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First-line immune checkpoint inhibitors plus chemotherapy for advanced triple-negative breast cancer: A network meta-analysis and cost-effectiveness analysis

Shuo Kang
Second Hospital of Hebei Medical University
Shuo Yang
Hebei Medical University
Yize Jia
Hebei Medical University
Shan Zhao
28301483@hebmu.edu.cn

Second Hospital of Hebei Medical University

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Abstract

Background

There are no head-to-head randomized trials comparing first-line immune checkpoint inhibitor (ICI) regimens for advanced triple-negative breast cancer (TNBC). We evaluated the comparative evidence and model-based economic outcomes of three ICI-containing regimens from the Chinese healthcare system perspective.

Methods

We systematically searched bibliographic databases, ClinicalTrials.gov, and oncology conference proceedings through September 1, 2026. A fixed-effect network meta-analysis (NMA) synthesized progression-free survival and overall survival hazard ratios from eligible phase III randomized trials. A decision tree combined with a three-state partitioned survival model estimated costs and quality-adjusted life-years (QALYs) over 10 years. Pembrolizumab plus chemotherapy was the primary absolute-risk survival anchor; alternative trial-specific anchors were assessed as structural scenarios.

Results

Three randomized trials (IMpassion130, KEYNOTE-355, and TORCHLIGHT), involving 2,280 patients, were included. Indirect comparisons did not show statistically significant differences among ICI regimens in progression-free or overall survival; the small, loop-free network limited certainty. In the base-case economic model, toripalimab plus chemotherapy had the lowest modeled cost (US$40,972.13) and highest QALYs (2.27), compared with atezolizumab plus chemotherapy (US$115,286.53; 1.82 QALYs) and pembrolizumab plus chemotherapy (US$124,952.00; 1.90 QALYs). The economic ordering was maintained across alternative survival-anchor scenarios, although absolute QALYs differed.

Conclusions

Under the specified Chinese health-system costs and model assumptions, toripalimab plus chemotherapy was the economically preferred strategy. This finding does not establish clinical superiority; between-trial differences and uncertainty in long-term survival extrapolation limit its interpretation and generalizability.

Background

Breast cancer is the most commonly diagnosed cancer among women worldwide, with approximately 2.3 million new cases and 666,000 deaths estimated in 2022 [1]. Triple-negative breast cancer (TNBC) is

defined by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression [2] and accounts for approximately 15%-20% of breast cancers [1]. Historically, chemotherapy was the predominant systemic treatment for advanced TNBC, and outcomes remained poor, with a median overall survival (OS) of approximately 9–12 months and a 5-year survival rate of about 12% [3,4]. The aggressive biology of TNBC and the lack of classical actionable receptors have therefore driven the development of immune-based therapeutic strategies.

Immune checkpoint inhibitors (ICIs) can restore antitumor T-cell activity by attenuating inhibitory signaling within the tumor immune microenvironment, particularly through the programmed cell death 1 (PD-1)/programmed death ligand 1 (PD-L1) axis [5,6]. Chemotherapy may complement checkpoint inhibition by promoting tumor-antigen release and modifying the immune microenvironment, providing a biological rationale for combined immunochemotherapy. Phase III trials including IMpassion130 [7], KEYNOTE-355 [8,9], and TORCHLIGHT [10] evaluated atezolizumab-, pembrolizumab-, and toripalimab-based first-line strategies, respectively. Their populations, PD-L1 assessment methods, and chemotherapy backbones were not identical, which complicates indirect comparison. Recent reviews have highlighted the expanding role of immune checkpoint blockade in TNBC, while emphasizing persistent uncertainties regarding biomarker selection and optimization of treatment strategies [11]. Previous China-based economic evaluations have generally assessed individual ICI regimens against chemotherapy [12,13,14,15], whereas direct head-to-head evidence among these ICI-containing strategies is unavailable. We therefore integrated a systematic review and NMA with a cost-effectiveness model to compare their relative clinical effects and economic value while explicitly examining structural uncertainty related to the choice of absolute-risk survival anchor.

Methods

Network meta-analysis

Study selection and risk of bias

PubMed, Embase, Web of Science, the Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov were systematically searched from database inception through September 1, 2026. Conference proceedings from the American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), American Association for Cancer Research (AACR), and relevant breast-cancer meetings were also screened. Eligible studies were English-language phase III RCTs evaluating first-line ICI plus chemotherapy versus chemotherapy in adults with previously untreated unresectable locally advanced, recurrent, or metastatic TNBC and reporting PFS and/or OS. Neoadjuvant- or adjuvant-only studies, non-randomized studies, and studies without an eligible first-line ICI comparison were excluded. When multiple publications reported the same trial, the most mature and informative report for each outcome was used. The full search strategies and eligibility criteria are provided in Supplementary File 1, and the prespecified inclusion and exclusion criteria are summarized in Supplementary Table 1.

Risk of bias was assessed in RevMan version 5.3 using the Cochrane risk-of-bias tool [16]. The systematic review was reported in accordance with PRISMA 2020 [17] and the PRISMA extension for NMA, and was registered in PROSPERO (CRD420261366915).

Data collection

Two reviewers independently screened titles/abstracts and full texts and independently extracted study characteristics and HRs for PFS and OS. Disagreements were resolved by discussion, with consultation of a third reviewer when consensus could not be reached. When essential information was unavailable, the corresponding authors were contacted; studies with unresolved essential missing data were excluded. Study-level data were cross-checked against the source publication before synthesis. The characteristics of the included phase III RCTs are summarized in Supplementary Table 2. Studies judged to be at high risk of bias were retained and were prespecified for sensitivity assessment where the evidence structure permitted.

Synthesis of data and statistical analysis

An NMA was conducted to estimate relative HRs for PFS and OS among ICI-containing regimens for advanced TNBC. Because the evidence network was sparse and contained only three RCTs, between-study heterogeneity could not be estimated reliably; therefore, a fixed-effect model was used for the primary analysis. The network contained no closed loop, so formal assessment of inconsistency between direct and indirect evidence was not possible [18,19]. The network structure is shown in Supplementary Fig. 1. Surface under the cumulative ranking curve (SUCRA) values were used to summarize treatment-ranking probabilities; rankings were interpreted as exploratory and not as evidence of statistically significant clinical superiority. Analyses were performed using the gemtc package in R version 4.5.0.

Cost-effectiveness analysis

Analytical overview

The economic evaluation was conducted from the perspective of the Chinese healthcare system and was reported in accordance with CHEERS 2022. A decision-analytic model combining a treatment-selection decision tree and a partitioned survival model evaluated pembrolizumab plus chemotherapy, atezolizumab plus chemotherapy, and toripalimab plus chemotherapy (Fig. 1). The partitioned survival model comprised three mutually exclusive health states: progression-free survival (PFS), progressed disease (PD), and death. The cycle length was 3 weeks and the time horizon was 10 years. All patients entered the model in the PFS state, and state occupancy was derived from the PFS and OS functions. Outcomes included total costs, life-years (LYs), QALYs, and ICERs. Costs were expressed in 2025 US

dollars using an exchange rate of CNY 7.122 = US$1. Costs and health outcomes were discounted at 5% annually [20]. The willingness-to-pay (WTP) threshold was set at three times China's 2025 per-capita gross domestic product [21,22].

Clinical data

Clinical efficacy and safety inputs were obtained from the included trials. Pseudo-individual patient data were reconstructed from published Kaplan-Meier curves, and exponential, gamma, Weibull, log-normal, log-logistic, and Gompertz functions were fitted to extrapolate survival beyond the observed follow-up [23]. Candidate models were assessed by visual fit and Akaike information criterion (AIC); AIC values and selected distributions are reported in Supplementary Table 3. Pembrolizumab plus chemotherapy was prespecified as the primary absolute-risk survival anchor because it had the most mature follow-up among the included trials. Each NMA HR was expressed consistently as the target regimen versus the selected anchor, such that an HR < 1 indicated a lower hazard for the target regimen. Reverse contrasts were derived algebraically rather than entered as independent model inputs. Alternative analyses replaced the complete trial-specific absolute-risk function with the atezolizumab or toripalimab survival function and were treated as structural scenarios. Because each anchor implies a different baseline hazard, absolute survival, QALYs, treatment duration, and costs were interpreted within, rather than directly compared across, scenario blocks. After disease progression, gemcitabine plus carboplatin was used as a simplified subsequent treatment assumption based on trial appendices and the Chinese Society of Clinical Oncology Breast Cancer Guidelines (2025 edition).

Cost and utility data

The model included direct medical costs for first-line and subsequent anticancer therapy, routine follow-up, best supportive care, end-of-life care, and management of grade ≥ 3 treatment-related adverse events. Drug doses were estimated for a representative patient with a body surface area of 1.72 m^2 (height 1.64 m; weight 65 kg) [24].

Health-state utilities were assigned on a scale from 0 (death) to 1 (perfect health). Utility values for PFS, PD, and death were 0.86, 0.73, and 0, respectively, based on published evidence for Chinese women with breast cancer [25]. Unit costs, parameter ranges, and probability distributions are summarized in Table 1.

Table 1
Model inputs: base-case values and ranges used in sensitivity analyses.

Parameter	**Range**			**Distribution**	**Reference**
Parameter	Base-case value	Lower bound	Upper bound	Distribution	Reference
Cost values (US$)					
Pembrolizumab (0.1 g)	2516.57	2013.26	3019.88	Gamma	Local charge
Atezolizumab (1.2 g)	4606.74	3685.39	5528.09	Gamma	Local charge
Toripalimab (240 mg)	244.72	195.78	293.66	Gamma	Local charge
Capecitabine (0.5 g)	1.85	1.48	2.22	Gamma	Local charge
Nab-paclitaxel (0.1 g)	18.96	15.17	22.75	Gamma	Local charge
Paclitaxel (30 mg)	5.33	4.27	6.40	Gamma	Local charge
Gemcitabine (1 g)	28.88	23.10	34.66	Gamma	Local charge
Carboplatin (150 mg)	15.31	12.25	18.37	Gamma	Local charge
supportive treatment	274.36	219.49	329.23	Gamma	26
routine follow-up	73.9	59.12	88.68	Gamma	27
Palliative care	685.9	548.72	823.08	Gamma	27
Anemia	138.57	110.86	166.28	Gamma	27
Neutropenia	354	283.2	424.8	Gamma	28
Neutrophil count decreased	435.21	348.17	522.25	Gamma	29
Neuropathy peripheral	1.45	1.16	1.74	Gamma	27
Fatigue	81.57	65.26	97.88	Gamma	30

PFS, progression-free survival; PD, progressed disease; AEs, adverse events; HR, hazard ratio; NMA, network meta-analysis; Atec, atezolizumab plus chemotherapy; Pemc, pembrolizumab plus chemotherapy; Torc, toripalimab plus chemotherapy; OS, overall survival. HR contrast labels were cross-checked against the NMA league table; the first-named treatment is the numerator and the second-named treatment is the denominator.

Parameter	Range			Distribution	Reference
Leukopenia	115.01	92.01	138.01	Gamma	31
Utility values					
PFS	0.86	0.69	1	Beta	25
PD	0.73	0.58	0.88	Beta	25
Risk of grade ≥ 3 adverse events: pembrolizumab					
Anemia	0.16	0.128	0.192	Beta	8
Neutropenia	0.30	0.24	0.36	Beta	8
Neutrophil count decreased	0.17	0.136	0.204	Beta	8
Risk of grade ≥ 3 adverse events: toripalimab					
Fatigue	0.04	0.032	0.048	Beta	10
Anaemia	0.03	0.024	0.036	Beta	10
Neuropathy peripheral	0.06	0.048	0.072	Beta	10
Neutropenia	0.08	0.064	0.096	Beta	10
Neutrophil count decreased	0.05	0.04	0.06	Beta	10
Risk of grade ≥ 3 adverse events: atezolizumab					
Leukopenia	0.252	0.2016	0.3024	Beta	7
Neutropenia	0.263	0.2104	0.3156	Beta	7
Discount rate	0.05	0.04	0.06	Beta	20
HR of PFS (Atec versus Pemc)	0.98	0.78	1.2	Log-normal	NMA

PFS, progression-free survival; PD, progressed disease; AEs, adverse events; HR, hazard ratio; NMA, network meta-analysis; Atec, atezolizumab plus chemotherapy; Pemc, pembrolizumab plus chemotherapy; Torc, toripalimab plus chemotherapy; OS, overall survival. HR contrast labels were cross-checked against the NMA league table; the first-named treatment is the numerator and the second-named treatment is the denominator.

Parameter	Range			Distribution	Reference
HR of PFS (Atec versus Torc)	1.0	0.78	1.4	Log-normal	NMA
HR of PFS (Pemc versus Atec)	1.0	0.82	1.3	Log-normal	NMA
HR of PFS (Pemc versus Torc)	1.1	0.79	1.4	Log-normal	NMA
HR of PFS (Torc versus Pemc)	0.94	0.69	1.3	Log-normal	NMA
HR of PFS (Torc versus Atec)	0.96	0.72	1.3	Log-normal	NMA
HR of OS (Atec versus Pemc)	0.97	0.76	1.2	Log-normal	NMA
HR of OS (Atec versus Torc)	1.2	0.88	1.8	Log-normal	NMA
HR of OS (Pemc versus Torc)	1.3	0.92	1.8	Log-normal	NMA
HR of OS (Pemc versus Atec)	1.0	0.82	1.3	Log-normal	NMA
HR of OS (Torc versus Pemc)	0.78	0.55	1.1	Log-normal	NMA
HR of OS (Torc versus Atec)	0.8	0.57	1.1	Log-normal	NMA

PFS, progression-free survival; PD, progressed disease; AEs, adverse events; HR, hazard ratio; NMA, network meta-analysis; Atec, atezolizumab plus chemotherapy; Pemc, pembrolizumab plus chemotherapy; Torc, toripalimab plus chemotherapy; OS, overall survival. HR contrast labels were cross-checked against the NMA league table; the first-named treatment is the numerator and the second-named treatment is the denominator.

Sensitivity analyses

Deterministic one-way and probabilistic sensitivity analyses were conducted to characterize parameter uncertainty. In one-way analyses, parameters were varied across reported 95% confidence intervals or, when these were unavailable, ± 20% of the base-case value; results were summarized in tornado diagrams. In the probabilistic sensitivity analysis, 1,000 Monte Carlo simulations simultaneously sampled HRs from log-normal distributions, proportions and utility values from beta distributions, and costs from gamma distributions. Cost-effectiveness acceptability curves were generated across a range of WTP thresholds. Structural uncertainty was evaluated separately by repeating the analysis with alternative trial-specific survival anchors.

Results

Network meta-analysis

The searches identified 8,816 records; after screening and full-text assessment, three phase III RCTs (IMpassion130, KEYNOTE-355, and TORCHLIGHT), comprising 2,280 participants, were included in the NMA (Fig. 2). Overall risk of bias was low across most assessed domains (Supplementary Fig. 2). All relative HR estimates for OS and PFS had 95% confidence intervals that included 1 (Table 2), indicating that the indirect comparisons did not identify statistically significant differences among the evaluated ICI-containing regimens. Toripalimab plus chemotherapy had the highest SUCRA ranking probability (Supplementary Fig. 3).

Table 2
Hazard ratios from the exploratory network meta-analysis for progression-free and overall survival.

	Pemc	Torc	Atec
Progression-free survival			
Pemc	1	1.1 (95% CI: 0.79–1.4)	1.0 (95% CI: 0.82–1.3)
Torc	0.94 (95% CI: 0.69–1.3)	1	0.96 (95% CI: 0.72–1.3)
Atec	0.98 (95% CI: 0.78–1.2)	1.0 (95% CI: 0.78–1.4)	1
Overall survival			
Pemc	1	1.3 (95% CI: 0.92–1.8)	1.0 (95% CI: 0.82–1.3)
Torc	0.78 (95% CI: 0.55–1.1)	1	0.8 (95% CI: 0.57–1.1)
Atec	0.97 (95% CI: 0.76–1.2)	1.2 (95% CI: 0.88–1.8)	1

Atec, atezolizumab plus chemotherapy; Pemc, pembrolizumab plus chemotherapy; Torc, toripalimab plus chemotherapy. Each hazard ratio compares the row treatment with the column treatment; values below 1 favor the row treatment.

Cost-effectiveness analysis

Base-case analysis

In the primary analysis using pembrolizumab plus chemotherapy as the survival anchor, toripalimab plus chemotherapy generated 2.27 QALYs at a total cost of US$40,972.13. Atezolizumab plus chemotherapy generated 1.82 QALYs at US$115,286.53, and pembrolizumab plus chemotherapy generated 1.90 QALYs at US$124,952.00. Under these model assumptions, both atezolizumab- and pembrolizumab-containing strategies were dominated by toripalimab because they were more costly and generated fewer QALYs (Table 3).

Table 3
Cost-effectiveness results under alternative survival-anchor scenarios.

Strategy	Total cost (US$)	QALYs	Incremental cost (US$)	Incremental QALYs	Economic interpretation
Primary base case (pembrolizumab survival anchor)					
Torc	40972.13	2.27			Reference strategy
Atec	115286.53	1.82	74314.40	-0.45	Dominated
Pemc	124952.00	1.90	83979.88	-0.37	Dominated
Structural scenario 1 (atezolizumab survival anchor)					
Torc	29662.45	2.49			Reference strategy
Atec	108191.49	2.16	78529.04	-0.33	Dominated
Pemc	115849.26	2.11	86186.81	-0.38	Dominated
Structural scenario 2 (toripalimab survival anchor)					
Torc	47222.32	3.01			Reference strategy
Pemc	161933.96	2.57	114711.65	-0.44	Dominated
Atec	166911.61	2.72	119689.29	-0.29	Dominated

Atec, atezolizumab plus chemotherapy; Pemc, pembrolizumab plus chemotherapy; Torc, toripalimab plus chemotherapy; QALYs, quality-adjusted life-years. “Dominated” indicates a strategy that is more costly and generates fewer QALYs than the reference strategy.

Sensitivity analyses

One-way sensitivity analyses identified the acquisition costs of atezolizumab and pembrolizumab, together with the PFS and PD utility values, as key drivers of model outcomes (Supplementary Fig. 4A-B). Across the evaluated parameter ranges, toripalimab plus chemotherapy generally retained the most favorable economic profile. The cost-effectiveness acceptability analysis indicated that toripalimab plus chemotherapy had the highest probability of being cost-effective across WTP thresholds from US$0/QALY to US$100,000/QALY (Fig. 3).

Scenario analyses

Using atezolizumab plus chemotherapy as the survival anchor preserved the same economic ordering: toripalimab plus chemotherapy remained less costly and generated more QALYs than the alternative strategies. The same pattern was observed when toripalimab plus chemotherapy was used as the anchor. However, absolute QALY estimates varied across anchor scenarios, with higher values when TORCHLIGHT supplied the absolute-risk function. This variation demonstrates structural uncertainty associated with anchor selection. The direction of the toripalimab survival estimates is consistent with

the favorable outcomes observed in TORCHLIGHT versus its chemotherapy control, but TORCHLIGHT did not directly compare toripalimab with pembrolizumab or atezolizumab.

In the structural scenarios, tornado diagrams again identified ICI acquisition costs and the utility of PD as influential parameters (Supplementary Fig. 4C-F). The persistent model-based economic advantage of toripalimab was therefore driven primarily by its lower acquisition cost in the Chinese setting, supporting robustness of the relative economic conclusion while highlighting uncertainty in absolute health-benefit estimates.

Discussion

The exploratory NMA did not detect statistically significant differences in progression-free or overall survival among the evaluated ICI-containing regimens. Although toripalimab plus chemotherapy had the most favorable treatment-ranking probabilities, these rankings should not be interpreted as evidence of comparative clinical superiority. The economic model instead suggested that toripalimab plus chemotherapy could offer better value under the modeled Chinese costs and treatment pathways, primarily because of lower drug acquisition costs. This distinction is relevant to decisions about affordability and resource allocation, but the economic results should not be extrapolated directly to other health systems with different prices, reimbursement arrangements, or treatment patterns. The included trials differed in PD-L1 assays, scoring thresholds, chemotherapy backbones, and patient characteristics, which restricts the transitivity assumption needed for indirect treatment comparisons .[7–10]

A methodological challenge for NMA-informed economic evaluation is the application of relative treatment effects to an absolute-risk survival function. The base-case model anchored survival to pembrolizumab plus chemotherapy, whereas scenario analyses substituted survival estimates from the atezolizumab or toripalimab trials. The economic ordering was maintained, but absolute QALYs differed among scenarios, showing that the choice of anchor was a source of structural uncertainty. This sensitivity cannot be resolved by probabilistic parameter sampling alone. A previous Chinese cost-effectiveness analysis based on the TORCHLIGHT trial reported broadly comparable costs for toripalimab plus chemotherapy[12]; differences in model structures, data maturity, and survival extrapolation may affect estimated benefits.

Several limitations should be considered. First, only three phase III trials contributed to the NMA, and there was no closed loop; statistical assessment of inconsistency was therefore not feasible. Differences in PD-L1 definitions and chemotherapy comparators were not adjusted for, and the results should be considered exploratory. Second, long-term survival estimates were extrapolated from reconstructed published Kaplan-Meier curves; the relative-hazard extrapolation may be unreliable if treatment effects vary over time. Third, the model assumed a simplified subsequent treatment regimen and relied on some literature-derived cost and utility inputs rather than prospectively collected Chinese resource-use data. Fourth, the adverse-event cost model excluded grade 1–2 events, and external

validation of long-term survival projections was limited. Further research should examine biomarker-harmonized evidence, updated long-term trial data, and real-world Chinese treatment pathways and costs.

Conclusions

Among the three evaluated first-line ICI-containing regimens for advanced TNBC, indirect comparisons did not demonstrate statistically significant differences in OS or PFS. Under the assumptions of the Chinese healthcare system model, toripalimab plus chemotherapy was less costly and generated more QALYs than the pembrolizumab- and atezolizumab-containing strategies. This economic result was driven largely by drug acquisition costs.

Abbreviations

AACR
American Association for Cancer Research
AIC
Akaike information criterion
ASCO
American Society of Clinical Oncology
CENTRAL
Cochrane Central Register of Controlled Trials
CHEERS
Consolidated Health Economic Evaluation Reporting Standards
CI
confidence interval
CNY
Chinese yuan
ER
estrogen receptor
ESMO
European Society for Medical Oncology
HER2
human epidermal growth factor receptor 2
HR
hazard ratio
ICI
immune checkpoint inhibitor
ICER
incremental cost-effectiveness ratio
LY

life-year
NMA
network meta-analysis
OS
overall survival
PD
progressed disease
PD-1
programmed cell death 1
PD-L1
programmed death ligand 1
PFS
progression-free survival
PR
progesterone receptor
PRISMA
Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY
quality-adjusted life-year
RCT
randomized controlled trial
SUCRA
surface under the cumulative ranking curve
TNBC
triple-negative breast cancer
WTP
willingness-to-pay.

Declarations

Ethics approval and consent to participate

Not applicable. This study used aggregate data from published studies and did not involve recruitment of human participants, use of identifiable individual-level data, or collection of human tissue; therefore, additional ethics approval and participant consent were not required.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Supplementary information

Additional file 1 (DOCX): Electronic Supplementary Material containing Supplementary Tables 1–3, Supplementary Figs. 1–4, and Supplementary File 1.

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Author Contribution

S.K.: Data curation, Validation, Writing – original draft. S.Y.: Investigation, Data curation, Validation, Writing – original draft. Y. J.: Investigation, Writing – original draft. S.Z.: Writing – review & editing. All authors read and approved the final manuscript.

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Data Availability

All clinical-effect data used in the NMA were derived from published studies cited in this article. Model inputs and results necessary to interpret the analysis are reported in the manuscript and Supplementary Information. The analytic model, parameterisation files, and calculation sheets are available from the corresponding author on reasonable request.

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Figures

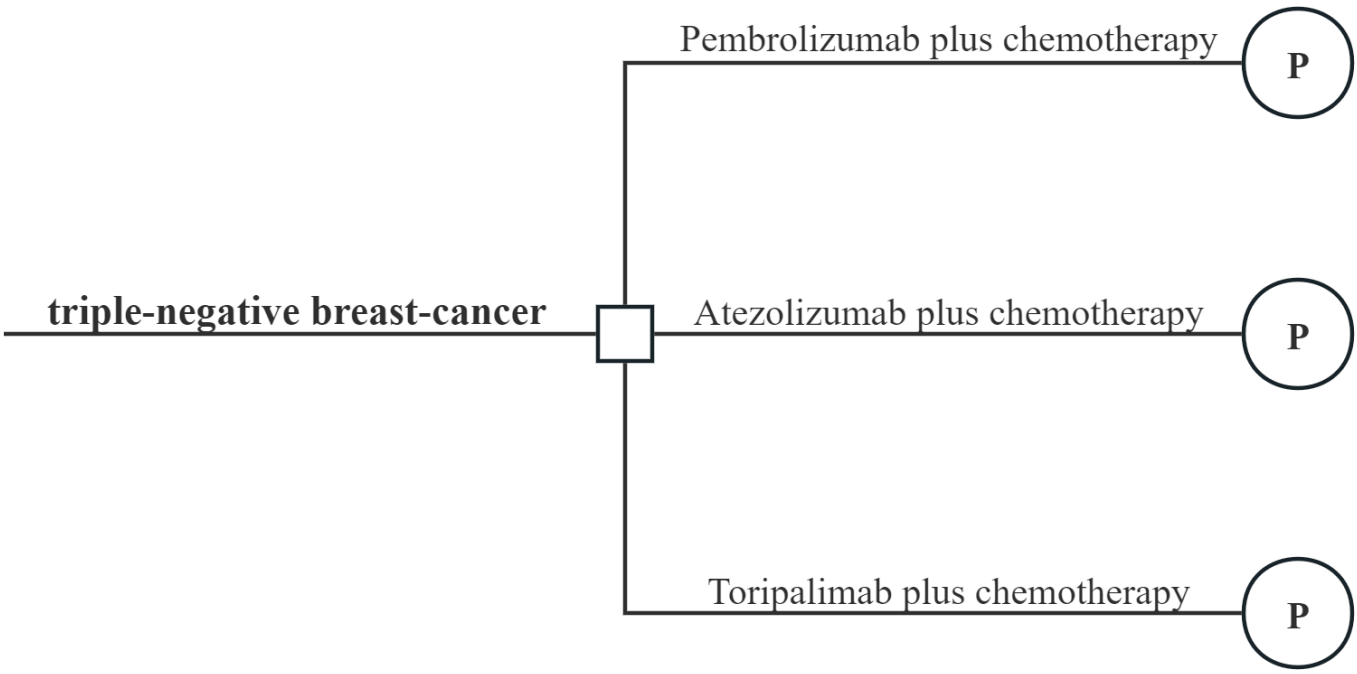


Figure 1

Figure 1 Structure of the decision tree (A) and partitioned survival model

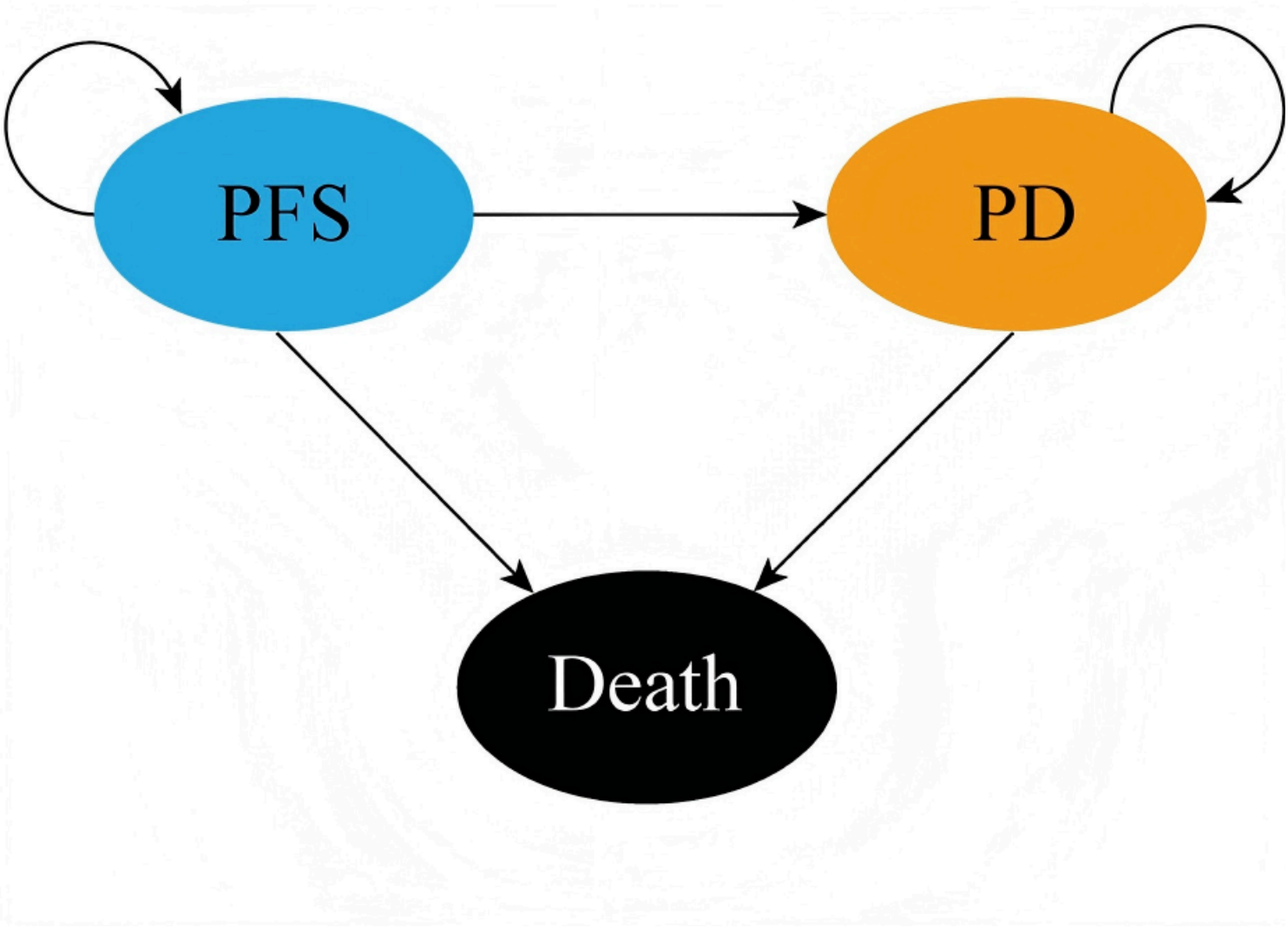


Figure 2

Figure 1 Structure of the decision tree (B). PFS, progression-free survival; PD, progressed disease.

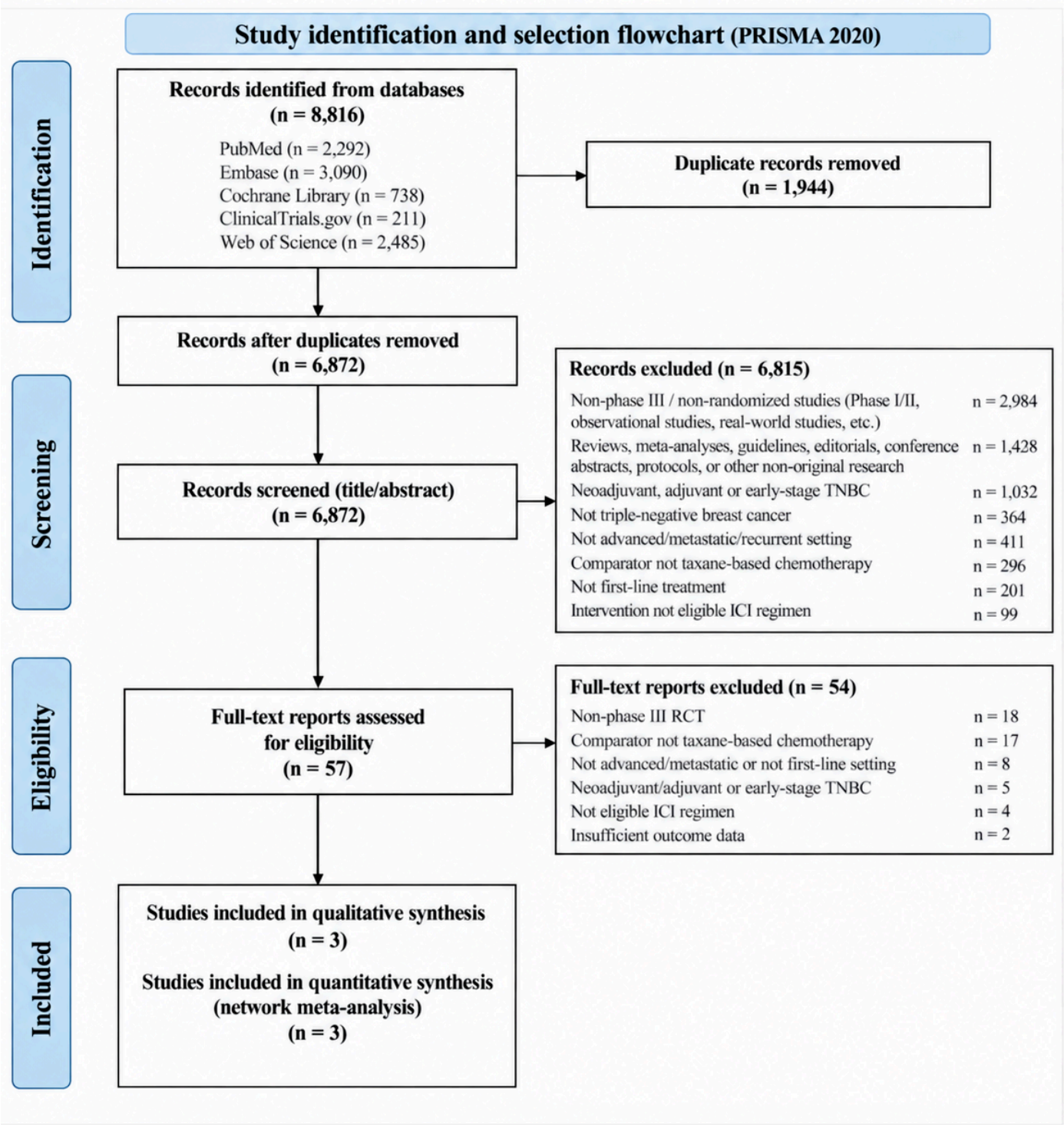


Figure 3

Figure 2 PRISMA 2020 flow diagram of study selection.

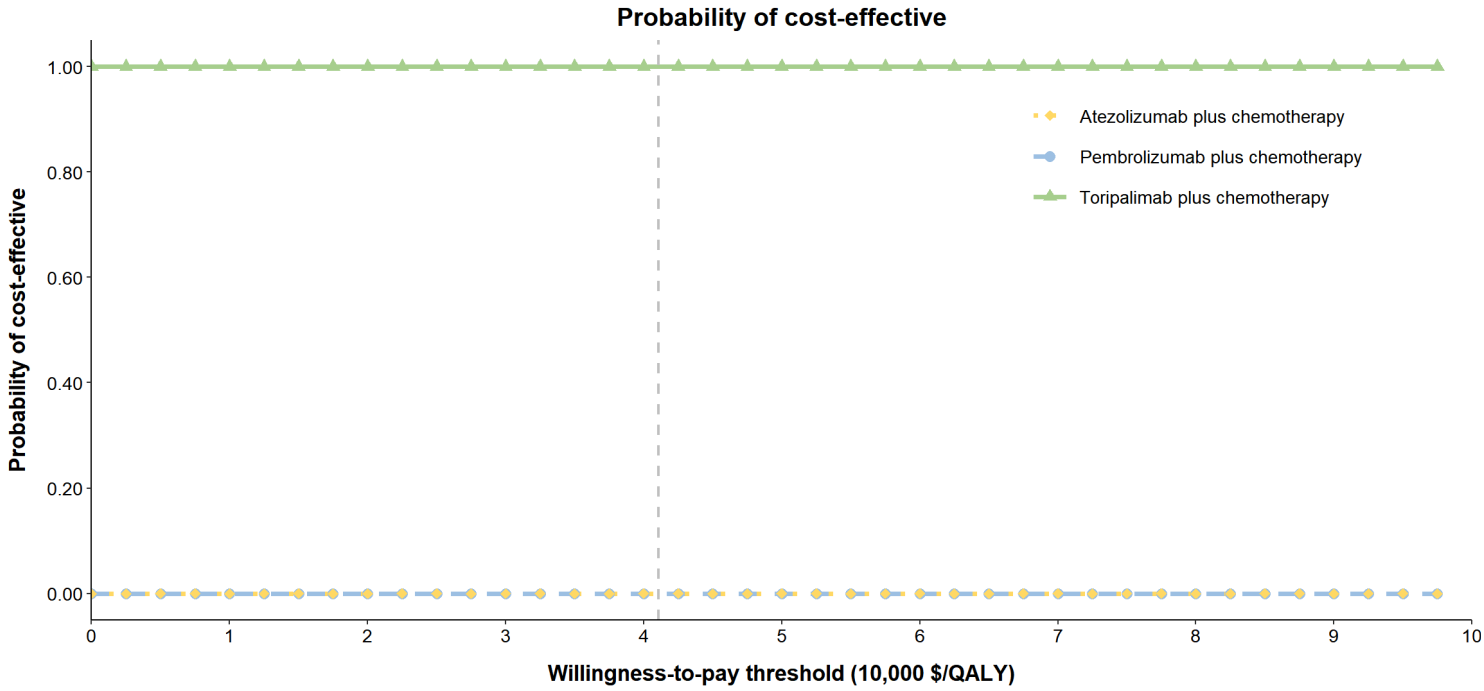


Figure 4

Figure 3 Cost-effectiveness acceptability curves. QALY, quality-adjusted life-year.

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