

**Clinical trial results:
A Phase I/II Study of Danusertib in Combination with Romidepsin in
Adult Patients with Mature Peripheral T Cell Lymphoma (PTCL)
Summary**

EudraCT number	2012-005157-23
Trial protocol	IT
Global end of trial date	15 December 2016

Results information

Result version number	v1 (current)
This version publication date	13 May 2020
First version publication date	13 May 2020
Summary attachment (see zip file)	Final Study Report_Synopsis (DART_Clinical Study Report_Synopsis-5-14.pdf)

Trial information**Trial identification**

Sponsor protocol code	DART
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Fondazione IRCCS Istituto Nazionale dei Tumori
Sponsor organisation address	via Venezian 1, Milano, Italy, 20133
Public contact	Clinical Trials Center, Fondazione IRCCS Istituto Nazionale dei Tumori, +39 0223903146, trialcenter@istitutotumori.mi.it
Scientific contact	Prof. Paolo Corradini and Dr Anna Guidetti, Fondazione IRCCS Istituto Nazionale dei Tumori, +39 0223902950, paolo.corradini@unimi.it

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	12 September 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 September 2016
Global end of trial reached?	Yes
Global end of trial date	15 December 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

(Ph I) To determine the maximum tolerated dose/recommended phase two dose (MTD/RP2D) and the associated dose-limiting toxicities (DLTs) observed during the first cycle of treatment with romidepsin in combination with danusertib in patients with relapsed or refractory Hodgkin and Non-Hodgkin Lymphoma.

(Ph II - NOT PERFORMED) To evaluate antitumor activity of romidepsin in combination with danusertib in patients with relapsed or refractory Peripheral T-Cell Lymphomas who have received at least one prior systemic therapy.

Protection of trial subjects:

This study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Each subject, or the subject's representative, signed an informed consent form prior to screening.

In the dose-escalation phase, patients were allocated to cohorts of 3 to 6 patients receiving a fixed dose of romidepsin combined with different doses of danusertib. The first two patients in each cohort should have been treated with at least 2 weeks of delay between the first and the second patient. In absence of 1st cycle DLT in the first patient, the third patient could be enrolled at any time.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 December 2013
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	Italy: 12
Worldwide total number of subjects	12
EEA total number of subjects	12

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	8
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between 11 December 2013 and 04 February 2016, 12 patients with relapsed or refractory Hodgkin and Non Hodgkin lymphoma, in the absence or unable or who refused to undergo alternative salvage regimens of proven efficacy, were enrolled in the Phase I part of the study. Two Italian centers conducted the study.

Pre-assignment

Screening details:

In the Phase I of the study both Hodgkin and non-Hodgkin lymphomas were included, while in the Phase II only patients with Peripheral T-cell lymphomas should have been enrolled. However, the study was closed on 15 December 2016 at the end of the Phase I part for Sponsor decision.

Period 1

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

Blinding implementation details:

not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	Dose level 1 (starting dose): DN200 - RM12

Arm description:

Danusertib 200 mg/m² given in association with Romidepsin at 12 mg/m² on Days 1 and 8 q4wks until disease progression, patient refusal to continue study treatment, withdrawal of patient consent, or the occurrence of unacceptable toxicity.

Arm type	Experimental
Investigational medicinal product name	Danusertib
Investigational medicinal product code	PHA-739358
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Danusertib was administered as 3-hr IV infusion on Days 1 and 8 q4wks. The starting dose of danusertib was 200 mg/m² (corresponding to a cumulative dose of 400 mg/m² in a 4-week cycle). The proposed starting dose was chosen based on the tolerability seen in the ongoing and completed clinical trials with similar or higher total doses.

Investigational medicinal product name	Romidepsin
Investigational medicinal product code	
Other name	Istodax
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Romidepsin was administered at the fixed dose of 12 mg/m² as 4-hr IV infusion on Days 1 and 8 q4wks, while dose escalation of danusertib was performed.

Arm title	Dose level -1: DN160 - RM12
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Arm description:

Danusertib 160 mg/m² given in association with Romidepsin at 12 mg/m² on Days 1 and 8 q4wks until disease progression, patient refusal to continue study treatment, withdrawal of patient consent, or the occurrence of unacceptable toxicity.

Arm type	Experimental
Investigational medicinal product name	Danusertib
Investigational medicinal product code	PHA-739358
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dosage and administration details Danusertib was administered as 3-hr IV infusion on Days 1 and 8 q4wks. The starting dose was 200 mg/m² and it was expected that at least two different doses of danusertib (i.e., 200 mg/m², 300 mg/m²) would have been tested, but due to dose limiting toxicities in 2/6 patients treated at the first dose level of danusertib (200 mg/m²) with romidepsin (12 mg/m²) the following 6 patients were treated at 160 mg/m² of danusertib plus romidepsin at 12 mg/m². No DLTs occurred among the 6 patients of the dose level -1 who completed the first cycle of treatment.

Investigational medicinal product name	Romidepsin
Investigational medicinal product code	
Other name	Istodax
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Romidepsin was administered at the fixed dose of 12 mg/m² as 4-hr IV infusion on Days 1 and 8 q4wks, while dose escalation of danusertib was performed.

Number of subjects in period 1	Dose level 1 (starting dose): DN200 - RM12	Dose level -1: DN160 - RM12
	Started	6
Completed	6	6

Baseline characteristics

Reporting groups

Reporting group title	Dose level 1 (starting dose): DN200 - RM12
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Reporting group description:

Danusertib 200 mg/m² given in association with Romidepsin at 12 mg/m² on Days 1 and 8 q4wks until disease progression, patient refusal to continue study treatment, withdrawal of patient consent, or the occurrence of unacceptable toxicity.

Reporting group title	Dose level -1: DN160 - RM12
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Reporting group description:

Danusertib 160 mg/m² given in association with Romidepsin at 12 mg/m² on Days 1 and 8 q4wks until disease progression, patient refusal to continue study treatment, withdrawal of patient consent, or the occurrence of unacceptable toxicity.

Reporting group values	Dose level 1 (starting dose): DN200 - RM12	Dose level -1: DN160 - RM12	Total
Number of subjects	6	6	12
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)	4	4	8
From 65-84 years	2	2	4
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	3	1	4
Male	3	5	8
Race Units: Subjects			
White	5	6	11
Black	1	0	1
Histological Diagnosis Units: Subjects			
Diffuse large B-cell lymphoma (DLBCL) NOS	1	2	3
Primary mediastinal large B-cell lymphoma	1	0	1
Nodular sclerosis classical Hodgkin lymphoma	1	0	1
Peripheral T-cell lymphoma NOS	1	2	3
Angioimmunoblastic T-cell lymphoma	2	0	2
Anaplastic large cell lymphoma (ALCL) ALK-	0	2	2

Stage at study entry			
Units: Subjects			
stage I	0	0	0
stage II	1	2	3
stage III	0	0	0
stage IV	5	4	9
ECOG at study entry			
ECOG (Eastern Cooperative Oncology Group) Performance Status			
Units: Subjects			
ECOG 0	4	2	6
ECOG 1	2	3	5
ECOG 2	0	1	1

End points

End points reporting groups

Reporting group title	Dose level 1 (starting dose): DN200 - RM12
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Reporting group description:

Danusertib 200 mg/m² given in association with Romidepsin at 12 mg/m² on Days 1 and 8 q4wks until disease progression, patient refusal to continue study treatment, withdrawal of patient consent, or the occurrence of unacceptable toxicity.

Reporting group title	Dose level -1: DN160 - RM12
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Reporting group description:

Danusertib 160 mg/m² given in association with Romidepsin at 12 mg/m² on Days 1 and 8 q4wks until disease progression, patient refusal to continue study treatment, withdrawal of patient consent, or the occurrence of unacceptable toxicity.

Primary: MTD/RP2D and first cycle DLTs (Phase I part)

End point title	MTD/RP2D and first cycle DLTs (Phase I part) ^[1]
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End point description:

Phase I part: determination of the maximum tolerated dose/recommended phase II dose (MTD/RP2D) and the associated dose-limiting toxicities (DLTs) observed during the first cycle of treatment with romidepsin in combination with danusertib in patients with relapsed or refractory Hodgkin and NonHodgkin Lymphoma.

End point type	Primary
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End point timeframe:

Cycle 1 (i.e. 4wks)

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: Descriptive analyses. In the dose-escalation phase, pts were allocated to cohorts of 3 to 6 pts, as follows: If 0/3 pts experienced 1st cycle DLT, the next cohort would start one dose level higher; If 1/3 pts experienced 1st cycle DLT, up to 3 more pts would start at the same dose level; If 1/6 experienced 1st cycle DLT, the next cohort would start one dose level higher. If $\geq 2/3$ or $\geq 2/6$ pts experienced DLTs in the 1st cycle, the then the MTD have been considered to be exceeded.

End point values	Dose level 1 (starting dose): DN200 - RM12	Dose level -1: DN160 - RM12		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: subjects who experienced DLT	2	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective tumor response defined by Cheson's Criteria (Phase I part)

End point title	Objective tumor response defined by Cheson's Criteria (Phase I part)
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End point description:

Best Overall Response

End point type

Secondary

End point timeframe:

All study period (disease response was be assessed every 2 cycles).

End point values	Dose level 1 (starting dose): DN200 - RM12	Dose level -1: DN160 - RM12		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: subjects				
Complete Response	0	0		
Partial Response	1	1		
Stable Disease	1	2		
Progressive Disease	3	3		
Not Evaluable	1	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From enrollment to 28 days after last treatment.

Adverse event reporting additional description:

Overall safety profile characterized by type, frequency, severity, timing of adverse events and laboratory abnormalities (coded using MedDRA 16.1, and graded according to NCI CTCAE version 4.03). The most frequent non serious adverse events (i.e. occurring in 15% or more of the treated patients) are reported in the table below.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Dose level 1 (starting dose): DN200 - RM12
Reporting group description:	-
Reporting group title	Dose level -1: DN160 - RM12
Reporting group description:	-
Reporting group title	All patients
Reporting group description:	-

Serious adverse events	Dose level 1 (starting dose): DN200 - RM12	Dose level -1: DN160 - RM12	All patients
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 12 (8.33%)
number of deaths (all causes)	1	0	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Death from lymphoma	Additional description: 3 SAEs occurred in one patient treated with danusertib at 200 mg/m ² and romidepsin at 12 mg/m ² : nausea (G3), neutropenic fever (G3) and death due to progressive disease. Only the neutropenic fever was considered related to the study drugs.		
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Blood and lymphatic system disorders			
Neutropenic fever (Grade 3)	Additional description: 3 SAEs occurred in one patient treated with danusertib at 200 mg/m ² and romidepsin at 12 mg/m ² : nausea (G3), neutropenic fever (G3) and death due to progressive disease. Only the neutropenic fever was considered related to the study drugs.		
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Nausea (Grade 3)	Additional description: 3 SAEs occurred in one patient treated with danusertib at 200 mg/m2 and romidepsin at 12 mg/m2: nausea (G3), neutropenic fever (G3) and death due to progressive disease. Only the neutropenic fever was considered related to the study drugs.		
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Dose level 1 (starting dose): DN200 - RM12	Dose level -1: DN160 - RM12	All patients
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	6 / 6 (100.00%)	12 / 12 (100.00%)
Investigations			
Neutropenia			
subjects affected / exposed	4 / 6 (66.67%)	1 / 6 (16.67%)	5 / 12 (41.67%)
occurrences (all)	4	1	5
Leukopenia			
subjects affected / exposed	2 / 6 (33.33%)	1 / 6 (16.67%)	3 / 12 (25.00%)
occurrences (all)	2	1	3
Thrombocytopenia			
subjects affected / exposed	2 / 6 (33.33%)	1 / 6 (16.67%)	3 / 12 (25.00%)
occurrences (all)	2	1	3
Anaemia			
subjects affected / exposed	3 / 6 (50.00%)	0 / 6 (0.00%)	3 / 12 (25.00%)
occurrences (all)	3	0	3
Hypokalaemia			
subjects affected / exposed	2 / 6 (33.33%)	1 / 6 (16.67%)	3 / 12 (25.00%)
occurrences (all)	2	1	3
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	2 / 12 (16.67%)
occurrences (all)	1	1	2
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	4 / 6 (66.67%)	2 / 6 (33.33%)	6 / 12 (50.00%)
occurrences (all)	4	2	6
Asthenia			

subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	3 / 6 (50.00%) 3	4 / 12 (33.33%) 4
Fatigue subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	1 / 6 (16.67%) 1	2 / 12 (16.67%) 2
Gastrointestinal disorders			
Nausea subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 2	4 / 6 (66.67%) 4	6 / 12 (50.00%) 6
Diarrhoea subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 2	3 / 6 (50.00%) 3	5 / 12 (41.67%) 5
Vomiting subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 2	2 / 6 (33.33%) 2	4 / 12 (33.33%) 4
Decreased appetite subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	2 / 6 (33.33%) 2	3 / 12 (25.00%) 3
Constipation subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 2	1 / 6 (16.67%) 1	3 / 12 (25.00%) 3
Abdominal pain subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 2	0 / 6 (0.00%) 0	2 / 12 (16.67%) 2
Dyspepsia subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	1 / 6 (16.67%) 1	2 / 12 (16.67%) 2
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 2	1 / 6 (16.67%) 1	3 / 12 (25.00%) 3
Dyspnoea subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 2	0 / 6 (0.00%) 0	2 / 12 (16.67%) 2
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	1 / 6 (16.67%)	2 / 6 (33.33%)	3 / 12 (25.00%)
occurrences (all)	1	2	3
Pain in extremity			
subjects affected / exposed	1 / 6 (16.67%)	2 / 6 (33.33%)	3 / 12 (25.00%)
occurrences (all)	1	2	3
Oedema peripheral			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	2 / 12 (16.67%)
occurrences (all)	2	0	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 December 2014	Only one protocol Amendment was issued (Am. 1, 19 December 2014). The main propose for this Amendment was to notify a change in Coordinating Investigator and Sponsor study management personnel. The amendment did not have any impact on the study procedures.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
21 September 2016	The Phase II part was not activated because the pharmacokinetics parameters of romidepsin could not be evaluated.	-

Notes:

Limitations and caveats

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

The primary end point of the Phase I was reached and the RP2D was defined as Danusertib 160 mg/m²+ Romidepsin 12 mg/m². The Phase II was not activated because it was not possible to evaluate the activity of romidepsin in combination with danusertib.

Notes: