Assessment of Clinically Meaningful Benefits and Incremental Costs of Adding Bevacizumab to Trifluridine/Tipiracil for Metastatic Colorectal Cancer: A Comparison with Other Combination Regimens

EE637

Robert Epstein[1], Tehseen Salimi[2], Nadeem Khan[2], Lisa Abramovitz[3], Rebecca Bornheimer[3], Derek Weycker[3], Christopher Cann[4]

[1]Epstein Health, Woodcliff Lake, NJ, USA; [2]Taiho Oncology, Princeton, NJ, USA; [3]Avalere Health, Boston, MA, USA; [4]Fox Chase Cancer Center, Philadelphia, PA, USA

INTRODUCTION

- Trifluridine/tipiracil (FTD/TPI; Lonsurf®)—a fixed-dose combination tablet—was approved as third-line treatment for adults with metastatic colorectal cancer (mCRC) who previously received fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy:[1]
  - By the US Food and Drug Administration (FDA), 2015.
  - By the European Commission (EC), 2016.
- In 2023, based on findings from the Phase III SUNLIGHT trial, the US FDA and EC expanded the indication for FTD/TPI to include its use in combination with bevacizumab:[2]
  - SUNLIGHT also met both ESMO-MCBS and ASCO recommended targets for improvements in overall survival and progression-free survival.[3]
- While the SUNLIGHT trial demonstrated the safety and efficacy of FTD/TPI+BEV (vs. FTD/TPI), evidence assessing clinically meaningful benefits and incremental costs of adding BEV to FTD/TPI, relative to other regimens for advanced gastrointestinal cancers (aGIC), is not available.

OBJECTIVE

- To review and compare differences in clinical benefits and incremental costs of adding BEV to FTD/TPI versus addition of single agents to other approved chemotherapy regimens currently used for the treatment of aGIC in US clinical practice.[4]

METHODS

Study Design

- Comparative and comprehensive evaluation of efficacy, safety, and costs based on a targeted literature review.

Overview

- Benchmarking of incremental clinical benefits/economic costs was based on Phase III trial data for qualifying regimens that included ≥1 branded agent, were approved for aGIC in the US, and comprised combination therapies for which a single agent was added to an existing regimen.
- Qualifying regimens were identified by selecting:
  - All branded drugs currently approved for GIC from the National Cancer Institute (NCI) website.
  - From the list of branded drugs, those included in combination chemotherapy regimens that are currently recommended by the National Comprehensive Cancer Network (NCCN) for aGIC.
  - From the list of recommended regimens, those approved by the US FDA for aGIC based on a review of package inserts.
  - From the list of approved regimens, those that were evaluated in Phase III clinical trials versus regimens with one fewer agent.

Study Measures

- Clinical benefits included overall survival (OS), progression-free survival (PFS), and objective response rate (ORR):
  - Adverse events (AEs) and treatment discontinuation were also summarized
- Economic costs included drugs and their administration; drug costs were based on projected utilization of chemotherapy regimens and unit prices, and administration costs were based on published fee schedules:
  - Projected utilization was based on recommended dosages and administration, relative dose intensity (RDI), median duration of treatment.

Statistical Analyses

- Absolute and percentage differences in costs (2024USD) were calculated for each chemotherapy regimen.

LIMITATIONS

- Due to insufficient numbers of comparison regimens indicated for mCRC, the literature search was expanded to qualifying regimens for aGIC.
- Some measures (eg, treatment discontinuation, RDI, dose modifications) were not reported in all trial publications:
  - Estimation of regimen costs thus required certain assumptions (eg, for regimens where RDI was not available, assumed same as average across all reported values, 89.5%).
- Drug utilization was based on data from Phase III clinical trials, which may not reflect clinical practice.

CONCLUSIONS

- **Addition of BEV to FTD/TPI (vs. single-agent FTD/TPI) for mCRC yielded greater clinically meaningful benefits in terms of OS/PFS, and substantially lower incremental costs, compared with addition of single agents to other approved chemotherapy regimens for aGIC.[4]**
- **FTD/TPI+BEV thus has the potential to yield substantive patient health benefits with relatively low marginal costs to patients and health plans.**

RESULTS

- Seven regimens qualified for inclusion after the targeted literature review (**Table 1**).
- Addition of BEV to FTD/TPI yielded greatest improvements in clinical benefits vs. single agents added to comparator regimens: increase in OS (median), 3.3 vs. 1.3 – 2.5 months; increase in PFS (median), 3.2 vs. 0.2 – 2.2 months (**Table 2, Figure 1**):
  - Differences in AEs and treatment discontinuation were generally favorable/comparable for FTD/TPI + BEV.
- Incremental cost of adding BEV to FTD/TPI was lower than addition of single agents to other regimens: absolute increment, $26,441 vs. $74,373–$332,705; percentage increment, 32% vs. 346%–6,080% (**Figure 2**)

Table 1. Characteristics of Phase III trials for qualifying chemotherapy regimens

Trial Name	Enrollment Years	LOT	Cancer Type/Severity	Prior Treatment	Intervention	Control
SUNLIGHT	2020-2022	3rd	Histologically confirmed unresectable adenocarcinoma of colon/rectum	≤2 previous chemotherapy regimens for advanced CRC	FTD/TPI + bevacizumab	FTD–TPI
VELOUR	2007-2010	2nd	Colorectal adenocarcinoma with metastatic disease not amenable to potentially curative treatment; ECOG of 0, 1, or 2	1 prior oxaliplatin-based regimen (+ BEV)	FOLFIRI + Ziv-aflibercept	FOLFIRI
RAINBOW	2010-2012	2nd	Advanced gastric or gastro-esophageal junction adenocarcinoma	Disease progression ≤4 months after 1st-line chemotherapy	Paclitaxel + ramucirumab	Paclitaxel
RAISE	2010-2013	2nd	Colorectal carcinoma; ECOG 0 or 1	Disease progression ≤6 months of the last dose of 1st-line therapy	FOLFIRI + ramucirumab	FOLFIRI
CHECKMATE-648	2017-2019	1st	Unresectable advanced, recurrent, or metastatic esophageal squamous-cell carcinoma	Untreated	Chemo[1] + nivolumab	Chemo[1]
CHECKMATE-649	2017-2019	1st	Advanced gastric/gastroesophageal junction adenocarcinomas/esophageal adenocarcinoma	Untreated	Chemo[2] + nivolumab	Chemo[2]
TOPAZ-1	2019-2020	1st	Unresectable or metastatic biliary tract cancer or with recurrent disease	Untreated	Gemcitabine + cisplatin + durvalumab	Gemcitabine + cisplatin

ECOG: Eastern Cooperative Oncology Group; FOLFIRI: fluorouracil + irinotecan + leucovorin; FOLFOX: fluorouracil + leucovorin + oxaliplatin, FTD/TPI: tipiracil + trifluridine; LOT: line of therapy; N/R: not reported; XELOX: capecitabine + oxaliplatin
[1]fluorouracil + cisplatin; [2]FOLFOX or XELOX

Table 2. Efficacy results from Phase III clinical trials for qualifying chemotherapy regimens

Trial Name	Arm	N (ITT)	Median Follow-Up, Mths	Efficacy Measures: Overall Survival: Median (95% CI), Mths	Overall Survival: % Alive at 6/12 Mths	Progression-Free Survival: Median (95% CI), Mths	Progression-Free Survival: % PF at 6/12 Mths	ORR, %
SUNLIGHT	FTD/TPI + bevacizumab	246	14.2	10.8 (9.4-11.8)	77.0% / 43.0%	5.6 (4.5-5.9)	43.0% / 16.0%	6.1%
	FTD/TPI	246	13.6	7.5 (6.3-8.5)	61.0% / 30.0%	2.4 (2.1-3.2)	16.0% / 1.0%	1.2%
VELOUR	FOLFIRI + ziv-aflibercept	612	22.3	13.5 (12.5-15.0)	80.0% / 56.0%	6.9 (6.5-7.2)	56.0% / 17.0%	19.8%
	FOLFIRI	614		12.1 (11.1-13.1)	80.0% / 51.0%	4.7 (4.2-5.4)	40.0% / 17.0%	11.1%
RAINBOW	Paclitaxel + ramucirumab	330	7.9	9.6 (8.5-10.8)	72.0% / 40.0%	4.4 (4.2-5.3)	36.0% / 12.0%	28.0%
	Paclitaxel	335		7.4 (6.3-8.4)	57.0% / 30.0%	2.9 (2.8-3.0)	17.0% / 4.0%	16.0%
RAISE	FOLFIRI + ramucirumab	536	21.7	13.3 (12.4-14.5)	84.0% / 60.0%	5.7 (5.5-6.2)	55.0% / 18.0%	13.4%
	FOLFIRI	536		11.7 (10.8-12.7)	80.0% / 50.0%	4.5 (4.2-5.4)	45.0% / 13.0%	12.5%
CHECKMATE-648	Chemo[1]+ nivolumab	321	12.1	13.2 (11.1-15.7)	81.0% / 54.0%	5.8 (5.6-7.0)	50.0% / 24.0%	47.0%
	Chemo[1]	324	9.5	10.7 (9.4-11.9)	75.0% / 44.0%	5.6 (4.3-5.9)	43.0% / 16.0%	27.0%
CHECKMATE-649	Chemo[2] + nivolumab	789	13.1	13.8 (12.6-14.6)	N/R / 55.0%	7.7 (7.1-8.5)	N/R / 36.0%	58.0%
	Chemo[2]	792	11.1	11.6 (10.9-12.5)	N/R / 48.0%	6.9 (6.6-7.1)	N/R / 22.0%	46.0%
TOPAZ-1	Gemcitabine + cisplatin + durvalumab	341	16.8	12.8 (11.1-14.0)	79.0% / 54.1%	7.2 (6.7-7.4)	58.0% / 16.0%	26.7%
	Gemcitabine + cisplatin	344	15.9	11.5 (10.1-12.5)	77.0% / 48.0%	5.7 (5.6-6.7)	47.0% / 7.0%	18.7%

CI: confidence interval; FOLFIRI: fluorouracil + irinotecan + leucovorin; FTD/TPI: tipiracil + trifluridine; HR: hazard ratio, ITT: intention-to-treat; LOT: line of therapy; mths: months; N/R: not reported; ORR: objective response rate; PF: progression-free
[1]fluorouracil + cisplatin; [2]FOLFOX or XELOX

Figure 1. Hazard ratios (95% CIs) for time to death and time to progression from Phase III clinical trials for qualifying chemotherapy regimens

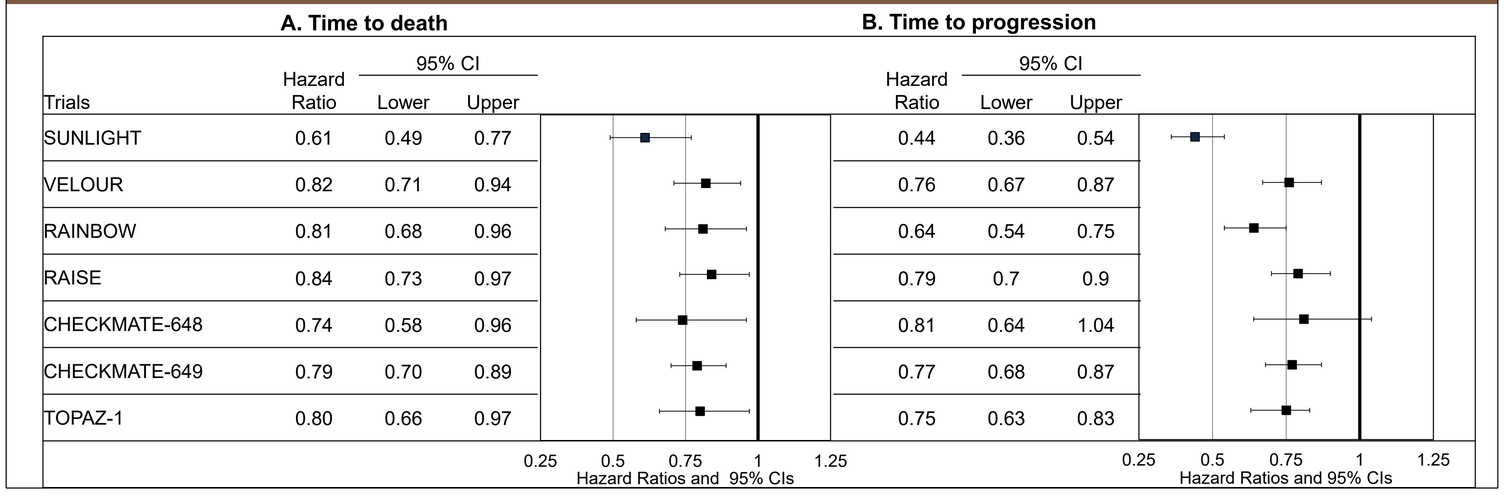
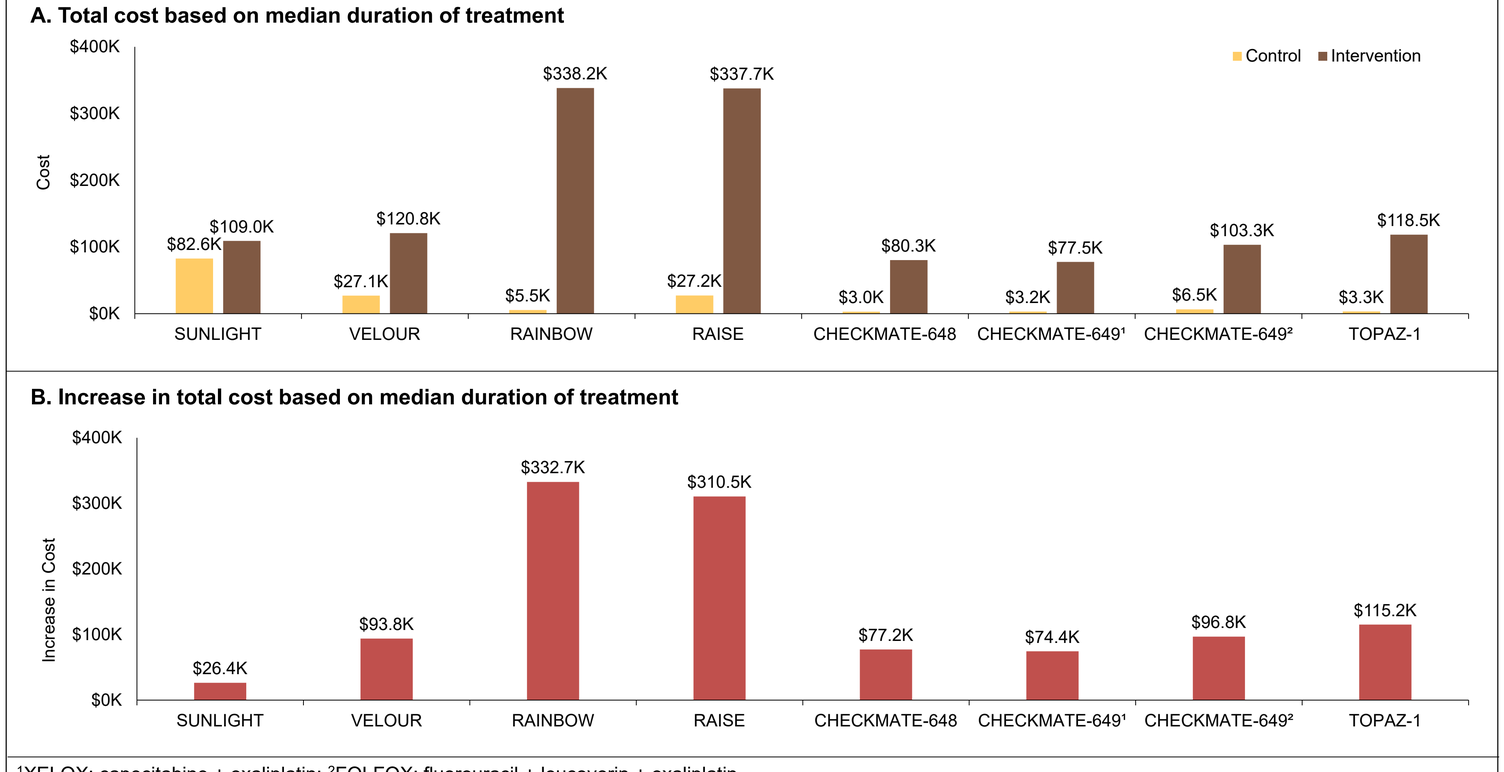


Figure 2. Cost of qualifying chemotherapy regimens, based on median treatment durations



[1]XELOX: capecitabine + oxaliplatin; [2]FOLFOX: fluorouracil + leucovorin + oxaliplatin

References

1) LONSURF (trifluridine and tipiracil). Prescribing Information. Taiho Oncology, Inc. 2015. 2) LONSURF (trifluridine and tipiracil). Prescribing Information. Taiho Oncology, Inc. 2023. 3) Fakih M, et al. *ESMO Open.* 2024; 9(11): 103931. [Online ahead of print.] 4) Ellis LM, et al. *J Clin Oncol.* 2014; 32(12): 1277-1280.

This study was sponsored by Taiho Oncology, Inc.

Poster presented at International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Europe Conference, Barcelona, Spain & online, November 17-20, 2024.