of Bias Assessment

The risk of bias was evaluated using the Cochrane Risk of Bias 2.0 (RoB 2) (26) tool across five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. The graphical summary of the risk of bias assessment for each included trial is presented in Supplementary Figures 1.

Overall, four of the six trials were judged to be at low risk of bias, with all domains adequately addressed, including adequate random sequence generation, allocation concealment, and complete outcome reporting. Two study (NeoTRIP, IMPesion031) (18, 19) presented some concerns, primarily due to lack of detailed reporting on the randomization process and blinding procedures. No trial was judged to be at high risk of bias in any domain. This high methodological quality strengthens the confidence in the reported safety outcomes across studies.

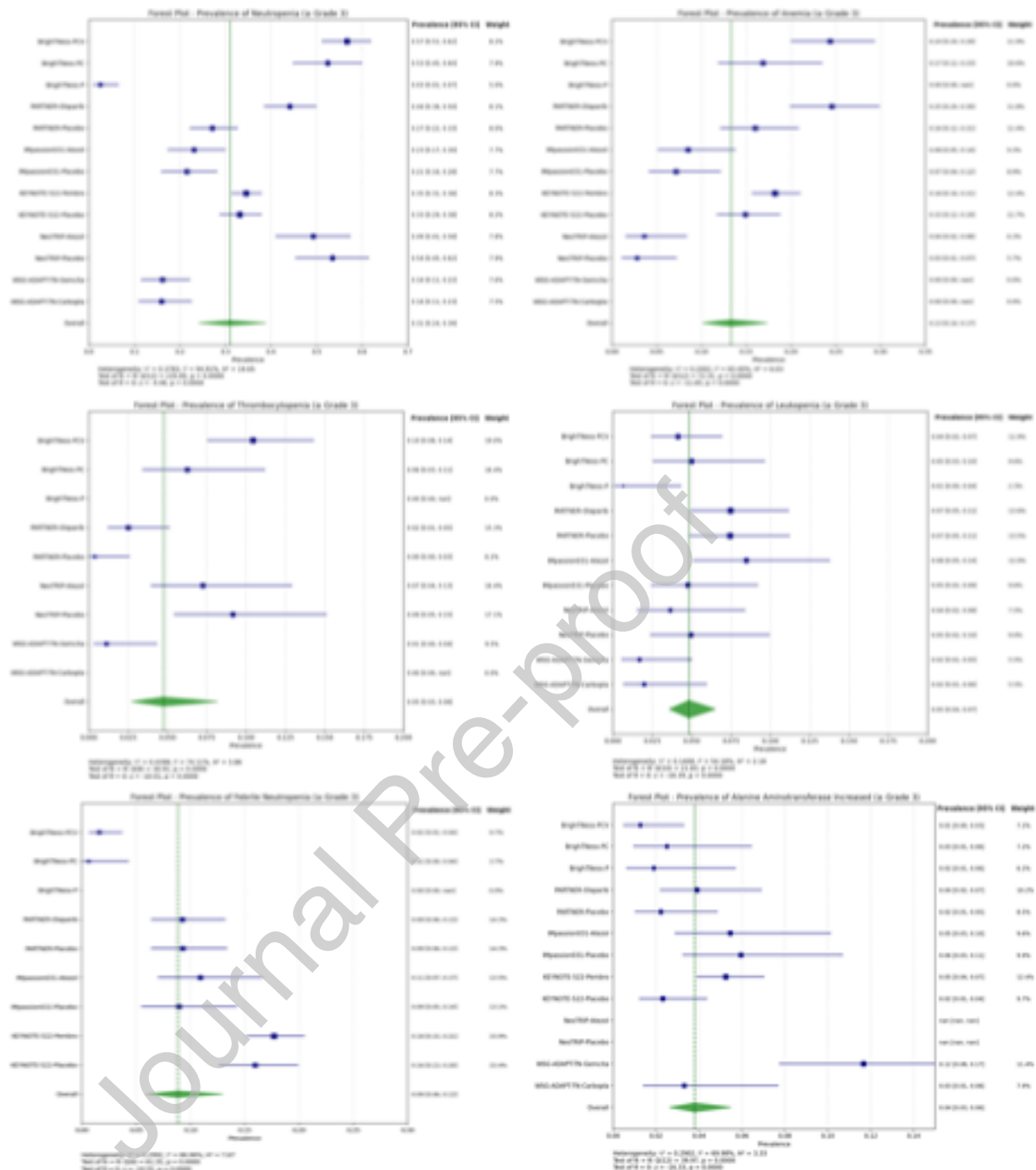


Figure 2 - Prevalence of Grade ≥ 3 Adverse Events in TNBC Patients Receiving Neoadjuvant Therapy: Forest Plot Meta-Analyses.

Legend: Forest plots displaying pooled prevalence estimates (95% confidence intervals) of grade ≥ 3 adverse events among patients with triple-negative breast cancer undergoing neoadjuvant chemotherapy. Outcomes include neutropenia, anemia, thrombocytopenia, leukopenia, febrile neutropenia, and elevated alanine aminotransferase levels. Squares represent individual study estimates weighted by sample size, and diamonds indicate overall pooled prevalence. High heterogeneity was observed across most outcomes. Studies included BrighTNess, PARTNER, IMpassion031, KEYNOTE-522, NeoTRIP, and WSG-ADAPT-TN.

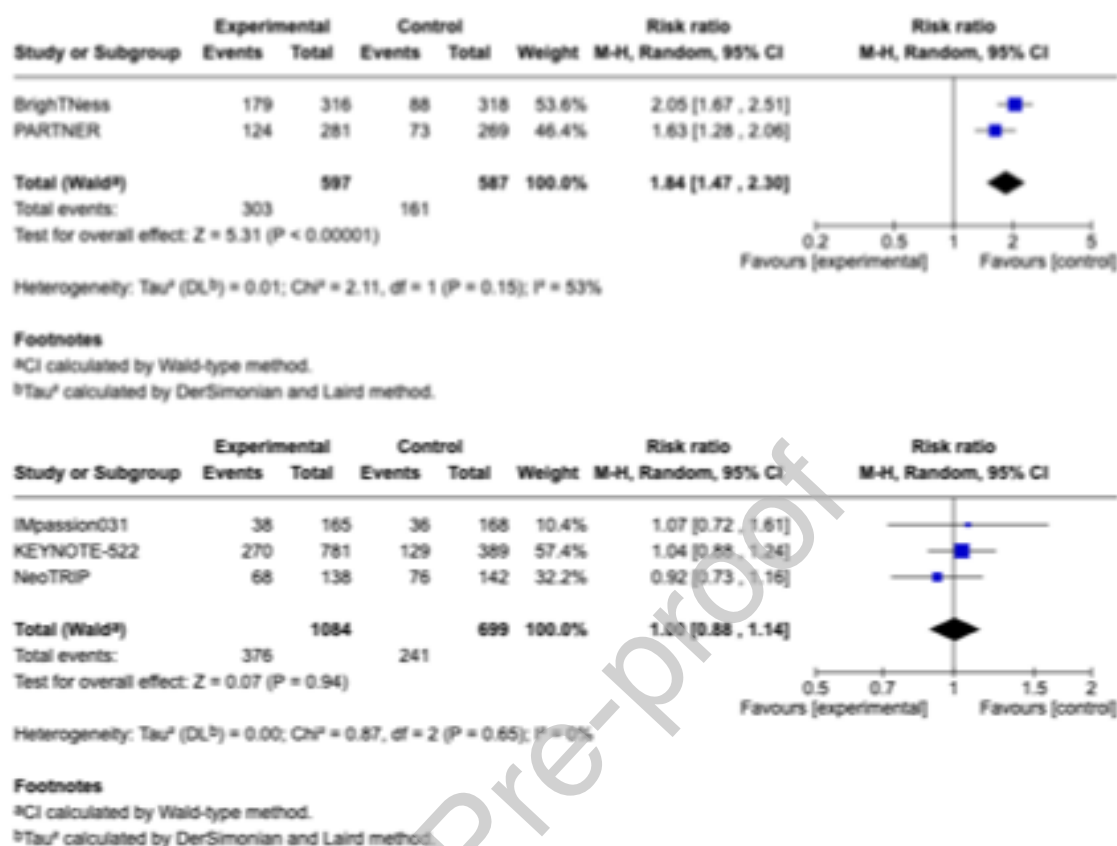


Figure 3 - Risk Ratio of Grade ≥ 3 Neutropenia in TNBC Patients Receiving Neoadjuvant Therapy

Legend: Forest plots comparing the risk of grade ≥ 3 neutropenia between experimental and control arms in randomized controlled trials of neoadjuvant therapy for triple-negative breast cancer. The upper plot shows pooled risk ratios for studies evaluating platinum or PARP inhibitors (BrighTNess and PARTNER), indicating a significantly increased risk in experimental arms (RR 1.84, 95% CI 1.47–2.30; $I^2=53\%$). The lower plot displays results for trials evaluating immune checkpoint inhibitors (IMpassion031, KEYNOTE-522, NeoTRIP), showing no significant difference in risk compared to controls (RR 1.00, 95% CI 0.88–1.14; $I^2=0\%$). Squares represent individual study estimates weighted by sample size, and diamonds indicate pooled risk ratios with 95% confidence intervals.

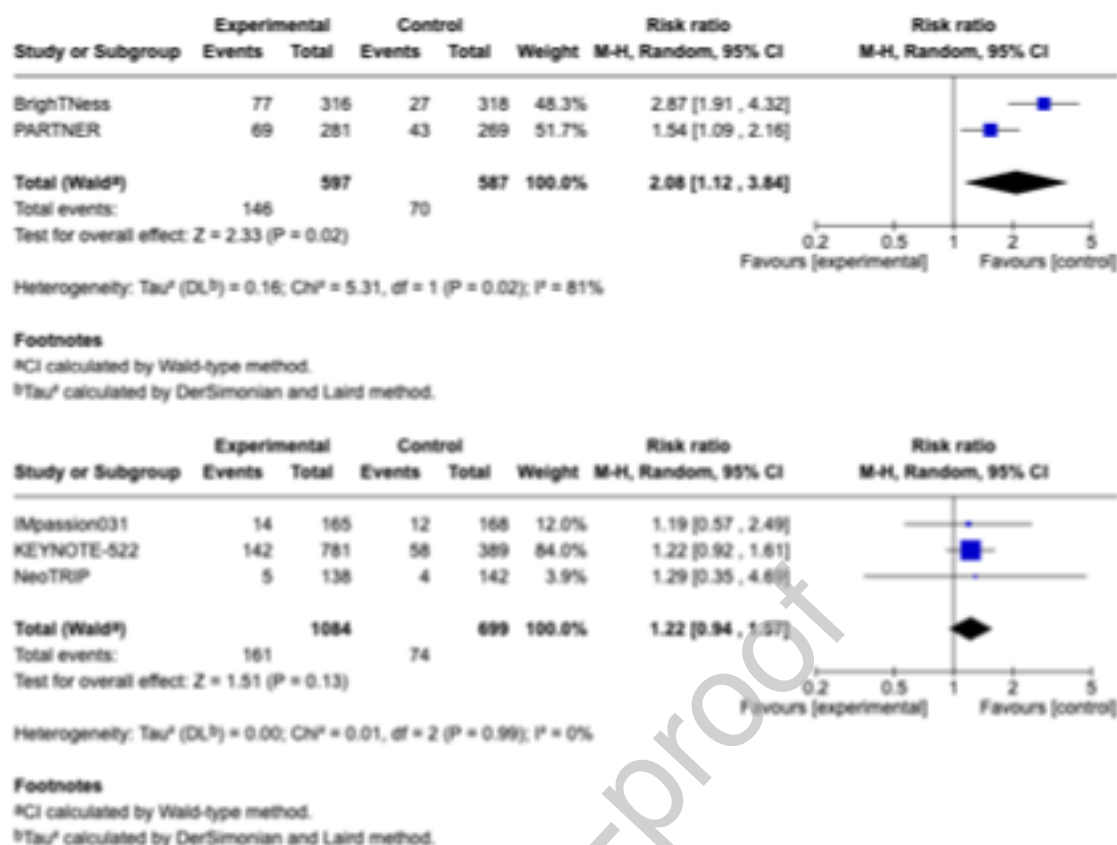


Figure 4 - Risk Ratio of Grade ≥ 3 Anemia in TNBC Patients Receiving Neoadjuvant Therapy

Legend: Forest plots comparing the risk of grade ≥ 3 anemia between experimental and control arms in randomized controlled trials of neoadjuvant therapy for triple-negative breast cancer. The upper plot shows pooled risk ratios for studies evaluating platinum or PARP inhibitors (BrighTNess and PARTNER), indicating a significantly increased risk in experimental arms (RR 2.08, 95% CI 1.12–3.84; $I^2=81\%$). The lower plot displays results for trials evaluating immune checkpoint inhibitors (IMpassion031, KEYNOTE-522, NeoTRIP), showing no significant difference in risk compared to controls (RR 1.22, 95% CI 0.94–1.57; $I^2=0\%$). Squares represent individual study estimates weighted by sample size, and diamonds indicate pooled risk ratios with 95% confidence intervals.

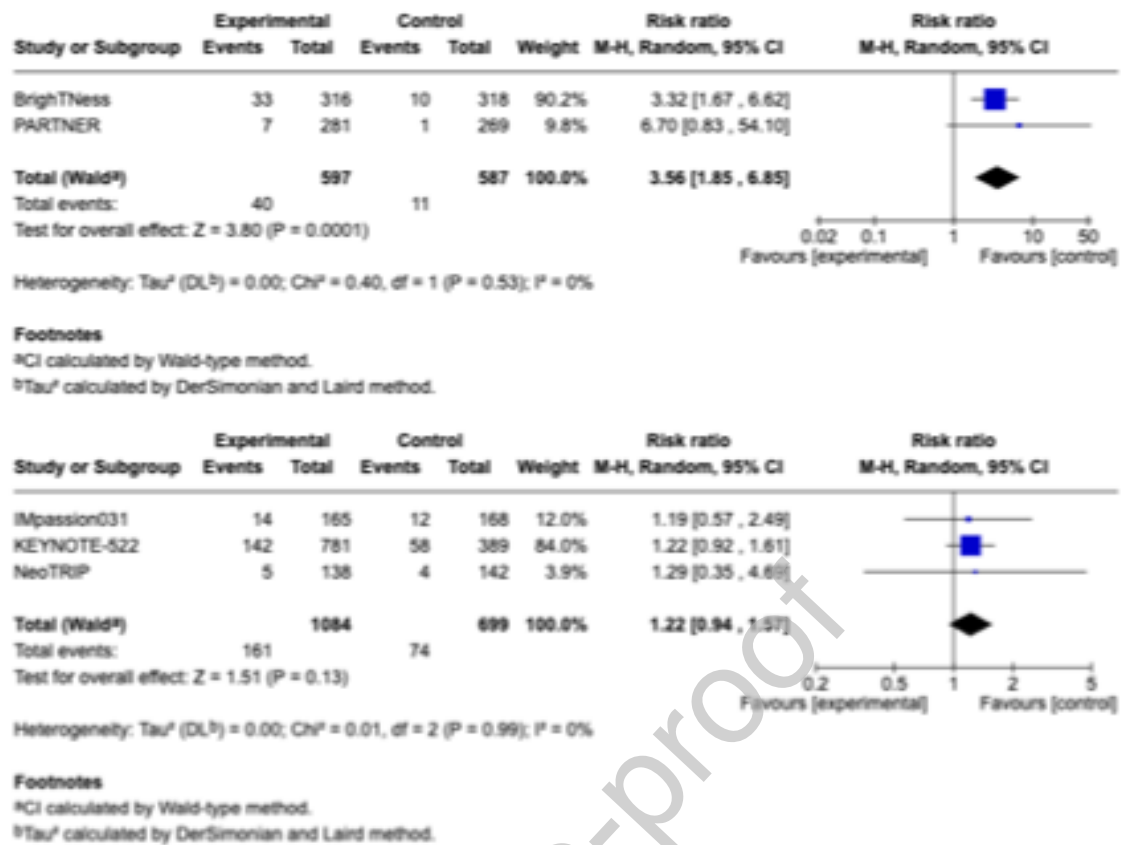


Figure 5 - Risk Ratio of Grade ≥ 3 Thrombocytopenia in TNBC Patients Receiving Neoadjuvant Therapy

Legend: Forest plots comparing the risk of grade ≥ 3 thrombocytopenia between experimental and control arms in randomized controlled trials of neoadjuvant therapy for triple-negative breast cancer. The upper plot shows pooled risk ratios for studies evaluating platinum or PARP inhibitors (BrighTNess and PARTNER), indicating a significantly increased risk in experimental arms (RR 3.56, 95% CI 1.85–6.85; $I^2=0\%$). The lower plot displays results for trials evaluating immune checkpoint inhibitors (IMpassion031, KEYNOTE-522, NeoTRIP), showing no significant difference in risk compared to controls (RR 1.22, 95% CI 0.94–1.57; $I^2=0\%$). Squares represent individual study estimates weighted by sample size, and diamonds indicate pooled risk ratios with 95% confidence intervals.

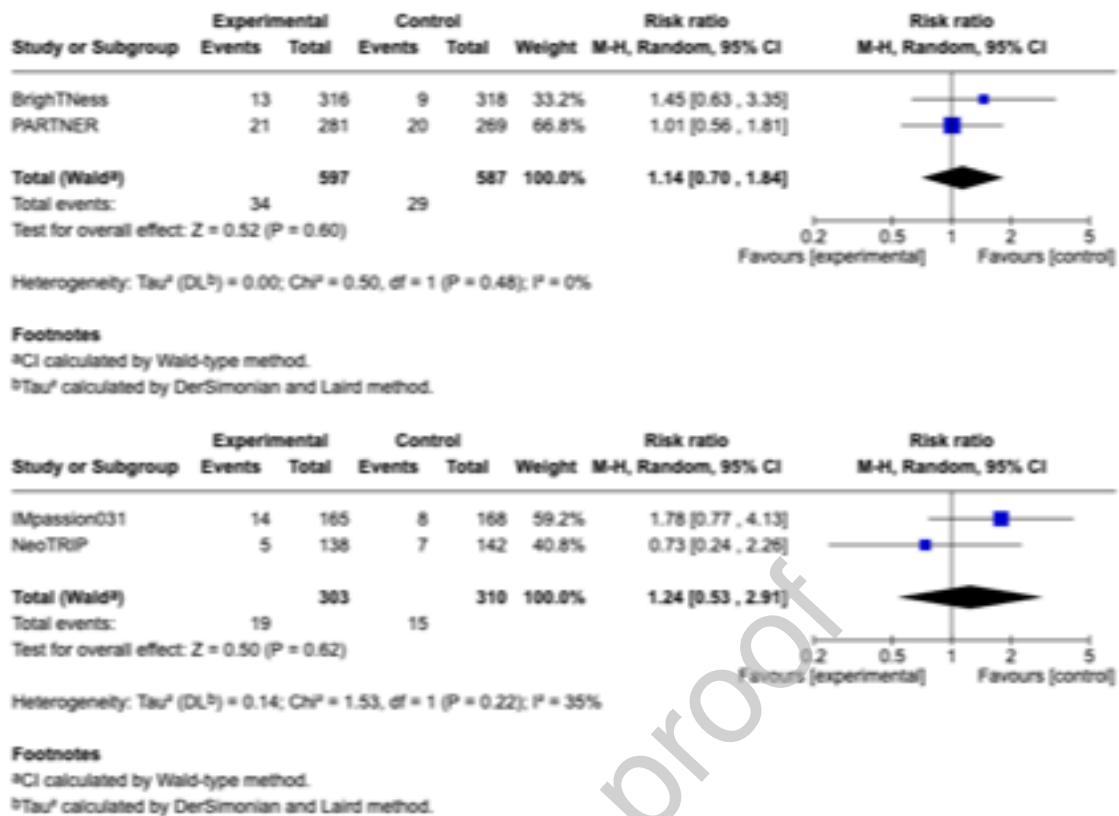


Figure 6 - Risk Ratio of Grade ≥ 3 Leukopenia in TNBC Patients Receiving Neoadjuvant Therapy

Legend: Forest plots comparing the risk of grade ≥ 3 leukopenia between experimental and control arms in randomized controlled trials of neoadjuvant therapy for triple-negative breast cancer. The upper plot shows pooled risk ratios for studies evaluating platinum or PARP inhibitors (BrighTNess and PARTNER), indicating no significant difference in risk between experimental and control arms (RR 1.14, 95% CI 0.70–1.84; $I^2=0\%$). The lower plot displays results for trials evaluating immune checkpoint inhibitors (IMpassion031, NeoTRIP), also showing no significant difference in risk compared to controls (RR 1.24, 95% CI 0.53–2.91; $I^2=35\%$). Squares represent individual study estimates weighted by sample size, and diamonds indicate pooled risk ratios with 95% confidence intervals.

Table 3. Security outcomes reported on the studies

Study name and authors		BrightNess, Loibl (29) and Geyer (27)	IMpassion031, Mittendorf (19)	KEYNOTE-522; Schmid (17, 30, 31)	Neo-RP, Gianni (18)	PARTNER, Abraham (8, 9)	WSG-ADAPT-TN, Gluz (28)
Neutropenia	GRADE 3 or 4	PCV= 179 (57%) PC=84 (53%) P<5%	Atezol= 38 (23%) Placebo= 36 (22%)	Pembro= 270 (34.6%) Placebo= 129 (33.2%)	Atezo= 68 (49%) Placebo= 76 (54%)	Olaparib= 124 (44%) Placebo=73 (27.2%)	Gemcita= 29 (16.1%) Carbopla= 24 (15.8%)
	GRADE 4	PCV=41 (13%) PC=18 (11%) P<5%	Not reported	Not reported	Not reported	Olaparib= 29 (10.3%) Placebo=23 (8.6%)	Not reported
Anaemia	GRADE 3 or 4	PCV=77 (25%) PC=27 (17%) P=0	Atezol= 14 (9%) Placebo= 12 (7%)	Pembro= 142 (18.2%) Placebo= 58 (14.9%)	Atezo= 5 (4%) Placebo= 4 (3%)	Olaparib= 69 (24.5%) Placebo= 43 (16%)	Gemcita= 0 Carbopla= 0
	GRADE 4	PCV=0 PC=0 P=0	Not reported	Not reported	Not reported	Olaparib= 1 (0.4%) Placebo= 0	Not reported
Thrombocytopenia	GRADE 3 or 4	PCV=33 (11%) PC=10 (6%) P=0	Not reported	Not reported	Atezo= 10 (7%) Placebo= 13 (9%)	Olaparib= 7 (2.5%) Placebo= 1 (0.4%)	Gemcita= 2 (1.3%) Carbopla=0
	GRADE 4	PCV=6 (2%) PC=2 (1%) P=0	Not reported	Not reported	Not reported	Olaparib= 0 Placebo= 1 (0.4%)	Not reported
Leukopenia	GRADE 3 or 4	PCV=13 (5%) PC=8 (5%) P<5%	Atezol= 14 (9%) Placebo= 8 (5%)	Not reported	Atezo= 5 (4%) Placebo= 7 (5%)	Olaparib= 21 (7.4%) Placebo= 20 (7.4%)	Gemcita= 3 (2.0%) Carbopla= 3 (2.0%)
	GRADE 4	PCV=1 (<1%) PC=1 (1%) P=0	Not reported	Not reported	Not reported	Olaparib= 2 (0.7%) Placebo= 7 (2.6%)	Not reported
Febrile neutropenia	GRADE 3 or 4	<5%	Atezol= 18 (11%) Placebo= 15 (9%)	Pembro= 138 (17.7%) Placebo= 62 (15.9%)	Not reported	Olaparib= 26 (9.3%) Placebo= 25 (9.3%)	Not reported
	GRADE 4	0	Not reported	Not reported	Not reported	Olaparib= 3 (1.1%) Placebo= 5 (1.9%)	Not reported
Hypertension	GRADE 3 or 4	<5%	Atezol= 10 (6%) Placebo= 12 (7%)	Not reported	Not reported	<5%	<5%

	GRADE 4	0	Not reported	Not reported	Not reported	Not reported	Not reported
Fatigue	GRADE 3 or 4	<5%	<5%	<5%	<5%	Olaparib= 27 (9.6%) Placebo= 28 (10.4%)	<5%
	GRADE 4	0	Not reported	Not reported	Not reported	Not reported	Not reported
Hypokalemia	GRADE 3 or 4	<5%	Not reported	Not reported	Not reported	Not reported	Not reported
	GRADE 4	PCV= 0 PC= 1 (1%) P= 1 (1%)	Not reported	Not reported	Not reported	Not reported	Not reported
Sepsis / Septic shock	GRADE 3 or 4	Not reported	Not reported	Only Grade 4	Not reported	Only Grade 4	Not reported
	GRADE 4	Not reported	Not reported	Pembro= 1 (0.3%) Placebo= 1 (0.3%)	Not reported	Olaparib= 1 (0.4%) Placebo= 8 (3.0%)	Not reported
Vomiting	GRADE 3 or 4	<5%	<5%	<5%	<5%	<5%	Not reported
	GRADE 4	0	Not reported	Not reported	Not reported	Olaparib= 0 (0%) Placebo= 1 (0.4%)	Not reported
Hypomagnesemia	GRADE 3 or 4	Not reported	Not reported	Not reported	Not reported	<5%	Not reported
	GRADE 4	Not reported	Not reported	Not reported	Not reported	Olaparib= 0 (0%) Placebo= 1 (0.4%)	Not reported
Hyperglycemia	GRADE 3 or 4	<5%	Not reported	Not reported	Not reported	Not reported	Not reported
	GRADE 4	PCV= 0 PC= 1 (1%) P=0	Not reported	Not reported	Not reported	Not reported	Not reported
Alanine aminotransferase increased	GRADE 3 or 4	<5%	Atezo= 9 (5%) Placebo= 10 (6%)	Pembro= 41 (5.2%) Placebo= 9 (2.3%)	Not reported	<5%	Gemcita= 21 (11.7%) Carbopla= 5 (3.3%)
	GRADE 4	0	Not reported	Not reported	Not reported	Olaparib= 1 (0.4%) Placebo= 0	Not reported
Aspartate aminotransferase increased	GRADE 3 or 4	<5%	<5%	<5%	Not reported	Not reported	<5%
	GRADE 4	0	Not reported	Not reported	Not reported	Not reported	Not reported
Platelet count decrease	GRADE 3 or 4	Not reported	Not reported	Not reported	Not reported	Olaparib= 32 (11.4%) Placebo= 14 (5.2%)	Not reported
	GRADE 4	Not reported	Not reported	Not reported	Not reported	Olaparib= 3 (1.1%) Placebo= 3 (1.1%)	Not reported
	GRADE 3 or 4	Not reported	Atezo= 20 (12%)	Pembro= 146 (18.7%)	Not reported	Not reported	Not reported

Neutrophil count decreased			Placebo= 19 (11%)	Placebo= 90 (23.1%)			
	GRADE 4	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Pulmonary embolism	GRADE 3 or 4	Not reported	Not reported	Only Grade 4	Not reported	Not reported	Not reported
	GRADE 4	Not reported	Not reported	Pembro= 1 (0.3%) Placebo= 0	Not reported	Not reported	Not reported
Pneumonitis	GRADE 3 or 4	Not reported	Not reported	Only Grade 4	Not reported	Not reported	Not reported
	GRADE 4	Not reported	Not reported	Pembro= 1 (0.3%) Placebo= 0	Not reported	Not reported	Not reported

Legends: PCV= paclitaxel plus carboplatin plus veliparib; PC: paclitaxel plus carboplatin plus veliparib placebo; P= paclitaxel plus carboplatin placebo plus veliparib placebo.

4.0 Discussion

4. Discussion

This study represents the first systematic review and meta-analysis specifically focused on phase 3 studies and high-grade (grade ≥ 3) adverse events associated with NAT in TNBC. While several prior publications have evaluated the efficacy of NAT strategies in TNBC, no previous synthesis has comprehensively quantified and compared the toxicity burden across contemporary phase 3 RCTs. Our findings provide critical insight into the safety profile of intensified treatment regimens, including those incorporating platinum agents, PARP inhibitors, and ICIs, that are increasingly used in routine clinical practice.⁽⁵⁾ Across six trials and over 3,300 patients, ^(8, 9, 17-19, 27-31) hematologic toxicities, particularly neutropenia, anemia, and thrombocytopenia, were the most frequent severe adverse events.

4.1 Key Toxicity Patterns

PARP inhibitors demonstrated the highest hematologic risks, significantly increasing neutropenia (RR=1.84), anemia (RR=2.08), and thrombocytopenia (RR=3.56). This reflects DNA repair pathway targeting affecting normal hematopoietic cells. The PARTNER trial's 48-hour interval between carboplatin and olaparib reduced myelosuppression while preserving efficacy,^(8,9) demonstrating how pharmacodynamic scheduling can mitigate toxicity.

These findings are consistent with prior studies demonstrating that platinum salts significantly increase the risk of severe hematologic adverse events.^(32,33) ICIs did not significantly increase hematologic toxicity risk but introduced immune-related adverse events affecting multiple organ systems. While most irAEs are manageable with corticosteroids, they can be severe and life-threatening, requiring vigilant monitoring protocols.⁽²¹⁻²³⁾

Platinum-based regimens showed the lowest severe adverse event rates, suggesting combination regimens amplify individual agent toxicities.

Severe hematologic toxicities remain a major consideration when intensifying neoadjuvant regimens for TNBC. While strategies incorporating platinum agents, PARP inhibitors, and immunotherapy have improved pathological response rates in several trials, these approaches may also increase treatment-related toxicity and require careful monitoring during therapy. Therefore, understanding the toxicity profiles associated with each therapeutic strategy is essential for optimizing treatment selection and ensuring that potential benefits outweigh the risks in individual patients.

4.2 Biomarker-Driven Selection

PARP inhibitor efficacy is largely restricted to BRCA-mutated patients, yet toxicity occurs regardless of mutation status. The PARTNER trial showed olaparib in BRCA wild-type patients increased toxicity without survival benefit,^(8,9) emphasizing the importance of biomarker-guided selection to avoid exposing patients to avoidable harm.

The recent integration of ICIs has redefined the therapeutic landscape for TNBC. The KEYNOTE-522 trial demonstrated significant improvement in pCR rates and overall survival with pembrolizumab addition to standard chemotherapy.(17,30,31,34) A recent meta-analysis confirmed that adding ICIs to chemotherapy in early-stage TNBC increases the risk of grade 3-4 toxicities compared to chemotherapy alone.(35)

4.3 Clinical Implications

The substantial toxicity burden necessitates: (1) personalized risk assessment incorporating predictive biomarkers (BRCA status, PD-L1 expression) for treatment selection; (2) proactive monitoring with regimen-specific toxicity protocols; (3) supportive care optimization utilizing growth factors and irAE management guidelines;(21-23) and (4) shared decision-making in this curative-intent setting.

In clinical practice, treatment selection for patients with early-stage TNBC often requires balancing efficacy and toxicity among multiple available therapeutic strategies. For instance, a patient presenting with both a germline BRCA mutation and PD-L1–positive disease may theoretically be eligible for platinum-based chemotherapy, PARP inhibitor strategies, or immunotherapy-containing regimens. In such scenarios, toxicity profiles should be interpreted alongside key efficacy outcomes reported in clinical trials, including pathological complete response (pCR), disease-free survival (DFS), and overall survival (OS). Integrating safety and efficacy data may help clinicians individualize treatment decisions and optimize the risk–benefit balance in this curative-intent setting.

Treatment-related deaths were rare (<1%) but occurred in KEYNOTE-522 and IMpassion031,(17,19,30,31) emphasizing the need for experienced multidisciplinary teams and institutional protocols for managing severe toxicities. No toxicity-related deaths were reported in BrighTNess, NeoTRIP, WSG-ADAPT-TN, or PARTNER.(8,9,18,27-29)

4.6 Emerging Therapies and Safety Considerations

Novel agents continue to reshape the therapeutic landscape. In 2025 a phase 3 trial combining sacituzumab govitecan with pembrolizumab demonstrated promising efficacy in patients with PD-L1–positive advanced TNBC (ASCENT-04/KEYNOTE-D19). (36) While early results indicate slowed disease progression, the combination was also associated with substantial toxicity, including neutropenia and severe diarrhea—adverse effects already observed in prior studies of antibody-drug conjugates.(37) These data reinforce the complexity of adding new agents to established backbones and the importance of balancing efficacy with toxicity, especially as neoadjuvant regimens grow increasingly multimodal.

4.5 Limitations

Heterogeneity existed in chemotherapy backbones, toxicity reporting schedules, and grading criteria across trials. Substantial heterogeneity was observed across several toxicity outcomes, particularly neutropenia and anemia. This variability likely reflects

important differences among the included trials, including variations in chemotherapy backbones, incorporation of platinum agents, treatment scheduling, and supportive care practices such as prophylactic granulocyte colony-stimulating factor (G-CSF). Additionally, the trials evaluated distinct therapeutic strategies—including PARP inhibitors, immune checkpoint inhibitors, and platinum-based regimens—combined with different chemotherapy platforms. These variations in treatment composition and toxicity monitoring are inherent to contemporary TNBC trials and may partly explain the high I^2 values observed in several analyses.

5. Conclusion

This meta-analysis demonstrates that neoadjuvant therapy for TNBC carries substantial grade ≥ 3 toxicity burden, particularly hematologic events. PARP inhibitors showed the highest hematologic risks, ICIs added immune-related toxicities without significant hematologic impact, and platinum-based regimens demonstrated the lowest severe adverse event rates.

These findings emphasize the critical importance of biomarker-driven treatment selection, particularly restricting PARP inhibitors to BRCA-mutated patients. Vigilant toxicity monitoring, proactive supportive care, and multidisciplinary management are essential for optimizing outcomes in this curative-intent setting.

As novel agents and combinations continue emerging, balancing efficacy with safety through precision-based approaches will remain central to TNBC care. The substantial toxicity burden identified here underscores the need for individualized risk-benefit assessment and shared decision-making to ensure optimal patient outcomes while minimizing harm.

5. Conclusion

This systematic review and meta-analysis demonstrate that neoadjuvant therapy for triple-negative breast cancer is associated with a significant burden of Grade ≥ 3 toxicities, especially hematologic events such as neutropenia and anemia. Platinum-based regimens consistently showed the lowest prevalence of severe adverse events across endpoints analyzed. These findings emphasize the importance of individualized treatment planning based on biomarkers to optimize therapeutic benefit while minimizing harm. Close toxicity monitoring remains essential, particularly when integrating PARP inhibitors, which showed the highest hematologic toxicity risks, and immune checkpoint inhibitors, which add unique immune-related adverse events.

As new agents and combinations continue to emerge in the neoadjuvant setting, balancing efficacy with safety will remain a central challenge in the care of patients with TNBC. A precision-based, multidisciplinary approach—integrating individualized risk-benefit assessment, early toxicity recognition and management, and shared decision-making—is crucial to ensure optimal clinical outcomes in this aggressive breast cancer subtype.

Acknowledgements

The authors thank all investigators, research staff, and participating institutions involved in the conduct of the included trials. We also acknowledge the support of the BBREAST Group (Brazilian Breast Cancer Association Team) for collaborative discussions and critical review of the manuscript.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of Interest

The authors declare no potential conflicts of interest related to this work.

Author Contributions

- **Marcelo Antonini:** Conceptualization, Methodology, Data curation, Formal analysis, Supervision, Writing – original draft, Writing – review & editing.
- **André Mattar:** Conceptualization, Methodology, Investigation, Validation, Writing – original draft, Writing – review & editing.
- **Marcelo Madeira:** Data curation, Formal analysis, Visualization, Writing – original draft, Writing – review & editing.
- **Francisco Pimentel Cavalcante, Felipe Zerwes, Fabricio Palermo Brenelli, Antonio Luis Frasson, Eduardo Camargo Millen, Giuliano Tavares Tosello, Marina Diógenes Teixeira, Gil Facina, Sabrina Monteiro Rondelo, Renata Arakelian, Larissa Chrispim de Oliveira, Lucas Miyake Okumura, Patrícia Carvalho Baruel, Henrique Lima Couto, Marina Fleury de Figueiredo, Rogério Fenile, Renata Montarroyos Leite, Pedro Paulo de Andrade Gomes, Gabriela de Oliveira Gomes, Leonardo Ribeiro Soares, Ruffo de Freitas Júnior, Luiz Henrique Gebrim:** Investigation, Validation, Visualization, Writing – review & editing.

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Supplemental Material

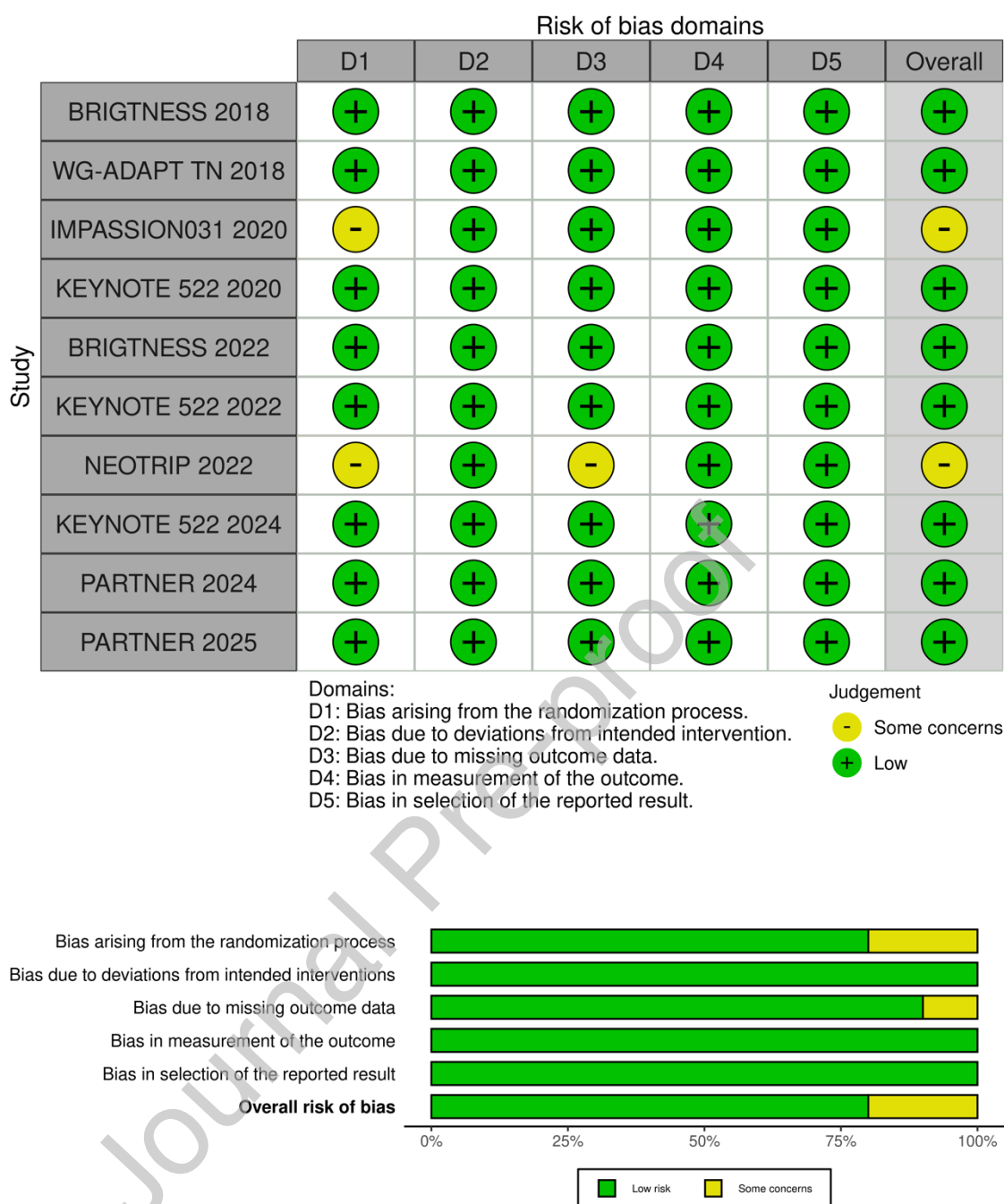


Figure S1 - Risk of Bias Assessment of Included Randomized Controlled Trials Using the Cochrane RoB 2 Tool.

Legend: Summary of risk of bias assessment for each included phase 2–3 randomized controlled trial evaluating neoadjuvant therapy in non-metastatic triple-negative breast cancer. Domains assessed include: (1) randomization process; (2) deviations from intended interventions; (3) missing outcome data; (4) measurement of the outcome; and (5) selection of the reported result. Most trials were judged as low risk of bias across all domains. Two studies (NeoTRIP, IMPassion031) showed some concerns due to insufficient information on the randomization process.