A GUIDE FOR PHARMACISTS

Treatment management with LONSURF

Dosing and safety tips for your patients taking LONSURF® tablets—FTD/TPI

LONSURF is indicated for the treatment of adult patients with metastatic colorectal cancer (mCRC) previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy.

LONSURF is indicated for the treatment of adult patients with metastatic gastric or gastroesophageal junction (GEJ) 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.

FTD/TPI=trifluridine/tipiracil.

Selected Important Safety Information

Severe Myelosuppression:

LONSURF caused severe and life-threatening myelosuppression (Grade 3-4) consisting of neutropenia (38%), anemia (18%), thrombocytopenia (5%), and febrile neutropenia (3%). Two patients (0.2%) died due to neutropenic infection. A total of 12% of LONSURF-treated 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 febrile neutropenia, absolute neutrophil count less than 500/mm^3, or platelets less than 50,000/mm^3. Upon recovery, resume LONSURF at a reduced dose as clinically indicated.

Embryo-Fetal Toxicity:

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

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

Lonsurf®
(trifluridine and tipiracil) tablets

Actor portrayal.

Dosing with LONSURF[1]

Dosing guidelines for LONSURF® tablets—FTD/TPI

Indicated dosage	35 mg/m^2 twice daily[ab]
Active treatment days	Days 1 to 5 and 8 to 12 of each 28-day treatment cycle
BSA-based calculation	• Round up to the nearest 5-mg increment • Do not exceed 80 mg/dose[a] or 160 mg/day[a]
Administration	• Taken orally twice daily with food, swallowed whole • No restriction on food type
Missed or vomited doses	The patient should not make up for these doses
Storage & Handling	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

[a]Based on the trifluridine component.
[b]In patients with severe renal impairment (CLcr of 15 to 29 mL/min), the recommended dosage is 20 mg/m^2.

4-week dosing cycle (28 days)

Week 1	Twice daily for 5 days with food	2 days rest
Week 2	Twice daily for 5 days with food	2 days rest
Week 3	Rest	
Week 4	Rest	

- Obtain complete blood cell counts prior to and on day 15 of each cycle

2 tablet strengths

15 mg trifluridine/
6.14 mg tipiracil tablet

20 mg trifluridine/
8.19 mg tipiracil tablet

Tablets shown at actual size.

Calculate your patient's dose at **LONSURFhcp.com/therightdose**

Selected 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 breast-fed infant or the effects on milk production. Because of the potential for serious adverse reactions in breast-fed infants, advise women not to breastfeed during treatment with LONSURF and for 1 day following the final dose.

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

Delay or withhold treatment before determining whether a dose reduction is needed to manage patients' AEs[1]

- Obtain complete blood cell counts prior to and on day 15 of each cycle

When to delay the dose:

At treatment initiation, delay the cycle start of LONSURF until:

- Absolute neutrophil count (ANC) is ≥1500/mm^3 or febrile neutropenia is resolved
- Platelet count is ≥75,000/mm^3
- Grade 3 or 4 non-hematological AEs are resolved to Grade 0 or 1

During treatment, withhold LONSURF for:

- ANC <500/mm^3 or febrile neutropenia
- Platelet count <50,000/mm^3
- Grade 3 or 4 non-hematological AEs

When to reduce the dose:

After recovery, resume LONSURF after reducing the dose by 5 mg/m^2/dose from the previous dose level for:

- Febrile neutropenia
- Uncomplicated Grade 4 neutropenia (which has recovered to ≥1500/mm^3) or thrombocytopenia (which has recovered to ≥75,000/mm^3) that results in more than 1-week delay in start of next cycle
- Non-hematologic Grade 3 or 4 AEs 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 to a minimum dose of 20 mg/m^2 twice daily. Do not escalate LONSURF dose after it has been reduced.

These are the only AEs that require a dose reduction.

In patients with severe renal impairment who are unable to tolerate a dose of 20 mg/m^2 twice daily, reduce dose to 15 mg/m^2 twice daily. Permanently discontinue treatment with LONSURF if patient cannot tolerate reduced dose.

AEs=adverse events; BSA=body surface area.

Lonsurf®
(trifluridine and tipiracil) tablets

Actor portrayal.

For patients with previously treated mCRC

Finding the right dose

Dose calculation case study in metastatic colon cancer patient with complications[1-3]

Height: 172.7 cm (5′8″)

Weight: 68.9 kg (152 lb)

BSA: 1.82 m^2

Estimated Dose: 63.7 mg
LONSURF® tablets—FTD/TPI (2x daily)

Round dose to the nearest 5-mg increment.

The recommended dose is 35 mg/m^2.
Calculate your patient's dose at:
LONSURFhcp.com/therightdose

Complete blood cell counts were obtained prior to and on day 15 of each cycle.

Prescribed dose 65 mg* (2x daily) 15 15 15 20

Complication 1, before treatment initiation of cycle 2: Developed Grade 3 neutropenia (ANC=950/mm^3)†

Dosing modification

- Dose was delayed until ANC rose to ≥1500/mm^3 within 4 days
- Dose was initiated at 65 mg,* **100% of the prescribed dose**

15 15 15 20

Complication 2, in week 2 of cycle 3: Developed Grade 4 neutropenia (ANC=450/mm^3)†

Dosing modification

- Dose was delayed until ANC rose to ≥1500/mm^3 within 4 days
- Dose was initiated at 65 mg,* **100% of the prescribed dose**

15 15 15 20

Final dose 65 mg* 15 15 15 20

In the RECOURSE trial:

- **~86%** of patients taking LONSURF did <u>not</u> require a dose reduction‡
  - The most common adverse events or lab abnormalities leading to dose reduction were neutropenia, anemia, febrile neutropenia, fatigue, and diarrhea
- **3.6%** of patients taking LONSURF discontinued treatment due to an AE

RECOURSE=**<u>Re</u>**fractory **<u>Co</u>**lo**<u>re</u>**ctal Cancer **<u>S</u>**tudy.
*Based on the trifluridine component.
†Delay treatment at cycle start for Grade 2-4 neutropenia or until febrile neutropenia has resolved. Withhold treatment during cycle for Grade 4 neutropenia or febrile neutropenia.
‡In the RECOURSE trial, 14% of patients required a dose reduction.
Tablets shown are not actual size.
Case study is fictional and is intended for discussion only.

Selected Important Safety Information

USE IN SPECIFIC POPULATIONS (cont'd)
Male Contraception: Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use condoms during treatment with LONSURF and for at least 3 months after the final dose.

Geriatric Use: Patients 65 years of age or over who received LONSURF had a higher incidence of the following compared to patients younger than 65 years: Grade 3 or 4 neutropenia (46% vs 32%), Grade 3 anemia (22% vs 16%), and Grade 3 or 4 thrombocytopenia (7% vs 4%).

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

Lonsurf® (trifluridine and tipiracil) tablets

LONSURF is a balanced choice for patients with previously treated mCRC

LONSURF® tablets—FTD/TPI—provided a statistically significant reduction in risk of mortality (31%)[4]

- mOS (95% CI): 7.2 months (6.6-7.8) vs 5.2 months (4.6-5.9) for placebo (HR=0.69 [95% CI: 0.59-0.81]; *P*<0.0001)*

LONSURF helped prolong progression-free survival (PFS)[1,3,5]

- mPFS (95% CI): 2.0 months vs 1.7 months for placebo (HR=0.47 [95% CI: 0.40-0.55]; *P*<0.001)*
- Number (%) of events was 472 (88) for LONSURF and 251 (94) for placebo†

Actor portrayal.

Study design[1-3]

RECOURSE was an international, randomized, double-blind, placebo-controlled phase 3 study in 800 patients.‡ All patients were ≥18 years of age, had histologically confirmed mCRC, had Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and had received ≥2 prior regimens of standard chemotherapy and were refractory to or were failing all of the following within 3 months: a fluoropyrimidine, irinotecan, and oxaliplatin; an anti-VEGF biological therapy; and, if *RAS* wild type, an anti-EGFR therapy. The primary endpoint was OS. Key secondary endpoints included PFS and safety and tolerability.

OS was defined as the time (in months) from randomization until death.
BSC=best supportive care; mOS=median OS; mPFS=median PFS; OS=overall survival.

*In the *Kaplan-Meier estimates.
†Prespecified study endpoint.
‡Treatment arms were LONSURF plus BSC vs placebo plus BSC.

Selected Important Safety Information

USE IN SPECIFIC POPULATIONS (cont'd)

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

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

A demonstrated safety profile can help manage expectations

AEs* in ≥5% of patients receiving LONSURF and occurring more commonly (>2%) than in patients receiving placebo[1]

	LONSURF + BSC (n=533), %		Placebo + BSC (n=265), %	
	All Gr	Gr 3-4[a]	All Gr	Gr 3-4[a]
General				
Asthenia/fatigue	52	7	35	9
Pyrexia	19	1	14	<1
Gastrointestinal				
Nausea	48	2	24	1
Diarrhea	32	3	12	<1
Vomiting	28	2	14	<1
Abdominal pain	21	2	18	4
Stomatitis	8	<1	6	0
Metabolism and nutrition				
Decreased appetite	39	4	29	5
Infections[b]	27	6	16	5
Nervous system				
Dysgeusia	7	0	2	0
Skin and subcutaneous tissue				
Alopecia	7	0	1	0

[a]No Grade 4 definition for nausea, abdominal pain, or fatigue in National Cancer Institute Common Terminology.
[b]Incidence reflects 64 preferred terms in the Infections and Infestations system organ class.
*Treatment arms were LONSURF plus BSC vs placebo plus BSC.

Lonsurf® (trifluridine and tipiracil) tablets

Actor portrayal.

For patients with previously treated metastatic gastric or GEJ cancer

Finding the right dose

Dose calculation case study in metastatic gastric cancer patient with complications[1,6]

Height: 170.2 cm (5′7″)

Weight: 71.7 kg (158 lb)

BSA: 1.83 m^2

Estimated Dose: 64.05 mg
LONSURF® tablets—FTD/TPI (2x daily)

Round dose to the nearest 5-mg increment.

The recommended dose is 35 mg/m^2.
Calculate your patient's dose at:
LONSURFhcp.com/therightdose

Selected Important Safety Information

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

ADVERSE REACTIONS

Most Common Adverse Drug Reactions in Patients Treated With LONSURF (≥5%): The most common adverse drug reactions in LONSURF-treated patients vs placebo-treated patients with mCRC, respectively, were asthenia/fatigue (52% vs 35%), nausea (48% vs 24%), decreased appetite (39% vs 29%), diarrhea (32% vs 12%), vomiting (28% vs 14%), infections (27% vs 16%), abdominal pain (21% vs 18%), pyrexia (19% vs 14%), stomatitis (8% vs 6%), dysgeusia (7% vs 2%), and alopecia (7% vs 1%). In metastatic gastric cancer or gastroesophageal junction (GEJ), the most common adverse drug reactions, respectively were, nausea (37% vs 32%), decreased appetite (34% vs 31%), vomiting (25% vs 20%), infections (23% vs 16%) and diarrhea (23% vs 14%).

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

Complete blood cell counts were obtained prior to and on day 15 of each cycle.

Prescribed dose 65 mg* (2x daily) 15 15 15 20

Complication 1, before treatment initiation of cycle 2: Developed Grade 3 nausea/vomiting and diarrhea not controlled by antiemetic therapy and unresponsive to antidiarrheal medication†

Dosing modification

- Dose was delayed until nausea/vomiting and diarrhea resolved to Grade 0 or 1
- After recovery, dose was initiated at 55 mg,* **85% of the prescribed dose**

15 20 20

Complication 2, in week 2 of cycle 3: Developed Grade 4 nausea/vomiting and diarrhea not controlled by antiemetic therapy and unresponsive to antidiarrheal medication†

Dosing modification

- Dose was withheld until nausea/vomiting and diarrhea resolved to Grade 0 or 1
- After recovery, dose was resumed at 45 mg,* **69% of the prescribed dose**

15 15 15

Final dose 45 mg* 15 15 15

In the TAGS trial:

- **~89%** of patients taking LONSURF did not require a dose reduction‡
  - The most common adverse events or lab abnormalities leading to dose reduction were neutropenia, anemia, febrile neutropenia, and diarrhea
- **13%** of patients taking LONSURF discontinued treatment due to an AE vs **17%** of patients taking placebo

TAGS=TAS-102 Gastric Study.
*Based on the trifluridine component.
†Delay treatment at cycle start for all Grade 3 or 4 AEs except for Grade 3 nausea and/or vomiting controlled by antiemetic therapy or Grade 3 diarrhea responsive to antidiarrheal medication.
‡In the TAGS trial, **11%** of patients required a dose reduction.
Tablets shown are not actual size.
Case study is fictional and is intended for discussion only.

Lonsurf® (trifluridine and tipiracil) tablets

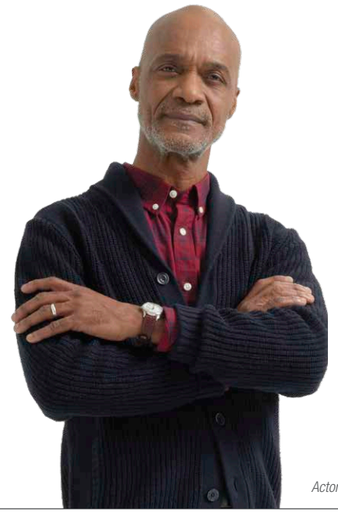
LONSURF is a balanced choice for patients with previously treated metastatic gastric or GEJ cancer

LONSURF® tablets—FTD/TPI—provided a statistically significant reduction in risk of mortality (31%)[1,5,6]

- mOS (95% CI): 5.7 months (4.8-6.2) vs 3.6 months (3.1-4.1) for placebo (HR=0.69 [95% CI: 0.56-0.85]; *P*=0.0006)*†

LONSURF helped prolong progression-free survival (PFS)[1,5]

- mPFS (95% CI): 2.0 months (1.9-2.3) vs 1.8 months (1.7-1.9) for placebo (HR=0.56 [95% CI: 0.46-0.68]; *P*<0.0001)*
- Number (%) of events was 287 (85) for LONSURF and 156 (92) for placebo‡



Actor portrayal.

Study design[1,6]

TAGS was a multinational, randomized, double-blind, placebo-controlled, phase 3 trial in 507 patients.§ All patients were ≥18 years of age (≥20 years of age in Japan), had histologically confirmed, nonresectable, metastatic gastric adenocarcinoma or GEJ, had ECOG performance status of 0 or 1, had previously received ≥2 regimens of standard chemotherapy, and were refractory to or intolerant of their last previous therapy. Previous regimens must have included a fluoropyrimidine, a platinum agent, a taxane or irinotecan, or both, and, if HER2 positive, an anti-HER2 therapy. Adjuvant chemotherapy could be counted as 1 prior regimen in patients who had recurrence during or within 6 months of completion of the adjuvant chemotherapy. Both patients and investigators were masked to treatment allocation. The primary endpoint was OS. Key secondary endpoints included PFS and safety and tolerability.

OS was defined as the time (in months) from randomization until death.
*Kaplan-Meier estimates.
†Methodology of Brookmeyer and Crowley.
‡Prespecified study endpoint.
§Treatment arms were LONSURF plus BSC vs placebo plus BSC.

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

A demonstrated safety profile can help manage expectations

AEs* in ≥5% of patients receiving LONSURF and occurring more commonly (>2%) than in patients receiving placebo[1]

	LONSURF + BSC (n=335), %		Placebo + BSC (n=168), %	
	All Gr	Gr 3-4[a]	All Gr	Gr 3-4[a]
Gastrointestinal				
Nausea	37	3	32	3
Vomiting	25	4	20	2
Diarrhea	23	3	14	2
Metabolism and nutrition				
Decreased appetite	34	9	31	7
Infections[b]	23	5	16	5

[a]No Grade 4 definition for nausea or fatigue in National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03.
[b]Incidence reflects 46 preferred terms in the Infections and Infestations system organ class.
*Treatment arms were LONSURF plus BSC vs placebo plus BSC.

Selected Important Safety Information

ADVERSE REACTIONS (cont'd)
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.

Laboratory Test Abnormalities in Patients Treated With LONSURF: The most common laboratory test abnormalities in LONSURF-treated patients vs placebo-treated patients with mCRC, respectively, were anemia (77% vs 33%), neutropenia (67% vs 1%), and thrombocytopenia (42% vs 8%). In metastatic gastric cancer or GEJ, the test abnormalities, respectively, were neutropenia (66% vs 4%), anemia (63% vs 38%), and thrombocytopenia (34% vs 9%).

Lonsurf®
(trifluridine and tipiracil) tablets

TAIHO ONCOLOGY PATIENT SUPPORT
A partner in your cancer care.

Taiho Oncology Patient Support™: Designed to simplify patient access to LONSURF

We know getting patients access to LONSURF® tablets—FTD/TPI—is a critical step in their treatment. We strive to make this process as simple as possible.

Co-pay support

- Eligible, privately insured patients can receive a Taiho Oncology Patient Support™ Co-pay Card for a $0 co-pay, no matter the dosage strength. This card can help with out-of-pocket expenses for LONSURF, to make access easier for patients. Register your patient at **TaihoOncologyCopay.com**
- For more information, visit **TaihoPatientSupport.com** or call **1-844-TAIHO-4U** (1-844-824-4648)

Additional resources for patients include:

- Access and reimbursement support
- Specialty pharmacy (SP) prescription coordination
- Patient Assistance Program
- Alternate funding support
- Personalized nurse support for treatment plan adherence upon request

To help your patients stay on track, visit **LONSURFhcp.com/therightdose**

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

References: 1. LONSURF [package insert]. Princeton, NJ: Taiho Oncology, Inc.; 2019. **2.** National Cancer Institute. Common terminology criteria for adverse events v4.03 (CTCAE). Bethesda, MD: US Department of Health and Human Services; 2010. NIH publication 09-5410. **3.** Mayer RJ, Van Cutsem E, Falcone A, et al; for the RECOURSE Study Group. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. *N Engl J Med*. 2015; 372(20):1909-1919. **4.** Van Cutsem E, Mayer RJ, Laurent S, et al; for the RECOURSE Study Group. The subgroups of the phase III RECOURSE 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. **5.** Data on file. Taiho Oncology, Inc., Princeton, NJ. **6.** 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.

TAIHO ONCOLOGY

Lonsurf® (trifluridine and tipiracil) tablets