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Efficacy and Safety of First-Line Treatment for Advanced Triple- Negative Breast Cancer: A Network Meta-Analysis of Randomized Controlled Trials

junxiao wang
the second hospital of sanming
tantan fang
Fuzhou First General Hospital
xiaolan wu
the second hospital of sanming
qisheng lin
the second hospital of sanming
ezhang liu
liuez1971@hotmail.com

the second hospital of sanming

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Abstract

Background: Various therapeutic regimens have emerged as first-line treatments for advanced triple-negative breast cancer (TNBC); however,the optimal choice remains uncertain. This study employeda network meta-analysis to comprehensively evaluate the efficacy and safety of different treatment strategies.

Methods: A systematic literature search without restrictions was conducted in PubMed, Embase, and the Cochrane Library from inception to November 2, 2025. Manual searches of conference abstracts from American Society of Clinical Oncology, European Society for Medical Oncology, and San Antonio Breast Cancer Symposium (2020-2025) were also performed. Identified randomized controlled trials were analyzed using a network meta-analysis with a random-effects model. Results are expressed as hazard ratios (HR) and odds ratios with 95% confidence intervals (CI). Treatments were ranked by the surface under the cumulative ranking curve (SUCRA), with progression-free survival (PFS) designated as the primary endpoint.

Results: A total of 3,279 articles were screened, of which 26 clinical studies involving 8,447 patients with advanced TNBC were included. Bevacizumab combined with capecitabine and vinorelbine demonstrated superior PFS in the entire study population (vs paclitaxel: HR 0.24, 95% CI 0.11–0.49). Despite achieving the highest SUCRA for overall survival, the benefit of bevacizumab plus chemotherapy was not statistically significant (HR 0.44, 95% CI 0.16–1.17). Subgroup analysis indicated that the combination of sacituzumab govitecan (SG) and pembrolizumab achieved the most favorable PFS outcomes among PD-L1 positive patients (SG vs paclitaxel: HR 0.54, 95% CI 0.40–0.75). The paclitaxel plus platinum-based regimen achieves an optimal balance between efficacy and safety.

Conclusions: Therapeutic strategies for advanced TNBC should be personalized. The combination of SG and pembrolizumab may offer greater benefit in PD-L1 positive subgroups, while paclitaxel-platinum regimens may represent a relatively balanced option in terms of efficacy and safety, particularly for patients with unknown PD-L1 status.

Highlights

- For patients who are PD-L1 positive , the combination of sacituzumab govitecan and pembrolizumab represents a potentially promising therapeutic option.
- For the overall population or PD-L1-negative patients, bevacizumab combined with chemotherapy may be considered a preferable treatment regimen.
- Considering both efficacy and safety, paclitaxel plus platinum-based chemotherapy regimen represents an acceptable option.

Background

Breast cancer is the second most commonly diagnosed malignancy globally and is the leading cause of cancer-related mortality in women[1]. Triple-negative breast cancer (TNBC), accounting for approximately 10–15% of all breast cancer cases, is defined by the absence of estrogen receptor, progesterone receptor, and HER2 amplification. This biological profile renders the disease insensitive to endocrine and targeted anti-HER2 therapies[2]. Consequently, cytotoxic chemotherapy, primarily based on taxanes, anthracyclines, or platinum agents, has long served as the first-line standard for advanced disease[3]. However, owing to its aggressive clinical behavior, genomic heterogeneity, and historically poor prognosis, patients often experience rapid development of therapeutic resistance, limited progression-free survival (PFS), and considerable treatment-related toxicity with these conventional regimens[4].

A paradigm shift has occurred with the introduction of immune checkpoint inhibitors (ICIs) as first-line therapy. Pivotal trials, including IMpassion130[5] and KEYNOTE-355[6], demonstrated that combining pembrolizumab (Pembro) or atezolizumab with chemotherapy significantly improved survival outcomes in patients with programmed death-ligand 1 (PD-L1)-positive tumors, establishing a new standard of care for this subset. Nevertheless, a substantial therapeutic challenge remains for patients whose tumors lack PD-L1 expression or for whom biomarker testing is not feasible, highlighting a critical unmet need in this population.

In recent years, numerous strategies have been developed to address this gap. Novel agents targeting distinct pathways, such as antibody-drug conjugates, AKT inhibitors, PARP inhibitors, and anti-angiogenic agents such as bevacizumab (Bev), have shown preliminary efficacy in various settings. This expanding therapeutic strategy raises several pivotal yet unresolved clinical questions: which regimens among these emerging options hold the greatest potential for meaningful improvement in PFS or overall survival (OS) in patients? Furthermore, can an optimal balance between efficacy and tolerability be achieved? Can immunotherapy achieve further transformative breakthroughs?

Various treatment strategies exhibit substantial variations in both efficacy and safety profiles, and there is a notable paucity of high-quality evidence for direct comparison. Furthermore, the impact of different therapeutic options on patients' quality of life and tolerability must be carefully considered in clinical decision-making.

Consequently, integrating existing data from randomized controlled trials (RCTs) through a network meta-analysis (NMA) allows for an indirect comparison of the efficacy and safety of various treatment regimens, thereby offering more comprehensive evidence to support clinical practice[7]. Although these two NMA[8–9] provided initial insights into the efficacy of immunotherapy and platinum-based regimens for first-line metastatic TNBC, they have several notable limitations. First, their analyses were restricted to a limited number of treatment regimens. Second, a systematic evaluation of treatment-related adverse events was lacking.

In contrast, our study offers comprehensive treatment coverage for all patients. Furthermore, by including only RCTs, systematically assessing both efficacy and safety, and incorporating subgroup

analyses of PD-L1-positive patients, our rigorous NMA provides more reliable evidence for clinical decision-making in this setting.

Materials and Methods

This research was conducted in accordance with the PRISMA guidelines [10] and registered with PROSPERO (ID: CRD420251179399) (Supplementary File A).

Eligibility and Exclusion Criteria

Inclusion criteria were as follows: 1. mTNBC; 2. Patients had at least two treatment arms, reported HR or presented Kaplan-Meier curves, and must include PFS data; 4. Articles published in English; 5. Each treatment group contained more than 10 participants. Exclusion Criteria: 1. Data specifically for first-line treatment could not be extracted in isolation, as the study reported pooled results from both first-line and second-line patient cohorts; 2. Single-arm and retrospective studies.

Information Sources

A comprehensive and systematic literature search was performed in three major electronic databases: PubMed, Embase, and the Cochrane Library. The search period spanned from the inception of each database to November 2, 2025, with no restrictions. To ensure the inclusion of the most recent and potentially unpublished data, the electronic search was supplemented by a manual review of conference abstracts from key oncology meetings, including American Society of Clinical Oncology, European Society for Medical Oncology, and San Antonio Breast Cancer Symposium, covering the years 2020 to 2025.

Search Strategy

A literature search was conducted using the following search terms in PubMed, Embase, and Cochrane Library: Adjustments were made for each electronic database without applying any additional filtering criteria: (metastasis OR metastases OR metastatic OR advanced OR recurrent OR stage IV OR unresectable) AND (breast OR mammary) AND (cancer OR carcinoma OR malignant OR neoplasm OR tumour) AND (triple negative OR TNBC) AND (randomized controlled trial OR randomised controlled trial).

Study Selection

After removing duplicate records using EndNote (version 22), two researchers independently screened the literature records using a two-stage process. First, the titles and abstracts were assessed for eligibility. If sufficient information was available, a decision to include or exclude the study was made at this stage. When a judgment could not be reached based on the title and abstract alone, the full text was

retrieved for in-depth evaluation. In the case of disagreement or uncertainty between the first two reviewers, a third reviewer was consulted to arbitrate and reach a final decision. All studies meeting the inclusion criteria were assessed for methodological quality using the Review Manager 5.4 software. To ensure the validity of the network meta-analysis, network connectivity was confirmed by verifying that the evidence structure formed a connected graph. A complete flow diagram (Fig. 1) details the number of studies included and excluded at each stage, along with the exclusion reasons. Studies that used the number of prior treatment lines as a stratification factor but did not report outcome data specifically for the first-line treatment population were excluded from the study. Furthermore, to avoid bias from overlapping patient populations, only the most recent data from each clinical trial were used.

Data Collection Process

We extracted the necessary data from published papers, supplementary materials and conference abstracts. When the Hazard Ratio (HR) was not provided, we utilized the Engauge Digitizer software to extract the relevant information from the Kaplan-Meier curve. Some of these studies enrolled patients with HER2-negative breast cancer, from which we specifically extracted data for the HR-negative subgroup. Studies that did not report these data were excluded. All data included in this analysis were publicly available.

Data Items

The following data were extracted from the articles identified in our final search: article title, first author, publication year, treatment, lines, PD-L1 status, PFS, OS, HR and 95% confidence interval (CI), objective response rate (ORR), and ≥ 3 adverse events (AEs). The primary endpoint was PFS, which included analyses of all participants and participants with PD-L1 positivity. The secondary endpoints comprised OS, ORR, and ≥ 3 AEs (Supplementary File B).

Study Risk of Bias Assessment

Review Manager 5.4 was used to assess various types of bias. For each domain in each study, judgments were made according to the tool's handbook guidelines as "low risk", "high risk", or "unclear risk". The rules for determining the overall risk of bias judgment were as follows: if a study was judged as "low risk" across all domains, its overall risk of bias was "low"; if it was judged as "high risk" in one or more key domains, the overall risk was "high"; in all other situations (i.e., no domains with high risk, but one or more domains with "unclear risk"), the overall risk was "unclear". The assessment process was completed independently by two investigators (WJX and FTT). Both had received prior training in using this assessment tool. After completion, the two investigators cross-checked and discussed their assessments to resolve discrepancies. If consensus could not be reached through discussion, a third investigator (LEZ) arbitrated and made the final decision.

No adaptations were made to the existing Cochrane tool during this process. We used the 'Risk of Bias' module in Review Manager 5.4 to record, manage, and summarize the independent judgments of the two reviewers and to generate risk of bias summary figures. It is crucial to emphasize that the software was used solely to assist in data recording and visualization; all risk of bias judgments originated from manual assessment by the investigators, not from automated processing by the software.

Summary Measures

We utilized HR and 95% CI to illustrate PFS and OS, while odds ratios (OR) and 95% CI were utilized to present ORR and grade ≥ 3 AEs. We ranked the various treatment protocols based on their surface under the cumulative ranking curve (SUCRA) values, which ranged from 0 to 100, with higher scores indicating more effective treatments. Finally, both PFS and ≥ 3 AEs were assigned a maximum score of 50, and these two endpoints were combined to evaluate the efficacy and safety of each treatment protocol, with sensitivity analyses performed to maintain the robustness of the results. Statistical significance was set at $p < 0.05$.

Synthesis Methods

Following the identification of the treatment measures, we categorized them into their respective therapeutic classes. The complete list of drugs and their corresponding categories is provided in Supplementary File C.

Ethics Consideration

The Ethics Committee of Sanming Second Hospital confirmed that all data were obtained from publicly available publications; therefore, no ethical approval was required.

Statistical Analysis

Literature screening was conducted using EndNote (version 22) for initial deduplication and management. Subsequent title/abstract screening, full-text review, and data extraction were systematically performed and recorded using the Cochrane Review Manager software (RevMan Version 5.4). The risk of bias in the included RCTs was assessed using the Cochrane RoB 2 tool.

The NMA for continuous outcomes was performed using R software (version 4.5.0) with the meta and netmeta packages. The consistency within the network was assessed using the design-by-design decomposition of the Q statistic. In cases of significant global inconsistency (between-designs Q test p-value < 0.10), potential sources were identified by sequentially detaching individual direct comparison estimates using the decomp.design function. A random-effects NMA model was fitted to the data. Treatment rankings were evaluated using the SUCRA, calculated directly via the built-in functionality of the netmeta package. Higher SUCRA values represent superior efficacy, while also indicating a lower incidence of adverse events in safety analyses. The results were visualized using the ggplot2 package.

The NMA for dichotomous outcomes was conducted using Stata (version 18.0) and the network suite of commands. Data were preprocessed using the command "network setup r n, study(id) trt(t) format(augment) or". A frequentist random-effects consistency model was then fitted "network meta c". Treatment rankings were derived using the command "network rank max, all zero reps(50000)", which estimates ranking probabilities via 5,0000 Monte Carlo simulations, specifying that larger effect sizes are preferable (max) and using the baseline treatment as a reference (zero). SUCRA values were generated based on the resulting probability matrices.

Results

Study selection

Database searches identified 3,279 records, with 2,905 remaining after duplicate removal criteria. Following rigorous screening, 29 eligible studies were included in the review. However, only 26 studies contributed to closed loops in the network and were included in the final NMA. The remaining three studies were excluded because of a lack of connectivity (Supplementary File D). When multiple publications reported on the same study, the most recent and comprehensive data were retained. The PRISMA flow diagram is presented in Fig. 1, and the completed PRISMA 2020 checklist is provided in Supplementary File E.

Study characteristic

This study included 26 research articles[5, 6, 11–34] published between 2009 and 2025, encompassing 60 groups with a combined total of 8,890 patients (Table 1). Of these, two studies were limited to PD-L1-positive patients, 22 enrolled only HR-negative patients, six evaluated ICIs, and four assessed Bev.

Table 1
Characteristics of Included Studies.

No	Study/Author (Year)	Treatment	PFS			
			HR, 95%CI		Patients (n)	
1	IMpassion130 (2021)	Placebo + nab-paclitaxel			451	
		Atezolizumab + nab-paclitaxel	0.80 (0.69–0.92)		451	
2	KEYNOTE355 (2022)	Placebo + nab-paclitaxel			281	
		Pembrolizumab + nab-paclitaxel	0.82 (0.70–0.98)		566	
3	ASCENT03 (2025)	nab-paclitaxel/paclitaxel		/	155	
		gemcitabine+carboplatin	/			124
		Sacituzumab	0.51 (0.38–0.68)	0.89 (0.64–1.22)	154	125
4	ASCENT04 (2025)	nab-paclitaxel/paclitaxel+pembrolizumab		/	114	/
		gemcitabine+carboplatin+pembrolizumab	/		/	108
		Sacituzumab+pembrolizumab	0.82 (0.58–1.17)	0.52 (0.36–0.75)	116	105
5	BOOG 2013-01 (2021)	Paclitaxel			15	
		Paclitaxel+bevacizumab	0.74 (0.32–1.70)		15	
6	CALGB40502 (2015)	Paclitaxel			197	
		Ixabepilone	1.57 (1.08–2.29)		223	
7	CARIN (2016)	Capecitabine+bevacizumab			61	
		Capecitabine+bevacizumab+vinorelbine	0.57 (0.39–0.84)		61	
8	CBCSG006 (2015)	Paclitaxel+gemcitabine			118	
		Cisplatin+gemcitabine	0.69 (0.52–0.91)		118	
9	E2100	paclitaxel			111	

	(2009)	Paclitaxel+bevacizumab	0.49 (0.34–0.70)		121	
10	CBCSG018 (2022)	Gemcitabine+cisplatin			126	
		Nab-paclitaxel+cisplatin	0.67 (0.50–0.88)		127	
11	Xiaodong Liu (2024)	Gemcitabine+carboplatin			94	
		Gemcitabine+capecitabine	1.15 (0.86–1.54)		93	
12	IMpassion131 (2021)	Placebo+paclitaxel			220	
		Atezolizumab+paclitaxel	0.86 (0.70–1.05)		431	
13	IMpassion132 (2024)	Gemcitabine+carboplatin			149	
		Atezolizumab+gemcitabine+carboplatin	0.72 (0.56–0.94)		148	
14	Joyce O'Shaughnessy (2014)	Gemcitabine+carboplatin			114	
		Gemcitabine+carboplatin+iniparib	0.88 (0.67–1.17)		42	
15	Olivier Trédan (2015)	Ixabepilone			40	
		Ixabepilone+cetuximab	1.12 (0.69–1.79)		39	
16	PAKT (2019)	Placebo+paclitaxel			70	
		Capivasertib+paclitaxel	0.74 (0.50–1.08)		70	
17	tnAcity (2018)	Nab-paclitaxel+gemcitabine		/	61	/
		Gemcitabine+carboplatin	/		/	66
		Nab-paclitaxel+carboplatin	0.59 (0.38–0.92)	0.58 (0.37–0.90)	64	64
18	TROPION-Breast02 (2025)	Paclitaxel, nab-paclitaxel			321	
		Dato-Dxd	0.57 (0.47–0.69)		323	
19	TURANDOT (2016)	Bevacizumab+capecitabine			64	
		Bevacizumab+paclitaxel	1.23 (0.75–2.01)		63	

20	TORCHLIGHT (2024)	Placebo + nab-paclitaxel		178
		Toripalimab + nab-paclitaxel	0.65 (0.47–0.91)	353
21	IPATunity130 (2024)	Placebo+paclitaxel		87
		Ipatasertib+paclitaxel	1.02 (0.71–1.45)	168
22	LOTUS (2021)	Placebo+paclitaxel		62
		Ipatasertib+paclitaxel	0.60 (0.37–0.98)	62
23	fRida (2021)	Placebo+paclitaxel		61
		Paclitaxel+reparixin	1.14 (0.71–1.81)	62
24	COLET (2021)	Placebo+paclitaxel		43
		Cobimetnib+paclitaxel	0.73 (0.43–1.24)	47
25	Chengcheng Gong (2024)	Gemcitabine+carboplatin		75
		Gemcitabine+cisplatin	0.93 (0.64–1.34)	75
26	CAPItello290 (2025)	Placebo+paclitaxel		408
		Capivasertib+paclitaxel	0.72 (0.61–0.84)	404

Risk of bias within studies

The funnel plot indicated no publication bias (Fig. 2). According to the Cochrane risk of bias assessment tool, 12 of the included RCTs were designed as open-label studies and were rated as high risk in the domain of “blinding of participants and personnel”. Risk ratings for the remaining domains are presented in Fig. 3.

Assessment of Heterogeneity

The initial random-effects model incorporating all included studies revealed a statistically significant global inconsistency (between-designs $Q = 18.66$, $p < 0.0001$), indicating a conflict between direct and indirect evidence. The decomposition of inconsistency suggested that this conflict was primarily concentrated within an evidence loop involving sacituzumab govitecan (SG) and ICIs. Consequently, a sensitivity analysis was performed to investigate its impact on the conclusions drawn. Tracing the source of inconsistency identified the direct comparison evidence from the IMpassion132 trial as the key contributor (detailed analysis of the reasons can be found in the Discussion section). The NMA was repeated after excluding this study, and the results demonstrated that global inconsistency was no

longer significant (between-designs Q = 1.24, p = 0.266). Heterogeneity was also substantially reduced (I^2 = 30.7% vs. 68.9%) (Supplementary File F). These findings indicate good internal consistency within the remaining studies. Therefore, all subsequent comparisons and rankings of treatment effects were based on this consistent model (dataset excluding IMpassion132).

Primary endpoint PFS

PFS in the Overall Population

A network meta-analysis of PFS in the overall population was performed based on data from 25 trials (Fig. 4A). The SUCRA rankings are shown in Fig. 5A. The league table of hazard ratios (Table 2) provides detailed pairwise comparisons. Regimens containing Bev combined with chemotherapy consistently achieved the highest probability of being the most effective treatment. The combination of capecitabine (Cap), vinorelbine (Vin), and Bev ranked first (SUCRA: 96.8), Cap plus Bev (SUCRA: 77.0) ranked fourth. Paclitaxel-based platinum doublets also demonstrated high efficacy, with paclitaxel plus cisplatin (Cis) (SUCRA: 92.7) and paclitaxel plus carboplatin (Car) (SUCRA: 89.0) ranking second and third, respectively. Among the highest-ranked regimens, Cap + Vinorelbine + Bev significantly improved PFS compared with paclitaxel (HR 0.24, 95% CI 0.11–0.49), the current first-line standard of care.

In contrast, gemcitabine (Gem)-based platinum regimens (Gem + Cis, SUCRA: 72.7; Gem + Car, SUCRA: 56.9) and single-agent therapies such as paclitaxel (SUCRA: 17.8), ixabepilone (SUCRA: 6.7), or combinations with reparixin (SUCRA: 15.3) or cobimetinib (SUCRA: 38.9) occupied lower ranks.

Antibody-drug conjugates (ADCs) (SG, SUCRA: 69.0) and datopotamab deruxtecan (Dato-DXd, SUCRA: 58.5) showed moderate efficacy Notably, SG demonstrated a statistically significant efficacy benefit over paclitaxel monotherapy (paclitaxel vs SG: 1.96, 1.60–2.40). However, no significant differences were observed when comparing paclitaxel plus Car with SG (vs SG: 0.70, 0.46–1.06) or comparing paclitaxel plus Cis with SG (vs SG: 0.62, 0.38–1.02).

Consistent with the expected population effect, ICIs combinations showed limited efficacy in the overall population, including PD-L1-negative patients. Paclitaxel plus ICIs ranked lower (SUCRA: 30.5), and the combination of Gem, Car, and ICIs (SUCRA: 10.8) did not demonstrate a significant advantage over paclitaxel plus ICIs (1.58, 1.05–2.36).

PFS in the PD-L1 Positive Subgroup

The PFS network meta-analysis for the PD-L1-positive subgroup (seven trials) yielded the following results: network plot (Fig. 4B), SUCRA rankings (Fig. 5B), and league table of hazard ratios (Supplemental File G.A). SG combined with Pembro had a higher SUCRA value (82.1) than paclitaxel combined with Pembro (0.610), corresponding to an HR of 1.22 (0.91–1.64) for this comparison; however, the difference was not statistically significant. Regimens containing paclitaxel with an AKT inhibitor (SUCRA: 69.4) or with the PD-1 inhibitor toripalimab (SUCRA: 63.3) were also ranked highly. In contrast to the overall population, all top-ranked regimens in this subgroup incorporated targeted or immunotherapy. Notably,

when added to immunotherapy, doublet chemotherapy (SUCRA: 15.8) did not demonstrate superior efficacy over single-agent chemotherapy (SUCRA: 61.0) (Gem + Car+Pembro vs paclitaxel+Pembro: HR 1.58, 95% CI 0.91–2.74).

The combination of paclitaxel with ICIs significantly improved PFS compared to paclitaxel monotherapy (Atezolizumab+paclitaxel vs paclitaxel = 0.70, 0.54–0.91; Paclitaxel vs Pembro+paclitaxel = 1.52, 1.06–2.16; Paclitaxel vs toripalimab+paclitaxel = 1.54, 1.06–2.23). Dato-DXd (SUCRA: 0.438) showed a non-significant trend towards benefit compared to paclitaxel plus Pembro (HR: 1.17, 0.58–2.34).

Secondary endpoint OS

The results regarding OS (17 trials) are presented in the network plot (Fig. 4C), along with the corresponding SUCRA rankings (Fig. 5C) and league table of hazard ratios (Supplemental File G.B). Paclitaxel plus ICIs yielded the highest SUCRA value for overall survival (91.9), suggesting the greatest probability of being the most effective regimen. This was supported by a significant OS benefit compared with non-paclitaxel chemotherapy (HR 0.68, 0.49–0.93). Although the difference versus paclitaxel monotherapy did not reach statistical significance, the HR favored the addition of ICIs (HR 0.85, 0.70–1.04), with a confidence interval approaching unity, indicating a consistent trend toward improved survival. Paclitaxel monotherapy ranked second (SUCRA: 80.4), followed by paclitaxel plus Bev (SUCRA: 67.6). Non-paclitaxel-based regimens, including non-paclitaxel chemotherapy (SUCRA: 64.3) and non-paclitaxel plus PARP inhibitor (SUCRA: 61.1), occupied the middle ranks. Regimens based on reparixin or cobimetnib demonstrated lower SUCRA values for OS, ranking at the bottom of the hierarchy, a pattern consistent with their PFS performance. Dato-Dxd did not show a statistically significant OS benefit compared to paclitaxel monotherapy (HR: 0.79, 0.54–1.51).

Secondary endpoint ORR

The ORR was assessed across 17 studies (network plot: Fig. 4D), with SUCRA rankings (Fig. 5D) and league tables of ORs (Supplementary G.C). Dato-Dxd yielded the highest SUCRA value, followed by the paclitaxel plus Car regimen. ICIs plus Gem and Car demonstrated the lowest SUCRA value among all treatments. Consistent with the SUCRA ranking results, Dato-Dxd and paclitaxel plus Car demonstrated superiority over the other treatment regimens, with statistically significant differences. For the overall population, the use of immunotherapy without knowledge of PD-L1 expression status did not demonstrate superiority over chemotherapy alone (paclitaxel + Car vs paclitaxel+ICIs: OR 3.15, 1.29–7.65). The combination of Gem, Car, and ICIs did not demonstrate a significant advantage over paclitaxel plus ICIs, and similar to the PFS findings, this difference was not statistically significant (OR 0.68, 0.40–1.15).

Secondary endpoint Safety

All 23 studies that reported grade ≥ 3 adverse events were included in the network meta-analysis for this outcome. The network plot is shown in Fig. 4E, the SUCRA ranking results are presented in Fig. 5E, and the league table of comparisons is provided in Supplementary G.D. Gem plus Cis (SUCRA: 83.8),

paclitaxel plus Gem (82.9), and paclitaxel plus Cis (81.7) demonstrated the most favorable safety profiles. In contrast, the regimens with the lowest SUCRA values—and therefore the highest probability of adverse events—were all Bev-containing combinations: Cap plus Vin and BEV (2.9), paclitaxel plus Bev (4.3), and Cap plus Bev (14.5). In contrast, the regimens with the lowest SUCRA values, indicating the highest probability of adverse events, were all Bev-containing combinations: capecitabine plus vinorelbine and bevacizumab (2.9), paclitaxel plus bevacizumab (4.3), and capecitabine plus bevacizumab (14.5). Furthermore, these regimens demonstrated statistically significant differences compared to first-line chemotherapy regimens: paclitaxel plus cisplatin versus capecitabine plus vinorelbine and bevacizumab (OR 0.08, 0.01–0.44) and paclitaxel plus cisplatin versus paclitaxel plus bevacizumab (OR 0.09, 0.02–0.43). Thus, Bev-based combination therapies were consistently associated with the greatest likelihood of adverse events in the network meta-analysis. Several treatments, including paclitaxel plus Car (75.9), Gem plus Car (64.9), and ixabepilone (63.3), demonstrated intermediate safety.

Combined analysis of PFS and ≥ 3 AEs

The composite efficacy-toxicity profile was evaluated by integrating both PFS and ≥ 3 AEs, with each endpoint weighted at 50% (Fig. 6). Sensitivity analyses confirmed that this weighting scheme was robust, as the overall rankings remained stable across a range of proportions (Supplementary File H). Accordingly, the paclitaxel plus Cis regimen achieved the highest SUCRA score, followed by the paclitaxel plus Car and Gem plus Cis strategies. SG, SG plus ICIs, and Dato-Dxd demonstrated intermediate efficacy-toxicity rankings (reflected by moderate SUCRA values), whereas cobimetinib, reparixin, and ixabepilone plus cetuximab yielded notably low SUCRA values.

Discussion

Conducted in strict adherence to the PRISMA guidelines, this analysis exclusively incorporated randomized controlled trials, thereby ensuring a high level of evidence. By comprehensively encompassing major first-line strategy categories, including chemotherapy, immunotherapy, anti-angiogenic therapy, ADCs, and targeted agents, our study provides an evidence-based framework to inform personalized treatment decisions for metastatic TNBC. The main findings were as follows: in the overall population, regimens containing Bev demonstrated the highest potential for prolonging PFS but were associated with higher toxicity risks; in the PD-L1-positive subgroup, SG combined with Pembro ranked first in efficacy; and paclitaxel combined with platinum-based chemotherapy achieved a relatively optimal balance between efficacy and safety.

The Dilemma of Bevacizumab in TNBC

In the overall population (including both PD-L1-negative and PD-L1-positive patients) analysis of PFS, the regimen combining Cap, Vin, and Bev—representing an anti-angiogenic plus chemotherapy strategy—ranked the highest. This outcome underscores the critical role of the vascular endothelial growth factor pathway in TNBC, particularly in the basal-like subtype, and supports ongoing clinical trials enrolling

patients in this setting[35]. Although a trend toward improved OS was observed, the difference did not reach statistical significance, suggesting that longer follow-up and additional data are required to confirm OS benefits. Among Bev-containing regimens, particularly those combined with multiple chemotherapeutic agents, the toxicity profile was most pronounced, with a significantly higher incidence of grade ≥ 3 AEs, consistent with the established side effect spectrum, including hypertension and proteinuria[36].

Among the Bev-based combination therapies, Cap + Vin + Bev and Cap + Bev regimens demonstrated the most favorable PFS outcomes (SUCRA values of 0.968 and 0.770, respectively). However, these regimens were associated with relatively lower OS rankings (non-paclitaxel + Bev regimens had a SUCRA of 0.341), suggesting that although intensive chemotherapy combinations may provide short-term disease control, clear long-term survival benefits have yet to be established, accompanied by considerable toxicity burdens. Therefore, a careful balance between efficacy and safety must be considered in clinical decision making.

The PD-L1-positive subgroup

In the PD-L1-positive subgroup, the value of immunotherapy was prominently highlighted. The combination of SG and Pembro emerged as the top-ranked regimen for PFS in this subgroup, demonstrating a statistically significant improvement compared to doublet chemotherapy combined with ICIs (Pembro + Gem+Car vs. Pembro + SG: HR 1.92, 1.35–2.75). This finding has substantial clinical implications. SG monotherapy has already demonstrated significant survival benefits in later-line settings[37]; its combination with immunotherapy establishes a synergistic strategy that integrates "targeted cytotoxic drug delivery" with "immune suppression reversal". ADCs can induce immunogenic cell death, potentially enhancing the immunogenicity of the tumor microenvironment and thereby augmenting immunotherapy efficacy. This provides a highly promising new direction for the first-line treatment of PD-L1-positive metastatic TNBC[38]. Concurrently, intensifying chemotherapy backbone in the context of immunotherapy did not yield additional PFS benefit (Pembro + Gem+Car vs. Pembro+Paclitaxel: HR 1.58, 0.91–2.74). This underscores that, in the era of immunotherapy, the role of chemotherapy may pivot more towards immune modulation rather than cytotoxicity, and that excessively intensive chemotherapy could potentially exert adverse effects on immune cell function, thereby undermining the effectiveness of immunotherapy[39].

PFS and Grade ≥ 3 AEs

The paclitaxel-platinum (Cis or Car) regimen demonstrated a distinct clinical profile in this analysis. It ranked among the top regimens in terms of PFS in the overall population (second only to the Bev-containing regimen), while also exhibiting a favorable safety ranking with a low risk of ≥3AEs. When efficacy and safety were integrated into a weighted comprehensive assessment, the paclitaxel-platinum combination achieved the highest composite score. This indicates that the regimen offers a balanced clinical profile with reliable efficacy and relatively good tolerability. Platinum agents induce DNA crosslinking damage, rendering them particularly effective against TNBC harboring homologous recombination repair deficiencies, such as BRCA mutations. For patients with unknown PD-L1 status who

may not clearly benefit from first-line immunotherapy, or for those with significant concerns regarding treatment toxicity, the paclitaxel-platinum regimen represents a rational and robust therapeutic option in the first-line setting.

Inconsistency Analysis of ORR

There were notable differences between the SUCRA rankings for ORR and those for PFS. For instance, Dato-DXd ranked highest for ORR but only in the mid-range for PFS. This divergence may reflect differences in therapeutic mechanisms: certain treatments, such as potent ADCs or high-dose chemotherapy, can induce substantial tumor regression (reflected in a higher ORR), but resistance may emerge relatively quickly, limiting the extension of PFS. Conversely, other therapies, such as immunotherapy or anti-angiogenic therapy, may not achieve the highest initial response rates but can provide more sustained disease control by modifying the tumor microenvironment (reflected in a longer PFS). These findings highlight the limitations of ORR as a surrogate endpoint and underscore the greater importance of PFS when evaluating the long-term effectiveness of a treatment strategy.

Data Adjustment in the IMpassion 132 Study

Data from the IMpassion132 clinical trial were extracted solely for the PD-L1-positive population, which investigated the benefit of combining immunotherapy with chemotherapy. As expected, this combination demonstrated favorable efficacy in this subgroup. However, these data could not be included in the progression-free survival (PFS) analysis for the overall population, as the overall population also included PD-L1-negative patients. Moreover, in the network meta-analysis subgroup of PD-L1-positive populations, this study could not form a closed loop of comparisons with other clinical trials and was therefore excluded. Following sensitivity analysis, the removal of this study resulted in both the between-designs Q statistic and heterogeneity reaching acceptable levels, allowing for further analysis.

Limitations

Several limitations of this analysis should be acknowledged. First, heterogeneity in baseline patient characteristics across the included studies—such as the proportion of visceral metastases, BRCA mutation rates, and prior treatment histories—may affect the precision of the comparisons. Second, SG plus Pembro were evaluated in only single studies, necessitating validation in larger populations. Third, as a NMA is fundamentally based on indirect statistical comparisons, the strength of evidence it provides is inherently lower than that from large-scale, head-to-head randomized trials. Finally, our analysis did not assess other critically important outcomes, such as health-related quality of life and patient-reported outcomes.

Conclusions

The first-line treatment for metastatic TNBC has entered an era of increasing diversification and precision. For patients with PD-L1-positive disease, immunotherapy combined with SG demonstrates

potential superior to traditional chemotherapy plus immunotherapy, representing a critical direction for future development. For the overall population, while Bev-containing regimens significantly prolong PFS, they are associated with considerable toxicity. In contrast, the paclitaxel-platinum combination achieves a satisfactory balance between efficacy and tolerability, establishing itself as a core therapeutic option. Ultimately, regimen selection should be guided by biomarker-driven stratification and thoroughly integrated with individual patient characteristics and treatment goals to achieve truly personalized care.

Abbreviations

TNBC	Triple-negative breast cancer
PFS	progression-free survival
ICIs	Immune checkpoint inhibitors
Pembro	Pembrolizumab
PD-L1	Programmed death-ligand 1
Bev	Bevacizumab
OS	Overall survival
RCTs	Randomized controlled trials
NMA	Network meta-analysis
HR	Hazard ratio
CI	Confidence interval
ORR	Objective response rate
AEs	Adverse events
OR	Odds ratios
SUCRA	Surface under the cumulative ranking curve
SG	Sacituzumab govitecan
Cap	Capecitabine
Vin	Vinorelbine
Cis	Cisplatin
Car	Carboplatin
Gem	Gemcitabine
ADCs	Antibody-drug conjugates
Dato-DXd	Datopotamab deruxtecan

Declarations

Ethics approval

The Ethics Committee of Sanming Second Hospital confirmed that all data were obtained from publicly available publications.

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files.

Competinginterests

The authors declare that they have no competing interests.

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Author contributions

Conceptualization: WJX/FTT/LEZ

Data curation: WJX/FTT/WXL

Formal analysis: WJX/FTT

Investigation: WJX/WXL

Methodology: WJX

Project administration: LQS

Resources: LQS

Software: WJX

Supervision: LQS/LEZ

Validation: WJX/FTT/WXL

Visualization: WJX

Writing – original draft: WJX

Writing – review & editing: WJX/FTT/WXL/LQS/LEZ

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Table 2

Table 2 is available in the Supplementary Files section.

Figures

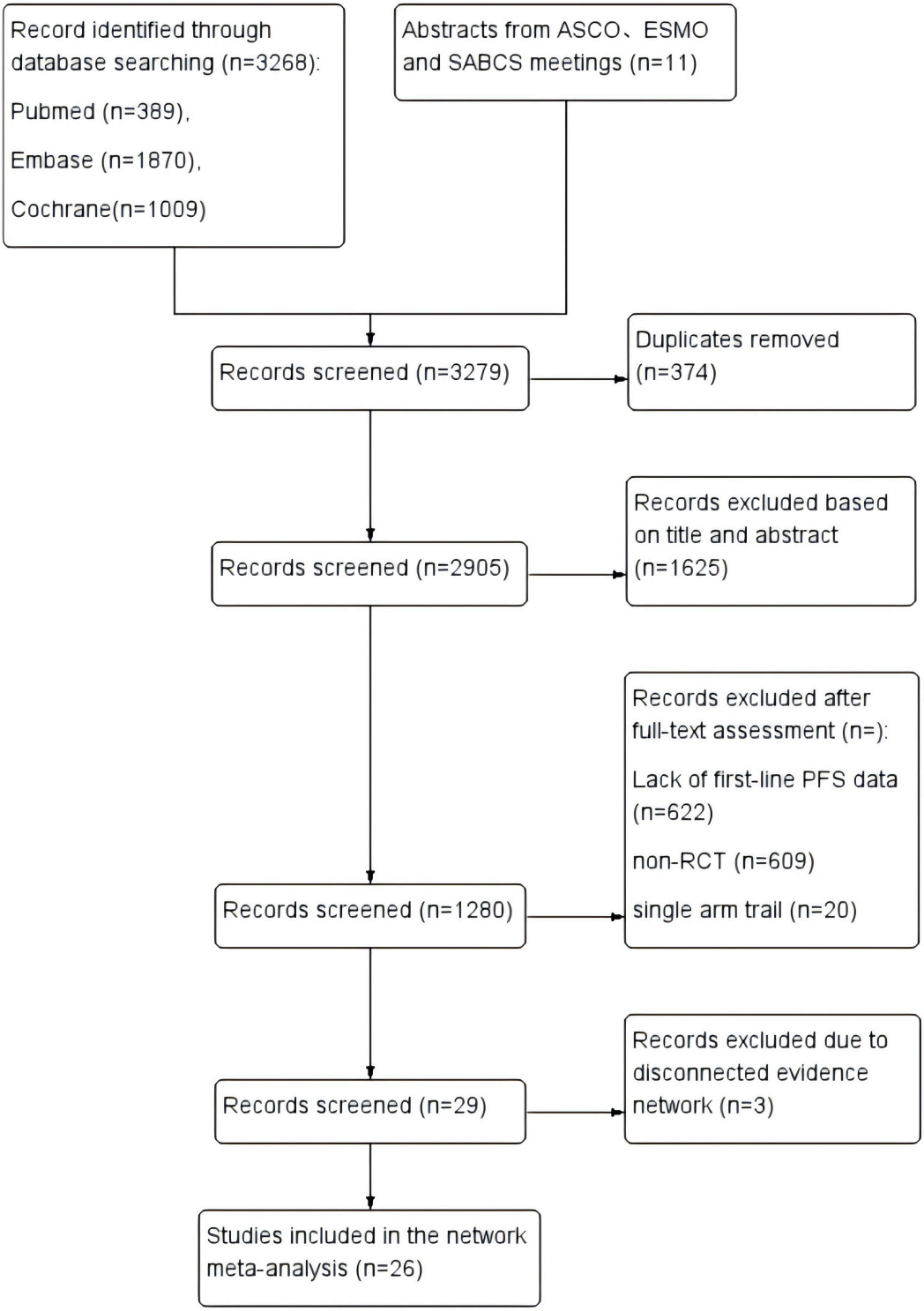


Figure 1 PRISMA flow diagram of theliterature search and studyselection process

Figure 1

See image above for figure legend

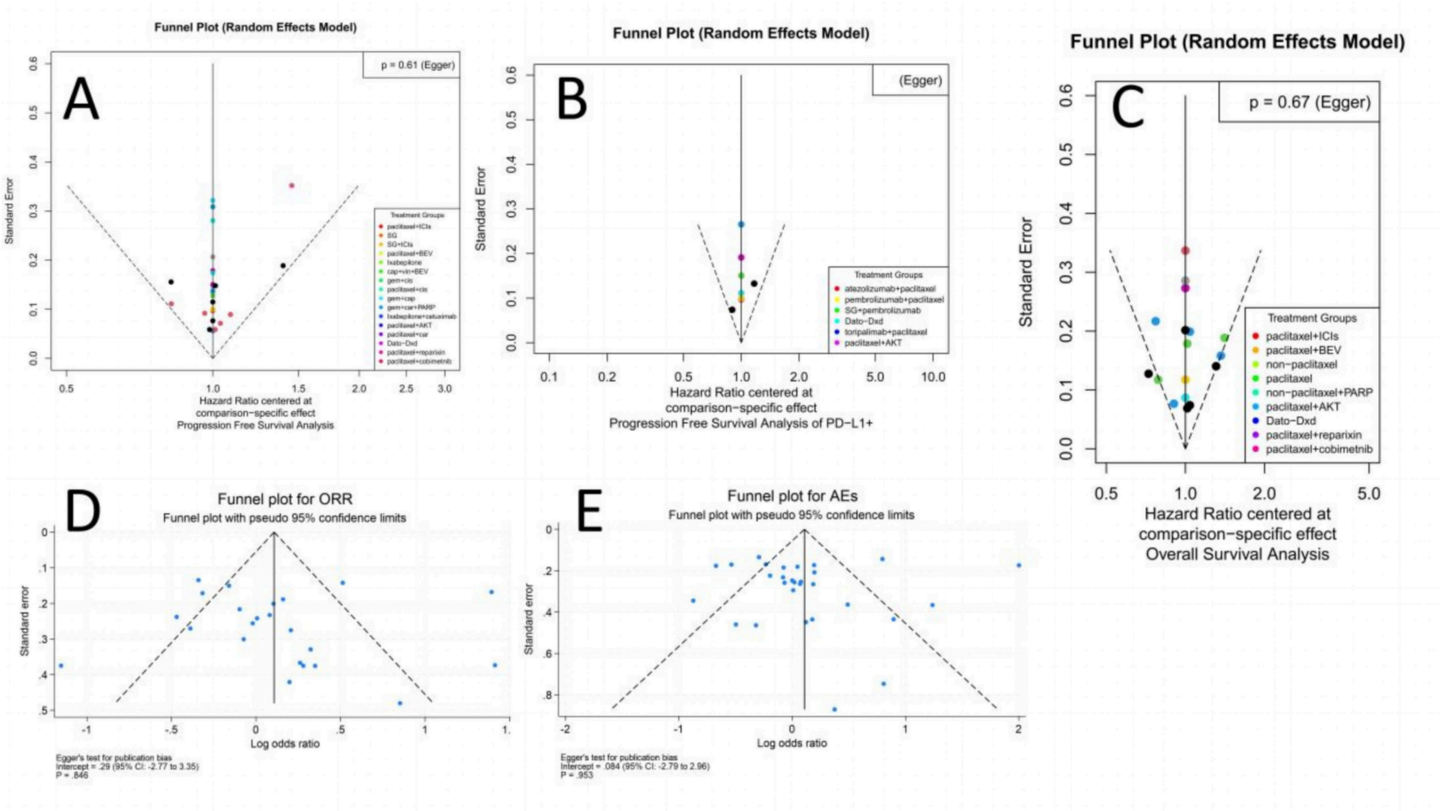


Figure 2

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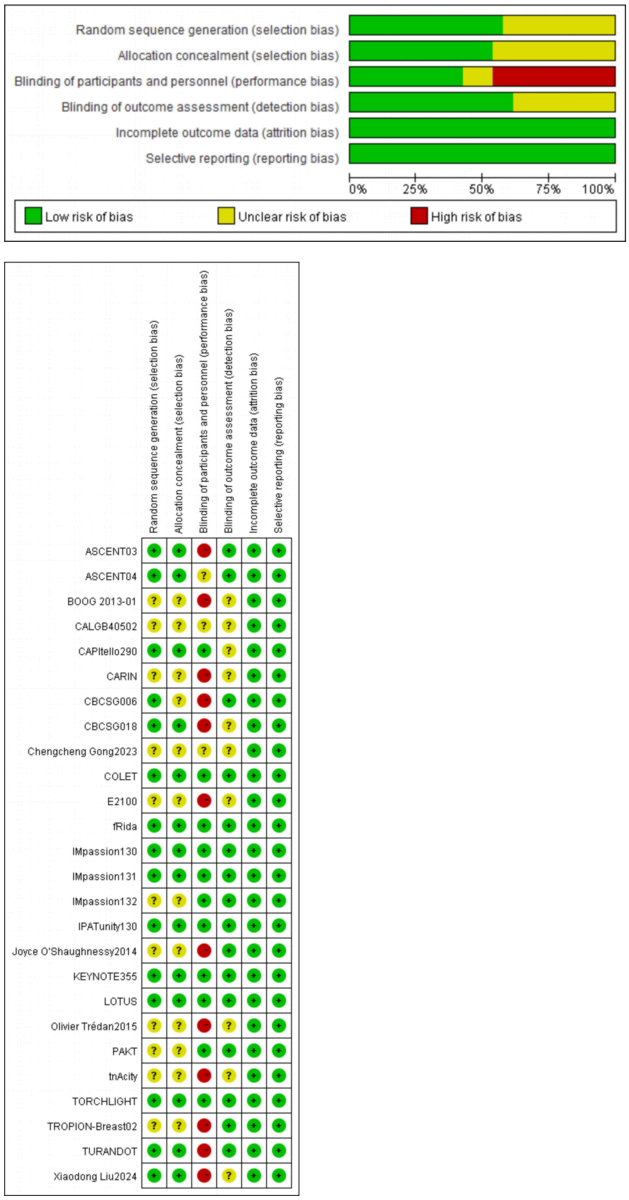


Figure 3. Risk of bias for all included studies.

Figure 3

See image above for figure legend

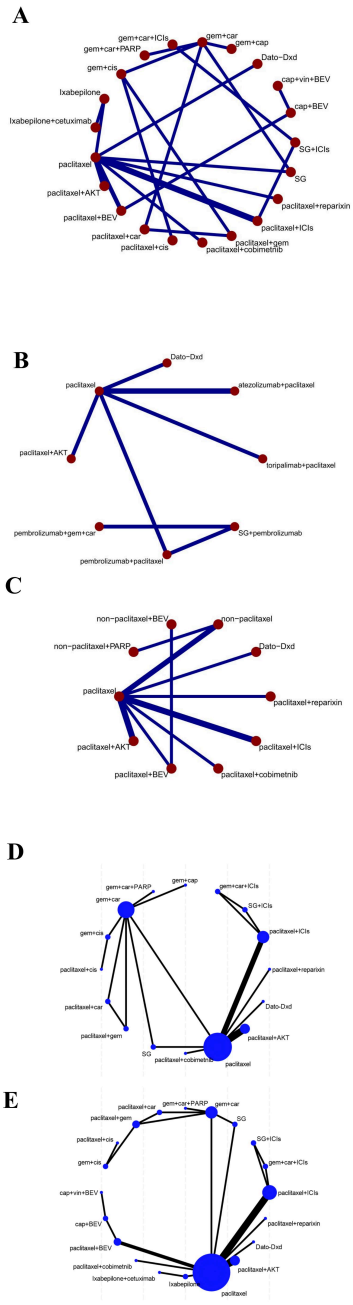
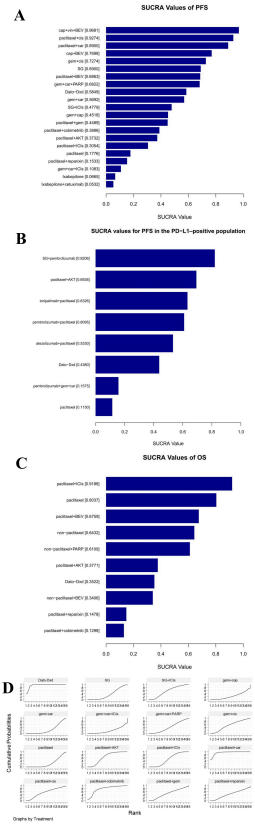


Figure 4. Network diagrams for each predefined endpoint: A. PFS of overall populations; B. PFS of PD-L1 positive populations; C. OS of overall populations; D. ORR of overall populations; E.≥3AEs of overall populations.

Figure 4

See image above for figure legend



Treatment	SUCRA
Dato-Dxd	95.2
paclitaxel+car	94.7
paclitaxel+sobzmetinib	77.6
paclitaxel+AKT	64.3
SG+ICIs	56.2
paclitaxel+cis	53.0
gem+cis	52.6
paclitaxel+ICIs	50.7
paclitaxel+gem	48.2
paclitaxel+reparixin	42.9
gem+car+PARP	40.5
SG	34.5
gem+car	24.3
paclitaxel	23.3
gem+cap	23.2
gem+car+ICIs	17.7

Treatment	SUCRA
gem+cis	83.8
paclitaxel+gem	82.9
paclitaxel+cis	81.7
paclitaxel+car	75.9
gem+car+PARP	68.7
paclitaxel	68.5
gem+car	64.9
lvabepilone	63.3
paclitaxel+reparixin	58.0
Dato-Dxd	54.6
SG	53.0
gem+car+ICIs	48.5
paclitaxel+ICIs	47.4
SG+ICIs	44.3
lvabepilone+cetuximab	30.4
paclitaxel+AKT	27.6
paclitaxel+sobzmetinib	24.8
cap+BEV	14.5
paclitaxel+BEV	4.3
cap+vin+BEV	2.9

Figure 5. SUCRA values and rankings for each predefined endpoint: A. PFS of overall populations; B. PFS of PD-L1 positive populations; C. OS of overall populations; D. ORR of overall populations; E. ≥3AEs of overall populations.

Figure 5

See image above for figure legend

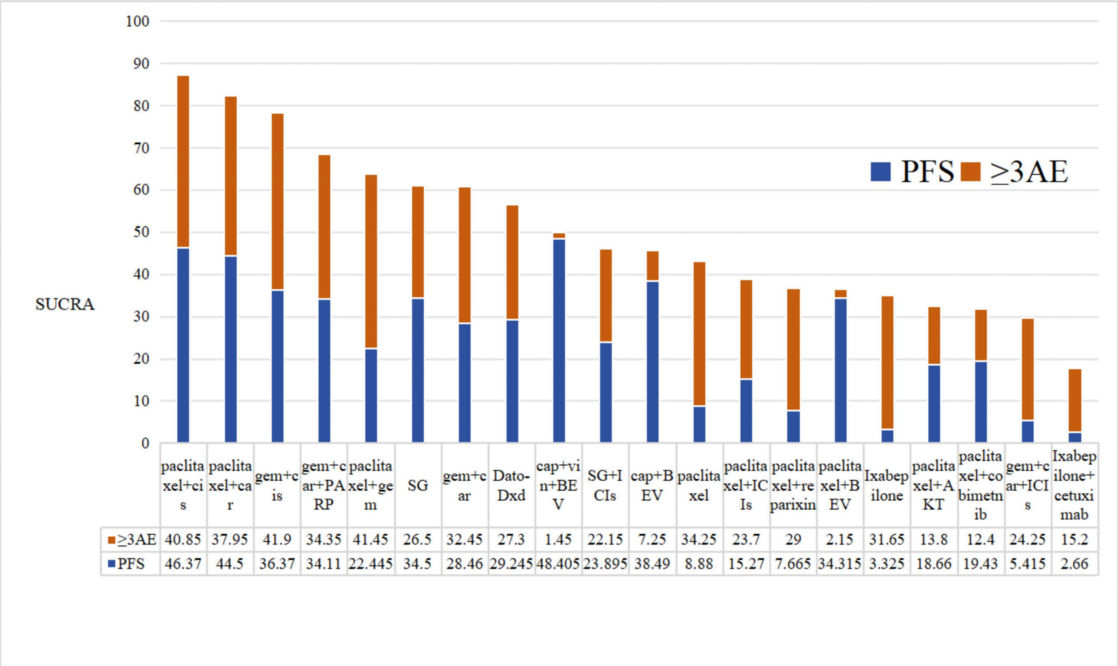


Figure 6. Rankings derived from combining PFS and ≥3AEs. The maximum values of PFS and ≥3AEs are 50 each, and they are added together and ranked in order of score.

Figure 6

See image above for figure legend

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table2.docx
- SupplementalFileA.pdf
- SupplementalFileB.xlsx
- SupplementalFileC.docx
- SupplementalFileD.docx
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- SupplementalFileH.docx