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RESEARCH**

APPLICATION NUMBER:

207981Orig1s000

SUMMARY REVIEW

Division Director Summary Review

Date	September 21, 2015
From	Patricia Keegan
Subject	Division Director Summary Review
NDA #	NDA 207981
Applicant Name	Taiho
Date of Submission	December 19, 2014
PDUFA Goal Date	December 18, 2015
Proprietary Name / Established (USAN) Name	Lonsurf/ trifluridine/tipiracil
Dosage Forms / Strength	Tablets for oral use/ 15-mg and 20-mg
Proposed Indication(s)	“for the treatment of patients with metastatic colorectal cancer who have been previously treated with, (b) (4) fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and an anti-EGFR therapy”
Recommended Action for NME	<i>Approval</i>

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Regulatory Project Manager Review	Meredith Libeg
Medical Officer Review	Leigh Marcus
Statistical Review	Weishi (Vivian) Yuan
Nonclinical Pharmacology/Toxicology Review	G. Sachia Khasar & Emily M. Fox
Quality Review	Erika Englund & Rajiv Agarwal;
Microbiology Review	Quamrul Majumder & Marisa Heayn
Biopharmaceutics Review	Salaheldin Hamed
Clinical Pharmacology/Pharmacometrics Review	Xianhua (Walt) Cao & Jingyu (Jerry) Yu
OSI Review	Lauren Iacono-Connors
CDTL Review	Steven Lemery
OPDP Consult Review	Carole Broadnax
OSE/DMEPA Consult Review	Otto Townsend
OSE/DRISK Consult Review	Mona Patel
DPMH Consult review	Ethan Hausman
Patient Labeling Team review	Morgan Walker

OND=Office of New Drugs

OSI=Office of Scientific Investigations

CDTL=Cross-Discipline Team Leader

OPDP=Office of Prescription Drug Promotion

OSE= Office of Surveillance and Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

DRISK=Division of Risk Management

DPMH= Division of Pediatric and Maternal Health

Division Director Summary Review

1. Introduction

Lonsurf, is a new molecular entity consisting of two drugs, trifluorithymidine (FTD; trifluridine) and tipiracil (TPI), in a fixed molar ratio of 1.0:0.5 that is supplied as tablets for oral administration in strengths of 15-mg and 20-mg, based on the trifluridine component. Trifluridine is a thymidine-based nucleoside analog, which can be incorporated into deoxyribonucleic acid (DNA) following phosphorylation and inhibit cell proliferation. Tipiracil is a thymidine phosphorylase inhibitor, which contributes to the action of Lonsurf by inhibiting degradation of trifluridine, leading to increased systemic exposure to trifluridine. Trifluridine was approved on April 10, 1980, under the proprietary name, Viroptic (trifluridine ophthalmic solution) 1% Sterile (NDA 018299). Viroptic is “indicated for the treatment of primary kerato-conjunctivitis and recurrent epithelial keratitis due to herpes simplex virus, types 1 and 2.”

This NDA relied on the results of a single multicenter, randomized (2:1), double-blind, placebo-controlled trial, Study TPU-TAS-102-301 (RECOURSE). Key eligibility criteria were histologically documented metastatic colorectal cancer (mCRC); prior treatment with at least two chemotherapy regimens containing a fluoropyrimidine, oxaliplatin, irinotecan, a VEGF-directed biologic, and, for those with *KRAS* wild-type mCRC, an anti-EGFR therapy, or evidence of intolerance to one or more such agents; ECOG PS 0-1; absence of CNS metastases; and absence of ascites requiring drainage. Patients were randomized to trifluridine/tipiracil or placebo (2:1); 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). Patients were randomized to receive trifluridine/tipiracil at a dose of 35 mg/m² based on the trifluridine component or matching placebo administered orally twice daily after meals on Days 1 through 5 and Days 8 through 12 of each 28-day cycle until disease progression or unacceptable toxicity. The primary endpoint was overall survival (OS) and key secondary efficacy endpoints were progression-free survival (PFS) and overall response rate (ORR).

A total of 800 patients were enrolled and randomized; 534 patients were randomized to trifluridine/tipiracil and 266 patients were randomized to placebo. The median age was 63 years, 61% were male, 58% and 35% were White and Asian respectively, and all patients had baseline ECOG PPS 0 or 1. The primary site of disease was colon (62%) or rectum (38%). All patients had received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy and all but one patient received prior bevacizumab. Approximately half (49%) of the study population had *KRAS* wild-type mCRC; all but two patients with *KRAS* wild-type mCRC received panitumumab or cetuximab.

Study TAS-102-301 demonstrated a clinically important and statistically significant improvement in overall survival [hazard ratio (HR) 0.68 (95% confidence interval (CI): 0.58, 0.81); $p < 0.001$] with median survival times of 7.1 months in the trifluridine/tipiracil arm

compared to 5.3 months in the placebo arm. In addition, progression-free survival was also significantly prolonged in the trifluridine/tipiracil arm as compared to placebo [HR 0.47 (95% CI: 0.40, 0.55); $p < 0.001$].

There were 533 patients treated with trifluridine/tipiracil in Study-102-301, which is sufficient to detect adverse reactions occurring at an incidence of approximately 1%. The most common adverse drug reactions or laboratory abnormalities (all Grades and greater than or equal to 10% in incidence) in patients treated with trifluridine/tipiracil 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. However the incidence of Grade 3 or 4 adverse events, with the exception of myelosuppression, was low with 7% Grade 3-4 asthenia/fatigue and 4% Grade 3-4 decreased appetite, 3% Grade 3-4 diarrhea, and other Grade 3-4 adverse reactions occurring at an incidence of 2% or less.

The most serious safety concerns identified for trifluridine/tipiracil were severe myelosuppression, with 0.2% fatality due to neutropenic sepsis and an incidence of Grade 3-4 neutropenia of 38%, Grade 3-4 anemia of 18%, Grade 3-4 thrombocytopenia of 5% and incidence of febrile neutropenia of 3.8%. Across Study 102-301, 9.4% of patients receiving trifluridine/tipiracil required granulocyte-colony stimulating factors. In Study 102-301, 3.6% of patients discontinued trifluridine/tipiracil for an adverse event and 13.7% of patients required a dose reduction. The most common adverse reactions leading to dose reduction were neutropenia, anemia, febrile neutropenia, fatigue, and diarrhea.

The major issue considered in this application was whether this single randomized trial provided substantial evidence of effectiveness and whether the risk:benefit ratio was favorable. The demonstration of a modest but clinically important improvement in overall survival and progression-free survival was statistically robust. The adverse reaction profile is similar to drugs which patients would have already received as part of their prior treatment. The incidence and severity of the gastrointestinal and myelosuppressive toxicity observed in this study would be considered acceptable in light of the benefits and is supported by the relatively low incidence of dose reductions (13.7%) and 3.6% discontinuation rate for an adverse reaction. I concur with the review team members that this application should be approved.

2. Background

Indicated Population and Alternative Therapy

Based on SEER data, there will be an estimated 132,700 new cases of colorectal cancer and 49,700 deaths due to colorectal cancer in 2015.¹ Approximately 20% of colorectal cancers have distant metastases disease at diagnosis and the 5-year survival rate for those with metastatic disease is 13%.

¹ <http://seer.cancer.gov/statfacts/html/colorect.html>. Accessed on September 19, 2015.

The proposed indication is “for the treatment of patients with metastatic colorectal cancer who have been previously treated with, (b) (4) fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and an anti-EGFR therapy.”

Available therapy for this population is limited to one FDA-approved drug, Stivarga (regorafenib), which was approved on September 27, 2012, for “the treatment of patients with metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy.” This approval was based on demonstration of a single, randomized, multicenter, placebo-controlled clinical trial (CORRECT trial), comparing regorafenib to a matching placebo. The CORRECT trial demonstrated statistically significant improvements in both overall survival [HR = 0.77 (0.64, 0.94)] with KM-estimated median survival times 6.4 and 5.0 months and in progression-free survival [HR = 0.49 (0.42, 0.58)] with estimated median PFS of 2.0 and 1.7 months, in the regorafenib and placebo arms, respectively. The overall response rates were similar between arms (1% vs. 0.4%).

Based on the proposed indication, other drugs approved for the treatment of metastatic colorectal cancer cannot be approved available therapy due to the requirement to have prior receipt of, or intolerance to, such therapy.

Pre-submission Regulatory History

December 28, 1998: IND 57674 submitted to FDA for the clinical investigation of TAS-102; initial studies evaluated the safety and tolerability of TAS-102 in patients with various cancers. (b) (4)

Based on the results of an exploratory randomized trial (Study J003/10040030) in patients with refractory colorectal cancer conducted in Japan, Taiho requested reactivation of IND 57674 on June 24, 2011.

November 29, 2011: teleconference to discuss the CMC and non-clinical development program for TAS-102. FDA agreed with the proposed starting materials and the bridging study to support the intended manufacturing site. FDA requested that Taiho designate a primary manufacturing site and an alternate site, both of which should have 12-month real time and 6-month accelerated stability studies in the NDA. In addition, FDA stated that Taiho should include acceptance criteria for both “specified” and “unspecified” impurities as well as heavy metals testing in the drug substance specifications.

December 12, 2011: meeting was held to discuss the proposed clinical trial of TAS-102 in refractory colorectal cancer patients (Study TAS-102-301) and ancillary studies required in support of the clinical development and plans to support an NDA for TAS-102. Key agreements reached were:

- Taiho would provide adequate data to support the safety of the proposed dose (30-35 mg BID) in Study TAS-102-301, which exceeds the maximum tolerated dose of 25 mg BID identified in the dose-finding trial (TAS-102-101) previously conducted in the US.

- Taiho will need to justify that the results are applicable to the U.S. population. FDA expects that Taiho will enroll adequate numbers of patients in the TAS-102-301 trial who received prior therapy applicable to a U.S. population and who reflect an ethnic composition sufficiently similar to that of the U.S. population.
- Study TAS-102-301, a single randomized trial intended to support an NDA should be well designed, well-conducted, and internally consistent, and provide statistically persuasive efficacy findings such that a second trial would be ethically or practically impossible to perform.
- Taiho will need to provide adequate justification that TPI is a necessary component of TAS-102 and that FTD alone (e.g., at a higher dose or more frequent schedule) is not sufficient to provide the proposed treatment effect.
- The general study design for the proposed pharmacokinetics study to characterize the pharmacokinetics of FTD with and without TPI and of the proposed renal and hepatic impairment trials appear to be acceptable.
- Until a dedicated QT clinical trial is conducted that rules out serious risks, Taiho will conduct ECG monitoring in all clinical trials.
- Taiho agreed to provide the proposed analysis plan to specify event-based analysis, provide underlying assumptions justifying the sample size, and clarity on testing of secondary endpoints. Taiho also agreed to provide safety data to support dosing recommendations in the event of toxicity.

October 25, 2013: letter was issued notifying Taiho that the proposed proprietary name “Lonsurf” was conditionally acceptable.

December 2, 2013: letter issued confirming FDA’s acknowledgment that pre-NDA meeting scheduled on December 5, 2013, was cancelled by Taiho based on receipt of FDA’s preliminary responses to the meeting questions.

June 10, 2014: letter issued confirming FDA’s acceptance of the agreed initial Pediatric Study Plan (iPSP).

July 31, 2014: interdisciplinary pre-NDA meeting held to review the summary results of Study TAS-102-301 and reach agreement on the content and format of the proposed NDA. Key comments and agreements reached were:

- FDA advised a request for Fast Track designation to permit submission of a rolling NDA and facilitate timely review.
- The proposed non-clinical studies would support filing of an NDA; all nonclinical study reports should be submitted in Module 4.
- As revised and agreed-upon during the meeting, FDA stated that the content and format of the proposed NDA would support filing. Taiho agreed to submit the safety update at Day 90, regardless of the review designation.
- FDA advised Taiho that a justification should be provided in the NDA to support their request for review designation.
- FDA agreed that REMS would not be required in order to file the NDA; a final decision regarding the requirement for REMS would be made during review of the NDA.

September 12, 2014: letter issued designating as a Fast Track development program the investigation of TAS-102 for the treatment of patients with metastatic colorectal cancer who have been previously treated with, (b) (4), fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and an anti-EGFR therapy (b) (4)

October 3, 2014: letter allowing Protocol TO-TAS-102- 104 entitled, “An Open-label Expanded Access Study of TAS-102 in Patients with Metastatic Colorectal Cancer Refractory to or Failing Standard Chemotherapy” submitted under the provisions of 21 CFR 312.320, to proceed.

3. CMC

I concur with the conclusions reached by the quality review team (chemistry, biopharmaceutics, microbiology and facilities reviewers) regarding the acceptability of the manufacturing of the drug product and drug substance. Lonsurf will be marketed as film-coated immediate release tablets for oral administration in two strengths: a white “15 mg” tablet containing 15 mg trifluridine and 6.14 mg tipiracil and a pale red “20 mg” tablet containing 20 mg trifluridine 8.20 mg tipiracil. The quality review team granted a categorical exclusion from the preparation of an environmental assessment (EA) for trifluridine/tipiracil film-coated tablets, 15/6.14 mg, and 20/8.19 mg, according to section 505(b) of the Federal Food, Drug, and Cosmetic Act. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months. There are no outstanding issues that would preclude approval.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the nonclinical pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

The NDA contained the results of in vitro and in vivo studies assessing the pharmacodynamic effects of trifluridine and of tipiracil, individually. Trifluridine is incorporated into the DNA of mammalian cells; trifluridine was incorporated into the DNA of cancer cells as early as 4 hours after exposure at concentrations achievable with the recommended dose of Lonsurf (35 mg/m² twice daily) and transient depletion of the intracellular pool of thymidine was observed, attributed to inhibit thymidylate synthase. Incubation with trifluridine inhibited the in vitro proliferation of human cancer cell lines at IC₅₀ values of 0.2 µM to 24 µM. Administration of trifluridine:tipiracil (1:0.5 M) inhibited tumor growth and improved survival relative to controls in human colorectal cancer xenograft models.

Pharmacology studies confirmed the inhibition of thymidine phosphorylase by tipiracil. Concomitant administration of tipiracil and trifluridine resulted in increases in trifluridine

exposure of ≥ 100 -fold as compared to trifluridine alone in non-human primates chronic (13-week) toxicology studies. Tipiracil, as a single agent, did not inhibit tumor growth in tumor xenograft models.

In chronic toxicology studies in rats and monkeys, the major target organs were the hematopoietic system and gastrointestinal (GI) tract. Safety pharmacology studies indicate that trifluridine/tipiracil does not have significant effects on the neurologic, cardiovascular, or respiratory systems. Trifluridine/tipiracil crossed the placenta and was detectable in breast milk in rats. Trifluridine/tipiracil was embryotoxic and teratogenic when at exposures comparable to that achieved with the recommended human dose administered early in gestation, but did not alter fertility in female rates. In vitro studies indicate that trifluridine is genotoxic.

5. Clinical Pharmacology/Pharmacometrics

I concur with the conclusions reached by the clinical pharmacology and pharmacometrics reviewers that there are no outstanding clinical pharmacology issues that preclude approval.

The pharmacokinetics of trifluridine/tipiracil were characterized, demonstrating that systemic exposure (AUC) of trifluridine increased more than dose proportionally over the dose range of 15 to 35 mg/m². The mean elimination half-life of trifluridine at steady state was 2.1 hours and of tipiracil was 2.4 hours. The clinical pharmacology program provided a nearly complete assessment of the pharmacokinetics of Lonsurf; the program contained dose-finding studies establishing the tolerability of the dosage regimen, the contribution of the tipiracil hydrochloride component as a pharmacokinetic modulator, the food effects on pharmacokinetic profile, the effects of Lonsurf on cardiophysiology, ADME (absorption, distribution, metabolism, excretion) of Lonsurf, relative bioavailability of Lonsurf in patients with cancer, and effects of organ (renal, hepatic) on pharmacokinetics. These study results supported the specific labeling recommendation that TAS-102 be administered under fed conditions (*e.g.*, within 1 hour after completion of morning and evening meals). In addition, no dose adjustments are required when Lonsurf is administered with concomitant medications because neither trifluridine nor tipiracil are metabolized by cytochrome P450 (CYP) enzymes (b) (4) had no clinically meaningful effect on exposure to trifluridine or tipiracil.

A population pharmacokinetic (PopPK) analyses that included data from 239 patients who received the proposed dosage regimen identified that body size and renal function are the primary intrinsic factors affecting the exposure to trifluridine and tipiracil. Based on the PopPK analysis, the proposed adjustment for the dose by body surface area (BSA) was determined to be appropriate and supported the labeling recommendation that dose adjustment is required for patients with mild hepatic impairment, and mild to moderate renal impairment.

The exploratory exposure-response (E-R) analyses were inconclusive data from only 138 Lonsurf-treated patients enrolled in Study TAS-102-301 trial were included in these analyses and the survival in this subgroup appeared better than in the ITT population, suggesting that

this subgroup might not be representative of the overall population. In E-R analyses, the 138 patients were divided evenly into a “high trifluridine AUC” and a “low trifluridine AUC” subgroup. There was a suggestion that survival was longer and the incidences of Grade ≥ 3 neutropenia and of all Grade ≥ 3 drug related adverse events were higher in the subgroup of patients with “high trifluridine AUC” than in those with “low trifluridine AUC”.

An ECG substudy was incorporated into Study TAS-102-301 to assess effects on cardiac electrophysiology. Based on the results of this study, given the absence of clinically significant effects in the hERG assay or in a nonclinical safety cardiology study, the QT-IRT consultant concluded that trifluridine/tipiracil is unlikely to cause clinically relevant QT prolongation.

6. Clinical Microbiology

I concur with the conclusions reached by the clinical microbiology reviewer that there are no outstanding clinical microbiology or sterility issues that preclude approval.

7. Clinical/Statistical-Efficacy

This NDA relied primarily on the results of a single, multicenter, international, randomized (2:1), placebo-controlled trial (TPU-TAS-102-301), with supportive evidence provided in a randomized, activity-estimating trial conducted in Japan (Study J003/10040030). There were no concerns regarding the study design or appropriateness of the dosage regimen. Based on the results observed in the primary efficacy trial, there are no concerns with regards to the robustness of the findings, which provide substantial evidence of effectiveness.

Six clinical sites were chosen for inspection based on enrollment of large numbers of study subjects, and significant primary efficacy results pertinent to decision making. Based on the review of preliminary inspectional findings, the data obtained at these six clinical study sites appear reliable for use in support of the NDA.

Study Design

Title: TPU-TAS-102-301 (RECOURSE), titled “A Randomized, Double-Blind, Phase 3 Study of TAS-102 plus Best Supportive Care (BSC) Versus Placebo plus BSC in Patients with Metastatic Colorectal Cancer Refractory to Standard Chemotherapies”.

Key eligibility criteria were histologically documented metastatic colorectal cancer (mCRC); prior treatment with at least two chemotherapy regimens containing a fluoropyrimidine, oxaliplatin, irinotecan, a VEGF-directed biologic, and, for those with *KRAS* wild-type mCRC, an anti-EGFR therapy, or evidence of intolerance to one or more such agents; ECOG PS 0-1; absence of CNS metastases; and absence of ascites requiring drainage.

The primary objective was to demonstrate improvement in overall survival among patients randomized to receive trifluridine/tipiracil compared to those randomized to receive placebo.

Secondary objectives included demonstration of an improvement in progression-free survival for those randomized to receive trifluridine/tipiracil compared to those randomized to receive placebo, to further characterize the adverse reaction profile and drug-related toxicity, and to confirm the tolerability of the trifluridine/tipiracil dosage regimen administered in this trial.

Patients were randomized to trifluridine/tipiracil or placebo (2:1); randomization was stratified by KRAS status (wild-type vs. mutant), time since diagnosis of first metastasis (<18 months vs. \geq 18 months), and region (Japan vs. US, Europe and Australia).

Treatment regimen: Trifluridine/tipiracil 35 mg/m² (based on trifluridine component), or matching placebo, orally twice daily on Days 1-5 and 8-12 of a 28-day treatment cycle continuing until disease progression or unacceptable toxicity.

Analysis plan: The sample size of 800 patients was based on the following assumptions: 1) a 2:1 randomization, 2) 90% power to detect an effect on overall survival at a one-sided type I error rate of 0.025 after 571 events, 3) median OS of 5 months in placebo arm, and 4) hazard ratio of 0.75. There were not planned interim analyses for overall survival; the analysis of overall survival was to occur at 571 deaths. PFS was the key secondary endpoint and would be tested at the 1-sided 0.025 level, if the study met the primary endpoint. The analyses of OS and PFS were to be conducted in the intent-to-treat population (all randomized). The comparison of overall response rate was to be conducted in the “tumor response population” defined as all randomized patients with measurable disease (at least one target lesion) at baseline and with at least one tumor evaluation while on treatment.

Results

The study was initiated on June 17, 2012 and the data cut-off date for primary analysis was January 24, 2014. The trial enrolled 800 patients, of whom 534 patients were randomized to trifluridine/tipiracil and 266 patients were randomized to placebo. Approximately two-thirds of patients were enrolled in sites in Western Europe and one-third of patients were enrolled in Asia. The median age was 63 years, 61% were male, 58% and 35% were White and Asian respectively, 56% has a baseline ECOG PS of 0 and 44% had an ECOG PS of 1, and 79% were more than 18 months from identification of metastatic disease. The primary site of disease was colon (62%) or rectum (38%). All patients had received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy and all but one patient received prior bevacizumab. Approximately half (49%) of the study population had KRAS wild-type mCRC; all but two patients with KRAS wild-type mCRC received panitumumab or cetuximab. Most (61%) patients had received 4 or more prior lines of chemotherapy.

The efficacy results from Study 102-301 are summarized in the table and figure below. The median PFS times are not provided in the table as these do not reflect the improvement observed; the mean PFS was 3.2 months (95% CI: 3.0, 3.4) in the trifluridine/tipiracil arm and 1.9 months (95% CI: 1.8, 2.1) in the placebo arm. FDA calculated the overall response rates in the intent-to-treat population, consistent with usual conventions. The ORR was 1.5% (8/534) in the trifluridine/tipiracil arm and 0.4% (1/266) in the placebo arm. The median duration of response among the 8 responders in the trifluridine/tipiracil arm was 7.4 months (95% CI: 1.9, 7.5).

Table 3 Efficacy Results

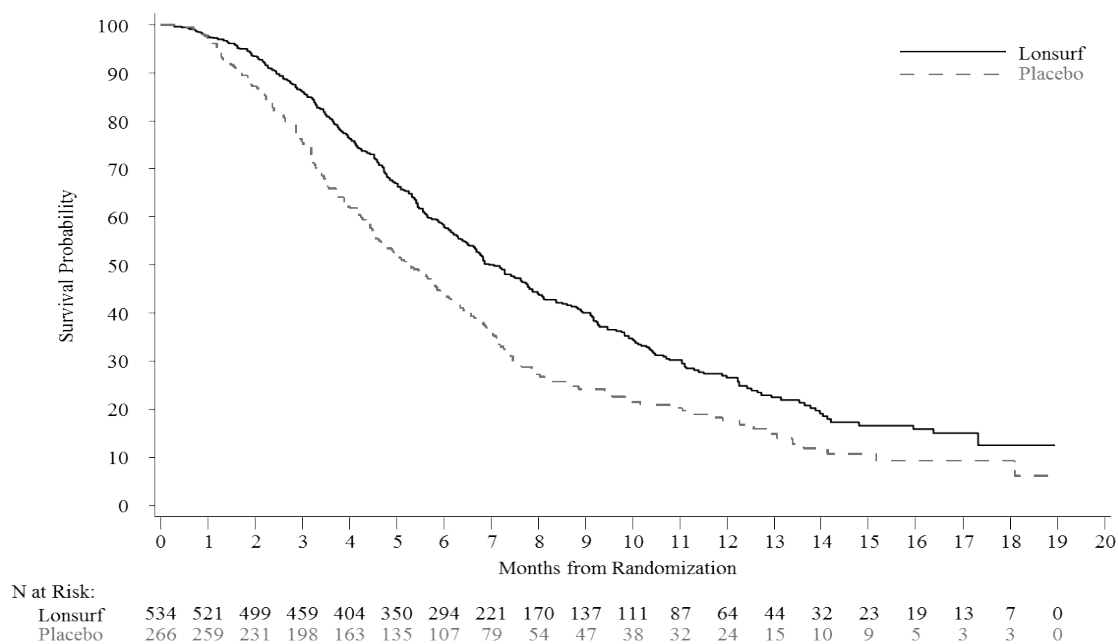
	trifluridine/tipiracil (N=534)	placebo (N=266)
Overall Survival		
Number of deaths, N (%)	364 (68)	210 (79)
Median OS (months) ^a [95% CI] ^b	7.1 [6.5, 7.8]	5.3 [4.6, 6.0]
Hazard ratio [95% CI]	0.68 [0.58, 0.81]	
P-value ^c	<0.001	
Progression-Free Survival		
Number of Progression or Death, N (%)	472 (88)	251 (94)
Hazard ratio [95% CI]	0.47 (0.40, 0.55)	
P-value ^c	<0.001	

^a Kaplan-Meier estimates

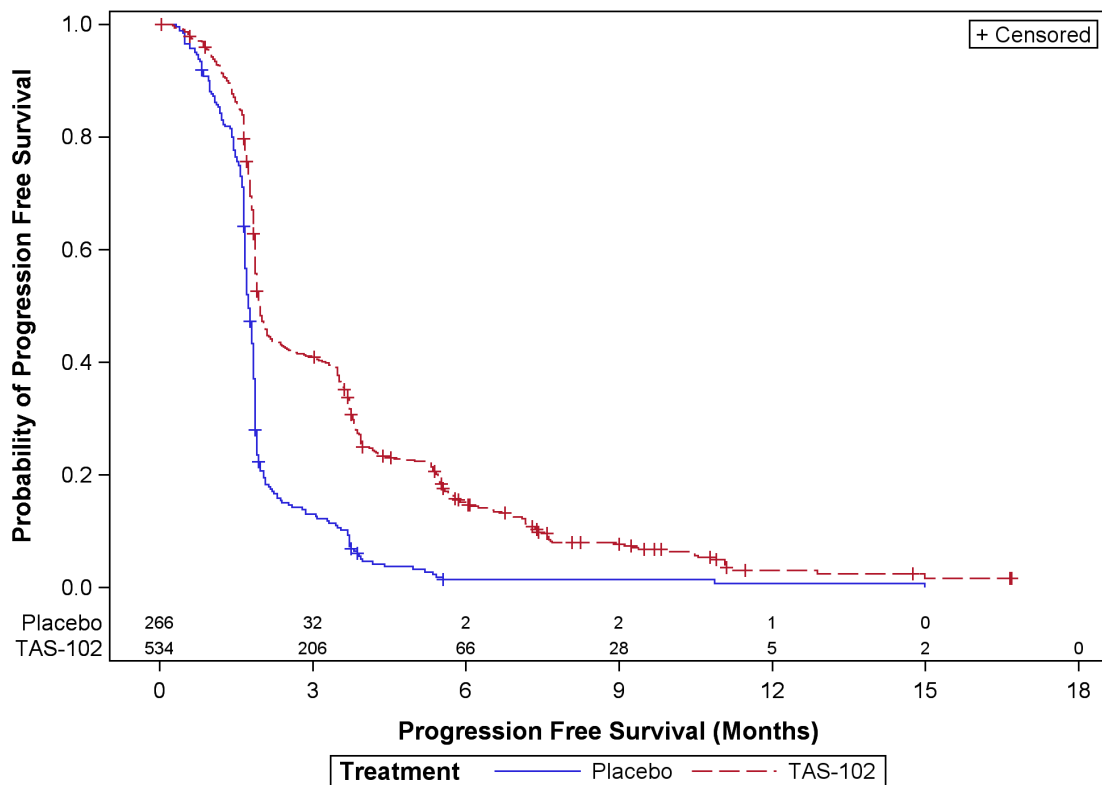
^b Methodology of Brookmeyer and Crowley

^c Stratified log-rank test (strata: KRAS status, time since diagnosis of first metastasis, region)

K-M Curves of Overall Survival



K-M Curves of Progression-free Survival



8. Safety

Size of the database

The size of the safety database was adequate. There were 533 patients treated with trifluridine/tipiracil in Study-102-301, which is sufficient to detect adverse reactions occurring at an incidence of approximately 1%. The most common adverse drug reactions or laboratory abnormalities (all Grades and greater than or equal to 10% in incidence) in patients treated with trifluridine/tipiracil 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. However the incidence of Grade 3 or 4 adverse events, with the exception of myelosuppression, was low with 7% Grade 3-4 asthenia/fatigue and 4% Grade 3-4 decreased appetite, 3% Grade 3-4 diarrhea, and other Grade 3-4 adverse reactions occurring at an incidence of 2% or less.

In Study 102-301, 3.6% of patients discontinued trifluridine/tipiracil for an adverse event and 13.7% of patients required a dose reduction. The most common adverse reactions leading to dose reduction were neutropenia, anemia, febrile neutropenia, fatigue, and diarrhea.

Major safety concerns:

The most serious safety concerns identified for trifluridine/tipiracil were severe myelosuppression, with 0.2% fatality due to neutropenic sepsis and an incidence of Grade 3-4 neutropenia of 38%, Grade 3-4 anemia of 18%, Grade 3-4 thrombocytopenia of 5%) and incidence of febrile neutropenia of 3.8%. Across Study 102-301, 9.4% of patients receiving trifluridine/tipiracil required granulocyte-colony stimulating factors. The other significant risk is embryofetal toxicity in pregnant women exposed to trifluridine at the recommended dose. Both of these risks are adequately addressed with product labeling.

REMS

Both the DRISK consultant and the clinical review team agreed that Risk Evaluation and Mitigation Strategies are not required to ensure safe use. Taiho submitted their proposed Risk Management Program, which consists of agreed-upon physician package insert describing the serious risks of severe neutropenia and embryofetal toxicity and the common risk of gastrointestinal toxicity (vomiting, diarrhea) and a pharmacovigilance plan. I concur that these risks, which are common to many anti-neoplastic agents, have been effectively mitigated with product labeling describing the risks and dose modifications in the event of such adverse reactions.

PMRs and PMCs

The only post-marketing requirements were identified by the clinical pharmacology review team, to complete ongoing studies assessing whether, and how, pharmacokinetics are altered in patients with severe renal impairment and moderate to severe hepatic impairment. There were no clinical adverse reactions that required post-marketing studies for further investigation.

9. Advisory Committee Meeting

The NDA for this new molecular entity was not referred to an FDA advisory committee because the safety profile is acceptable for the treatment of patients with unresectable advanced or recurrent colorectal cancer. The application did not raise significant public health questions on the role of Lonsurf for this indication and outside expertise was not necessary as there were no controversial issues that would benefit from an advisory committee discussion.

10. Pediatrics

Taiho requested a full waiver from the requirements of the Pediatric Research Equity Act (PREA) for all age groups because pediatric studies are impossible or highly impractical due to the small number of pediatric patients diagnosed with colorectal cancer annually. As stated in the Division of Pediatric and Maternal Health (DPMH) review, the estimated incidence is 1 per million in the United States (159 pediatric cases; reported ages 4 to 20 years, from 1973 through 2005) in children. The Pediatric Review Committee (PeRC) granted approval of this waiver on July 8, 2015.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

- Proprietary name: Based on the review by the Division of Medication Error and Prevention and Analysis (DMEPA), DMEPA determined that the proposed proprietary trade name, Lonsurf, did not pose risks of medication error; the Office of Prescription Drug Promotion did not identify concerns of potential promotional claims. All review team members concurred that the proposed tradename was acceptable. A letter notifying Taiho of this determination was issued on March 5, 2015.
- Physician labeling
 - Boxed Warnings: Taiho did not propose a Boxed Warning and the review team did not find the seriousness of the adverse reactions sufficient to require inclusion of one.
 - Indications and Usage: edited for brevity (b) (4) and inclusion of clarification that only patients with RAS wild-type therapy should have received a prior anti-EGFR therapy.
 - Dosage and Administration: The DMEPA consult reviewer noted potential risks of medication errors given that Lonsurf dosing is based on the trifluridine component and dosing is complex requiring the a combination of 15-mg and 20-mg tablets to achieve the prescribed dose and that dosing is rounded to the nearest 5 mg. This section of labeling was edited for clarity and brevity.
 - Dosage Forms and Strengths: tipiracil dose based on free-base rather than hydrochloride salt.
 - (b) (4)
 - Warnings and Precautions: Edited subsection on “Severe Myelosuppression” to provide information on the risks observed in clinical experience, edited recommendations on actions to be taken to mitigate risk for brevity and to remove (b) (4)
(b) (4) Subsection on “Embryofetal Toxicity” revised for conformance with the Pregnancy and Lactation Labeling Rule (PLLR).
 - Adverse Reactions: Revised text describing clinical trial safety results for conformance with FDA guidance on this section of product labeling; limited adverse reactions and laboratory abnormality tables to those events occurring at a higher rate than in the placebo arm (and thus possibly related to the underlying disease rather than the drug). Included a subsection on the incidence of infections in Study 102-301, by pooling all data and describing the most frequent infections. Added subsection incidence of interstitial lung disease observed across 7000 patients, which includes the marketing of this drug in Asia.

- Drug Interactions: Edited for brevity and essential information. Cautionary statements that are not supported by clinical data were removed.
 - Use in Specific Populations: Subsections 8.1-8.3 revised in accordance with PLLR; animal data in juvenile animals included in subsection 8.4 (b) (4); editorial edits to subsection 8.5 to conform to language specified in 21 CFR 201.57; subsections 8.6 and 8.7 revised for brevity and essential information; subsections 8.5, 8.6, and 8.7 revised to state that there are no recommended dose modification based on age or end-organ impairment.
 - Overdosage: Edited for brevity and essential information; added statement that there is known antidote for Lonsurf (b) (4).
 - Description: added pharmacologic class and route of administration. Strength revised to include strength of tipiracil free base.
 - Clinical Pharmacology: Extensively edited for brevity, limited to essential information per FDA Guidance and regulations for this section.
 - Nonclinical Pharmacology/Toxicology: Modified to clarify that effects on female reproductive organs are dose-related and not limited to the highest dose tested. (b) (4)
- (b) (4)
- Clinical Studies: Edited to provide additional description of the trial design (b) (4)
- (b) (4)
- References: Added reference to OSHA website because trifluridine is genotoxic.
 - How Supplied/Storage and Handling: added detailed description to 16.1 per 21 CFR 201.57 on description of tablets. Added statement with regard to need for special handling since trifluridine is genotoxic.
 - Patient Counseling: Modified in accordance with FDA Guidance on this section; edited for brevity and essential information.
- Carton and immediate container labels: The carton and immediate container labeling was revised in accordance with applicable regulations and to minimize the risk of medication errors.
 - Patient labeling: Patient labeling was submitted by Taiho. This was edited to reflect modifications to the physician package insert and to conform to FDA Guidances for this labeling.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: I concur with the recommendations of the review team that this NDA be approved with the agreed-upon labeling.
- Risk Benefit Assessment
Metastatic colorectal cancer is a serious and life-threatening disease with a 5-year survival rate of 16% from diagnosis of metastatic disease. In the major efficacy trial, the median survival in the control arm was 5.1 months.

This NDA relied on the results of a single multicenter, randomized (2:1), double-blind, placebo-controlled trial, which enrolled 800 patients. This trial demonstrated a clinically important and statistically significant improvement in overall survival [hazard ratio (HR) 0.68 (95% confidence interval (CI): 0.58, 0.81); $p < 0.001$] with median survival times of 7.1 months in the trifluridine/tipiracil arm compared to 5.3 months in the placebo arm. In addition, progression-free survival was also significantly prolonged in the trifluridine/tipiracil arm as compared to placebo [HR 0.47 (95% CI: 0.40, 0.55); $p < 0.001$]. The adverse reaction profile of trifluridine/tipiracil is similar to drugs which patients would have already received as part of their prior treatment. The most common adverse reactions of this combination drug were anemia, neutropenia, asthenia/fatigue, nausea, thrombocytopenia, decreased appetite, diarrhea, vomiting, abdominal pain, and pyrexia. However the incidence of Grade 3 or 4 adverse events, with the exception of myelosuppression, was low with 7% Grade 3-4 asthenia/fatigue and 4% Grade 3-4 decreased appetite, 3% Grade 3-4 diarrhea, and other Grade 3-4 adverse reactions occurring at an incidence of 2% or less. The most serious safety concerns identified for trifluridine/tipiracil were severe myelosuppression, with 0.2% fatality due to neutropenic sepsis and an incidence of Grade 3-4 neutropenia of 38%, Grade 3-4 anemia of 18%, Grade 3-4 thrombocytopenia of 5%) and incidence of febrile neutropenia of 3.8%. Across Study 102-301, 9.4% of patients receiving trifluridine/tipiracil required granulocyte-colony stimulating factors.

This patient population has only one effective, alternative therapy (regorafenib) which provides and improvement in survival of a similar magnitude. Thus there is a continued unmet need for effective treatments, where patients may choose treatment based on the adverse reaction profile or in light of other co-morbid conditions. The incidence and severity of the gastrointestinal and myelosuppressive toxicity observed in this study would be considered acceptable by the oncology community and patients in light of the benefits. The tolerability of this agent is supported by the relatively low incidence of dose reductions (13.7%) and 3.6% discontinuation rate for an adverse reaction.

I concur with the review team members that this application should be approved.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

I concur with the recommendations of the DRISK consultant and the clinical team that REMS are not required to ensure safe use of Lonsurf in the indicated population.

- Recommendation for other Postmarketing Requirements and Commitments
Hepatic and renal impairments studies are required to determine the appropriate dose adjustments, if any, for patients with end-organ impairment, as follows:
 - Complete the ongoing clinical pharmacokinetic trial to determine an appropriate dose of Lonsurf (trifluridine and tipiracil) in patients with moderate to severe hepatic impairment in accordance with the FDA Guidance for Industry entitled “Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.”
 - Complete the ongoing clinical pharmacokinetic trial to determine an appropriate dose of Lonsurf (trifluridine and tipiracil) in patients with severe renal impairment in accordance with the FDA Guidance for Industry entitled “Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.”

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/s/

PATRICIA KEEGAN
09/21/2015