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# TAS-102 with or without bevacizumab treatment for patients with metastatic colorectal cancer: a multi-country cost-effectiveness analysis

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***Abstract***

**Background:** TAS-102 (trifluridine/tipiracil) plus bevacizumab demonstrated a significant survival benefit in patients with refractory metastatic colorectal cancer (mCRC). Physicians and patients are uncertain whether this treatment option is clinically acceptable in different countries, underscoring the need for analyses of the cost-effectiveness of this regimen.

**Objectives:** To guide doctors and patients to choose TAS-102 plus bevacizumab or TAS-102 monotherapy in cancer treatment.

**Design:** The cost-effective analysis.

**Methods:** A comprehensive Markov model of the 10-year horizon for three health states was established using data from the SUNLIGHT trial to evaluate the cost and health effects of TAS-102 with or without bevacizumab at particular willingness-to-pay (WTP) thresholds, analyzing parameters including quality-adjusted life-years (QALYs), incremental cost-effectiveness ratios (ICERs), incremental net monetary benefit, as well as incremental net-health benefit (INHB). Sensitivity and subgroup analyses were additionally conducted.

**Results:** Treatment with TAS-102 plus bevacizumab versus TAS-102 monotherapy increased effectiveness (cost) by 0.39 ($151,474), 0.38 ($26,794), and 0.41 ($8596) QALYs, with an ICER of $388,171, $69,617, and $20,919 per QALY and an INHB of −0.62, −0.03, and 0.18 QALYs in the United States, United Kingdom, and China, respectively. The utility of progression-free survival was the most important factor in this model. At respective WTP thresholds of $150,000, $65,000, and $37,653 per QALY in the United States, United Kingdom, and China, the odds of TAS-102 plus bevacizumab being the dominant treatment were 0%, 49.6%, and 87.8%, respectively. In addition, mCRC patients with an Eastern Oncology Cooperative Group performance status $\geqslant 1$ may be the best candidates for treatment.

**Conclusion:** TAS-102 plus bevacizumab treatment represents a cost-effective third-line treatment for refractory mCRC from a Chinese payers' perspective, although the same was not true in the United States or United Kingdom at current drug prices.

## Plain language summary

### TAS-102-bevacizumab for metastatic colorectal cancer

TAS-102 plus bevacizumab treatment represents a cost-effective third-line treatment for refractory metastatic colorectal cancer in China, although the same was not true in the US or UK at current drug prices.

***Keywords:*** bevacizumab, cost-effectiveness, incremental cost-effectiveness ratio, metastatic colorectal cancer, TAS-102 (trifluridine/tipiracil)

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## Introduction

Colorectal cancer (CRC) is the third most prevalent malignancy and exhibits the second highest death rate globally.[1] In 2020, there were approximately 1.93 million new CRC diagnoses globally and over 930,000 deaths worldwide. These included 286,162, 244,824, and 54,443 deaths in China, Europe, and the United States, respectively, accounting for about 30% of total global CRC-related mortality, and the incidence of this form of cancer and associated mortality is increasing rapidly.[1,2] Roughly 20% of patients with CRC have metastatic disease when initially diagnosed, and metastatic progression ultimately arises in 20%–50% of patients who are diagnosed with early-stage disease, with a 5-year survival rate of under 10%.[3,4]

Currently, third-line treatment options for metastatic CRC (mCRC) patients include regorafenib, trifluridine/tipiracil (TAS-102) monotherapy, and fruquintinib, which may provide some antitumor efficacy. Despite advances in these therapies, survival outcomes remain poor, with respective expected median overall survival (OS) and progression-free survival (PFS) intervals of just 6–9 and 1–3 months.[5–9] In patients with refractory disease, treatment goals largely center on mitigating tumor progression and increasing survival without adversely impacting patient quality of life (QoL). As a result, there remains a pressing need to develop novel antitumor agents or treatment strategies for refractory mCRC, and existing treatment regimens may require further updating.

TAS-102 is an orally active chemotherapeutic drug consisting of thymine analogs (trifluridine) and thymine phosphorylase inhibitors (tipiracil) that is generally well tolerated. As it exhibits a favorable safety profile, TAS-102 has emerged as a new antitumor treatment option that could potentially be combined with other drugs. The most likely combination drug is bevacizumab, a monoclonal antibody targeting VEGF-A. A phase II randomized controlled trial (EudraCT, 2016-005241-23) performed by a research group in Denmark found that TAS-102 plus bevacizumab exhibited good activity in 46 patients with refractory or intolerant mCRC, providing more promising clinical evidence.[10] However, randomized studies are crucial to validate these findings. Recent results from the global phase III SUNLIGHT (NCT04737187) trial showed TAS-102 plus bevacizumab significantly extended patient median OS (10.8 vs 7.5 months; hazard ratio (HR), 0.61; 95% confidence interval (CI), 0.49–0.77; $p < 0.001$) and PFS (5.6 vs2.4 months; HR, 0.44; 95% CI, 0.36–0.54; $p < 0.001$) relative to TAS-102 monotherapy in refractory mCRC patients when used as a third-line treatment, with a serious adverse event (AE) incidence rate of ~13% and without treatment-related deaths.[11] Based on promising survival data, this protocol was recommended under the guidelines of the National Comprehensive Cancer Network and the Chinese Society of Clinical Oncology.[12,13]

While TAS-102 significantly improved survival outcomes and had a good safety profile, given that it is an expensive drug and the population of eligible patients is relatively limited, there is a clear need for economic analyses focused on determining whether the clinical benefits afforded by this treatment are justifiable from a cost perspective to support to the broader application of this promising oncology drug, as high costs may limit public access to innovative anticancer drugs or therapeutic strategies. Determining the value of TAS-102 plus bevacizumab in mCRC patient populations helps guide its rational use at an appropriate price point in multiple international settings. Therefore, this study explored the cost-effectiveness and potential economic impacts of TAS-102 with or without bevacizumab strategies as a third-line treatment option for refractory mCRC patients from the perspective of health services in several different countries including the United States, representative European countries (United Kingdom), and middle-income countries (China).

## Materials and methods

The reporting of this study conforms to the CHEERS (Consolidated Health Economic Evaluation Reporting Standards) statement[14] (Supplemental Table S1).

### *Population and intervention*

As it was based on the same characteristics as in the SUNLIGHT trial, the simulated population for this study consisted of 492 mCRC patients who had received 1–2 previous chemotherapy or targeted therapy regimens in an advanced setting. These patients were randomized at a 1:1 ratio into TAS-102 monotherapy ($n = 246$) or

TAS-102 plus bevacizumab ($n = 246$) groups.[15] The majority of patients (92.1%) had been treated with two regiments and 2.6% had been treated with three or more regiments. Patients received TAS-102 (35 mg/m$^2$ b.i.d. on days 1–5 and 8–12 of each 28-day cycle) either as single-agent treatment or plus bevacizumab (5 mg/kg on days 1 and 15). When progressive disease (PD) or intolerable toxicity was observed in all patients receiving third-line therapy, 31 (13%) and 31 (13%) patients in the TAS-102 alone and TAS-102 plus bevacizumab groups respectively received the best supportive care (BSC) (Table 1).[15] Patients near death receive terminal care. Average body weight values for American, Chinese, and British patients were 74, 65, and 77.3 kg, and mean body surface area values were 1.82, 1.72, and 1.88 m$^2$, respectively (Table 2).[16–19] The detailed medication regimen is found in Supplemental Table S2.

### *Decision model and transition probabilities*

A Markov decision model with a 2-month cycle length extending over a 10-year time horizon, more than 99% of the cohort died, was established using TreeAge Software (version TreeAge Pro 2022, Williamstown, MA, https://www.treeage.com). The model included three independent health states: PFS, PD, and mortality (Supplemental Figure S1). To build a survival model, graph data from the SUNLIGHT trial were extracted by GetData Graph Digitizer (version 2.26, Graph Digitizer Pty Ltd, available at: http://www.getdata-graph-digitizer.com/index.php). Using the Akaike Information Criterion and Bayesian Information Criterion, the best-fitting parameter models for the reconstructed data were assessed from among exponential, log-logistic, log-normal, Gompertz, and Weibull distributions (Supplemental Figure S2 and Supplemental Table S3).[20] Ultimately, a flexible and effective Weibull distribution was selected, and the two parameters scale ($\lambda$) and shape ($\gamma$) were obtained using R (version 4.1.1, R Foundation, available at: http://www.rproject.org) calculation. The time-dependent transition probability in each period was calculated with the following formula: $(1-\exp\ \{\lambda(t-u)\gamma-\lambda t\gamma\})$.[20] Details of the estimated model parameters are shown in Table 1.

### *Measurement of utilities and costs*

Utility is used to reflect a patient's QoL over the course of a natural disease, ranging from 0 (death) to 1 (perfect health status). Since the SUNLIGHT trial did not report detailed data on efficacy or QoL in patients treated with TAS-102 plus bevacizumab, we referred to a previously published article on refractory mCRC. The utility values for the PFS and PD states were 0.73 and 0.59, 0.73 and 0.59, and 0.78 and 0.69 for American, British, and Chinese patients, respectively.[16,19,21] We assessed the impact of the deterioration of QoL contingent on clinical events by multiplying disutility by AE incidence (Table 1).[22]

Only the following direct costs were considered for this study: the costs of medicines, administration, BSC, management for treatment-related severe AEs, and terminal care (Table 2). Costs for post-progression care and other routine care (office visits, imaging tests, laboratory tests, and follow-up) were not considered incremental between the two groups and were therefore not included in the study. US drug prices were derived from the Centers for Medicare & Medicaid Services and similar resources.[23,24] UK drug prices were searched in the Monthly Index of Medical Specialities.[25] Chinese drug prices were obtained through Xiangya Hospital of Central South University. Other direct medical expenses were obtained from previously published articles.[17,19,26–29] In addition, only grade 3 or higher treatment-related AEs (anemia, neutropenia) with incidence rates $\geqslant 5\%$ were considered in this study.[15] AE costs were estimated by multiplying AE incidence rates by the costs associated with each AE treatment event.[22,27–29] Using the American and British consumer price indices, the costs associated with the relevant medical services were inflation-adjusted to 2022 prices.[30] Since the Chinese government controls healthcare costs such that they remain stable, they were not subject to inflation adjustment in the current analysis, which only considers the China Primary Health Care Foundation that offers a Patient Assistance Program (PAP). All prices were converted into US dollars at an exchange rate of \$1 = ¥6.8297 and \$1 = £0.8302 (February 2023).

### *Main outcomes*

Overall costs, expected life years (LYs), quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios (ICERs) were calculated as primary outcomes for this study. ICERs were computed based on the incremental cost divided by the incremental QALYs

**Table 1.** Key clinical and health preference data.

| Parameters | Baseline value | Range | | References | Distribution |
|---|---|---|---|---|---|
| | | Minimum | Maximum | | |
| Weibull survival model | | | | | |
| OS of TAS-102 plus bevacizumab | Scale = 0.017935, Shape = 1.508591 | — | — | 11 | — |
| OS of bevacizumab | Scale = 0.043557, Shape = 1.34468 | — | — | | — |
| PFS of TAS-102 plus bevacizumab | Scale = 0.095291, Shape = 1.195668 | — | — | | — |
| PFS of bevacizumab | Scale = 0.237067, Shape = 1.139692 | — | — | | — |
| Risk for main AEs (grade ⩾3) in TAS-102 plus bevacizumab | | | | | |
| Anemia | 0.060 | 0.344 | 0.516 | 11 | Beta |
| Neutropenia | 0.430 | 0.048 | 0.07 | 11 | Beta |
| Risk for main AEs (grade ⩾3) in bevacizumab | | | | | |
| Anemia | 0.110 | 0.088 | 0.132 | 11 | Beta |
| Neutropenia | 0.320 | 0.256 | 0.384 | 11 | Beta |
| Rate of treatment discontinuation | | | | | |
| TAS-102 plus bevacizumab | 0.130 | 0.104 | 0.156 | 11 | Beta |
| TAS-102 | 0.130 | 0.104 | 0.156 | 11 | Beta |
| Utility and disutility | | | | | |
| Utility of PFS in the United States or United Kingdom | 0.730 | 0.584 | 0.876 | 15,18 | Beta |
| Utility of PD in the United States or the United Kingdom | 0.590 | 0.472 | 0.708 | 15,18 | Beta |
| Utility of PFS in China | 0.780 | 0.624 | 0.936 | 20 | Beta |
| Utility of PD in China | 0.690 | 0.552 | 0.828 | 20 | Beta |
| Disutility due to AEs (grade 1 and 2) | 0.105 | 0.084 | 0.126 | 21 | Beta |
| Disutility due to AEs (grade ⩾3) | 0.183 | 0.146 | 0.220 | 21 | Beta |

AEs, adverse events; OS, overall survival; PD, progressive disease; PFS, progression-free survival; TAS-102, trifluridine/tipiracil.

obtained, and compared to willingness-to-pay (WTP) thresholds of $150,000/QALY, $65,000/QALY, and $37,653/QALY (3 times the Chinese GDP per capita in 2021) of the United States, United Kingdom, and China, respectively.[27,31] In addition, the incremental monetary benefit (INMB) and incremental net-health benefit (INHB) were analyzed in detail and calculated as follows: $\mathrm{INMB} = (\mu E1 - \mu E0) \times \mathrm{WTP} - (\mu C1 - \mu C0)$ and $\mathrm{INHB} = (\mu E1 - \mu E0) - (\mu C1 - \mu C0)/\mathrm{WTP}$, where $\mu Ei$ and $\mu Ci$ are the efficacy and cost associated with TAS-102 plus bevacizumab

**Table 2.** Cost estimates.

| Parameters | United States | | China | | United Kingdom | | Distribution |
|---|---|---|---|---|---|---|---|
| | Mean[Ref.] | Range | Mean[Ref.] | Range | Mean[Ref.] | Range | |
| Drugs per cycle, $ | | | | | | | |
| TAS102 | 35,672[22] | 28,538–42,806 | 4810[a] | 3848–5772 | 5264[24] | 4211.2–6317 | Gamma |
| Bevacizumab | 5236[23] | 4189–6283 | 429[a] | 343–515 | 2260[24] | 1808–2712 | Gamma |
| AEs, $ | | | | | | | |
| TAS-102 | 10,598[21] | 8478–12,718 | 120[26,27] | 96–144 | 636[27,28] | 509–763 | Gamma |
| TAS-102 plus bevacizumab | 13,011[21] | 10,399–15,613 | 117[26,27] | 94–140 | 566[27,28] | 453–679 | Gamma |
| Administration per cycle, $ | 75[25] | 60–90 | 18[26] | 14–22 | 354[28] | 283–425 | Gamma |
| Best supportive care per cycle, $ | 1460[26] | 1168–1752 | 2413[27] | 1930–2896 | 91[26] | 73–109 | Gamma |
| Terminal care per patient, $ | 12,890[26] | 10,312–15,468 | 1967[16] | 1574–2360 | 9392[18] | 7514–11,270 | Gamma |
| Body weight, kg | 74.0[15] | 59.2–88.8 | 65.0[16] | 52.0–78.0 | 77.3[17] | 61.8–92.8 | Normal |
| Body surface area, $m^2$ | 1.82[15] | 1.81–1.83 | 1.72[16] | 1.71–1.73 | 1.88[18] | 1.87–1.89 | Normal |
| Discount rate, % | 3.0[26] | — | 5.0[26] | — | 3.5[26] | — | Uniform |

[a]The costs of drugs were estimated based on the price of Xiangya Hospital of Central South University, 2023.
AEs, adverse events; TAS-102, trifluridine/tipiracil.

($i=1$) or TAS-102 alone ($i=0$), respectively.[32] In the United States, United Kingdom, and China, the major cost and efficacy outcomes were analyzed with assumed annual discount rates of 3%, 3.5%, and 5%, respectively.[27]

### *Sensitivity and scenario analyses*

Sensitivity analyses were utilized to test model uncertainty and stability. In the one-way sensitivity analysis, key parameters were varied by ±20% and used as inputs in the model to identify those parameters that have a substantial impact on model results.[33] T with resultant data being presented using a tornado diagram. As recommended, we applied gamma and beta distributions for AE rates and all utility values, respectively. For probabilistic sensitivity analyses, the parameters were sampled using the Monte Carlo method with 10,000 repeat samplings, and results were plotted in the form of cost-effectiveness acceptability curves and scatter plots.[34]

In scenario analyses, cost-effectiveness for the three national subgroups was explored based on forest plots from the SUNLIGHT trial.[15] Patients were stratified based on age, sex, Eastern Oncology Cooperative Group performance status (ECOG PS), tumor location, RAS mutation status, previous bevacizumab treatment, and time since metastatic cancer diagnosis.[15] It was assumed that the data were identical to the general population except for the OS and PFS HR values for individuals in these three countries, using the approach previously employed by Zhu et al.[35] We also explored the probability and ICER values associated with TAS-102 plus bevacizumab being cost-effective at prices that were 100%, 90%, 50%, and 10% of the current drug price in the United States and United Kingdom.

## Results

### *Base-case analysis*

Based on results generated using a Markov model with a 10-year horizon, TAS-102 plus bevacizumab and TAS-102 monotherapy regimens produced 2.16, 2.09, and 2.14 LYs and 1.56, 1.52, and 1.55 LYs, respectively, with 1.37, 1.50, and

**Table 3.** Results of the base-case analysis.

| Treatment | Total cost, $ | Overall LYs | Overall QALYs | ICER, $ | | INMB, $ | INHB, QALY |
|---|---|---|---|---|---|---|---|
| | | | | Per LY | Per QALY | | |
| The United States | | | | | | | |
| TAS-102 | 152,694 | 1.56 | 0.98 | — | — | — | — |
| TAS-102 plus bevacizumab | 304,168 | 2.16 | 1.37 | 253,487 | 388,171 | −92,974 | −0.62 |
| China | | | | | | | |
| TAS-102 | 10,190 | 1.52 | 1.09 | — | — | — | — |
| TAS-102 plus bevacizumab | 18,786 | 2.09 | 1.50 | 15,243 | 20,919 | 6842 | 0.18 |
| The United Kingdom | | | | | | | |
| TAS-102 | 20,484 | 1.55 | 0.97 | — | — | — | — |
| TAS-102 plus bevacizumab | 47,279 | 2.14 | 1.36 | 45,502 | 69,617 | −2094 | −0.03 |

ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; INHB, incremental net-health benefits; LYs, life-years; QALY, quality-adjusted life-year; TAS-102, trifluridine/tipiracil.

1.36 QALYs versus 0.98, 1.09, and 0.97 QALYs in the United States, China, and the United Kingdom when taking QoL into consideration. The cost of TAS-102 plus bevacizumab treatment was $304,168, $18,786, and $47,279 as compared to $152,694, $10,190, and $20,484 for TAS-102 monotherapy in the United States, China, and the United Kingdom, respectively. The ICER, negative INHBs, and negative INMBs for TAS-102 plus bevacizumab relative to TAS-102 alone were $388,171/QALY ($253,487 per year) and $69,617/QALY ($45,502 per year), −0.62 and −0.03 QALYs, and −$92,974 and −$2094 in the United States and United Kingdom, with these values being higher than the conventional WTP thresholds. In China, the ICER, positive INHBs, and positive INMBs of TAS-102 plus bevacizumab relative to TAS-102 alone were $20,919/QALY ($17,635 per year), 0.18 QALYs, and $6842, with these values being lower than the conventional WTP thresholds (Table 3).

### *Sensitivity analysis*

One-way sensitivity analyses yielded similar results for the Chinese and British patient models, with the utility of PFS having the most significant effect on model results (range 0.584–0.876, ICER range $18,274/QALY to $388,170/QALY), followed by the costs of medicines and the utility of PD (Figure 1). In American patient models, PFS utility had the greatest impact, followed by the incidence of neutropenia in the TAS-102 plus bevacizumab group and the cost of TAS-102 (Figure 1). Probabilistic sensitivity analyses indicated that the odds of TAS-102 plus bevacizumab being cost-effective relative to TAS-102 monotherapy were 0%, 87.8%, and 49.6%, respectively, under the corresponding traditional WTP thresholds in the United States, China, and the United Kingdom (Figure 2 and Supplemental Figure S3). In addition, the probability of TAS-102 plus bevacizumab being cost-effective was greater than 50% at the WTP values of 36,000 and 6700 per QALY in the United States and United Kingdom, respectively (Figure 2).

### *Subgroup and scenario analysis*

In the subgroup analysis, TAS-102 plus bevacizumab remained a cost-effective treatment regimen from a Chinese payer perspective, however, whereas the opposite was true from the American perspective. Treatment of Chinese patients with an ECOG PS $\geq$ 1 was most likely to be cost-effective, with an ICER of $15,429/QALY, a positive INHB of 0.32 QALY, and a probability of 93.9%, followed by patients who had not previously undergone bevacizumab therapy and RAS

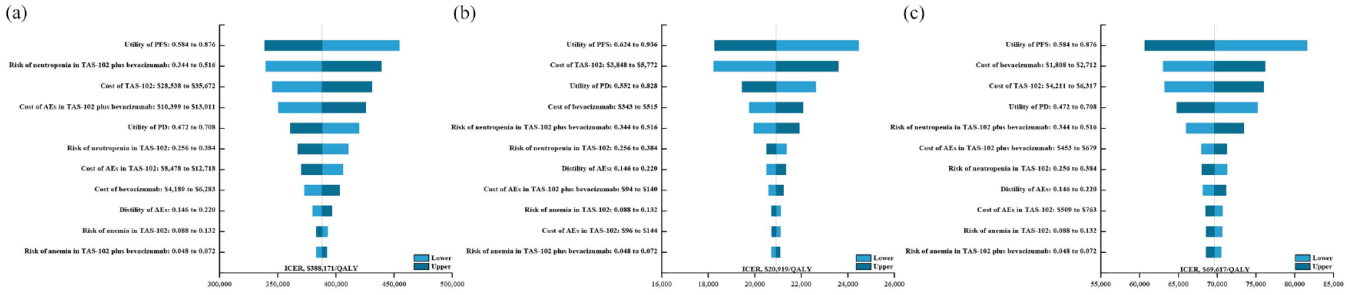


**Figure 1.** The one-way sensitivity analyses for TAS-102 plus bevacizumab strategy compared to TAS-102 strategy in the United States (a), China (b), and the United Kingdom (c).
AEs, adverse events; PD, progressive disease; PFS, progression-free survival; QALY, quality-adjusted life-year; TAS-102, trifluridine/tipiracil.

mutations (Figure 3). In addition, patients in the UK patient subgroups exhibited similar outcomes to those for Chinese patient subgroups, with such treatment being most cost-effective in patients with an ECOG PS $\geqslant$ 1 ($49,791/QALY, 0.12, and 69.9%), followed by patients without a history of prior bevacizumab therapy ($53,658/QALY, 0.14, and 67.7%), and patients diagnosed with mCRC <18 months previously ($62,892/QALY, 0.02, and 56.7%) (Supplemental Table S4).

A scenario analysis revealed that when the cost of TAS-102 plus bevacizumab was reduced by 90% and 10% in the United States and the United Kingdom, the resultant ICERs were $128,202/QALY and $63,157/QALY, respectively, both of which were lower than the corresponding WTP value, thus demonstrating cost-effectiveness in these two countries (Supplemental Table S5).

## Discussion

Patient CRC-related healthcare expenditures in 2015 in the United States, China, and Europe were $11.57, ¥25.65, and €7.50 billion, respectively.[36–38] In addition, the significant increase in morbidity due to lifestyle changes and population aging trends, as well as the updating of treatment regimens for mCRC, have significantly improved the survival rate and survival durations of affected patients, inevitably increasing the associated CRC-related medical expenditures.[37,39] Given the rising cost of health care and the limited medical resources available in different countries, individuals and societies must conduct economic assessments focused on the cost-effectiveness of cancer treatment. We herein conducted the first cost-effectiveness analysis of the internationally approved TAS-102 plus bevacizumab regimen for refractory mCRC patients from the perspectives of payers in the United States, the United Kingdom, and China.

Based on the current decision analysis model, TAS-102 plus bevacizumab treatment gained 0.41, 0.39, and 0.38 QALYs compared with TAS-102 alone, providing ICER values of $20,919/QALY in China, $388,171/QALY in the United States, and $69,617/QALY in the United Kingdom, respectively. At a WTP threshold of $37,653/QALY in China, these analyses showed that TAS-102 plus bevacizumab treatment was cost-effective. However, given current local drug prices, TAS-102 plus bevacizumab was less cost-effective than TAS-102 monotherapy at WTP thresholds of $150,000 in the United States and $65,000/QALY in the United Kingdom. One-way sensitivity analyses revealed that PFS utility was the most sensitive parameter driving the results of this model, followed by the cost of anticancer drugs. Probabilistic sensitivity analyses found that the odds of TAS-102 plus bevacizumab being cost-effective were 87.8% and 49.6% in China and the United Kingdom, respectively, while in the United States these odds were close to zero. A comprehensive sensitivity analysis found this model to be stable. To achieve the same cost–benefit probability in these three countries, a cost reduction of 90% and 10% may be required in the United States and the United Kingdom. Thus, this study provides information on drug discounts, which is a key driver of the balance between affordability for patients in different countries or regions and the financial costs imposed on the public healthcare system.

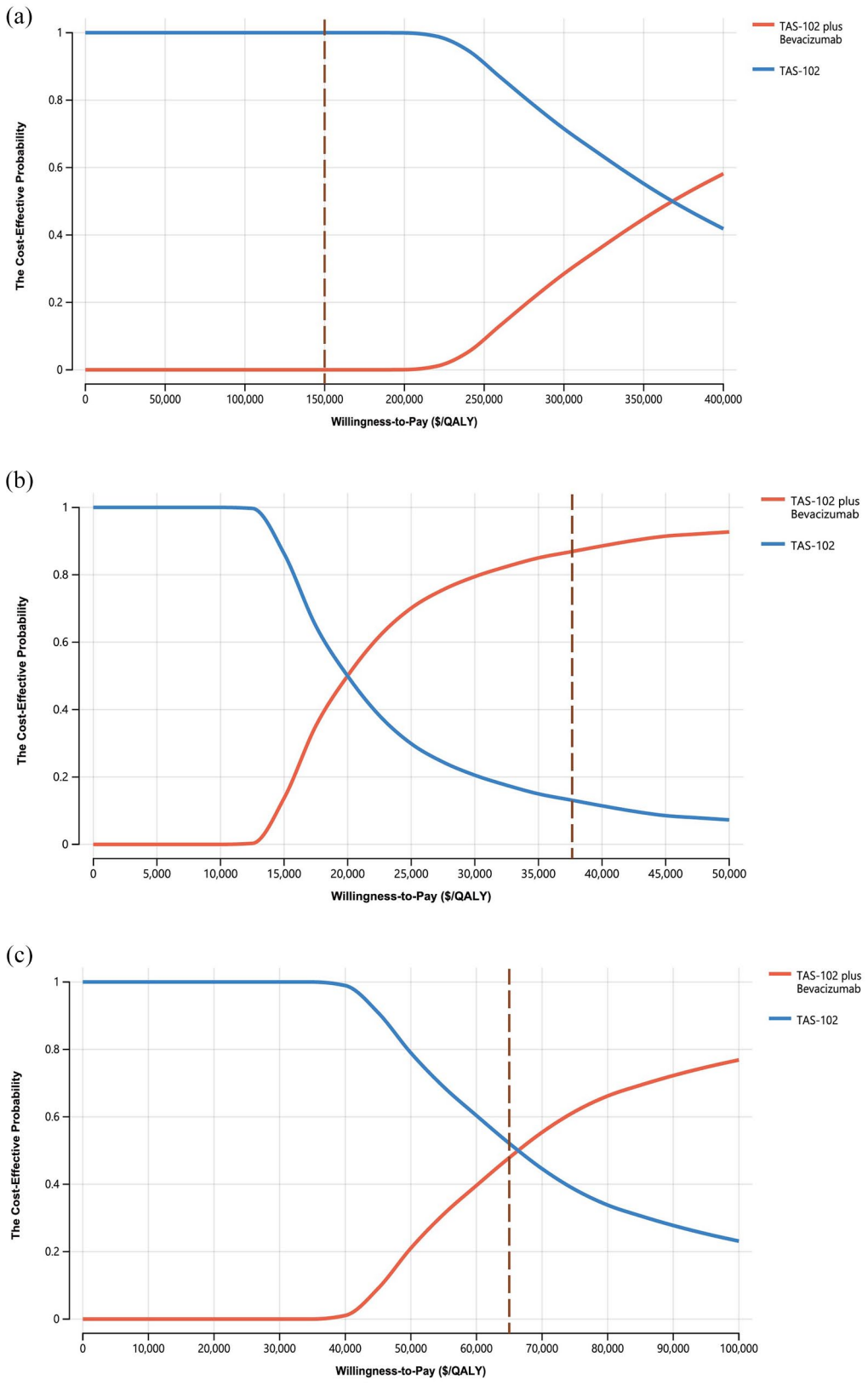


**Figure 2.** The cost-effectiveness acceptability curves for the TAS-102 plus bevacizumab strategy compared to TAS-102 strategy in the United States (a), China (b), and the United Kingdom (c).
QALY, quality-adjusted life-year; TAS-102, trifluridine/tipiracil.

| Subgroups | HR of OS (95% CI) | HR of PFS (95% CI) | ICER Median (range), $/QALY | INHB Median (range), QALY | Probability of cost-effectiveness, % |
|---|---|---|---|---|---|
| **Age, years** | | | | | |
| <65 | 0.65 (0.48 - 0.87) | 0.41 (0.31 - 0.53) | 25,075 (19,843 - 55,251) | 0.12 (0.05 to 0.31) | 79.1 |
| ≥65 | 0.69 (0.42 - 0.81) | 0.46 (0.34 - 0.62) | 25,732 (16,145 - 30,752) | 0.09 (0.03 to 0.47) | 78.3 |
| **Sex** | | | | | |
| Male | 0.62 (0.45 - 0.84) | 0.42 (0.32 - 0.56) | 22,439 (18,081 - 41,670) | 0.16 (-0.01 to 0.38) | 83.3 |
| Femalea | 0.62 (0.46 - 0.85) | 0.46 (0.35 - 0.61) | 20,662 (17,304 - 40,068) | 0.18 (-0.01 to 0.38) | 87.8 |
| **ECOG PS** | | | | | |
| 0 | 0.74 (0.53 - 1.02) | 0.37 (0.27 - 0.49) | 37,610 (-254,221 - 24,641) | 0.00 (-0.16 to 0.19) | 60.1 |
| ≥1 | 0.54 (0.41 - 0.73) | 0.50 (0.39 - 0.65) | 15,429 (14,186 - 20,243) | 0.32 (0.11 to 0.53) | 93.9 |
| **Location of tumour** | | | | | |
| Left-sided tumour | 0.65 (0.50 - 0.85) | 0.44 (0.35 - 0.56) | 23,546 (19,020 - 44,573) | 0.13 (-0.02 to 0.31) | 81.7 |
| Right-sided tumour | 0.59 (0.40 - 0.87) | 0.44 (0.31 - 0.64) | 19,789 (16,520 - 43,598) | 0.21 (-0.02 to 0.49) | 89.4 |
| **RAS mutation status** | | | | | |
| Wild-type | 0.64 (0.43 - 0.96) | 0.29 (0.20 - 0.42) | 31,767 (23,370 - 268,741) | 0.06 (-0.15 to 0.30) | 68.4 |
| Mutant | 0.62 (0.43 - 0.81) | 0.51 (0.41 - 0.64) | 18,693 (14,240 - 29,492) | 0.20 (0.03 to 0.49) | 91.2 |
| **Previous bevacizumab** | | | | | |
| Yes | 0.72 (0.52 - 0.92) | 0.51 (0.41 - 0.63) | 25,849 (17,573 - 74,891) | 0.08 (-0.06 to 0.31) | 78.3 |
| No | 0.40 (0.25 - 0.63) | 0.29 (0.19 - 0.43) | 17,316 (16,340 - 22,629) | 0.47 (0.15 to 0.85) | 93.2 |
| **Time since diagnosis of metastasic cancer, months** | | | | | |
| <18 | 0.52 (0.37 - 0.72) | 0.36 (0.26 - 0.49) | 19539 (17,443 - 26,939) | 0.28 (0.07 to 0.52) | 89.2 |
| ≥18 | 0.70 (0.53 - 0.94) | 0.51 (0.39 - 0.65) | 24,043 (18,782 - 98,863) | 0.10 (-0.06 to 0.28) | 81.5 |

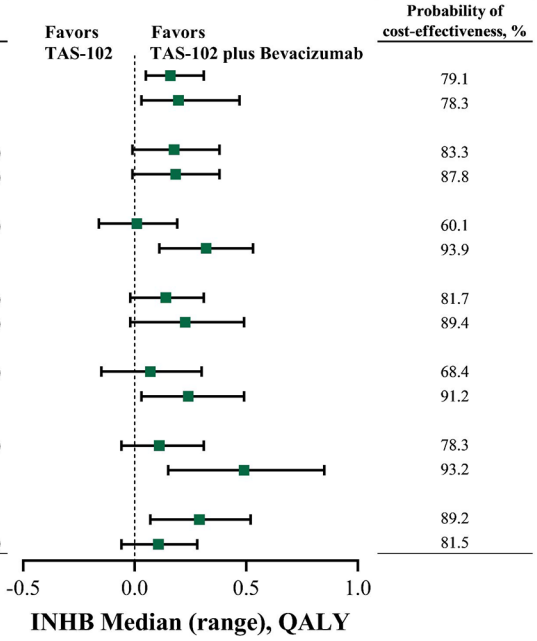


**Figure 3.** Subgroup analysis results in China.
CI, confidence interval; ECGO PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; INHB, incremental net-health benefit; OS, overall survival; PFS, progression-free survival; QALYs, quality-adjusted life-years.

Multiple cost-effectiveness analyses of TAS-102 have been conducted from the perspective of payers in the United States, the United Kingdom, Japan, and Greece to date, which have focused primarily on monotherapy for colorectal and gastric cancers (GCs).[26,40–46] In the United States, two studies analyzed TAS-102 monotherapy cost-effectiveness for patients with refractory mCRC and pretreated metastatic GC, respectively, which produced ICERs of $330,000/QALY and $986,333/QALY compared with BSC, indicating that it was not cost-effective.[40,41] Ramaekers et al. found an ICER of £49,392/QALY for TAS-102 monotherapy for mCRC from a UK payers' perspective, suggesting that TAS-102 is a cost-effective use of NHS resources.[42] Two studies analyzing mCRC and GC patient treatment showed that the ICERs of TAS-102 monotherapy were $432,734/QALY and $294,113/QALY compared to BSC or nivolumab, respectively, suggesting that it was cost-effective in Japan.[43,44] Most of these findings are similar to the present results, suggesting that although TAS-102 treatment seems promising in clinical practice, there is some variation in the degree to which it represents a cost-effective substitute for the standard of care in different countries or healthcare systems. There are several reasons for this observation. In the United States, treatment cost-effectiveness is not a legal mandate, and potential costs are not taken into consideration by the FDA when making regulatory decisions regarding marketing applications[47,48]; European countries such as the United Kingdom have policies that allow national authorities to negotiate drug prices directly and drug pricing is usually supervised or directly regulated by each national government[49]; in addition, the State Council of China released the 13th Five-Year Plan for advancing healthcare system reform in January 2017, highlighting the key importance of economic evaluation when conducting multilateral negotiations and providing PAPs for the launch of the China Primary Health Care Foundation for cancer drugs in China.[48] Differences in bargaining power and pricing rules could explain why cancer drugs launched in China or European countries tend to be cheaper than in the United States. The present results are thus expected to provide information for policy regulators in multiple countries when making decisions regarding insurance approvals.

There have been few economic evaluations of TAS-102 combinations to date, with only one study having analyzed it from the perspective of the Japanese health system. TAS-102 plus bevacizumab was associated with an ICER of $21,534/QALY relative to TAS-102 monotherapy, indicating that TAS-102 plus bevacizumab is a cost-effective strategy.[26] The study had several shortcomings. The model was constructed and analyzed based on a small number of patients and incomplete phase I/II trial data, and the disutility of AEs was not considered in this analysis. As a result, these methods are less precise and lack analyses of key factors, such as the incidence, cost, and one-way sensitivity analyses of AEs. In addition, the results may not be generalizable to other countries as they focus on the payer's perspective of the healthcare system of a single country. By contrast, our analysis is based on comprehensive long-term data from SUNLIGHT phase III clinical trials, improving the robustness of the survival estimates in this model. Second, we considered the incidence and cost of grade ⩾3 AEs, which are closely related to QoL, and employed their disutility values to correct for average utility values. Our analysis thus more accurately reflects the utility of these treatment methods. Third, we examined the relative cost-effectiveness of these therapeutic regimens in a range of patient subgroups, potentially providing a valuable clinical reference. Finally, we performed these analyses from the perspectives of health systems in multiple countries, including the United States as a high-income country, the United Kingdom as a representative European nation, and the middle-income country of China. These results can thus not only be applied to a single country but also can be generalized across multiple health systems.

A subgroup analysis found that TAS-102 combined with bevacizumab had a higher chance of being cost-effective for patients with right-sided tumors and RAS mutant mCRC. This is consistent with previous findings. A CALGB/SWOG study involving 80,405 patients found that bevacizumab treatment of patients with left-sided tumors was inferior to patients with right-sided mCRC regardless of RAS mutation status (OS, HR,1.26; 95% CI, 1.00–1.58 and PFS, HR, 1.03, 95% CI, 0.83–1.28).[50] The main reason for the different prognosis of the patients with right- and left-sided CRC may be due to their embryological origins, with the right and left colon, respectively, originating in the midgut and hindgut, resulting in molecular, biological, and anatomical differences.[51,52] Another retrospective analysis of a community sample found that the addition of bevacizumab as a treatment for KRAS mutant mCRC may provide a significant PFS benefit (0.41 months; 95% CI 9.0–11.3). One of the reasons for these uncertain results can also be attributed to cancer heterogeneity. Therefore, in the era of personalized medicine, further research exploring biomarkers is needed, as the screening-based identification of more suitable patients with heterogeneous diseases will make innovative treatment options more likely to be cost-effective.

Our model has several limitations due to the simplification of disease processes, costs, and model assumptions. First, our simulation model, like many others, was derived from clinical trial data and hence necessarily vulnerable to uncertainty. However, the Weibull models showed a good fit to the survival data and were validated in the sensitivity analysis. The long-term benefits of TAS-102 plus bevacizumab for refractory mCRC patients remain an open question. Further updated data reported from the SUNLIGHT trial are needed to reduce these uncertainties in the future. Second, the costs of grade 1 or 2 AEs were not considered in this model, which might have some impact on our results. However, the sensitivity analysis revealed that no matter how these parameters related to AEs varied within the predefined range, the results remained unchanged. Third, since the utility values of patients were not detailed in the SUNLIGHT trial, the utility values for this study were derived from previously published articles related to mCRC. However, sensitivity analyses demonstrated that the model was robust and held positive evidence. Finally, survival curves for all subgroups were not reported in the SUNLIGHT study. We conducted subgroup analyses in three countries based on the HRs of subgroups, which may differ somewhat from real survival outcomes. Therefore, further subgroup analyses will be necessary in the future to generate stronger evidence.

## Conclusion

In summary, these economic evaluation results based on a decision analysis model suggested that TAS-102 plus bevacizumab is cost-effective as a third-line treatment for refractory mCRC from

the perspective of the Chinese healthcare system, but not from the US or UK healthcare systems. In addition, we also potential patient subgroups in which such treatment may be more cost-effective, providing opportunities for the personalized optimization of cancer care. This study can provide stronger evidence for guideline recommendations and may inform decision-making for patients, clinicians, governments, and healthcare finance structures in different countries.

## Declarations

### *Ethics approval and consent to participate*

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors, it does not require the approval of the independent ethics committee.

### *Consent for publication*

Not applicable.

### *Author contributions*

**Youwen Zhu:** Conceptualization; Formal analysis; Investigation; Methodology; Validation; Visualization; Writing – original draft; Writing – review & editing.

**Kun Liu:** Conceptualization; Formal analysis; Investigation; Validation; Visualization; Writing – original draft; Writing – review & editing.

**Hong Zhu:** Conceptualization; Data curation; Funding acquisition; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

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### *Competing interests*

The authors declare that there is no conflict of interest.

### *Availability of data and materials*

All authors had full access to all of the data in this study and took complete responsibility for the integrity of the data and the accuracy of the data analysis. The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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## Supplemental material

Supplemental material for this article is available online.

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