Clinical trial results:
Prospective, Multicenter, Open-label Phase IV trial of Trifluridine/Tipiracil to Evaluate the Health-related Quality of Life in Patients with Metastatic Colorectal Cancer

Summary

EudraCT number	2017-000292-83
Trial protocol	DE
Global end of trial date	24 December 2020

Results information

Result version number	v1 (current)
This version publication date	11 January 2022
First version publication date	11 January 2022

Trial information

Trial identification

Sponsor protocol code	Tallisur

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Servier Deutschland GmbH
Sponsor organisation address	Elsenheimerstraße 53, München, Germany, 80687
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 July 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 December 2020
Global end of trial reached?	Yes
Global end of trial date	24 December 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of treatment with FTD/TPI on HRQoL as measured by EORTC QLQ-C30 (global health status/quality of life scale)

Protection of trial subjects:

The clinical study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and in accordance with the International Council on Harmonisation (ICH) guideline for good clinical practice (GCP).
The investigator obtained written informed consent of a patient prior to any study-related procedures including the documentation of results of clinical routine procedures for study purposes as set forth in the ICH-GCP guidelines and the respective European Union's and national legislation. Subjects had the right to withdraw consent at any time and without giving any reasons without prejudice to his or her future medical care by the investigator or other medical health care personnel at the institution. The investigator discussed with the subject the most appropriate way to withdraw to ensure the subject's health.

Background therapy:

Not applicable.

Evidence for comparator:

Not applicable. To evaluate the effect of treatment with trifluridine/tipiracil on quality of life, a controlled study with best supportive care (BSC) was chosen and considered appropriate comparative treatment according to the advice from the German Federal Joint Committee (G-BA) on 29 September 2016.

Actual start date of recruitment	22 September 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 195
Worldwide total number of subjects	195
EEA total number of subjects	195

Notes:

Subjects enrolled per age group

In utero	0

Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	76
From 65 to 84 years	116
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

The recruitment period of this clinical study lasted from 22 September 2017 (first patient registered) to 08 January 2019 (last patient registered). 202 patients were recruited to 44 study centres in Germany, 7 of which did not enter the treatment / close observation phase (2 deaths, 3 patient`s wish, 1 AE, 1 violation of selection criteria).

Pre-assignment

Screening details:

Adult patients with histologically or cytologically confirmed UICC stage IV carcinoma of the colon or rectum with metastatic colorectal cancer, at least one measurable or non-measurable lesion as defined by RECIST version 1.1, any ECOG performance status, previously treated with or not considered candidates for available therapies.

Period 1

Period 1 title	Overall period (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not applicable.

Arms

Are arms mutually exclusive?	Yes
Arm title	FTD/TPI (trifluridine/tipiracil)

Arm description:

FTD/TPI (starting dose 35 mg/m2 BSA/dose) was taken orally twice daily (BID) on Days 1 to 5 and Days 8 to 12 of each 28-day cycle as long as a benefit was observed or until unacceptable toxicity occurred.

Arm type	Experimental
Investigational medicinal product name	Trifluridine/tipiracil
Investigational medicinal product code	
Other name	Lonsurf (R)
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

The daily FTD/TPI dosage was calculated according to the body surface area (BSA). FTD/TPI (starting dose 35 mg/m2 BSA/dose) was taken orally twice daily (BID) on Days 1 to 5 and Days 8 to 12 of each 28-day cycle as long as a benefit was observed or until unacceptable toxicity occurred. The dosage was not allowed to exceed 80 mg per dose. In case of haematological or non-haematological toxicities, criteria for dose interruption and dose modification applied. A maximum of 3 dose reduction levels (30 mg/m2 BSA BID, 25 mg/m2 BSA BID, and 20 mg/m2 BSA BID) was permitted to a minimum dose of 20 mg/m2 BID.

Arm title	BSC (Best Supportive Care)

Arm description:

Best supportive care, tailored to the patient`s individual needs.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	FTD/TPI (trifluridine/tipiracil)	BSC (Best Supportive Care)
Started	186	9
Completed	0	0
Not completed	186	9
Disease progression (clinical)	23	-
Consent withdrawn by subject	12	1
Physician decision	6	-
Adverse event, non-fatal	25	1
Death	10	3
Patient non-compliance	1	-
Other / unknown	10	-
Lost to follow-up	2	1
Start of further anti-tumour therapy	-	2
Disease progression (RECIST 1.1)	95	1
Protocol deviation	2	-

Baseline characteristics

Reporting groups	
Reporting group title	FTD/TPI (trifluridine/tipiracil)
Reporting group description:	
FTD/TPI (starting dose 35 mg/m2 BSA/dose) was taken orally twice daily (BID) on Days 1 to 5 and Days 8 to 12 of each 28-day cycle as long as a benefit was observed or until unacceptable toxicity occurred.	
Reporting group title	BSC (Best Supportive Care)
Reporting group description:	
Best supportive care, tailored to the patient`s individual needs.	

Reporting group values	FTD/TPI (trifluridine/tipiracil)	BSC (Best Supportive Care)	Total
Number of subjects	186	9	195
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	74	2	76
From 65-84 years	109	7	116
85 years and over	3	0	3
Age continuous Units: years			
median	67.0	78.0	
full range (min-max)	40 to 88	54 to 82	-
Gender categorical Units: Subjects			
Female	69	4	73
Male	117	5	122
ECOG Performance Status Units: Subjects			
ECOG PS 0	72	0	72
ECOG PS 1	94	4	98
ECOG PS 2	18	3	21
ECOG PS 3	0	1	1
Unknown	2	1	3
Number of previouis therapy lines of mCRC			
Only systemic anticancer therapies; a new therapy was defined as administration of a substance that was not part of the preceding therapy line.			
Units: Subjects			
0 previous therapy lines	8	2	10
1 previous therapy line	23	1	24
2 previous therapy lines	71	3	74
3 previous therapy lines	49	0	49

≥ 4 previous therapy lines	35	3	38

Subject analysis sets	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
All enrolled patients who received at least one dose of FTD/TPI (Group A) or started the close observation period (Group B).	
Subject analysis set title	FAS-C30
Subject analysis set type	Full analysis
Subject analysis set description:	
FAS HR QoL subset 1: Patients of the FAS who answered the baseline and at least one additional EORTC QLQ-C30 questionnaire between start of FTD/TPI treatment (Group A) or the start of the close observation period (Group B) and the end of treatment/close observation.	
Subject analysis set title	FAS-EQ
Subject analysis set type	Full analysis
Subject analysis set description:	
FAS HR QoL subset 2: Patients of the FAS who answered the baseline and at least one additional EQ-5D-5L questionnaire between start of FTD/TPI treatment (Group A) or the start of the close observation period (Group B) and the end of treatment/close observation.	
Subject analysis set title	FAS-C30 (pe)
Subject analysis set type	Full analysis
Subject analysis set description:	
FAS-C30 evaluable for the primary endpoint (pe): a subset of the FAS-C30 comprising all patients who received at least two cycles of FTD/TPI and who completed the baseline EORTC-QLQ-C30 questionnaire and at least one more questionnaire AFTER Cycle 1 (i.e., the earliest within two days before Day 1 of Cycle 2).	
Subject analysis set title	Per protocol
Subject analysis set type	Per protocol
Subject analysis set description:	
All patients of the FAS/SAF without any relevant violation of selection criteria; moreover, patients from two centres were excluded from the PP due to inspection findings.	

Reporting group values	Full Analysis Set (FAS)	FAS-C30	FAS-EQ
Number of subjects	195	129	128
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)	76		
From 65-84 years	116		
85 years and over	3		
Age continuous Units: years			
median	67.0		

full range (min-max)	40 to 88		

Gender categorical Units: Subjects			
Female	73		
Male	122		
ECOG Performance Status Units: Subjects			
ECOG PS 0	72		
ECOG PS 1	98		
ECOG PS 2	21		
ECOG PS 3	1		
Unknown	3		
Number of previouis therapy lines of mCRC			
Only systemic anticancer therapies; a new therapy was defined as administration of a substance that was not part of the preceding therapy line.			
Units: Subjects			
0 previous therapy lines	10		
1 previous therapy line	24		
2 previous therapy lines	74		
3 previous therapy lines	49		
≥ 4 previous therapy lines	38		

Reporting group values	FAS-C30 (pe)	Per protocol	
Number of subjects	112	171	
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years median full range (min-max)			
Gender categorical Units: Subjects			
Female Male			
ECOG Performance Status Units: Subjects			
ECOG PS 0 ECOG PS 1			

ECOG PS 2 ECOG PS 3 Unknown			
Number of previouis therapy lines of mCRC			
Only systemic anticancer therapies; a new therapy was defined as administration of a substance that was not part of the preceding therapy line.			
Units: Subjects			
0 previous therapy lines 1 previous therapy line 2 previous therapy lines 3 previous therapy lines ≥ 4 previous therapy lines			

End points

End points reporting groups

Reporting group title	FTD/TPI (trifluridine/tipiracil)

Reporting group description:

FTD/TPI (starting dose 35 mg/m2 BSA/dose) was taken orally twice daily (BID) on Days 1 to 5 and Days 8 to 12 of each 28-day cycle as long as a benefit was observed or until unacceptable toxicity occurred.

Reporting group title	BSC (Best Supportive Care)

Reporting group description:

Best supportive care, tailored to the patient`s individual needs.

Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

All enrolled patients who received at least one dose of FTD/TPI (Group A) or started the close observation period (Group B).

Subject analysis set title	FAS-C30
Subject analysis set type	Full analysis

Subject analysis set description:

FAS HR QoL subset 1: Patients of the FAS who answered the baseline and at least one additional EORTC QLQ-C30 questionnaire between start of FTD/TPI treatment (Group A) or the start of the close observation period (Group B) and the end of treatment/close observation.

Subject analysis set title	FAS-EQ
Subject analysis set type	Full analysis

Subject analysis set description:

FAS HR QoL subset 2: Patients of the FAS who answered the baseline and at least one additional EQ-5D-5L questionnaire between start of FTD/TPI treatment (Group A) or the start of the close observation period (Group B) and the end of treatment/close observation.

Subject analysis set title	FAS-C30 (pe)
Subject analysis set type	Full analysis

Subject analysis set description:

FAS-C30 evaluable for the primary endpoint (pe): a subset of the FAS-C30 comprising all patients who received at least two cycles of FTD/TPI and who completed the baseline EORTC-QLQ-C30 questionnaire and at least one more questionnaire AFTER Cycle 1 (i.e., the earliest within two days before Day 1 of Cycle 2).

Subject analysis set title	Per protocol
Subject analysis set type	Per protocol

Subject analysis set description:

All patients of the FAS/SAF without any relevant violation of selection criteria; moreover, patients from two centres were excluded from the PP due to inspection findings.

Primary: Rate of responders with unchanged or improved HRQoL

End point title	Rate of responders with unchanged or improved HRQoL

End point description:

Response was calculated as the mean of the score of the EORTC QLQ C30 global health status/quality of life scale (QL2) at all scheduled time points of HR-QoL analysis in the time interval from two days before start of Cycle 2 until the end of treatment/end of close observation compared to the baseline score of the global health status/quality of life (QL2) scale. The rate of responders was defined as the proportion of patients with response, i.e. improvement (≥10 scores) or stabilization (>-10 and <10 scores) of the EORTC QLQ C30 global health status/ quality of life (QL2) score compared to the baseline score.

CAVE: Only the analyses in FAS-C30 (pe) are the primary endpoint of the study.

End point type	Primary

End point timeframe:

From two days before start of Cycle 2 until the end of treatment/end of close observation.

End point values	FTD/TPI (trifluridine/tipiracil)	BSC (Best Supportive Care)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106[1]	6[2]		
Units: Response rate, %				
number (confidence interval 95%)				
FAS-C30 pe, Group A: 62/106	58.5 (48.5 to 68.0)	0 (0 to 0)		
FAS-C30 pe, Group B: 3/6	0 (0 to 0)	50.0 (11.8 to 88.2)		
FAS-C30 pe, Group A, ECOG 0: 24/43	55.8 (39.9 to 70.9)	0 (0 to 0)		
FAS-C30 pe, Group A, ECOG 1: 33/54	61.1 (46.9 to 74.1)	0 (0 to 0)		
FAS-C30 pe, Group B, ECOG 1: 1/3	0 (0 to 0)	33.3 (0.8 to 90.6)		
FAS-C30 pe, Group A, ECOG 2-3: 4/8	50.0 (15.7 to 84.3)	0 (0 to 0)		
FAS-C30 pe, Group B, ECOG 2-3: 1/2	0 (0 to 0)	50.0 (1.3 to 98.7)		
FAS-C30 pe, Grp. A, 0 prev. therapy lines: 4/6	66.7 (22.3 to 95.7)	0 (0 to 0)		
FAS-C30 pe, Grp. B, 0 prev. therapy lines: 1/1	0 (0 to 0)	100.0 (2.5 to 100.0)		
FAS-C30 pe, Grp. A, 1-2 prev. therapy lines: 29/54	53.7 (39.6 to 67.4)	0 (0 to 0)		
FAS-C30 pe, Grp. B, 1-2 prev. therapy lines: 2/4	0 (0 to 0)	50.0 (6.8 to 93.2)		
FAS-C30 pe, Grp. A, 2 prev. therapy lines: 23/42	54.8 (38.7 to 70.2)	0 (0 to 0)		
FAS-C30 pe, Grp. B, 2 prev. therapy lines: 1/3	0 (0 to 0)	33.3 (0.8 to 90.6)		
FAS-C30 pe, Grp. A, > 2 prev. therapy lines: 29/46	63.0 (47.5 to 76.8)	0 (0 to 0)		
FAS-C30 pe, Grp. B, > 2 prev. therapy lines: 0/1	0 (0 to 0)	0.0 (0 to 0)		
PP pe, Group A: 56/96	58.3 (47.8 to 68.3)	0 (0 to 0)		
PP pe, Group B: 3/6	0 (0 to 0)	50.0 (11.8 to 88.2)		

Notes:

[1] - 106 in FAS-C30 pe; subgroup numbers identified in category headers.

[2] - 6 in FAS-C30 pe; subgroup numbers identified in category headers.

Statistical analyses

Statistical analysis title	Primary endpoint analysis

Statistical analysis description:

Calculation of the 2-sided 95% confidence interval for the response rate separately for both groups.

Comparison groups	FTD/TPI (trifluridine/tipiracil) v BSC (Best Supportive Care)

Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	equivalence[3]
Parameter estimate	Confidence interval
Point estimate	58.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	48.5
upper limit	68

Notes:

[3] - A response rate of 45% ± 10% was assessed as appropriate in Group A (patients with ≥ 2 cycles FTD/TPI).
A response rate of 45% ± 20% was assessed as appropriate in Group B (patients with ≥ 2 cycles BSC).

Note: Number of patients needed was not achieved in Group B. Parameter estimate presented is estimate for Group A.

Secondary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)

End point description:

PFS (based on RECIST version 1.1) was defined as the duration from the first administration of FTD/TPI (Group A) or Day 1 of observation Cycle 1 (Group B) to the day of radiological or clinical tumour progression or death of any cause, whichever came first.
Patients who were not known to have had a radiological or clinical progression were censored for PFS analysis at the last date they were known not to have experienced progression.

End point type	Secondary

End point timeframe:

Patients were followed until the end of study, at least one year after start of FTD/TPI / close observation.

End point values	FTD/TPI (trifluridine/tipiracil)	BSC (Best Supportive Care)	Full Analysis Set (FAS)	Per protocol
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	186	9	195	171
Units: months				
median (confidence interval 95%)	2.5 (2.1 to 2.9)	3.7 (2.2 to 4.7)	2.5 (2.2 to 3.1)	2.5 (2.1 to 3.2)

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Duration from first administration of FTD/TPI (Group A) or Day 1 of observation Cycle 1 (Group B) to the day of death from any cause.
Patients who were not known to have died were censored for OS analysis on the last day they were known to have been alive.

End point type	Secondary

End point timeframe:

Patients were followed until the end of study, at least one year after start of FTD/TPI / close observation.

End point values	FTD/TPI (trifluridine/tipiracil)	BSC (Best Supportive Care)	Full Analysis Set (FAS)	Per protocol
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	186	9	195	171
Units: months				
median (confidence interval 95%)	6.9 (6.1 to 8.3)	4.7 (3.6 to 11.6)	6.8 (6.0 to 8.2)	6.8 (5.9 to 8.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Average EORTC QLQ-C30 scores

End point title	Average EORTC QLQ-C30 scores

End point description:

EORTC QLQ-C30 consists of
the global health status (QL2) scale,
the functional scales physical functioning (PF2), role functioning (RF2), emotional functioning (EF), cognitive functioning (CF), and social functioning (SF),
and the symptom scales / items fatigue (FA), nausea and vomiting (NV), pain (PA), dyspnoea (DY), insomnia (SL), appetite loss (AP), constipation (CO), diarrhoea (DI), and financial difficulties (FI).
For the global health status and functional scales higher scores (on a scale of 0 - 100) represent a higher QoL / higher/healthier level of functioning.
For a symptom scale/item, higher scores represent a higher level of symptomatology/problems.

End point type	Secondary

End point timeframe:

At baseline, during and after treatment/close observation. After treatment includes all questionnaires completed at the end of treatment visit and during follow-up. Only questionnaires completed within prespecified time windows were considered.

End point values	FTD/TPI (trifluridine/tipiracil)	BSC (Best Supportive Care)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123[4]	6[5]		
Units: Score points				
arithmetic mean (standard deviation)				
QL2 at baseline	59.4 (± 20.5)	50.0 (± 14.9)		
QL2 during treatment	54.2 (± 22.3)	61.8 (± 31.0)		
QL2 after treatment	45.0 (± 25.1)	52.8 (± 21.0)		
PF2 at baseline	65.1 (± 24.5)	33.3 (± 34.8)		

PF2 during treatment	60.1 (± 25.2)	43.3 (± 47.0)		
PF2 after treatment	52.8 (± 28.5)	39.7 (± 44.8)		
RF2 at baseline	57.9 (± 31.6)	25.0 (± 39.1)		
RF2 during treatment	51.8 (± 31.1)	43.1 (± 51.0)		
RF2 after treatment	39.5 (± 34.0)	42.2 (± 51.8)		
EF at baseline	67.7 (± 23.9)	62.5 (± 35.3)		
EF during treatment	66.8 (± 26.4)	80.6 (± 21.2)		
EF after treatment	63.5 (± 26.5)	75.8 (± 29.7)		
CF at baseline	79.2 (± 23.2)	75.0 (± 23.0)		
CF during treatment	76.2 (± 22.7)	59.7 (± 37.8)		
CF after treatment	74.6 (± 23.3)	82.8 (± 9.2)		
SF at baseline	63.1 (± 30.7)	61.1 (± 44.3)		
SF during treatment	60.0 (± 31.5)	68.1 (± 31.5)		
SF after treatment	56.0 (± 33.7)	76.7 (± 20.3)		
FA at baseline	46.0 (± 27.0)	72.2 (± 23.0)		
FA during treatment	52.3 (± 26.9)	56.5 (± 34.4)		
FA after treatment	57.8 (± 30.6)	61.7 (± 33.0)		
NV at baseline	9.6 (± 19.1)	19.4 (± 19.5)		
NV during treatment	14.1 (± 16.5)	8.3 (± 16.7)		
NV after treatment	16.3 (± 20.5)	8.6 (± 7.5)		
PA at baseline	34.3 (± 32.7)	41.7 (± 27.4)		
PA during treatment	43.7 (± 34.0)	31.9 (± 25.0)		
PA after treatment	47.2 (± 34.9)	48.6 (± 35.4)		
DY at baseline	29.8 (± 30.7)	55.6 (± 34.4)		
DY during treatment	38.3 (± 30.1)	38.9 (± 43.0)		
DY after treatment	43.7 (± 34.3)	40.0 (± 43.7)		
SL at baseline	30.1 (± 31.2)	38.9 (± 25.1)		
SL during treatment	36.8 (± 31.5)	25.0 (± 31.9)		
SL after treatment	40.9 (± 35.0)	60.6 (± 47.2)		
AP at baseline	29.8 (± 33.3)	38.9 (± 49.1)		
AP during treatment	39.2 (± 31.9)	25.0 (± 50.0)		
AP after treatment	42.0 (± 30.9)	47.2 (± 33.7)		
CO at baseline	18.9 (± 28.7)	11.1 (± 17.2)		
CO during treatment	19.5 (± 26.3)	8.3 (± 16.7)		
CO after treatment	16.4 (± 23.6)	8.9 (± 15.4)		
DI at baseline	19.4 (± 27.0)	16.7 (± 27.9)		
DI during treatment	19.5 (± 27.2)	0.0 (± 0.0)		
DI after treatment	24.2 (± 27.6)	10.6 (± 12.9)		
FI at baseline	17.8 (± 27.2)	5.6 (± 13.6)		
FI during treatment	19.9 (± 26.9)	0.0 (± 0.0)		
FI after treatment	20.2 (± 26.5)	0.0 (± 0.0)		

Notes:

[4] - 123 in FAS-C30; 123 (121-123 per item) at BL, 92 (91-92) during, 55 (54-55) after treatment.

[5] - 6in FAS-C30; 6 at baseline, 4 during treatment, 3 after treatment.

Statistical analyses

No statistical analyses for this end point

Secondary: Average EQ-5D-5L index and EQ VAS scores

End point title	Average EQ-5D-5L index and EQ VAS scores

End point description:

EQ-5D-5L consists of the EQ-5D descriptive system comprising 5 dimensions mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, and the EQ 20 cm vertical visual anlogue scale (VAS). EQ-5D-5L results are represented by an index value between 0 and 1 computed by the Crosswalk Index Value Calculator, where a higher value represents a higher level of problems; EQ VAS scores are presented as continuous parameter (0-100) where a high value represents a high health profile.

End point type	Secondary

End point timeframe:

At baseline, during and after treatment/close observation. After treatment includes all questionnaires completed at the end of treatment visit and during follow-up. Only questionnaires completed within prespecified time windows were considered.

End point values	FTD/TPI (trifluridine/tipiracil)	BSC (Best Supportive Care)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122[6]	6[7]		
Units: score points				
arithmetic mean (standard deviation)				
EQ-5D-5L index at baseline	0.8 (± 0.2)	0.7 (± 0.4)		
EQ-5D-5L index during treatment	0.7 (± 0.2)	0.6 (± 0.4)		
EQ-5D-5L index after treatment	0.6 (± 0.3)	0.5 (± 0.5)		
EQ VAS at baseline	62.7 (± 20.0)	65.0 (± 15.8)		
EQ VAS during treatment	58.1 (± 23.1)	68.5 (± 26.1)		
EQ VAS after treatment	49.5 (± 27.1)	61.9 (± 18.9)		

Notes:

[6] - 122 in FAS-EQ; EQ-5D-5L index n=120 at BL, 86 during, 57 after treatment; VAS n=120, 90, and 57.
[7] - 6 in FAS-EQ; EQ-5D-5L index n=5 and VAS n=6 at BL; both n=4 during and n=3 after treatment.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to deterioration of HR-QoL according to EORTC QLQ-C30 global health status QL2

End point title	Time to deterioration of HR-QoL according to EORTC QLQ-C30 global health status QL2

End point description:

From day 1 of cycle 1 of treatment with FTD/TPI / close observation to first change of global health/quality of life scale of ≤-10 scores compared to the baseline score.

End point type	Secondary

End point timeframe:

From day 1 of cycle 1 of treatment with FTD/TPI / close observation to end of treatment / close observation (EoT) and end of follow-up (EoF), respectively.

End point values	FTD/TPI (trifluridine/tipiracil)	BSC (Best Supportive Care)	FAS-C30	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	123[8]	6[9]	129[10]	
Units: months				
median (confidence interval 95%)				
until end of treatment/close observation	84.0 (64.0 to 391.0)	9999 (60.0 to 9999)	84.0 (64.0 to 391.0)	
until end of follow-up	121.0 (84.0 to 172.0)	104.0 (60.0 to 9999)	121.0 (87.0 to 172.0)	

Notes:

[8] - 123 in FAS-C30. Deteriorations n=39 (31.7%) until EoT, n=63 (51.2%) until EoF.

[9] - 6 in FAS-C30. Deteriorations n=1 (16.7%) until EoT, n=2 (33.3%) until EoF.

[10] - N=40 deteriorations until EoT, n=65 (50.4%) deteriorations until EoF.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

End point type	Other pre-specified

End point timeframe:

Proportion of patients experiencing a response (complete [CR] or partial response [PR] based on RECIST version 1.1) in the period from start of Cycle 1 until the last administration of FTD/TPI (Group A) or close observation (Group B) plus 28 days.

End point values	FTD/TPI (trifluridine/tipiracil)	BSC (Best Supportive Care)	Full Analysis Set (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	186	9	195	
Units: Responders	4	0	4	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first administration of FTD/TPI (Group A) or Day 1 of the close observation Cycle 1 (Group B) to 28 days after the last administration of FTD/TPI (Group A) or until the end of close observation (Group B)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	A: FTD/TPI (trifluridine/tipiracil) (SAF)

Reporting group description:

FTD/TPI (starting dose 35 mg/m2 BSA/dose) was taken orally twice daily (BID) on Days 1 to 5 and Days 8 to 12 of each 28-day cycle as long as a benefit was observed or until unacceptable toxicity occurred.

Reporting group title	B: BSC (Best Supportive Care) (SAF)

Reporting group description:

Best supportive care, tailored to the patient`s individual needs.

Serious adverse events	A: FTD/TPI (trifluridine/tipiracil) (SAF)	B: BSC (Best Supportive Care) (SAF)	
Total subjects affected by serious adverse events			
subjects affected / exposed	83 / 186 (44.62%)	5 / 9 (55.56%)	
number of deaths (all causes)	147	7	
number of deaths resulting from adverse events	25	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant ascites			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	23 / 186 (12.37%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 23	0 / 1	
deaths causally related to treatment / all	0 / 13	0 / 1	
Metastases to central nervous system			
subjects affected / exposed	3 / 186 (1.61%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Metastases to lung			
subjects affected / exposed	3 / 186 (1.61%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastases to spine			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 186 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	2 / 186 (1.08%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pain			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pyrexia			
subjects affected / exposed	2 / 186 (1.08%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	4 / 186 (2.15%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Reproductive system and breast disorders			
Female genital tract fistula			
subjects affected / exposed	0 / 186 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 186 (1.08%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiccups			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonitis			

subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 186 (1.08%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Stridor			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis radiation			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	0 / 186 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Urinary tract stoma complication			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	2 / 186 (1.08%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Coma hepatic			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Monoparesis			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorder			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Radiculopathy			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 186 (2.15%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	5 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	2 / 186 (1.08%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 186 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	2 / 186 (1.08%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Diarrhoea			
subjects affected / exposed	3 / 186 (1.61%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal stenosis			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ileus			
subjects affected / exposed	2 / 186 (1.08%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal stenosis			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mechanical ileus			
subjects affected / exposed	2 / 186 (1.08%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			

subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	2 / 186 (1.08%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal varices haemorrhage			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis chronic			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	4 / 186 (2.15%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stenosis			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			

subjects affected / exposed	4 / 186 (2.15%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis			
subjects affected / exposed	5 / 186 (2.69%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	2 / 186 (1.08%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	4 / 186 (2.15%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	3 / 4	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bladder perforation			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract disorder			

subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 186 (1.08%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	2 / 186 (1.08%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal wall abscess			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Arthritis infective			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cholangitis infective			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic infection			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	3 / 186 (1.61%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney infection			
subjects affected / exposed	0 / 186 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ophthalmic herpes zoster			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis bacterial			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 186 (1.61%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			

subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 186 (1.08%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Superinfection			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 186 (1.08%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 186 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vestibular neuronitis			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound abscess			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dehydration			

subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 186 (0.54%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	A: FTD/TPI (trifluridine/tipiracil) (SAF)	B: BSC (Best Supportive Care) (SAF)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	170 / 186 (91.40%)	6 / 9 (66.67%)	
Nervous system disorders			
Polyneuropathy	Additional description: Includes PTs polyneuropathy (n=8, FTD/TPI), neuropathy peripheral (n=1, FTD/TPI) and peripheral motor neuropathy (n=1, FTD/TPI).		
subjects affected / exposed	10 / 186 (5.38%)	0 / 9 (0.00%)	
occurrences (all)	10	0	
Blood and lymphatic system disorders			
Anaemia	Additional description: Includes PTs anaemia (n=39, FTD/TPI; n=1, BSC) and haemoglobin decreased (n=4, FTD/TPI).		
subjects affected / exposed	43 / 186 (23.12%)	1 / 9 (11.11%)	
occurrences (all)	56	1	
Leukopenia	Additional description: Includes PTs leukopenia (n=29, FTD/TPI) and white blood cell count decreased (n=8, FTD/TPI).		
subjects affected / exposed	37 / 186 (19.89%)	0 / 9 (0.00%)	
occurrences (all)	79	0	
Neutropenia	Additional description: Includes PTs neutropenia (n=48, FTD/TPI) and neutrophil count decreased (n=8, FTD/TPI).		
subjects affected / exposed	55 / 186 (29.57%)	0 / 9 (0.00%)	
occurrences (all)	117	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	42 / 186 (22.58%)	2 / 9 (22.22%)	
occurrences (all)	53	3	
Oedema	Additional description: Includes PTs oedema (n=3, FTD/TPI) and oedema peripheral (n=17, FTD/TPI).		

subjects affected / exposed	19 / 186 (10.22%)	0 / 9 (0.00%)	
occurrences (all)	22	0	
Pain			
subjects affected / exposed	8 / 186 (4.30%)	2 / 9 (22.22%)	
occurrences (all)	9	2	
Pyrexia			
subjects affected / exposed	16 / 186 (8.60%)	0 / 9 (0.00%)	
occurrences (all)	24	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	13 / 186 (6.99%)	1 / 9 (11.11%)	
occurrences (all)	14	1	
Ascites			
subjects affected / exposed	9 / 186 (4.84%)	1 / 9 (11.11%)	
occurrences (all)	13	1	
Constipation			
subjects affected / exposed	22 / 186 (11.83%)	0 / 9 (0.00%)	
occurrences (all)	25	0	
Diarrhoea			
subjects affected / exposed	38 / 186 (20.43%)	0 / 9 (0.00%)	
occurrences (all)	45	0	
Nausea			
subjects affected / exposed	42 / 186 (22.58%)	1 / 9 (11.11%)	
occurrences (all)	49	1	
Vomiting			
subjects affected / exposed	24 / 186 (12.90%)	1 / 9 (11.11%)	
occurrences (all)	32	1	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea	Additional description: Includes PTs dyspnoea (n=16, FTD/TPI) and dyspnoea exertional (n=2, FTD/TPI).		
subjects affected / exposed	18 / 186 (9.68%)	0 / 9 (0.00%)	
occurrences (all)	21	0	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	13 / 186 (6.99%)	0 / 9 (0.00%)	
occurrences (all)	13	0	
Infections and infestations			

Infection subjects affected / exposed occurrences (all)	7 / 186 (3.76%) 8	0 / 9 (0.00%) 0	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	28 / 186 (15.05%) 31	0 / 9 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 March 2018	Amendment 1, Protocol version 3.0: Change of allowed periods and time points for study procedures during treatment phase: Study procedures on 'Day 1 of each treatment cycle before administration of FTD/TPI in the respective cycle/start of the observation cycle or within previous 3 days (maximum 72 hours) unless otherwise indicated below' (previously 2 days). Addition of a note: In case of any delay of the treatment start in the following treatment cycle, restaging has to be performed after 8 weeks or within previous 7 days (equivalent to duration of two treatment cycles with FTD/TPI without any treatment delay). Adjustment of text according to schedule of assessments (Section 2): Questionnaires EORTC-QLQ C30 and EQ-5D-5L including EQ VAS as paper version on Day 1 of the respective cycle or within previous 2 days. Update of information according to new SmPC for Lonsurf®: Update of one sentence on hepatic impairment: FTD/TPI is not recommended for use in patients with baseline moderate or severe hepatic impairment (National Cancer Institute [NCI] Criteria Group C and D defined by total bilirubin > 1.5 x ULN), as a higher incidence of Grade 3 or 4 hyperbilirubinaemia is observed in patients with baseline moderate hepatic impairment, although this is based on very limited data. Update of information on interactions: Deletion of one sentence: Inductive effect of tipiracil on human CYP isoforms cannot be excluded.
30 July 2018	Amendment 2, Protocol version 4.0: Updated information: Extension of the limitation of the early benefit assessment for Lonsurf® to 1 April 2020 (previously two years from 02 Feb 2017). The 1st of October 2018 as an optional data extract date for interim analysis – depending on whether this date or the time point of 50 evaluable patients permanently termination study treatment is earlier – was deleted. The following sentence was deleted: An interim report in the format of an integrated clinical study report will be prepared within three months after data extract date of the interim statistical analysis.
07 December 2018	Amendment 3, Protocol version 5.0: Change of study duration: Extension of the estimated accrual period from 1 year to 15 months. Extension of estimated study duration from 24 to 27 months. Change of Planned end of study from QII 2019 to QIV 2019. Change of sample size calculation: Addition of a table for sample sizes for alternative values of type I error if recruitment of 24 patients in Group B could not be achieved.
29 April 2019	Amendment 4, Protocol version 6.0: Change of duration of questioning quality of life: Extension of the time period for questioning of quality of life for patients treated with FTD/TPI for more than one year: questioning for the duration of treatment, at the end-of-treatment visit and at Month 1 of follow up.

31 January 2020	Amendment 5, Protocol version 7.0: Extension of the study duration until the end of 2020. Additional analysis, study report and annual safety report (required because of extension of study duration).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported