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Efficacy and safety of atezolizumab combined with bevacizumab-based chemotherapy in advanced malignancies: a systematic review and meta-analysis of randomized trials

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Abstract

Background The integration of immune checkpoint inhibitors with anti-angiogenic therapy has transformed the management of advanced malignancies. Atezolizumab (ATZ), a PD-L1 inhibitor, combined with Bevacizumab (BEV) and chemotherapy, may exert synergistic antitumor effects via immune activation and vascular normalization. However, the comparative efficacy and safety of this triplet regimen across cancer types remain uncertain.

Methods A systematic search of PubMed, Embase, Scopus, the Cochrane Library, and major clinical trial registries was conducted from inception to July 31, 2025, to identify randomized controlled trials (RCTs) evaluating ATZ + BEV + chemotherapy versus BEV + chemotherapy alone. Primary endpoints included objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS). Safety outcomes encompassed all-grade and grade III-IV adverse events based on CTCAE. Pooled risk ratios (RRs) and hazard ratios (HRs) were calculated using a random-effects model. Evidence certainty was assessed via GRADE.

Results A total of eight RCTs comprising 3707 participants were analyzed. Incorporation of ATZ into the treatment protocol led to a notable increase in ORR (RR = 1.10; 95% CI: 1.00–1.21) and produced significant gains in both PFS (adjusted HR = 0.73; 95%CI: 0.63–0.84) and OS (adjusted HR = 0.83; 95%CI: 0.76–0.92). In contrast, changes in DCR were modest and did not achieve statistical significance (RR = 1.02; *P* = 0.324). The addition of ATZ did not substantially elevate the frequency of most adverse events relative to BEV plus chemotherapy alone. However, a statistically significant increase was observed in diarrhea (RR = 1.24; 95%CI: 1.06–1.46), predominantly driven by low-grade events, and in grade III-IV nausea (RR = 1.66; 95%CI: 1.03–1.84). Rates of other grade III-IV toxicities were generally comparable

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between treatment groups. Sensitivity analyses and assessments for publication bias supported the stability of the results, and the overall certainty of the evidence was judged to be high.

Conclusion The ATZ + BEV + chemotherapy regimen demonstrated OS benefits in multiple malignancies, although the magnitude of benefit appears to vary across tumor types. Toxicity was generally manageable, although selective increases in low-grade gastrointestinal events and grade III-IV nausea were observed. Immune-related adverse event profiles differed among indications. These findings support the biologic rationale for concurrent immune and angiogenic targeting; however, tumor-specific factors should be considered when integrating this strategy into contemporary oncology practice. Future biomarker-driven studies are warranted to refine patient selection and optimize therapeutic sequencing.

Keywords Immune checkpoint inhibitors, Monoclonal antibody, Antineoplastic agents, Drug therapy, Cancer

Introduction

Cancer continues to represent a major global health challenge, accounting for a significant proportion of illness and death and imposing considerable societal and economic strain. According to the most recent global estimates, nearly 20 million new cancer cases are diagnosed annually, resulting in approximately 10 million deaths each year [1]. Beyond mortality, the profound morbidity associated with cancer and its treatments continues to impose extensive pressure on healthcare systems worldwide [1, 2]. Despite significant therapeutic advances in recent decades, disparities in survival outcomes persist, particularly across low- and middle-income countries [3]. Nevertheless, continuous progress in oncology, including molecularly targeted therapy and immunotherapy, has substantially improved survival and quality of life in many patient populations [4, 5].

Among anti-angiogenic agents, Bevacizumab (BEV), a recombinant humanized monoclonal antibody targeting vascular endothelial growth factor A (VEGFA), has demonstrated robust efficacy across multiple neoplasms such as colorectal cancer, renal cell carcinoma, glioblastoma, and ovarian cancer [6, 7]. By inhibiting tumor angiogenesis, BEV enhances cytotoxic chemotherapy delivery and has become a cornerstone in several first-line oncologic regimens. In parallel, Atezolizumab (ATZ), a programmed death-ligand 1 (PD-L1) inhibitor, has emerged as an important advance in immuno-oncology [8]. As a member of the immune checkpoint inhibitor (ICI) class, ATZ potentiates anti-tumor immune responses by blocking PD-L1 interactions with PD-1 and B7.1 receptors, thus reversing T-cell exhaustion and restoring immune surveillance [9]. Combining ATZ with anti-angiogenic therapy such as BEV provides a biologically rational approach, as VEGF inhibition may normalize tumor vasculature and enhance immune cell infiltration, synergistically improving anti-tumor activity.

Extensive clinical evidence has underscored the enhanced therapeutic performance of ATZ combined with BEV compared with traditional treatment strategies. In patients with unresectable hepatocellular carcinoma, the ATZ–BEV regimen used in the first-line setting has been shown to yield meaningful gains in both PFS and overall survival (OS) when evaluated against sorafenib [10]. Likewise, findings from the IMpower150 study demonstrated that adding ATZ to a backbone of BEV, carboplatin, and paclitaxel produced more favorable outcomes in metastatic non-squamous NSCLC than the standard BEV–carboplatin–paclitaxel protocol, although this intensified approach was associated with higher rates of adverse events, including dermatologic reactions and immune-related toxicities [11].

While these findings underscore the potential therapeutic advantage of ATZ + BEV combinations, concerns regarding safety, toxicity profiles, and heterogeneous responses across cancer types persist. Consequently, a comprehensive quantitative assessment comparing BEV plus chemotherapy regimens with or without ATZ remains necessary. To address this gap, we performed this study to assess the relative efficacy and safety of adding ATZ to BEV + chemotherapy combinations across various malignancies. The results obtained from this analysis aim to offer a unified evidence base that can support clinical decision-making and guide the refinement of therapeutic approaches for individuals with cancer.

Materials and methods

Study design

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure transparency and rigor in reporting (see Table S1). Also, The methodological quality of the review was appraised using the AMSTAR 2 checklist [12, 13]. Furthermore, the study protocol was prospectively registered in the PROSPERO database (Registration ID: CRD420251125783).

Search strategy and data sources

A comprehensive and systematic literature search was performed across major databases and trial registries, including PubMed/MEDLINE, Scopus, Embase,

Cochrane Library, Web of Science, the International Clinical Trials Registry Platform (ICTRP), and ClinicalTrials.gov. The timeline of our search was from inception to July 31, 2025. The search strategy was meticulously customized to the unique syntax and indexing systems of each database, employing a combination of controlled vocabulary and free-text terms to maximize sensitivity and specificity. Relevant keywords and Medical Subject Headings (MeSH) were identified through the MeSH database and refined using terminology extracted from previously published systematic reviews on similar topics. The search was conducted without any language or time restrictions, ensuring comprehensive coverage of both older and recent literature. The primary search terms included "Bevacizumab," "Atezolizumab," and "Neoplasms." In addition, Google Scholar was screened to capture gray literature, and citation tracking was undertaken through reference lists of related systematic reviews to identify further eligible studies (Table S2).

Study selection process

All studies retrieved from database searches, Google Scholar, and relevant review papers were imported into EndNote X9 (Clarivate Analytics, Philadelphia, PA, USA) for organizational management. Duplicate citations were detected and eliminated using the software's automated deduplication tool. After this process, two independent reviewer pairs (S.M. with A.E.S., and K.P. with A.M.S.) evaluated the titles and abstracts based on the predefined eligibility criteria. Any disagreements concerning study selection were addressed through discussion and subsequently resolved with input from the corresponding author (P.E.).

Eligible studies included published randomized controlled trials (RCTs) with full-text availability that compared ATZ plus BEV and chemotherapy (ATZ + BEV + chemotherapy) as the intervention arm versus BEV and chemotherapy alone (BEV + chemotherapy) as the control arm. Exclusion criteria encompassed secondary analyses, book chapters, study protocols, conference abstracts, in vivo or in vitro experimental studies, cross-sectional, case–control, and cohort designs. Records that did not include the specified treatment regimens or that focused on non-cancer populations were excluded. In addition, duplicate publications or overlapping datasets were carefully examined, and in such cases, the most complete and recent report was retained for data extraction.

Data extraction and variables

After the screening process, the full-text versions of all eligible studies were retrieved for detailed data extraction. Data were extracted independently by two investigators (K.P. and A.E.S.) using Microsoft Excel 2019 (Microsoft Corp., Redmond, WA, USA). Each reviewer completed a separate data sheet, and discrepancies were resolved through discussion and adjudication by the corresponding author.

A predefined data extraction framework was employed to ensure consistency across studies. Extracted variables included the first author's name, year of publication, study acronym, data collection period, mean ± standard deviation of age for both groups, sex distribution, cancer type, treatment details, and the composition of the intervention (ATZ + BEV + chemotherapy) and control (BEV + chemotherapy) arms. For efficacy evaluation, the following outcomes were analyzed: Objective Response Rate (ORR), Disease Control Rate (DCR), Progression-Free Survival (PFS), and OS. These endpoints were extracted as reported in the primary studies, all defined according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 [14]. In addition to efficacy outcomes, safety endpoints were systematically collected for the following adverse events: neutropenia, diarrhea, nausea, decreased appetite, vomiting, alopecia, constipation, fatigue, hypertension, asthenia, proteinuria, anemia, and pyrexia. Adverse events were extracted and categorized according to their grading systems as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 [15], and were grouped into Grade 1–2 and Grade III-IV. To address potential sources of heterogeneity related to chemotherapy composition and study design, two categorical subgroup variables were established. The chemotherapy Backbone variable classified regimens as either platinum-based (e.g., cisplatin- or carboplatin-containing combinations) or fluoropyrimidine-based (e.g., 5-fluorouracil or capecitabine-based) [16]. The Comparator Type variable distinguished trials with placebo-controlled versus active comparator arms (without ICIs) [17, 18], enabling a clearer assessment of both the absolute and incremental benefits of ATZ-based combinations across diverse study designs.

Quality appraisal (risk of bias assessment)

The methodological rigor and risk of bias for all included randomized trials were evaluated using the Cochrane Risk of Bias 2.0 (RoB 2.0) framework. This tool examines five principal sources of potential bias: adequacy of the randomization process, adherence to intended interventions, completeness of outcome data, accuracy of outcome measurements, and selective reporting of results. In accordance with Cochrane Handbook guidance [19], each study was subsequently assigned an overall judgment of low risk, high risk, or some concerns. Two reviewers (K.P. and A.A.N.) conducted the quality appraisal independently, and any inconsistencies in their assessments were addressed through discussion with the

corresponding author (P.E.) to ensure consensus across all evaluations.

Statistical analyses

After data extraction was completed, statistical analyses were performed using STATA version 17.0 (StataCorp, College Station, TX, USA). Given the anticipated variability across the included trials, a random-effects framework was adopted, employing restricted maximum likelihood (REML) for parameter estimation. For binary endpoints, risk ratios (RRs) with corresponding 95% confidence intervals (CIs) were generated to compare treatment arms. For time-dependent outcomes, including PFS and OS, available hazard ratios (HRs) along with their 95%CI were utilized. Studies reporting both adjusted and unadjusted effect measures were analyzed separately to account for potential confounding effects. Studies presenting continuous efficacy outcomes as medians with 95% CIs were excluded from the quantitative synthesis, as such summary statistics do not permit valid computation of pooled effect estimates. Only studies providing means and standard deviations, or sufficient data to allow conversion to these metrics, were considered suitable for meta-analysis [20–22]. Between-study heterogeneity was evaluated using Cochran's Q test and quantified with the I^2 statistic, where values of 25%, 50%, and 75% were interpreted as low, moderate, and high heterogeneity, respectively [23, 24]. In addition to the main efficacy and safety analyses, multiple subgroup analyses were performed according to publication year, start date of data collection, cancer type, chemotherapy backbone, comparator type, ATZ dosing schedule, and risk of bias; for safety outcomes, additional stratification was performed based on disease grade to enhance interpretative depth. To evaluate the stability of the meta-analytic findings, sensitivity testing was conducted using a leave-one-out procedure, allowing us to determine the extent to which each individual study affected the pooled effect estimates. Potential publication bias was examined through both graphical and statistical techniques, including Egger's weighted regression analysis and inspection of funnel plot symmetry [25, 26]. A p-value exceeding 0.05 for these assessments was interpreted as evidence against significant publication bias. The certainty of evidence for the primary efficacy endpoints, ORR, DCR, PFS, and OS, was further appraised using the GRADE framework, which synthesizes confidence in the cumulative evidence across five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias [27]. All analytic procedures adhered to the methodological standards set forth in the Cochrane Handbook for Systematic Reviews of Interventions, ensuring compliance with best-practice guidelines for conducting and interpreting meta-analyses of randomized controlled trials [22].

Results

Study selection

As depicted in Fig. 1, the systematic search yielded a total of 6231 records from major electronic databases, including Scopus ($n = 2841$), Embase ($n = 1400$), Web

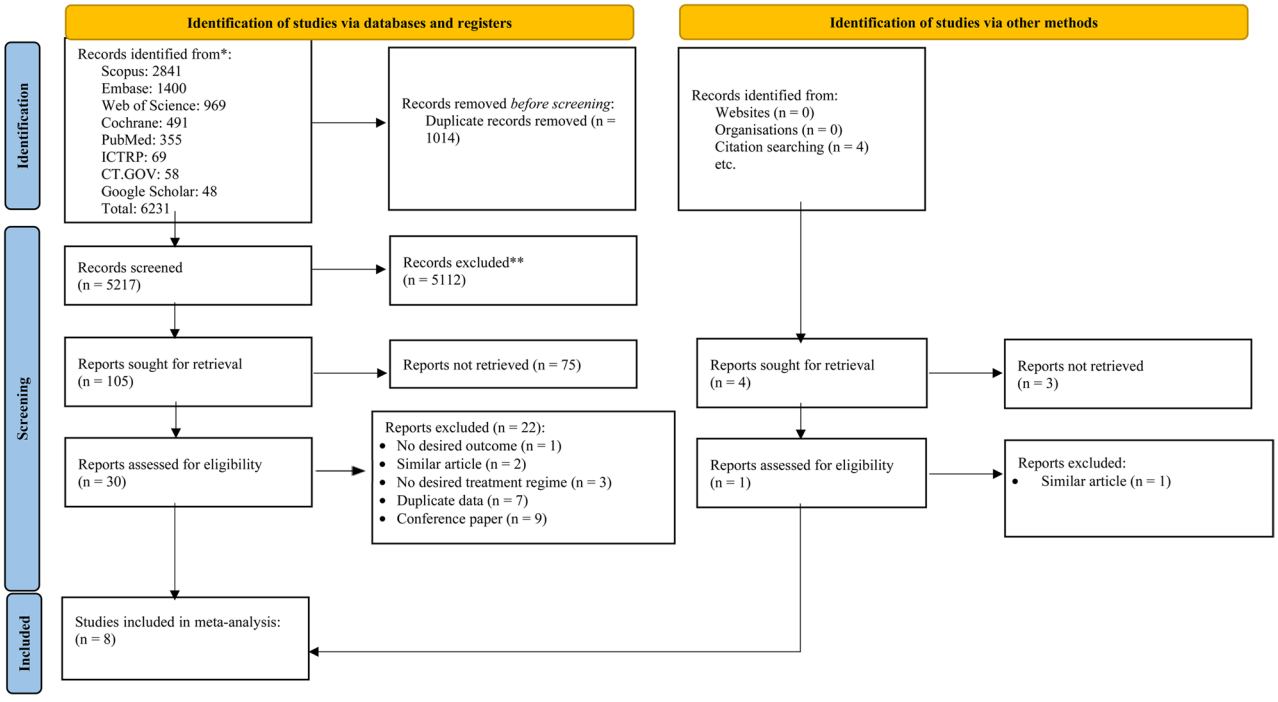


Fig. 1 PRISMA flow diagram for new systematic reviews, including database and other source searches

of Science ($n = 969$), the Cochrane Library ($n = 491$), PubMed ($n = 355$), ICTRP ($n = 69$), ClinicalTrials.gov ($n = 58$), and Google Scholar ($n = 48$). Four additional records were retrieved through manual citation screening. After eliminating 1014 duplicate entries, 5217 unique references proceeded to title and abstract review. Of these, 5112 were excluded due to clear irrelevance, most commonly non-randomized study designs, or non-applicable therapeutic regimens. The remaining 105 articles underwent full-text evaluation. During this phase, 22 studies were excluded for predefined reasons, including incompatible outcomes ($n = 1$), unsuitable therapeutic protocols ($n = 2$), duplicate publications ($n = 5$), overlapping datasets ($n = 7$), and conference abstracts lacking complete data ($n = 9$). A detailed summary of exclusions is presented in Table S3. Ultimately, eight studies satisfied all eligibility criteria and were included in the final quantitative synthesis (Fig. 1).

Study characteristics and quality appraisal (risk of bias assessment)

Overall, eight RCTs [28–35] were included in the quantitative synthesis, encompassing a combined population of 3707 patients across multiple cancer types and geographic regions. The studies were published between 2018 and 2025, with data collection periods ranging from 2015 to 2022. Most trials were international, multicenter investigations conducted across Europe, Asia, and North America, reflecting broad patient representation and treatment diversity. The sample sizes of individual studies varied from 128 to 1301 participants, with mean participant ages ranging from approximately 51 to 70 years across both treatment and control arms. Included studies investigated several tumor types, primarily metastatic colorectal cancer, non-squamous non–small cell lung cancer, epithelial ovarian cancer, advanced mesothelioma, and metastatic or recurrent cervical cancer. Dosing regimens for ATZ ranged from 800 to 1200 mg administered intravenously every two or three weeks, typically in combination with platinum-based doublets such as carboplatin–paclitaxel, FOLFOXIRI, or capecitabine– BEV protocols. Most studies included patients with advanced (stage III-IV) or metastatic disease. Among these, the IMpower150 [30] and IMagyn050 [34] trials contributed the largest patient samples, while smaller phase II studies such as BACCI [32] and AtezoTRIBE [29] provided additional data on refractory or metastatic settings. Notably, all included studies were open-label, randomized, controlled trials evaluating the efficacy and safety of adding ATZ to BEV-based chemotherapy regimens in various malignancies (Table 1).

In the assessment of risk of bias across the included studies, seven studies were rated as having a low risk of bias, while one study was rated as having a moderate risk of bias. Further details on the risk of bias are presented in Fig. 2.

Results of the meta-analysis: efficacy of ATZ + BEV + chemotherapy versus BEV + chemotherapy in cancer patients

The pooled random-effects analysis demonstrated that the intervention group achieved a significantly higher ORR compared with the control group (RR = 1.10; 95%CI: 1.00–1.21; $P = 0.041$). Although the DCR was numerically greater in the intervention arm, this difference did not reach statistical significance (RR = 1.02; 95%CI: 0.98–1.07; $P = 0.324$). Furthermore, the intervention group exhibited a markedly prolonged progression-free survival (PFS) relative to the control arm. Treatment with ATZ plus BEV + chemotherapy reduced the risk of disease progression or death by approximately 27% (adjusted HR = 0.73; 95%CI: 0.63–0.84; $P < 0.001$). Similarly, patients in the intervention arm demonstrated superior OS, with an estimated 24% reduction in the risk of death compared with those receiving BEV + chemotherapy alone (adjusted HR = 0.83; 95%CI: 0.76–0.92; $P < 0.001$) (Table 2).

Results of the subgroup meta-analysis for efficacy of ATZ + BEV + chemotherapy versus BEV + chemotherapy in cancer patients

Subgroup analyses were conducted across seven prespecified variables, including publication year, data collection period, cancer type, chemotherapy backbone, comparator type, ATZ dosing schedule, and risk of bias (Table 3). For ORR, the pooled analysis favored ATZ plus BEV + chemotherapy over BEV + chemotherapy alone, particularly in studies published after 2022 (RR = 1.13, 95%CI: 1.04–1.23) and those using platinum-based regimens (RR = 1.13, 95%CI: 1.02–1.24), with moderate heterogeneity (I^2 = 61–72%). Trials with every-three-week dosing also demonstrated improved ORR (RR = 1.13, 95%CI: 1.03–1.24), whereas fluoropyrimidine-based combinations showed no significant difference (RR = 0.95, 95%CI: 0.78–1.16). For DCR, subgroup effects were modest across all categories, with pooled RRs ranging from 1.02 to 1.05, indicating broadly comparable disease stabilization between regimens. In contrast, PFS consistently favored the ATZ combination across subgroups, especially in studies initiated before 2019 (HR = 0.71, 95%CI: 0.57–0.85) and in platinum-based regimens (HR = 0.73, 95%CI: 0.61–0.86), with substantial heterogeneity (I^2 = 72–83%). Notably, benefit in OS was most apparent in studies published after 2022 (HR = 0.78, 95%CI: 0.65–0.93) and those using active comparators rather than placebo (HR = 0.78, 95%CI: 0.68–0.87). Across cancer types, the OS and PFS advantages were particularly pronounced in non-squamous NSCLC (OS HR = 0.82; PFS HR = 0.70) and pleural mesothelioma (PFS HR = 0.72) (Table 3).

Table 1 Demographic characteristics of the included studies in the systematic review and meta-analysis

ID	Author, (Published year)	Study Acronym	Data collection Start - End	Age (mean ± SD) (Intervention Group)	Age (mean ± SD) (Control Group)	Sex Ratio for Intervention Group (M/F)	Sex Ratio for Control Group (M/F)	Cancer type	Intervention (Atezolizumab Added to Bevacizumab and Chemotherapy) Dose	Control (Bevacizumab and Chemotherapy) Dose	Atezolizumab Cycles	Grade	Total patients included	Number of Intervention Group	Number of Control Group
1	Oaknin et al. (2023) [28]	BEATcc	2018–2021	51.33 ± 12.69	52.33 ± 13.07	0/206	0/204	Metastatic, recurrent, or persistent cervical cancer.	Intravenous platinum (cisplatin 50 mg/m2 or carboplatin area under the curve of 5), intravenous paclitaxel 175 mg/m2, and intravenous bevacizumab 15 mg/kg + intravenous atezolizumab 1200 mg	Intravenous platinum (cisplatin 50 mg/m2 or carboplatin area under the curve of 5), intravenous paclitaxel 175 mg/m2, and intravenous bevacizumab 15 mg/kg	Every 3 weeks	I-IV	410	206	204
2	Antoniott et al. (2022) [29]	AtezoTRIBE	2018–2020	59.67 ± 11.23	60.33 ± 9.08	83/62	42/31	Metastatic colorectal cancer	FOLFOXIRI (intravenous 165 mg/m2 irinotecan, 85 mg/m2 oxaliplatin, 200 mg/m2 leucovorin, and 3200 mg/m2 fluorouracil as a 48 h infusion) plus bevacizumab (5 mg/kg intravenously) + atezolizumab (840 mg intravenously)	FOLFOXIRI (intravenous 165 mg/m2 irinotecan, 85 mg/m2 oxaliplatin, 200 mg/m2 leucovorin, and 3200 mg/m2 fluorouracil as a 48 h infusion) plus bevacizumab (5 mg/kg intravenously)	Every 2 weeks	I-IV	218	145	73
3	Zhou et al. (2025) [30]	IMpower151	2020–2022	55.67 ± 34.43	55.67 ± 32.93	90/62	91/62	Metastatic Non-squamous NSCLC	atezolizumab, bevacizumab, carboplatin and paclitaxel or pemetrexed	placebo plus bevacizumab, carboplatin and pemetrexed or paclitaxel	Every 3 weeks	I-IV	305	152	153
4	Taberner et al. (2022) [31]	MODUL	2015–2021	59 ± 10.83	58.5 ± 10.629	177/120	94/54	BRAF wild-type/unknown status metastatic colorectal cancer	5-FU 1600–2400 mg/m2 46-h IVinfusion and LV 400 mg/m2 2-h IV infusion plus bevacizumab 5 mg/kg 15-30-min IV infusion on day 1 every 2 weeks or capecitabine 1000 mg/m2 twice-daily orally on days 1–14 every 21 days plus bevacizumab 5 mg/kg 15-30-min IV infusion every 2 weeks + atezolizumab 800 mg 60-min IV infusion	5-FU 1600–2400 mg/m2 46-h IV infusion and LV 400 mg/m2 2-h IV bevacizumab 5 mg/kg 15-30-min IV infusion on day 1 every 2 weeks or capecitabine 1000 mg/m2 twice-daily orally on days 1–14 every 21 days plus bevacizumab 5 mg/kg 15-30-min IV infusion every 2 weeks	Every 2 weeks	I-IV	445	297	148
5	Mettu et al. (2022) [32]	BACCI	2017–2018	59.33 ± 9.81	56.17 ± 9.95	47/35	30/16	Refractory metastatic colorectal cancer	oral capecitabine (850 or 1000 mg/m2, per investigator choice and institutional standards) twice daily on days 1 to 14, intravenous bevacizumab (7.5 mg/kg) on day 1, and intravenous atezolizumab 1200 mg	oral capecitabine (850 or 1000 mg/m2, per investigator choice and institutional standards) twice daily on days 1 to 14, intravenous bevacizumab (7.5 mg/kg) on day 1, and placebo on day 1.	Every 3 weeks	I-IV	128	82	46

Table 1 (continued)

ID	Author, (Published year)	Study Acronym	Data collection Start - End	Age (mean ± SD) (Intervention Group)	Age (mean ± SD) (Control Group)	Sex Ratio for Intervention Group (M/F)	Sex Ratio for Control Group (M/F)	Cancer type	Intervention (Atezolizumab Added to Bevacizumab and Chemotherapy) Dose	Control (Bevacizumab and Chemotherapy) Dose	Atezolizumab Cycles	Grade	Total patients included	Number of Intervention Group	Number of Control Group
6	Socinski et al. (2018) [33]	IMpower150	2015–2016	61.5 ± 9.813	61.75 ± 9.982	240/160	239/161	Metastatic Non-squamous NSCLC	Atezolizumab was administered at a dose of 1200 mg, bevacizumab at a dose of 15 mg per kilogram of body weight, paclitaxel at a dose of 200 mg per square meter of body-surface area (175 mg per square meter for Asian patients), and carboplatin at an area under the concentration–time curve of 6 mg per milliliter per minute.	bevacizumab at a dose of 15 mg per kilogram of body weight, paclitaxel at a dose of 200 mg per square meter of body-surface area (175 mg per square meter for Asian patients), and carboplatin at an area under the concentration–time curve of 6 mg per milliliter per minute.	Every 3 weeks	I-IV	800	400	400
7	Moore et al. (2021) [34]	IMagyn050	2017–2019	58.25 ± 8.864	54.75 ± 10.477	0/651	0/650	Stage III or IV epithelial ovarian, fallopian tube, or primary peritoneal cancer	Atezolizumab 1200 mg (day 1, cycles 1–22), with paclitaxel plus carboplatin (day 1, cycles 1–6) plus bevacizumab 15 mg/kg (day 1, cycles 2–22), omitting perioperative bevacizumab in neoadjuvant patients	placebo (day 1, cycles 1–22), with paclitaxel plus carboplatin (day 1, cycles 1–6) plus bevacizumab 15 mg/kg (day 1, cycles 2–22), omitting perioperative bevacizumab in neoadjuvant patients	Every 3 weeks	I-IV	1301	651	650
8	Felip et al. (2025) [35]	BEAT-meso	2019–2022	69.9 ± 7.94	68.8 ± 7.94	160/40	156/44	Advanced diffuse pleural mesothelioma	standard chemotherapy [4–6 cycles of carboplatin area under the curve with pemetrexed 500 mg/m2, on day 1 of 3-week cycle (q3w)], and bevacizumab (15 mg/kg intravenously, on day 1 q3w until progression, toxicity, or patient refusal) + atezolizumab 1200 mg intravenously, on day 1 q3w until progression, toxicity, or patient refusal	standard chemotherapy [4–6 cycles of carboplatin area under the curve with pemetrexed 500 mg/m2, on day 1 of 3-week cycle (q3w)], and bevacizumab (15 mg/kg intravenously, on day 1 q3w until progression, toxicity, or patient refusal)	Every 3 weeks	I-IV	400	200	200

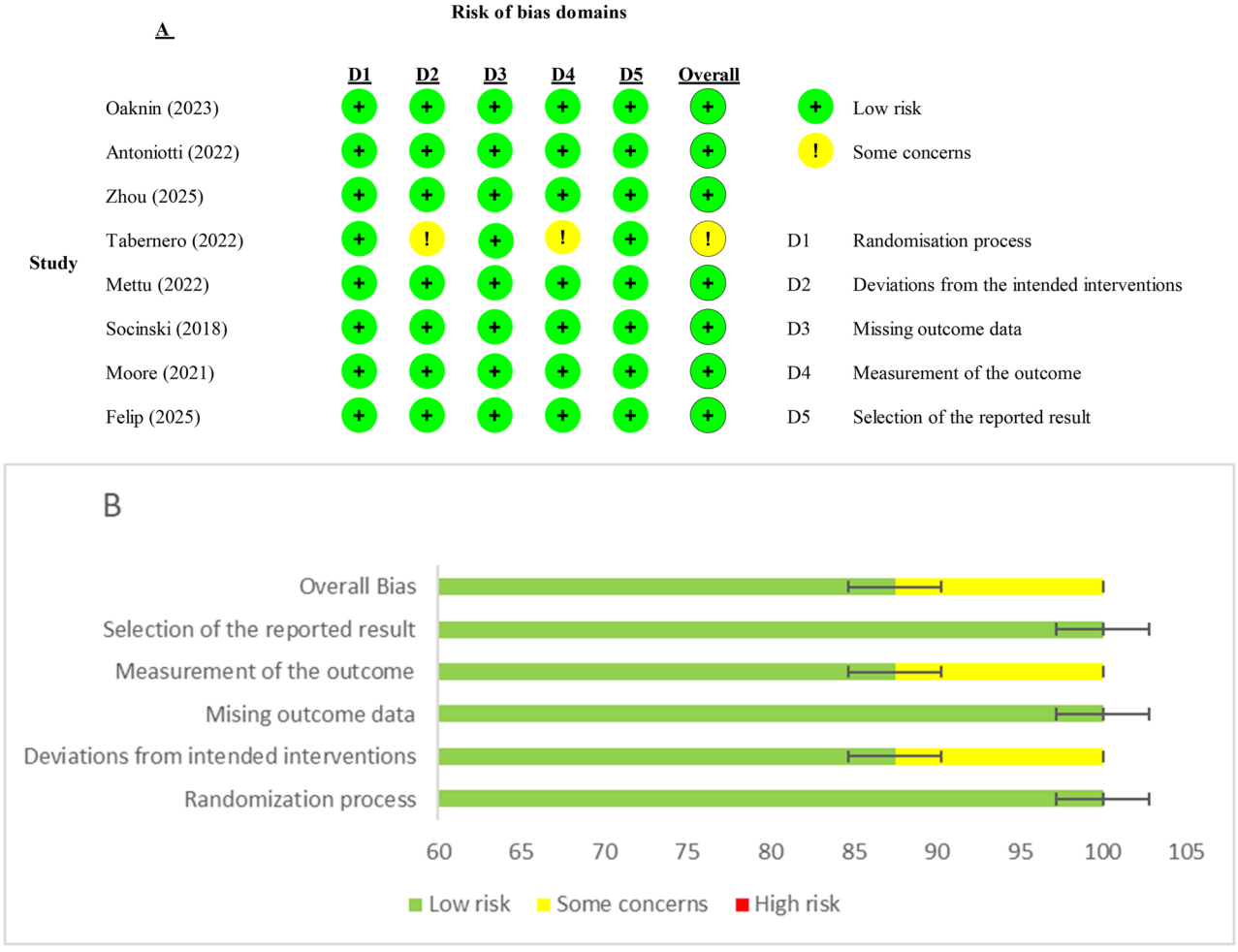


Fig. 2 Risk of bias Assessment; Risk of bias assessment of included randomized control trials (RCTs). (**A**) Risk of bias summary of all included RCTs; (**B**) risk of bias

Table 2 Efficacy, survival outcomes and heterogeneity measures for atezolizumab plus bevacizumab and chemotherapy vs. bevacizumab and chemotherapy alone in cancer patients

Variable	Number of datasets	Effect estimate	95% CI	*P*-value	Heterogeneity		
					Q	I^2	*P*-value
ORR (number)	8	**RR = 1.10**	**1.00–1.21**	**0.041**	15.42	59.81%	**0.031**
DCR (number)	4	RR = 1.02	0.98–1.07	0.324	4.03	0.0%	0.258
PFS (month) unadjusted	2	$HR_{unadjusted}$ = 0.88	0.72–1.10	0.265	1.18	15.0%	0.278
PFS (month) adjusted	6	**$HR_{adjusted}$ = 0.73**	**0.63–0.84**	**< 0.001**	16.78	70.2%	**0.005**
OS (month) unadjusted	2	$HR_{unadjusted}$ = 0.86	0.70–1.06	0.157	0.35	0.0%	0.553
OS (month) adjusted	5	**$HR_{adjusted}$ = 0.83**	**0.76–0.92**	**< 0.001**	4.31	0.0%	0.366

ORR Objective Response rate, *DCR* Disease Control Rate, *PFS* Progression Free Survival, *OS* Overall Survival, *RR* Risk Ratio, *CI* Confidence Interval, *HR* Hazard Ratio, Note: Bold values indicate statistical significance ($P < 0.05$)

Results of the meta-analysis for safety of ATZ + BEV + chemotherapy versus BEV + chemotherapy in cancer patients

The pooled safety analysis, based on data from 4 to 7 RCTs per adverse event, revealed no statistically significant increase in most treatment-related toxicities with the addition of ATZ to BEV + chemotherapy (Table 4). The overall incidence of neutropenia (RR = 1.03; 95%CI: 0.95–1.12; $P = 0.901$), nausea (RR = 1.04; 95%CI: 0.94–1.14; $P = 0.348$), and fatigue (RR = 1.03; 95%CI: 0.94–1.13; $P = 0.894$) was comparable between groups, with negligible heterogeneity (I^2 = 0%). Similarly, events such as anemia, asthenia, hypertension, and alopecia showed no significant between-group difference (RRs ranging from 0.97 to 1.06). A statistically significant increase was observed only for diarrhea in the intervention group (RR = 1.24; 95%CI:

Table 3 Subgroup meta-analysis results of the efficacy of atezolizumab plus bevacizumab and chemotherapy with bevacizumab and chemotherapy alone in cancer patients based on different categorical variables

Variables*	Number of datasets	Effect estimates	95% CI	Test of group difference		Heterogeneity		
				chi2	*P*-value	Q	I^2	*P*-value
ORR[#]								
Published year[***]								
≤ 2022	5	1.10	0.93–1.31	0.05	0.824	12.38	72.01	**0.015**
> 2022	3	**1.13**	**1.04–1.23**			2.11	0.00	0.348
Start date of data collection[***]								
< 2019	6	1.12	0.99–1.27	0.34	0.559	14.29	71.10	**0.014**
≥ 2019	2	1.06	0.91–1.22			0.97	0.00	0.326
Cancer type								
Gynecologic cancers **	2	1.09	0.99–1.21	1.87	**0.600**	3.16	68.35	0.075
Colorectal cancer	3	0.95	0.78–1.16			1.46	0.00	0.481
NSCLC	2	1.15	0.85–1.55			5.23	80.86	**0.022**
Pleural mesothelioma	1	1.12	0.93–1.36			0.00	-	-
Chemotherapy Backbone								
Platinum-based	5	**1.13**	**1.02–1.24**	2.17	0.140	12.19	66.29	**0.016**
Fluoropyrimidine-based	3	0.95	0.78–1.16			1.46	0.00	0.481
Comparator Type								
Placebo-controlled	3	1.04	0.99–1.10	1.71	0.191	1.09	0.00	0.580
Active comparator	5	**1.14**	**1.01–1.30**			8.26	58.00	0.082
Atezolizumab Cycles								
Every 2 weeks	2	0.94	0.77–1.15	2.54	0.111	0.59	0.00	0.442
Every 3 weeks	6	**1.13**	**1.03–1.24**			12.75	61.11	**0.026**
Risk of Bias								
Low	7	**1.10**	**1.00–1.21**	0.01	0.911	15.40	64.86	**0.017**
Some concern	1	1.14	0.68–1.91			0.00	-	-
DCR[#]								
Published year								
≤ 2022	2	1.03	0.97–1.09	0.08	0.782	0.03	0.00	0.872
> 2022	2	1.05	0.89–1.25			3.94	74.62	**0.047**
Start date of data collection								
< 2019	2	1.03	0.97–1.09	0.08	0.782	0.03	0.00	0.872
≥ 2019	2	1.05	0.89–1.25			3.94	74.62	**0.047**
Cancer type								
Gynecologic cancers **	0	-	-	3.05	0.218	-	-	-
Colorectal cancer	1	1.02	0.91–1.14			0.00	-	-
NSCLC	2	1.01	0.96–1.06			0.98	0.05	0.321
Pleural mesothelioma	1	**1.17**	**1.00–1.36**			0.00	-	-
Chemotherapy Backbone								
Platinum-based	3	1.03	0.96–1.11	0.03	0.868	0.00	-	-
Fluoropyrimidine-based	1	1.02	0.91–1.14			4.03	45.66	0.134
Comparator Type								
Placebo-controlled	1	0.98	0.90–1.06	1.73	0.188	-	-	-
Active comparator	3	1.04	0.99–1.10			2.30	0.00	0.317
Atezolizumab Cycles								
Every 2 weeks	1	1.02	0.91–1.14	0.03	0.868	0.00	-	-
Every 3 weeks	3	1.03	0.96–1.11			4.03	45.66	0.134
Risk of Bias								
Low	3	1.03	0.96–1.11	0.03	0.868	0.00	-	-
Some concern	1	1.02	0.91–1.14			4.03	45.66	0.134

Table 3 (continued)

Variables*	Number of datasets	Effect estimates	95% CI	Test of group difference		Heterogeneity		
				chi2	*P*-value	Q	I^2	*P*-value
PFS#								
Published year								
≤ 2022	3	**0.74**	**(0.56–0.92)**	0.10	0.752	12.50	83.31	**0.002**
> 2022	3	**0.71**	**(0.60–0.82)**			2.79	23.91	0.247
Start date of data collection								
< 2019	4	**0.71**	**(0.57–0.85)**	0.26	0.613	13.73	78.19	**0.003**
≥ 2019	2	**0.76**	**(0.63–0.88)**			0.78	0.00	0.377
Cancer type								
Gynecologic cancers **	2	0.77	(0.48–1.07)	0.19	0.979	8.51	88.25	**0.004**
Colorectal cancer	1	**0.70**	**(0.55–0.85)**			-	-	-
NSCLC	2	**0.70**	**(0.48–0.93)**			3.48	71.26	0.062
Pleural mesothelioma	1	**0.72**	**(0.57–0.87)**			-	-	-
Chemotherapy Backbone								
Platinum-based	4	**0.73**	**(0.61–0.86)**	0.11	0.741	15.32	72.78	**0.004**
Fluoropyrimidine-based	1	**0.70**	**(0.55–0.85)**			-	-	-
Comparator Type								
Placebo-controlled	2	0.90	(0.77–1.02)	12.93	**< 0.001**	0.36	0.00	0.548
Active comparator	4	**0.65**	**(0.59–0.72)**			2.04	0.00	0.564
Atezolizumab Cycles								
Every 2 weeks	1	**0.70**	**(0.55–0.85)**	0.11	0.741	-	-	-
Every 3 weeks	5	**0.73**	**(0.61–0.86)**			15.32	72.78	**0.004**
OS#								
Published year								
≤ 2022	2	**0.85**	**(0.74–0.97)**	0.51	0.477	1.31	23.62	0.253
> 2022	3	**0.78**	**(0.65–0.93)**			2.46	21.76	0.292
Start date of data collection								
< 2019	3	**0.81**	**(0.68–0.93)**	0.33	0.568	3.96	49.35	0.138
≥ 2019	2	**0.87**	**(0.70–1.03)**			-0.33	0.00	0.629
Cancer type								
Gynecologic cancers **	2	0.81	(0.57–1.04)	0.05	0.974	3.92	74.50	**0.048**
Colorectal cancer	0	-	-			-	-	-
NSCLC	2	**0.82**	**(0.70–0.95)**			0.58	0.00	0.445
Pleural mesothelioma	1	0.84	(0.64–1.04)			-	-	-
Comparator Type								
Placebo-controlled	2	0.92	(0.78–1.06)	2.93	0.087	0.00	0.00	0.954
Active comparator	3	**0.78**	**(0.68–0.87)**			1.61	0.00	0.448

ORR Objective Response rate, *DCR* Disease Control Rate, *PFS* Progression Free Survival, *OS* Overall Survival, *CI* Confidence Interval

* Some subgroups were excluded from analysis due to insufficient study numbers or lack of comparable data between treatment arms, specifically, study quality subgroups for PFS and OS, as well as Chemotherapy Backbone and Comparator Type subgroups for OS

** The term gynecologic cancers refer to cervical, ovarian/fallopian tube, and peritoneal malignancies

*** The categorization of these variables was determined not only by data availability within each group but also by temporal considerations related to the onset and conclusion of the COVID-19 pandemic period

The analytical unit for ORR and DCR was the number of patients, and effect sizes were expressed as risk ratios (RRs); whereas for PFS and OS, outcomes were measured in months and effect estimates were reported as adjusted hazard ratios (HRs). Note: Bold values indicate statistical significance ($P < 0.05$)

1.09–1.48; $P = 0.0096$), with moderate heterogeneity (I^2 = 49%). Although decreased appetite (RR = 1.17; 95%CI: 0.96–1.42) and proteinuria (RR = 1.13; 95%CI: 0.97–1.32) tended to be more frequent with ATZ-containing regimens, these differences were not statistically significant. The pooled risk for pyrexia showed the greatest variability (RR = 1.50; 95%CI: 0.93–2.40; I^2 = 74.9%), suggesting potential heterogeneity across trials (Table 4).

Results of the subgroup meta-analysis for safety of ATZ added to BEV and chemotherapy versus BEV and chemotherapy alone in cancer patients

Subgroup analyses across cancer type, chemotherapy backbone, comparator type, ATZ dosing cycle, and adverse event grade revealed broadly consistent safety profiles between treatment arms, with few statistically significant variations (Table S4). The incidence

Table 4 Meta-analysis results and heterogeneity of adverse events (safety) of atezolizumab added to bevacizumab and chemotherapy versus bevacizumab and chemotherapy alone in cancer patients

Adverse events	Number of studies	RR [a]	95% CI [b]	Heterogeneity		
				Q	I^2	*P.value*
Neutropenia	6	1.03	(0.95–1.12)	1.60	0.00	0.901
Diarrhea	6	**1.27**	**(1.09–1.48)**	9.35	49.1	0.096
Nausea	7	1.04	(0.94–1.14)	6.71	23.87	0.348
Decreased Appetite	4	1.17	(0.96–1.42)	4.87	41.02	0.182
Vomiting	6	1.12	(0.91–1.39)	10.26	38.71	0.068
Alopecia	4	0.99	(0.90–1.10)	5.96	24.82	0.114
Constipation	6	1.06	(0.92–1.21)	8.44	41.11	0.133
Fatigue	6	1.03	(0.94–1.13)	1.66	0.00	0.894
Hypertension	7	0.97	(0.85–1.11)	8.99	31.91	0.174
Asthenia	4	0.99	(0.86–1.14)	1.38	0.00	0.710
Proteinuria	6	1.13	(0.97–1.32)	4.96	16.01	0.421
Anemia	6	1.02	(0.95–1.10)	3.67	0.00	0.598
Pyrexia	4	1.50	(0.93–2.40)	10.77	74.92	**0.013**

RR Risk Ratio, *CI* Confidence Interval

It should be noted that the adverse events presented in this table refer to the occurrence of any reported toxicity, as described in the studies by Oaknin et al. [28], Antoniotti et al. [29], Felip et al. [30], Zhou et al. [31], and Mettu et al. [32]. In the trial by Tabernero et al. [33], adverse events were reported according to treatment-emergent adverse events (TEAEs), whereas in the study by Socinski et al. [34] they were classified as treatment-related adverse events (TRAEs). In contrast, Moore et al. [35] only referred to the occurrence of "clinical adverse events" without further specification. Note: Bold values indicate statistical significance ($P < 0.05$)

of diarrhea remained significantly higher in the ATZ combination group across several strata, particularly in studies using platinum-based chemotherapy (RR = 1.29; 95%CI: 1.08–1.56) and those employing an active comparator (RR = 1.34; 95%CI: 1.12–1.61). A notable increase in pyrexia was also observed among gynecologic cancer populations (RR = 2.11; 95%CI: 1.65–2.70) and in platinum-based regimens (RR = 2.11; 95%CI: 1.65–2.70). Conversely, hypertension appeared slightly lower in placebo-controlled trials (RR = 0.85; 95%CI: 0.74–0.97), while no significant differences were detected for neutropenia, fatigue, nausea, anemia, or proteinuria across any subgroup. For most grade III-IV events, the relative risk estimates approached unity, suggesting that the addition of ATZ did not exacerbate severe toxicity (Table S4).

Sensitivity analysis

Figures S1–S19 summarize the sensitivity analyses assessing the robustness of pooled efficacy and safety outcomes. For ORR, removing individual studies caused only minor variations, while the overall direction and magnitude of effect remained stable. Similarly, adjusted PFS and OS estimates were unaffected by the exclusion of any single study, confirming the reliability of the survival results. For safety outcomes, the direction of association was generally consistent across analyses, particularly for diarrhea, which remained unchanged regardless of study removal. However, some adverse events, including nausea, alopecia, hypertension, and asthenia, showed shifts in effect direction when certain studies were excluded, indicating that these specific results should be interpreted with caution (Figures S1–S19).

Publication bias

Funnel plots were constructed for each efficacy outcome to evaluate potential publication bias between the two therapeutic regimens. Visual inspection of the plots revealed symmetrical distributions, suggesting an absence of small-study effects. Consistently, the results of Egger's regression test indicated no significant evidence of publication bias across all efficacy endpoints, including ORR (bias = 0.16; SE = 0.78; $P = 0.835$), DCR (bias = 2.33; SE = 1.90; $P = 0.220$), adjusted PFS (bias = − 0.91; SE = 4.13; $P = 0.826$), and OS (bias = − 0.67; SE = 2.02; $P = 0.740$) (Figures S20–S25).

Certainty of evidence

According to the GRADE assessment, the overall certainty of evidence for all primary efficacy outcomes, including ORR, DCR, PFS, and OS, was rated as high. All included trials were randomized controlled studies with minimal risk of bias and no evidence of indirectness or imprecision. Moderate heterogeneity was observed for ORR (I^2 = 59.8%) and substantial heterogeneity for PFS (I^2 = 70.2%), whereas DCR and OS showed negligible heterogeneity (I^2 = 0%). No evidence of publication bias was detected (Table 5).

Discussion

This systematic review and meta-analysis of eight randomized trials including 3707 patients provides a comprehensive evaluation of adding ATZ to a BEV-based chemotherapy regimen across multiple tumor types. The pooled evidence indicates that incorporating ATZ significantly improves key clinical outcomes, particularly

Table 5 Certainty of evidence of efficacy outcomes to GRADE approach

Outcomes	Risk of bias*	Inconsistency**	Indirectness***	Imprecision****	Publication bias*****	Intervention vs. control 95%CI	Participants		Certainty of evidence #
							Intervention	Control	
ORR	No	Serios (-1)	No	No	No	RR = 1.10 (1.00–1.21)	2133	1874	⊕⊕⊕⊕ (High)
DCR	No	No	No	No	No	RR = 1.02 (0.98–1.07)	1049	901	⊕⊕⊕⊕ (High)
PFS	No	Serios (-1)	No	No	No	$HR_{adjusted}$ = 0.73 (0.63–0.84)	1754	1680	⊕⊕⊕⊕ (High)
OS	No	No	No	No	No	$HR_{adjusted}$ = 0.83 (0.76–0.92)	1609	1607	⊕⊕⊕⊕ (High)

ORR Objective Response rate, *DCR* Disease Control Rate, *PFS* Progression Free Survival, *OS* Overall Survival, *RR* Risk Ratio, *CI* Confidence Interval, *HR* Hazard Ratio

* As all included studies were randomized controlled trials (RCTs), none were judged to have a risk of bias in reporting their respective outcomes

** The evaluated heterogeneity was negligible for DCR and OS (I^2 = 0%), whereas moderate and substantial heterogeneity were observed for ORR (I^2 = 59.8%) and PFS (I^2 = 70.2%), respectively

*** According to the prespecified PICO framework; P: patients with cancer, I: intervention group (ATZ + BEV + chemotherapy), C: control group (BEV + chemotherapy), and O: efficacy outcomes, all included studies fully met these criteria, and thus no indirectness was identified

**** To assess imprecision, the number of studies and the width of the 95% confidence intervals (CIs) were examined for each outcome. Specifically, eight studies contributed data to ORR, four to DCR, six to PFS, and five to OS. None of these outcomes exhibited wide 95% CIs, indicating acceptable precision across analyses

***** Evaluation of publication bias, based on funnel plot inspection and Begg's test (reported in the Publication Bias section and Supplementary Materials), revealed no evidence of asymmetry or publication bias across outcomes: ORR (bias = 0.16; SE = 0.78; P = 0.835), DCR (bias = 2.33; SE = 1.90; P = 0.220), adjusted PFS (bias = −0.91; SE = 4.13; P = 0.826), and OS (bias = −0.67; SE = 2.02; P = 0.740)

Although no extreme effect sizes (RR > 2 or RR < 0.5) were observed, an overall upgrade by one level was warranted due to the presence of a plausible dose–response relationship across outcomes and potential residual confounding arising from unadjusted ORR and DCR estimates

ORR, PFS, and OS. The regimen was associated with a 27% reduction in the risk of progression or death and a 24% reduction in overall mortality, underscoring a clinically meaningful survival effect. However, the magnitude of benefit varied across tumor types, reflecting underlying biological and clinical heterogeneity. Although the improvement in DCR was not statistically significant, the consistent trend favoring ATZ suggests a genuine antitumor effect. This discrepancy likely reflects inherent differences between endpoints: DCR includes stable disease and is less sensitive to treatment-induced cytoreduction, whereas ORR more directly captures pronounced radiologic responses driven by synergistic immune activation and vascular normalization resulting from PD-L1 inhibition combined with VEGF blockade [36, 37]. From a clinical standpoint, these findings support the biological rationale for integrating immunotherapy with antiangiogenic therapy and chemotherapy in selected advanced cancer settings [38]. Overall toxicity profiles were broadly comparable between treatment arms. Nevertheless, selective increases in gastrointestinal events were observed, including predominantly low-grade diarrhea and a higher incidence of grade III-IV nausea, while most other severe toxicities remained similar across groups. These findings suggest that treatment intensification with ATZ modestly increases certain adverse events but does not substantially exacerbate overall high-grade toxicity. Although the direction of effect was generally consistent across subgroup analyses, several subgroup comparisons were based on a limited number of trials and should therefore be interpreted as exploratory and hypothesis-generating rather than definitive. Accordingly, these findings warrant confirmation in adequately powered tumor-specific studies.

The survival and response benefits demonstrated in our meta-analysis are consistent with results from pivotal randomized trials assessing the incorporation of ATZ into BEV + chemotherapy backbones across multiple tumor types. Evidence from pivotal randomized trials further reinforces the clinical advantages of integrating ATZ into BEV-based regimens. In the IMpower150 study, the addition of ATZ to BEV, carboplatin, and paclitaxel resulted in superior outcomes for patients with non-squamous NSCLC, extending median PFS to 8.3 months compared with 6.8 months in the control arm and prolonging median OS from 14.7 to 19.2 months [11]. A comparable pattern was observed in metastatic or recurrent cervical cancer, where the BEATcc trial demonstrated a 39% reduction in progression risk (HR = 0.61) and an improved ORR of 64% versus 51% with the addition of ATZ to BEV plus platinum-based chemotherapy [28]. Likewise, in colorectal cancer, the AtezoTRIBE trial showed that incorporating ATZ into the FOLFOXIRI–BEV regimen decreased the risk of disease progression by 28% (HR = 0.72) [29]. By contrast, the IMagyn050 study in advanced ovarian cancer failed to reach statistical significance for PFS improvement (19.5 vs. 18.4 months; HR = 0.92), despite a modest trend favoring the immunotherapy arm [34]. Beyond these RCTs, multiple systematic reviews and meta-analyses reinforce the efficacy

advantage of immunotherapy–antiangiogenic combinations. For instance, a network meta-analysis in unresectable HCC positioned ATZ + BEV as the most effective first-line option, with pooled OS and PFS benefits over lenvatinib, sorafenib, and durvalumab-based regimens [39]. Another large-scale systematic review reported consistent HRs favoring this combination across 12 comparative studies, supporting its broad efficacy and tolerability [10]. Similarly, meta-analyses of ICI + anti-VEGF strategies across multiple malignancies, including renal cell carcinoma and urothelial cancer, show pooled PFS improvements of approximately 25–35%, underscoring the generalizability of this therapeutic concept [40–42]. When viewed collectively, these randomized and pooled data confirm that adding ATZ to BEV + chemotherapy confers a reproducible survival and response advantage in advanced cancers. However, the magnitude of benefit appears context dependent. The moderate heterogeneity detected for PFS ($I^2 \approx 70\%$) and OS ($I^2 \approx 60\%$) in our meta-analysis likely stems from biologic and trial-level variation rather than contradictory findings. Differences in tumor immunogenicity, tumor mutational burden (TMB), PD-L1 expression, and immune-cell infiltration patterns strongly influence checkpoint inhibitor responsiveness [43, 44]. For example, tumors with high TMB or mismatch-repair deficiency exhibit stronger sensitivity to PD-1/PD-L1 blockade, while "immune-cold" cancers such as many ovarian tumors often display limited responsiveness even with concurrent anti-angiogenic therapy [45]. Additionally, differences in chemotherapy backbones, prior therapy exposure, and timing of immunotherapy initiation may modulate the observed effect size.

Mechanistically, VEGF inhibition reprograms the tumor microenvironment in ways that enhance immune checkpoint activity. BEV-mediated VEGF blockade transiently normalizes tumor vasculature, reduces hypoxia, and increases T-cell infiltration, thereby improving cytotoxic lymphocyte function within tumors [38, 46]. Simultaneously, ATZ restores exhausted T-cell activity by inhibiting PD-L1–PD-1 signaling, amplifying immune-mediated tumor clearance [47]. This dual targeting suppresses additional immunosuppressive elements, including myeloid-derived suppressor cells and regulatory T cells, further strengthening antitumor immunity [48, 49]. Preclinical studies have shown that this synergy augments chemotherapy-induced antigen release and promotes adaptive immune responses [50]. These mechanisms align with the clinical efficacy observed in our analysis, where the ATZ + BEV + chemotherapy combination consistently improved ORR, PFS, and OS without compromising tolerability. Study-level inconsistencies, such as the lack of statistical significance in IMagyn050 or variability in DCR, may reflect differences in tumor biology and treatment sequencing. For example, ovarian cancer exhibits low $CD8^+$ T-cell infiltration and reduced interferon-γ signaling, limiting checkpoint inhibitor efficacy despite VEGF blockade [45]. Additionally, the timing of immunotherapy (concurrent vs. sequential) and treatment line may influence the strength of immuno-angiogenic synergy [29, 51]. Our findings also indicate that chemotherapy backbone modulates treatment benefit. Trials using platinum-based regimens showed greater synergy with ATZ, likely due to platinum-induced immunogenic cell death, increased antigen release, and dendritic cell activation [52], which enhance responsiveness to PD-L1 inhibition and VEGF-mediated vascular normalization [53]. In contrast, fluoropyrimidine-based regimens exert weaker immunogenic pressure and may provide a less favorable immune milieu [54]. Overall, these mechanistic and clinical data support ATZ + BEV + chemotherapy as a biologically rational and potent therapeutic strategy across multiple cancers.

The pooled safety analysis from our meta-analysis demonstrated that adding ATZ to BEV + chemotherapy did not substantially increase the overall incidence of treatment-related adverse events, although selective increases in specific toxicities were observed. Among the evaluated toxicities, the frequency of diarrhea was modestly but significantly higher in the ATZ-containing group ($RR \approx 1.24$), whereas most other adverse events, including neutropenia, fatigue, anemia, hypertension, and alopecia, were comparable between arms; however, grade III-IV nausea occurred more frequently in the ATZ-containing group. Although the majority of severe (grade III-IV) toxicities were not statistically different between groups, an increased risk of grade III-IV nausea was observed, while other high-grade events remained comparable. Collectively, these findings suggest that the incremental efficacy gain achieved by combining ATZ is associated with a modest increase in selected adverse events but does not substantially compromise overall tolerability.

The safety profile observed in this meta-analysis closely aligns with major RCTs. In IMpower150, rates of grade ≥ 3 adverse events were comparable between the ATZ + BEV + chemotherapy group and the BEV + chemotherapy control (57% vs. 49%), with slightly higher frequencies of diarrhea, rash, and immune-related hepatitis in the ATZ arm [11]. Similar findings were reported in AtezoTRIBE, where grade ≥ 3 toxicities occurred in 63% of patients receiving the triplet regimen versus 57% in controls [29]. BEATcc and IMagyn050 likewise demonstrated similar toxicity patterns and no unexpected safety signals or treatment-related deaths attributable to ATZ [28, 34]. Recent systematic reviews further support the favorable risk–benefit profile of PD-L1 inhibitors

combined with antiangiogenic agents, reporting pooled grade ≥ 3 toxicity rates of 60–65%, comparable to standard regimens [10, 41, 42]. The selective increase in diarrhea in our analysis is biologically plausible. Immune-mediated colitis is a recognized complication of PD-1/PD-L1 blockade, driven by heightened T-cell activity, mucosal immune infiltration, and disruption of epithelial tolerance [55, 56]. BEV may further sensitize the intestinal mucosa by impairing microvascular repair and epithelial healing, modestly amplifying GI effects [57]. Nevertheless, the absence of significant increases in high-grade diarrhea suggests these events are largely mild and manageable. Other toxicities, including hypertension and proteinuria, reflect VEGF inhibition and were not significantly intensified by ATZ, consistent with pharmacovigilance data [58]. Hematologic effects also remained comparable, indicating no antagonism between immunotherapy and cytotoxic agents. Across most adverse events, relative risk estimates for grade III-IV toxicities approximated unity, while any observed differences were primarily confined to lower-grade events, reinforcing that the addition of ATZ did not substantially exacerbate severe toxicity. An exception was observed for grade III-IV nausea (RR 1.66), representing a statistically significant increase despite low heterogeneity; however, the absolute incidence remained limited, and no parallel increase was seen in other high-grade gastrointestinal toxicities. Across subgroup and sensitivity analyses, the triplet regimen maintained a generally manageable safety profile; however, several subgroup comparisons were derived from a small number of trials and should be considered exploratory, requiring validation in larger, indication-specific datasets. Also, the observed variation in diarrhea and pyrexia across specific tumor types and chemotherapy backbones suggests that immune-related toxicity patterns may not be entirely uniform across malignancies and should be interpreted within tumor-specific clinical contexts. Immune-related events were generally reversible, responded to corticosteroids or brief interruptions, and showed no evidence of cumulative or synergistic toxicity [51, 59]. Importantly, accumulating evidence suggests that the relationship between immune-related adverse events (IREAs) and therapeutic efficacy is grade- and organ-specific. A large pooled analysis of atezolizumab across multiple indications demonstrated that low-grade (G1–2) IREAs, particularly dermatologic events and thyroid dysfunction, were significantly associated with improved OS, whereas certain high-grade IREAs, such as pneumonitis and colitis, correlated with poorer outcomes, likely reflecting treatment interruption and the need for immunosuppression [60]. Endocrine IREAs, especially thyroid dysfunction, represent the most common immune-mediated toxicities and may exhibit tumor- and treatment-specific risk patterns, particularly in combination regimens [61, 62]. These findings underscore that IREAs should not be interpreted solely as safety liabilities but rather as context-dependent markers of immune activation requiring careful monitoring and individualized management. Overall, current evidence indicates that adding ATZ to BEV + chemotherapy enhances efficacy while maintaining an acceptable safety profile, although selective increases in specific adverse events and the context-dependent implications of IREAs warrant continued clinical vigilance.

Study limitations and future directions

This meta-analysis possesses several noteworthy strengths that enhance the credibility and clinical relevance of its findings. It represents the most comprehensive quantitative synthesis to date directly comparing ATZ plus BEV + chemotherapy versus BEV + chemotherapy alone across multiple malignancies. By integrating data from eight RCTs encompassing over 3700 patients, our analysis provides a robust pooled estimate of efficacy and safety outcomes with high statistical power. Methodological rigor was ensured through the use of GRADE criteria to assess the certainty of evidence. Moreover, extensive subgroup, sensitivity, and publication bias analyses confirmed the internal consistency and stability of the results. The simultaneous evaluation of both efficacy and safety endpoints in a single framework offers a balanced perspective that strengthens clinical interpretability and supports evidence-based decision-making in oncology practice.

However, several limitations should be acknowledged. First, despite including only RCTs, between-study heterogeneity was moderate for PFS and OS, likely reflecting variations in tumor type, chemotherapy backbone, PD-L1 expression, and prior treatment exposure across studies. This heterogeneity likely reflects not only methodological differences but also substantial biological variability across tumor types, including differences in intrinsic immunogenicity, tumor microenvironment composition, and angiogenic dependence. Accordingly, pooling results within a pan-cancer framework may obscure tumor-specific differences in the magnitude of therapeutic benefit. Second, the number of eligible trials was relatively limited for certain outcomes, particularly within subgroup analyses, which may have constrained the precision of pooled estimates. Consequently, subgroup findings should be interpreted with caution, as several analyses were underpowered and not designed to provide definitive evidence of differential treatment effects. These exploratory observations primarily serve to generate hypotheses regarding tumor-specific variability rather than establish conclusive subgroup effects. Third, most included trials were conducted in advanced or metastatic settings, and therefore the applicability of our findings to earlier disease stages

remains uncertain. Additionally, patient-level data were not available, preventing adjustment for confounding variables such as performance status, genetic drivers, and biomarker-defined subgroups. Moreover, key predictive biomarkers such as PD-L1 expression and tumor mutational burden were not consistently reported or stratified in a manner that allowed extraction of comparable quantitative data across the included trials. Consequently, biomarker-based subgroup analyses were not feasible within the scope of this meta-analysis. Such factors may differentially influence treatment efficacy and immune-related toxicity patterns across distinct malignancies. Finally, although no significant publication bias was detected, the possibility of selective reporting or unpublished negative results cannot be fully excluded. In light of these considerations, while our findings should be interpreted with caution in heterogeneous tumor contexts, the overall methodological robustness, consistency across multiple endpoints, and concordance with established biological rationale collectively affirm the validity and clinical significance of the observed outcomes.

Future perspectives

Future research should aim to refine the clinical application of ATZ plus BEV + chemotherapy through biomarker-driven patient selection and optimized treatment sequencing. Identifying predictive factors such as PD-L1 expression, tumor mutational burden, microsatellite instability, and angiogenic signatures will be crucial to determine which subgroups derive the most durable benefit. Further trials are warranted to explore this combination in earlier disease stages and across underrepresented tumor types, while integrating translational endpoints to clarify mechanisms of immune–angiogenic synergy. Given the observed toxicity patterns, prospective studies incorporating pharmacogenomic or immunogenomic profiling may help predict and mitigate adverse events. Ultimately, the integration of immune checkpoint blockade with anti-angiogenic therapy represents a promising frontier in precision oncology, and future efforts should focus on refining these regimens to maximize efficacy while maintaining safety and quality of life for cancer patients.

Conclusion

In summary, this systematic review and meta-analysis indicates that the addition of ATZ to BEV + chemotherapy is associated with significant improvements in ORR, PFS, and OS across multiple malignancies. However, the magnitude and consistency of benefit varied among tumor types, likely reflecting underlying biological and clinical heterogeneity. Overall toxicity was generally acceptable, although selective increases in specific adverse events, including predominantly low-grade gastrointestinal toxicity and a higher incidence of grade III-IV nausea, were observed. Moreover, the clinical implications of immune-related adverse events may be grade- and organ-specific, warranting tumor-contextualized interpretation and careful management. The combination leverages complementary immune and angiogenic mechanisms, providing a biologically rational therapeutic strategy in appropriately selected advanced cancer settings. Nevertheless, given inter-tumor variability and limited data in certain subgroups, these findings should be applied with clinical contextualization rather than uniform pan-cancer extrapolation. Future research should prioritize predictive biomarker development, clarification of tumor-specific benefit, and optimization of patient selection to further personalize therapy and improve long-term outcomes.

Abbreviations

AMSTAR	A MeaSurement Tool to Assess systematic Reviews
ATZ	Atezolizumab
BEV	Bevacizumab
CI	Confidence Interval
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
FOLFOXIRI	Combination regimen of folinic acid, fluorouracil, oxaliplatin, and irinotecan
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
HCC	Hepatocellular Carcinoma
HR	Hazard Ratio
ICI	Immune Checkpoint Inhibitor
ICTRP	International Clinical Trials Registry Platform
IMmotion / IMpower / Imagyn	Acronyms for clinical trial programs involving Atezolizumab
MET	Mesenchymal Epithelial Transition factor
MeSH	Medical Subject Headings
NSCLC	Non–Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
PD-1	Programmed Cell Death Protein 1
PD-L1	Programmed Death-Ligand 1
PFS	Progression-Free Survival
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized Controlled Trial
RECIST	Response Evaluation Criteria in Solid Tumors
RCC	Renal Cell Carcinoma
RR	Risk ratio
SD	Standard Deviation
STATA	Statistical Analysis Software (StataCorp, TX, USA)
TMB	Tumor Mutational Burden
VEGF	Vascular Endothelial Growth Factor
WHO	World Health Organization
IREAs	Immune-Related Adverse Events

Supplementary Information

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Supplementary Material 1.

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None.

Authors' contributions
The concept and design of the study were developed by K.P. and P.E. Literature search and screening were conducted by A.A.N., A.E.S., S.M., and A.M.S. Data extraction was performed by A.E.S. and K.P., while qualitative assessment and methodological appraisal were carried out by A.A.N. and K.P. The preliminary data analysis was conducted by A.A.N. All stages of the study, including analysis and manuscript preparation, were supervised by P.E. and M.H.A. The manuscript was drafted by K.P., P.E., and A.A.N., and critically revised for important intellectual content by all authors. All contributors read and approved the final version of the manuscript before submission.

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Data availability
Comprehensive data can be found within the manuscript and its supplementary files. The corresponding author is available to provide further data upon a reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Due to nature of the study there is no need for publication concept.

Competing interests
The authors declare no competing interests.

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