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RESEARCH**

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STATISTICAL REVIEW(S)



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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

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Indication(s): (b) (4) Metastatic Colorectal Cancer

Applicant: Taiho

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Biometrics Division: V

Statistical Reviewer: Weishi Yuan

Concurring Reviewers: Kun He, Team Leader
Rajeshwari Sridhara, Division Director

Medical Division: Oncology Products 2

Clinical Team: Leigh Marcus, Clinical Reviewer
Steven Lemery, Team Leader
Patricia Keegan, Division Director

Project Manager: Gina Davis

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Table of Contents

LIST OF TABLES	3
LIST OF FIGURES	4
1. EXECUTIVE SUMMARY	5
2. INTRODUCTION	6
2.1 OVERVIEW	6
2.1.1. <i>Class and Indication</i>	6
2.1.2. <i>Regulatory History</i>	6
2.1.3. <i>Study Reviewed</i>	6
2.2 DATA SOURCES	7
3. STATISTICAL EVALUATION	8
3.1 DATA AND ANALYSIS QUALITY	8
3.2 EVALUATION OF EFFICACY	8
3.2.1. Study Design and Endpoints.....	8
3.2.2. Efficacy Measures	8
3.2.3. Sample Size Consideration.....	9
3.2.4. Statistical Methodologies	9
3.2.5. Patient Disposition, Demographic and Baseline Characteristics	10
3.2.6. Results and Conclusions.....	12
3.3 EVALUATION OF SAFETY.....	16
4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS.....	17
4.1 GENDER, RACE, AGE, AND GEOGRAPHIC REGION.....	17
4.2 OTHER SPECIAL/SUBGROUP POPULATIONS	18
5. SUMMARY AND CONCLUSIONS.....	19
5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE.....	19
5.2 CONCLUSIONS AND RECOMMENDATIONS.....	19
5.3 LABELING RECOMMENDATIONS.....	19

LIST OF TABLES

Table 1. Patient Disposition	10
Table 2. Demographics.....	11
Table 3. Baseline Characteristics	11
Table 4. Primary analysis of OS.....	13
Table 5. Analysis of PFS.....	14
Table 6. Analysis of ORR	16
Table 7. Subgroups Analyses of OS: Gender, Age, Race and Region	17
Table 8. Subgroup Analyses of OS: Baseline Characteristics	18

LIST OF FIGURES

Figure 1. K-M Curves of OS Analysis	13
Figure 2. K-M Curves of PFS Analysis.....	15

1. EXECUTIVE SUMMARY

The applicant submitted data and final study reports of a randomized study to support approval for TAS-102 as the treatment of patients with metastatic colorectal cancer who have been previously treated with, (b) (4) fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and an anti-EGFR therapy. This is the first indication for TAS-102.

This application was based on a single randomized study, Study TPU-TAS-102-301 (Study 301), titled “randomised, 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 primary endpoint was overall survival (OS). Secondary endpoints included progression free survival (PFS) and overall response rate (ORR). The study planned to enroll 800 patients.

A total of 800 patients were randomized in a 2:1 allocation with 534 in the TAS-102 arm and 266 in the placebo arm. Randomization was stratified by KRAS gene status (wild-type, mutant), time since diagnosis of first metastasis (<18 months, ≥18 months), geographical region (Asia [Japan], Western [US, Europe and Australia]). TAS-102 was shown to prolong OS compared with placebo with p-value < 0.0001 based on a stratified log-rank test. The median OS was 7.1 months in the TAS-102 arm and 5.3 months in the placebo arm. The estimated hazard ratio (HR) was 0.68 with 95% CI (0.58, 0.81) based on a stratified Cox model.

Based on the data and analyses, TAS-102 showed a statistically significant improvement in OS compared with placebo. Whether the data and analyses provided in this submission showed an overall favorable benefit/risk profile in supporting a regulatory approval is deferred to the clinical review team.

2. INTRODUCTION

The applicant submitted data and final study report to seek regular approval for a new indication for TAS-102. This application was based on Study TPU-TAS-102-301 (Study 301), a Phase 3, randomized, double blind, placebo controlled, multi-center study to assess the effect of TAS-102 administered orally plus best supportive care (BSC) on overall survival in patients with refractory metastatic colorectal cancer (mCRC).

2.1 Overview

2.1.1. Class and Indication

TAS-10 is a combination of 1M trifluridine (FTD) and 0.5 M tipiracil hydrochloride (TPI). FTD is a thymidine-based nucleoside, which is incorporated into deoxyribonucleic acid (DNA) in tumor cells following phosphorylation. TPI inhibits degradation of FTD by inhibiting thymidine phosphorylase (TPase).

2.1.2. Regulatory History

TAS-102 is investigated under IND 57,674. This is the first indication TAS-102 is seeking under Section 505(b)(1) of the Food, Drug and Cosmetic Act.

In December 2011, FDA and the applicant held an End-of-Phase-II meeting to discuss the development program for TAS-102. In September 2014, FDA granted fast-track designation to TAS-102. A pre-NDA meeting was held at the end of July, 2014 and a rolling submission plan was agreed.

The NDA was completely submitted on December 19, 2014.

2.1.3. Study Reviewed

Study TPU-TAS-102-301 (Study 301), a Phase 3, randomized, double blind, placebo controlled, multi-center study to compare the efficacy and safety of TAS-102 plus BSC versus BSC in patients with metastatic colorectal cancer who have been previously treated with, (b)(4) fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and an anti-EGFR therapy. A total of 800 patients were randomized in a 2:1 ratio to receive either TAS-102 plus BSC or placebo plus BSC. Randomization was stratified by KRAS gene status (wild-type, mutant), time since diagnosis of first metastasis (<18 months, ≥18 months), geographical region (Asia [Japan], Western [US, Europe and Australia]).

The primary objective of this study was to compare the treatment effect of TAS-102 with that of placebo on overall survival (OS). The secondary objectives were to compare the treatment effect of TAS-102 with that of placebo on progression free survival (PFS), and overall response rate (ORR).

A total of 800 patients were randomized with 534 in the TAS-102 arm and 266 in the placebo arm. The study was initiated on June 17, 2012 and the data cut-off date for primary analysis was January 24, 2014.

2.2 Data Sources

Data used for review is from the electronic submission received on October 16, November 7, and December 19, 2014. The network path is

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3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Data and reports of this submission were submitted electronically. The applicant submitted data for both studies as well as the related SAS programs for analysis.

The reviewer was able to perform most of the analyses using the submitted data.

3.2 Evaluation of Efficacy

3.2.1. Study Design and Endpoints

Study TPU-TAS-102-301 (Study 301) was a multinational, double-blind, parallel-group, randomized Phase 3 study evaluating the efficacy and safety of TAS-102 versus placebo in patients with refractory metastatic colorectal cancer.

A total of 800 patients were randomly assigned in a 2:1 ratio to TAS-102 plus BSC or placebo plus BSC. Randomization were conducted via an Interactive Voice/Web Response System (IWRS) and stratified by:

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

TAS-102 or placebo was administered in 28-day cycles until any of the study treatment discontinuation criteria were met, which include disease progression, severe adverse events, pregnancy, patient withdrawal, or physician's decision. CT scans were performed every 8 weeks during study treatment. Patients were followed for survival every 8 weeks until death, or until 12 months after the first dose of study medication for the last patient randomized in the study

The primary objective of this study was to compare the treatment effect of TAS-102 with placebo based on OS. The secondary objectives were to compare the treatment effect of TAS-102 with placebo on PFS and ORR.

A DMC was set up to undertake interim safety review of the study's progress, approximately every 3 months.

3.2.2. Efficacy Measures

The primary endpoint OS was defined as the time 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, whichever is earlier.

Secondary endpoint included

- PFS, defined as the time from the date of randomization until the date of the investigator-assessed radiological disease progression or death due to any cause; and
- ORR, defined as the proportion of patients with objective evidence of complete response (CR) or partial response (PR).

3.2.3. Sample Size Consideration

In the final Study 301 protocol, the sample size consideration was based on the following estimates and assumptions:

- 2:1 randomization scheme.
- One-sided type I error rate of 0.025 and 90% power.
- A median OS of 5 months in placebo arm,
- A constant hazard ratio of 0.75 over time.

The planned sample size was 800 patients with 571 OS events for the final analysis. A total of 800 patients were randomized with 534 in the TAS-102 arm and 266 in the placebo arm.

No interim efficacy analysis was planned for this study.

3.2.4. Statistical Methodologies

The Intent-to-Treat (ITT) population was used for the primary efficacy analysis. The ITT population comprise of all randomized patients regardless of whether or not treatment was administered. A total of 798 patients in the study were treated with one in each arm was not treated.

OS and PFS were summarized using the Kaplan-Meier estimates and the difference between the two treatment arms was tested using a stratified log-rank test, stratifying for stratification factors at randomization. If OS demonstrated significance at the 1-sided 0.025 level, PFS could subsequently be tested at the 1-sided 0.025 level.

ORR analysis would be based on the tumor response population which includes 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. The analysis used Fisher's exact test. Treatment estimates and differences would be presented along with the associated 95% CIs.

Reviewer's Comment

- There were minor amendments to the protocol during the study, and the statistical analysis plan was not amended.
- The ORR analysis was not based on the ITT population.

3.2.5. Patient Disposition, Demographic and Baseline Characteristics

A total of 800 patients were randomized to one of two treatment arms using a 2:1 randomization ratio with 534 patients in the TAS-102 arm and 266 patients in the placebo arm. A total of 101 study centers enrolled patients in 13 countries including 21 in the United States, 20 in Japan, 11 in Spain, 9 in Italy, 8 in Germany, 6 in Belgium, 6 in France, 5 in Australia, 5 in the United Kingdom, 4 in Austria, 3 in Ireland, 2 in Sweden, and 1 in Czech Republic.

The study was initiated (first patient randomized) on June 17, 2012 and the data cut-off date for the submitted Clinical Study Report was January 24, 2014 for overall survival data, and January 31, 2014 for other clinical data. As of January 31, 2014, there were 39 patients remaining on treatment with 37 in the TAS-102 arm and 2 in the placebo arm.

A total of 1002 patients were screened and 800 patients were randomized into the study. Two patients were not treated, with 1 in each treatment arm. A total of 99 patients were enrolled in the USA. Japan enrolled 266 patients, the most number of patients. The patient disposition is summarized in Table 1.

Table 1. Patient Disposition

	TAS-102	Placebo
Randomized	N = 534 (100)	N = 266 (100)
Received Investigational Product	533 (99.8)	265 (99.6)
Still Being Treated, Jan 31, 2014	37 (6.9)	2 (0.8)
Discontinued	496 (92.9)	263 (98.9)
Radiologic Progression	416 (77.9)	222 (83.5)
Clinical Progression	33 (6.2)	31 (11.7)
Death	7 (1.3)	4 (1.5)
Adverse Event	19 (3.6)	4 (1.5)
Withdrawal of Consent	12 (2.2)	1 (0.4)
Other	9 (1.7)	1 (0.4)

Demographic characteristics at baseline are summarized in Table 2.

Table 2. Demographics

	TAS-102	Placebo
	N = 534	N = 266
Randomized	534 (100)	266 (100)
Gender		
Male	326 (61.0)	165 (62.0)
Female	208 (39.0)	101 (38.0)
Race		
Caucasian	306 (57.3)	155 (58.3)
Non-Caucasian	228 (42.7)	111 (41.7)
Age		
< 65	300 (56.2)	148 (55.6)
≥ 65	234 (43.8)	118 (44.4)
Region		
Asia	178 (33.3)	88 (33.1)
Western EU	356 (66.7)	178 (66.9)

Disease characteristics at baseline are summarized in Table 3.

Table 3. Baseline Characteristics

	TAS-102	Placebo
	N = 534	N = 266
Randomized	534 (100)	266 (100)
ECOG Status		
0	301 (56.4)	147 (55.3)
1	233 (43.6)	119 (44.7)
KRAS Status		
Mutant	272 (50.9)	135 (50.8)
Wild	262 (49.1)	131 (49.2)
Time since Metastasis		
< 18 Months	111 (20.8)	55 (20.7)
≥ 18 Months	423 (79.2)	211 (79.3)
BRAF Status		
Mutant	4 (0.7)	4 (1.5)
Wild	75 (14.0)	41 (15.4)
Missing	455 (85.2)	221(83.1)

Table 3. Baseline Characteristics (Continued)

	TAS-102	Placebo
	N = 534	N = 266
Randomized	534 (100)	266 (100)
Baseline Renal Function		
Normal	307 (57.5)	145 (54.1)
Mild Impairment	47 (8.8)	27 (10.2)
Moderate Impairment	178 (33.3)	91 (34.2)
Missing	2 (0.4)	3 (1.1)
Baseline eGFR		
Normal	335 (62.7)	160 (60.2)
Mild Impairment	153 (28.7)	82 (30.8)
Moderate Impairment	33 (6.2)	16 (6.0)
Missing	13 (2.4)	8 (3.0)
Primary Tumor Location		
Colon	338 (63.3)	161 (60.5)
Rectal	196 (36.7)	105 (39.5)
Number of Metastatic Sites		
1-2	324 (60.7)	153 (57.2)
≥ 3	210 (39.3)	113 (42.5)
Number of Prior Regimens*		
2	95 (17.8)	45 (16.9)
3	119 (22.3)	54 (20.3)
≥4	320 (59.9)	167 (62.8)

* Includes neoadjuvant, adjuvant, metastatic.

Reviewer's comments:

The demographic and baseline characteristics of the ITT population are generally balanced over the two arms.

3.2.6. Results and Conclusions

Primary Endpoint Analysis: OS

There were 800 patients in the ITT population, with 534 in the TAS-102 arm and 266 in the placebo arm. A total of 574 patients died at time of the primary analysis, of which 364 were in the TAS-102 arm and 210 in the placebo arm.

Table 4 summarizes the efficacy analysis results of the OS. TAS-102 was shown prolonging OS 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)

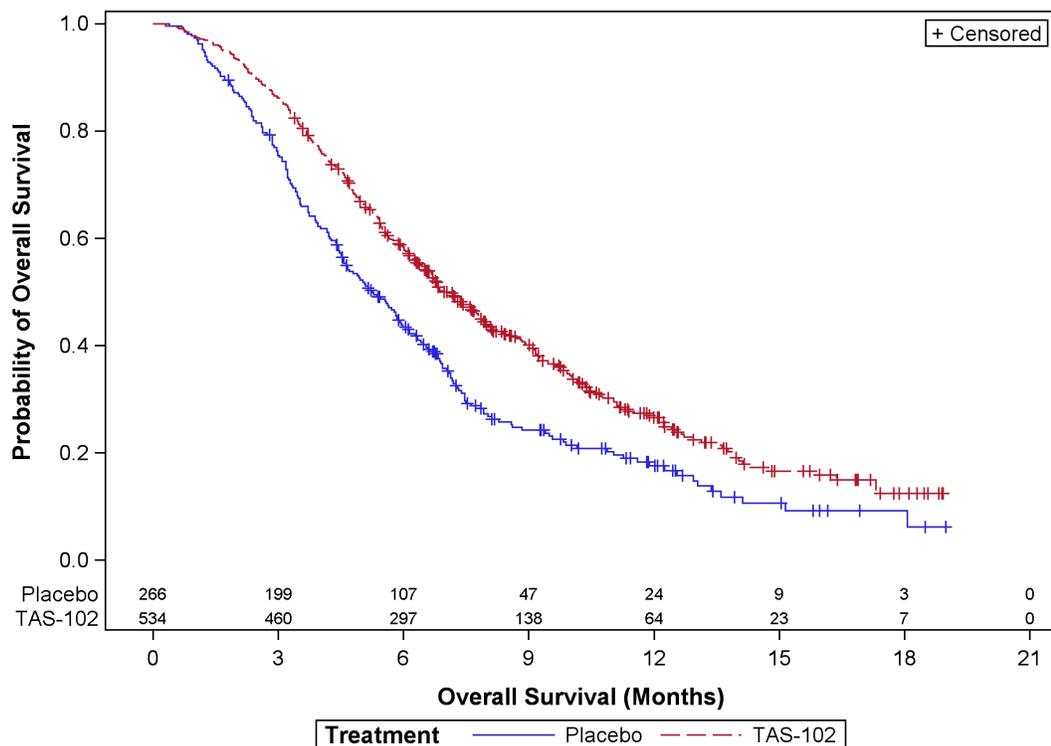
based on a Cox model stratified by KRAS gene status, time since diagnosis of first metastasis, and geographical region.

Table 4. Primary analysis of OS

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

Figure 1 shows the estimated Kaplan-Meier curves for the distribution of OS.

Figure 1. K-M Curves of OS Analysis



Reviewer's comments:

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

Secondary Endpoints Analysis: PFS

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

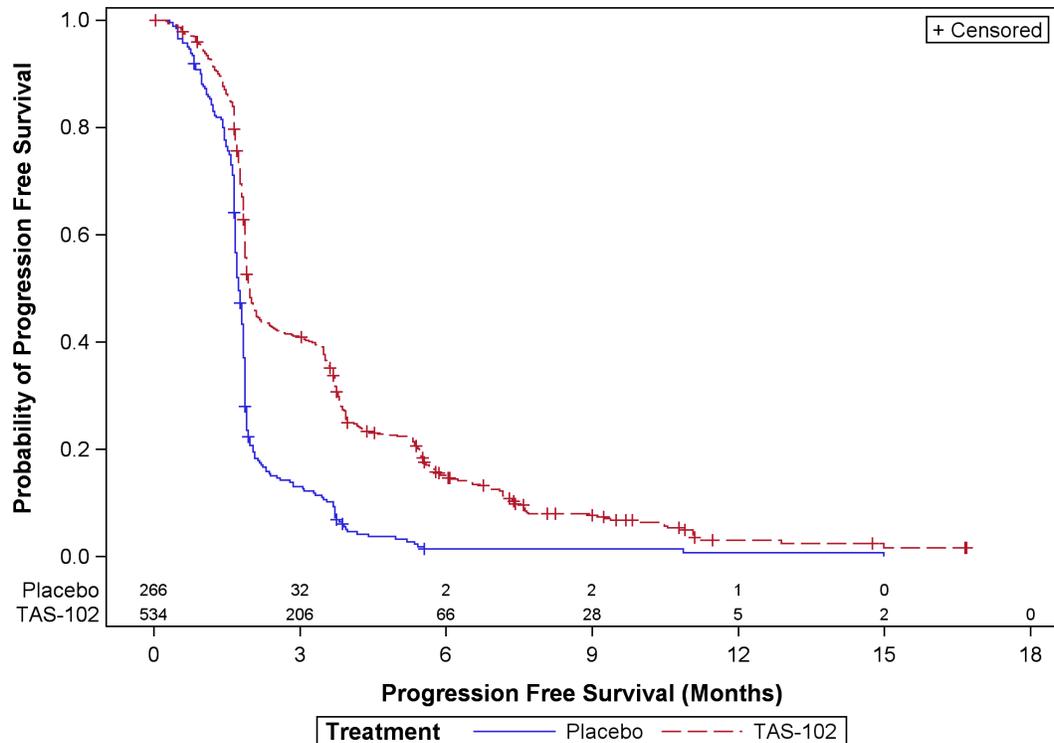
Table 5 summarizes the main efficacy analysis results of the primary endpoint. TAS-102 was shown prolonging PFS to placebo with p-value < 0.0001 based on a stratified log-rank test stratified by KRAS gene status, time since diagnosis of first metastasis, and geographical region. The median PFS was 2.0 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.

Table 5. Analysis of PFS

	TAS-102 N = 534	Placebo N = 266
Number of Events (%)	472 (88.4%)	251 (94.4%)
Median PFS (95% CI)	2.0 (1.9, 2.1)	1.7 (1.7, 1.8)
HR (95% CI)	0.47 (0.40, 0.55)	
p-value	<0.0001	

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

Figure 2. K-M Curves of PFS Analysis



Reviewer's comments:

The absolute PFS improvement in median was small. The Kaplan-Meier curves suggest that the data did not follow a constant hazard ratio over time. Since 90% of the patients progressed at time of the analysis, the PFS data was mature. This reviewer calculated the mean of the PFS as an additional measurement of the treatment effect on PFS. The means of PFS was 3.2 months with 95% CI (3.0, 3.4) in the TAS-102 arm and 1.9 months with 95% CI (1.8, 2.1)

Secondary Endpoints Analysis: ORR

The ORR analysis is summarized in the following table.

Table 6. Analysis of ORR

	TAS-102	Placebo
	N = 534	N = 266
Number of Responders (%)	8 (1.5)	1 (0.4)
95%CI of ORR	(0.7, 2.9)	(0.0, 2.1)
CR(%)	0	1 (0.4)
PR(%)	8 (1.5)	0
Difference in ORR (95% CI)	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 response at time of analysis, 4 had radiologic progression, and 1 had clinical progression. The one responder in the placebo arm had a DoR of 13.1 months and radiologic progression.

Reviewer's comments:

1. There were few responders observed.
2. The applicant conducted ORR analysis based on the tumor response (TR) population, which contains 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.
3. Since there was no adjustment for multiplicity ORR, the results of the ORR analyses are considered exploratory.

3.3 Evaluation of Safety

Please refer to the clinical review of this application for details of the safety evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Since no hypothesis and power calculation are pre-specified in the subgroups presented in this section, all results are considered exploratory.

Table 7 summarizes the subgroup analysis of OS based the ITT population.

Table 7. Subgroups Analyses of OS* : Gender, Age, Race and Region

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

*These analyses were not adjusted for multiplicities.

Reviewer's comments:

There was no outlier observed among the subgroups analyzed for OS.

4.2 Other Special/Subgroup Populations

The following table summarizes other important subgroup analysis of OS based on the ITT population.

Table 8. Subgroup Analyses of OS* : Baseline Characteristics

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

*These analyses were not adjusted for multiplicities.

^a TM: Time since Metastasis

^b Includes neoadjuvant, adjuvant, metastatic

Reviewer's comments:

No outlier subgroup was observed except for the group of patients with 2 prior regimens reported a HR point estimate greater than 1. For this subgroup, the median OS was improved. However the Kaplan-Meier curves were crossed back and forth after 10 months with about 25% patients still at risk at 10 months point in this subgroup.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

A total of 800 patients were randomized to in 2:1 allocation with 534 in the TAS-102 arm and 266 in the placebo arm. A total of 574 patients died at time of the primary analysis, of which 364 were in the TAS-102 arm and 210 in the placebo arm. TAS-102 was shown prolonging OS 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.

For the PFS analysis, a total of 723 patients progressed or died at time of the primary analysis, of which 472 were in the TAS-102 arm and 251 in the placebo arm. TAS-102 was shown a 0.3 month improvement in PFS 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.

There were 8 partial responders in the TAS-102 arm and 1 complete responder in the placebo arm.

5.2 Conclusions and Recommendations

Based on the data and analyses, TAS-102 showed a statistically significant improvement in OS compared with placebo. Whether the data and analyses provided in this submission showed an overall favorable benefit/risk profile in supporting a regulatory approval is deferred to the clinical review team.

5.3 Labeling Recommendations

1. The OS results should be included in the label.
2. The PFS results may be included in the label.
3. The results of ORR on the ITT population may be included in the label but the p-value should not be included.
4. All other secondary endpoints are considered exploratory and should not be included in the label.

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/s/

WEISHI YUAN
08/05/2015

KUN HE
08/05/2015

RAJESHWARI SRIDHARA
08/05/2015