22 June 2023
EMA/CHMP/221594/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lonsurf

International non-proprietary name: trifluridine / tipiracil

Procedure No. EMEA/H/C/003897/II/0026

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE	:	Adverse event
AESI	:	Adverse event of special interest
Bev	:	Bevacizumab
BID	:	bis in die (twice a day)
BRAF	:	v-Raf murine sarcoma viral oncogene homolog B
CI	:	Confidence interval
CR	:	Complete response
CRC	:	Colorectal cancer
CrCl	:	Creatinine clearance
CPH model	:	Cox proportional hazard model
CSR	:	Clinical study report
CT	:	Combined term
CTCAE	:	Common terminology criteria for adverse events
DNA	:	Deoxyribonucleic acid
DCR	:	Disease Control Rate
e.g.	:	Exempli Gratia (For Example)
EAE	:	Emergent adverse event
ECOG PS	:	Eastern Cooperative Oncology Group Performance Status
e-CRF	:	Electronic Case Report Form
EGFR	:	Epidermal growth factor receptor
EMA	:	European Medicines Agency
EORTC	:	European organisation for research and treatment of cancer
EQ-5D-5L	:	5-level version of the EQ-5D instrument
ESMO	:	European society of medical oncology
EU	:	European Union
FAS	:	Full analysis set
FDA	:	Food and Drug Administration
FTD/TPI	:	Trifluridine/Tipiracil
FU	:	Follow-up
G-CSF	:	Granulocyte-colony stimulating factor
GHS	:	Global health status

HR	:	Hazard Ratio
i.e.	:	id est (that is)
IPD	:	Important protocol deviation
I.R.I.S.	:	Institut de Recherches Internationales Servier
IU	:	International unit
IV	:	IntraVenous (route)
IWRS	:	Interactive web response system
KM	:	Kaplan-Meier
KRAS	:	V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
kg	:	kilogram
L	:	Liter
LLT	:	Lower level term
m^2	:	Square meter
mmol	:	Millimole
MAH	:	Marketing authorisation holder
mCRC	:	Metastatic colorectal cancer
MedDRA	:	Medical Dictionary For Regulatory Activities
MSI-H	:	Microsatellite instability high
mL	:	Milliliter
mg	:	Milligram
min	:	Minute
mmol	:	Millimole
mOS	:	Median OS
mPFS	:	Median PFS
NA	:	Not Applicable
NCCN	:	National Comprehensive Cancer Network
ORR	:	Overall response rate
OS	:	Overall survival
PD	:	Progressive disease
PFS	:	Progression-free survival
PI	:	Product Information
QTc	:	QT interval corrected for heart rate
PR	:	Partial Response

PT	:	Preferred Term
QLQ-C30	:	Quality of Life Questionnaire Core questionnaire
QoL	:	Quality of Life
RAS (*i.e.* gene RAS)	:	Rat sarcoma viral oncogene homolog
RCT	:	Randomised clinical trial
RDI	:	Relative dose intensity
RECIST	:	Response Evaluation Criteria In Solid Tumours
RMP	:	Risk management plan
SEAE	:	Serious emergent adverse event
SAP	:	Statistical analysis plan
SCS	:	Summary of clinical safety
SD	:	Standard Deviation
SMQ	:	Standard MedDRA Queries
SOC	:	System organ class
SS	:	Safety Set
TK	:	Thymidine kinase
TOI	:	Taiho Oncology Inc.
TPase	:	Thymidine phosphorylase
TUDD	:	Time until definitive deterioration
ULN	:	Upper limit of normal
USA	:	United States of America
VEGF	:	Vascular endothelial growth factor
vs	:	*Versus*
µmol	:	micromole

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Les Laboratoires Servier submitted to the European Medicines Agency on 1 February 2023 an application for a variation.

The following variation was requested:

Variation requested	Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	I and IIIB

Extension of indication to include treatment of patients with refractory metastatic colorectal cancer, for LONSURF in combination with bevacizumab based on results from study SUNLIGHT (CL3-95005-007); This is an open-label, randomised, phase III study comparing trifluridine/tipiracil in combination with bevacizumab to trifluridine/tipiracil monotherapy in patients with refractory metastatic colorectal cancer. As a consequence, sections 4.1, 4.2, 4.4, 4.8, and 5.1 of the SmPC. The package leaflet is updated in accordance. The updated RMP version 9.1 has also been submitted. In addition, the MAH took the opportunity to update section 4.6 of the SmPC and the Package leaflet accordingly.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) CW/0001/2015 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	1 February 2023
Start of procedure:	25 February 2023
CHMP Rapporteur Assessment Report	21 April 2023
PRAC Rapporteur Assessment Report	26 April 2023
PRAC Outcome	3 May 2023
CHMP members comments	15 May 2023
Updated CHMP Rapporteur(s) (Joint) Assessment Report	19 May 2023
Request for supplementary information	25 May 2023
MAH's responses submitted to the CHMP on:	30 May 2023
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	6 June 2023
Comments	12 June 2023
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	15 June 2023
CHMP opinion:	22 June 2023

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

The marketing authorisation holder (MAH) proposes to add the following new indication for Lonsurf in combination with bevacizumab:

"*Lonsurf is indicated in combination with bevacizumab for the treatment of adult patients with metastatic colorectal cancer (CRC) who have received two prior anticancer treatment regimens (see section 5.1).*"

Epidemiology and risk factors

Colorectal cancer (CRC) is the third most common cancer in terms of incidence and second in terms of mortality in the world. Globally more than 1.85 million new CRC cases and 916 000 deaths were estimated to occur in 2020. There is an approximately 9-fold variation in colon cancer incidence rates by world regions, with the highest rates in European regions, Australia/ New Zealand, and Northern America. Rectal cancer incidence rates have a similar regional distribution, although rates in Eastern Asia rank among the highest (Sung, 2021).

Clinical presentation, and prognosis

Approximately 25% of patients present with metastases at initial CRC diagnosis and almost 50% of patients with CRC will develop metastases, contributing to the high mortality rates reported for CRC (Ayez, 2011; Cervantes, 2022).

The overall prognosis of patients with mCRC has improved significantly in the past decades, and the average survival is 30 months (Formica, 2015). Although some patients with mCRC can be cured through surgical and ablative techniques, the disease remains incurable in most cases, and there is clearly a need for new therapeutic approaches.

Management

In patients with unresectable disease, chemotherapy is the mainstay of treatment. Various combinations of drugs may be used for the treatment of these patients at some point during the duration of their disease based on European Society for Medical Oncology (ESMO) guidelines (Cervantes, 2022) and National Comprehensive Cancer Network (NCCN) guidelines (NCCN, 2019; NCCN, 2021) for the United States of America (USA). The choice of chemotherapy is based upon the consideration of the goals of therapy, the type and timing of prior therapies, and the differing toxicity profiles of the constituent drugs. Historically, a combined regimen containing a fluoropyrimidine formed the backbone of chemotherapy for decades. However, the introduction of monoclonal antibodies targeting VEGF receptor and the use of epidermal growth factor receptor (EGFR) inhibitors for a subset of mCRC patients with RAS wild-type tumours, have shown to improve clinical outcomes when combined with chemotherapy (Baldus, 2010).

Following progression after treatment with standard chemotherapies (i.e. a fluoropyrimidine, oxaliplatin, irinotecan, and as applicable, anti-VEGF and/or anti-EGFR antibodies), the estimated OS with best supportive care treatment alone is around 5 months (RECOURSE trial). However, an increasing number of patients with mCRC can receive 3 or more lines of therapy (Bekaii-Saab, 2018). Treatments in this setting include regorafenib (a multitargeted tyrosine kinase inhibitor), FTD/TPI (trifluridine/tipiracil) monotherapy, and for specific subgroups of patients, antibodies that target EGFR for patients with RAS wild-type tumours (if no prior exposure), and anti-programmed cell death protein 1 inhibitors for patients with microsatellite instability-high mCRC (Cervantes, 2022; NCCN, 2019; NCCN, 2021). Clinical trials of emerging agents, new treatment combinations, and novel therapies are still needed to continue the efforts to improve outcomes for patients with mCRC (Cervantes, 2022).

In the USA, the most recently updated NCCN guidelines include the possibility of using FTD/TPI with the addition of bevacizumab (NCCN, 2021) based on the results of the Danish trial, a randomised Phase 2 trial conducted in Denmark (Pfeiffer, 2020). The combination is not approved for the treatment of refractory mCRC in any region.

2.1.1. About the product

FTD/TPI

Trifluridine/tipiracil (FTD/TPI) is a combination of FTD and TPI at a molar ratio 1:0.5. Results of in vivo studies show FTD incorporation into deoxyribonucleic acid (DNA) to be the primary mechanism of anti-tumour activity with oral administration. FTD is incorporated into DNA in tumour cells following three phosphorylation steps. The first phosphorylation is mediated by thymidine kinase (TK). TPI inhibits degradation of FTD by inhibiting TPase, thus increasing systemic exposure to FTD.

FTD/TPI monotherapy is currently approved for the treatment of adult patients with metastatic colorectal cancer (CRC) who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and anti EGFR agents in the European Union ([EU], 2016).The recommended starting dose of FTD/TPI is 35 mg/m2/dose administered orally twice daily (BID) on days 1 to 5 and days 8 to 12 of each 28-day cycle until disease progression or unacceptable toxicity occurs (Lonsurf EU PI).

Rationale for the combination of trifluridine/tipiracil with bevacizumab in mCRC

Bevacizumab is approved for treatment of mCRC in combination with fluoropyrimidine-based chemotherapy. Continuation of bevacizumab beyond first progression has an, albeit modest, OS benefit and administration of bevacizumab in addition to chemotherapy in both first- and second-line settings is mentioned in the recent ESMO guideline (Cervantes et al. Ann Oncol. 2023). See also the results of Study ML18147 in which the addition of bevacizumab to fluoropyrimidine-based chemotherapy resulted in a prolongation of survival in patients with mCRC who have progressed on a first-line bevacizumab-containing regimen (Avastin SmPC).

The combination of FTD/TPI and bevacizumab has shown activity against CRC xenografts in mice and in two preliminary investigator-initiated clinical trials conducted in refractory mCRC patients.

The approved indication:

Lonsurf is indicated in combination with bevacizumab for the treatment of adult patients with metastatic colorectal cancer (CRC) who have received two prior anticancer treatment regimens including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and/or anti-EGFR agents.

The recommended starting dose of Lonsurf in adults, as monotherapy or in combination with bevacizumab, is 35 mg/m2/dose administered orally twice daily on Days 1 to 5 and Days 8 to 12 of each 28-day cycle as long as benefit is observed or until unacceptable toxicity occurs.

When Lonsurf is used in combination with bevacizumab for the treatment of metastatic CRC, the dose of bevacizumab is 5 mg/kg of body weight given once every 2 weeks. Please refer to the full product information for bevacizumab.

2.1.2. The development programme/compliance with CHMP guidance/scientific advice

There was no scientific advice for this product in the current indication.

2.1.3. General comments on compliance with GCP

The Applicant stated that the pivotal trial for the current application, the SUNLIGHT study, was conducted in accordance with the ethical principles stated in the Declaration of Helsinki, 1964, as revised in 2013, as revised in Fortaleza, 2013 with the GCP and with the applicable regulatory requirements.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

The MAH presented an ERA for a new therapeutic indication of Lonsurf in combination with bevacizumab for the treatment of adult patients with metastatic colorectal cancer (CRC) who have received two prior anticancer treatment regimens.

Lonsurf is a drug containing two active pharmaceutical ingredients (API), trifluridine and tipiracil hydrochloride. It is currently indicated as monotherapy for the treatment of metastatic CRC and metastatic gastric cancer (GC).

The assessment was based upon the recommendations in Article 8(3) of Directive 2001/83/EC, as amended, and in the principles laid out in the European Medicines Agency (EMA) guideline on the environmental risk assessment of medicinal products for human use (EMA, 2006) abbreviated "the guideline" in the following. Moreover, the recommendations as published in EMA Questions and answers on Guideline on the environmental risk assessment of medicinal products for human use (EMA, 2016) use abbreviated "the Q&A document", as well as the draft for the revised EMA guideline (EMA, 2018), abbreviated "the draft guideline".

A Phase I evaluation of the two APIs of Lonsurf was performed, including screening for Persistence, Bioaccumulation and Toxicity (PBT) by experimentally determining the octanol water coefficient (log Kow) and calculation of the predicted environmental concentration (PEC) in surface water.

The log Kow value fell below the Action Limit of 4.5 specified in the guideline for both APIs over a wide range of pH values, indicating no relevant risk of PBT.

$PEC_{SURFACE\ WATER\ TOTAL} = PEC_{SURFACE\ WATER\ CRC} + PEC_{SURFACE\ WATER\ GC}$

$PEC_{SURFACE\ WATER\ TOTAL\ trifluridine} = 0.00333\ \mu g/L + 0.0016\ \mu g/L = 0.0049\ \mu g/L$

$PEC_{SURFACE\ WATER\ TOTAL\ tipiracil\ hydrochloride} = 0.00157\ \mu g/L + 0.00075\ \mu g/L = 0.00232\ \mu g/L$

For each API, the $PEC_{SURFACE\ WATER}$ fell below the Action Limit of 0.01 µg/L, as defined in the guideline. Therefore, a Phase II assessment is regarded as not necessary. The assessment can stop after Phase I.

Table 1: Log K_{ow} values for trifluridine and tipiracil hydrochloride in dependence of pH pH	**Log K_{ow} trifluridine**	**Log K_{ow} tipiracil (as hydrochloride)**
2	-0.434	-4.25
4	-0.430	-3.16
6	-0.425	-2.30
7	-0.453	-2.03
8	-0.543	-1.97
10	-1.030	-1.95
12	-2.340	-2.01

2.2.2. Discussion on non-clinical aspects

An updated ERA was submitted to support this application for an extension of indication. The Fpen refinement has taken the existing and new indications into account. The resulting total PECSURFACE WATER does not exceed the action limit and therefore a phase II assessment is not needed.

2.2.3. Conclusion on the non-clinical aspects

The updated ERA submitted in this application does not indicate a significant increase in environmental exposure further to the use of trifluridine and tipiracil hydrochloride.

- Considering the above data, trifluridine and tipiracil hydrochloride are not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH. The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies, see *Table 2*.

2.3.2. Pharmacokinetics

The combination regimen of FTD/TPI with bevacizumab was initially studied in the C-TASK FORCE Phase 1/2 study conducted in Japanese patients with mCRC refractory to standard chemotherapies. Using a dose de-escalation design in Phase 1, the recommended dose for Phase 2 was determined for FTD/TPI as 35 mg/m²/dose BID on Days 1-5 and Days 8-12 in a 4-week cycle plus bevacizumab (5 mg/kg, IV) on Days 1 and 15 in a 4-week cycle (Kuboki, 2017), which is the same as the FTD/TPI monotherapy dose per product information (PI). Pharmacokinetic analyses were performed for FTD during cycle 1 of the Phase 1 part of the *C-TASK FORCE* study. The combination of FTD/TPI with bevacizumab (*C-TASK FORCE* trial) did not increase the FTD and TPI exposure in plasma as compared to that of previously reported FTD/TPI monotherapy (*TAS102-J001* trial), as shown in Table 1. The differences in C_{max}, AUC_{0-t} and AUC_{inf} were statistically insignificant (p=0.98, p=0.92, and p=0.92, respectively). The geometric mean ratios (i.e., *C-TASK FORCE* trial/*TAS102-J001* trial) of TPI C_{max} and AUC_{inf} were 1.1 and 0.96, respectively.

Table 1 - Comparison of the pharmacokinetic parameters between C-TASK-FORCE and TAS102-J001.

Compound	PK Parameters	C-TASK FORCE Geometric Mean	TAS102-J001 Geometric Mean	Geometric Mean Ratio (C-TASK/TAS102-J001)	90% 2-sided Confidence Interval Lower	Upper
FTD	C_{max} (ng/mL)	3286	3273	0·996	0·752	1·319
	AUC_{0-t} (ng·h/mL)	8350	8446	1·012	0·83	1·234
	AUC_{inf} (ng·h/mL)	8446	8544	1·012	0·821	1·246
TPI	C_{max} (ng/mL)	63·1	69·7	1·105	0·729	1·675
	AUC_{0-t} (ng·h/mL)	279	270	0·970	0·66	1·425
	AUC_{inf} (ng·h/mL)	295	282	0·955	0·645	1·415

2.3.3. Discussion on clinical pharmacology

No new PK data for FTD/TPI in combination with bevacizumab was included in the dossier to support this Type II variation. This is considered acceptable as 1) no interaction between FTD/TPI and bevacizumab is expected based on the mechanisms of action and pharmacokinetic characteristics described in the SmPCs of FTD/TPI (LONSURF) and bevacizumab; and 2) earlier research (Kuboki, 2017) reported comparable FTD and TPI exposure between combined FTD/TPI with bevacizumab and FTD/TPI monotherapy, which indicates no drug interaction between FTD/TPI and bevacizumab.

In regard to this type II variation, no pharmacokinetic adjustments are proposed for the Lonsurf SmPC, is acceptable.

2.4. Clinical efficacy

2.4.1. Dose response study

No dose response study was performed with the proposed combination therapy in the proposed indication. The proposed doses of FTD/TPI and bevacizumab are the same as in the already approved indications.

2.4.2. Main study – SUNLIGHT

The efficacy data for the current application come from a single pivotal trial, CL3-95005-007, abbreviated as SUNLIGHT (NCT04737187). This was a multinational, open-label, two-arm, randomised phase 3 study comparing treatment with FTD/TPI in combination with bevacizumab to FTD/TPI monotherapy in patients with refractory mCRC. The study design is summarized in *Table 2*.

The data cut-off dates were 05 July 2022 for clinical data (i.e. non-survival) and 19 July 2022 (occurrence of 331st death) for survival data. The median follow-up duration was 14.1 months.

Table 2: Efficacy study of FTD/TPI in combination with bevacizumab in patients with refractory mCRC (SUNLIGHT study)

Study design	**Study drugs** Dose, route, regimen	**Primary study objective**	**Number of patients** Randomised / off treatment	**Duration of treatment and follow-up**	**Diagnosis** Main inclusion criteria	**Main efficacy endpoint(s)**
Phase 3, Multinational, open-label, controlled two-arm, randomised (1:1) with stratification factors[1] study 13 countries, 492 patients On-going study CSR NP42261	**Test Drug: FTD/TPI + Bev** FTD/TPI 35 mg/m²/dose orally BID (tablet) 5 days on 2 days off for 2 weeks, 14 days rest with Bev 5 mg/kg, IV at Day 1 and Day 15 of each cycle. Repeated every 4 weeks **Comparator: FTD/TPI** FTD/TPI 35 mg/m²/dose orally BID (tablet) 5 days on 2 days off for 2 weeks, 14 days rest. Repeated every 4 weeks	To demonstrate the superiority of the combination FTD/TPI + Bev over FTD/TPI monotherapy in terms of OS in patients with mCRC	**FTD/TPI + Bev** 246/214 patients **FTD/TPI** 246/242 patients	Treatment period: cycles of treatment until patients met discontinuation criteria[2] FU period until the end of study *i.e.* 19 months after the first study treatment intake of last randomised patient	M/F ≥ 18 years, with histologically confirmed unresectable metastatic adenocarcinoma of the colon or rectum, who have received a maximum of 2 prior chemotherapy regimens for advanced CRC (including a fluoropyrimidine, irinotecan, oxaliplatin, an anti-VEGF monoclonal antibody[3] and/or an anti-EGFR monoclonal antibody for RAS wild type patients), and had demonstrated progressive disease or intolerance to their last regimen Patients with ECOG PS ≤ 1.	**Primary endpoint**: **OS** defined as the time between the randomisation and death due to any cause **Key secondary endpoint**: **PFS**[4] based on investigator assessment, defined as the time between the randomisation and radiological tumour progression or death Other secondary endpoints: - ORR, DCR - Time to worsening of ECOG PS to ≥ 2 - Quality of Life Clinical data cut-off of 05 July 2022 and survival data cut-off of 19 July 2022 for primary OS analysis (occurrence of the 331st death).

Abbreviations: Bev: bevacizumab; BID: twice a day; CRC: colorectal cancer; CSR: Clinical Study Report; IV: intravenous; DCR, disease control rate; ECOG: eastern cooperative oncology group; EGFR: epidermal growth factor receptor; FU: follow-up; M/F: male/female; FTD: trifluridine; mCRC: metastatic CRC; ORR: overall response rate; OS: overall survival; PFS: progression free survival; PS: performance status; QoL: quality of life; RAS (i.e. gene RAS): rat sarcoma virus; RECIST: response evaluation criteria in solid tumours; TPI: tipiracil hydrochloride; VEGF: vascular endothelial growth factor
1. Geographic region (North America, European Union, Rest of the World), time since first metastasis diagnosis (< 18 months, ≥ 18 months), RAS status (wild type, mutant)
2. Patients were considered on treatment as long as the patient continued FTD/TPI. Bevacizumab monotherapy was not allowed
3. Prior anti-VEGF monoclonal antibody was optional except in France, where it was mandated
4. Tumour assessment according to RECIST version 1.1

Methods

Study participants

The key eligibility criteria for the study were as follows.

Inclusion criteria:

- Male or female participant aged ≥ 18 years old at the time of ICF signature
- Had histologically confirmed unresectable adenocarcinoma of the colon or rectum (all other histological types were excluded).
- RAS status had been previously determined (mutant or wild type) based on local assessment of tumour biopsy. Wild type was defined as KRAS (exon 2, 3 and 4) and NRAS (exon 2, 3 and 4) wild type. Mutant was defined as at least KRAS or NRAS mutant (any exon, any mutation).
- Had received a maximum of 2 prior chemotherapy regimens for the treatment of advanced colorectal cancer and had demonstrated progressive disease or intolerance to their last regimen:

- Prior treatment regimens for the treatment of advanced colorectal cancer had included a fluoropyrimidine, irinotecan, oxaliplatin, an anti-VEGF monoclonal antibody and/or an anti-EGFR monoclonal antibody for RAS wild type patients.
- Patients who had received adjuvant/neoadjuvant chemotherapy and had recurrence during or within 6 months of completion of the adjuvant/neoadjuvant chemotherapy could count the adjuvant/neoadjuvant therapy as one regimen of chemotherapy for advanced disease.

- Had measurable or non-measurable disease as defined by RECIST version 1.1.
- Estimated life expectancy ≥ 12 weeks.
- Had an ECOG PS ≤ 1. ECOG had to remain ≤ 1 during all the screening period (from screening visit to randomisation).
- Had an adequate organ function as defined by the following laboratory values obtained within 7 days prior to the randomisation:
  - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L.
  - Haemoglobin ≥ 9 g/dL. In case of blood transfusion, the haemoglobin assessment had to be performed 2 weeks or more after the transfusion.
  - Platelet count ≥ 100 x 109/L.
  - Creatinine clearance ≥ 50 mL/min assessed using the Cockcroft & Gault formula.
  - Total serum bilirubin < 1.5 x upper limit of normal (ULN) (unless Gilbert disease confirmed).
  - Aspartate aminotransferase (AST; SGOT) and alanine aminotransferase (ALT; SGPT) ≤ 2.5 x ULN (unless if liver function abnormalities were due to underlying liver metastasis, AST and ALT ≤ 5 x ULN).
  - Adequate coagulation function for all patients. For patients receiving anti-coagulant therapy (except platelet anti-aggregates) the adequate therapeutic levels of INR had to be confirmed.
- Female of childbearing potential (as defined in Section 5.3 of study protocol) had to be tested negative in a serum pregnancy test within 7 days prior to the randomisation and all participants had to use a highly effective method of birth control as well as their partners lasting at least 6 months after the last dose of IMP.
- Had provided a written informed consent prior any study-specific procedure.

  Of note: prior anti-VEGF monoclonal antibody was optional except in France, where it was mandated.

<u>Exclusion criteria</u>

General criteria

- More than 2 prior chemotherapy regimens for the treatment of advanced colorectal cancer.
- Patients receiving or having received anticancer therapies within 4 weeks prior to randomisation.

Medical and therapeutic criteria

- Had not recovered from clinically relevant non-hematologic CTCAE grade ≥ 3 toxicity of previous anticancer therapy prior to the randomisation (excluding alopecia and skin pigmentation).
- Had symptomatic central nervous system metastases that were neurologically unstable or requiring increasing doses of steroids to control CNS disease.
- Had major surgery within 4 weeks prior to the randomisation (the surgical incision should be fully healed prior to study drug administration), or had not recovered from side effects of previous surgery, or patient that may require major surgery during the study.
- Had severe or uncontrolled active acute or chronic infection.
- Had active or history of interstitial lung disease.
- In the investigator's opinion, uncontrolled diabetes mellitus even under treatment.
- Confirmed uncontrolled arterial hypertension (defined as systolic blood pressure ≥ 150 mmHg and/or diastolic blood pressure ≥ 100 mmHg) or uncontrolled or symptomatic arrhythmia.
- Deep arterial thromboembolic event including cerebrovascular accident or myocardial infarction within the last 6 months prior to randomisation.
- Severe/unstable angina, symptomatic congestive heart failure New York Heart Association (NYHA) class III or IV.
- Drainage for ascites, pleural effusion or pericardial fluid within 4 weeks prior to randomisation.
- Treatment with systemic immunosuppressive therapy (except steroids given in prophylactic setting or at a chronic low dose (≤ 20 mg/day prednisone equivalent)).
- Prior radiotherapy if completed less than 4 weeks before randomisation, except if provided as a short course for symptoms palliation only. Tumour lesions if previously irradiated should not have been chosen as target lesions for response evaluation.

Criteria related to bevacizumab administration

- History of allergic reactions or hypersensitivity to bevacizumab or any of its excipients.
- Serious non-healing wound, non-healing ulcer or non-healing bone fracture.
- Known coagulopathy that increases risk of bleeding, bleeding diatheses. Any other haemorrhage/bleeding event CTCAE grade ≥ 3 within 4 weeks prior to randomisation.
- History of any life-threatening VEGF-related adverse event.
- Proteinuria ≥ 1 g/24 hours or 2+ by dipstick.

Treatments

FTD/TPI was administered at the starting dose and schedule recommended in the treatment of patients with mCRC, 35 mg/m^2 BID on days 1 to 5 and days 8 to 12 of each 28-day cycle. Bevacizumab in combination with FTD/TPI was administered intravenously (IV) at 5 mg/kg of body weight given once every 2 weeks of a 4-week cycle, which is one approved posology of bevacizumab in the treatment of

mCRC. The study was open-label and no placebo for the intravenous bevacizumab injection was given to patients in the comparator arm.

Patients were treated until disease progression or unacceptable toxicity.

If a medical condition developed that required bevacizumab to be permanently withdrawn the patient could continue with FTD/TPI alone. Bevacizumab was not to be administered alone in case of dose delay due to FTD/TPI toxicities. The cycle was to be delayed, and bevacizumab was to be restarted at the same time of FTD/TPI. IF FTD/TPI treatment was permanently discontinued, bevacizumab monotherapy was not allowed. FTD/TPI missed doses were not to be replaced.

All toxicities related to FTD/TPI had to be resolved to Grade 1 or baseline before the start of a new treatment cycle. In the event of haematological and/or non-haematological toxicities, rules for FTD/TPI dose interruption and resumption were provided as in *Table 3*; rules for dose modifications were provided as in *Table 4*. No dose reductions for bevacizumab were recommended. Bevacizumab therapy should either be permanently discontinued or temporarily suspended in case of toxicity.

Table 3: Dose interruption and resumption criteria for haematological toxicities related to myelosuppression

Parameter	Interruption criteria*	Resumption criteria**
Neutrophils	$< 0.5 \times 10^9$/L	$\geq 1.5 \times 10^9$/L
Platelets	$< 50 \times 10^9$/L	$\geq 75 \times 10^9$/L

** Interruption criteria applied only during active treatment intake period (i.e. D1-5 and D8-12) based on an unscheduled laboratory assessment*

*** Resumption criteria applied to the start of the next cycle for all patients regardless of whether or not the interruption criteria were met.*

Table 4: Recommended dose modifications for Lonsurf in case of haematological and non-haematological adverse reactions

Adverse reaction	Recommended dose modifications
• Febrile neutropenia • CTCAE* Grade 4 neutropenia (< 0.5 x 10^9/L) or thrombocytopenia (< 25 × 10^9/L) that results in more than 1 week's delay in start of next cycle • CTCAE* non-haematologic Grade 3 or Grade 4 adverse reaction; except for Grade 3 nausea and/or vomiting controlled by antiemetic therapy or diarrhoea responsive to antidiarrhoeal medicinal products	• Interrupt dosing until toxicity resolves to Grade 1 or baseline. • When resuming dosing, decrease the dose level by 5 mg/m^2/dose from the previous dose level (Table 4). • Dose reductions are permitted to a minimum dose of 20 mg/m^2/dose twice daily (or 15 mg/m^2/dose twice daily in severe renal impairment). • Do not increase dose after it has been reduced.

* Common terminology criteria for adverse events

If the patient recovered from toxicities requiring treatment interruption:

During the 2-week active treatment intake period of a cycle (treatment D1-D12):

- If no dose reduction was required, FTD/TPI could be resumed during that cycle.
- If a dose reduction was required, FTD/TPI had to be resumed at the start of the next cycle at the appropriate dose level.

During the rest period (D13-D28):

- The next cycle was to be started on schedule at the appropriate FTD/TPI dose level.

If the toxicities did not resolve during the given cycle to Grade 1 or baseline, the start of the next cycle had to be delayed for a maximum of 28 days from the scheduled start date of next cycle. If more than 28 days were needed to recover, the patient had to be withdrawn from treatment.

The criteria for discontinuation from treatment were:

- Adverse events incompatible with continuation of the study treatments according to the judgment of the investigator, including no recovery in safety parameters or according to the following predefined criteria:
    - A maximum dose delay of more than 28 days from the scheduled start date of the next cycle.
    - Need for more than 3 dose reductions of FTD/TPI (maximum of 3 dose reductions allowed).
- Protocol deviation if it interfered with the study evaluations and/or if it jeopardised participant's safety, e.g. any medical event requiring administration of an unauthorised concomitant treatment.
- Radiologic progressive disease documented by CT-scan or Magnetic Resonance Imaging (MRI).
- Clinical progressive disease manifested by symptomatic deterioration.
- Non-medical reason (to be carefully described) e.g. consent withdrawal, patient's removal.
- Other, physician decision (for medical reasons that could not be included in any of the criteria listed above).

Objectives

The primary objective was to demonstrate the superiority of FTD/TPI in combination with bevacizumab over FTD/TPI monotherapy in terms of OS in patients with refractory mCRC.

The secondary objectives were to estimate the effect of FTD/TPI in combination with bevacizumab versus FTD/TPI monotherapy in terms of PFS, ORR, and DCR in patients with refractory mCRC. Other secondary objectives were to compare the safety and tolerance, and the impact on QoL of FTD/TPI in combination with bevacizumab to FTD/TPI monotherapy in patients with refractory mCRC.

Outcomes/endpoints

The primary endpoint was overall survival (OS), defined as the observed time between the date of randomisation and the date of death due to any cause.

The most important secondary endpoint was progression-free survival (PFS). PFS was based on investigator judgment and was defined as the time between the randomisation and the date of radiologic tumour progression according to RECIST version 1.1 or death from any cause.

Overall response rate (ORR) was defined as the proportion of patients who achieved a complete response (CR) or partial response (PR) based investigator's assessment of tumour response. Disease control rate (DCR) was defined as the proportion of patients who achieved a CR or PR or stable disease based on the investigator's assessment of tumour response.

The Best Overall Response (BOR) as per RECIST 1.1 was defined as the best response recorded from the start of the study treatment until the end of treatment. In this study, the minimum time from baseline to assess a response of "stable disease" was 6 weeks.

Safety assessments included recording of adverse events (AEs) including serious AEs (graded by NCI-CTCAE, version 5.0), and concomitant treatments. Other safety assessments were evaluation of clinical laboratory tests, 12-lead ECG, ECOG PS, vital signs, weight, height, physical examination findings, and, if the patient was female of childbearing potential, pregnancy testing.

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core Questionnaire (EORTC QLQ-C30) and the EQ-5D-5L tools were used to assess quality of life.

Sample size

A maximum of 331 events (deaths for any cause) were required for the primary analysis to detect a HR of 0.70 with 90% power using a log-rank test at one-sided cumulative 2.5% level of significance. Based on the data from the RECOURSE study (Mayer, 2015), the median OS (mOS) in the control group was expected to be around 7.1 months.

A hazard ratio (HR) of 0.70 translates into a 3-month increase of the mOS in the experimental arm (10.1 months) compared to the control arm. Based on the assumption that enrolment would have continued for approximately 12 months, and that about 5% per year of the patients would drop out, a total of 490 patients randomized in a 1:1 ratio were needed to observe the 331st OS event approximately 9 months after the last patient randomisation.

Randomisation

The treatment group was allocated via IWRS using a central randomisation (1:1) to FTD/TPI in combination with bevacizumab or FTD/TPI monotherapy with stratification factors being the geographic region (North America, European Union, Rest of the World), the time since first metastasis diagnosis (< 18 months, ≥ 18 months) and the RAS status (wild type, mutant).

Blinding (masking)

This was an open-label study; the investigators and patients were not blinded to study treatment.

Statistical methods

Study periods

The study was divided into the following periods for each patient (*Figure 1*):

- Screening visit (up to 28 days prior to randomisation) was to obtain informed consent.
- Screening period and inclusion: the eligibility of the patient to be included and randomised in the study was checked.
- Randomisation: included patients were randomly assigned to one of the two treatment groups: FTD/TPI + Bev or FTD/TPI.

- Treatment period: randomised patients received the first dose of study treatments (C1D1) within 3 days after randomisation and continued until they met a discontinuation criterion as described above.
- Withdrawal visit occurred within 4 weeks following the date of IMPs withdrawal and before the start of a new anticancer therapy.
- Post-withdrawal follow-up period: after the withdrawal visit, the patient was followed:
    - For tumour assessment (unless patient had discontinued study treatments for radiologic disease progression or withdrawal of consent) every 8 weeks until radiologic progression regardless of initiation of a new anticancer therapy.
    - For survival status every 8 weeks until death or the end of the study (whichever first occurred).

The end of study was planned 19 months after the first investigational medical product (IMP) intake of the last patient randomised and defined as the date of the last follow-up of the last patient (including a phone contact) or the date of the last contact attempt if the last patient was declared lost to follow-up.

Once the study is completed, patients still being treated will be offered the option to continue the treatments outside the study.

Measurements

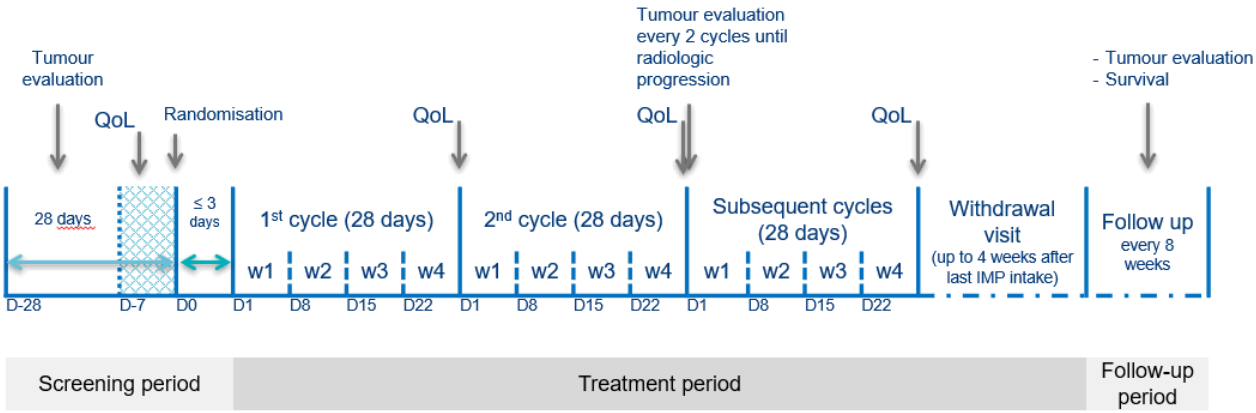
Tumour assessments were performed by the investigator according to the revised RECIST 1.1 criteria (Eisenhauer 2009; RECIST 1.1 update and clarification Schwartz 2016).

Tumour assessments/imaging studies of the chest, abdomen, and pelvis at a minimum (other localisations if clinically indicated) were obtained at each time point listed below for all patients:

- Baseline: within 28 days prior to randomisation. Images obtained prior to the patient signing the ICF could be used if the date of the images was within 28 days of randomisation and if in line with methods and techniques that were used during study.
- Every 2 cycles from Day 1 Cycle 1 until radiologic progression was documented (including at the withdrawal visit if not done in the previous 8 weeks).
- For patients who discontinued treatment for reasons other than radiologic disease progression or consent withdrawal, every 8 weeks during the follow up period until the patient experienced radiologic progression, regardless of the initiation of new anticancer therapy.

If the investigator determined that a patient developed clinical progression manifested by symptomatic deterioration but not supported by radiologic evidence of progression, the patient had to stop treatment. Symptoms of clinical progression were documented in the patient's source documents and in AE form. Tumour assessments continued every 8 weeks until radiologic progression was documented.

Figure 1: Study periods and measurements



Analysis sets

- Screened set: All patients screened.
- Included set (IS): All included patients.
- Full analysis set (FAS): In accordance with the intention-to-treat principle and Section 5.2.1 of the ICH E9 guideline, all patients to whom a therapeutic unit was randomly assigned using IWRS. Patients in the FAS were analysed in the arm they were assigned by randomisation.
- Safety set (SS): All patients having taken at least one dose of FTD/TPI. Patients were analysed according to the treatment actually received.

Primary endpoint OS analysis (FAS population)

OS in the FAS population was compared between the 2 treatment groups using the stratified log-rank test one-sided 2.5% level of significance (stratification factors based on IWRS data). The hazard ratio of OS with its 95% confidence interval was estimated with a stratified Cox proportional hazard model (stratification factors based on IWRS data).

During the study the following intercurrent events (IE) could have occurred:

- Administration of further anti-cancer therapy.
- Treatment discontinuation.
- Treatment switch (from FTD/TPI in combination with bevacizumab to FTD/TPI monotherapy and from FTD/TPI monotherapy to FTD/TPI in combination with bevacizumab (i.e. planned arm different from actual arm).

The primary estimand of interest for OS was the effect of the randomised treatments on the survival duration in all patients regardless of whether or not intercurrent events occur (treatment policy strategy). All data collected during the trial regardless of any intercurrent event were used.

Supportive analyses for OS, conducted in the FAS population (unless otherwise noted), included:

- an unstratified log-rank test and an unstratified Cox proportional hazards model.
- An OS analysis which excluded patients who had not fulfilled at least one of the following criteria:
    - Has histologically confirmed unresectable adenocarcinoma of the colon or rectum.

- Has received a maximum of 2 prior chemotherapy regimens for the treatment of advanced colorectal cancer and had demonstrated progressive disease or intolerance to their last regimen.
- Has measurable or non-measurable metastatic lesion(s) as defined by Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1.
- Has an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1.
- More than 2 prior chemotherapy regimens for the treatment of advanced colorectal cancer.
- Has previously received trifluridine/tipiracil.
- Did not currently receive or has not received anticancer therapies within 4 weeks prior to randomisation.

- Restricted Mean Survival Time (RMST) for OS was to be estimated with its 95% confidence interval in each treatment group and the difference in RMST between treatment groups tested.

A secondary estimand strategy based on OS was defined in order to assess the effect of the randomised treatments on the survival time in all subjects before patients received further anti-cancer therapy. The aim of this estimand was to evaluate the effect of the study treatment without taking into account any potential effects of another anti-cancer therapy. For the intercurrent event (IE) "administration of further anti-cancer therapy" and "treatment switch", data obtained post-IE was not to be used for the analysis and OS times were to be censored at the time of administration of further anti-cancer therapy. For the intercurrent event of "treatment discontinuation", patients were followed up under a treatment policy strategy approach unless they received further anti-cancer therapy.

Secondary endpoint analysis

The analysis approach for **PFS** was the same as the approach specified for the primary endpoint, OS. A treatment policy estimand approach was also specified for PFS: patients were censored if they were alive without documented radiological progression, lost to follow-up without documented radiological progression; or had no baseline or post-baseline tumour assessment.

The following additional analyses were pre-specified for PFS:

- an unstratified log-rank test and an unstratified Cox proportional hazards model.
- A secondary estimand strategy, for which clinical progression and administration of further anti-cancer therapy were defined as PFS events in addition to the radiological progression or death.
- In line with FDA guidance, an analysis in which it was planned to censor PFS at the time of administration of further anti-cancer therapy, and in cases where patients had radiological progression or died after ≥ 2 consecutive missed radiological assessments.

Other secondary endpoint analyses

ORR and **DCR** were to be described using 2-sided 95% Clopper-Pearson CIs in each treatment arm. A Fisher's exact test and a 2-sided 95% CI for the difference in ORR between the two treatment arms was also to be provided based on the normal approximation. If a stratified analysis is required a Cochran-Mantel-Haenszel test will be used.

Multiplicity adjustments

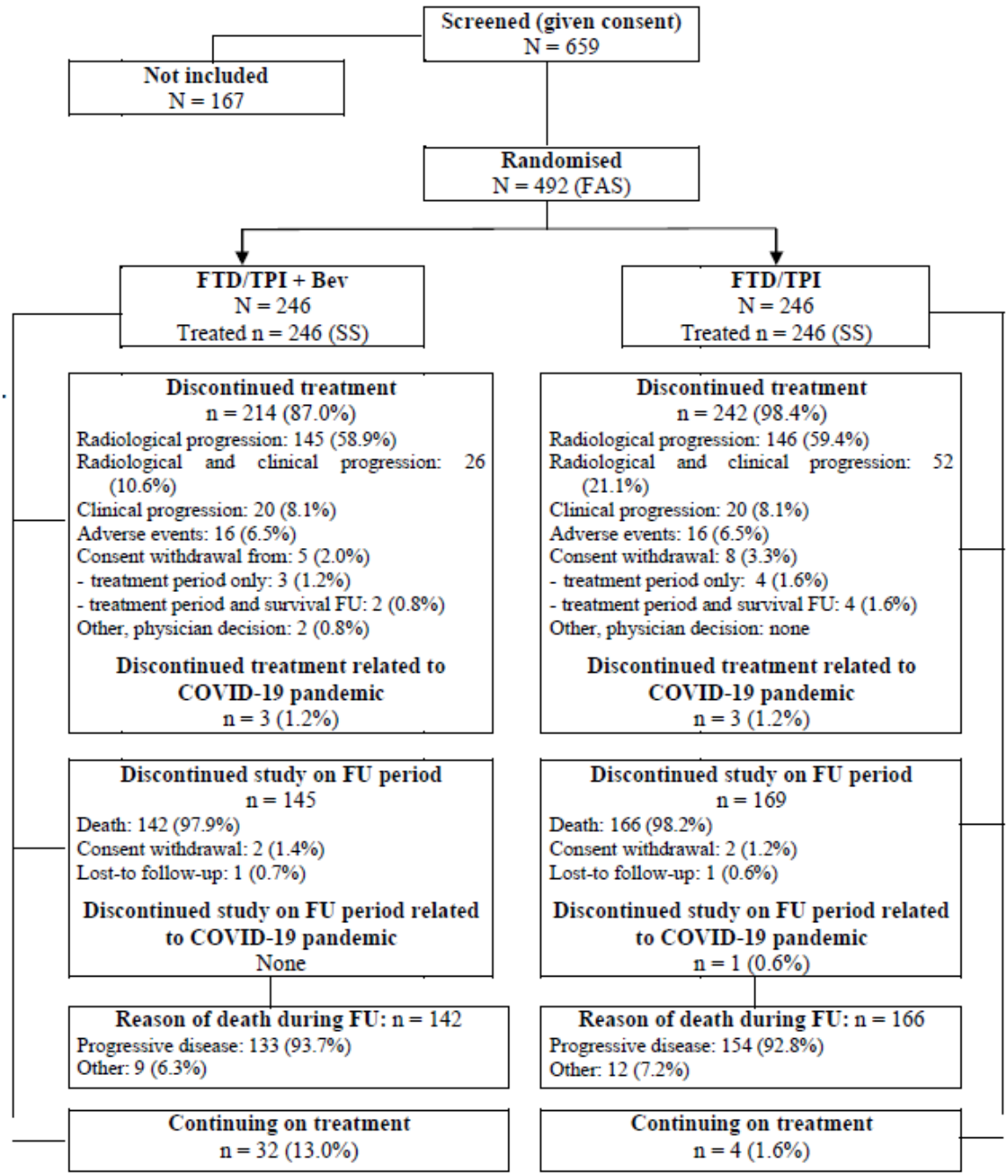
A hierarchical testing strategy, where PFS was to be statistically evaluated and interpreted only if the primary efficacy estimand OS is significantly different between the 2 treatment groups, was specified to control the overall type-I error rate. The other secondary endpoints were not included in the testing hierarchy. No interim analysis for efficacy was planned.

Results

Participant flow

The overall disposition of randomised patients by group in the FAS is presented in *Figure 2*.

Figure 2: Disposition of patients



Percentages are based on n
FAS: Full Analysis Set; SS: Safety Set; FU: follow-up

A total of 659 patients provided consent and were screened. Among them, 167 (25.3%) were not included due to not meeting the eligibility criteria (24.3%) or withdrawal of consent (1.1%).

Of the 160 patients that entered screening but were not randomized because of not meeting the eligibility criteria, most screen failures were because of not having received a maximum of 2 prior chemotherapy treatments, including all standard treatment lines, and showing PD or intolerance to the last regimen (40%). Also, many patients did not have adequate organ function as defined in the protocol (24.4%), and some did not have an adequate performance status during the entire screening period (6.9%).

All included patients were randomised. Of the total of 492 randomised patients (i.e. the FAS), 246 were assigned to FTD/TPI + bevacizumab and 246 were assigned to FTD/TPI. All randomised patients received study treatment as assigned at randomisation. As of clinical data cut-off, 36 (7.3%) patients were still on treatment (13.0% in the FTD/TPI + bevacizumab group, 1.6% in the FTD/TPI group). The main reason for study treatment discontinuation was clinical and/or radiological disease progression (77.6% vs 88.6%). For patients having both radiological and clinical progressive disease, the rate of withdrawal for this reason was higher in the FTD/TPI group than in the FTD/TPI + bevacizumab group (21.1% vs 10.6%). The other most frequent reason for treatment withdrawal was adverse events (6.5% in each group). The percentage of patients who withdrew consent was 2.0% in the FTD/TPI + bevacizumab group and 3.2% in the FTD/TPI group.

Recruitment

Patients were recruited at 102 sites in 13 countries. European patients were predominantly represented in the study with 315 (64.0%) patients from the EU (Austria, Belgium, Denmark, France, Germany, Hungary, Italy, Poland, Spain). Additionally, 161 (32.7%) patients were from Brazil, Russian Federation and Ukraine, and 16 (3.3%) patients were from North America (USA).

The study started on 25 November 2020 (first visit of first patient) and the last patient was randomised on 18 February 2022.

Conduct of the study

One global protocol amendment including substantial changes was issued for this study: Amendment No. 1, dated 30 December 2020 was applicable in all countries. It mainly concerned:

- New exclusion criteria for patients with uncontrolled hypertension, patients with history of any life-threatening VEGF related adverse event and patients with proteinuria.
- Sponsorship of TOI for the investigational sites in USA.
- Change of the time window to perform the tumour assessment.
- Baseline ECG obtained prior to patient having signed the ICF could be used if the date of ECG was within 28 days of randomisation.
- Clarifications were made. They concerned mainly:
    - Inclusion criterion number 4: to clarify that the considered prior treatment regimens were those for advanced CRC setting.
    - Definition of the end of study.
    - Reasons for discontinuation and restart of treatment period, in case of COVID-19 infection.
    - Follow-up procedures in case of withdrawal of consent.
    - All fatal events occurring between ICF signature and IMP administration were to be reported on AE form.
    - Precisions in statistical and safety parts of the protocol.

- Inclusion of local amendment issued for France to specify that all patients in France should have received an anti-VEGF monoclonal antibody before entry in the study.

One global protocol amendment including non-substantial changes was issued on 08 June 2022 to update instructions for restarting treatment after COVID infection: restart could be done if patient was asymptomatic and a period of at least 7 days after the diagnosis has been respected, and with a negative test (if testing was required by the institutional site).

Changes in the statistical analyses

The original SAP version 1.0 was released on 06 November 2020. Prior to database lock, the SAP was amended once; version 2.0 was issued on 02 August 2022. The main changes to the SAP were the following:

- Update of subgroup categories (Section 2.3).
- Addition of methodology for data handling according to a survival cut-off date (Section 3.1).
- Addition of 'Time from first metastasis diagnosis to randomisation' definition and addition of precision on staging classifications (Sections 3.2.4.2 & 4.2.1.3.2).
- Updates of previous therapies descriptive analyses (Section 3.2.4.5).
- Update of covariate categories (Section 3.4.1.3.2).
- Addition of a sensitivity analysis (supportive 3) for secondary estimand based on PFS (FDA IND 57674) (Section 3.4.1.3.1).
- Addition of EAEs related to disease progression and leading to death analyses (Section 3.5.2).
- Addition of figures displaying mean changes in QoL from baseline by scheduled assessment timepoint (Section 3.6).
- Update of categories of changes from baseline (Section 3.6.1).
- Update of the treatment period and after treatment period definitions considering both IMPs and a time window of 30 days (Sections 6 & 6.1).
- Update of scheduled QoL assessment timepoint definitions to take into account information from ePRO and eCRF; addition of withdrawal questionnaire definition (Sections 7.1 & 7.2).

Changes or analyses decided after study database lock

In the multivariate OS analysis, two factors were identified with potential predictive value based on the interaction p-value: time since first metastasis diagnosis (< 18, ≥ 18 months) and prior bevacizumab use (yes, no). Unplanned analyses based on the final multivariate model for OS were performed to confirm that the benefit from the combination therapy remained significant in the corresponding subgroups for both factors.

Protocol deviations

Overall, 51 patients had 57 important protocol deviations (IPDs) before or at inclusion with similar frequency in the treatment groups (10.2% and 10.6%). The most frequent IPDs before or at inclusion were those belonging to a predefined subset of IPDs as follows:

- Patient who received anticancer therapies within 4 weeks prior to randomisation (13 patients, 2.6%).

- Patient who received more than 2 prior chemotherapy regimens for the treatment of advanced CRC (12 patients, 2.4%).

In addition, 3 patients (1.2%) in the FTD/TPI + bevacizumab group and 2 patients (0.8%) in the FTD/TPI group had 'Proteinuria ≥ 2+ by dipstick'. Other IPDs were reported in less than 1% of the patients globally. One patient in the FTD/TPI group signed consent after first investigation and 2 patients in the FTD/TPI + bevacizumab group had total serum bilirubin ≥ 1.5 ULN (i.e. not fulfilling eligibility criteria for inclusion).

Overall, 49 patients had 87 IPDs after inclusion with higher frequency in the FTD/TPI + bevacizumab group than in the FTD/TPI group: 14.2% vs 5.7%. The most frequent deviations concerned the deviation class 'Safety Possibly Affected' with higher frequency in the FTD/TPI + bevacizumab group (11.4%) than in the FTD/TPI group (5.3%). This difference was mainly related to the occurrence of two deviations: blood sample for laboratory safety measurements not taken within 2 days prior to FTD/TPI intake (7.7% vs 4.5%) and not taken within 2 days prior to bevacizumab administration at Day 15 (4.9% in the FTD/TPI + bevacizumab group; IPD not applicable for patients in the FTD/TPI group).

Baseline data

Baseline patients and disease characteristics are listed in *Table 6* and *Table 7*.

Table 5: Baseline demographic characteristics - SUNLIGHT – full analysis set (N=492)

			FTD/TPI + Bev (N = 246)	FTD/TPI (N = 246)	All (N = 492)
Age (years)		n	246	246	492
		Mean ± SD	61.01 ± 11.11	62.36 ± 11.17	61.68 ± 11.15
		Median	62.00	64.00	63.00
		Min ; Max	20.0 ; 84.0	24.0 ; 90.0	20.0 ; 90.0
	< 65	n (%)	146 (59.35)	129 (52.44)	275 (55.89)
	≥ 65	n (%)	100 (40.65)	117 (47.56)	217 (44.11)
	[65;75[	n (%)	76 (30.89)	83 (33.74)	159 (32.32)
	≥ 75	n (%)	24 (9.76)	34 (13.82)	58 (11.79)
Sex		n	246	246	492
	Female	n (%)	124 (50.41)	112 (45.53)	236 (47.97)
	Male	n (%)	122 (49.59)	134 (54.47)	256 (52.03)
Ethnic origin		n	228	229	457
	White	n (%)	215 (94.30)	220 (96.07)	435 (95.19)
	Black/African American	n (%)	4 (1.75)	3 (1.31)	7 (1.53)
	Asian	n (%)	-	1 (0.44)	1 (0.22)
	American Indian or Alaska	n (%)	1 (0.44)	-	1 (0.22)
	Other	n (%)	8 (3.51)	5 (2.18)	13 (2.84)
Geographic Region		n	246	246	492
	North America	n (%)	8 (3.25)	8 (3.25)	16 (3.25)
	European Union	n (%)	158 (64.23)	157 (63.82)	315 (64.02)
	Rest of the world	n (%)	80 (32.52)	81 (32.93)	161 (32.72)
ECOG PS		n	246	246	492
	0	n (%)	119 (48.37)	106 (43.09)	225 (45.73)
	1	n (%)	127 (51.63)	139 (56.50)	266 (54.07)

			FTD/TPI + Bev (N = 246)	FTD/TPI (N = 246)	All (N = 492)
	2	n (%)	-	1 (0.41)	1 (0.20)

Percentages are based on n
ECOG PS: Eastern Cooperative Oncology Group Performance Status

Table 6: Baseline disease characteristics - SUNLIGHT – full analysis set (N = 492)

			FTD/TPI + Bev (N = 246)	FTD/TPI (N = 246)	All (N = 492)
Primary diagnosis (adenocarcinoma)		n	246	246	492
Colon		n (%)	180 (73.17)	181 (73.58)	361 (73.37)
Rectum		n (%)	66 (26.83)	65 (26.42)	131 (26.63)
Primary tumour site		n	246	246	492
Right		n (%)	62 (25.20)	77 (31.30)	139 (28.25)
Left		n (%)	184 (74.80)	169 (68.70)	353 (71.75)
Number of metastatic organ sites		n	246	246	492
	1-2	n (%)	152 (61.79)	141 (57.32)	293 (59.55)
	≥ 3	n (%)	94 (38.21)	105 (42.68)	199 (40.45)
Time from first metastasis diagnosis to randomisation (months)		n	246	246	492
		Mean ± SD	22.61 ± 14.05	24.09 ± 14.66	23.35 ± 14.36
		Median	21.025	21.124	21.091
		Min ; Max	0.62 ; 133.15	2.99 ; 86.01	0.62 ; 133.15
	< 18 months	n (%)	103 (41.87)	101 (41.06)	204 (41.46)
	≥ 18 months	n (%)	143 (58.13)	145 (58.94)	288 (58.54)
Number of prior metastatic drug regimens[1]		Mean ± SD	1.98 ± 0.26	1.97 ± 0.32	1.98 ± 0.29
		Median	2.00	2.00	2.00
		Min ; Max	1.0 ; 3.0	1.0 ; 4.0	1.0 ; 4.0
	1	n (%)	11 (4.47)	15 (6.10)	26 (5.28)
	2	n (%)	229 (93.09)	224 (91.06)	453 (92.07)
	≥ 3	n (%)	6 (2.44)	7 (2.85)	13 (2.64)
Previous metastatic drug treatment[1]					
Fluoropyrimidine		n (%)	246 (100)	246 (100)	492 (100)
Irinotecan		n (%)	246 (100)	245 (99.59)	491 (99.80)
Oxaliplatin		n (%)	241 (97.97)	243 (98.78)	484 (98.37)
Anti-VEGF monoclonal antibody		n (%)	178 (72.36)	176 (71.54)	354 (71.95)
Anti-EGFR monoclonal antibody in RAS wild type patients		n (%)*	67 (94.37)	66 (92.96)	133 (93.66)

- *Percentages are based on N except (*) based on the number of patients for whom RAS status was wild type*
- *EGFR: Epidermal Growth Factor Receptor; VEGF: Vascular Endothelial Growth Factor. Regarding prior anti-VEGF monoclonal antibodies, those included bevacizumab and ramucirumab*
- *1Defined for the previous drug treatment (a) given in palliative indication or (b) given in adjuvant or neoadjuvant indication and with a progression during or within 6 months of the drug treatment completion*

One patient in the FTD/TPI group had an ECOG rated 2 at baseline prior to treatment while it was rated 1 at inclusion.

Thirteen (2.6%) patients received more than 2 prior regimens for advanced CRC which was reported as an important protocol deviation.

Numbers analysed

Efficacy analyses were carried out in the FAS (n=492) by treatment arm, following the intention-to-treat principle. Both study arms consisted of 246 patients.

Outcomes and estimation

Primary outcome: overall survival

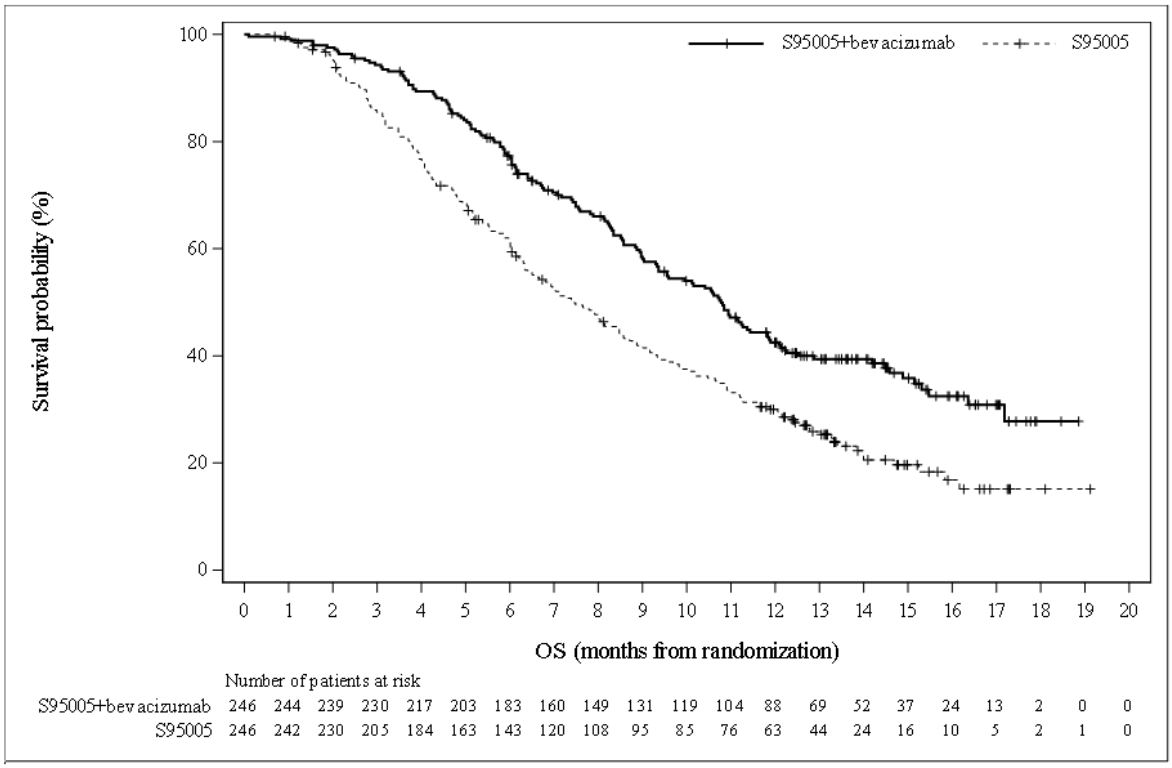
The median follow-up duration at DCO for survival was 14.1 months. OS is summarised by treatment group for the FAS population in *Table 8* as of the survival cut-off date of 19 July 2022.

Table 7: Overall survival - full analysis set (N = 492)

		FTD/TPI + Bev (N = 246)	**FTD/TPI (N = 246)**
Number of censors	n (%)	98	63
Alive	n (%)	98 (39.84)	63 (25.61)
Number of events	n (%)	148	183
Death	n (%)	148 (60.16)	183 (74.39)
Survival (months)			
Median (months)[1]		10.78	7.46
95% confidence interval[2]		[9.36 ; 11.83]	[6.34 ; 8.57]
p-value[3]		< 0.001	
Survival probability			
Survival probability at 6 months[1]		0.77	0.61
95% confidence interval[4]		[0.72 ; 0.82]	[0.55 ; 0.67]
Survival probability at 12 months[1]		0.43	0.30
95% confidence interval[4]		[0.36 ; 0.49]	[0.24 ; 0.36]
Survival probability at 18 months[1]		0.28	0.15
95% confidence interval[4]		[0.19 ; 0.37]	[0.09 ; 0.22]
Hazard ratio* (relative to FTD/TPI monotherapy)		0.61	
95% confidence interval		[0.49 ; 0.77]	

- *Percentages are based on n*
- *1. Kaplan-Meier estimates*
- *2. Methodology of Brookmeyer and Crowley*
- *3. Stratified Log-Rank Test (IWRS stratification factors: geographic region, time since first metastasis diagnosis, RAS status)*
- *4 Using log-log transformation methodology of Kalbfleisch and Prentice*
- ** Stratified Cox proportional hazard model using IWRS stratification factors*

Figure 3: Kaplan-Meier curves of overall survival - full analysis set (N = 492)



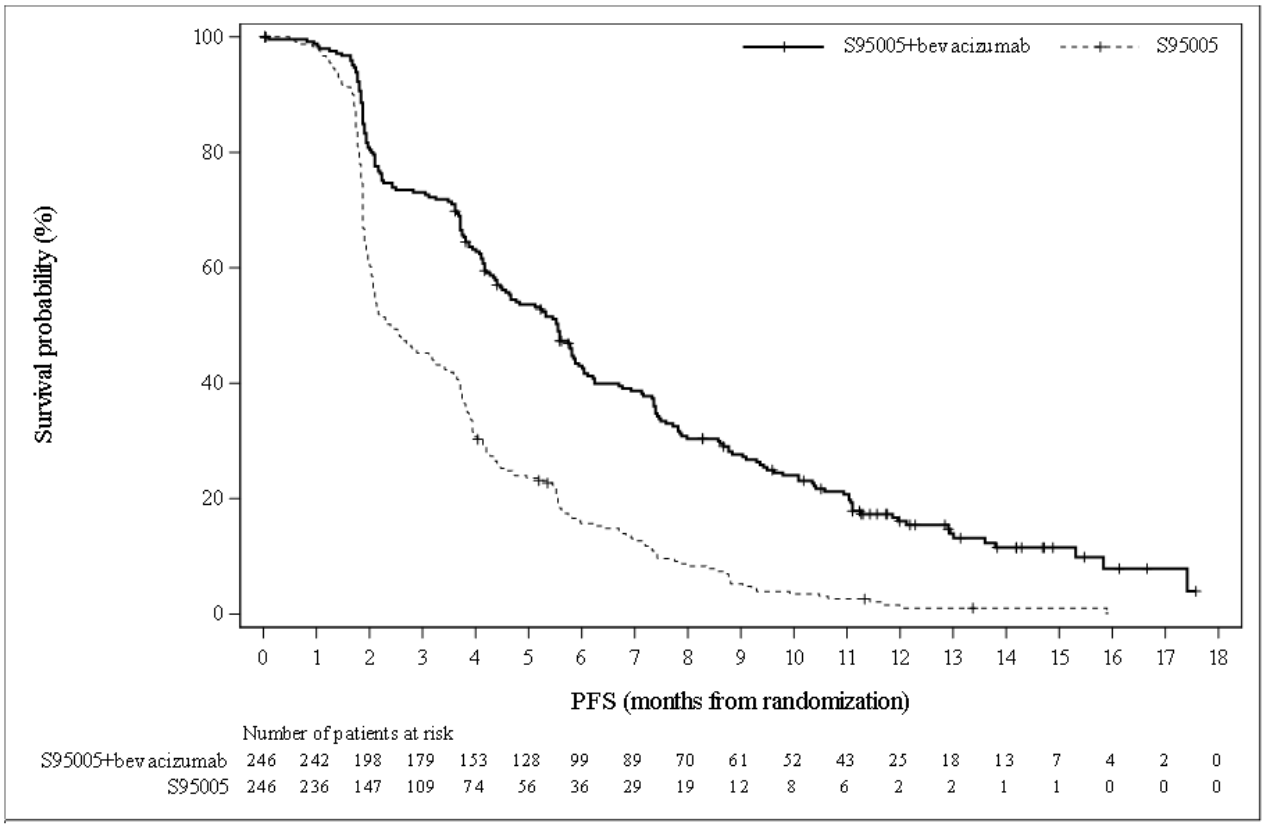
Key secondary outcome: progression free survival

Table 8: Summary of Progression-Free Survival - Investigator assessment - full analysis set (N=492)

		FTD/TPI + Bev (N = 246)	FTD/TPI (N = 246)
Number of censors	n (%)	40 (16.26)	10 (4.07)
Lost to follow-up without documented radiological progression	n (%)	2 (0.81)	4 (1.63)
Alive without documented radiological progression	n (%)	38 (15.45)	5 (2.03)
No baseline or post-baseline tumour assessment	n (%)	-	1 (0.41)
Number of events	n (%)	206 (83.74)	236 (95.93)
Radiological PD	n (%)	178 (72.36)	206 (83.74)
Death	n (%)	28 (11.38)	30 (12.2)
Progression Free Survival (months)			
Median (months) [1]		5.55	2.40
95% confidence interval[2]		[4.50 ; 5.88]	[2.07 ; 3.22]
p-value[3]		< 0.001	
Progression Free Survival probability			
Survival probability at 3 months[1]		0.73	0.45
95% confidence interval[4]		[0.67 ; 0.78]	[0.39 ; 0.51]
Survival probability at 6 months[1]		0.43	0.16
95% confidence interval[4]		[0.37 ; 0.49]	[0.11 ; 0.21]
Survival probability at 9 months[1]		0.28	0.05
95% confidence interval[4]		[0.22 ; 0.34]	[0.03 ; 0.09]
Survival probability at 12 months[1]		0.16	0.01
95% confidence interval[4]		[0.12 ; 0.21]	[0.00 ; 0.03]
Hazard ratio* (relative to FTD/TPI monotherapy)		0.44	
95% confidence interval		[0.36 ; 0.54]	

- *Percentages are based on N*
- *1. Kaplan-Meier estimates*
- *2. Methodology of Brookmeyer and Crowley*
- *3. Stratified Log-Rank Test at one-sided 2.5% level of significance (IWRS stratification factors: geographic region, time since first metastasis diagnosis, RAS status)*
- *4. Using log-log transformation methodology of Kalbfleisch and Prentice*
- ** Stratified Cox proportional hazard model using IWRS stratification factors*

Figure 4: Kaplan-Meier curves of progression-free survival - Investigator assessment -full analysis set (N=492)



Other secondary outcomes: overall response rate and disease control rate

Table 9: Summary of tumour response (BOR, ORR and DCR) - Investigator assessment - full analysis set

		FTD/TPI + Bev (N = 246)	FTD/TPI (N = 246)
Best overall response	n	246	246
Complete response (CR)	n (%)	-	1 (0.41)
Partial response (PR)	n (%)	15 (6.1)	2 (0.81)
Stable disease	n (%)	156 (63.41)	100 (40.65)
Non-CR / Non- Progressive disease (Non-PD)	n (%)	3 (1.22)	3 (1.22)
Progressive disease (PD)	n (%)	61 (24.8)	126 (51.22)

Non evaluable (NE)	n (%)	11 (4.47)	14 (5.69)
Statistical analysis			
ORR[1]	n (%)	15 (6.10)	3 (1.22)
	95% CI[3]	[3.45 , 9.86]	[0.25 , 3.52]
	Difference[4]	4.88	
	95% CI[5]	[1.59 , 8.17]	
DCR[2]	n (%)	171 (69.51)	103 (41.87)
	95% CI[3]	[63.35 , 75.2]	[35.63 , 48.31]
	Difference[4]	27.64	
	95% CI[5]	[19.21 , 36.07]	

- *BOR: Best Overall Response; ORR: Overall Response Rate; DCR; disease Control Rate*
- *Percentages are based on n*
- *Non-CR/non-PD only for patients with non-measurable disease*
- *1. ORR (BOR = CR or PR)*
- *2. DCR (BOR = CR or PR or Stable Disease)*
- *3. 95% Confidence interval of the estimate using Clopper Pearson method*
- *4. FTD/TPI + Bev minus FTD/TPI*
- *5. 95% Confidence interval of the difference using the normal approximation*

Time to worsening of ECOG-PS

Analysis of the time from randomisation to worsening of ECOG PS to ≥ 2 was performed in the FAS using Kaplan-Meier methodology to estimate median time of worsening ECOG PS ≥ 2 in each treatment group with a stratified log-rank test. To be considered as worsening, ECOG PS had to be increased by at least 1 from baseline and to be at least of 2 on treatment. Death was considered as worsening of ECOG PS ≥ 2.

In the FAS, the FTD/TPI + Bev group showed a numerical difference in time to worsening of ECOG PS to ≥ 2 compared to the FTD/TPI group ($p < 0.001$, stratified log rank test). The median time to worsening of ECOG PS to ≥ 2 was 9.3 months (95% CI: 8.34, 10.61) vs 6.3 months (95% CI: 5.55, 7.23), respectively.

Quality of life

Quality of life (QoL) was assessed based on the EORTC QLQ-C30 and EQ-5D-5L assessment instruments. The EORTC QLQ-C30 questionnaire and EQ-5D-5L were completed at the beginning of each visit by the patient:

- Within 7 days prior to randomisation (baseline).
- At Day 1 of cycles ≥ 2 (every cycle) prior to any study procedure.
- At withdrawal visit.

EORTC QLQ-C30

The QoL scores were analysed as change from baseline. Global health status (GHS) was the primary QoL variable of interest. Any absolute change from baseline greater than 10 points was considered a clinically meaningful difference.

For global health status (GHS), the completion rate (i.e. patients of the FAS with a non-missing score) decreased with each visit in the two treatment groups as treatment discontinuations reduced the sample size. Among patients expected to complete the questionnaire i.e. still on treatment, the compliance rate was ≥ 86% across the timepoints up to cycle 11 (questionnaire completed by 34 patients in FTD/TPI + Bev group, 6 patients FTD/TPI group) and similar in the two treatments groups, except at cycle 7 with lower compliance rate in the FTD/TPI + Bev group than in the FTD/TPI group (86.2% vs 100%, respectively). The reasons for non-completion were mostly questionnaire not available, institutional error or other reasons.

Considering any absolute change from baseline greater than 10 points as a clinically meaningful difference, no relevant change was detected in mean scores for the GHS in either group during treatment, as well as for the functioning and symptom/single items, except for appetite loss at cycle 4: mean change of 9.0 ± 26.5 in the FTD/TPI + Bev group and 11.2 ± 32.7 in the FTD/TPI group.

The comparison of the two treatment groups with respect to changes from baseline of the QoL scores was performed longitudinally over time using a repeated-measures mixed-effects model analysis. The terms included in the model were treatment groups, baseline stratification factors, baseline score and assessment timepoints. Results did not show clinically relevant between-group difference for any of the QoL items and no clinically relevant difference in treatment effect across all assessment timepoints was found.

EQ-5D-5L

Among patients of the FAS with evaluable EQ-5D-5L assessment, questionnaire and VAS completion rates decreased with each visit post-baseline, due to stopping study treatment because of disease progression. The reasons for non-compliance were the same as for the EORTC QLQ-C30.

At baseline, the median EQ-5D-5L utility score were almost identical in the two treatment groups: 0.942 in the FTD/TPI + Bev group; 0.940 in the FTD/TPI group. Up to cycle 8, the median change from baseline in EQ-5D-5L score was null in the two groups. Based on a visual analogue scale (VAS) score, also no clinically relevant change from baseline was detected at post-baseline timepoints in either group.

Ancillary analyses

Sensitivity analyses

- For Overall survival:

In order to evaluate the robustness of the observed result, the following sensitivity analyses were performed:

- Unstratified analysis of OS

This OS analysis showed a HR of 0.62 (95% CI: 0.50, 0.77). The p-value from the unstratified log-rank test was still <0.001 as for the primary analysis.

- Analysis of OS excluding patients not fulfilling one of the following eligibility criteria:
    - Inclusion criteria #2: had histologically confirmed unresectable adenocarcinoma of the colon or rectum.
    - Inclusion criteria #4a: had received a maximum of 2 prior chemotherapy regimens for the treatment of advanced colorectal cancer and had demonstrated progressive disease or intolerance to their last regimen.
    - Inclusion criteria #5: measurable or non-measurable metastatic lesion(s) as defined by RECIST version 1.1.
    - Inclusion criteria #8: had an ECOG PS ≤ 1.
    - Exclusion criteria #13: more than 2 prior chemo regimens for treatment of advanced colorectal cancer.
    - Exclusion criteria #17: currently receiving or having received anticancer therapies within 4 weeks prior to randomisation.

- Exclusion criteria #37: previously received FTD/TPI.

This OS analysis showed a HR of 0.59 (95% CI: 0.47, 0.74) and median OS of 10.8 months (95% CI: 9.56,12.12) for the FTD/TPI + Bev group vs 7.2 months (95% CI: 6.31, 8.51) for the FTD/TPI group ($p < 0.001$; stratified log-rank test).

These two sensitivity analyses were consistent with the primary analysis of OS in the FAS.

Additional estimand based on OS: new anticancer therapy

Overall, in the FAS, 44.9% of patients received at least one new anticancer therapy with similar frequency in the FTD/TPI + Bev group than in the FTD/TPI group: 43.9% vs 45.9%.

Additional analyses were performed to evaluate the effect of the study treatment without taking into account any potential effects of the administration of new anticancer therapy by censoring survival at the initiation of new anticancer therapy.

This OS analysis demonstrated a HR of 0.40 (95% CI: 0.30, 0.55) and median OS of 14.5 months (95% CI: 10.41, upper bound not calculated) vs 7.8 months (95% CI: 6.21, 8.77), respectively, ($p < 0.001$; stratified log-rank test).

- For progression free survival

Sensitivity analyses of PFS were performed taking into account clinical progression and administration of new anticancer therapy. As shown in *Table 10*, the results of all sensitivity analyses were statistically significant and consistent with the primary analysis of PFS in the FAS population.

Table 10: Sensitivity analyses of Progression-Free Survival – investigator assessment – FAS:

PFS event	FTD/TPI + Bev (N = 246) PFS (months) Median (CI95%)	FTD/TPI (N = 246) PFS (months) Median (CI95%)	Log-rank p-value*	Hazard Ratio* (95%CI)
Unstratified analysis (supportive analysis 1)	5.55 (4.50, 5.88)	2.40 (2.07, 3.22)	< 0.001	0.44 (0.36; 0.53)
Including clinical progression or new anticancer therapy as PFS events (supportive analysis 2)	5.26 (4.34, 5.81)	2.15 (2.04, 2.69)	< 0.001	0.44 (0.36; 0.53)
Including new anticancer therapy or ≥ 2 consecutive missing tumour assessments as PFS censors (supportive analysis 3, FDA recommended analysis)	5.55 (4.47, 5.88)	2.30 (2.07, 3.12)	< 0.001	0.44 (0.36; 0.54)

PD: progression disease
** Stratified log rank test and stratified Cox proportional hazard model using IWRS stratification factors (geographic region, time since first metastasis diagnosis, RAS status)*

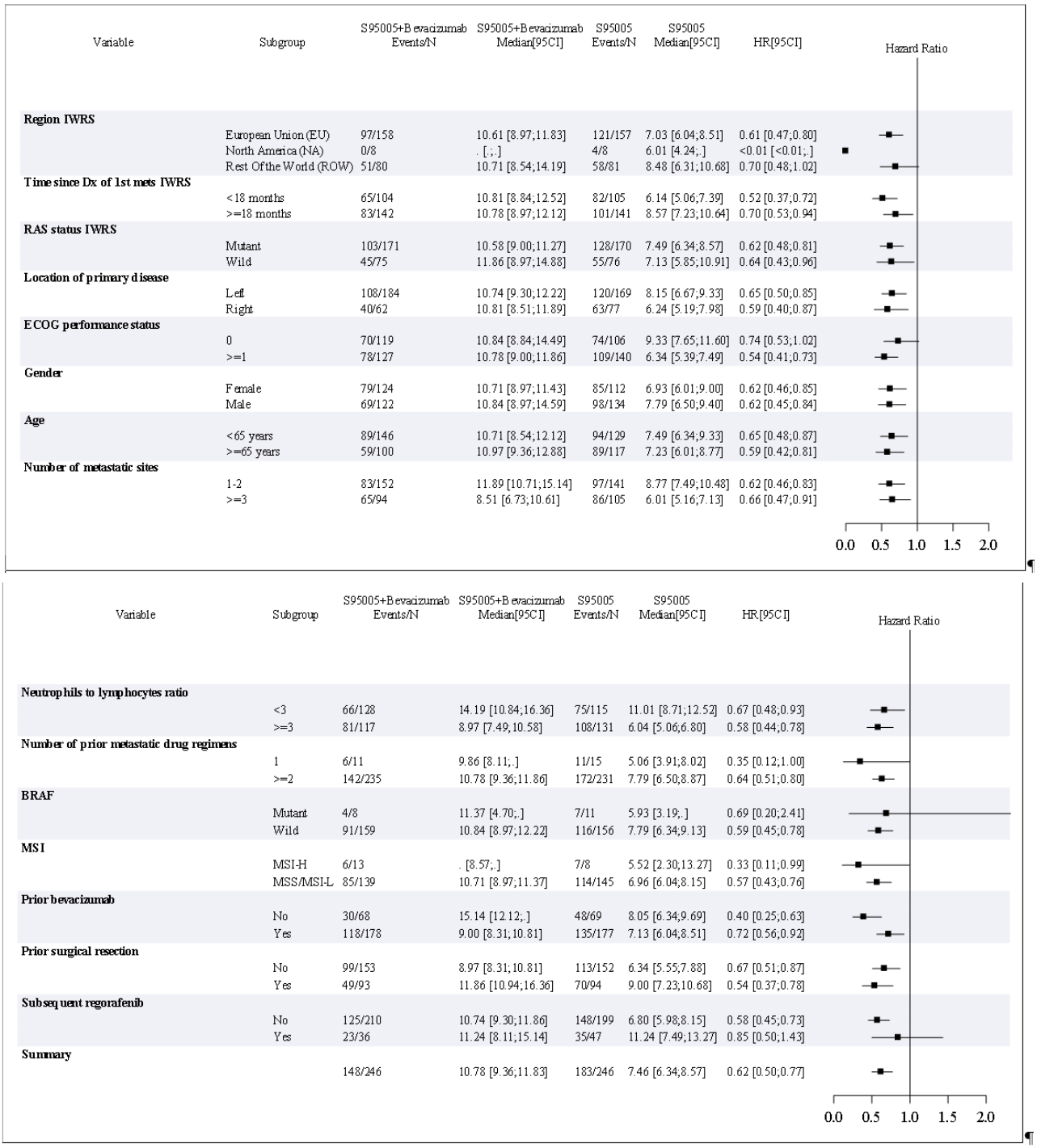
Subgroup analyses for overall survival

OS was analysed across the stratification subgroups and for additional subgroups as pre-specified in the SAP. The results of these analyses are summarised in Figure 5.

The HRs were consistently in favour of the FTD/TPI + Bev treatment group in all subgroups examined, including the stratification factors subgroups, and ranging from 0.33 to 0.85.

For some subgroups (1 prior metastatic drug regimen, BRAF mutant, MSI-H, no subsequent regorafenib), the results should be interpreted with caution due to small sample sizes.

Figure 5: Forest plot of subgroup analyses of overall survival - SUNLIGHT - FAS population (N = 492)



Variable	Subgroup	S95005+Bevacizumab Events/N	S95005+Bevacizumab Median[95CI]	S95005 Events/N	S95005 Median[95CI]	HR[95CI]
Region IWRS						
	European Union (EU)	97/158	10.61 [8.97;11.83]	121/157	7.03 [6.04;8.51]	0.61 [0.47;0.80]
	North America (NA)	0/8	. [.;.]	4/8	6.01 [4.24;.]	<0.01 [<0.01;.]
	Rest Of the World (ROW)	51/80	10.71 [8.54;14.19]	58/81	8.48 [6.31;10.68]	0.70 [0.48;1.02]
Time since Dx of 1st mets IWRS						
	<18 months	65/104	10.81 [8.84;12.52]	82/105	6.14 [5.06;7.39]	0.52 [0.37;0.72]
	>=18 months	83/142	10.78 [8.97;12.12]	101/141	8.57 [7.23;10.64]	0.70 [0.53;0.94]
RAS status IWRS						
	Mutant	103/171	10.58 [9.00;11.27]	128/170	7.49 [6.34;8.57]	0.62 [0.48;0.81]
	Wild	45/75	11.86 [8.97;14.88]	55/76	7.13 [5.85;10.91]	0.64 [0.43;0.96]
Location of primary disease						
	Left	108/184	10.74 [9.30;12.22]	120/169	8.15 [6.67;9.33]	0.65 [0.50;0.85]
	Right	40/62	10.81 [8.51;11.89]	63/77	6.24 [5.19;7.98]	0.59 [0.40;0.87]
ECOG performance status						
	0	70/119	10.84 [8.84;14.49]	74/106	9.33 [7.65;11.60]	0.74 [0.53;1.02]
	>=1	78/127	10.78 [9.00;11.86]	109/140	6.34 [5.39;7.49]	0.54 [0.41;0.73]
Gender						
	Female	79/124	10.71 [8.97;11.43]	85/112	6.93 [6.01;9.00]	0.62 [0.46;0.85]
	Male	69/122	10.84 [8.97;14.59]	98/134	7.79 [6.50;9.40]	0.62 [0.45;0.84]
Age						
	<65 years	89/146	10.71 [8.54;12.12]	94/129	7.49 [6.34;9.33]	0.65 [0.48;0.87]
	>=65 years	59/100	10.97 [9.36;12.88]	89/117	7.23 [6.01;8.77]	0.59 [0.42;0.81]
Number of metastatic sites						
	1-2	83/152	11.89 [10.71;15.14]	97/141	8.77 [7.49;10.48]	0.62 [0.46;0.83]
	>=3	65/94	8.51 [6.73;10.61]	86/105	6.01 [5.16;7.13]	0.66 [0.47;0.91]
Neutrophils to lymphocytes ratio						
	<3	66/128	14.19 [10.84;16.36]	75/115	11.01 [8.71;12.52]	0.67 [0.48;0.93]
	>=3	81/117	8.97 [7.49;10.58]	108/131	6.04 [5.06;6.80]	0.58 [0.44;0.78]
Number of prior metastatic drug regimens						
	1	6/11	9.86 [8.11;.]	11/15	5.06 [3.91;8.02]	0.35 [0.12;1.00]
	>=2	142/235	10.78 [9.36;11.86]	172/231	7.79 [6.50;8.87]	0.64 [0.51;0.80]
BRAF						
	Mutant	4/8	11.37 [4.70;.]	7/11	5.93 [3.19;.]	0.69 [0.20;2.41]
	Wild	91/159	10.84 [8.97;12.22]	116/156	7.79 [6.34;9.13]	0.59 [0.45;0.78]
MSI						
	MSI-H	6/13	. [8.57;.]	7/8	5.52 [2.30;13.27]	0.33 [0.11;0.99]
	MSS/MSI-L	85/139	10.71 [8.97;11.37]	114/145	6.96 [6.04;8.15]	0.57 [0.43;0.76]
Prior bevacizumab						
	No	30/68	15.14 [12.12;.]	48/69	8.05 [6.34;9.69]	0.40 [0.25;0.63]
	Yes	118/178	9.00 [8.31;10.81]	135/177	7.13 [6.04;8.51]	0.72 [0.56;0.92]
Prior surgical resection						
	No	99/153	8.97 [8.31;10.81]	113/152	6.34 [5.55;7.88]	0.67 [0.51;0.87]
	Yes	49/93	11.86 [10.94;16.36]	70/94	9.00 [7.23;10.68]	0.54 [0.37;0.78]
Subsequent regorafenib						
	No	125/210	10.74 [9.30;11.86]	148/199	6.80 [5.98;8.15]	0.58 [0.45;0.73]
	Yes	23/36	11.24 [8.11;15.14]	35/47	11.24 [7.49;13.27]	0.85 [0.50;1.43]
Summary		148/246	10.78 [9.36;11.83]	183/246	7.46 [6.34;8.57]	0.62 [0.50;0.77]

Hazard Ratio

0.0 0.5 1.0 1.5 2.0

Additional analyses

A supplementary analysis for ORR and DCR was performed in all patients of the FAS with measurable disease (at least one target lesion) at baseline and with at least one tumour evaluation while on treatment (222/246 patients in the FTD/TPI + Bev group and 215/246 patients in the FTD/TPI group).

Results were similar to those of the overall FAS population: ORR was 6.3% in the FTD/TPI + Bev group (14 patients, all with PR) vs 0.9% in the FTD/TPI group (2 patients, both with PR).

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 11: Summary of Efficacy for the SUNLIGHT trial

Title: An open-label, randomised, phase III study comparing trifluridine/tipiracil in combination with bevacizumab to trifluridine/tipiracil monotherapy in patients with refractory metastatic colorectal cancer (SUNLIGHT study)		
Study identifier	CL3-95005-007	
Design	A multinational, open-label, two-arm, randomised phase 3 study comparing treatment with trifluridine/tipiracil (FTD/TPI) in combination with bevacizumab to FTD/TPI monotherapy in patients with refractory mCRC. 492 patients with advanced colorectal cancer, who had received a maximum of 2 prior chemotherapy regimens, including a fluoropyrimidine, irinotecan, oxaliplatin, an anti-VEGF monoclonal antibody and/or an anti-EGFR monoclonal antibody for patients with a RAS wild type tumour, were treated with FTD/TPIl + bevacizumab (n=246) or FTD/TPI monotherapy (n=246) until disease progression or unacceptable toxicity.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Treatment continued until disease progression, withdrawal of consent, or until unacceptable toxicity occurred. Not applicable Not applicable
Hypothesis	FTD/TPI in combination with bevacizumab is superior in terms of OS compared to FTD/TPI monotherapy	
Treatments groups	FTD/TPI	Trifluridine/tipiracil 35 mg/m2 orally BID on days 1 to 5 and days 8 to 12 of a 28-day cycle, as long as clinical benefit was observed, or until unacceptable toxicity, n= 246
	FTD/TPI + bevacizumab	Trifluridine/tipiracil 35 mg/m2 orally BID on days 1 to 5 and days 8 to 12, plus bevacizumab 5 mg/kg intravenously once every 2 weeks of a 28-day cycle, as long as clinical benefit was observed, or until unacceptable toxicity, n= 246
Endpoints and definitions	Primary endpoint Overall survival (OS)	Time between the date of randomisation and the date of death due to any cause

	Key secondary endpoint Progression-free survival (invPFS)		Time between randomisation and the date of radiologic tumour progression according to RECIST version 1.1 or death from any cause, assessed by the investigator	
	Secondary endpoint Overall response rate (ORR)		Proportion of patients who achieved a complete response (CR) or partial response (PR) based on investigator's assessment	
Database lock	05 July 2022 for clinical data (i.e. non-survival) and 19 July 2022 for survival data.			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	All randomised patients (full analysis set, FAS) received study treatment as assigned at randomisation. As of clinical DCO, 36 (7.3%) patients were still on treatment (13.0% in the FTD/TPI + bevacizumab group, 1.6% in the FTD/TPI group). The primary endpoint was analysed in the FAS using the intent to treat principle. The median follow-up duration at DCO for analysis of the primary endpoint was 14.1 months. The study started on 25 November 2020 (first visit of first patient) and the last patient was randomized on 18 February 2022.			
Effect estimate per comparison	Primary endpoint	Comparison groups	FTD/TPI (n=246)	FTD/TPI + bevacizumab (n=246)
		OS median, months (95% CI)	7.46 (6.34-8.57)	10.78 (9.36-11.83)
		HR (95% CI)	0.61 (0.49-0.77)	
		P-value	<0.001 one-sided, stratified log-rank test	
	Secondary endpoint	invPFS median, months (95% CI)	2.40 (2.07-3.22)	5.55 (4.50-5.88)
		HR (95% CI)	0.44 (0.36-0.54)	
		P-value	<0.001 one-sided, stratified log-rank test	
	Secondary endpoint	ORR, % (95% CI)	1.2	6.1
		between group difference (95% CI)	4.9% (1.59-8.17)	

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

Clinical studies in special populations

Not applicable.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy data for the current application come from the single **pivotal trial** CL3-95005-007 or **SUNLIGHT** (NCT04737187). This was a multinational, open-label, two-arm, randomised phase 3 study comparing treatment with FTD/TPI in combination with bevacizumab to FTD/TPI monotherapy in patients with refractory mCRC. Treatment with FTD/TPI and with bevacizumab followed the doses and dosing schedule of the already approved other indications in advanced CRC, which is considered acceptable. Treatment could be continued until disease progression or unacceptable toxicity. FTD/TPI could be continued as monotherapy in case of intolerable toxicity of bevacizumab, but bevacizumab monotherapy was not allowed.

All patients had to have received a maximum of two chemotherapy regimens, including the standard available treatments including a fluoropyrimidine, oxaliplatin, irinotecan and a monoclonal antibody targeting either VEGF or EGFR (for patients with a KRAS-wildtype tumour). This third line treatment setting is consistent with the approved indication for FTD/TPI monotherapy. This comparator can therefore be considered adequate.

The **patient population** for the SUNLIGHT study consisted of patients relatively fit for the third-line disease setting, reflected by an ECOG-PS of 0 or 1, the ability to have received all available standard treatment options for advanced CRC and the absence of significant comorbidity. Patients with severe renal impairment were excluded from the trial, eGFR as estimated by the Cockcroft-Gault equation had to be ≥50 ml/min. Some other exclusion criteria are related to known bevacizumab toxicity, such as recent thrombo-embolic events, non-healed wounds, uncontrolled hypertension and proteinuria.

Most patients included in the trial were from Europe. The trial included the planned number of participants in 15 months at 102 sites. Of the total of 492 randomised patients (i.e. the full analysis set, FAS), 246 were assigned to FTD/TPI + bevacizumab and 246 were assigned to FTD/TPI.

The used **stratification factors** for randomisation (geographic region, time since first metastasis diagnosis (< 18 months, ≥ 18 months) and RAS status) are acceptable as they are related to prognosis. It has become clear in recent literature that the location of the primary tumour (left or right sidedness) is also prognostic and might also be predictive of the effect of chemotherapy treatment in advanced CRC, however, the criterium 'time since first metastasis diagnosis' also reflects possible differences in inherent disease course.

The **primary endpoint** of the pivotal study was overall survival, which is the most relevant endpoint considering the poor prognosis of the included patients in a last line treatment setting. There was no placebo for bevacizumab in the comparator arm (open-label design). The fact that treating physicians were aware of the assigned treatment arm, could influence their response assessments and timing of declaring clinical or radiological disease progression. This hampers the interpretation of investigator-assessed PFS, the key secondary endpoint of the trial.

The proposal to specify a **treatment policy estimand** approach for both OS and PFS is agreed. For the secondary estimand approach for OS, data collected after any use of additional anti-cancer

medication are not included in the analysis through the use of censoring. The Applicant describes this as a "while on treatment" estimand, however, it is considered to more closely represent a hypothetical estimand approach (i.e. if patients had not received additional anti-cancer medication). For OS the primary estimand of interest is the treatment policy estimand and therefore this secondary estimand for OS is not considered relevant for the assessment. For PFS the decision to censor patients lost to follow up or without a post-baseline tumour assessment may lead to informative censoring. Given the trial is open-label, the additional estimand approach for PFS, in which clinical progression and administration of further anti-cancer therapies are counted as events is considered relevant for the assessment. The PFS analysis in which patients are censored upon receiving anti-cancer therapy or progress or die after 2 or more missed assessments is not relevant to the CHMP assessment.

A rather large proportion of patients that had given informed consent for participation in the trial were not included due to not meeting the eligibility criteria (25%). Most screen failures were because of not having received a maximum of 2 prior chemotherapy treatments, including all standard treatment lines, and showing PD or intolerance to the last regimen. Also, many patients did not have adequate organ function as defined in the protocol, and some did not have an adequate performance status during the entire screening period. These are the inclusion criteria which have led to a selected, relatively fit patient population. All included patients were randomised and treated with the assigned therapy. At the clinical DCO, only a small proportion of patients was still on treatment (13.6% for FTD/TPI + bevacizumab and 1.6% for FTD/TPI monotherapy). The main reason was disease progression.

There was one global **protocol amendment** including substantial changes to the protocol, which was issued shortly (1 month) after the first patient was included. The statistical analysis plan was amended once, this amendment is dated 6 months after the last patient was included in the study but before the database lock. Both amendments appear not to impact the (interpretation of the) results. The frequency of important protocol deviations was similar between treatment groups both before and after inclusion to the study. It is considered unlikely that these protocol deviations have influenced the study results in a relevant manner.

Efficacy data and additional analyses

The **data cut-off** dates were 05 July 2022 for clinical data (i.e. non-survival) and 19 July 2022 (occurrence of 331st death) for survival data. The median follow-up duration was 14.1 months.

The primary analysis of the primary endpoint of **OS** showed a statistically significant longer median OS in the patients treated with FTD/TPI with bevacizumab compared to FTD/TPI monotherapy, with a HR of 0.61 (95% CI: 0.49 -0.77) and a p<0.001 by stratified log-rank test, which was lower than the target p-value (p<0.025) that was prespecified to reach statistical significance. The OS Kaplan-Meier curves for both treatment arms separate early and stay separated throughout the follow-up period of the trial. The observed 3.3 months difference in median OS (10.8 versus 7.5 months) can be considered clinically relevant in this last-line patient population without other relevant treatment options.

Consent withdrawal and lost-to-follow-up of a few percent seems reassuring. It is noted in the protocol that *"If all these attempts to contact the patient fail, the investigator can then declare the patient "lost to follow-up".* Most patients had been followed up for OS within 6 months of data cut-off and there was no indication of different censoring patterns among the treatment arms though.

Two sensitivity analyses for OS in the FAS were performed: an unstratified analysis and an analysis excluding patients that should have been excluded from participating in the trial based on the exclusion criteria. These two analyses showed results consistent with the primary analysis. The

subgroup analysis for OS does not raise any concerns regarding a possible lack of effect in certain subgroups of patients. This includes the subgroup of patients that were previously treated with the VEGF-inhibitor bevacizumab (72% of patients).

The key secondary endpoint of **PFS** showed a statistically significant longer PFS in the patients treated with FTD/TPI with bevacizumab compared to FTD/TPI monotherapy, with a HR of 0.44 (95% CI: 0.36 - 0.54) and a p<0.001 by stratified log-rank test, which was lower than the target p-value (p<0.025) for statistical significance. Median PFS was 3.2 months longer with the addition of bevacizumab to FTD/TPI chemotherapy (5.6 versus 2.4 months). Because of the open-label design of the trial, the additional estimand approach for PFS, in which clinical progression and administration of further anti-cancer therapies are counted as events, is considered to be of relevance. This additional analysis shows the same hazard ratio and almost the same estimates for median PFS as the primary analysis.

Only the primary and key secondary endpoint were type-1 error controlled, therefore the analyses of the additional secondary endpoints are considered descriptive.

Overall response rate was low both for FTD/TPI monotherapy (3 patients, 1.2%) and for FTD/TPI with bevacizumab (15 patients, 6.1%). The percentage of patients with stable disease was numerically higher for the combination therapy (63.4% versus 40.7%). The result of the addition of bevacizumab to FTD/TPI therefore mainly appears to be prolongation of disease stabilisation.

The interpretation of the results of the analysis for 'time to worsening of ECOG-PS' should be done cautiously, because the open-label design of the trial might have influenced the evaluation of this endpoint.

With regards to the **QoL** endpoints, the analysis of global health status (GHS) as change from baseline was the primary variable of interest. Any absolute change from baseline greater than 10 points was considered a clinically meaningful difference. No relevant change was detected in mean scores for GHS in either group during treatment (within group differences) and there were also no clinically relevant between-group differences in GHS. It should be noted that the open-label design of the trial might have influenced the evaluation of QoL by the patients as well as the investigators. It is also not clear how missing data was handled in this analysis. The results of the QoL analysis, therefore, do not qualify for inclusion in section 5.1 of the SmPC.

The SUNLIGHT inclusion criteria explicitly specified that the prior anticancer treatments had to include a fluoropyrimidine, irinotecan, oxaliplatin, an anti-VEGF monoclonal antibody and/or an anti-EGFR monoclonal antibody (for patients with a RAS wild type tumour). This is adequately reflected in the **indication wording**. The previous therapies are also specified in the already approved indication for Lonsurf monotherapy. Of note, the two mCRC indications were not combined because of the wording "*patients ... not considered candidates for, available therapies*" included in the monotherapy indication (Lonsurf SmPC). Such patients were not allowed to enrol in SUNLIGHT and seeing the additional toxicity of adding bevacizumab to Lonsurf the positive B/R cannot be extrapolated to such patients.

Additional expert consultation

Not applicable.

2.4.4. Conclusions on the clinical efficacy

The addition of bevacizumab to FTD/TPI monotherapy showed a statistically significant and clinically relevant 3.3 months longer median OS in patients with refractory metastatic colorectal cancer who had received two prior anticancer treatment regimens including fluoropyrimidine-, oxaliplatin- and

irinotecan based chemotherapies, anti-VEGF agents, and/or anti-EGFR agents. The OS outcome is supported by the secondary endpoint of PFS.

2.5. Clinical safety

Introduction

Trifluridine/tipiracil (FTD/TPI), also named S95005, TAS-102 or Lonsurf, was approved as monotherapy for the treatment of adult patients with previously treated advanced metastatic colorectal cancer (mCRC). Bevacizumab (Bev) is an anti-vascular endothelial growth factor (VEGF) therapy approved for various oncology indications, including treatment of mCRC in combination with fluoropyrimidine-based chemotherapy.

The known adverse drug reactions (ADRs) observed for FTD/TPI at rates ≥1/10 are neutropenia, leukopenia, anaemia, thrombocytopenia, decreased appetite, diarrhoea, nausea, vomiting, and fatigue.

For bevacizumab the reported ADRs are: hypertension, gastrointestinal perforation, bleeding/haemorrhages, arterial/venous thromboembolic events, proteinuria and wound healing complication.

The safety data discussed below in this document are based on the single pivotal study CL3-95005-007 (SUNLIGHT; NCT04737187).

Standard safety monitoring was performed (vital signs, haematology and chemistry laboratory tests, electrocardiogram [ECG]) and AEs were graded using Common Toxicity Criteria for Adverse Event (CTCAE) Version 5.0.

Patient exposure

The data cut-off dates were 05 July 2022 for clinical data (i.e. non-survival) and 19 July 2022 (occurrence of 331st death) for survival data. As of the clinical cut-off date, the mean ± SD (median) treatment duration was longer in the FTD/TPI + Bev group than in the FTD/TPI group: 6.1 ± 4.3 (5.0) months vs 3.4 ± 2.5 (2.1) months (Table 13).

Table 12 Extent of exposure - SUNLIGHT - Safety Set (N = 492)

		FTD/TPI + Bev (N = 246)	FTD/TPI (N = 246)
Treatment duration (months)	n	246	246
	Mean ± SD	6.12 ± 4.31	3.42 ± 2.49
	Median	4.96	2.07
	Min ; Max	0.1 ; 18.5	0.6 ; 14.3
≤ 2	n (%)	48 (19.51)	101 (41.06)
]2; 4]	n (%)	48 (19.51)	70 (28.46)
]4; 6]	n (%)	55 (22.36)	41 (16.67)
]6; 8]	n (%)	24 (9.76)	18 (7.32)
]8; 10]	n (%)	19 (7.72)	10 (4.07)
> 10	n (%)	52 (21.14)	6 (2.44)
Number of cycles initiated	n	246	246
	Mean ± SD	5.99 ± 4.12	3.42 ± 2.42
	Median	5.00	2.00
	Min ; Max	1.0 ; 17.0	1.0 ; 15.0
1	n (%)	15 (6.10)	24 (9.76)
2	n (%)	50 (20.33)	113 (45.93)
3	n (%)	19 (7.72)	18 (7.32)
4	n (%)	32 (13.01)	38 (15.45)
5	n (%)	17 (6.91)	9 (3.66)
6	n (%)	26 (10.57)	20 (8.13)
7	n (%)	10 (4.07)	4 (1.63)
8	n (%)	18 (7.32)	10 (4.07)
9	n (%)	7 (2.85)	2 (0.81)
10	n (%)	13 (5.28)	2 (0.81)
> 10	n (%)	39 (15.85)	6 (2.44)

Dose intensity

The treatment compliance was assessed by the relative dose intensity (RDI) during the overall treatment duration. The RDI (%) per patient was defined as the ratio of the dose intensity to the planned starting dose intensity at inclusion.

Table 14 summarises the cumulative dose, dose intensity and relative dose intensity of FTD/TPI by treatment group and those of bevacizumab in the FTD/TPI + Bev group.

Table 13 Cumulative dose, dose intensity and relative dose intensity - SUNLIGHT - Safety Set (N = 492)

		FTD/TPI + Bev		FTD/TPI (N = 246)
		FTD/TPI (N = 246)	Bev (N = 246)	
Cumulative dose	n	245*	246	246
(FTD/TPI mg /m^2; Bev: mg/kg)	Mean ± SD	3907.35 ± 2695.59	55.14 ± 39.67	2246.52 ± 1662.31
	Median	3309.54	40.13	1387.52
	Min ; Max	16.9 ; 11769.0	5.0 ; 170.0	137.8 ; 9970.5
Dose intensity	n	245*	246	246
(FTD/TPI: mg/m^2/week;	Mean ± SD	148.76 ± 23.09	2.17 ± 0.68	152.69 ± 24.78
Bev: mg/m/week)	Median	154.59	2.19	158.13
	Min ; Max	27.8 ; 180.8	0.9 ; 11.6	34.4 ; 277.1
Relative dose intensity[(a)] (%)	n	245*	246	246
	Mean ± SD	85.00 ± 13.20	86.90 ± 27.31	87.25±14.16
	Median	88.34	87.61	90.36
	Min ; Max	15.9 ; 103.3	36.4 ; 463.0**	19.7 ; 158.4**

a:ratio of actual to planned dose intensity
** missing for one patient who had only one treatment cycle and for whom the real dose taken for FTD/TPI was not evaluable*
***highest value explained by low treatment durations due to early deaths*

Adverse events

Emergent AEs on treatment (EAEs) are defined as AEs with onset or worsening during the treatment period as defined in the statistical analysis plan (SAP) of the SUNLIGHT study i.e. between the first study treatment intake and up to 30 days after the last study treatment intake.

For the safety analysis, the follow-up period was defined as the time from the 31st day after the last treatment intake and up to the patient study withdrawal. An overall summary for emergent adverse events in the Safety Set (N = 492) is provided in Table 15.

Table 14 Overall summary for emergent adverse events in the Safety Set (N = 492) as of clinical data cut-off 05 July 2022

		FTD/TPI + Bev (N = 246)	FTD/TPI (N = 246)
Patients having reported at least one:			
EAE	n (%)	241 (98.0)	241 (98.0)
Treatment-related[1] EAE	n (%)	223 (90.7)	200 (81.3)
Severe (Grade ≥ 3) EAE	n (%)	178 (72.4)	171 (69.5)
Severe treatment-related[1] EAE	n (%)	145 (58.9)	112 (45.5)
Serious EAE (including death) (SEAE)	n (%)	61 (24.8)	77 (31.3)
Serious treatment-related[1] EAE	n (%)	13 (5.3)	20 (8.1)
EAE leading to FTD/TPI withdrawal	n (%)	31 (12.6)	31 (12.6)
Treatment-related EAE leading to FTD/TPI withdrawal[2]	n (%)	6 (2.4)	5 (2.0)
Severe EAE leading to FTD/TPI withdrawal[2]	n (%)	22 (8.9)	20 (8.1)
Serious EAE leading to FTD/TPI withdrawal[2]	n (%)	20 (8.1)	17 (6.9)
EAE leading to FTD/TPI treatment delayed	n (%)	167 (67.9)	147 (59.8)
EAE leading to FTD/TPI dose reduction	n (%)	18 (7.3)	20 (8.1)
EAE leading to FTD/TPI treatment delayed and dose reduction	n (%)	31 (12.6)	11 (4.5)
EAE leading to FTD/TPI temporary interruption	n (%)	27 (11.0)	21 (8.5)

EAE leading to bevacizumab withdrawal	n (%)	36 (14.6)	NA
EAE leading to bevacizumab treatment delayed	n (%)	172 (69.9)	NA
EAE leading to bevacizumab temporary interruption	n (%)	64 (26.0)	NA
Patients who died during the study[3]			
During treatment period	n (%)	13 (5.3)	24 (9.8)
During the follow-up period	n (%)	133 (54.1)	153 (62.2)
Treatment-related[1] EAE leading to death	n (%)	-	-

NA: not applicable
1. In the FTD/TPI + Bev group, EAEs related to the combination i.e. related to FTD/TPI and/or bevacizumab
2; FTD/TPI withdrawal corresponded to treatment withdrawal as bevacizumab monotherapy was not allowed.
3. As of the clinical cut-off, a total of 323 deaths were reported and used for safety analysis. As of the survival cut-off, a total of 331 deaths were reported and used for the OS analysis.

EAEs with incidence ≥ 5% in either group are presented by preferred term (PT) in Table 16.

The incidence of hypertension (as preferred term [PT]) was notably higher in the FTD/TPI + Bev than in the FTD/TPI group.

Table 15 Emergent adverse events for ≥ 5% of patients - SUNLIGHT - Safety Set (N = 492)

Preferred Term	FTD/TPI + Bev (N = 246)		FTD/TPI (N = 246)	
	All grade n (%)	Grade ≥ 3 n (%)	All grade n (%)	Grade ≥ 3 n (%)
ALL	**241 (98.0)**	**178 (72.4)**	**241 (98.0)**	**171 (69.5)**
Neutropenia	153 (62.2)	106 (43.1)	126 (51.2)	79 (32.1)
Nausea	91 (37.0)	4 (1.6)	67 (27.2)	4 (1.6)
Anaemia	71 (28.9)	15 (6.1)	78 (31.7)	27 (11.0)
Asthenia	60 (24.4)	10 (4.1)	55 (22.4)	10 (4.1)
Fatigue	53 (21.5)	3 (1.2)	40 (16.3)	9 (3.7)
Diarrhoea	51 (20.7)	2 (0.8)	46 (18.7)	6 (2.4)
Decreased appetite	50 (20.3)	2 (0.8)	38 (15.4)	3 (1.2)
Vomiting	46 (18.7)	2 (0.8)	36 (14.6)	4 (1.6)
Thrombocytopenia	42 (17.1)	7 (2.8)	28 (11.4)	3 (1.2)
Neutrophil count decreased	34 (13.8)	22 (8.9)	17 (6.9)	13 (5.3)
Abdominal pain	29 (11.8)	5 (2.0)	27 (11.0)	4 (1.6)
Constipation	27 (11.0)	-	28 (11.4)	2 (0.8)
Stomatitis	27 (11.0)	1 (0.4)	9 (3.7)	-
Hypertension	25 (10.2)	14 (5.7)	5 (2.0)	3 (1.2)
Abdominal pain upper	22 (8.9)	1 (0.4)	10 (4.1)	2 (0.8)
Platelet count decreased	22 (8.9)	3 (1.2)	5 (2.0)	-
Alanine aminotransferase increased	21 (8.5)	7 (2.8)	14 (5.7)	-
Aspartate aminotransferase increased	21 (8.5)	6 (2.4)	14 (5.7)	3 (1.2)
Weight decreased	20 (8.1)	2 (0.8)	12 (4.9)	1 (0.4)
Headache	20 (8.1)	-	9 (3.7)	-
COVID-19	17 (6.9)	3 (1.2)	8 (3.3)	3 (1.2)
Arthralgia	17 (6.9)	1 (0.4)	6 (2.4)	1 (0.4)
Leukopenia	16 (6.5)	4 (1.6)	21 (8.5)	7 (2.8)
Back pain	16 (6.5)	1 (0.4)	13 (5.3)	2 (0.8)
Proteinuria	15 (6.1)	2 (0.8)	3 (1.2)	-
Blood bilirubin increased	14 (5.7)	4 (1.6)	14 (5.7)	2 (0.8)
Pyrexia	12 (4.9)	-	15 (6.1)	1 (0.4)

Preferred Term	FTD/TPI + Bev (N = 246)		FTD/TPI (N = 246)	
	All grade n (%)	Grade ≥ 3 n (%)	All grade n (%)	Grade ≥ 3 n (%)

Percentages are based on N
Grade ≥ 3: Severe EAE
Adverse events were coded using MedDRA 25.0

Adverse events of special interest (AESI)

AESI are known adverse reactions associated with FTD/TPI or bevacizumab. For each AESI, analysis was performed based on a list of pre-defined PTs of similar medical concept, including Standard MedDRA Queries (SMQ) for bevacizumab.

AESI for FTD/TPI

Bone marrow suppression events

Overall, incidence of bone marrow suppression events did not show relevant between-group difference (between-group difference < 10%: 80.9% in the FTD/TPI + Bev group vs 73.2% in the FTD/TPI group). Regarding the categories of EAEs, incidences were higher in the FTD/TPI + Bev than FTD/TPI group for treatment-related events, severe events, treatment-related severe events, and events leading to treatment delayed and events leading to treatment delayed/dose reduction (between-group difference > 5%).

Infections

Infection events that occurred in ≥ 2 patients (0.8%) in either group are shown by PT in Table 17. Incidences of events did not show relevant between-group differences, neither for overall infection events (between-group difference < 10%: 30.9% in the FTD/TPI + Bev group vs 23.2% in the FTD/TPI group) nor for the EAE categories (between-group difference < 5%). Fatal infections occurred in 2.0% of patients in the FTD/TPI + Bev group and 0.8% in the FTD/TPI group; none of these were considered treatment-related.

Table 16 Infections and Infestations - Emergent adverse events in ≥ 2 patients - SUNLIGHT - Safety Set (N = 492)

Preferred Term	FTD/TPI + Bev (N = 246)		FTD/TPI (N = 246)	
	All grade n (%)	Grade ≥ 3 n (%)	All grade n (%)	Grade ≥ 3 n (%)
ALL	**76 (30.9)**	**19 (7.7)**	**57 (23.2)**	**18 (7.3)**
COVID-19	17 (6.9)	3 (1.2)	8 (3.3)	3 (1.2)
Urinary tract infection	11 (4.5)	-	7 (2.8)	1 (0.4)
Upper respiratory tract infection	6 (2.4)	-	6 (2.4)	-
Urinary tract infection bacterial	6 (2.4)	-	1 (0.4)	1 (0.4)
Viral upper respiratory tract infection	5 (2.0)	-	1 (0.4)	-
Pneumonia	4 (1.6)	2 (0.8)	6 (2.4)	2 (0.8)
Asymptomatic COVID-19	4 (1.6)	-	2 (0.8)	-
Oral infection	3 (1.2)	-	-	-
Cystitis	2 (0.8)	-	4 (1.6)	-
Infection	2 (0.8)	1 (0.4)	4 (1.6)	2 (0.8)
Nasopharyngitis	2 (0.8)	-	3 (1.2)	-
Escherichia urinary tract infection	2 (0.8)	-	1 (0.4)	-
Oral herpes	2 (0.8)	-	1 (0.4)	-
Vascular device infection	2 (0.8)	1 (0.4)	1 (0.4)	1 (0.4)
Furuncle	2 (0.8)	1 (0.4)	-	-
Gingivitis	2 (0.8)	-	-	-
Respiratory tract infection	2 (0.8)	-	-	-
Respiratory tract infection viral	2 (0.8)	-	-	-
Septic shock	2 (0.8)	2 (0.8)	-	-
Tooth infection	2 (0.8)	-	-	-
Bacterial pyelonephritis	-	-	2 (0.8)	1 (0.4)

Percentages are based on N
Grade ≥ 3: Severe EAE
Adverse events were coded using MedDRA 25.0

Gastrointestinal events

No gastrointestinal perforation events were reported in the FTD/TPI group. The incidence of gastrointestinal perforation events was 2.4% in the FTD/TPI + Bev group. The incidence was 1.6% for treatment-related events.

Overall incidence of gastrointestinal events did not show a relevant between-group difference (< 10%: 48.4% in the FTD/TPI + Bev group vs 41.1% in the FTD/TPI group). Regarding the categories of EAEs, incidence was higher in the FTD/TPI + Bev than FTD/TPI group for treatment-related events (between-group difference > 5%).

AESIs for bevacizumab

The following AESIs are associated with bevacizumab: hypertension, gastrointestinal perforation, bleeding/haemorrhages, arterial/venous thromboembolic events, proteinuria and wound healing complication.

The overall incidence for each of these bevacizumab AESIs was higher with the combination FTD/TPI plus bevacizumab than FTD/TPI monotherapy. However, between-group differences were all < 10% with greatest differences observed for hypertension (11.0% vs 2.0, respectively) and haemorrhages (11.8% vs 3.7%, respectively). No gastrointestinal perforation events were reported in the FTD/TPI group.

In the FTD/TPI + Bev group the incidence of gastrointestinal perforation events was 2.4%. The incidence of severe gastrointestinal perforation events was 1.6%.

The incidence of haemorrhagic events was higher in the FTD/TPI + Bev than FTD/TPI group (11.8% vs 3.7%), as well as for incidence of treatment-related events (5.3% vs none). The incidence of thromboembolic events was 4.9% in the FTD/TPI + Bev group and 3.7% in the FTD/TPI group. Treatment-related thromboembolic events occurred at 2.8% in the FTD/TPI + Bev group and none occurred in the FTD/TPI group.

Overall, incidence of proteinuria AEs was 6.1% in the FTD/TPI + Bev and 1.2% in the FTD/TPI group. Treatment-related proteinuria events were reported only in the FTD/TPI + Bev group in 4.9% of patients.

No wound healing complication events were reported.

For patients treated with the combination FTD/TPI plus bevacizumab, the rates of severe AESIs were < 2%, except for hypertension (6.1%), and the rates for AESIs leading to treatment withdrawal or treatment modification were ≤ 2%.

Analysis of treatment-related emergent adverse events

For patients who received the combination FTD/TPI plus bevacizumab, treatment-related EAEs described are events considered related to the combination i.e. related to FTD/TPI and/or bevacizumab (i.e. FTD/TPI only or bevacizumab only or both FTD/TPI and bevacizumab), unless specified otherwise.

Treatment-related EAEs with incidence ≥ 5% in either group are presented by PT in Table 18.

When FTD/TPI was combined with bevacizumab, treatment-related EAEs were consistent with the known adverse reactions of FTD/TPI monotherapy and bevacizumab.

Among other treatment-related EAEs, hypertension occurred at higher frequency in the FTD/TPI + Bev group than FTD/TPI group: 7.3% vs none.

Table 17 Treatment-related emergent adverse events for ≥ 5% of patients - SUNLIGHT - Safety Set (N = 492)

Preferred Term	FTD/TPI + Bev (N = 246)		FTD/TPI (N = 246)	
	All grade n (%)	Grade ≥ 3 n (%)	All grade n (%)	Grade ≥ 3 n (%)
ALL	**223 (90.7)**	**145 (58.9)**	**200 (81.3)**	**112 (45.5)**
Neutropenia	148 (60.2)	102 (41.5)	119 (48.4)	72 (29.3)
Nausea	82 (33.3)	3 (1.2)	51 (20.7)	3 (1.2)
Anaemia	58 (23.6)	12 (4.9)	62 (25.2)	20 (8.1)
Asthenia	47 (19.1)	6 (2.4)	35 (14.2)	2 (0.8)
Vomiting	41 (16.7)	2 (0.8)	27 (11.0)	3 (1.2)
Fatigue	40 (16.3)	2 (0.8)	30 (12.2)	6 (2.4)

Preferred Term	FTD/TPI + Bev (N = 246)		FTD/TPI (N = 246)	
	All grade n (%)	Grade ≥ 3 n (%)	All grade n (%)	Grade ≥ 3 n (%)
Diarrhoea	38 (15.4)	1 (0.4)	38 (15.4)	5 (2.0)
Thrombocytopenia	38 (15.4)	5 (2.0)	22 (8.9)	1 (0.4)
Neutrophil count decreased	34 (13.8)	22 (8.9)	17 (6.9)	13 (5.3)
Decreased appetite	30 (12.2)	1 (0.4)	18 (7.3)	-
Stomatitis	26 (10.6)	1 (0.4)	9 (3.7)	-
Platelet count decreased	22 (8.9)	3 (1.2)	4 (1.6)	-
Hypertension	18 (7.3)	10 (4.1)	-	-
Leukopenia	14 (5.7)	3 (1.2)	19 (7.7)	5 (2.0)

Percentages are based on N
Grade ≥ 3: Severe EAE
Adverse events were coded using MedDRA 25.0

Serious adverse event/deaths/other significant events

Serious adverse events

The percentage of patients who experienced at least one serious EAE (SEAE) was lower in the FTD/TPI + Bev group than the FTD/TPI group (24.8% vs 31.3%).

SEAEs reported by at least 2 (0.8%) patients in either group are presented in Table 19.

Table 18 Serious emergent adverse events for ≥ 2 patients - SUNLIGHT - Safety Set (N = 492)

Preferred Term	FTD/TPI + Bev (N = 246)		FTD/TPI (N = 246)	
	n	%	n	%
ALL	**61**	**24.8**	**77**	**31.3**
Intestinal obstruction	7	2.8	5	2.0
Malignant neoplasm progression	6	2.4	11	4.5
COVID-19	5	2.0	6	2.4
Jaundice cholestatic	3	1.2	-	-
Jaundice	2	0.8	5	2.0
Acute kidney injury	2	0.8	2	0.8
Vomiting	2	0.8	2	0.8
Abdominal pain	2	0.8	1	0.4
Cholangitis	2	0.8	1	0.4
Neutropenia	2	0.8	1	0.4
Bile duct stenosis	2	0.8	-	-
Biliary dilatation	2	0.8	-	-
Blood bilirubin increased	2	0.8	-	-
Hyperbilirubinaemia	2	0.8	-	-
Large intestinal obstruction	2	0.8	-	-
Metastases to meninges	2	0.8	-	-
Nausea	2	0.8	-	-
Septic shock	2	0.8	-	-
Stoma site haemorrhage	2	0.8		-

Preferred Term	FTD/TPI + Bev (N = 246)		FTD/TPI (N = 246)	
	n	%	n	%
Anaemia	1	0.4	8	3.3
Febrile neutropenia	1	0.4	6	2.4
Pulmonary embolism	1	0.4	4	1.6
Abdominal pain upper	1	0.4	2	0.8
Ascites	1	0.4	2	0.8
Dehydration	1	0.4	2	0.8
Pneumonia	1	0.4	2	0.8
Hepatic failure	-	-	5	2.0
Metastases to central nervous system	-	-	4	1.6
Diarrhoea	-	-	3	1.2
Fatigue	-	-	3	1.2
Bacterial pyelonephritis	-	-	2	0.8
Cachexia	-	-	2	0.8
Constipation	-	-	2	0.8
Infection	-	-	2	0.8
Multiple organ dysfunction syndrome	-	-	2	0.8
Pyrexia	-	-	2	0.8

Percentages are based on N
Treatment emergent serious AE include sponsor upgrade
Adverse events were coded using MedDRA 25.0

Treatment-related SEAEs were reported for 13 patients (5.3%) in the FTD/TPI + Bev group and 20 (8.1%) in the FTD/TPI group. Treatment-related SEAEs that occurred in more than 2 (0.8%) patients were febrile neutropenia and anaemia (0.4% vs 2.4% for each).

Deaths

The data cut-off dates were 05 July 2022 for clinical data (i.e. non-survival) and 19 July 2022 (occurrence of 331st death) for survival data.

As of the survival cut-off, 331 deaths were reported and used for the overall survival primary analysis. For the safety analysis, only deaths that occurred as of the clinical cut-off date are described in this section.

As of the clinical cut-off, a total of 323 patients had died: 59.4% of patients in the FTD/TPI + Bev group and 72.0% of patients in the FTD/TPI group (Table 20).

Table 19 Summary of deaths - SUNLIGHT - Safety Set (N = 492)

		FTD/TPI + Bev (N = 246)	FTD/TPI (N = 246)
Death	n (%)	146 (59.4)	177 (72.0)
Death during the treatment period	n (%)	13 (5.3)	24 (9.8)
Death during the follow-up period	n (%)	133 (54.1)	153 (62.2)

		FTD/TPI + Bev (N = 246)	FTD/TPI (N = 246)
Reason of death during the follow-up period	n	132	149
Progressive disease	n (%*)	127 (96.2)	139 (93.3)
Other	n (%*)	5 (3.8)	10 (6.7)

** % based on the number of deaths during the follow-up period with a reported reason of death*
Clinical data cut-off for SUNLIGHT: 05 July 2022

Deaths were reported either as fatal outcome of EAE or as withdrawal reason from the follow-up period. Fatal EAEs occurred during the treatment period, but the resulting death could have occurred during either the treatment period or the follow-up period.

Analysis of fatal EAEs

The analysis of EAEs leading to death is presented by system organ class (SOC) and PT in Table 21. Fatal EAEs occurred during the treatment period, but the resulting death could have occurred during either treatment period or follow-up period. The percentage of patients who experienced a fatal EAE (regardless of whether death occurred during treatment or follow-up period) was lower in the FTD/TPI + Bev group than in the FTD/TPI group: 5.3% vs 11.0% (Table 21). Fatal EAEs reported in more than one patient were malignant neoplasm progression (2.4% vs 4.5%), hepatic failure (none vs 1.2%), septic shock (0.8% vs none), multiple organ dysfunction syndrome and cachexia (none vs 0.8% for each). Deaths due to reason(s) other than disease progression occurred in 5 patients in the FTD/TPI + Bev group (due to abdominal sepsis, septic shock, COVID-19, COVID-19 pneumonia, and cardiac failure congestive), and in 5 patients in the FTD/TPI group (due to COVID-19, respiratory failure, cerebrovascular accident, cardiac failure acute and death [as PT]).

Table 20 Emergent adverse events leading to death - SUNLIGHT - Safety Set (N = 492)

System Organ Class Preferred Term	FTD/TPI + Bev (N = 246)		FTD/TPI (N = 246)	
	n	%	n	%
ALL	13	5.3	27	11.0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	6	2.4	12	4.9
Malignant neoplasm progression	6	2.4	11	4.5
Metastases to central nervous system	-	-	1	0.4
Infections and infestations	5	2.0	2	0.8
Septic shock	2	0.8	-	-
COVID-19	1	0.4	1	0.4
Abdominal sepsis	1	0.4	-	-
COVID-19 pneumonia	1	0.4	-	-
Urosepsis	-	-	1	0.4
Cardiac disorders	2	0.8	1	0.4
Cardiac failure	1	0.4	-	-
Cardiac failure congestive	1	0.4	-	-
Cardiac failure acute	-	-	1	0.4
Gastrointestinal disorders	1	0.4	1	0.4
Intestinal obstruction	1	0.4	-	-
Subileus	-	-	1	0.4
General disorders and administration site conditions	-	-	5	2.0
Multiple organ dysfunction syndrome	-	-	2	0.8
Death	-	-	1	0.4
Fatigue	-	-	1	0.4
General physical health deterioration	-	-	1	0.4
Hepatobiliary disorders	-	-	3	1.2
Hepatic failure	-	-	3	1.2
Jaundice	-	-	1	0.4
Metabolism and nutrition disorders	-	-	2	0.8
Cachexia	-	-	2	0.8
Nervous system disorders	-	-	1	0.4
Cerebrovascular accident	-	-	1	0.4
Respiratory, thoracic and mediastinal disorders	-	-	1	0.4
Respiratory failure	-	-	1	0.4

Percentages are based on N
Adverse events were coded using MedDRA 25.0
Note: EAEs leading to death during the follow-up period were as follows:
- 2 patients (0.8%) in the FTD/TPI + Bev group: cardiac failure congestive and malignant neoplasm progression (1 patient each)
- 5 patients (2.0%) in the FTD/TPI group: malignant neoplasm progression (2 patients), general physical health deterioration, cachexia and cerebrovascular accident (1 patient each).

Deaths which resulted from fatal EAEs were predominantly due to disease progression for 8 out of 13 patients in the FTD/TPI + Bev group and 22 out of 27 patients in the FTD/TPI group (Table 22). None of the deaths were treatment-related in either treatment group.

Table 21 Deaths during treatment or follow-up period - EAEs leading to death according to disease progression and/or other reasons - SUNLIGHT - Safety Set (N = 492)

Type of Adverse Events	FTD/TPI + Bev (N = 246)			FTD/TPI (N = 246)		
	NEAE	n	%	NEAE	n	%
All patients having at least one EAE leading to death	14	13	5.3	29	27	11.0
Due to disease progression only* and not treatment-related	9	8	3.3	24	22	8.9
Due to other reason(s) than disease progression and not treatment-related	5	5	2.0	5	5	2.0
Due to other reason(s) than disease progression and treatment-related	-	-	-	-	-	-

EAE: emergent adverse event; NEAE: Number of emergent adverse events; Percentages are based on N
Treatment-related refers to relationship to combination (FTD/TPI and/or bevacizumab)
**as reported by investigator*

Deaths during the follow-up period

Out of the 286 patients who died during follow-up period, most of the deaths were attributed to progressive disease: 96.2% in the FTD/TPI + Bev group and 93.3% in the FTD/TPI group. For 5 patients (3.8%) in the FTD/TPI + Bev group and 10 patients (6.7%), the cause of death during follow-up period was reported as 'Other'. Among those deaths for 'Other' reason, one was reported as fatal outcome of an EAE in the FTD/TPI + Bev group (cardiac failure congestive).

Adverse drug reactions (ADRs)

The identification of ADRs and their frequency are based on:

- **For Lonsurf as monotherapy:** the safety pool of 1114 patients consisting of 533 treated patients with metastatic colorectal cancer in the placebo-controlled Phase III (RECOURSE) clinical study, 335 treated patients with metastatic gastric cancer in the placebo-controlled Phase III (TAGS) clinical study and 246 patients with metastatic colorectal cancer in the controlled Phase III (SUNLIGHT) clinical study.

The most common adverse reactions (≥ 30%) are neutropenia (53% [34% ≥ Grade 3]), nausea (31% [1% ≥ Grade 3]), fatigue (31% [4% ≥ Grade 3]), and anaemia (30% [11% ≥ Grade 3]).

The most common adverse reactions (≥ 2%) that resulted in treatment discontinuation, dose reduction, dose delay, or dose interruption were neutropenia, anaemia, fatigue, leukopenia, thrombocytopenia, diarrhoea, and nausea.

- **For Lonsurf in combination with bevacizumab:** 246 patients with metastatic colorectal cancer in the controlled Phase III (SUNLIGHT) clinical study.

The most common adverse reactions (≥ 30%) are neutropenia (69% [48% ≥ Grade 3]), fatigue (35% [3% ≥ Grade 3]), and nausea (33% [1% ≥ Grade 3]).

The most common adverse reactions (≥ 2%) that resulted in treatment discontinuation, dose reduction, dose delay, or dose interruption of Lonsurf when used in combination with bevacizumab were neutropenia, fatigue, thrombocytopenia, nausea and anaemia.

When Lonsurf is used in combination with bevacizumab, the frequency of the following adverse reactions was increased compared to Lonsurf as monotherapy: neutropenia (69% vs 53%), severe neutropenia (48% vs 34%), thrombocytopenia (24% vs 16%), stomatitis (11% vs 6%).

Table 22: Treatment-related EAE reported in clinical studies in patients treated with Lonsurf - Safety Set (N = 1793)

System Organ Class (MedDRA)[a]	Treatment-related EAE	Frequency		Incidences	
		Monotherapy	Combination with bevacizumab	Monotherapy (N=1114) n (%)	Combination with bevacizumab (N=246) n (%)
	Lymphopenia	Common	Common	53 (4.76)	6 (2.44)
	Pancytopenia	Uncommon	Uncommon	8 (0.72)	1 (0.41)
	Erythropenia	Uncommon	-	5 (0.45)	-
	Leukocytosis	Uncommon	-	2 (0.18)	-
	Monocytopenia	Uncommon	-	2 (0.18)	-
	Monocytosis	Uncommon	-	7 (0.63)	-
	Granulocytopenia	Rare	-	1 (0.09)	-
Metabolism and nutrition disorders	Decreased appetite	Very common	Very common	220 (19.75)	30 (12.20)
	Hypoalbuminaemia	Common	Uncommon	17 (1.53)	1 (0.41)
	Dehydration	Uncommon	-	6 (0.54)	-
	Hyperglycaemia	Uncommon	Uncommon	3 (0.27)	1 (0.41)
	Hyperkalaemia	Uncommon	-	4 (0.36)	-
	Hypocalcaemia	Uncommon	-	6 (0.54)	-
	Hypokalaemia	Uncommon	-	7 (0.63)	-
	Hyponatraemia	Uncommon	-	6 (0.54)	-
	Hypophosphataemia	Uncommon	-	3 (0.27)	-
	Gout	Rare	-	1 (0.09)	-
	Hypernatraemia	Rare	-	1 (0.09)	-
Psychiatric disorders	Anxiety	Uncommon	-	2 (0.18)	-
	Insomnia	Uncommon	-	8 (0.72)	-
Nervous system disorders	Dysgeusia	Common	Common	39 (3.50)	8 (3.25)
	Dizziness	Uncommon	Common	9 (0.81)	3 (1.22)
	Headache	Uncommon	Common	9 (0.81)	4 (1.63)
	Neuropathy peripheral	Uncommon	Uncommon	11 (0.99)	1 (0.41)
	Paraesthesia	Uncommon	Uncommon	9 (0.81)	1 (0.41)
	Lethargy	Uncommon	-	2 (0.18)	-
	Neurotoxicity	Uncommon	-	3 (0.27)	-
	Burning sensation	Rare	-	1 (0.09)	-
	Dysaesthesia	Rare	-	1 (0.09)	-
	Hyperaesthesia	Rare	-	1 (0.09)	-
	Hypoaesthesia	Rare	-	1 (0.09)	-
	Syncope	Rare	-	1 (0.09)	-
Eye disorders	Cataract	Rare	-	1 (0.09)	-
	Diplopia	Rare	-	1 (0.09)	-
	Dry eye	Rare	-	1 (0.09)	-
	Vision blurred	Rare	-	1 (0.09)	-
	Visual acuity reduced	Rare	-	1 (0.09)	-
Ear and labyrinth disorders	Vertigo	Uncommon	-	3 (0.27)	-
	Ear discomfort	Rare	-	1 (0.09)	-
Cardiac disorders	Angina pectoris	Uncommon	-	2 (0.18)	-
	Arrhythmia	Uncommon	-	3 (0.27)	-
	Palpitations	Uncommon	-	5 (0.45)	-
Vascular disorders	Hypertension	Uncommon	Common	4 (0.36)	4 (1.63)
	Flushing	Uncommon	-	8 (0.72)	-
	Hypotension	Uncommon	-	3 (0.27)	-
	Embolism	Rare	-	1 (0.09)	-

	Neuropathy peripheral	Uncommon	Uncommon	11 (0.99)	1 (0.41)
	Paraesthesia	Uncommon	Uncommon	9 (0.81)	1 (0.41)
	Lethargy	Uncommon	-	2 (0.18)	-
	Neurotoxicity	Uncommon	-	3 (0.27)	-
	Burning sensation	Rare	-	1 (0.09)	-
	Dysaesthesia	Rare	-	1 (0.09)	-
	Hyperaesthesia	Rare	-	1 (0.09)	-
	Hypoaesthesia	Rare	-	1 (0.09)	-
	Syncope	Rare	-	1 (0.09)	-
Eye disorders	Cataract	Rare	-	1 (0.09)	-
	Diplopia	Rare	-	1 (0.09)	-
	Dry eye	Rare	-	1 (0.09)	-
	Vision blurred	Rare	-	1 (0.09)	-
	Visual acuity reduced	Rare	-	1 (0.09)	-
Ear and labyrinth disorders	Vertigo	Uncommon	-	3 (0.27)	-
	Ear discomfort	Rare	-	1 (0.09)	-
Cardiac disorders	Angina pectoris	Uncommon	-	2 (0.18)	-
	Arrhythmia	Uncommon	-	3 (0.27)	-
	Palpitations	Uncommon	-	5 (0.45)	-
Vascular disorders	Hypertension	Uncommon	Common	4 (0.36)	4 (1.63)
	Flushing	Uncommon	-	8 (0.72)	-
	Hypotension	Uncommon	-	3 (0.27)	-
	Embolism	Rare	-	1 (0.09)	-
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Common	Common	15 (1.35)	3 (1.22)
	Pulmonary embolism	Uncommon	-	3 (0.27)	-
	Dysphonia	Uncommon	Uncommon	5 (0.45)	1 (0.41)
	Cough	Uncommon	-	9 (0.81)	-
	Epistaxis	Uncommon	-	6 (0.54)	-
	Rhinorrhoea	Rare	Uncommon	1 (0.09)	1 (0.41)
	Oropharyngeal pain	Rare	-	1 (0.09)	-
	Pleural effusion	Rare	-	1 (0.09)	-
Gastrointestinal disorders	Diarrhoea	Very common	Very common	218 (19.57)	38 (15.45)
	Vomiting	Very common	Very common	170 (15.26)	41 (16.67)
	Nausea	Very common	Very common	346 (31.06)	82 (33.33)
	Abdominal pain	Common	Common	51 (4.58)	17 (6.91)
	Stomatitis	Common	Very common	62 (5.57)	27 (10.98)
	Constipation	Common	Common	56 (5.03)	4 (1.63)
	Ileus	Uncommon	-	3 (0.27)	-
	Gastrointestinal haemorrhage	Uncommon	-	6 (0.54)	-
	Colitis	Uncommon	Uncommon	2 (0.18)	1 (0.41)
	Mouth ulceration	Uncommon	Common	2 (0.18)	3 (1.22)
	Oral disorder	Uncommon	Common	11 (0.99)	4 (1.63)
	Abdominal distension	Uncommon	Uncommon	4 (0.36)	1 (0.41)
	Anal inflammation	Uncommon	Uncommon	2 (0.18)	1 (0.41)
	Dyspepsia	Uncommon	Uncommon	10 (0.90)	2 (0.81)

	Flatulence	Uncommon	Uncommon	3 (0.27)	1 (0.41)
	Gastritis	Uncommon	-	4 (0.36)	-
	Gastrooesophageal reflux disease	Uncommon	-	4 (0.36)	-
	Glossitis	Uncommon	-	2 (0.18)	-
	Impaired gastric emptying	Uncommon	-	2 (0.18)	-
	Retching	Uncommon	-	2 (0.18)	-
	Tooth disorder	Uncommon	-	2 (0.18)	-
	Ascites	Rare	-	1 (0.09)	-
	Pancreatitis acute	Rare	-	1 (0.09)	-
	Subileus	Rare	-	1 (0.09)	-
	Breath odour	Rare	-	1 (0.09)	-
	Buccal polyp	Rare	-	1 (0.09)	-
	Enterocolitis haemorrhagic	Rare	-	1 (0.09)	-
	Gingival bleeding	Rare	-	1 (0.09)	-
	Oesophagitis	Rare	-	1 (0.09)	-
	Periodontal disease	Rare	-	1 (0.09)	-
	Proctalgia	Rare	-	1 (0.09)	-
	Reflux gastritis	Rare	-	1 (0.09)	-
Hepatobiliary disorders	Hyperbilirubinaemia	Common	Common	23 (2.06)	10 (4.07)
	Hepatotoxicity	Uncommon	-	3 (0.27)	-
	Biliary dilatation	Rare	-	1 (0.09)	-
Skin and subcutaneous tissue disorders	Alopecia	Common	Common	50 (4.49)	7 (2.85)
	Dry skin	Common	Common	19 (1.71)	3 (1.22)
	Pruritus	Common	Uncommon	19 (1.71)	2 (0.81)
	Rash	Common	Uncommon	22 (1.97)	2 (0.81)
	Nail disorder	Uncommon	Uncommon	6 (0.54)	2 (0.81)
	Palmar-plantar erythrodysaesthesia syndrome[c]	Uncommon	Uncommon	11 (0.99)	2 (0.81)
	Acne	Uncommon	-	3 (0.27)	-
	Hyperhidrosis	Uncommon	-	6 (0.54)	-
	Urticaria	Uncommon	-	2 (0.18)	-
	Blister	Rare	-	1 (0.09)	-
	Erythema	Rare	-	1 (0.09)	-
	Photosensitivity reaction	Rare	-	1 (0.09)	-
	Skin exfoliation	Rare	-	1 (0.09)	-
Musculoskeletal and connective tissue disorders	Arthralgia	Uncommon	Common	5 (0.45)	4 (1.63)
	Myalgia	Uncommon	Common	4 (0.36)	3 (1.22)
	Muscular weakness	Uncommon	Uncommon	2 (0.18)	1 (0.41)
	Pain in extremity	Uncommon	Uncommon	3 (0.27)	1 (0.41)
	Bone pain	Uncommon	-	2 (0.18)	-
	Limb discomfort	Uncommon	-	2 (0.18)	-
	Muscle spasms	Uncommon	-	2 (0.18)	-
	Joint swelling	Rare	-	1 (0.09)	-
Renal and urinary disorders	Proteinuria	Common	Uncommon	16 (1.44)	1 (0.41)

	Renal failure	Uncommon	-	3 (0.27)	-
	Haematuria	Uncommon	-	4 (0.36)	-
	Micturition disorder	Uncommon	-	5 (0.45)	-
	Cystitis noninfective	Rare	-	1 (0.09)	-
	Leukocyturia	Rare	-	1 (0.09)	-
Reproductive system and breast disorders	Menstrual disorder	Rare	Uncommon	1 (0.09)	1 (0.41)
General disorders and administration site conditions	Fatigue	Very common	Very common	343 (30.79)	86 (34.96)
	Pyrexia	Common	Uncommon	40 (3.59)	1 (0.41)
	Mucosal inflammation	Common	Uncommon	34 (3.05)	2 (0.81)
	Malaise	Common	-	28 (2.51)	-
	Oedema	Common	-	17 (1.53)	-
	General physical health deterioration	Uncommon	-	3 (0.27)	-
	Pain	Uncommon	Uncommon	6 (0.54)	1 (0.41)
	Feeling of body temperature change	Uncommon	-	7 (0.63)	-
	Xerosis	Rare	-	1 (0.09)	-
Investigations	Weight decreased	Common	Common	28 (2.51)	8 (3.25)
	Hepatic enzyme increased	Common	Common	36 (3.23)	11 (4.47)
	Blood alkaline phosphatase increased	Common	Uncommon	20 (1.80)	2 (0.81)
	Blood lactate dehydrogenase increased	Uncommon	-	4 (0.36)	-
	C-reactive protein increased	Uncommon	-	2 (0.18)	-
	Blood creatinine increased	Uncommon	-	10 (0.90)	-
	Blood urea increased	Uncommon	-	8 (0.72)	-
	Haematocrit decreased	Uncommon	-	3 (0.27)	-
	International normalised ratio increased	Uncommon	-	2 (0.18)	-
	Activated partial thromboplastin time prolonged	Rare	-	1 (0.09)	-
	Electrocardiogram QT prolonged	Rare	-	1 (0.09)	-
	Protein total decreased	Rare	-	1 (0.09)	-

[a] Different MedDRA preferred terms that were considered clinically similar have been grouped into a single term.
[b] Fatal cases have been reported.
[c] Hand-foot skin reaction.
Treatment-related EAE include sponsor upgrade

Laboratory findings

Emergent severe abnormal biochemical parameters occurring in ≥ 5% of patients while on treatment were observed for high bilirubin with identical incidence in the two treatment groups (5.8%), including Grade 4 of 1.7% in both groups (Table 23).

Table 23 Biochemical parameters - Counts of patients with emergent severe abnormal values (Grade 3 or 4) on treatment in the Safety Set (N = 492)

	Worst post-baseline CTCAE Grade							
	FTP/TPI + Bev (N = 246)				FTP/TPI (N = 246)			
Parameter (Unit)	Na	GRADE 3	GRADE 4	ALL	Na		GRADE 3	GRADE 4	ALL
High ALP (IU/L)	242 n (%)	2* (0.8)	-	2* (0.8)	241	n (%)	3* (1.2)	-	3* (1.2)
High ALAT (IU/L)	242 n (%)	8* (3.3)	-	8* (3.3)	241	n (%)	1* (0.4)	-	1* (0.4)
High ASAT(IU/L)	242 n (%)	5* (2.1)	-	5* (2.1)	241	n (%)	3* (1.2)	-	3* (1.2)

Parameter (Unit)	Worst post-baseline CTCAE Grade								
	FTP/TPI + Bev (N = 246)				FTP/TPI (N = 246)				
	Nª		GRADE 3	GRADE 4	ALL	Nª		GRADE 3	GRADE 4	ALL
High Bilirubin (µmol/L)	242	n (%)	10* (4.1)	4* (1.7)	14* (5.8)	241	n (%)	10* (4.1)	4* (1.7)	14* (5.8)
High Creatinine (µmol/L)	242	n (%)	2 (0.8)	-	2 (0.8)	241	n (%)	-	-	-
High GGT (IU/L)	239	n (%)	7* (2.9)	-	7* (2.9)	238	n (%)	10* (4.2)	1* (0.4)	11* (4.6)
High Magnesium (mmol/L)	242	n (%)	2 (0.8)	-	2 (0.8)	241	n (%)	1 (0.4)	-	1 (0.4)
High Sodium (mmol/L)	242	n (%)	-	1 (0.4)	1 (0.4)	242	n (%)	-	-	-
Low Albumin (g/L)	242	n (%)	-	-	-	242	n (%)	2 (0.8)	-	2 (0.8)
Low Glucose (mmol/L)	242	n (%)	1 (0.4)	-	1 (0.4)	242	n (%)	1 (0.4)	1 (0.4)	2 (0.8)
Low Potassium (mmol/L)	242	n (%)	2 (0.8)	-	2 (0.8)	242	n (%)	5 (2.1)	1 (0.4)	6 (2.5)
Low Sodium (mmol/L)	242	n (%)	4 (1.7)	1 (0.4)	5 (2.1)	242	n (%)	6 (2.5)	2 (0.8)	8 (3.3)

n: number of patients switching from Grade < 3 or missing (*) at baseline to Grade 3 or 4 post-baseline
Nª: number of patients with at least one post-baseline value on treatment
*%: [n (including *)/Nª]*100*

For creatinine clearance, treatment-emergent moderate impairment was detected in 11.6% of patients in the FTD/TPI + Bev group vs 13.2% in the FTD/TPI group, and severe impairment in 2 patients 0.8% vs 1 patient, 0.4%, respectively

Haematological parameters rated according to the CTCAE grading

Counts of patients with treatment emergent severe abnormal values (Grade 3 or 4) for haematological parameters are presented in Table 24.

Table 24 Haematological parameters - Counts of patients with emergent severe abnormal values (Grade 3 or 4) on treatment in the Safety Set (N = 492)

Parameter (Unit)	Worst post-baseline CTCAE Grade									
	FTP/TPI + Bev (N = 246)					FTP/TPI (N = 246)				
	Nª		GRADE 3	GRADE 4	ALL	Nª		GRADE 3	GRADE 4	ALL
Low Hemoglobin (g/L)	242	n (%)	13 (5.4)	-	13 (5.4)	240	n (%)	27 (11.3)	-	27 (11.3)
Low Lymphocytes (10^9/L)	242	n (%)	30 (12.4)	1 (0.4)	31 (12.8)	241	n (%)	25 (10.4)	3 + 1° (1.7)	28 + 1° (12.0)
Low Neutrophils (10^9/L)	242	n (%)	81 (33.5)	44 (18.2)	125 (51.7)	241	n (%)	64 (26.6)	29 (12.0)	93 (38.6)
Low Platelets (10^9/L)	242	n (%)	7 (2.9)	3 (1.2)	10 (4.1)	241	n (%)	2 (0.8)	-	2 (0.8)
Low Leukocytes (10^9/L)	242	n (%)	47 (19.4)	4 (1.7)	51 (21.1)	241	n (%)	30 (12.4)	3 (1.2)	33 (13.7)

n: number of patients switching from Grade < 3 or (°) switching from Grade 3 at baseline to Grade 4 post-baseline
Nª: number of patients with at least one post-baseline value on treatment
*%: [n (including °)/Nª]*100*

Previous radiotherapy was given to 38 out of 246 patients (15.4%) in the FTP/TPI + Bev arm and to 51 out of 246 patients (20.7%) in the FTP/TPI arm. The incidence of overall haematological and

myelosuppression-related adverse reactions for patients who received prior radiotherapy compared to patients without prior radiotherapy was 73.7% versus 77.4% in the FTP/TPI + Bev arm and 64.7% versus 67.7% in the FTP/TPI arm, respectively.

Safety in special populations

Age

A summary of EAEs is provided for patients < 65 years and ≥ 65 years and by treatment group in Table 25. Differences ≥ 10% between the subgroups < 65 years and ≥ 65 years for overall EAEs and by category are as follows:

- In the FTD/TPI group, severe EAEs were of higher frequency for patients ≥ 65 years (76.1%) than patients < 65 years (63.6%), also for treatment-related severe EAEs (53.0% vs 38.8%, respectively).

- In the FTD/TPI + Bev group, serious EAEs were more frequent for patients ≥ 65 years (31.0%) than patients < 65 years (20.5%).

Neutropenia occurred more frequently in patients ≥ 65 years than for patients < 65 years in both treatment groups: 68.0% vs 58.2%, respectively, in FTD/TPI + Bev group; 56.4% and 46.5%, respectively, in FTD/TPI group. A similar trend was observed for severe neutropenia: 51.0% vs 37.7%, respectively, in FTD/TPI + Bev group; 40.2% and 24.8%, respectively, in FTD/TPI group. Nausea was more frequent in patients < 65 vs ≥ 65 years in both treatment groups (41.1% vs 31.0%, respectively, in the FTD/TPI + Bev group; 33.3% vs 20.5%, respectively, in FTD/TPI group).

Table 25 Summary of EAEs by age subgroups in the Safety Set (N = 492)

		< 65 years		≥ 65 years	
		FTD/TPI + Bev (N = 146)	FTD/TPI (N = 129)	FTD/TPI + Bev (N = 100)	FTD/TPI (N = 117)
Patients who reported at least one:					
EAE	n (%)	97.3	97.7	99.0	98.3
Treatment-related EAE	n (%)	88.4	82.9	94.0	79.5
Severe (Grade ≥ 3) EAE	n (%)	69.2	63.6	77.0	76.1
Treatment-related severe EAE	n (%)	55.5	38.8	64.0	53.0
Serious EAE	n (%)	20.5	31.0	31.0	31.6
Treatment-related serious EAE	n (%)	3.4	5.4	8.0	11.1

Based on pooled data from monotherapy studies, patients 65 years of age or older who received Lonsurf as monotherapy (n=1114) had a higher incidence (≥ 5%) of the following treatment-related adverse events compared to patients younger than 65 years: neutropenia (58.9% vs 48.2%), severe neutropenia (41.3% vs 27.9%), anaemia (36.5% vs 25.2%), severe anaemia (14.1% vs 8.9%), decreased appetite (22.6% vs 17.4%), and thrombocytopenia (21.4% vs 12.1%).
When Lonsurf is used in combination with bevacizumab (n=246), patients 65 years of age or older had a higher incidence (≥ 5%) of the following treatment-related adverse events compared to patients younger than 65 years: neutropenia (75.0% vs 65.1%), severe neutropenia (57.0% vs 41.8%), fatigue (39.0% vs 32.2%), thrombocytopenia (28.0% vs 20.5%), and stomatitis (14.0% vs 8.9%).

Gender

A summary of EAEs is provided for male and female patients and by treatment group in Table 26.

There were no differences ≥ 10% between subgroups of male and female patients for overall EAEs and by category. Of note, nausea occurred at ≥ 10% higher frequency in females (45.2%) than in males (28.7%) in the FTD/TPI + Bev group.

Table 26 Summary of EAEs by sex subgroups in the Safety Set (N = 492)

		Male		Female	
		FTD/TPI + Bev (N = 122)	FTD/TPI (N = 134)	FTD/TPI + Bev (N = 124)	FTD/TPI (N = 112)
Patients who reported at least one:					
EAE	n (%)	97.5	98.5	98.4	97.3
Treatment-related EAE	n (%)	87.7	79.9	93.5	83.0
Severe (Grade ≥ 3) EAE	n (%)	71.3	70.1	73.4	68.8
Treatment-related severe EAE	n (%)	55.7	45.5	62.1	45.5
Serious EAE	n (%)	23.8	33.6	25.8	28.6
Treatment-related serious EAE	n (%)	4.9	9.0	5.6	7.1

ECOG PS at baseline

There were no differences of ≥ 10% between the subgroups of patients with ECOG PS = 0 and ECOG PS ≥ 1 for overall EAEs and by category, except a higher frequency of serious EAEs for patients with ECOG PS ≥ 1 than for patients with ECOG PS = 0 in both groups (29.9% vs 19.3% in FTD/TPI + Bev group; 36.4% vs 24.5% in the FTD/TPI group).

Creatinine clearance at baseline

Patients were required to have a creatinine clearance ≥ 50 mL/min assessed using the Cockcroft & Gault formula for inclusion. Analyses were performed for patients with baseline CrCl < 60 mL/min and CrCl ≥ 60 mL/min. 30 patients in the FTD/TPI + Bev group and 28 patients in the FTD/TPI group had a CrCl < 60 mL/min. A summary of EAEs is provided for patients with baseline CrCl < 60 mL/min and CrCl ≥ 60 mL/min and by treatment group is shown in Table 27.

Table 27 Summary of EAEs by baseline creatinine clearance subgroups in the Safety Set (N = 492)

		CrCl < 60 mL/min		CrCl ≥ 60 mL/min	
		FTD/TPI + Bev (N = 30)	FTD/TPI (N = 28)	FTD/TPI + Bev (N = 215)	FTD/TPI (N = 218)
Patients who reported at least one:					
EAE	n (%)	100	100	97.7	97.7
Treatment-related EAE	n (%)	96.7	89.3	89.8	80.3
Severe (Grade ≥ 3) EAE	n (%)	73.3	89.3	72.1	67.0
Treatment-related severe EAE	n (%)	60.0	71.4	58.6	42.2

Serious EAE	n (%)	40.0	28.6	22.8	31.7
Treatment-related serious EAE	n (%)	10.0	14.3	4.7	7.3

CrCl: creatinine clearance

There was a ≥ 10% higher frequency of the following EAEs for patients with baseline CrCl < 60 mL/min than for patients with baseline CrCl ≥ 60 mL/min:

- In both groups for anaemia: 43.3% vs 27.0%, respectively, in FTD/TPI + Bev group; 42.9% vs 30.3%, respectively, in FTD/TPI group.
- In FTD/TPI + Bev group for decreased appetite (43.3% vs 17.2% respectively), asthenia (40.0% vs 22.3%, respectively), abdominal pain (23.3% vs 10.2%, respectively), neutrophil count decreased (23.3% vs 12.6%, respectively).

On the contrary, there was a ≥ 10% lower frequency for patients with baseline CrCl < 60 mL/min than for patients with baseline CrCl ≥ 60 mL/min in the FTD/TPI + Bev group for neutropenia (50.0% vs 63.7%, respectively) and nausea (26.7% vs 38.6%, respectively).

Safety related to drug-drug interactions and other interactions

No update to the previously submitted material has been provided.

Discontinuation due to adverse events

EAEs leading to treatment withdrawal and EAEs leading to treatment modification are summarised by treatment groups in Table 15 and Table 28.

Table 28 Summary of emergent adverse events leading to treatment withdrawal

	FTD/TPI + Bev (N = 246)		FTD/TPI (N = 246)	
	n	**%**	**n**	**%**
Patients with at least one EAE leading to:				
Treatment withdrawal[1]	31	12.6	31	12.6
Treatment delayed[2]	167	67.9	147	59.8
Dose reduction[3]	18	7.3	20	8.1
Treatment delayed and dose reduced	31	12.6	11	4.5
Temporary interruption[4]	27	11.0	21	8.5

Percentages are based on N

1: FTD/TPI withdrawal; 2: FTD/TPI delay of cycle initiation; 3: dose of FTD/TPI; 4: FTD/TPI intra-cycle interruption

EAEs leading to treatment withdrawal

For patients who received the combination of FTD/TPI plus bevacizumab, when an event led to FTD/TPI withdrawal, bevacizumab also had to be withdrawn (bevacizumab monotherapy was not allowed); in this summary, EAEs leading to treatment withdrawal are those leading to FTD/TPI withdrawal.

EAEs leading to treatment withdrawal were reported with the same frequency in both treatment groups (12.6%). These EAEs that occurred in more than 1 patient in either group were asthenia (3.3% in the FTD/TPI + Bev group vs 0.4% in the FTD/TPI group), or jaundice, decreased appetite, biliary dilatation, blood bilirubin increased, pain, anaemia, intestinal obstruction, malignant neoplasm progression, metastases to central nervous system and fatigue (each at a frequency of ≤ 0.8% in either group).

Of note: EAEs leading to bevacizumab withdrawal were reported for 14.6% of patients in the FTD/TPI + Bev group. These EAEs that occurred in more than 1 patient were asthenia (3.3%), pain, biliary dilatation, jaundice, blood bilirubin increased, decreased appetite, proteinuria and pulmonary embolism, each at frequency of 0.8%

EAEs leading to treatment modification

Overall, the most common EAEs leading to FTD/TPI treatment modification (delay, dose reduction or interruption) with the combination of FTD/TPI plus bevacizumab were either myelosuppressive events or, at a lower frequency, gastrointestinal disorders. Regarding incidence of those events leading to FTD/TPI treatment modification, between-group differences observed were ≤ 10%.

In the FTD/TPI + Bev group, incidence of EAEs leading to bevacizumab temporary interruption was 26.0%. The incidence of EAEs leading to bevacizumab treatment delay was 69.9%. As per study protocol, bevacizumab was not allowed to be administered alone in case of FTD/TPI dose delay. Consequently, the latter incidence of EAEs leading to bevacizumab treatment delay is consistent with the incidence of EAEs leading to FTD/TPI treatment delayed of similar magnitude (67.9%).

Post marketing experience

The combination of FTD/TPI and bevacizumab is currently not approved for the treatment of refractory mCRC in any region.

2.5.1. Discussion on clinical safety

The randomised, open-label, controlled two-arm, Phase 3 SUNLIGHT study compared FTD/TPI + Bev to FTD/TPI monotherapy. The safety of the following dosing regimens is discussed:

- FTD/TPI + Bev group: FTD/TPI at 35 mg/m² orally twice a day (BID), 5 days on/2 days off, over 2 weeks, followed by a 14-day rest with bevacizumab (5 mg/kg, IV) administered every 2 weeks (Day 1 and Day 15). This treatment cycle was repeated every 4 weeks.
- FTD/TPI group: FTD/TPI at 35 mg/m² orally twice a day (BID), 5 days on/2 days off, over 2 weeks.

As of the clinical cut-off date, the mean ± SD (median) treatment duration was longer in the FTD/TPI + Bev group than in the FTD/TPI group: 6.1 ± 4.3 (5.0) months vs 3.4 ± 2.5 (2.1) months. In the FTD/TPI + Bev group, 15.8% of patients initiated > 10 cycles of treatment compared to 2.4% of patients in the FTD/TPI group. The mean ± SD (median) relative **dose intensity** of FTD/TPI was

similar in the FTD/TPI + Bev and FTD/TPI groups: 85.0 ± 13.2 (88.3%) vs 87.2 ± 14.2 (90.4%), respectively; it was 86.9 ± 27.3 (87.6%) for bevacizumab in the FTD/TPI + Bev group.

Editorial changes were introduced in the section 4.6 of the SmPC and section 2 of PL on fertility following the Safety Working Party (SWP) recommendations on the duration of contraception following the end of treatment with a genotoxic drug (EMA/CHMP/SWP/74077/2020 corr. 3). Patients who wish to conceive a child should be advised to seek reproductive counselling and cryo-conservation of either the ovum or sperm prior to starting Lonsurf treatment.

Almost all patients experienced at least one adverse event (AE) in the pivotal study. The **adverse events of special interest (AESI)** were the known adverse reactions associated with FTD/TPI or bevacizumab. The AESI for FTD/TPI were bone marrow suppression events, infections, gastrointestinal events. The AESI for bevacizumab were hypertension, gastrointestinal perforation, bleeding/haemorrhages, arterial/venous thromboembolic events, proteinuria and wound healing complication.

The **most frequent EAEs** (> 20% in either group) reported were generally myelosuppressive and gastrointestinal events: neutropenia (62.2% in the FTD/TPI + Bev group vs 51.2% in the FTD/TPI group), nausea (37.0% vs 27.2%), anaemia (28.9% vs 31.7%), asthenia (24.2% vs 22.4%), fatigue (21.5% vs 16.3%), diarrhoea (20.7% vs 18.7%) and decrease appetite (20.3% vs 15.4%). Among those EAEs, the frequencies were similar in the two treatment groups, except for neutropenia, nausea and fatigue that occurred at higher frequencies in the FTD/TPI + Bev group (between-group difference > 5%). The safety profile of the combination FTD/TPI with bevacizumab was generally consistent with that of FTD/TPI monotherapy, except for an increased incidence of neutropenia events compared to FTD/TPI monotherapy, and with the of known safety profile of bevacizumab. The incidence of hypertension (as preferred term [PT]) was notably higher in the FTD/TPI + Bev (10.2%) than in the FTD/TPI group (2%).

Incidences of infection events did not show relevant between-group differences, neither for overall infection events (between-group difference < 10%: 30.9% in the FTD/TPI + Bev group vs 23.2% in the FTD/TPI group) nor for the EAE categories (between-group difference < 5%).

The percentage of patients who experienced **severe (Grade ≥ 3) EAEs** was similar in the FTD/TPI + Bev and FTD/TPI groups: 72.4% vs 69.5%. The most frequent (> 10% in either group) severe EAEs were neutropenia, which occurred at higher frequency in the FTD/TPI + Bev group (43.1% vs 32.1% in the FTD/TPI group) and anaemia, which occurred at lower frequency in the FTD/TPI + Bev group (6.1% vs 11.0% in the FTD/TPI group).

The percentage of patients who experienced at least one **treatment-related EAE** was higher in the FTD/TPI + Bev group than in the FTD/TPI group: 90.7% vs 81.3%. The most frequent (> 20 % in either group) treatment-related EAEs were neutropenia, nausea and anaemia. Among those EAEs, neutropenia and nausea occurred at higher (between-group difference > 5%) frequency in the FTD/TPI + Bev group than in the FTD/TPI group (neutropenia: 60.2% vs 48.4%; nausea: 33.3% vs 20.7%) and anaemia occurred with similar frequency in the two treatment groups (23.6% vs 25.2%).

The percentage of patients who experienced **severe treatment-related EAEs** was higher in the FTD/TPI + Bev than FTD/TPI group: 58.9% vs 45.5%. The most frequent (> 5% in either group) severe treatment-related EAEs reported with > 2% between-group differences were neutropenia and neutrophil count decreased that occurred a higher frequency in the FTD/TPI + Bev group, and anaemia that occurred at lower frequency in the FTD/TPI + Bev group.

The percentage of patients who experienced at least one **serious EAE (SEAE)** was lower in the FTD/TPI + Bev group than the FTD/TPI group (24.8% vs 31.3%). **Treatment-related SEAEs** were reported for 13 patients (5.3%) in the FTD/TPI + Bev group and 20 (8.1%) in the FTD/TPI group.

Among other severe treatment-related EAEs, hypertension was reported with > 2% between-group difference: 4.1% in the FTD/TPI + Bev group while not reported in the FTD/TPI group; all those hypertension events were related to bevacizumab only, except 1 related both to FTD/TPI and bevacizumab. This was consistent with the known adverse reactions of bevacizumab.

Fatal EAEs occurred during the treatment period, but the resulting death could have occurred during either treatment period or follow-up period. The percentage of patients who experienced at least one fatal EAE (regardless of whether death occurred during treatment or follow-up period) was lower in the FTD/TPI + Bev group than in the FTD/TPI group: 5.3% vs 11.0%. Deaths which resulted from fatal EAEs were predominantly due to disease progression. None of the deaths were treatment-related in either treatment group.

Analysis of common EAEs indicated no unexpected safety signal. The safety profile of the combination FTD/TPI with bevacizumab was generally consistent with that of FTD/TPI monotherapy, except for an increased incidence of neutropenia events compared to FTD/TPI monotherapy. According to the study protocol hematologic support was based on the institutional site standards. The SmPC of FTD/TPI contains adequate precautions for use regarding the monitoring and treatment of **bone marrow suppression**. Serious infections have been reported following treatment with FTD/TPI. Given that the majority were reported in the context of bone marrow suppression, the patient's condition should be monitored closely, and appropriate measures, such as antimicrobial agents and granulocyte-colony stimulating factor (G-CSF), should be administered as clinically indicated (Lonsurf SmPC).

Severe EAEs were of higher frequency for **patients ≥ 65 years** (76.1%) than patients < 65 years (63.6%), also for treatment-related severe EAEs (53.0% vs 38.8%, respectively) in the FTD/TPI group. In the FTD/TPI + Bev group, serious EAEs were also more frequent for patients ≥ 65 years (31.0%) than patients < 65 years (20.5%).
There were no differences of ≥ 10% between the subgroups of patients with **ECOG PS** = 0 and ECOG PS ≥ 1 for overall EAEs and by category, except a higher frequency of serious EAEs for patients with ECOG PS ≥ 1 than for patients with ECOG PS = 0 in both groups (29.9% vs 19.3% in FTD/TPI + Bev group; 36.4% vs 24.5% in the FTD/TPI group).
Patients were required to have a **creatinine clearance** ≥ 50 mL/min for inclusion in SUNLIGHT and there were 30 patients in the FTD/TPI + Bev group and 28 patients in the FTD/TPI group with a CrCl 50 to 60 mL/min. An overall increase in toxicity seems apparent in both treatment arms for patients with baseline CrCl < 60 mL/min compared with patients with baseline CrCl ≥ 60 mL/min. Plus, for some EAEs there was a ≥ 10% higher frequency for patients with baseline CrCl < 60 mL/min than for patients with baseline CrCl ≥ 60 mL/min. However, due to small size of the subgroup with baseline CrCl < 60 mL/min for each treatment group, the between-subgroup differences should be interpreted with caution. The SmPC does not include specific recommendations for the starting dose of the combination of FTD/TPI + Bev in patients with renal impairment. According to the already included information in section 4.2 of the Lonsurf SmPC, no adjustment of the FTD/TPI starting dose is recommended in patients with moderate renal impairment (CrCl 30 to 59 mL/min) and a reduced starting dose of FTD/TPI is recommended for patients with severe renal impairment (CrCl 15 to 29 mL/min). These recommendations are considered acceptable. Of note, the safety and efficacy of bevacizumab have not been studied in patients with renal impairment (Avastin SmPC).

EAE leading to **discontinuation** of FTD/TPI occurred in 12.6% of patients in both groups. Monotherapy with bevacizumab was not allowed. EAE leading to bevacizumab withdrawal occurred in 14.6% of the patients. EAE leading to FTD/TPI treatment delay were slightly higher for FTF/TPI + Bev

(67.9%) than for FTF/TPI (59.8%). EAE leading to FTD/TPI dose reduction occurred in 7.3% and 8.1% of the patients.

2.5.2. Conclusions on clinical safety

Adding bevacizumab to trifluridine/tipiracil resulted in limited additional toxicity. The overall safety profile of trifluridine/tipiracil in combination with bevacizumab did not result in unexpected safety findings compared to what is already known from the safety profiles of trifluridine/tipiracil or bevacizumab as monotherapy. The most frequent treatment-related EAEs (> 20% in either group) were myelosuppression (neutropenia, anaemia) and gastrointestinal (nausea) events with higher frequency in the FTD/TPI + Bev group vs FTD/TPI group for neutropenia and nausea. Treatment related hypertension was reported for 7.3% of patients treated with the combination FTD/TPI plus bevacizumab.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an 10 RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 10 is acceptable.

The CHMP endorsed the Risk Management Plan version 10.
No changes were proposed in Module SVIII – Summary of the safety concerns or in Part V. Risk minimisation measures.

Safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Safety in patients with moderate or severe renal impairment
Important potential risks	Developmental toxicity/Use in pregnant women
Missing information	Use in patients in worse condition than ECOG 0-1.

No changes were proposed as part of the summary of the safety concerns.

Pharmacovigilance plan

Table Part III.1: On-going and planned additional pharmacovigilance activities

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 3 – Required additional pharmacovigilance activities				
DIM-95005-001 (PROMETCO-EUPAS33865) – A Real World Evidence Prospective Cohort Study in the Management of Metastatic Colorectal Cancer: A Clinical and Patient Perspective On-going	Provide real world data on treatment patterns, associated effectiveness and safety, and impact on patients with mCRC after two disease progressions. **The study might further characterise the safety profile of Lonsurf with respect to the area of missing information "Use in patients in worse condition than ECOG 0-1".**	Use in patients in a worse condition than ECOG 0-1	Final report	September 2024

Part IV: Plans for post-authorisation efficacy studies
Not applicable

An editorial change (highlighted) was made in Part III Pharmacovigilance plan.

Risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Safety in patients with moderate or severe renal impairment.	Routine risk minimisation measures: SmPC sections 4.2 , 4.4 Legal status Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Developmental toxicity/Use in pregnant women	Routine risk minimisation measures: SmPC section 4.6 PL section 2 Legal status Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Use in patients in a worse condition than ECOG 0-1	Routine risk minimisation measures: None Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study DIM-95005-001 (PROMETCO)

The existing Risk Minimisation Measures remain sufficient to address the risks of Trifluridine/Tipiracil. No changes were proposed in Part V. of the Risk minimisation measures as part of this extension of indication.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.6, 4.8, 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

"Lonsurf is indicated in combination with bevacizumab for the treatment of adult patients with metastatic colorectal cancer (CRC) who have received two prior anticancer treatment regimens including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and/or anti-EGFR agents.".

The proposed posology for both components is in line with their approved posology (Lonsurf SmPC; Avastin SmPC).

The recommended starting dose of Lonsurf in adults, as monotherapy or in combination with bevacizumab, is 35 mg/m2/dose administered orally twice daily on Days 1 to 5 and Days 8 to 12 of each 28-day cycle until disease progression or unacceptable toxicity.

When Lonsurf is used in combination with bevacizumab for the treatment of metastatic CRC, the dose of bevacizumab is 5 mg/kg of body weight given once every 2 weeks.

3.1.2. Available therapies and unmet medical need

In patients with mCRC, chemotherapy is the mainstay of treatment with the goal of prolonging overall survival. Standard treatments include (combinations of) a fluoropyrimidine, oxaliplatin, irinotecan, and as applicable, anti-VEGF and/or anti-EGFR antibodies. Following progression after treatment with these standard chemotherapies the estimated OS with best supportive care alone is around 5 months. Treatments with limited efficacy in this third-line setting include regorafenib (a multitargeted tyrosine kinase inhibitor), FTD/TPI monotherapy, and for specific subgroups of patients, antibodies that target EGFR for patients with RAS wild-type tumours (if no prior exposure), and anti-programmed cell death protein 1 inhibitors for patients with microsatellite instability-high mCRC (Cervantes, 2022; NCCN, 2019; NCCN, 2021) (Baldus, 2010).

3.1.3. Main clinical study

The efficacy and safety data for the current application come from the single pivotal trial CL3-95005-007 or SUNLIGHT (NCT04737187). This was a multinational, open-label, two-arm, randomized phase 3 study comparing treatment with FTD/TPI in combination with bevacizumab to FTD/TPI monotherapy in patients with refractory mCRC.

The included patient population had an ECOG-PS of 0 or 1, and had to have received a maximum of two chemotherapy regimens, including the standard available treatments including a fluoropyrimidine, oxaliplatin, irinotecan and a monoclonal antibody targeting either VEGF or EGFR (for patients with a KRAS-wildtype tumour).

The primary endpoint of the pivotal study was overall survival, the key secondary endpoint was investigator-assessed PFS.

3.2. Favourable effects

Median OS was 3.3 months longer with the addition of bevacizumab to FTD/TPI chemotherapy (10.8 versus 7.5 months). This was a statistically significant difference, with a HR of 0.61 (95% CI: 0.49 - 0.77) and a p<0.001 by stratified log-rank test, which was lower than the target p-value (p<0.025) that was pre-specified to reach statistical significance.
With 60.2% of events (deaths) in the FTD/TPI + Bev group and 74.4% in the FTD/TPI group, OS data can be considered mature.
Two sensitivity analyses for OS showed results consistent with the primary analysis. Further. the subgroup analysis for OS does not raise any concerns regarding a possible lack of effect in certain subgroups of patients, including the subgroup of patients that were previously treated with the VEGF-inhibitor bevacizumab (72% of patients).

Median investigator-assessed PFS was 3.2 months longer with the addition of bevacizumab to FTD/TPI chemotherapy (5.6 versus 2.4 months). This was a statistically significant difference, with a HR of 0.44 (95% CI: 0.36 -0.54) and a p<0.001 by stratified log-rank test, which was lower than the target p-value (p<0.025) for statistical significance.

3.3. Uncertainties and limitations about favourable effects

The patient population for the SUNLIGHT study consisted of relatively fit patients, reflected by an ECOG-PS of 0 or 1, the ability to have received all available standard treatment options for advanced CRC in the first and second line and the absence of significant comorbidity. Patients with moderate and severe renal impairment were excluded from the trial, i.e. the eGFR as estimated by the Cockcroft-Gault equation had to be ≥50 ml/min. It is uncertain whether the reported OS benefit can be extrapolated to less fit patients with comorbidity. These limitations have been reflected in the SmPC.

The pivotal study was open label. The fact that treating physicians were aware of the assigned treatment arm, could influence their response assessments and timing of declaring clinical or radiological disease progression. In addition, for PFS the decision to censor patients lost to follow up or without a post-baseline tumour assessment may lead to informative censoring. Because of these problems, the additional estimand approach for PFS, in which clinical progression and administration of further anti-cancer therapies are counted as events, is considered to be of relevance. This additional analysis shows the same hazard ratio and almost the same estimates for median PFS as the primary analysis.

3.4. Unfavourable effects

The incidence of AEs in the different AE categories for FTD/TPI + Bev vs FTD/TPI were: any EAE 98.0% vs 98.0%; TREAE 90.7% vs 81.3%; grade 3 EAE≥72.4% vs 69.5%; severe treatment-related EAEs 58.9% vs 45.5%; SEAE 24.8% vs. 31.3%; TSEAEs 5.3% vs. 8.1%; EAEs leading to treatment withdrawal 12.6% vs 12.6% EAE leading to death 5.3% vs 11.0%. None of the deaths were considered treatment-related in either treatment group.

The most frequently observed AEs for FTD/TPI + Bev were: neutropenia (62.2%), nausea (37.0%), anaemia (28.9%), asthenia (24.4%), fatigue (21.5%), and diarrhoea (20.7%).

The frequencies of neutropenia (all grade: 62.2% vs 51.2%; grade ≥3 43.1% vs 32.1%), nausea (37.0% vs 27.2%) and fatigue (21.5% vs 16.3%) were higher in the FTD/TPI + Bev than in the FTD/TPI group, respectively.

The frequency of all grade hypertension was higher in the FTD/TPI + Bev than in the FTD/TPI group 10.2% vs 2% (5.7% vs. 1.2% grade ≥3).

An overall increase in toxicity seems apparent in both treatment arms for patients with baseline CrCl < 60 mL/min compared with patients with baseline CrCl ≥ 60 mL/min. Plus, for some EAEs there was a ≥ 10% higher frequency for patients with baseline CrCl < 60 mL/min than for patients with baseline CrCl ≥ 60 mL/min.

There were no unexpected safety findings compared to the known safety profiles of trifluridine/tipiracil and bevacizumab.

3.5. Uncertainties and limitations about unfavourable effects

Not applicable.

3.6. Effects Table

Table 29 Effects Table for Lonsurf + bevacizumab for treatment of adult patients with metastatic colorectal cancer who have received two prior anticancer treatment regimens (data cut-off: 19 July 2022)

Effect	Short description	Unit	Treatment FTD/TPI + Bev (n=246)	Control FTD/TPI (n=246)	Uncertainties / Strength of evidence	References
Favourable Effects						
Overall survival		Median, months (95% CI)	10.8 (9.36-11.83) Hazard ratio (95% CI) 0.61 (0.49-0.77) p<0.001 (1-sided)	7.5 (6.34-8.57)	Uncertainties: Study population was fit and highly selected. Strength: Mature data. Two sensitivity analyses for OS showed results consistent with primary analysis.	*Table 8*
Progression-free survival	Assessed by investigator	Median, months (95% CI)	5.6 (4.50-5.88) Hazard ratio (95% CI) 0.44 (0.36-0.54) p<0.001 (1-sided)	2.4 (2.07-3.22)	Uncertainties: Open-label design and possible informative censoring. Strength: Additional estimand approach for PFS shows results consistent with primary analysis.	*Table 9*
Unfavourable Effects						
Grade ≥3 EAE		%	72.4	69.5		Table 15

Effect	Short description	Unit	Treatment FTD/TPI + Bev (n=246)	Control FTD/TPI (n=246)	Uncertainties / Strength of evidence	References
Serious treatment-related EAE		%	5.3	8.1		Table 15
Neutropenia	All grade (Grade ≥ 3)	%	62.2 (43.1)	51.2 (32.1)		Table 16
Hypertension	All grade (Grade ≥ 3)	%	10.2 (5.7)	2 (1.2)		Table 16

Abbreviations: CI: confidence interval; DCO: data cut-off; EAE: emergent adverse event; HR: hazard ratio; OS: overall survival; PFS: progression-free survival

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The patient population for the SUNLIGHT study consisted of relatively fit patients, reflected by an ECOG-PS of 0 or 1, the ability to have received all available standard treatment options for advanced CRC and the absence of significant comorbidity. Nevertheless, in the target patient population the observed 3.3-month difference in median OS (10.8 versus 7.5 months) can be considered clinically relevant, because it concerns a last-line treatment setting without other relevant treatment options. The reported OS-benefit cannot be extrapolated to less fit patients with comorbidity, but the study population is adequately described in the SmPC.

The key secondary endpoint of investigator-assessed PFS provides support for the primary endpoint, with a median invPFS that was 3.2 months longer with the addition of bevacizumab to FTD/TPI chemotherapy (5.6 versus 2.4 months). Because of the open-label design of the trial, the additional estimand approach for PFS, in which clinical progression and administration of further anti-cancer therapies are counted as events, is considered to be of relevance. This additional analysis shows the same hazard ratio and almost the same estimates for median PFS as the primary analysis.

There were no unexpected safety findings in the assessment of emergent adverse events. The safety profile is consistent with the known safety profile of FTD/TPI monotherapy and bevacizumab.

3.7.2. Balance of benefits and risks

The observed benefit in overall survival of 3.3 months for the addition of bevacizumab to FTD/TPI chemotherapy in fit patients with refractory mCRC outweighs the risks. No unexpected safety findings of the combination were observed.

3.8. Conclusions

The overall B/R of Lonsurf is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of patients with refractory metastatic colorectal cancer for LONSURF in combination with bevacizumab based on results from study SUNLIGHT (CL3-95005-007); This is an open-label, randomised, phase III study comparing trifluridine/tipiracil in combination with bevacizumab to trifluridine/tipiracil monotherapy in patients with refractory metastatic colorectal cancer. As a consequence, sections 4.1, 4.2, 4.4, 4.8, and 5.1 of the SmPC. The package leaflet is updated in accordance. The updated RMP version 10 has also been submitted. In addition, the MAH took the opportunity to update section 4.6 of the SmPC and the Package leaflet accordingly.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion ‘Product Name-H-C-003897-II-0026

1.