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SUNLIGHT

Phase III Study of trifluridine/tipiracil in combination with bevacizumab vs trifluridine/tipiracil single agent in patients with refractory metastatic colorectal cancer

Effect of $KRAS^{G12}$ mutations on overall survival in patients with refractory metastatic colorectal cancer: a post-hoc analysis of the phase 3 SUNLIGHT trial

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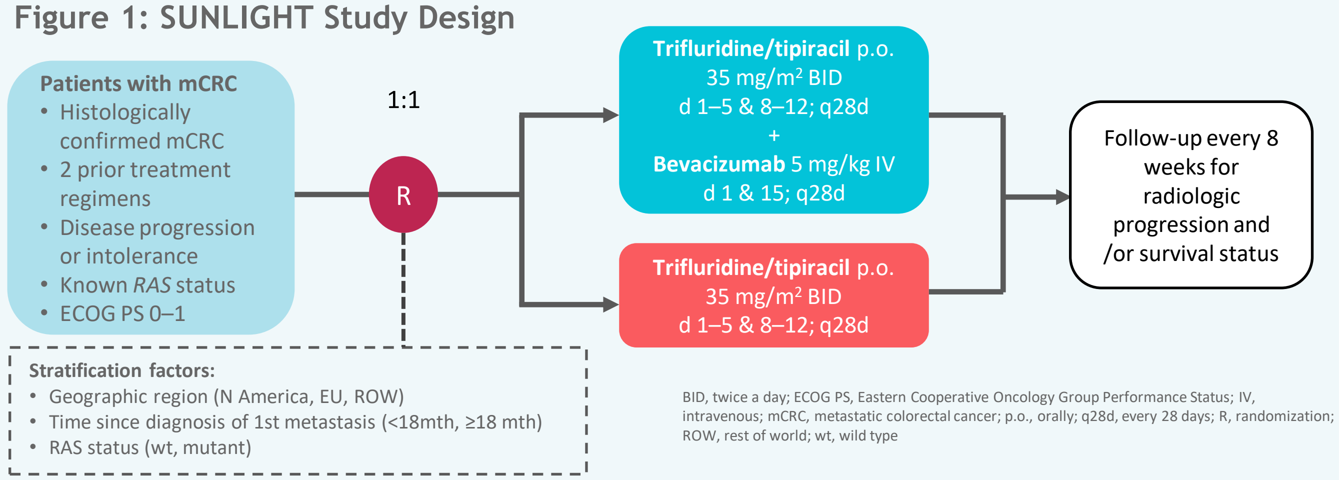
Background

- SUNLIGHT was an international, open-label, randomized, phase 3 study comparing trifluridine/tipiracil (FTD/TPI) in combination with bevacizumab versus FTD/TPI monotherapy, as third-line treatment in patients with refractory metastatic colorectal cancer (mCRC)[1]
- In SUNLIGHT, median overall survival (OS) was improved by 3.3 months with FTD/TPI + bevacizumab (10.8 months with FTD/TPI + bevacizumab vs. 7.5 months with FTD/TPI, HR: 0.61 [95% CI: 0.49,0.77] P<0.001)[1]
- This has led to the approval of this combination for the treatment of previously treated mCRC by the European Medicines Agency,[2] and the U.S. Food & Drug Administration[3]
- 44% of mCRC patients harbor mutations in *KRAS*, with mutations occurring most frequently at codon G12 ($KRAS^{G12}$)[4]
- A meta-analysis reported no effect of $KRAS^{G12}$ mutations on OS in patients treated with FTD/TPI monotherapy[5]
- The aim of this analysis was to investigate the effects of $KRAS^{G12}$ mutational status on OS in patients with mCRC treated with FTD/TPI + bevacizumab, utilizing data from the SUNLIGHT study

Methods

- This was a post-hoc analysis of data from the SUNLIGHT trial (NCT04737187; trial design overview shown in **Figure 1**)

Figure 1: SUNLIGHT Study Design


Patients with mCRC
Histologically confirmed mCRC
2 prior treatment regimens
Disease progression or intolerance
Known RAS status
ECOG PS 0–1
1:1
R
Trifluridine/tipiracil p.o. 35 mg/m² BID d 1–5 & 8–12; q28d + Bevacizumab 5 mg/kg IV d 1 & 15; q28d
Trifluridine/tipiracil p.o. 35 mg/m² BID d 1–5 & 8–12; q28d
Follow-up every 8 weeks for radiologic progression and /or survival status
Stratification factors:
Geographic region (N America, EU, ROW)
Time since diagnosis of 1st metastasis (<18mth, ≥18 mth)
RAS status (wt, mutant)
BID, twice a day; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IV, intravenous; mCRC, metastatic colorectal cancer; p.o., orally; q28d, every 28 days; R, randomization; ROW, rest of world; wt, wild type

- OS was compared between patients with and without a $KRAS^{G12}$ mutation in the SUNLIGHT population
- A subgroup analysis according to $KRAS^{G12}$ mutational status was conducted to assess the effect of $KRAS^{G12}$ mutation on the treatment benefit associated with FTD/TPI + bevacizumab vs FTD/TPI monotherapy on OS

Results

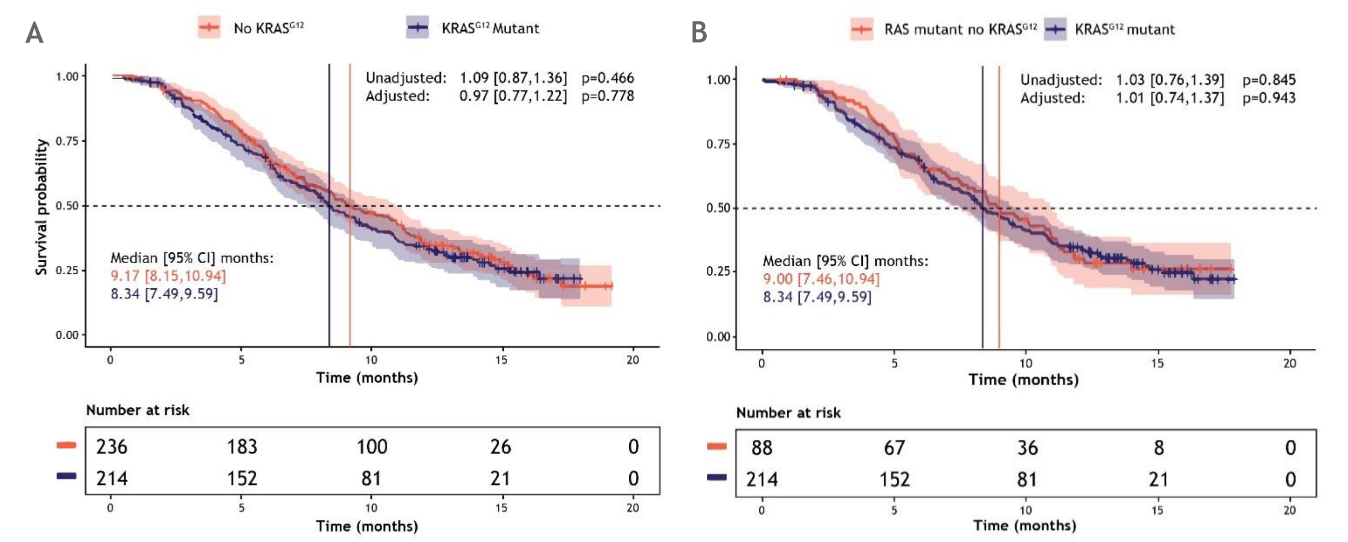
Effect of $KRAS^{G12}$ mutational status on OS in total SUNLIGHT population (treated with combination therapy or with monotherapy)

- In the overall population, a similar OS trend was observed in patients regardless of $KRAS^{G12}$ mutational status (**Figure 2A**)
- Patients with a $KRAS^{G12}$ mutation had a median OS of 8.34 months [95% CI: 7.49,9.59], while patients without a $KRAS^{G12}$ mutation had median OS of 9.17 months [95% CI: 8.15,10.94]
- A non-detrimental effect on OS was observed in patients with a $KRAS^{G12}$ mutation compared with patients without a $KRAS^{G12}$ mutation, shown by an OS HR of 1.09 [95% CI: 0.87,1.36]

Effect of $KRAS^{G12}$ mutational status on OS in *RAS* mutant patients

- In a subgroup analysis of patients with a *RAS* mutation, patients had a similar OS trend independent of $KRAS^{G12}$ mutational status (**Figure 2B**)
- *RAS* mutant patients without a $KRAS^{G12}$ mutation has a median OS of 9.00 months [95% CI: 7.46,10.94], while median OS for *RAS* mutant patients with mutated $KRAS^{G12}$ was 8.34 months [95% CI: 7.49,9.59]

Figure 2: Kaplan-Meier analysis of OS in the A) overall SUNLIGHT population, with or without a $KRAS^{G12}$ mutation, and in a B) *RAS* mutant patient subgroup, with or without a $KRAS^{G12}$ mutation

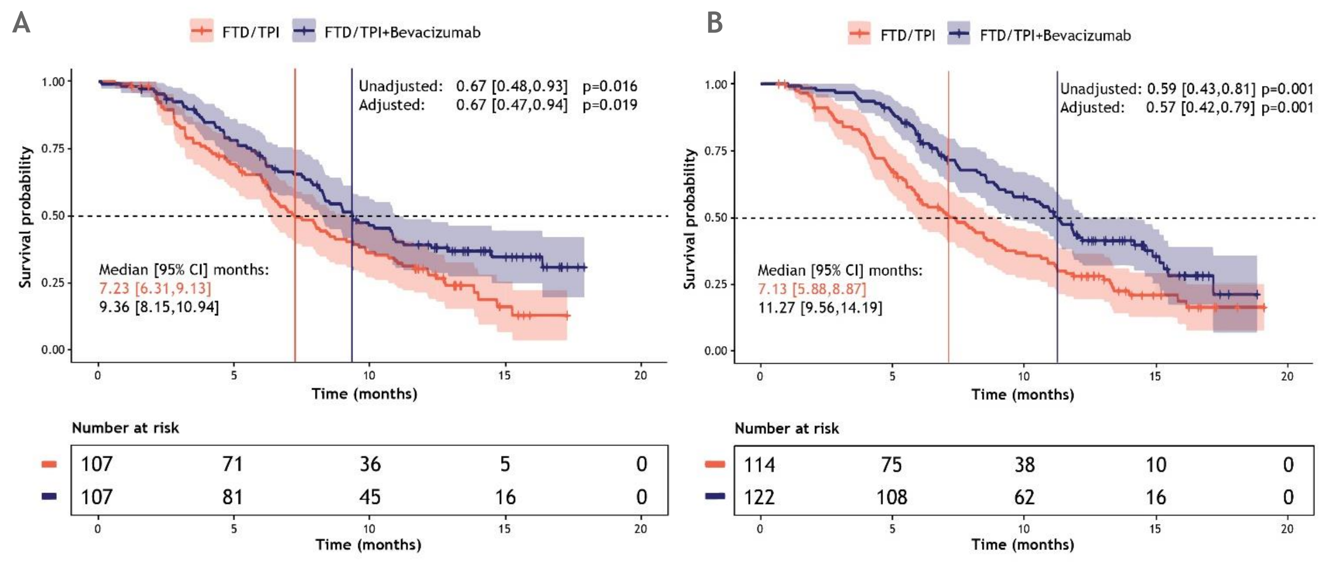

A
No KRAS G12
KRAS G12 Mutant
Unadjusted: 1.09 [0.87,1.36] p=0.466
Adjusted: 0.97 [0.77,1.22] p=0.778
Survival probability
Median [95% CI] months:
9.17 [8.15,10.94]
8.34 [7.49,9.59]
Time (months)
Number at risk
236 183 100 26 0
214 152 81 21 0
B
RAS mutant no KRAS G12
KRAS G12 mutant
Unadjusted: 1.03 [0.76,1.39] p=0.845
Adjusted: 1.01 [0.74,1.37] p=0.943
Median [95% CI] months:
9.00 [7.46,10.94]
8.34 [7.49,9.59]
Number at risk
88 67 36 8 0
214 152 81 21 0

A) With $KRAS^{G12}$ mutation N = 214; Without a $KRAS^{G12}$ mutation N=236 B) With RAS mutation, no $KRAS^{G12}$ mutation N=88; With $KRAS^{G12}$ mutation N = 214

Effect of $KRAS^{G12}$ mutational status on treatment benefit associated with FTD/TPI + bevacizumab vs FTD/TPI monotherapy on OS

- Patients treated with FTD/TPI + bevacizumab had prolonged OS compared with patients that received FTD/TPI monotherapy, regardless of $KRAS^{G12}$ mutational status (**Figure 3**)
- In the $KRAS^{G12}$ mutant subgroup, mOS was 9.36 months (95% CI: 8.15,10.94) with FTD/TPI + bevacizumab vs 7.23 months [95% CI: 6.31,9.13] with FTD/TPI monotherapy (HR, 0.67; [95% CI: 0.48,0.93])
- In the subgroup without a $KRAS^{G12}$ mutation, median OS was 11.27 months (95% CI: 9.56 - 14.19) with FTD/TPI + bevacizumab vs 7.13 months [95% CI: 5.88,8.87] with FTD/TPI monotherapy (HR, 0.59; [95% CI: 0.43,0.81])

Figure 3: Kaplan-Meier analysis of OS in patients treated with FTD/TPI + bevacizumab or FTD/TPI monotherapy (A) with $KRAS^{G12}$ mutation or (B) without a $KRAS^{G12}$ mutation


A
FTD/TPI
FTD/TPI+Bevacizumab
Unadjusted: 0.67 [0.48,0.93] p=0.016
Adjusted: 0.67 [0.47,0.94] p=0.019
Survival probability
Median [95% CI] months:
7.23 [6.31,9.13]
9.36 [8.15,10.94]
Time (months)
Number at risk
107 71 36 5 0
107 81 45 16 0
B
Unadjusted: 0.59 [0.43,0.81] p=0.001
Adjusted: 0.57 [0.42,0.79] p=0.001
Median [95% CI] months:
7.13 [5.88,8.87]
11.27 [9.56,14.19]
114 75 38 10 0
122 108 62 16 0

A) Treated with FTD/TPI + Bevacizumab N=107; Treated with FTD/TPI N=107 B) Treated with FTD/TPI + Bevacizumab N=122; Treated with FTD/TPI N=114

Conclusions

- $KRAS^{G12}$ mutational status has no detrimental effect on OS in patients with mCRC who are receiving FTD/TPI (as a monotherapy or in combination with bevacizumab) as third-line treatment
- Patients receiving a combination of FTD/TPI + bevacizumab showed an increase in OS compared to FTD/TPI monotherapy, independently of $KRAS^{G12}$ mutational status

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Corresponding Author & Disclosures