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Safety, efficacy, and cost-effectiveness evaluation of systemic treatments for refractory colorectal cancer: a systematic review and modeling study

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Abstract

Objectives To conduct pooled estimates and comparative evaluations of safety and efficacy, alongside cost-effectiveness and value-based pricing analyses, for systemic treatments recommended by the National Comprehensive Cancer Network in refractory colorectal cancer.

Methods A comprehensive search for related randomized controlled trials was conducted on PubMed, EMBASE, the Cochrane Library, and ClinicalTrials.gov. Safety was evaluated by aggregating treatment-related adverse events (TRAEs) and performing Bayesian network meta-analysis (NMA) for indirect comparisons. Pooled survival estimates of overall survival (OS) and progression-free survival (PFS) were conducted to assess treatment efficacy. For NMA of OS and PFS, time-variant fractional polynomial models were employed as the primary analysis, with Cox proportional hazards models used for result validation. Economic evaluations were performed using partitioned survival models from the US public sector perspective. Clinical parameters were sourced from meta-analyses; cost parameters included drug treatment, follow-up and administration, end-of-life care, and adverse event management expenses, which were obtained from the Federal Supply Schedule, public databases or published literature. Utility values were sourced from the CORRECT trial. Price simulations were also conducted. Robustness of results was confirmed by sensitivity and scenario analyses

Results We included nine studies comprising 3,978 patients and incorporating six treatments recommended by NCCN, including best supportive care (BSC), regorafenib, regorafenib dose optimization (REDo), trifluridine/tipiracil (TAS-102), TAS-102 with bevacizumab (TAS-BEV), and fruquintinib. Targeted treatments increased serious TRAEs and grade 3 + TRAEs compared to BSC. However, no significant safety differences were found among the targeted therapies. Regarding efficacy, REDo led in median OS, while fruquintinib led in median PFS. NMA indicated that TAS-BEV had the greatest PFS and OS survival benefit, followed by fruquintinib and REDo. Cost-effectiveness analysis favored BSC as the least expensive and the most cost-effective profile. TAS-BEV had the greatest effectiveness, with

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TAS-102 being the most cost-effective among targeted therapies. For cost-effectiveness against BSC, the price reductions of TAS-102, fruquintinib, REDoS, regorafenib, and TAS-BEV were 39%, 24%, 14%, 8%, and 7%, respectively.

Conclusions Targeted therapies have comparable safety; TAS-BEV is highly effective, TAS-102 is the top cost-effective targeted therapy. Treatment choice should balance individual patient needs with safety, efficacy, and cost.

Key points

- Our pioneering meta-analysis introduces reconstructed IPD to derive robust survival metrics for refractory CRC, setting a new standard by accounting for event censoring. Consistent OS and PFS estimates from high-quality studies provide precise treatment insights and aid in designing future trial sample sizes.
- As the first to apply NMA with reconstructed IPD for refractory CRC, we overcome the limitations of proportional hazards assumptions. Our dynamic model delivers timely efficacy assessments of various treatments, bolstering the clinical relevance and trustworthiness of our results.
- Our analysis is the first to compare the effectiveness and cost-efficiency of all NCCN-recommended regimens for refractory CRC from a US public payer perspective. With price simulations for value-based pricing, we offer crucial evidence for optimizing clinical drug use and resource allocation, facilitating informed healthcare decisions.

Keywords Refractory colorectal cancer, Individual patient data meta-analysis, Cost-effectiveness, Efficacy, Safety

Introduction

Globally, cancer is a primary cause of mortality and represents a significant obstacle to enhancing life expectancy across all nations [1]. In the United States, among all cancers, colorectal cancer (CRC) is the second leading cause of cancer-related mortality, and is the most common cause of death for men under the age of 50 [2]. The impact of cancer on society is substantial and transcends economic boundaries, affecting both more and less economically developed nations [1].

Advanced CRC treatment is customized based on individual disease features and treatment history [3]. First-line CRC treatment commonly consists of chemotherapy like FOLFOX (folinic acid, fluorouracil, and oxaliplatin) or FOLFIRI (folinic acid, fluorouracil, and irinotecan), paired with bevacizumab generally, or cetuximab/panitumumab for non-mutated RAS patients [4–6]. Pembrolizumab is the selected immunotherapy for patients with high microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR) [7, 8]. Once disease progresses, second-line treatments are tailored, possibly changing chemotherapy, maintaining bevacizumab, or starting anti-EGFR antibodies in RAS wild-type tumors if not yet used [9, 10]. For refractory CRC, the recommended in the National Comprehensive Cancer Network (NCCN, Version 1.2025)-approved systemic treatments encompass regorafenib, regorafenib dose optimization (REDo), trifluridine/tipiracil (TAS-102), TAS-102 with bevacizumab (TAS-BEV), and fruquintinib. Additionally, biomarker-driven therapies are recommended for specific molecular subtypes, including PD-1 inhibitors (pembrolizumab, nivolumab ± ipilimumab) for MSI-H/dMMR tumors, encorafenib + cetuximab for BRAF V600E-mutant tumors, and HER2-directed therapies (trastuzumab + tucatinib or trastuzumab + pertuzumab) for HER2-positive tumors [11, 12]. Per the CORRECT trial, regorafenib improved median overall survival (mOS) to 2.8 months over BSC's 1.8 months [13]. The REDoS study indicated REDo increased OS over regorafenib and was safer [14]. The RECOURSE trial demonstrated that TAS-102 significantly improved OS compared to BSC, with an HR of 0.68 and a 95% confidence interval (CI) of 0.58 to 0.81 [15]. Recent SUNLIGHT study results revealed that TAS-BEV notably enhanced survival over TAS-102 alone, with an mOS of 10.8 months compared to 7.5 months [16]. Recent data from the FRESCO and FRESCO-2 trials showed that fruquintinib improved OS compared with BSC, with HRs of 0.65 and 0.66 respectively [17, 18]. As a result, the U.S. Food and Drug Administration (FDA) has approved fruquintinib for treating patients with refractory CRC.

Employing individual patient data (IPD) meta-analysis, regarded as the best practice for analyzing time-to-event data, allows for nuanced treatment outcome evaluation while addressing data censoring [19]. In the context of refractory CRC, trials such as CONCUR and CORRECT have investigated the efficacy of a consistent treatment. Leveraging IPD meta-analysis in this case can yield more precise survival estimates. Furthermore, while numerous clinical studies have explored different treatment options, BSC frequently served as the control arm in these trials [13–18, 20–22]. Without direct comparisons of treatments, guideline committees are reluctant to prefer one drug over others. Hence, conducting a network meta-analysis (NMA) is essential to determine the relative effectiveness of different treatment options [23]. Given the substantial differences in drug prices ($11,826 for TAS-102 versus $25,200 for fruquintinib per 28-day cycle) and the modest survival gains over BSC (e.g., TAS-102 extends the mOS by only 1.8 months), cost

considerations are critical [15]. Economic evaluations of different regimens should be evidence-based to establish their value.

Accordingly, we aimed to merge data to analyse the pooled clinical efficacy and safety of different treatments and to use NMAs to determine their relative effectiveness and safety. Finally, variations in cost-effectiveness among regimens were determined, and value-based pricing strategies were derived.

Methods

Search strategy

Literature synthesis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Individual Patient Data (PRISMA-IPD) guidelines [24]. The search strategy is provided in Additional File Part 1. Researchers conducted a systematic search for relevant trials in PubMed, EMBASE, the Cochrane Library, and ClinicalTrials.gov up to December 2023.

Study selection and data extraction

Two researchers, Zhao and Jiang, initially screened the titles and abstracts of articles. Discrepancies were resolved through discussion with a panel including an oncology expert. The inclusion criteria were guided by the PICOS criteria:

(1) Population: Adults with histologically or cytologically confirmed colon or rectal adenocarcinoma, refractory or intolerant to at least two prior chemotherapy lines.
(2) Interventions and comparisons: Treatment options recommended by the NCCN for refractory CRC patients unresponsive to chemotherapy include regorafenib, ReDO, TAS-102, TAS-BEV, fruquintinib, and BSC.
(3) Outcomes: The primary outcomes of this study were PFS, OS, and adverse events (adverse events [AEs] of grade 3 or higher, and serious AEs). The inclusion criteria mandated published Kaplan–Meier curves for OS or PFS to facilitate IPD reconstruction from survival curves.
(4) Study design: Priority was given to phase II-III RCTs that provided the necessary data. We included only the most recent and comprehensive trials to prevent data duplication.
(5) The extracted data included PFS, OS, and AE. Furthermore, details such as the publication year, first author, trial registration, participant demographics (age, sample size, countries), and intervention specifics (treatments, endpoint outcomes) were also gathered.

Quality assessment

The quality of the studies included was assessed using the Cochrane Collaboration's risk of bias (ROB) tool [25]. The quality of the eligible studies was classified as high, low, or unclear. Egger's regression test was used to assess publication bias, with p values less than 0.05 indicating publication bias [26].

Statistical analyses

Guyot's method was employed to acquire IPD [27]. We digitalized published Kaplan-Meier curves via the GetData Graph Digitizer software version 2.24.

Pooled estimates of safety and survival, and network meta-analysis

After reconstructing IPD, a pooled analysis of OS and PFS was performed via the MetaSurv approach. This involved aggregating arcsine-transformed survival probabilities with a random-effects model to produce a summary survival curve without assuming a specific distribution [28]. Given that AEs reported in various studies are categorized as treatment-related or of all-cause, with a notable absence of all-cause AEs reported in the majority of studies [13, 15, 20–22]. To enable a more thorough comparison, we compared treatment-related adverse events (TRAEs). Moreover, we employed a random-effects model from the Meta package to amalgamate the incidence rates of TRAEs.

For NMAs of PFS and OS, both fixed-effects and random-effects models were used, with the random-effects model accounting for inter-study variability. The presence of low heterogeneity prompted the reporting of results from the fixed-effects models. Time-to-event data analysis revealed that hazard ratios (HRs) often varied over time, and deviations from the proportional hazards (PH) assumption were noted, as exemplified by the OS curve in the FRESCO-2 [18]. Hence, relying exclusively on HRs derived from Cox-PH models as effect size measures in NMA is unsuitable. To address this issue, we estimated time-varying HRs and projected long-term survival rates using Bayesian fractional polynomial (FP) models [29], first-order FP models were fitted using power parameters – 2, -1, -0.5, 0.5, 1, 2, and 3. Model fit was evaluated using the Akaike information criterion (AIC) and visual inspection. In the sensitivity analyses, Asian trials were excluded. This exclusion was conducted to account for potential differences in patient characteristics, treatment responses, healthcare systems, and drug pricing structures between Asian and Western populations, which could influence both clinical and economic outcomes [30, 31]. FP models were executed using the 'survival' package. Survival outcomes and life-years gained (LYG) were the selected outcome measures. LYG was calculated using Wiksten's method, employing a two-step approach

for NMA [29]. OS and PFS curves for the reference treatment were developed and extended using parametric models such as the exponential, gamma, Gompertz, Weibull, generalized gamma, log-normal, log-logistic, FP, restricted cubic spline (RCS), and Royston-Parmar spline (RP) models. Model selection hinged on the AIC and visual assessment. Next, time-varying HRs between various treatments and the reference were derived using the FP model, enabling the generation of survival curves to estimate life-years for each regimen. Additionally, Cox-PH models were applied via the 'Netmeta' package. This method yielded cautious results, confirming the robustness of the primary analyses. The Cox-PH models used HRs with 95% CIs. For safety assessment, Bayesian NMAs were performed using the 'BUGSnet' package, and ORs with 95% CIs represented the effect sizes.

We performed subgroup analyses of OS and PFS stratified by RAS mutation status (wild-type vs. mutant) and the number of prior systemic treatments (≤3 vs. >3). Given the unavailability of subgroup survival curves, we obtained only HR estimates using Cox-PH models.

Heterogeneity was gauged using Cochran's Q test and the I^2 statistic. An I^2 greater than 40% or a Q test p-value less than 0.1 denoted significant heterogeneity [32]. Model inconsistency was evaluated using the edge-splitting method, which incorporates both direct and indirect evidence [33, 34]. Markov chain convergence was checked using trace plots and the Gelman-Rubin statistic [35]. Data analysis was performed using R 4.1.0.

Cost-effectiveness analysis

Model structure A partitioned survival model with three health states was utilized to calculate total costs and QALYs for each treatment option (BSC, RSD, ReDO, TAS-102, TAS-BEV, and fruquintinib). Patients began in the PFS state and transitioned to progressive disease (PD) or death. The model used a 28-day cycle over 10 years, covering 99% of patient transitions to death. Outcomes were measured from the US public sector perspective (Veterans Affairs, VA), discounting costs and QALYs annually at 3% [36]. A half-cycle correction was implemented.

Clinical and economic parameters All parameters are detailed in Table S1. Data on the efficacy and safety for various regimens were derived from the initial part of this study [37]. AEs of grade 3 + with incidence rates of 1% or higher were incorporated into the model. The utility values for the PFS and PD states were sourced from the CORRECT trial, which provided EuroQol 5-Dimension Health Questionnaire (EQ-5D) scores of 0.73 for PFS and 0.59 for PD [15]. Treatment duration for different regimens was equated to time in PFS, indicated by time until treatment discontinuation [38]. The economic parameters included drug treatment expenses, AE management, follow-up and administrative costs, and end-of-life care costs. Drug costs were based on Federal Supply Schedule (FSS) pricing, reflecting VA-negotiated prices with drug firms. Compared with list drug prices, FSS drug costs more accurately reflect the true treatment burden [36]. Direct drug costs were calculated for an 80 kg patient with a body surface area of 1.78 m^2. The BSC costs were derived from existing literature [39]. For follow-up and administrative cost calculations, it was assumed that patients attended biweekly physician visits and underwent complete blood counts with differential and comprehensive metabolic panel tests [40]. Furthermore, following the NICE guidelines, patients were assumed to receive a CT scan quarterly [41]. Prices were derived from Medicare's Current Procedural Terminology (CPT) codes [42]. Post-progression costs were assessed for refractory CRC patients, upon advancing to the PD state, they received BSC, adhering to NICE guideline recommendations [41]. In scenario analysis, we accounted for the possibility that patients in the PD state might continue receiving active systemic therapy rather than exclusively receiving BSC. AE treatment costs were primarily derived from the Healthcare Cost and Utilization Project by the Agency for Healthcare Research and Quality [43], and were applied in the initial cycle of the model. The end-of-life care cost originated from real-world data of cancer patients from the perspective of the United States [44]. Costs were adjusted to 2023 U.S. dollars using the Personal Consumption Expenditures Price Index for healthcare services [45]. The willingness-to-pay threshold for each QALY was set at $150,000 ($100,000-200,000) [40]. For more details, refer to Table S1.

Sensitivity analyses, scenario analyses and price simulation Deterministic sensitivity analysis (DSA) was used to assess the effects of key parameters on the incremental net monetary benefit (INMB), and the results are displayed in tornado diagrams. Parameters varied within set ranges from the literature or databases, or within ± 20% of base-case values where specific limits were unavailable. A probabilistic sensitivity analysis (PSA) using Monte Carlo simulation with 10,000 iterations was conducted on the base-case. Costs were modeled with a gamma distribution, and probabilities, proportions, and utilities were modeled with a beta distribution. The cost-effectiveness acceptability curves (CEAC) explored cost-effectiveness probabilities over a $0 to $500,000 willingness-to-pay threshold. Table S1 details the sources of uncertainty.

Our study included scenario analyses to address uncertainties in model structure, parameter and utility values, survival extrapolation, and treatment patterns. The following scenarios were considered: (1) excluding Asian RCTs from the NMA; (2) assuming PH, modeling used Cox-PH model outcomes; (3) in the PD state, active

treatment primarily consisting of chemotherapy was permitted (predominantly chosen subsequent active treatments were informed by RCTs); [13–18, 20–22] (4) utility values were derived from the UK advanced CRC patients; [46] (5) according to the NICE guidelines, BSC was assumed to incur no cost [41].

From a cost-effectiveness standpoint, reasonable pricing strategies were evaluated using BSC and TAS-102 as benchmarks, with assumed intervention prices ranging from no reduction to a full discount. The willingness-to-pay threshold was set at $150,000/QALY in the price simulation.

Results

Characteristics of the included studies

Figure S1 presents the flowcharts. Of the 3979 records found in the specified databases, 3614 were excluded initially due to the selection criteria. Subsequently, 365 studies were considered for full-text review. After applying the eligibility criteria, 9 studies were included in our network, 3 of which were exclusively from the Western Pacific region [17, 20, 22]. This study included 3978 patients and six NCCN-recommended treatments: regorafenib, REDo, TAS-102, TAS-BEV, and fruquintinib [47]. Additional characteristics are summarized in Table 1. The evidence network plot is shown in Fig. 1.

Risk of Bias

The assessment of ROB is presented in Additional File Part 2. All RCTs had a low risk of bias, although some open-label trials raised concerns about blinding and allocation concealment [14, 16, 21]. The Egger test results suggested no publication bias within our network, and funnel plots can be found in Additional File Part 3.

Safety results

The pooled safety estimates, illustrated in Fig. 2A, revealed that the incidence of serious TRAEs across targeted therapies, ranked from lowest to highest were fruquintinib (0.06, 95% CI [0.04–0.10]), REDo (0.11, 0.04–0.23), regorafenib (0.19, 0.05–0.51), TAS-102 (0.31, 0.16–0.5), and TAS-BEV (0.45, 0.3–0.6). For grade 3 + TRAEs, fruquintinib had the lowest incidence (0.41, 95% CI [0.31–0.51]), followed by TAS-102 (0.46, 0.4–0.52), and regorafenib (0.54, 0.5–0.58).

The NMA results (Fig. 2B) indicated that, for serious TRAEs, targeted treatments do not significantly increase the risk compared to BSC. The safety profiles, from best to worst, were as follows: TAS-102 (OR 1.02, 95% CI[0.63–1.7]), REDo (1.03, 0.31–3.38), fruquintinib (1.12, 0.83–1.57), TAS-BEV (1.18, 0.45–3.13), and regorafenib (1.24, 0.92–1.67). In terms of Grade 3 + TRAEs relative to BSC, the safety ranking was: fruquintinib (OR 6.63, 95% CI [1.55–31.57]), followed by regorafenib (7.34, 1.62–32.9), and TAS-BEV (7.51, 0.88–65.32). The league table revealed no significant differences in the safety profiles of targeted therapies for either serious or grade 3 + AEs (Table S2).

Efficacy and effectiveness

The pooled survival estimates (Fig. 3) indicated that the mOS for the regimens varied, ordered from the lowest to highest: BSC (5.92 months, 95% CI [4.76–7.09]), TAS-102 (7.23, 6.32-8), regorafenib (7.37, 5.18–9.11), fruquintinib (8.19, 6.36–10.51), TAS-BEV (8.27, 5.08–11.73), and REDo (9.8, 7.5–11.9). In terms of PFS, from lowest to highest were BSC (1.58 months, 95% CI [1.51–1.67]), regorafenib (2.24, 1.87–3.31), TAS-102 (2.52, 1.91–2.91), REDo (2.8, 2–5), TAS-BEV (3.58, 2.08–5.23), and fruquintinib (3.62, 3.34–3.82). Heterogeneity was low in this analysis, all under 40%.

For NMA, OS and PFS curves for BSC were extrapolated using log-normal and log-logistic models, respectively. For the second step, we applied a first-order FP model (P=-2) to derive time-varying HRs for OS and PFS across treatments versus BSC. The model fit results are shown in Tables S3-S4. Figure 4 shows 60-month OS LYG, ranked from most to least: TAS-BEV (17.04 months), fruquintinib (15.27), TAS-102 (12.5), REDo (11.45), regorafenib (8.87), and BSC (8.18); For 24-month PFS LYG, from highest to lowest: TAS-BEV (10.85 months), fruquintinib (7.03), regorafenib (6.29), TAS-102 (5.69), REDo (4.78), and BSC (2.05). Excluding Asian-only trials, 60-month OS life-year gains ranked as follows: TAS-BEV (18.3 months), fruquintinib (13.84), REDo (12.03), TAS-102 (11.27), regorafenib (9.32), and BSC (8.21). For PFS at 24 months, LYG ranked as follows from highest to lowest: TAS-BEV (9.9 months), fruquintinib (6.02), regorafenib (5.75), REDo (4.87), TAS-102 (4.85), and BSC (2.05). Assuming that the PH assumption held, the results based on the Cox-PH model indicated that TAS-BEV had a notable lead in both OS and PFS. For OS, the rankings from highest to lowest against TAS-BEV were: REDo (HR 1.18, 95% CI [0.7–1.99]), fruquintinib (1.53, 1.14–2.04), regorafenib (1.64, 1.22–2.22), TAS-102 (1.66, 1.35–2.05), and BSC (2.33, 1.81–2.99). For PFS, the rankings from highest to lowest against TAS-BEV were: fruquintinib (HR 1.45, 95% CI [1.11–1.9]), REDo (1.85, 1.16–2.98), regorafenib (2.21, 1.69–2.9), TAS-102 (2.26, 1.88–2.72), and BSC (4.89, 3.89–6.15). Similarly, low heterogeneity was observed in both PFS and OS, as detailed in Fig. 5. See Table S5 for subgroup analysis results.

Cost-effectiveness

Clinical experts assessed the model's structure, assumptions, data sources, and outcomes for face validity. PFS and OS survival rates matched trial data, confirming model robustness. The right-censoring percentages for all

Table 1 Characteristics of the included studies

Trial	Study arms		Number of patients		Age (mean, range)		Sex (Male,%)		Region	Median duration/month (mean, 95%CI or SD)		Median PFS/month (mean, 95%CI)	
	I	C	I	C	I	C	I	C		I	C	I	C
CONCUR [20]	Regorafenib	BSC	136	68	57.5 (50.0–66.0)	55.5 (48.5–62.0)	63	49	Asian	2.4 (1.6–5.3)	1.6 (1.1–1.6)	3.2 (2-3.7)	1.7 (1.6–1.8)
Correct [11]	Regorafenib	BSC	505	255	61(54.0–67.0)	61(54.0–68.0)	62	60	global	2.8 (1.4–3.7)	1.8 (1.3–1.7)	1.9 (1.6–3.9)	1.7 (1.4–1.9)
FRESCO [15]	Fruquintinib	BSC	278	138	55.0 (23–75)	57.0 (24–74)	57	70	Asian	3.7 (0.1–21.9)	1.8(0.1–11.1)	3.7 (3.7–4.6)	1.8 (1.8–1.8)
FRESCO-2 [16]	Fruquintinib	BSC	461	230	64 (56–70)	64 (56–69)	53	61	global	3.1 (1.8–5.6)	1.8 (1.0-2.3)	3.7 (3.5–3.8)	1.8 (1.8–1.9)
RECOURSE [13]	Regorafenib	BSC	534	266	63(27–82)	63(27–82)	61	62	global	1.6 (0–18)	1.3 (0.1–14.7)	2.0 (1.9–2.1)	1.7 (1.7–1.8)
REDOS [12]	REDoS	Regorafenib	54	62	62 (53–68)	61 (53–68)	67	56	global	NA	NA	2.8 (2.0–5.0)	2.0 (1.8–2.8)
SUNLIGHT [14]	TAS-BEV	TAS-102	246	246	62 (20–84)	64 (24–90)	50	55	global	5.0 (0.1–18.5)	2.1 (0.6–14.3)	5.6 (4.5–5.9)	2.4 (2.1–3.2)
C-TASKFORCE [19]	TAS-BEV	TAS-102	46	47	64 (57–69)	67 (58–72)	52	64	Europe	4.9 (3.7–6.8)	2.4 (1.3–3.4)	4.6 (3.5–6.5)	2.6 (1.5–3.5)
TERRA [18]	TAS-102	BSC	271	135	58 (26–81)	56 (24–80)	63	62	Asian	3.2 (2.6)	2 (1)	2 (1.9–2.8)	1.8 (1.7–1.8)

Trial	Study arms		Median OS/month (mean, 95%CI)		HR PFS (Mean, 95%CI)	HR OS (Mean, 95%CI)	Any grade TRAE, N		grade 3 +TRAE, N		Any Serious TRAE, N	
	I	C	I	C	I	C	I	C	I	C	I	C
CONCUR [20]	Regorafenib	BSC	8.8 (7.3–9.8)	6.3 (4.3–7.6)	0.31 (0.22–0.44)	0.55 (0.40–0.77)	136	60	74	10	12	3
Correct [11]	Regorafenib	BSC	6.4 (3.6–11.8)	5.0 (2.8–10.4)	0.49 (0.42–0.58)	0.77 (0.64–0.94)	465	154	270	35	219	100
FRESCO [15]	Fruquintinib	BSC	9.3 (8.2–10.5)	6.6 (5.9–8.1)	0.26 (0.21–0.34)	0.65 (0.51–0.83)	266	97	128	10	17	2
FRESCO-2 [16]	Fruquintinib	BSC	7.4 (6.7–8.2)	4.8 (4.0-5.8)	0.32 (0.27–0.39)	0.66 (0.55–0.80)	395	130	164	26	NA	NA
RECOURSE [13]	Regorafenib	BSC	7.1 (6.5–7.8)	5.3 (4.6- 6.0)	0.48 (0.41–0.57)	0.68 (0.58–0.81)	524	247	370	137	158	89
REDOS [12]	REDoS	Regorafenib	9.8 (7.5–11.9)	6 (4.9–10.2)	0.84 (0.57–1.24)	0.72 (0.47–1.10)	NA	NA	NA	NA	6	8
SUNLIGHT [14]	TAS-BEV	TAS-102	10.8 (9.4–11.8)	7.5 (6.3–8.6)	0.44 (0.36 to 0.54)	0.61 (0.49–0.77)	NA	NA	NA	NA	NA	NA
C-TASKFORCE [19]	TAS-BEV	TAS-102	9.4 (7.6–10.7)	6.7 (4.9–7.6)	0.45 (0.29–0.72)	0.55 (0.32–0.94)	NA	NA	NA	NA	21	19
TERRA [18]	TAS-102	BSC	7.8 (7.1–8.8)	7.1 (5.9–8.2)	0.43 (0.34–0.54)	0.79 (0.62–0.99)	244	70	124	14	63	31

BSC, Best Supportive Care; C, control group; I, intervention group; HR, hazards ratio; N, number of patients; NA, not available; PFS, progression-free survival; OS, overall surviva; RCT, Randomized Controlled Trial; REDo, regorafenib dose optimization; TAS-102, trifluridine/tipiracil; TAS-BEV, TAS-102 with bevacizumab; TRAE, treatment-related adverse event

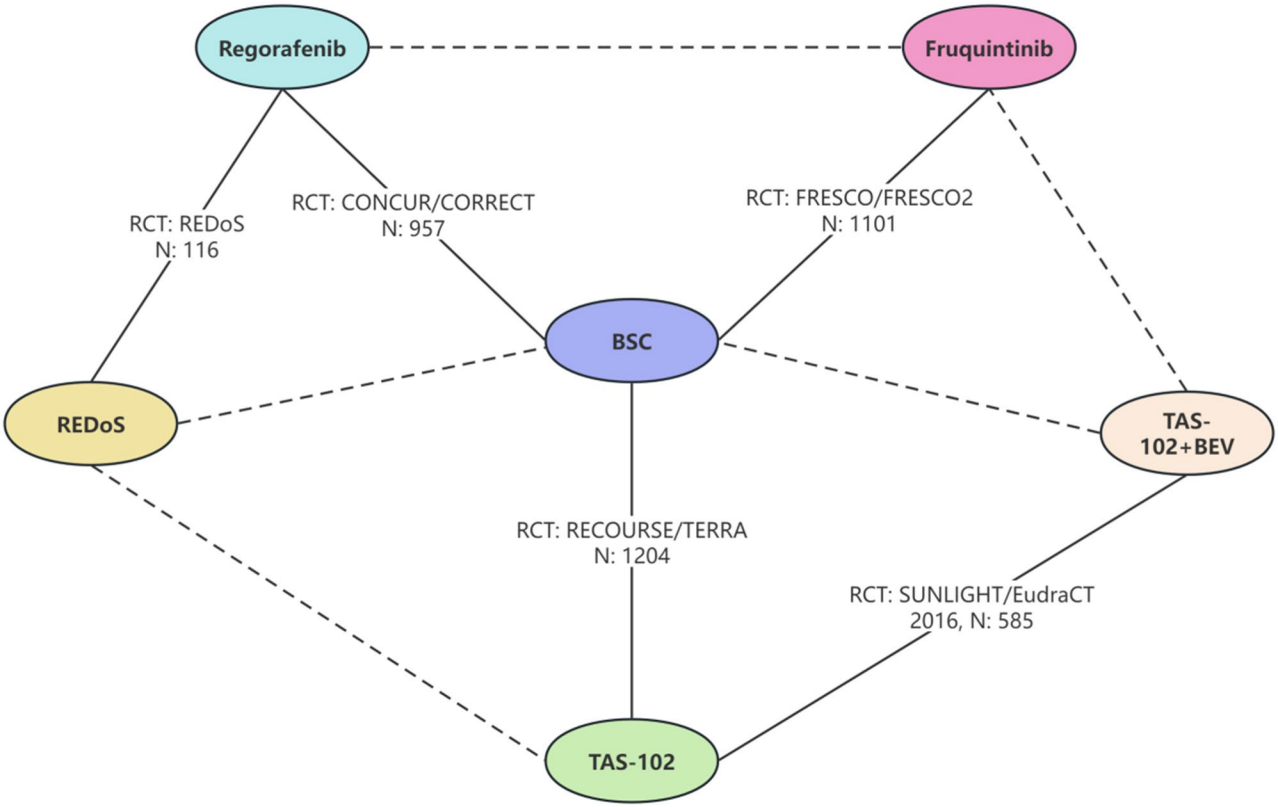


Fig. 1 Evidence network plot. BSC, Best Supportive Care; N, number of patients; RCT, Randomized Controlled Trial; REDo, regorafenib dose optimization; TAS-102, trifluridine/tipiracil; TAS-BEV, TAS-102 with bevacizumab

OS and PFS curves were under 20% (except for TAS-BEV in SUNLIGHT at 30%) [16], suggesting minimal uncertainty in extrapolation [13–18].

Baseline analysis revealed that treatment costs increased from BSC at $41,242 to TAS-102 at $140,656, REDo at $177,069, regorafenib at $186,803, TAS-BEV at $320,452, and fruquintinib topping at $334,799. The effectiveness ranged from 0.69 QALYs for BSC to 0.85 for regorafenib, 0.99 for REDo, 1.1 for TAS-102, and 1.39 for fruquintinib to 1.59 QALYs for TAS-BEV. BSC has historically been the most cost-effective option, with ICERs for other regimens relative to BSC escalating from TAS-102 at $349,254/QALY to TAS-BEV at $451,853/QALY, fruquintinib at $588,347/QALY, REDo at $682,534/QALY, and regorafenib at $1,317,383/QALY. TAS-102 emerged as the leading cost-effective active treatment, more details are provided in Table 2. The DSA results shown in Fig. 6 revealed that treatment costs, including drug pricing and patient body size factors, were the main drivers behind the highest INMB across regimens. Nevertheless, the foundational conclusions of the baseline analysis held firm: the five treatments, when compared to BSC, failed to be cost-effective when parameters varied within their specified ranges. Moreover, the cost-effectiveness advantage of TAS-102 over the other four targeted therapies remained unchanged amid variations in parameter values. The PSA results indicated that when the willingness-to-pay threshold was within the range of $100,000-200,000, BSC consistently remained the most cost-effective option (Fig. 7A); comparative results among targeted therapies showed (Fig. 7B) that TAS-102 was the most cost-effective option within the specified threshold range. Similarly, after excluding Asian trials, the conclusions remained unchanged (Fig. 7C-D). The scenario analysis results (Table 2) also indicated that the baseline analysis findings were stable. Among the five scenarios, BSC was the lowest-cost option, while TAS-BEV was the most effective choice. Additionally, BSC was the most cost-effective option, and TAS-102 was the most cost-effective targeted therapy.

At a willingness-to-pay threshold of $150,000/QALY, the pricing simulation suggested that, compared to BSC, TAS-102, fruquintinib, REDoS, regorafenib, and TAS-BEV would need to decrease their prices to 39%, 24%, 14%, 8%, and 7% of their original prices, respectively, to potentially be cost-effective. In comparison to TAS-102, a price reduction of 40% for REDoS, 56% for fruquintinib, and 59% for regorafenib would be required to potentially achieve economic viability (Fig. 8).

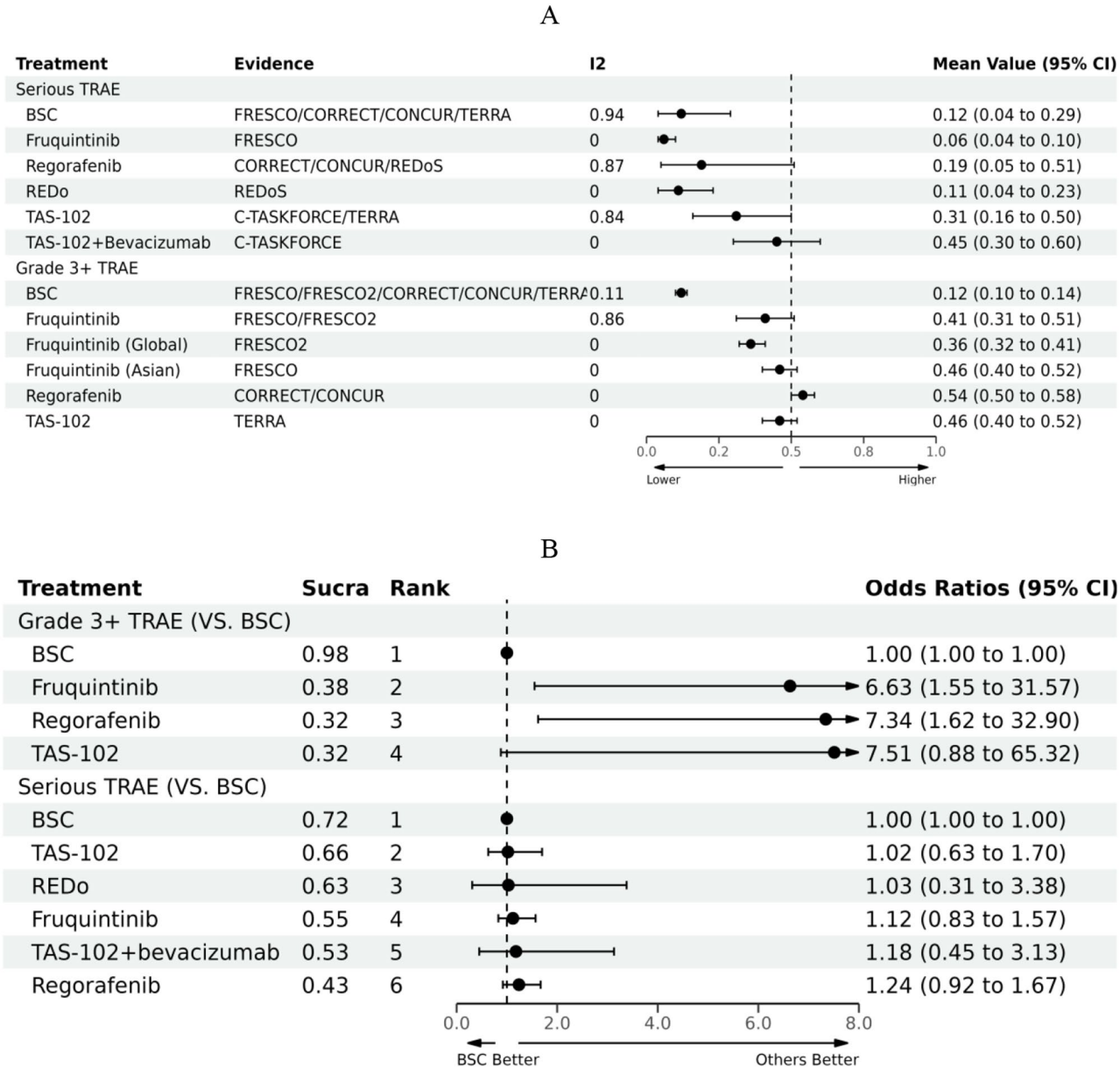


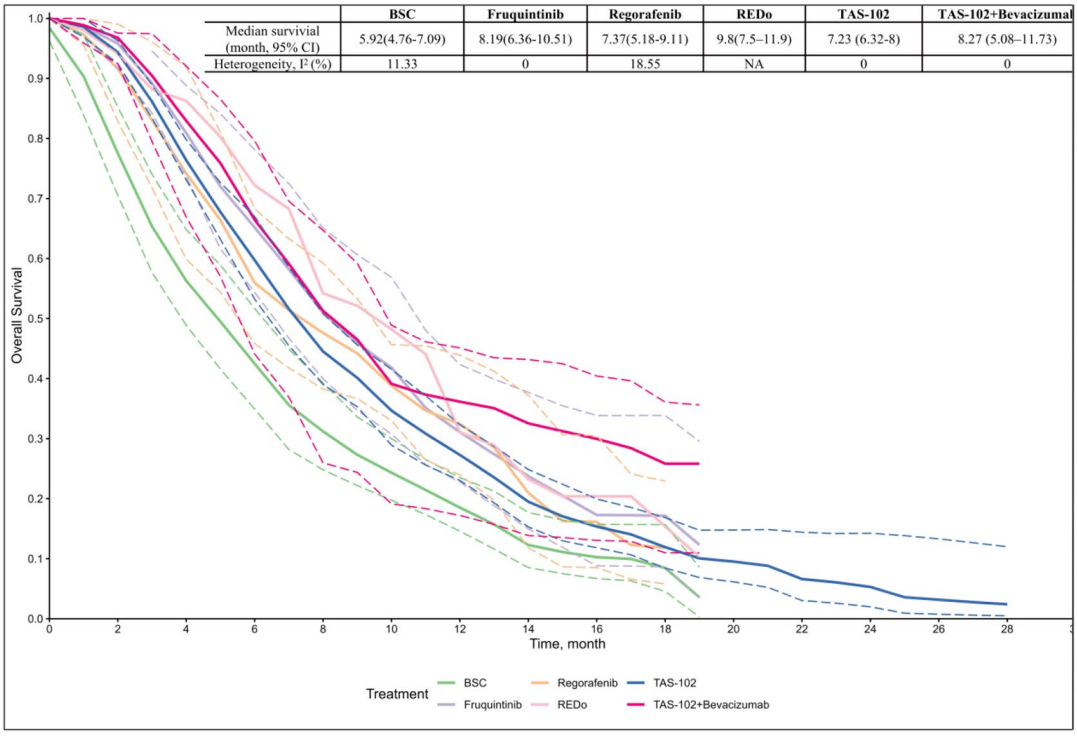
Fig. 2 Summarized results of safety analysis. **A** Pooled Incidence of Adverse Events; **B**. Network Meta-Analysis Results of Adverse Events. BSC, Best Supportive Care; REDo, regorafenib dose optimization; TAS-102, trifluridine/tipiracil; TAS-BEV, TAS-102 with bevacizumab; TRAE, treatment-related adverse event

Discussion

Main findings

In this study, we systematically evaluated 9 studies involving 3978 patients to explore the safety, efficacy, and cost-effectiveness of different treatment regimens for refractory CRC. This study examined six NCCN-endorsed treatments: BSC, regorafenib, REDo, TAS-102, TAS-BEV, and fruquintinib [47]. Regarding safety, our meta-analysis showed the pooled incidences of serious TRAEs and grade 3 + TRAEs across treatment regimens. Targeted treatments, compared with BSC, variably raised serious TRAEs and grade 3 + TRAE incidence rates. For serious TRAEs, the incidence rates ranked from highest to lowest were as follows: TAS-BEV (45%), TAS-102 (31%), regorafenib (19%), REDo (11%), and fruquintinib (6%). However, the NMA analysis indicated that, among targeted therapies, there were no significant differences in either serious TRAEs or grade 3 + TRAEs. The ranking discrepancy between direct incidence rates and NMA-derived Odd Ratios resulted from heterogeneity across trials, particularly the large variation in serious TRAEs incidence rates in the BSC arms. In the FRESCO trial, the BSC group had an SAE incidence of only 1.5%, while in TERRA and CONCUR, it was 23% and 4.4%, respectively.

A



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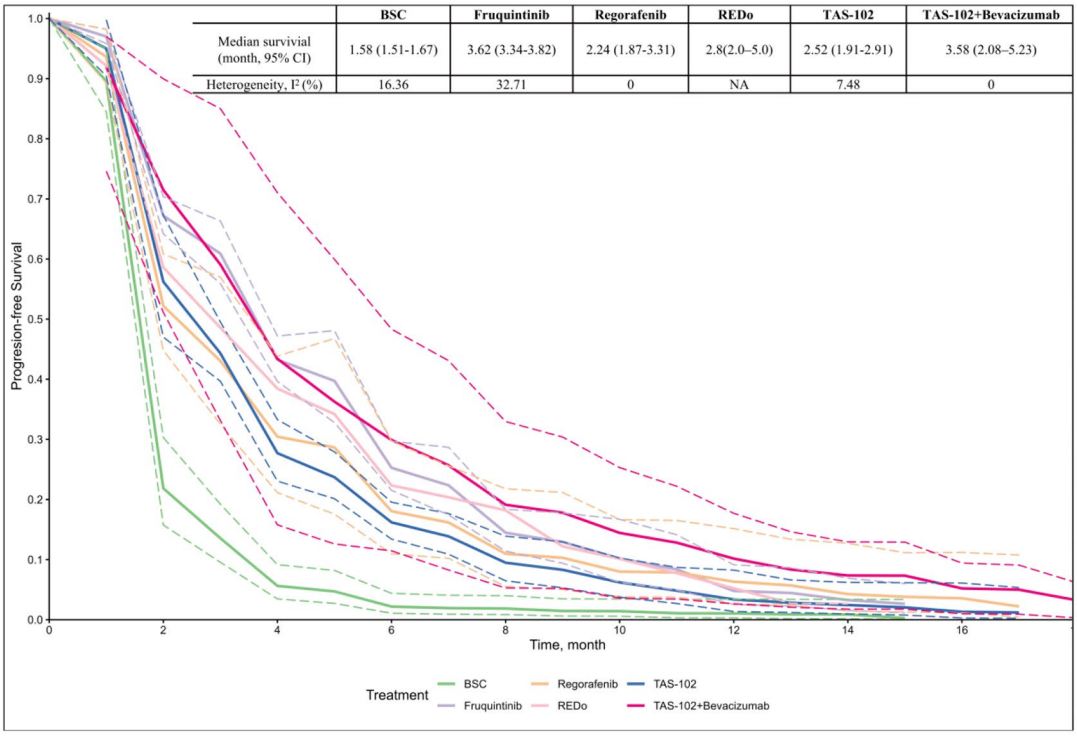

Fig. 3 Pooled estimates of overall survival and progression-free survival. BSC, Best Supportive Care; REDo, regorafenib dose optimization; TAS-102, trifluridine/tipiracil; TAS-BEV, TAS-102 with bevacizumab

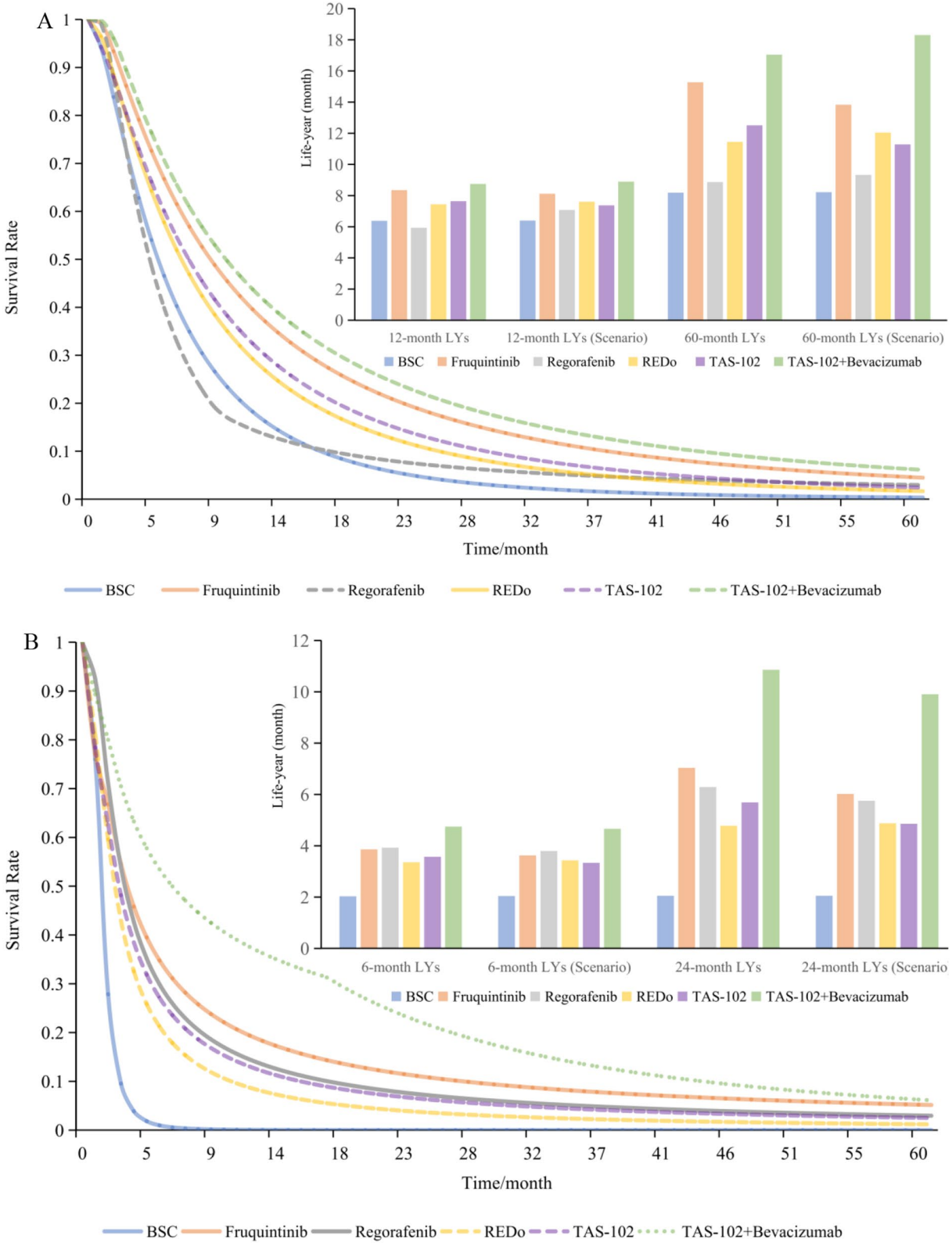

Fig. 4 Summary of network meta-analysis results for PFS and OS analysis. (**A**) OS; (**B**) PFS. BSC, Best Supportive Care; OS, overall survival; PFS, progression-free survival; REDo, regorafenib dose optimization; TAS-102, trifluridine/tipiracil; TAS-BEV, TAS-102 with bevacizumab

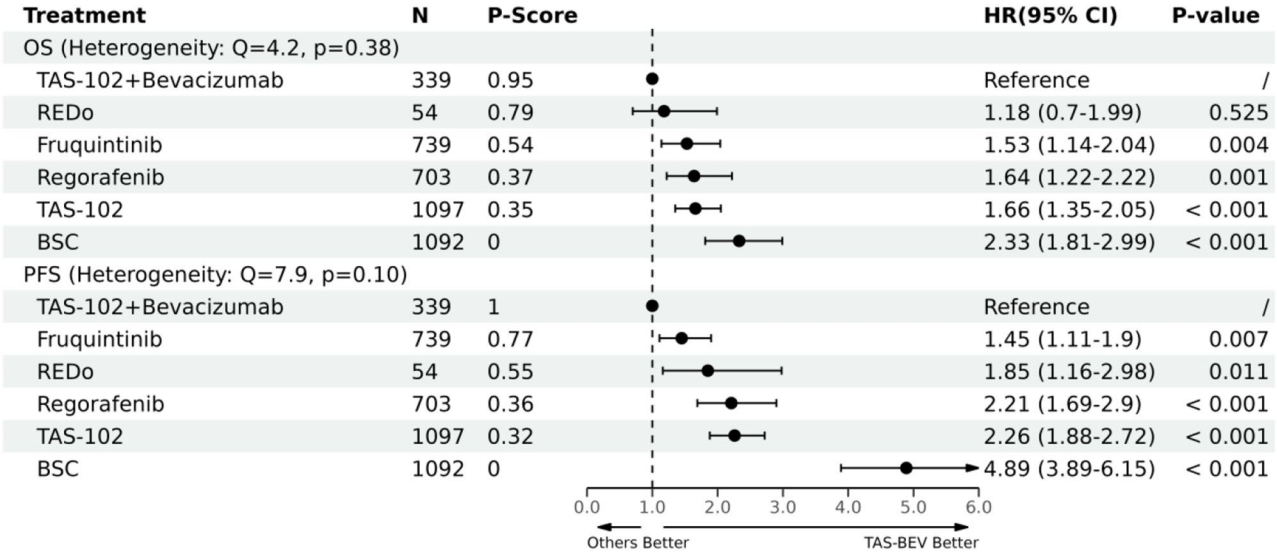

Fig. 5 Network meta-analysis results based on the cox proportional hazards model for OS and PFS. BSC, Best Supportive Care; N, number of patients; HR, Hazards ratios; OS, Overall Survival; PFS, Progression-free survival; RCT, Randomized Controlled Trial; REDo, regorafenib dose optimization; TAS-102, trifluridine/tipiracil; TAS-BEV, TAS-102 with bevacizumab

Regarding efficacy, treatment regimens significantly affect the OS and PFS. BSC had the shortest median survival times for OS and PFS. REDo reported the longest mOS at 9.8 months, followed by TAS-BEV at 8.27 months. For PFS, fruquintinib led to a median survival of 3.63 months, closely followed by TAS-BEV at 3.58 months. The NMA results suggested that for OS, TAS-BEV offered the greatest survival benefit, with fruquintinib and REDo trailing behind. In terms of PFS, TAS-BEV again surpassed other regimens, with fruquintinib being its closest competitor. Assuming PH, the results once again validated the significant advantages of TAS-BEV over other regimens in terms of OS and PFS. Fruquintinib and REDo outperformed regorafenib and TAS-102 but without statistical significance. Moreover, we observed low heterogeneity across treatment regimens, enhancing the reliability of our analysis findings.

From a public payer's view, baseline analysis revealed BSC to be the lowest-cost, most cost-effective choice, with TAS-BEV being most effective. Among the five targeted therapies, TAS-102 was the most cost-effective option. DSA results indicated a stable baseline analysis that was impervious to parameter shifts, model choices, or base assumptions. Similarly, PSA demonstrated that within $100,000/QALY to $200,000/QALY thresholds, BSC was consistently the most cost-effective, with TAS-102 as the optimal active treatment. Price-simulation results indicated that, for cost-effectiveness compared to BSC, TAS-102, fruquintinib, REDoS, regorafenib, and TAS-BEV should reduce prices to 39%, 24%, 14%, 8%, and 7% of their original values, respectively. Moreover, REDoS, fruquintinib, and regorafenib required 40%, 56%, and 59% price cuts, respectively, for economic viability against TAS-102.

This study revealed substantial efficacy of TAS-BEV over alternative regimens, with corroborative evidence from the C-TASKFORCE and SUNLIGHT clinical trials [16, 21]. According to SUNLIGHT, the superiority of TAS-BEV over TAS-102 was confirmed across most subgroups, including factors like age, sex, primary disease location, metastatic sites count, and RAS mutation status [16]. The efficacy of the TAS-BEV comes from TAS-102's dual action—combining trifluridine, which attacks cancer cells, with tipiracil, which prevents trifluridine's breakdown—and bevacizumab's ongoing VEGF blockage, a clinically proven approach to extend survival in refractory CRC [9, 48]. Fruquintinib is an oral, selective, and potent inhibitor of VEGF receptors 1, 2, and 3, which are crucial for angiogenesis and thus for tumor growth and metastasis [49]. As the latest drug approved by the FDA, its success is tied to the publication of the global multicenter FRESCO-2 study [18]. Fruquintinib was initially launched in China for refractory colorectal cancer treatment, following the findings of the FRESCO study [17]. Unlike the SUNLIGHT study, where 24% of patients were VEGF-naïve, those in the FRESCO-2 study were treated with a more advanced line of therapy [18]. Therefore, this study may have somewhat underestimated the efficacy of fruquintinib. However, fruquintinib has retained its status as a leading choice for efficacy and safety among targeted single-agent treatments. Furthermore, patient diversity in the FRESCO and FRESCO-2 studies suggested a broader application for fruquintinib [17, 18]. However, its higher price in the United States has somewhat restricted its widespread clinical use [50].

Table 2 Summary of cost-effectiveness analysis results

Drug	Cost/$	Effectiveness/QALY	Life-year(year)	ICER (VS. BSC)	ICER (VS. TAS-102)
Base-case analysis					
BSC	41,242	0.39	0.69	/	/
TAS-102	140,656	0.68	1.10	349,254	/
REDo	177,069	0.59	0.99	682,534	dominated
Regorafenib	218,487	0.53	0.85	1,317,383	dominated
Fruquintinib	334,799	0.89	1.39	588,347	905,914
TAS-BEV	320,452	1.01	1.59	451,853	539,481
Scenario 1: Excluding Asian Trials					
BSC	41,242	0.39	0.69	/	/
TAS-102	117,707	0.58	0.97	404,972	/
REDo	179,312	0.62	1.04	610,787	1,654,400
Regorafenib	193,508	0.52	0.85	1,154,533	dominated
Fruquintinib	265,279	0.76	1.22	611,923	832,311
TAS-BEV	453,092	1.47	2.43	382,009	377,134
Scenario 2: Time-invariant HR					
BSC	41,242	0.39	0.69	--	--
TAS-102	90,440	0.57	1.00	280,550	--
REDo	159,849	0.84	1.51	261,924	250,152
Regorafenib	120,589	0.58	1.01	418,158	2,095,059
Fruquintinib	221,387	0.67	1.10	653,564	1,305,919
TAS-BEV	270,568	1.11	1.85	317,885	329,875
Scenario 3: Allowance for Active Treatment upon Disease Progression					
BSC	41,242	0.39	0.69	/	/
TAS-102	179,335	0.68	1.10	485,140	--
REDo	204,790	0.59	0.99	821,831	dominated
Regorafenib	222,751	0.53	0.85	1,349,073	dominated
Fruquintinib	367,228	0.89	1.39	653,341	876,748
TAS-BEV	333,405	1.01	1.59	472,816	462,290
Scenario 4: Change utilities					
BSC	41,242	0.45	0.69	/	/
TAS-102	140,656	0.76	1.10	321,344	/
REDo	177,069	0.66	0.99	620,769	dominated
Regorafenib	218,487	0.57	0.85	1,382,855	dominated
Fruquintinib	334,799	0.99	1.39	541,896	835,551
TAS-BEV	320,452	1.10	1.59	425,831	519,172
Scenario 5: Assuming cost of BSC to be 0					
BSC	37,423	0.39	0.69	/	/
TAS-102	138,077	0.68	1.10	353,613	/
REDo	174,190	0.59	0.99	687,260	dominated
Regorafenib	218,044	0.53	0.85	1,342,479	dominated
Fruquintinib	332,132	0.89	1.39	590,656	905,500
TAS-BEV	319,589	1.01	1.59	456,637	544,627

BSC, Best Supportive Care; N, number of patients; RCT, Randomized Controlled Trial; REDo, regorafenib dose optimization; TAS-102, trifluridine/tipiracil; TAS-BEV, TAS-102 with bevacizumab

Compared to prior regorafenib, REDo had lower rates of side effects such as fatigue, hand-foot skin reaction, and hypertension, and it offered marginal OS and PFS benefits and enhanced patients' quality of life [14]. Additionally, REDo has somewhat decreased treatment expenses, making it an effective alternative to regorafenib when considering these factors.

Balancing safety, efficacy, and cost-effectiveness is key in refractory CRC treatment. While targeted therapies improve survival, they also raise adverse event risks and costs. Thus, treatment selection should consider disease traits, patient health, prior treatments, side effect tolerance, and patient preferences [51]. For instance, despite TAS-BEV's effectiveness in life extension, it also carries a risk of heightened adverse events [16], like severe

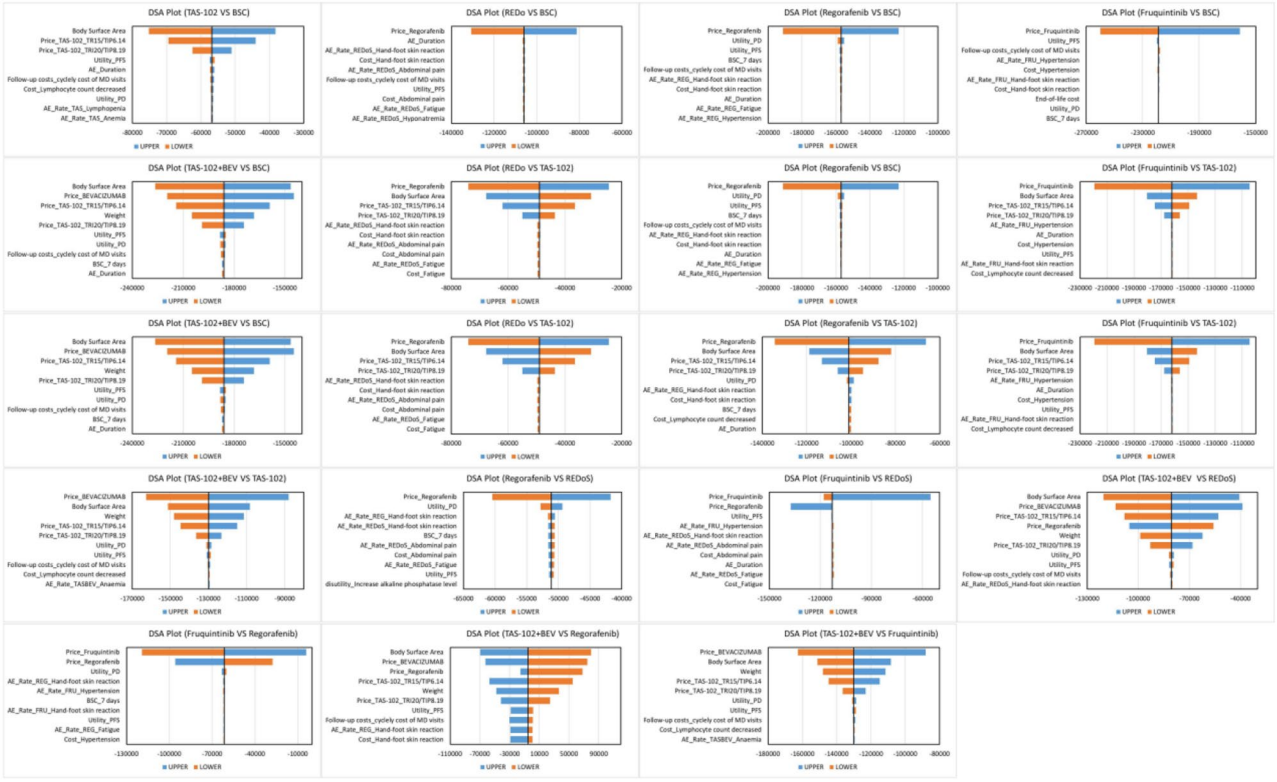

Fig. 6 One-way sensitivity analysis tornado diagram. BSC, Best Supportive Care; DSA, Deterministic Sensitivity Analysis; REDo, regorafenib dose optimization; TAS-102, trifluridine/tipiracil; TAS-BEV, TAS-102 with bevacizumab

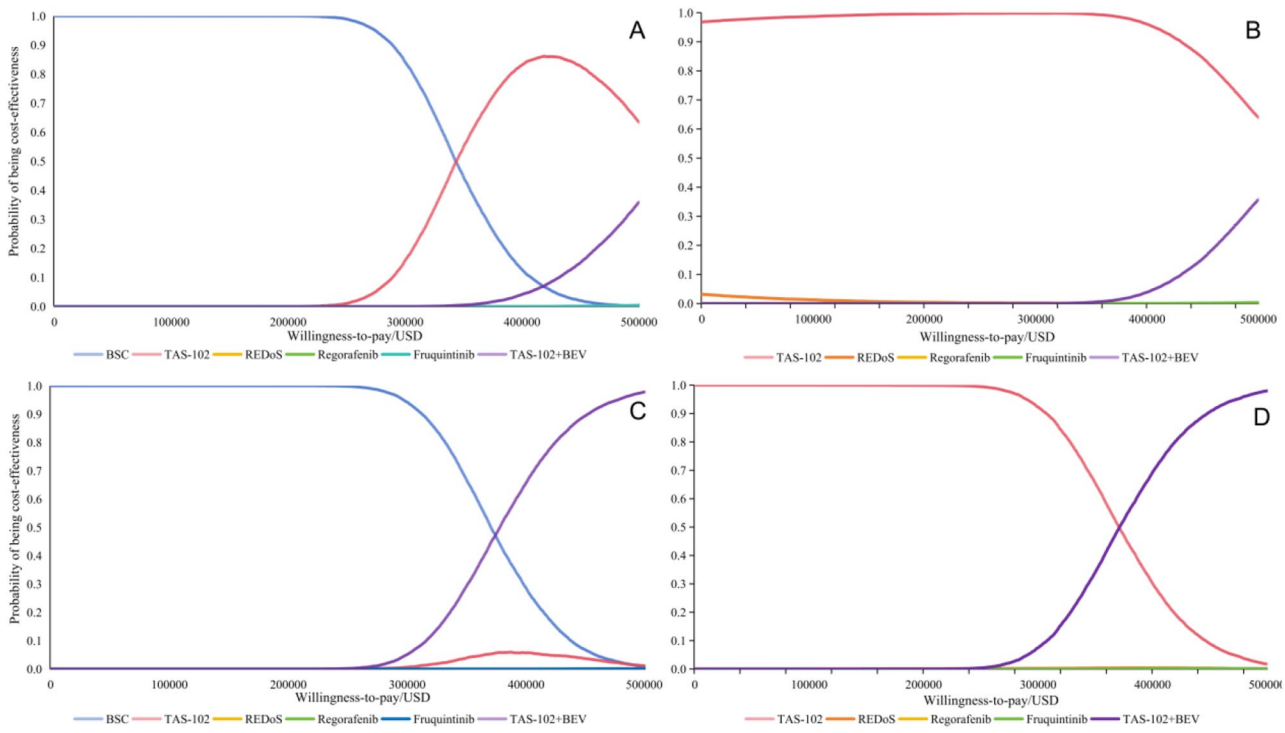

Fig. 7 Cost-effectiveness acceptability curves from probabilistic sensitivity analysis. **A.** Primary Analysis, All Treatments; **B.** Primary Analysis, Excluding BSC; **C.** Scenario Analysis, Excluding Asian Trials, All Treatments; **D.** Scenario Analysis, Excluding Asian Trials, Excluding BSC. BSC, Best Supportive Care; REDo, regorafenib dose optimization; TAS-102, trifluridine/tipiracil; TAS-BEV, TAS-102 with bevacizumab

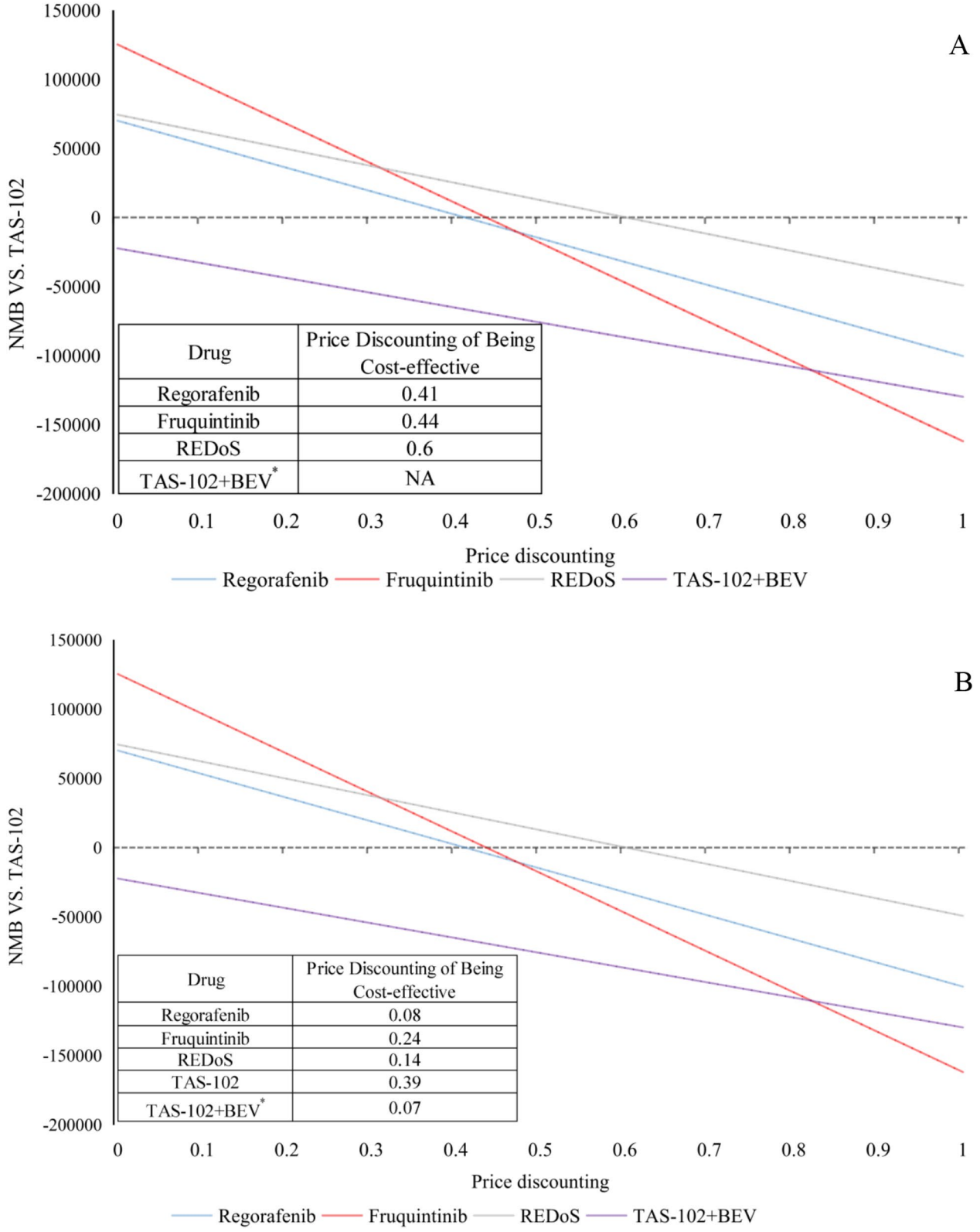

Fig. 8 Evidence-based pricing simulation outcomes. **A.** VS. BSC; **B.** VS. TAS-102. BSC, Best Supportive Care; REDo, regorafenib dose optimization; TAS-102, trifluridine/tipiracil; TAS-BEV, TAS-102 with bevacizumab

neutropenia. Hence, TAS-BEV might not suit patients valuing quality of life over extended survival, or those with severe comorbidities or frail health [52]. On the other hand, TAS-BEV may appeal to patients aiming for the longest survival, particularly if they are healthy and can manage side effects. For those concerned with costs or in resource-limited healthcare settings, BSC might be favored for its affordability. Moreover, TAS-102, a cost-effective targeted regimen, could balance patient expenses with treatment effectiveness. When choosing TAS-102, it is crucial for doctors and patients to jointly consider the effectiveness-side effect trade-off and its cost-effectiveness relative to alternatives. TAS-BEV showed notable survival benefits, indicating that it is an optimal option for patients who can afford it. Doctors needed to ensure that the higher costs were in line with patients' financial means and treatment goals. Effective communication was key so that patients comprehended the benefits, risks, and financial implications of their options. Ongoing monitoring of treatment efficacy and side effects is also crucial for doctors to adapt plans to enhance patient quality of life and overall well-being.

A previous study by Cho et al. assessed the cost-effectiveness of regorafenib and TAS-102 compared to BSC from a US payer perspective, finding that neither was cost-effective at the standard willingness-to-pay threshold of $150,000/QALY [53]. Sang et al.'s study analyzed ReDO against regorafenib, TAS-102, and TAS-BEV from a US payer standpoint and concluded that ReDO was the most cost-effective option at the $150,000/QALY threshold [40]. The discrepancies between these results and those of the current article may stem from limitations in Sang et al.'s study. First, they sourced efficacy data directly from clinical trials without indirect comparison adjustments, resulting in an ostensibly greater effectiveness for ReDO over TAS-BEV, which was arguably implausible [36, 38]. Second, our analysis included additional clinical data, such as the SUNLIGHT study, which impacted the results [16]. Finally, we employed a more suitable parametric extrapolation model, unlike prior studies that relied only on exponential models [54].

While our analysis is based on a WTP threshold of $150,000/QALY, it is important to note that WTP varies significantly across countries, influencing cost-effectiveness assessments. For example, the UK applies a threshold of $25,000-$38,000/QALY [55], while Germany does not have a fixed WTP threshold but often considers values around $55,000/QALY in price negotiations [56]. Japan generally applies a threshold of $35,000-$50,000/QALY, whereas Australia typically considers $33,000/QALY in health technology assessments [57]. China often adopts a threshold of $12,000-$36,000/QALY, based on 1–3 times GDP per capita [58]. In contrast, the US does not have a standardized WTP threshold, but estimates range from $100,000 to $150,000/QALY, with higher values sometimes considered for severe or rare diseases [59]. Given these differences, the cost-effectiveness of TAS-102 and similar therapies may vary across healthcare systems, depending on local WTP thresholds, healthcare budgets, and reimbursement policies. Additionally, drug pricing strategies differ across countries, with some nations implementing centralized price negotiations, while others, like the US, rely on market-driven pricing. These factors highlight the importance of country-specific economic evaluations to ensure that cost-effectiveness assessments align with local healthcare priorities and budget constraints.

Strengths and limitations

This study not only provides critical insights into the safety and efficacy of various targeted treatment regimens but also presents a nuanced cost-effectiveness analysis pivotal for clinical decision-making. The findings are vital for crafting treatment approaches and distributing resources, especially in settings constrained by healthcare availability. The value of this article is multifaceted: This article is the first of its kind to implement a meta-analysis of reconstructed IPD for survival data in refractory CRC patients, setting a gold standard by effectively accounting for event censoring. The pooled estimates for OS and PFS showed minimal heterogeneity, and all incorporated studies were of high quality. These robust, homogeneous survival data can accurately reflect the performance of treatment regimens and provide a basis for calculating sample sizes in future clinical trials. Second, this study is the first to conduct an NMA for refractory CRC using reconstructed IPD, a noteworthy advancement since traditional NMA based on HR requires the PH assumption which was proven inapplicable here. By employing a time-varying model, we leveraged IPD to evaluate regimen efficacy at various time points, enriching the use of clinical evidence and bolstering result reliability [60]. Third, for the first time in this study, an effectiveness and cost-effectiveness comparison of all regimens recommended by the NCCN guidelines was conducted from the perspective of a US public payer. This study provides valuable evidence for rational clinical drug use, rational allocation of healthcare resources, and decision-making. In addition, price simulations were conducted to inform value-based drug pricing.

Like most modeling study, our research also has several limitations. First, when evaluating regimen safety, due to limited evidence, we only used grade 3 + TRAEs and ignored other dimensions of safety indicators, such as grade 1–2 AEs and all-cause AEs. Second, the evidence for safety analysis exhibited significant heterogeneity, necessitating a cautious interpretation of some results. Furthermore, to enhance evidence quality, this

study exclusively included phase II-III RCTs, excluding single-arm studies and disregarding real-world evidence. Therefore, the relevant findings require further validation in real-world clinical practice. Third, indirect comparisons might encounter variations in baseline patient characteristics across different RCTs. Lacking access to individual patient data, our IPD meta-analysis could not account for factors beyond survival status. Consequently, further head-to-head RCTs comparing targeted therapies are essential to confirm our study's conclusions. Fourth, we only used a VA perspective and did not consider other payers, further research is needed to supplement this in the future. Finally, this study did not study the availability and affordability, implying that further research is required.

Conclusion

Compared to BSC, targeted therapies markedly increase AEs without significant safety differences among themselves. In terms of efficacy, TAS-BEV leads substantially, with furqutinib and REDo as secondary choices. For cost-effectiveness, BSC is the frontrunner, with TAS-102 as the preferred targeted therapy. Regimens differ in safety, efficacy, and cost-effectiveness, necessitating a balanced decision by healthcare providers based on individual patient circumstances and therapeutic aims.

Abbreviations

AEs	Adverse events
AIC	Akaike information criterion
BSC	Best Supportive Care
C	Control group
CRC	Colorectal cancer
I	Intervention group
HR	Hazard ratio
N	Number of patients
NA	Not available
NCCN	National Comprehensive Cancer Network
NMA	Network meta-analysis
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
QALY	Quality-Adjusted life year
RCT	Randomized controlled trial
REDo	Regorafenib dose optimization
ROB	Risk of bias
TAS-102	Trifluridine/tipiracil
TAS-BEV	TAS-102 with bevacizumab
TRAE	Treatment-related adverse event

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13561-025-00622-x.

Supplementary Material 1

Author contributions

Prof. Tang, Mr Zhao, Dr Jiang and Mr Shao had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Mr Zhao and Dr Jiang contributed equally to this work. Concept and design: Tang; Acquisition of data: Zhao, Jiang; Analysis and interpretation of data: Zhao, Shao; Drafting of manuscript: Zhao, Jiang; Critical revision of the manuscript for important intellectual content: Tang, Zhao, Jiang, Shao; Statistical analysis: Zhao, Jiang; Obtaining funding: Tang; Administrative and technical support: Tang; Supervision: Tang.

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Data availability

Data sharing statement Full data set is available, on request from the corresponding author, e-mail, tokammy@cpu.edu.cn.

Declarations

Ethical approval

This study does not involve human participants or animal subjects.

Patient consent for publication

Not required.

Provenance and peer review

Not commissioned; externally peer reviewed.

Patient and public involvement

No patient involved.

Permission to reproduce material from other sources

NA.

Competing interests

The authors declare no competing interests.

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