

# REDEFINE EXPECTATIONS

In 3L mCRC with the results of the SUNLIGHT trial

The combined effect of LONSURF + bevacizumab was proven in SUNLIGHT—a phase 3 study that demonstrated efficacy and safety compared with single-agent LONSURF in patients with refractory metastatic colorectal cancer (mCRC)<sup>1,2</sup>

## 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.<sup>1</sup>

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.<sup>1</sup>

3L=third-line.

## 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%).



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## SUNLIGHT study design

SUNLIGHT was an open-label randomized, phase 3 study that investigated the efficacy and safety of LONSURF® (trifluridine and tipiracil) tablets in combination with bevacizumab compared with single-agent LONSURF in patients with refractory mCRC.<sup>1,2</sup>

### Key inclusion criteria<sup>2</sup>

- Histologically confirmed unresectable adenocarcinoma of the colon or rectum
- Disease progression or intolerance
- No more than 2 previous chemotherapy regimens\*
  - Previous treatment must have included a fluoropyrimidine, irinotecan, oxaliplatin, an anti-VEGF monoclonal antibody (not necessarily bevacizumab), or an anti-EGFR monoclonal antibody (for patients with RAS wild-type disease)
- Known RAS status
- Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0-1

### 1:1 Randomization<sup>1,2</sup>

#### FTD-TPI + bevacizumab (n=246)

**FTD-TPI** administered orally, BID at a starting dose of 35 mg/m<sup>2</sup> of BSA on days 1-5 and on days 8-12 every 28 days

**Bevacizumab** administered intravenously at dose of 5 mg/kg of body weight on days 1 and 15

#### FTD-TPI (n=246)

**FTD-TPI** administered orally, BID at a starting dose of 35 mg/m<sup>2</sup> of BSA on days 1-5 and on days 8-12 every 28 days

- **Primary endpoint:** Overall survival (OS)
- **Key secondary endpoints:** Progression-free survival (PFS), objective response rate (ORR), time to worsening of ECOG PS score from 0 or 1 to 2, adverse reactions (ARs)

- The 28-day cycle continued until disease progression, unacceptable toxic effects, or consent was withdrawn
- Follow-up was every 8 weeks for radiologic progression and/or survival status

BID=twice daily; BSA=body surface area; EGFR=epidermal growth factor receptor.

\*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.<sup>2</sup>

## Key baseline characteristics<sup>2</sup>

Characteristic		LONSURF + bevacizumab (n=246)	LONSURF (n=246)
Age	Median, years (range)	62 (20-84)	64 (24-90)
	<65 years, n (%)	146 (59)	129 (52)
	≥65 years, n (%)	100 (41)	117 (48)
Sex, n (%)	Male	122 (50)	134 (55)
Race or ethnic group, n (%)	White	215 (87.4)	220 (89.4)
	Black	4 (1.6)	3 (1.2)
	Asian	0	1 (0.4)
	American Indian or Alaska Native	1 (0.4)	0
	Other	8 (3.3)	5 (2.0)
	Unknown	18 (7.3)	17 (6.9)
Region, n (%)	European Union	158 (64)	157 (64)
	North America	8 (3)	8 (3)
	Rest of the world	80 (33)	81 (33)
Prior treatment with anti-VEGF monoclonal antibody (mainly bevacizumab), n (%)	Yes	178 (72)	176 (72)
ECOG PS, n (%)	0	119 (48)	106 (43)
	1	127 (52)	139 (57)
	2	0	1 (0.4) <sup>a</sup>

<sup>a</sup>The patient had an ECOG PS of 1 at randomization, but was assessed as having a score of 2 on day 1 of the first cycle of treatment.<sup>2</sup>

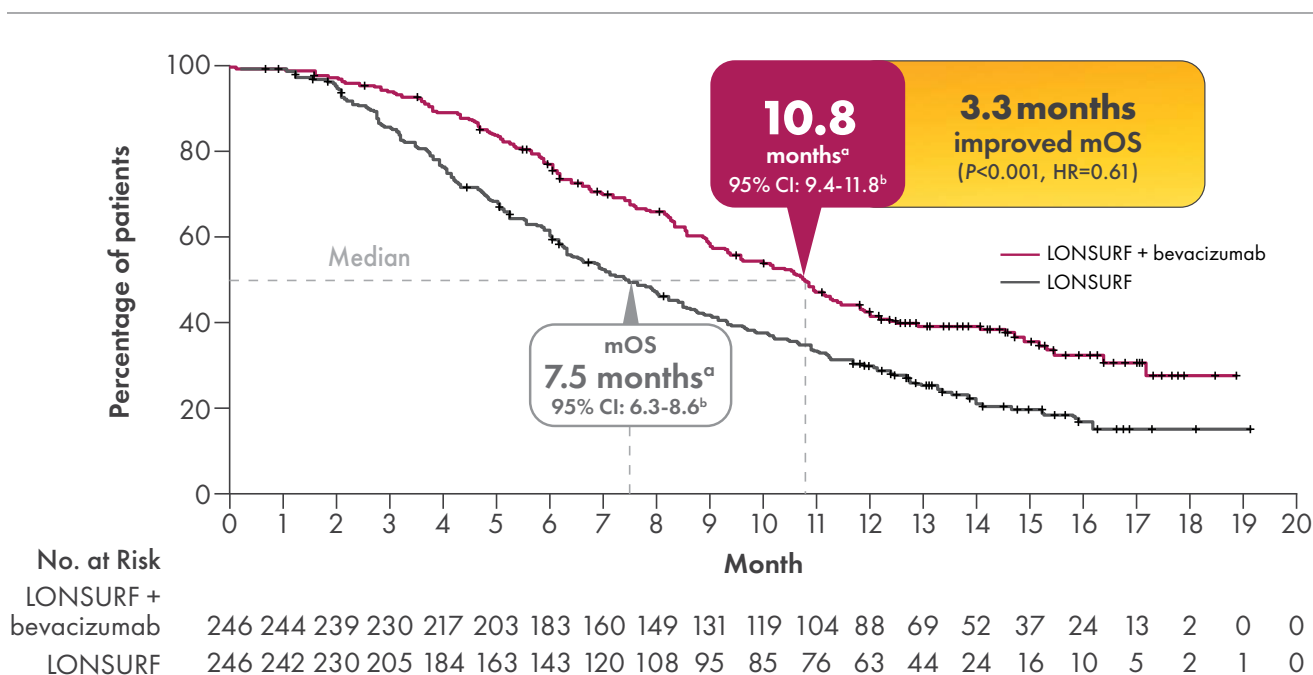
### IMPORTANT SAFETY INFORMATION WARNINGS AND PRECAUTIONS (continued)

**Severe Myelosuppression (continued):** 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.

## Redefine extended survival in 3L mCRC

SUNLIGHT is the first and only phase 3 study with an active control that demonstrated statistically significant efficacy in 3L mCRC<sup>3-8</sup>

Primary endpoint: **Overall Survival (OS)** (N=492)<sup>1,2</sup>



OS was defined as the time (in months) from randomization until death.<sup>2</sup>

HR and P values refer to the entire OS curve, and not any individual timepoint.

<sup>a</sup>Kaplan-Meier estimates.

<sup>b</sup>The widths of the confidence intervals have not been adjusted for multiplicity.<sup>2</sup>

- **39% reduction** in risk of mortality with LONSURF® (trifluridine and tipiracil) tablets + bevacizumab vs single-agent LONSURF<sup>1</sup>

CI=confidence interval; HR=hazard ratio; mOS=median OS.

### 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.

**4** Please see additional Important Safety Information throughout and full [Prescribing Information](#).

# OS across select clinically relevant subgroups of patients<sup>2</sup>



	LONSURF + bevacizumab	LONSURF	LONSURF + bevacizumab	LONSURF		
Subgroup	Number of events/total number		Median OS (95% CI)			Hazard Ratio
Time from diagnosis of first metastasis, months						
<18	65/104	82/105	10.8 (8.8-12.5)	6.1 (5.1-7.4)	■	0.52 (0.37-0.72)
≥18	83/142	101/141	10.8 (9.0-12.1)	8.6 (7.2-10.6)	■	0.70 (0.53-0.94)
RAS status						
Mutant	103/171	128/170	10.6 (9.0-11.3)	7.5 (6.3-8.6)	■	0.62 (0.48-0.81)
Wild	45/75	55/76	11.9 (9.0-14.9)	7.1 (5.9-10.9)	■	0.64 (0.43-0.96)
Location of primary disease						
Left side	108/184	120/169	10.7 (9.3-12.2)	8.2 (6.7-9.3)	■	0.65 (0.50-0.85)
Right side	40/62	63/77	10.8 (8.5-11.9)	6.2 (5.2-8.0)	■	0.59 (0.40-0.87)
ECOG PS						
0	70/119	74/106	10.8 (8.8-14.5)	9.3 (7.7-11.6)	■	0.74 (0.53-1.02)
≥1	78/127	109/140	10.8 (9.0-11.9)	6.3 (5.4-7.5)	■	0.54 (0.41-0.73)
Sex						
Female	79/124	85/112	10.7 (9.0-11.4)	6.9 (6.0-9.0)	■	0.62 (0.46-0.85)
Male	69/122	98/134	10.8 (9.0-14.6)	7.8 (6.5-9.4)	■	0.62 (0.45-0.84)
Age, years						
<65	89/146	94/129	10.7 (8.5-12.1)	7.5 (6.3-9.3)	■	0.65 (0.48-0.87)
≥65	59/100	89/117	11.0 (9.4-12.9)	7.2 (6.0-8.8)	■	0.69 (0.42-0.81)
Number of metastatic sites						
1 or 2	83/152	97/141	11.9 (10.7-15.1)	8.8 (7.5-10.5)	■	0.62 (0.46-0.83)
≥3	65/94	86/105	8.5 (6.7-10.6)	6.0 (5.2-7.1)	■	0.66 (0.47-0.91)
Number of prior metastatic drug regimens						
1	6/11	11/15	9.9 (8.1-NE)	5.1 (3.9-8.0)	■	0.35 (0.12-1.0)
≥2	142/235	172/231	10.8 (9.4-11.9)	7.8 (6.5-8.9)	■	0.64 (0.51-0.80)
Prior bevacizumab						
No	30/68	48/69	15.1 (12.1-NE)	8.1 (6.3-9.7)	■	0.40 (0.25-0.63)
Yes	118/178	135/177	9.0 (8.3-10.8)	7.1 (6.0-8.5)	■	0.72 (0.56-0.92)
Prior surgical resection						
No	99/153	113/152	9.0 (8.3-10.8)	6.3 (5.6-7.9)	■	0.67 (0.51-0.87)
Yes	49/93	70/94	11.9 (10.9-16.4)	9.0 (7.2-10.7)	■	0.54 (0.37-0.78)
Overall	148/246	183/246	10.8 (9.4-11.8)	7.5 (6.3-8.6)	■	0.62 (0.50-0.77)

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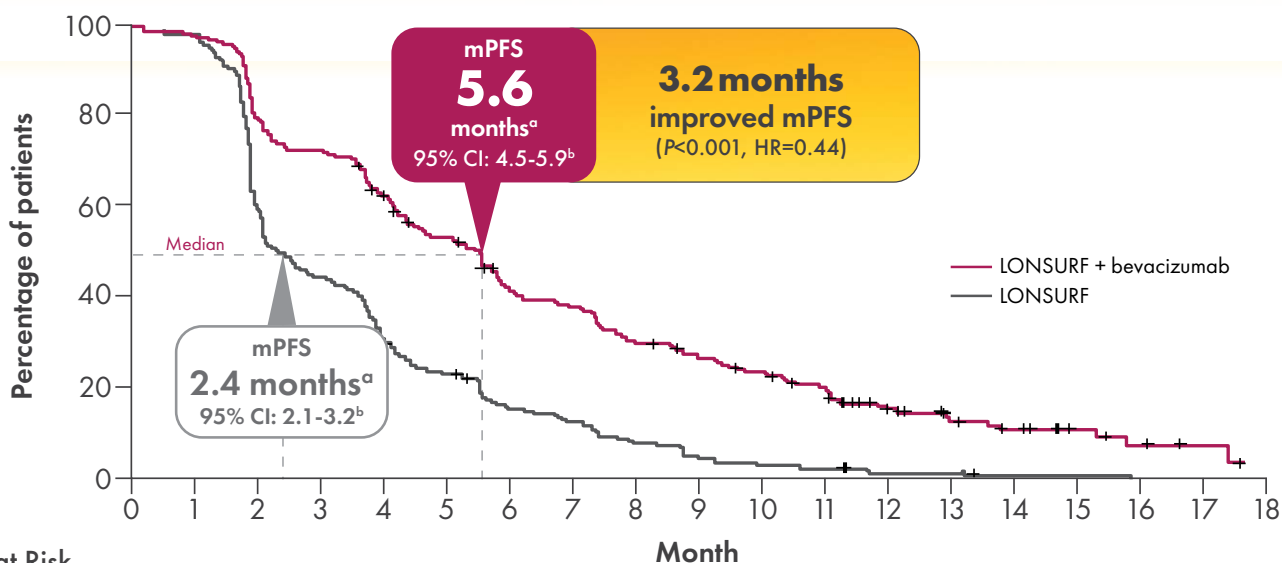
Within individual subgroups, it is difficult to apply statistical weight due to potential multiplicity issues, so these results should be interpreted with caution and no conclusions should be drawn.

NE=not evaluable.

**Results were consistent across all clinically relevant subgroups regardless of age, sex, location of primary disease, number of metastatic sites, RAS mutation status, and prior bevacizumab treatment<sup>2</sup>**

# Redefine prolonged PFS in 3L mCRC

Secondary endpoint: **Progression-free Survival (PFS) (N=492)<sup>1,2</sup>**



No. at Risk	Month																		
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

HR and P values refer to the entire PFS curve, and not any individual timepoint.

<sup>a</sup>Kaplan-Meier estimates.

<sup>b</sup>The widths of the confidence intervals have not been adjusted for multiplicity.<sup>1</sup>

- **56% reduction** in risk of progression with LONSURF® (trifluridine and tipiracil) tablets + bevacizumab vs single-agent LONSURF<sup>1</sup>

mPFS=median PFS.

## 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.

**6** Please see additional Important Safety Information throughout and full [Prescribing Information](#).



# PFS across select clinically relevant subgroups of patients<sup>2</sup>



	LONSURF + bevacizumab	LONSURF	LONSURF + bevacizumab	LONSURF		
Subgroup	Number of events/total number		Median PFS (95% CI)			Hazard Ratio
Time from diagnosis of first metastasis, months						
<18	86/104	100/105	5.6 (4.4-6.0)	2.0 (1.9-2.1)	■—	0.36 (0.26-0.49)
≥18	120/142	136/141	5.5 (4.3-6.2)	3.7 (2.5-3.8)	■—	0.51 (0.39-0.65)
RAS status						
Mutant	147/171	162/170	5.1 (4.2-5.8)	2.5 (2.1-3.6)	■—	0.51 (0.41-0.64)
Wild	59/75	74/76	6.0 (4.8-7.9)	2.3 (2.0-3.1)	■—	0.29 (0.20-0.42)
Location of primary disease						
Left side	155/184	160/169	5.6 (4.6-6.1)	2.6 (2.1-3.6)	■—	0.44 (0.35-0.56)
Right side	51/62	76/77	5.2 (3.8-6.2)	2.1 (2.0-3.7)	■—	0.44 (0.31-0.64)
ECOG PS						
0	96/119	103/106	5.8 (4.7-7.4)	2.6 (2.1-3.8)	■—	0.37 (0.27-0.49)
≥1	110/127	133/140	5.3 (4.1-5.9)	2.1 (2.0-3.1)	■—	0.50 (0.39-0.65)
Sex						
Female	102/124	108/112	5.6 (4.1-6.2)	2.1 (1.9-3.7)	■—	0.46 (0.35-0.61)
Male	104/122	128/134	5.5 (4.4-6.0)	2.6 (2.1-3.6)	■—	0.42 (0.32-0.56)
Age, years						
<65	124/146	122/129	5.3 (4.2-5.9)	2.1 (1.9-2.7)	■—	0.41 (0.31-0.53)
≥65	82/100	114/117	5.8 (4.5-7.5)	3.1 (2.1-3.8)	■—	0.46 (0.34-0.62)
Number of metastatic sites						
1 or 2	121/152	137/141	5.9 (5.5-7.4)	2.7 (2.1-3.7)	■—	0.39 (0.31-0.51)
≥3	85/94	99/105	4.1 (3.5-4.8)	2.1 (1.9-3.2)	■—	0.54 (0.40-0.72)
Number of prior metastatic drug regimens						
1	8/11	13/15	4.9 (3.6-11.1)	1.9 (1.7-2.1)	■—	0.37 (0.15-0.93)
≥2	198/235	223/231	5.6 (4.6-5.9)	2.6 (2.1-3.5)	■—	0.44 (0.36-0.54)
Prior bevacizumab						
No	52/68	65/69	7.7 (6.2-9.4)	2.6 (2.0-3.9)	■—	0.29 (0.19-0.43)
Yes	154/178	171/177	4.5 (4.1-5.5)	2.2 (2.1-3.4)	■—	0.51 (0.41-0.63)
Prior surgical resection						
No	132/153	145/152	4.7 (4.1-5.6)	2.1 (1.9-2.3)	■—	0.43 (0.33-0.55)
Yes	74/93	91/94	7.4 (5.6-8.0)	3.7 (2.6-4.2)	■—	0.43 (0.31-0.59)
Overall	206/246	236/246	5.6 (4.5-5.9)	2.4 (2.1-3.2)	■—	0.44 (0.36-0.53)

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Within individual subgroups, it is difficult to apply statistical weight due to potential multiplicity issues, so these results should be interpreted with caution and no conclusions should be drawn.

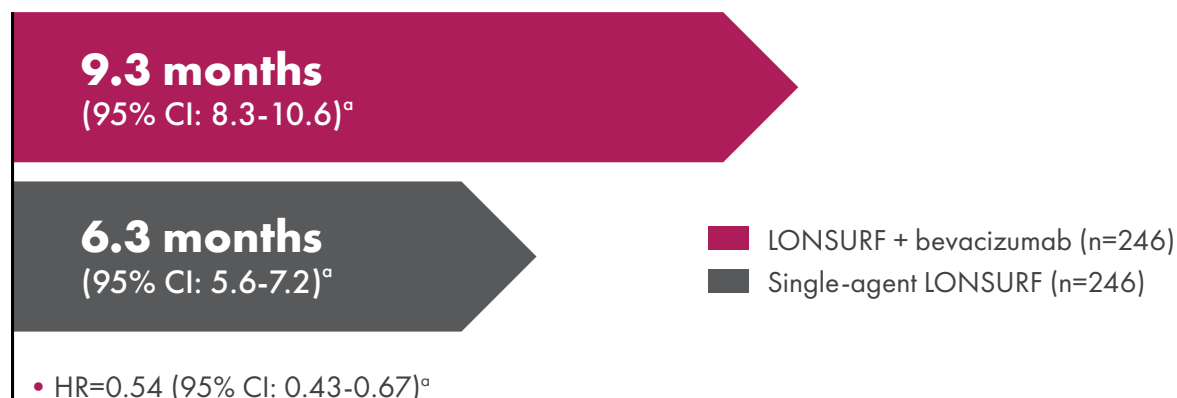
## Additional efficacy results

Secondary endpoint: **Objective Response Rate (ORR)<sup>2</sup>**

- Objective response rate was **6.1%** in LONSURF<sup>®</sup> (trifluridine and tipiracil) tablets + bevacizumab and **1.2%** in single-agent LONSURF
- ORR was a secondary endpoint that was studied in SUNLIGHT and is not reflected in the full Prescribing Information

## Time to worsening of ECOG Performance Status (PS)<sup>2</sup>

Additional secondary endpoint: **Median time to worsening to an ECOG PS of  $\geq 2$ , months**



<sup>a</sup>The widths of the confidence intervals have not been adjusted for multiplicity.

- LONSURF + bevacizumab provided a **46% reduction** in risk of deterioration to ECOG PS  $\geq 2$  vs single-agent LONSURF<sup>2</sup>
  - Since analysis not adjusted for multiplicity, results should be interpreted with caution and conclusions should be limited



## An established and consistent safety profile



Adverse reaction (AR) profile of LONSURF + bevacizumab combination was consistent with the independent AR profiles of each product<sup>1,9</sup>

Select laboratory abnormalities ( $\geq 10\%$ ) in patients receiving LONSURF + bevacizumab and single-agent LONSURF<sup>1</sup>

Hematologic abnormalities	LONSURF + bevacizumab (n=246)		LONSURF (n=246)	
	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 who received LONSURF + bevacizumab received granulocyte-colony stimulating factors (G-CSF) vs 14% with single-agent LONSURF<sup>1</sup>
- Febrile neutropenia occurred in 1 patient (**0.4%**) who received LONSURF + bevacizumab and in 6 patients who received single-agent LONSURF<sup>2</sup>

### IMPORTANT SAFETY INFORMATION USE IN SPECIFIC POPULATIONS (continued)

**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%).

## An established and consistent safety profile (continued)

Adverse reactions (ARs) in  $\geq 5\%$  of patients treated with LONSURF<sup>®</sup> (trifluridine and tipiracil) tablets + bevacizumab and single-agent LONSURF<sup>1</sup>

Adverse reaction	LONSURF + bevacizumab (n=246)		LONSURF (n=246)	
	All grades (%)	Grade 3-4 (%)	All grades (%)	Grade 3-4 (%)
<b>General disorders and administration site conditions</b>				
Fatigue <sup>a</sup>	45	5	37	8
Pyrexia	4.9	0	6	0.4
<b>Gastrointestinal disorders</b>				
Nausea	37	1.6	27	1.6
Diarrhea <sup>a</sup>	21	1.2	19	2.4
Vomiting <sup>a</sup>	19	0.8	15	1.6
Abdominal pain <sup>a</sup>	20	2.8	18	3.7
Constipation	11	0	11	0.8
Stomatitis <sup>a</sup>	13	<0.4	4.1	0
<b>Infections and infestations<sup>a</sup></b>	<b>31</b>	<b>8</b>	<b>24</b>	<b>8</b>

<sup>a</sup>Represents a composite of multiple related terms.

### IMPORTANT SAFETY INFORMATION USE IN SPECIFIC POPULATIONS (continued)

**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<sup>2</sup>.

**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.

10 Please see additional Important Safety Information throughout and full [Prescribing Information](#).

Adverse reactions (ARs) in  $\geq 5\%$  of patients treated with LONSURF + bevacizumab and single-agent LONSURF (continued)<sup>1</sup>

Adverse reaction	LONSURF + bevacizumab (n=246)		LONSURF (n=246)	
	All grades (%)	Grade 3-4 (%)	All grades (%)	Grade 3-4 (%)
<b>Metabolism and nutrition disorders</b>				
Decreased appetite	20	<0.8	15	1.2
<b>Musculoskeletal and connective tissue disorders</b>				
Musculoskeletal pain <sup>a</sup>	18	1.2	11	2
<b>Nervous system disorder</b>				
Headache	8	0	3.7	0
<b>Vascular disorders</b>				
Hypertension <sup>a</sup>	11	6	2	1.2
Hemorrhage <sup>a</sup>	10	1.2	3.7	0.8
<b>Renal and urinary disorders</b>				
Proteinuria	6	0.8	1.2	0

<sup>a</sup>Represents a composite of multiple related terms.

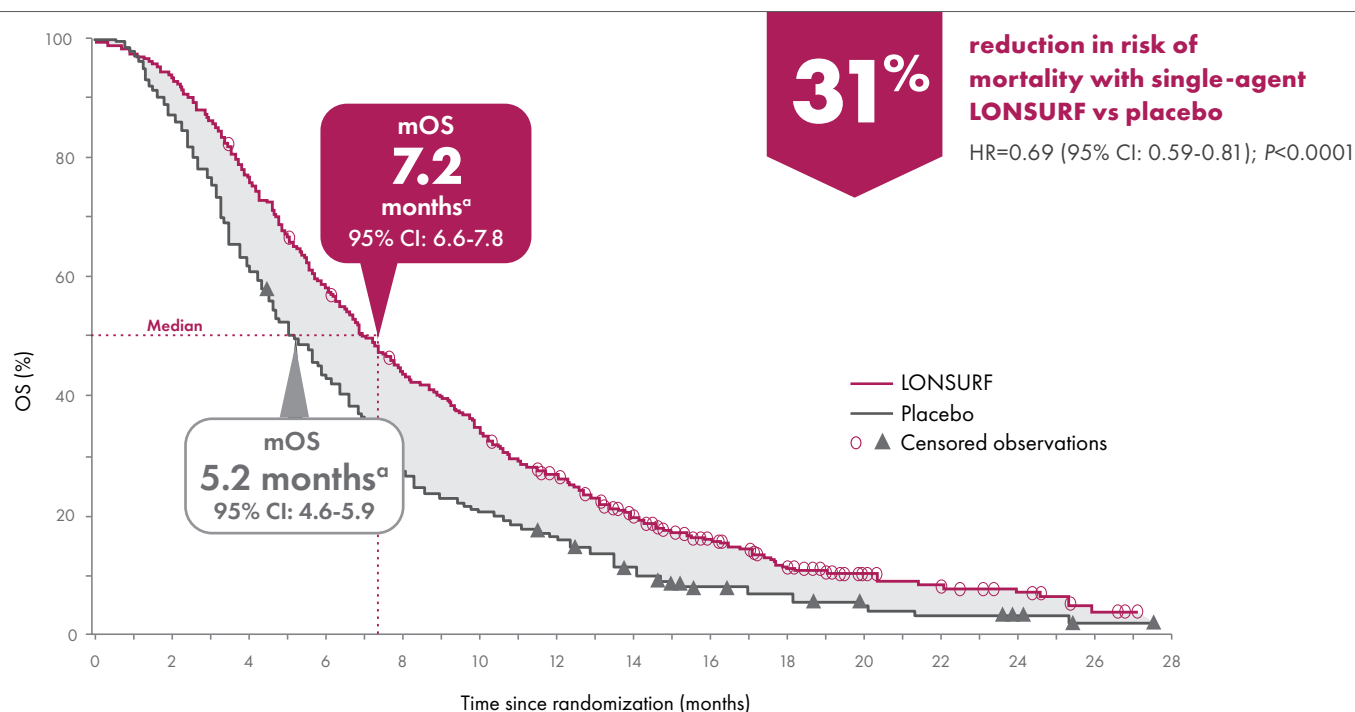
- **Dose delays** due to an AR occurred in **70%** of patients with LONSURF + bevacizumab<sup>2</sup>
- **Dosage interruptions** due to an AR occurred in **11%** of patients who received LONSURF + bevacizumab<sup>1</sup>
- **Dosage reductions** due to an AR or laboratory abnormality occurred in **7%** of patients with LONSURF + bevacizumab<sup>1</sup>
- **Discontinuation** due to an AR occurred in **13%** of patients in both treatment arms<sup>2</sup>

# OS with single-agent LONSURF

## RECOURSE study design

RECOURSE was an international, randomized, double-blind, placebo-controlled, phase 3 trial. The primary efficacy endpoint was OS. Key secondary endpoints included PFS and safety and tolerability. Patients were randomized 2:1 to receive either LONSURF® (trifluridine and tipiracil) tablets (n=534) or placebo (n=266) plus best supportive care (BSC).<sup>1,10,11</sup>

Primary endpoint: Overall Survival (OS) (N=800)<sup>10,12</sup>



n at risk:

LONSURF	534	521	499	459	406	355	308	267	231	212	180	156	137	117	95	74	59	49	38	29	20	17	14	12	10	7	4	1	0
Placebo	266	259	232	198	163	137	114	94	71	62	56	51	43	36	27	21	16	15	14	10	8	7	6	6	4	3	1	1	0

OS was defined as the time (in months) from randomization until death.<sup>10</sup>

<sup>a</sup>Kaplan-Meier estimates.

## IMPORTANT SAFETY INFORMATION ADVERSE REACTIONS

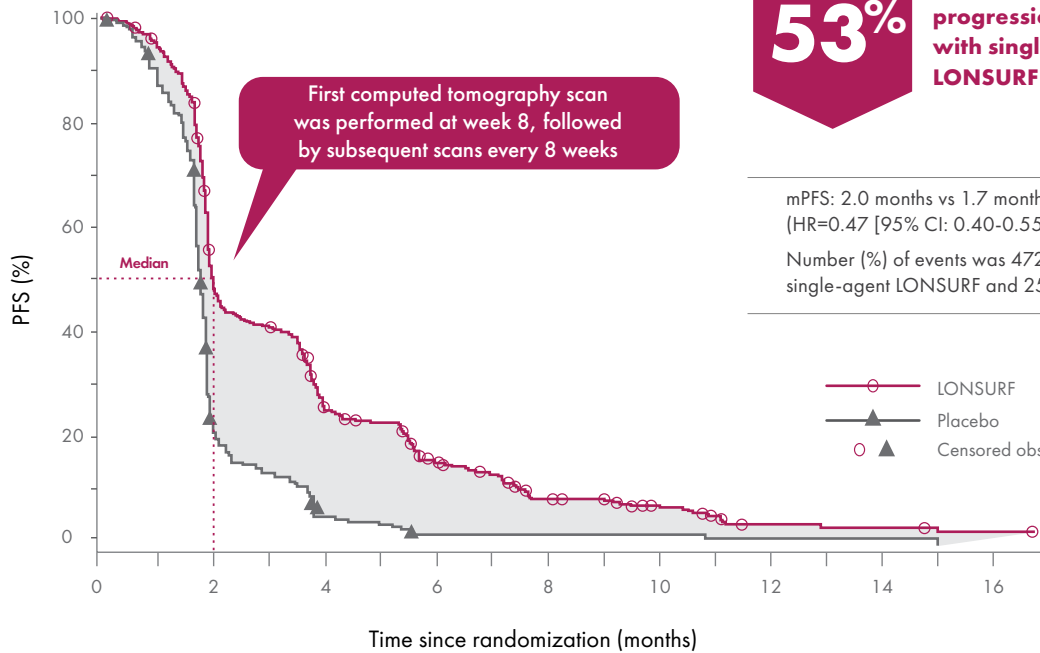
**Serious adverse reactions** occurred in 25% of patients. The most frequent serious adverse reactions ( $\geq 2\%$ ) were intestinal obstruction (2.8%), and COVID-19 (2%). Fatal adverse reactions occurred in 1.2% of patients who received LONSURF in combination with bevacizumab, including rectal fistula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

**12** Please see additional Important Safety Information throughout and full [Prescribing Information](#).

# PFS with single-agent LONSURF



Prespecified secondary endpoint: Progression-free Survival (PFS) (N=800)<sup>10,11</sup>



n at risk:

LONSURF	534	488	238	205	121	107	66	52	30	26	18	11	5	4	4	2	2	0
Placebo	266	227	51	32	10	7	2	2	2	2	2	1	1	1	1	0		

PFS was defined as the time (in months) from randomization to the first radiologic confirmation of disease progression or death from any cause.<sup>10</sup>

## Secondary endpoints (LONSURF vs placebo)

- **Disease control rate (DCR):** 44% in the LONSURF group vs 16% in the placebo group ( $P<0.001$ )<sup>10</sup>
- **Median time to deterioration of ECOG PS to  $\geq 2$ :** 5.7 months in the LONSURF group vs 4.0 months in the placebo group based on a prespecified analysis<sup>10</sup>

DCR is defined as the proportion of patients with a complete response, a partial response, or stable disease.

## Consider an option with a demonstrated safety profile

### Hematologic abnormalities<sup>1</sup>

	LONSURF + BSC (n=533)		Placebo + BSC (n=265)	
	All grades <sup>a</sup> (%)	Grade 3-4 (%)	All grades <sup>a</sup> (%)	Grade 3-4 (%)
Anemia <sup>b</sup>	77	18	33	3
Neutropenia	67	38	0.8	0
Thrombocytopenia	42	5	8	0.4

<sup>a</sup>Worst grade  $\geq 1$  grade higher than baseline, with percentages based on number of patients with postbaseline samples, which may be <533 (single-agent LONSURF) or 265 (placebo).<sup>1</sup>

<sup>b</sup>One grade 4 anemia AR based on clinical criteria was reported.<sup>1</sup>

- **69%** of patients who developed neutropenia (any grade) during the RECOURSE trial developed it during cycle 1<sup>11</sup>
- **14%** of patients in the single-agent LONSURF group received G-CSF<sup>1</sup>
- Hand-foot syndrome was reported in **2%** of patients in both treatment arms. No grade 3-4 was reported<sup>10</sup>
- **Dose delays** of  $\geq 4$  days due to an AR occurred in **53%** of patients treated with LONSURF<sup>®</sup> (trifluridine and tipiracil) tablets<sup>10</sup>
- **Dosage reductions** due to an AR or laboratory abnormality occurred in **14%** of patients with single-agent LONSURF<sup>1</sup>
  - The most common ARs or laboratory abnormalities leading to dose reduction were neutropenia, anemia, febrile neutropenia, fatigue, and diarrhea
- **Discontinuation** due to an AR occurred in **3.6%** of patients taking single-agent LONSURF<sup>1</sup>

### IMPORTANT SAFETY INFORMATION ADVERSE REACTIONS (continued)

The most common adverse reactions or laboratory abnormalities ( $\geq 10\%$  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%).

Adverse reactions (ARs) in  $\geq 5\%$  of patients treated with single-agent LONSURF and occurring more commonly ( $>2\%$ ) than in patients taking placebo<sup>1</sup>

Adverse reaction	LONSURF + BSC (n=533)		Placebo + BSC (n=265)	
	All grades (%)	Grade 3-4 <sup>a</sup> (%)	All grades (%)	Grade 3-4 <sup>a</sup> (%)
<b>General</b>				
Asthenia/fatigue	52	7	35	9
Pyrexia	19	1.3	14	0.4
<b>Gastrointestinal</b>				
Nausea	48	1.9	24	1.1
Diarrhea	32	3	12	0.4
Vomiting	28	2.1	14	0.4
Abdominal pain	21	2.4	19	3.8
Stomatitis	8	0.4	6	0
<b>Metabolism and nutrition</b>				
Decreased appetite	39	3.6	29	4.9
<b>Infections<sup>b</sup></b>	27	7	16	4.9
<b>Nervous system</b>				
Dysgeusia	7	0	2.3	0
<b>Skin and subcutaneous tissue</b>				
Alopecia	7	0	1.1	0

<sup>a</sup>No grade 4 definition for nausea, abdominal pain, or fatigue in National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE).<sup>1</sup>

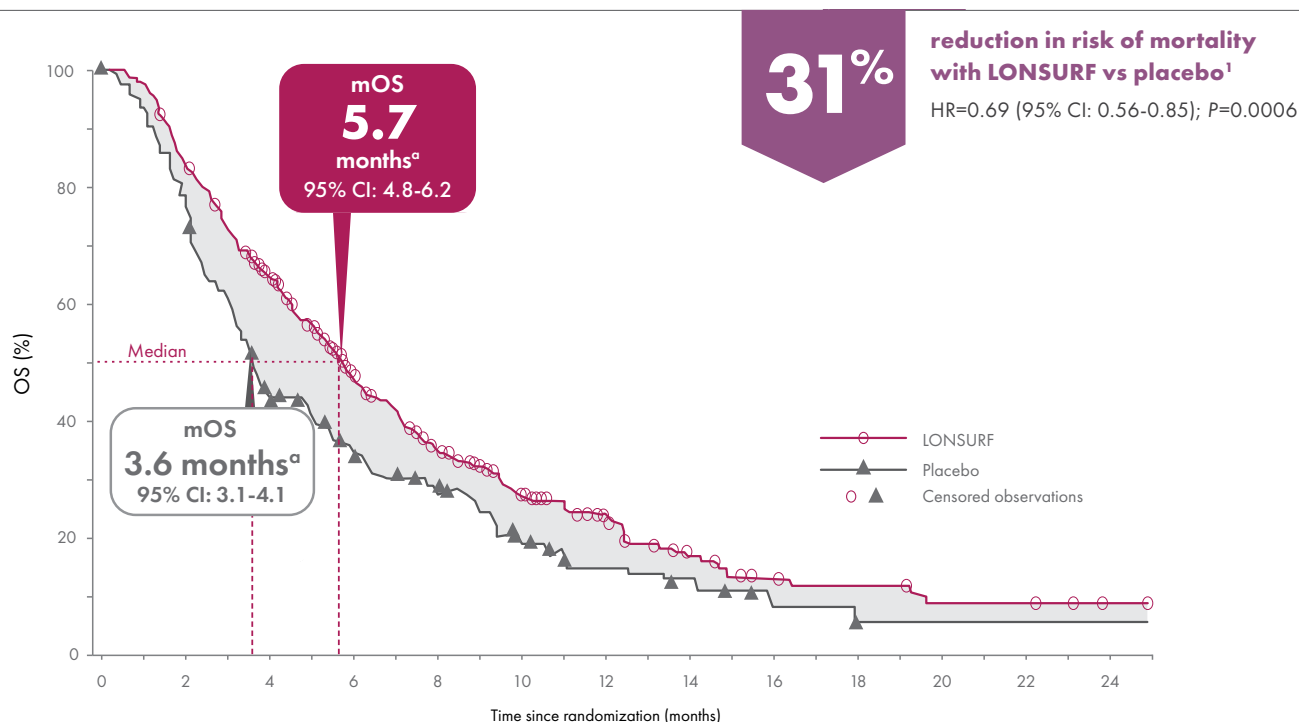
<sup>b</sup>Incidence reflects 64 preferred terms in the Infections and Infestations system organ class.<sup>1</sup>



## Overall survival in metastatic gastric or gastroesophageal junction (GEJ) cancer

TAGS was a multinational, randomized, double-blind, placebo-controlled, phase 3 trial. The primary endpoint was OS. Key secondary endpoints included PFS and safety and tolerability. Patients were randomized 2:1 to receive either LONSURF® (trifluridine and tipiracil) tablets (n=337) or placebo (n=170) plus BSC.<sup>13</sup>

**Primary endpoint: Overall Survival (OS) (N=507)<sup>1,11,13</sup>**



n at risk:

LONSURF	337	328	282	240	201	161	124	102	80	66	51	40	31	22	16	11	9	7	7	7	4	4	4	3	1	0
Placebo	170	158	131	101	71	60	47	40	34	29	17	12	10	9	7	5	2	2	0	0	0	0	0	0	0	0

OS was defined as the time (in months) from randomization until death.

<sup>a</sup>Kaplan-Meier estimates.

## Secondary endpoints (LONSURF vs placebo)

- **mPFS (95% CI):** 2.0 months vs 1.8 months (HR=0.56 [95% CI: 0.46-0.68]; P<0.0001)<sup>1,11</sup>
  - **44%** reduction in risk of progression or death with LONSURF vs placebo<sup>1,11</sup>
- **Disease control rate:** 44% (128/290) vs 14% (21/145)<sup>13</sup>
- **Median time to deterioration of ECOG PS to ≥2:** 4.3 months vs 2.3 months (HR=0.69 [95% CI: 0.56-0.85]; P=0.00053)<sup>13</sup>

# No new safety signals for LONSURF in TAGS trial



## Hematologic abnormalities<sup>1,13</sup>

	LONSURF + BSC (n=335)		Placebo + BSC (n=168)	
	All grades <sup>a</sup> (%)	Grade 3-4 (%)	All grades <sup>a</sup> (%)	Grade 3-4 (%)
Neutropenia	66	38	4	0
Anemia <sup>b</sup>	63	19	38	7
Thrombocytopenia	34	6	9	0
Febrile neutropenia	2	2	0	0

<sup>a</sup>Worst grade  $\geq 1$  grade higher than baseline, with percentage based on number of patients with postbaseline samples, which may be  $< 335$  (LONSURF) or 168 (placebo).<sup>1</sup>

<sup>b</sup>Anemia: No grade 4 definition in NCI-CTCAE, v4.03.<sup>1</sup>

- In the TAGS trial, **16%** of patients in the LONSURF group received G-CSF<sup>13</sup>
- **Dose delays** of  $>4$  days due to an AR occurred in **42%** of patients treated with LONSURF<sup>11</sup>
- **Dosage reductions** due to an AR or laboratory abnormality occurred in **11%** of patients with LONSURF<sup>1</sup>
- **Discontinuation** due to an AR (any grade) occurred in **13%** of patients with LONSURF vs 17% of patients receiving placebo<sup>1,13</sup>

Adverse reactions (ARs) in  $\geq 5\%$  of patients treated with LONSURF and occurring more commonly ( $>2\%$ ) than in patients taking placebo<sup>1</sup>

Adverse reaction	LONSURF + BSC (n=335)		Placebo + BSC (n=168)	
	All grades (%)	Grade 3-4 <sup>a</sup> (%)	All grades (%)	Grade 3-4 <sup>a</sup> (%)
<b>Gastrointestinal</b>				
Nausea	37	3	32	3
Vomiting	25	4	20	2
Diarrhea	23	3	14	2
<b>Metabolism and nutrition</b>				
Decreased appetite	34	9	31	7
Infections <sup>b</sup>	23	5	16	5

<sup>a</sup>No grade 4 definition for nausea in NCI CTCAE, version 4.03.<sup>1</sup>

<sup>b</sup>Incidence reflects 46 preferred terms in the Infections and Infestations system organ class.<sup>1</sup>

Please see additional Important Safety Information throughout and full [Prescribing Information](#).

## Achieving therapy goals depends on proper dosing

- Indicated dosage: 35 mg/m<sup>2</sup>\* twice daily with food (no food restrictions)<sup>1</sup>
  - Round dose up to the nearest 5-mg increment
  - Do not exceed 80 mg per dose (160 mg per day)
  - In patients with severe renal impairment (CLcr of 15 to 29 mL/min), the recommended dosage is 20 mg/m<sup>2</sup>\*
- Active treatment days include days 1 through 5 and days 8 through 12 of each 28-day treatment cycle<sup>1</sup>
- Obtain complete blood cell counts prior to and on day 15 of each cycle<sup>1</sup>

Two tablet strengths<sup>1</sup>



15 mg trifluridine/6.14 mg tipiracil tablet<sup>1</sup>  
Tablet shown is not actual size.



20 mg trifluridine/8.19 mg tipiracil tablet<sup>1</sup>  
Tablet shown is not actual size.

Instruct patients to swallow LONSURF® (trifluridine and tipiracil) tablets whole. Patients should not retake any doses that are missed or vomited, and should continue with the next scheduled dose.<sup>1</sup>

**When adding bevacizumab to LONSURF 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 Prescribing Information for bevacizumab for additional dosing information.<sup>2</sup>**

CLcr=creatinine clearance.

\*Based on the trifluridine component.<sup>1</sup>

	LONSURF <sup>1</sup>		Bevacizumab <sup>2</sup>
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.<sup>1</sup>



Scan the QR code for LONSURF Dosage Calculator and Personalized Treatment Calendar or visit [LONSURFhcp.com/dosing/dosage-calculator](https://LONSURFhcp.com/dosing/dosage-calculator)

## IMPORTANT SAFETY INFORMATION

### ADVERSE REACTIONS (continued)

**The most common adverse reactions or laboratory abnormalities (≥10% in incidence) in patients treated with single-agent LONSURF (continued)** 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%).

## Dose modifications with LONSURF<sup>1</sup>

Withhold treatment before determining whether a dose reduction is needed to manage patients with Adverse Reactions (ARs)



### When to *withhold* LONSURF

Do not initiate the cycle of LONSURF until:

- Absolute neutrophil count (ANC) is  $\geq 1,500/\text{mm}^3$  or febrile neutropenia is resolved
- Platelet count is  $\geq 75,000/\text{mm}^3$
- Grade 3 or 4 nonhematologic ARs are resolved to grade 0 or 1

Within a treatment cycle, withhold LONSURF if the following occur:

- ANC  $< 500/\text{mm}^3$  or febrile neutropenia
- Platelet count is  $< 50,000/\text{mm}^3$
- Grade 3 or 4 nonhematologic AR



### When and how to *resume* LONSURF

After recovery, resume LONSURF after reducing the dose by 5 mg/m<sup>2</sup>/dose from the previous dose, if the following\* occur:

- Febrile neutropenia
- Uncomplicated Grade 4 neutropenia which has recovered to  $\geq 1,500/\text{mm}^3$  that results in more than 1-week delay in start of next cycle
  - If it takes less than 1 week to recover to  $\geq 1,500/\text{mm}^3$  – do not reduce and resume at previous dose
- Uncomplicated Grade 4 thrombocytopenia which has recovered to  $\geq 75,000/\text{mm}^3$  that results in more than 1-week delay in start of next cycle
  - If it takes less than 1 week to recover to  $\geq 75,000/\text{mm}^3$  – do not reduce and resume at previous dose
- Nonhematologic Grade 3 or 4 ARs
  - Except for Grade 3 nausea and/or vomiting controlled by antiemetic therapy or Grade 3 diarrhea responsive to antidiarrheal medication

\*These are the only ARs that require a dose reduction.

**A maximum of 3 dose reductions are permitted to a minimum dose of 20 mg/m<sup>2</sup> orally twice daily. But, in patients with severe renal impairment, only 1 dose reduction is permitted to a minimum dose of 15 mg/m<sup>2</sup> orally twice daily**

- Do not escalate LONSURF dosage after it has been reduced
- Permanently discontinue LONSURF in patients who are unable to tolerate a dose of 20 mg/m<sup>2</sup> orally twice daily
  - But, in patients with severe renal impairment, permanently discontinue LONSURF in patients who are unable to tolerate a dose of 15 mg/m<sup>2</sup> orally twice daily

**For combination treatment in mCRC, modify the dosage of LONSURF as above and/or modify bevacizumab administration as appropriate. Refer to the Prescribing Information for bevacizumab dosing administration information<sup>1</sup>**

## **IMPORTANT SAFETY INFORMATION**

### **ADVERSE REACTIONS (continued)**

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%).

## Taiho Oncology Patient Support™

Taiho Oncology Patient Support offers personalized services to help patients, caregivers, and healthcare professionals access Taiho Oncology products. This includes insurance coverage determination and help with medication affordability.



**TAIHO ONCOLOGY  
PATIENT SUPPORT**  
*Supporting your treatment journey*

## How to enroll

We offer 3 convenient ways to enroll in Taiho Oncology Patient Support services:



### Via the HCP Portal

- **Enroll online**, directly through our HCP portal at [TaihoPatientSupport.com](http://TaihoPatientSupport.com)
- **NOTE:** Login required. Please register prior to enrolling

OR



### Download, Print, and Fax

- Download and fill in the **Enrollment Form**, and print it out to complete
- Fax the completed form to **1-844-287-2559**

OR



### By Phone

- Call **1-844-TAIHO-4U** (1-844-824-4648) for help with enrollment

HCP=healthcare professional.



## Taiho Oncology Patient Support can assist with:



### Insurance Coverage Support

- Benefits investigation
- Prior authorization assistance
- Appeals assistance
- Coordination of prescriptions with pharmacies



### Patient Affordability Assistance<sup>a</sup>

- \$0 co-pay program enrollment for eligible commercially insured patients
- Patient assistance program designed to provide free medication to eligible patients who are uninsured or underinsured
- Referrals to third-party foundations for co-pay or other assistance based on eligibility and additional criteria
- Referrals to Medicare Part D Low-Income Subsidy (LIS)/Extra Help Program



### Personalized Nurse Support<sup>b</sup>

- One-on-one nurse educational support for patients, available via opt-in

<sup>a</sup>Visit [TaihoPatientSupport.com](https://TaihoPatientSupport.com) to see full eligibility criteria.

<sup>b</sup>If this option is selected on the Patient Enrollment Form, a Nurse Navigator will be assigned to provide telephone support and will address general inquiries about LONSURF<sup>®</sup> (trifluridine and tipiracil) tablets treatment.

# 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<sup>2</sup>.

**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.

**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. doi:10.3390/ijms23084427. **5.** Li J, Qin S, Xu RH, 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 randomized, 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.** Mayer RJ, Van Cutsem E, Falcone A, et al; RECURSE Study Group. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. *N Engl J Med.* 2015;372(20):1909-1919. **11.** Data on file. Taiho Oncology, Inc., Princeton, NJ. **12.** Van Cutsem E, Mayer RJ, Laurent S, et al; RECURSE Study Group. The subgroups of the phase III RECURSE trial of trifluridine/tipiracil (TAS-102) versus placebo with best supportive care in patients with metastatic colorectal cancer. *Eur J Cancer.* 2018;90:63-72. **13.** Shitara K, Doi T, Dvorkin M, et al. Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2018;19(11):1437-1448. **14.** Ferrara N. Vascular endothelial growth factor: basic science and clinical progress. *Endocr Rev.* 2004;25(4):581-611. **15.** Referenced with permission from the *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines<sup>®</sup>) for Colon Cancer V.4.2023*. © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. Accessed November 21, 2023. To view the most recent and complete version of the guideline, go online to NCCN.org. **16.** Referenced with permission from the *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines<sup>®</sup>) for Rectal Cancer V.6.2023*. © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. Accessed November 21, 2023. To view the most recent and complete version of the guideline, go online to NCCN.org. **17.** Referenced with permission from the *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines<sup>®</sup>) for Gastric Cancer V.2.2023*. © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. Accessed August 31, 2023. To view the most recent and complete version of the guideline, go online to NCCN.org. **18.** Referenced with permission from the *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines<sup>®</sup>) for Esophageal and Esophagogastric Junction Cancers V.3.2023*. © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. Accessed August 31, 2023. To view the most recent and complete version of the guideline, go online to NCCN.org.

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Please see additional Important Safety Information throughout and full [Prescribing Information](#).

# REDEFINE EXPECTATIONS WITH LONSURF

SUNLIGHT is the first and only phase 3 study with an active control that demonstrated statistically significant efficacy and proven safety in 3L mCRC<sup>3-8</sup>

LONSURF interferes with DNA synthesis and prevents cell proliferation, while bevacizumab starves the tumor by preventing angiogenesis.<sup>1,14</sup>



To learn more about LONSURF,  
visit [LONSURFhcp.com](https://LONSURFhcp.com)

The National Comprehensive Cancer Network® (NCCN®) recommends trifluridine and tipiracil (LONSURF) +/- bevacizumab as NCCN Category 2A recommended options for a potential third-line or subsequent treatment in mCRC patients.<sup>15,16</sup>

The NCCN recommends trifluridine and tipiracil (LONSURF) as a Category 1 third-line or subsequent treatment option for certain patients with metastatic gastric or GEJ cancer.<sup>17,18</sup>

## IMPORTANT SAFETY INFORMATION ADVERSE REACTIONS (continued)

The most common adverse reactions or laboratory abnormalities ( $\geq 20\%$  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 phosphatase (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 additional Important Safety Information throughout  
and full [Prescribing Information](#).

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12/2023

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LON-PM-US-1770

**Lonsurf**<sup>®</sup>  
(trifluridine and tipiracil) tablets

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LONSURF safely and effectively. See full prescribing information for LONSURF.

LONSURF (trifluridine and tipiracil) tablets, for oral use  
Initial U.S. Approval: 2015

### RECENT MAJOR CHANGES

Indications and Usage (1.1)	8/2023
Dosage and Administration (2)	8/2023
Warnings and Precaution (5.1)	8/2023

### INDICATIONS AND USAGE

LONSURF is a combination of trifluridine, a nucleoside metabolic inhibitor, and tipiracil, a thymidine phosphorylase inhibitor, indicated for the treatment of adult patients with:

- metastatic colorectal cancer as a single agent or in combination with bevacizumab who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy. (1.1)
- 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. (1.2)

### DOSAGE AND ADMINISTRATION

- Recommended Dosage:** 35 mg/m<sup>2</sup>/dose orally twice daily with food on Days 1 through 5 and Days 8 through 12 of each 28-day cycle. (2.1)

### DOSAGE FORMS AND STRENGTHS

Tablets:

- 15 mg trifluridine/6.14 mg tipiracil (3)
- 20 mg trifluridine/8.19 mg tipiracil (3)

### CONTRAINDICATIONS

None. (4)

### WARNINGS AND PRECAUTIONS

- Severe Myelosuppression:** Obtain complete blood counts prior to and on Day 15 of each cycle. Withhold and resume at next lower LONSURF dosage as recommended. (2.1, 5.1)
- Embryo-Fetal Toxicity:** Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.2, 8.1, 8.3)

### ADVERSE REACTIONS

The most common adverse reactions or laboratory abnormalities for single agent LONSURF (≥10%) are neutropenia, anemia, thrombocytopenia, fatigue, nausea, decreased appetite, diarrhea, vomiting, abdominal pain, and pyrexia. (6.1)

The most common adverse reactions or laboratory abnormalities for LONSURF in combination with bevacizumab (≥20%) are neutropenia, anemia, thrombocytopenia, fatigue, nausea, increased AST, increased ALT, increased alkaline phosphatase, decreased sodium, diarrhea, abdominal pain, and decreased appetite. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Taiho Oncology, Inc. at 1-844-878-2446 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### USE IN SPECIFIC POPULATIONS

- Lactation:** Advise not to breastfeed. (8.2)
- Geriatric Use:** For LONSURF as a single agent, Grade 3 or 4 neutropenia, Grade 3 anemia and Grade 3 or 4 thrombocytopenia occurred more commonly in patients 65 years or older. (8.5) For LONSURF in combination with bevacizumab Grade 3 or 4 neutropenia and Grade 3 or 4 thrombocytopenia occurred more commonly in patients 65 years or older. (8.5)
- Hepatic Impairment:** Do not initiate LONSURF in patients with baseline moderate or severe hepatic impairment. (8.7)
- Renal Impairment:** Reduce LONSURF dose in patients with severe renal impairment. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 8/2023

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## **FULL PRESCRIBING INFORMATION**

### **1 INDICATIONS AND USAGE**

#### **1.1 Metastatic Colorectal Cancer**

LONSURF, as a single agent or in combination with bevacizumab, is indicated 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.

#### **1.2 Metastatic Gastric Cancer**

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.

### **2 DOSAGE AND ADMINISTRATION**

#### **2.1 Recommended Dosage**

The recommended dosage of LONSURF as a single agent or in combination with bevacizumab is 35 mg/m<sup>2</sup> up to a maximum of 80 mg per dose (based on the trifluridine component) orally twice daily with food on Days 1 through 5 and Days 8 through 12 of each 28-day cycle until disease progression or unacceptable toxicity. Round dose to the nearest 5 mg increment.

Refer to the Prescribing Information for bevacizumab dosing information.

Instruct patients to swallow LONSURF tablets whole.

Instruct patients not to retake doses of LONSURF that are vomited or missed and to continue with the next scheduled dose.

LONSURF is a cytotoxic drug. Follow applicable special handling and disposal procedures.<sup>1</sup>

[Table 1](#) shows the calculated initial daily dose based on body surface area (BSA).

**Table 1: Recommended Dosage According to Body Surface Area (BSA)**

BSA (m <sup>2</sup> )	Total daily dose (mg)	Dose (mg) administered twice daily	Tablets per dose	
			15 mg	20 mg
< 1.07	70	35	1	1
1.07 – 1.22	80	40	0	2
1.23 – 1.37	90	45	3	0
1.38 – 1.52	100	50	2	1
1.53 – 1.68	110	55	1	2
1.69 – 1.83	120	60	0	3
1.84 – 1.98	130	65	3	1
1.99 – 2.14	140	70	2	2
2.15 - 2.29	150	75	1	3
≥2.30	160	80	0	4

## 2.2 Dosage Modifications for Adverse Reactions

Obtain complete blood cell counts prior to and on Day 15 of each cycle [see *Warnings and Precautions (5.1)*].

Do not initiate the cycle of LONSURF until:

- Absolute neutrophil count (ANC) greater than or equal to 1,500/mm<sup>3</sup> or febrile neutropenia is resolved
- Platelets greater than or equal to 75,000/mm<sup>3</sup>
- Grade 3 or 4 non-hematological adverse reactions are resolved to Grade 0 or 1

Within a treatment cycle, withhold LONSURF for any of the following:

- Absolute neutrophil count (ANC) less than 500/mm<sup>3</sup> or febrile neutropenia
- Platelets less than 50,000/mm<sup>3</sup>
- Grade 3 or 4 non-hematologic adverse reaction

After recovery, resume LONSURF after reducing the dose by 5 mg/m<sup>2</sup>/dose from the previous dose, if the following occur:

- Febrile neutropenia
- Uncomplicated Grade 4 neutropenia (which has recovered to greater than or equal to 1,500/mm<sup>3</sup>) or thrombocytopenia (which has recovered to greater than or equal to 75,000/mm<sup>3</sup>) that results in more than 1 week delay in start of next cycle



- Non-hematologic Grade 3 or Grade 4 adverse reaction except for Grade 3 nausea and/or vomiting controlled by antiemetic therapy or Grade 3 diarrhea responsive to antidiarrheal medication

A maximum of 3 dose reductions are permitted. Permanently discontinue LONSURF in patients who are unable to tolerate a dose of 20 mg/m<sup>2</sup> orally twice daily. Do not escalate LONSURF dosage after it has been reduced.

Refer to the bevacizumab prescribing information for dose modifications for adverse reactions associated with bevacizumab.

## **2.3 Recommended Dosage for Renal Impairment**

### **Severe Renal Impairment**

In patients with severe renal impairment [creatinine clearance (CL<sub>cr</sub>) of 15 to 29 mL/min as determined by the Cockcroft-Gault formula], the recommended dosage is 20 mg/m<sup>2</sup> (based on the trifluridine component) orally twice daily with food on Days 1 through 5 and Days 8 through 12 of each 28-day cycle ([Table 2](#)) [*see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)*]. Reduce dose to 15 mg/m<sup>2</sup> twice daily in patients with severe renal impairment who are unable to tolerate a dose of 20 mg/m<sup>2</sup> twice daily ([Table 2](#)). Permanently discontinue LONSURF in patients who are unable to tolerate a dose of 15 mg/m<sup>2</sup> twice daily.

**Table 2: Recommended Dosage for Severe Renal Impairment According to BSA**

BSA (m <sup>2</sup> )	Total daily dose (mg)	Dose (mg) administered twice daily	Tablets per dose	
			15 mg	20 mg
<b>For a dose of 20 mg/m<sup>2</sup> twice daily:</b>				
< 1.14	40	20	0	1
1.14 – 1.34	50	25*	2 in the evening*	1 in the morning*
1.35 – 1.59	60	30	2	0
1.60 – 1.94	70	35	1	1
1.95 – 2.09	80	40	0	2
2.10 – 2.34	90	45	3	0
≥ 2.35	100	50	2	1
<b>For a dose of 15 mg/m<sup>2</sup> twice daily:</b>				
< 1.15	30	15	1	0
1.15 – 1.49	40	20	0	1
1.50 – 1.84	50	25*	2 in the evening*	1 in the morning*
1.85 – 2.09	60	30	2	0
2.10 – 2.34	70	35	1	1
≥ 2.35	80	40	0	2

\* For a total daily dose of 50 mg, instruct patients to take 1 x 20-mg tablet in the morning and 2 x 15-mg tablets in the evening.

### 3 DOSAGE FORMS AND STRENGTHS

Tablets:

- 15 mg trifluridine/6.14 mg tipiracil: white, biconvex, round, film-coated, imprinted with '15' on one side, and '102' and '15 mg' on the other side, in gray ink.
- 20 mg trifluridine/8.19 mg tipiracil: pale red, biconvex, round, film-coated, imprinted with '20' on one side, and '102' and '20 mg' on the other side, in gray ink.

### 4 CONTRAINDICATIONS

None.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 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 [*see Dosage and Administration (2.2)*].

### 5.2 Embryo-Fetal Toxicity

Based on animal studies and its mechanism of action, LONSURF can cause fetal harm when administered to a pregnant woman. Trifluridine/tipiracil caused embryo-fetal lethality and embryo-fetal toxicity in pregnant rats when orally administered during gestation at dosage levels resulting in exposures lower than those achieved at the recommended dosage of 35 mg/m<sup>2</sup> twice daily. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use an effective method of contraception during treatment with LONSURF and for at least 6 months after the final dose [*see Use in Specific Populations (8.1, 8.3)*].

## 6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Severe Myelosuppression [*see Warnings and Precautions (5.1)*]

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described in the WARNINGS AND PRECAUTIONS section and below reflect exposure to LONSURF at the recommended dose in 533 patients with metastatic colorectal cancer in RECURSE, 246 patients with metastatic colorectal cancer treated with LONSURF as monotherapy in SUNLIGHT and 335 patients with metastatic gastric cancer in TAGS. Among the 1114 patients who received LONSURF as a single agent, 12% were exposed for 6 months or longer and 1% were exposed for 12 months or longer. The most common adverse reactions or laboratory abnormalities ( $\geq 10\%$ ) were neutropenia, anemia, thrombocytopenia, fatigue, nausea, decreased appetite, diarrhea, vomiting, abdominal pain, and pyrexia.

Among the 246 patients with metastatic colorectal cancer treated with LONSURF in combination with bevacizumab in SUNLIGHT, 39% were exposed for 6 months or longer, and 14% were exposed for 12 months or longer. The most common adverse reactions or laboratory abnormalities ( $\geq 20\%$ ) were neutropenia, anemia, thrombocytopenia, fatigue, nausea, increased AST, increased ALT, increased alkaline phosphatase, decreased sodium, diarrhea, abdominal pain, and decreased appetite.

### Metastatic Colorectal Cancer

#### *LONSURF as a single agent*

The safety of LONSURF was evaluated in RECURSE, a randomized (2:1), double-blind, placebo-controlled trial in patients with previously treated metastatic colorectal cancer [see *Clinical Studies (14.1)*]. Patients received LONSURF 35 mg/m<sup>2</sup>/dose (n=533) or placebo (n=265) twice daily on Days 1 through 5 and Days 8 through 12 of each 28-day cycle. In RECURSE, 12% of patients received LONSURF for more than 6 months and 1% of patients received LONSURF for more than 1 year.

The study population characteristics were: median age 63 years; 61% male; 57% White, 35% Asian, and 1% Black.

The most common adverse reactions or laboratory abnormalities ( $\geq 10\%$  in incidence) in patients treated with LONSURF at a rate that exceeds the rate in patients receiving placebo were anemia, neutropenia, asthenia/fatigue, nausea, thrombocytopenia, decreased appetite, diarrhea, vomiting, abdominal pain, and pyrexia.

In RECURSE, 3.6% of patients discontinued LONSURF for an adverse reaction and 14% of patients required a dose reduction. The most common adverse reactions or laboratory abnormalities leading to dose reduction were neutropenia, anemia, febrile neutropenia, fatigue, and diarrhea.

[Table 3](#) and [Table 4](#) list the adverse reactions and laboratory abnormalities (graded using CTCAE v4.03), respectively, observed in RECURSE.

**Table 3: Adverse Reactions ( $\geq 5\%$ ) in Patients Receiving LONSURF and at a Higher Incidence ( $>2\%$ ) than in Patients Receiving Placebo in RECOURSE**

Adverse Reactions	LONSURF (N=533)		Placebo (N=265)	
	All Grades (%)	Grades 3-4* (%)	All Grades (%)	Grades 3-4* (%)
<b>General</b>				
Asthenia/fatigue	52	7	35	9
Pyrexia	19	1.3	14	0.4
<b>Gastrointestinal</b>				
Nausea	48	1.9	24	1.1
Diarrhea	32	3	12	0.4
Vomiting	28	2.1	14	0.4
Abdominal pain	21	2.4	19	3.8
Stomatitis	8	0.4	6	0
<b>Metabolism and nutrition</b>				
Decreased appetite	39	3.6	29	4.9
<b>Infections<sup>†</sup></b>	27	7	16	4.9
<b>Nervous system</b>				
Dysgeusia	7	0	2.3	0
<b>Skin and subcutaneous tissue</b>				
Alopecia	7	0	1.1	0

\*No Grade 4 definition for nausea, abdominal pain, or fatigue in National Cancer Institute Common Terminology

<sup>†</sup>Incidence reflects 64 preferred terms in the Infections and Infestations system organ class.

**Table 4: Select Laboratory Abnormalities in RECOURSE**

Laboratory Parameter*	LONSURF		Placebo	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
<b>Hematologic</b>				
Anemia <sup>†</sup>	77	18	33	3
Neutropenia	67	38	0.8	0
Thrombocytopenia	42	5	8	0.4

\* Worst Grade at least one grade higher than baseline, with percentages based on number of patients with post-baseline samples, which may be <533 (LONSURF) or 265 (placebo)

<sup>†</sup> One Grade 4 anemia adverse reaction based on clinical criteria was reported

In RECOURSE, pulmonary emboli occurred more frequently in LONSURF-treated patients (2%) compared to no patients on placebo.

#### *LONSURF in combination with bevacizumab*

The safety of LONSURF in combination with bevacizumab was evaluated in SUNLIGHT, an international, randomized, open label study in patients with previously treated metastatic colorectal cancer [see *Clinical Studies (14.1)*].

The study population characteristics were: median age 63 years (20 to 90 years); 52% male; 88% White, 1.4% Black, 0.2% Asian, 0.2% American Indian or Alaska Native, and 9.6% were unknown; and baseline ECOG performance status 0 (46%), 1 (54%), or 2 (0.2%).

Serious adverse reactions occurred in 25% of patients. The most frequent serious adverse reactions ( $\geq 2\%$ ) 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%).

Permanent treatment discontinuation due to an adverse reaction occurred in 13% of patients. The adverse reaction which resulted in permanent treatment discontinuation in  $\geq 2\%$  of patients was fatigue.

Dosage reductions due to an adverse reaction or laboratory abnormality occurred in 7% of patients. At least one dose reduction in 3.7% of patients was required for neutropenia.

Dosage interruptions due to an adverse reaction occurred in 11% of patients who received LONSURF in combination with bevacizumab. The adverse reaction that required dosage interruption in  $\geq 2\%$  of patients was nausea.

The most common adverse reactions or laboratory abnormalities ( $\geq 20\%$  in incidence) in patients treated with LONSURF in combination with bevacizumab were neutropenia, anemia, thrombocytopenia, fatigue, nausea, increased aspartate aminotransferase, increased alanine aminotransferase, increased alkaline phosphatase, decreased sodium, diarrhea, abdominal pain, and decreased appetite. [Table 5](#) and [Table 6](#) list the adverse reactions and laboratory abnormalities, respectively, observed in SUNLIGHT.

**Table 5: Adverse Reactions (≥5%) in SUNLIGHT**

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

\*Represents a composite of multiple related terms



**Table 6: Select Laboratory Abnormalities ( $\geq 10\%$ ) in SUNLIGHT**

Laboratory parameters	LONSURF + Bevacizumab <sup>a</sup>		LONSURF <sup>a</sup>	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
<b>Hematology</b>				
Neutrophils decreased	80	52	68	39
Hemoglobin decreased	68	5	73	11
Platelets decreased	54	4.1	29	0.8
<b>Chemistry</b>				
Aspartate aminotransferase increased	34	2.1	28	1.2
Alanine aminotransferase increased	33	3.3	23	0.4
Alkaline phosphatase increased	31	0.8	36	1.2
Sodium decreased	25	2.1	20	3.3
Potassium increased	17	0	15	0
Potassium decreased	12	0.8	12	2.5
Creatinine increased	12	0.8	15	0

<sup>a</sup>Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: LONSURF + bevacizumab group (n=242 patients) and LONSURF group (range: 240 to 242 patients).

### Metastatic Gastric Cancer

The safety of LONSURF was evaluated in TAGS, an international, randomized (2:1), double-blind, placebo-controlled trial in patients with metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma who were previously treated with at least 2 prior chemotherapy regimens for advanced disease [see *Clinical Studies (14.2)*]. Previous treatments must have included a fluoropyrimidine, a platinum, and either a taxane or irinotecan. Patients with HER2/neu-positive tumors must have received prior HER2/neu-targeted therapy, if available. Adjuvant chemotherapy could be counted as one prior regimen in patients who had recurrence during or within 6 months of completion of the adjuvant chemotherapy. Patients received LONSURF 35 mg/m<sup>2</sup>/dose (n=335) or placebo (n=168) twice daily on Days 1 through 5 and Days 8 through 12 of each 28-day cycle with best supportive care. In TAGS, 10% of patients received LONSURF for more than 6 months and 0.9% of patients received LONSURF for more than 1 year.

The study population characteristics were: median age 63 years (24 to 89 years); 73% male; 70% White, 16% Asian, and 1% Black.

The most common adverse reactions or laboratory abnormalities ( $\geq 10\%$  in incidence) in patients treated with LONSURF at a rate that exceeds the rate in patients receiving placebo were neutropenia, anemia, nausea, decreased appetite, thrombocytopenia, vomiting, and diarrhea.

In TAGS, 13% of patients discontinued LONSURF for an adverse reaction and 11% of patients required a dose reduction. The most common adverse reactions or laboratory abnormalities leading to dose reduction were neutropenia, anemia, febrile neutropenia, and diarrhea.

Table 7 and 8 list the adverse reactions and laboratory abnormalities (graded using CTCAE v4.03), respectively, observed in TAGS.

**Table 7: Adverse Reactions (≥5%) in Patients Receiving LONSURF and at a Higher Incidence (>2%) than in Patients Receiving Placebo in TAGS**

Adverse Reactions	LONSURF (N=335)		Placebo (N=168)	
	All Grades (%)	Grades 3-4* (%)	All Grades (%)	Grades 3-4* (%)
<b>Gastrointestinal</b>				
Nausea	37	3	32	3
Vomiting	25	4	20	2
Diarrhea	23	3	14	2
<b>Metabolism and nutrition</b>				
Decreased appetite	34	9	31	7
<b>Infections<sup>†</sup></b>	23	5	16	5

\*No Grade 4 definition for nausea or fatigue in NCI CTCAE, version 4.03.

<sup>†</sup>Incidence reflects 46 preferred terms in the Infections and Infestations system organ class.

**Table 8: Laboratory Abnormalities in TAGS**

Laboratory Parameter*	LONSURF		Placebo	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
<b>Hematologic</b>				
Neutropenia	66	38	4	0
Anemia <sup>†</sup>	63	19	38	7
Thrombocytopenia	34	6	9	0

\* Worst Grade at least one Grade higher than baseline, with percent based on number of patients with post-baseline samples which may be <335 (LONSURF) or 168 (placebo)

<sup>†</sup> Anemia: No Grade 4 definition in CTCAE, v4.03

In TAGS, pulmonary emboli occurred more frequently in LONSURF-treated patients (3.1%) compared to 1.8% for patients on placebo.

#### Additional Clinical Experience

Interstitial lung disease was reported in 15 (0.2%) patients, 3 of which were fatal, among approximately 7,000 patients exposed to LONSURF in clinical studies and clinical practice settings in Asia.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

Based on animal data and its mechanism of action [see *Clinical Pharmacology (12.2)*], LONSURF can cause fetal harm. LONSURF caused embryo-fetal lethality and embryo-fetal toxicity in pregnant rats when given during gestation at doses resulting in exposures lower than or similar to human exposures at the recommended clinical dose (see Data). There are no available data on LONSURF use in pregnant women. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

#### Data

##### *Animal Data*

Trifluridine/tipiracil was administered orally once daily to female rats during organogenesis at dose levels of 15, 50, and 150 mg/kg [trifluridine (FTD) equivalent]. Decreased fetal weight was observed at FTD doses  $\geq 50$  mg/kg (approximately 0.33 times the FTD exposure at the clinical dose of 35 mg/m<sup>2</sup> twice daily). At the FTD dose of 150 mg/kg (approximately 0.92 times the FTD exposure at the clinical dose of 35 mg/m<sup>2</sup> twice daily) embryoletality and structural anomalies (kinked tail, cleft palate, ectrodactyly, anasarca, alterations in great vessels, and skeletal anomalies) were observed.

### 8.2 Lactation

#### Risk Summary

There are no data on the presence of trifluridine, tipiracil or its metabolites in human milk or its effects on the breastfed child or on milk production. In nursing rats, trifluridine and tipiracil or their metabolites were present in breast milk (*see Data*). 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.

#### Data

Radioactivity was excreted in the milk of nursing rats dosed with trifluridine/tipiracil containing <sup>14</sup>C-FTD or <sup>14</sup>C-tipiracil (TPI). Levels of FTD-derived radioactivity were as high as approximately 50% of the exposure in maternal plasma an hour after dosing with trifluridine/tipiracil and were approximately the same as those in maternal plasma for up to 12 hours following dosing. Exposure to TPI-derived radioactivity was higher in milk than in maternal plasma beginning 2 hours after dosing and continuing for at least 12 hours following administration of trifluridine/tipiracil.

### **8.3 Females and Males of Reproductive Potential**

#### Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating LONSURF [see *Use in Specific Populations (8.1)*].

#### Contraception

LONSURF can cause fetal harm when administered to a pregnant woman [see *Use in Specific Populations (8.1)*].

#### *Females*

Advise females of reproductive potential to use effective contraception during treatment with LONSURF and for at least 6 months after the final dose.

#### *Males*

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 [see *Nonclinical Toxicology (13.1)*].

### **8.4 Pediatric Use**

Safety and effectiveness of LONSURF in pediatric patients have not been established.

#### Juvenile Animal Toxicity Data

Dental toxicity including whitening, breakage, and malocclusion (degeneration and disarrangement in the ameloblasts, papillary layer cells and odontoblasts) were observed in rats treated with trifluridine/tipiracil at doses  $\geq 50$  mg/kg (approximately 0.33 times the exposure at the clinical dose of 35 mg/m<sup>2</sup> twice daily).

### **8.5 Geriatric Use**

Of the 1114 patients with metastatic colorectal cancer or gastric cancer who received single agent LONSURF in clinical studies, 45% were 65 years of age or over, and 11% were 75 and over. In the 246 patients who received LONSURF in combination with bevacizumab; 41% were 65 years of age or over, and 10% were 75 and over. While these studies were not designed to detect a difference in efficacy, no overall differences were observed in patients 65 or older versus younger patients with either LONSURF as a single agent or LONSURF in combination with bevacizumab.

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%).

## 8.6 Renal Impairment

No dose adjustment is recommended for patients with mild or moderate renal impairment (CLcr of 30 to 89 mL/min as determined by the Cockcroft-Gault formula). Reduce the dose of LONSURF for patients with severe renal impairment (CLcr of 15 to 29 mL/min) [see *Dosage and Administration (2.3)*]. The pharmacokinetics of trifluridine and tipiracil have not been studied in patients with end stage renal disease.

## 8.7 Hepatic Impairment

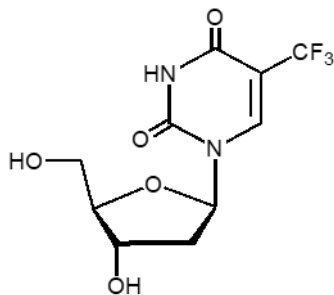
No adjustment to the starting dosage of LONSURF is recommended for patients with mild hepatic impairment. Do not initiate LONSURF in patients with baseline moderate or severe (total bilirubin >1.5 times ULN and any AST) hepatic impairment [see *Clinical Pharmacology (12.3)*].

## 11 DESCRIPTION

LONSURF contains trifluridine and tipiracil hydrochloride at a molar ratio of 1:0.5.

### Trifluridine

Trifluridine, a nucleoside metabolic inhibitor, is described chemically as 2'-deoxy-5-(trifluoromethyl) uridine and has the following structural formula:

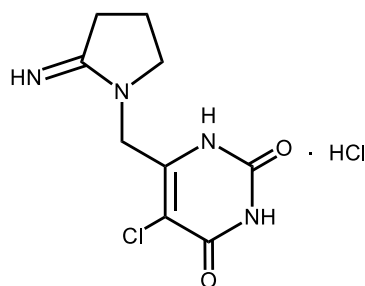


Trifluridine has a molecular formula C<sub>10</sub>H<sub>11</sub>F<sub>3</sub>N<sub>2</sub>O<sub>5</sub> and a molecular weight of 296.20.

Trifluridine is a white crystalline powder, soluble in water, ethanol, 0.01 mol/L hydrochloric acid, 0.01 mol/L sodium hydroxide solution; freely soluble in methanol, acetone; sparingly soluble in 2-propanol, acetonitrile; slightly soluble in diethyl ether; and very slightly soluble in isopropyl ether.

### Tipiracil hydrochloride

Tipiracil hydrochloride, a thymidine phosphorylase inhibitor, is described chemically as 5-chloro-6-[(2-iminopyrrolidin-1-yl)methyl]pyrimidine-2,4-(1*H*,3*H*)-dione monohydrochloride or 2,4(1*H*,3*H*)-Pyrimidinedione, 5-chloro-6-[(2-imino-1-pyrrolidinyl)methyl]-, hydrochloride (1:1) and has the following structural formula:



Tipiracil hydrochloride has a molecular formula  $C_9H_{11}ClN_4O_2 \cdot HCl$  and a molecular weight of 279.12. Tipiracil hydrochloride is a white crystalline powder, soluble in water, 0.01 mol/L hydrochloric acid, and 0.01 mol/L sodium hydroxide; slightly soluble in methanol; very slightly soluble in ethanol; and practically insoluble in acetonitrile, 2-propanol, acetone, diisopropyl ether, and diethyl ether.

LONSURF (trifluridine and tipiracil) tablets for oral use contain 15 mg of trifluridine and 6.14 mg of tipiracil equivalent to 7.065 mg of tipiracil hydrochloride or 20 mg of trifluridine and 8.19 mg of tipiracil equivalent to 9.420 mg of tipiracil hydrochloride.

LONSURF tablets contain the following inactive ingredients: lactose monohydrate, pregelatinized starch, stearic acid, hypromellose, polyethylene glycol, titanium dioxide, ferric oxide, and magnesium stearate. The tablets are imprinted with ink containing shellac, ferric oxide red, ferric oxide yellow, titanium dioxide, FD&C Blue No. 2 Aluminum Lake, carnauba wax, and talc.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

LONSURF consists of a thymidine-based nucleoside analog, trifluridine, and the thymidine phosphorylase inhibitor, tipiracil, at a molar ratio 1:0.5 (weight ratio, 1:0.471). Inclusion of tipiracil increases trifluridine exposure by inhibiting its metabolism by thymidine phosphorylase.

Following uptake into cancer cells, trifluridine is incorporated into DNA, interferes with DNA synthesis and inhibits cell proliferation. Trifluridine/tipiracil demonstrated anti-tumor activity against *KRAS* wild-type and mutant human colorectal cancer xenografts in mice.

### 12.2 Pharmacodynamics

#### Cardiac Electrophysiology

LONSURF administered to 42 patients with advanced solid tumors at the recommended dosage had no large effect (i.e. >20 ms) in the mean QTc interval when compared to placebo and no exposure-QT relationship was identified. Two of 42 patients (4.8%) had QTc >500 msec and 2.4% had a QTc increase from baseline >60 msec.

## 12.3 Pharmacokinetics

After twice daily dosing of LONSURF, systemic exposure (AUC) of trifluridine increased more than dose-proportionally over the dose range of 15 mg/m<sup>2</sup> (0.43 times the recommended dose) to 35 mg/m<sup>2</sup>.

The accumulation of trifluridine was 3-fold for AUC<sub>0-12hr</sub> and 2-fold for C<sub>max</sub> at steady state while no accumulation was observed for tipiracil.

Administration of a single dose of LONSURF 35 mg/m<sup>2</sup> increased the mean AUC<sub>0-last</sub> of trifluridine by 37-fold and C<sub>max</sub> by 22-fold with reduced variability compared to administration of a single dose of trifluridine 35 mg/m<sup>2</sup> alone.

### Absorption

Following a single oral administration of LONSURF at 35 mg/m<sup>2</sup> in patients with cancer, the mean time to peak plasma concentration (T<sub>max</sub>) of trifluridine was around 2 hours.

### *Food Effect*

A standardized high-fat, high-calorie meal decreased trifluridine C<sub>max</sub>, tipiracil C<sub>max</sub> and AUC by approximately 40%, but did not change trifluridine AUC compared to those in a fasting state in patients with cancer following administration of a single dose of LONSURF 35 mg/m<sup>2</sup>.

### Distribution

Trifluridine mainly binds to human serum albumin. The in vitro protein binding of trifluridine in human plasma is >96%, independent of drug concentration and presence of tipiracil. Plasma protein binding of tipiracil is below 8%.

### Elimination

After administration of LONSURF 35 mg/m<sup>2</sup>, the mean elimination half-life (t<sub>1/2</sub>) of trifluridine was 1.4 hours and of tipiracil was 2.1 hours after a single dose. The mean elimination half-life at steady state of trifluridine was 2.1 hours and of tipiracil was 2.4 hours.

### *Metabolism*

Trifluridine and tipiracil are not metabolized by cytochrome P450 (CYP) enzymes. Trifluridine is mainly eliminated by metabolism via thymidine phosphorylase to form an inactive metabolite, 5-(trifluoromethyl) uracil (FTY). No other major metabolites were detected in plasma or urine.

### *Excretion*

After single oral administration of LONSURF (60 mg) with [<sup>14</sup>C]-trifluridine, the total cumulative excretion of radioactivity was 60% of the administered dose. The majority of recovered radioactivity was eliminated into urine (55% of the dose) as FTY and trifluridine glucuronide isomers within 24 hours and the excretion into feces and expired air was <3% for both. The unchanged trifluridine was <3% of administered dose recovered in the urine and feces.

After single oral administration of LONSURF (60 mg) with [<sup>14</sup>C]-tipiracil hydrochloride, recovered radioactivity was 77% of the dose, which consisted of 27% urinary excretion and 50% fecal excretion. Tipiracil was the major component and 6-HMU was the major metabolite in urine, and feces.

## Specific Populations

Based on the population pharmacokinetic analysis, there is no clinically relevant effect of age, sex, or race (White or Asian) on the pharmacokinetics of trifluridine or tipiracil.

### *Patients with Renal Impairment*

In a dedicated renal impairment study, all patients received LONSURF 35 mg/m<sup>2</sup> twice daily except for patients with severe renal impairment who received 20 mg/m<sup>2</sup> twice daily. Mild renal impairment (CLcr of 60 to 89 mL/min as determined by the Cockcroft-Gault formula) had no clinically important effect on steady-state AUC<sub>0-last</sub> of trifluridine and tipiracil. Moderate renal impairment (CLcr of 30 to 59 mL/min) increased steady-state AUC<sub>0-last</sub> of trifluridine by 56% and tipiracil by 139% compared to normal renal function (CLcr ≥ 90 mL/min). Severe renal impairment (CLcr of 15 to 29 mL/min) increased the dose-normalized steady-state AUC<sub>0-last</sub> of trifluridine by 140% and tipiracil by 614% compared to normal renal function. The pharmacokinetics of trifluridine and tipiracil have not been studied in patients with end stage renal disease.

### *Patients with Hepatic Impairment*

No clinically important differences in the mean exposures of trifluridine and tipiracil were observed between patients with mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN or total bilirubin <1 to 1.5 times ULN and any AST) to moderate hepatic impairment (total bilirubin >1.5 to 3 times ULN and any AST) and patients with normal hepatic function (total bilirubin and AST ≤ ULN); however, 5 of 6 patients with moderate hepatic impairment experienced Grade 3 or 4 increased bilirubin levels. The pharmacokinetics of trifluridine and tipiracil have not been studied in patients with severe hepatic impairment [*see Dosage Modifications (2.2), Use in Specific Populations (8.6)*].

## Drug Interaction Studies

In vitro studies indicated that trifluridine, tipiracil, and FTY did not inhibit the CYP enzymes and had no inductive effect on CYP1A2, CYP2B6, or CYP3A4/5.

In vitro studies indicated that trifluridine was not an inhibitor of or substrate for human uptake and efflux transporters.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

No long-term studies evaluating the carcinogenic potential of trifluridine/tipiracil in animals have been performed. Trifluridine/tipiracil was genotoxic in a reverse mutation test in bacteria, a chromosomal aberration test in mammalian-cultured cells, and a micronucleus test in mice.

Animal studies did not indicate an effect of trifluridine/tipiracil on male fertility in rats. Dose-related increases in the corpus luteum count and implanted embryo count were observed, but female fertility was not affected.



## 14 CLINICAL STUDIES

### 14.1 Metastatic Colorectal Cancer

#### Previously treated metastatic colorectal cancer (single agent LONSURF)

##### *RECOURSE*

The efficacy of LONSURF was evaluated in RECOURSE (NCT01607957), an international, randomized, double-blind, placebo-controlled study conducted in patients with previously treated metastatic colorectal cancer (mCRC). Key eligibility criteria included prior treatment with at least 2 lines of standard chemotherapy for metastatic CRC, ECOG performance status (PS) 0-1, absence of brain metastasis, and absence of ascites requiring drainage in the past four weeks. Patients were randomized 2:1 to receive LONSURF 35 mg/m<sup>2</sup> or matching placebo orally twice daily after meals on Days 1-5 and 8-12 of each 28-day cycle until disease progression or unacceptable toxicity. Randomization was stratified by KRAS status (wild-type vs. mutant), time since diagnosis of first metastasis (<18 months vs. ≥ 18 months), and region (Japan vs. US, Europe and Australia). The major efficacy outcome measure was overall survival (OS) and an additional efficacy outcome measure was progression-free survival (PFS).

A total of 800 patients were randomized to LONSURF (N=534) with best supportive care (BSC) or matching placebo (N=266) plus BSC. The median age was 63 years, 61% were male, 58% and 35% were White and Asian respectively, and all patients had baseline ECOG PS of 0 or 1. The primary site of disease was colon (62%) or rectum (38%). KRAS status was wild-type (49%) or mutant (51%) at study entry. All patients received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy. All but one patient received bevacizumab and all but two patients with KRAS wild-type tumors received panitumumab or cetuximab.

Efficacy results are summarized in [Table 9](#) and [Figure 1](#).

**Table 9: Efficacy Results from RECOURSE**

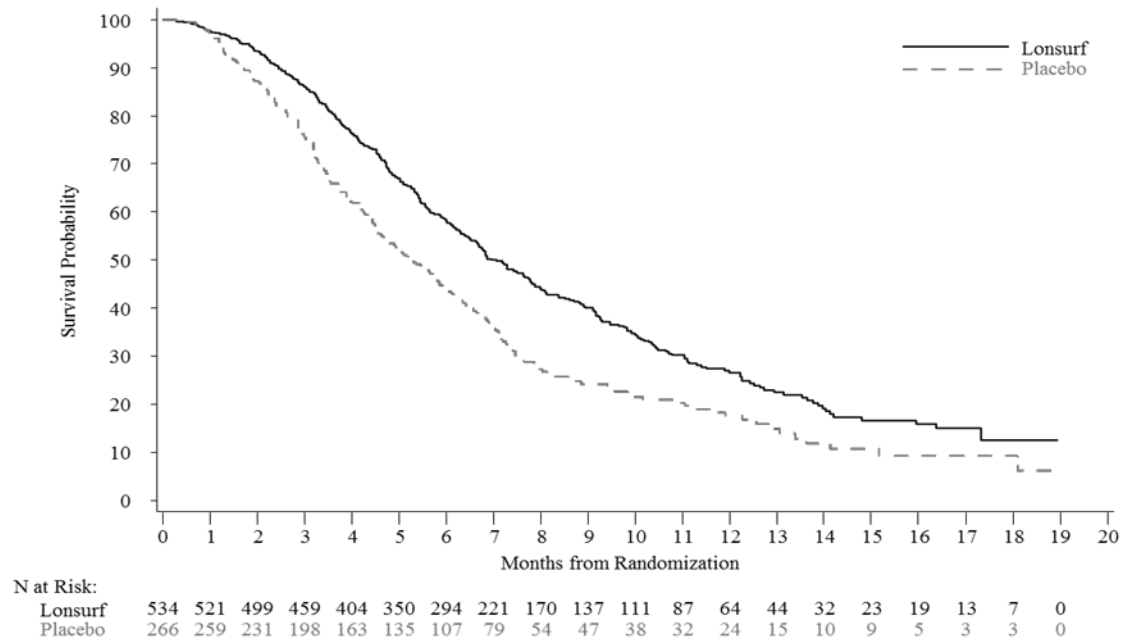
	<b>LONSURF (N=534)</b>	<b>Placebo (N=266)</b>
<b>Overall Survival</b>		
Number of deaths, N (%)	364 (68)	210 (79)
Median OS (months) <sup>a</sup> (95% CI) <sup>b</sup>	7.1 (6.5, 7.8)	5.3 (4.6, 6.0)
Hazard ratio (95% CI)	0.68 (0.58, 0.81)	
p-value <sup>c</sup>	<0.001	
<b>Progression-Free Survival</b>		
Number of events, N (%)	472 (88)	251 (94)
Hazard ratio (95% CI)	0.47 (0.40, 0.55)	
p-value <sup>c</sup>	<0.001	

<sup>a</sup> Kaplan-Meier estimates

<sup>b</sup> Methodology of Brookmeyer and Crowley

<sup>c</sup> Stratified log-rank test (strata: KRAS status, time since diagnosis of first metastasis, region), 2-sided

**Figure 1: Kaplan-Meier Curves of Overall Survival in RECOURSE**



Previously treated metastatic colorectal cancer (LONSURF in combination with bevacizumab)

*SUNLIGHT*

The efficacy of LONSURF in combination with bevacizumab was evaluated in SUNLIGHT (NCT 04737187), an international, randomized (1:1), open label study in patients with previously treated metastatic colorectal cancer. Patients were required to have received no more than 2 prior treatments for advanced disease, including a fluoropyrimidine, irinotecan, oxaliplatin, an anti-VEGF monoclonal antibody (optional) and an anti-EGFR monoclonal antibody for patients with RAS wild-type. Other key eligibility criteria included ECOG performance status (PS) 0-1, absence of symptomatic brain metastases, absence of ascites requiring drainage in the past 4 weeks, absence of uncontrolled hypertension, absence of non-healing wound, and absence of deep venous thromboembolic event in the past 4 weeks. Patients were randomized to receive LONSURF 35 mg/m<sup>2</sup> administered orally twice daily on Days 1 to 5 and 8 to 12 of each 28-day cycle with or without bevacizumab 5 mg/kg administered intravenously every 2 weeks (on Day 1 and Day 15) of each 4-week cycle until disease progression or unacceptable toxicity. Randomization was stratified by geographic region (North America, European Union, Rest of the World), time since diagnosis of metastatic disease (<18 months, ≥18 months) and RAS status (wild-type, mutant). The major efficacy outcome was overall survival (OS), and an additional efficacy outcome measure was progression-free survival (PFS).

A total of 492 patients were randomized to receive LONSURF in combination with bevacizumab (N=246) or LONSURF as a single agent (N=246). The trial population characteristics were as follows: median age 63 years, 52% male, 88% White, 1.4% Black, 0.2% Asian, 0.2% American Indian or Alaska Native, and 9.6% were unknown, 46% had ECOG PS 0 and 54% had ECOG PS 1. The primary site of disease was colon (73%) or rectum (27%). Seventy-one percent of patients had a RAS mutant status. A total of 92% of patients received 2 prior anticancer treatment

regimens for advanced CRC; all patients received prior fluoropyrimidine; 99.8% of patients received prior irinotecan; 98% of patients received prior oxaliplatin. Among all 492 treated patients, 76% received prior anti-VEGF treatment, and 72% received an anti-VEGF monoclonal antibody. Among the 142 patients with RAS wild-type mCRC, 94% received prior anti-EGFR monoclonal antibody.

Efficacy results are summarized in [Table 10](#) and [Figure 2](#).

**Table 10: Efficacy Results from SUNLIGHT**

	<b>LONSURF plus Bevacizumab (N=246)</b>	<b>LONSURF (N=246)</b>
<b>Overall survival</b>		
Number of deaths, N (%)	148 (60)	183 (74)
Median OS (months) <sup>a</sup> (95% CI) <sup>b</sup>	10.8 (9.4, 11.8)	7.5 (6.3, 8.6)
Hazard ratio (95% CI) <sup>c</sup>	0.61 (0.49, 0.77)	
p-value <sup>d</sup>	<0.001	
<b>Progression-free survival (per investigator)</b>		
Number of events N (%)	206 (84)	236 (96)
Median PFS (months) <sup>a</sup> (95% CI) <sup>b</sup>	5.6 (4.5, 5.9)	2.4 (2.1, 3.2)
Hazard ratio (95% CI) <sup>d</sup>	0.44 (0.36, 0.54)	
p-value <sup>d</sup>	<0.001	

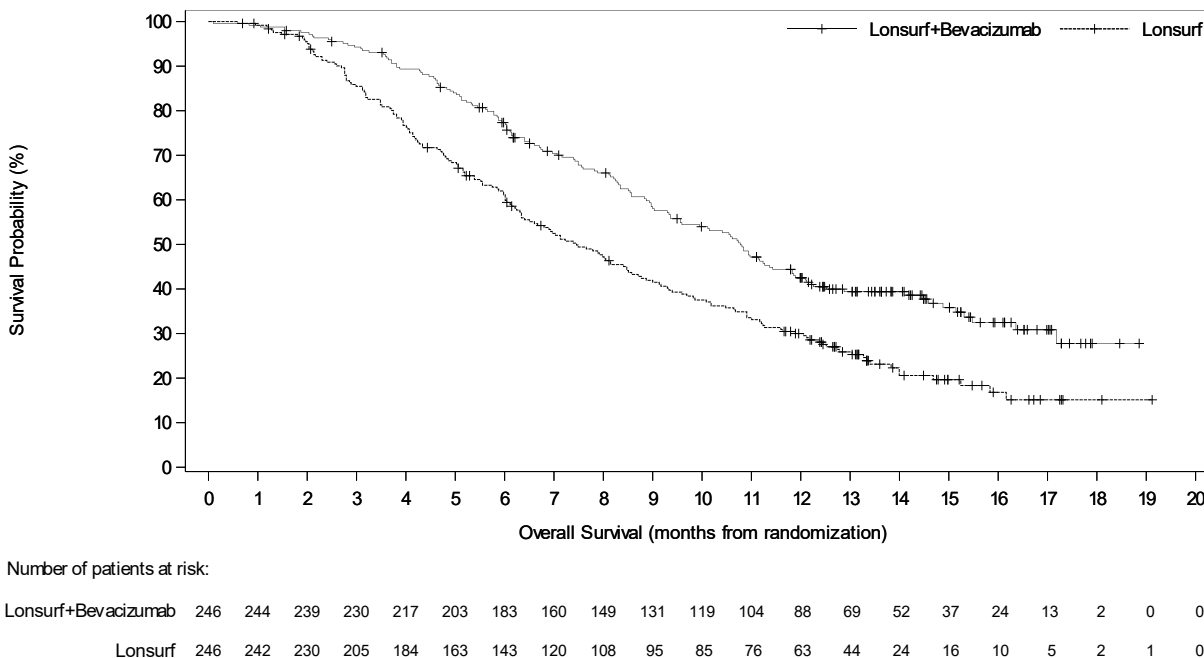
a Kaplan-Meier estimates

b Methodology of Brookmeyer and Crowley

c Stratified proportional hazards model (strata: region, time since first metastasis diagnosis, RAS status)

d Stratified log-rank test (strata: region, time since first metastasis diagnosis, RAS status), 1-sided p-value

**Figure 2: Kaplan-Meier Curves of Overall Survival in SUNLIGHT**



## 14.2 Metastatic Gastric Cancer

The efficacy of LONSURF was evaluated in TAGS (NCT02500043), an international, randomized, double-blind, placebo-controlled study in patients with metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma previously treated with at least 2 prior regimens for advanced disease. Previous treatments must have included a fluoropyrimidine, a platinum, and either a taxane or irinotecan. Patients with HER2/neu-positive tumors must have received prior HER2/neu-targeted therapy, if available. Adjuvant chemotherapy could be counted as one prior regimen in patients who had recurrence during or within 6 months of completion of the adjuvant chemotherapy. Other key eligibility criteria included ECOG performance status (PS) 0 or 1. Patients were randomized 2:1 to receive LONSURF 35 mg/m<sup>2</sup> orally twice daily on Days 1-5 and 8-12 of each 28-day cycle with best supportive care (BSC) or matching placebo with BSC until disease progression or unacceptable toxicity. Randomization was stratified by ECOG PS at baseline (0 vs. 1), prior ramucirumab (yes vs. no), and geographic region (Japan vs. rest of world). The major efficacy outcome measure was OS and an additional outcome measure was PFS.

A total of 507 patients were randomized to LONSURF (N=337) or placebo (N=170). The median age was 63 years, 73% were male, 70% and 16% were White and Asian respectively, and 38% had a baseline ECOG PS of 0. Seventy-one percent of patients had gastric tumors, 29% had GEJ tumors, and two patients had gastric/GEJ tumors. All patients received platinum-based chemotherapy, 99% received fluoropyrimidine-based therapy, 91% received a taxane, 55% received irinotecan, and 33% received ramucirumab. The HER2 status was negative in 62%,

positive in 19%, and unknown in 20% of patients. Among the 94 patients with HER2 positive tumors, 89% received prior anti-HER2 therapy.

Efficacy results are summarized in [Table 11](#) and [Figure 3](#).

**Table 11: Efficacy Results from TAGS**

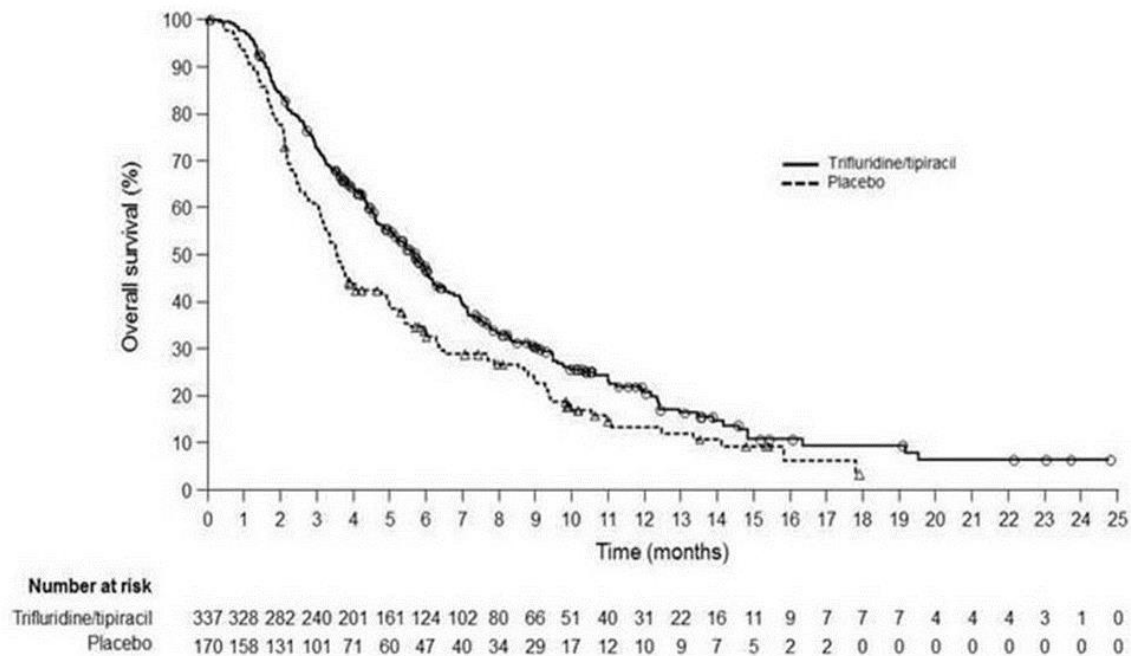
	<b>LONSURF (N=337)</b>	<b>Placebo (N=170)</b>
<b>Overall Survival</b>		
Number of deaths, N (%)	244 (72)	140 (82)
Median OS (months) <sup>a</sup> (95% CI) <sup>b</sup>	5.7 (4.8, 6.2)	3.6 (3.1, 4.1)
Hazard ratio (95% CI)	0.69 (0.56, 0.85)	
p-value <sup>c</sup>	0.0006	
<b>Progression-Free Survival</b>		
Number of events, N (%)	287 (85)	156 (92)
Hazard ratio (95% CI)	0.56 (0.46, 0.68)	
p-value <sup>c</sup>	<0.0001	

<sup>a</sup> Kaplan-Meier estimates

<sup>b</sup> Methodology of Brookmeyer and Crowley

<sup>c</sup> Stratified log-rank test (strata: ECOG PS, prior ramucirumab treatment, region), 2-sided

**Figure 3: Kaplan-Meier Curves of Overall Survival in TAGS**



## 15 REFERENCES

1. “OSHA Hazardous Drugs”. OSHA.  
<http://www.osha.gov/SLTC/hazardousdrugs/index.html>

## 16 HOW SUPPLIED/STORAGE AND HANDLING

LONSURF 15 mg/6.14 mg tablets are supplied as white, biconvex, round, film-coated tablet, imprinted with ‘15’ on one side, and ‘102’ and ‘15 mg’ on the other side, in gray ink. The tablets are packaged in HDPE bottles with child resistant closures in the following presentations:

- 20 count: NDC 64842-1025-1
- 40 count: NDC 64842-1025-2
- 60 count: NDC 64842-1025-3

LONSURF 20 mg/8.19 mg tablets are supplied as pale red, biconvex, round, film-coated tablet, imprinted with ‘20’ on one side, and ‘102’ and ‘20 mg’ on the other side, in gray ink. The tablets are packaged in HDPE bottles with child resistant closures in the following presentations:

- 20 count: NDC 64842-1020-1
- 40 count: NDC 64842-1020-2
- 60 count: NDC 64842-1020-3

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) [See USP Controlled Room Temperature].

LONSURF is a cytotoxic drug. Follow applicable special handling and disposal procedures.<sup>1</sup>  
If stored outside of original bottle, discard after 30 days.

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling ([Patient Information](#)).

### Severe Myelosuppression

Advise patients to immediately contact their healthcare provider if they experience signs or symptoms of infection and advise patients to keep all appointments for blood tests [*see Warnings and Precautions (5.1)*].

### Gastrointestinal Toxicity

Advise patients to contact their healthcare provider for severe or persistent nausea, vomiting, diarrhea, or abdominal pain [*see Adverse Reactions (6.1)*].

### Administration Instructions

Advise patients that LONSURF is available in two strengths and they may receive both strength tablets to provide the prescribed dosage.

Advise patients to take LONSURF with food [*see Dosage and Administration (2.1)*].

Advise patients not to retake doses of LONSURF that are vomited or missed and to continue with the next scheduled dose.

Advise patients that anyone else who handles their medication should wear gloves [*see References (15)*].

#### Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential of the potential risk to the fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy [*see Warnings and Precautions (5.2), Use in Specific Populations (8.3)*].

Advise female patients of reproductive potential to use effective contraception during treatment with LONSURF and for at least 6 months after the final dose [*see Warnings and Precautions (5.2), Use in Specific Populations (8.3)*].

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 [*see Use in Specific Populations (8.3), Nonclinical Toxicology (13.1)*].

#### Lactation

Advise women not to breastfeed during treatment with LONSURF and for 1 day following the final dose [*see Use in Specific Populations (8.2)*].

Manufactured by: Taiho Pharmaceutical Co., Ltd., Japan

Manufactured for: Taiho Oncology, Inc., Princeton, NJ 08540 USA

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