Clinical trial results:
Phase II study of first-line therapy with Thalidomide in combination with Peg-introna and decrescendo IL-2 in patients with metastatic malignant melanoma

Summary

EudraCT number	2004-005166-20
Trial protocol	DK
Global end of trial date	01 April 2014

Results information

Result version number	v1 (current)
This version publication date	10 October 2021
First version publication date	10 October 2021

Trial information

Trial identification

Sponsor protocol code	04.10

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 2, entrance 140, basement, Odense C, Denmark, 5000
Public contact	Ida Coordt Elle, Odense University Hospital, 45 29335922, ida.coordt.elle@rsyd.dk
Scientific contact	Lars Bastholt, Odense University Hospital, 45 24849408, lars.bastholt@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	31 December 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 April 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Determination of efficacy and toxicity of a new combination of drugs

Protection of trial subjects:

Patients were treated only at three specialized centres in Denmark, with personnel trained in handling the specific known toxicities of this type of treatment.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 January 2007
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Scientific research
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 464
Worldwide total number of subjects	464
EEA total number of subjects	464

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)	1
Adults (18-64 years)	200
From 65 to 84 years	263
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between January 2007 and April 2014, 464 Danish patients received high-dose (HD) interleukin-2 (IL-2) and interferon (IFN) as first-line treatment
for metastatic melanoma. Our data represent the largest cohort of patients with metastatic melanoma worldwide, with relevant data on all patients and no patients lost to follow-up.

Pre-assignment

Screening details:

Baseline staging included patient history; physical examination, ECOG performance status (PS); CT of the brain, neck, chest
and abdomen); and blood chemistry, CRP, sodium, potassium, creatinine, ALAT,
LDH and alkaline phosphatase.

Period 1

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

Blinding implementation details:

With the availability of ipilimumab in July 2010 and later also with the approval of drugs targeting BRAF mutations, relevant second-line treatment option after IL-2 became available. To test the hypothesis of positive impact of these new treatment options, we divided our material into two subgroups, before and after July 1, 2010. We compared the aforementioned biomarkers in
the two groups and subsequent analyses of response rate(RR), PFS and OS were performed.

Arms

Are arms mutually exclusive?	Yes
Arm title	Before July 1, 2010

Arm description:

Patients treated before July 1st, 2010

Arm type	Experimental
Investigational medicinal product name	Aldesleukin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The HD IL-2 regimen started in week 2 and consisted of aldesleukin (Proleukin, Novartis): 18 MU/m2 in the first 6 h, 18 MU/m2 in the next 12 h, 18 MU/m2 in the subsequent 24 h and followed by 4.5 MU/m2 per day for the next 3 days. IL-2 was administered as continuous intravenous infusions.

Investigational medicinal product name	IFN alpha 2b
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Until July 2009, the IFN
dose was given as IFN alpha 2b (IntronA, ScheringPlough), 10 MU subcutaneous (s.c.), on days 1, 3 and 5.
Thereafter, IFN was given as pegylated IFN alpha 2b,
(PEG-Intron, Schering-Plough), 300 mg s.c., on day 1.

Arm title	After July 1st, 2010
Arm description: Patients treated after July 1st, 2010.	
Arm type	Experimental
Investigational medicinal product name	Aldesleukin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: The HD IL-2 regimen started in week 2 and consisted of aldesleukin (Proleukin, Novartis): 18 MU/m2 in the first 6 h, 18 MU/m2 in the next 12 h, 18 MU/m2 in the subsequent 24 h and followed by 4.5 MU/m2 per day for the next 3 days. IL-2 was administered as continuous intravenous infusions.	
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Number of subjects in period 1	Before July 1, 2010	After July 1st, 2010
Started	232	232
Completed	232	232

Baseline characteristics

Reporting groups

Reporting group title	Trial

Reporting group description: -

Reporting group values	Trial	Total	
Number of subjects	464	464	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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 65-84 years		0	
85 years and over		0	
Age		0	
Age continuous Units: years			
median	59		
full range (min-max)	17 to 76	-	
Gender categorical Units: Subjects			
Female	185	185	
Male	279	279	

Subject analysis sets

Subject analysis set title	Before July 1st, 2010
Subject analysis set type	Full analysis

Subject analysis set description:

Baseline demographics and disease characteristics of the treated population.

Subject analysis set title	After July 1st, 2010
Subject analysis set type	Full analysis

Subject analysis set description:

Patients treated after July 1st, 2010.

Reporting group values	Before July 1st, 2010	After July 1st, 2010	
Number of subjects	232	232	
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			
Age continuous Units: years median full range (min-max)	 59 17 to 76		
Gender categorical Units: Subjects			
Female	185		
Male	279		

End points

End points reporting groups

Reporting group title	Before July 1, 2010
Reporting group description: Patients treated before July 1st, 2010	
Reporting group title	After July 1st, 2010
Reporting group description: Patients treated after July 1st, 2010.	
Subject analysis set title	Before July 1st, 2010
Subject analysis set type	Full analysis
Subject analysis set description: Baseline demographics and disease characteristics of the treated population.	
Subject analysis set title	After July 1st, 2010
Subject analysis set type	Full analysis
Subject analysis set description: Patients treated after July 1st, 2010.	

Primary: Overall response rate

End point title	Overall response rate[1]
End point description:	
End point type	Primary
End point timeframe: 5 years	

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 attached publication for statistical analysis.

End point values	Before July 1, 2010	After July 1st, 2010	Before July 1st, 2010	After July 1st, 2010
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	232	232	232	232
Units: percent				
arithmetic mean (standard deviation)	23.3 (± 1)	27.6 (± 1)	23.3 (± 1)	27.6 (± 1)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
No data on toxicity were collected	
Adverse event reporting additional description:	
No data on toxicity were collected.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups	
Reporting group title	Patients
Reporting group description:	
No data on toxicity were collected. The number of affected subjects is made up.	

Serious adverse events	Patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 464 (0.22%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Immune system disorders			
Capillary leak syndrome	Additional description: No data on toxicity were collected. The number of affected subjects is made up.		
subjects affected / exposed	1 / 464 (0.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		

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

Non-serious adverse events	Patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 464 (0.22%)		
General disorders and administration site conditions			
Fatigue	Additional description: No data on toxicity were collected. The number of affected subjects is made up.		
subjects affected / exposed	1 / 464 (0.22%)		
occurrences (all)	1		

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

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31108244