



Clinical trial results:

Lonsurf - RII

Lonsurf (TAS-102) with or without bevacizumab in patients with chemo-refractory metastatic colorectal cancer.

A randomized phase II study

Summary

EudraCT number	2016-005241-23
Trial protocol	DK
Global end of trial date	24 June 2019

Results information

Result version number	v1 (current)
This version publication date	26 January 2022
First version publication date	26 January 2022

Trial information

Trial identification

Sponsor protocol code	16.37
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Odense University Hospital
Sponsor organisation address	J. B. Winsløvs Vej 4, entrance 140, basemenet, Odense C, Denmark,
Public contact	Ida Coordt Elle, Odense Universitetshospital, 45 29335922, ida.coordt.elle@rsyd.dk
Scientific contact	Per Pfeiffer, Odense Universitetshospital, 45 26283844, per.pfeiffer@rsyd.dk

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	24 June 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	24 June 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective:

- Progression-free survival (PFS)

Protection of trial subjects:

Pre-medication was administered to minimize adverse events and discomfort.

A safety analysis focusing on toxicity, treatment duration, and dose intensity was done when the first 42 patients had completed two cycles of therapy.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 August 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 93
Worldwide total number of subjects	93
EEA total number of subjects	93

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)	46
From 65 to 84 years	47

Subject disposition

Recruitment

Recruitment details:

Eligible patients were aged 18 years or older with histopathologically confirmed colorectal adenocarcinoma, had non-resectable metastatic colorectal cancer, had a WHO performance status of 0 or 1, had a life expectancy of at least 3 months, and were refractory or intolerant to fluoropyrimidines, irinotecan, oxaliplatin, and cetuximab or panitumumab

Pre-assignment

Screening details:

Liver and renal function had to be within normal ranges and bilirubin no higher than 1.5-times the upper limit of normal, glomerular filtration rate above 50 mL/min, neutrophil cell count of at least 1.5×10^9 cells per L, and a platelet count of at least 100×10^9 per L.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Lonsurf

Arm description:

Monotherapy with TAS-102 35 mg/m² orally twice daily on days 1–5 and 8–12 every 28 days.

Arm type	Active comparator
Investigational medicinal product name	trifluridine-tipiracil
Investigational medicinal product code	
Other name	Lonsurf, TAS-102
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

35 mg/m² orally twice daily on days 1–5 and 8–12 every 28 days.

Arm title	Lonsurf+bevacizumab
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Arm description:

Lonsurf 35 mg/m² orally twice daily on days 1–5 and 8–12 every 28 days. Bevacizumab (5 mg/kg intravenously) on days 1 and 15 every 28 days. The bevacizumab dose was administered as a 30-min intravenous infusion before the TAS-102 dose.

Arm type	Experimental
Investigational medicinal product name	trifluridine-tipiracil
Investigational medicinal product code	
Other name	Lonsurf, TAS-102
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

35 mg/m² orally twice daily on days 1–5 and 8–12 every 28 days.

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	Avastin
Pharmaceutical forms	Solution for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

(5 mg/kg intravenously) on days 1 and 15 every 28 days.

The bevacizumab dose was administered as a 30-min intravenous infusion before the TAS-102 dose. If dose reduction was needed during treatment because of toxicity, the dose of TAS-102 was reduced in increments of 5 mg/m². If patients had unacceptable toxicities related to bevacizumab, treatment with TAS-102 monotherapy could be continued according to protocol without bevacizumab. Dose reduction of bevacizumab was not recommended.

Number of subjects in period 1	Lonsurf	Lonsurf+bevacizumab
Started	47	46
Completed	47	46

Baseline characteristics

Reporting groups

Reporting group title	Lonsurf
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Reporting group description:

Monotherapy with TAS-102 35 mg/m² orally twice daily on days 1–5 and 8–12 every 28 days.

Reporting group title	Lonsurf+bevacizumab
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Reporting group description:

Lonsurf 35 mg/m² orally twice daily on days 1–5 and 8–12 every 28 days.

Bevacizumab (5 mg/kg intravenously) on days 1 and 15 every 28 days. The bevacizumab dose was administered as a 30-min intravenous infusion before the TAS-102 dose.

Reporting group values	Lonsurf	Lonsurf+bevacizumab	Total
Number of subjects	47	46	93
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)	22	24	46
From 65-84 years	25	22	47
85 years and over	0	0	0
Gender categorical			
Units: Subjects			
Female	17	22	39
Male	30	24	54

End points

End points reporting groups

Reporting group title	Lonsurf
Reporting group description:	
Monotherapy with TAS-102 35 mg/m ² orally twice daily on days 1–5 and 8–12 every 28 days.	
Reporting group title	Lonsurf+bevacizumab
Reporting group description:	
Lonsurf 35 mg/m ² orally twice daily on days 1–5 and 8–12 every 28 days. Bevacizumab (5 mg/kg intravenously) on days 1 and 15 every 28 days. The bevacizumab dose was administered as a 30-min intravenous infusion before the TAS-102 dose.	

Primary: Progression-free survival

End point title	Progression-free survival ^[1]
End point description:	
End point type	Primary
End point timeframe:	
24 months	
Notes:	
[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: Please see the publication for complete statistical analysis.	

End point values	Lonsurf	Lonsurf+bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	46		
Units: months				
median (confidence interval 95%)	2.6 (1.6 to 3.5)	4.6 (3.5 to 6.5)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

30 days after last treatment

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.1
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Reporting groups

Reporting group title	Lonsurf
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Reporting group description:

Monotherapy with TAS-102 35 mg/m² orally twice daily on days 1–5 and 8–12 every 28 days.

Reporting group title	Lonsurf+bevacizumab
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Reporting group description:

Lonsurf 35 mg/m² orally twice daily on days 1–5 and 8–12 every 28 days.

Bevacizumab (5 mg/kg intravenously) on days 1 and 15 every 28 days. The bevacizumab dose was administered as a 30-min intravenous infusion before the TAS-102 dose.

Serious adverse events	Lonsurf	Lonsurf+bevacizumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 47 (14.89%)	14 / 46 (30.43%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	7 / 47 (14.89%)	12 / 46 (26.09%)	
occurrences causally related to treatment / all	7 / 7	12 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 47 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 47 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Lonsurf	Lonsurf+bevacizuma b	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 47 (100.00%)	46 / 46 (100.00%)	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	24 / 47 (51.06%)	27 / 46 (58.70%)	
occurrences (all)	24	27	
Anaemia			
subjects affected / exposed	34 / 47 (72.34%)	31 / 46 (67.39%)	
occurrences (all)	34	31	
Thrombocytopenia			
subjects affected / exposed	8 / 47 (17.02%)	18 / 46 (39.13%)	
occurrences (all)	8	18	
Diarrhoea			
subjects affected / exposed	15 / 47 (31.91%)	16 / 46 (34.78%)	
occurrences (all)	15	16	
Febrile neutropenia			
subjects affected / exposed	1 / 47 (2.13%)	2 / 46 (4.35%)	
occurrences (all)	1	2	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	40 / 47 (85.11%)	39 / 46 (84.78%)	
occurrences (all)	40	39	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	33 / 47 (70.21%)	27 / 46 (58.70%)	
occurrences (all)	33	27	
Vomiting			
subjects affected / exposed	13 / 47 (27.66%)	16 / 46 (34.78%)	
occurrences (all)	13	16	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 July 2017	CT scan after cycle 1. CBC deleted. Use of OPEN facilities for randomization and eCRF. Bevacizumab dose modification section added. Monitoring of SUSARs deleted.
15 November 2017	Hillerød, Rigshospitalet and Sønderborg sites added. Baseline scan should be maximum two weeks old instead of four. Hematology blood samples on day 15 for both arms. Maximum eight days between registration and treatment start. Examples added to exclusion criterion. Minor corrections.
12 December 2017	Hillerød site removed from protocol. Changes in section 7 regarding personnel handling medication.
03 August 2018	Inclusion of 124 patients instead of 80 patients.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/31999946>