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RESEARCH**

*APPLICATION NUMBER:*

**207981Orig1s000**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

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Priority or Standard	Standard
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Division / Office	DOP2/OHOP
Reviewer Name(s)	Leigh Marcus Steven Lemery, Team Leader
Review Completion Date	21 August 2015
Established Name	Trifluridine/tipiracil hydrochloride (TAS-102)
(Proposed) Trade Name	Lonsurf
Therapeutic Class	Antitumor nucleoside
Applicant	Taiho Oncology, Inc.
Formulation(s)	Tablets
Dosing Regimen	35mg/m <sup>2</sup> orally twice daily for 5 days, and 2 days of rest, for 2 weeks followed by 14 days of rest, every 4 weeks
Indication(s)	Treatment of patients with unresectable advanced or recurrent colorectal cancer
Intended Population(s)	≥ 18 years of age

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## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

This reviewer recommends approval of new drug application (NDA) 207981 for TAS-102 tablets 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 <sup>(b)</sup><sub>(4)</sub>RAS wild type, an anti-EGFR therapy. The recommendation for approval is contingent upon final agreement on labeling and post-marketing commitments with Taiho and contingent upon final inspection results.

This NDA is primarily supported by a single, multicenter, randomized (2:1), double-blind, placebo-controlled trial, TPU-TAS-102-301 (RECOURSE, as described in the remainder of this review), that randomized 800 patients with previously treated metastatic CRC. 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 CRC received panitumumab or cetuximab. Eight hundred patients were randomized to receive 35 mg/m<sup>2</sup> TAS-102 orally twice daily for 5 days, and 2 days of rest, for 2 weeks followed by 14 days of rest, every 4 weeks (n=534) plus best supportive care (BSC) or placebo (n=266) plus BSC (will be referred to just as placebo for the remainder of this review); of these, 1 in each group did not receive study medication, thus 798 patients were treated (533, TAS-102; 265, placebo). Treatment continued until disease progression, unacceptable toxicity, or death.

The assessment of benefit in this application is based on the primary endpoint of overall survival (OS). This recommendation for approval is based on review of the clinical data, which support the conclusion that TAS-102 modestly prolongs overall survival in patients who have failed standard chemotherapy (a population for whom only one therapy is currently approved). A statistically significant, clinically meaningful prolongation in OS was observed in patients randomized to receive TAS-102; median OS was 7.1 months in the TAS-102 arm compared to 5.3 months in the placebo arm, hazard ratio (HR) of 0.68 (95% CI: 0.58, 0.81), p<0.0001 (2-sided).

The secondary efficacy endpoints were progression free survival (PFS) and overall response rate (ORR). The addition of TAS-102 to BSC (will be referred to as just TAS-102 for the remainder of this review) resulted in a modest statistically significant improvement in PFS compared to placebo with HR of 0.48 (95% CI: 0.41, 0.57), p<0.001 (2-sided stratified log-rank test). The median PFS for the TAS-102 group was 2.0 months versus 1.7 months for the placebo group. There was no difference between treatment groups with respect to ORR (8 patients with partial response in the TAS-102 group; 1 patient with complete response in the placebo group).

The results of RECURSE were supported by the results of a randomized trial in patients with colorectal cancer conducted in Japan (Study J003/10040030). The trial was a randomized (2:1), double-blind, placebo-controlled study of patients with chemotherapy-refractory advanced colorectal cancer who progressed or failed to respond to more than two chemotherapeutic regimens including a fluoropyrimidine, irinotecan, and oxaliplatin. TAS-102 plus was administered at a dose of 70 mg/m<sup>2</sup>/day (35 mg/m<sup>2</sup>/dose twice daily) for 5 consecutive days with 2 days rest weekly for 2 weeks followed by a 2-week recovery period. Patients in the placebo arm received BSC. The primary endpoint was OS and the study was designed with a one-sided alpha of 0.10. One hundred seventy-two patients were enrolled; however the full analysis set consisted of 169 patients. Two patients were excluded by the applicant who discontinued prior to receiving study drug. HR for OS was 0.56 with a p-value of 0.0011 for OS (median difference of 2.4 months). PFS was 2 months for the TAS-102 group versus 1 month for placebo as assessed by independent review committee and 2.7 months for TAS-102 as assessed by the investigators (median difference of 1-1.7 months). There was no difference between treatment groups with respect to ORR (0.9% in the treatment arm versus 0% in the control arm). Some baseline differences in prognostic factors were observed in the trial between arms (57% of patients were men in the treatment arm versus 49% in the placebo arm; 44% of patients had rectal cancer in the treatment arm versus 37% in the placebo arm).

The FDA Guidance for Industry entitled “*Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*” states that for approval, “reliance on only a single study will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with a potentially serious outcome, and confirmation of the result in a second trial would be practically or ethically impossible”. RECURSE was a large randomized trial which demonstrated robust and consistent results across most patient subsets and achieved more than one endpoint including a clinically meaningful, statistically significant overall survival benefit providing sufficient basis for approval as set forth in the guidance.

## 1.2 Risk Benefit Assessment

The benefit-risk assessment for this NDA was based on data from the RECURSE trial, which enrolled 800 patients with metastatic colorectal cancer whose disease progressed after receiving treatment with (b) (4) fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and an anti-EGFR therapy (for patients with KRAS wild-type tumors). RECURSE was a prospective, multicenter, multinational, randomized (2:1), double-blind, placebo-controlled trial of TAS-102 versus placebo. Randomization stratification factors were geographic region (Asia versus U.S. and Europe), KRAS status (wild type versus mutant), and time since diagnosis of first metastasis (<18 months versus ≥ 18 months). The primary objective was to compare overall survival of the TAS-102 arm versus the

placebo arm.

The trial demonstrated a statistically significant and clinically meaningful improvement in OS in favor of the TAS-102 arm with a HR of 0.68 [95% CI: 0.58, 0.81; p-value < 0.0001). Median OS was 7.1 months in the TAS-102 arm and 5.3 months in the placebo arm. The median survival time was increased by a 1.8 months in the TAS-102 arm. This is comparable to the modest effect size demonstrated in a clinical study investigating regorafenib for the treatment of patients with third line metastatic CRC. The statistical significance, magnitude of treatment effect, and robustness of the primary OS analysis were all supported by sensitivity analyses (refer to FDA biostatistical review) and by the results of a phase 2 clinical study conducted in Japan.

The progression-free survival analysis was supportive of the primary analysis results. There was a statistically significant reduction in the risk of disease progression or death in the TAS-102 arm [HR = 0.48, 95% CI (0.41; 0.57); p-value < 0.0001 compared with the placebo arm. The ORR analysis was exploratory (1.5% versus 0.4%) for the TAS-102 and placebo arms respectively.

The improvement in overall survival was associated with a higher incidence of treatment-related Grade 3–4 adverse events (49% versus 10% in the TAS-102 and placebo arms, respectively). The most common adverse drug reactions or laboratory abnormalities (all Grades and greater than or equal to 10% in incidence) in patients treated with TAS-102 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. Treatment discontinuations due to AEs were more frequent in the TAS-102 arm (3.6% versus 1.5% in the placebo arm).

In both arms, the leading cause of deaths was progressive disease (83% and 94% in the TAS-102 and placebo arms respectively). The overall safety profile was manageable.

### **Analysis of Condition:**

TAS-102 is proposed as a treatment for patients with metastatic colorectal cancer (CRC) whose disease progressed after (b) (4) treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and an anti-EGFR therapy ( (b) (4) RAS wild-type). The current goals of treatment for patients with (non-oligometastatic) metastatic is to prolong survival and improve quality of life. The standard of care is to administer chemotherapy until the disease progresses, recurs, or the toxicity of therapy is deemed intolerable or detrimental to quality of life. In the U.S., treatment of metastatic disease progresses along multiple lines of anti-neoplastic drugs. Median survival of patients with metastatic CRC can vary based on certain factors and is approximately 30 months in patients with KRAS wild-type disease (Venhook, 2014).

According to Surveillance, Epidemiology and End Results (SEER) data accessed on 7 Jan 2015 (<http://seer.cancer.gov/statfacts/html/colorect.html>), based on cases and deaths from 2007-11, the incidence rate of CRC is approximately 43.7 new cases diagnosed per 100,000 people in the United States (U.S.), and mortality rate is approximately 15.9 deaths per 100,000 people. CRC is the third most common cause of death due to cancer in the U.S. At least 50% of patients develop metastases, and most patients with metastatic CRC are unresectable.

For the vast majority of patients, metastatic colorectal carcinoma is a progressive disease with a fatal outcome. Median survival of patients with metastatic CRC can vary based on certain factors including tumor specific factors (e.g., KRAS or BRAF mutations).

### **Current Treatment Options:**

In general, patients with metastatic CRC receive (in the first- and second-line settings) treatment with a fluoropyrimidine (fluorouracil with leucovorin or capecitabine) in combination with irinotecan or oxaliplatin. Monoclonal antibodies are generally added to these regimens (e.g., an anti-VEFG pathway drug or if KRAS wild-type, an anti-EGFR antibody). For patients refractory to these agents, The National Comprehensive Cancer Network (NCCN) guideline version 2.2015 accessed on 7 Jan 2015 ([http://www.nccn.org/professionals/physician\\_gls/pdf/colon.pdf](http://www.nccn.org/professionals/physician_gls/pdf/colon.pdf)) recommend regorafenib, best supportive care, or participation in a clinical trial. Regorafenib demonstrated a modest improvement in OS (less than 2 months) although it also causes adverse reactions including fatigue, diarrhea, hand-foot syndrome, etc.

Regorafenib is the only FDA-approved drug for the treatment of patients with metastatic 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. There is no head-to-head comparison clinical trial between regorafenib and TAS-102.

### **Benefit:**

The efficacy of TAS-102 for the treatment of patients with metastatic CRC who had progressed after receiving treatment with or are not candidates for fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and an anti-EGFR biological therapy, was demonstrated in one adequate and well controlled study, TPU-TAS-102-301 (RECOURSE). RECOURSE was a prospective, multicenter, multinational, randomized (2:1), double-blind, placebo-controlled trial of TAS-102 versus placebo.

The efficacy analyses of RECOURSE were based on the intention-to-treat population (ITT), which consisted of 800 patients (TAS-102: 534; placebo: 266).

Patient demographics and baseline characteristics were balanced between the two treatment arms. The primary site of disease was colon for 63% of patients, and rectum for 37% of patients. Median age at randomization was 63.0 years, 61% of patients were men, 57% were White and 34% were Asian; all patients had a baseline ECOG performance status of 0 or 1. Fifty-one percent of patients had tumors reported by investigators as KRAS mutant. The majority of patients (60%) had received  $\geq 4$  prior systemic cancer therapies.

As of the cutoff date for non-survival data, the mean duration of treatment was 12.7 weeks for patients in the TAS-102 group and 6.8 weeks for patients in placebo group. A total of 574 deaths were included in the primary analysis of OS based on a cut-off date of 24 January 2014 (TAS-102: 367; placebo: 211; 4 patients died (b) (6)). Of the 220 patients who were alive at the time of the data cutoff date, a total of 39 patients (37 and 2 patients in the TAS-102 and placebo arms respectively) remained on treatment.

A total of 29 (6%) patients in the TAS-102 arm and 18 (7%) patients in the placebo arm were reported to have major protocol violations, and the frequency and nature of the protocol deviations appeared to be similar between the treatment arms.

The primary endpoint of OS from randomization was met. The median OS was 7.1 months for the TAS-102 group versus 5.3 months for the placebo group with a hazard ratio (HR) of 0.68 (95% confidence interval [CI]: 0.58, 0.81), and 2-sided  $p < 0.0001$ . The statistical significance, magnitude of treatment effect, and robustness of the primary OS analysis were all supported by sensitivity analyses. This is comparable to the effect size demonstrated in a clinical trial with regorafenib for third-line treatment for patients with metastatic CRC.

The secondary endpoint of PFS was met. There was a statistically significant reduction in the risk of disease progression or death in the TAS-102 arm [HR = 0.48, 95% CI (0.41; 0.57);  $p$ -value  $< 0.0001$  compared with the placebo arm. The ORR was exploratory (1.5% versus 0.4%) for the TAS-102 and placebo arms respectively.

In summary, the primary benefit that patients receive from taking TAS-102 is that they live longer.

RECOURSE was a well conducted study that demonstrated that TAS-102 compared to placebo resulted in a modest survival benefit, with a statistically significant  $p$ -value of 0.0001 using a stratified log-rank test (which met the pre specified efficacy boundary) and an estimated hazard ratio of 0.68 (95% confidence interval [CI]: 0.58, 0.81). Treatment with TAS-102 resulted in a median prolongation of survival of 1.8 months. Median overall survival in the TAS-102 arm was 7.1 months, compared to 5.3 months in the placebo arm. The robustness of the findings was supported by subgroup and sensitivity analyses. Internal consistency between the primary endpoint of OS and secondary endpoint of PFS was also observed.

Although modest, the treatment effect of TAS-102 was comparable to the effect observed in a clinical study of regorafenib in a similar study population. The primary efficacy endpoint was overall survival (OS). A statistically significant OS improvement was observed in patients who received regorafenib compared to those receiving placebo [HR 0.77 (95% CI: 0.64, 0.94),  $p=0.005$ , stratified log-rank test]. Median OS was 6.4 and 5 months for patients on the regorafenib arm and placebo, respectively. The submission was of adequate quality for the clinical review. There were no issues that questioned the integrity of the data in the submission.

TAS-102 resulted in a clinically meaningful and statistically significant improvement in the primary endpoint of OS compared to placebo. The increase in median overall survival is considered clinically meaningful by the community.

**Risk:**

The safety analysis was based on the safety population of the RECOURSE study (533 patients and 265 patients in the TAS-102 and placebo arms, respectively). Overall, the incidence rate of adverse events of any grade (TAS-102 98% versus placebo 93%) was similar, although there was a higher incidence of treatment Grade 3–4 adverse events (49% versus 10% in the TAS-102 and placebo arms, respectively). The most common adverse drug reactions or laboratory abnormalities (all Grades and greater than or equal to 10% in incidence) in patients treated with TAS-102 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.

Gastrointestinal (GI) AEs of all grades were more frequent in the TAS-102 group than in the placebo group, including diarrhea, nausea, vomiting, and abdominal pain. However, the overall incidence of  $\geq$  Grade 3 GI events was similar in the two treatment groups. The overall incidence of blood and lymphatic disorder AEs (all grades) was higher in the TAS-102 group than in the placebo group, as was the incidence of AEs  $\geq$  Grade 3. This was primarily due to a higher incidence of AEs associated with myelosuppression, a well described effect of TAS-102, including anemia, leukopenia, neutropenia and thrombocytopenia. GI toxicity was managed with supportive care. Fifty subjects (9.4%) treated with TAS-102 were identified as using granulocyte-colony stimulating factors, while there was no concomitant use of this medicine on the placebo arm.

The median duration of therapy was 6.7 weeks on the TAS-102 arm and 5.7 weeks on the placebo arm. Treatment discontinuations due to AE were more frequent in the TAS-102 arm (3.6% versus 1.5% in the placebo arm). A dose reduction was required in 13.7% of patients on TAS-102. The most common adverse reactions leading to dose reduction were neutropenia, anemia, febrile neutropenia, neutrophil count decreased, fatigue, and diarrhea.

The leading cause of death on both arms was progressive disease (83% and 94% in the TAS-102 and placebo arms respectively).

Grade 3-4 AEs of myelosuppression and diarrhea were observed more frequently in the TAS-102 arm compared to placebo. Fifty subjects (9.4%) treated with TAS-102 were identified as using granulocyte-colony stimulating factors compared to none on placebo. The toxicity profile of the RECURSE study was manageable.

The results of the safety analyses demonstrated that the safety profile of TAS-102 35mg/m<sup>2</sup> twice daily in a patient population with advanced metastatic CRC who have limited treatment options is favorable based on the effect observed on overall survival.

### **Risk Management:**

The risks of TAS-102 use in the treatment of patients with metastatic colorectal carcinoma are well known to prescribers and managed through product labeling. The risks are also managed in that this drug will be administered by oncologists who have specific training in the administration of anti-neoplastic drugs and in the management of toxicities related to these drugs. Two PMRs will be requested to obtain data in order to determine an appropriate dose of TAS-102 in patients with hepatic and renal impairment. These studies are ongoing at this time.

The risk of TAS-102 use can be managed through product labeling and administration of the drug in specialized settings.

### **1.3 Recommendations for Post market Risk Evaluation and Mitigation Strategies**

The applicant will not be required to provide REMS for this submission.

### **1.4 Recommendations for Post market Requirements and Commitments**

There are no clinical recommendations for additional PMC/PMRs. The Applicant is required to complete the following (ongoing) clinical pharmacology trials in Table 1 under the PMR provision. The PMR trials will be included in the Approval letter with milestones agreed upon. These trials are requested by Office of Clinical Pharmacology (OCP) to ensure that a safe dose can be recommended to patients with renal or hepatic impairment.

Table 1: Clinical Pharmacology Post market Requirements

Drug Development Question	Rationale	PMR
Should the dose of TAS-102 be modified in patients with moderate or severe hepatic impairment?	The active component trifluridine (FTD) in TAS-102 is mainly eliminated by metabolism via thymidine phosphorylase (TPase) to form an inactive metabolite, 5-(trifluoromethyl) uracil (FTY). Because TPase is found in the liver and gastrointestinal tract, patients with hepatic impairment may have higher FTD exposures than patients with normal hepatic function, which may lead to more treatment-limiting severe toxicity.	Complete a pharmacokinetic study to determine the appropriate dose of TAS-102 in patients with hepatic impairment.  Final Protocol Submission: Submitted  Trial Completion: 9/30/ 2017  Final Report Submission: 12/31/2017
Should the dose of TAS-102 be modified in patients with severe renal impairment?	The pharmacokinetic modulator tipiracil (TPI) in TAS-102 is a thymidine phosphorylase (TPase) inhibitor, which is primarily eliminated by urinary excretion in its unchanged form. Patients with renal impairment may have increased TPI exposure leading to increasing in trifluridine (FTD) exposure due to increased inhibition of FTD metabolism (via TPase) by TPI, which may lead to more treatment-limiting severe toxicity.	Complete a pharmacokinetic study to determine the appropriate dose of TAS-102 in patients with renal impairment.  Final Protocol Submission: Submitted  Trial Completion: 9/30/ 2017  Final Report Submission: 12/31/2017

## 2 Introduction and Regulatory Background

According to Surveillance, Epidemiology and End Results (SEER) data accessed on 7 Jan 2015 (<http://seer.cancer.gov/statfacts/html/colorect.html>), based on cases and deaths from 2007-11, the incidence rate of CRC is approximately 43.7 new cases diagnosed per 100,000 people in the U.S., and mortality rate is approximately 15.9 deaths per 100,000 people. CRC is the third highest cause of death due to cancer in the U.S. At least 50% of patients develop metastases, and most patients with metastatic CRC are unresectable.

In general, patients with metastatic CRC receive (in the first- and second-line settings) treatment with a fluoropyrimidine (fluorouracil with leucovorin or capecitabine) in

combination with irinotecan or oxaliplatin. Monoclonal antibodies are added to these regimens (e.g., an anti-VEFG pathway drug or if KRAS wild-type, an anti-EGFR antibody). For patients refractory to these agents, The National Comprehensive Cancer Network (NCCN) guideline version 2.2015 accessed on 7 Jan 2015 ([http://www.nccn.org/professionals/physician\\_gls/pdf/colon.pdf](http://www.nccn.org/professionals/physician_gls/pdf/colon.pdf)) recommend regorafenib, BSC, or participation in a clinical trial.

## 2.1 Product Information

TAS-102 (trifluridine/tipiracil hydrochloride), proprietary name TAS-102, is a fixed combination (1:0.5) of  $\alpha,\alpha,\alpha$ -trifluorothymidine (FTD) and 5-chloro-6-(2-iminopyrrolidin-1-yl) methyl-2,4 (1H,3H)-pyrimidinedione hydrochloride [thymidine phosphorylase inhibitor (TPI)]. The bioavailability of FTD after oral administration is extremely low due to a first-pass effect by TPase, which results in the rapid degradation of FTD to its major metabolite, 5-trifluoromethyl-2,4(1H,3H)-pyrimidinedione (FTY). FTY is an inactive metabolite as its growth inhibitory activity against tumor cells *in vitro* is  $\geq 100$ -fold lower than that of FTD. TPI is a specific inhibitor of TPase that inhibits the metabolism of FTD in the intestinal tract and liver. Therefore, co-administration of TPI with FTD increases the concentration of FTD in the body and enables the attainment of effective and consistent levels of FTD that, from a clinical feasibility perspective, could not be reached by oral FTD administration alone. Following uptake into cancer cells, FTD is phosphorylated by thymidine kinase, further metabolized in cells to a DNA substrate, and incorporated directly into DNA, thereby interfering with DNA function to prevent cell proliferation.

TAS-102 is a new molecular entity (NME) and is supplied in two strengths: immediate release film-coated 15 mg white round tablets and 20 mg pale-red round tablets. The applicant's indication for TAS-102 is for treatment of patients age  $\geq 18$  years old with unresectable, advanced, or recurrent CRC who have previously been treated with, (b) (4) fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and an anti-EGFR therapy.

## 2.2 Currently Available Treatments for Proposed Indications

First- and second-line therapy of advanced or metastatic CRC usually consists of the administration of oxaliplatin or irinotecan in combination with leucovorin and fluorouracil. Monoclonal antibodies can also be added to chemotherapy. With the exception of metastatic disease confined to the liver and completely resected, metastatic CRC is generally considered incurable and the aim of therapy is to prolong survival and improve quality of life. The standard of care is to administer chemotherapy in first-line until the disease progresses, recurs, or the toxicity of therapy is deemed intolerable or detrimental to the patient's quality of life. Treatment of metastatic disease is a continuum of care, and if disease progresses during first line treatment, treatment continues with a different chemotherapy regimen that has not been used before in that

particular patient (for example, if a patient received an oxaliplatin-based regimen for first line, an irinotecan-based regimen may be used for the second-line treatment).

The applicant's proposed indication for TAS-102 is treatment of metastatic CRC after third progression, or for patients who previously received, (b) (4) fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and an anti-EGFR therapy. NCCN guidelines [Version 2.2015 accessed on 7 Jan 2015 ([http://www.nccn.org/professionals/physician\\_gls/pdf/colon.pdf](http://www.nccn.org/professionals/physician_gls/pdf/colon.pdf))] recommend regorafenib, BSC, or participation in a clinical trial for third-line treatment of metastatic CRC.

FDA approved regorafenib (Stivarga) in September 2012 for the treatment of patients with metastatic 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, according to the package insert (PI) (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Overview&DrugName=STIVARGA> accessed on 7 Jan 2015). Regorafenib is a small-molecule multi-kinase inhibitor that blocks the activity of several protein kinases, including VEGFR1 (also known as FLT1), VEGFR2, VEGFR3, TIE2, KIT, RET, RAF1, BRAF, BRAFV600E, PDGFR and FGFR. Regorafenib demonstrated safety and efficacy in a randomized, placebo-controlled, trial in 16 countries in North America, Europe, Asia, and Australia (CORRECT trial). Enrolled patients had adenocarcinoma of the colon or rectum, had received standard therapies, and had disease progression. The primary endpoint was overall survival (OS) with median OS of 6.4 months in the regorafenib group (N=505) versus 5.0 months in the placebo group (N=255), hazard ratio 0.77; 95% CI 0.64–0.94; one-sided p=0.0052. The most common ≥ Grade 3 adverse reactions following the use of regorafenib (versus placebo) in patients with metastatic CRC were hand-foot skin reaction (17% versus 0), fatigue (15% versus 9%), infection (9% versus 6%), diarrhea (8% versus 2%), hypertension (8% versus <1%), and rash or desquamation (6% versus < 1%).

### **2.3 Availability of Proposed Active Ingredient in the United States**

TAS-102 is a NME and is not currently marketed in the U.S.

### **2.4 Important Safety Issues with Consideration to Related Drugs**

TAS-102 is a combined form of 1M  $\alpha,\alpha,\alpha$ -trifluorothymidine (FTD) and 0.5 M thymidine phosphorylase inhibitor (TPI). FTD was FDA approved in 1980 as an antiviral drug for topical treatment of epithelial keratitis caused by herpes simplex virus. The package insert reports that the most frequent adverse reactions were ocular. TPI inhibits degradation of FTD and does not have a related (approved) drug counterpart.

FTD is an antineoplastic antimetabolite and FTD, after phosphorylation and metabolization, is incorporated into DNA, interfering with DNA function and cell proliferation. The applicant stated that incorporation into DNA is the primary anti-tumor mechanism of action (as opposed to thymidylate synthase inhibition with other fluoropyrimidines). Like other fluoropyrimidines, gastrointestinal and myelotoxicity occurs following the use of TAS-102. TAS-102 differs in that it is not metabolized by dihydropyrimidine dehydrogenase and thus dihydropyrimidine dehydrogenase deficiency (DPD) does not appear to be a risk factor for severe toxicity following the use of TAS-102.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

The following summarizes key regulatory history for TAS-102:

- **November 29, 2011: Type B meeting, End of Phase 2, CMC**, Teleconference
  - FDA recommended that the applicant designate a primary manufacturing site with a single manufacturing process for the drug substance. An additional site may be used as an alternate manufacturing site.
    - At the time of NDA submission, both sites should have 12 months long term and 6 months accelerated stability data in accordance with ICH.
    - FDA informed the applicant that insufficient stability data at the time of submission is a filing issue.
    - FDA stated that forced degradation studies for drug substance are necessary from only one site.
    - The applicant indicated that the (b) (4) site has a manufacturing inspection record, while no inspection record exists for (b) (4).
  - The applicant's proposal for different test methods for each impurity profile based on source could be acceptable based on scientific justification submitted in NDA; however, FDA recommended one single drug substance specification regardless of drug substance source.
    - FDA expressed concerns regarding the impact of drug product supply chain with dual sources for drug substance, specifically, with lot to lot drug substance traceability in the drug product.
    - Dependent upon the assessment of comparability between the two manufacturing sites and the two manufacturing methods, a determination of the retest period (the applicant will submit as (b) (4) months) will be made during the NDA review.
  - FDA expressed concerns about change controls (e.g., if a change in a vendor were to occur, would a change in impurities also occur, thereby impacting the drug substance and product quality).

- FDA recommended that the specifications ensure control of all impurities and that an impurity evaluation be performed for materials from different vendors.
- FDA requested the following in the applicant's NDA submission:
  - Acceptance specifications for the starting materials (b) (4) including any proposed critical quality attributes (such as impurity acceptance criteria)
  - Complete impurity profiles of (b) (4) manufactured by the intended supplier(s). If the starting material (b) (4) is provided by multiple suppliers, provide comparative impurity profiles of the starting material manufactured by the different suppliers
  - Test data to demonstrate that your proposed synthetic process in your NDA submission is capable of removing the impurities carried over from the starting material to the final drug substance
  - Test data to demonstrate that your proposed analytical methods are capable of detecting these impurities (see above bullet) during the synthetic process as well as in the final drug substance
  - Information supporting well characterized reference starting materials
- FDA stated that in the event that a request for a BCS Class-1 classification for the drug substance/drug product and/or a request for a BA/BE waiver for any strength of the proposed drug product is/are made, the complete data supporting such request(s) should be provided.
- **December 12, 2011: Type B meeting, End of Phase 2**
  - This meeting was held to obtain the Agency's guidance on the proposed pivotal clinical trial of TAS-102 (RECOURSE) in patients with refractory colorectal cancer and on the ancillary studies required to support the clinical development and registration of TAS-102. Major agreements reached during this meeting include:
    - FDA stated that to support an NDA, the applicant will need to justify that the results are applicable to the U.S. population and the dosing regimen in TAS-102-301 (RECOURSE) is reasonably safe for the US population.
    - FDA stated that in an NDA submission, the applicant will need to provide adequate justification that TPI is a necessary component of TAS-102 and why FTD alone (e.g., at a higher dose or more frequent schedule) is not sufficient to provide the proposed treatment effect.
    - FDA agreed that the general study design for the proposed renal and hepatic impairment trials appeared to be acceptable.
    - FDA stated that the overall QT risk evaluation plan is inadequate to support TAS-102 marketing registration.

- The applicant provided justification to support the administration of TAS-102 under fed conditions in the ongoing and proposed clinical trials, and agreed to submit data to FDA.
  - FDA asked the applicant to conduct population PK studies, sparse PK studies in the Phase 3 trial to explore the exposure-response relationships for FTD and TPI (and metabolites), validate the analytical methods used to determine the concentrations of FTD and TPI (and metabolites), and evaluate the *in vitro* studies of FTD and TPI.
  - FDA stated that the applicant will need to provide justification regarding not conducting BA studies for individual components. Taiho agreed to submit justification to the IND.
- *November 29, 2013 (December 5, 2013): Type B meeting, pre-NDA, CMC; (meeting was not held because November 29, 2013 written responses were considered adequate).* The written responses were:
    - It is expected that Taiho will provide 12 months of LTSS data for all three primary stability batches within the 30 days from the NDA submission.
    - It is recommended that Taiho select the annual stability batches using the lowest count configuration (20 counts) for each strength (15 mg and 20 mg) of the drug product for the annual stability testing program.
    - The Agency cannot reach a conclusion on the acceptability of the process validation activities until the actual protocols, acceptance criteria and study outcomes are evaluated during an inspection.
      - FDA does not approve process validation plans, protocols, or specific batches used in process validation studies.
    - Determination of acceptability of the acceptance criteria for related substances in (b) (4) will be made during the NDA review when all CMC information and relevant data have been evaluated.
    - Final determination of the acceptability of the proposed starting materials for TP1 drug substance will be made during the NDA review. In the NDA, Taiho should include:
      - Appropriate change controls for the manufacturing of TPI
      - Validated analytical methods to detect and quantitate impurities in the drug substance, intermediates, and the proposed starting materials.
      - Impurity profile data from all available batches of the proposed starting material, (b) (4) and their corresponding intermediate and drug substance batch analysis data.
  - *March 14, 2014:* In accordance with **PREA**, Taiho submitted an agreed upon **iPSP**, and FDA acknowledged that Taiho did not intend to conduct studies in pediatric subjects for this indication of colorectal cancer (*June 10, 2014*). A disease specific waiver from all requirements of PREA in a marketing application for TAS-102 for the proposed indication of colorectal cancer was granted.

- *July 31, 2014: Type B meeting, pre-NDA*
  - FDA recommended submission of the safety update 90 days after submission of the NDA.
  - FDA agreed that based on a preliminary evaluation of the data provided in the meeting package, a REMS will not be required for filing. However, a formal determination on the need for a REMS will be determined during the review of the NDA.
  - Taiho agreed to provide information supporting the metabolism of TAS-102 in the NDA to support the omission of a Warning based on dihydropyrimidine dehydrogenase deficiency (DPD).
  - FDA recommended that Taiho submit a request for Fast Track designation in order to support a rolling submission.
- *September 12, 2014: Granted Fast Track*, submitted by Taiho on August 22, 2014 for the development of TAS-102 for the treatment of patients with metastatic CRC who have been previously treated with, (b) (4) fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and an anti-EGFR therapy to demonstrate an improvement in overall survival.
- *December 19, 2014*: Taiho submitted the complete NDA.
- *January 5, 2015*: Taiho submitted an agreed upon **iPSP**, and requested a waiver from all requirements of PREA for the proposed indication of colorectal cancer.

## 2.6 Other Relevant Background Information

### 2.6.1 Metastatic colorectal cancer

#### Epidemiology

CRC is the third most common cancer in men and women in the U.S. SEER data (<http://seer.cancer.gov/statfacts/html/colorect.html#incidence-mortality>) accessed on 7 Jan 2015 state that approximately 4.7 percent of men and women will be diagnosed with colon and rectum cancer at some point during their lifetime. The median age at diagnosis for cancer of the colon and rectum (all stages) from 2007-2011 was 68 years. As the U.S. population ages, the CRC incidence rates have also increased: 14.2% of patients are being diagnosed between 45 and 54 years; 21.2% between 55 and 64; 23.9% between 65 and 74; 23.2% between 75 and 84; and 12.1% ≥ 85 years of age.

More men than women are frequently diagnosed with CRC (50.6 per 100,000 males versus 38.2 per 100,000 women). Distribution varies among ethnicities: the lowest incidence rates are found in Hispanic (44.3 and 30.6 per 100,000 males and females, respectively) and Asian populations (43.1 and 32.0 per 100,000 males and females, respectively). The incidence rates are higher in Whites (49.6 and 37.3 per 100,000 males and females, respectively) and even higher in Black populations (62.3 and 47.3 per 100,000 males and females, respectively).

Approximately 20% of patients are diagnosed in the metastatic stage. Mortality rates for CRC have continued to decline and are at an all-time low of 15.1 deaths per 100,000 for all races and all sexes. The median age at death for cancer of the colon and rectum from 2007-2011 for all races and both sexes was 74 years. The age-adjusted death rate was 15.9 per 100,000 men and women per year. These rates are based on patients who died in 2007-2001 in the US.

Table 2 summarizes the American Cancer Society (ACS) (Cancer Facts and Figures 2014 <http://www.cancer.org/research/cancerfactsstatistics/cancerfactsfigures2014/>) estimates of colon, rectal and the most common cancers incidence rates in the U.S. population for the year 2014. Projected cases are based on 1995-2010 incidence rates from 49 states and DC as reported by the North American Association of Central Cancer Registries (NAACCR).

Table 2: Estimated new cancer cases and deaths by sex, U.S. 2014

	Estimated new cases			Estimated deaths		
	Both sexes	Male	Female	Both sexes	Male	Female
All sites	1,665,540	855,220	810,320	585,720	310,010	275,710
Colon	96,830	48,450	48,380	50,310	26,270	24,040
Rectum	40,000	23,380	16,620	No data	No data	No data
Lung	224,210	116,000	108,210	159,260	86,930	72,330
Breast	235,030	2,360	232,670	40,430	430	40,000
Prostate	233,000	233,000	-	29,480	29,480	-

### Treatment

Depending on the patient's performance status, the first-line treatment of metastatic CRC can be palliative, or in select cases, curative. Palliative therapy aims to prolong survival while preserving or improving the quality of life, whereas select isolated organ metastases (typically limited to hepatic metastases) can be resected with curative intent. The reported 5-year survival rate after the complete resection of hepatic metastases is 20% to 30% (Schmiegel, 2009). Thus, treatment is chosen depending on the clinical subgroup to which the patient belongs.

After decades of treating metastatic CRC with 5-fluorouracil (5-FU) alone or in combination with leucovorin (LV), newer agents introduced in the 1990s have resulted in improvements in overall survival rates. These improvements stem from combinations of cytotoxic agents (irinotecan and oxaliplatin) and therapies targeting the VEGFR pathway (bevacizumab or zif-aflibercept) and the EGFR pathway (cetuximab or panitumumab).

In the third-line setting (i.e., after a patient progresses on oxaliplatin- and irinotecan-containing regimens), treatment options are more limited and include regorafenib, an

EGFR inhibitor (in RAS wild type patients who have yet to receive an EGFR inhibitor), best supportive care, or a clinical trial.

Regorafenib is an inhibitor of multiple tyrosine kinase pathways including vascular endothelial growth factor (VEGF). In September 2012, the FDA granted approval for the use of regorafenib in patients who had progressed on prior therapy (including an EGFR inhibitor). The safety and effectiveness of regorafenib were evaluated in a single, clinical study of 760 patients with previously treated metastatic CRC. Patients were randomly assigned 2:1 regorafenib or placebo in addition to BSC. Patients treated with regorafenib had a statistically significant improvement in OS (6.4 months in the regorafenib group vs. 5.0 months in the placebo group; HR, 0.77; 95% CI, 0.64–0.94; one-sided  $p=0.0052$ ).

Regorafenib is the only FDA-approved drug for the treatment of patients with metastatic 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 is the same study population that was investigated in both TAS-102 trials. A placebo-controlled design was selected for this study since, at the time the study was initiated, there were no standard therapies for patients with metastatic CRC who had been previously treated with fluoropyrimidines, oxaliplatin, irinotecan, monoclonal anti-VEGF and anti-EGFR antibodies, and had become refractory or intolerant to those chemotherapies. Regorafenib became authorized for the treatment of patients with metastatic CRC in all participating RECURSE countries/regions (Australia, EU, Japan and the U.S.) only after most of the study enrollment was complete (>80%). There is no head-to-head comparison clinical trial between regorafenib and TAS-102.

### **2.6.2 Foreign Market Authorization**

Japan approved TAS-102 on 24 Mar 2014 for the treatment in patients with unresectable, advanced, or recurrent CRC. This approval was based on the results of the randomized (2:1), double-blind, placebo-controlled clinical trial conducted in Japan (J003-10040030). J003-10040030 randomized 170 patients with metastatic CRC who progressed or failed to respond to at least two prior chemotherapy regimens that included a fluoropyrimidine, irinotecan, and oxaliplatin. Patients in the experimental arm received TAS-102 35 mg/m<sup>2</sup> orally twice daily for five days a week with two days rest followed by a 14 day rest interval (repeated every four weeks). OS was the primary endpoint of the trial and demonstrated that TAS-102 improved OS with a HR of 0.56 and p-value of 0.0011 (median difference of 2.4 months).

### 3 Ethics and Good Clinical Practices

#### 3.1 Submission Quality and Integrity

The submission was of adequate quality for the clinical review.

For RECOURSE, the applicant appeared to do a thorough job requesting information from investigators, and the CRFs and narratives were complete and provided the information needed to supplement the databases.

This reviewer could not identify any issue that questioned the integrity of the data in the submission.

In RECOURSE, 2 subjects had missing death flags and death dates in at least one dataset. In J003-10040030, 1 subject has 2 records of death (10040030-017). The death analysis was therefore subset to give a complete count of subject death.

Table 3 shows the number of instances with missing race data, ethnicity data, or both from the RECOURSE study. The sites in France did not have this information collected; and Japan also did not have this data listed (0%).

Table 3: Missing Race and Ethnicity Data in RECOURSE trial

Race	Ethnicity	TAS-102 (N=533)	Placebo (N=265)
Missing	Not reported	40 (0.08% of arm)	12 (0.05% of arm)
White	Not reported	6 (0.01% of arm)	2 (0.008% of arm)
<b>Total</b>		46 (0.09% of arm)	14 (0.05% of arm)

There were also duplicate laboratory values reported for subject 351-009 in RECOURSE for bilirubin; clinically, this did not trigger a safety signal. About 15% of the J003-10040030 data for adverse events were missing a start date.

#### 3.2 Compliance with Good Clinical Practices

The submission (module 2, section 2.5 [Clinical Overview], page 12 as well as the RECOURSE clinical study report, section 5 page 31) contained a statement that all completed and ongoing clinical trials of TAS-102 have been performed in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines.

Because TAS-102 is an NME, an Office of Scientific Investigations (OSI) consult was requested for the clinical inspection of 6 trial sites. Sites were selected based upon analyses of site-specific efficacy data, types and quantity of protocol violations, patient

## Clinical Review

Leigh Marcus

NDA 207981

TAS-102 (Lonsurf) for the treatment of patients with metastatic colorectal cancer

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enrollment per site, and investigator financial conflict of interest disclosures. This reviewer also used the JMP Clinical tool to analyze for possible fraud at sites including searching for excessive patient visits on Saturday/Sundays or holidays, searching for patients with the same birthdates, or with blood pressures ending with the same value. No patterns were identified in these analyses. Table 4 lists the sites for clinical inspection.

Table 4: Office of Scientific Investigations Clinical Inspections

Site Number	PI/Site address	Number of Patients
356	Carbonero, Rocio Avenida Manuel Siurot s/n. Sevilla, SPAIN	21
706	Denda, Tadamichi Chiba-city, Chiba JAPAN	14
604	Falcone, Alfredo ITALY	35
355	Tabernerero, Josep Barcelona, SPAIN	20
704	Yamaguchi, Kensei Kita-adachi-gun, Saitama JAPAN	15
705	Yoshino, Takayuki Kashiwa-city, Chiba JAPAN	30

### **Protocol Violations**

The sponsor stated that major protocol violations occurred during study conduct in 47 subjects (6%). There were 33 subjects (4%) at study entrance who did not receive all required prior chemotherapies, were not refractory to their last chemotherapy regimen, or who had anticancer therapy within 3-4 weeks of study medicine. There were 14 subjects (2%) during the study period who received radiation, cancer surgery, or chemotherapy while receiving study drug. Table 5 summarizes the protocol violations as per the protocol violation dataset. The table shows that the proportion of protocol violations were similar between arms. It is unlikely that these violations qualitatively affected the overall outcome of the study.

Table 5: Protocol Violations in RECURSE (ITT population)

	<b>TAS-102 N=534 (%)</b>	<b>Placebo N=266 (%)</b>	<b>Total N=800</b>
Subjects with protocol violations	29 (5.4)	18 (6.8)	47 (5.9)
Received wrong treatment	0	0	0
Compliance with protocol procedures	10 (1.9)	4 (1.5)	14 (1.8)
Violation of entry criteria	19 (3.6)	14 (5.3)	33 (4.1)

### 3.3 Financial Disclosures

For RECURSE:

A total of 100 investigators and 654 sub-investigators participated in RECURSE. Of these, financial disclosure information was obtained from all 100 investigators. A total of 654 sub-investigators were involved in the trial, of those, 644 signed the Financial Disclosure Form, one of whom reported a conflict of interest.

- Participation was defined as sites that enrolled patients into the study
- One Investigator enrolled patients at 2 clinical sites. (Sites #559 and 577)

For further information, see the separate financial disclosure form.

For supportive study J003 (study not conducted under the IND):

A total of 23 investigators and 178 sub-investigators at 20 sites participated in Study J003. Of these, financial disclosure information was obtained from 18 investigators (none was collected for sub investigators), 3 of who reported a conflict of interest (Sites #1, 13, and 20). Site #3 had 3 principal investigators; however, two of the investigators did not sign any case report forms (CRF) before the cut-off date of the clinical study report (CSR), therefore financial disclosure was not collected for those two investigators. Site #18 had 2 principal investigators; however, one of the investigators did not sign any CRF before the cut-off date of the clinical study report CSR, therefore financial disclosure was collected only for the other investigator. Site #11 did not enroll any patients and no financial disclosure form was collected. Another investigator passed away and financial disclosure could not be collected.

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls

The pharmaceutical development followed a comprehensive manufacturing science paradigm to demonstrate that a quality product could be manufactured. Provided information appeared adequate to facilitate the review. Refer to the Quality Reviews of trifluridine (DMF (b) (4)) and tipiracil (DMF 28368) for a full discussion of the controls and manufacturing process. Original CMC information, amendments, and responses to the CMC deficiencies related to the drug product in the NDA have been reviewed and found "Adequate."

### 4.2 Clinical Microbiology

Refer to the microbiology review by Quamrul Majumder for a full discussion. The specifications for TPI do not include a test for microbiological attributes testing. This was considered adequate because there is a test for microbial enumeration in the drug product specifications.

### 4.3 Preclinical Pharmacology/Toxicology

Toxicology assessment of trifluridine/tipiracil was performed in rats, dogs and monkeys. The target organs identified were the lymphatic and hematopoietic systems and the gastrointestinal tract. The approximate lethal dose after a single administration was 2000 mg/kg and the gastrointestinal tract was identified as the primary target organ. Similarly, in repeated dose toxicity studies, the gastrointestinal tract was again identified as one of the primary target organs, in addition to the lymphatic and hematopoietic systems. 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 (degeneration and disarrangement in the ameloblasts, papillary layer cells and odontoblasts) were observed in teeth of rats treated with trifluridine/tipiracil. An effect on growing teeth in humans cannot be excluded, but this finding was not evident in young adult monkeys, and therefore may be rodent-specific.

The below assessment is from the reviews written by Drs. Emily Fox and G. Sachia Khasar. The Applicant conducted *in vitro* and *in vivo* studies demonstrating the pharmacological activity of both FTD and TPI, the two components of trifluridine:tipiracil

(FTD:TPI). FTD itself was previously approved for the treatment of epithelial keratitis caused by herpes simplex virus and was shown to interfere with DNA synthesis in cultured mammalian cells. Consistent with its activity as a thymidine analog, FTD was incorporated into the DNA of human cancer cells following 4 and 24 hours of incubation with concentrations of FTD that have been achieved clinically at the recommended dose of 35 mg/m<sup>2</sup> FTD:TPI given twice daily. Incubation with FTD also resulted in transient depletion of the intracellular pool of thymidine, consistent with its ability to non-covalently bind and inhibit thymidylate synthase. FTD inhibited the *in vitro* proliferation of various human cancer cell lines with IC<sub>50</sub> values ranging from 0.214 μM to 24.4 μM. FTD:TPI exhibited *in vivo* anti-tumor activity in various human colorectal cancer xenograft models in nude mice, including KRAS wild-type (COL-1) and cetuximab-resistant KRAS mutant (HCT-116) xenografts. Further, FTD:TPI exhibited *in vivo* anti-tumor activity against MX-1 human breast cancer xenografts relatively insensitive to the oral fluoropyrimidine anticancer drug TS-1.

TPI inhibits the activity of thymidine phosphorylase. In contrast to FTD, the Applicant showed that treatment of mice implanted with various tumor models with TPI alone resulted in no effect on tumor growth compared to control-treated mice, though FTD:TPI still had anti-tumor activity. In pharmacokinetic analyses, the administration of TPI along with FTD resulted in *in vivo* FTD exposures of ≥ 100-fold higher than those following administration of FTD alone. Significant increases in FTD exposure following FTD:TPI administration compared to FTD alone also occurred in the 13-week repeat-dose toxicology study in the monkey. Thus, the presented data support the conclusion that the major role of TPI in FTD:TPI is to enhance the exposure of FTD.

FTD and TPI preferentially distributed to plasma rather than blood cells in rat, monkey, and human blood. Following single oral administration of ([<sup>14</sup>C]FTD)FTD:TPI or ([<sup>14</sup>C]TPI)FTD:TPI to lactating rats, radioactivity was excreted into milk. Thus, women should be advised to avoid breastfeeding during treatment with FTD:TPI. TPI was not substantially metabolized *in vitro* in human hepatocytes, although the minor metabolite 6-hydroxymethyluracil (6-HMU) was detected in human plasma and urine at trace levels. 6-HMU was also detected in rat plasma, urine, and feces following single oral administration of [<sup>14</sup>C-TPI]FTD:TPI or <sup>14</sup>C-TPI, providing nonclinical exposure for this metabolite. In human hepatocytes, FTD was metabolized *in vitro* using human hepatocytes to FTY, uracil-5-carboxylic acid (5-CU), and 5-carboxy-2'-deoxyuridine (5-CdUrd), with FTY being the major metabolite. In keeping with this, trifluridine was metabolized to FTY in human plasma along with 5-CU and 5-CdUrd at low or trace levels. Following a single oral administration of radiolabeled FTD:TPI to rats and monkeys, the majority of FTD-associated radioactivity was excreted in the urine, whereas TPI-associated radioactivity was excreted primarily in the feces. Consistent with clinical findings, the major FTD metabolite detected in rat and monkey plasma and urine was 5-(trifluoromethyl) uracil (FTY). Adequate exposure to FTY occurred in animals to account for potential metabolite-mediated toxicity. Although 5-CU and 5-CdUrd were not detected in rat or monkey plasma or urine in the nonclinical PK studies

conducted by the Applicant, published studies have demonstrated that 5-CU and 5-CdUrd have been detected in urine following single intravenous administration of <sup>14</sup>C-FTD to monkeys. Given these published data, the low amounts of 5-CU and 5-CdUrd detected in human plasma, and the advanced cancer indication, further metabolite evaluation is not warranted at this time.

The rat and monkey were the major species used to test the safety of FTD:TPI in toxicology studies. Following 13 weeks of administration at the high dose level, animal exposure to FTD in FTD:TPI was approximately equal to or greater than (0.92-fold in the rat at 221 mg/kg FTD:TPI, 2.3-fold in the monkey at 29.42 mg/kg) the clinical exposure measured by AUC of 23697 ng•h/mL at the recommended dose of 35 mg/m<sup>2</sup> twice daily. Major target organs of toxicity in both species included the hematopoietic system and gastrointestinal tract. Following single oral administration of [<sup>14</sup>C-FTD]FTD:TPI to rats, tissue distribution was high in the GI tract, also consistent with clinical findings of GI toxicity. In *in vivo* safety pharmacology studies in male Sprague-Dawley rats, single oral doses of FTD:TPI up to 640 mg/kg had no significant effect on general physical condition, respiratory rate, tidal volume, or minute volume. Similarly, FTD:TPI had no significant effect on CNS up to 24 hours post administration, though its distribution to the brains of rats was ~7% of that in plasma, suggesting that FTD:TPI is able to cross the blood-brain barrier, at least at low levels. FTD:TPI did not significantly inhibit *in vitro* hERG-mediated potassium current in stably transfected HEK293 cells at concentrations up to 300 μM, which is much higher than the clinical C<sub>max</sub> achieved at the recommended human dose of FTD:TPI (~16 μM). In keeping with this, single and repeated administration of FTD:TPI had no significant effect on QT/QTc prolongation in *in vivo* animal studies and no clear effects of FTD:TPI on QTc prolongation have been reported in clinical trials. FTD:TPI and FTD were positive in genetic toxicology tests, while TPI was negative. The major toxicity of myelosuppression (including decreased white blood cells and red blood cells); mild bone marrow hypocellularity, as well as the gastrointestinal tract toxicities reported clinically were predictable from nonclinical toxicology studies in rats and monkeys.

In pharmacokinetic studies in pregnant rats, both FTD and TPI were able to cross the placental barrier. FTD:TPI had no effect on fertility in male or female rats; however, administration of the drug either early in development or during the period of organogenesis resulted in decreased numbers of viable fetuses. Toxicokinetic data was not collected in the rat embryofetal development (EFD) study, but, the same doses were used in the rat EFD study and the 13-week repeat-dose toxicology study, allowing for clinical exposure comparison. Based on the toxicokinetic data from the long-term study in rats, increased embryo-fetal lethality occurred at maternal exposures similar to clinical exposures at the clinically recommended dose. Other observations included decreased fetal weights at doses ≥74 mg/kg, as well as delayed ossification, and visceral and skeletal abnormalities at the 221 mg/kg dose level. A warning for the risk of effects on embryofetal development is warranted in the label for FTD:TPI. In addition, based on the embryofetal risk, a clinical half-life of the drug of approximately 2

hours, and positive findings for genotoxicity, patients are advised to use contraception during treatment with FTD:TPI and, in males, for 3 months following the final dose of the drug. Please see review by Drs. Emily Fox and G. Sachia Khasar review for full details.

## 4.4 Clinical Pharmacology

### 4.4.1 Mechanism of Action

TAS-102, an antitumor nucleoside, is a fixed combination of 1M trifluridine (FTD;  $\alpha,\alpha,\alpha$ -trifluorothymidine) and 0.5 M tipiracil hydrochloride (TPI; 5-chloro-6-[(2-iminopyrrolidin-1-yl)methyl]pyrimidine-2,4-(1H,3H)-dione monohydrochloride). FTD, an antineoplastic antimetabolite, is a thymidylate synthase inhibitor. TPI is a specific inhibitor of TPase that inhibits the metabolism of FTD in the intestinal tract and liver. When orally administered, FTD is rapidly degraded to an inactive form, 5-trifluoromethyluracil or 5-trifluoromethyl-2,4(1H,3H)-pyrimidinedione (FTY) by thymidine phosphorylase (TPase), which is present in gastrointestinal tract, liver, and tumor tissue. Co-administration of TPI, which inhibits TPase, with FTD prevents the rapid degradation of FTD in the body. Following uptake into cancer cells, FTD is phosphorylated by thymidine kinase, further metabolized in cells to a DNA substrate, and incorporated directly into DNA, thereby interfering with DNA function to prevent cell proliferation.

### 4.4.2 Pharmacodynamics

#### **Cardiac Electrophysiology**

TAS-102 at 35 mg/m<sup>2</sup> (based on trifluridine component) administered twice daily had no clinically relevant effect on QT/QT<sub>c</sub> prolongation in patients with cancer.

### 4.4.3 Pharmacokinetics

For a complete review, please refer to Drs. Xianhua Cao and Jungyu Yu's review. TAS-102 consists of an antineoplastic thymidine-based nucleoside analogue, trifluridine, and the thymidine phosphorylase inhibitor, tipiracil, at a molar ratio 1:0.5 (weight ratio, 1:0.471). Following uptake into cancer cells, trifluridine is phosphorylated by thymidine kinase, further metabolized in cells to a DNA substrate, and incorporated directly into DNA, thereby interfering with DNA function to prevent cell proliferation. However, trifluridine is rapidly degraded by thymidine phosphorylase (TPase) and readily metabolized by a first-pass effect following oral administration, hence the inclusion of the thymidine phosphorylase inhibitor, tipiracil.

In nonclinical studies, trifluridine/tipiracil demonstrated antitumor activity against both 5-fluorouracil (5-FU) sensitive and resistant colorectal cancer cell lines. The cytotoxic activity of trifluridine/tipiracil against several human tumor xenografts correlated highly with the amount of trifluridine incorporated into DNA, confirming this as the primary mechanism of action.

The dosing levels ranged from 50 to 180 mg/m<sup>2</sup>/day in the U.S. trials and from 30 to 70 mg/m<sup>2</sup>/day in the trial conducted in Japan. The half-life of FTD was approximately 2 hours, and depends on whether or not TPI is present. After administration of TAS-102 35 mg/m<sup>2</sup> twice daily, the mean elimination half-life ( $t_{1/2}$ ) of trifluridine was 1.4 hours and of tipiracil was 2.1 hours after a single dose. The  $t_{1/2}$  at steady state of trifluridine was 2.1 hours and of tipiracil was 2.4 hours. Both the maximum observed plasma concentration ( $C_{max}$ ) and the area under the plasma concentration-time curve (AUC) of FTD tended to increase after repeated administration to 2- to 3-fold higher than after initial dosing of TAS-102. After twice daily dosing of TAS-102, 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<sup>2</sup>. The accumulation of trifluridine was 3-fold for AUC<sub>0-last</sub> and 2-fold for peak plasma concentration ( $C_{max}$ ) at steady-state while no accumulation was observed for tipiracil. Administration of a single dose of TAS-102 containing tipiracil and trifluridine 35 mg/m<sup>2</sup> increased the mean AUC<sub>0-last</sub> of trifluridine by 37-fold and  $C_{max}$  by 22-fold with reduced variability compared to trifluridine 35 mg/m<sup>2</sup> alone. The mechanism for accumulation of FTD has not been clarified.

No pharmacokinetic drug-drug interaction studies have been conducted with TAS-102. Trifluridine is a substrate of thymidine phosphorylase, and is not metabolized by cytochrome P450 (CYP) enzymes. Tipiracil is not metabolized in either human liver or hepatocytes. *In vitro* studies indicated that trifluridine, tipiracil, and FTY did not inhibit the CYP enzymes and had no inductive effect on CYP1A2, CYP2B6 or CYP3A4/5. *In vitro* studies indicated that trifluridine was not an inhibitor of or substrate for human uptake and efflux transporters.

No dedicated clinical studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of TAS-102. No dose adjustment is recommended for patients with mild hepatic impairment: total bilirubin (TB) less than or equal to the upper limit of normal (ULN) and AST greater than ULN or TB less than 1 to 1.5 times ULN and any AST. Patients with moderate (TB greater than 1.5 to 3 times ULN and any AST) or severe (TB greater than 3 times ULN and any AST) hepatic impairment were not enrolled in RECOURSE.

No dedicated clinical studies have been conducted to evaluate the effect of renal impairment on the pharmacokinetics of TAS-102. In RECOURSE, patients with moderate renal impairment (CL<sub>Cr</sub> = 30 to 59 mL/min, n= 47) had a higher incidence (difference of at least 5%) of ≥ Grade 3 adverse events, serious adverse events, and dose delays and reductions compared to patients with normal renal function (CL<sub>Cr</sub> ≥ 90 mL/min, n= 306) or patients with mild renal impairment (CL<sub>Cr</sub> = 60 to 89 mL/min, n= 178). No dose adjustment to the starting dose of TAS-102 is recommended in patients with mild or moderate renal impairment (CL<sub>Cr</sub> of 30 to 89 mL/min); however patients with moderate renal impairment may require more frequent dose modification for

increased toxicity. No patients with severe renal impairment (CL<sub>cr</sub> <30 mL/min) were enrolled in RECURSE.

### **Absorption**

Following a single oral administration of TAS-102 at 35 mg/m<sup>2</sup> in patients with cancer, the mean time to peak plasma concentration (T<sub>max</sub>) of trifluridine was around 2 hours. A standardized high-fat, high-calorie meal decreased trifluridine C<sub>max</sub>, tipiracil C<sub>max</sub> and AUC by approximately 40%, but did not change trifluridine AUC compared to those in a fasting state in patients with cancer following a single dose of TAS-102 at 35 mg/m<sup>2</sup>.

### **Distribution**

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

### **Elimination**

#### ***Metabolism***

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

#### ***Excretion***

Following a single dose of TAS-102 at 60 mg, the mean 48-hour cumulative urinary excretion was 1.5 % for unchanged trifluridine, 19.2 % for FTY, and 29.3% for unchanged tipiracil.

## **5 Sources of Clinical Data**

### **5.1 Tables of Studies/Clinical Trials**

One adequate and well controlled trial was submitted in the NDA (RECURSE). A second trial was used to provide supportive evidence of efficacy (J003-10040030). Refer to Section 7 below regarding studies used to support safety. The trials used in support of this NDA application are in Table 6.

Table 6: Listing of clinical trials and role in review

Study Design	Study Name	Function
Randomized, placebo-controlled, double-blind	<b>TPU-TAS-102-301</b> <b>(“RECOURSE”)</b>	<b>Pivotal</b>
	J003-10040030 (Japan Phase 2)	
Open-label	J001-10040010 (Dose escalation; Japan Phase 1)	Supportive
	J004-10040040 (Food-Effect; Japan Phase 1)	
	TPU-TAS-102-101 (Dose escalation; US Phase 1)	
	TPU-TAS-102-102 (TPI PK contribution; US Phase 1)	
	TPU-TAS-102-103 (QTc; US/UK Phase 1)	
	TPU-TAS-102-104 (Bioavailability; US Phase 1)	

## 5.2 Review Strategy

The review of efficacy will primarily be based on the evaluation of the pivotal trial, **RECOURSE**: 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. The trial analyzed efficacy data using the intent-to-treat (ITT) population, which included all randomized patients.

The safety analyses were performed using the as-treated (AT) analysis population. This population includes all patients who took part of any dose of the study medication. All analyses using this population are based on the treatment actually received.

The results of RECOURSE were supported by a randomized phase 2 trial in patients with colorectal cancer in Japan (Study J003/10040030).

Datasets were submitted from legacy studies, with the focus on pivotal trial RECOURSE and Study J003/10040030. Signals were similar across all groups (see Table 13), including patients with metastatic CRC who received at least one dose of the study drug at the recommended dose of 35 mg/m<sup>2</sup> BID for 5 days a week with 2 days rest for 2 weeks followed by a 14-day rest (1 treatment cycle). Safety analysis will be explored based on analysis of integrated safety data from the 2 randomized placebo-controlled studies (called “Safety Data Group 2), which consisted of 646 patients receiving TAS-102 and 322 patients receiving placebo. Integrated safety data from the larger group of

761 CRC patients receiving this dosage of TAS-102 (called "Safety Data Group 1") confirmed the safety profile observed for Safety Data Group 2.

### 5.3 Discussion of Individual Studies/Clinical Trials

**5.3.1 RECURSE** 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.

The following protocol synopsis is based on the latest version of the protocol, Amendment #4.

#### **Study Design**

RECURSE was a multinational, double-blind, two-arm, parallel, randomized study evaluating the efficacy and safety of TAS-102 versus placebo in patients with refractory metastatic CRC. Patients were randomly assigned (2:1) to TAS-102 (experimental arm) or placebo (control arm).

Treatment assignment was performed centrally using a dynamic allocation method (biased coin) via an Interactive Voice/Web Response System (IXRS) stratified by:

- KRAS gene type (wild, mutant)
- Time since diagnosis of first metastasis (<18 months, ≥18 months)
- Geographical region (Region 1: Asia [Japan]; Region 2: Western [U.S. and Europe])

Patients were treated until disease progression, unacceptable adverse events, or irreversible treatment-related Grade 4 clinically relevant non-hematologic event. Patients were followed for tumor response until radiologic disease progression or initiation of new anticancer therapy and for survival up until 1 year after the last patient was randomized or target number of events was met.

#### **Objectives**

The **primary objective** was to demonstrate improvement in overall survival with TAS-102 and BSC in comparison to placebo and BSC in patients with refractory metastatic CRC.

**Secondary objectives** were determination of progression-free survival, safety, and tolerability endpoints.

**Inclusion and Exclusion Criteria** (copied from the protocol with modifications for brevity)

#### ***Inclusion criteria***

- Age ≥ 18 years old
- Histologically or cytologically confirmed adenocarcinoma of the colon or rectum

- KRAS status must have been determined (mutant or wild)
- ECOG performance status 0-1
- Measurable or non-measurable metastatic lesions by RECIST v1.1
- Organ function as defined by the following laboratory values obtained within 7 days prior to study drug administration on Day 1 of Cycle 1:
  - Hemoglobin value of  $\geq 9.0$  g/dL
  - Absolute neutrophil count of  $\geq 1,500/\text{mm}^3$  ( $\geq 1.5 \times 10^9/\text{L}$  by International Units [IU])
  - Platelet count  $\geq 100,000/\text{mm}^3$  (IU:  $\geq 100 \times 10^9/\text{L}$ )
  - Total serum bilirubin of  $\leq 1.5$  mg/dL (except for Grade 1 hyperbilirubinemia due solely to a medical diagnosis of Gilbert's syndrome)
  - Aspartate aminotransferase (AST/SGOT) and alanine aminotransferase (ALT/SGPT)  $\leq 3.0 \times$  upper limit of normal (ULN); if liver function abnormalities are due to underlying liver metastasis, AST and ALT  $\leq 5 \times$  ULN
  - Serum creatinine of  $\leq 1.5$  mg/dL

#### **Exclusion criteria**

- Brain or leptomeningeal metastases
- Other concurrently active malignancies excluding malignancies that are disease free  $> 5$  years or carcinoma-*in-situ* deemed cured by adequate treatment
- Ascites, pleural effusion or pericardial fluid requiring drainage in last 4 weeks
- Intestinal obstruction, pulmonary fibrosis, renal failure, liver failure, or cerebrovascular disorder
- Myocardial infarction within the last 12 months, severe/unstable angina, symptomatic congestive heart failure New York Heart Association (NYHA) class III or IV
- Patients with autoimmune disorders or history of organ transplantation who require immunosuppressive therapy
- Major surgery within prior 4 weeks (the surgical incision should be fully healed prior to study drug administration)
- Any anticancer therapy within prior 3 weeks (except for bevacizumab within prior 4 weeks)
- Extended field radiation within prior 4 weeks or limited field radiation within prior 2 weeks
- Any investigational agent received within prior 4 weeks
- Has unresolved toxicity of greater than or equal to CTCAE Grade 2 attributed to any prior therapies (excluding anemia, alopecia, skin pigmentation, and platinum-induced neurotoxicity)
- Pregnant or lactating

#### **Treatment Plan**

Trial medication (35 mg/m<sup>2</sup>/dose of TAS-102 or placebo) was administered orally twice daily on Days 1 through 5, with the first dose administered in the morning of Day 1 of

each cycle and the last dose administered in the evening of Day 5, followed by a recovery period from Day 6 through Day 7. TAS-102 or placebo was administered orally twice daily on Days 8 through 12, with the first dose administered in the morning of Day 8 of each cycle and the last dose administered in the evening of Day 12, followed by a recovery period from Day 13 through Day 28. Each cycle was 28 days.

### **Dose adjustments/modifications**

Table 7 summarizes the planned dose level modifications for RECURSE. There were to be no dose reductions below 20mg/m<sup>2</sup> po BID.

Table 7: Dose level modifications

Dose reduction level	Dose given po BID
-1	30 mg/m <sup>2</sup>
-2	25
-3	20

Table 8 summarizes the non-hematological toxicity dosing modifications for RECURSE.

Table 8: TAS-102 or placebo dosing modification for non-hematologic drug-related toxicities (modified from submission)

Grade	Dose Hold/Resumption within a 28-day Treatment Cycle	Dose Adjustment for Next Cycle
Grade ≤ 2		
Any occurrence	Maintain at same level	None
Grade ≥ 3 (except nausea/vomiting)		
1 <sup>st</sup> , 2 <sup>nd</sup> , or 3 <sup>rd</sup> occurrence	Suspend until Grade ≤ 1	Reduce by 1 dose level from previous level
4 <sup>th</sup> occurrence	Discontinue	Discontinue

Table 9 summarizes the hematological toxicity dosing modifications for RECURSE.

Table 9: TAS-102 or placebo dosing modification for hematologic drug-related toxicities (modified from submission)

Parameter	Hold Criteria		Resumption Criteria
	Conventional Units	International System (IS) units	
Neutrophil	< 500/mm <sup>3</sup>	< 0.5 x 10 <sup>9</sup> /L	≥ 1500/mm <sup>3</sup> (IU: ≥ 1.5 x 10 <sup>9</sup> /L)
Platelets	< 50,000/mm <sup>3</sup>	< 50 x 10 <sup>9</sup> /L	≥ 75,000/mm <sup>3</sup> (IU: ≥ 75 x 10 <sup>9</sup> /L)

Uncomplicated neutropenia or thrombocytopenia  $\leq$  Grade 3 did not require a reduction in the dose of study medication. Uncomplicated Grade 4 neutropenia or thrombocytopenia that resulted in a  $>1$  week delay of the start of the next cycle initiated the next cycle at one reduced dose level. If the delay was  $\leq 1$  week, the patient started the next cycle at the same dose level.

### **Efficacy Assessments**

Patients were evaluated for efficacy, including OS, PFS, and ORR. Tumor assessments were performed based on Response Evaluation Criteria in Solid Tumors (RECIST). Computed tomography (CT) scans were performed every 8 weeks.

### **Safety Monitoring**

Safety assessments were done at screening including (but not limited to) histological confirmation, KRAS and BRAF status, Eastern Cooperative Oncology Group (ECOG) Performance status (PS), ECG, and screening laboratories. ECGs were repeated during cycle 1 at day 1 and day 12, and then again at end of treatment (EOT) and the 30-day safety follow-up visit. AE/SAE assessments were done at baseline, cycle 1-2 days 1, 12, 15, and at recovery/end of cycle, EOT and the safety follow-up visit. The severity of adverse events was assessed using CTCAE v. 4.03. The schedule of monitoring is listed in Table 10.

Table 10: Study Schedule

Visit ID / Procedure	Baseline Period		On-Treatment Period								End of Treatment/ End of Study Period		
	Baseline Day		CYCLE				SUBSEQUENT CYCLES				End of Treatment	30-Day Safety Follow-up Visit	Survival Follow-up
			Day of Cycle				Day of Cycle						
	-28 to -1	-7 to -1	1	12	15	End of Recover	1	12	15	End of Recovery			
Sign ICF	X												
Enrollment	X												
Randomization			X										
Medical History	X												
Histological Confirmation	X												
KRAS Status	X												
BRAF Status	X												
Physical Examination		X					X				X	X	
Baseline Signs & Symptoms	X												
ECG	X		X	X							X	X	
Height		X											
Vital Signs & Weight		X					X				X	X	
ECOG Performance Status	X		X				X				X	X	
Hematology		X			X		X		X		X	X	
Serum Chemistry		X			X		X		X		X	X	
Urinalysis		X									X	X	
Pregnancy Test		X											
PK Blood Sampling				X									
Chest X-ray (optional)	X												
Tumor Measurements	X									X	X		X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X
AE/SAE Assessment	X	X	X	X	X	X	X	X	X	X	X	X	
TAS-102 or Placebo Treatment			X (D 1-5)	X (D 8-12)			X (D 1-5)	X (D 8-12)					
Survival Status			X	X	X	X	X	X	X	X	X	X	X

### **Statistical Considerations**

The safety and efficacy study populations were defined by the applicant as follows:

- Intent-to-Treat (ITT) population: This population included all randomized patients and was the primary population for all efficacy parameters. All analyses using this population were based on the treatment assigned by randomization.
- Tumor Response (TR) evaluable population: This population included all patients in the ITT population with measurable disease (at least one target lesion) at baseline and with at least one tumor evaluation while on treatment. Patients who have disease progression or have a cancer related death prior to their 1st tumor evaluation were considered evaluable. All analyses using this population were based on the treatment assigned by randomization.
- As-Treated (AT) population: This population included all patients who took part of any dose of the study treatment. This population was used for safety analyses. All analyses using this population were based on the treatment actually received.
- Pharmacokinetic (PK) population: This population included patients at selected sites participating in the PK assessment who had evaluable plasma measurements with no significant protocol deviations that may impact the data.

Overall survival (OS) was the primary endpoint of this study and was defined as the time (in months) from the date of randomization to the death date. In the absence of death confirmation or for patients alive as of the OS cut-off date, survival time was censored at the date of last study follow-up, or the cut-off date. The OS cut-off date used for the primary analysis was based on the observations of the 571st death in the study.

Progression free survival (PFS) was defined as the time (in months) from the date of randomization until the date of the investigator-assessed radiological disease progression or death due to any cause. Patients who were alive with no disease progression as of the analysis cut-off date were censored at the date of the last tumor assessment. Patients who received non-study cancer treatment before disease progression, or patients with clinical but not radiologic evidence of progression were censored at the date of the last evaluable tumor assessment before the non-study cancer treatment was initiated.

The assessment of overall response rate (ORR) was based on Investigator review of the images. ORR was defined as the proportion of patients with objective evidence of complete response (CR) or partial response (PR). At the analysis stage, the best overall response was assigned for each patient as the best response recorded from all responses recorded after study randomization. When applicable, responses recorded after disease progression or initiation of non-study cancer treatment were excluded. A patient's best response assignment of stable disease (SD) needed to be maintained for at least 6 weeks after study randomization.

Duration of response was derived for those patients with objective evidence of PR or CR. DR was defined as the time from the first documentation of response (CR or PR) to the first documentation of objective tumor progression or to death due to any cause. Patients alive and progression free as of the analysis cut-off date were censored at their last evaluable tumor response assessment prior to initiation of any non-study cancer treatment.

A target of 571 deaths were required to detect a treatment effect (hazard ratio) of 0.75 with 90% power and a 1-sided type 1 error rate of 0.025. Based on these assumptions, the goal was to randomize 800 patients assuming a variable accrual period of 18 months and a 3% per year loss to survival follow-up. No interim analyses were planned.

The primary analysis of OS included follow-up data (including death events) through the date of the 571st death. The difference in survival between the two treatment arms was assessed in the ITT population using the stratified log-rank test (Score statistic from PHREG and ties=Breslow) from a Cox proportional hazards (CPH) model including treatment and the 3 stratification factors in the model. Survival for each arm was summarized using Kaplan Meier curves and was further characterized by the applicant in terms of the median and survival probability at 3, 6, 9 and 12 months, along with the corresponding 2-sided 95% confidence intervals for the estimates. Confidence intervals for median survival were based upon the methods of Brookmeyer and Crowley.

Comparisons for all secondary endpoints were made at the 2-sided 0.05 significance level. OS was assumed to demonstrate significance at the 1-sided 0.025 level, such that PFS was subsequently tested at the 1-sided 0.025 level. ORR and disease control rate (DCR=CR+PR+SD) was compared between treatment arms using Fisher's Exact test in the subset of patients in the ITT population with measurable disease at baseline (the tumor response [TR] population). ORR was defined as the proportion of patients with objective evidence of CR or PR. Treatment estimates and differences were presented along with the associated 2-sided 95% confidence intervals constructed using the Clopper-Pearson approximation.

Table 11 lists the amendments for RECURSE with clinical changes.

Table 11: RECURSE Amendments

Amendment	Date	Clinical changes noted
1	28 March 2012	<ol style="list-style-type: none"> <li>Added an exclusion criterion regarding concomitant medical conditions</li> <li>Added inclusion criteria exception of serum bilirubin <math>\geq 1.5</math> mg/dL in Gilbert's syndrome</li> <li>Added exclusion criteria for patients with autoimmune disorders or history of organ transplantation who required immunosuppressive therapy</li> <li>Added that the best overall response as per RECIST Criteria (version 1.1, 2009) is the best response recorded from the start of the study treatment until the end of treatment</li> </ol>
2	22 April 2012	<ol style="list-style-type: none"> <li>Addition of mobile phone number of Medical Monitor for Japan.</li> <li>Removal of carbon dioxide from required serum chemistry tests.</li> </ol>
3	13 November 2012	<ol style="list-style-type: none"> <li>Modification of exclusion criterion regarding unresolved toxicities associated with prior therapies</li> <li>Addition of a caution statement when using human thymidine analogues concomitantly with TAS-102</li> <li>Addition of generic name and updated chemical name for TPI</li> <li>Clarification of timing of end of treatment assessments of ECG, urinalysis, and tumor measurements.</li> </ol>
4	01 April 2014	As outlined in this NDA

The Japanese trial (**Study J003/10040030**) was a phase 2, randomized (2:1), double-blind, placebo-controlled trial of patients with chemotherapy refractory advanced colorectal cancer who progressed or failed to respond to more than two chemotherapeutic regimens including a fluoropyrimidine, irinotecan, and oxaliplatin. TAS-102 was administered at a dose of 70 mg/m<sup>2</sup>/day (35 mg/m<sup>2</sup>/dose twice daily) for 5 consecutive days with 2 days rest weekly for 2 weeks followed by a 2-week recovery period. Patients in the placebo arm received BSC. Eligibility criteria were similar to RECURSE with the exception of inclusion only of patients age  $\geq 20$  years old, and allowing inclusion of ECOG PS of 2 on J003/10040030. Patients were risk stratified according to PS (0, 1/2). The primary endpoint was OS and designed with the Full Analysis Set (FAS) as 102 patients in the TAS-102 group and 51 patients in the placebo group, for a total of 153 patients, with a one-sided alpha of 0.10 and a test power of

80%. The investigational drug continued until any of the “Discontinuation standards for administration of the study drug.” AEs were assessed with CTCAE Ver. 3.0 Japanese translation JCOG/JSCO edition. AEs were recorded as events that developed up to the post-treatment observation/follow-up period (30 days after administration of the investigational drug is completed).

## 6 Review of Efficacy

### **Efficacy Summary**

Evidence of the effectiveness of TAS-102 for the treatment of patients with refractory metastatic colorectal cancer is derived from one adequate and well controlled trial and a single randomized and controlled supportive study.

The review of efficacy will primarily be based on the evaluation of the pivotal trial, **RECOURSE**: 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.

RECOURSE was an open label, multinational, double-blind, two-arm, parallel group, randomized trial in patients with metastatic CRC who were previously treated with a fluoropyrimidine, oxaliplatin, irinotecan, and monoclonal anti-VEGF and anti-EGFR antibodies (if the patient’s tumor was KRAS wild-type). A total of 800 patients were randomized (2:1) to receive TAS-102 or placebo at a total of 101 study sites in 13 countries. Patients were stratified by KRAS status (wild-type, mutant), time since diagnosis of metastasis (<18 months, ≥18 months), and geographic region (Region 1: Asia [Japan]; Region 2: Western [Australia, Europe, U.S.]). Patients received TAS-102 35 mg/m<sup>2</sup>/dose or placebo based on body surface area (BSA), administered orally twice daily (BID) after morning and evening meals for 5 days a week with 2 days rest for 2 weeks, followed by a 14-day rest interval (1 treatment cycle), repeated every 4 weeks.

Treatment continued until disease progression or unacceptable toxicity. Safety assessments, including monitoring of adverse events (AEs), physical examination, vital signs, ECOG performance status, 12-lead ECG and clinical laboratory evaluations were performed from the time of signed informed consent through 30 days after the last dose of study medication or until the start of new antitumor therapy (whichever was earlier). Tumor assessments were performed every 8 weeks during study treatment using Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1, 2009). After the end of treatment, all patients were followed for survival at scheduled 8-week intervals until death.

The primary endpoint was overall survival (OS) based on data collected as of the date of the 571st death observed in the study. The study was designed to detect with 90% power an OS hazard ratio of 0.75 (25% risk reduction) for TAS-102 compared to

placebo with a 1-sided type I error of 0.025. The key secondary endpoints were progression-free survival (PFS), safety and tolerability. Other protocol-defined secondary efficacy endpoints included: time to treatment failure (TTF), overall response rate (ORR), disease control rate (DCR) and duration of response (DR). In addition, an analysis of time to ECOG performance status (PS) of 2 or higher was described in the statistical analysis plan.

In RECURSE, demographic and baseline characteristics were comparable for the two treatment groups. In the intent-to-treat (ITT) population, median age was 63.0 years, 61% of patients were men, 57% were White and 34% were Asian; all patients had a baseline ECOG performance status of 0 or 1. The primary site of disease was colon for 63% of patients, and rectum for 37% of patients. Fifty-one percent of patients had tumors reported by investigators as KRAS mutant. The majority of patients (60%) had received  $\geq 4$  prior systemic cancer therapies.

As of the cutoff date for non-survival data, the mean duration of treatment was 12.7 weeks for patients in the TAS-102 group and 6.8 weeks for patients in placebo group. A total of 574 deaths were included in the primary analysis of OS based on a date cutoff date of 24 January 2014 (4 patients died [REDACTED] (b) (4)). Among patients with censored survival data, the median follow-up for OS was 8.29 months (range: 1.8 to 19.0 months). The overall median follow-up for all patients was 11.8 months. The median OS was 7.1 months for the TAS-102 group versus 5.3 months for the placebo group with a hazard ratio (HR) of 0.68 (95% confidence interval [CI]: 0.58, 0.81), and 2-sided  $p < 0.0001$  (stratified log-rank test). The percentage of patients surviving at 1 year was 26.6% in the TAS-102 group and 17.6% in the placebo group. The effect on OS was generally consistent across all randomization strata and pre-specified subgroups (although subgroups were pre-specified, alpha was not allocated for these analyses). In an exploratory multivariate Cox regression analysis, none of the pre-specified factors were identified by the applicant as predictive, with all treatment interaction p-values being more than 0.20.

Results for PFS supported the OS results with a statistically significant improvement for TAS-102 compared to placebo (HR=0.48, 95% CI: 0.41-0.57,  $p < 0.0001$ ); median PFS was 2.0 months for the TAS-102 group versus 1.7 months for the placebo group. The absolute magnitude of the effect at the median was small; however, the curves appeared to separate after median PFS was reached. The effect of increased PFS was generally consistent across randomization strata and pre-specified subgroups. Results obtained for other secondary efficacy endpoints (TTF, ORR, DCR and DR) were also supportive. In an exploratory analysis, time to worsening of ECOG PS to  $\geq 2$  was longer in the TAS-102 group compared to the placebo group (HR=0.66, 95% CI: [0.56, 0.78],  $p < 0.0001$ ).

In summary, the addition of TAS-102 resulted in a clinically meaningful and statistically significant improvement in the primary endpoint of OS compared to placebo.

Supportive study **J003-10040030** was a randomized, double-blind, placebo-controlled, multicenter study evaluating the efficacy and safety of TAS-102 versus placebo in patients with metastatic CRC who had progressed on or following two or more chemotherapeutic regimens including fluoropyrimidine, irinotecan, and oxaliplatin. One hundred and seventy-two (172) patients were randomized (2:1) to receive TAS-102 (35 mg/m<sup>2</sup>/dose) given orally twice daily for 5 days a week with 2 days rest for 2 weeks, repeated every 4 weeks; or placebo. Patients were stratified by baseline ECOG performance status (PS=0, PS=1 or 2).

Tumor assessments were performed every 4 weeks for the first 12 weeks of study treatment and thereafter every 8 weeks during study treatment. Tumor response was assessed by an independent review committee according to RECIST, version 1.0, as well as by investigators. After the end of treatment, patients were followed for survival at scheduled 12-week intervals until death.

The primary endpoint was overall survival. Secondary endpoints included ORR, duration of response, DCR, PFS, and TTF; safety and tolerability of TAS-102; relationship between effect of TAS-102 and KRAS gene status. The primary analysis of OS by the applicant was based on the full analysis set (FAS), i.e., all patients who received at least one dose of investigational drug and had at least one post-baseline efficacy assessment. A target sample size of 162 patients was required to detect with 80% power an expected hazard ratio of 0.67 for TAS-102 compared to placebo with a one-sided significance level of 10%. The cutoff date for analysis of OS was 04 February 2011 (event driven as the date of confirmation of 121<sup>st</sup> event required for OS analysis). The data cut-off for other analyses of efficacy and safety was 13 April 2011.

Per the clinical efficacy summary, a total of 172 patients were randomized; study drug was administered to 170 patients (113, TAS-102; 57, placebo) and 2 patients were discontinued before treatment with study drug. One treated patient was not eligible; therefore, the FAS consisted of 169 patients (112, TAS-102; 57, placebo). Patient characteristics and prior cancer therapies were comparable for the two treatment groups. In the FAS population, median age was 63.0 years in the TAS-102 group and 62.0 years in the placebo group; 54.4% of patients were men; 63.3% had baseline PS=0, 34.3% had baseline PS=1, and 2.4% had baseline PS=2. The primary site of disease was colon for 58.6% of patients, and rectum for 41.4% of patients. The KRAS gene status was confirmed for 99 of 112 patients in the TAS-102 group, of which 54 (54.5%) were wild-type and 45 (45.5%) were mutant; and 50 of 57 patients in the placebo group, of which 24 (48.0%) were wild-type and 26 (52.0%) were mutant. Eighty-two percent (82%) of patients had received  $\geq 3$  prior chemotherapy regimens.

At the cutoff date for OS analysis, 75 patients in the TAS-102 group and 48 patients in the placebo group had died. Median OS was 9.0 months in the TAS-102 group and 6.6 months in the placebo group (HR=0.56; 95% CI: [0.39, 0.81]; p = 0.0011). The effect of

TAS-102 on OS was consistent across pre-specified subgroup analyses. Median PFS assessed by independent review committee was 2.0 months in the TAS-102 group compared with 1.0 month in the placebo group (HR=0.41; 95% CI: [0.28, 0.59];  $p < 0.0001$ , stratified log-rank test). Median PFS assessed by investigators was 2.7 months in the TAS-102 group compared with 1.0 month in the placebo group (HR=0.34; 95% CI: [0.24, 0.49];  $p < 0.0001$ , stratified log-rank test). For the best tumor response assessed by independent review committee, ORR was 0.9% (1/112) in the TAS-102 group and 0.0% (0/57) in the placebo group. The protocols were overall well conducted, and protocol violations were minimal and did not impact the integrity of the data.

The efficacy results obtained in the pivotal Phase 3 study (RECOURSE) and the supportive Phase 2 study (J003-10040030) were consistent in demonstrating a statistically significant risk reduction and clinically meaningful impact in patients on treatment with TAS-102 compared to placebo in regards to OS. The two study populations were generally comparable with respect to baseline demographic and disease characteristics except that all patients enrolled in Study J003-10040030 were Asian.

## 6.1 Indication

The proposed indication is for treatment of patients with metastatic CRC who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if <sup>(b)</sup><sub>(4)</sub>RAS wild type, an anti-EGFR therapy.

### 6.1.1 Methods

Evidence of the effectiveness of TAS-102 for the treatment of patients with refractory metastatic colorectal cancer is derived from a Phase 3 pivotal study and a Phase 2 supportive study.

### 6.1.2 Demographics

The first patient was randomized on 17 June 2012. The study data cut-off date was 31 January 2014; 571 patients had died at the time of data cut-off.

A total of 1002 patients were screened for this study, and 202 (20%) patients were considered screening failures and consequently were not randomized. The screening failures did not meet eligibility criteria and were not randomized.

Eight hundred patients from 101 sites in 13 countries (U.S., Sweden, Japan, Italy, Ireland, Great Britain, France, Spain, Germany, Czech Republic, Belgium, Austria, and Australia) were randomized in the RECOURSE study. Japan had the highest number of subjects enrolled (267, 33% of subjects randomized), with a male predominance. There

Clinical Review

Leigh Marcus

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TAS-102 (Lonsurf) for the treatment of patients with metastatic colorectal cancer

were 534 (67%) patients randomized to the TAS-102 arm and 266 (33%) patients randomized to the placebo arm. Of the 800 patients, 2 patients (1, TAS-102; 1, placebo) did not receive study medication. Patient 202-006 (TAS-102 group) discontinued prior to receiving treatment due to ascites; Patient 312-002 (placebo group) was found to be ineligible for the study (entry criteria for serum bilirubin not met).

Patient demographic characteristics were balanced between the two treatment arms (Table 12). Median age at randomization was 63 years in both arms, and the mean was 62. The majority of the patients were men (61% and 62% in the TAS-102 and placebo arms respectively) and White (62% and 61% in the TAS-102 and placebo arms respectively). Black subjects were under-represented in the trial (1% and 2% in the TAS-102 and placebo arms respectively) as compared to the proportion of Black patients with CRC in the U.S. The treatment groups were well balanced (2:1) with respect to KRAS status, time since diagnosis of metastasis, geographic region, and ECOG performance status. More patients had colon cancer than rectal cancer.

Table 12 summarizes the patient demographics and baseline disease characteristics in the ITT population for RECURSE:

Table 12: RECURSE Demographics and Baseline Disease Characteristics in ITT population

	<b>TAS-102 N=534 (%)</b>	<b>Placebo N=266 (%)</b>
<b>Age</b>		
Median age (range)	63 (27-82)	63 (27-82)
Mean age (±SD)	62 (10)	62 (11)
Age ≥ 65	234 (44)	118 (44)
Age ≥ 75	36 (7)	24 (9)
<b>Gender</b>		
Male	326 (61)	165 (62)
Female	208 (39)	101 (38)
<b>Race</b>		
White	306 (57)	155 (58)
Black	4 (1)	5 (2)
Asian	184 (34)	94 (35)
Not collected	40 (7)	12 (5)
<b>Geographic Region</b>		
Region 1 (Japan)	178 (33)	88 (33)
Region 2 (U.S./Europe)	356 (67)	178 (67)
<b>KRAS gene type</b>		
Wild	262 (49)	131 (49)
Mutant	272 (51)	135 (51)
<b>Time since diagnosis of first metastasis</b>		

	<b>TAS-102 N=534 (%)</b>	<b>Placebo N=266 (%)</b>
< 18 months	111 (21)	55 (21)
≥ 18 months	423 (79)	211 (79)
<b>ECOG PS</b>		
0	301 (56)	147 (55)
1	233 (44)	119 (45)
<b>Location</b>		
Colon	338 (63)	161 (61)
Rectum	196 (37)	105 (39)

Demographics were analyzed using the analysis dataset for subject level (ADSL), which included subject disposition, demographic and baseline characteristics. Data was subset for treatment arm.

To be eligible for RECURSE, subjects must have been treated with at least 2 prior regimens of standard chemotherapies including fluoropyrimidines, irinotecan and oxaliplatin, an anti-VEGF monoclonal antibody (bevacizumab), and at least one of the anti-EGFR monoclonal antibodies (cetuximab or panitumumab) for KRAS wild-type patients. The majority of the patients (61%) had received ≥ 4 prior systemic regimens. All but 1 patient received bevacizumab as prior therapy. Table 13 describes details of prior therapy in the ITT population for RECURSE. The two groups were balanced with respect to prior therapies. Of note, regorafenib was FDA approved after >80% study enrollment was complete. There were 83 (16%) subjects in the TAS-102 arm and 41 (15%) subjects on placebo that went on to treatment with regorafenib after therapy on this trial.

Table 13: Prior Cancer Therapies (ITT population)

	<b>TAS-102 N= 534 (%)</b>	<b>Placebo N= 266 (%)</b>
<b>Number of prior treatment regimens*</b>		
1	0	0
2	95 (18)	45 (17)
3	119 (22)	54 (20)
≥ 4	320 (60)	167 (63)
<b>Treatment class</b>		
Anti-EGFR therapy (Cetuximab/Panitumumab)	278 (52)	144 (54)
Bevacizumab	534 (100)	265 (>99)
Fluoropyrimidine	534 (100)	266 (100)
Irinotecan	534 (100)	266 (100)
Oxaliplatin	534 (100)	266 (100)
Regorafenib	91 (17)	53 (20)

Prior therapy was analyzed in the ITT population from the analysis dataset concomitant medication (ADCM), and subset by treatment arm. \*Number of prior regimens includes both neoadjuvant and adjuvant.

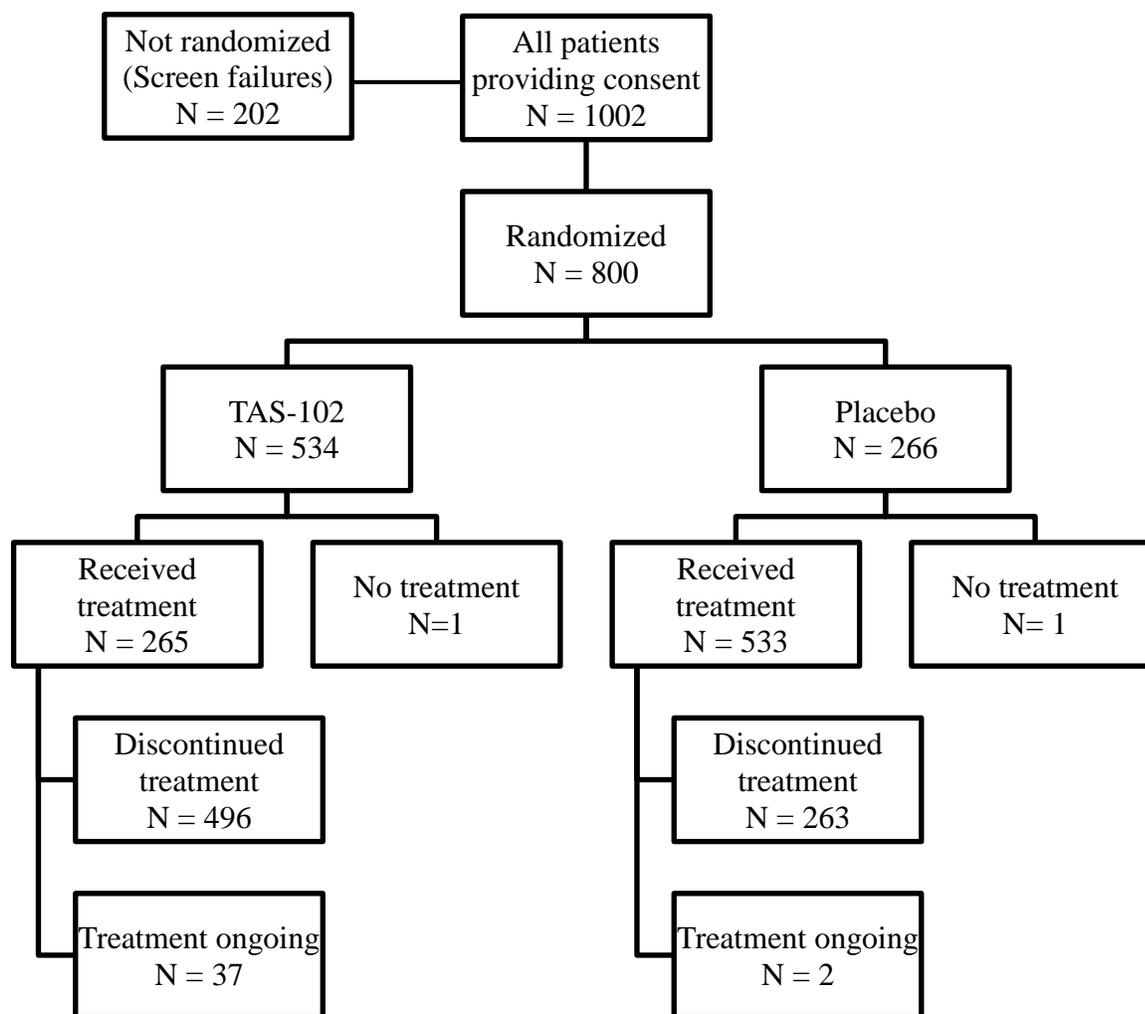
### 6.1.3 Subject Disposition

The first patient was randomized on 17 June 2012. The study data cut-off date was 31 January 2014; 571 patients had died at the time of data cut-off.

A total of 1002 patients were screened for this study, and 202 (20%) patients were considered screening failures and consequently were not randomized. The screening failures did not meet eligibility criteria and were not randomized.

Eight hundred patients from 101 sites in 13 countries were randomized in the RECURSE study; 534 (67%) patients in the TAS-102 arm and 266 (33%) patients in the placebo arm. Of the 800 patients randomized, 2 patients (1, TAS-102; 1, placebo) did not receive study medication. Patient 202-006 (TAS-102 group) discontinued prior to receiving treatment due to ascites; Patient 312-002 (placebo group) was found to be ineligible for the study (entry criteria for serum bilirubin not met). Therefore there were 800 patients in the intent-to-treat population (ITT) and analyzed for efficacy, and 798 patients in the as-treated (AT) population analyzed for safety. The flow diagram for subject disposition is in Figure 1.

Figure 1: Schema of Subject Disposition for RECOURSE



There was only a 2 subject difference between the as treated (AT) safety population and the intent-to-treat (ITT) efficacy population.

Table 14 summarizes the reasons for treatment and study discontinuation based on the ITT population, although the applicant based their assessments of discontinuation in the AT population. There was 1 subject difference in each arm between the ITT and AT datasets, with no clinically meaningful differences.

There were 759 (95%) patients who discontinued study treatment; 496 (93%) in TAS-102 arm and 263 (99%) in the placebo arm. There were 162 patients in the TAS-102 arm (30%) and 51 patients in the placebo arm (19%) who were continuing on study at

the time of data cut-off; 39 (37 patients in the TAS-102 arm and 2 in the placebo arm) were still receiving treatment (or placebo) at the time of data cut off.

There were 2 subjects (405-012, 150-011) with “need for radiotherapy” listed as the reason for discontinuation in the “other” category. There were also subjects (in the “other” category that discontinued due to lack of compliance (608-007) and principle investigator decision (103-002, 400-002, 572-004, 608-009). Table 14 describes the reasons for study and treatment discontinuation. Most of the discontinuations were due to disease progression or death. There were more patients with adverse events leading to discontinuation on the TAS-102 arm (3.6%) as compared to placebo arm (1.5%). In 7.3.3 Dropouts and/or Discontinuations, AE contributed to 10% of discontinuation of TAS-102 and 14% of discontinuation of placebo. The reason for the disagreement is that in the disposition dataset, adverse event/SAE indicated as the “primary reason” for discontinuation of study treatment was based on the treatment discontinuation page of the CRF. This discrepancy is attributable to the fact that AEs that were symptoms of disease progression were assessed as leading to discontinuation of treatment on the AE page of the CRF, while the patient was indicated as having discontinued due to disease progression on the treatment discontinuation page of the CRF.

Table 14: Treatment and study discontinuation for RECURSE as per ITT

	<b>TAS-102 N=534 (%)</b>	<b>Placebo N=266 (%)</b>
<b>Study discontinuation</b>		
Death	367 (69)	211 (79)
Lost to follow-up	3 (<1)	3 (1)
<b>Treatment discontinuation</b>		
Patients who discontinued treatment	496 (93)	263 (99)
Administrative decision	4 (<1)	0
Adverse event	19 (3.6)	4 (1.5)
Death	7 (1)	4 (2)
Disease progression (clinical and radiological progression)	450 (84)	254 (95)
Consent withdrawal	13 (2)	1 (<1)
Other	8 (1.5)	0

Analysis was performed by treatment arm in the disposition dataset.

#### 6.1.4 Analysis of Primary Endpoint(s)

The following section is copied with permission from Dr. Yuan, FDA biostatistical reviewer. Table 15 summarizes the efficacy analysis results of PFS. TAS-102 was shown to prolong OS compared to placebo with p-value < 0.0001 based on a stratified log-rank test stratified by KRAS gene status, time since diagnosis of first metastasis, and

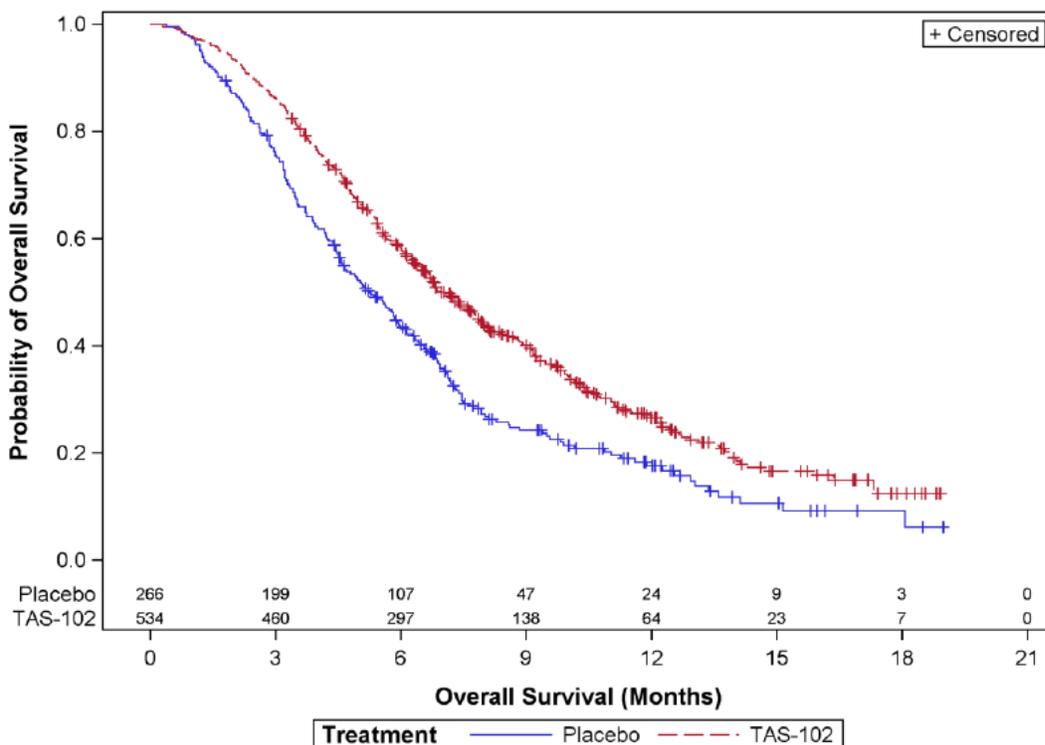
geographical region. The median OS was 7.1 months in the TAS-102 arm and 5.3 months in the placebo arm. The estimated HR was 0.68 with 95% CI (0.58, 0.81) based on a Cox model stratified by KRAS gene status, time since diagnosis of first metastasis, and geographical region.

Table 15: Primary analysis of OS

	<b>TAS-102</b> N = 534	<b>Placebo</b> N = 266
<b>Number of Deaths (%)</b>	364 (68.2%)	210 (78.9%)
<b>Median OS (95% CI)</b>	7.1 (6.5, 7.8)	5.3 (4.6, 6.0)
<b>HR (95% CI)</b>	0.68 (0.58, 0.81)	
<b>p-value</b>	<0.0001	

Figure 2 shows the estimated Kaplan-Meier curves for the distribution of OS.

Figure 2: Kaplan-Meier curves of OS Analysis



The randomization was based on three stratification factors via the IVRS system. A sensitivity analysis was conducted based on the stratification factors captured in the CRFs, and the results were consistent with those of the primary analysis. The statistical

reviewer also conducted other sensitivity analysis, including using an unstratified log-rank test, stratified and unstratified log-rank test based on the as treated population, stratified and unstratified log-rank test based on the actual treatment assignments, and excluding patients who did not meet the inclusion criteria, to check the robustness of the primary analysis results and the sensitivity analysis results were consistent with those of the primary analysis.

#### 6.1.5 Analysis of Secondary Endpoints(s)

For the PFS analysis, a total of 723 patients progressed or died at the time of the primary analysis, of which 472 were in the TAS-102 arm and 251 were in the placebo arm.

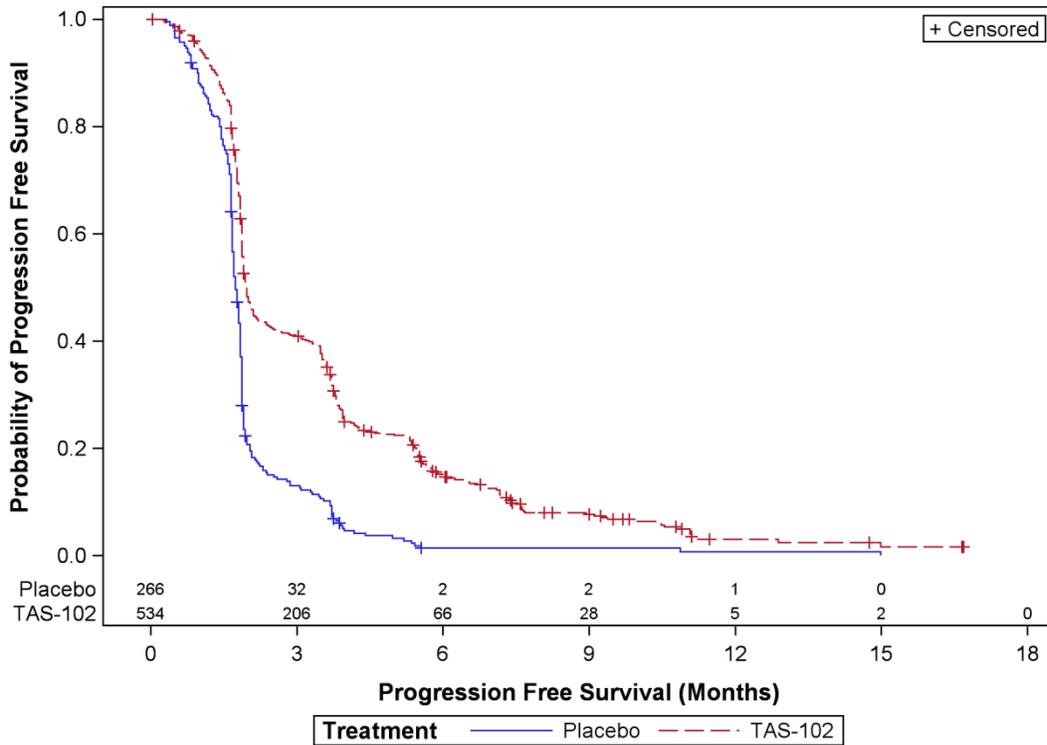
TAS-102 was shown to prolong PFS compared to placebo with p-value < 0.0001 based on a stratified log-rank test stratified by KRAS gene status, time since diagnosis of first metastasis, and geographical region. The median PFS was 2.0 months in the TAS-102 arm and 1.7 months in the placebo arm. The estimated HR was 0.48 with 95% CI (0.41, 0.57) based on a Cox model stratified by KRAS gene status, time since diagnosis of first metastasis, and geographical region. The analysis of PFS is summarized in Table 16.

Table 16: Analysis of PFS

	<b>TAS-102</b> N = 534	<b>Placebo</b> N = 266
<b>Number of Events (%)</b>	472 (88.4%)	251 (94.4%)
<b>Median PFS (95% CI)</b>	2.0 (1.9, 2.1)	1.7 (1.7, 1.8)
<b>HR (95% CI)</b>	0.48 (0.41, 0.57)	
<b>p-value</b>	<0.0001	

Figure 3 shows the estimated Kaplan-Meier curves for the distribution of PFS. Note that the curves separate after the median, so the median difference in PFS is not necessarily the most accurate description of the effect on PFS.

Figure 3: K-M Curves of PFS Analysis



### 6.1.6 Other Endpoints

The ORR is summarized in Table 17.

Table 17: Analyses of ORR

	<b>TAS-102</b> N = 534	<b>Placebo</b> N = 266
<b>ORR (%)</b>	8 (1.5)	1 (0.4)
<b>95%CI of ORR</b>	(0.7, 2.9)	(0.0, 2.1)
<b>CR(%)</b>	0	1 (0.4)
<b>PR(%)</b>	8 (1.5)	0
<b>Difference in ORR (95% CI)</b>	1.1 (-0.1, 2.4)	

Of the 8 responders in the TAS-102 arm, the median duration of response (DoR) was 7.4 months with 95% CI (1.9, 7.5). Among them, 3 had on-going responses at time of the analysis, 4 had radiologic progression, and 1 had clinical progression. The one responder in the placebo arm had a DoR of 13.1 months followed by radiologic progression. The applicant conducted ORR analyses based on the tumor response (TR) population, which contained all patients in the ITT population with measurable disease (at least one target lesion) at baseline and with at least one tumor evaluation while on treatment. There were 760 patients in the TR population, with 502 in the TAS-102 arm and 258 in the placebo arm.

### 6.1.7 Subpopulations

Since no hypotheses were pre-specified in the subgroups presented in this section, all results are considered exploratory. Table 18 summarizes the results of the FDA biostatistics subgroup analysis of the ITT population.

Table 18: Subgroups Analyses of OS: Gender, Age, Race, and Region

<b>Subgroups</b>	<b>Events/N</b>		<b>Median PFS</b>		<b>HR (95% CI)</b>
	<b>TAS-102</b>	<b>Placebo</b>	<b>TAS-102</b>	<b>Placebo</b>	
<b>Male</b>	220/326	128/165	7.3	5.0	0.69 (0.55, 0.87)
<b>Female</b>	144/208	82/101	6.8	5.6	0.68 (0.51, 0.90)
<b>Age &lt; 65</b>	203/300	113/148	7.1	5.7	0.74 (0.59, 0.94)
<b>Age ≥ 65</b>	161/234	97/118	7.0	4.6	0.62 (0.48, 0.80)
<b>Caucasian</b>	185/306	115/155	6.3	4.9	0.66 (0.52, 0.83)
<b>Non-Caucasian</b>	179/228	95/111	7.8	5.8	0.71 (0.55, 0.92)
<b>Asia</b>	215/356	132/178	6.5	4.8	0.64 (0.52, 0.80)
<b>Western</b>	149/178	78/88	7.8	6.7	0.75 (0.57, 1.00)

The analyses showed that the OS results for subgroups were generally consistent with the primary result. Table 19 summarizes stratification factors and other important subgroup analyses of OS based on ITT population.

Table 19: Subgroup Analyses of OS: Baseline Characteristics

Subgroups	Events/N		Median OS		HR (95% CI)
	TAS-102	Placebo	TAS-102	Placebo	
<b>Kras Wild</b>	191/272	103/135	6.5	4.9	0.80 (0.63, 1.02)
<b>Kras Mutant</b>	173/262	107/131	8.0	5.7	0.58 (0.45, 0.74)
<b>TM* &lt;18 Months</b>	85/111	46/55	4.9	3.7	0.84 (0.58, 1.21)
<b>TM* ≥18 Months</b>	279/423	164/211	7.8	5.8	0.64 (0.53, 0.78)
<b>ECOG=0</b>	191/301	107/147	8.5	6.1	0.73 (0.57, 0.93)
<b>ECOG=1</b>	173/233	103/119	5.5	4.4	0.61 (0.48, 0.79)
<b>Primary Tumor Colon</b>	234/338	127/161	6.8	4.5	0.68 (0.55, 0.85)
<b>Primary Tumor Rectal</b>	130/196	83/105	7.8	6.0	0.64 (0.48, 0.85)
<b>2 Prior Regimens</b>	70/95	36/45	6.2	4.8	1.05 (0.68, 1.63)
<b>3 Prior Regimens</b>	93/119	44/54	6.7	4.7	0.74 (0.51, 1.08)
<b>≥4 Prior Regimens</b>	201/320	130/167	7.9	5.6	0.59 (0.47, 0.73)
<b>1-2 Metastatic Sites</b>	201/324	111/153	8.8	6.3	0.69 (0.54, 0.87)
<b>≥3 Metastatic Sites</b>	163/210	99/113	5.3	3.9	0.68 (0.52, 0.88)

\* TM: Time since Metastasis

Most of the subgroup analyses showed that the OS results for subgroups were consistent with the primary result except patients with 2 prior regimens reported a HR point estimate greater than 1. For this small subgroup, the median OS was improved. However the Kaplan-Meier curves crossed back and forth after 10 months with about 25% patients still at risk in this subgroup.

#### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

A series of initial dose-finding studies were conducted in the U.S. in patients with solid tumors. Based on preclinical findings (Study M96-029), these studies used daily dosing of TAS-102 in order to facilitate FTD incorporation into tumor cells. In the first 3 studies initiated (Studies TAS102-9801, TAS102-9802, and TAS102-9803), TAS-102 was administered once daily using various dosing schedules of 3- or 4-week cycles. The initial starting dose in the first human study (TAS102-9801) was 100 mg/m<sup>2</sup>/day, which was 1/3 the toxic low dose in a 4-week toxicity study in monkeys. The results of these studies indicated that TAS-102 was better tolerated when administered for 5 consecutive days rather than for 14 consecutive days, and a dose regimen of 5 days a week with 2 days rest for 2 weeks, repeated every 4 weeks was determined to be the optimal dosing regimen. While these initial 3 studies were ongoing, results of nonclinical studies became available that demonstrated significantly greater tumor

reduction in mice following twice daily dosing compared with daily dosing. Therefore, 2 additional studies were initiated to evaluate twice daily and three times daily dosing (Studies TAS102-9804 and TAS102-9805, respectively) using the regimen of 5 days a week with 2 days rest for 2 weeks, repeated every 4 weeks. In Study TAS102-9804, which was conducted in heavily pretreated patients with breast cancer, the MTD was 50 mg/m<sup>2</sup>/day, while in study TAS102-9805, which was conducted in primarily in patients with metastatic CRC, the MTD was 70 mg/m<sup>2</sup>/day. In a subsequent dose-finding study conducted in Japan (Study J001-10040010), a TAS-102 regimen of 35 mg/m<sup>2</sup> twice daily (70 mg/m<sup>2</sup>/day) administered for 5 days a week with 2 days rest for 2 weeks, repeated every 4 weeks, was well tolerated in patients with advanced solid tumors. The efficacy and safety of this regimen was established in the Japanese Phase 2 study in patients with metastatic CRC (Study J003-10040030). The tolerability of this regimen in Western patients with refractory metastatic CRC was confirmed in a dose-finding study conducted in the U.S. (Study TPU-TAS-102-101). Therefore, this regimen was selected for evaluation in the pivotal, global, study (RECOURSE).

#### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable.

#### 6.1.10 Additional Efficacy Issues/Analyses

The NDA is based on the submission of a single adequate and well controlled clinical trial, RECOURSE. The results of RECOURSE were supported by the results of a randomized trial in patients with metastatic CRC conducted in Japan (Study J003/10040030). Both trials were randomized (2:1), double-blind, placebo-controlled studies of patients with chemotherapy-refractory advanced CRC who progressed or failed to respond to more than two chemotherapeutic regimens including a fluoropyrimidine, irinotecan, and oxaliplatin. Demographic and baseline characteristics were similar in both trials, with the exception of only Asian subjects enrolled in the Japanese trial. TAS-102 was administered at a dose of 35 mg/m<sup>2</sup>/dose twice daily for 5 consecutive days with 2 days rest weekly for 2 weeks followed by a 2-week recovery period on both trials.

The RECOURSE statistical plan included 90% power for OS HR 0.75 (25% risk reduction) for TAS-102 compared to placebo with 1-sided type I error of 0.025. The primary endpoint in the Japanese trial was OS and the study was designed with a one-sided alpha of 0.10. Both trials were statistically significant at their designated alpha levels.

There was a difference in median PFS durations in the placebo arms observed between the two studies (1.7 months in RECOURSE versus 1.0 months in J003/10040030). This difference appeared to be related to differences in scheduling of imaging for response. In the RECOURSE study, the earliest planned radiologic evaluation was after 2 cycles

of treatment (about 8 weeks), whereas in J003-10040030, the patients underwent the first radiologic evaluation after their first cycle of therapy (about 4 weeks), so the corresponding placebo medians reflect these differences.

In summary, RECURSE was a large, well-controlled, randomized trial which demonstrated robust and consistent results across most patient subsets and achieved more than one endpoint including a clinically meaningful, statistically significant prolongation of life providing sufficient basis for approval.

## 7 Review of Safety

### **Safety Summary**

The main safety analyses were performed on RECURSE the pivotal study supporting the proposed indication. Additional safety data contained in the application (i.e., integrated data including legacy data) were reviewed and the safety profile of TAS-102 in other trials appeared similar to that in the pivotal placebo controlled trial (RECURSE).

#### **Pivotal trial: RECURSE**

RECURSE was a multinational, double-blind, placebo controlled study of TAS-102 35mg/m<sup>2</sup> orally twice daily on day 1-5 and 8-12 versus placebo. The protocol required that patients have metastatic CRC who have been previously treated with, or are not candidates for fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and an anti-EGFR therapy. Patients received treatment until disease progression, unacceptable adverse events, or irreversible treatment-related Grade 4 clinically relevant non-hematologic adverse events (AE).

A total of 798 patients received either TAS-102 or placebo in the RECURSE trial (constituting the safety analysis dataset). At the time of cutoff, 95% of these patients discontinued TAS-102 or placebo (analyzed in ITT population). In the analysis of disposition using the disposition dataset (n=800; all patients in the ITT population), the main reason for treatment discontinuation was disease progression, which occurred with a greater frequency in the placebo arm (95%) than in the TAS-102 arm (84%). Adverse events leading to discontinuation (including adverse events with an outcome of treatment discontinuation, using the disposition dataset) occurred with a higher frequency in the TAS-102 arm (3.6%) than in the placebo arm (1.5%). However, analyses of narratives and CRFs did not always allow for a clear distinction of the causes of withdrawal, because in the advance metastatic CRC setting, progression of disease and some adverse events (for example bowel perforation) could not be distinguished.

There were 68 patients (35 patients in the TAS-102 arm and 33 patients in the placebo arm) who died within 30 days of the last dose of study medication. Of these patients, 83% in the TAS-102 arm and 94% in the placebo arm died of reasons considered by the investigator as directly related to CRC (e.g., terms included “disease progression”). There were more deaths related to an AE on placebo (11%) than TAS-102 (3%).

Generally, patients remained on treatment longer on the TAS-102 arm. Median (range) duration of treatment was 47 days (1, 546) in the TAS-102 arm and 40 days (1, 446) for placebo. The average number of days of exposure was 89 days for TAS-102 and 47 days for placebo.

Sixty percent of patients on the TAS-102 treatment arm underwent a dose modification, including dose reduction, delay, or interruption, while 22% of subjects on the placebo arm had dose modifications. Ten percent of subjects on TAS-102 withdrew study medicine due to an AE, while 14% of patients on the placebo arm discontinued due to an AE.

Almost all patients in both arms of RECURSE experienced adverse events (AEs). The most common AEs by preferred term (PT) in the TAS-102 treatment arm were nausea (48%), anemia (38.8%), decreased appetite (38.6%), fatigue (35.1%), diarrhea (31.9%), neutropenia (29.3%), and neutrophil count decreased (27.8%). Grade 3-4 AEs of myelosuppression and diarrhea were observed more frequently in the TAS-102 arm compared to placebo (incidence rates are reported in 7.4.2 Laboratory Findings; incidence of PT diarrhea was 3% versus 0.4% respectively). The incidence of non-fatal serious adverse events (SAE) occurred more frequently in patients who received placebo (33%) compared to patients in the TAS-102 arm (29%).

The most common AEs by system organ class (SOC) in both treatment arms were gastrointestinal disorders, infections and infestations, and general disorders and administration site conditions. Gastrointestinal (GI) AEs of all grades were more frequent in the TAS-102 group than in the placebo group, including diarrhea, nausea, vomiting, and abdominal pain. However, the overall incidence of  $\geq$  Grade 3 GI events was similar in the two treatment groups. The overall incidence of blood and lymphatic disorder AEs (all grades) was higher in the TAS-102 group than in the placebo group, as was the incidence of AEs  $\geq$  Grade 3. This was primarily due to a higher incidence of AEs associated with myelosuppression, a well described effect of TAS-102, including anemia, leukopenia, neutropenia and thrombocytopenia.

## **EVENTS OF SPECIAL INTEREST:**

### **Myelosuppressive Effects**

TAS-102 treatment was associated with an increased frequency of adverse events and laboratory abnormalities associated with myelosuppression including anemia, neutropenia, and thrombocytopenia. These events were generally manageable with

reductions in dose, delays in cycle initiation, and use of G-CSF/GM-CSF (9.4% of patients receiving TAS-102).

### **Infections**

Infection-related AEs were more frequent in the TAS-102 group compared to the placebo group; the most frequently reported types of infection were nasopharyngitis, upper respiratory tract infection, and urinary tract infection. Three patients experienced fatal infections, one of which occurred in the setting of neutropenia.

### **Other Adverse Events**

Other frequently occurring events with TAS-102 treatment were gastrointestinal disorders including diarrhea, nausea and vomiting. However, Grade  $\geq 3$  events of this type were infrequent and had similar incidence rates compared to placebo.

Although there was no difference between the 2 treatment groups in incidence of DVTs, PE was reported for 8 patients (the applicant counted 9) in the TAS-102 group versus 0 in the placebo group. TAS-102 was not associated with an increase in incidence of arrhythmogenic events or events of cardiac ischemia.

There was no imbalance between the TAS-102 and placebo groups with respect to incidence of skin reactions including hand-foot syndrome, pruritus and rash.

### **Hepatobiliary Abnormalities**

There were no differences between the two treatment groups in hepatobiliary abnormality-related AEs or in hepatobiliary laboratory abnormalities.

### **Renal Abnormalities**

Renal abnormality-related AEs were more frequent in the TAS-102 group than in the placebo group due primarily to an increased incidence of AEs of proteinuria (4.1% versus 1.9%, respectively), all of which were Grade 1 or 2 in severity. Seven (1.3%) patients in the TAS-102 group and 2 (0.8%) in the placebo group had AEs of renal failure, acute renal failure, or renal impairment.

### **Other Laboratory Abnormalities**

Increased frequency of hypokalemia observed with TAS-102 treatment appears to be associated at least in part with the occurrence of gastrointestinal disturbances including vomiting and diarrhea.

### **Subgroup Analyses**

Subgroup analyses of AEs and clinical laboratory abnormalities indicated an increased incidence of hematologic abnormalities among patients  $\geq 65$  years of age compared to younger patients, and among females compared to males. Differences in incidence of AEs observed for patients enrolled at sites in Asia versus those enrolled at Western sites appear to be due more to differences in verbatim terms used to describe

laboratory-related events than to any actual differences in tolerability. There were no consistent differences between Asian and Western patients with respect to Grade 3 or 4 hematology abnormalities.

In summary, serious AEs and fatal AEs were less frequent in the TAS-102 group than in the placebo group; there was one death considered by the investigator as related to TAS-102 treatment. The most frequent toxicities observed with TAS-102 treatment were hematologic abnormalities including anemia, neutropenia, febrile neutropenia and thrombocytopenia, which were managed with reductions in dose and delays in cycle initiation. Other frequent toxicities were gastrointestinal events including nausea, vomiting and diarrhea, with an associated increase in hypokalemia in patients who developed vomiting/diarrhea.

**Supportive Study:**

A total of 172 patients in Japan were enrolled onto study J003-10040030 and data from 170 were included in the safety analysis: 113 on TAS-102 and 57 patients on placebo. No deaths occurred within 30 days after the start of study treatment, either in the TAS-102 or placebo groups. Forty-nine SAEs were reported in 26 patients (15%) across both treatment groups; 41 events were reported in 21 patients (19%) in the TAS-102 group. Among the SAE in the TAS-102, 25 events reported in 13 patients were determined to be adverse drug reactions by the investigator. Three patients discontinued due to AE in the TAS-102 group and 1 patient in the placebo group discontinued the study due to an AE. AE occurred in 98.2% of patients on TAS-102 and 91.2% on placebo.

In the TAS-102 group the SOCs with the highest incidences (50% or higher) were "Investigations," "Gastrointestinal disorders," "General disorders and administration site conditions" and "Metabolism and nutrition disorders." The PTs with the highest incidences (30% or higher) were bone marrow depression (white blood cell count decreased, hemoglobin decreased, neutrophil count decreased); nausea, vomiting, diarrhea, and decreased appetite (gastrointestinal disorders) and fatigue. There were high incidence of decreased appetite and fatigue in placebo group (30% or higher) as well.

AE that were Grade 3 or higher were mainly related to myelosuppression.

In conclusion, the results of the safety analyses demonstrated that the safety profile of TAS-102 35mg/m<sup>2</sup> twice daily in a patient population with advanced metastatic CRC who have limited treatment options is favorable based on the effect observed on overall survival. Although there were small numerical differences in the frequencies of adverse events observed between arms, there was no new pattern or trend in the toxicities identified with the exception of myelotoxicity and gastrointestinal abnormalities.

## 7.1 Methods

Adverse events were coded using MedDRA, Version 16.0, and were categorized by system organ class (SOC) and preferred term (PT). Only treatment emergent adverse events (AEs) were included in summary tabulations.

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The trials included in the safety review and ISS are listed in Table 20. Due to the similarity of the adverse event profile of TAS-102 between the pivotal RECURSE trial and legacy data, this safety review will focus on the pivotal trial (see justification in Section 5.2 Review Strategy).

Table 20: Trials used to evaluate safety

Study Number	Number of treated patients	
	TAS-102	Placebo
<b>TPU-TAS-102-301 RECURSE pivotal Phase 3</b>	<b>533</b>	<b>265</b>
J003-10040030 Phase 2, Japan	113	57
J001-10040010	5	0
J004-10040040	5	0
TPU-TAS-102-101	24	0
TPU-TAS-102-102	29	0
TPU-TAS-102-103	33	0
TPU-TAS-102-104	19	0
<i>Total</i>	<i>1407</i>	<i>322</i>

In addition, serious adverse events (SAE) were reported from non-integrated studies (legacy studies, ongoing studies) and from patients who did not have metastatic CRC, and/or received TAS-102 at doses other than 35mg/m<sup>2</sup> twice daily.

### 7.1.2 Categorization of Adverse Events

The severity of the events was documented using NCI CTCAE version 4.03. The MedDRA 16.0 dictionary was used to code AE data. A total of 7471 preferred terms (PT) in 24 system organ classes (SOC) described all AEs. Table 21 lists the reasons for exclusion of certain AEs contained within the AE dataset from certain analyses of safety.

Table 21: Adverse Events Data Validation Summary

Reason for Exclusion	Placebo N=1,616		TAS-102 N=6,118	
	Event Count	%	Event Count	%
1. Date missing or incomplete	0	0.0	1	0.0
2. Date before study analysis period	70	4.3	193	3.2
3. Date after study analysis period	7	0.4	46	0.8

Verbatim terms in the AE dataset were reviewed to determine whether MedDRA PTs were appropriately coded. Information in case report forms from 20% of patients were compared to the data in the datasets. Based on this analysis, the data in the datasets appeared reliable for analysis.

A total of 4310 out of 7471 PTs in the as treated (AT) safety population (including the AEs reported after the study analysis period) did not identically match the verbatim terms (note that this analysis was to the preferred term and not the lower level term). Some discrepancies were related to misspelled verbatim terms or due to a typo that appeared to be corrected in the MedDRA dictionary PT. Overall, the coding of adverse events to MedDRA was acceptable.

The applicant defined an AE in Section 9.1.1 of RECURSE as any untoward medical condition that occurs in a patient while participating in a clinical study and does not necessarily have a causal relationship with the use of the product. Treatment emergent adverse events are AEs that occur from the initiation of any study medication administration, and do not necessarily have a causal relationship to the use of the study medication.

Two-hundred sixty-three adverse events that occurred during in the screening period (prior to treatment) were not included in the analysis of safety. The 53 AEs that occurred after the study analysis period ended were included in the analysis as this reviewer felt that they could contribute to the safety information submitted in the application and because there were more reported in the TAS-102 arm. There were 5879 adverse events in 533 patients in the TAS-102 arm and 1539 AEs in 265 patients in the placebo arm for a total of 7471 adverse events.

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Datasets were submitted from legacy studies, with the focus on pivotal trial RECURSE and Study J003/10040030. Signals were similar across all groups (see Table 20), including patients with metastatic CRC who received at least one dose of the study drug

at the recommended dose. Therefore, this review will focus on the RECURSE safety group as the representative sample.

## 7.2 Adequacy of Safety Assessments

Overall, the applicant's monitoring of the clinical safety was adequate and the datasets are of very good quality. See Section 3.1 Submission Quality and Integrity for further details.

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Of 800 randomized patients, 798 received at least one dose of study medication (533 received TAS-102 and 265 received placebo). Reasons for not receiving treatment were: adverse event (1) and ineligibility (1).

Median (range) duration of treatment was 47 days (1, 546) in the TAS-102 arm and 40 days (1, 446) for placebo. The average number of days of exposure was 89 days for TAS-102 and 47 days for placebo. Generally, patients stayed on treatment longer on the TAS-102 arm. Table 22 summarizes the exposure analysis.

Table 22: Summary of Treatment Exposure for RECURSE (AT population)

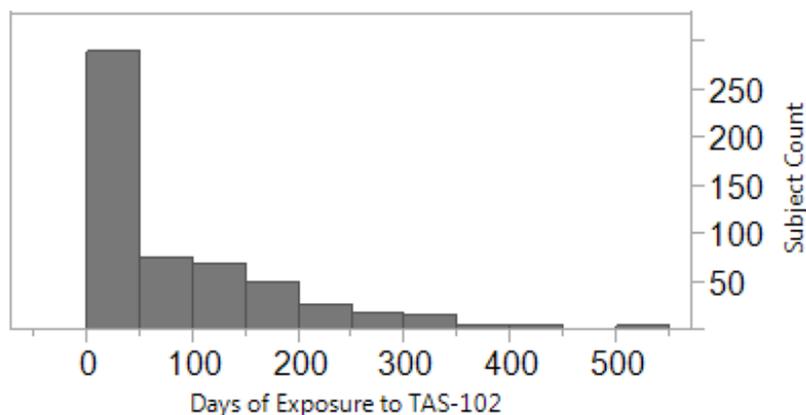
	TAS-102 (N = 533)	Placebo (N = 265)
<b>Duration of treatment in days</b>		
Mean (SD)	89 (84)	47 (43)
Median	47	40
Min, Max	1, 546	1, 446
<b>Duration of treatment by maximum period (n %)</b>		
<1 month	67 (12.6)	50 (18.9)
1-<2 months	234 (43.9)	165 (62.3)
2-<3 months	36 (6.8)	19 (7.2)
3-<6 months	117 (22)	27 (10.2)
≥6 months	79 (15)	4 (1.5)
<b>Dose modification</b>	<b>321 (60)</b>	<b>59 (22)</b>
<b>Dose reduction</b>	<b>73 (13.7)</b>	<b>3 (1)</b>
<b>Discontinuation due to AE</b>	<b>54 (10)</b>	<b>36 (14)</b>
<b>Dose held/delay/interruption</b>	Non-contributory based on non-continuous oral dosing	

The analysis dataset for exposure (ADEX) was used to identify treatment start date and end date, I calculated the number of days a subject was on treatment, divided by month or cycles on therapy, and subset by each subject and treatment arm. I confirmed the exposure based on days on therapy. The results for cycles/months on therapy were very close to the applicants, but they used initiation of and end of cycle versus actual dates.

Based on an analysis using the adverse events dataset, 60% of subjects on the TAS-102 treatment arm (N=321) underwent a dose modification, including dose reduction, delay, or interruption, while 22% of subjects on the placebo arm had dose modifications (N=59). Ten percent of subjects on TAS-102 (N=54) withdrew study medicine due to an AE, while 14% of subjects on the placebo arm (N=36) discontinued due to AE.

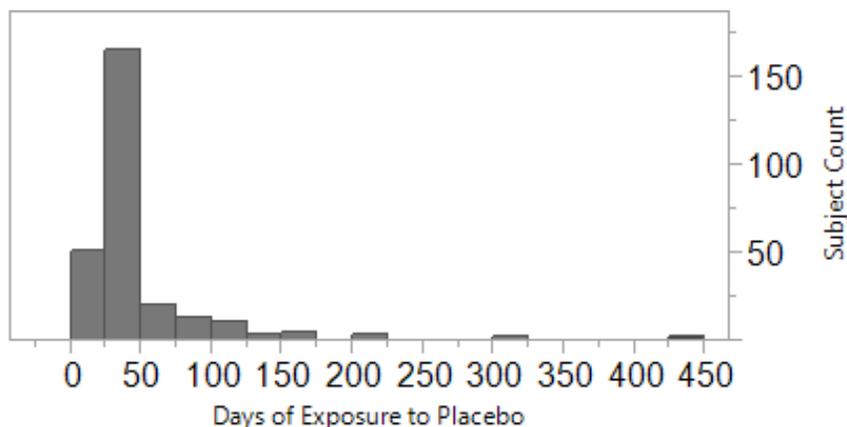
Figure 4 and Figure 5 are histograms representing the number of subjects treated with TAS-102 and placebo, respectively, and their duration on treatment in days. Patients treated with TAS-102 were exposed to study drug for longer duration. Both histograms are right skewed and more patients were on treatment during the earlier course of therapy.

Figure 4: Duration of Exposure to TAS-102 in RECOURSE (AT population)



Analysis was done by assessing the days of exposure of TAS-102 in the subject disposition, demographic and baseline characteristics dataset (ADSL).

Figure 5: Duration of Exposure to Placebo in RECOURSE (AT population)



Analysis was done by assessing the days of exposure of placebo in the subject disposition, demographic and baseline characteristics dataset (ADSL).

Using the exposure dataset, 87% of patients in the TAS-102 group and 81% of patients in the placebo group continued to Cycle 2; 43% of patients in the TAS-102 group and 18% of patients in the placebo group continued to Cycle 3. The median dose intensity was 155 mg/m<sup>2</sup>/week in the TAS-102 group and 165 mg/m<sup>2</sup>/week in the placebo group.

Table 23 lists the demographic data in the AT safety population for RECURSE. Demographics were well balanced between arms. Mean age was the same in both arms (62 years old). The majority of patients were younger than 65 years (56% in both arms) which shows that RECURSE enrolled a younger population than the average American population with metastatic CRC [the median age at diagnosis for metastatic CRC according to SEER data is 68 years of age (accessed on 6 April 2015, <http://seer.cancer.gov/statfacts/html/colorect.html>)]. There was a gender imbalance with more men than women in the trial (61% versus 37%). Additionally, according to ACS, CRC incidence rates are highest in Black men and women. There is a health disparity with enrollment of minorities onto clinical trials. As such, there were not enough Black subjects to make inferences about the clinical effects of TAS-102 compared to non-Black subjects. Incidence rates among other major racial/ ethnic groups are lower than those among Whites. In RECURSE, Asian patients represented 35% of the population while White patients represented 57%. Aside from the small numbers of Black patients, the demographical profile of the patient population on RECURSE was applicable to the U.S. population with metastatic CRC.

Table 23: RECURSE demographics in AT safety population

Demographic Baseline Characteristics		TAS-102		Placebo		Overall	
		N=533		N=265		N=798	
<b>Age</b>	<b>Mean (SE)</b>	61.5 (10.2)		61.5 (10.5)		61.5 (10.3)	
		<b>Count</b>	<b>%</b>	<b>Count</b>	<b>%</b>	<b>Count</b>	<b>%</b>
<b>Age Group</b>	<b>Age under 65 years</b>	299	56.1	147	55.5	446	55.9
	<b>65 &lt;= Age &lt;75</b>	198	37.1	94	35.5	292	36.6
	<b>Age 75 and over</b>	36	6.8	24	9.1	60	7.5
<b>Sex</b>	<b>F</b>	207	38.8	101	38.1	308	38.6
	<b>M</b>	326	61.2	164	61.9	490	61.4
<b>Race</b>	<b>Asian</b>	184	34.5	94	35.5	278	34.8
	<b>Black Or African American</b>	4	0.8	5	1.9	9	1.1
	<b>White</b>	305	57.2	154	58.1	459	57.5
	<b>Missing</b>	40	7.5	12	4.5	52	6.5
<b>Ethnicity</b>	<b>Hispanic Or</b>	10	1.9	6	2.3	16	2.0

Demographic Baseline Characteristics	TAS-102		Placebo		Overall	
	N=533		N=265		N=798	
Latino						
Not Hispanic Or Latino	477	89.5	245	92.5	722	90.5
Not Reported	46	8.6	14	5.3	60	7.5

The demographics tables for the AT and ITT populations (Table 12, Table 23) are almost identical, because only 2 patients (1 in TAS-102 arm and 1 in placebo arm) were randomized but did not receive study drug.

### 7.2.2 Explorations for Dose Response

Only one dose was investigated in the clinical trials designed to assess the safety and efficacy of TAS-102; therefore conclusions regarding the effectiveness of lower (or higher) starting doses cannot be made. Please refer to the clinical pharmacology review for population-PK analyses and exposure-response analyses.

### 7.2.3 Special Animal and/or In Vitro Testing

TAS-102 was tested as separate drugs FTD and TPI in preclinical cardiac safety models. FTD had no effect on hERG current at concentrations up to 300 µmol/L. Oral administration of FTD at dose levels of up to 108.8 mg/kg produced no effects on assessed cardiovascular parameters in the conscious monkey. TPI had no effect on hERG current at concentrations up to 100 µmol/L. Oral administration of TPI at dose levels of up to 1000 mg/kg produced no effects on assessed cardiovascular parameters in the conscious monkey.

### 7.2.4 Routine Clinical Testing

Routine clinical testing and monitoring were analyzed, and the results of these analyses are described in the Safety and Laboratory Sections of this review (Sections 7.3 Major Safety Results and 7.4 Supportive Safety Results).

### 7.2.5 Metabolic, Clearance, and Interaction Workup

For a complete review, refer to the clinical pharmacology reviews and also to 4.4.3 Pharmacokinetics. TAS-102 and placebo were administered with best supportive care (i.e., treatments aimed at ameliorating symptoms, improve function, or treat complications from the disease and/or treatment). No formal analysis of interaction was conducted for this NME.

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

hepatocytes. *In vitro* studies indicated that trifluridine, tipiracil, and FTY did not inhibit the CYP enzymes and had no inductive effect on CYP1A2, CYP2B6 or CYP3A4/5. *In vitro* studies indicated that trifluridine was not an inhibitor of or substrate for human uptake and efflux transporters.

#### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

TAS-102 is a combined product, and contains  $\alpha,\alpha,\alpha$ -trifluorothymidine (FTD). Like other fluoropyrimidines, gastrointestinal and myelotoxicity occurs following the use of TAS-102. A review of gastrointestinal and myelotoxicity found with use of TAS-102 is described in Section 7.3.5 Submission Specific Primary Safety Concerns. One difference between TAS-102 and 5-fluorouracil and capecitabine is that TAS-102 is not metabolized via dihydropyrimidine dehydrogenase.

### 7.3 Major Safety Results

There were a total of 771 subjects (96%) who experienced AEs: 524 subjects (98%) on the TAS-102 arm and 247 subjects (93%) on the placebo arm. With the exception of the analysis of AEs in Table 24, the analysis of AEs below included all AEs reported after TAS-102 or placebo was initiated. This included 53 AEs that occurred in 29 subjects  $\geq$  30 days after the last dose of study drug/placebo. Although including these later reported AEs constitutes a more conservative approach, for most of the analyses, incidence rates were the same; clinically, no signal was detected based on including the additional adverse events, and the analyses corresponded to the incidence rates documented by the applicant.

All AEs listed Table 24 were treatment emergent AEs. AEs with onset dates on or after the first dose of study medication and within 30 days following the last dose of study medication were considered “on-therapy” or equivalently “treatment emergent.” There were cases where an event started prior to the first dose of study medication and continued into the treatment period, and the applicant counted this as treatment-emergent if the maximum grade was higher than onset grade (for example with 2 subjects with SAEs on TAS-102 and 1 on placebo). The difference of rates of AEs  $\geq$  Grade 3 in this analysis compared to the applicant’s was also attributable to an event that occurred prior to the first dose of study drug and CTCAE Grade increased during the treatment period (the applicant counted the additional 4 subjects on TAS-102 and 3 subjects on placebo). The applicant’s analysis had 2 more subjects with Grade 3 or 4 treatment-related AEs (TRAE) on TAS-102 (261) and 1 more TRAE on placebo (26); this is the same clinically and their results were more conservative. The treatment-related AEs were identified by investigator reporting in CRFs.

In summary, the applicant took a conservative approach with regards to accounting for AEs as did this reviewer.

Table 24: Summary of AEs

	TAS-102; n (%) N=533	Placebo; n (%) N=265
Subjects who experienced an AE	524 (98.3)	247 (93.2)
Subjects who experienced an AE Grade 3-5	366 (68.7)	134 (50.6)
Subjects who experienced a SAE	156 (29.3)	88 (33.2)
Subjects who experienced a treatment-related AE	457 (85.7)	145 (54.7)
Subjects who experienced a treatment-related AE Grade 3-4	259 (48.6)	25 (9.4)
AE resulting in discontinuation	54 (10)	36 (13.6)
Deaths related to an AE	17	30

All AE analyses were performed using the adverse events dataset (ADAE). The ≥ Grade 3 AEs did not include AEs which preceded the study medicine and then increased in CTCAE toxicity during therapy. The analysis of serious adverse events did not include SAEs prior to first dose of study drug. For the analysis of deaths, SAEs were grouped by subject level and identified by a variable that resulted in death. The treatment-related AEs were identified by investigator reporting in CRFs, flagged in the ADAE dataset, and subset by Grade and treatment arm.

**REVIEWER COMMENT:** *The applicant included subjects who had events prior to receiving the first dose and had maximum toxicity grade higher than onset grade. This reviewer finds this comprehensive and acceptable.*

### 7.3.1 Deaths

There were 68 patients (35 patients in the TAS-102 arm and 33 patients in the placebo arm) who died within 30 days of the last dose of study medication. Of these patients, 29 of the 35 patients (83%) in the TAS-102 arm and 31 of the 33 patients (94%) in the placebo arm died of reasons considered by the investigator as directly related to CRC (e.g., terms included “disease progression”). This section will review the adverse events leading to death. Table 25 summarizes all reported deaths in the AT population, including all deaths within 30 days of receiving the last dose of TAS-102 or placebo.

Table 25: All Reported Deaths (AT population)

	TAS-102 (N=533) n (%)	Placebo (N=265) n (%)
<i>Deaths &lt; 30 days of last dose</i>	35 (6.5%)	33 (12.5%)
Clinical disease progression	19 (3.6%)	21 (8%)
Radiological disease progression	10 (1.9%)	10 (3.8%)

Other	6 (1.1%)	2 (0.8%)
<i>Death &gt; 30 days after last dose</i>	332 (62%)	178 (67%)
Total number of deaths in reporting period	367 (69%)	211 (80%)

This analysis was conducted by identifying deaths that occurred within 30 days of the last dose of TAS-102 (or placebo) and examining the analysis value (reason for death) by treatment arm in the disposition dataset (ADDS).

The applicant’s analysis described one fewer patient who died due to clinical progression (Patient 200-006) as this patient died due to Klebsiella pneumonia/septic shock considered related to study medication, such that the applicant listed it as “toxicity.” However, the investigator indicated clinical disease progression as the primary category of death. The applicant also listed all deaths in the ITT population, such that there was 1 additional patient in each arm reported as dying in the 30 day interval, however both of these patients never received drug/placebo. Patient 202-006 discontinued prior to receiving treatment due to an AE of ascites, and Patient 312-002 was found to be ineligible for the study.

There were 6 patients in the TAS-102 group for which the category of death was “Other”; details for these patients are as follows:

- Patient 150-008 died 25 days after discontinuing treatment due to radiologic progression (29 days after last dose of study medication).
- Patient 200-004 had an ongoing AE of staphylococcal pneumonia (considered unrelated) at the time of death, which the investigator considered to be a symptom of disease progression.
- Patient 355-013 had fatal staphylococcal pneumonia (considered unrelated).
- Patient 562-016 withdrew consent for study treatment after Cycle 1, Day 4 (no AEs reported; site was notified of patient’s death by a family member).
- Patient 575-003 had fatal pulmonary edema (considered not related).
- Patient 602-003 had fatal pulmonary embolism (considered not related).

For the 2 patients in the placebo group whose category of death was “Other,” both had fatal AEs considered not related to study treatment. Details for these patients are as follows:

- Patient 150-007 (respiratory arrest);
- Patient 562-024 (cardio-respiratory arrest, acidosis, hemorrhage intracranial and renal failure).

The causes of mortality captured as not directly attributed to cancer in the placebo arm were general physical health deterioration (8 patients), followed by hepatic failure (6 patients) and dyspnea (4 patients); however, when looking at narratives and CRFs of these patients, most appeared to die of progression of their cancer.

In the analysis conducted using the adverse event dataset, only including patients who had received a dose of study drug within 30 days, 47 patients (5.9%) had AEs that resulted in death: 17 (3%) in the TAS-102 arm and 30 (11%) in the placebo arm. Table 26 summarizes the AEs with a fatal outcome within 30 days of treatment, by PT. This analysis is considered a more conservative analysis than the analysis described above that used the disposition dataset. The analysis below included patients considered by the investigator as having died due to disease progression. However, because investigator attribution may not be accurate, the analysis below may be a better representation of causes of death in the trial. Nevertheless, the table below shows that an imbalance in fatal adverse events was not evident among patients treated with TAS-102.

Table 26: Fatal AEs &lt; 30 days after last dose of drug by PT (AT population)

<b>MedDRA Preferred Term</b>	<b>TAS-102 (N = 533) n</b>	<b>Placebo (N = 265) n</b>
<i>Total = 47</i>	<i>17 (3%)</i>	<i>30 (11%)</i>
General physical health deterioration	6	8
Hepatic failure	2	6
Renal failure acute	2	0
Dyspnea	1	4
Pleural effusion	1	1
Liver abscess	1	0
Pneumonia staphylococcal	1	0
Pulmonary embolism	1	0
Pulmonary edema	1	0
Sepsis	1	0
Septic shock	1	0
Abdominal pain	0	1
Acidosis	0	1
Bile duct obstruction	0	1
Cardio-respiratory arrest	0	1
Cognitive disorder	0	1
Gastrointestinal hemorrhage	0	1
Hematemesis	0	1
Hemorrhage intracranial	0	1

<b>MedDRA Preferred Term</b>	<b>TAS-102 (N = 533) n</b>	<b>Placebo (N = 265) n</b>
Hepatic encephalopathy	0	1
Intestinal perforation	0	1
Jaundice	0	1
Lymphangiosis carcinomatosa	0	1
Malignant ascites	0	1
Pulmonary congestion	0	1
Renal failure	0	1
Renal impairment	0	1
Respiratory arrest	0	1
Small intestinal obstruction	0	1

The analysis was performed by using a per-subject rate, dictionary-derived terms resulting in death, by treatment arm in the adverse events dataset (ADAE).

Because deaths could be attributed to more than one adverse event, the number of AEs causing deaths were higher than the number of deaths. For example, there were 39 PTs for 30 subjects on the placebo arm that contributed to toxic deaths within 30 days.

Even when PTs are grouped together that are clinically similar, such as acute renal failure, renal failure, and renal impairment, the TAS-102 arm still had fewer deaths attributable to AE.

In the review of the narratives from the non-cancer-attributed cases, a majority of the patients listed with fatal AEs actually had progressive disease. For example, Patient 102-001 had dyspnea listed as a PT for the fatal AE; however at the time of randomization, the patient had bilateral pleural effusions with Grade 2 dyspnea. Most likely the effusions were from the underlying metastases to the lungs as described in the autopsy report although thoracentesis only revealed granulocytes and fibrin.

Patient 104-001 had a fatal AE listed as “General physical health deterioration”; however, the patient had a rectal ultrasound that showed progressive disease. The narrative stated that “General physical health deterioration” was considered as a symptom of disease progression. The Investigator believed the fatal event was not related to study medication and indicated clinical disease progression as the primary cause of death.

Patient 302-002 had metastatic CRC to the liver and lung. The Investigator assessed the event, hepatic failure, as not related to the study medication and noted that hepatic

failure was a symptom of disease progression, and that death was caused by clinical disease progression.

### 7.3.2 Nonfatal Serious Adverse Events

Serious adverse events were defined as an adverse event that

- is fatal
- is life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

Although this definition is standard (i.e., defined in CFR 312.32), in oncology, and particularly in the treatment of advanced disease, attribution of seriousness to an adverse event is highly variable, and for the same event with the same severity and similar outcome, investigators sometimes differed in their interpretation of seriousness.

After excluding adverse events that occurred prior to investigational drug administration and that occurred 30 or more days after the last dose of TAS-102/placebo, there were a total of 370 nonfatal serious adverse events (SAE) in 244 patients across both arms: in 156 (29%) patients in the TAS-102 arm, 88 (33%) in the placebo arm. Of these, 47 patients had a fatal outcome: 30 patients in the placebo arm died from a SAE and 17 patients in the TAS-102 arm died. However, when analyzing the fatal events, a majority were most likely directly related to disease progression (e.g., lymphangiosis carcinomatosa, malignant effusions).

Table 27 summarizes the most frequent non-fatal SAEs by SOC. The most frequent SAEs by SOC were gastrointestinal disorders (7.5% in the TAS-102 arm; 9.8% in the placebo arm), general physical health deterioration (5.1% in the TAS-102 arm; 6% in the placebo arm), infections and infestations (4.5% in the TAS-102 arm; 4% in the placebo arm), hepatobiliary disorders (3.4% in the TAS-102 arm; 4.9% in the placebo arm) and general disorders and administration site conditions (2.8% in the TAS-102 arm; 4.2% in the placebo arm). However, the only AEs that occurred more frequently in the TAS-102 arm were blood and lymphatic system disorders.

Table 27: RECURSE non-fatal SAEs incidence  $\geq 2\%$  in AT population by SOC

System Organ Class	TAS-102 N=533		Placebo N=265	
	Subject Count	%	Subject Count	%
Gastrointestinal disorders	40	7.5	26	9.8
Blood and lymphatic system disorders	28	5.3	0	0
General disorders and administration site conditions	27	5.1	16	6
Infections and infestations	24	4.5	11	4
Hepatobiliary disorders	18	3.4	13	4.9
Respiratory, thoracic and mediastinal disorders	14	2.6	12	4.5
Renal and urinary disorders	12	2.3	2	0.8

Analyzed all SAE not grade 5 by treatment arm and SOC in the adverse event dataset (ADAE). Note that the applicant included patients that SAE occurred prior to first study dose, which is why their analysis differs only slightly.

Table 28 summarizes the most frequent non-fatal SAEs by HLT. The most frequent SAEs by HLT were general signs and symptoms NEC (3% in TAS-102 the arm; 4.5% in the placebo arm), and neutropenia (3.4% in the TAS-102 arm; none in placebo arm).

Table 28: RECURSE non-fatal SAEs incidence  $\geq 2\%$  in AT population by HLT

High Level Term	TAS-102 N=533		Placebo N=265	
	Subject Count	%	Subject Count	%
Neutropenias	18	3.4	0	0
General signs and symptoms NEC	16	3	12	4.5
Breathing	2	0.4	7	2.6

High Level Term	TAS-102 N=533		Placebo N=265	
	Subject Count	%	Subject Count	%
abnormalities				
Gastrointestinal stenosis and obstruction NEC	8	1.5	6	2.3
Hepatic failure and associated disorders	3	0.6	6	2.3
Musculoskeletal and connective tissue pain and discomfort	3	0.6	6	2.3

Analyzed all SAE not grade 5 by treatment arm and HLT from MAED in the adverse event dataset (ADAE).

Table 29 summarizes the most frequent non-fatal SAEs by PT. The most frequent SAEs by PT was general physical health deterioration (2.8% in the TAS-102 arm; 4.2% in the placebo arm).

Table 29: RECOURSE non-fatal SAEs incidence  $\geq$  2% in AT population by PT

Preferred Term	TAS-102 N=533		Placebo N=265	
	Subject Count	%	Subject Count	%
General physical health deterioration	15	2.8	11	4.2
Febrile neutropenia	14	2.6	0	0
Hepatic failure	3	0.6	6	2.3
Dyspnea	2	0.4	6	2.3

Analyzed all SAE not grade 5 by treatment arm and PT in the adverse event dataset (ADAE).

The most frequently affected systems were the gastrointestinal system and blood and lymphatic systems. There was a similar per patient incidence rate of infectious SAEs in both arms (4.5% in the TAS-102 arm; 4% in the placebo arm); however, febrile neutropenia (as a SAE) was reported in 2.6% of the patients in the TAS-102 arm versus

none in the placebo arm. Febrile neutropenia SAEs occurred more frequently among TAS-102 treated patients.

### 7.3.3 Dropouts and/or Discontinuations

Based on an analysis of the adverse event dataset (and AE page of the CRF), 54 subjects (10%) on TAS-102 and 36 subjects (14%) on placebo discontinued study medicine due to AE. This analysis differed when the analysis was conducted using data from the treatment discontinuation page of the CRF and disposition dataset. Using the disposition dataset, 3.6% of patients in the TAS-102 group and 1.5% of patients in the placebo group had an adverse event/SAE indicated as the primary reason for discontinuation of study treatment. Please refer to 6.1.3 Subject Disposition for more details.

The majority of reasons for dropout were due to disease progression or death from disease progression. There were 4 patients (<1 %) that discontinued treatment with TAS-102 for reasons due to “administrative” or “investigator”, and none on the placebo arm. Table 30 lists the dropout profile by treatment group for RECOURSE in ITT.

Table 30: RECOURSE dropout profile in ITT population

Reasons for Dropout	Treatment Groups	
	TAS-102 N=534 n (%)	Placebo N=266 n (%)
Adverse Event	19 (3.6)	4 (1.5)
Lost to Follow-Up*	3 (< 1)	3 (1)
Other (progression, death)	482 (90)	97
Total Dropouts	496 (93)^	263 (99)

Data analyzed from treatment arm in disposition dataset (ADDS). \*“Lost to follow-up” was a term analyzed in “Study discontinuation” in the AT population, but did not appear in “Treatment discontinuation” analysis. Therefore, total dropouts^ could be higher by 1%.

### 7.3.4 Significant Adverse Events

There were 72 subjects with AEs reported as reasons for dose reduction in the TAS-102 arm and 2 subjects with AEs that led to dose reduction in placebo; however 1 subject in each treatment arm failed to report the reason in the CRF. Adverse events were

considered the reason for dose reductions in all but 2 subjects the TAS-102 arm. The majority of the dose reductions were due to myelosuppression, specifically neutropenia. Fatigue, nausea, vomiting, and diarrhea were also evident as reasons for dose reduction in the TAS-102 arm. There were no new safety signals identified in analyzing AEs that resulted in dose reduction. Anemia and bronchopneumonia were listed as reasons for dose reduction in the placebo arm. The incidence rates of adverse events leading to dose reduction are grouped by SOC and PT in Table 31. Note that a comprehensive analysis of neutropenia could be described by combining PT “neutropenia”, “febrile neutropenia”, and “neutrophil count decreased.”

Table 31: RECOURSE AE Reasons for Dose Reduction incidence in AT population by PT and SOC

Preferred Term	System Organ Class	TAS-102 N=533		Placebo N=265	
		Subject Count	%	Subject Count	%
Neutropenia	Blood and lymphatic system disorders	17	3.2	0	0
Anemia		10	1.9	1	0.4
Febrile neutropenia		10	1.9	0	0
Neutrophil count decreased	Investigations	10	1.9	0	0
Fatigue	General disorders and administration site conditions	8	1.5	0	0
Diarrhea	Gastrointestinal disorders	7	1.3	0	0
Nausea		5	0.9	0	0
Decreased appetite	Metabolism and nutrition disorders	5	0.9	0	0
Vomiting	Gastrointestinal disorders	4	0.8	0	0
Asthenia	General disorders and administration site conditions	3	0.6	0	0
Mucosal inflammation		2	0.4	0	0
Blood alkaline phosphatase increased	Investigations	2	0.4	0	0
Platelet count decreased		2	0.4	0	0

In the adverse events dataset, incidence was analyzed per subject per AE based on terms “dose reduction” or dose “interruption/reduction;” note a subject could have had a few dose reductions and different AE reason for each reduction (and be counted more than once); a dose reduction for the same AEs would only be counted once.

There were 366 subjects (69%) listed in the TAS-102 arm with non-fatal Grade 3-4 AEs and 134 subjects (51%) listed in the placebo arm. The non-fatal Grade 3-4 AE by SOC are listed in Table 32. The TAS-102 arm had more AEs in the investigations and blood and lymphatic system disorders SOCs, which were both driven by neutropenia. Gastrointestinal disorders, general disorders and administration site conditions, and metabolism and nutritional disorders were balanced as far as AE across both treatment arms.

Table 32: RECOURSE Non-fatal Grades 3-4 AEs by SOC  $\geq$  6% in AT population

System Organ Class	TAS-102 N=533		Placebo N=265	
	Subject Count	%	Subject Count	%
Investigations	262	49.2	53	20.0
Blood and lymphatic system disorders	261	49.0	11	4.2
Gastrointestinal disorders	85	15.9	42	15.8
General disorders and administration site conditions	68	12.8	30	11.3
Metabolism and nutrition disorders	57	10.7	31	11.7
Infections and infestations	35	6.6	12	4.5
Hepatobiliary disorders	32	6.0	11	4.2
Respiratory, thoracic and mediastinal disorders	26	4.9	12	4.5
Musculoskeletal and connective tissue disorders	17	3.2	8	3.0
Renal and urinary disorders	13	2.4	7	2.6
Nervous system disorders	12	2.3	9	3.4

System Organ Class	TAS-102 N=533		Placebo N=265	
	Subject Count	%	Subject Count	%
Vascular disorders	11	2.1	16	6.0

Analyses were performed using the adverse event dataset and grouping by SOC and treatment arm. Note that subjects could have had Grade 3 and then Grade 4 neutropenia, and the analysis counted each subject one time for each SOC. Analyses vary minimally with the applicant who counted multiple occurrences of a PT only once for that term as either “all grades” or  $\geq$  grade 3 (which also included fatal AE).

The non-fatal Grade 3-4 AEs by PT are listed in Table 33. Neutropenia (and all PT related to neutropenia) and anemia were reported in the TAS-102 arm with almost no occurrences in the placebo arm. Grade 3-4 diarrhea and vomiting were also observed more frequently in patients who received TAS-102. Hypokalemia was seen more frequently in the TAS-102 arm and this could be attributable to factors such as diuretic and concomitant medicine, or potassium loss from diarrhea. When potassium levels were analyzed in the laboratory values dataset, about a third of patients in each treatment group experienced potassium abnormalities. When analyzing the more objective laboratory findings, Grade  $\geq$  3 hyperkalemia was higher in placebo (5%) than TAS-102 (3.8%). See 7.4.2 Laboratory Findings for more details.

Grade 3 hyperglycemia was noted in 6 subjects (1.1%) on TAS-102 and none on placebo. There were more patients with hyperglycemia on TAS-102 at study entry than on placebo.

Table 33: RECURSE Non-fatal Grades 3-4 AEs by PT  $\geq$  2% in AT population

Preferred Term	TAS-102 N=533		Placebo N=265	
	Subject Count	%	Subject Count	%
Neutropenia	127	23.8	0	0.0
Neutrophil count decreased	101	18.9	0	0.0
Anemia	83	15.6	7	2.6
White blood cell count decreased	58	10.9	0	0.0
Fatigue	21	3.9	13	4.9
Blood bilirubin increased	20	3.8	9	3.4
Febrile neutropenia	20	3.8	0	0.0

Preferred Term	TAS-102 N=533		Placebo N=265	
	Subject Count	%	Subject Count	%
Decreased appetite	19	3.6	12	4.5
Asthenia	18	3.4	8	3.0
Blood alkaline phosphatase increased	17	3.2	11	4.2
Gamma-glutamyltransferase increased	16	3.0	10	3.8
Diarrhea	16	3.0	1	0.4
Leukopenia	13	2.4	0	0.0
Platelet count decreased	13	2.4	0	0.0
Dyspnea	12	2.3	5	1.9
General physical health deterioration	12	2.3	4	1.5
Abdominal pain	11	2.1	8	3.0
Hypokalemia	11	2.1	2	0.8
Thrombocytopenia	11	2.1	1	0.4
Vomiting	11	2.1	1	0.4

Analyses were performed using the adverse events dataset, Grades 3 and 4 by treatment arm, to compare PT incidence greater than 2%.

Designated Medical Events (DME) were reviewed using MedDRA-Based Adverse Event Diagnostics (MAED) and did not show any unknown safety signals, including standardized MedDRA Queries (SMQs) and high level terms (HLT). SMQs are groupings of MedDRA terms that relate to a defined medical condition or area of interest.

Thromboembolic events were investigated at PT, HLT and SMQ levels. There was Grade 3-4 pulmonary emboli (PE) noted in 8 subjects (1.5%) on TAS-102 and no subjects on placebo. Two subjects were reported as related to TAS-102: subject 709-015 was listed as non-serious and resolved while subject 604-024 had concurrent disease progression and the CRF narrative said that PE could be due to underlying disease.

Minimal gliosis was reported in the brain and spinal cord of monkeys, so SMQs were queried for seizures. There were 2 subjects in each arm with generalized convulsive

seizures. Other PTs such as “neurological decompensation” and “neurotoxicity” were balanced between arms, if not more events occurred on placebo.

### 7.3.5 Submission Specific Primary Safety Concerns

To assess Hy’s law for potential hepatotoxicity, the dataset was queried to identify patients with ALT or AST > 3x ULN, total bilirubin  $\geq$  2 x ULN and alkaline phosphates  $\leq$  2 x ULN. Although these represent the laboratory criteria for Hy’s law, interpretation of these laboratory abnormalities in a patient population with metastatic CRC is challenging because these patients often experience hepatic dysfunction due to metastatic disease in the liver.

Thirty-one (5.8%) patients in the TAS-102 group and 24 (9.1%) patients in the placebo group had increased aminotransferase values (AT >3x ULN) in conjunction with increased bilirubin (>2x ULN), including 3 (0.6%) patients in the TAS-102 group and 2 (0.8%) patients in the placebo group with alkaline phosphatase (ALP) <2 x ULN or missing. Subject 566-001, who was treated on TAS-102, met criteria at the end of cycle 1 with the presentation of fever and neutropenia, and worsening of baseline biliary tree dilatation. For cycle 2, the patient was rechallenged at a reduced dose and went on to receive 8 cycles of TAS-102. Subject 705-005 was treated with TAS-102 and had baseline liver and hepatic nodal lesions, and was found to have jaundice on ultrasound at a regular visit for initiation of cycle 2. After stent placement, repeat imaging showed progressive disease and the patient was removed from study. Subject 707-001 on the TAS-102 treatment arm had SAE of bile duct stenosis on CT which presented with nausea and vomiting at the end of cycle 1. Imaging of the abdomen also revealed progressive disease and the patient was removed from study.

Fifty subjects (9.4%) treated with TAS-102 were identified as using granulocyte-colony stimulating factors, while there was no concomitant use of this medicine on the placebo arm.

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

The most common adverse events (AEs) in the TAS-102 treatment arm were nausea (48%), anemia (38.8%), decreased appetite (38.6%), fatigue (35.1%), diarrhea (31.9%), neutropenia (29.3%), and neutrophil count decreased (27.8%), as shown in Table 34.

The most common AEs in the placebo treatment arm were decreased appetite (28.7%), nausea (23.8%), fatigue (22.6%), constipation (15.1%), vomiting (14.3%), and diarrhea (12.5%). There was no subject with neutropenia and only one subject (0.4%) with

neutrophil count decreased, and it was low grade. The common AEs by preferred term (PT) for TAS-102 and placebo are summarized in Table 34.

Table 34: AEs by PT (incidence >10%) in descending order of frequency in AT population

Preferred Term	TAS-102 N=533				Placebo N=265			
	All Grades		Grades 3/4/5		All Grades		Grades 3/4/5	
	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%
Nausea	256	48.0	10	1.9	63	23.8	3	1.1
Anemia	207	38.8	83	15.6	22	8.3	7	2.6
Decreased appetite	206	38.6	19	3.6	76	28.7	12	4.5
Fatigue	187	35.1	21	3.9	60	22.6	13	4.9
Diarrhea	170	31.9	16	3.0	33	12.5	1	0.4
Neutropenia	156	29.3	107	20.1	0	0.0	0	0.0
Neutrophil count decreased	148	27.8	85	15.9	1	0.4	0	0.0
Vomiting	147	27.6	11	2.1	38	14.3	1	0.4
White blood cell count decreased	146	27.4	55	10.3	1	0.4	0	0.0
Pyrexia	98	18.4	6	1.1	37	14.0	1	0.4
Asthenia	94	17.6	18	3.4	30	11.3	8	3.0
Platelet count decreased	81	15.2	13	2.4	6	2.3	0	0.0
Constipation	80	15.0	1	0.2	40	15.1	3	1.1
Abdominal pain	79	14.8	11	2.1	34	12.8	9	3.4
Cough	55	10.3	2	0.4	30	11.3	2	0.8
Dyspnea	55	10.3	13	2.4	33	12.5	9	3.4
Edema peripheral	53	9.9	1	0.2	27	10.2	2	0.8
Blood alkaline phosphatase increased	46	8.6	17	3.2	24	9.1	11	4.2
Blood bilirubin increased	44	8.3	20	3.8	19	7.2	9	3.4
Stomatitis	42	7.9	2	0.4	16	6.0	0	0.0
Back pain	42	7.9	9	1.7	18	6.8	2	0.8

Preferred Term	TAS-102 N=533				Placebo N=265			
	All Grades		Grades 3/4/5		All Grades		Grades 3/4/5	
	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%
Weight decreased	41	7.7	1	0.2	27	10.2	0	0.0
Abdominal pain upper	38	7.1	1	0.2	12	4.5	1	0.4

The denominator used was for all patients in the AT population, and analyses were performed using the adverse events dataset. Incidences differ slightly from the applicant's and for the most part, are identical; both are clinically equivalent.

Abdominal pain was reported by the applicant in the proposed label using a composite term (preferred terms abdominal pain [14.8% in all grades TAS-102; 12.8% in placebo] plus abdominal pain upper [7.1% in all grades TAS-102; 4.5% in placebo] such that it appears that it occurred more frequently in patients receiving TAS-102 (21% in TAS-102 for all grades; 18% in placebo all grades), and as such this reviewer does not object to the more conservative analysis in labeling.

A total of 366 subjects (69%) on TAS-102 and 134 subjects (51%) on placebo experienced a  $\geq$  Grade 3 adverse event. The high incidence of  $\geq$  Grade 3 adverse events in the placebo arm most likely reflects disease progression, concomitant medicines, or other factors that could be reported as AEs.

**AE of special interest:**

Exploratory analyses were performed for terms related to coronary artery disease including acute myocardial infarction, angina pectoris, myocardial ischemia, and increased troponin. There were 3 subjects (0.6%) on the TAS-102 arm and 1 (0.4%) subject on placebo with PTs that met these criteria. When searching for terms related to arrhythmia including arrhythmia, atrial fibrillation, atrioventricular block, bradycardia, bundle branch block right, cardio-respiratory arrest, sinus bradycardia, sinus tachycardia, tachycardia, and ventricular arrhythmia, 15 subjects (2.8%) on TAS-102 and 9 subjects (3.8%) on placebo matriculated. There was 1 subject (559-004) on TAS-102 with 2 AEs in this category, sinus tachycardia and ventricular arrhythmia. Both were Grade 1 and there was no CRF available for review; however the AE was listed as not related to study medication. Subjects 562-024 and 360-007 on TAS-102 had SAEs with PTs listed above. Both were reported as not related to study medicine and related to non-study medication. Subject 307-002 had Grade 3 toxicity that was not related to study medicine or non-study medicine. The rest of the AEs were  $\leq$  toxicity Grade 2.

Nineteen subjects (3.6%) on TAS-102 and 4 (1.5%) on placebo had an AE described by one of the PTs listed: thrombosis in device, portal vein thrombosis, pulmonary embolism

(PE), axillary vein thrombosis, deep vein thrombosis, jugular vein thrombosis, pelvic venous thrombosis, superior vena cava syndrome, thrombosis, or venous thrombosis limb. Seven of the subjects on TAS-102 were reported as SAEs. Subjects 604-024 and 709-015 were reported as experiencing pulmonary embolism related to TAS-102 and were Grade 3 in severity. One subject's PE did not resolve (604-024) while the other subject's did (709-015).

Forty-two (7.9%) subjects on TAS-102 arm and 23 (8.7%) subjects on placebo arm experienced any PT listed as enterocolitis hemorrhagic, gastrointestinal hemorrhage, gingival bleeding, hematemesis, hematochezia, lower gastrointestinal hemorrhage, peritoneal hemorrhage, rectal hemorrhage, upper gastrointestinal hemorrhage, post procedural hemorrhage, hematuria, metrorrhagia, vaginal hemorrhage, or epistaxis. All subjects with these PTs considered related to TAS-102 were Grade  $\leq 2$  in severity and none were flagged as SAEs. Subject 202-008 had Grade 1 hemorrhagic enterocolitis reported as related, and recovered after 1 day.

The most common AEs by high-level term (HLT) in the TAS-102 treatment arm were: white blood cell analyses (37%), neutropenias (32%), and platelet analyses (15%), as shown in Table 35.

The most common AEs by HLT in the placebo treatment arm were white blood cell analyses (3%), and platelet analyses (2%). The common AEs by HLT are shown in Table 35.

Table 35: AEs by HLT in descending order of incidence in AT population

High Level Term	TAS-102 N=533		Placebo N=265	
	Subject Count	%	Subject Count	%
White blood cell analyses	195	37	7	3
Neutropenias	171	32	0	0
Platelet analyses	81	15	6	2
Thrombocytopenias	37	7	1	0.4
Alopecias	36	7	3	1
Leukopenias NEC	32	6	2	1
Dyspeptic signs and symptoms	16	3	1	0.4
Non-site specific injuries NEC	9	2	0	0
Pulmonary	9	2	0	0

High Level Term	TAS-102 N=533		Placebo N=265	
	Subject Count	%	Subject Count	%
thrombotic and embolic conditions				
Red blood cell analyses	8	2	0	0
Conjunctival infections, irritations and inflammations	6	1	0	0
Medication errors NEC	6	1	0	0
Anal and rectal pains	5	1	0	0
Muscle weakness conditions	5	1	0	0

Analyses were performed in the adverse event dataset and used HLT by treatment arm.

*REVIEWER COMMENT: In general, most of the HLTs in Table 35 were driven by a single preferred term. Therefore, the draft labelling described the more granular PTs rather than HLTs, with the exception of “asthenia/fatigue”, and this reviewer finds this clinically acceptable.*

The most common AEs by system organ class (SOC) in both treatment arms were gastrointestinal disorders, infections and infestations, and general disorders and administration site conditions, as shown in Table 36. The AEs occurred more frequently in the TAS-102 arm, and markedly so for blood and lymphatic system disorders, and investigations.

Table 36: AEs by SOC (incidence >5%) in descending order of frequency in AT population

Body System or Organ Class	TAS-102 N=533				Placebo N=265			
	All Grades		Grades 3/4/5		All Grades		Grades 3/4/5	
	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%
<b>Blood and lymphatic system disorders</b>								
<i>Anemia</i>	207	38.8	83	15.6	22	8.3	7	2.6
<i>Neutropenia</i>	156	29.3	107	20.1	0	0.0	0	0.0

Body System or Organ Class  Preferred Term	TAS-102 N=533				Placebo N=265			
	All Grades		Grades 3/4/5		All Grades		Grades 3/4/5	
	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%
<i>Thrombocytopenia</i>	37	6.9	11	2.1	1	0.4	1	0.4
<i>Leukopenia</i>	29	5.4	13	2.4	0	0.0	0	0.0
<b>Gastrointestinal disorders</b>								
<i>Nausea</i>	256	48.0	10	1.9	63	23.8	3	1.1
<i>Diarrhea</i>	170	31.9	16	3.0	33	12.5	1	0.4
<i>Vomiting</i>	147	27.6	11	2.1	38	14.3	1	0.4
<i>Constipation</i>	80	15.0	1	0.2	40	15.1	3	1.1
<i>Abdominal pain</i>	79	14.8	11	2.1	34	12.8	9	3.4
<i>Stomatitis</i>	42	7.9	2	0.4	16	6.0	0	0.0
<i>Abdominal pain upper</i>	38	7.1	1	0.2	12	4.5	1	0.4
<i>Ascites</i>	21	3.9	5	0.9	14	5.3	8	3.0
<b>General disorders and administration site conditions</b>								
<i>Fatigue</i>	187	35.1	21	3.9	60	22.6	13	4.9
<i>Pyrexia</i>	98	18.4	6	1.1	37	14.0	1	0.4
<i>Asthenia</i>	94	17.6	18	3.4	30	11.3	8	3.0
<i>Edema peripheral</i>	53	9.9	1	0.2	27	10.2	2	0.8
<i>Mucosal inflammation</i>	30	5.6	2	0.4	12	4.5	0	0.0
<i>General physical health deterioration</i>	21	3.9	18	3.4	15	5.7	12	4.5
<b>Investigations</b>								
<i>Neutrophil count decreased</i>	148	27.8	85	15.9	1	0.4	0	0.0
<i>White blood cell count decreased</i>	146	27.4	55	10.3	1	0.4	0	0.0
<i>Platelet count decreased</i>	81	15.2	13	2.4	6	2.3	0	0.0
<i>Blood alkaline phosphatase increased</i>	46	8.6	17	3.2	24	9.1	11	4.2
<i>Blood bilirubin increased</i>	44	8.3	20	3.8	19	7.2	9	3.4
<i>Weight decreased</i>	41	7.7	1	0.2	27	10.2	0	0.0
<i>Aspartate aminotransferase increased</i>	28	5.3	6	1.1	22	8.3	7	2.6
<i>Gamma-glutamyltransferase increased</i>	24	4.5	16	3.0	13	4.9	10	3.8
<b>Metabolism and nutrition disorders</b>								

Body System or Organ Class	TAS-102 N=533				Placebo N=265			
	All Grades		Grades 3/4/5		All Grades		Grades 3/4/5	
	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%
<i>Decreased appetite</i>	206	38.6	19	3.6	76	28.7	12	4.5
<i>Hyponatremia</i>	16	3.0	7	1.3	14	5.3	4	1.5
<b>Musculoskeletal and connective tissue disorders</b>								
<i>Back pain</i>	42	7.9	9	1.7	18	6.8	2	0.8
<b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b>								
<i>Tumor pain</i>	30	5.6	3	0.6	23	8.7	5	1.9
<b>Nervous system disorders</b>								
<i>Dysgeusia</i>	36	6.8	0	0.0	6	2.3	0	0.0
<i>Headache</i>	29	5.4	0	0.0	13	4.9	0	0.0
<b>Psychiatric disorders</b>								
<i>Insomnia</i>	24	4.5	0	0	25	9.4	0	0
<b>Respiratory, thoracic and mediastinal disorders</b>								
<i>Cough</i>	55	10.3	2	0.4	30	11.3	2	0.8
<i>Dyspnea</i>	55	10.3	13	2.4	33	12.5	9	3.4
<b>Skin and subcutaneous tissue disorders</b>								
<i>Alopecia</i>	36	6.8	0	0	3	1.1	0	0
<b>Vascular disorders</b>								
<i>Hypertension</i>	19	3.6	8	1.5	14	5.3	10	3.8

Table 34 and Table 36 were generated using STDM data and performed by FDA's Office of Computational Science. The numbers differ from the applicant's which were generated using analysis data (AdAM); however, in most cases the applicant's analyses were more conservative. In general, the differences were attributed to differences in determining which adverse events were "treatment emergent" and the applicant included more events in their analysis. In the draft label submitted, all analyses had < 1% absolute difference.

The overall incidence of blood and lymphatic disorder AEs (all grades) was higher in the TAS-102 group than in the placebo group, as was the incidence of AEs ≥ Grade 3. This was primarily due to a higher incidence of AEs associated with myelosuppression, a well described effect of TAS-102, including anemia, leukopenia, neutropenia and thrombocytopenia. The AE term "febrile neutropenia" was reported in 20 (3.8%) patients in the TAS-102 group compared to none in the placebo group. This was described in the label submitted by Taiho.

Gastrointestinal (GI) AEs of all grades were more frequent in the TAS-102 group than in the placebo group, including diarrhea, nausea, vomiting, and abdominal pain. However, the overall incidence of ≥ Grade 3 GI events was similar in the two treatment groups.

Adverse events of asthenia and fatigue (all grades) were more frequent in the TAS-102 group than in the placebo group; however, there was no difference between the groups in  $\geq$  Grade 3 AEs of asthenia and fatigue.

Other AEs that occurred more frequently with TAS-102 with a frequency of 5-10% (frequency of placebo in parentheses) include HLT “upper respiratory tract infection” 8% (3%) and “sensory abnormalities NEC” 7% (2%); and PTs “dysgeusia” 7% (2%), “alopecia” 7% (1%), stomatitis 8% (6%), mucosal inflammation 6% (5%), and back pain 8% (7%). Nine patients (1.7%) in the TAS-102 group had AEs of pulmonary embolism while there were none reported in the placebo arm.

#### 7.4.2 Laboratory Findings

Treatment with TAS-102 can lead to myelosuppression. As expected, treatment with TAS-102 resulted in a higher incidence of neutropenia, including a higher incidence of severe neutropenia, compared to placebo. Toxicity of neutrophils are summarized in Table 37 and Table 38.

Table 37: Neutrophil count by toxicity grades in RECOURSE

Treatment Arm	N (%) All toxicity grades	N (%) Toxicity Grade 0	N (%) Toxicity Grade 1	N (%) Toxicity Grade 2	N (%) Toxicity Grade 3	N (%) Toxicity Grade 4
TAS-102 N=533	353 (66)	180 (34)	36 (7)	117 (22)	140 (26)	60 (11)
Placebo N=265	3 (1)	262 (99)	1 (<1)	1 (0.4)	0	1 (<1)

Analysis was performed using the laboratory dataset (ADLB), and then subset by toxicity grade per subject and treatment arm. Incidence rates were rounded to the next integer except in cases where <1%. The neutropenia results are the same as the applicant has in their draft labelling, with incidence of Grade 3-4 neutropenia 38% in TAS-102.

The shift tables were generated by using subjects in the ADLB (laboratory) dataset (identified using a safety flag), then taking the minimum toxicity grade at baseline and comparing it to the maximum toxicity grade for however long the subject was on treatment, by treatment arm.

Table 38: Shift Table for Neutrophils on RECOURSE

Baseline	TAS-102 N=524; n (%)					Placebo N=263; n (%)				
	Grade					Grade				
Grade	0	1	2	3	4	0	1	2	3	4
Normal/0	173 (33)	36 (7)	116 (22)	136 (26)	59 (11)	261 (99)	1 (<1)	1 (<1)	0	0
1	0	0	1 (<1)	2 (<1)	1 (<1)	0	0	0	0	0

In order to perform an exploratory analysis of clinically relevant laboratory values, this reviewer used the minimum screening laboratory value to account for the possibility of a patient having more than one baseline value. The applicant had a slightly different denominator (varied from 1-3 subjects) for each shift table as they included the number of patients with at least one post-baseline measurement during treatment including patients with missing baseline, but all values were similar and the applicant's analysis was more conservative.

In this analysis, there was a higher incidence of patients treated with TAS-102 who developed higher grade neutropenia than compared to placebo, where there was minimal neutropenia observed. Thirty-seven percent of patients treated with TAS-102 experienced Grade 3-4 neutropenia. Note that there were 4 subjects who had ANC Grade > 1 at baseline (Grade 2=1, Grade 3=2, Grade 4=1) and were entered onto the trial even though the inclusion criteria required subjects to have ANC  $\geq$  1500 (or < Grade 1), and as such was a protocol violation.

Time to recovery from Grade 3-4 neutropenia to  $\geq$  Grade 1 ranged from 2-56 days, with a median of 8 days and a mean of 11 days. For the 188 patients with neutrophil laboratory values recorded as recovered from Grade 3 or 4, all were treated with TAS-102. Three quarters of the patients with Grade 3 or 4 neutropenia took less than 14 days to recover. Sixty patients had Grade 4 neutropenia. Note that any analysis of time to recovery in hematology parameters was limited by the fact that the protocol mandated hematology testing only on Week 2 and Week 4 of each cycle.

Fifty subjects (9.4%) treated with TAS-102 were identified in the concomitant medicine dataset (ADCM) as using granulocyte-colony stimulating factors, while there was no concomitant use of this medicine on the placebo arm. This is not surprising based on the myelosuppression observed with TAS-102 use and the duration of neutropenia as just described.

The analysis for anemia was performed using the ADLB (laboratory) dataset with the same methodology as described above for neutrophils, in Table 39. This methodology was applied across the entire laboratory section described here and below.

The incidence of Grade 3 anemia (18%) in the TAS-102 treatment arm was described in the applicant's draft label, and verified in the analysis below. Results were similar to the applicant's; however, as described above (based on the different methodology), the applicant's analyses in the CSR were more conservative based on inclusion of more subjects and can differ by a few subjects.

Table 39: Anemia by toxicity grades in RECURSE

Treatment Arm	N (%) All toxicity grades	N (%) Toxicity Grade 0	N (%) Toxicity Grade 1	N (%) Toxicity Grade 2	N (%) Toxicity Grade 3
TAS-102 N=528	404 (77)	166 (31)	190 (36)	260 (49)	95 (18)
Placebo N=263	86 (33)	132 (50)	49 (19)	35 (13)	8 (3)

Note: there is no CTCAE Grade 4 for anemia based on laboratory value. Toxicity grade analysis was performed using applicant's flagged baseline values per patient per treatment arm. Note that one patient could have had many toxicity Grades, such that the "All toxicity grades N" would exceed 100%.

Table 40: Shift Table for Anemia on RECURSE

Baseline	TAS-102 N=525; n (%)				Placebo N=263; n (%)			
	Grade				Grade			
Grade	0	1	2	3	0	1	2	3
Normal/0	20	127 (24)	61 (12)	14 (3)	55 (21)	48 (18)	4 (2)	1 (<1)
1	0	83 (16)	121 (23)	63 (12)	7 (2.7)	98 (37)	30 (11)	2 (1)
2	0	1 (<1)	16 (3)	19 (4)	0	3 (1)	10 (4)	5 (2)

This reviewer conducted the analysis of platelets using the laboratory datasets as described above for neutrophils and anemia. The incidence of Grade 3 or 4 thrombocytopenia (5%) in the TAS-102 treatment arm was confirmed and these results were described in the draft label submitted by the applicant. The Grade 3 and 4 toxicities (27 subjects, 5%) are listed by subject and percentage in each toxicity grade below (Table 41).

Table 41: Platelets by toxicity grades in RECOURSE

Treatment Arm	N (%) All toxicity grades	N (%) Toxicity Grade 0	N (%) Toxicity Grade 1	N (%) Toxicity Grade 2	N (%) Toxicity Grade 3	N (%) Toxicity Grade 4
TAS-102 N=533	223 (42)	498 (93)	194 (36)	62(12)	27 (5)	3 (<1)
Placebo N=265	19 (7)	252 (95)	17 (6)	1 (<1)	1 (<1)	1 (<1)

Table 42: Shift Table for Thrombocytopenia on RECOURSE

Baseline	TAS-102 N=525; n (%)					Placebo N=263; n (%)				
	Grade					Grade				
Grade	0	1	2	3	4	0	1	2	3	4
Normal/0	262 (50)	156 (30)	20 (4)	15 (3)	1 (<1)	216 (82)	20 (8)	0	0	1 (<1)
1	1 (<1)	41 (8)	18 (3)	9 (2)	2 (<1)	4 (2)	21 (8)	1 (<1)	0	0

As described above for neutrophils and anemia, the applicant's results described in the CSR were more conservative based on the methodology used. The applicant found that among patients with normal platelet counts at baseline, 4.5% experienced Grade 3 thrombocytopenia and 0.6% Grade 4 thrombocytopenia. The above analyses confirm that 5% experienced Grade 3 (3% from baseline and 2% from Grade 1) and 0.6% experienced Grade 4. The incidence of Grade 3 or 4 thrombocytopenia (5%) in the TAS-102 treatment arm was confirmed and these results were described in the draft label submitted by the applicant.

Table 43: Sodium by toxicity grades in RECOURSE

Treatment Arm	N (%) All toxicity grades	N (%) Toxicity Grade 0	N (%) Toxicity Grade 1	N (%) Toxicity Grade 2	N (%) Toxicity Grade 3	N (%) Toxicity Grade 4
TAS-102 N=533	264 (50)	269 (50)	230 (43)	1 (<1)	33 (6)	0
Placebo N=265	120 (45)	145 (55)	101 (38)	0	16 (6)	3 (<1)

Due to the common AE of diarrhea in all Grades (31.9% in TAS-102; 12.5% in placebo), and vomiting (27.6%, 14.3%, respectively) sodium and potassium abnormalities were explored. Both hyponatremia and hypernatremia were analyzed together, but the majority of toxicity was hyponatremia. The incidences in toxicities were similar in both

treatment arms. Shifts from baseline were also similar between arms. About half of patients in each treatment arm experienced sodium abnormalities. Six percent of patients had  $\geq$  Grade 3 toxicity, as seen in Table 43. The shift from normal to abnormal sodium was comparable for both treatment arms, while only grade 4 sodium abnormalities were seen in the placebo group, in which there was a total of 3 patients that shifted up to Grade 4, and summarized in see Table 44.

Table 44: Shift Table for hyponatremia on RECOURSE

Baseline	TAS-102 N=521; n (%)					Placebo N=261; n (%)				
	Grade					Grade				
Grade	0	1	2	3	4	0	1	2	3	4
Normal/0	280 (54)	165 (32)	0	17 (3)	0	151 (58)	73 (28)	0	10 (4)	1 (<1)
1	17 (3)	29 (6)	0	10 (2)	0	6 (2)	14 (5)	0	3 (1)	1 (<1)
3	0	0	0	3 (0.6)	0	0	0	0	1 (<1)	1 (<1)

Table 45: Potassium by toxicity grades in RECOURSE

Treatment Arm	N (%) All toxicity grades	N (%) Toxicity Grade 0	N (%) Toxicity Grade 1	N (%) Toxicity Grade 2	N (%) Toxicity Grade 3	N (%) Toxicity Grade 4
TAS-102 N=533	203 (38)	330 (62)	169 (32)	12 (2)	18 (3)	4 (1)
Placebo N=265	93 (35)	172 (65)	64 (24)	17 (6)	12 (5)	0

Hypo and hyperkalemia were analyzed together, and toxicity results may be confounded by concomitant medicines such as diuretics. Never the less, about a third of patients in each treatment group experienced potassium abnormalities. Grade  $\geq$  3 toxicity was higher in placebo (5%) than TAS-102 (3%), but only marginally so. There were 4 patients (1%) who experienced Grade 4 potassium levels, all of whom were receiving TAS-102. Half of these patients shifted to a maximum toxicity of Grade 4 (total incidence of Grade 4 shift was <1%, see Table 46). The shift to a higher toxicity grade was greater on the TAS-102 arm, which was most likely attributable to the higher AE rates of diarrhea and vomiting seen with TAS-102.

Table 46: Shift Table for potassium on RECOURSE

Baseline	TAS-102 N=521; n (%)					Placebo N=261; n (%)				
	Grade					Grade				
Grade	0	1	2	3	4	0	1	2	3	4
Normal/0	337 (65)	115 (22)	8 (2)	11 (2)	1 (<1)	174 (67)	46 (18)	8 (3)	9 (3)	0
1	14 (3)	27 (5)	1 (<1)	5 (1)	0	7 (3)	7 (3)	7 (3)	2 (1)	0
2	0	0	1 (0.2)	0	0	0	0	0	0	0
3	0	0	0	0	1 (<1)	1 (<1)	0	0	0	0

While the toxicity for sodium and potassium was relatively balanced between treatment arms on RECOURSE, hypocalcemia was more prevalent in the TAS-102 arm (42%) as compared to placebo (30%). There was a higher incidence of hypocalcemia in toxicity Grade 1 (32%), Grade 2 (9%) and Grade 4 (<1%) in TAS-102 subjects compared with placebo, as shown in Table 47. The only grade 4 toxicity in calcium was seen in TAS-102 (<1%) with 2 patients shifting to Grade 4 toxicity, which is summarized in Table 48.

Table 47: Calcium by toxicity grades in RECOURSE

Treatment Arm	N (%) All toxicity grades	N (%) Toxicity Grade 0	N (%) Toxicity Grade 1	N (%) Toxicity Grade 2	N (%) Toxicity Grade 3	N (%) Toxicity Grade 4
TAS-102 N=530	222 (42)	308 (58)	169 (32)	49 (9)	2 (<1)	2 (<1)
Placebo N=264	80 (30)	184 (70)	60 (23)	18 (7)	2 (1)	0

Table 48: Shift Table for calcium in RECOURSE

Baseline	TAS-102 N=507; n (%)					Placebo N=251; n (%)				
	Grade					Grade				
Grade	0	1	2	3	4	0	1	2	3	4
Normal/0	298 (59)	126 (25)	30 (6)	1 (0.2)	1 (0.2)	180 (72)	47 (19)	8 (3)	1 (<1)	0
1	11 (2)	23 (5)	11 (2)	1 (<1)	0	2 (1)	5 (2)	5 (2)	1 (<1)	0
2	2 (<1)	2 (<1)	0	0	0	0	0	0	0	0
3	0	0	0	0	1 (<1)	1 (<1)	0	1	0	0

Clinical Review

Leigh Marcus

NDA 207981

TAS-102 (Lonsurf) for the treatment of patients with metastatic colorectal cancer

								( $<1$ )		
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Note that there may be slight differences of 1-2 subjects between this analysis for Grades 1 and the applicant due to combining hyper- and hypo- toxicities. Grades 2-4 matched in both reviews.

Diarrhea can cause hypomagnesemia, so magnesium levels were evaluated, and abnormalities in TAS-102 (all grades, 25%) might be more pronounced than in placebo (all grades, 17%). Table 49 summarizes magnesium toxicities in TAS-102 arm versus placebo.

Table 49: Magnesium by toxicity grades in RECURSE

Treatment Arm	N (%) All toxicity grades	N (%) Toxicity Grade 0	N (%) Toxicity Grade 1	N (%) Toxicity Grade 2	N (%) Toxicity Grade 3	N (%) Toxicity Grade 4
TAS-102 N=177	45 (25)	132 (75)	39 (22)	1 (0.6)	4 (2)	1 (1)
Placebo N=89	15 (17)	73 (82)	14 (16)	1 (1)	0	0

Renal toxicity, as assessed by creatinine levels, was similar in each treatment arm with an incidence of about 20%, as shown in Table 50. Four patients (1%) shifted from baseline to Grade 3 creatinine toxicity on TAS-102 while there was 1 patient ( $<1\%$ ) that shifted to Grade 3 and 4 each, respectively, on the placebo arm, which is summarized in Table 51.

Table 50: Creatinine by toxicity grades in RECURSE

Treatment Arm	N (%) All toxicity grades	N (%) Toxicity Grade 0	N (%) Toxicity Grade 1	N (%) Toxicity Grade 2	N (%) Toxicity Grade 3	N (%) Toxicity Grade 4
TAS-102 N=533	107 (20)	426 (80)	80 (15)	20 (4)	6 (1)	1 ( $<1$ )
Placebo N = 265	51 (19)	214 (81)	41 (15)	8 (3)	1 ( $<1$ )	1 ( $<1$ )

Table 51: Shift Table for creatinine on RECOURSE

Baseline	TAS-102 N=525; n (%)					Placebo N=261; n (%)				
	Grade					Grade				
Grade	0	1	2	3	4	0	1	2	3	4
Normal/0	426 (81)	49 (9)	10 (2)	4 (0.8)	0	213 (82)	24 (9)	6 (2)	1 (<1)	(<1)
1	3 (0.6)	25 (5)	7 (1)	1 (0.2)	0	3 (1)	12 (5)	1 (0.4)	0	0

The incidence of transaminitis was balanced between arms with aspartate aminotransferase (AST) all grades toxicity at about 60%, and alanine aminotransferase (ALT) all grades toxicity at 42%, as shown in Table 52 and Table 54. However, the shift tables were imbalanced between treatment arms, both with worse levels in patients who received placebo. Patients' AST levels shifted to Grades 3 and 4 on placebo (6%) more often than while on TAS-102 (4.6%), shown in Table 53. Patients' ALT levels shifted to Grades 3 and 4 on placebo (2%) more often than while on TAS-102 (4%), as shown in Table 55.

Table 52: Aspartate aminotransferase (AST) by toxicity grades in RECOURSE

Treatment Arm	N (%) All toxicity grades	N (%) Toxicity Grade 0	N (%) Toxicity Grade 1	N (%) Toxicity Grade 2	N (%) Toxicity Grade 3	N (%) Toxicity Grade 4
TAS-102 N=533	321 (60)	212 (40)	246 (46)	48 (9)	25 (5)	2 (<1)
Placebo N=265	161 (61)	104 (39)	110 (42)	32 (12)	16 (6)	3 (1)

Table 53: Shift Table for AST in RECOURSE

Baseline	TAS-102 N=521; n (%)					Placebo N=260; n (%)				
	Grade					Grade				
Grade	0	1	2	3	4	0	1	2	3	4
Normal/0	222 (43)	99 (19)	3 (0.6)	5 (1)	2 (0.4)	108 (42)	50 (19)	8 (3)	2 (0.8)	0
1	15 (3)	120 (23)	29 (6)	10 (2)	0	2 (0.8)	56 (22)	18 (7)	8 (3)	1 (<1)
2	0	5 (1)	4 (1)	6 (1)	0	0	0	2 (1)	3 (1)	2 (1)
3	0	0	0	1 (<1)	0	0	0	0	0	0

Table 54: Alanine aminotransferase (ALT) by toxicity grades in RECURSE

Treatment Arm	N (%) All toxicity grades	N (%) Toxicity Grade 0	N (%) Toxicity Grade 1	N (%) Toxicity Grade 2	N (%) Toxicity Grade 3	N (%) Toxicity Grade 4
TAS-102 N=533	222 (42)	311 (58)	183 (34)	29 (5)	9 (2)	1 (<1)
Placebo N=265	110 (42)	155 (58)	87 (33)	12 (5)	9 (3)	2 (1)

Table 55: Shift Table for ALT in RECURSE

Baseline	TAS-102 N=523; n (%)					Placebo N=262; n (%)				
	Grade					Grade				
Grade	0	1	2	3	4	0	1	2	3	4
Normal/0	314 (60)	92 (18)	10 (2)	6 (1)	1 (<1)	157 (60)	53 (20)	6 (2)	3 (1)	1 (<1)
1	15 (3)	64 (12)	12 (2)	3 (1)	0	6 (2)	27 (10)	2 (1)	2 (1)	0
2	0	2 (<1)	4 (1)	0	0	0	0	1 (<1)	3 (1)	1 (<1)

Hyperbilirubinemia was found with a higher incidence in the TAS-102 arm (all Grades toxicity of 39%) compared to placebo (31%). Grade 3 or greater hyperbilirubinemia was seen in placebo more frequently in patients who received placebo (Grade 3 toxicity was 9% and Grade 4 toxicity was 4%) compared to TAS-102 (Grade 3 was 8% and Grade 4 was 2%). Full details of total bilirubin toxicity are listed below in Table 56.

Table 56: Hyperbilirubinemia by toxicity grades in RECURSE

Treatment Arm	N (%) All toxicity grades	N (%) Toxicity Grade 0	N (%) Toxicity Grade 1	N (%) Toxicity Grade 2	N (%) Toxicity Grade 3	N (%) Toxicity Grade 4
TAS-102 N=532	206 (39)	326 (61)	90 (17)	65 (12)	42 (8)	9 (2)
Placebo N=265	83 (31)	182 (69)	29 (11)	20 (8)	24 (9)	10 (4)

Shifts in bilirubin to higher grade toxicity were slightly higher in the placebo arm (Grade 3 was 9% and Grade 4 was 3%) compared to TAS-102 (Grade 3 was 7% and Grade 4 was 1%).

Table 57: Shift Table for Hyperbilirubinemia in RECOURSE

Baseline	TAS-102 N=520; n (%)					Placebo N=257; n (%)				
	Grade					Grade				
Grade	0	1	2	3	4	0	1	2	3	4
Normal/0	323 (62)	82 (16)	47 (9)	33 (6)	5 (1)	181 (70)	23 (9)	11 (4)	16 (6)	6 (2)
1	4 (1)	6 (1)	13 (3)	5 (1)	1 (<1)	2 (1)	3 (1)	4 (2)	5 (2)	2 (1)
2	0	0	0	1 (<1)	0	0	0	2 (1)	2 (1)	0

Note that the applicant had more subjects in the total denominator, and had a more conservative analysis however the analysis above matched the applicant for Grades 3-4.

In order to further explore TAS-102 toxicity in the setting of metastatic CRC, the laboratory dataset was queried to search for subjects with increased AST and ALT  $\geq 3x$  ULN and TB  $\geq 2x$  ULN with ALP  $\leq 2x$  ULN (Hy's law). There were 3 subjects who met laboratory criteria for Hy's law, summarized in Table 58. None of these subjects met the complete criteria for Hy's law because the liver dysfunction could be explained due to causes other than drug toxicity.

Table 58: Subject's treated on TAS-102 arm meeting Hy's Law

Subject on TAS-102	Time point	Narrative	Rechallenged? Why?
566-001	End of Cycle 1	Presented with fever and neutropenia, and worsening of baseline biliary tree dilatation.	Yes Reduced Dose Cycle 2-8
705-005	End of Cycle 1	Baseline liver and hepatic nodal lesions, was found to have jaundice on ultrasound at a regular visit.	No After stent placement, repeat imaging showed PD. Removed from study
707-001	End of Cycle 1	SAE of bile duct stenosis on CT which presented with nausea and vomiting.	No Imaging of the abdomen revealed PD. Removed from study

#### 7.4.3 Vital Signs

No clinically relevant differences between arms were observed in mean or median changes in body weight or vital signs.

#### 7.4.4 Electrocardiograms (ECGs)

Cardiac safety was investigated in Study TPU-TAS-102-103, a Phase 1, non-randomized, open-label study in patients with advanced solid tumors conducted in Europe (United Kingdom [UK]) and the US. A total of 30 patients were evaluated for both cardiac safety and pharmacokinetics (PK). TAS-102 had no clinically relevant QTc prolongation effect compared with placebo based on the results of the linear model for the relationship between plasma FTD, FTY, and TPI concentrations and placebo-adjusted baseline-subtracted QTc intervals. No patient had a QT, QTcF, or QTcB interval >500 msec at any time point, and there were no morphological changes for T waves or U waves for any patients. No clinically relevant changes from baseline or differences between treatment groups were observed. TAS-102 did not appear to be arrhythmogenic as evidenced by the absence of AEs of ventricular tachycardia, ventricular fibrillation, syncope, and seizure. Please refer to QT Interdisciplinary Review Team review for additional details.

#### 7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were conducted or reported.

#### 7.4.6 Immunogenicity

This section is not applicable to this drug product.

### 7.5 Other Safety Explorations

#### 7.5.1 Dose Dependency for Adverse Events

Patients in both the pivotal trial and supportive trial received 35mg/m<sup>2</sup> TAS-102 given twice daily for 5 days with 2 days rest, then 5 days again with 2 days rest, followed by 14 days off drug (28 day cycle).

#### 7.5.2 Time Dependency for Adverse Events

Using the exposure dataset, following the first tumor assessment at the end of Cycle 1, 87% of patients in the TAS-102 group and 81% of patients in the placebo group continued to Cycle 2; 43% of patients in the TAS-102 group and 18% of patients in the placebo group continued to Cycle 3. The median time on TAS-102 was 84 days. Eighty-four percent of subjects on TAS-102 discontinued treatment due to disease progression. This was difficult to interpret exploratory analyses of AEs correct for time on treatment.

Grade 4 neutropenia was reported in 60 patients (11%) on the TAS-102 arm; there was no Grade 4 neutropenia events on placebo. Table 59 summarizes the subjects with Grade 4 neutropenia by cycle on therapy.

Table 59: Grade 4 neutropenia in RECURSE, TAS-102 arm only

Cycle	TAS-102 N=533 n/%
1	19/3.6
2	26/5.6
3	12/5.2
4	8/4.2
5	5/4.3
6	7/7.2
7	6/10
8	2/4.5
9	1/3.1
10	1/4

Analysis performed using the laboratory dataset, Grade 4 neutropenia by cycle number by subject. Patients can have multiple events, for example, neutropenia in both cycle 1 and 2 (there were 88 Grade 4 neutropenia events in total).

Four percent of subjects on TAS-102 and 1.5% on placebo listed AE as reason for discontinuation. Below are tabular listings of key adverse events by duration on therapy, up to just beyond the median time on therapy (84 days or 3 cycles).

There were 13 patients (1.6%) with Grade 3 nausea: 10 (1.9%) on the TAS-102 arm and 3 (1.1%) on placebo. Of note, there was no Grade 4 nausea events reported in either arm. Table 60 summarizes Grade 3 nausea by cycle length.

Table 60: Grade 3 Nausea by Cycle

Cycle	TAS-102 N=533 n/%	Placebo N=233 n/%
1	3/0.6	1/0.4
2	2/0.4	2/0.9
3	3/1.3	0
4	2/1	0

Analysis was performed per event, so it is possible that the same subject reported nausea during cycles 1, 2, and so forth. The denominator is how many patients initiated that cycle.

There were 16 subjects with Grade 3-4 diarrhea on TAS-102 and 1 subject experienced Grade 3 diarrhea on placebo. To note, there was one Grade 4 diarrhea event on TAS-102. Table 61 summarizes Grade 3-4 diarrhea by cycle.

Table 61: Grade 3-4 Diarrhea by Cycle

Cycle	TAS-102 N=533 n/%	Placebo N=265 n/%
1	6/1.1	1/0.4
2	5/1.1	0
3	2/0.9	0
4	1/0.5	0

Analysis was performed per event (not subject), so it is possible that the same subject reported diarrhea during cycles 1, 2, and so forth.

### 7.5.3 Drug-Demographic Interactions

In order to allow for a more substantive analysis, this review of adverse events related to drug-demographic interactions will focus on adverse reactions potentially related to TAS-102. Primarily they are analyses of myelotoxicity and gastrointestinal disorders.

#### Age

There were 299 patients (56%) in the TAS-102 arm who were <65 years old and 234 (44%) who were ≥ 65 years of age. There were no clinically meaningful differences in the incidence rates of AEs per arm based on age category. There were 2 subjects on TAS-102 and 1 subject on placebo who the applicant counted as having a SAE due to the event starting prior to the first dose with an increase in toxicity grade after dosing. There were no signals observed when reviewing the applicant's summary table versus Table 62 below. SAEs were near balanced between arms and across age categories. There were more deaths in general on placebo and age category did appear to influence the number of deaths.

Table 62: Summary Table of AEs by age in RECURSE:

Age	TAS-102; n (%) N=533		Placebo; n (%) N=265	
	< 65 N=299	≥ 65 N=234	< 65 N=147	≥ 65 N=118
Subjects who experienced an AE	293 (98)	231 (99)	137 (93)	110 (93)
Subjects who experienced a SAE	84 (28)	72 (31)	45 (31)	43 (37)
Deaths related to an AE	12 (4)	5 (2)	16 (11)	14 (12)

The subject disposition and demographic dataset was analyzed for all ages, and then the adverse event dataset was analyzed for all AE, deaths, and serious adverse events.

There were more reported adverse events in TAS-102-treated subjects caused by nausea, decreased appetite, fatigue, diarrhea, vomiting, anemia, neutropenia, pyrexia, asthenia, abdominal pain, and decreased platelet counts regardless of age.

In general, adverse events occurred at a similar incidence rate in TAS-102 treated patients irrespective of age. The only category of adverse reactions that had greater than 5% difference in incidence rate in TAS-102-treated patients was myelotoxicity.

Based on clinical laboratory assessments, patients  $\geq 65$  years of age in the TAS-102 group had a higher incidence (difference of at least 5%) of Grade 3 or 4 neutropenia (47% vs 30.1%), Grade 3 anemia (25.6% vs 13%) and Grade 3 or 4 thrombocytopenia (8.5% vs 2.3%) than younger patients. The applicant used the toxicity grade for the exact number of subjects per age category, while my analysis used all comer subjects in the appropriate age category, which explains the  $<1\%$  difference.

Table 63: Selected AEs by age group in RECURSE

Preferred Term	TAS-102 N=533				Placebo N=265			
	Age < 65 N=299		Age $\geq 65$ N=234		Age < 65 N=147		Age $\geq 65$ N=118	
	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%
Nausea	154	51.5	102	43.6	40	27.2	23	19.5
Decreased appetite	109	36.5	97	41.5	47	32.0	29	24.6
Fatigue	102	34.1	85	36.3	36	24.5	24	20.3
Diarrhea	95	31.8	75	32.1	21	14.3	12	10.2
Vomiting	89	29.8	58	24.8	27	18.4	11	9.3
Anemia	94	31.4	113	48.3	11	7.5	11	9.3
Neutropenia	79	26.4	77	32.9	0	0	0	0
Neutrophil count decreased	75	25.1	73	31.2	1	0.7	0	0
Pyrexia	55	18.4	43	18.4	20	13.6	17	14.4
White blood cell count decreased	72	24.1	74	31.6	1	0.7	0	0
Asthenia	50	16.7	44	18.8	16	10.9	14	11.9
Constipation	46	15.4	35	15.0	20	13.6	20	16.9
Abdominal pain	42	14.0	37	15.8	18	12.2	16	13.6
Platelet count decreased	31	10.4	50	21.4	3	2.0	3	2.5
Weight decreased	18	6.0	23	9.8	15	10.2	12	10.2

In adverse events dataset, incidence was analyzed per subject per AE based on treatment arm, age category, and PT.

There were more deaths on placebo than on the TAS-102 arm attributable to AEs. Upon review of CRFs, many AE in the TAS-102 arm might have been due to disease progression. Table 64 summarizes the AEs with fatal outcomes by age group and arm. There were no identifiable trends regarding age and fatal outcome.

Table 64: Fatal AEs by age group in RECOURSE

Preferred Term	TAS-102 N=533				Placebo N=265			
	Age < 65 N=299		Age ≥ 65 N=234		Age < 65 N=147		Age ≥ 65 N=118	
	Subject Count	%						
General physical health deterioration	5	1.7	1	0.4	6	4.1	2	1.7
Hepatic failure	2	0.7	0	0	4	2.7	2	1.7
Renal failure acute	2	0.7			0	0		
Dyspnea	1	0.3	0	0	2	1.4	2	1.7
Pleural effusion	1	0.3	0	0	0	0	1	0.8
Pneumonia staphylococcal	1	0.3	0	0	0	0	0	0
Abdominal pain	0	0	0	0	1	0.7	0	0
Bile duct obstruction	0	0	0	0	1	0.7	0	0
Cognitive disorder	0	0	0	0	1	0.7	0	0
Hepatic encephalopathy	0	0	0	0	1	0.7	0	0
Intestinal perforation	0	0	0	0	1	0.7	0	0
Respiratory arrest	0	0	0	0	1	0.7	0	0
Small intestinal obstruction	0	0	0	0	1	0.7	0	0
Liver Abscess	0	0	1	0.4	0	0	0	0
Pulmonary Embolism	0	0	1	0.4	0	0	0	0
Pulmonary Edema	0	0	1	0.4	0	0	0	0
Sepsis	0	0	1	0.4	0	0	0	0
Septic Shock	0	0	1	0.4	0	0	0	0
Acidosis	0	0	0	0	0	0	1	0.8
Cardio-respiratory arrest	0	0	0	0	0	0	1	0.8
Gastrointestinal hemorrhage	0	0	0	0	0	0	1	0.8
Hematemesis	0	0	0	0	0	0	1	0.8
Hemorrhage intracranial	0	0	0	0	0	0	1	0.8
Jaundice	0	0	0	0	0	0	1	0.8
Lymphangiosis carcinomatosa	0	0	0	0	0	0	1	0.8
Malignant ascites	0	0	0	0	0	0	1	0.8
Pulmonary congestion	0	0	0	0	0	0	1	0.8
Renal failure	0	0	0	0	0	0	1	0.8
Renal impairment	0	0	0	0	0	0	1	0.8

In adverse events dataset, incidence was analyzed per subject per death based on treatment arm, age category, and PT.

**Gender**

There were a high number of AEs overall in both sexes, only slightly higher in TAS-102. There were fewer SAEs in TAS-102 for males compared to placebo. There were fewer deaths overall on TAS-102 compared to placebo and gender did not appear to have any association with this outcome. Table 65 summarizes the summary incidences of AEs and gender.

Table 65: Summary Table of AEs by gender in RECOURSE

Gender	TAS-102; n (%) N=533		Placebo; n (%) N=265	
	Male N=326	Female N=207	Male N=164	Female N=101
Subjects who experienced an AE	322 (99)	202 (98)	152 (93)	95 (94)
Subjects who experienced a SAE	88 (27)	68 (33)	60 (37)	28 (28)
Deaths related to an AE	21 (6)	4 (2)	13 (8)	9 (9)

The subject disposition and demographic dataset was analyzed for gender, and then the adverse event dataset was analyzed for all AE, deaths, and serious adverse events.

Women exposed to TAS-102 experienced more gastrointestinal toxicity including nausea (54.6% versus 43.9%) and vomiting (42% versus 18.4%) than men. There were 5 women (2.5%) on the TAS-102 arm that had Grade 3 vomiting, 2 of which had Grade 3 vomiting at the start of study medicine; there were 6 men (1.8%) with Grade 3 vomiting, 5 of which had Grade 3 vomiting at the starting dose of TAS-102. Women also experienced more diarrhea (37.2% versus 28.5%) and abdominal pain (see Table 66) than men. The incidence rate of gastrointestinal toxicity also was higher in women in the placebo arm; however, the difference in magnitude appeared larger in the TAS-102 arm.

In general the rates of myelotoxicity between men and women by AE were comparable. However, based on clinical laboratory assessments, female patients who received TAS-102 had a higher incidence (difference of at least 5%) of Grade 3 or 4 neutropenia (42% vs 34.7%), and Grade 3 anemia (24.2% vs 15%) than male patients, with a similar incidence of Grade 3 or 4 thrombocytopenia (4.3% vs 5.5%). Table 66 lists AE by PT and gender.

Table 66: Selected AEs by gender in RECOURSE:

Preferred Term	TAS-102 N=533				Placebo N=265			
	Male N=326		Female N=207		Male N=164		Female N=101	
	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%
Nausea	143	43.9	113	54.6	31	18.9	32	31.7
Decreased appetite	120	36.8	86	41.5	43	26.2	33	32.7

Preferred Term	TAS-102 N=533				Placebo N=265			
	Male N=326		Female N=207		Male N=164		Female N=101	
	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%
Anemia	118	36.2	89	43.0	10	6.1	12	11.9
Fatigue	110	33.7	77	37.2	31	18.9	29	28.7
Neutropenia	97	29.8	59	28.5	0	0.0	0	0
Diarrhea	93	28.5	77	37.2	19	11.6	14	13.9
Neutrophil count decreased	86	26.4	62	30.0	1	0.6	0	0
White blood cell count decreased	86	26.4	60	29.0	1	0.6	0	0
Vomiting	60	18.4	87	42.0	18	11.0	20	19.8
Pyrexia	59	18.1	39	18.8	22	13.4	15	14.9
Asthenia	54	16.6	40	19.3	20	12.2	10	9.9
Platelet count decreased	52	16.0	29	14.0	4	2.4	2	2
Constipation	45	13.8	36	17.4	24	14.6	16	15.8
Abdominal pain	41	12.6	38	18.4	21	12.8	13	12.9
Edema peripheral	27	8.3	26	12.6	17	10.4	10	9.9
Weight decreased	26	8.0	15	7.2	16	9.8	11	10.9
Abdominal pain upper	13	4.0	25	12.1	7	4.3	5	5.0
Alopecia	16	4.9	20	9.7	0	0	3	3.0

In adverse events dataset, incidence was analyzed per subject per AE based on treatment arm, gender, and PT. The applicant included subjects with toxicity grade that increased after the first dose of drug, which is more comprehensive and this reviewer find this acceptable.

The most frequent cause of death in all subgroups was disease progression. Based on Table 67, there was no difference in fatal outcomes due to gender.

Table 67: Fatal AEs by gender group in RECOURSE:

Preferred Term	TAS-102 N=533				Placebo N=265			
	Male N=326		Female N=207		Male N=164		Female N=101	
	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%
General physical health deterioration	4	1.2	2	1	6	3.7	2	2
Hepatic failure	2	0.6	0	0	3	1.8	3	3
Dyspnea	1	0.3	0	0	3	1.8	1	1
Liver abscess	1	0.3	0	0	0	0	0	0
Pneumonia staphylococcal	1	0.3	0	0	0	0	0	0
Pulmonary embolism	1	0.3	0	0	0	0	0	0
Pulmonary edema	1	0.3	0	0	0	0	0	0
Renal failure acute	1	0.3	1	0.5	0	0	0	0

Preferred Term	TAS-102 N=533				Placebo N=265			
	Male N=326		Female N=207		Male N=164		Female N=101	
	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%
Sepsis	1	0.3	0	0	0	0	0	0
Septic shock	1	0.3	0	0	0	0	0	0
Acidosis	0	0	0	0	1	0.6	0	0
Bile duct obstruction	0	0	0	0	1	0.6	0	0
Cardio-respiratory arrest	0	0	0	0	1	0.6	0	0
Gastrointestinal hemorrhage	0	0	0	0	1	0.6	0	0
Hemorrhage intracranial	0	0	0	0	1	0.6	0	0
Intestinal perforation	0	0	0	0	1	0.6	0	0
Lymphangiosis carcinomatosa	0	0	0	0	1	0.6	0	0
Pleural effusion	0	0	1	0.5	1	0.6	0	0
Pulmonary congestion	0	0	0	0	1	0.6	0	0
Renal failure	0	0	0	0	1	0.6	0	0
Renal impairment	0	0	0	0	1	0.6	0	0
Respiratory arrest	0	0	0	0	1	0.6	0	0
Abdominal Pain	0	0	0	0	0	0	1	1
Cognitive disorder	0	0	0	0	0	0	1	1
Hematemesis	0	0	0	0	0	0	1	1
Hepatic encephalopathy	0	0	0	0	0	0	1	1
Jaundice	0	0	0	0	0	0	1	1
Malignant ascites	0	0	0	0	0	0	1	1
Small intestinal obstruction	0	0	0	0	0	0	1	1

In adverse events dataset, incidence was analyzed per subject per death based on treatment arm, gender, and PT.

### **Race**

Only 9 Black patients were randomized (4 TAS-102, 5 placebo). The analysis of adverse events in Asian patients were assessed in the “Geographic Region” analysis, below.

### **Geographic Region**

Subjects were stratified by geographic region (Region 1: Asia [Japan]; Region 2: Western [Australia, Europe, U.S.]). There were equal numbers of subjects who experienced an AE on each treatment arm, which was universal between geographic regions. There was little difference in SAEs between Western region (31%) and Asia (26%) in subjects on the TAS-102 arm. Deaths were balanced according to region, and there were more deaths related to AE on placebo.

Table 68: Summary Table of AEs by geographic region in RECOURSE

Geographic Region	TAS-102; n (%) N=533		Placebo; n (%) N=265	
	Western N=355	Asia N=178	Western N=177	Asia N=88
Subjects who experienced an AE	347 (98)	177 (99)	166 (94)	81 (92)
Subjects who experienced a SAE	109 (31)	47 (26)	54 (31)	34 (39)
Deaths related to an AE	14 (4)	3 (2)	20 (11)	10 (11)

The subject disposition and demographic dataset was analyzed for geographic region, and then the adverse event dataset was analyzed for all AE, deaths, and serious adverse events. There were a few more SAEs in the analysis by the applicant for SAEs that started prior to the first dose of study medicine, which this reviewer finds acceptable.

Differences in the rates of adverse events related to myelotoxicity were noted in Table 69; however, these differences are difficult to interpret. For example, there seems to be an imbalance of neutropenia between arms, however, neutropenia was not consistently reported by investigators between regions within the MedDRA hierarchy. For example, the PT “neutropenia” was reported in 152 subjects (43%) in the West (HLT “neutropenias” incidence 44%) and in 4 subjects (2%) in Asia (HLT incidence is 8%). The incidence of PT “neutrophil count decreased” was 112 subjects (63%) in Asia (HLT “white blood cell analyses” incidence 75%) while the incidence of “neutrophil count decreased” was 36 subjects (10%) in the Western region (HLT “white blood cell analyses” incidence 17%).

Patients from Asia who received TAS-102 had a higher incidence rate of “nausea,” “fatigue,” and “decreased appetite,” (54.5%; 41%; 52.2%) as compared to Western patients (44.8; 32.1%; 31.8%); however, the incidence rates of nausea and decreased appetite were also higher in the placebo arm.

Western patients had higher incidence rates of abdominal pain across both arms compared to patients enrolled in Asia.

Table 69: Selected AEs by geographic region in RECOURSE

Preferred Term	TAS-102 N=533				Placebo N=265			
	Western N=355		Asia N=178		Western N=177		Asia N=88	
	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%
Nausea	159	44.8	97	54.5	39	22	24	27.3
Neutropenia	152	42.8	4	2.2	0	0	0	0
Anemia	115	32.4	92	51.7	17	9.6	5	5.7

Preferred Term	TAS-102 N=533				Placebo N=265			
	Western N=355		Asia N=178		Western N=177		Asia N=88	
	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%
Fatigue	114	32.1	73	41.0	45	25.4	15	17.0
Decreased appetite	113	31.8	93	52.2	44	24.9	32	36.4
Diarrhea	112	31.5	58	32.6	24	13.6	9	10.2
Vomiting	99	27.9	48	27.0	20	11.3	18	20.5
Asthenia	94	26.5	0	0	30	16.9	0	0
Abdominal pain	63	17.7	16	9	27	15.3	7	8
Pyrexia	57	16.1	41	23.0	24	13.6	13	14.8
Constipation	55	15.5	26	14.6	28	15.8	12	13.6
Thrombocytopenia	37	10.4	0	0	0	0	1	1.1
Neutrophil count decreased	36	10.1	112	62.9	0	0	1	1.1
Weight decreased	28	7.9	13	7.3	20	11.3	7	8
White blood cell count decreased	30	8.5	116	65.2	0	0	1	1.1
Platelet count decreased	21	5.9	60	33.7	4	2.3	2	2.3

In adverse events dataset, incidence was analyzed per subject per AE based on treatment arm, geographic region, and PT. The applicant included subjects with toxicity grade that increased after the first dose of drug, which is more comprehensive and this reviewer find this acceptable

#### 7.5.4 Drug-Disease Interactions

There were no unexpected clinical differences between patient subgroups based on location of tumor (colon or rectum), time of metastasis (greater or equal to 18 months versus less than 18 months), or KRAS status (wild type versus mutant).

#### 7.5.5 Drug-Drug Interactions

Based on *in vitro* drug interaction studies, the applicant concluded that FTD, FTY, and TPI do not demonstrate the potential to inhibit CYP enzymes and are unlikely to induce CYP1A1, CYP2B6, and CYP3A4/5. The applicant also concluded that TAS-102 is unlikely to cause interactions with other drugs due to inhibition of ACT2 by TPI but the transport of TPI by OCT2 might be affected when TAS-102 is administered concomitantly with drugs that inhibit the OCT2 transporter. Refer to the clinical pharmacology review for a more extensive analysis and discussion of drug-drug interactions.

## 7.6 Additional Safety Evaluations

### 7.6.1 Human Carcinogenicity

No long term studies evaluating the carcinogenic potential of trifluridine/tipiracil in animals have been performed. Trifluridine/tipiracil 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, TAS-102 should be treated as a potential carcinogen.

Results of animal studies did not indicate an effect of trifluridine and tipiracil on male fertility in rats. In female rats, increases in the corpus luteum count and implanting embryo count were observed at high doses, but female fertility was not affected.

### 7.6.2 Human Reproduction and Pregnancy Data

TAS-102 can cause fetal harm when administered to a pregnant woman. There were no studies conducted in pregnant women. Based on its mechanism of action and findings from animal reproduction studies, TAS-102 can cause fetal harm when administered to a pregnant woman. TAS-102 caused embryo-fetal lethality and embryo-fetal toxicity in pregnant rats when orally administered during gestation at dose levels lower than the clinical exposure at the recommended human dose.

TAS-102 was administered orally once daily to female rats during gestation (GD7 to GD17) at dose levels of 15, 50, and 150 mg/kg. Inhibition of fetal growth was observed after administration at doses of 50 mg/kg or higher, and a lethal effect on embryos and a teratogenic effect were observed at 150 mg/kg. Maternal rats exhibited suppressed body weight gain at  $\geq 50$  mg/kg/day and decreased food consumption at 150 mg/kg/day. The AUCs of FTD in rats at these dose levels were lower than that in human at the recommended dose of TAS-102.

There are no data available for the effect of TAS-102 on human fertility. Results of animal studies did not indicate an effect of trifluridine and tipiracil hydrochloride on male fertility in rats. In female rats, increases in the corpus luteum count and implanting embryo count were observed at high doses, but female fertility was not affected.

### 7.6.3 Pediatrics and Assessment of Effects on Growth

Safety and effectiveness of TAS-102 in pediatric patients have not been established because studies have not been conducted in the pediatric patients.

Colorectal carcinoma is a disease of adulthood, and its incidence increases with age. In pediatrics, colorectal carcinoma is usually associated with conditions such as familial

adenomatous polyposis and ulcerative colitis. The diagnosis of polyp syndrome is often made in the first or second decade of life, long before the risk of intestinal neoplasia.

In the SEER report from 2004-2008 (<http://seer.cancer.gov/statfacts/html/colorect.html>), 0.1% of all colorectal cancers were diagnosed under the age of 20 (around 1 per million people younger than 20 years, or fewer than 100 cases annually).

The applicant requested a waiver of the requirement to assess TAS-102 in all pediatric age groups because studies would be impossible or highly impracticable. This reviewer agrees that the request meets the criteria for a waiver and recommends granting the applicant a waiver for TAS-102 in the third line metastatic colorectal carcinoma indication.

#### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable

### 7.7 Additional Submissions / 90-day Safety Update

On 19 March 2015, Taiho Oncology, Inc. submitted the 90-day safety update. Datasets, programs, and listings of SAEs and deaths reported from 25 July 2014 through 19 January 2015 were submitted. Table 70 summarizes the 32 SAEs in 28 subjects that were submitted from RECOURSE, all of which occurred in patients who received TAS-102.

Table 70: SAEs in the 90-day safety update in RECOURSE

Preferred Term	N
Pyrexia	6
Febrile neutropenia	3
Abdominal pain lower	2
Anemia	2
Intestinal obstruction	2
Abdominal pain	1
Ascites	1
Atrial fibrillation	1
Bacteremia	1
Blood bilirubin increased	1
Chest pain	1
Colitis	1
Diarrhea	1
Gastric ulcer	1
Neutropenia	1
Pelvic pain	1

<b>Preferred Term</b>	<b>N</b>
Renal failure acute	1
Sciatica	1
Sepsis	1
Small intestinal obstruction	1
Upper gastrointestinal hemorrhage	1
Urinary tract infection	1

There were no fatalities reported in the 90-day safety update for RECOURSE. Grade 3 events occurred in 11 subjects. Grade 4 events occurred in 1 subject (301-016) who had febrile neutropenic urosepsis, and Grade 3 acute renal failure. Note that Grade 4 anemia based on clinical findings was described for subject 301-007, however there is no Grade 4 anemia within CTCAE.

Based on the additional safety information provided in the report, the safety data is generally consistent with the previous cumulative experience of TAS-102. However, there were two new SAEs identified which the applicant included in their draft label. Colitis was identified from a cumulative review of the safety data, and interstitial lung disease had been reported and observed from the post marketing experience in Japan. One subject had Grade 2 colitis in RECOURSE in the safety update and none reported lung disease.

## **8 Post market Experience**

Not applicable for this new molecular entity.

## 9 Appendices

### 9.1 Literature Review/References

American Cancer Society (ACS) (Cancer Facts and Figures 2014 <a href="http://www.cancer.org/research/cancerfactsstatistics/cancerfactsfigures2014/">http://www.cancer.org/research/cancerfactsstatistics/cancerfactsfigures2014/</a> )
Grothey A., Van Cutsem E., Sobrero A., Siena S., Falcone A., et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. <i>The Lancet</i> 2013 Jan; 381 (9863): 303-12.
Regorafenib Label/Package Insert: <a href="http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Overview&amp;DrugName=STIVARGA">http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Overview&amp;DrugName=STIVARGA</a> accessed on 7 Jan 2015
Schmiegel W., Pox C., Arnold D., Porschen R., Rödel C. et al. Colorectal carcinoma: the management of polyps, (neo) adjuvant therapy, and the treatment of metastases. <i>Dtsch Arztebl Int.</i> 2009 Dec;106 (51-52): 843-8.
Surveillance, Epidemiology and End Results (SEER) data accessed on 7 Jan 2015 ( <a href="http://seer.cancer.gov/statfacts/html/colorect.html">http://seer.cancer.gov/statfacts/html/colorect.html</a> ), accessed on 6 April 2015, <a href="http://seer.cancer.gov/statfacts/html/colorect.html">http://seer.cancer.gov/statfacts/html/colorect.html</a> )
The National Comprehensive Cancer Network (NCCN) guideline version 2.2015 accessed on 7 Jan 2015 ( <a href="http://www.nccn.org/professionals/physician_gls/pdf/colon.pdf">http://www.nccn.org/professionals/physician_gls/pdf/colon.pdf</a> )
Venhook A., Weiser M., Tepper J. Colorectal Cancer: All Hands on Deck. <i>Am Soc Clin Oncol Educ Book.</i> 2014:83-9. doi: 10.14694/EdBook_AM.

### 9.2 Labeling Recommendations

The following table summarizes the recommended changes to the TAS-102 label. As this review will be completed prior to the PDUFA goal date, some changes to the labeling may occur subsequent to the completion of this review that may be addressed in an amendment to the clinical review.

- Recommended dose: Asked Taiho to provide evidence that (b) (4) the bioavailability of the product in a clinically significant manner.
- Contraindications: Deleted (b) (4) as this was a theoretical risk.
- Clinical trials experience: Added All Grades AEs greater than 10% rather than (b) (4) adverse drug reactions greater than 5% in TAS-102 more commonly >2% than in patients receiving placebo were incorporated in Table 1 and split the formatting to include Grades 3 and 4 separately. In Table 2 (b) (4) was deleted as this likely does not result in clinical squeal. (b) (4) was also deleted as it was likely related to underlying disease. The remainder of terms was deleted

Clinical Review

Leigh Marcus

NDA 207981

TAS-102 (Lonsurf) for the treatment of patients with metastatic colorectal cancer

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or moved into a Tables 1 and 2 to focus on significant clinical events. Pulmonary emboli were inserted.

- Clinical studies: Focused on primary endpoints (Taiho to decide on keeping PFS in label (b) (4)).

### **9.3 Advisory Committee Meeting**

Not applicable.

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/s/  
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LEIGH J MARCUS  
08/21/2015

STEVEN J LEMERY  
08/21/2015

I agree with the recommendations in this review. My full secondary review will be contained in the CDTL memo.

Clinical Investigator Financial Disclosure  
Review Template

Application Number: 207981

Submission Date(s): 12/19/2014 Last module, Module 5 received (Rolling)

Applicant: Taiho, Inc.

Product: TAS-102 “Lonsurf”

Reviewer: Leigh Marcus, MD

Date of Review: 3/26/2015

Covered Clinical Study (Name and/or Number): TPU-TAS-102-301 (RECOURSE), Japan (Study J003/10040030).

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: RECOURSE: <u>100 investigators, 654 sub-investigators.</u> Study J003/10040030: <u>23 investigators, 178 sub-investigators.</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>None</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>4 (there was just one investigator in the pivotal RECOURSE study who had a disclosable financial conflict of interest).</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p style="padding-left: 40px;">Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>None</u></p> <p style="padding-left: 40px;">Significant payments of other sorts: <u>4</u></p> <p style="padding-left: 40px;">Proprietary interest in the product tested held by investigator: <u>None</u></p> <p style="padding-left: 40px;">Significant equity interest held by investigator in sponsor of covered study: <u>None</u></p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) RECOURSE: 100, 643 from sub-investigators; Study J003/10040030: <u>15</u>		
Is an attachment provided with the	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation

reason:		from applicant)
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Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.<sup>1</sup> Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements) (See below)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

Taiho Oncology, Inc. does not believe any bias, intentional or unintentional, was introduced by these arrangements. The primary study submitted in support of the NDA was double-blinded and OS was the primary endpoint (not subjective measure) and the contribution of randomized patients by Dr. [REDACTED]<sup>(b) (6)</sup> site was 2.5% of the total randomized, and even eliminating the results of Dr. [REDACTED]<sup>(b) (6)</sup> site would not change any conclusions of the study.

Based on the financial disclosures submitted by the applicant, this reviewer does not find that the results for the submission could be biased due to financial interests. See Amendment 0018 (SDN 19) received 3/13/2015.

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<sup>1</sup> See [web address].

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/s/  
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LEIGH J MARCUS  
03/27/2015

STEVEN J LEMERY  
03/27/2015

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA/BLA Number: 207981      Applicant: Taiho Oncology, Inc.      Stamp Date: 19 Dec 2014**

**Drug Name: TAS-102      NDA/BLA Type:NDA**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
<b>FORMAT/ORGANIZATION/LEGIBILITY</b>					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			Electronic CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			Japanese to English translation is certified
6.	Is the clinical section legible so that substantive review can begin?	X			
<b>LABELING</b>					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			Draft label was not consistent with PLR guidelines. Sent back to applicant for revisions. This will not preclude filing.
<b>SUMMARIES</b>					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			In Module 2.5
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).	X			505(b)(1)
<b>505(b)(2) Applications</b>					
13.	If appropriate, what is the reference drug?			X	
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?			X	
15.	Describe the scientific bridge (e.g., BA/BE studies)			X	
<b>DOSE</b>					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)?	X			Multiple dose finding studies including J001-10040010; TPU-TAS-102-101; and TPU-TAS-102-102
<b>EFFICACY</b>					
17.	Do there appear to be the requisite number of adequate and	X			

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	well-controlled studies in the application?  Pivotal Study #1: TPU-TAS-102-301 (RECOURSE)  Indication: TAS-102 is indicated for treatment of patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if <sup>(b)</sup> <sub>(4)</sub> RAS wild type, an anti-EGFR therapy.				
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
<b>SAFETY</b>					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
22.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	X			QT interval study submitted
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>1</sup> ) been exposed at the dose (or dose range) believed to be efficacious?	X			Although there were fewer patients enrolled than the ICH guideline for exposure, based on the trial population of end stage cancer patients, the sample size is adequate for the proposed indication
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
26.	Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?	X			MedDRA v 16.0

<sup>1</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

<sup>2</sup> The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			This is a cytotoxic drug. The applicant has evaluated common side effects of cytotoxic therapy including myelosuppression and gastrointestinal
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
<b>OTHER STUDIES</b>					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
<b>PEDIATRIC USE</b>					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Pediatric waiver request has been submitted for the indication of colorectal cancer
<b>ABUSE LIABILITY</b>					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
<b>FOREIGN STUDIES</b>					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
<b>DATASETS</b>					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
<b>CASE REPORT FORMS</b>					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
<b>FINANCIAL DISCLOSURE</b>					
41.	Has the applicant submitted the required Financial Disclosure information?				

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
<b>GOOD CLINICAL PRACTICE</b>					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? \_\_Yes\_\_**

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

There are no comments at this time.

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/s/  
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LEIGH J MARCUS  
01/30/2015

STEVEN J LEMERY  
01/30/2015