SUNLIGHT
Data Highlights

Lonsurf®
(trifluridine and tipiracil) tablets

Redefine expectations in 3L mCRC with LONSURF + bevacizumab

SUNLIGHT is the first and only Phase 3 study with an **active comparator** that demonstrated statistically significant efficacy and proven safety while maintaining quality of life (QoL) in third-line (3L) metastatic colorectal cancer (mCRC).[1-10]

STUDY DESIGN

SUNLIGHT was an open-label, randomized, Phase 3 study that investigated the efficacy and safety of LONSURF tablets in combination with bevacizumab compared with single-agent LONSURF in patients with refractory mCRC. The primary endpoint was overall survival (OS). Secondary endpoints were progression-free survival (PFS), objective response, disease control, QoL, and safety, including time to worsening of Eastern Cooperative Oncology Group performance status (ECOG PS) from 0 or 1 to 2 or more.[1,2]

INDICATION

LONSURF is indicated as a single agent or in combination with bevacizumab for the treatment of adult patients with metastatic colorectal cancer previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if *RAS* wild-type, an anti-EGFR therapy.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Severe Myelosuppression: In the 1114 patients who received LONSURF as a single agent, LONSURF caused severe or life-threatening myelosuppression (Grade 3-4) consisting of neutropenia (38%), anemia (17%), thrombocytopenia (4%) and febrile neutropenia (3%). Three patients (0.3%) died due to neutropenic infection/sepsis; four other patients (0.5%) died due to septic shock.

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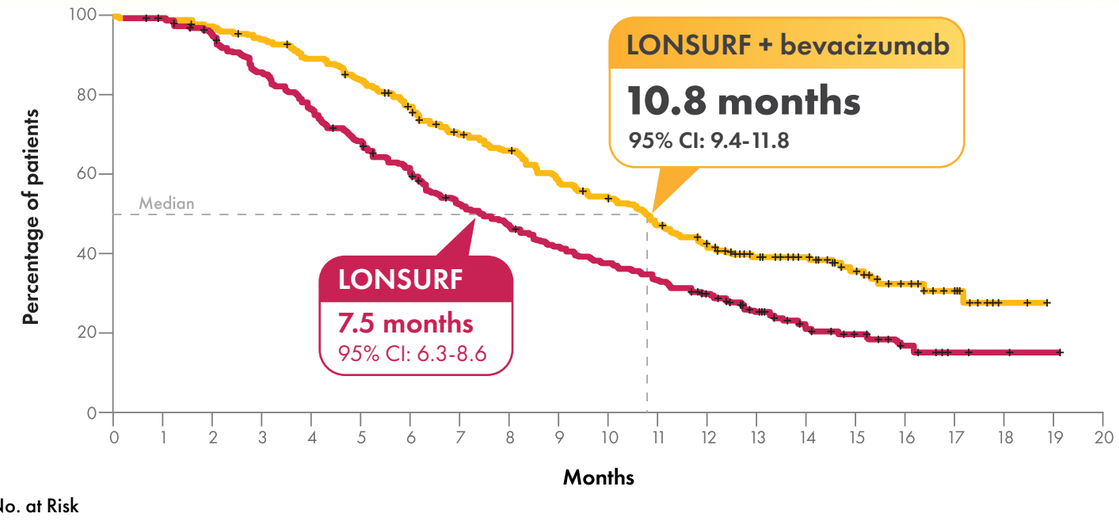
~11 months median OS

Primary Endpoint: Overall Survival (OS) (N=492)[1,2]

Hazard ratio (HR)=0.61, *P*<0.001



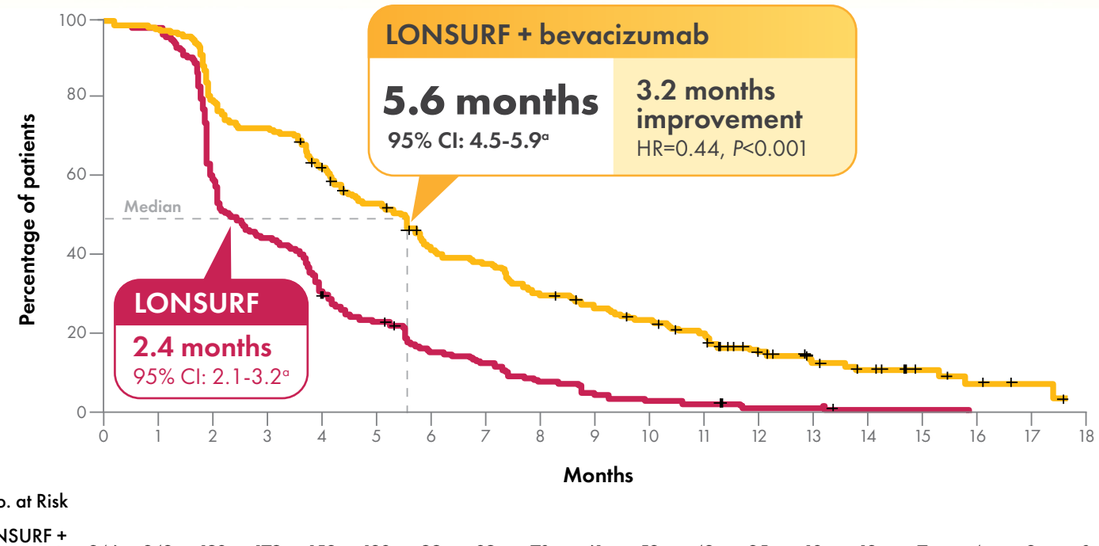
No. at Risk

LONSURF + bevacizumab	246	244	239	230	217	203	183	160	149	131	119	104	88	69	52	37	24	13	2	0	0
LONSURF	246	242	230	205	184	163	143	120	108	95	85	76	63	44	24	16	10	5	2	1	0

39% reduction in the risk of death[1]

Median PFS more than doubled

Progression-free Survival (PFS) (N=492)[1,2]



No. at Risk

LONSURF + bevacizumab	246	242	198	179	153	128	99	89	70	61	52	43	25	18	13	7	4	2	0		
LONSURF	246	236	147	109	74	56	36	29	19	12	8	6	2	2	1	1	0	0	0		

[b]Not adjusted for multiplicity.[2]

Additional endpoints

Disease control rate (DCR)[11]

77% LONSURF + bevacizumab vs 47% LONSURF alone

Objective response rate (ORR)[2]

6% LONSURF + bevacizumab vs 1% LONSURF alone

DCR=objective response + stable disease; ORR=complete response + partial response.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (continued)

Severe Myelosuppression (continued): A total of 14% of patients received granulocyte-colony stimulating factors. In the 246 patients who received LONSURF in combination with bevacizumab, LONSURF caused severe or life-threatening myelosuppression (Grade 3-4) consisting of neutropenia (52%), anemia (5%), thrombocytopenia (4%) and febrile neutropenia (0.4%). One patient (0.4%) died due to abdominal sepsis and two other patients (0.8%) died due to septic shock. A total of 29% of patients received granulocyte-colony stimulating factors. Obtain complete blood counts prior to and on Day 15 of each cycle of LONSURF and more frequently as clinically indicated. Withhold LONSURF for severe myelosuppression and resume at the next lower dosage.

Please see additional Important Safety Information throughout and full Prescribing Information at LONSURF.com/PI.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (continued)

Embryo-Fetal Toxicity: LONSURF can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment and for at least 6 months after the final dose.

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LONSURF + bevacizumab maintained QoL across all studied measures

In the SUNLIGHT trial, QoL and Time to Worsening of Eastern Cooperative Oncology Group performance status (ECOG PS) from 0 or 1 to 2 or more were secondary endpoints. QoL was assessed through the patient-completed European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC-QLQ-C30) and EuroQol 5-Dimension 5-Level (EQ-5D-5L) questionnaire. Time to definitive deterioration (TTDD) was determined for each treatment arm. However, while TTDD of the QLQ-C30 subscales was a predefined secondary endpoint, TTDD of the EQ-5D-5L measures was not predefined.[2,10]

Patients treated with LONSURF + bevacizumab experienced a longer TTDD in all questionnaire measures and a delayed worsening of ECOG PS vs those treated with LONSURF alone.[10]

Cancer-specific patient-reported outcome (PRO): EORTC QLQ-C30

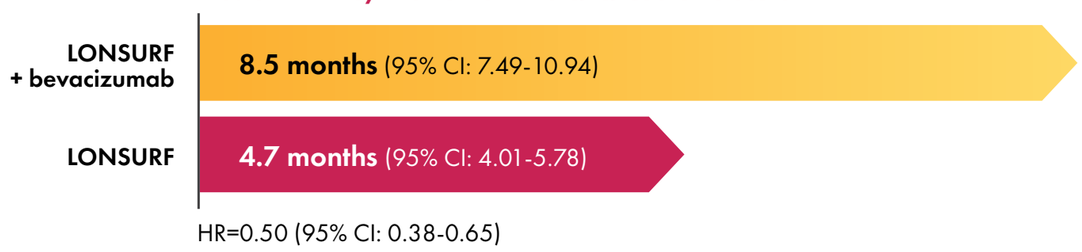
The QLQ-C30 assesses health-related QoL in patients with cancer using 30 questions across 15 subscales (global health status [GHS], 5 functional, and 9 symptom).[10]

TTDD was compared for each treatment arm, defined as the interval from baseline to the first QoL score worsening by ≥10 points, with no subsequent improvement above this threshold during the study.[10]

Global Health Status[10]

The GHS subscale of the QLQ-C30 questionnaire assesses a patient's overall perception of their health and QoL.

Median TTDD by ≥10 Points in the QLQ-C30 GHS Score



HR=0.50 (95% CI: 0.38-0.65)

IMPORTANT SAFETY INFORMATION

USE IN SPECIFIC POPULATIONS

Lactation: It is not known whether LONSURF or its metabolites are present in human milk. There are no data to assess the effects of LONSURF or its metabolites on the breastfed child or the effects on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with LONSURF and for 1 day following the final dose.

Male Contraception: Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use condoms during treatment with LONSURF and for at least 3 months after the final dose.

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Functional subscales[10]

Physical functioning
HR=0.41 (95% CI: 0.32-0.54)
9.0 months vs 4.5 months
(95% CI: 8.15-11.83) (95% CI: 3.71-5.62)

Cognitive functioning
HR=0.43 (95% CI: 0.33-0.56)
9.4 months vs 4.7 months
(95% CI: 8.34-12.25) (95% CI: 4.07-6.11)

Role functioning
HR=0.46 (95% CI: 0.36-0.60)
8.6 months vs 4.4 months
(95% CI: 7.49-10.94) (95% CI: 3.78-5.06)

Social functioning
HR=0.46 (95% CI: 0.35-0.60)
9.0 months vs 4.9 months
(95% CI: 7.85-11.86) (95% CI: 4.14-5.88)

Emotional functioning
HR=0.42 (95% CI: 0.31-0.55)
10.0 months vs 5.9 months
(95% CI: 8.51-12.12) (95% CI: 4.70-6.60)

Symptom subscales[10]

Fatigue
HR=0.54 (95% CI: 0.42-0.69)
8.2 months vs 4.0 months
(95% CI: 6.11-9.95) (95% CI: 3.19-4.83)

Appetite loss
HR=0.50 (95% CI: 0.39-0.65)
8.3 months vs 4.7 months
(95% CI: 6.70-10.94) (95% CI: 3.94-6.04)

Nausea and vomiting
HR=0.41 (95% CI: 0.31-0.54)
9.4 months vs 5.1 months
(95% CI: 8.51-11.86) (95% CI: 4.27-6.31)

Constipation
HR=0.44 (95% CI: 0.33-0.58)
9.5 months vs 5.6 months
(95% CI: 8.34-12.12) (95% CI: 4.63-6.67)

Pain
HR=0.46 (95% CI: 0.35-0.59)
8.6 months vs 4.3 months
(95% CI: 6.96-10.41) (95% CI: 3.29-5.16)

Diarrhea
HR=0.41 (95% CI: 0.31-0.55)
10.4 months vs 5.5 months
(95% CI: 8.84-14.49) (95% CI: 4.70-6.60)

Dyspnea
HR=0.41 (95% CI: 0.31-0.54)
9.4 months vs 5.7 months
(95% CI: 8.54-12.25) (95% CI: 4.40-6.60)

Financial difficulties
HR=0.47 (95% CI: 0.36-0.62)
9.4 months vs 6.1 months
(95% CI: 8.34-12.12) (95% CI: 5.06-6.93)

Insomnia
HR=0.42 (95% CI: 0.32-0.56)
9.4 months vs 5.8 months
(95% CI: 8.54-12.25) (95% CI: 4.70-6.80)

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LONSURF + bevacizumab maintained QoL across all studied measures

General health PRO: EQ-5D-5L

The EQ-5D-5L questionnaire measures general QoL across 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with 5 levels of severity. It converts these into a single index utility score from 1 (full health) to 0 (death) and includes a visual analog scale (VAS) ranging from 100 (best imaginable health) to 0 (worst imaginable health).[11]

This data presentation is neither intended to draw conclusions regarding the impact of LONSURF + bevacizumab on QoL nor to imply that there is a treatment effect of LONSURF + bevacizumab on these time-to-event QoL endpoints. These results should be interpreted with caution.

TTDD was compared for each treatment arm, defined as the interval from baseline to the first worsening in EQ-5D-5L index utility score by ≥0.08 or VAS score by ≥7 points, with no subsequent improvement above this threshold during the study.[10]

Index utility score[10]
HR=0.39 (95% CI: 0.30-0.52)

10.0 months (95% CI: 8.34-12.25) **vs 5.5 months** (95% CI: 4.63-6.34)

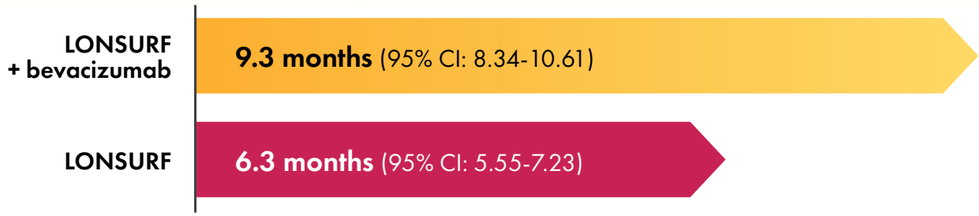
Visual analog scale[10]
HR=0.51 (95% CI: 0.40-0.66)

8.3 months (95% CI: 7.16-9.56) **vs 4.0 months** (95% CI: 3.32-4.93)

In SUNLIGHT, health-related QoL (assessed by QLQ-C30 and EQ-5D-5L) was maintained throughout treatment, with no clinically relevant difference between patients treated with LONSURF + bevacizumab and LONSURF alone.[10]

Slower time to ECOG PS deterioration

Median Time to Worsening to ECOG PS ≥2[2,10]*



HR=0.54 (95% CI: 0.43-0.67)

*Not adjusted for multiplicity.

46% reduction in the risk of worsening to ECOG PS ≥2[10]

There was a significant association between time to ECOG PS deterioration to ≥2 and clinically relevant change in mean GHS score (QLQ-C30) over time. A worsening of ≥10 points in mean GHS score increased the risk of ECOG PS deterioration by 53%.[10]

44% of patients treated with LONSURF + bevacizumab went on to receive subsequent therapy following the trial.[10]

IMPORTANT SAFETY INFORMATION

USE IN SPECIFIC POPULATIONS (continued)

Geriatric Use: Patients 65 years of age or older who received LONSURF in combination with bevacizumab had a higher incidence of the following hematologic laboratory abnormalities compared to patients younger than 65 years: Grade 3 or 4 neutropenia (60% vs 46%) and Grade 3 or 4 thrombocytopenia (5% vs 4%).

Renal Impairment: No adjustment to the starting dosage of LONSURF is recommended in patients with mild or moderate renal impairment (CLcr of 30 to 89 mL/min). Reduce the starting dose of LONSURF for patients with severe renal impairment (CLcr of 15 to 29 mL/min) to a recommended dosage of 20 mg/m^2.

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IMPORTANT SAFETY INFORMATION

USE IN SPECIFIC POPULATIONS (continued)

Hepatic Impairment: Do not initiate LONSURF in patients with baseline moderate or severe (total bilirubin > 1.5 times ULN and any AST) hepatic impairment. Patients with severe hepatic impairment (total bilirubin > 3 times ULN and any AST) were not studied. No adjustment to the starting dosage of LONSURF is recommended for patients with mild hepatic impairment.

ADVERSE REACTIONS

Serious adverse reactions occurred in 25% of patients. The most frequent serious adverse reactions (≥2%) were intestinal obstruction (2.8%), and COVID-19 (2%). Fatal adverse reactions occurred in 1.2% of patients who received LONSURF in combination with bevacizumab, including rectal fistula (0.4%), bowel perforation (0.4%) and atrial fibrillation (0.4%).

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Safety profile was generally manageable and predictable[2,11]

Select laboratory abnormalities (≥10%) in patients

	LONSURF + bevacizumab (n=246)		LONSURF (n=246)	
Hematologic abnormality	**All grades (%)**	**Grade 3-4 (%)**	**All grades (%)**	**Grade 3-4 (%)**
Neutropenia	80	52	68	39
Anemia	68	5	73	11
Thrombocytopenia	54	4.1	29	0.8

- **29%** of patients treated with LONSURF + bevacizumab received granulocyte-colony stimulating factors (G-CSF) vs 19.5% treated with LONSURF alone[1,2]
- Febrile neutropenia occurred in 1 patient (**<1%**) treated with LONSURF + bevacizumab and in 6 patients treated with LONSURF alone[2]

Dose modifications

- **Dose delays** due to adverse events occurred in **70%** of patients treated with LONSURF + bevacizumab[2]
- **Dosage interruptions** due to an AR occurred in **11%** of patients treated with LONSURF + bevacizumab[1]
- **Dose reduction** due to an AR or laboratory abnormality occurred in **7%** of patients treated with LONSURF + bevacizumab[1]
- **Discontinuation** due to an AR occurred in **13%** of patients in both treatment arms[1]

Do not initiate treatment with LONSURF until the absolute neutrophil count (ANC) is ≥1,500 mm^3. Within a cycle, withhold LONSURF if the ANC is <500 mm^3. A maximum of 3 dose reductions are permitted to a minimum dose of 20 mg/m^2 orally twice daily. See Section 2.2 Dosage Modifications for Adverse Reactions of the LONSURF PI for specific guidance on dose adjustments for ARs.[1]

The AR profile of LONSURF + bevacizumab combination was consistent with the independent AR profiles of each product.[1]

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Adverse reactions (ARs) in ≥5% of patients[1]

	LONSURF + bevacizumab (n=246)		LONSURF (n=246)	
Adverse reaction	**All grades (%)**	**Grade 3-4 (%)**	**All grades (%)**	**Grade 3-4 (%)**
General disorders and administration site conditions				
Fatigue[a]	45	5	37	8
Pyrexia	4.9	0	6	0.4
Gastrointestinal disorders				
Nausea	37	1.6	27	1.6
Diarrhea[a]	21	1.2	19	2.4
Vomiting[a]	19	0.8	15	1.6
Abdominal pain[a]	20	2.8	18	3.7
Constipation	11	0	11	0.8
Stomatitis[a]	13	<0.4	4.1	0
Infections and infestations[a]	31	8	24	8
Metabolism and nutrition disorders				
Decreased appetite	20	<0.8	15	1.2
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain[a]	18	1.2	11	2
Nervous system disorder				
Headache	8	0	3.7	0
Vascular disorders				
Hypertension[a]	11	6	2	1.2
Hemorrhage[a]	10	1.2	3.7	0.8
Renal and urinary disorders				
Proteinuria	6	0.8	1.2	0

[a]Represents a composite of multiple related terms.

Extended survival and prolonged PFS while maintaining QoL[1,2,10]

In the SUNLIGHT trial, patients treated with LONSURF + bevacizumab vs LONSURF alone experienced:

~11 months OS and more than double the PFS

OS: 10.8 months (95% CI: 9.4-11.8) vs 7.5 months (95% CI: 6.3-8.6) (HR=0.61, *P*<0.001)[1,2]

PFS: 5.6 months (95% CI: 4.5-5.9) vs 2.4 months (95% CI: 2.1-3.2) (HR=0.44, *P*<0.001)[1,2]

Maintained QoL across all studied measures

QoL was maintained across all patient-reported measures of the QLQ-C30 and EQ-5D-5L questionnaires, while the time to deterioration to ECOG PS ≥2 was significantly delayed.[10]

A generally manageable and predictable safety profile

The AR profile of LONSURF + bevacizumab was consistent with the independent AR profiles of each product.[1,2,9,11]

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IMPORTANT SAFETY INFORMATION

ADVERSE REACTIONS

The most common adverse reactions or laboratory abnormalities (≥20% in incidence) in patients treated with LONSURF in combination with bevacizumab vs LONSURF alone were neutropenia (80% vs 68%), anemia (68% vs 73%), thrombocytopenia (54% vs 29%), fatigue (45% vs 37%), nausea (37% vs 27%), increased aspartate aminotransferase (34% vs 28%), increased alanine aminotransferase (33% vs 23%), increased alkaline phosphate (31% vs 36%), decreased sodium (25% vs 20%), diarrhea (21% vs 19%), abdominal pain (20% vs 18%), and decreased appetite (20% vs 15%).

References: 1. LONSURF [package insert]. Princeton, NJ: Taiho Oncology, Inc.; 2023. **2.** Prager GW, Taieb J, Fakih M, et al. Trifluridine–tipiracil and bevacizumab in refractory metastatic colorectal cancer. *N Engl J Med.* 2023;388(18):1657-1667. **3.** Dasari NA, Lonardi S, Garcia-Carbonero R, et al. FRESCO-2: a global phase III multiregional clinical trial (MRCT) evaluating the efficacy and safety of fruquintinib in patients with refractory metastatic colorectal cancer [abstract]. *Ann Oncol.* 2022;33(suppl 7):S1391-S1392. **4.** Evrard C, Messina S, Sefrioui D, et al. Heterogeneity of mismatch repair status and microsatellite instability between primary tumour and metastasis and its implications for immunotherapy in colorectal cancers. *Int J Mol Sci.* 2022;23(8):4427. **5.** Li J, Qin S, Xu R-H, et al. Effect of fruquintinib vs placebo on overall survival in patients with previously treated metastatic colorectal cancer: the FRESCO randomized clinical trial. *JAMA.* 2018;319(24):2486-2496. **6.** Kim TW, Shen L, Xu JM, et al. TERRA: a randomized, double-blind, placebo-controlled phase 3 study of TAS-102 in Asian patients with metastatic colorectal cancer [abstract]. *Ann Oncol.* 2016;27(suppl 6):vi149-vi206. **7.** Li J, Qin S, Yau T, et al. CONCUR: a randomised, double-blind, placebo-controlled phase 3 study of regorafenib monotherapy in Asian patients with previously treated metastatic colorectal cancer (mCRC) [abstract]. *Ann Oncol.* 2014;25(2):ii105-ii117. **8.** Grothey A, Van Cutsem E, Sobrero A, et al; CORRECT Study Group. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet.* 2013;381(9863):303-312. **9.** AVASTIN [package insert]. South San Francisco, CA: Genentech, Inc.; 2022. **10.** Taieb J, Fakih M, Tabernero J, et al. Impact of treatment with trifluridine/tipiracil in combination with bevacizumab on health-related quality of life and performance status in refractory metastatic colorectal cancer: an analysis of the phase III SUNLIGHT trial. Published online December 11, 2024. **11.** Fakih M, Prager GW, Tabernero J, Amellal N, Calleja E, Taieb J. Clinically meaningful outcomes in refractory metastatic colorectal cancer: a decade of defining and raising the bar. *ESMO Open.* 2024;9(11):103931.

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