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Therapeutic landscape of advanced cervical cancer: comparative efficacy of emerging versus established combination regimens using reconstructed survival data

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Abstract

Objective

To compare the survival, response, and safety of therapeutic regimens for advanced cervical cancer using reconstructed individual patient data (IPD), organized into clinically coherent evidence networks to avoid implausible comparisons between arms of unrelated trials.

Methods

Fifty-nine studies (10,734 patients) were included. Survival outcomes were analyzed within three pre-specified networks by clinical setting, locally advanced disease, first-line recurrent/metastatic disease, and previously treated disease, anchored to published hazard ratios (HRs), with within-trial IPD reconstruction used only for Cox-model cross-checks and restricted mean survival time (RMST). Response and safety outcomes were pooled by random-effects meta-analysis and ranked via generalized linear models. PROSPERO ID: CRD420251172090.

Results

In first-line disease, adding bevacizumab (GOG-240; OS HR = 0.71, PFS HR = 0.67), pembrolizumab (KEYNOTE-826; OS HR = 0.63, PFS HR = 0.61), atezolizumab (BEATcc; OS HR = 0.68, PFS HR = 0.62), or cadonilimab (COMPASSION-16; OS HR = 0.64, PFS HR = 0.62) to chemotherapy significantly improved survival. In locally advanced disease, pembrolizumab plus chemoradiotherapy improved OS (HR = 0.73) and PFS (HR = 0.72), whereas durvalumab did not (OS HR = 0.73; PFS HR = 0.84), except in PD-L1-high tumors (PFS HR = 0.62). In previously treated disease, tisotumab vedotin (OS HR = 0.70) and cemiplimab (OS HR = 0.67) showed comparable randomized benefit. On a 29.6-month horizon, pembrolizumab-chemotherapy-bevacizumab achieved the longest RMST (18.80 months). For response, immunotherapy-anti-angiogenic-chemotherapy triplets achieved up to 83.3% objective response (OR = 4.63); immune-checkpoint-based regimens carried the lowest grade ≥ 3 toxicity (OR as low as 0.08 vs reference).

Conclusion

Randomized evidence supports survival benefits from anti-angiogenic and immune-checkpoint-based treatment intensification in selected clinical settings of cervical cancer, although the optimal regimen remains setting- and biomarker-dependent. Reconstructed cross-trial analyses should be considered exploratory.

Synopsis

Reconstructed IPD from 59 studies (10,734 patients) formed three survival networks.

Adding anti-angiogenic or immune-checkpoint agents improved survival across all settings.

Pembrolizumab plus chemotherapy and bevacizumab achieved the longest restricted mean survival time.

1. INTRODUCTION

Cervical cancer (CC) remains a major global health burden, especially in low- and middle-income countries (LMICs), where over 85% of cases and deaths occur [1]. In 2022, there were approximately 660,000 new cases and 350,000 deaths globally, with the highest incidence and mortality observed in sub-Saharan Africa and Southeast Asia (IARC/WHO)[2]. In Eastern Africa, rates can exceed 40 cases and 30 deaths per 100,000 women. The high burden of advanced-stage disease, coupled with limited access to effective therapies, highlights the urgent need for improved treatment strategies in these regions[3]. According to NCCN (2024)[4] and ESMO (2023), first-line therapy is typically platinum-based chemotherapy (PBC), often combined with bevacizumab or chemoradiotherapy (CCRT)[3]. In PD-L1-positive disease, immune checkpoint inhibitors (ICIs) such as pembrolizumab are recommended[5, 6]. However, these guidelines are largely based on a few phase III trials (notably GOG 240) and lag behind the rapid development of novel strategies[7, 8]. Recent phase II studies have explored chemotherapy-free approaches, including dual ICIs (nivolumab + ipilimumab) and targeted biologic combinations, offering promising efficacy and better tolerability, particularly in patients unfit for cytotoxic therapy[9, 10]. However, the majority of such studies remain in early-phase development, often as single-arm trials without control groups[11], making it difficult to directly compare them to standard therapies or perform network meta-analyses due to the absence of common comparators and heterogeneity in trial design[12].

Inconsistent reporting of survival and toxicity outcomes further hampers cross-study comparison. Traditional meta-analyses based on aggregated hazard ratios (HRs) or response rates fail to capture granular time-to-event dynamics or cumulative toxicities, limiting their clinical applicability.

To address these gaps, we performed a systematic review of trials published in the past decade and reconstructed individual patient-level survival curves from digitized Kaplan-Meier plots. This approach enables standardized comparison of efficacy and toxicity across heterogeneous regimens, even without direct head-to-head trials.

2. METHODS

Study design and population

This study was conducted as a systematic review with reconstructed survival data, in accordance with PRISMA 2020 guidelines. PROSPERO ID: CRD420251172090. Eligible publications were required to meet

the following criteria:

- Included studies reported survival (OS/PFS) and ≥1 standardized tumor-response endpoint (per RECIST 1.1/iRECIST: ORR, CR/PR, SD, DCR, CBR, BOR, DoR, TTR), published Jan-2014-Apr-2024; 2014 reflects the post-GOG-240 era [13].

- Employ systemic treatment regimen including chemoradiotherapy, immunotherapy, targeted therapy, combination therapy, or other advanced approaches.

Exclusion criteria included preclinical studies, case reports, and studies lacking sufficient OS/PFS data or involving populations outside the defined disease scope.

Search strategy and study selection

A comprehensive literature search was performed using PubMed, Embase, Cochrane Library, Web of Science, and *ClinicalTrials.gov* to identify eligible studies. Detailed search terms and study characteristics are provided in **Suppl. Table S1**. Using Covidence [14], four reviewers independently screened studies, with discrepancies resolved by consensus (**Suppl. Table S1-2**).

Eligible studies were Phase Ib to III trials evaluating systemic therapies (immunotherapy, anti-angiogenic agents, or chemotherapy) with accessible Kaplan-Meier (KM) curves. We excluded studies with poor KM resolution to ensure high-fidelity IPD reconstruction. Selection results and reasons for exclusion are summarized in the PRISMA flow diagram (**Suppl. Figure S1**).

Quality assessment

Quality and risk of bias were assessed using the PEDro Scale [15] for randomized controlled trials (RCTs) and the Newcastle-Ottawa Scale (NOS) [16] for non-randomized studies. Studies with poor methodological quality (NOS < 5, PEDro < 4) were excluded or flagged for sensitivity analysis.

Data extraction and endpoint definitions

From each included study, two investigators independently extracted study-level characteristics: first author and year, phase, NCT number, design, sample size, age, histology, LA/M stages, presence of metastasis, interventions and comparators (with dosages), population type, follow-up duration, and outcomes. Discrepancies in data extraction were resolved by a third reviewer to ensure scientific rigor.

Survival outcomes encompassed OS, PFS, and other time-to-event endpoints (EFS, DFS, DMFS, LRFS, ppOS). For each treatment group, the numbers at risk, deaths, and survivors at defined time points were extracted from KM risk tables. This enabled reconstruction of individual patient-level survival curves for quantitative analysis.

The data was extracted from a pooled response dataset in which the number of responders (EI) and the total number of patients (NI) were recorded for each treatment arm at multiple follow-up time points.

The response rate was calculated as EI/NI and organized by clinical endpoint (overall response, objective response).

Statistical Analysis

*Evidence networks***.** Survival analysis (OS, PFS) was organized into three pre-specified networks by clinical setting: locally advanced disease (CALLA, KEYNOTE-A18), first-line persistent/recurrent/metastatic disease (GOG-240, KEYNOTE-826, BEATcc, COMPASSION-16, JCOG0505; randomized trials only), and previously treated disease (single-arm studies, descriptive only; randomized trials analyzed separately). A hazard ratio (HR) was never computed between arms of different, unrelated trials.

IPD reconstruction. For each eligible arm, pseudo individual patient data were reconstructed from the published number-at-risk table: censored observations per interval were calculated as the drop in number-at-risk minus recorded events, and event/censoring times were assigned by uniform random sampling within each interval (conceptually analogous to the Guyot algorithm [12], applied to exact reported counts rather than digitized curve coordinates). Sub-population series sharing identical labels were separated using label and follow-up-time discontinuity, cross-verified against each trial's published baseline N where labels were ambiguous. Reconstruction was performed strictly within one trial at a time and never combined across trials. Fidelity was confirmed by comparing the reconstructed Kaplan-Meier curve against the exact stepwise function from the raw counts; a reconstructed HR was nonetheless classified low-reliability, and not used to override the published estimate, if the sparser arm had <8 timepoints or the reconstructed HR fell outside the published 95% CI.

Survival comparisons. Published HRs (95% CI) were primary evidence throughout. Reconstructed pseudo-IPD served only as a within-trial Cox-model cross-check and to estimate restricted mean survival time (RMST) differences (bootstrap 95% CI, both arms resampled jointly). Trials reporting the same regimen pair were pooled via trial-stratified Cox models; trials sharing a comparator but not each other were linked via anchored indirect comparison (Bucher method [17]). Proportional hazards were assessed via Schoenfeld residuals.

Response outcomes. ORR, disease control rate, and best-response categories were pooled per regimen by random-effects logit-scale meta-analysis (I^2, tau^2, Cochran's Q; Wilson interval for single-study regimens), ranked via fixed-effect binomial GLM (adjusted OR, 95% CI, Wald p) with a mixed-effects sensitivity model [18]. Within-trial comparisons used unpooled odds ratios (Haldane-Anscombe correction). Publication bias was assessed by funnel plot and Egger's test.

Safety outcomes. Any-grade and grade ≥3 AEs were extracted per arm; internally inconsistent rows were excluded. AE terms were grouped into system-organ-class categories by keyword matching, with category counts taken as the maximum (not sum) across constituent terms to avoid double-counting. Pooling and ranking followed the response-outcome methods.

Software. R (≥4.x): survival/survminer, metafor, lme4, ggplot2/patchwork. Two-sided p<0.05 was significant.

3. RESULTS

3.1. Study characteristics and outcome reporting

A total of 59 studies were included, enrolling 10,734 patients overall; the median sample size per study was 64 patients (range 3-1,060), and the median reported age across studies was 51 years. Most studies were phase II (30/59, 50.8%) or phase III (18/59, 30.5%), with fewer early-phase trials reported as phase I-II / Ib-II (4/59, 6.8%), phase I (3/59, 5.1%), or phase II-III (1/59, 1.7%); 3/59 (5.1%) did not clearly report trial phase. Regarding design, 31/59 studies (52.5%) were single-arm or other non-randomized interventional studies, 23/59 (39.0%) were randomized controlled trials, and 5/59 (8.5%) were observational cohort studies. Most studies enrolled mixed histology populations including *squamous cell carcinoma, adenocarcinoma,* and *adenosquamous carcinoma* (51/59, 86.4%), while squamous-only cohorts accounted for 5/59 (8.5%) and adenocarcinoma-only cohorts for 1/59 (1.7%). Disease stage at enrollment was predominantly advanced: among the 25/59 studies (42.4%) that reported metastatic status numerically, 4,716 of 6,278 patients (75.1%) had metastatic disease; among the 14/59 studies (23.7%) that reported recurrent/persistent disease explicitly, 2,259 of 3,588 patients (63.0%) had recurrent disease. Lymph node involvement (regional nodal metastasis) was documented as present/allowed in 16/59 studies (27.1%), whereas 43/59 studies (72.9%) documented “NO” nodal metastasis in the eligibility/description column. For outcome distribution, tumor-response endpoints dominated: ORR in 51/59 (86.4%). Time-to-event outcomes were similarly common-PFS 50/59 (84.7%) and OS 48/59 (81.4%)-with safety reported in 37/59 (62.7%) and durability of response in 22/59 (37.3%). Less frequently reported were DCR 10/59 (16.9%), QoL 1/59 (1.7%), and DFS/local-control metrics ≈1/59 (≈1.7%) (**Suppl. Table S3**).

Quality assessment showed RCTs generally scored ≥7 on the PEDro scale, while non-RCTs had NOS scores of 6-8, despite limitations in blinding and follow-up. These trials provide a heterogeneous but valuable evidence base for reconstructing survival outcomes and exploring efficacy patterns of emerging therapies, **Suppl. Table S4-5**.

3.2. Pooled Survival and Restricted Mean Survival Time Analyses of Reconstructed Cohorts Under Quality Control

The survival evidence was organized into three clinically distinct networks (**Figure 1):** locally advanced cervical cancer (Network 1), first-line persistent/recurrent/metastatic disease (Network 2) and previously treated recurrent/metastatic disease (Network 3/3b). In Network 1, pembrolizumab plus chemoradiotherapy significantly improved OS (HR 0.73, 95% CI 0.57-0.94; p=0.004) and PFS (HR 0.72, 95% CI 0.59-0.87) versus placebo plus chemoradiotherapy in KEYNOTE-A18. In contrast, CALLA showed no significant OS or PFS benefit with durvalumab plus chemoradiotherapy in the overall population,

although a favorable PFS signal was observed in patients with PD-L1 TAP ≥20% (HR 0.62, 95% CI 0.42-0.91) (**Table S8; Figure S2**).

In Network 2, randomized within-trial evidence consistently supported the addition of antiangiogenic and immune-checkpoint therapies to standard chemotherapy. GOG-240 demonstrated improved OS (HR 0.71, 95% CI 0.54-0.95) and PFS (HR 0.67, 95% CI 0.54-0.82) with bevacizumab plus chemotherapy. KEYNOTE-826 showed significant benefits with pembrolizumab plus chemotherapy ± bevacizumab for OS (HR 0.63, 95% CI 0.52-0.77) and PFS (HR 0.61, 95% CI 0.50-0.74), with broadly consistent effects across bevacizumab-use and PD-L1 CPS ≥1 subgroups. BEATcc similarly favored atezolizumab plus bevacizumab and chemotherapy for OS (HR 0.68, 95% CI 0.52-0.88) and PFS (HR 0.62, 95% CI 0.49-0.78), while COMPASSION-16 favored cadonilimab plus chemotherapy ± bevacizumab for OS (HR 0.64, 95% CI 0.48-0.86) and PFS (HR 0.62, 95% CI 0.49-0.80) (**Table S9; Figure S3**). Chemotherapy-backbone comparisons were generally non-significant, except for inferior PFS with topotecan-paclitaxel versus cisplatin-paclitaxel in GOG-240 (HR 1.39, 95% CI 1.09-1.77).

The anchored Bucher comparison between pembrolizumab plus chemotherapy plus bevacizumab and atezolizumab plus bevacizumab plus chemotherapy showed no significant OS difference (indirect HR 0.882, 95% CI 0.600-1.297; p=0.524; **Figure 1D; Table S13**). In previously treated disease (Network 3b), tisotumab vedotin improved OS (HR 0.70, 95% CI 0.54-0.89) and PFS (HR 0.67, 95% CI 0.54-0.82) versus investigator-choice chemotherapy in innovaTV 301[19], while cemiplimab also improved OS (HR 0.67, 95% CI 0.56-0.80) and PFS (HR 0.75, 95% CI 0.63-0.89) in EMPOWER-Cervical1 (**Table S10; Figure S7**). Single-arm Network 3 studies were therefore treated descriptively only; median OS ranged from 12.8 months with balstilimab plus zalifrelimab to 24.7 months with nivolumab plus ipilimumab (**Figure 1A; Table S14**).

Exploratory reconstructed survival analyses are summarized in **Figure 2.** Kaplan–Meier curves for selected regimens are shown for OS **(Figure 2A)** and PFS **(Figure 2B)**. Forest plots of statistically significant reconstructed HRs relative to the prespecified reference regimen are presented for OS **(Figure 2C)** and PFS **(Figure 2D)**. Marked cross-regimen differences were observed, although these estimates should be interpreted cautiously because they represent cross-trial comparisons across heterogeneous populations rather than randomized head-to-head effects (**Tables S16–S17**). Among the highest reconstructed median OS estimates were atezolizumab–bevacizumab–chemotherapy (39.13 months) and bevacizumab–chemotherapy (38.51 months); however, both were classified as low-reliability estimates and were excluded after data-quality sensitivity analysis **(Table S19**).

RMST analyses provided complementary estimates where proportional hazards were questionable. At τ=29.6 months, pembrolizumab plus chemotherapy plus bevacizumab had the highest exploration OS RMST (18.80 months), followed by placebo plus chemotherapy plus bevacizumab (16.21 months) **(Figure S17**). More importantly, within-trial ΔRMST analyses demonstrated significant gains for COMPASSION-16 OS (+3.05 months, 95% CI 1.19-4.61), GOG-240 OS (+2.80 months, 95% CI 0.46-5.39), KEYNOTE-826 ITT PFS (+2.12 months, 95% CI 1.02-2.96), and BEATcc OS (+2.01 months, 95% CI 0.38-

3.31), whereas KEYNOTE-A18 OS and the KEYNOTE-826 no-bevacizumab OS subgroup were not significant (**Figure S4).**

Trial-stratified reconstructed analyses produced a non-significant pooled HR for pembrolizumab plus chemoradiotherapy in Network 1 (HR 0.930, 95% CI 0.854-1.013; p=0.094; **Table S11**) and a significant pooled effect for cadonilimab plus chemotherapy ± bevacizumab in Network 2 (HR 0.724, 95% CI 0.634-0.827; p<0.001; **Table S12).** Although global cross-regimen Cox analyses showed extensive PH violations (global Schoenfeld $p=3.06\times10^{-42}$; **Table S20; Figure S19**), PH assumptions were generally satisfied in the key within-trial reconstructed comparisons, including COMPASSION-16, BEATcc, KEYNOTE-826, KEYNOTE-A18, and GOG-240 (**Table S15**).

Reconstruction quality varied across trial arms (**Figure 1B-C).** Several series showed inconsistencies between baseline sample size, final numbers at risk, and cumulative events (**Figures S6 and S20**). Excluding flagged series removed the two highest exploratory OS-ranked bevacizumab-based regimens and altered some absolute survival estimates, although most remaining rankings were stable (**Table S19**). Finally, funnel plots showed no statistically significant evidence of small-study effects for OS (Egger p=0.22) or PFS (p=0.0842) **(Figures S21-S22).**

3.3. Efficacy Analysis of Objective Response and Disease Control Across Reconstructed IPD Cohorts

This pooled analysis evaluated tumor response outcomes across clinical trials, analyzing 27 regimens (total N=7,092 patients; 3,581 events) across 103 clinical trial arms for ORR and 13 regimens (total N=673 patients; 431 events) across 17 arms for Disease Control Rate (DCR) (**Table S23**). For ORR, Placebo 200 + Chemotherapy ± Bevacizumab 15 (Pbo 200 + Chemo ± Bev 15) served as the reference treatment, demonstrating a pooled ORR of 51.95% (574/1105), while for DCR, Balstilimab 3 (Balsti 3) served as the reference, demonstrating a pooled DCR of 42.86% (69/161) (**Table S21,23; Figure S24**). Compared with Pbo 200 + Chemo ± Bev 15, seven regimens achieved statistically significant improvements in objective tumor response (**Table S23; Figure S23,25; Figure 3 B, C & D),** led by Toripalimab 240 + Bevacizumab 7.5 + Paclitaxel 175 + Cisplatin 50 Or Carboplatin AUC 5 (Tori 240 + Bev 7.5 + Pac 175 + Cis 50 Or Carbo AUC 5; pooled ORR=83.33%; OR=4.63; 95% CI=1.74-15.98; p=0.005) and Durvalumab 1500 + (SOC) + (CCRT) (Durva 1500 + (SOC) + (CCRT); pooled ORR=82.60%; OR=4.39; 95% CI=3.31-5.90; p<0.001), followed by Placebo 1500 + (SOC) + (CCRT) (pooled ORR=80.26%; OR=3.76; 95% CI=2.86-4.99; p<0.001) and Pembrolizumab 200 + Chemotherapy (Pembro 200 + Chemo; pooled ORR=80.00%; OR=3.70; 95% CI=2.17-6.70; p<0.001) (**Figure 3C).** Significant ORR improvements were also demonstrated by Pembro 200 + CRT (Cis 40 + EBRT + BT) + Pembro 400 (OR=3.29; 95% CI=2.61-4.19; p<0.001), Pbo 200 + CRT (Cis 40 + EBRT + BT) + Pembro 400 (OR=2.71; 95% CI=2.16-3.42; p<0.001), and Pembro 200 + Chemo ± Bev 15 (OR=1.91; 95% CI=1.61-2.28; p<0.001). Conversely, 14 regimens demonstrated significantly lower ORR compared with the reference (**Table S23; Figure S31; Figure 3D**), led by Ipilimumab IV (pooled ORR=2.38%; OR=0.02; 95% CI=0.004-0.07; p<0.001) and Chemotherapy: Pemetrexed 500 + Topotecan 1 Or Irinotecan 100 + Gemcitabine 1000 + Vinorelbine 30 (pooled ORR=6.25%; OR=0.06; 95% CI=0.04-0.10; p<0.001), while five regimens showed non-significant

differences. For DCR, compared with Balsti 3, eight regimens demonstrated significantly superior disease control (**Table S23**), led by Tori 240 + Bev 7.5 + Pac 175 + Cis 50 Or Carbo AUC 5 (pooled DCR=95.83%; OR=30.67; 95% CI=6.23-555.31; p<0.001) and Camrelizumab 200 + Albumin-Binding Paclitaxel 260 + Carboplatin + Maintenance Therapy (pooled DCR=91.43%; OR=14.22; 95% CI=4.84-60.89; p<0.001), whereas Pembro 200 + RT + An Immunomodulatory Fve-Drug Cocktail showed significantly worse DCR (pooled DCR=16.28%; OR=0.26; 95% CI=0.10-0.59; p=0.002), and three regimens yielded non-significant results. Direct pairwise within-trial comparisons confirmed adding immunotherapies significantly improved response; in Monk 2023, Pembro 200 + Chemo ± Bev 15 compared with Pbo 200 + Chemo ± Bev 15 significantly increased complete response (OR=1.97; 95% CI=1.31-2.98; p=0.001) and objective response (OR=2.10; 95% CI=1.48-2.97; p<0.001) while reducing progressive disease (OR=0.43; 95% CI=0.23-0.81; p=0.009), whereas other direct comparisons (Durva 1500 + (SOC) + (CCRT) vs Pbo 1500 + (SOC) + (CCRT) in Mayadev 2020) were non-significant (**Table S22**). In overall rankings (**Table S21; Figure S26; Figure 3B & C**), Tori 240 + Bev 7.5 + Pac 175 + Cis 50 Or Carbo AUC 5 achieved the highest pooled proportion for ORR (83.33%), followed closely by Durva 1500 + (SOC) + (CCRT) (82.60%) and Pbo 1500 + (SOC) + (CCRT) (80.26%), with Ipi IV ranking lowest (2.38%); notably, the joint efficacy landscape demonstrated that regimens combining immunotherapy, anti-angiogenic agents, and chemotherapy occupied the most favorable therapeutic space **(Figure 3A**). Minimal heterogeneity (I^2=0%) was observed across most pooled regimens, with substantial heterogeneity restricted only to TV 0.3 And 2.2 (I^2=48.44%; Q p=0.16) and Balsti 3 (I^2=36.14%; Q p=0.21) **(Figure S28, S32).** Finally, random-effects mixed-effects models validated the primary GLM estimates, showing highly stable odds ratios for key treatments including Durva 1500 + (SOC) + (CCRT) (OR=4.39; 95% CI=3.29-5.86; p<0.001) (Table S24), while Egger's test indicated significant publication bias across the pooled studies (p<0.001) **(Figure S27).**

3.4. Safety Profile and Tolerability of Oncology Regimens

This pooled safety analysis evaluated IPD cohorts comprising 21 oncology regimens (total N=3,777 patients) to compare severe Grade3 adverse events (AEs; 2,230 events) and Any-Grade AEs (3,379 events) across clinical trial arms (**Figure S35-36).** Utilizing Placebo 200 + Chemoradiotherapy (Cisplatin 40 + External Beam Radiotherapy + Brachytherapy) + Pembrolizumab 400 (Pbo 200 + CRT (Cis 40 + EBRT + BT) + Pembro 400) as the reference treatment, which demonstrated a pooled Grade3 AE rate of 68.68% (364/530) (**Figure 4C**) and an Any-Grade AE rate of 99.25% (526/530) (**Figure 4B**), five regimens showed significantly higher severe toxicity odds (OR>1, p<0.05) (**Figure S37,42; Figure 4D).** The highest severe toxicity risk was observed with Cadonilimab 10 + Chemotherapy (Cisplatin 50 OR Carboplatin AUC 4-5 + Paclitaxel 175) + Bevacizumab 15 (Cado 10 + Chemo (Cis 50 OR Carbo AUC 4-5 + Pac 175) + Bev 15; pooled Grade3 AE rate=85.40% [193/226]; OR=2.67; 95% CI=1.79-4.08; p<0.001) (Figure 4 C & D), followed by Placebo 10 + Chemotherapy + Bevacizumab 15 (pooled Grade3 AE rate=80.37%; OR=1.87; 95% CI=1.29-2.76; p=0.001), Placebo 200 + Chemotherapy Bevacizumab 15 (pooled Grade3 AE rate=75.08%; OR=1.37; 95% CI=1.004-1.89; p=0.049), Pembrolizumab 200 + Chemotherapy Bevacizumab 15 (pooled Grade3 AE rate=74.85%; OR=1.36; 95% CI=1.002-1.85; p=0.050), and Pembro 200 + CRT (Cis 40 + EBRT + BT) + Pembro 400 (pooled Grade3 AE rate=74.62%; OR=1.34; 95% CI=1.03-1.76; p=0.032).

Conversely, nine regimens demonstrated significantly lower severe toxicity odds than the reference (OR<1, p<0.05), led by Nivolumab 240 (Nivo 240; pooled Grade3 AE rate=14.46% [12/83]; OR=0.08; 95% CI=0.04-0.14; p<0.001), Balstilimab 3 + Zalifrelimab 1 (pooled Grade3 AE rate=20.00%; OR=0.11; 95% CI=0.07-0.17; p<0.001), and Pembrolizumab 200 + Radiotherapy + Immunomodulatory 5 drug cocktail (pooled Grade3 AE rate=23.26%; OR=0.14; 95% CI=0.06-0.28; p<0.001) **(Figure S38),** while three regimens—Balstilimab 3 (Balsti 3; 0% [0/161]; OR=1.44e-13; p=1.000), Camrelizumab 200 + Apatinib 250 (0% [0/45]; OR=5.05e-13; p=1.000), and Pembrolizumab 200 after CRT (0% [0/24]; OR=9.25e-13; p=1.000)—yielded general findings of zero severe events. For Any-Grade AEs, compared with the reference rate (**Figure 4B**), twelve regimens showed significantly lower toxicity odds (p<0.05), led by Carboplatin AUC 5 + Paclitaxel 175 + Bevacizumab 15 (Any-Grade AE rate=54.67% [82/150]; OR=0.009; 95% CI=0.003-0.023; p<0.001) and Nivo 240 (Any-Grade AE rate=57.83% [48/83]; OR=0.010; 95% CI=0.003-0.027; p<0.001) (**Figure S36).** Head-to-head within-trial safety comparisons were not separately conducted because all trial safety data were pooled directly in this IPD meta-cohort; however, the relative toxicity of active regimens was robustly established by GLM-adjusted odds ratios versus the shared reference (Figure 4D). In overall safety rankings (**Figure 4C; Figure S43),** Cado 10 + Chemo + Bev 15 ranked as the most toxic regimen, whereas Balsti 3 ranked safest (0% severe AE), and the joint safety landscape clearly mapped the low-toxicity profile of immunotherapies compared with heavy platinum-chemotherapy and anti-angiogenic combinations (**Figure S41; Figure 4A**). Across organ systems (**Table S25)**, Other_Unclassified (21.21% of classified rows), Gastrointestinal (14.11%), General_Constitutional (8.64%), and Cardiovascular (7.71%) were the most commonly affected categories (**Figure S40; Figure 4B**), with Anaemia (68 study-rows) and Diarrhoea (67 study-rows) being the most frequent specific adverse events**; Figure S39.** Cross-study heterogeneity for Grade3 adverse events was low to moderate (median I^2=0%, mean I^2=25.39%) (**Figure S45**). However, influence analysis excluding these flagged series did not alter the global GLM safety ranking, demonstrating high robustness of the primary safety landscape. Finally, Egger's test revealed a significant funnel-plot asymmetry across the pooled studies (p<0.001), indicating potential publication bias or study heterogeneity among the reported trials (**Figure S44).**

3. RESULTS

3.1. Study characteristics and outcome reporting

A total of 59 studies were included, enrolling 10,734 patients overall; the median sample size per study was 64 patients (range 3 − 1,060), and the median reported age across studies was 51 years. Most studies were phase II (30/59, 50.8%) or phase III (18/59, 30.5%), with fewer early-phase trials reported as phase I-II / Ib-II (4/59, 6.8%), phase I (3/59, 5.1%), or phase II-III (1/59, 1.7%); 3/59 (5.1%) did not clearly report trial phase. Regarding design, 31/59 studies (52.5%) were single-arm or other non-randomized interventional studies, 23/59 (39.0%) were randomized controlled trials, and 5/59 (8.5%) were observational cohort studies. Most studies enrolled mixed histology populations including *squamous cell carcinoma, adenocarcinoma*, and *adenosquamous carcinoma* (51/59, 86.4%), while squamous-only

cohorts accounted for 5/59 (8.5%) and adenocarcinoma-only cohorts for 1/59 (1.7%). Disease stage at enrollment was predominantly advanced: among the 25/59 studies (42.4%) that reported metastatic status numerically, 4,716 of 6,278 patients (75.1%) had metastatic disease; among the 14/59 studies (23.7%) that reported recurrent/persistent disease explicitly, 2,259 of 3,588 patients (63.0%) had recurrent disease. Lymph node involvement (regional nodal metastasis) was documented as present/allowed in 16/59 studies (27.1%), whereas 43/59 studies (72.9%) documented “NO” nodal metastasis in the eligibility/description column. For outcome distribution, tumor-response endpoints dominated: ORR in 51/59 (86.4%). Time-to-event outcomes were similarly common-PFS 50/59 (84.7%) and OS 48/59 (81.4%)-with safety reported in 37/59 (62.7%) and durability of response in 22/59 (37.3%). Less frequently reported were DCR 10/59 (16.9%), QoL 1/59 (1.7%), and DFS/local-control metrics ≈ 1/59 (≈ 1.7%) (**Suppl. Table S3**).

Quality assessment showed RCTs generally scored ≥ 7 on the PEDro scale, while non-RCTs had NOS scores of 6–8, despite limitations in blinding and follow-up. These trials provide a heterogeneous but valuable evidence base for reconstructing survival outcomes and exploring efficacy patterns of emerging therapies, **Suppl. Table S4-5**.

3.2. Pooled Survival and Restricted Mean Survival Time Analyses of Reconstructed Cohorts Under Quality Control

The survival evidence was organized into three clinically distinct networks (Fig. 1): locally advanced cervical cancer (Network 1), first-line persistent/recurrent/metastatic disease (Network 2) and previously treated recurrent/metastatic disease (Network 3/3b). In Network 1, pembrolizumab plus chemoradiotherapy significantly improved OS (HR 0.73, 95% CI 0.57–0.94; p = 0.004) and PFS (HR 0.72, 95% CI 0.59–0.87) versus placebo plus chemoradiotherapy in KEYNOTE-A18. In contrast, CALLA showed no significant OS or PFS benefit with durvalumab plus chemoradiotherapy in the overall population, although a favorable PFS signal was observed in patients with PD-L1 TAP ≥ 20% (HR 0.62, 95% CI 0.42–0.91) (**Table S8; Figure S2**).

In Network 2, randomized within-trial evidence consistently supported the addition of antiangiogenic and immune-checkpoint therapies to standard chemotherapy. GOG-240 demonstrated improved OS (HR 0.71, 95% CI 0.54–0.95) and PFS (HR 0.67, 95% CI 0.54–0.82) with bevacizumab plus chemotherapy. KEYNOTE-826 showed significant benefits with pembrolizumab plus chemotherapy ± bevacizumab for OS (HR 0.63, 95% CI 0.52–0.77) and PFS (HR 0.61, 95% CI 0.50–0.74), with broadly consistent effects across bevacizumab-use and PD-L1 CPS ≥ 1 subgroups. BEATcc similarly favored atezolizumab plus bevacizumab and chemotherapy for OS (HR 0.68, 95% CI 0.52–0.88) and PFS (HR 0.62, 95% CI 0.49–0.78), while COMPASSION-16 favored cadonilimab plus chemotherapy ± bevacizumab for OS (HR 0.64, 95% CI 0.48–0.86) and PFS (HR 0.62, 95% CI 0.49–0.80) (**Table S9; Figure S3**). Chemotherapy-backbone comparisons were generally non-significant, except for inferior PFS with topotecan-paclitaxel versus cisplatin-paclitaxel in GOG-240 (HR 1.39, 95% CI 1.09–1.77).

The anchored Bucher comparison between pembrolizumab plus chemotherapy plus bevacizumab and atezolizumab plus bevacizumab plus chemotherapy showed no significant OS difference (indirect HR 0.882, 95% CI 0.600-1.297; p = 0.524; Fig. 1D; **Table S13**). In previously treated disease (Network 3b), tisotumab vedotin improved OS (HR 0.70, 95% CI 0.54–0.89) and PFS (HR 0.67, 95% CI 0.54–0.82) versus investigator-choice chemotherapy in innovaTV 301[19], while cemiplimab also improved OS (HR 0.67, 95% CI 0.56–0.80) and PFS (HR 0.75, 95% CI 0.63–0.89) in EMPOWER-Cervical1 (**Table S10; Figure S7**). Single-arm Network 3 studies were therefore treated descriptively only; median OS ranged from 12.8 months with balstilimab plus zalifrelimab to 24.7 months with nivolumab plus ipilimumab (Fig. 1A; **Table S14**).

Exploratory reconstructed survival analyses are summarized in Fig. 2. Kaplan–Meier curves for selected regimens are shown for OS **(**Fig. 2A**)** and PFS **(**Fig. 2B**)**. Forest plots of statistically significant reconstructed HRs relative to the prespecified reference regimen are presented for OS **(**Fig. 2C**)** and PFS **(**Fig. 2D**)**. Marked cross-regimen differences were observed, although these estimates should be interpreted cautiously because they represent cross-trial comparisons across heterogeneous populations rather than randomized head-to-head effects (**Tables S16–S17**). Among the highest reconstructed median OS estimates were atezolizumab–bevacizumab–chemotherapy (39.13 months) and bevacizumab–chemotherapy (38.51 months); however, both were classified as low-reliability estimates and were excluded after data-quality sensitivity analysis **(Table S19**).

RMST analyses provided complementary estimates where proportional hazards were questionable. At τ = 29.6 months, pembrolizumab plus chemotherapy plus bevacizumab had the highest exploration OS RMST (18.80 months), followed by placebo plus chemotherapy plus bevacizumab (16.21 months) **(Figure S17**). More importantly, within-trial ΔRMST analyses demonstrated significant gains for COMPASSION-16 OS (+ 3.05 months, 95% CI 1.19–4.61), GOG-240 OS (+ 2.80 months, 95% CI 0.46–5.39), KEYNOTE-826 ITT PFS (+ 2.12 months, 95% CI 1.02–2.96), and BEATcc OS (+ 2.01 months, 95% CI 0.38–3.31), whereas KEYNOTE-A18 OS and the KEYNOTE-826 no-bevacizumab OS subgroup were not significant (**Figure S4).**

Trial-stratified reconstructed analyses produced a non-significant pooled HR for pembrolizumab plus chemoradiotherapy in Network 1 (HR 0.930, 95% CI 0.854–1.013; p = 0.094; **Table S11**) and a significant pooled effect for cadonilimab plus chemotherapy ± bevacizumab in Network 2 (HR 0.724, 95% CI 0.634–0.827; p < 0.001; **Table S12).** Although global cross-regimen Cox analyses showed extensive PH violations (global Schoenfeld $p = 3.06\times10^{-42}$; **Table S20; Figure S19**), PH assumptions were generally satisfied in the key within-trial reconstructed comparisons, including COMPASSION-16, BEATcc, KEYNOTE-826, KEYNOTE-A18, and GOG-240 (**Table S15**).

Reconstruction quality varied across trial arms (Fig. 1B-C**).** Several series showed inconsistencies between baseline sample size, final numbers at risk, and cumulative events (**Figures S6 and S20**). Excluding flagged series removed the two highest exploratory OS-ranked bevacizumab-based regimens and altered some absolute survival estimates, although most remaining rankings were stable (**Table**

S19). Finally, funnel plots showed no statistically significant evidence of small-study effects for OS (Egger p = 0.22) or PFS (p = 0.0842) **(Figures S21-S22).**

3.3. Efficacy Analysis of Objective Response and Disease Control Across Reconstructed IPD Cohorts

This pooled analysis evaluated tumor response outcomes across clinical trials, analyzing 27 regimens (total N = 7,092 patients; 3,581 events) across 103 clinical trial arms for ORR and 13 regimens (total N = 673 patients; 431 events) across 17 arms for Disease Control Rate (DCR) (**Table S23**). For ORR, Placebo 200 + Chemotherapy ± Bevacizumab 15 (Pbo 200 + Chemo ± Bev 15) served as the reference treatment, demonstrating a pooled ORR of 51.95% (574/1105), while for DCR, Balstilimab 3 (Balsti 3) served as the reference, demonstrating a pooled DCR of 42.86% (69/161) (**Table S21,23; Figure S24**). Compared with Pbo 200 + Chemo ± Bev 15, seven regimens achieved statistically significant improvements in objective tumor response (**Table S23; Figure S23,25;** Fig. 3B, C **& D)**, led by Toripalimab 240 + Bevacizumab 7.5 + Paclitaxel 175 + Cisplatin 50 Or Carboplatin AUC 5 (Tori 240 + Bev 7.5 + Pac 175 + Cis 50 Or Carbo AUC 5; pooled ORR = 83.33%; OR = 4.63; 95% CI = 1.74–15.98; p = 0.005) and Durvalumab 1500 + (SOC) + (CCRT) (Durva 1500 + (SOC) + (CCRT); pooled ORR = 82.60%; OR = 4.39; 95% CI = 3.31–5.90; p < 0.001), followed by Placebo 1500 + (SOC) + (CCRT) (pooled ORR = 80.26%; OR = 3.76; 95% CI = 2.86–4.99; p < 0.001) and Pembrolizumab 200 + Chemotherapy (Pembro 200 + Chemo; pooled ORR = 80.00%; OR = 3.70; 95% CI = 2.17–6.70; p < 0.001) (Fig. 3C**).** Significant ORR improvements were also demonstrated by Pembro 200 + CRT (Cis 40 + EBRT + BT) + Pembro 400 (OR = 3.29; 95% CI = 2.61–4.19; p < 0.001), Pbo 200 + CRT (Cis 40 + EBRT + BT) + Pembro 400 (OR = 2.71; 95% CI = 2.16–3.42; p < 0.001), and Pembro 200 + Chemo ± Bev 15 (OR = 1.91; 95% CI = 1.61–2.28; p < 0.001). Conversely, 14 regimens demonstrated significantly lower ORR compared with the reference (**Table S23; Figure S31;** Fig. 3D), led by Ipilimumab IV (pooled ORR = 2.38%; OR = 0.02; 95% CI = 0.004–0.07; p < 0.001) and Chemotherapy: Pemetrexed 500 + Topotecan 1 Or Irinotecan 100 + Gemcitabine 1000 + Vinorelbine 30 (pooled ORR = 6.25%; OR = 0.06; 95% CI = 0.04–0.10; p < 0.001), while five regimens showed non-significant differences. For DCR, compared with Balsti 3, eight regimens demonstrated significantly superior disease control (**Table S23**), led by Tori 240 + Bev 7.5 + Pac 175 + Cis 50 Or Carbo AUC 5 (pooled DCR = 95.83%; OR = 30.67; 95% CI = 6.23-555.31; p < 0.001) and Camrelizumab 200 + Albumin-Binding Paclitaxel 260 + Carboplatin + Maintenance Therapy (pooled DCR = 91.43%; OR = 14.22; 95% CI = 4.84–60.89; p < 0.001), whereas Pembro 200 + RT + An Immunomodulatory Fve-Drug Cocktail showed significantly worse DCR (pooled DCR = 16.28%; OR = 0.26; 95% CI = 0.10–0.59; p = 0.002), and three regimens yielded non-significant results. Direct pairwise within-trial comparisons confirmed adding immunotherapies significantly improved response; in Monk 2023, Pembro 200 + Chemo ± Bev 15 compared with Pbo 200 + Chemo ± Bev 15 significantly increased complete response (OR = 1.97; 95% CI = 1.31–2.98; p = 0.001) and objective response (OR = 2.10; 95% CI = 1.48–2.97; p < 0.001) while reducing progressive disease (OR = 0.43; 95% CI = 0.23–0.81; p = 0.009), whereas other direct comparisons (Durva 1500 + (SOC) + (CCRT) vs Pbo 1500 + (SOC) + (CCRT) in Mayadev 2020) were non-significant (**Table S22**). In overall rankings (**Table S21; Figure S26;** Fig. 3B **& C**), Tori 240 + Bev 7.5 + Pac 175 + Cis 50 Or Carbo AUC 5 achieved the highest pooled proportion for ORR (83.33%), followed closely by Durva 1500 + (SOC) + (CCRT) (82.60%)

and Pbo 1500 + (SOC) + (CCRT) (80.26%), with Ipi IV ranking lowest (2.38%); notably, the joint efficacy landscape demonstrated that regimens combining immunotherapy, anti-angiogenic agents, and chemotherapy occupied the most favorable therapeutic space **(**Fig. 3A). Minimal heterogeneity (I^2=0%) was observed across most pooled regimens, with substantial heterogeneity restricted only to TV 0.3 And 2.2 (I^2=48.44%; Q p = 0.16) and Balsti 3 (I^2=36.14%; Q p = 0.21) **(Figure S28, S32).** Finally, random-effects mixed-effects models validated the primary GLM estimates, showing highly stable odds ratios for key treatments including Durva 1500 + (SOC) + (CCRT) (OR = 4.39; 95% CI = 3.29–5.86; p < 0.001) (Table S24), while Egger's test indicated significant publication bias across the pooled studies (p < 0.001) **(Figure S27).**

3.4. Safety Profile and Tolerability of Oncology Regimens

This pooled safety analysis evaluated IPD cohorts comprising 21 oncology regimens (total N = 3,777 patients) to compare severe Grade3 adverse events (AEs; 2,230 events) and Any-Grade AEs (3,379 events) across clinical trial arms (**Figure S35-36).** Utilizing Placebo 200 + Chemoradiotherapy (Cisplatin 40 + External Beam Radiotherapy + Brachytherapy) + Pembrolizumab 400 (Pbo 200 + CRT (Cis 40 + EBRT + BT) + Pembro 400) as the reference treatment, which demonstrated a pooled Grade3 AE rate of 68.68% (364/530) (Fig. 4C) and an Any-Grade AE rate of 99.25% (526/530) (Fig. 4B), five regimens showed significantly higher severe toxicity odds (OR > 1, p < 0.05) (**Figure S37,42;** Fig. 4D**).** The highest severe toxicity risk was observed with Cadonilimab 10 + Chemotherapy (Cisplatin 50 OR Carboplatin AUC 4–5 + Paclitaxel 175) + Bevacizumab 15 (Cado 10 + Chemo (Cis 50 OR Carbo AUC 4–5 + Pac 175) + Bev 15; pooled Grade3 AE rate = 85.40% [193/226]; OR = 2.67; 95% CI = 1.79–4.08; p < 0.001) (Fig. 4C & D), followed by Placebo 10 + Chemotherapy + Bevacizumab 15 (pooled Grade3 AE rate = 80.37%; OR = 1.87; 95% CI = 1.29–2.76; p = 0.001), Placebo 200 + Chemotherapy Bevacizumab 15 (pooled Grade3 AE rate = 75.08%; OR = 1.37; 95% CI = 1.004–1.89; p = 0.049), Pembrolizumab 200 + Chemotherapy Bevacizumab 15 (pooled Grade3 AE rate = 74.85%; OR = 1.36; 95% CI = 1.002–1.85; p = 0.050), and Pembro 200 + CRT (Cis 40 + EBRT + BT) + Pembro 400 (pooled Grade3 AE rate = 74.62%; OR = 1.34; 95% CI = 1.03–1.76; p = 0.032). Conversely, nine regimens demonstrated significantly lower severe toxicity odds than the reference (OR < 1, p < 0.05), led by Nivolumab 240 (Nivo 240; pooled Grade3 AE rate = 14.46% [12/83]; OR = 0.08; 95% CI = 0.04–0.14; p < 0.001), Balstilimab 3 + Zalifrelimab 1 (pooled Grade3 AE rate = 20.00%; OR = 0.11; 95% CI = 0.07–0.17; p < 0.001), and Pembrolizumab 200 + Radiotherapy + Immunomodulatory 5 drug cocktail (pooled Grade3 AE rate = 23.26%; OR = 0.14; 95% CI = 0.06–0.28; p < 0.001) **(Figure S38)**, while three regimens—Balstilimab 3 (Balsti 3; 0% [0/161]; OR = 1.44e-13; p = 1.000), Camrelizumab 200 + Apatinib 250 (0% [0/45]; OR = 5.05e-13; p = 1.000), and Pembrolizumab 200 after CRT (0% [0/24]; OR = 9.25e-13; p = 1.000)—yielded general findings of zero severe events. For Any-Grade AEs, compared with the reference rate (Fig. 4B), twelve regimens showed significantly lower toxicity odds (p < 0.05), led by Carboplatin AUC 5 + Paclitaxel 175 + Bevacizumab 15 (Any-Grade AE rate = 54.67% [82/150]; OR = 0.009; 95% CI = 0.003–0.023; p < 0.001) and Nivo 240 (Any-Grade AE rate = 57.83% [48/83]; OR = 0.010; 95% CI = 0.003–0.027; p < 0.001) (**Figure S36).** Head-to-head within-trial safety comparisons were not separately conducted because all trial safety data were pooled directly in this IPD meta-cohort; however,

the relative toxicity of active regimens was robustly established by GLM-adjusted odds ratios versus the shared reference (Fig. 4D). In overall safety rankings (Fig. 4C; **Figure S43)**, Cado 10 + Chemo + Bev 15 ranked as the most toxic regimen, whereas Balsti 3 ranked safest (0% severe AE), and the joint safety landscape clearly mapped the low-toxicity profile of immunotherapies compared with heavy platinum-chemotherapy and anti-angiogenic combinations (**Figure S41;** Fig. 4A). Across organ systems (**Table S25)**, Other_Unclassified (21.21% of classified rows), Gastrointestinal (14.11%), General_Constitutional (8.64%), and Cardiovascular (7.71%) were the most commonly affected categories (**Figure S40;** Fig. 4B), with Anaemia (68 study-rows) and Diarrhoea (67 study-rows) being the most frequent specific adverse events; **Figure S39.** Cross-study heterogeneity for Grade3 adverse events was low to moderate (median I^2=0%, mean I^2=25.39%) (**Figure S45**). However, influence analysis excluding these flagged series did not alter the global GLM safety ranking, demonstrating high robustness of the primary safety landscape. Finally, Egger's test revealed a significant funnel-plot asymmetry across the pooled studies ($p < 0.001$), indicating potential publication bias or study heterogeneity among the reported trials (**Figure S44).**

4. DISCUSSION

This reconstructed-IPD synthesis of 59 studies and 10,734 patients set out to answer a question that the pace of drug approval in cervical cancer has outrun: across locally advanced, first-line recurrent/metastatic, and previously-treated disease, which regimens most convincingly extend survival, and how much of that apparent advantage survives rigorous scrutiny? By deliberately partitioning the evidence into three clinically coherent networks, rather than forcing every regimen onto a single comparator, as our earlier exploratory approach did, we were able to let each network answer the question its own trials were designed to ask, while still permitting a transparent, quality-controlled view of the wider landscape.

The clearest signal emerged in the first-line setting. Bevacizumab (GOG-240) [20], pembrolizumab (KEYNOTE-826) [21, 22], atezolizumab (BEATcc) [22–25], and cadonilimab (COMPASSION-16) [27] each independently reduced the hazard of death or progression by roughly 30–40% when added to a platinum-taxane backbone, with 95% CIs that never crossed unity. The broadly similar effect sizes observed across these trials suggest that treatment intensification through anti-angiogenic or immune-checkpoint strategies may provide clinically meaningful benefit, although cross-trial differences preclude attributing this similarity to a common biological mechanism. Restricted mean survival time reinforced this picture on a scale clinicians can act on directly: at a common 29.6-month horizon, pembrolizumab plus chemotherapy and bevacizumab yielded the greatest expected survival gain of any regimen evaluated, and within-trial ΔRMST confirmed real, non-artefactual separation in COMPASSION-16, GOG-240, KEYNOTE-826, and BEATcc alike.

The locally advanced setting told a more instructive, and more sobering, story. Pembrolizumab added to chemoradiotherapy (KEYNOTE) [28] produced a significant improvement in both OS and PFS, while durvalumab in the same setting (CALLA) [29] did not, except in the PD-L1-high subgroup, where a PFS signal emerged. Placed side by side, these two trials are less a contradiction than a natural experiment:

they suggest that the durable systemic control achieved by checkpoint blockade in metastatic disease does not automatically transfer to the curative-intent, radiation-dominated context of locally advanced cervical cancer, and that PD-L1 expression may matter more here than it does downstream. Any future network of locally advanced trials should be built expecting this kind of heterogeneity, not treating a single positive or negative trial as generalizable to the whole class.

Extending the survival question beyond first line, we found that both tisotumab vedotin and cemiplimab, agents typically discussed only in the language of single-arm response rates, in fact rest on genuinely randomized evidence with hazard ratios (0.70 and 0.67 for OS, respectively) fully comparable in magnitude to the first-line intensification trials. This is a point easily lost when previously treated disease is summarized as "phase II, single arm": a meaningful fraction of that evidence base is randomized and deserves to be analyzed as such rather than folded into a purely descriptive bucket.

Running alongside this network-based analysis, an exploratory cross-trial ranking, built from reconstructed IPD and subjected to the same data-quality and Schoenfeld diagnostics, identified an overlapping set of favorable regimens, but also generated several implausibly extreme hazard ratios that a naive reading would have mistaken for outsized treatment effects. We regard this divergence as a finding in its own right rather than a failure of the exploratory method: it is precisely the scenario that anchored, within-trial and indirect (Bucher) comparisons are designed to guard against, and it argues for reporting such exploratory rankings only alongside, never instead of, their quality-controlled, trial-respecting counterparts.

The response and safety analyses added dimensions that survival data alone cannot capture. Regimens combining anti-angiogenic and immunotherapeutic agents with chemotherapy occupied the most favorable region of the response landscape, while immune-checkpoint monotherapy and dual-checkpoint combinations were consistently the safest, and heavily platinum- or bevacizumab-intensified regimens the most toxic, a trade-off familiar from the toxicity literature of these drug classes individually, now quantified explicitly, and by organ system, within a single comparative framework. The very low heterogeneity observed for most pooled response estimates (I^2 near 0% for all but two regimens) lends further credibility to these rankings; the significant Egger's asymmetry detected for both the response and safety networks most plausibly reflects the predominance of small, early-phase, single-arm studies in that portion of the evidence base rather than classical publication bias, though the two cannot be fully disentangled with the data at hand.

Several limitations warrant mention. The IPD were reconstructed, not observed, and validation revealed a systematic pattern, reconstructed OS diverged materially from published medians for some large trials even when PFS reconstruction matched well and baseline N was verified, suggesting extraction artefacts specific to OS curves rather than random error, which is why published HRs, not reconstructed ones, anchored every conclusion. Over half of the included studies were single-arm, limiting Network 3 to descriptive synthesis. The exploratory cross-trial ranking, though flagged and quality-controlled, still produced implausible outliers and should be read as hypothesis-generating only. AE categorization relied

on automated keyword matching rather than MedDRA, and Egger's test cannot fully separate true heterogeneity from publication bias when per-regimen study counts are small. Finally, several clinically relevant comparisons (CALLA OS by PD-L1 subgroup, JCOG0505 PFS) [30] lacked both published HR and reconstructable data and were left unreported rather than estimated.

Taken together, these three largely independent analytical lenses, within-trial network evidence anchored to published hazard ratios, RMST as a proportional-hazards-free complement, and a transparently flagged exploratory cross-trial synthesis, converge on the same conclusion: intensifying a platinum-taxane backbone with an anti-angiogenic and/or immune-checkpoint agent is the most consistent route to meaningful survival gain across the spectrum of advanced cervical cancer. What differs by setting is not whether intensification helps, but which agent, in which biomarker-defined population, and at what cost in toxicity, questions that only prospective, adequately powered trials can ultimately resolve.

5. CONCLUSION

This reconstructed-IPD synthesis across three clinically coherent survival networks shows that Across the clinically distinct treatment settings examined, randomized trials provide the strongest evidence that selected anti-angiogenic and immune-checkpoint-based combinations improve survival relative to their respective trial-specific controls. Reconstructed IPD and cross-trial rankings provide complementary, hypothesis-generating information but should not be interpreted as direct comparative evidence. Prospective randomized studies remain necessary to determine the optimal regimen for each treatment setting and biomarker-defined population. Conclusions were anchored to published hazard ratios and corroborated by restricted mean survival time, deliberately avoiding hazard ratios between unrelated trials; a parallel exploratory synthesis, reported only alongside this framework, reinforced the same pattern while also illustrating the implausible estimates such comparisons can produce if used uncritically. Response and safety analyses indicate these same strategies achieve the most favourable efficacy-toxicity balance overall. What remains uncertain is not whether intensification helps, but which agent best suits which biomarker-defined population at which line of therapy, questions only prospective, adequately powered randomized trials can definitively resolve.

Declarations

Conflict of 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.

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Data visualizations

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

Supplementary materials

Supplementary data is available upon reasonable requested

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Figures

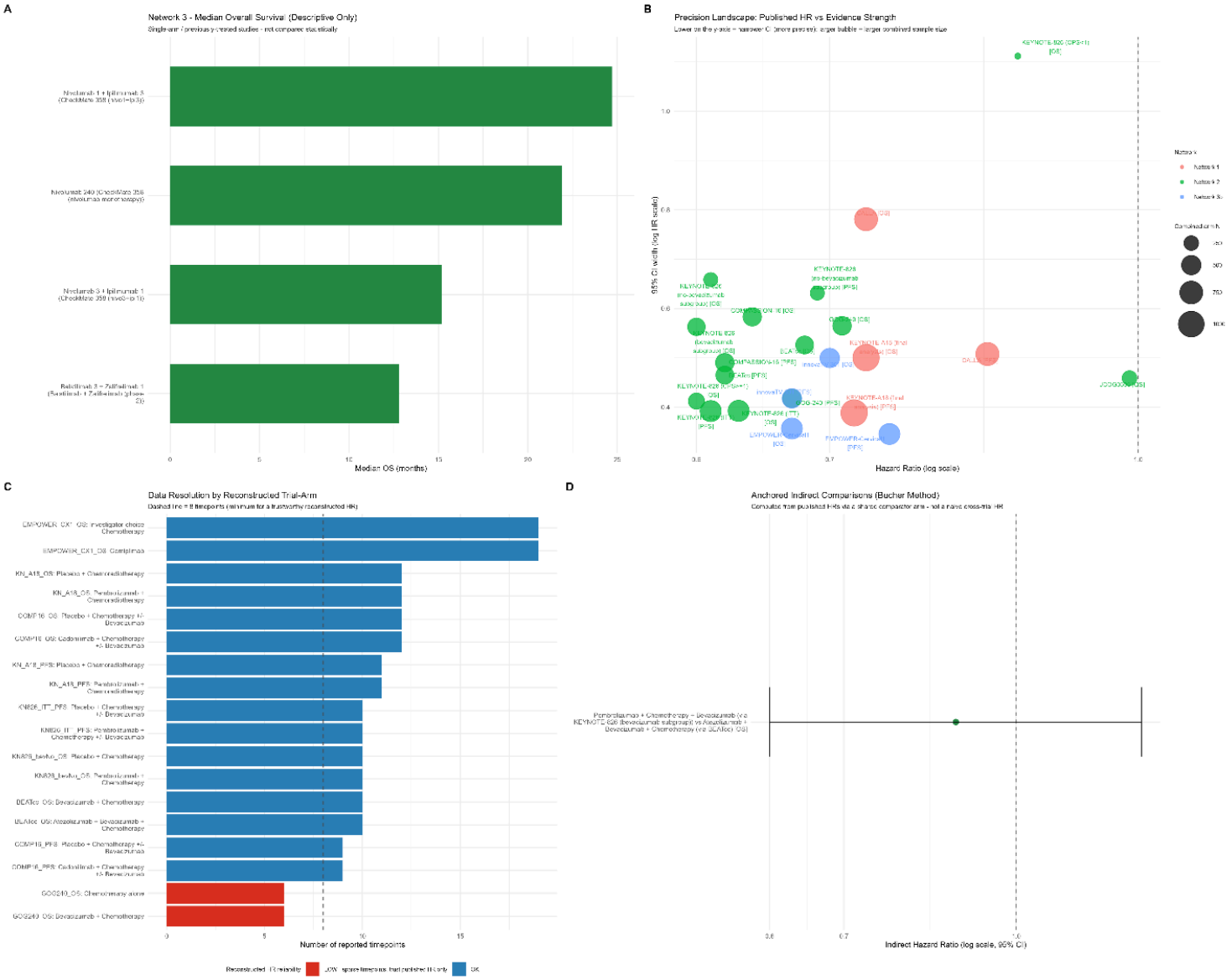


Figure 1

Integrated evidence landscape across cervical cancer treatment networks

Note:

(A) Median overall survival (OS) reported in single-arm studies of previously treated recurrent/metastatic disease (Network 3); these estimates are descriptive and were not statistically compared across regimens. **(B)**Precision landscape of published hazard ratios (HRs) across the three randomized clinical networks; the x-axis represents the published HR, the y-axis represents 95% CI width on the log-HR scale, bubble size reflects the combined sample size, and colors indicate the clinical network. **(C)** Data resolution of reconstructed trial arms according to the number of reported survival time points; the dashed line indicates eight time points, used as a practical threshold for higher-resolution reconstruction. **(D)** Anchored indirect comparison of pembrolizumab + chemotherapy + bevacizumab versus atezolizumab + bevacizumab + chemotherapy using the Bucher method and their respective shared comparator evidence. The dashed vertical line represents HR = 1.0.

Abbreviations:CI, confidence interval; HR, hazard ratio; OS, overall survival.

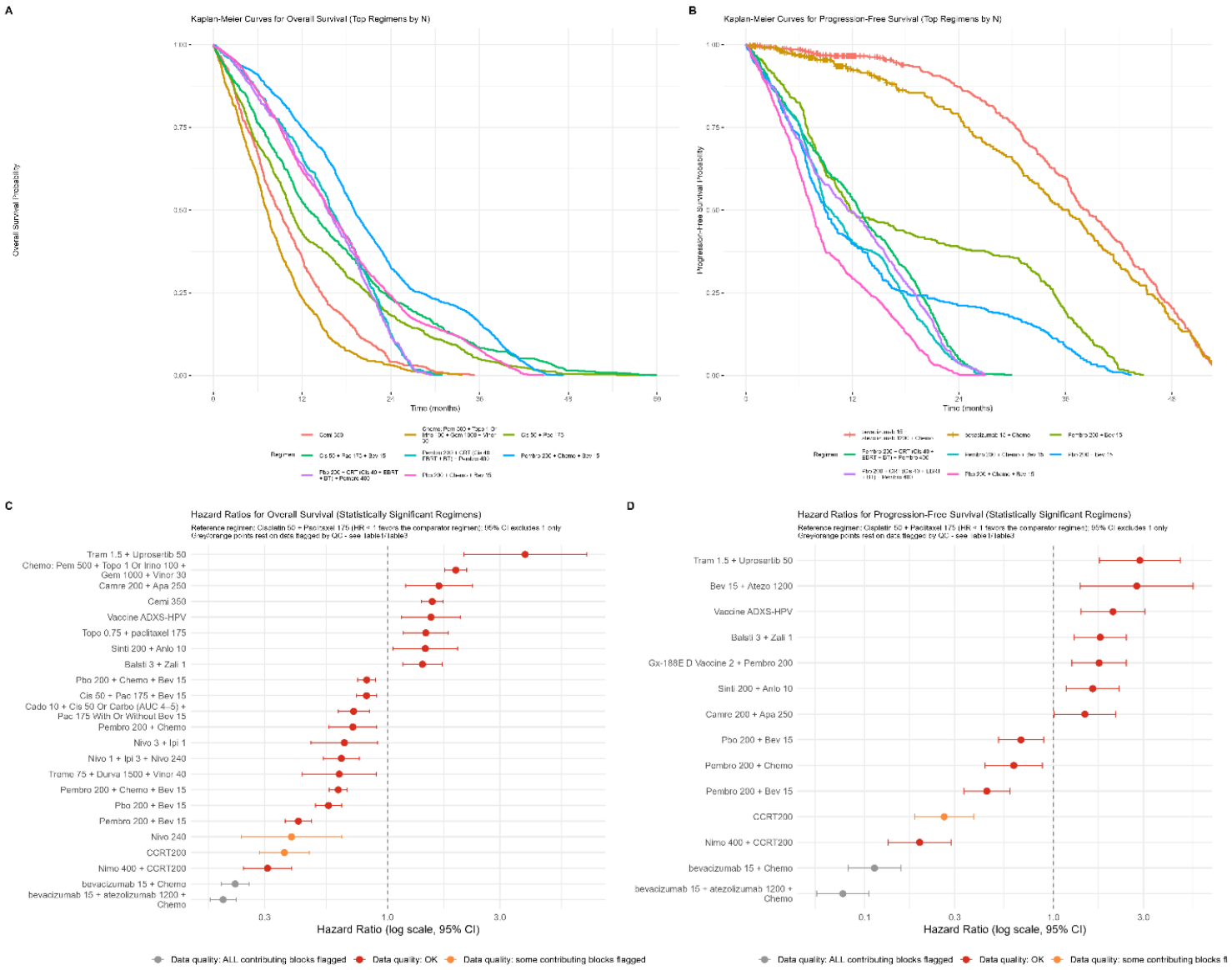


Figure 2

Comparative survival outcomes across treatment regimens in cervical cancer

Note:

(A–B) Kaplan–Meier curves derived from reconstructed pseudo-individual patient data for overall survival (OS) and progression-free survival (PFS), respectively, for selected regimens with the largest available sample sizes. **(C–D)**Forest plots of statistically significant HRs for OS and PFS relative to the prespecified reference regimen, cisplatin 50 mg/m² + paclitaxel 175 mg/m². HR <1 favors the evaluated regimen, whereas HR >1 favors the reference. Point and interval colors indicate reconstruction data-quality status, distinguishing datasets with no identified quality concern, partially flagged data, and regimens for which all contributing reconstruction blocks were flagged. Error bars represent 95% confidence intervals.

Abbreviations:CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; KM, Kaplan–Meier.

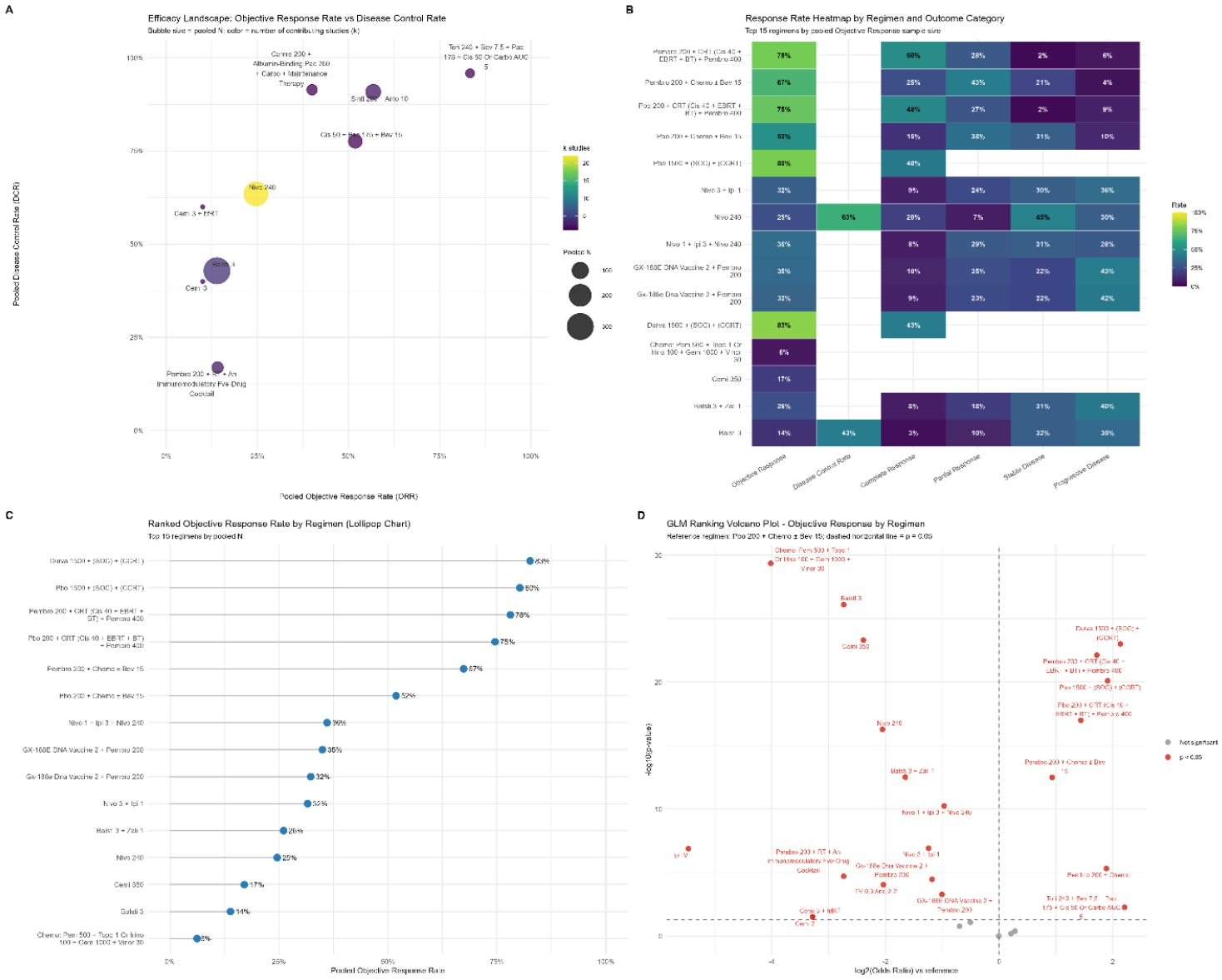


Figure 3

Comparative tumor response landscape across treatment regimens in cervical cancer

Note:

(A) Integrated efficacy landscape comparing pooled objective response rate (ORR) and disease control rate (DCR); bubble size represents pooled sample size and color indicates the number of contributing studies. **(B)** Heatmap of pooled response outcomes for the 15 regimens with the largest objective-response sample sizes, including ORR, DCR, complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). **(C)**Ranking of the same leading regimens according to pooled ORR. **(D)**Volcano plot of generalized linear model (GLM)-derived odds ratios for objective response relative to the reference regimen (placebo + chemotherapy + bevacizumab); the x-axis shows

log2(OR), the y-axis shows −log10(p-value), and the dashed horizontal line denotes p = 0.05. Positive log2(OR) values indicate higher odds of objective response than the reference, whereas negative values indicate lower odds.

Abbreviations:CR, complete response; DCR, disease control rate; GLM, generalized linear model; OR, odds ratio; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.



Figure 4

Comparative safety and toxicity landscape across treatment regimens in cervical cancer

Note:

(A) Integrated safety landscape comparing pooled any-grade and grade ≥3 adverse-event (AE) rates; bubble size represents pooled sample size and color indicates the number of contributing studies. **(B)**

Heatmap of any-grade AE rates by organ-system category for the 15 regimens with the largest pooled samples. Because individual patients could experience multiple AEs within the same category, the category-level rate was conservatively represented by the maximum single-term AE rate within each regimen rather than by summing events. **(C)**Ranking of treatment regimens according to pooled grade ≥3 AE rates. **(D)**Volcano plot of GLM-derived odds ratios for grade ≥3 toxicity relative to the prespecified reference regimen; the x-axis represents log2(OR), the y-axis represents −log10(p-value), and the dashed horizontal line denotes p = 0.05. Positive log2(OR) values indicate greater odds of severe toxicity than the reference, whereas negative values indicate lower odds.

Abbreviations:AE, adverse event; CI, confidence interval; GLM, generalized linear model; OR, odds ratio.