Clinical trial results:
HD-R3i - A prospective, randomized, placebo-controlled, international, multicenter phase I/II trial of RAD001 (everolimus) in combination with DHAP as induction therapy in patients with relapsed or refractory Hodgkin Lymphoma

Summary

EudraCT number	2010-021086-73
Trial protocol	DE
Global end of trial date	31 December 2018

Results information

Result version number	v1 (current)
This version publication date	09 April 2020
First version publication date	09 April 2020

Trial information

Trial identification

Sponsor protocol code	Uni-Koeln-1443

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01453504
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Cologne
Sponsor organisation address	Albertus Magnus-Platz, Köln, Germany, 50923
Public contact	Trial Coordination Center of the German Hodgkin Study Group (GHSG), German Hodgkin Study Group (GHSG), 0049 221478 88 200, ghsg@uk-koeln.de
Scientific contact	Trial Coordination Center of the German Hodgkin Study Group (GHSG), German Hodgkin Study Group (GHSG), 0049 221478 88 200, ghsg@uk-koeln.de

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	18 January 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 December 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Phase I: To identify the recommended phase-II dose of RAD001 in combination with DHAP (Ever-DHAP)
Phase II: To demonstrate the efficacy of Ever-DHAP as induction therapy

Protection of trial subjects:

Written informed consent prior to study entry; IDMC monitoring; Phase I: 3+3 design with recruitment pause after completion of each dose level; start of phase II only after approval of ethics committee following review of phase I results.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 August 2012
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	Germany: 73
Worldwide total number of subjects	73
EEA total number of subjects	73

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)	73
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between 13Aug2012 and 24Jan2014, 14 patients were enrolled into phase I according to a modified 3+3 design. Enrollment for phase II started on 04Jul2014, with randomization between verum and placebo. Due to slow recruitment, the placebo arm was closed after 9 patients, and enrollment to verum continued up to a total of 50 patients on 07Mar2018.

Pre-assignment

Screening details:

Main inclusion criteria: Histologically confirmed first relapse of HL, HL refractory to first-line treatment or multiple relapse without prior HDCT/SCT; Age 18-60 years; ECOG<=2; normal organ function. Main exclusion criteria: Relevant concurrent disease; pregnancy or lactation.

Period 1

Period 1 title	Phase I and II (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Phase I was not randomized; patients received Ever-DHAP with everolimus on different dose levels according to a modified 3+3 design. Phase II started randomized between Ever-DHAP and Placebo-DHAP. After enrollment of 9 patients per arm, the placebo arm was closed and all subsequent patients were enrolled into the verum arm without randomization or blinding.

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase I, 2.5 mg

Arm description:

Two cycles of Ever-DHAP combination chemotherapy in 14-day intevals with everolimus at a dose of 2.5 mg

Arm type	Experimental
Investigational medicinal product name	Everolimus
Investigational medicinal product code	
Other name	RAD001
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2.5 mg everolimus administered on days 1-14 of each cycle

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

40 mg dexamethasone administered on days 1-4 of each cycle

Investigational medicinal product name	Cytarabine
Investigational medicinal product code	
Other name	Ara-C
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use

Dosage and administration details: 2000 mg cytarabine per m² BSA administered every 12 hours on day 2 of each cycle	
Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 100 mg cisplatin per m² BSA administered on day 1 of each cycle over 24 hours	
Arm title	Phase I, 5 mg
Arm description: Two cycles of Ever-DHAP combination chemotherapy in 14-day intevals with everolimus at a dose of 5 mg	
Arm type	Experimental
Investigational medicinal product name	Everolimus
Investigational medicinal product code	
Other name	RAD001
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 5 mg everolimus administered on days 1-14 of each cycle	
Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use
Dosage and administration details: 40 mg dexamethasone administered on days 1-4 of each cycle	
Investigational medicinal product name	Cytarabine
Investigational medicinal product code	
Other name	Ara-C
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use
Dosage and administration details: 2000 mg cytarabine per m² BSA administered every 12 hours on day 2 of each cycle	
Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 100 mg cisplatin per m² BSA administered on day 1 of each cycle over 24 hours	
Arm title	Phase I, 7.5 mg
Arm description: Two cycles of Ever-DHAP combination chemotherapy in 14-day intevals with everolimus at a dose of 7.5 mg	
Arm type	Experimental

Investigational medicinal product name	Everolimus
Investigational medicinal product code	
Other name	RAD001
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

7.5 mg everolimus administered on days 1-14 of each cycle

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

40 mg dexamethasone administered on days 1-4 of each cycle

Investigational medicinal product name	Cytarabine
Investigational medicinal product code	
Other name	Ara-C
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

2000 mg cytarabine per m² BSA administered every 12 hours on day 2 of each cycle

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

Dosage and administration details:

100 mg cisplatin per m² BSA administered on day 1 of each cycle over 24 hours

Arm title	Phase I, 10 mg

Arm description:

Two cycles of Ever-DHAP combination chemotherapy in 14-day intevals with everolimus at a dose of 10 mg

Arm type	Experimental
Investigational medicinal product name	Everolimus
Investigational medicinal product code	
Other name	RAD001
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

10 mg everolimus administered on days 1-14 of each cycle

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

40 mg dexamethasone administered on days 1-4 of each cycle

Investigational medicinal product name	Cytarabine
Investigational medicinal product code	
Other name	Ara-C
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use

Dosage and administration details: 2000 mg cytarabine per m² BSA administered every 12 hours on day 2 of each cycle	
Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 100 mg cisplatin per m² BSA administered on day 1 of each cycle over 24 hours	
Arm title	Phase II, Ever-DHAP
Arm description: Two cycles of Ever-DHAP combination chemotherapy in 14-day intevals with everolimus at a dose of 10 mg	
Arm type	Experimental
Investigational medicinal product name	Everolimus
Investigational medicinal product code	
Other name	RAD001
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 10 mg everolimus administered on days 1-14 of each cycle	
Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use
Dosage and administration details: 40 mg dexamethasone administered on days 1-4 of each cycle	
Investigational medicinal product name	Cytarabine
Investigational medicinal product code	
Other name	Ara-C
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use
Dosage and administration details: 2000 mg cytarabine per m² BSA administered every 12 hours on day 2 of each cycle	
Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 100 mg cisplatin per m² BSA administered on day 1 of each cycle over 24 hours	
Arm title	Phase II, Plac-DHAP
Arm description: Two cycles of DHAP chemotherapy in 14-day intevals with placebo	
Arm type	Active comparator
Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details: 40 mg dexamethasone administered on days 1-4 of each cycle	
Investigational medicinal product name	Cytarabine
Investigational medicinal product code	
Other name	Ara-C
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use
Dosage and administration details: 2000 mg cytarabine per m² BSA administered every 12 hours on day 2 of each cycle	
Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 100 mg cisplatin per m² BSA administered on day 1 of each cycle over 24 hours	

Number of subjects in period 1	Phase I, 2.5 mg	Phase I, 5 mg	Phase I, 7.5 mg
Started	3	3	5
Start of treatment	3	3	5
Completed	3	3	3
Not completed	0	0	2
Consent withdrawn by subject	-	-	-
Adverse event, non-fatal	-	-	2
HL diagnosis disconfirmed	-	-	-

Number of subjects in period 1	Phase I, 10 mg	Phase II, Ever-DHAP	Phase II, Plac-DHAP
Started	3	50	9
Start of treatment	3	48	9
Completed	3	45	9
Not completed	0	5	0
Consent withdrawn by subject	-	1	-
Adverse event, non-fatal	-	3	-
HL diagnosis disconfirmed	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Phase I, 2.5 mg
Reporting group description:	
Two cycles of Ever-DHAP combination chemotherapy in 14-day intevals with everolimus at a dose of 2.5 mg	
Reporting group title	Phase I, 5 mg
Reporting group description:	
Two cycles of Ever-DHAP combination chemotherapy in 14-day intevals with everolimus at a dose of 5 mg	
Reporting group title	Phase I, 7.5 mg
Reporting group description:	
Two cycles of Ever-DHAP combination chemotherapy in 14-day intevals with everolimus at a dose of 7.5 mg	
Reporting group title	Phase I, 10 mg
Reporting group description:	
Two cycles of Ever-DHAP combination chemotherapy in 14-day intevals with everolimus at a dose of 10 mg	
Reporting group title	Phase II, Ever-DHAP
Reporting group description:	
Two cycles of Ever-DHAP combination chemotherapy in 14-day intevals with everolimus at a dose of 10 mg	
Reporting group title	Phase II, Plac-DHAP
Reporting group description:	
Two cycles of DHAP chemotherapy in 14-day intevals with placebo	

Reporting group values	Phase I, 2.5 mg	Phase I, 5 mg	Phase I, 7.5 mg
Number of subjects	3	3	5
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)	3	3	5
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	1	0	3
Male	2	3	2

Reporting group values	Phase I, 10 mg	Phase II, Ever-DHAP	Phase II, Plac-DHAP
Number of subjects	3	50	9

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)	3	50	9
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	2	17	2
Male	1	33	7

Reporting group values	Total		
Number of subjects	73		
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)	73		
From 65-84 years	0		
85 years and over	0		
Gender categorical Units: Subjects			
Female	25		
Male	48		

End points

End points reporting groups

Reporting group title	Phase I, 2.5 mg
Reporting group description:	
Two cycles of Ever-DHAP combination chemotherapy in 14-day intevals with everolimus at a dose of 2.5 mg	
Reporting group title	Phase I, 5 mg
Reporting group description:	
Two cycles of Ever-DHAP combination chemotherapy in 14-day intevals with everolimus at a dose of 5 mg	
Reporting group title	Phase I, 7.5 mg
Reporting group description:	
Two cycles of Ever-DHAP combination chemotherapy in 14-day intevals with everolimus at a dose of 7.5 mg	
Reporting group title	Phase I, 10 mg
Reporting group description:	
Two cycles of Ever-DHAP combination chemotherapy in 14-day intevals with everolimus at a dose of 10 mg	
Reporting group title	Phase II, Ever-DHAP
Reporting group description:	
Two cycles of Ever-DHAP combination chemotherapy in 14-day intevals with everolimus at a dose of 10 mg	
Reporting group title	Phase II, Plac-DHAP
Reporting group description:	
Two cycles of DHAP chemotherapy in 14-day intevals with placebo	

Primary: Rate of patients experiencing dose-limiting toxicities

End point title	Rate of patients experiencing dose-limiting toxicities[1][2]

End point description:

DLTs were divided into known toxicities of DHAP (category A) and putative toxicities of Ever-DHAP (category B). Initially, only category B toxicities were counted as DLTs. Once a certain toxicity of category A had been reported, this toxicity was henceforth categorized as DLT for all subsequent cases. If it occured again in any patient, it was counted as DLT.
Category A) grade III/IV infections; grade III/IV neurotoxicity; grade III/IV ototoxicity; grade III/IV nausea/vomiting despite appropriate antiemetics; grade III/IV nephrotoxicity; neutropenia grade IV for more than 10 days despite GCSF; thrombocytopenia grade IV for more than 5 days.
Category B) other non-haematological grade III/IV toxicities with the exception of grade III infections, grade III hyperglycemia and of nausea/vomiting in the absence of appropriate antiemetic therapy; unsuccessful stem cell mobilization (<2 x 106 CD34+ cells/kg) after 2 cycles.

End point type	Primary

End point timeframe:

DLTs were measured during 2 cycles of study treatment in combination with chemotherapy (Ever-DHAP) in phase I.

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: This was a phase I study with a modified 3+3 design. No dose-limiting toxicities were observed, thus dose escalation was done after 3 patients each and 10 mg of everolimus per day was chosen as recommended phase-II dose. It was decided not to treat additional 3 patients at that dose level because no DLTs had occurred thus far and the probability of observing DLTs in each of these 3 patients (the only scenario that would lead to a change in recommended dose) was low.
[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The end point "Rate of patients experiencing dose-limiting toxicities" was only analyzed in

phase I of the study. Thus, it is not reported for phase II patients.

End point values	Phase I, 2.5 mg	Phase I, 5 mg	Phase I, 7.5 mg	Phase I, 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3[3]	3
Units: patients				
Any DLT	0	0	0	0
No DLT	3	3	3	3

Notes:

[3] - 2 patients excluded from analysis due to treatment termination before end of cycle 2 (both no DLT).

Statistical analyses

No statistical analyses for this end point

Primary: Rate of CT-based complete remission after induction

End point title	Rate of CT-based complete remission after induction[4][5]

End point description:

Based on the exact binomial distribution, the null hypothesis "CR rate after Ever-DHAP < 21%" was to be tested with an exact single-stage phase-II design, assuming a CR rate after Ever-DHAP of 40% or higher. The Plac-DHAP arm was analyzed descriptively due to the small sample size after early closure.

End point type	Primary

End point timeframe:

Primary endpoint of phase II was the rate of patients with complete remission according to the CT-based final restaging which was to be performed ideally on day 21 of the second (Ever-)DHAP cycle.

Notes:

[4] - 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: Primary statistical analysis was to test H0 "CR rate after Ever-DHAP < 21%" against a one-sided alternative. It is not possible to enter this single-arm analysis in the system.
The observed CR rate of 27% (95% CI 15-42) with Ever-DHAP failed to reach this target and was not significantly superior to the historical benchmark for insufficient efficacy of 21% (p=0.23, exact one-sided binomial test).
[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The end point "Rate of CT-based complete remission after induction" was only analyzed in phase II of the study. Thus, it is not reported for phase I patients.

End point values	Phase II, Ever-DHAP	Phase II, Plac-DHAP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45[6]	9		
Units: patients				
CR	12	2		
Non-CR	33	7		

Notes:

[6] - 2 patients dropped out before start of treatment; 3 patients discontinued before restaging

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were assessed from start of treatment until the 28-day follow-up visit or start of a new HL therapy, whichever occured first.

Adverse event reporting additional description:

Expected AEs of CTCAE grades 3/4 were assessed on the therapy administration CRFs. Unexpected and serious AEs were (additionally) assessed on specific forms. Please note that SAEs may be reported twice (therapy administration and SAE form). Thus, non-serious AEs and SAEs might include duplicate events and do not add up to a total number of AEs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.1

Reporting groups

Reporting group title	Phase II, Ever-DHAP

Reporting group description:

Two cycles of Ever-DHAP combination chemotherapy in 14-day intevals with everolimus at a dose of 10 mg

Reporting group title	Phase II, Plac-DHAP

Reporting group description:

Two cycles of DHAP chemotherapy in 14-day intevals with placebo

Reporting group title	Phase I, 2.5 mg

Reporting group description:

Two cycles of Ever-DHAP combination chemotherapy in 14-day intevals with everolimus at a dose of 2.5 mg

Reporting group title	Phase I, 5 mg

Reporting group description:

Two cycles of Ever-DHAP combination chemotherapy in 14-day intevals with everolimus at a dose of 5 mg

Reporting group title	Phase I, 7.5 mg

Reporting group description:

Two cycles of Ever-DHAP combination chemotherapy in 14-day intevals with everolimus at a dose of 7.5 mg

Reporting group title	Phase I, 10 mg

Reporting group description:

Two cycles of Ever-DHAP combination chemotherapy in 14-day intevals with everolimus at a dose of 10 mg

Serious adverse events	Phase II, Ever-DHAP	Phase II, Plac-DHAP	Phase I, 2.5 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 48 (37.50%)	0 / 9 (0.00%)	0 / 3 (0.00%)
number of deaths (all causes)	3	0	1
number of deaths resulting from adverse events	0	0	0
Investigations			
Blood creatine increased			

subjects affected / exposed	1 / 48 (2.08%)	0 / 9 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	1 / 48 (2.08%)	0 / 9 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 48 (2.08%)	0 / 9 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Oculogyric crisis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 9 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	2 / 48 (4.17%)	0 / 9 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	1 / 48 (2.08%)	0 / 9 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 48 (4.17%)	0 / 9 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Nausea			

subjects affected / exposed	1 / 48 (2.08%)	0 / 9 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 48 (2.08%)	0 / 9 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Non-cardiac chest pain			
subjects affected / exposed	1 / 48 (2.08%)	0 / 9 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 48 (2.08%)	0 / 9 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 9 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 9 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	1 / 48 (2.08%)	0 / 9 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral candidiasis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 9 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumonia			
subjects affected / exposed	1 / 48 (2.08%)	0 / 9 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 48 (2.08%)	0 / 9 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Phase I, 5 mg	Phase I, 7.5 mg	Phase I, 10 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Blood creatine increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oculogyric crisis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			

subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Non-cardiac chest pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			

subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral candidiasis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Phase II, Ever-DHAP	Phase II, Plac-DHAP	Phase I, 2.5 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 48 (89.58%)	8 / 9 (88.89%)	2 / 3 (66.67%)
Cardiac disorders			
Cardiac disorder			
alternative dictionary used: NCI CTCAE 4.0			
alternative assessment type: Non-systematic			

subjects affected / exposed[1]	1 / 42 (2.38%)	0 / 8 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Neurotoxicity			
alternative dictionary used: NCI CTCAE 4.0			
alternative assessment type: Non-systematic			
subjects affected / exposed[2]	0 / 42 (0.00%)	0 / 8 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
alternative dictionary used: NCI CTCAE 4.0			
alternative assessment type: Non-systematic			
subjects affected / exposed[3]	7 / 42 (16.67%)	1 / 8 (12.50%)	0 / 3 (0.00%)
occurrences (all)	9	1	0
Thrombocytopenia			
alternative dictionary used: NCI CTCAE 4.0			
alternative assessment type: Non-systematic			
subjects affected / exposed[4]	38 / 42 (90.48%)	7 / 8 (87.50%)	2 / 3 (66.67%)
occurrences (all)	68	11	4
Leukopenia			
alternative dictionary used: NCI CTCAE 4.0			
alternative assessment type: Non-systematic			
subjects affected / exposed[5]	37 / 42 (88.10%)	7 / 8 (87.50%)	2 / 3 (66.67%)
occurrences (all)	55	7	3
Ear and labyrinth disorders			
Ototoxicity			
alternative dictionary used: NCI CTCAE 4.0			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 48 (0.00%)	0 / 9 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Nausea or vomiting			
alternative dictionary used: NCI CTCAE 4.0			
alternative assessment type: Non-systematic			

subjects affected / exposed[6]	6 / 42 (14.29%)	0 / 8 (0.00%)	0 / 3 (0.00%)
occurrences (all)	7	0	0
Mucositis			
alternative dictionary used: NCI CTCAE 4.0			
alternative assessment type: Non-systematic			
subjects affected / exposed[7]	3 / 42 (7.14%)	0 / 8 (0.00%)	0 / 3 (0.00%)
occurrences (all)	3	0	0
Gastrointestinal disorder			
alternative dictionary used: NCI CTCAE 4.0			
alternative assessment type: Non-systematic			
subjects affected / exposed[8]	2 / 42 (4.76%)	0 / 8 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Skin and subcutaneous tissue disorders			
Skin disorder			
alternative dictionary used: NCI CTCAE 4.0			
alternative assessment type: Non-systematic			
subjects affected / exposed[9]	1 / 42 (2.38%)	0 / 8 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Infection			
alternative dictionary used: NCI CTCAE 4.0			
alternative assessment type: Non-systematic			
subjects affected / exposed[10]	5 / 42 (11.90%)	0 / 8 (0.00%)	0 / 3 (0.00%)
occurrences (all)	5	0	0

Non-serious adverse events	Phase I, 5 mg	Phase I, 7.5 mg	Phase I, 10 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	5 / 5 (100.00%)	3 / 3 (100.00%)
Cardiac disorders			
Cardiac disorder			
alternative dictionary used: NCI CTCAE 4.0			
alternative assessment type: Non-systematic			
subjects affected / exposed[1]	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			

Neurotoxicity			
alternative dictionary used: NCI CTCAE 4.0			
alternative assessment type: Non-systematic			
subjects affected / exposed[2]	0 / 3 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
alternative dictionary used: NCI CTCAE 4.0			
alternative assessment type: Non-systematic			
subjects affected / exposed[3]	0 / 3 (0.00%)	2 / 5 (40.00%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Thrombocytopenia			
alternative dictionary used: NCI CTCAE 4.0			
alternative assessment type: Non-systematic			
subjects affected / exposed[4]	3 / 3 (100.00%)	5 / 5 (100.00%)	3 / 3 (100.00%)
occurrences (all)	4	8	5
Leukopenia			
alternative dictionary used: NCI CTCAE 4.0			
alternative assessment type: Non-systematic			
subjects affected / exposed[5]	3 / 3 (100.00%)	5 / 5 (100.00%)	3 / 3 (100.00%)
occurrences (all)	5	6	3
Ear and labyrinth disorders			
Ototoxicity			
alternative dictionary used: NCI CTCAE 4.0			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Nausea or vomiting			
alternative dictionary used: NCI CTCAE 4.0			
alternative assessment type: Non-systematic			
subjects affected / exposed[6]	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Mucositis			
alternative dictionary used: NCI CTCAE 4.0			

alternative assessment type: Non-systematic			
subjects affected / exposed[7]	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorder			
alternative dictionary used: NCI CTCAE 4.0			
alternative assessment type: Non-systematic			
subjects affected / exposed[8]	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Skin disorder			
alternative dictionary used: NCI CTCAE 4.0			
alternative assessment type: Non-systematic			
subjects affected / exposed[9]	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Infection			
alternative dictionary used: NCI CTCAE 4.0			
alternative assessment type: Non-systematic			
subjects affected / exposed[10]	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: 2 patients enrolled in the phase II Ever-DHAP arm did not receive any study therapy and were thus not exposed to AEs.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: 2 patients enrolled in the phase II Ever-DHAP arm did not receive any study therapy and were thus not exposed to AEs.

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: 2 patients enrolled in the phase II Ever-DHAP arm did not receive any study therapy and were thus not exposed to AEs.

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: 2 patients enrolled in the phase II Ever-DHAP arm did not receive any study therapy and were thus not exposed to AEs.

[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: 2 patients enrolled in the phase II Ever-DHAP arm did not receive any study therapy and were thus not exposed to AEs.

[6] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: 2 patients enrolled in the phase II Ever-DHAP arm did not receive any study therapy and were thus not exposed to AEs.

[7] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: 2 patients enrolled in the phase II Ever-DHAP arm did not receive any study therapy and were thus not exposed to AEs.
[8] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: 2 patients enrolled in the phase II Ever-DHAP arm did not receive any study therapy and were thus not exposed to AEs.
[9] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: 2 patients enrolled in the phase II Ever-DHAP arm did not receive any study therapy and were thus not exposed to AEs.
[10] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: 2 patients enrolled in the phase II Ever-DHAP arm did not receive any study therapy and were thus not exposed to AEs.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 November 2013	Implementation of current information regarding trial medication and editorial changes
03 June 2014	Implementation of current information regarding trial medication and editorial changes
16 January 2015	Implementation of current information regarding trial medication and editorial changes
06 October 2015	Closure of the placebo arm of the randomized phase II study due to insufficient patient recruitment, replacement of the study drug (everolimus) by commercially available everolimus
19 August 2016	Update of ICF, editorial changes

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Although recruitment of the placebo arm did not succeed, conclusions from this phase I/II trial are evident: adding everolimus to time-intensified DHAP is safe and feasible, but does not relevantly improve response to induction therapy.

Notes: