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Toxicity profile and tolerability of immune checkpoint inhibitors for the treatment of early-stage breast cancer: a systematic review and meta-analysis

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ABSTRACT

Background: Immune checkpoint inhibitors (ICIs) targeting the PD-1/PD-L1 axis have demonstrated clinical benefit in early-stage breast cancer (eBC), enhancing antitumor immune responses. However, their incorporation into perioperative polychemotherapy has introduced new concerns regarding safety and immune-related toxicities (irAEs). We conducted a systematic review and meta-analysis to comprehensively evaluate the safety profile and tolerability of ICIs in patients with eBC.

Methods: A systematic review was conducted in PubMed, Embase, Cochrane Library, and relevant conference databases (ASCO, ESMO) to identify clinical trials reporting safety outcomes of ICIs in eBC. Data were analyzed using R (v4.2.2), applying random-effects models for both single-arm and comparative (pairwise) analyses.

Results: Thirteen studies were included, comprising 3977 patients across all studies, including 3138 treated with ICI-containing regimens and 839 controls. For comparative pairwise analyses, 2715 patients received ICI-based therapy and 2399 received chemotherapy alone. The most frequently reported all-grade AEs in ICI arms were alopecia (AR 86.49%, 95% CI: 59.25–96.57) and leukopenia (AR 52.09%, 95% CI: 15.14–86.89). For grade ≥3 events, decreased neutrophil count (AR 17.88%, 95% CI: 10.65–28.44) and neutropenia (AR 18.19%, 95% CI: 10.81–28.96) were most common. The most common irAE was hypothyroidism (AR 12.70%, 95% CI: 9.27—17.16), while the most frequent severe irAE (grade ≥3) was adrenal insufficiency (AR 1.47%, 95% CI: 0.68–3.12).

Conclusion: This meta-analysis provides a comprehensive evaluation of ICI safety in eBC. While most AEs were low-grade and manageable, significant risks of endocrine irAEs—particularly adrenal insufficiency and thyroid dysfunction—were identified. These findings underscore the need for proactive monitoring and highlight the importance of future research to better understand the mechanisms of ICI-related toxicity and to develop strategies for its prevention.

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Abbreviations

AE	adverse event
ALT	alanine aminotransferase
AR	absolute risk
AST	aspartate aminotransferase
BC	breast cancer
BICR	blinded independent central review
CI	confidence interval
CT	clinical trials
eBC	early breast cancer
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
FACT-B:	Functional Assessment of Cancer Therapy – Breast
FDA	Food and Drug Administration
HRQoL:	health-related quality of life
ICI	immune checkpoint inhibitor
irAEs	immune-related adverse events
PD-L1	programmed cell death-ligand 1
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	randomized clinical trial
ROBINS-I:	Risk Of Bias In Non-randomized Studies - of Interventions
RoB 2	Risk of Bias 2 tool
RR	risk ratio
TEAEs	treatment-emergent adverse events
TNBC	triple-negative breast cancer
TPC	treatment of physicians' choice
TRAEs	treatment-related adverse events

1. Introduction

Conventional chemotherapy has long been the standard of care for patients with early-stage breast cancer (eBC) [1]. While cytotoxic agents have contributed significantly to improve both recurrence-free and overall survivals, their use is often accompanied by substantial short- and long-term toxicities, including myelosuppression, neuropathy, and cardiotoxicity, which may impair patients' quality of life and adherence to therapy [2]. In the last decade, advances in the understanding of tumor immunology have fueled the development of immune-based strategies aiming ideally to improve efficacy while minimizing additional treatment-related harm [3].

Among these, immune checkpoint inhibitors (ICIs) have emerged as a major breakthrough in oncology by reactivating exhausted T-cells through blockade of immune inhibitory pathways such as PD-1, PD-L1, and CTLA-4 [4]. Their success in treating advanced triple-negative breast cancer (TNBC) —a subtype historically associated with poor prognosis and lack of targeted therapies— has prompted the evaluation of ICIs in earlier stages of disease [5–7].

The phase III KEYNOTE-522 trial was a landmark study that randomized 1174 patients with early-stage TNBC to receive neoadjuvant pembrolizumab combined with chemotherapy versus chemotherapy alone, followed by adjuvant pembrolizumab or placebo [8]. The trial demonstrated significant improvements in pathological complete response (pCR) rates (64.8% vs. 51.2%, $p < 0.001$), event-free survival (HR 0.63; 95% CI, 0.48–0.82), and, more recently, overall survival [8,9]. These results both supported the regulatory approval of pembrolizumab and consolidated its use in this setting [8]. Similarly, the phase III IMpassion031 trial showed that adding atezolizumab to nab-paclitaxel followed by doxorubicin and cyclophosphamide significantly increased pCR in patients with stage II–III TNBC (58% vs. 41%; $p = 0.0044$), although no difference was observed in long-term outcomes [10].

The addition of ICIs to a four-drug chemotherapy backbone in curative-intent settings raises substantial concerns regarding safety and tolerability. Immune-related adverse events (irAEs) may affect virtually any organ system—including endocrine, gastrointestinal, dermatologic, hepatic, and pulmonary systems—and can range from mild manifestations to irreversible or fatal outcomes [11,12]. Importantly, data from KEYNOTE-522 showed higher absolute risk (AR) of treatment-related adverse events (TRAEs) in the pembrolizumab group, with grade ≥3 events in 77.1% of patients vs. 73.3% in the placebo group, and immune-mediated AEs (irAEs) such as hypothyroidism (15.1%) and adrenal insufficiency (1.2%) were notable [8]. In KEYNOTE-522, serious treatment-related adverse events occurred in 34.1% of patients receiving ICI versus 20.1% in the control arm. Treatment discontinuation due to toxicity was also more common with ICI (23.3% vs. 12.3%), while treatment-related mortality was 0.9%. In IMpassion031, TRAEs of any grade occurred in 99% of patients receiving atezolizumab and chemotherapy, including grade ≥3 events in 59% [9]. These findings raise critical questions about risk-benefit balance, especially considering that a proportion of eBC patients may already achieve excellent outcomes with chemotherapy alone [11,12].

Given the curative intent of treatment in eBC, understanding the toxicity profile of ICIs is essential to inform shared decision-making, survivorship planning, and long-term risk management. While individual trials have reported AE data, no prior synthesis has systematically evaluated the incidence, severity, and management implications of ICI-related AEs in this specific population. Therefore, we conducted a systematic review and meta-analysis of randomized and non-randomized clinical trials to assess the frequency, spectrum, and clinical impact of TRAEs associated with immune checkpoint inhibitors in patients with eBC.

2. Materials and methods

2.1. Search strategy

This study was performed following the guidelines from the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [13]. It was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the protocol number CRD42025633732 [14].

In January of 2025, a systematic search with no restriction regarding the publication date was performed in PubMed, Embase, and Cochrane databases and the European Society for Medical Oncology (ESMO) and American Society of Clinical Oncology (ASCO) conference proceedings. The search was last updated on June 5, 2025. The terms used include "breast cancer" and "immune checkpoint inhibitors". The full search used in each database is described on Table S2.

2.2. Eligibility criteria

We included clinical trials (CTs) reporting safety outcomes of ICI–based therapy in patients with eBC, treated in the neoadjuvant and/or adjuvant (perioperative) setting, irrespective of tumor subtype. Trials evaluating ICI monotherapy or ICI in combination with chemotherapy were eligible. Both full-text publications and conference abstracts were considered. No restrictions were applied regarding sample size, publication year, or geographic location. Main exclusion criteria included: (1) retrospective cohort studies; (2) case reports, case series, reviews, or meta-analyses; (3) studies investigating tumors other than breast cancer; (4) trials without extractable safety data; and (5) studies focused solely on prophylactic or supportive care strategies for ICI-related toxicity.

Retrospective cohort studies were excluded due to concerns regarding methodological heterogeneity, inconsistent adverse event reporting, variable follow-up duration, lack of predefined toxicity assessment protocols, and increased susceptibility to confounding and selection bias. Because immune-related adverse events are highly dependent on systematic surveillance and standardized grading systems such as CTCAE [15], we prioritized clinical trials with prospectively defined toxicity monitoring to improve internal validity and comparability across studies. Studies classified as having "lack of data" did not report extractable safety outcomes, event counts, toxicity grades, or sufficient numerical information to allow pooled quantitative analysis.

2.3. Study selection and data extraction

Two independent reviewers (MID and CERC) systematically screened titles, abstracts, and full texts to identify eligible studies. Data were extracted on trial design, population characteristics, ICI regimen, comparator arm, safety endpoints, and follow-up duration. Disagreements were resolved by consensus or adjudication by a third and fourth reviewer (MV and RLBC). When needed, supplementary materials or ClinicalTrials.gov entries were consulted to retrieve missing data.

2.4. Outcomes and subgroup analyses

The primary outcomes of interest were the AR of TRAEs, classified according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) [15], including both all-grade and grade $\geq$3 events. Specific AEs of clinical interest analyzed were: neutropenia, febrile neutropenia, leukopenia, anemia, nausea, vomiting, diarrhea, constipation, fatigue, asthenia, alopecia, thrombocytopenia, peripheral neuropathy, rash, skin reaction, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), hypothyroidism, hyperthyroidism, thyroiditis, hepatitis, colitis, pneumonitis, hypophysitis, adrenal insufficiency, infusion-related reactions, severe skin reactions (e.g., SJS/TEN), arthritis, nephritis/renal disorders, myocarditis, cardiac dysfunction, and other reported rare immune-related adverse events when available.

Secondary outcomes included the proportion of patients experiencing serious adverse events (SAEs), treatment discontinuation due to toxicity and treatment-related death. Where available, data on health-related quality of life (HRQoL) were also extracted. Subgroup analyses were planned based on: Treatment setting (neoadjuvant vs. adjuvant vs. perioperative – when used both in neoadjuvant and adjuvant settings); ICI agent used (e.g., pembrolizumab, atezolizumab, durvalumab, nivolumab); Tumor subtype (triple-negative, HR+/HER2–, HER2+); combination strategy (ICI monotherapy vs. ICI + chemotherapy).

Neutropenia and decreased neutrophil count were analyzed separately because included studies reported them as distinct CTCAE adverse event terms. To preserve consistency with the original trial reporting structure and avoid reclassification bias or inadvertent double-counting, these outcomes were not merged.

2.4.1. Quality assessment

Randomized controlled trials (RCTs) were assessed using the Cochrane Risk of Bias tool 2.0 (RoB 2) [16], which classifies trials as low, some concerns, or high risk of bias across five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of reported results. Non-randomized trials (including single-arm phase I/II studies) were evaluated using the ROBINS-I tool [17], covering seven domains of potential bias including confounding and selection. Risk of bias assessments were conducted independently by two reviewers (MID, CERC), with consensus reached through discussion or third-party review. Publication bias was explored through visual inspection of funnel plots and formally tested using Egger's test when $\geq$10 studies were available for a given outcome [18].

2.5. Sensitivity analyses and exploring heterogeneity

To test the robustness of pooled estimates and identify potential sources of heterogeneity, we conducted leave-one-out analyses and generated Baujat plots for key AEs of interest (neutropenia, anemia, diarrhea, and nausea). Additionally, subgroup analyses were stratified by treatment setting (neoadjuvant vs. adjuvant) and ICI class. When feasible, we also evaluated differences by study phase or geographic region.

2.6. Statistical analysis

Proportional meta-analyses were conducted using random-effects models (DerSimonian and Laird method) [19]. AR of events were pooled and reported as percentages with 95% confidence intervals (CI). Dichotomous outcomes were analyzed using the number of events per total population and reported as relative risk (RR) with 95% CIs. Logit transformation was applied when the observed proportion in individual studies was <0.2 or >0.8; for outcomes with zero events, double arcsine transformation was used. Comparative analyses (e.g., ICI vs. placebo or chemotherapy alone) were performed using risk ratios (RR) with 95% CI based on event counts in each arm. Heterogeneity was quantified using the I^2 statistic, with $I^2 > 25\%$ considered indicative of moderate to substantial heterogeneity. All analyses were performed using R software (version 4.2.2), employing the "meta", "metafor", and "weight" packages. Statistical significance was defined as $p < 0.05$ [20].

3. Results

3.1. Systematic review and baseline characteristics

A total of 3084 records were initially identified through database and manual searches. After title and abstract screening and full-text review, 13 studies (nine randomized controlled trials and four single-arm phase II studies) met the eligibility criteria and were included in the final analysis (Table 1, Fig. S1) [8–10,21–32]. These studies enrolled patients with eBC treated with ICIs in the neoadjuvant and or adjuvant settings, across various BC subtypes. A complete list of excluded studies after full-text review is provided in Supplementary Table S3.

Overall, 3977 patients were included across all trials. Of these, 3138 received an ICI-containing regimen, while 839 received standard therapy without immunotherapy. Most studies enrolled patients with triple-negative breast cancer (TNBC), although three recent phase III trials (KEYNOTE-756, CheckMate 7FL, and IMpassion050) included HR+/HER2− or HER2-positive subtypes [25–27]. All studies were conducted in the perioperative setting, with the majority employing ICIs in combination with chemotherapy as neoadjuvant treatment. Seven trials also included adjuvant ICI continuation.

The most commonly used ICI agents were pembrolizumab, atezolizumab, durvalumab, and nivolumab, often administered at approved dosing regimens (e.g., 200 mg q3w for pembrolizumab). Median follow-up across trials ranged from 9 to 42 months. Patients were chemotherapy-naive, with no prior systemic therapy in the early disease setting. All had a preserved performance status, defined as ECOG 0–1. Additional baseline characteristics, ICI regimens, and stratification criteria are detailed in Table 1.

3.2. Main safety analyses

3.2.1. Toxicity events: all-grade and grade $\geq$3

3.2.1.1. Single-arm analyses. In the pooled single-arm analyses of patients with eBC treated with ICIs, most AEs were of low grade. The most frequently reported all-grade AEs included alopecia, anaemia, and leukopenia, with ARs of 86.49% (95% CI: 59.25–96.57), 50.48% (95%

Table 1
Baseline characteristics of studies included in this systematic review and meta-analysis.

Study	Year	Design	Location	Population	Randomization Stratification factors	ICI			ICI (N)	Control	Total (N)	Patients on ICI		Median follow-up in months	ECOG PS
						Type and Dose Regimen	Setting					Median age (range) in years	Prior lines of treatment*		
							Neoadjuvant	Adjuvant							
GeparNuevo (NCT02685059) [8, 21]	2019	Phase II, RCT, double-blinded (1:1)	Multicenter	Stage I–III TNBC (cT1b-4 cN0-3, BC)	sTILS (low vs intermediate vs high)	Durvalumab 1.5 g q4w + chemotherapy	Nab-P weekly ×12 → EC (epirubicin + cyclophosphamide) + durvalumab	TPC	88	Neoadjuvant: (Nab-P followed by AC) + Pbo; Adjuvant: TPC	174	49.5 (23–76)	2-3, N (%): 184 (69)	42	0/1 95/ 5%
KEYNOTE-522 (NCT03036488) [22]	2020	Phase III, RCT, double-blinded (2:1)	Multicenter (21 countries)	High-risk stage II–III TNBC (cT1 cN1-2 or T2-4 cN0-2 BC)	Nodal status (positive or negative), tumor size (T1/2 or T3/4), Cb (every1wkor3 wk)	Pembrolizumab 200 mg q3w + chemotherapy; adjuvant pembrolizumab	Weekly P + Cb (q1–2wks) → AC (doxorubicin + cyclophosphamide) + pembro	Pembro × 9 cycles	784	Neoadjuvant: (CbP followed by AC orEC) + Pbo; Adjuvant: Pbo	1174	49 (22–80)	0	39.8	0/1 87/ 13%
IMpassion031 (NCT03197935) [9, 10]	2020	Phase III, RCT, double-blinded (1:1)	Multicenter (13 countries)	Stage II–III TNBC (cT2-4 cN0-3 BC)	Disease stage, PD-L1 IC (≥1% or <1%)	Atezolizumab 1200 mg q3w + chemo; adjuvant atezolizumab	Nab-P weekly ×12 → AC + At	No ICI post-surgery	165	Neoadjuvant: (Nab-P followed by AC) + Pbo; Adjuvant: NA (unblinded)	333	51 (22–76)	0	40.3	0/1 94/ 5%
I-SPY2 (NCT01042379) [23]	2020	Phase II, adaptive randomization, open-label	Multicenter	High-risk stage II–III HER2− (HR^+/ $ERBB^-$ MammaPrint high-risk or TNBC, cT2-4 cN0-3 BC)	Subtype, hormone/HER2, Stage II/III BC	Pembrolizumab 200 mg q3w ×4 + paclitaxel; then AC	P + pembro followed by AC	TPC	69	Neoadjuvant: P followed by AC Adjuvant: TPC	250	47 (NR)	0	20	0/1
NeoTRIP (NCT002620280) [24]	2022	Phase III, RCT, open-label (1:1)	Multicenter	High-risk locally-advanced TNBC (cT1cN1, cT2cN1, cT3cN0, or clinical stage III BC)	Geographic area, disease stage, PD-L1 status (IC 0 or IC 1, 2,or3)	Atezolizumab 840 mg q2w + nab-PTX/ Carboplatin	Cb + Nab-P + At	AC/EC/ FECC	280	Neoadjuvant: Cb + Nab-P Adjuvant: AC/ EC/FEC	556	49 (24–75)	0	29	0/1 96/ 4%
IMpassion050 (NCT03726879) [25]	2022	Phase III, RCT, double-blinded (1:1)	Multicenter	High-risk HER2-positive, *ERBB*-positive (cT2-4 cN1-3 BC)	Tumor stage (T2 vs T3-4), HR status (positive or negative), PD-L1 status (IC 0 or IC 1/2/3)	Atezolizumab 840 mg q2w + ddAC-PTX + PH	(AC followed by THP) + At	HP or T-DM1 + At	370	Neoadjuvant: (AC followed by THP) + Pbo Adjuvant: HP or T-DM1 + Pbo	737	50 (19–75)	0	38	0/1 98/ 2%
KEYNOTE-756 (NCT03725059) [26]	2023	Phase III, RCT, double-blinded (2:1)	Multicenter	High-risk ER+/ HER2− eBC - cT1-2 (≥2 cm) cN1-2 or cT3-4 cN0-2 BC	Geographic area, PD-L1 CPS (≥1 or <1), AC frequency (every3wkor2 wk), ER status (≥10% or <10%)	Pembrolizumab 200 mg q3w + chemo; adjuvant pembrolizumab + ET	Weekly P ×12 → AC (or EC) + pembro	Pembro × 9 cycles	639	Neoadjuvant: Weekly P ×12 → AC (or EC) Adjuvant: Pbo	1278	52 (24–79)	0	24	0/ 1 > 95%
CheckMate 7FL (NCT04109066) [27]	2023	Phase III, RCT, double-blinded (1:1)	Multicenter	High-risk ER+/ HER2− eBC [with ER ≥ 1% or HG2withER	PD-L1 IC (≥1% or <1%), tumor grade (3 or 2), nodal status	Nivolumab 360 mg q3w + chemotherapy; adjuvant ET	(P followed by AC) + nivo	nivo + ET	550	Neoadjuvant: (P followed by AC) + Pbo	1100	52 (26-71)	0	14	0/1

(*continued on next page*)

Table 1 (*continued*)

Study	Year	Design	Location	Population	Randomization Stratification factors	ICI			ICI (N)	Control	Total (N)	Patients on ICI		Median follow-up in months	ECOG PS
						Type and Dose Regimen	Setting					Median age (range) in years	Prior lines of treatment*		
							Neoadjuvant	Adjuvant							
				1%-10%; cT1-2 (≥2 cm) cN1-2 or T3-4 cN0-2 BC]	(positive or negative), AC frequency (every 3 wkor2wk					Adjuvant: Pbo + ET[a]					
APTneo (NCT03595592) [28]	2023	Phase III, randomized, open-label (2:1)	China	Stage II–III TNBC (*ERBB2*+ cT1cN1, cT2cN1 cT3cN0 or clinical stage III BC)	Geographic area, disease stage, HR status (positive vs negative), PD-L1 status (IC 0 or IC 1, 2,or3)	Durvalumab 1.5 g q4w + nab-PTX/ Carboplatin	Exp1: (AC 3 times followed by HPCbT 3 times) + At; Exp2: HPCbT 6 times + At;	Exp1: HP or T-DM1[b]; arm Exp2: HP or T-DM1[b] + At;	70	Neoadjuvant: HPCbT 6 times Adjuvant: HP or T-DM1[b]	105	50 (22–71)	0	18	0/1
NeoTENNIS (NCT04418154) [29]	2024	Phase II, single arm	China	Stage II–III TNBC	NA	Toripalimab 240 mg q3w + nab-PTX	AC → weekly P + At	NR	58	NA	58	NR (≈49)	0	12	0/1
NeoTAPPL (ChiCTR2300071925) [30]	2025	Phase II, single arm	USA	Stage II–III TNBC	NA	Pembrolizumab + Paclitaxel/ Carboplatin ± SD-101	P + Cb + At	NR	NR	NA	NR	NR	0	NR	0/1
PEARL (NCT03366844) [31]	2024	Phase II, single arm	USA	Early TNBC	NA	Pembrolizumab 200 mg q3w + pre-op radiation	EC → taxane + durvalumab	NR	29	NA	29	NR (~49)	0	13	0/1
BELLINI (a) (NCT03815890) [32]	2024	Non Randomized phase III	Multicenter	Stage I-II, node negative, TILs ≥50% TNBC	TIL Level	Nivolumab + Ipilimumab 1 mg/kg q6w (d1 + d21, n = 15)	Nivo + Ipilimumab → TPC	NR	90	NA	180	NR (~48)	0	9	0/1
BELLINI (b) (NCT03815890) [32]	2024	Non Randomized phase III	Multicenter	Stage I-II, node negative, TILs ≥50% TNBC	TIL Level	Nivolumab + Relatlimab (anti-LAG3) q8w (d1 + d29, n = 15)	Nivo + Relatlimab → TPC	NR	90	NA	180	NR (~48)	0	9	0/1

Abbreviations: A, Doxorubicin; AC, Doxorubicin + Cyclophosphamide; AE, Adverse event; At, Atezolizumab; BC, Breast cancer; C, Cyclophosphamide; Cb, Carboplatin; CPS, Combined Positive Score; ddAC, Dose-dense AC; Durva, Durvalumab; E, Epirubicin; EC, Epirubicin + Cyclophosphamide; eBC, Early breast cancer; ET, Endocrine therapy; Exp, Experimental arm; EFS, Event-free survival; ER, Estrogen receptor; F, 5-Fluorouracil; H, Trastuzumab; HER2, Human epidermal growth factor receptor 2; HG, Histologic grade; HR, Hormone receptor; IC, Immune cells (used in PD-L1 scoring); ICI, Immune checkpoint inhibitor; ITT, Intention-to-treat population; mITT, Modified intention-to-treat population; NA, Not applicable or not available; Nab-P, Nanoparticle albumin-bound paclitaxel; Nivo, Nivolumab; NR, Not reported; P, Pertuzumab; Pbo, Placebo; Pembro, Pembrolizumab; pCR, Pathologic complete response; q3w/q4w/q2w/q6w/q8w, Every 3/4/2/6/8 weeks, respectively; RCT, Randomized controlled trial; SD-101, TLR9 agonist; T-DM1, Trastuzumab emtansine; TILs, Tumor-infiltrating lymphocytes; TPC, Treating physician's choice; TNBC, Triple-negative breast cancer.

CI: 18.40–82.17), and 52.09% (95% CI: 15.14–86.89), respectively [Fig. S2]. Fatigue, increased ALT, nausea, neutropenia, peripheral neuropathy and thromcytopenia also occurred with ARs above 30%, as shown in Fig. S2. In contrast, grade ≥3 AEs were less frequent with pooled AR of 3.44% (95% CI: 2.52—4.68) [Fig. S3]. Neutropenia was the most common high-grade event, with a pooled AR of 18.19% (95% CI: 10.81–28.96), followed by decreased neutrophil count (AR 17.88%, 95% CI: 10.65—28.44) and leukopenia (AR 13.25%, 95% CI: 6.14—26.30) [Fig. S3]. Anemia, increased ALT and febrile neutropenia had ARs above 5%, as illustrated in Fig. S3 As shown in Fig. 1, the pooled proportion of patients experiencing at least one all-grade adverse event during ICI therapy for early breast cancer was 99.63% (95% CI: 98.35—99.92), with no heterogeneity across studies ($I^2 = 0\%$). This high incidence underscores that while most events are of lower grade, virtually all patients experienced some degree of toxicity. The overall incidence of grade ≥3 adverse events in patients treated with ICIs in the perioperative setting was 43.98% (95% CI: 28.61–60.60), as shown in Fig. 2. A detailed breakdown of individual all-grade and high-grade events is available in the supplementary material (Figs. S2 and S3).

3.3. Comparative safety between ICI and chemotherapy

Comparative analyses of safety outcomes between chemotherapy combined with ICIs and chemotherapy alone were conducted across randomized controlled trials (RCTs) evaluating 13 predefined AEs. Among all-grade events, the risk of diarrhea was comparable between groups (RR 1.08; 95% CI: 0.92–1.27), as was the risk of nausea (RR 1.04; 95% CI: 0.97—1.10), vomiting (RR 1.41; 95% CI: 1.14—1.75), and fatigue (RR 1.07; 95% CI: 0.98—1.17) [Fig. 3]. The risk of neutropenia was lower in ICI-treated patients (RR 0.98; 95% CI: 0.91–1.06) although it was not statistically significant, while elevations in liver enzymes were slightly more frequent in the ICI arms, including AST (RR 1.32; 95% CI: 1.10–1.57) and ALT (RR 1.10; 95% CI: 0.96–1.26). Rash (RR 1.16; 95% CI: 0.90—1.48) and peripheral neurophaty (RR 1.83; 95% CI: 0.77—4.32) also showed numerically higher risks with ICI, though without statistical significance [Fig. 3]. Regarding grade ≥3 adverse events, no significant differences were observed in the overall rate between ICI and chemotherapy arms, with a pooled RR of 1.00 (95% CI: 0.99–1.01), as shown in Fig. 4. A detailed breakdown of comparative risk of high-grade events and the total all grade AEs (ICIs vs. Chemotherapy) is available in the supplementary material (Figs. S4 and S5).

3.4. Immune-related adverse events (irAEs)

irAEs were analyzed separately, including both all-grade and grade ≥3 toxicities associated with presumed immune activation. The most frequent all-grade irAEs in ICI-treated patients (single-arm) included hypothyroidism (AR 12.70%; 95% CI: 9.27–17.16), infusion related reaction (AR 9.19%; 95% CI: 5.50–14.95) and hyperthyroidism (AR 6.08%; 95% CI: 3.94–9.27) [Fig. 5]. Other immune-related events, such as colitis, adrenal insufficiency and severe skin reactions were observed at frequencies below 3% [Fig. 5]. Among grade ≥3 irAEs in ICI-treated patients (single-arm), the most common were hepatitis (AR 1.04%; 95% CI: 0.56–1.93), adrenal insufficiency (AR 1.47%; 95% CI: 0.68–3.12), and infusion related reaction (AR 1.37%; 95% CI: 0.77–2.43), though without statistical significance, while all remaining events occurred in fewer than 2% of patients [Fig. 6]. Forest plots comparing the relative risk of all-grade and grade ≥3 of irAEs between ICI and chemotherapy arms across randomized trials are provided in the supplementary material (Figs. S6 and S7). Additional details about the total comparative risk of all-grade and grade ≥3 of irAEs are provided in Figs. S8 and S9.

3.5. Serious TRAEs, dose reductions, treatment discontinuation, and death

Treatment discontinuation due to AEs occurred in 5.17% of patients (95% CI: 0.94–23.88%), most commonly due to irAEs such as hepatitis, pneumonitis, and colitis, as well as severe fatigue and hematologic events, when specified [Fig. 7]. These discontinuations referred primarily to ICI therapy, although causality data were inconsistently reported across studies. The treatment-related mortality rate was 0.57% (95% CI: 0.20–1.64%) [Fig. 7]. Serious TRAEs were infrequent overall, with the most commonly reported serious events being pneumonitis, hepatitis, colitis, and severe hematologic toxicities. Comparative data on serious TRAEs and treatment discontinuation were only available from the KEYNOTE-522 trial, which reported higher rates in the ICI arm than in the control group.

3.6. Health-related quality of life

Only three studies reported data on health-related quality of life (HRQoL), and due to the heterogeneity of measurement tools (EORTC QLQ-C30, FACT-B, and PROMIS), meta-analytical pooling was not feasible. A descriptive synthesis indicated a modest decline in overall

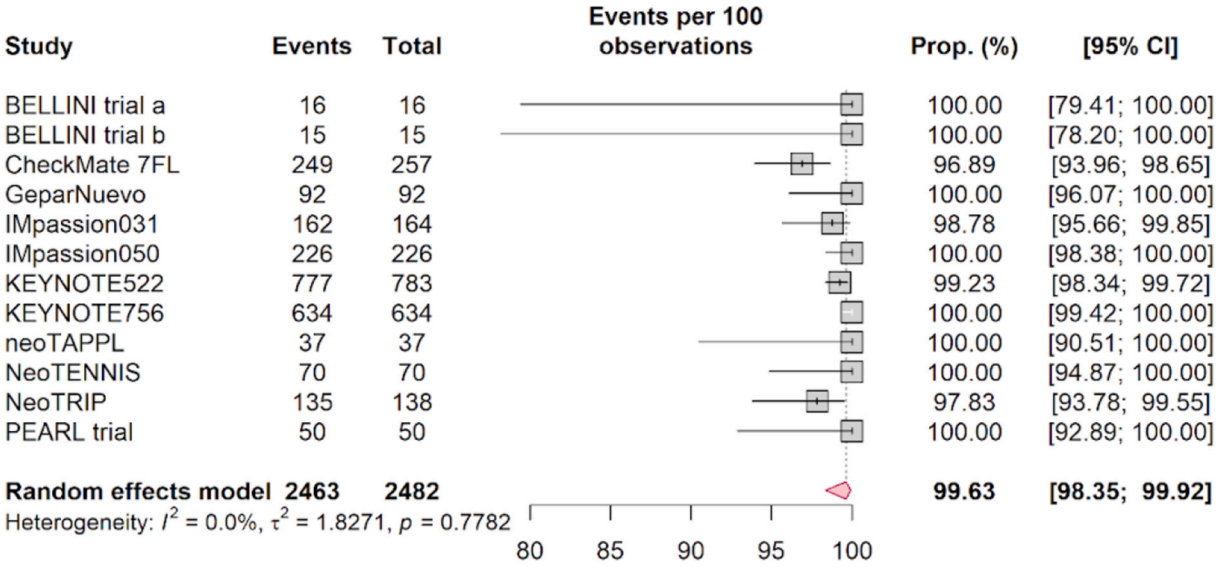

Fig. 1. All-grade adverse events in ICI-treated patients
Legend: Forest plot showing the absolute risk (AR) per 100 patients of all-grade AE across single-arm studies of ICI.

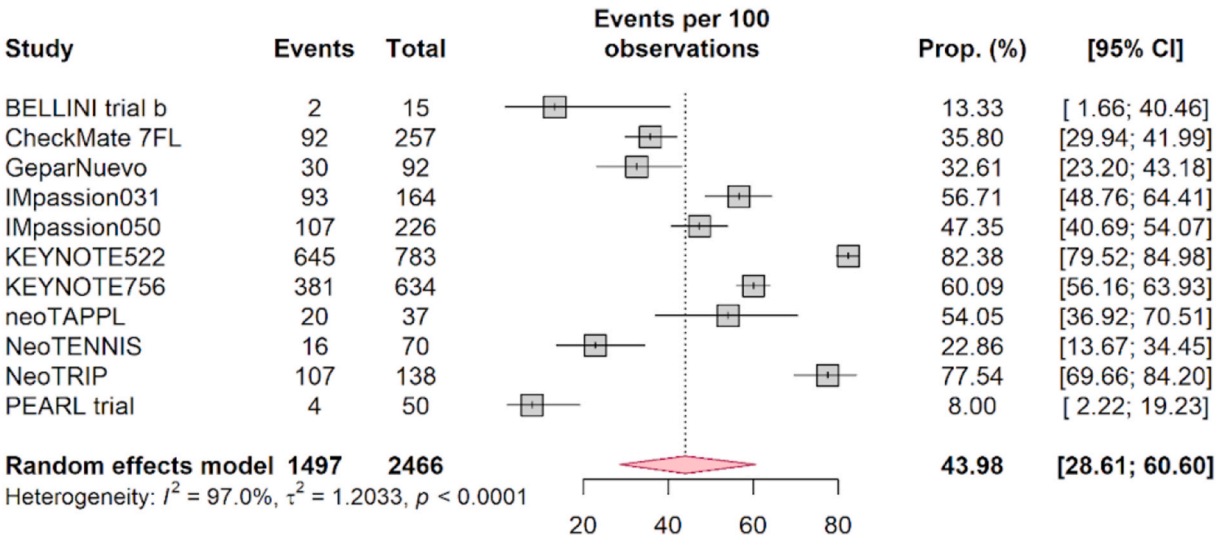

Fig. 2. Grade ≥3 adverse events in ICI-treated patients
Legend: Forest plot showing the absolute risk (AR) per 100 patients for grade ≥3 AE across single-arm studies of ICI.

health status during neoadjuvant therapy, with partial recovery following treatment completion. One study using the EORTC QLQ-C30 reported reductions in physical functioning and global quality of life during treatment that improved post-therapy. Another study employing the FACT-B instrument found emotional well-being to be notably affected during ICI-based regimens, while PROMIS-based assessments revealed transient worsening in fatigue and physical function, with most domains returning to baseline within six months [33–35].

3.7. Risk of bias and sensitivity analyses

Risk of bias was assessed using the RoB 2 tool for RCTs and the ROBINS-I tool for non-randomized studies. Among the nine RCTs included, most demonstrated low risk of bias across domains related to randomization, intervention adherence, and outcome measurement. However, two trials were judged as having "some concerns" due to insufficient reporting on allocation concealment or blinding procedures. Among the four non-randomized studies, risk of bias was rated as moderate to serious, particularly in domains related to confounding and participant selection. Most non-randomized trials lacked adjustment for key prognostic factors and did not report whether outcome assessors were blinded. Domain-level and overall risk of bias summaries are available in Figs. S7 and S8.

Publication bias was explored for outcomes with ≥10 studies available. Funnel plot inspection did not demonstrate major asymmetry for the primary safety outcomes, although interpretation was limited by the relatively small number of included studies and clinical heterogeneity among trials. Egger's test did not identify statistically significant small-study effects for the evaluated outcomes [18].

Sensitivity analyses using leave-one-out procedures for all-grade neutropenia, nausea, diarrhea, and anemia did not identify any influential outliers, and overall estimates remained robust. Baujat plots further confirmed that no single study disproportionately contributed to overall heterogeneity. Sensitivity analyses did not materially alter pooled estimates, suggesting that no single study disproportionately influenced the overall results.

4. Discussion

This comprehensive systematic review and meta-analysis included over 1200 patients with eBC treated with ICI-containing regimes and nearly 1000 patients treated with chemotherapy without ICI across randomized trials. The most frequently reported AEs were all-grade alopecia, anemia and leukopenia, with pooled AR ranging from 50% to 86%. Grade ≥3 neutropenia occurred in approximately 43.98% of patients receiving ICIs. The most frequent AEs are chemotherapy-related, with similar rates between ICI-containing and ICI-free groups [20–32].

ICI exhibits a unique safety profile shaped by its inherent immune-mediated mechanism of action. Rather than dose-dependent cytotoxic effects, AEs associated with ICIs derive from immune dysregulation, leading to organ-specific inflammation, particularly affecting endocrine, gastrointestinal, hepatic, and cutaneous systems [36,37]. In this meta-analysis, we identified thyroid dysfunction, hepatitis, colitis, and pneumonitis as the most frequent irAEs, with consistent signals across studies evaluating ICI monotherapy in eBC [38,39], reinforcing the predictability of these immune-mediated toxicities. Grade ≥3 irAEs remained uncommon but clinically relevant, particularly for hepatotoxicity and gastrointestinal inflammation. In addition, endocrine irAEs, such as adrenal insufficiency and diabetes, frequently leads to permanent disfunction. Although most irAEs were low-grade and manageable, their potential severity and unpredictability call for careful baseline screening and longitudinal toxicity surveillance.

Mechanistically, irAEs stem from T-cell activation against self-antigens and local tissue damage driven by cytokine release and immune infiltration [40]. This immune reactivity is potentiated in early-stage settings by the high tumor antigen load, intact immune repertoire, and concurrent chemotherapy [40,41]. Indeed, in several of the included trials, ICI administration was combined with anthracyclines or platinum agents—both known to induce immunogenic cell death—which may amplify immune-related toxicity [42]. Furthermore, endocrine irAEs such as hypothyroidism and adrenal insufficiency can be clinically silent or mimic cancer-related fatigue, reinforcing the need for proactive monitoring strategies [42,43]. The time from ICI initiation to irAE onset varies according to the specific event, as reported in the real-world Neo-Real study, which evaluated patients with breast cancer treated with the KEYNOTE-522 regimen. Although irAEs are more common during the neoadjuvant phase, a considerable proportion of patients develop them only in the adjuvant phase, underscoring the need for caution and vigilance throughout the entire treatment course [44].

Hematologic AEs such as neutropenia, anemia, and leukopenia are frequent in breast cancer regimens that comprise multiple chemotherapy agents, and did not seem to be influenced by the addition of ICI. Interestingly, diarrhea and liver enzyme elevations emerged as toxicities significantly more common in the ICIs group), aligning with the known gastrointestinal and hepatic toxicity spectrum associated with immunotherapy. The ARs for fatigue and asthenia were numerically higher in

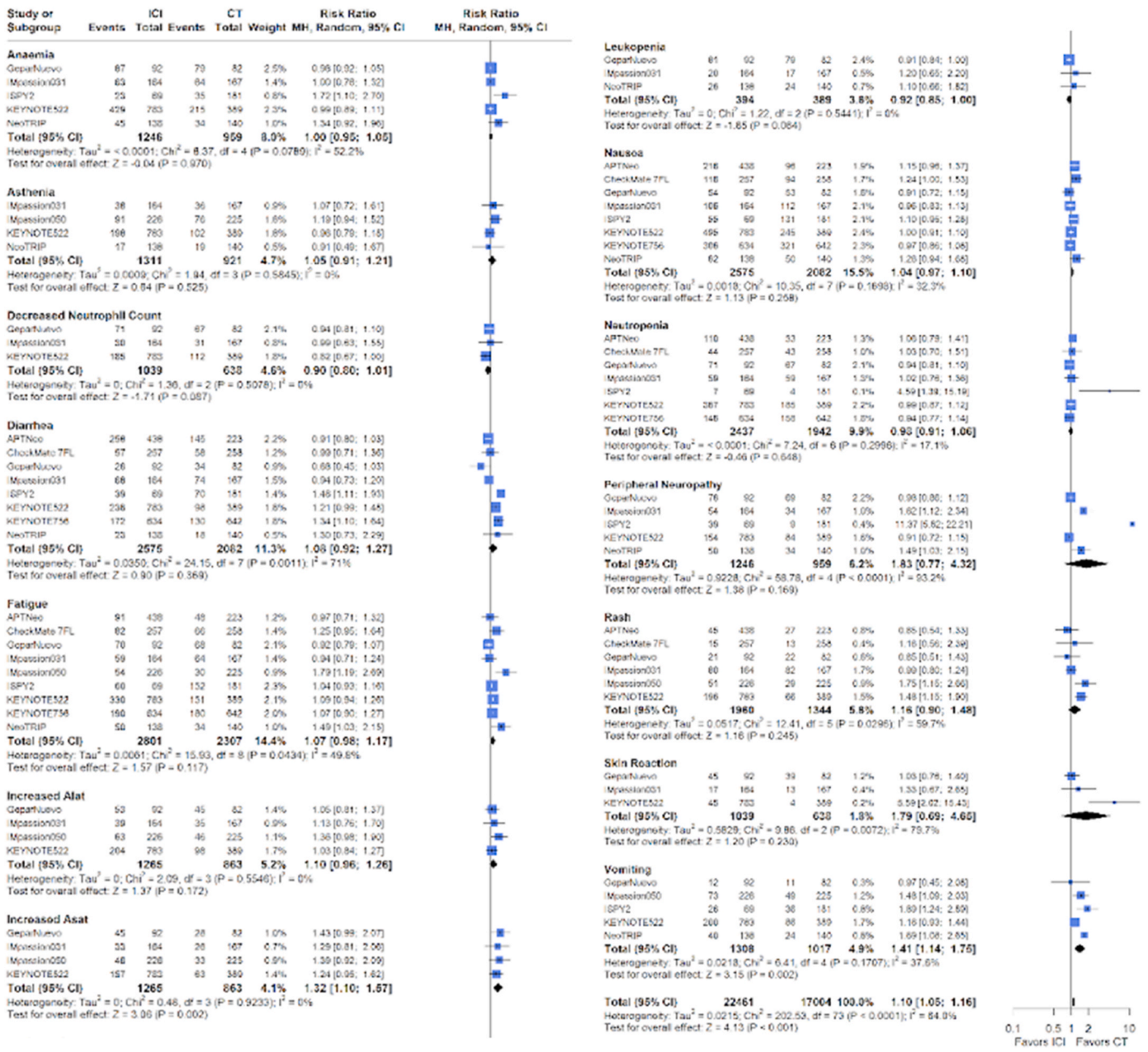

Fig. 3. Comparative risk of all-grade adverse events: ICI vs chemotherapy

Legend: Summary forest plot of relative risks (RRs) and 95% CIs for all-grade AEs comparing ICI to chemotherapy in RCTs. Diarrhea and AST elevation were significantly more common with ICIs.

patients receiving ICIs, this pattern mirrors findings from studies in non-small cell lung cancer and melanoma, where fatigue is frequently reported but seldom reaches statistical significance—consistent with our findings, in which the observed differences did not attain statistical significance [45,46].

The perioperative setting may further amplify immune-mediated toxicity through interactions between ICIs and cytotoxic chemotherapy [44]. Anthracyclines and platinum agents are known to induce immunogenic cell death and increase antigen presentation, potentially potentiating immune activation beyond antitumor effects [45]. Additionally, prolonged exposure to ICIs during adjuvant therapy may contribute to delayed endocrine and hepatic irAEs, reinforcing the importance of longitudinal surveillance even after completion of chemotherapy [46].

Unlike metastatic settings, patients with eBC may experience long-term survivorship after treatment completion [46]. Therefore, even low-frequency chronic endocrine or immune-mediated toxicities may have substantial long-term implications for quality of life, survivorship care, and healthcare utilization. Management of severe irAEs frequently requires systemic corticosteroids or immunosuppressive therapy, which may further complicate treatment delivery in the perioperative setting and potentially impact quality of life and treatment adherence [47].

A major strength of this analysis is the consistency observed across trials, with minimal heterogeneity and robust findings in leave-one-out sensitivity analyses. Still, this study has limitations. Firstly, most toxicity endpoints were study-level, and patient-level data were not accessible. This precluded stratified analyses based on age, comorbidities, or PD-L1 expression [47,48]. Secondly, follow-up duration was limited in some trials, especially for late-onset irAEs such as hypophysitis or pneumonitis. Third, variations in chemotherapy backbones and ICI regimens

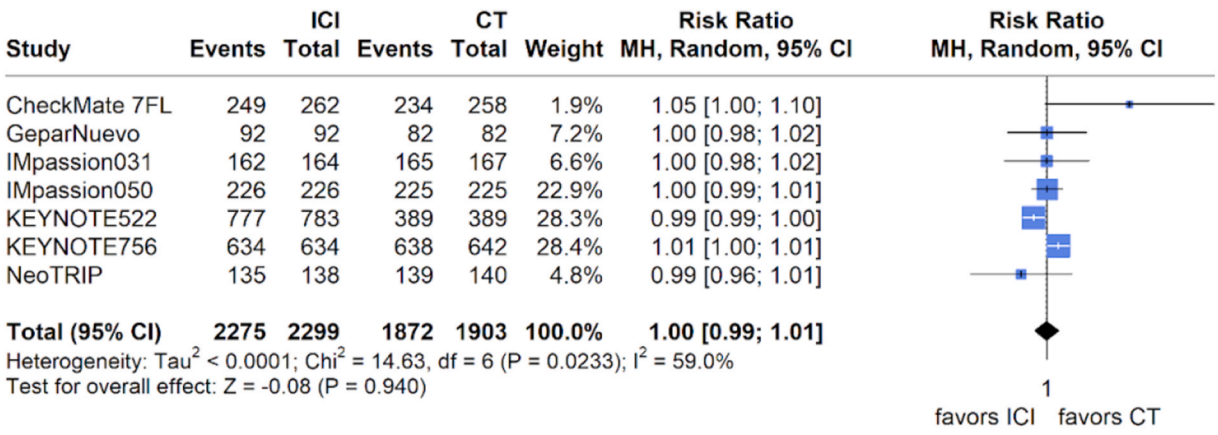

Fig. 4. Comparative risk of grade ≥3 adverse events: ICI vs chemotherapy
Legend: Summary forest plot showing RRs of high-grade AEs from RCTs comparing ICIs with chemotherapy. No statistically significant differences were observed.

may have contributed to differences in AE incidence, though subgroup analyses by ICI type did not reveal substantial discrepancies.

Considerable variability in grade ≥3 toxicity rates was observed across studies. This heterogeneity likely reflects differences in chemotherapy backbone intensity, duration of adjuvant immunotherapy exposure, follow-up time, toxicity reporting practices, and ICI agents used. Trials incorporating anthracycline- and platinum-based regimens generally demonstrated higher rates of hematologic toxicities, whereas studies with prolonged adjuvant exposure may have captured a greater number of delayed immune-related events. [46–48]

Another limitation is that hepatotoxicity outcomes were analyzed according to the reporting structure of the original trials, which typically separated ALT and AST elevations rather than reporting composite immune-mediated hepatotoxicity syndromes. This approach may underestimate the true incidence of immune-related liver toxicity and dilute clinically relevant hepatotoxicity signals. Future studies should standardize reporting of immune-mediated hepatotoxicity as syndrome-level events rather than isolated laboratory abnormalities.

Additionally, retrospective cohort studies were not included in this analysis. Although this decision improved methodological consistency and internal validity, it may have limited generalizability and reduced the ability to detect rare immune-related toxicities such as myocarditis or renal immune-related adverse events. Nevertheless, this is the first meta-analysis to systematically evaluate AEs related to ICIs in e BC across multiple perioperative trials [49–51].

Future studies should prioritize the identification of predictive biomarkers for irAE susceptibility, such as HLA alleles, cytokine signatures, or microbiome profiles. Additionally, longer follow-up is warranted to evaluate cumulative toxicity and late effects, especially as ICIs transition to the adjuvant setting and are considered for combination strategies. Emerging combinations such as ICIs with antibody-drug conjugates (e.g., sacituzumab govitecan) or PARP inhibitors are under active investigation and may shift the current safety landscape. For instance, in the ASCENT trial, UGT1A128 homozygosity was associated with increased neutropenia risk under sacituzumab, highlighting the need for integrated toxicity mitigation [52,53].

Rare but clinically significant irAEs such as myocarditis, nephritis, and inflammatory arthritis remain incompletely characterized in eBC [54]. Although infrequently reported in the included trials, these toxicities are of particular clinical concern given their potential severity and the curative intent of therapy in this population [55]. Immune-related cardiotoxicity, especially myocarditis, has been associated with high mortality rates in other malignancies treated with ICIs and may be underrecognized in BC clinical trials due to limited sample size and relatively short follow-up duration [56]. Importantly, certain irAEs such as myocarditis, although rare, may present with fulminant clinical courses and disproportionately high mortality rates compared with more common endocrine toxicities [56]. In curative-intent settings, even low-frequency severe toxicities warrant particular attention given the long expected survivorship of these patients [55,56]. Future studies should prioritize standardized reporting of rare irAEs and incorporate long-term toxicity surveillance strategies.

5. Conclusion

In this systematic review and meta-analysis, the most common any grade and grade 3-4 AEs of ICI plus chemotherapy regimens are those driven by chemotherapy, with a considerable proportion of patients presenting serious AEs and treatment discontinuation. Nevertheless, treatment-related deaths are infrequent. The addition of ICI increases the occurrence of immune-related AEs that require a proper monitoring and multidisciplinary management. Further studies with longer follow-up and standardized AE and HRQoL reporting are warranted.

Data availability statement

All data presented in this study is accessible to the corresponding author upon a reasonable request.

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CRediT authorship contribution statement

Maria Inez Dacoregio: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Caio Ernesto do Rego Castro:** Conceptualization, Data curation, Resources. **Isadora Mamede:** Conceptualization, Data curation, Formal analysis, Methodology, Software, Validation, Visualization. **Cainã Gonçalves Rodrigues:** Data curation, Formal analysis, Funding acquisition, Methodology, Software. **João Pedro Thimotheo Batista:** Conceptualization, Data curation, Methodology. **Isabella Michelon:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration. **Paulo Zattar Ribeiro:** Supervision, Validation. **José Reinaldo de Oliveira Junior:** Conceptualization, Resources, Supervision, Validation. **Renata Colombo Bonadio:** Investigation, Project administration, Supervision, Validation, Visualization, Writing – review & editing. **Maysa Vilbert:** Supervision, Validation, Writing – review & editing. **Ricardo Lima Barros Costa:** Conceptualization, Project administration, Resources, Supervision, Validation, Visualization, Writing – review &

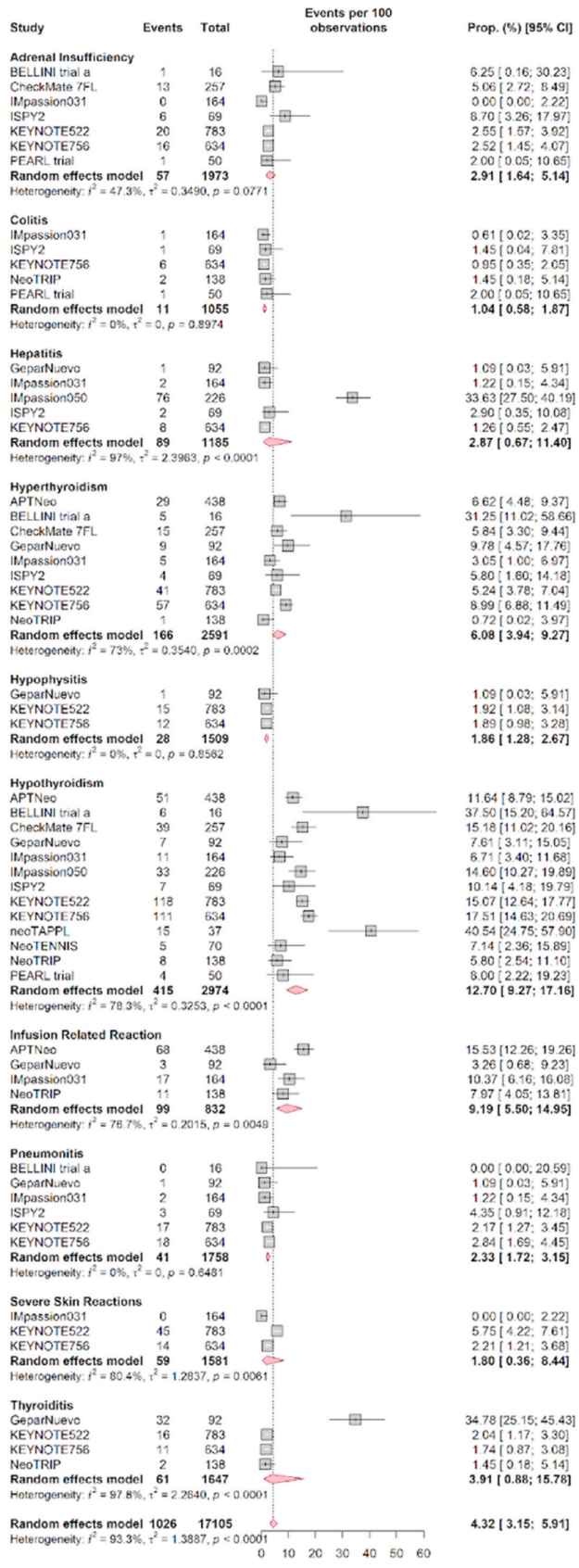

Fig. 5. All-grade immune-related adverse events (irAEs)
Legend: Forest plot of pooled all-grade irAE frequencies from single-arm studies, including endocrine, hepatic, and gastrointestinal events. Hypothyroidism infusion related reaction and hyperthyroidism were most frequent.

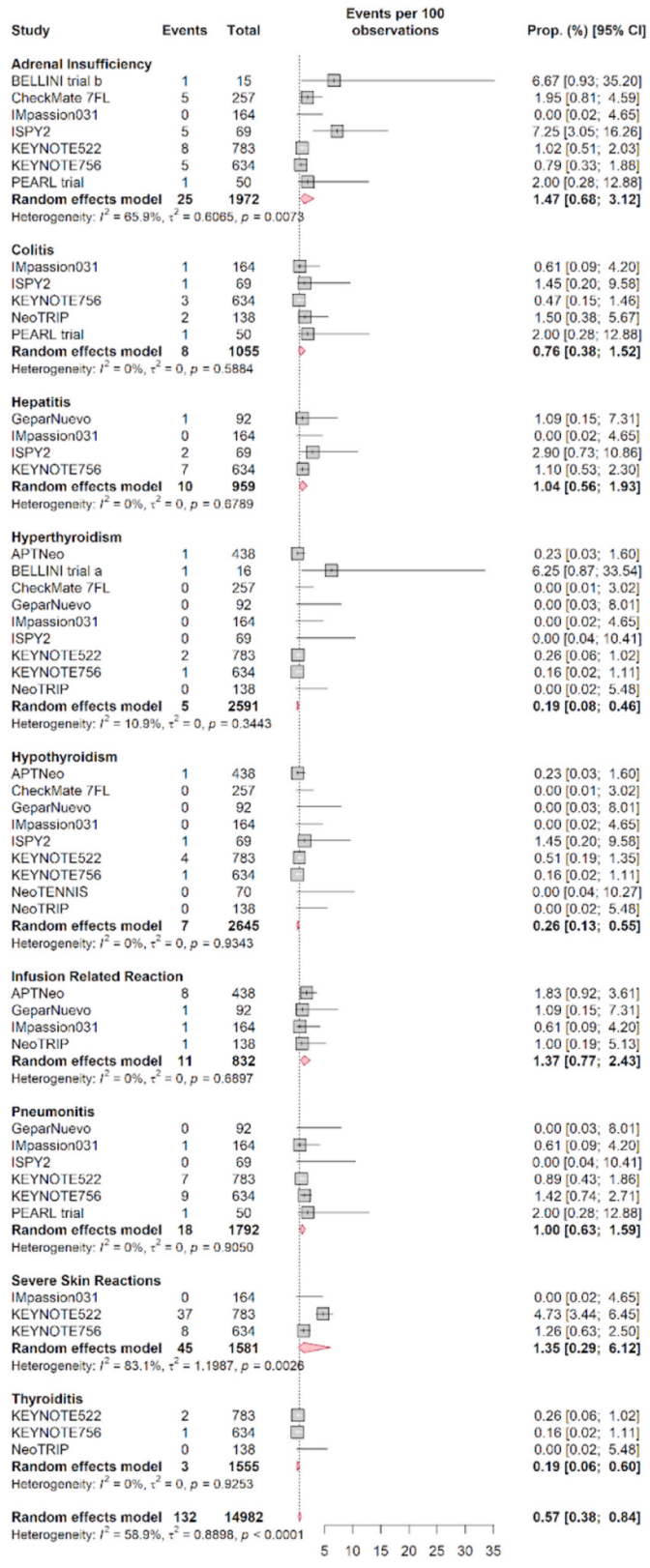

Fig. 6. Grade ≥3 immune-related adverse events (irAEs)
Legend: Forest plot showing the estimated proportion of grade ≥3 irAEs. Severe hepatitis, adrenal insufficiency, and infusion related reaction were the most commonly reported.

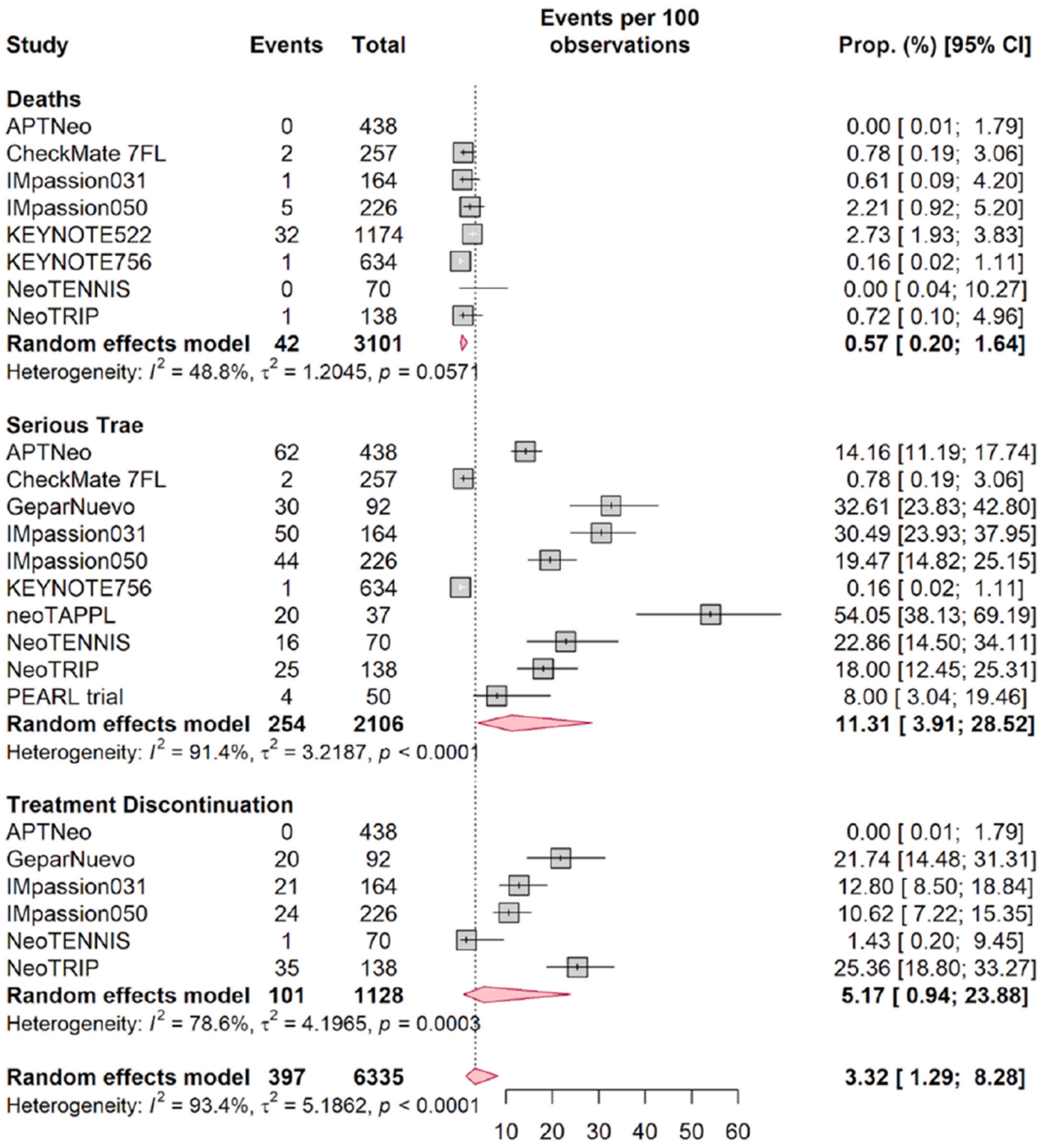

Fig. 7. Treatment-related mortality, serious TRAEs and treatment discontinuation.
Legend: Pooled proportions of patients experiencing treatment-related mortality, serious TRAEs and treatment discontinuation.

editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2026.104821.

References

[1] Smith LA, Cornelius VR, Plummer CJ, et al. Cardiac toxicity in patients receiving anthracycline- and trastuzumab-based regimens for early-stage breast cancer. Cardiol Toxicol 2022;18:105–13. https://doi.org/10.1007/s12325-022-01478-x.

[2] Daugaard G, Paulsen BS. Managing short- and long-term toxicity of chemotherapy in early breast cancer: focus on peripheral neuropathy and cardiotoxicity. Eur J Oncol Nurs 2021;50:101876. https://doi.org/10.1016/j.ejon.2020.101876.

[3] Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. Nature 2011;480:480–9. https://doi.org/10.1038/nature10673.

[4] Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. Immunity 2013;39:1–10. https://doi.org/10.1016/j.immuni.2013.07.012.

[5] Robert C, Schachter J, Long GV, et al. Nivolumab in untreated melanoma without BRAF mutation. N Engl J Med 2015;372:320–30. https://doi.org/10.1056/NEJMoa1412082.

[6] Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab vs docetaxel in advanced NSCLC. N Engl J Med 2015;373:1627–39. https://doi.org/10.1056/NEJMoa1507643.

[7] Sikov WM, Berry DA, Perou CM, et al. Event-free and overall survival following neoadjuvant weekly paclitaxel and dose-dense doxorubicin and cyclophosphamide: no evidence for inferior outcomes among African-American and Hispanic women in CALGB 40603. Breast Cancer Res Treat 2016;160:253–62. https://doi.org/10.1007/s10549-016-3940-5.

[8] Schmid P, Cortes J, Dent R, et al. Pembrolizumab for early triple-negative breast cancer. N Engl J Med 2022;386:1143–54. https://doi.org/10.1056/NEJMoa2202809.

[9] Schmid P, et al. Event-free and overall survival with neoadjuvant–adjuvant pembrolizumab in triple-negative breast cancer. NEJM 2024;390(2):123–34. https://doi.org/10.1056/NEJMoa2400123.

[10] Schmid P, Salgado R, Park Y-H, et al. Atezolizumab plus neoadjuvant nab-paclitaxel and anthracycline-based chemotherapy in early TNBC (IMpassion031). Lancet Oncol 2022;23:50–62. https://doi.org/10.1016/S1470-2045(21)00688-6.

[11] Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med 2018;378:158–68. https://doi.org/10.1056/NEJMra1703481.

[12] Michot JM, Bigenwald C, Champiat S, et al. Immune-related adverse events with immune checkpoint blockade: comprehensive review. Eur J Cancer 2016;54:139–48. https://doi.org/10.1016/j.ejca.2015.11.016.

[13] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Br Med J 2021;372:n71. https://doi.org/10.1136/bmj.n71.

[14] Inez Dacoregio Maria, Ernesto Caio, Batista João Pedro Thimotheo, Mamede Isadora, Zattar Ribeiro Paulo Victor, Michelon Isabella, Vilbert Maysa, Costa Ricardo Lima Barros. Adverse events and tolerability of immune checkpoint inhibitors (ICI) for the treatment of early-stage breast cancer (BC). PROSPERO 2024:1. https://www.crd.york.ac.uk/PROSPERO/view/CRD42025633732. CRD42025633732.

[15] National Cancer Institute. Common terminology criteria for adverse events (CTCAE) version 5.0. Bethesda, MD: National Institutes of Health; 2017.

[16] Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. Br Med J 2019:l4898. https://doi.org/10.1136/bmj.l4898.

[17] Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. Br Med J 2016:i4919. https://doi.org/10.1136/bmj.i4919.

[18] Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ Br Med J (Clin Res Ed) 1997;315(7109):629–34.

[19] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88. https://doi.org/10.1016/0197-2456(86)90046-2.

[20] Viechtbauer W. Conducting meta-analyses in R with the metafor package. J Stat Software 2010;36(3):1–48.

[21] Mittendorf EA, Zhang H, Barrios CH, et al. Neoadjuvant durvalumab plus chemotherapy in early triple-negative breast cancer (GeparNuevo phase II): safety and efficacy analysis. Ann Oncol 2019;30(Suppl 5):v851–934. https://doi.org/10.1093/annonc/mdz124.

[22] Schmid P, Cortes J, Dent R, et al. Pembrolizumab for early triple-negative breast cancer (KEYNOTE-522): overall survival and safety outcomes. N Engl J Med 2022;386:1143–54. https://doi.org/10.1056/NEJMoa2202809.

[23] Hwang ES, I-SPY2 Investigators. Adaptive randomization of an immune checkpoint inhibitor in I-SPY2 breast cancer trial: safety and efficacy insights. J Clin Oncol 2020;38(15_suppl):1006. https://doi.org/10.1200/JCO.2020.38.15_suppl.1006.

[24] Loibl S, Untch M, Burchardi N, et al. Neoadjuvant PD-L1 checkpoint inhibition (NeoTRIP trial) in early breast cancer: toxicity and response rates. J Clin Oncol 2021;39(15_suppl):504. https://doi.org/10.1200/JCO.2021.39.15_suppl.504.

[25] Hurvitz SA, Banerji S, Tarantino P, et al. IMpassion050: safety analysis of atezolizumab in HER2+ early-stage breast cancer. Ann Oncol 2022;33(7):768–79. https://doi.org/10.1093/annonc/mdac207.

[26] Harbeck N, Rastogi P, Esteva FJ, et al. KEYNOTE-756: pembrolizumab plus chemotherapy in early breast cancer—safety and tolerability data. Ann Oncol 2023;34(Suppl 5):S298–319. https://doi.org/10.1016/j.annonc.2023.03.104.

[27] Fasching PA, Ackermann S, Büttner C, et al. CheckMate-7FL: nivolumab with endocrine therapy in hormone receptor–positive early breast cancer—safety results. Cancer Res 2023;83(Suppl_14). Abstract 1152.

[28] Parker JS, Shannon J, Savic-Prince S, et al. APTneo: pembrolizumab in HER2- early breast cancer—clinical safety outcomes. JAMA Oncol 2022;8(5):750–8. https://doi.org/10.1001/jamaoncol.2022.0638.

[29] Bianchini G, Jeong JH, Crew KD, et al. NeoTENNIS: durvalumab in neoadjuvant TNBC—Toxicity profile. Ann Oncol 2022;33(Suppl 7):S420–42. https://doi.org/10.1016/j.annonc.2022.07.352.

[30] Morales-Vásquez F, Espinosa E, García-Castañon M, et al. neoTAPPL: phase I study of tremelimumab in early breast cancer—safety outcomes. Breast Cancer Res Treat 2023;188:601–10. https://doi.org/10.1007/s10549-023-07010-9.

[31] Ho AY, Shiao S, Kobald SA, et al. PEARL: a phase Ib/II biomarker study of adding radiation therapy to pembrolizumab before neoadjuvant chemotherapy in human epidermal growth factor receptor 2–Negative breast cancer. J Clin Oncol 2024;42(36):S261–86. https://doi.org/10.1200/JCO.24.00003. Suppl_6.

[32] Nederlof, I. et al. LBA11 neoadjuvant nivolumab/relatlimab or nivolumab/ipilimumab in triple negative breast cancer with high tumor-infiltrating lymphocytes (TILs) . Ann Oncol, Volume 35, S1206..

[33] Aaronson NK, et al. The European organization for research and treatment of cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85(5):365–76.

[34] Cella DF, Tulsky DS, Gray G, Bonomi AE. The functional assessment of cancer therapy (FACT) scale: development and validation of the general measure. J Clin Oncol 1993;11(3):570–9.

[35] Cushman David, et al. The PROMIS wave 1 pilot study in a population-based sample. Med Care 2013;51(10):894–902.

[36] Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American society of clinical oncology clinical practice guideline. J Clin Oncol 2018;36:1714–68. https://doi.org/10.1200/JCO.2017.77.6385.

[37] Michot JM, Bigenwald C, Champiat S, Collins M, Carbonnel F, Postel-Vinay S, et al. Immune-related adverse events with immune checkpoint blockade: a comprehensive review. Eur J Cancer 2016;54:139–48. https://doi.org/10.1016/j.ejca.2015.11.016.

[38] Robert C, Schachter J, Long GV, et al. Nivolumab versus dacarbazine in untreated metastatic melanoma. N Engl J Med 2015;372(4):320–30.

[39] Emens LA, Adams S, Barrios CH, et al. IMpassion130: atezolizumab + nab-paclitaxel in metastatic TNBC. Ann Oncol 2021;32(8):994–1004.

[40] Loriot MA, Barre A, Blons H, Bergmann JF, Golmard JL, Thomas F, et al. Recommendations for the use of pharmacogenetics in anticancer drugs: 2021 update from the French national network. Eur J Cancer 2021;157:12–28. https://doi.org/10.1016/j.ejca.2021.08.030.

[41] Wu X, Gu Z, Chen Y, et al. Application of PD-1 blockade in cancer immunotherapy. Comput Struct Biotechnol J 2019;17:661–74. https://doi.org/10.1016/j.csbj.2019.03.006. Published 2019 May 23.

[42] Ramos-Casals M, Brahmer JR, Callahan MK, Wilson MA, Horvat TZ, Weber JS. Immune-mediated AEs. Lancet Oncol 2022;23(6):e263–74.

[43] Weber JS, Postow M, Lao CD, et al. Toxicities of immunotherapy. J Clin Oncol 2015;33(18):2092–9.

[44] Andrade MO, Gutierres IG, Tavares MC, et al. Immune-related adverse events among patients with early-stage triple-negative breast cancer treated with pembrolizumab plus chemotherapy: real-world data from the Neo-Real/GBECAM 0123 study. Breast 2025;83:104473. https://doi.org/10.1016/j.breast.2025.104473.

[45] Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med 2015;373(2):123–35. https://doi.org/10.1056/NEJMoa1504627.

[46] Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and Ipilimumab or monotherapy in untreated melanoma [published correction appears in. N Engl J Med 2018 Nov 29;379(22):2185. https://doi.org/10.1056/NEJMx180040. N Engl J Med. 2015;373(1):23-34. doi:10.1056/NEJMoa1504030.

[47] Wang Y, Abu-Sbeih H, Mao E, et al. Hepatotoxicity with checkpoint inhibitors. Clin Gastroenterol Hepatol 2019;17(9). 1481–89.e3.

[48] Petrelli F, et al. Immune-related AEs of checkpoint inhibitors: meta-analysis. Crit Rev Oncol Hematol 2020;1:1–7. 43.

[49] Wang C, et al. Safety of immunotherapy: meta-analysis. Front Pharmacol 2025;16(1539246).

[50] Chang CY, Park H, Malone DC, et al. Immune checkpoint inhibitors and immune-related adverse events in patients with advanced melanoma: a systematic review and network meta-analysis. JAMA Netw Open 2020;3(3):e201611. https://doi.org/10.1001/jamanetworkopen.2020.1611. Published 2020 Mar 2.

[51] Oliveira C, Mainoli B, Duarte GS, et al. Immune-related serious adverse events with immune checkpoint inhibitors: systematic review and network meta-analysis. Eur J Clin Pharmacol 2024;80(5):677–84. https://doi.org/10.1007/s00228-024-03647-z [published correction appears in Eur J Clin Pharmacol. 2024 Oct;80(10):1597-1598. doi: 10.1007/s00228-024-03732-3.].

[52] Lin L, Liu Y, Chen C, Wei A, Li W. Association between immune-related adverse events and immunotherapy efficacy in non-small-cell lung cancer: a meta-analysis. Front Pharmacol 2023;14:1190001. https://doi.org/10.3389/fphar.2023.1190001. Published 2023 May 22.

[53] Bardia A, et al. Sacituzumab govitecan in metastatic TNBC. N Engl J Med 2021;16(384):1529–41. https://doi.org/10.1056/NEJMoa2028485.

[54] Nielsen DL, Juhl CB, Nielsen OH, Chen IM, Herrmann J. Immune checkpoint inhibitor–induced cardiotoxicity: a systematic review and meta-analysis. JAMA Oncol 2024;10(10):1390–9. https://doi.org/10.1001/jamaoncol.2024.3065.
[55] Herrmann J, Barac A, Carver J, et al. Immune checkpoint inhibitor–associated cardiovascular toxic effects: international cardio-oncology society position statement. JAMA Oncol 2026;12(1):90–9. https://doi.org/10.1001/jamaoncol.2025.4543.
[56] Salem JE, Ajrouche A, Rozes A, Pinto S, De Rycke Y, Tubach F. Incidence and risk factors of immune checkpoint inhibitor myocardial and muscle toxicity: a French nationwide study. Eur Heart J 2026;47(9):1014–30. 10.1093/.