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Efficacy and safety of trifluridine/tipiracil in combination with bevacizumab in older and younger patients with refractory metastatic colorectal cancer: a subgroup analysis of the phase 3 SUNLIGHT trial

Julien Taieb,[1] Gerald W. Prager,[2] Marwan Fakih,[3] Fortunato Ciardiello,[4] Eric Van Cutsem,[5] Elena Elez,[6] Felipe Melo Cruz,[7] Lucjan Wyrwicz,[8] Daniil Stroyakovskiy,[9] Zsuzsanna Pápai,[10] Pierre-Guillaume Poureau,[11] Gabor Liposits,[12] Chiara Cremolini,[13] Igor Bondarenko,[14] Dominik Paul Modest,[15] Lucas Roby,[16] Valentine Barboux,[16] Nadia Amellal,[16] Josep Tabernero[6]

[1]Université Paris-Cité, (Paris Descartes), Georges Pompidou European Hospital, SIRIC CARPEM, Paris, France. [2]Medical University Vienna, Department of Medicine I, Vienna, Austria. [3]City of Hope Comprehensive Cancer Center, Duarte, CA 910106, USA. [4]Department of Precision Medicine, Università degli Studi della Campania Luigi Vanvitelli, Naples, Italy. [5]Department of Digestive Oncology, University Hospitals, Leuven and KU Leuven, Leuven, Belgium. [6]Vall d'Hebron University Hospital and Institute of Oncology (VHIO), UVic-UCC, IOB-Quiron, Barcelona, Spain. [7]Núcleo de Pesquisa e Ensino da Rede São Camilo, Sao Paulo, Brazil. [8]Department of Oncology and Radiotherapy, Maria Sklodowska-Curie National Cancer Research Institute, Warsaw, Poland. [9]Moscow City Oncological Hospital #62, Moscow, Russian Federation. [10]Medical Oncology, Duna Medical Centre, Budapest, Hungary. [11]Institut de Cancérologie, Brest, France. [12]Department of Clinical Research, University of Southern Denmark, Odense, Denmark. [13]Department of Translational Research and New Technologies; University of Pisa, Pisa, Italy. [14]Dnipro State Medical University, Dnipro, Ukraine. [15]Charité Universitätsmedizin, Berlin, Germany. [16]Servier International Research Institute, Suresnes, France.

Background

- Trifluridine/tipiracil (FTD/TPI) is an orally administered treatment that comprises trifluridine, a thymidine-based antineoplastic nucleoside analog, combined with tipiracil, a thymidine phosphorylase inhibitor that increases the bioavailability of trifluridine[1]
- SUNLIGHT was a large, international, open-label, randomized, phase 3 study evaluating FTD/TPI plus bevacizumab (bev) vs. FTD/TPI monotherapy as third-line treatment in patients with refractory metastatic colorectal cancer (mCRC)[2,3]
- In SUNLIGHT, median overall survival (OS) was improved by 3.3 months with FTD/TPI + bev (10.8 months with FTD/TPI + bev vs. 7.5 months with FTD/TPI monotherapy; hazard ratio [HR] 0.61 [95% CI: 0.49, 0.77]; p<0.001)[2]
- Progression-free survival (PFS) was improved by 3.2 months (5.6 months with FTD/TPI + bev vs. 2.4 months with FTD/TPI monotherapy; HR 0.44 [95% CI: 0.36, 0.54]; p<0.001)[2]
- Demonstrated OS benefit in SUNLIGHT led to the approval of FTD/TPI + bev for the treatment of previously treated mCRC patients by the European Medicines Agency[4] and the U.S. Food & Drug Administration[5]

Objective

- The aim of this subgroup analysis from SUNLIGHT was to examine efficacy and safety outcomes in patients with refractory mCRC by age (<65, 65–74, and ≥75 years)

Methods

Study design and patient population

- In SUNLIGHT (NCT04737187), eligible patients were randomized (1:1) to receive FTD/TPI (35 mg/m^2 twice daily on days 1-5 and 8-12 of each 28-day cycle) alone, or combined with bev (5 mg/kg on days 1 and 15)
- SUNLIGHT enrolled patients with mCRC who had disease progression or intolerance to two prior treatment regimens, known *RAS* status, and Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0/1
  - ECOG-PS was evaluated at baseline, at each treatment cycle, and at withdrawal visit

Post-hoc analysis

- This post-hoc analysis of SUNLIGHT in patients categorized according to age (<65 [18-64], 65-74, and ≥75 years) was not powered for statistical significance, and therefore, no formal comparisons were made between age groups
- For each age group, OS (primary endpoint), PFS and time to worsening of ECOG PS (from 0 or 1 to ≥2) were compared between treatment groups in the full analysis set (FAS) using Kaplan-Meier survival estimates and calculated HRs and 95% CIs from unstratified Cox proportional hazard models
- The incidence of emergent adverse events (EAE) across age groups in the safety set is summarized descriptively

Results

- Of the 492 randomized patients (n=246 FTD/TPI + bev; n=246 FTD/TPI), 56%, 32%, and 12% were aged <65, 65-74, and ≥75 years, respectively
- Median duration of treatment with FTD/TPI + bev was 4.6, 5.7, and 4.4 months in the <65, 65-74, and ≥75 age groups, respectively, and duration of FTD/TPI monotherapy was 2.1, 2.1, and 2.0 months in those aged <65, 65-74, and ≥75 years, respectively
- Baseline characteristics were well balanced between treatments across age groups **(Table 1)**

Table 1: Baseline characteristics

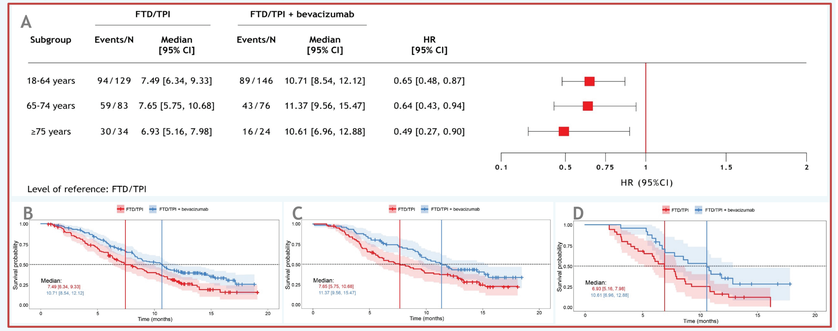
Characteristic	<65 years		65-74 years		≥75 years	
	FTD/TPI + bev (n=146)	FTD/TPI (n=129)	FTD/TPI + bev (n=76)	FTD/TPI (n=83)	FTD/TPI + bev (n=24)	FTD/TPI (n=34)
Age, years, mean (SD)	54.0 (8.4)	54.0 (8.2)	69.0 (2.7)	69.1 (3.1)	78.3 (2.6)	77.7 (2.9)
Male gender, %	52.1	44.2	51.3	45.8	37.5	50.0
ECOG PS 0/1, %	54.1/45.9	49.6/50.4	40.8/59.2	44.6/54.2‡	37.5/62.5	14.7/85.3
Mutant *RAS* status, %	68.5	70.5	76.3	66.3	54.2	70.6
<18 months since 1st diagnosis, %	43.2	51.2	43.4	32.5	33.3	35.3
Right-sided primary disease, %	19.2	27.1	29.0	31.3	50.0	47.1
Renal function, n (%) Normal/mild impairment/moderate impairment*	68.5/27.4/4.1	69.0/27.9/3.1	38.7/42.7/18.7	43.4/41.0/15.7	16.7/41.7/41.7	20.6/47.1/32.4
Hepatic dysfunction (NCI ODWG), n (%) Normal/mild dysfunction/moderate dysfunction	54.1/44.5/1.4	58.1/41.9/-	64.5/34.2/1.3	72.3/27.7/-	58.3/33.3/8.3	82.4/14.7/-†

‡One patient had ECOG PS 2 at baseline (not shown here). *Normal (≥90 ml/min), mild impairment (60-89 ml/min), and moderate impairment (30-59 ml/min). †Hepatic functional status was unknown in one patient (2.9%). Bev, bevacizumab; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FTD, trifluridine; NCI ODWG, National Cancer Institute – Organ Dysfunction Working Group; SD, standard deviation; TPI, tipiracil.

Effect of FTD/TPI + bev on OS in age subgroups

- In all age groups, FTD/TPI + bev prolonged median OS vs. FTD/TPI monotherapy **(Figure 1)**; a wider 95% CI in the ≥75 years age group was attributed to the small sample size

Figure 1: Subgroup analysis of OS: (A) forest plot according to age group, and Kaplan-Meier analysis in patients aged (B) <65 years, (C) 65-74 years, and (D) ≥75 years

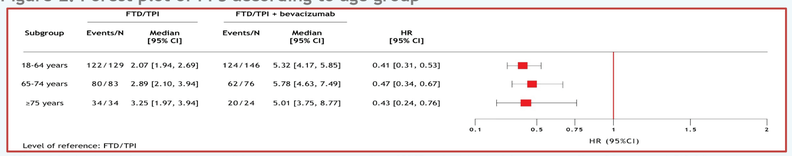


OS was defined as the time from randomization to death from any cause. CI, confidence interval; FAS, full analysis set; FTD, trifluridine; HR, hazard ratio; OS, overall survival; TPI, tipiracil.

Effect of FTD/TPI + bev on PFS in age subgroups

- Median PFS was prolonged in all age groups treated with FTD/TPI + bev vs. those treated with FTD/TPI monotherapy **(Figure 2)**

Figure 2: Forest plot of PFS according to age group

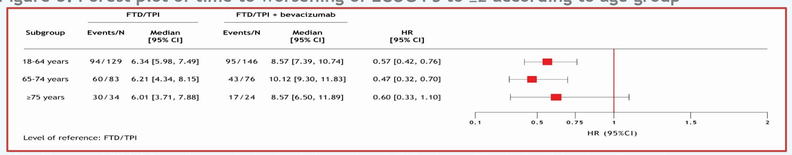


PFS was defined as the time from randomization to radiologic tumour progression according to RECIST version 1.1 or death from any cause. CI, confidence interval; FAS, full analysis set; FTD, trifluridine; HR, hazard ratio; PFS, progression-free survival; TPI, tipiracil.

Effect of FTD/TPI + bev on time to worsening of ECOG PS in age subgroups

- FTD/TPI + bev prolonged median time to ECOG PS worsening compared with FTD/TPI monotherapy **(Figure 3)**

Figure 3: Forest plot of time to worsening of ECOG PS to ≥2 according to age group



CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FAS, full analysis set; FTD, trifluridine; HR, hazard ratio; TPI, tipiracil.

Incidence of adverse events

- EAE frequencies during the treatment period were similar across age groups **(Table 2)**
- The most common EAEs with FTD/TPI + bev in the <65, 65-74, and ≥75 age groups included neutropenia (58.2, 67.1, 70.8%), nausea (41.1, 30.3, 33.3%), anemia (27.4, 30.3, 33.3%), asthenia (22.6, 25.0, 33.3%), decreased appetite (15.8, 25.0, 33.3%), fatigue (21.2, 23.7, 16.7%), and neutrophil count decrease (11.6, 15.8, 20.8%), respectively

Table 2: Summary of EAEs

	<65 years		65-74 years		≥75 years	
	FTD/TPI + bev (n=146)	FTD/TPI (n=129)	FTD/TPI + bev (n=76)	FTD/TPI (n=83)	FTD/TPI + bev (n=24)	FTD/TPI (n=34)
EAE	97.3	97.7	98.7	97.6	100.0	100.0
Severe (grade ≥3) EAE	69.2	63.6	80.3	74.7	66.7	79.4
Serious EAE	20.5	31.0	31.6	27.7	29.2	41.2
Treatment-related EAE	88.4	82.9	92.1	80.7	100.0	76.5
Severe (grade ≥3)	55.5	38.8	65.8	54.2	58.3	50.0
Serious	3.4	5.4	7.9	13.3	8.3	5.9

EAE, treatment-emergent adverse event; FTD, trifluridine; TPI, tipiracil.

Conclusions

The results of this age-based subgroup analysis of SUNLIGHT demonstrate the efficacy benefit in OS, PFS and time to ECOG PS worsening, and the tolerability of FTD/TPI + bev treatment, regardless of age in refractory mCRC patients

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Corresponding Author & Disclosures

Julien Taieb: jtaieb75@gmail.com

Disclosure

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