PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr**LONSURF**®

trifluridine and tipiracil tablet

15 mg trifluridine/ 6.14 mg tipiracil (as tipiracil hydrochloride)
20 mg trifluridine / 8.19 mg tipiracil (as tipiracil hydrochloride)

Antineoplastic Agent
Thymidine phosphorylase inhibitor/nucleoside metabolic inhibitor

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RECENT MAJOR LABEL CHANGES

INDICATIONS (1)	11-2019
WARNINGS AND PRECAUTIONS (6), Geriatrics (6.1.4)	11-2019
DOSAGE AND ADMINISTRATION (3.3)	10-2020
WARNINGS AND PRECAUTIONS (6), Renal	10-2020

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Lonsurf® (trifluridine and tipiracil [as tipiracil hydrochloride] tablets) is indicated for the treatment of adult patients with metastatic colorectal cancer who have been previously treated with, or are not candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF biological agents, and, if RAS wild-type, anti-EGFR agents.

Lonsurf monotherapy is indicated for the treatment of adult patients with metastatic gastric cancer or adenocarcinoma of the gastroesophageal junction, who have been previously treated with at least two prior lines of chemotherapy including a fluoropyrimidine, a platinum, and either a taxane or irinotecan and if appropriate with HER2/neu-targeted therapy.

Clinical effectiveness of Lonsurf is based on benefit observed in a pivotal study in patients who had been previously treated with all of the above available therapies.

1.1 Pediatrics

Pediatrics (0 – 18 years): No pediatric data have been made available to Health Canada; therefore, Health Canada has not approved an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥ *65* years of age):

In elderly (65 years or older) versus younger patients (less than 65 years) no overall differences in effectiveness of Lonsurf were reported in metastatic colorectal cancer and in metastatic gastric cancer.

Elderly gastric cancer patients (with 65 years of age or older) who received Lonsurf had a higher incidence of the hematologic laboratory abnormalities compared to younger than 65 years of age.

Efficacy and safety data in patients ≥ 75 years old is limited.

2 CONTRAINDICATIONS

Lonsurf is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, or component of the container closure. For a complete listing (see **DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING)**.

3 DOSAGE AND ADMINISTRATION

3.1 Dosing Considerations

Complete blood cell counts must be obtained prior to initiation of therapy and as needed to monitor blood counts, but at a minimum, prior to each treatment cycle.

Treatment must not be started if the absolute neutrophil count is < 1.5 $\times 10^9$/L, if the platelet counts are < 75$\times$ 10^9/L, or if the patient has an unresolved Grade 3 or 4 non-hematological clinically relevant toxicity from prior therapies and/or prior Lonsurf cycles.

Lonsurf is a cytotoxic drug. Follow applicable special handling and disposal procedures (see **WARNINGS AND PRECAUTIONS, NON-CLINICAL TOXICOLOGY, CARCINOGENESIS AND MUTAGENESIS**).

3.2 Recommended Dose and Dosage Adjustment

The recommended starting dose of Lonsurf for adults is 35 mg/m^2/dose administered orally with water, twice daily, within 1 hour after completion of morning and evening meals, on Days 1 to 5 and Days 8 to 12 of each 28-day cycle. This treatment cycle is repeated every 4 weeks as long as benefit is observed or until unacceptable toxicity occurs. See Table 1 for dose calculation based on body surface area (BSA). The dosage must not exceed 80 mg/dose based on the trifluridine component.

Lonsurf should not be administered in children less than 18 years of age (See **TOXICOLOGY**)

Table 1 Lonsurf Starting Dose Calculation According to Body Surface Area (BSA)

Lonsurf Dose	BSA (m^2)	Dose in mg (2x daily)	Tablets per dose		Total daily dose (mg)
			15/6.14 mg	20/8.19 mg	
35 mg/m^2	< 1.07	35	1	1	70
	1.07 - 1.22	40	0	2	80
	1.23 - 1.37	45	3	0	90
	1.38 - 1.52	50	2	1	100
	1.53 - 1.68	55	1	2	110
	1.69 - 1.83	60	0	3	120
	1.84 - 1.98	65	3	1	130
	1.99 - 2.14	70	2	2	140
	2.15 - 2.29	75	1	3	150
	≥ 2.30	80	0	4	160

Dosing adjustments may be required based on individual safety and tolerability.

A maximum of 3 dose reductions are permitted to a minimum dose of 20 mg/m^2 twice daily. Dose escalation is not permitted after it has been reduced.

In the event of hematological and/or non-hematological toxicities patients should follow the dose interruption, resumption and reduction criteria stated in Table 2, Table 3 and Table 4.

Table 2 Dose interruption and resumption criteria for hematological toxicities related to myelosuppression

Parameter	Interruption Criteria	Resumption Criteria[a]
Neutrophils	< 0.5 x 10^9/L	≥ 1.5 x 10^9/L
Platelets	< 50 x 10^9/L	≥ 75 x 10^9/L

[a] Resumption criteria applied to the start of the next cycle for all patients regardless of whether or not the interruption criteria were met

Table 3 Recommended dose modifications for Lonsurf in case of hematological and non-hematological Treatment Emergent Adverse Events

Treatment Emergent Adverse Events (TEAEs)	Recommended dose modifications
• Febrile neutropenia • CTCAE* Grade 4 neutropenia (< 0.5 x 10^9/L) or thrombocytopenia (< 25 X 10^9/L) that results in more than 1 week's delay in start of next cycle • CTCAE* non-hematologic Grade 3 or Grade 4 TEAEs; except for Grade 3 nausea and/or vomiting controlled by antiemetic therapy or diarrhea responsive to antidiarrheal medicinal products	• Interrupt dosing until toxicity resolves to Grade 1 or baseline. • When resuming dosing, decrease the dose level by 5 mg/m^2/dose from the previous dose level (Table 4). • Dose reductions are permitted to a minimum dose of 20 mg/m^2/dose twice daily (or 15 mg/m^2/dose twice daily in severe renal impairment) (Table 5). • Do not increase dose after it has been reduced.

* Common terminology criteria for adverse events

Table 4 Lonsurf dose reductions according to body surface area (BSA)

Lonsurf dose	BSA (m^2)	Dose in mg (2x daily)	Tablets per dose (2x daily)		Total daily dose (mg)
			15/6.14 mg	20/8.19 mg	
Level 1 dose reduction: From 35 mg/m^2 to 30 mg/m^2					
30 mg/m^2	< 1.09	30	2	0	60
	1.09 - 1.24	35	1	1	70
	1.25 - 1.39	40	0	2	80
	1.40 - 1.54	45	3	0	90
	1.55 - 1.69	50	2	1	100
	1.70 - 1.94	55	1	2	110
	1.95 - 2.09	60	0	3	120
	2.10 - 2.28	65	3	1	130
	≥ 2.29	70	2	2	140
Level 2 dose reduction: From 30 mg/m^2 to 25 mg/m^2					
25 mg/m^2	< 1.10	25[a]	2[a]	1[a]	50[a]
	1.10 - 1.29	30	2	0	60
	1.30 - 1.49	35	1	1	70
	1.50 - 1.69	40	0	2	80
	1.70 - 1.89	45	3	0	90
	1.90 - 2.09	50	2	1	100
	2.10 - 2.29	55	1	2	110
	≥ 2.30	60	0	3	120
Level 3 dose reduction: From 25 mg/m^2 to 20 mg/m^2					
20 mg/m^2	< 1.14	20	0	1	40
	1.14 – 1.34	25[a]	2[a]	1[a]	50[a]
	1.35 – 1.59	30	2	0	60
	1.60 – 1.94	35	1	1	70
	1.95 – 2.09	40	0	2	80
	2.10 – 2.34	45	3	0	90
	≥ 2.35	50	2	1	100

[a] At a total daily dose of 50 mg, patients should take 1 x 20/8.19 mg tablet in the morning and 2 x 15/6.14 mg tablets in the evening.

Dose adjustments for special populations

Renal impairment

Mild renal impairment (creatinine clearance 60 to 89 mL/min) or moderate renal impairment (creatinine clearance 30 to 59 mL/min): No adjustment of the starting dose is recommended in patients with mild or moderate renal impairment. Patients with moderate renal impairment may require dose modification for increased hematological toxicity and should be closely monitored (See **WARNINGS AND PRECAUTIONS, SPECIAL POPULATIONS RENAL**).

Severe renal impairment (creatinine clearance 15 to 29 mL/min): In patients with severe renal impairment, administration of Lonsurf with a starting dose of 20 mg/m^2 (based on the trifluridine component) is recommended orally, twice daily with food on Days 1 through 5 and Days 8 through 12 of each 28-day cycle (Table 5) [See **ACTION AND CLINICAL PHARMACOLOGY]**. Reduce dose to 15 mg/m^2 twice daily in patients with severe renal

impairment who are unable to tolerate a dose of 20 mg/m^2 twice daily (Table 5). Dose escalation should not be considered after the dose has been reduced. Permanently discontinue Lonsurf in patients who are unable to tolerate a dose of 15 mg/m^2 twice daily. (**See WARNINGS AND PRECAUTIONS, SPECIAL POPULATIONS RENAL; ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**)

Table 5 Recommended Dosage for Severe Renal Impairment According to Body Surface Area

BSA (m^2)	Total daily dose (mg)	Dose (mg) administered twice daily	Tablets per dose	
			15mg	20mg
For a dose of 20 mg/m^2 twice daily:				
< 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
For a dose of 15 mg/m^2 twice daily:				
< 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.

End stage renal disease (creatinine clearance below 15 mL/min):
Administration of Lonsurf is not recommended as there is no data available for these patients.

Hepatic impairment

Mild hepatic impairment: No adjustment of the starting dose is recommended in patients with mild hepatic impairment.

Moderate or severe hepatic impairment: Administration is not recommended in patients with baseline moderate or severe hepatic impairment (National Cancer Institute [NCI] Criteria Group C and D defined by total bilirubin > 1.5 times the upper limit of normal). A higher incidence of Grade 3 or 4 hyperbilirubinemia has been observed in patients with baseline moderate hepatic impairment, based on limited data. Patients with severe hepatic impairment (total bilirubin >3 X ULN or any AST were not studied.

Elderly
No adjustment of the starting dose is required in patients ≥ 65 years old.

Paediatric population

Health Canada has not authorized an indication for paediatric use.

Race
No adjustment of the starting dose is required on the basis of patient's race. There is limited data on Lonsurf in Black/African American patients but there is no biological rationale to expect any difference between this subgroup and the overall population.

3.3 Administration

Lonsurf is for oral use. Lonsurf must be taken with a glass of water within 1 hour after completion of the morning and evening meals. (See **ACTION AND CLINICAL PHARMACOLOGY, PHARMACOKINETICS, ABSORPTION**).

3.4 Missed Dose

If doses were missed or held, the patient must not make up for missed doses.

4 OVERDOSAGE

The highest dose of Lonsurf administered in clinical trials was 180 mg/m^2 per day.

The TEAEs reported in association with overdoses were consistent with the established safety profile.

The primary anticipated complication of an overdose is bone marrow suppression.

There is no known antidote for an overdose of Lonsurf.

Medical management of an overdose should include customary therapeutic and supportive medical intervention aimed at correcting the presenting clinical manifestations and preventing their possible complications.

For management of a suspected drug overdose, contact your regional poison control centre.

5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	Tablet 15 mg trifluridine/6.14 mg tipiracil (as tipiracil hydrochloride)	hypromellose, lactose monohydrate, magnesium stearate, polyethylene glycol, pharmaceutical ink, pregelatinized starch, stearic acid, titanium dioxide
oral	Tablet 20 mg trifluridine/8.19 tipiracil mg (as tipiracil hydrochloride)	Ferric oxide, hypromellose, lactose monohydrate, magnesium stearate, polyethylene glycol, pharmaceutical ink, pregelatinized starch, stearic acid, titanium dioxide

Lonsurf 15 mg/6.14 mg tablets
Each tablet contains 15 mg trifluridine and 6.14 mg tipiracil (as 7.065 mg tipiracil hydrochloride). The tablet is a white, biconvex, round, film-coated tablet, with a diameter of 7.1 mm and a thickness of 2.7 mm, imprinted with ‘15’ on one side, and ‘102’ and ‘15 mg’ on the other side, in grey pharmaceutical ink.

Lonsurf 20 mg/8.19 mg tablets
Each tablet contains 20 mg trifluridine and 8.19 mg tipiracil (as 9.420 mg tipiracil hydrochloride). The tablet is a pale red, biconvex, round, film-coated tablet, with a diameter of 7.6 mm and a thickness of 3.2 mm, imprinted with ‘20’ on one side, and ‘102’ and ‘20 mg’ on the other side, in grey pharmaceutical ink.

Both tablets are imprinted with edible ink containing carnauba wax, FD&C Blue No. 2 Aluminum Lake, ferric oxide red, ferric oxide yellow, shellac, talc and titanium dioxide.

Lonsurf is available in aluminium/aluminium blister with laminated desiccant (calcium oxide) trays containing 10 tablets.

Each pack contains 20 tablets.

6 WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Lonsurf (trifluridine and tipiracil) tablets should be administered only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents.
- Myelosuppression (See **WARNINGS and PRECAUTIONS, ADVERSE REACTIONS**)
- Gastrointestinal toxicity (See **WARNINGS and PRECAUTIONS, ADVERSE**

General
Lonsurf is a cytotoxic drug. Applicable special handling and disposal procedures should be followed.

Carcinogenesis and Mutagenesis
Lonsurf should be treated as a potential carcinogen (See **NON-CLINICAL TOXICOLOGY**).

Driving and Operating Machinery
It is not known whether Lonsurf affects the patient's ability to drive or use machines. If patients experience symptoms such as fatigue, dizziness and or malaise affecting their ability to concentrate and react during treatment with Lonsurf, it is recommended that they do not drive or use machines until the effect subsides.

Gastrointestinal
Lonsurf caused an increase in the incidence of gastrointestinal toxicities including nausea, vomiting and diarrhea. Patients with nausea, vomiting, diarrhea and other gastrointestinal toxicities should be carefully monitored, and anti-emetic, anti-diarrheal and other measures, such as fluid/electrolyte replacement therapy, should be administered early and as clinically indicated. Dose modifications (delay and/or reduction) should be applied as necessary (See **RECOMMENDED DOSE AND DOSAGE ADJUSTMENTS**).

Lactose intolerance
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, congenital lactase deficiency or glucose-galactose malabsorption should consult with their physician and discuss whether the benefits outweigh the risks on an individual basis.

Hematologic
Bone Marrow Suppression: Lonsurf can cause severe and life-threatening myelosuppression. In the pivotal trial in metastatic colorectal cancer (RECOURSE), grades 3 or 4 neutropenia (38%), leukopenia (21%), anemia (18%), thrombocytopenia (5%) and febrile neutropenia (4%) were observed. One patient (0.2%) died due to neutropenic infection. In the pivotal trial in metastatic gastric cancer (TAGS), grades 3 or 4 neutropenia (38%), anemia (19%), leukopenia (21%), thrombocytopenia (6%) and febrile neutropenia (2%) were observed.

Complete blood cell counts must be obtained prior to initiation of therapy and as needed to monitor blood counts, but at a minimum, prior to each treatment cycle.

Treatment must not be started if the absolute neutrophil count is < 1.5 ×10^9/L, if the platelet counts are < 75× 10^9/L, or if the patient has an unresolved Grade 3 or 4 non-hematological clinically relevant toxicity from prior therapies and/or prior Lonsurf cycles.

Serious infections have been reported following treatment with Lonsurf. Given that the majority of infections in the RECOURSE and TAGS studies were reported in the context of bone marrow suppression, the patient's condition should be monitored closely, and appropriate measures, such as antimicrobial agents and granulocyte-colony stimulating factor, should be administered as clinically indicated. In the RECOURSE and TAGS studies, 9.4% and 17.3% of patients respectively in the Lonsurf groups received granulocyte-colony stimulating factor mainly for therapeutic use. (See **DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS**)

Hepatic/Biliary/Pancreatic
Lonsurf is not recommended for use in patients with moderate or severe hepatic impairment (National Cancer Institute [NCI] Criteria Group C and D defined by total bilirubin > 1.5 X ULN). A higher incidence of Grade 3 and Grade 4 hyperbilirubinemia has been observed in patients with baseline hepatic impairment. In a pharmacokinetic trial, Grade 3 or 4 hyperbilirubinemia was observed in 5 of 6 patients with baseline moderate hepatic impairment. Patients with severe hepatic impairment (total bilirubin >3 X ULN or any AST were not studied. (See **DOSAGE AND ADMINISTRATION**)

Monitoring and Laboratory Tests
Complete blood cell counts must be obtained prior to initiation of therapy and as needed to monitor blood counts, but at a minimum, prior to each treatment cycle.

Treatment must not be started if the absolute neutrophil count is < 1.5 ×10^9/L, if the platelet counts are < 75× 10^9/L, or if the patient has an unresolved Grade 3 or 4 non-hematological clinically relevant toxicity from prior therapies and/or prior Lonsurf cycles.

Monitoring of proteinuria by dipstick urinalysis is recommended prior to starting and during therapy.

Radiotherapy
There was a slightly higher incidence of overall haematological and myelosuppression-related TEAEs, including febrile neutropenia, for patients who received prior radiotherapy compared to patients without prior radiotherapy in RECOURSE (54.6% versus 49.2%, respectively).

Proteinuria: Monitoring of proteinuria by dipstick urinalysis is recommended prior to starting and during therapy.

Respiratory
Interstitial Lung Disease/Pneumonitis: Severe, life-threatening, or fatal interstitial lung disease (ILD)/pneumonitis have been rarely observed in one clinical trial of Asian patients as well as post marketing.

Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis. Exclude other potential causes of ILD/pneumonitis, and permanently discontinue Lonsurf in patients diagnosed with treatment-related ILD/pneumonitis (See **ADVERSE REACTIONS**).

6.1 Special Populations

6.1.1 Pregnant Women

There are no available data from the use of Lonsurf in pregnant women. Based on the mechanism of action, trifluridine has a potential to cause congenital malformations when administered during pregnancy. Studies in animals have shown reproductive toxicity. (See **NON-CLINICAL TOXICOLOGY**)

Lonsurf should not be used during pregnancy unless the clinical condition of the woman requires treatment with Lonsurf.

Based on findings in animals, trifluridine may cause fetal harm when administered to pregnant women. Women should avoid becoming pregnant while taking Lonsurf and for up to 6 months after ending treatment. Therefore, women of child-bearing potential must use highly effective contraceptive measures while taking Lonsurf and for 6 months after stopping treatment.

It is currently unknown whether Lonsurf may reduce the effectiveness of hormonal contraceptives, and therefore women using hormonal contraceptives should add a barrier contraceptive method.

Females and Males of Reproductive Potential

Contraception

Because of the potential for genotoxicity, males with female partners of reproductive potential should be advised to use an adequate form of contraception during treatment with Lonsurf and for up to 6 months after the final dose. (See **NON-CLINICAL TOXICOLOGY)**.

6.1.2 Breast-feeding

It is not known whether trifluridine (FTD) or tipiracil hydrochloride are excreted in human milk. Because of the potential for serious adverse reactions in breastfeeding infants, advise nursing women not to breastfeed during treatment with Lonsurf and for one day following the final dose (See **ACTION AND CLINICAL PHARMACOLOGY**, **Pharmacokinetics***).*

Studies in animals have shown excretion of trifluridine, tipiracil and/or their metabolites in milk. (See **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

6.1.3 Pediatrics

Pediatrics (0 to 18 years): Lonsurf should not be administered in children less than 18 years of age. No data are available to Health Canada; therefore, Health Canada has not approved an indication for pediatric use.

6.1.4 Geriatrics

Elderly should be monitored closely for hematologic abnormalities. Patients 65 years of age or older who received Lonsurf 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 (22% vs. 16%), and Grade 3 or 4 thrombocytopenia (7% vs. 4%). In RECOURSE and TAGS, 868 patients received Lonsurf; 45% were 65 years of age or over, while 10% were 75 and over.

6.1.5 Renal

In the RECOURSE and TAGS studies patients with moderate renal impairment (creatinine clearance = 30 to 59 mL/min) had a higher incidence (defined as a difference of at least 5%) of ≥ Grade 3 adverse events (hemoglobin (decrease) and leukocytes (decrease), serious adverse events, and dose delays and reductions compared to the patients with normal (creatinine clearance ≥ 90 mL/min) or mild renal impairment (creatinine clearance = 60 to 89 mL/min). In the dedicated renal impairment study in patients with all solid tumors, one dose reduction from 20 mg/m^2 to 15 mg/m^2 was reported from 25% (2/8) subjects with severe renal impairment. Treatment emergent adverse events (TEAEs) increased with the degree of renal impairment. Lonsurf is not recommended for use in patients with end-stage renal disease (creatinine clearance < 15 mL/min or requiring dialysis), as Lonsurf has not been studied in these patients.

No dose adjustment to the starting dose of Lonsurf is recommended in patients with mild or moderate renal impairment (creatinine clearance of 30 to 89 mL/min). Patients with moderate renal impairment should be monitored frequently for increased hematological toxicities as they may require dose modification. Reduce the starting dose of Lonsurf for patients with severe renal impairment (creatinine clearance of 15 to 29 mL/min). (See **DOSAGE AND ADMINISTRATION; PHARMACOKINETICS**, **SPECIAL POPULATIONS AND CONDITIONS**, **RENAL INSUFFICIENCY)**

7 ADVERSE REACTIONS

7.1 Adverse Reaction Overview

A total of 761 patients were exposed with Lonsurf at the recommended dose in patients with metastatic colorectal cancer in RECOURSE and 335 patients with metastatic gastric cancer in TAGS studies. The most common TEAE or laboratory abnormalities (≥10%) were anemia, neutropenia, fatigue/asthenia, nausea, thrombocytopenia, decreased appetite, diarrhea, vomiting, and pyrexia.

Colorectal Cancer
A total of 761 colorectal cancer patients who were administered Lonsurf at a dose of 35mg/m^2 BID. The most serious observed treatment emergent adverse events (TEAEs) in patients receiving Lonsurf were bone marrow suppression and gastrointestinal toxicity.

In clinical studies, the most frequently observed TEAEs in patients receiving Lonsurf were neutropenia 58.3% (444/761), grade ≥ 3 38.7% (295/761); nausea 50% (381/761), grade ≥ 3 2.4% (18/761); fatigue 37.8% (288/761), grade ≥ 3 3.5% (27/761); anemia 32.7% (249/761), grade ≥ 3 13.9% (106/761) and leukopenia 282/761 (37%) grade ≥ 3 114/761 (15%).

In clinical studies 8.9 % (68/761) of Lonsurf patients had TEAEs resulting in treatment discontinuation and 56.6% (431/761) of patients had TEAEs leading to study treatment interruption, delay or dose reduction.

In clinical studies 2.6% (20/761) of Lonsurf patients reported TEAEs with fatal outcomes.

The most common TEAEs in patients receiving Lonsurf that resulted in treatment discontinuation, dose reduction, dose delay, or dose interruption were neutropenia, general deterioration of health, anemia, febrile neutropenia, fatigue, diarrhea and dyspnoea.

Gastric Cancer

A total of 335 patients with gastric or GEJ adenocarcinoma received Lonsurf and Best Supportive Care (BSC) and 168 patients in placebo arm received BSC only. Lonsurf 35 mg/m^2/dose was administrated twice daily on Days 1 through 5 and Days 8 through 12 of each 28-day cycle with best supportive care.

In the clinical study, the most frequently observed TEAEs in patients (≥10% incidence and more than placebo), after the first dose and within 30 days of last dose, receiving Lonsurf were neutropenia 52.5% (176/335), grade ≥ 3 34.0% (114/335); anemia 44.5% (149/335), grade ≥ 3 18.8% (63/335); nausea 37% (124/335), grade ≥ 3 0% (10/335); decreased appetite 34.3% (115/335), grade ≥ 3 8.7%(29/335); fatigue 26.6% (89/335), grade ≥ 3 6.9% (23/335) vomiting 24.8%(83/335), grade ≥ 3 3.6% (12/335); diarrhea 22.7% (76/335), grade ≥ 3 2.7% (9/335) and leukopenia 17% (57/335), grade ≥ 3 6.9% (23/335).

In TAGS, 11% (37/335) of patients receiving Lonsurf required a dose reduction. The most common TEAEs or laboratory abnormalities leading to dose reduction were neutropenia, anemia, febrile neutropenia, pancytopenia, neutrophil count decrease, diarrhea and nausea.

Patients treated with Lonsurf having events leading to delay of 4 days was reported in 42% (322/773 total cycles) and delay of 8 days in 14% (105/773 total cycles).

In TAGS, 13% (43/335) of patients discontinued Lonsurf for a TEAE and 17% (28/168) patients in the placebo group.

Four (4)% (14/335) of Lonsurf patients reported adverse events with fatal outcomes.

Table 8 and Table 9 list the TEAEs and laboratory abnormalities (graded using CTCAE v4.03), respectively, observed in TAGS. Four (4)% (14/335) of Lonsurf patients reported adverse events with fatal outcomes.

Safety results seen in patients with gastric cancer, including Grade ≥ 3 TEAEs, were similar to those in patients with metastatic colorectal cancer. No new safety signals were seen in patients with metastatic gastric cancer.

7.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Colorectal Cancer

The data described below are from RECOURSE, a randomised (2:1), double-blind, placebo-controlled trial in which 533 patients (median age 63 years; 61% men; 57% White, 35% Asian, 1% Black) with previously treated metastatic colorectal cancer received Lonsurf as a single agent at a dose of 35 mg/m^2/dose administered twice daily on Days 1 through 5 and Days 8 through 12 of each 28-day cycle. The mean duration of Lonsurf therapy was 12.7 weeks.

The most frequently observed TEAEs or laboratory abnormalities (all Grades and ≥10% in incidence) in Lonsurf treated patients at a rate that exceeds the rate in patients receiving placebo were anemia, neutropenia, fatigue/asthenia, nausea, thrombocytopenia, decreased appetite, diarrhoea, vomiting, pyrexia, and abdominal pain.

TEAEs leading to discontinuation occurred in 55 (10.3%) patients in the Lonsurf group and 36 (13.6%) patients in the placebo group. In the Lonsurf group the most frequent were general physical health deterioration (2.3%), fatigue (1.1%) and dyspnoea (0.6%). In the placebo group, the most frequent TEAEs leading to discontinuation were blood bilirubin increased (2.3%), general physical health deterioration (1.9%), ascites (1.9%), decreased appetite (1.5%), hepatic failure (1.1%), abdominal pain (1.1%) and asthenia (1.1%).

At least 1 dose reduction during treatment was reported in 13.7% of patients in the Lonsurf group. TEAEs leading to dose reduction were reported for 72 of these patients. The most frequent TEAEs leading to dose reduction in the Lonsurf group were: neutropenia (17, 3.2%), anemia (11, 2.1%), neutrophil count decreased (10, 1.9%), febrile neutropenia (10, 1.9%), fatigue (8, 1.5%), and diarrhea (7, 1.3%). In the placebo group, 3 (1.1%) patients had a single dose reduction, with 2 reporting TEAEs leading to dose reduction (1, anemia; 1, bronchopneumonia).

Table 6 Very Common (≥ 10 %) and Common (≥ 1% and < 10%) Treatment Emergent Adverse Events Reported in Patients with Metastatic Colorectal Cancer in the RECOURSE study

	Lonsurf and BSC N=533 (%)		**Placebo and BSC N=255 (%)**	
	Any Grade	**Grade ≥ 3**	**Any Grade**	**Grade ≥ 3**
Blood and Lymphatic System Disorders				
Anemia	40	16	8	3
Neutropenia	29	20	0	0
Thrombocytopenia	7	2	0.4	0.4
Leukopenia	5	2	0	0
Febrile neutropenia	4	4	0	0
Gastrointestinal Disorders				
Nausea	48	1.9	24	1.1
Diarrhea	32	3	12	0.4
Vomiting	28	2	14	0.4
Abdominal Pain	15	2	14	4
Stomatitis	8	0.4	6	0
Dyspepsia	3	0	0.4	0
General Disorders and Administration Site Conditions				
Fatigue	35	4	23	6
Asthenia	18	3	11	3
Pyrexia	18	1.1	14	0.4

	Lonsurf and BSC N=533 (%)		Placebo and BSC N=255 (%)	
	Any Grade	**Grade ≥ 3**	**Any Grade**	**Grade ≥ 3**
Mucosal Inflammation	6	0.4	5	0
Malaise	4	0	2	0
Influenza like illness	1.7	0	0.4	0
Pain	2	0.8	1.1	0
Infections and Infestations				
Nasopharyngitis	4	0	1.5	0
Upper respiratory tract infection	3	0	1.5	0
Urinary tract infection	3	0.6	1.9	1.1
Herpes zoster	1.5	0.2	0	0
Investigations				
Neutrophil count decreased	28	16	0.4	0
White blood cell count decreased	27	10	0.4	0
Platelet count decreased	15	2	2	0
Lymphocyte count decreased	4	1.9	1.9	1.1
Metabolism and Nutrition Disorders				
Decreased appetite	39	4	29	5
Hypokalemia	4	2	1.9	0.8
Nervous System Disorders				
Dysgeusia	7	0	2	0
Renal and Urinary Disorders				
Proteinuria	4	0	1.9	0
Respiratory, Thoracic and Mediastinal Disorders				
Pulmonary embolism	2	2	0	0
Skin and Subcutaneous Tissue Disorders				
Alopecia	7	0	1	0
Rash	4	0	2	0.4

Gastric Cancer

A total of 507 patients were randomized to Lonsurf (N=337) or placebo (N=170) twice daily on Days 1 through 5 and Days 8 through 12 of each 28-day cycle with best supportive care. The median age was 63 years, 73% were male, 70% and 16% were White and Asian respectively.

The most frequently observed TEAEs or laboratory abnormalities (all Grades and ≥10% in incidence) in Lonsurf treated patients at a rate that exceeds the rate in patients receiving placebo were anemia, neutropenia, fatigue/asthenia, nausea, thrombocytopenia, decreased appetite, diarrhoea, vomiting, pyrexia, and abdominal pain.

In the Lonsurf group the most frequent TEAEs leading to discontinuation were general physical health deterioration (1.2%), diarrhea (0.6%), fatigue (0.6%), neutropenic sepsis (0.6%), blood bilirubin increased (0.6%), decreased appetite (0.6%), cachexia (0.6%), pulmonary embolism (0.6%) and dyspnoea (0.6%). In the placebo group, the most frequent TEAEs leading to discontinuation malaise (1.8%), general physical health deterioration (1.2%), asthenia (1.2%), decreased appetite (0.9%).

At least 1 dose reduction during treatment was reported in 11% of patients in the Lonsurf group. The most frequent TEAEs leading to dose reduction in the Lonsurf group were neutropenia (12, 3.6%), anemia (7, 2.1%), febrile neutropenia (3, 0.9%), pancytopenia (3,

0.9%), diarrhea (3, 0.9%) and neutrophil count decreased (3, 0.9%). In the placebo group, 1% patients had a single dose reduction, with 2 reporting TEAEs leading to dose reduction (1, asthenia; 1, rash maculo papular).

Table 7 Very Common (≥ 10 %) and Common (≥ 1 % and < 10%) Treatment Emergent Adverse Events Reported in Patients with Metastatic Gastric Cancer more commonly reported than in patients given placebo in the TAGS study

	Lonsurf and BSC N=335 (%)		Placebo and BSC N=168 (%)	
	Any Grade	**Grade ≥ 3**	**Any Grade**	**Grade ≥ 3**
Blood and Lymphatic System Disorders				
Anemia	45	19	19	8
Neutropenia	39	23	4	0
Leukopenia	17	7	2	0
Thrombocytopenia	10	2	1	0
Lymphopenia	6	2	5	2
Febrile neutropenia	2	2	0	0
Pancytopenia	2	2	0	0
Cardiac disorders				
Palpitations	2	0	1	0
Ear and labyrinth disorders				
Vertigo	1	0	1	0
Gastrointestinal disorders				
Nausea	37	3	32	3
Vomiting	25	4	20	2
Diarrhoea	23	3	14	2
Constipation	13	1	15	2
Dysphagia	6	2	5	2
Stomatitis	5	0	2	0
Gastrointestinal haemorrhage	2	1	1	1
Haematemesis	2	1	0	0
General disorders and administration site conditions				
Fatigue	27	7	21	6
Pyrexia	8	0	5	1
General physical health deterioration	7	7	10	9
Chills	1	0	0	0
Hepatobiliary disorders				
Hyperbilirubinemia	3	2	2	1
Liver disorder	1	0	0	0
Infections and infestations				
Upper respiratory tract infection	3	0	0	0
Oral candidiasis	2	0	1	0
Nasopharyngitis	2	0	0	0
Neutropenic sepsis	1	1	0	0
Metabolism and nutrition disorders				
Decreased appetite	34	9	31	7
Hypoalbuminaemia	7	1	6	1
Hypokalaemia	3	1	2	0
Hypocalcaemia	3	0	1	0

	Lonsurf and BSC N=335 (%)		Placebo and BSC N=168 (%)	
	Any Grade	**Grade ≥ 3**	**Any Grade**	**Grade ≥ 3**
Cachexia	1	0	1	1
Musculoskeletal and connective tissue disorders				
Back pain	8	1	7	2
Musculoskeletal pain	3	0	1	0
Arthralgia	2	0	1	1
Myalgia	2	0	0	0
Nervous system disorders				
Dysgeusia	3	0	1	0
Somnolence	3	0	1	0
Neuropathy peripheral	2	0	1	0
Paraesthesia	2	0	0	0
Psychiatric disorders				
Anxiety	3	0	2	0
Insomnia	3	0	6	0
Respiratory, thoracic and mediastinal disorders				
Pleural effusion	4	2	3	1
Pulmonary embolism	3	2	2	1
Epistaxis	1	0	1	0
Cough	3	0	4	0
Productive cough	1	0	1	0
Skin and subcutaneous tissue disorders				
Alopecia	4	0	1	0
Dry skin	2	0	1	0
Pruritus	2	0	1	0
Rash	1	0	1	0
Vascular disorders				
Hypotension	2	1	1	1

TEAEs and laboratory abnormalities were graded using CTCAE v4.03.

7.3 Less Common Clinical Trial Adverse Reactions

Clinically important TEAEs that occur in 0.1 to <1% of Lonsurf treated patients, and which are reported in 2 or more patients receiving Lonsurf are:

Gastrointestinal Disorders: abdominal tenderness, abnormal faeces, colitis, gastritis, gingival bleeding, ileus

Infections and Infestations: cellulitis, device related infection, ear infection, fungal infection, gastroenteritis, influenza, lower respiratory tract infection, oral candidiasis, paronychia, pneumonia staphylococcal, sepsis, fatal septic shock

Investigations: bilirubin conjugated increased, blood potassium decreased, haematocrit decreased, protein total decreased

7.4 Abnormal Hematologic Laboratory Findings

Table 8 Shifts from Baseline for Key Hematology Parameters - RECOURSE

	Lonsurf + Best Supportive Care			Placebo + Best Supportive Care		
Laboratory Parameter	**All Grades (%)**	**Grade† 3 (%)**	**Grade† 4 (%)**	**All Grades (%)**	**Grade† 3 (%)**	**Grade† 4 (%)**
Blood and lymphatic system disorders						
Anemia	77	18	NA	33	3	NA
Neutropenia	67	27	11	1	0	0
Thrombocytopenia	42	5	1	8	0	<1

† Common Terminology Criteria for Adverse Events (CTCAE), v4.03
NA Not applicable
One Grade 4 anemia TEAE based on clinical criteria was reported

Table 9 Shifts from Baseline for Key Hematology Parameters - TAGS

	Lonsurf + Best Supportive Care			Placebo + Best Supportive Care		
Laboratory Parameter	**All Grades (%)**	**Grade† 3 (%)**	**Grade† 4 (%)**	**All Grades (%)**	**Grade† 3 (%)**	**Grade† 4 (%)**
Blood and lymphatic system disorders						
Leukopenia	72	19	2	4	0	0
Neutropenia	66	27	11	4	0	0
Anemia	63	19	0	38	7	0
Thrombocytopenia	34	4	2	9	0	0

† Common Terminology Criteria for Adverse Events (CTCAE), v4.03

The frequency of hematological laboratory abnormalities associated with myelosuppression was much higher in the Lonsurf group than in the placebo group. Myelosuppression was generally manageable with reductions in dose, delays in cycle initiation and occasional use of granulocyte colony-stimulating factor.

7.5 Post-Market Adverse Reactions

Post marketing adverse reactions included interstitial lung disease (reported mainly in Japanese patients). 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 DRUG INTERACTIONS

8.1 Overview

In vitro studies indicated that trifluridine is a substrate for the nucleoside transporters CNT1, ENT1 and ENT2. Tipiracil was a substrate for OCT2 and MATE1. Therefore, caution is required when using medicinal products that interact with these transporters.

8.2 Drug-Drug Interactions

No clinical pharmacokinetic drug-drug interaction studies have been conducted with Lonsurf.

Trifluridine is a substrate of thymidine phosphorylase, and is not metabolized by cytochrome P450 (CYP) enzyme. Tipiracil is not metabolized in either human liver S9 or hepatocytes.

In vitro studies indicated that trifluridine, tipiracil hydrochloride and its metabolite 5-[trifluoromethyl] uracil did not inhibit the activity of human cytochrome P450 (CYP) isoforms. In vitro evaluation indicated that trifluridine, tipiracil hydrochloride and 5-[trifluoromethyl] uracil had no inductive effect on human CYP isoforms.

In vitro studies indicated that trifluridine is a substrate for the nucleoside transporters CNT1, ENT1 and ENT2. Therefore, caution is required when using medicinal products that interact with these transporters such as zidovudine. Tipiracil was a substrate for OCT2 and MATE1, therefore, the concentration might be increased when Lonsurf (trifluridine and tipiracil) is administered concomitantly with inhibitors of OCT2 or MATE1 such as cimetidine or dolutegravir.

Based on the results from in vitro study in human colon cancer cells, zidovudine (AZT) attenuated the cell growth inhibitory effects of trifluridine, mainly at near clinical concentration of zidovudine. There is a possibility of attenuation of anti-tumor activity of Lonsurf with zidovudine if used concomitantly in clinical practice.

Caution is required when using medicinal products that are human thymidine kinase substrates, e.g., zidovudine. Such medicinal products, if used concomitantly with Lonsurf, may compete with the effector, trifluridine, for activation via thymidine kinases. Therefore, when using antiviral medicinal products that are human thymidine kinase substrates, monitor for possible decreased efficacy of the antiviral medicinal product, and consider switching to an alternative antiviral medicinal product that is not a human thymidine kinase substrate, such as lamivudine, zalcitabine, didanosine and abacavir.

It is unknown whether Lonsurf may reduce the effectiveness of hormonal contraceptives. Therefore, women using a hormonal contraceptive must also use a barrier contraceptive method.

8.3 Drug-Food Interactions

It is recommended to take Lonsurf within 1 hour after completion of the morning and evening meals.

8.4 Drug-Herb Interactions

Interactions with herbal products have not been established.

8.5 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

9 ACTION AND CLINICAL PHARMACOLOGY

9.1 Mechanism of Action

Trifluridine/tipiracil is comprised of an antineoplastic thymidine-based nucleoside analogue, trifluridine, and the thymidine phosphorylase inhibitor, tipiracil (as tipiracil hydrochloride)).

Following uptake into cancer cells, trifluridine, is phosphorylated by thymidine kinase, further metabolised in cells to a deoxyribonucleic acid (DNA) substrate, and incorporated directly into DNA, thereby interfering with DNA function to prevent cell proliferation. However, trifluridine is rapidly degraded by thymidine phosphorylase and readily metabolised by a first-pass effect following oral administration, hence the inclusion of the thymidine phosphorylase inhibitor, tipiracil (as tipiracil hydrochloride).

In nonclinical studies, trifluridine/tipiracil demonstrated antitumour activity against both 5-fluorouracil sensitive and resistant colorectal cancer cell lines.

The cytotoxic activity of trifluridine/tipiracil against several human tumour xenografts correlated highly with the amount of trifluridine incorporated into DNA, suggesting this as the primary mechanism of action.

9.2 Pharmacodynamics

Lonsurf (trifluridine and tipiracil tablets) had no clinically relevant effect on QT/QTc prolongation compared with placebo in an open label study in patients with advanced solid tumours.

A thorough clinical QT study was performed in 30 patients with advanced solid tumours, Lonsurf 35 mg/m^2 as single and multiple doses (BID on Days 1 through 5 and Days 8 to 12) had no clinically relevant QT, QTcF, or QTcB prolongation effect compared with placebo. No patient had a QT, QTcF, or QTcB interval >500 msec at any time point. Lonsurf did not appear to be arrhythmogenic as evidenced by the absence of AEs of ventricular tachycardia, ventricular fibrillation, syncope, and seizure.

Studies of cardiovascular parameters in cynomolgus monkeys were found to have no effect at dose levels of up to 108.8 mg/kg of trifluridine, and up to 1000 mg/kg of tipiracil.

In addition, in a HEK293-hERG cell line assay trifluridine concentrations up to 300 mcmol/L and tipiracil at concentrations up to 100 mcmol/L for tipiracil, did not block the hERG potassium channel.

9.3 Pharmacokinetics

After twice daily dosing of Lonsurf (trifluridine and tipiracil tablets), systemic exposure (area under the concentration curve, AUC) of trifluridine more than dose-proportionally over the dose range of 15 to 35 mg/m^2 on Day 1. However tipiracil was generally dose proportional. After single-dose administration of Lonsurf 35 mg/m^2, the mean apparent half-life ($t_{1/2}$) of trifluridine

was 1.4 hours and of tipiracil was 1.7 hours based on a 10 hour sampling period. The mean apparent half-life at steady state of trifluridine was 2.0 hours and of tipiracil was 2.4 hours.

Administration of a single dose of Lonsurf containing tipiracil and trifluridine 35 mg/m^2 increased the mean AUC_{0-12} of trifluridine by 37-fold and C_{max} by 22-fold with reduced variability compared to trifluridine 35 mg/m^2 alone.

Absorption:
After oral administration of Lonsurf with [^{14}C]-trifluridine, at least 57% of the administered trifluridine was absorbed and only 3% of the dose was excreted into faeces. After oral administration of Lonsurf with [^{14}C]-tipiracil, at least 27% of the administered tipiracil was absorbed and 50% of the total radioactivity dose measured into faeces, suggestive of moderate gastrointestinal absorption of tipiracil.

Following a single dose of Lonsurf (35 mg/m^2) in patients with advanced solid tumours, the mean times to peak plasma concentrations (t_{max}) of trifluridine and tipiracil were around 2 hours and 3 hours, respectively.

In the pharmacokinetic analyses of the multiple dose administration of Lonsurf (35 mg/m^2/dose, twice daily for 5 days a week with 2 days rest for 2 weeks followed by a 14-day rest, repeated every 4 weeks), trifluridine area under the concentration-time curve during a dosing interval (AUC_{0-12}) was approximately 3-fold higher and maximum concentration (C_{max}) was approximately 2-fold higher after multiple dose administration (Day 12 of Cycle 1) of Lonsurf than after single-dose (Day 1 of Cycle 1).

However, there was no accumulation for tipiracil, and no further accumulation of trifluridine with successive cycles (Day 12 of Cycles 2 and 3) of administration of Lonsurf. Following multiple doses of Lonsurf (35 mg/m^2/dose twice daily) in patients with advanced solid tumours.

Contribution of tipiracil**:** Single-dose administration of Lonsurf (35 mg/m^2/dose) increased the mean AUC_{0-12} of trifluridine by 37-fold and C_{max} by 22-fold with reduced variability compared to trifluridine alone (35 mg/m^2/dose).

Linearity/non-linearity
After twice daily dosing of Lonsurf, systemic exposure (area under the concentration curve, AUC) of trifluridine increased more than dose-proportionally over the dose range of 15 to 35 mg/m^2. However tipiracil was generally dose proportional.

Effect of food: When Lonsurf at a single dose of 35 mg/m^2 was administered to 14 patients with solid tumours after a standardised high-fat, high-calorie meal, trifluridine area under the concentration-time curve (AUC) did not change, but trifluridine C_{max}, tipiracil C_{max} and AUC decreased by approximately 40% compared to those in a fasting state. In clinical studies Lonsurf was administered within 1 hour after completion of the morning and evening meals.

Distribution:
The protein binding of trifluridine in human plasma is over 96% and trifluridine bound mainly to human serum albumin. Plasma protein binding of tipiracil is below 8%.

Radioactivity was excreted in the milk of nursing rats dosed with trifluridine/tipiracil containing ^{14}C-FTD (trifluridine) or ^{14}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.

Metabolism:
Biotransformation
Trifluridine was mainly eliminated by metabolism via thymidine phosphorylase to form an inactive metabolite, 5-[trifluoromethyl] uracil. After a single 60 mg dose of Lonsurf with [^{14}C]-trifluridine, the analytes mostly recovered in urine were 5-[trifluoromethyl] uracil and trifluridine glucuronide isomers. Other minor metabolites, 5-carboxyuracil and 5-carboxy-2'-deoxyuridine, were detected, but those levels in plasma and urine were at low or trace levels.

Tipiracil was not metabolised in human liver S9 or in cryopreserved human hepatocytes. Tipiracil was the major component and 6-hydroxymethyluracil was the major metabolite consistently in human plasma, urine, and faeces.

Elimination:
Following the multiple-dose administration of Lonsurf at the recommended dose and regimen, the apparent mean half-lives ($t_{1/2}$) for trifluridine on Day 1 of Cycle 1 and on Day 12 of Cycle 1 were 1.4 hours and 2.0 hours, respectively based on 10 hours of sampling. Due to the 3 to 4 fold accumulation seen in AUC, the true terminal half life of trifluridine may be longer when in presence of tipiracil. The mean $t_{1/2}$ values for tipiracil on Day 1 of Cycle 1 and on Day 12 of Cycle 1 were 1.7 hours and 2.4 hours, respectively. No significant accumulation of tipiracil was seen between Day 1 and Day 12 of cycle 1.

Following twice daily dosing of Lonsurf (35 mg/m^2) for 5 days with 2 days rest for 2 weeks in patients with advanced solid tumours, the apparent oral clearance for trifluridine and tipiracil on Day 12 (day 5 of the second week of dosing) were approximately 3 L/hr and 90 L/hr, respectively. After single oral administration of Lonsurf with [^{14}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) within 24 hours, and the excretion into feces and expired air was less than 3% for both. After single oral administration of Lonsurf with [^{14}C]-tipiracil hydrochloride, recovered radioactivity was 77% of the dose, which consisted of 27% urinary excretion and 50% fecal excretion.

Special Populations and Conditions

Based on the population pharmacokinetics analysis, there is no clinically relevant effect of age, gender or race on the pharmacokinetics of trifluridine or tipiracil.

Gastrectomy:

In RECOURSE study for colorectal cancer the influence of gastrectomy on pharmacokinetics parameters was not able to be examined because very few patients (1% of overall) had undergone gastrectomy.

Hepatic Insufficiency: Based on the population pharmacokinetics analysis, liver function parameters including alkaline phosphatase (ALP, 36-2322 U/L), aspartate aminotransferase (AST, 11-197 U/L), alanine aminotransferase (ALT, 5-182 U/L), and total bilirubin (0.17-3.20 mg/dL) were not significant covariates for pharmacokinetics parameters of either

trifluridine or tipiracil. Serum albumin was found to significantly affect trifluridine clearance, with a negative correlation. For low albumin values ranging from 2.2 to 3.5 g/dL, the corresponding clearance values range from 4.2 to 3.1 L/h. No study in severe hepatic impairment (NCI Criteria Group C and D) has been conducted.

In a dedicated study the pharmacokinetics of trifluridine and tipiracil hydrochloride were evaluated in cancer patients with mild or moderate hepatic impairment (National Cancer Institute [NCI] Criteria Group B and C, respectively) and in patients with normal hepatic function. Based upon limited data with a considerable variability, no statistically significant differences were observed in the pharmacokinetics in patients with normal hepatic function versus patients with mild or moderate hepatic impairment. In patients with moderate hepatic impairment AUCt was 40-50% higher in patients with moderate hepatic impairment than in normal liver function. There is no need for a starting dose adjustment in patients with mild hepatic impairment.

Renal Insufficiency: Of the 533 patients in the RECOURSE study who received Lonsurf, 306 (57%) patients had normal renal function (creatinine clearance ≥ 90 mL/min), 178 (33%) patients had mild renal impairment (creatinine clearance 60 to 89 mL/min), and 47 (9%) had moderate renal impairment (creatinine clearance 30 to 59 mL/min), with data missing for 2 patients. Patients with severe renal impairment were not enrolled. In the population pharmacokinetic analyses from the patients enrolled in RECOURSE study, a clinically significant total exposure increase in trifluridine (43%) and tipiracil (65%) was reported in patients with moderate renal impairment as compared with patients with normal renal function.

A dedicated renal impairment study was conducted among 43 patients with solid organ tumours, 28% had normal, 28% mild, 26% had moderate and 19% severe renal impairment. All patients received Lonsurf 35 mg/m^2 twice daily except for patients with severe renal impairment who received 20 mg/m^2 twice daily. Mild renal impairment (creatinine clearance of 60 to 89 mL/min as determined by the Cockcroft-Gault formula) had no clinically significant difference on steady-state $AUC_{0\text{-last}}$ of trifluridine. In the moderate renal impairment (creatinine clearance of 30 to 59 mL/min) increased steady-state $AUC_{0\text{-last}}$ of trifluridine by 56% and tipiracil by139% compared to normal renal function (creatinine clearance ≥ 90 mL/min) was reported. In severe renal impairment (creatinine clearance of 15 to 29 mL/min) increased steady-state $AUC_{0\text{-last}}$ of of trifluridine by 37% and tipiracil by 308% compared to normal renal function was reported. One dose reduction from 20 mg/m^2 to 15 mg/m^2 was reported in 25% (2/8) subjects with severe renal impairment.

Trifluridine exposures from Phase 1 dedicated renal study in all solid tumors were comparable with POP PK analyses from colorectal cancer patients with mild and moderate renal impairment from RECOURSE study.

The pharmacokinetics of trifluridine and tipiracil have not been studied in patients with end-stage renal disease.

10 STORAGE, STABILITY AND DISPOSAL

Lonsurf should be stored at room temperature (15°C to 30°C).

Hands should be washed after handling tablets.

Any unused medicinal product or waste material should be disposed according to local requirements.

PART II: SCIENTIFIC INFORMATION

11 PHARMACEUTICAL INFORMATION

Drug Substance - Trifluridine

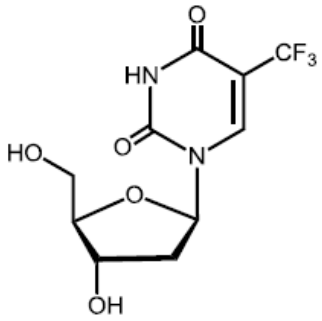
Proper name: Trifluridine

Chemical name: 2′-deoxy-5-(trifluoromethyl) uridine, Trifluorothymidine

Molecular formula: $C_{10}H_{11}F_3N_2O_5$

Molecular mass: 296.20

Structural formula:



Physicochemical properties:

Description	White crystalline, non-hygroscopic powder
Solubility	Trifluridine is 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.
Melting point	180°C (with decomposition)
pH	pH 4.81 (10 mg/mL, water, at 22.4°C)
pK_a	8.08

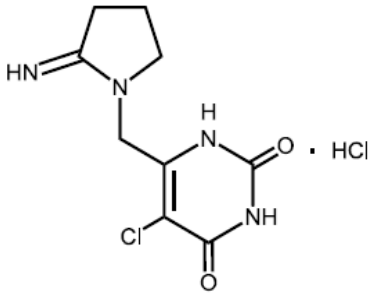
Drug Substance - Tipiracil (hydrochloride)

Chemical name: 2,4(*1H,3H*)-Pyrimidinedione, 5-chloro-6-[(2-imino-1-pyrrolidinyl)methyl]-, hydrochloride (1:1)

Molecular formula: $C_9H_{11}ClN_4O_2$•HCl

Molecular mass tipiracil hydrochloride: 279.12 (tipiracil free base:242.66)

Structural formula:



Physicochemical properties:

Description	White crystalline powder
Solubility	Tipiracil hydrochloride is very slightly soluble in ethanol, slightly soluble in methanol, practically insoluble in 2-propanol, acetonitrile, acetone, diisopropyl ether and diethyl ether. Tipiracil hydrochloride is soluble in 0.01 M hydrochloric acid and in 0.01 M sodium hydroxide solution.
Melting point	240°C (with decomposition)
pH	pH 3.74 (10 mg/mL, water)
pK_a	5.95

12 CLINICAL TRIALS

12.1 Trial Design and Study Demographics

Table 10 Summary of patient demographics for clinical trials

Study #	Trial design	Dosage, route of administration and duration	Study subjects (N = number)	Median age (Range)	Gender
TPU-TAS-102-301 (RECOURSE) Metastatic Colorectal Cancer	Multinational, double-blind, two-arm, parallel-group, randomised, Phase 3 study	Lonsurf, starting dose of 35 mg/m^2/dose bid or Placebo bid, x 5 days/week x 2 weeks, followed by a 14-day rest (one 28 day treatment cycle). Treatment continued until disease progression or unacceptable toxicity.	N = 800 Lonsurf: 534 Placebo: 266	63.0 years (27-82 years) 44.0% ≥65 years	61.4% Males 38.6% Females
TAS-102-302 (TAGS) Metastatic Gastric Cancer	Multinational, double-blind, parallel-group, randomised, Phase 3 study	Lonsurf, starting dose of 35 mg/m^2/dose bid or Placebo bid, x 5 days/week x 2 weeks, followed by a 14-day rest (one 28 day treatment cycle). Treatment continued until disease progression or unacceptable toxicity.	N = 507 Lonsurf: 337 Placebo: 170	63.0 years (24 to 89 years)	72.8% Males 27.2% Females

Study TPU-TAS-102-301 (RECOURSE) – Metastatic colorectal cancer

The clinical efficacy and safety of Lonsurf (trifluridine and tipiracil tablets) were evaluated in an international, randomised, double-blind, placebo-controlled Phase III study (RECOURSE) in patients with previously treated metastatic colorectal cancer. The primary efficacy endpoint was overall survival, and secondary efficacy endpoints included progression-free survival, and overall response rate and disease control rate.

In total, 800 patients were randomised 2:1 to receive Lonsurf (N = 534) plus best supportive care (BSC) or matching placebo (N = 266) plus BSC. 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. United States, Europe and Australia). Key eligibility criteria included prior treatment with at least 2 lines of standard chemotherapy for metastatic CRC and being refractory to or intolerant of those therapies, ECOG PS 0-1, absence of brain metastasis, and absence of ascites requiring drainage in the past four weeks.

Lonsurf dosing was based on BSA with a starting dose of 35 mg/m^2/dose. Study treatment was administered orally twice daily after morning and evening meals for 5 days a week with 2 days rest for 2 weeks, followed by 14 days rest, repeated every 4 weeks. Patients continued therapy until disease progression or unacceptable toxicity.

Of the 800 randomised patients, the median age was 63 years, 61% were male, 58% were Caucasian/White, 35% were Asian/Oriental, and 1% were Black/African American, and all patients had baseline Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 or 1. The primary site of disease was colon (62%) or rectum (38%). KRAS status was wild (49%) or mutant (51%) at study entry. The median number of prior lines of therapy for metastatic disease was 3. All patients received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy. All but 1 patient received bevacizumab, and all but 2 patients with KRAS wild type tumours received panitumumab or cetuximab. The 2 treatment groups were comparable with respect to demographic and baseline disease characteristics.

Study TAS-102-302 (TAGS) – Metastatic gastric cancer

The efficacy of Lonsurf was evaluated in Phase 3 TAGS, 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.

Five hundred and seven (507) patients were randomized 2:1 to Lonsurf (N=337) or placebo (N=170). Randomization was stratified by ECOG PS at baseline (0 vs. 1), prior ramucirumab (yes vs. no), and geographic region (Japan vs. rest of world). Patients received Lonsurf 35 mg/m^2 orally twice daily after morning and evening meals for 5 days a week with 2 days rest for 2 weeks, followed by 14 days rest, repeated every 4 weeks until disease progression or unacceptable toxicity. The major efficacy outcome measure was overall survival and an additional outcome measure was progression free survival.

The study population characteristics were: median age 63 years (24 to 89 years); 73% male; 70% White, 16% Asian, and 1% Black, and 38% had a baseline ECOG PS of 0 and 62% had a baseline of ECOG PS of 1. Patients administered Lonsurf who were refractory to irinotecan (98%), taxane (90%) fluoropyrimidine (88%) or platinum (86%). Patients received Lonsurf who were intolerant to fluoropyrimidine (11%), platinum (11%), taxane (10%) or irinotecan (2%). A similar number of patients in the Lonsurf arm [44%, (n=147)] and placebo arm [44% (n=74)] had undergone prior gastrectomy.

Patients with severe renal impairment and moderate and severe hepatic impairment were excluded. 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.

12.2 Study Results

Study TPU-TAS-102-301 (RECOURSE) – Metastatic colorectal cancer
An overall survival analysis of the study, carried out as planned at 72% (N = 574) of events, demonstrated a statistically significant survival benefit of Lonsurf (trifluridine and tipiracil) tablets plus best supportive care compared to placebo plus best supportive care. Progress Free Survival was significantly improved in patients receiving Lonsurf plus best supportive care (See Table 11, Figure 2 and Figure 3).

Table 11 Efficacy Results of RECOURSE Study

Primary Endpoints	**Lonsurf + BSC (N=534)**	**Placebo + BSC (N=266)**
Overall Survival (OS)		
Number of deaths, N (%)	364 (68.2)	210 (78.9)
Median OS (months)[a] [95% CI][b]	7.1 [6.5, 7.8]	5.3 [4.6, 6.0]
Hazard ratio [95% CI]	0.68 [0.58, 0.81]	
P-value[c]	< 0.0001 (1-sided and 2-sided)	
Progression-Free Survival (PFS)		
Number of Progression or Death, N (%)	472 (88.4)	251 (94.4)
Median PFS (months)[a] [95% CI][b]	2.0 [1.9, 2.1]	1.7 [1.7, 1.8]
Hazard ratio [95% CI]	0.48 [0.41, 0.575]	
P-value[c]	<0.0001 (1-sided and 2-sided)	

[a] Kaplan-Meier estimates
[b] Methodology of Brookmeyer and Crowley
[c] Stratified log-rank test (strata: KRAS status, time since diagnosis of first metastasis, region), 2-sided

Figure 1 Kaplan-Meier curves of overall survival, RECOURSE

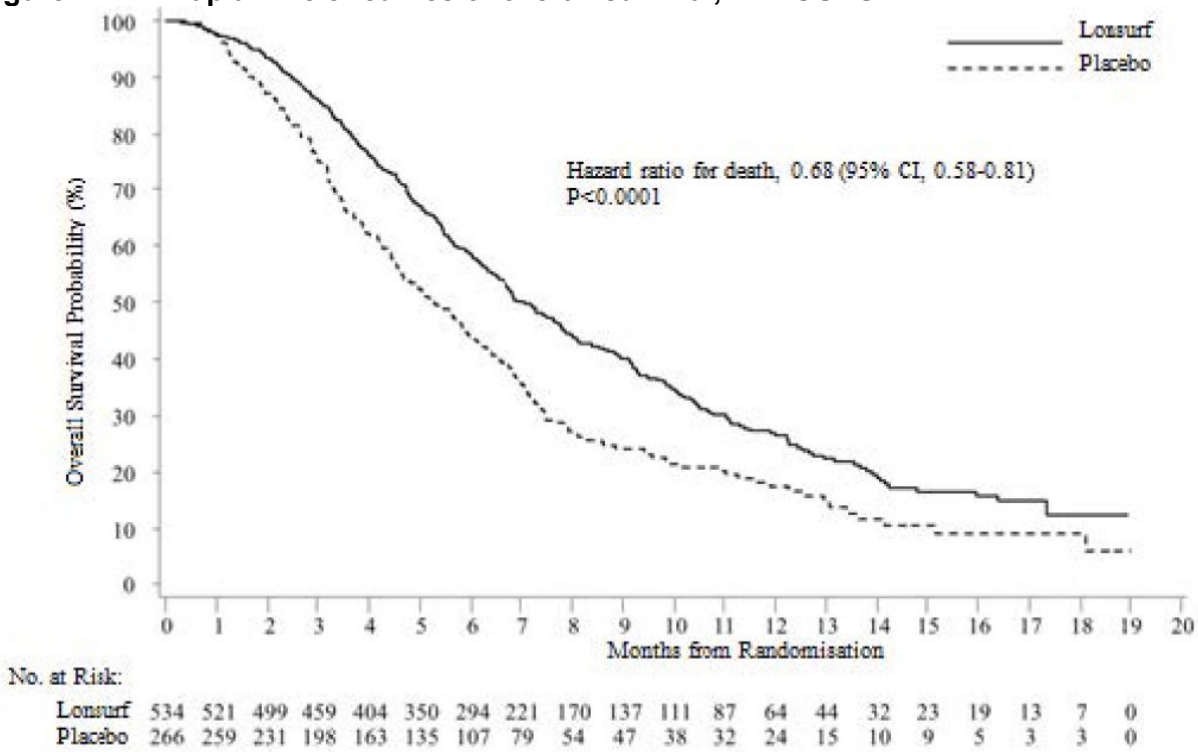
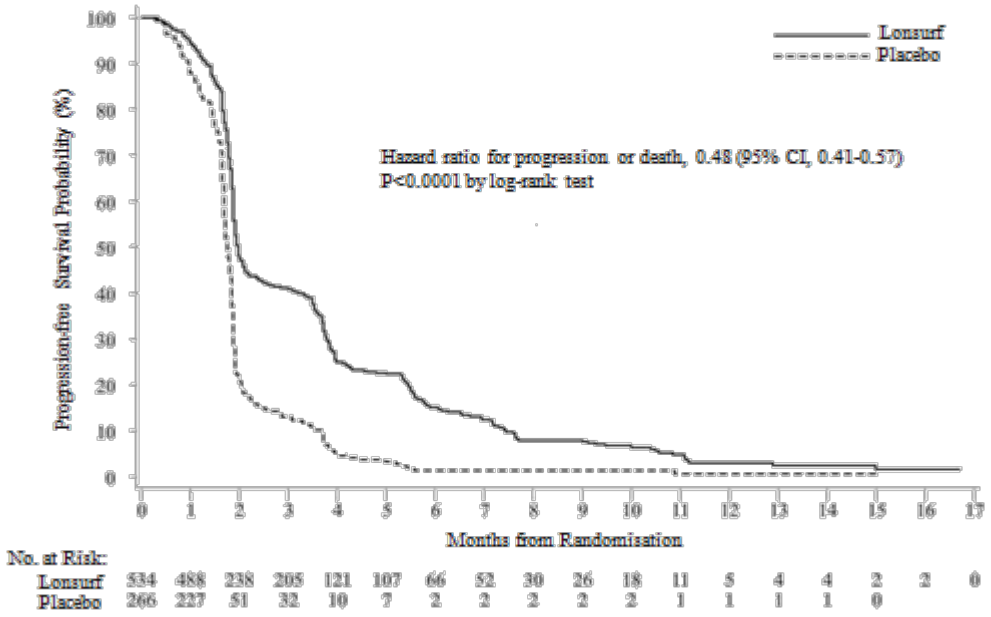


Figure 2 Kaplan-Meier curves of progression-free survival, RECOURSE



An updated overall survival analysis, carried out at 89% (N = 712) of events, confirmed the clinically meaningful and statistically significant survival benefit of Lonsurf plus best supportive care compared to placebo plus best supportive care (hazard ratio: 0.69; 95% with a confidence

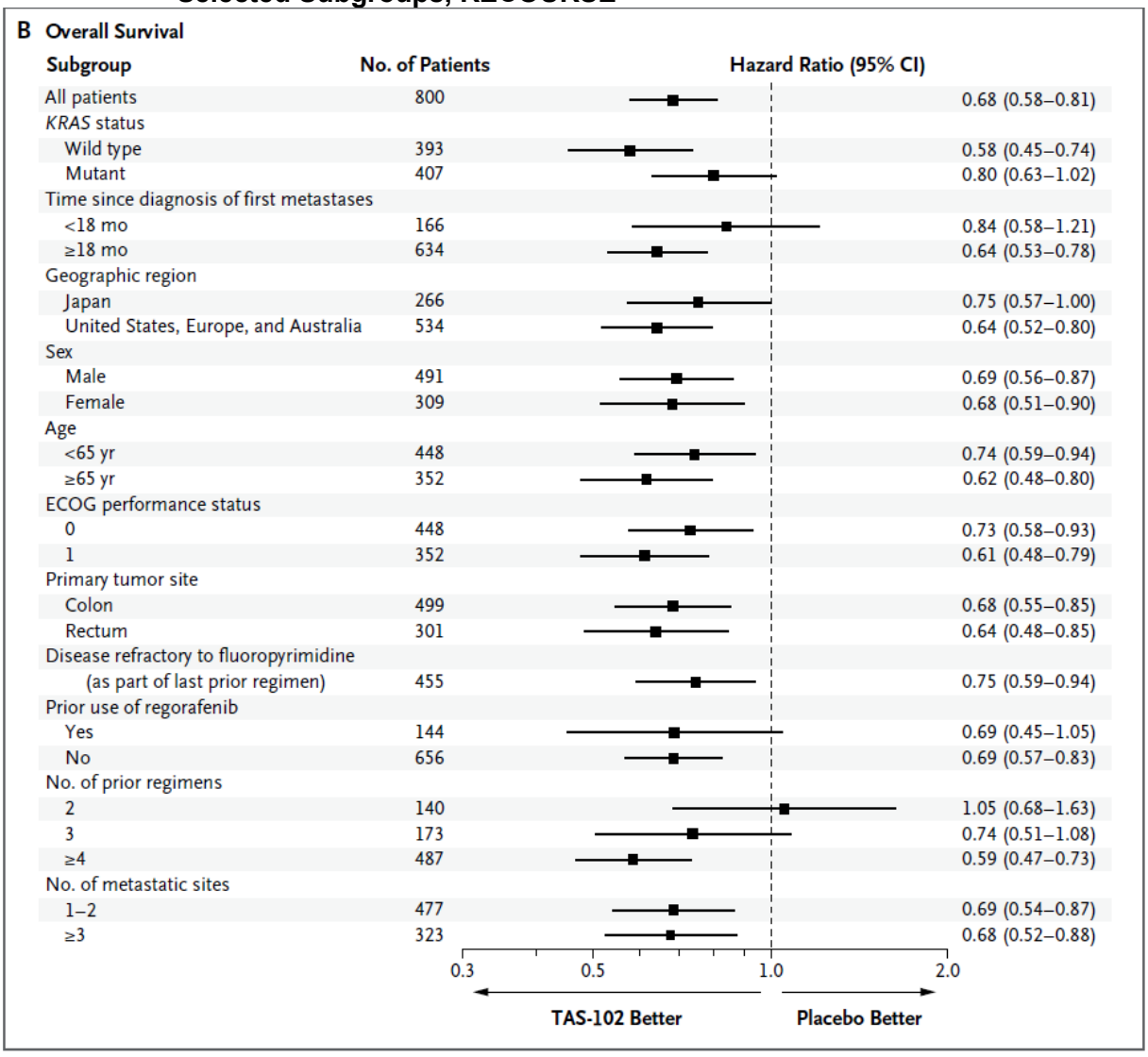
interval of 0.59 to 0.81; $p < 0.0001$) and a median overall survival of 7.2 months vs 5.2 months respectively.

The overall survival benefit was observed consistently in all pre-specified subgroups.

Sixty one percent (61%, N = 485) of all randomised patients received a fluoropyrimidine as part of their last treatment regimen prior to randomisation, of which 455 (94%) were refractory to the fluoropyrimidine at that time. Among these patients, the overall survival benefit with Lonsurf was maintained.

Eighteen percent (18%, N = 144) of all randomised patients received regorafenib prior to randomisation. Among these patients, the overall survival benefit with Lonsurf was maintained. The effect was also maintained in regorafenib-naive patients.

Figure 3 Forest Plot of Hazard Ratios for Treatment Effect on Overall Survival by Selected Subgroups, RECOURSE



The overall response rate (complete response or partial response) was 1.6% in patients treated with Lonsurf and 0.4% in patients treated with placebo.

Study TAS-102-302 (TAGS) – Metastatic gastric cancer

The primary endpoint of the TAGS study was overall survival. Secondary endpoints were progression-free survival (time from randomisation until investigator-assessed radiological disease progression or death from any cause) and safety and tolerability.

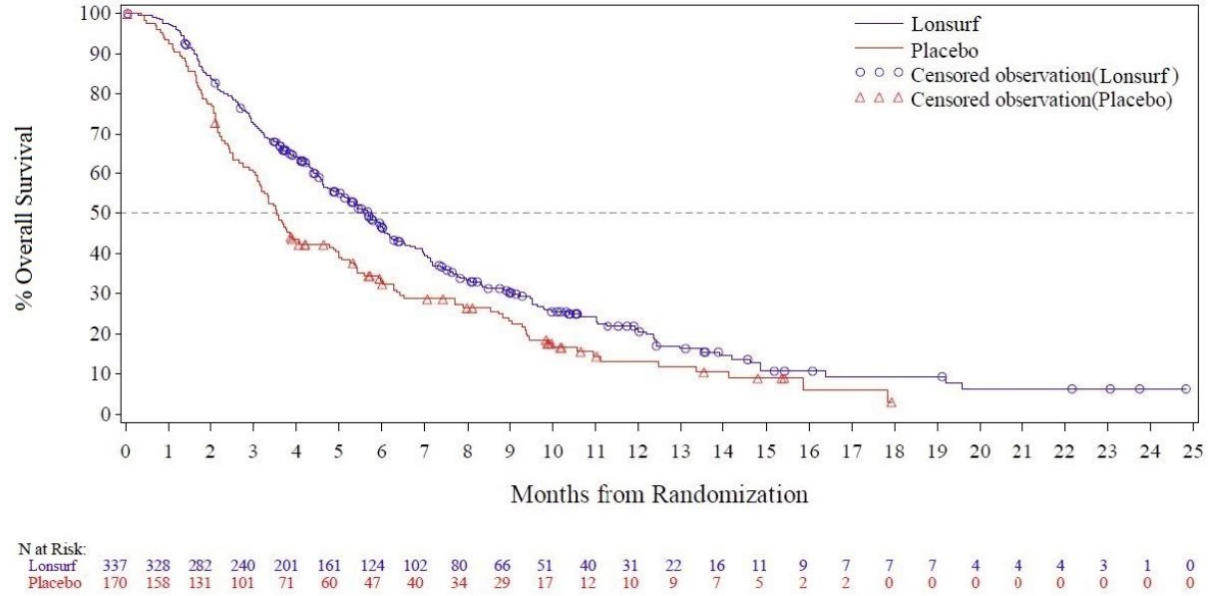
The overall survival analysis of the TAGS study, demonstrated a clinically meaningful and statistically significant survival benefit of Lonsurf plus best supportive care compared to best supportive care (hazard ratio: 0.69; 95% confidence interval of 0.56 to 0.85; $p < 0.0006$) and a median overall survival of 5.7 months vs 3.6 months respectively. PFS was significantly improved in patients receiving Lonsurf plus BSC (See Table 12, Figure 4, Figure 5).

Table 12 Efficacy Results of TAGS Study

Primary Endpoints	Lonsurf + BSC (N=337)	Placebo + BSC (N=170)
Overall Survival (OS)		
Number of deaths, N (%)	244 (72)	140 (82)
Median OS (months)[a] [95% CI]	5.7 [4.8, 6.2]	3.6 [3.1, 4.1]
Hazard ratio [95% CI]	0.69 [0.56, 0.85]	
P-value[b]	0.0006	
Progression-Free Survival (PFS)		
mPFS months [95% CI]	2.0 [1.9, 2.3]	1.8 [1.7, 1.9]
Hazard ratio [95% CI]	0.57 [0.47, 0.70]	
P-value[b]	<0.0001	
Number of events, N (%)	287 (85)	156 (92)

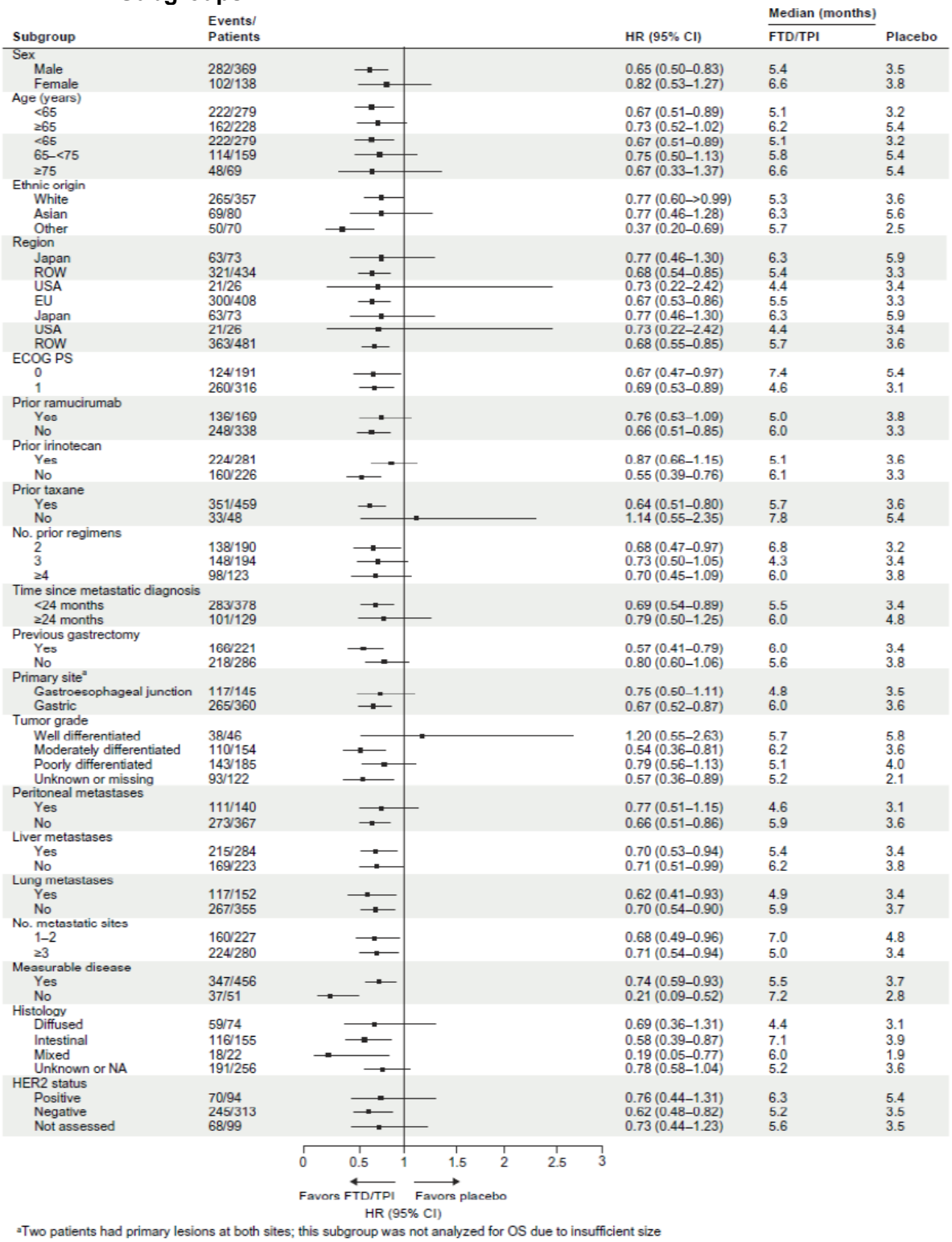
[a] Kaplan-Meier estimates
[b] Stratified log-rank test (strata: ECOG PS, prior ramucirumab treatment, region) 2-sided

Figure 4 Kaplan-Meier curves of overall survival, TAGS (ITT population)



The overall survival benefit was observed consistently in all pre-specified subgroups. See Figure 5.

Figure 5 Hazard Ratios for Treatment Effect on Overall Survival by Selected Subgroups



[a]Two patients had primary lesions at both sites; this subgroup was not analyzed for OS due to insufficient size

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group Performance Status; EU = European Union; FTD/TPI = TAS-102; HER 2 = human epidermal growth factor receptor 2; HR = hazard ratio; NA = not assessed; ROW = Rest of World; USA = United States of America

13 NON-CLINICAL TOXICOLOGY

Repeat-dose toxicity
Toxicology assessment of trifluridine/tipiracil hydrochloride was performed in rats, dogs and monkeys. The target organs identified were the lymphatic and hematopoietic systems and the gastrointestinal tract. All changes, i.e., leukopenia, anemia, bone marrow hypoplasia, atrophic changes in the lymphatic and hematopoietic tissues and the gastrointestinal tract, were reversible within 9 weeks of drug withdrawal. Whitening, breakage, and malocclusion were observed in teeth of rats treated with trifluridine/tipiracil hydrochloride, which are considered rodent specific and not relevant for human.

Carcinogenesis and mutagenesis
No long term studies evaluating the carcinogenic potential of trifluridine/tipiracil hydrochloride in animals have been performed. Trifluridine was shown to be genotoxic in a reverse mutation test in bacteria, a chromosomal aberration test in mammal-cultured cells, and a micronucleus test in mice. Therefore, Lonsurf should be treated as a potential carcinogen.

Reproductive toxicity
Animal studies did not indicate an effect of trifluridine and tipiracil hydrochloride on male fertility in rats. Dose related increases in the corpus luteum count and implanting embryo count observed in female rats but female fertility was not affected. Trifluridine/tipiracil hydrochloride has been shown to cause embryo-fetal lethality and embryo-fetal toxicity in pregnant rats when given at dose levels lower than the clinical exposure. No peri/post-natal developmental toxicity studies have been performed.

Juvenile Animals
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 greater than or equal to 50 mg/kg (approximately 0.33 times the exposure at the clinical dose of 35 mg/m^2 twice daily).