

**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
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**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?
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Notes:

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### 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:

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### General information about the trial

Main objective of the trial:

Avastin as monotherapy has effect in mRCC. Avastin in combination with interferon-alfa (IFN- $\alpha$ ) 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- $\alpha$  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:

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### 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:

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#### 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
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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

<b>Statistical analysis title</b>	Efficacy analysis
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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
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End point description:

End point type	Secondary
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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

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**Secondary: Objective respons rate (ORR)**

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End point title	Objective respons rate (ORR)
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End point description:

End point type	Secondary
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End point timeframe:

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

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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		

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Time-to-treatment failure (TTF)**

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

End point type	Secondary
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End point timeframe:

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

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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)		

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Frequency of no evidence of disease (NED)**

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End point title	Frequency of no evidence of disease (NED)
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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
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	current
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### Reporting groups

Reporting group title	IL2/IFN/BEV
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Reporting group description:

Experimental arm

Reporting group title	IL2/IFN-alfa
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Reporting group description:

Control arm

<b>Serious adverse events</b>	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	
<b>General disorders and administration site conditions</b>			
<b>Fatigue</b>			
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	
<b>flu like symptoms</b>			
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	
<b>Gastrointestinal disorders</b>			
<b>Diarrhoea</b>			
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	
<b>Nausea</b>			
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	
<b>vomiting</b>			
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	
<b>Dyspepsia</b>			
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	
<b>Respiratory, thoracic and mediastinal disorders</b>			
<b>Cough</b>			

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	
<b>Dyspnoea</b>			
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	
<b>Skin and subcutaneous tissue disorders</b>			
<b>Rash</b>			
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	
<b>Pruritus</b>			
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	
<b>Psychiatric disorders</b>			
<b>confusion</b>			
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	
<b>Depression</b>			
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	
<b>Metabolism and nutrition disorders</b>			
<b>Dehydration</b>			
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 %

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

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

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported