Clinical trial results:
Bevacizumab, Interleukin-2 and Interferon-alpha in metastathic renal cell carcinoma

Summary

EudraCT number	2009-012010-52
Trial protocol	DK
Global end of trial date	31 May 2017

Results information

Result version number	v1 (current)
This version publication date	03 December 2020
First version publication date	03 December 2020
Summary attachment (see zip file)	DaRenCa study-1 (Frede Donskov et al, a randomized phase II trial, DaRenCa study-1, Acta Oncologica, 2018.pdf)

Trial information

Trial identification

Sponsor protocol code	mRCC

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01274273
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Aarhus University
Sponsor organisation address	Noerrebrogade 44, Aarhus, Denmark,
Public contact	Frede Donskov, Aarhus University Hospital, +45 27147015, fd@oncology.au.dk
Scientific contact	Frede Donskov, Aarhus University Hospital, +45 27147015, fd@oncology.au.dk
Sponsor organisation name	Department of Oncology, Aarhus University Hospital
Sponsor organisation address	Noerrebrogade 44, Aarhus, Denmark,
Public contact	Frede Donskov , Aarhus university hospital, +45 27147015, fd@oncology.au.dk
Scientific contact	Frede Donskov , Aarhus university hospital, +45 27147015, fd@oncology.au.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	No

1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 May 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 May 2017
Global end of trial reached?	Yes
Global end of trial date	31 May 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Avastin as monotherapy has effect in mRCC. Avastin in combination with interferon-alfa (IFN-α) has significant efficacy in mRCC and has been approved by EMEA.
The present study assessed whether the combination of Interleukin-2 (IL-2) and IFN-α with Avastin may add efficacy in patients with mRCC with a tolerable safety profile.
Primary endpoint: Progression Free Survival

Protection of trial subjects:

No specific measures

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 October 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 118
Worldwide total number of subjects	118
EEA total number of subjects	118

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)	98
From 65 to 84 years	20
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

N/A

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	IL2/INF/BEV2
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: 10 mg/kg IV	
Arm title	IL2/INF
Arm description: -	
Arm type	Standard therapy
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	IL2/INF/BEV2	IL2/INF
Started	59	59
Completed	59	59

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	118	118	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	116	116	
From 65-84 years	2	2	
85 years and over	0	0	
Age continuous Units: years			
median	57		
full range (min-max)	28 to 70	-	
Gender categorical Units: Subjects			
Female	25	25	
Male	93	93	
IMDC			
IMDC risk classification			
Units: Subjects			
Favorable	26	26	
Intermediate	68	68	
Poor	24	24	
Karnofsky PS			
Karnofsky PS			
Units: Subjects			
100	68	68	
90	35	35	
80	10	10	
70	5	5	
MSKCC risk			
MSKCC risk classification			
Units: Subjects			
Favorable	61	61	
intermediate	57	57	
Metastasis -free interval Units: Subjects			

< 1 year	88	88	
>1	30	30	
Nephrectomy Units: Subjects			
yes	101	101	
No	17	17	

Subject analysis sets	
Subject analysis set title	IL2/IFN/BEV
Subject analysis set type	Intention-to-treat
Subject analysis set description: Patients treated with IL2/IFN/BEV	
Subject analysis set title	IL2/INF
Subject analysis set type	Intention-to-treat
Subject analysis set description: Patients treated with IL2/INF	

Reporting group values	IL2/IFN/BEV	IL2/INF	
Number of subjects	59	59	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	58	58	
From 65-84 years	1	1	
85 years and over	0	0	
Age continuous Units: years			
median	58	55	
full range (min-max)	28 to 70	37 to 69	
Gender categorical Units: Subjects			
Female	13	12	
Male	46	47	
IMDC			
IMDC risk classification			
Units: Subjects			
Favorable	14	12	
Intermediate	32	36	
Poor	13	11	
Karnofsky PS			
Karnofsky PS			
Units: Subjects			
100	31	37	
90	19	16	

80	6	4	
70	3	2	
MSKCC risk			
MSKCC risk classification			
Units: Subjects			
Favorable	30	31	
intermediate	29	28	
Metastasis -free interval Units: Subjects			
< 1 year	43	45	
>1	16	14	
Nephrectomy Units: Subjects			
yes	50	51	
No	9	8	

End points

End points reporting groups	
Reporting group title	IL2/INF/BEV2
Reporting group description: -	
Reporting group title	IL2/INF
Reporting group description: -	
Subject analysis set title	IL2/IFN/BEV
Subject analysis set type	Intention-to-treat
Subject analysis set description: Patients treated with IL2/IFN/BEV	
Subject analysis set title	IL2/INF
Subject analysis set type	Intention-to-treat
Subject analysis set description: Patients treated with IL2/INF	

Primary: Progression free survival (PFS)	
End point title	Progression free survival (PFS)
End point description:	
End point type	Primary
End point timeframe: Response evaluation (according to RECIST 1.1) every 12th week until week 104. Hereafter every 24th week until disease progression	

End point values	IL2/INF/BEV2	IL2/INF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	59		
Units: months				
median (confidence interval 95%)	8.0 (4.2 to 11.9)	8.1 (5.1 to 11.0)		

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	IL2/INF/BEV2 v IL2/INF
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 5
Method	Logrank
Parameter estimate	Hazard ratio (HR)

Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	Efficacy analysis

Statistical analysis description:

Differences in progression free survival in the two treatment arms will be tested with a two-sided log rank
test at the 5% alpha level. Kaplan Meier curves will be displayed, with median progression free survival estimates and confidence limits given.

Comparison groups	IL2/INF/BEV2 v IL2/INF
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 5
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Secondary: Overall survival

End point title	Overall survival

End point description:

End point type	Secondary

End point timeframe:

Response evaluation (according to RECIST 1.1) every 12th week until week 104. Hereafter every 24th week until disease progression or death

End point values	IL2/INF/BEV2	IL2/INF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	59		
Units: Months				
median (confidence interval 95%)	30.3 (20.6 to 40.0)	34.1 (19.9 to 48.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective respons rate (ORR)

End point title	Objective respons rate (ORR)

End point description:

End point type	Secondary

End point timeframe:

Response evaluation (according to RECIST 1.1) every 12th week until week 104. Hereafter every 24th week until disease progression

End point values	IL2/INF/BEV2	IL2/INF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	59		
Units: Rate	44	29		

Statistical analyses

No statistical analyses for this end point

Secondary: Time-to-treatment failure (TTF)

End point title	Time-to-treatment failure (TTF)

End point description:

End point type	Secondary

End point timeframe:

Response evaluation (according to RECIST 1.1) every 12th week until week 104. Hereafter every 24th week until disease progression

End point values	IL2/INF/BEV2	IL2/INF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	59		
Units: months				
median (confidence interval 95%)	7.4 (4.4 to 10.3)	5.6 (2.6 to 8.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of no evidence of disease (NED)

End point title	Frequency of no evidence of disease (NED)

End point description:

End point type	Secondary

End point timeframe:

Response evaluation (according to RECIST 1.1) every 12th week until week 104. Hereafter every 24th week until disease progression

End point values	IL2/INF/BEV2	IL2/INF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	59		
Units: patients	3	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of surgical residual disease

End point title	Frequency of surgical residual disease

End point description:

End point type	Secondary

End point timeframe:

Response evaluation (according to RECIST 1.1) every 12th week until week 104. Hereafter every 24th week until disease progression

End point values	IL2/INF/BEV2	IL2/INF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	59		
Units: patients	17	17		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse event was reported during the clinical study as per protocol	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	current

Reporting groups	
Reporting group title	IL2/IFN/BEV
Reporting group description:	
Experimental arm	
Reporting group title	IL2/IFN-alfa
Reporting group description:	
Control arm	

Serious adverse events	IL2/IFN/BEV	IL2/IFN-alfa	
Total subjects affected by serious adverse events			
subjects affected / exposed	50 / 59 (84.75%)	49 / 59 (83.05%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Weight decrease neonatal			
subjects affected / exposed	2 / 59 (3.39%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	15 / 59 (25.42%)	2 / 59 (3.39%)	
occurrences causally related to treatment / all	15 / 15	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypotension			
subjects affected / exposed	1 / 59 (1.69%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
thrombosis			

subjects affected / exposed	4 / 59 (6.78%)	11 / 59 (18.64%)	
occurrences causally related to treatment / all	4 / 4	11 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	38 / 59 (64.41%)	36 / 59 (61.02%)	
occurrences causally related to treatment / all	38 / 38	36 / 36	
deaths causally related to treatment / all	0 / 0	0 / 0	
flu like symptoms			
subjects affected / exposed	22 / 59 (37.29%)	24 / 59 (40.68%)	
occurrences causally related to treatment / all	22 / 22	24 / 24	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	5 / 59 (8.47%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	5 / 5	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	3 / 59 (5.08%)	4 / 59 (6.78%)	
occurrences causally related to treatment / all	3 / 3	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
vomiting			
subjects affected / exposed	2 / 59 (3.39%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	0 / 59 (0.00%)	3 / 59 (5.08%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Cough			

subjects affected / exposed	1 / 59 (1.69%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	3 / 59 (5.08%)	3 / 59 (5.08%)	
occurrences causally related to treatment / all	3 / 3	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 59 (1.69%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pruritus			
subjects affected / exposed	2 / 59 (3.39%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
confusion			
subjects affected / exposed	4 / 59 (6.78%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	4 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 59 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	15 / 59 (25.42%)	15 / 59 (25.42%)	
occurrences causally related to treatment / all	15 / 15	15 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	IL2/IFN/BEV	IL2/IFN-alfa	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	59 / 59 (100.00%)	59 / 59 (100.00%)	
Investigations			
Weight decreased			
subjects affected / exposed	33 / 59 (55.93%)	38 / 59 (64.41%)	
occurrences (all)	33	38	
Vascular disorders			
Hypertension			
subjects affected / exposed	17 / 59 (28.81%)	8 / 59 (13.56%)	
occurrences (all)	17	8	
Hypotension			
subjects affected / exposed	10 / 59 (16.95%)	5 / 59 (8.47%)	
occurrences (all)	10	5	
Thrombosis			
subjects affected / exposed	4 / 59 (6.78%)	11 / 59 (18.64%)	
occurrences (all)	4	11	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	19 / 59 (32.20%)	20 / 59 (33.90%)	
occurrences (all)	19	20	
flu like symptoms			
subjects affected / exposed	34 / 59 (57.63%)	31 / 59 (52.54%)	
occurrences (all)	34	31	
Injection site reaction			
subjects affected / exposed	34 / 59 (57.63%)	40 / 59 (67.80%)	
occurrences (all)	34	40	
Gastrointestinal disorders			
Diarrhea	Additional description: No new or unexpected toxicity was observed		
subjects affected / exposed	33 / 59 (55.93%)	42 / 59 (71.19%)	
occurrences (all)	33	42	
Nausea			
subjects affected / exposed	50 / 59 (84.75%)	48 / 59 (81.36%)	
occurrences (all)	50	48	
Vomiting			
subjects affected / exposed	31 / 59 (52.54%)	33 / 59 (55.93%)	
occurrences (all)	31	33	

Dyspepsia			
subjects affected / exposed	7 / 59 (11.86%)	18 / 59 (30.51%)	
occurrences (all)	7	18	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	11 / 59 (18.64%)	12 / 59 (20.34%)	
occurrences (all)	11	12	
Dyspnoea			
subjects affected / exposed	24 / 59 (40.68%)	18 / 59 (30.51%)	
occurrences (all)	24	18	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	25 / 59 (42.37%)	20 / 59 (33.90%)	
occurrences (all)	25	20	
Dry skin			
subjects affected / exposed	42 / 59 (71.19%)	48 / 59 (81.36%)	
occurrences (all)	42	48	
Rash			
subjects affected / exposed	11 / 59 (18.64%)	6 / 59 (10.17%)	
occurrences (all)	11	6	
Pruritus			
subjects affected / exposed	50 / 59 (84.75%)	35 / 59 (59.32%)	
occurrences (all)	50	35	
Psychiatric disorders			
confusion			
subjects affected / exposed	14 / 59 (23.73%)	17 / 59 (28.81%)	
occurrences (all)	14	17	
Depression			
subjects affected / exposed	19 / 59 (32.20%)	15 / 59 (25.42%)	
occurrences (all)	19	15	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	7 / 59 (11.86%)	0 / 59 (0.00%)	
occurrences (all)	7	0	
Musculoskeletal and connective tissue disorders			

Pain in extremity subjects affected / exposed occurrences (all)	10 / 59 (16.95%) 10	1 / 59 (1.69%) 1	
Infections and infestations Stomatitis subjects affected / exposed occurrences (all)	19 / 59 (32.20%) 19	10 / 59 (16.95%) 10	
Metabolism and nutrition disorders Dehydration subjects affected / exposed occurrences (all)	10 / 59 (16.95%) 10	8 / 59 (13.56%) 8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported