Clinical trial results:
Full dose S-1 monotherapy compared to reduced dose S-1/oxaliplatin combination therapy as first-line treatment for older patients with metastatic colorectal cancer.

Summary

EudraCT number	2014-000394-39
Trial protocol	DK NO FI
Global end of trial date	01 September 2018

Results information

Result version number	v1 (current)
This version publication date	19 January 2022
First version publication date	19 January 2022

Trial information

Trial identification

Sponsor protocol code	KFE 14.01

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. Winsløws Vej 4, entrance 140, basemenet, Odense C, Denmark, 5000
Public contact	Ida Coordt Elle, Odense University Hospital, +45 29335922, ida.coordt.elle@rsyd.dk
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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	01 September 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 September 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Progression-free survival (PFS)

Protection of trial subjects:

Pre-medication was administered to minmize adverse reactions.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 February 2015
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	Norway: 57
Country: Number of subjects enrolled	Sweden: 51
Country: Number of subjects enrolled	Denmark: 43
Country: Number of subjects enrolled	Finland: 9
Worldwide total number of subjects	160
EEA total number of subjects	160

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)	0
From 65 to 84 years	153
85 years and over	7

Subject disposition

Recruitment

Recruitment details:

Eligible patients were aged 70 years or older and had histopathologically proven colorectal adenocarcinoma,
non-resectable metastases, and a WHO performance status of 0–2.

Pre-assignment

Screening details:

Participants had received no prior chemotherapy except adjuvant fluoropyrimidine therapy completed more than 180 days before randomisation and had a life expectancy of at least 3 months.

Period 1

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

Blinding implementation details:

Patients were randomly assigned to sequential full-dose monotherapy (S-1 followed by irinotecan monotherapy at progression) or sequential dose-reduced combination chemotherapy (S-1 and oxaliplatin followed by S-1 and irinotecan at progression). Bevacizumab was optional in first-line therapy at the discretion of the treating physician but the decision had to be made before randomisation.

Arms

Are arms mutually exclusive?	Yes
Arm title	Full-dose monotherapy

Arm description:

Patients assigned to full-dose monotherapy were treated with S-1 30 mg/m² orally twice daily on days 1–14 every 3 weeks followed by second-line treatment at progression with irinotecan (250 mg/m² intravenously on day 1 every 3 weeks or 180 mg/m² intravenously on day 1 every 2 weeks). In the absence of toxicity above grade 1 (except alopecia), it was recommended to increase irinotecan in steps to 350 mg/m² intravenously on day 1 every 3 weeks or 250 mg/m² intravenously on day 1
every 2 weeks.

Arm type	Active comparator
Investigational medicinal product name	S1
Investigational medicinal product code	
Other name	Teysuno
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Patients assigned to full-dose monotherapy were treated with S-1 30 mg/m² orally twice daily on days 1–14 every 3 weeks followed by second-line treatment at progression with irinotecan (250 mg/m² intravenously on day 1 every 3 weeks or 180 mg/m² intravenously on day 1 every 2 weeks). In the absence of toxicity above grade 1 (except alopecia), it was recommended to increase irinotecan in steps to 350 mg/m² intravenously on day 1
every 3 weeks or 250 mg/m² intravenously on day 1 every 2 weeks.

Arm title	Reduced-dose combination therapy

Arm description:

Patients assigned to reduced-dose combination chemotherapy received S-1 20 mg/m² orally twice daily on days 1–14 and oxaliplatin 100 mg/m² intravenously on day 1 every 3 weeks followed by second-line treatment at progression with S-1 20 mg/m² orally twice daily on days 1–14 and irinotecan 180 mg/m² intravenously on day 1 every 3 weeks.

Arm type	Experimental

Investigational medicinal product name	S1
Investigational medicinal product code	
Other name	Teysuno
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Patients assigned to reduced-dose combination chemotherapy received S-1 20 mg/m² orally twice daily on
days 1–14 and oxaliplatin 100 mg/m² intravenously on day 1 every 3 weeks followed by second-line treatment at progression with S-1 20 mg/m² orally twice daily on days 1–14 and irinotecan 180 mg/m² intravenously on day 1 every 3 weeks.

Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients assigned to reduced-dose combination chemotherapy received S-1 20 mg/m² orally twice daily on
days 1–14 and oxaliplatin 100 mg/m² intravenously on day 1 every 3 weeks followed by second-line treatment at progression with S-1 20 mg/m² orally twice daily on days 1–14 and irinotecan 180 mg/m² intravenously on day 1 every 3 weeks.

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

Dosage and administration details:

Patients assigned to reduced-dose combination chemotherapy received S-1 20 mg/m² orally twice daily on
days 1–14 and oxaliplatin 100 mg/m² intravenously on day 1 every 3 weeks followed by second-line treatment at progression with S-1 20 mg/m² orally twice daily on days 1–14 and irinotecan 180 mg/m² intravenously on day 1 every 3 weeks.

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

Dosage and administration details:

Because bevacizumab was not standard of care in most Nordic countries at the time of study design, the addition
of bevacizumab to first-line chemotherapy was optional and given at the discretion of the treating physician. When used, bevacizumab was given at 7.5 mg/kg intravenously on day 1 every 3 weeks.

Number of subjects in period 1	Full-dose monotherapy	Reduced-dose combination therapy
Started	83	77
Completed	83	77

Baseline characteristics

Reporting groups	
Reporting group title	Full-dose monotherapy
Reporting group description:	
Patients assigned to full-dose monotherapy were treated with S-1 30 mg/m² orally twice daily on days 1–14 every 3 weeks followed by second-line treatment at progression with irinotecan (250 mg/m² intravenously on day 1 every 3 weeks or 180 mg/m² intravenously on day 1 every 2 weeks). In the absence of toxicity above grade 1 (except alopecia), it was recommended to increase irinotecan in steps to 350 mg/m² intravenously on day 1 every 3 weeks or 250 mg/m² intravenously on day 1 every 2 weeks.	
Reporting group title	Reduced-dose combination therapy
Reporting group description:	
Patients assigned to reduced-dose combination chemotherapy received S-1 20 mg/m² orally twice daily on days 1–14 and oxaliplatin 100 mg/m² intravenously on day 1 every 3 weeks followed by second-line treatment at progression with S-1 20 mg/m² orally twice daily on days 1–14 and irinotecan 180 mg/m² intravenously on day 1 every 3 weeks.	

Reporting group values	Full-dose monotherapy	Reduced-dose combination therapy	Total
Number of subjects	83	77	160
Age categorical Units: Subjects			
Age continuous Units: years			
median	78	78	
inter-quartile range (Q1-Q3)	76 to 81	75 to 80	-
Gender categorical Units: Subjects			
Female	40	38	78
Male	43	39	82

End points

End points reporting groups

Reporting group title	Full-dose monotherapy

Reporting group description:

Patients assigned to full-dose monotherapy were treated with S-1 30 mg/m² orally twice daily on days 1–14 every 3 weeks followed by second-line treatment at progression with irinotecan (250 mg/m² intravenously on day 1 every 3 weeks or 180 mg/m² intravenously on day 1 every 2 weeks). In the absence of toxicity above grade 1 (except alopecia), it was recommended to increase irinotecan in steps to 350 mg/m² intravenously on day 1 every 3 weeks or 250 mg/m² intravenously on day 1
every 2 weeks.

Reporting group title	Reduced-dose combination therapy

Reporting group description:

Patients assigned to reduced-dose combination chemotherapy received S-1 20 mg/m² orally twice daily on days 1–14 and oxaliplatin 100 mg/m² intravenously on day 1 every 3 weeks followed by second-line treatment at progression with S-1 20 mg/m² orally twice daily on days 1–14 and irinotecan 180 mg/m² intravenously on day 1 every 3 weeks.

Primary: Progression-free survival

End point title	Progression-free survival[1]

End point description:

End point type	Primary

End point timeframe:

Data-cut-off was 36 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 original publication for statistical analysis.

End point values	Full-dose monotherapy	Reduced-dose combination therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	77		
Units: months				
median (confidence interval 95%)	5.3 (4.1 to 6.8)	6.2 (5.3 to 8.3)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Last treatment + 30 days.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups	
Reporting group title	Full-dose monotherapy
Reporting group description: -	
Reporting group title	Reduced-dose combination therapy
Reporting group description: -	

Serious adverse events	Full-dose monotherapy	Reduced-dose combination therapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	33 / 83 (39.76%)	13 / 77 (16.88%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events	2	0	
General disorders and administration site conditions			
Dehydration			
subjects affected / exposed	1 / 83 (1.20%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 83 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	4 / 83 (4.82%)	2 / 77 (2.60%)	
occurrences causally related to treatment / all	4 / 4	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			

subjects affected / exposed	12 / 83 (14.46%)	2 / 77 (2.60%)	
occurrences causally related to treatment / all	12 / 12	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infection			
subjects affected / exposed	15 / 83 (18.07%)	8 / 77 (10.39%)	
occurrences causally related to treatment / all	15 / 15	8 / 8	
deaths causally related to treatment / all	2 / 2	0 / 0	
Mucositis management			
subjects affected / exposed	1 / 83 (1.20%)	0 / 77 (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: 3 %

Non-serious adverse events	Full-dose monotherapy	Reduced-dose combination therapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	83 / 83 (100.00%)	77 / 77 (100.00%)	
Investigations			
Hyponatraemia			
subjects affected / exposed	5 / 83 (6.02%)	1 / 77 (1.30%)	
occurrences (all)	5	1	
Vascular disorders			
Embolism			
subjects affected / exposed	7 / 83 (8.43%)	3 / 77 (3.90%)	
occurrences (all)	7	3	
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	18 / 83 (21.69%)	55 / 77 (71.43%)	
occurrences (all)	18	55	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	14 / 83 (16.87%)	16 / 77 (20.78%)	
occurrences (all)	14	16	
Anaemia			

subjects affected / exposed	54 / 83 (65.06%)	46 / 77 (59.74%)	
occurrences (all)	54	46	
Thrombocytopenia			
subjects affected / exposed	13 / 83 (15.66%)	20 / 77 (25.97%)	
occurrences (all)	13	20	
General disorders and administration site conditions			
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	13 / 83 (15.66%)	15 / 77 (19.48%)	
occurrences (all)	13	15	
Fatigue			
subjects affected / exposed	60 / 83 (72.29%)	60 / 77 (77.92%)	
occurrences (all)	60	60	
Dehydration			
subjects affected / exposed	4 / 83 (4.82%)	0 / 77 (0.00%)	
occurrences (all)	4	0	
Pain			
subjects affected / exposed	32 / 83 (38.55%)	25 / 77 (32.47%)	
occurrences (all)	32	25	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	37 / 83 (44.58%)	42 / 77 (54.55%)	
occurrences (all)	37	42	
Diarrhoea			
subjects affected / exposed	31 / 83 (37.35%)	30 / 77 (38.96%)	
occurrences (all)	31	30	
Vomiting			
subjects affected / exposed	24 / 83 (28.92%)	13 / 77 (16.88%)	
occurrences (all)	24	13	
Constipation			
subjects affected / exposed	10 / 83 (12.05%)	9 / 77 (11.69%)	
occurrences (all)	10	9	
Infections and infestations			
Mucositis management			
subjects affected / exposed	9 / 83 (10.84%)	8 / 77 (10.39%)	
occurrences (all)	9	8	
Infection			

subjects affected / exposed occurrences (all)	11 / 83 (13.25%) 11	6 / 77 (7.79%) 6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 January 2014	Questionnaire VES13 added, Barthel deleted. GFR clarified in relation to treatment.
17 February 2014	Corrections and comments from authorities.
14 April 2014	Elaboration of Safety section. Corrections in patient information.
03 November 2014	Author added to the protocol committee. General changes to protocol.
24 April 2017	Number of patients increased from 150 to 160. Number of sites changed, as Finland entered the study.
08 September 2017	Extension of inclusion period until Nov. 1st 2017. Extension of study period until LPLV May 1st 2019. Change of PI in Herning from Nina Keldsen to Halla Skuladottir.

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/30852136