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SUNLIGHT

Maintained ECOG-PS with trifluridine/tipiracil in combination with bevacizumab in refractory metastatic colorectal cancer: an analysis of the phase III SUNLIGHT trial

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Background

- Trifluridine/tipiracil (FTD/TPI) is an orally administered combination of trifluridine, a thymidine-based antineoplastic nucleoside analog, and tipiracil, a thymidine phosphorylase inhibitor that increases the bioavailability of trifluridine[1]
- Results from the phase 3 RECOURSE study showed that third-line FTD/TPI significantly improved overall survival (OS) and had a favorable safety profile in patients with refractory metastatic colorectal cancer (mCRC),[1] which established FTD/TPI as a recommended third-line treatment for mCRC
- In phase 2 randomized and single-arm studies, combination of FTD/TPI plus bevacizumab improved OS and progression-free survival (PFS) with a manageable safety profile[2-7]
- Therefore, SUNLIGHT, an international, open-label, randomized, phase 3 study comparing FTD/TPI in combination with bevacizumab versus FTD/TPI monotherapy in patients with refractory mCRC was conducted[8]
- In SUNLIGHT, median 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), hazard ratio (HR) of 0.61 (95% CI: 0.49, 0.77; P<0.001)[9]
- In addition, median PFS was 5.6 months and 2.4 months in the FTD/TPI + bevacizumab and FTD/TPI groups, respectively (HR 0.44 [95% CI: 0.36, 0.54]; P<0.001)[9]
- These results mean that FTD/TPI + bevacizumab could be considered as a new standard of care for third-line treatment of mCRC

Objective

- The objective of this analysis was to compare FTD/TPI in combination with bevacizumab versus FTD/TPI monotherapy in patients with refractory mCRC who had a maintained Eastern Cooperative Oncology Group performance status (ECOG-PS) during treatment using data from the SUNLIGHT study

Methods

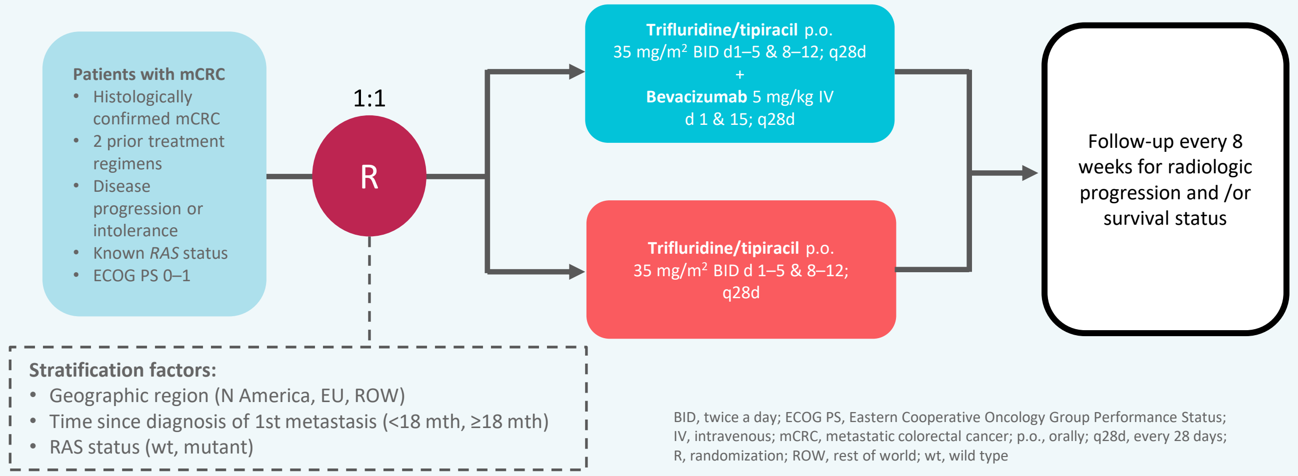
Study Design and Population

- This was a post-hoc analysis of data from the SUNLIGHT trial (NCT04737187; trial design overview shown in **Figure 1**)
- SUNLIGHT enrolled patients with ECOG-PS 0/1
  - ECOG-PS was evaluated at baseline, at each treatment cycle, and at withdrawal visit
  - Worst ECOG values and time to ECOG worsening from 0 or 1 to ≥2 were reported

Post-Hoc Analysis

- The following endpoints were compared between patients receiving FTD/TPI + bevacizumab and those receiving FTD/TPI monotherapy
  - OS and PFS in patients who remained at ECOG-PS 0 or 1

Figure 1: SUNLIGHT Study Design



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

Results

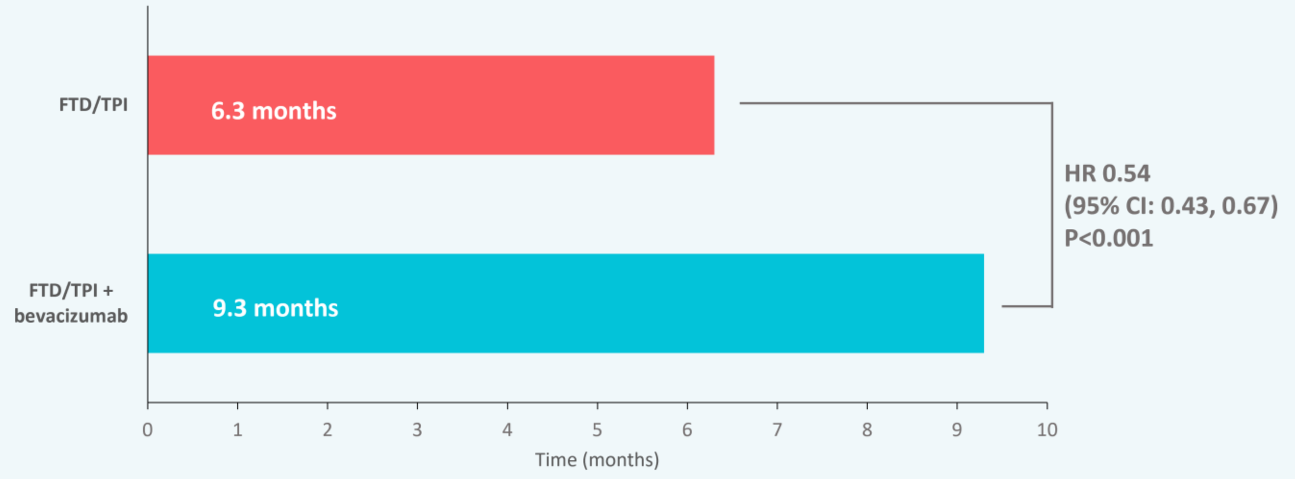
Key Patient Baseline Characteristics from SUNLIGHT

- Of 492 randomized patients (FTD/TPI + bevacizumab, n=246; FTD/TPI, n=246) from the SUNLIGHT study
  - 52% were male
  - 58% had ≥18 months from diagnosis of first metastasis to randomization
  - 69% had mutant *RAS*
  - 491 had ECOG-PS 0 or 1

Time to ECOG-PS Worsening

- FTD/TPI + bevacizumab significantly improved time to ECOG-PS worsening from 0 or 1 to ≥2 when compared with FTD/TPI monotherapy **(Figure 2)**

Figure 2: Time to ECOG-PS Worsening



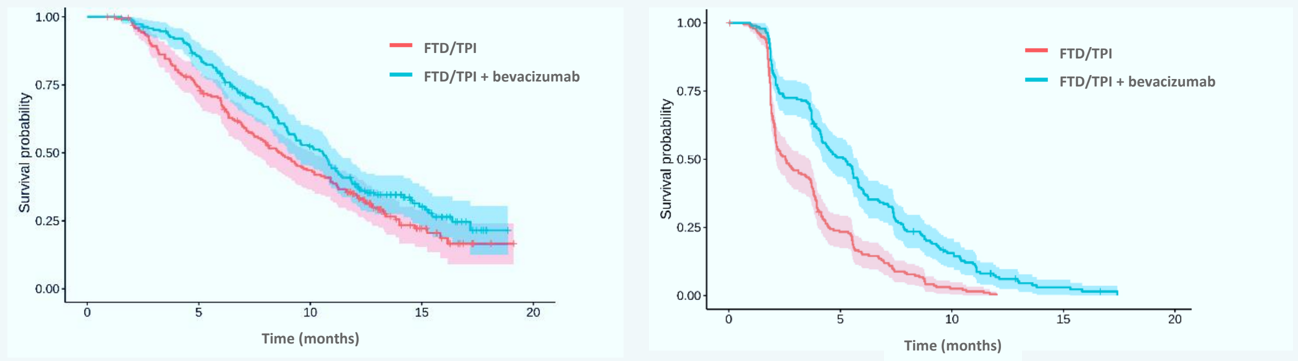
CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group performance status; FTD/TPI, Trifluridine/tipiracil; HR, hazard ratio

- Highest ECOG-PS distribution showed similar proportions over cycles with no clinically meaningful difference (>10%) in both treatment arms
- Considering patients who had discontinued study treatment as of the clinical cut-off date of July 5th, 2022, 189/208 (91%) FTD/TPI + bevacizumab recipients and 200/235 (85%) FTD/TPI recipients remained at ECOG-PS 0 or 1 at treatment discontinuation

OS and PFS in Patients With Maintained ECOG-PS (Post-Hoc Analysis)

- In patients with maintained ECOG-PS, median OS was prolonged in the FTD/TPI + bevacizumab group (10.58 months [95% CI: 9.03, 11.24]) vs the FTD/TPI group (8.71 months [95% CI: 7.39, 10.18]; HR 0.78 [95% CI: 0.61, 0.99; **Figure 3A**)
  - OS probability was consistently higher in patients with maintained ECOG-PS treated with FTD/TPI + bevacizumab versus those treated with FTD/TPI alone at 4 (0.92 [95% CI: 0.87, 0.95] vs 0.81 [0.74, 0.85]), 6 (0.79 [0.73, 0.84] vs 0.69 [0.62, 0.75]) and 9 months (0.58 [0.50, 0.65] vs 0.48 [0.41, 0.55])
- Likewise, median PFS in patients who remained at ECOG-PS 0 or 1 was increased in the FTD/TPI + bevacizumab group (5.22 months [95% CI: 4.17, 5.75]) vs the FTD/TPI group (2.55 months [95% CI: 2.10, 3.58]; HR 0.49 [95% CI: 0.40, 0.61; **Figure 3B**)
  - Probability of progression-free disease was consistently higher in patients with maintained ECOG-PS treated with FTD/TPI + bevacizumab vs those treated with FTD/TPI alone at 4 (0.61 [95% CI: 0.54, 0.68] vs 0.31 [0.25, 0.38]), 6 (0.39 [0.32, 0.46] vs 0.15 [0.10, 0.20]) and 9 months (0.20 [0.15, 0.26] vs 0.04 [0.02, 0.08])

Figure 3: Kaplan-Meier Analysis of (A) Overall Survival and (B) Progression-Free Survival in Patients with a Maintained ECOG-PS of 0 or 1 at Treatment Withdrawal



ECOG-PS, Eastern Cooperative Oncology Group performance status; FTD/TPI, trifluridine/tipiracil

Conclusions

- Consistent with the results of the overall study population,[9] FTD/TPI in combination with bevacizumab prolonged OS and PFS in patients with maintained ECOG-PS
- Maintenance of physical performance may allow patients to receive further therapeutic options during the continuum of care

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