

ORIGINAL RESEARCH

Impact of *KRAS*^{G12} mutations on survival with trifluridine/tipiracil plus bevacizumab in patients with refractory metastatic colorectal cancer: *post hoc* analysis of the phase III SUNLIGHT trial[☆]

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Background: In metastatic colorectal cancer (mCRC), *KRAS* mutations are often associated with poorer survival; however, the prognostic impact of specific point mutations is unclear. In the phase III SUNLIGHT trial, trifluridine/tipiracil (FTD/TPI) plus bevacizumab significantly improved overall survival (OS) versus FTD/TPI alone. We assessed the impact of *KRAS*^{G12} mutational status on OS in SUNLIGHT.

Patients and methods: In the global, open-label, randomized, phase III SUNLIGHT trial, adults with mCRC who had received no more than two prior chemotherapy regimens were randomized 1 : 1 to receive FTD/TPI alone or FTD/TPI plus bevacizumab. In this *post hoc* analysis, OS was assessed according to the presence or absence of a *KRAS*^{G12} mutation in the overall population and in patients with *RAS*-mutated tumors.

Results: Overall, 450 patients were analyzed, including 302 patients in the *RAS* mutation subgroup (214 with a *KRAS*^{G12} mutation and 88 with a non-*KRAS*^{G12} *RAS* mutation). In the overall population, similar OS outcomes were observed in patients with and without a *KRAS*^{G12} mutation [median 8.3 and 9.2 months, respectively; hazard ratio (HR) 1.09, 95% confidence interval (CI) 0.87-1.4]. Similar OS outcomes were also observed in the subgroup analysis of patients with a *KRAS*^{G12} mutation versus those with a non-*KRAS*^{G12} *RAS* mutation (HR 1.03, 95% CI 0.76-1.4). FTD/TPI plus bevacizumab improved OS compared with FTD/TPI alone irrespective of *KRAS*^{G12} mutational status. Among patients with a *KRAS*^{G12} mutation, the median OS was 9.4 months with FTD/TPI plus bevacizumab versus 7.2 months with FTD/TPI alone (HR 0.67, 95% CI 0.48-0.93), and in patients without a *KRAS*^{G12} mutation, the median OS was 11.3 versus 7.1 months, respectively (HR 0.59, 95% CI 0.43-0.81).

Conclusions: The presence of a *KRAS*^{G12} mutation had no detrimental effect on OS among patients treated in SUNLIGHT. The benefit of FTD/TPI plus bevacizumab over FTD/TPI alone was confirmed independently of *KRAS*^{G12} status.

Key words: bevacizumab, *KRAS* mutation, metastatic colorectal cancer, overall survival, phase III, trifluridine/tipiracil

INTRODUCTION

Activating mutations in members of the *RAS* gene family, comprising the *KRAS*, *NRAS*, and *HRAS* viral oncogene

homologs, are common in human cancers, including colorectal cancer (CRC).¹ *KRAS* proteins translated from mutated *KRAS* genes are thought to be defective in their interactions with guanosine triphosphatase-activating proteins, leading to constitutive activation of *KRAS* and disruption of multiple downstream cellular pathways, including those involved in cell survival and proliferation.² Mutations in *KRAS* are present in ~40% of CRC cases and most commonly involve a point mutation in exon 2 at glycine residues 12 (*KRAS*^{G12}; ~80%) or 13 (*KRAS*^{G13}; ~20%).^{3,4} There are 15 different *KRAS*^{G12} mutations, of which the most common in CRC is G12D (glycine to aspartic acid), followed by G12V (glycine to valine).³⁻⁵

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Patients with metastatic CRC (mCRC) harboring *KRAS* mutations have worse survival outcomes than individuals with *RAS* and *BRAF* wild-type tumors.⁶⁻⁸ Although *in vitro* data have shown different oncogenic activities for different *KRAS* codon mutations,⁹ there are sparse clinical data to definitively indicate whether one *KRAS* mutation is more prognostic than another. Results from a pooled analysis of five randomized controlled trials (RCTs) in mCRC reported an association between *KRAS* G12C (glycine to cysteine) and G13D tumors and poor survival.⁶ *KRAS* and *NRAS* mutations, however, are predictive of worse treatment outcomes with the epidermal growth factor receptor (EGFR) inhibitors cetuximab and panitumumab.^{7,10-12} In patients carrying a wild-type *KRAS* gene copy, the binding of anti-EGFR antibodies to the external part of the receptor induces conformational changes that directly inhibit tyrosine kinase activity and downstream signaling. *KRAS* mutations, however, induce constitutive activation of the intracellular domain of the *KRAS* protein, thus preventing the inhibition induced by anti-EGFR antibodies. Accordingly, national and international guidelines recommend that all patients with mCRC undergo testing for *RAS* (*KRAS* and *NRAS*) mutations in certified laboratories before initiating treatment.¹³⁻¹⁸

Trifluridine/tipiracil (FTD/TPI) is an oral combination of trifluridine (FTD), a cytotoxic thymidine-based nucleoside analog, and tipiracil hydrochloride (TPI), a thymidine phosphorylase inhibitor that prevents degradation of and improves systemic exposure to FTD.¹⁹ FTD/TPI is approved as a single agent or in combination with bevacizumab for patients with mCRC previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-vascular endothelial growth factor biologic therapy, and, if *RAS* wild-type, an anti-EGFR therapy. FTD/TPI was approved as monotherapy based on the results of the phase III RECURSE trial of FTD/TPI versus placebo.²⁰ Subsequently, FTD/TPI in combination with bevacizumab was approved based on data from the randomized phase III SUNLIGHT study, which showed statistically significant improvements in overall survival (OS; primary endpoint) and progression-free survival (PFS; secondary endpoint) with FTD/TPI plus bevacizumab versus FTD/TPI alone.²¹

In both RECURSE and SUNLIGHT, the survival benefits with FTD/TPI versus placebo and FTD/TPI plus bevacizumab versus FTD/TPI alone were observed in all prespecified subgroups, including those with and without *KRAS*-mutated disease.²⁰⁻²³ In line with these findings, guidelines advocate these regimens as third-line treatment options for patients with mCRC, regardless of *KRAS* mutation status.^{15,16,18} Recently, questions have been asked regarding the relevance of *KRAS* mutations to predicting outcomes with FTD/TPI, and they have received discrepant answers.²⁴⁻²⁸ The aim of this *post hoc* analysis was to use data from the SUNLIGHT trial to assess the potential impact of *KRAS*^{G12} mutations on survival when patients are treated with FTD/TPI plus bevacizumab, compared with the absence of *KRAS*^{G12} mutations or the presence of non-*KRAS*^{G12} *RAS* mutations, and to review the findings in the context of available literature.

PATIENTS AND METHODS

Study design and patients

Full details of the SUNLIGHT study design and eligibility criteria have been published previously.^{21,29} Briefly, SUNLIGHT was a global, open-label, randomized, phase III trial that enrolled adults with histologically confirmed, unresectable adenocarcinoma of the colon or rectum and known *RAS* status who had received no more than two prior chemotherapy regimens and had progressed on or were intolerant to their last line of treatment. Previous treatment included a fluoropyrimidine, irinotecan, oxaliplatin, anti-vascular endothelial growth factor, and/or (in patients with *RAS* wild-type tumors) anti-EGFR antibody therapy. Patients were randomized 1 : 1 to receive FTD/TPI 35 mg/m² orally twice daily on days 1-5 and 8-12 with or without bevacizumab 5 mg/kg intravenously on days 1 and 15 of each 28-day cycle. Randomization was stratified by geographic region (North America versus Europe versus the rest of the world), time since diagnosis of metastatic disease (<18 months versus ≥18 months), and *RAS* status (wild-type versus mutant). *RAS* mutational status was tested locally, and the data were reported by individual study sites. Treatment continued until disease progression, unacceptable toxicity, or withdrawal of consent. The primary endpoint was OS, defined as time from randomization to death from any cause.

The SUNLIGHT study was carried out in accordance with the principles of the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice guidelines. The study protocol was approved by the institutional review board(s) and/or independent ethics committee(s) at each participating site. All enrolled patients provided written informed consent.

Post hoc and statistical analysis

OS in the full analysis set (FAS; all randomized patients with confirmed *KRAS* mutational status) was assessed both across and within treatment groups according to the presence or absence of a *KRAS*^{G12} mutation (presence of a *KRAS*^{G12} mutation versus *RAS* wild-type or a non-*KRAS*^{G12} *RAS* mutation). Additionally, a subgroup analysis was conducted in patients with *RAS*-mutated tumors to assess the OS benefit with FTD/TPI plus bevacizumab versus FTD/TPI alone stratified by *KRAS*^{G12} mutational status (presence of a *KRAS*^{G12} mutation versus a non-*KRAS*^{G12} *RAS* mutation). Median OS was assessed using Kaplan–Meier methodology, hazard ratios (HRs) were calculated using Cox regression models, and confidence intervals (CIs) were calculated using Brookmeyer and Crowley's methodology.

A stratified log-rank test with a two-sided significance level of 0.05 was used to compare the distributions of OS between the *RAS* mutation subgroups and to derive *P* values. An unstratified Cox regression model with trial group as a predictor variable was fitted for each *RAS* mutation subgroup, and the HR and associated 95% CI were determined for the assigned treatment.

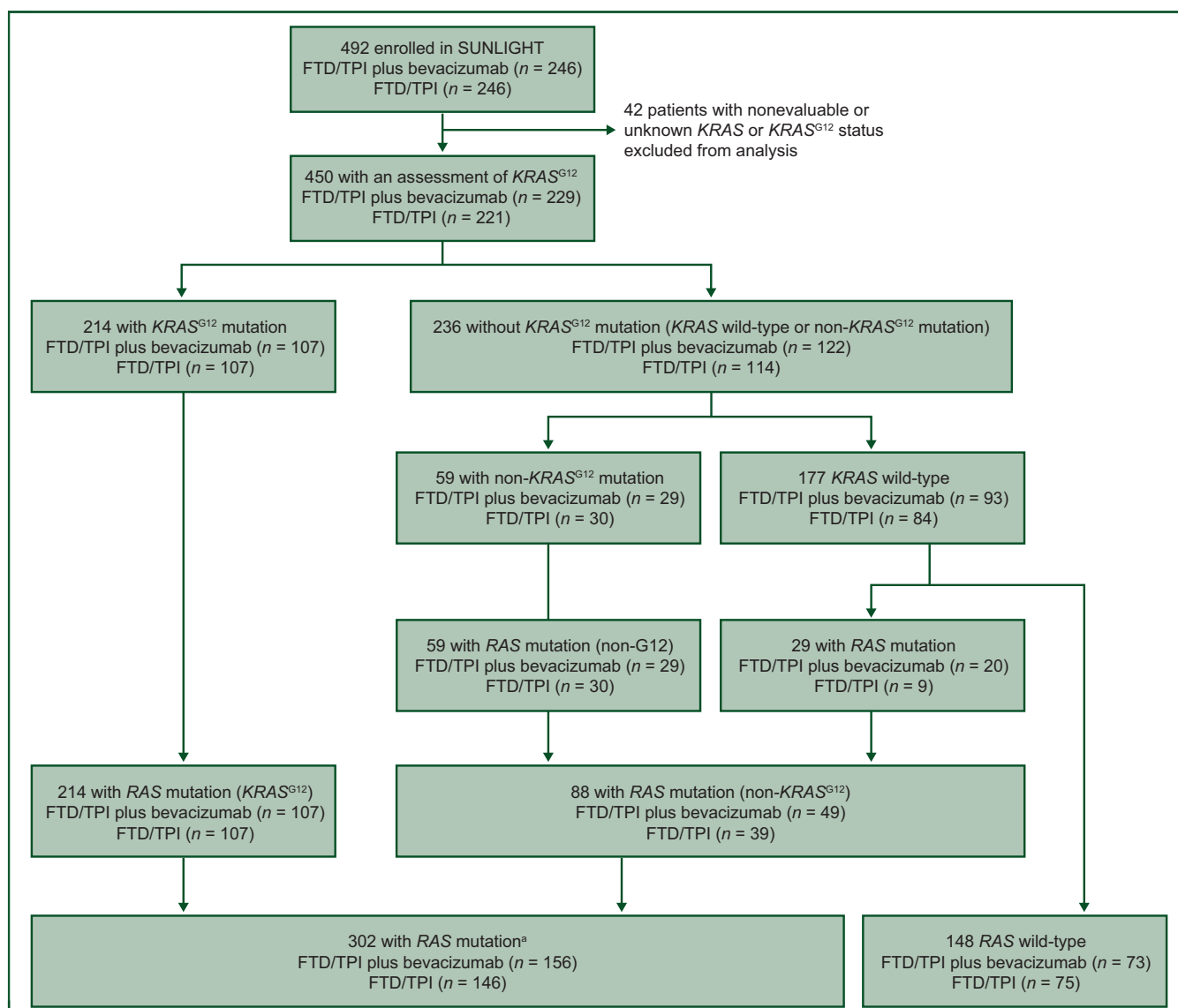


Figure 1. Patient analysis flowchart.

^aAmong the 302 patients with RAS mutations, 2 patients assessed as having wild-type disease were conserved in the analysis as having a *KRAS*^{G12} mutation. FTD/TPI, trifluridine and tipiracil.

RESULTS

A total of 450 patients were included in the FAS population (214 with a *KRAS*^{G12} mutation and 236 with *RAS* wild-type tumors or with a non-*KRAS*^{G12} *RAS* mutation), and 302 patients were included in the *RAS* mutation subpopulation (214 with a *KRAS*^{G12} mutation and 88 with a non-*KRAS*^{G12} *RAS* mutation) (Figure 1). Baseline patient demographics among the different subgroups are summarized in Table 1.

Overall, no significant difference in survival was observed between patients with *RAS* wild-type ($n = 148$) and *RAS*-mutated tumors ($n = 302$); median OS was 9.3 months versus 8.5 months, respectively (HR 1.12, 95% CI 0.88-1.4). FTD/TPI plus bevacizumab was associated with improved OS compared with FTD/TPI alone in both subgroups. In the population with a *RAS* mutation, median OS (95% CI) was 10.1 months (8.9-11.3 months) with FTD/TPI plus

bevacizumab versus 7.1 months (6.3-8.5 months) with FTD/TPI alone (HR 0.61, 95% CI 0.46-0.81). In the population with *RAS* wild-type disease, median OS (95% CI) was 11.4 months (8.6-14.9 months) with FTD/TPI plus bevacizumab versus 7.4 months (5.9-10.9 months) with FTD/TPI alone (HR 0.66, 95% CI 0.44-0.99).

No significant difference in survival was observed between patients with and without *KRAS*^{G12} mutations in the FAS (HR 1.09, 95% CI 0.87-1.4; Figure 2A), though there was a small numerical difference in the median OS (95% CI) between these two populations [8.3 months (7.5-9.6 months) versus 9.2 months (8.2-10.9 months), respectively]. Similar results were observed when the analysis was restricted to the *RAS* mutation subgroup (HR 1.03, 95% CI 0.76-1.4; Figure 2B). Of the 214 patients with *KRAS*^{G12} mutations, 24 had confirmed *KRAS*^{G12C} mutations (Table 1). Median OS (95% CI) in patients with *KRAS*^{G12C} mutations was 8.5 months (6.0-9.6 months).

Table 1. Baseline patient demographics and clinical characteristics

	<i>RAS</i> mutation (<i>n</i> = 302)	<i>KRAS</i> ^{G12} mutation (<i>n</i> = 214)	<i>KRAS</i> ^{G12C} mutation (<i>n</i> = 24)	Non- <i>KRAS</i> ^{G12} <i>RAS</i> mutation (<i>n</i> = 88)	<i>RAS</i> wild-type (<i>n</i> = 148)	<i>RAS</i> wild-type or a non- <i>KRAS</i> ^{G12} <i>RAS</i> mutation (<i>n</i> = 236)
Median age, years	63	64	60.5	62	62	62
Male, <i>n</i> (%)	153 (50.7)	112 (52.3)	12 (50.0)	41 (46.6)	80 (54.1)	121 (51.3)
Race or ethnic group, <i>n</i> (%)						
White	266 (88.1)	186 (86.9)	21 (87.5)	80 (90.9)	133 (89.9)	213 (90.3)
Black	6 (2.0)	6 (2.8)	0	0	1 (0.7)	1 (0.4)
Asian	0	0	0	0	1 (0.7)	1 (0.4)
Other	11 (3.6)	8 (3.7)	3 (12.5)	3 (3.4)	2 (1.4)	5 (2.1)
Missing	19 (6.3)	14 (6.5)	0	5 (5.7)	11 (7.4)	16 (6.8)
Geographic region, <i>n</i> (%)						
North America	8 (2.7)	6 (2.8)	1 (4.2)	2 (2.3)	6 (4.1)	8 (3.4)
European Union	199 (65.9)	140 (65.4)	17 (70.8)	59 (67.0)	98 (66.2)	157 (66.5)
Rest of the world	95 (31.5)	68 (31.8)	6 (25.0)	27 (30.7)	44 (29.7)	71 (30.1)
Primary diagnosis, <i>n</i> (%)						
Colon cancer	220 (72.9)	162 (75.7)	18 (75.0)	58 (65.9)	108 (73.0)	166 (70.3)
Rectal cancer	82 (27.1)	52 (24.3)	6 (25.0)	30 (34.1)	40 (27.0)	70 (29.7)
Location of primary tumor, <i>n</i> (%)						
Right side	91 (30.1)	65 (30.4)	7 (29.2)	26 (29.6)	35 (23.6)	61 (25.8)
Left side	211 (69.9)	149 (69.6)	17 (70.8)	62 (70.4)	113 (76.4)	175 (74.2)
Number of metastatic sites, <i>n</i> (%)						
1/2	182 (60.3)	132 (61.7)	14 (58.3)	50 (56.8)	90 (60.8)	140 (59.3)
≥3	120 (39.7)	82 (38.3)	10 (41.7)	38 (43.2)	58 (39.2)	96 (40.7)
ECOG performance status, <i>n</i> (%)						
0	129 (42.7)	93 (43.5)	13 (54.2)	36 (40.9)	74 (50.0)	110 (46.6)
1	173 (57.3)	121 (56.5)	11 (45.8)	52 (59.1)	73 (49.3)	125 (53.0)
2	0	0	0	0	1 (0.7)	1 (0.4)

ECOG, Eastern Cooperative Oncology Group.

No significant differences in OS were observed according to *KRAS*^{G12} mutation status within the individual treatment arms (FTD/TPI alone or FTD/TPI plus bevacizumab) in either the FAS or *RAS* mutation population (Figure 3).

In the FAS, FTD/TPI plus bevacizumab was associated with improved OS compared with FTD/TPI alone, irrespective of *KRAS*^{G12} mutational status (Figure 4). In the population with a *KRAS*^{G12} mutation, median OS (95% CI) was 9.4 months (8.2-10.9 months) with FTD/TPI plus bevacizumab versus 7.2 months (6.3-9.1 months) with FTD/TPI alone (HR 0.67, 95% CI 0.48-0.93). In the population without a *KRAS*^{G12} mutation, median OS (95% CI) was 11.3 months (9.6-14.2 months) with FTD/TPI plus bevacizumab versus 7.1 months (5.9-8.9 months) with FTD/TPI alone (HR 0.59, 95% CI 0.43-0.81).

DISCUSSION

The results of this *post hoc* analysis of SUNLIGHT data found no evidence to suggest that the addition of bevacizumab to FTD/TPI was less effective in improving survival outcomes in any *KRAS* subgroup. No significant differences in survival between patients with and without *KRAS*^{G12} mutations were observed in the FAS, either across treatments (both treatment arms) or within treatment arms (FTD/TPI plus bevacizumab and FTD/TPI alone), and similar effects were observed in the *RAS* mutation population. The improvements in survival with FTD/TPI plus bevacizumab versus FTD/TPI alone were confirmed to be independent of *KRAS* mutational status.

In the SUNLIGHT trial, OS outcomes in patients who received FTD/TPI alone were comparable between those with and without a *KRAS*^{G12} mutation (median 7.2 versus 7.1 months). These findings are consistent with those from a meta-analysis reported by Yoshino et al., which included updated OS data from 1375 patients enrolled in three RCTs of FTD/TPI versus placebo: RECURSE (global), TERRA (Asia), and J003 (Japan).²⁴ The results of the meta-analysis support the OS benefit of FTD/TPI as monotherapy in patients with *KRAS*^{G12} mutations, albeit potentially with a smaller magnitude compared with that observed in patients without *KRAS*^{G12} mutations. While univariate analyses suggested that the presence of a *KRAS*^{G12} mutation significantly reduced the OS benefit of FTD/TPI versus placebo compared with the absence of a *KRAS*^{G12} mutation (HR 0.86, 95% CI 0.70-1.05 and HR 0.62, 95% CI 0.53-0.72, respectively; interaction *P* = 0.0206), a multivariate analysis controlling for differences in baseline characteristics showed the OS benefit was maintained in patients with and without *KRAS*^{G12} mutations (HR 0.73, 95% CI 0.59-0.89 and HR 0.63, 95% CI 0.54-0.74, respectively; interaction *P* = 0.2939). PFS was also significantly longer with FTD/TPI versus placebo regardless of the presence of *KRAS*^{G12} mutations.²⁴

Our findings are also in agreement with the results of a systematic review and meta-analysis reported by Huang et al., which reported that FTD/TPI monotherapy was associated with improved OS and PFS irrespective of *KRAS* mutational status.²⁵ The meta-analysis included data from 2903 patients treated with FTD/TPI or placebo and/or best supportive care across the same three RCTs as in the

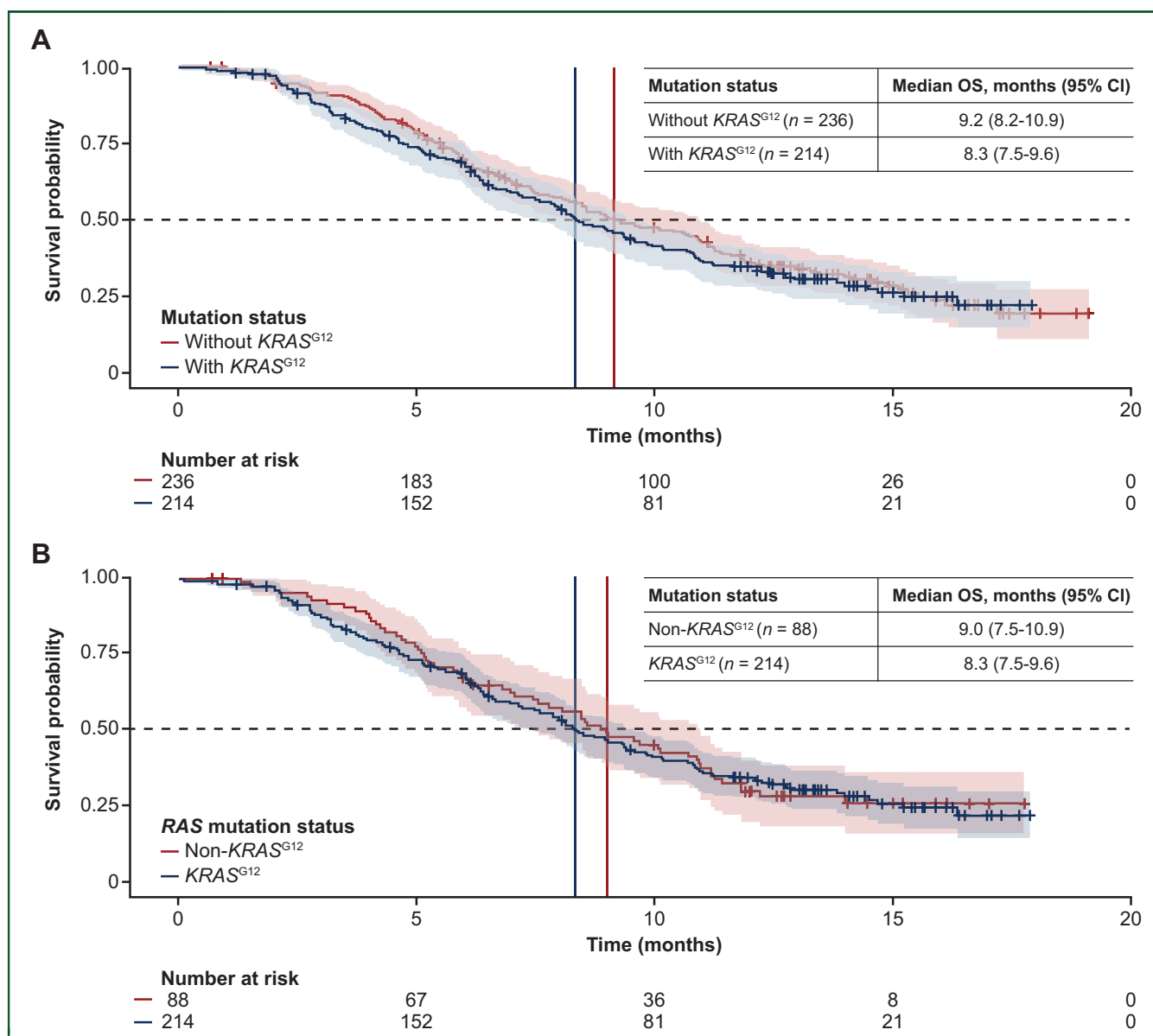


Figure 2. OS according to $KRAS^{G12}$ mutation status. (A) FAS population (FTD/TPI plus bevacizumab and FTD/TPI alone; $n = 450$). (B) RAS mutation population ($n = 302$). CI, confidence interval; FAS, full analysis set; FTD/TPI, trifluridine and tipiracil; OS, overall survival.

Yoshino et al. analysis, as well as three *post hoc* analyses and two prospective cohort studies. Analysis of OS according to $KRAS$ mutational status, however, was limited to results from the TERRA and J003 RCTs and a *post hoc* analysis of RECURSE. FTD/TPI showed significant OS benefits versus placebo/best supportive care in both $KRAS$ wild-type (HR 0.66, 95% CI 0.55-0.79; $P < 0.00001$) and $KRAS$ mutation subgroups (HR 0.75, 95% CI 0.62-0.91; $P = 0.004$), along with a significant PFS improvement in both subgroups (both, HR 0.47, 95% CI 0.38-0.58; $P < 0.00001$). Of note, the individual studies included in the meta-analyses of Yoshino et al. and Huang et al. were not designed to assess OS benefit according to $KRAS$ mutational status.^{24,25} Additionally, the latter did not include data on codon-specific $KRAS$ mutations.²⁵

Interestingly, the results of the current analysis differ from the findings from an observational subgroup analysis

conducted by van de Haar et al.²⁶ in a real-world cohort of 960 patients, which reported shorter OS following treatment with FTD/TPI in patients with $KRAS^{G12}$ mutations versus those with no $KRAS^{G12}$ mutation or with a $KRAS^{G13}$ mutation.²⁶ The same authors also conducted an exploratory *post hoc* analysis using data from the phase III RECURSE study, the results of which suggested that OS was not prolonged with FTD/TPI versus placebo in patients with a $KRAS^{G12}$ mutation (HR 0.97, 95% CI 0.73-1.20; $P = 0.85$). By contrast, patients with $KRAS^{G13}$ -mutant tumors had significantly improved OS (HR 0.29, 95% CI 0.15-0.55; $P < 0.001$). In this analysis, $KRAS^{G12}$ mutations ($n = 279$) were reported to be predictive of reduced OS benefit with FTD/TPI versus placebo (unadjusted interaction $P = 0.0031$, adjusted interaction $P = 0.015$); however, it should be noted that identification of a significant interaction term indicates that the degree of benefit with FTD/TPI

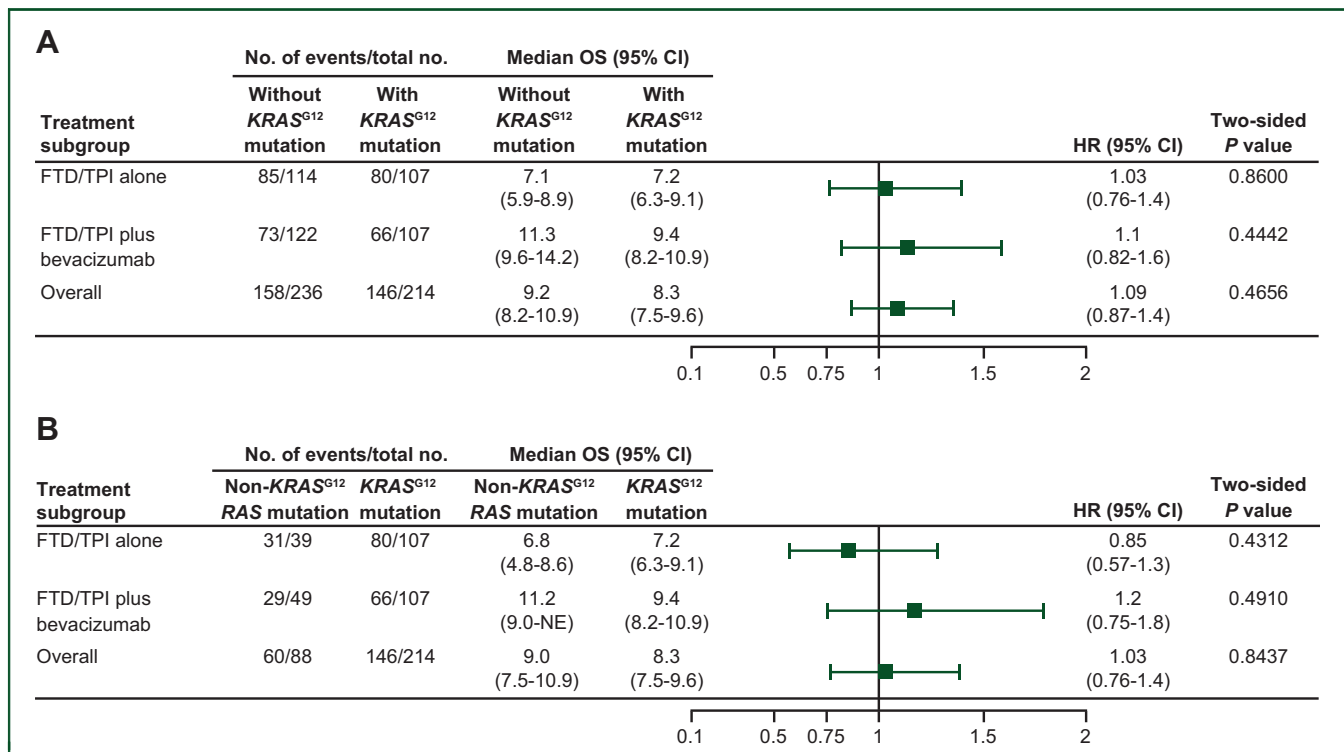


Figure 3. Forest plot of OS according to *KRAS*^{G12} mutation status in the individual treatment arms (FTD/TPI alone and FTD/TPI plus bevacizumab). (A) FAS population. (B) *RAS* mutation population. Interaction *P* values were not statistically significant [*P* = 0.6634 in the FAS population (versus patients without a *KRAS*^{G12} mutation) and *P* = 0.3074 in the *RAS* mutation population (versus patients with a non-*KRAS*^{G12} *RAS* mutation)]. CI, confidence interval; FAS, full analysis set; FTD/TPI, trifluridine and tipiracil; HR, hazard ratio; NE, not estimable; OS, overall survival.

versus placebo was different between the populations with and without *KRAS*^{G12} mutations, not that the *KRAS*^{G12} mutation subgroup did not benefit from treatment. The analyses reported by van de Haar et al. had some limitations, including the fact that the real-world study was not designed to identify the OS benefit in patients with or without codon-specific *KRAS* mutations. There were also potential confounding factors due to imbalances in baseline characteristics and prior treatment, and no sensitivity analysis was conducted to account for heterogeneity bias. Additional limitations of the real-world cohort analysis include the limited quality of documentation (e.g. a lack of detail on what inclusion and exclusion criteria were considered for data selection), and small patient numbers (*n* = 37) in the discovery cohort that identified *KRAS*^{G12} mutations as a potential biomarker of resistance. Interestingly, OS outcomes in the real-world cohort and the control arm of the RECURSE study appear discordant and inconsistent with historical data. Median OS in the *KRAS*^{G13} population, for example, was ~15 months in the real-world cohort treated with FTD/TPI, compared with 8.7 months for the *KRAS*^{G13} mutation FTD/TPI subgroup of the RECURSE population, and just 2.9 months in the *KRAS*^{G13} mutation placebo group. By comparison, median OS in a pooled analysis of 571 patients with *KRAS*^{G13}-mutant, chemorefractory mCRC treated with cetuximab-based treatment was 7.6 months.³⁰

As per the aforementioned analyses, the fact that the SUNLIGHT trial was not designed to assess the impact of

codon-specific *KRAS* mutations is also a limitation of the current analysis, along with the *post hoc* nature of the subgroup analysis. Furthermore, in the analysis restricted to the *RAS* mutation subgroup, patients with *KRAS*^{G12}-mutant tumors who were treated with FTD/TPI alone comprised <10% of the study population, thereby precluding meaningful interpretation of the comparison between populations with a *KRAS*^{G12} mutation versus a non-*KRAS*^{G12} *RAS* mutation. Moreover, data on *KRAS*^{G13} or specific *KRAS*^{G12} mutations were not reported because the numbers of patients with available data in the SUNLIGHT trial were too small to allow meaningful comparisons. Therefore, like the previously reported observational data and meta-analyses,²⁴⁻²⁶ it is not possible to speculate on the prognostic/predictive value of individual *KRAS*^{G12} point mutations in patients receiving FTD/TPI with or without bevacizumab. Further insights in this regard would be of value, particularly with respect to the *KRAS*^{G12C} mutation, which has been established as a strong negative prognostic factor in patients with mCRC.³¹ Lastly, data on *KRAS* mutational status were collected upon diagnosis of metastatic disease, whereas the SUNLIGHT study was conducted in the later-line setting; therefore, it is possible that *RAS* mutations may have emerged throughout treatment and some patients might have been misclassified. For example, in a recent analysis of the phase III FIRE-4 study of first-line folinic acid, fluorouracil, and irinotecan plus cetuximab in patients with *RAS* wild-type disease per tissue biopsy, serial liquid biopsy detected a *RAS* mutation in 13% of patients.³²

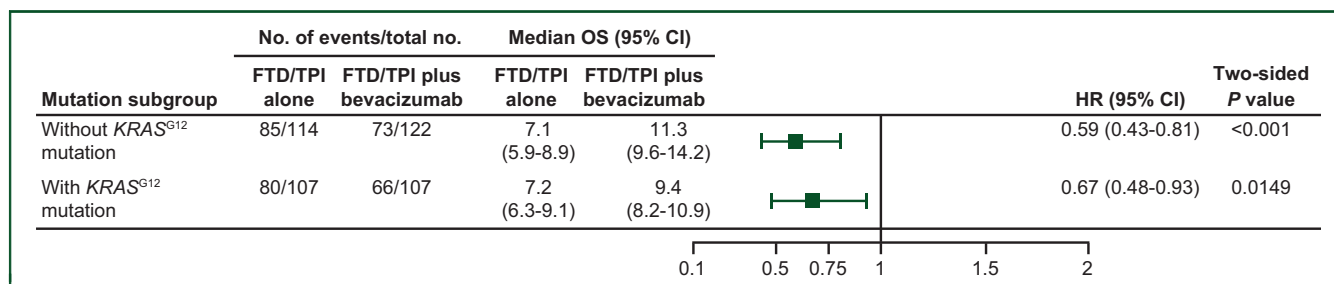


Figure 4. Forest plot of OS with FTD/TPI plus bevacizumab versus FTD/TPI alone according to *KRAS*^{G12} mutation status in the FAS population. CI, confidence interval; FAS, full analysis set; FTD/TPI, trifluridine and tipiracil; HR, hazard ratio; OS, overall survival.

Higher-sensitivity *KRAS* mutation testing methods may also be needed to support detailed interpretation of the tumor genotype. Hyperselective circulating tumor DNA analysis of baseline samples from the phase III PARADIGM trial of first-line panitumumab, for example, showed that 8% of patients had a *KRAS*/*NRAS* mutation.³³

Conclusions

The results of this *post hoc* analysis, based on results from an RCT that had a high quality of data collection and homogeneous patient population, show no evidence that *KRAS* mutations have an impact on OS with the combination of FTD/TPI plus bevacizumab. The combination provides clinical benefit to all patient populations, including those with or without *KRAS*^{G12}-mutant mCRC. Overall, based on available data, and to the best of our knowledge, *KRAS* mutations are not predictive of clinical outcomes with FTD/TPI either as monotherapy or in combination with bevacizumab.

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ROLE OF THE FUNDER

The sponsors (Servier International Research Institute and Taiho Oncology, Inc.) were involved in the study design and were responsible for the overall study management, data management, and statistical analysis. The sponsors were involved in the writing of this report, alongside the authors, all of whom had access to the raw data. The corresponding author had full access to all the data in the study and had the final responsibility for the decision to submit for publication.

DISCLOSURE

JTab has received fees for advisory/consultancy roles from Array BioPharma, AstraZeneca, Bayer, BeiGene, Biocartis,

Boehringer Ingelheim, Chugai Pharmaceutical Co., Ltd., F. Hoffmann-La Roche, Foundation Medicine, Genentech, Genmab A/S, HaliDX SAS, Halozyme, Imugene, Inflection Biosciences, Ipsen, Kura Oncology, Lilly, Menarini, Merck Serono, Merrimack Pharmaceuticals, Merus, Molecular Partners, MSD, Novartis, Peptomyc, Pfizer, Pharmacyclics, ProteoDesign SL, Rafael Pharmaceuticals, Roche Diagnostics, Sanofi, Seagen, Servier, Symphogen, Taiho, and VCN Biosciences. JTai has received honoraria for speaker or advisory role from Amgen, Astellas, AstraZeneca, Bristol Myers Squibb, Merck Serono, MSD, Novartis, Pierre Fabre, Roche, Servier, and Takeda. MF has received fees for consultancy or participation in advisory boards from AstraZeneca, Bayer Corporation, Bristol-Myers Squibb, Eisai Oncology, Entos Pharmaceuticals, Janssen, Merck, Mirati Therapeutics, Nouscom, Pfizer, Roche/Genentech, Taiho Oncology, and Xenthera; fees for an editorial board role from Mirati Therapeutics; and research grant support from Agenus, Bristol-Myers Squibb, Genentech/imCORE, and Verastem Oncology. GWP has received fees for advisory/consultancy roles from Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, CECOG, Daiichi Sankyo, Incyte, Lilly, Merck Serono, MSD, Novartis, Pierre Fabre, Roche, Sanofi, Servier, and Takeda. EVC has received grants or contracts from Amgen, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly and Company, Ipsen, Merck Sharp & Dohme, Merck KGaA, Novartis, Roche, and Servier; and consulting fees from AbbVie, ALX, Amgen, Array, Astellas, AstraZeneca, Bayer, Beigene, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly and Company, GlaxoSmithKline, Incyte, Ipsen, Merck Sharp & Dohme, Merck KGaA, Mirati, Novartis, Nordic, Pierre Fabre Oncologie, Pfizer, Roche, Seagen, Servier, Takeda, Terumo, Taiho Pharmaceutical, and Zymeworks. FC reports grants or contracts from Roche, Pfizer, and Pierre Fabre; and payment or honoraria from Merck KGaA, Bayer, Pierre Fabre, Servier, MSD, and Roche. NA and DS are employees of Servier. EC is an employee of Taiho Oncology, Inc. TY has received research grants from Amgen, Chugai Pharmaceutical Co., Ltd., Daiichi Sankyo, Eisai, FALCO Biosystems, Genomedia Inc., Molecular Health, MSD, Nippon Boehringer Ingelheim, Ono Pharmaceutical Co., Ltd., Pfizer, Roche Diagnostics, Sanofi, Sysmex, and Taiho Oncology; honoraria from Bayer Yakuin, Chugai Pharmaceutical Co., Ltd., Merck, MSD K.K., Ono Pharmaceutical Co., Ltd., and Takeda; and consulting fees from Sumitomo Corporation. RJM has declared no conflicts of interest.

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