Lonsurf®
(trifluridine and tipiracil) tablets

LONSURF® and VA Oncology Clinical Pathway Considerations

VA Oncology Pathway Recommended	**LONSURF ± bevacizumab is a recommended 3L therapy and fruquintinib could be considered after LONSURF in subsequent treatment lines[1-4,a]**
NCCN Category 2A[b]	**The National Comprehensive Cancer Network® (NCCN®) recommends trifluridine + tipiracil (LONSURF) ± bevacizumab as Category 2A[a] for 3L or subsequent treatment in mCRC patients.[5,6]**

3L=third-line; EGFR=epidermal growth factor receptor; mCRC=metastatic colorectal cancer; NCCN=National Comprehensive Cancer Network; VA=US Department of Veterans Affairs.

[a]Patients being considered for fruquintinib use in the 3L setting must have received prior treatment with or are not candidates to receive trifluridine + tipiracil (LONSURF) with or without bevacizumab.

[b]Category 2A: based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.[5,6]

INDICATIONS AND IMPORTANT SAFETY INFORMATION

INDICATIONS

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.

LONSURF is indicated for the treatment of adult patients with metastatic gastric or gastroesophageal junction adenocarcinoma previously treated with at least two prior lines of chemotherapy that included a fluoropyrimidine, a platinum, either a taxane or irinotecan, and if appropriate, HER2/neu-targeted 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. 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.

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.

Please see additional Important Safety Information throughout and full Prescribing Information.

TAIHO ONCOLOGY

How LONSURF and bevacizumab work

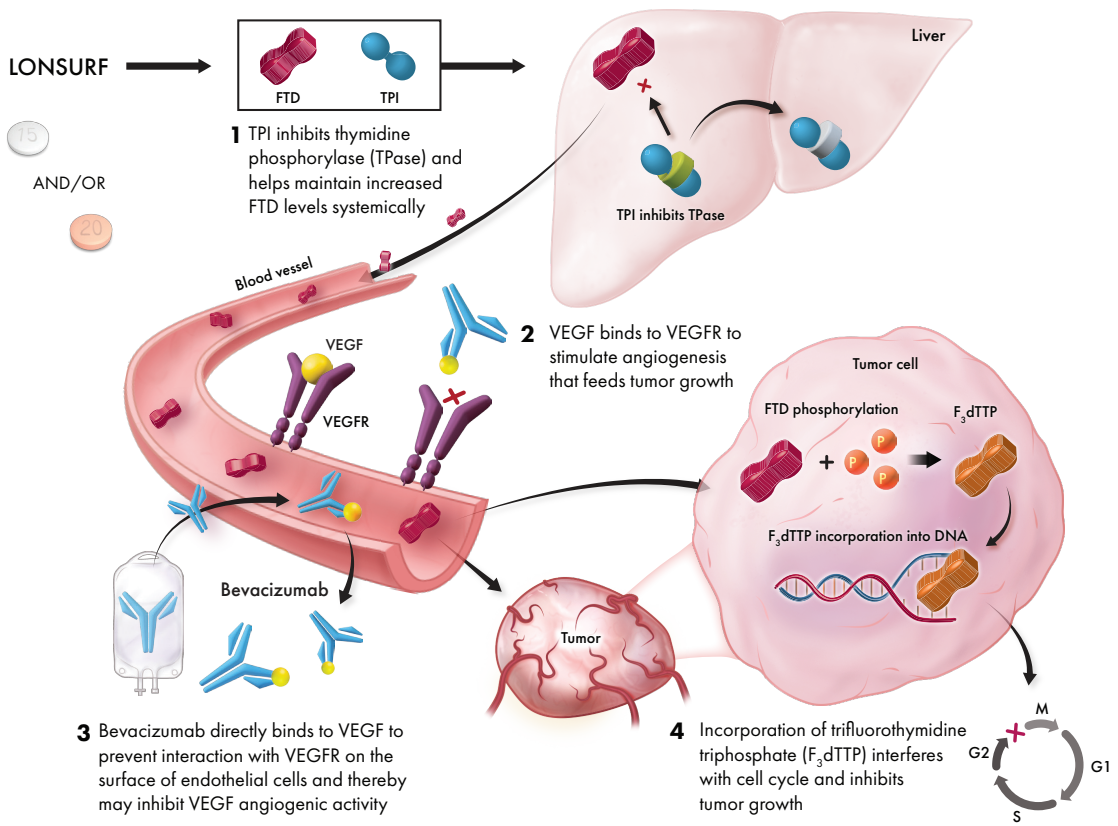
LONSURF (trifluridine and tipiracil) tablets is an antimetabolite combination agent.[7,8]

- **Trifluridine (FTD)** is a fluorinated thymidine analogue incorporated into the DNA, causing DNA dysfunction that leads to the death of cancer cells[7,9,a]
  - FTD is not a prodrug of 5-fluorouracil (5-FU)[10]
  - Pharmacokinetic pathway of trifluridine is independent of DPD[11]
- **Tipiracil (TPI)** inhibits the rapid degradation of FTD[7]

Bevacizumab is a vascular endothelial growth factor (VEGF) inhibitor.[10]

- VEGF inhibitors prevent angiogenesis (the growth of new blood vessels) by selectively binding to circulating VEGF and thus inhibiting the binding of VEGF to its cell surface receptors (VEGFR)[12]

Proposed mechanism of action (MOA)[7,9,11,13]



LONSURF interferes with DNA synthesis and prevents cell proliferation, while bevacizumab starves the tumor by preventing angiogenesis.[7,13]

This presentation is for illustrative purposes only. Not intended to imply clinical significance.
[a]LONSURF can also have toxic effects on healthy, nontumor cells.
DPD=dihydropyrimidine dehydrogenase.

IMPORTANT SAFETY INFORMATION (cont'd)

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.

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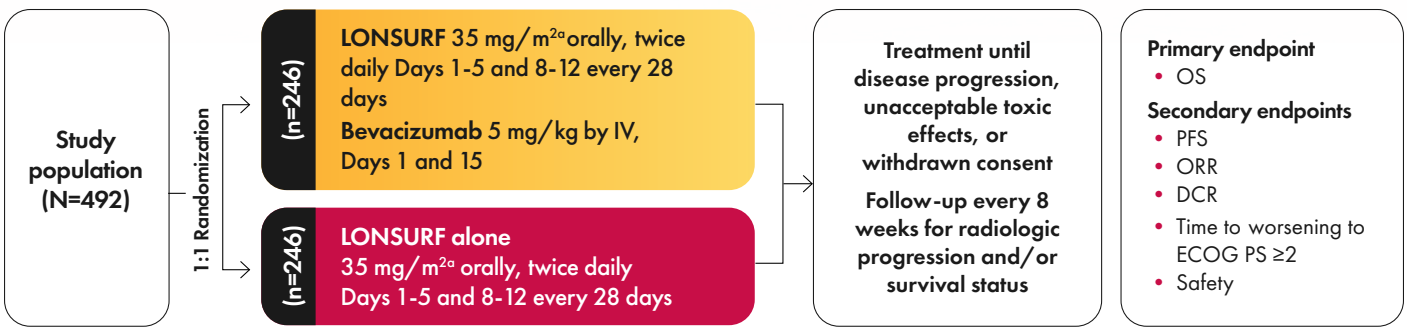
SUNLIGHT study design

SUNLIGHT was an open-label, randomized, Phase 3 study that investigated the efficacy and safety of LONSURF + bevacizumab vs LONSURF alone in patients with refractory mCRC.[7,14]



Key eligibility criteria[7]

- ECOG performance status (PS) 0-1
- Disease progression or intolerance
- Histologically confirmed unresectable adenocarcinoma of the colon or rectum
- No more than 2 previous chemotherapy regimens[b]
  - Prior treatment with a fluoropyrimidine, irinotecan, oxaliplatin, an anti–vascular endothelial growth factor (VEGF) monoclonal antibody (not necessarily bevacizumab), or an anti–epidermal growth factor receptor (EGFR) monoclonal antibody (for patients with *RAS* wild-type disease)
- Known *RAS* status

Stratification

Randomization was stratified according to:

- Geographic region (North America, the European Union, or the rest of the world)
- Time since diagnosis of first metastasis (<18 months or ≥18 months)
- *RAS* status (wild type or mutated)

Median duration of treatment:[14] **5.0 months** vs **2.1 months**

At the time of analysis, 13% of patients treated with LONSURF + bevacizumab and 1.6% treated with LONSURF alone were still receiving treatment.[14]

[a]Starting dose.[14]

[b]The treatment could have included neoadjuvant or adjuvant chemotherapy if disease had recurred during treatment or within 6 months after the last administration of neoadjuvant or adjuvant therapy.[14]

IMPORTANT SAFETY INFORMATION (cont'd)
USE IN SPECIFIC POPULATIONS (cont'd)

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.

Geriatric Use: Patients 65 years of age or older who received LONSURF as a single agent had a higher incidence of the following hematologic laboratory abnormalities compared to patients younger than 65 years: Grade 3 or 4 neutropenia (46% vs 32%), Grade 3 anemia (20% vs 14%), and Grade 3 or 4 thrombocytopenia (6% vs 3%). 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%).

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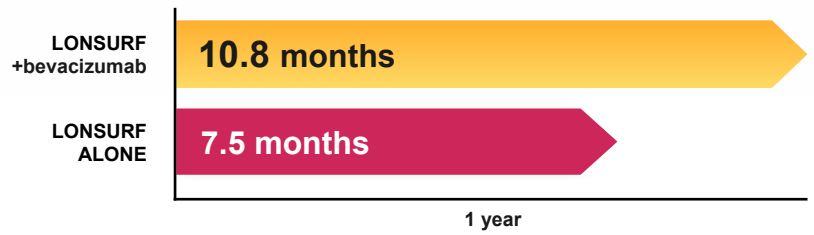
SUNLIGHT Efficacy

LONSURF + bevacizumab achieved ~11 months mOS in 3L mCRC treatment

Primary endpoint: median OS (N=492)[7,14,a]



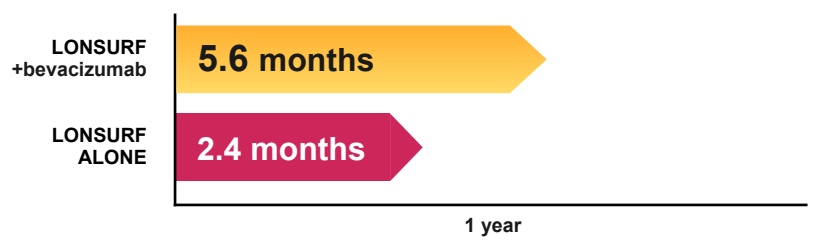
LONSURF + bevacizumab=95% CI; 9.4-11.8; LONSURF=95% CI; 6.3-8.6.

39%

Reduction in risk of death with LONSURF + bevacizumab vs active comparator (LONSURF monotherapy)
(HR=0.61 [95% CI: 0.49-0.77]; *P*<0.001)[7,14]

Median PFS more than doubled

Secondary endpoint: median PFS (N=492)[7,14]



LONSURF + bevacizumab=95% CI; 4.5-5.9; LONSURF=95% CI; 2.1-3.2.[b]

56%

Reduction in risk of progression with LONSURF + bevacizumab vs active comparator (LONSURF monotherapy)
(HR=0.44 [95% CI: 0.36-0.54]; *P*<0.001)[7,14]

Combination therapy (LONSURF + bevacizumab) offers superior benefits and PFS over monotherapy (LONSURF alone), reinforcing its role as an effective 3L+ treatment option for mCRC.[14]

[a]OS was defined as the time (in months) from randomization until death.[7]

[b]Not adjusted for multiplicity.[14]

3L=third-line; CI=confidence interval; HR=hazard ratio; mCRC=metastatic colorectal cancer; mOS=median overall survival; OS=overall survival; PFS=progression-free survival.

IMPORTANT SAFETY INFORMATION (cont'd)
USE IN SPECIFIC POPULATIONS (cont'd)

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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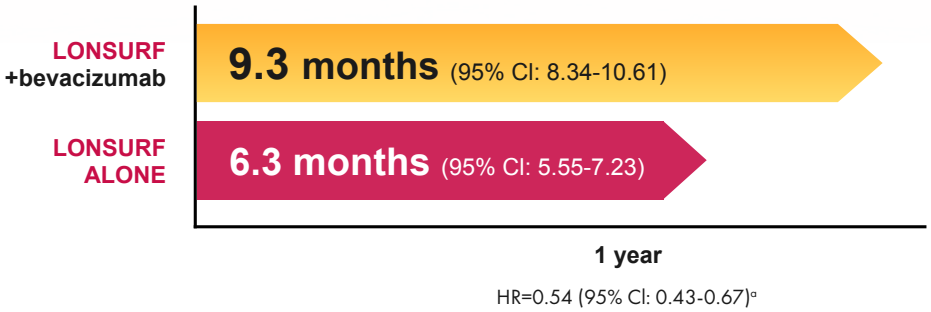
SUNLIGHT Efficacy (cont'd)

Slower time to ECOG PS deteriorations

Additional secondary endpoints:

Median time to worsening to ECOG PS ≥2 (N=492)[14,15]



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

46% reduction in the risk of worsening to ECOG PS ≥2[15]

44% of patients treated with LONSURF + bevacizumab went on to receive subsequent therapy following the trial[15]

Combination therapy (LONSURF + bevacizumab) helped mCRC patients stay functional[b] for a longer period compared with LONSURF alone.[15]

[a]Not adjusted for multiplicity.[14]
[b]Defined as ECOG PS of 0-1.[15]

CI=confidence interval; ECOG PS=Eastern Cooperative Oncology Group performance status; HR=hazard ratio; mCRC=metastatic colorectal cancer.

IMPORTANT SAFETY INFORMATION
USE IN SPECIFIC POPULATIONS (cont'd)

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.

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LONSURF ± bevacizumab is recommended in the VA Oncology Clinical Pathway as a 3L therapy for mCRC[1,2,a,b]

Potential treatment algorithm for *RAS* mutant population[1,2]

1L	2L	3L	4L
mFOLFOX6 or CAPOX + bevacizumab[c-e]	FOLFIRI ± bevacizumab[b,c]	Trifluridine and tipiracil (LONSURF) ± bevacizumab[b,c]	Fruquintinib

Potential treatment algorithm for *RAS* wild-type population[1,2]

1L	2L	3L	4L
mFOLFOX6 or CAPOX + panitumumab[c,f]	FOLFIRI ± bevacizumab[b,c]	Trifluridine and tipiracil (LONSURF) ± bevacizumab[b,c]	Fruquintinib

In the VA Oncology Clinical Pathway, LONSURF ± bevacizumab is a recommended 3L therapy and fruquintinib could be considered after LONSURF in subsequent treatment lines.[1-4,a,b]

[a]Patients being considered for fruquintinib use in the 3L setting must have received prior treatment with or are not candidates to receive LONSURF ± bevacizumab.

[b]These treatment algorithms are examples only; other treatment options may be recommended in the Oncology Clinical Pathway Guidelines. Each line of treatment (eg, 1L, 2L, 3L, and 4L) is for patients with specific assumptions, and HCPs should refer directly to the source material for all relevant details.

[c]Candidate for bevacizumab ECOG PS 0-2; ANC >1500/mm^3; due to anti-VEGF effects, patients with the following should not receive bevacizumab: non-healing wound/fracture, major surgery in prior 4 weeks, bleeding disorder or coagulopathy, recent history of GI perforation, unstable cardiac condition (uncontrolled HTN, arterial thromboembolism, symptomatic CHF [NYHA II-IV], or arrhythmia), or active cocaine use.[1,2]

[d]Candidate for oxaliplatin contraindication if any adjuvant treatment in the past 12 months or preexisting neuropathy >1 grade neuropathy; patient preference to avoid neuropathy.[1,2]

[e]Capecitabine: avoid capecitabine if adherence issues, unable to self-report toxicity, or severe renal impairment (CrCl <30 mL/min).[1,2]

[f]Left Sided Primary is defined as primary originating in splenic flexure and colon distal to that.[1,2]

1L=first-line; 2L=second-line; 3L=third-line; ANC=absolute neutrophil count; *BRAF*=B-Raf proto-oncogene; *BRAFwt*=B-Raf proto-oncogene wild-type; CHF=cardiac heart failure; CRC=colorectal cancer; CrCl=creatinine clearance; ECOG PS=Eastern Cooperative Oncology Group Performance Status; EGFR=epidermal growth factor receptor; HTN=hypertension; mut=mutation; *KRAS*=Kirsten rat sarcoma virus; mCRC=metastatic colorectal cancer; NYHA=New York hear association; pMMR=proficient mismatch repair; *RAS*=rat sarcoma virus; *RASwt*=rat sarcoma virus wild-type; VA=US Department of Veterans Affairs; VEGF=vascular endothelial growth factor; wt=wild-type.

IMPORTANT SAFETY INFORMATION

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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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommended treatment option for mCRC[5,6,a]

Potential treatment algorithm for 3L use (*KRAS/NRAS* mutant)[5,6]

Initial therapy	2L therapy	3L and subsequent therapies[b]		
FOLFOX ± bevacizumab	FOLFIRI ± bevacizumab	Trifluridine and tipiracil (LONSURF) ± bevacizumab	or	Fruquintinib, regorafenib, clinical trials, or best supportive care

Potential treatment algorithm for 3L use (*KRAS/NRAS* wild type)[5,6]

Initial therapy	2L therapy	3L and subsequent therapies[b]		
FOLFOX ± cetuximab[c,d]	FOLFIRI ± bevacizumab	Trifluridine and tipiracil (LONSURF) ± bevacizumab	or	Fruquintinib, regorafenib, clinical trials, or best supportive care

NCCN Category 2A

National Comprehensive Cancer Network® (NCCN®) recommends trifluridine + tipiracil (LONSURF) ± bevacizumab as Category 2A[e] recommended for 3L or subsequent treatment in mCRC patients.[5,6]

[a]These treatment algorithms are examples only; other treatment options are recommended in the NCCN Guidelines. See the full NCCN Guidelines for the footnotes.
[b]Fruquintinib or regorafenib or trifluridine and tipiracil ± bevacizumab are treatment options for patients who have progressed through all available regimens.[5,6]
[c]The left side of the colon is defined as splenic flexure to rectum. Evidence suggests that patients with tumors originating on the right side of the colon (hepatic flexure through cecum) are unlikely to respond to cetuximab and panitumumab in first-line therapy for metastatic disease. Data on the response to cetuximab and panitumumab in patients with primary tumors originating in the transverse colon (hepatic flexure to splenic flexure) are lacking.[5]
[d]Cetuximab or panitumumab should only be used for left-sided tumors.[5,6]
[e]Category 2A: based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.[5,6]

2L=second-line; 3L=third-line; CRC=colorectal cancer; *KRAS*=Kirsten rat sarcoma virus; mCRC=metastatic colorectal cancer; NCCN=National Comprehensive Cancer Network; *NRAS*=neuroblastoma *RAS* viral oncogene homolog.

IMPORTANT SAFETY INFORMATION (cont'd)

ADVERSE REACTIONS (cont'd)

The most common adverse reactions or laboratory abnormalities (≥10% in incidence) in patients treated with single-agent LONSURF at a rate that exceeds the rate in patients receiving placebo in mCRC: anemia (77% vs 33%), neutropenia (67% vs 0.8%), asthenia/fatigue (52% vs 35%), nausea (48% vs 24%), thrombocytopenia (42% vs 8%), decreased appetite (39% vs 29%), diarrhea (32% vs 12%), vomiting (28% vs 14%), abdominal pain (21% vs 19%), and pyrexia (19% vs 14%). In metastatic gastric cancer or gastroesophageal junction (GEJ): neutropenia (66% vs 4%), anemia (63% vs 38%), nausea (37% vs 32%), thrombocytopenia (34% vs 9%), decreased appetite (34% vs 31%), vomiting (25% vs 20%), infections (23% vs 16%) and diarrhea (23% vs 14%).

Pulmonary emboli occurred more frequently in LONSURF-treated patients compared to placebo: in mCRC (2% vs 0%) and in metastatic gastric cancer and GEJ (3% vs 2%).

Interstitial lung disease (0.2%), including fatalities, has been reported in clinical studies and clinical practice settings in Asia.

Please see additional Important Safety Information throughout and full Prescribing Information.

Lonsurf® (trifluridine and tipiracil) tablets

LONSURF + bevacizumab vs LONSURF alone

Safety profile was generally manageable[7]

Select laboratory abnormalities (≥10%) in patients[7]

	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 14% treated with LONSURF alone[7]
- Febrile neutropenia occurred in 1 patient (**<1%**) treated with LONSURF + bevacizumab and in 6 patients treated with LONSURF alone[7,14]

Dose modifications

- **Dose delays** due to adverse events occurred in **70%** of patients treated with LONSURF + bevacizumab[14]
- **Dosage interruptions** due to an AR occurred in **11%** of patients treated with LONSURF + bevacizumab[7]
- **Dosage reductions** due to an AR or laboratory abnormality occurred in **7%** of patients treated LONSURF + bevacizumab[7]
- **Discontinuation** due to an AR occurred in **13%** of patients in both treatment arms[7]

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.

The ARs profile of LONSURF + bevacizumab combination was consistent with the independent AR profiles of each product.[7,14]

Please see additional Important Safety Information throughout and full Prescribing Information.

Lonsurf® (trifluridine and tipiracil) tablets

LONSURF + bevacizumab vs LONSURF alone

Safety profile was generally manageable[7]

Adverse reactions (ARs) in ≥5% patients[7]

	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
Abdominal pain[a]	20	2.8	18	3.7
Vomiting[a]	19	0.8	15	1.6
Stomatitis[a]	13	<0.4	4.1	0
Constipation	11	0	11	0.8
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.[7]

Please see additional Important Safety Information throughout and full Prescribing Information.

Lonsurf® (trifluridine and tipiracil) tablets

LONSURF recommended dosing and administration[7]

Indicated dosage: 35 mg/m^2[a] twice daily with food (no food restrictions)
- Round dose up to the nearest 5-mg increment[7]
- Do not exceed 80 mg per dose (160 mg per day)[7]
- In patients with severe renal impairment (creatinine clearance of 15 to 29 mL/min), the recommended dosage is 20 mg/m^2[2,7]

Active treatment days include Days 1 through 5 and Days 8 through 12 of each 28-day treatment cycle

Obtain complete blood cell counts prior to and on Day 15 of each cycle[7]

Dosing Calculator & Treatment Calendar

Available in 2 strengths[7]:

15 mg trifluridine/6.14 mg tipiracil tablet
Tablet shown is not actual size

20 mg trifluridine/8.19 mg tipiracil tablet
Tablet shown is not actual size

Instruct patients to swallow LONSURF tablets whole. Patients should not retake any doses that are missed or vomited and should continue with the next scheduled dose.[7]

When adding bevacizumab to LONSURF (trifluridine and tipiracil) tablets in mCRC, the dose of bevacizumab is 5 mg/kg of body weight given once every 2 weeks (Day 1 and Day 15). Refer to the bevacizumab Prescribing Information for additional dosing information.[7,12]

	LONSURF[7]		bevacizumab[12]
Week 1	Twice daily for 5 days with food	2 days rest	IV dose (Day 1)
Week 2	Twice daily for 5 days with food	2 days rest	-
Week 3	Rest		IV dose (Day 15)
Week 4	Rest		-

Remind patients and their caregivers that LONSURF is a cytotoxic drug. Follow applicable special handling and disposal procedures. Store at 20°C to 25°C (68°F to 77°F); excursions are permitted from 15°C to 30°C (59°F to 86°F). If stored outside of original bottle, discard after 30 days.[7]

[a]Based on the trifluridine component.[7]

IMPORTANT SAFETY INFORMATION (cont'd)

ADVERSE REACTIONS (cont'd)

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%).

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INDICATIONS

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.

LONSURF is indicated for the treatment of adult patients with metastatic gastric or gastroesophageal junction adenocarcinoma previously treated with at least two prior lines of chemotherapy that included a fluoropyrimidine, a platinum, either a taxane or irinotecan, and if appropriate, HER2/neu-targeted 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. 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.

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.

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.

Geriatric Use: Patients 65 years of age or older who received LONSURF as a single agent had a higher incidence of the following hematologic laboratory abnormalities compared to patients younger than 65 years: Grade 3 or 4 neutropenia (46% vs 32%), Grade 3 anemia (20% vs 14%), and Grade 3 or 4 thrombocytopenia (6% vs 3%). 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.

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%).

The most common adverse reactions or laboratory abnormalities (≥10% in incidence) in patients treated with single-agent LONSURF at a rate that exceeds the rate in patients receiving placebo in mCRC: anemia (77% vs 33%), neutropenia (67% vs 0.8%), asthenia/fatigue (52% vs 35%), nausea (48% vs 24%), thrombocytopenia (42% vs 8%), decreased appetite (39% vs 29%), diarrhea (32% vs 12%), vomiting (28% vs 14%), abdominal pain (21% vs 19%), and pyrexia (19% vs 14%). In metastatic gastric cancer or gastroesophageal junction (GEJ): neutropenia (66% vs 4%), anemia (63% vs 38%), nausea (37% vs 32%), thrombocytopenia (34% vs 9%), decreased appetite (34% vs 31%), vomiting (25% vs 20%), infections (23% vs 16%) and diarrhea (23% vs 14%).

Pulmonary emboli occurred more frequently in LONSURF-treated patients compared to placebo: in mCRC (2% vs 0%) and in metastatic gastric cancer and GEJ (3% vs 2%).

Interstitial lung disease (0.2%), including fatalities, has been reported in clinical studies and clinical practice settings in Asia.

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%).

Please see full Prescribing Information.

Lonsurf®
(trifluridine and tipiracil) tablets

See 3L mCRC in a different light with LONSURF + bevacizumab

Lonsurf® (trifluridine and tipiracil) tablets

Nearly 11-month median OS and over 2x longer median PFS[7]

- In the Phase 3 SUNLIGHT trial, LONSURF + bevacizumab significantly improved OS and PFS vs LONSURF monotherapy
  - median OS: 10.8 months vs 7.5 months (HR=0.61 [95% CI: 0.49-0.77]; *P*<0.001)[a]
  - median PFS: 5.6 months vs 2.4 months (HR=0.44 [95% CI: 0.36-0.54]; *P*<0.001)[a]

Recommended by the VA Oncology Clinical Pathway, trifluridine and tipiracil (LONSURF) ± bevacizumab is:

- Recommended as a preferred 3L+ option for mCRC in the NCCN Guidelines® (combination recommended over trifluridine + tipiracil [LONSURF] alone)[5,6]:
- VA Oncology Clinical Pathway recommended for 3L therapy for mCRC[1-4]

On Formulary

- **VA:** Approved on formulary with a CFU[16]
- **TRICARE:** Listed on the Uniform Formulary; permitted via standard PA process[17]

[a]Not adjusted for multiplicity.

3L=third-line; CFU=criteria for use; CI=confidence interval; HR=hazard ratio; mCRC=metastatic colorectal cancer; NCCN=National Comprehensive Cancer Network; OS=overall survival; PA=prior authorization; PFS=progression-free survival; VA=US Department of Veterans Affairs.

References: 1. US Department of Veterans Affairs. Oncology Clinical Pathways. Colon cancer V.2.2026. Published April 2026. Access April 30, 2026. https://www.cancer.va.gov/assets/pdf/clinical-pathways/colon.pdf **2.** US Department of Veterans Affairs. Oncology Clinical Pathways. Rectal cancer V1.2026. Published April 2026. Accessed April 30, 2026. https://www.cancer.va.gov/assets/pdf/clinical-pathways/rectal.pdf **3.** Little NG. Fruquintinib (FRUZAQLA) in metastatic colorectal cancer, National Drug Mini-Monograph. Published May 2024. Accessed March 20, 2026. https://www.va.gov/formularyadvisor/DOC_PDF/MON_Fruquintinib_FRUZAQLA_Monograph_May_2024.pdf **4.** Fruquintinib (FRUZAQLA) Coverage & Formulary Criteria – May 2024. Veterans Affairs National Formulary Advisor. Published May 2024. Accessed March 20, 2026. https://www.va.gov/formularyadvisor/DOC_PDF/CFU_fruquintinib_FRUZAQLA_Criteria_May_2024.pdf **5.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Colon Cancer V.2.2026. © National Comprehensive Cancer Network, Inc. 2026. All rights reserved. Published April 7, 2026. Accessed April 30, 2026. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. **6.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Rectal Cancer V.2.2026. © National Comprehensive Cancer Network, Inc. 2026. All rights reserved. Published April 7, 2026. Accessed April 30, 2026. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. **7.** LONSURF [package insert]. Princeton, NJ: Taiho Oncology, Inc.; 2023. **8.** Uboha N, Hochster HS. TAS-102: a novel antimetabolite for the 21st century. *Future Oncol.* 2016;12(2):153-163. **9.** Matsuoka K, Iimori M, Niimi S, et al. Trifluridine induces p53-dependent sustained G 2 phase arrest with its massive misincorporation into DNA and few DNA strand breaks. *Mol Cancer Ther.* 2015;14(4):1004-1013. **10.** Lenz H-J, Stintzing S, Loupakis F. TAS-102, a novel antitumor agent: a review of the mechanism of action. *Cancer Treat Rev.* 2015;41(9):777-783. **11.** Schouten JF, Willems J, Sanders SJWJ, Creemers G-J, Deenen MJ. Standard-dose trifluridine/tipiracil as safe treatment alternative in metastatic colorectal cancer patients with DPD deficiency. *Clin Colorectal Cancer.* 2021;20(4):359-363. **12.** AVASTIN [package insert]. South San Francisco, CA: Genentech, Inc.; 2022. **13.** Ferrara N. Vascular endothelial growth factor: basic science and clinical progress. *Endocr Rev.* 2004;25(4):581-611. **14.** 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. **15.** 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. *Clin Colorectal Cancer.* 2025;24(2):180-187.e4. **16.** U.S. Department of Veterans Affairs. Tipiracil/trifluridine tablet. VA Formulary Advisor. Accessed March 24, 2026. https://www.va.gov/formularyadvisor/drugs/4035761-TIPIRACIL--TRIFLURIDINE-TAB **17.** Express Scripts. TRICARE formulary search tool: formulary pricing results. Accessed March 24, 2026. https://www.express-scripts.com/frontend/open-enrollment/tricare/fst/

IMPORTANT SAFETY INFORMATION (cont'd)

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. 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.

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