2. SYNOPSIS

Name of Sponsor: Fondazione IRCCS Istituto Nazionale Tumori **Name of Finished Product:** Not applicable and Istodax® **Name of Active Ingredient:** Danusertib Hydrochloride (PHA-739358) and Romidepsin	*(For National Authority Use only)*
Title of Study: A Phase I/II Study of Danusertib in Combination with Romidepsin in Adult Patients with Mature Peripheral T-cell Lymphoma (PTCL)	
Protocol Number: EUDRACT 2012-005157-23	
Investigator(s): Paolo Corradini, MD, Dipartimento di Oncologia Medica ed Ematologia,Struttura Complessa di Ematologia, Fondazione IRCCS Istituto Nazionale Tumori,Via G. Venezian, 1 – 20133 Milan (Italy) – Alessandro Massimo Gianni, MD up to 30th October 2014. Alessandro Rambaldi, MD, Haematology Unit, Papa Giovanni XXIII Hospital, Piazza OMS, 1 – 24127 Bergamo (Italy)	
Study Centers: Two Italian centers conducted the study.	
Publication Reference:	
Studied Period (Years): First subject enrolled 11-December 2013 Last subject completed: 20-Sep 2016	**Phase of Development:** I-II
Objectives: **Primary:** Phase I part: • To determine 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 Non-Hodgkin Lymphoma. Phase II part: • To evaluate antitumor activity of romidepsin in combination with danusertib in patients with relapsed or refractory Peripheral T-Cell Lymphomas (PTCL) who have received at least one prior systemic therapy. **Secondary:** Phase I part: • To define the safety profile of the combination • To monitor blood level of romidepsin and danusertib at the end of infusion • To document any antitumor activity of the combination Phase II part: • To further evaluate the efficacy of the combination • To characterize the safety profile of the combination	
Methodology: This was a Phase I/II, open-label multicenter study. In Phase I part of the study, patients with relapsed or refractory Hodgkin (HL) and Non Hodgkin lymphoma (NHL), in the absence, unable to undergo alternative salvage regimens of proven efficacy or who refuse them, were enrolled, with the aim to determine the MTD/RP2D of the combination. Romidepsin was administered at the fixed dose of 12 mg/m^2 as 4-hr IV infusion on Days 1 and 8 q4wks, while dose escalation of danusertib was performed. Danusertib was administered as 3-hr IV infusion on Days 1 and 8 q4wks. The starting dose of danusertib was 200 mg/m^2	

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(corresponding to a cumulative dose of 400 mg/m^2 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.

Number of Subjects (Planned and Analyzed):
Phase I part

An overall sample size of approximately 8-10 treated patients was anticipated for the phase I part. Since the trial design foresaw that sequential dose-escalation steps would have been applied to cohorts of 3 patients up to the identification of the MTD (defined on 6 treated patients) the total number of patients who should have been enrolled and treated could not be planned preventively depending upon the toxicity observed and the resulting influence on cohort size and number of dose levels tested.

Phase II part (not performed)
The study was designed to follow a Simon optimal two-stage design with 80% power and 10% type I error for detecting a 30% rate of overall response which is 15% point superior to the null rate of 15%. After testing the drug on 19 T-cell lymphoma patients in the first stage, the trial was scheduled to be terminated if 3 or fewer patients responded. If the trial went to the second stage, a total of 39 patients would have been scheduled to be studied. If the total number of responding patients was less than or equal to 8, the null hypothesis would have been rejected. Treatment success was defined, in the study protocol, as an attainment of either CR or PR (objective response rate) and the primary efficacy analysis was based on the proportion of successes out of the total number of eligible and treated patients (success rate). Based on the current clinical scenario, a success rate of 30% would have been considered of clinical interest against the null hypothesis of a clinically uninteresting success rate as low as 15%. Assuming that the analysis would be conducted at the level $\alpha = 0.10$ (1-sided) with power $1-\beta = 0.80$, 39 patients would have been required, and the null hypothesis was to be rejected if $\geq 9/39$ successes were counted. The exact type 1 error and power are $\alpha = 0.097$ and $1-\beta = 0.803$.

Diagnosis and Main Criteria for Inclusion:

The study aimed at evaluating whether the combination of romidepsin with danusertib was safe and clinically effective when used as salvage regimen in patients with relapsed or refractory aggressive lymphomas. Since also B-cell lymphomas might have responded to the combination , to expedite study implementation in the dose-finding 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.

Subject had to meet the following main inclusion criteria to be eligible for enrollment into the study:

1. Signed and dated IEC-approved Informed Consent.
2. Phase I part: histologically or cytologically confirmed lymphoid malignancy as per WHO classification (Hodgkin lymphoma or non-Hodgkin lymphoma, for which standard curative or palliative measures do not exist, are no longer effective or have been refused by the patient).
3. Phase II part: histologically or cytologically confirmed relapsed or refractory Peripheral T-cell lymphomas, as per WHO classification who have received at least one prior systemic therapy (not just steroids or local radiation), ineligible and/or unwilling to undergo second line high-dose chemotherapy with either autologous or allogeneic stem cell transplantation (according to local guidelines or physician's choice).
4. Measurable disease in two dimensions and measurable was intended as > 20 mm (or 15 mm if 5 mm slices were used, as in spiral computed tomography [CT] scans); lesions that were considered

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intrinsically non-measurable including bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses that were not confirmed and followed by imaging techniques, cystic lesions, lesions that were situated in a previously irradiated area were considered only assessable.

5. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2.
6. Adult (age ≥ 18 years) patients.
7. Life expectancy ≥ 12 weeks.
8. Resolution of all acute toxic effects (excluding alopecia) of any prior anticancer therapy to NCI CTC (Version 4.03) Grade ≤ 1 or to the baseline laboratory values as defined in Inclusion Criterion Number 9.
9. Baseline laboratory values fulfilling the following requirement :
    - Absolute Neutrophils Count (ANC) ≥ 1,500/mm^3 (≥ 1.5 x 10^9 /L)
    - Platelets ≥ 100,000/mm^3 (≥ 100 x 10^9 /L)
    - Hemoglobin > 9.0 g/dL
    - Serum Creatinine or Creatinine Clearance ≤ 1.5 x ULN > 60 mL/min
    - Total Serum Bilirubin ≤ 1.5 x ULN
    - Liver Transaminases (AST/ALT) ≤ 3 x ULN; ≤ 5 x ULN if liver metastasis are present
    - Alkaline Phosphatase (ALP) ≤ 2.5 x ULN; ≤ 5 x ULN if liver and/or bone metastasis are present Amylase and lipase Within the ULN
    - Potassium ≥ 3.8 mmol/L
    - Magnesium ≥ 1.8 mmol/L
    - LVEF (by MUGA) Above the LLN
    - QTc ≤ 480 milliseconds

    Pregnancy test if female with child bearing potential Negative within 7 days of starting treatment
10. For males and females of child-bearing potential, agreement upon the use of effective contraceptive methods prior to study entry, for the duration of study participation and in the following 90 days after discontinuation of study treatment.

The presence of any of the following would have excluded a subject from study enrollment:

1. Current enrollment in another therapeutic clinical trial.
2. *Phase II part*: Patients at first treatment failure (partial response, progression, relapse following first line chemotherapy) who are eligible for and willing to undergo high-dose salvage therapy with autologous or allogeneic stem cells rescue.
3. History of allergic reactions attributed to compounds of similar chemical composition to the study drugs.

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In case of doubt please refer to the Sponsor who will contact the manufactures.

4. Patients with known central nervous system or meningeal involvement.
5. Major surgery, other than diagnostic surgery, within 4 weeks prior to treatment start.
6. Patients who have had chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to treatment start or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier. Prior radiation therapy must not have been to more than 25% of the red bone marrow. Whole pelvic radiation is considered to be over 25%.
7. History of prolonged QTc interval or additional risk factors for torsade de pointes (e.g., heart failure, hypokalemia, family history of long QT syndrome).
8. A known history of sustained ventricular tachycardia (VT), ventricular fibrillation (VF), Torsade de Pointes, or cardiac arrest unless currently addressed with an automatic implantable cardioverter defibrillator (AICD).
9. Any cardiac arrhythmia requiring an anti-arrhythmic medication (excluding stable doses of beta-blockers).
10. Use of concomitant medications that increase or possibly increase the risk to prolong the QTc interval (see Appendix 3) and/or induce torsades de pointes, ventricular arrhythmia (see http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm).
11. Hypertrophic cardiomegaly or restrictive cardiomyopathy from prior treatments or other causes.
12. Other significant ECG abnormalities including 2nd degree atrio-ventricular (AV) block type II, 3rd degree AV block, or bradycardia (ventricular rate less than 50 beats/min).
13. Symptomatic coronary artery disease (CAD), e.g., angina Canadian Class II-IV (see Appendix 5) or suspected cardiac ischemia (i.e., ST depression of ≥2 mm, measured from isoelectric line to the ST segment). In any patient in whom there is doubt, the patient should have a stress imaging study and, if abnormal, angiography to define whether or not CAD is present.
14. Congestive heart failure (CHF) that meets New York Heart Association (NYHA) Class II to IV definitions (see Appendix 6).
15. Uncontrolled hypertension (i.e., blood pressure of ≥160/95 mmHg). Patients who have a history of hypertension controlled by medication must be on a stable dose (for at least one month).
16. Any of the following in the past 6 months: myocardial infarction, unstable angina, coronary/peripheral artery bypass graft, cerebrovascular accident or transient ischemic attack, pulmonary embolism, deep vein thrombosis.
17. Prior allogeneic stem cell transplant patients will be allowed to enroll if they are past day +100 of transplant, have no active graft-versus-host-disease, are not on any immunosuppressants, and have been off immunosuppressants for at least 4 weeks.
18. Prior autologous stem cell transplant patients will be allowed to enter this study if they are past their day +100 of transplant.
19. Prior use of valproic acid or any other histone deacetylase (HDAC) inhibitor for lymphoma treatment, including romidepsin
20. Known active infections (bacterial, fungal, viral), particularly active viral infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV). Patients who are seropositive because of HBV vaccine are eligible as well as patients HBV and HCV seropositive, but negative for viral DNA by RT-PCR.
21. History of previous cancer, except skin basal-cell carcinoma or in situ carcinoma of the cervix, within the previous 5 years
22. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the patient

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inappropriate for entry into this study or could compromise protocol objectives in the opinion of the Investigator and/or the Sponsor.

Test Product, Dose and Mode of Administration, Batch Number:

Phase I part: danusertib dose escalation

The starting dose of danusertib was 200 mg/m^2/day (corresponding to a cumulative dose of 400 mg/m^2 in a 4-week cycle). The proposed starting dose has been chosen based on the tolerability seen in the ongoing and completed clinical trials with similar or higher total doses. The dose escalation steps was scheduled to precede according to the design described below, guided by the safety results and the drug exposure observed at the previous dose levels, until MTD should have been attained. The dose escalation scheme of danusertib proposed was summarized in the table reported below, according to study protocol:

Dose Level	Drug	Dose (mg/m^2)	Day 1	Day 8	Day 15
-1	Romidepsin	12	X	X	
	Danusertib	160	X	X	
1 (starting dose)	Romidepsin	12	X	X	
	Danusertib	200	X	X	
2	Romidepsin	12	X	X	
	Danusertib	300	X	X	
3	Romidepsin	12	X	X	X
	Danusertib	300	X	X	

At any time during the study, the above anticipated dose levels might be modified, based on clinical and pharmacokinetic data acquired during study progress. The dose level was assigned by the Sponsor designee, at the time of patient registration.

In the dose-escalation phase, patients were scheduled to be allocated to cohorts of 3 to 6 patients receiving a fixed dose of romidepsin combined with progressively higher doses of danusertib, based on the rules specified below:

If 0/3 patient/s experienced first cycle DLT, the next cohort had to start one dose level higher.

If 1/3 patient/s experienced first cycle DLT, up to 3 more patients had to start at the same dose level; if 1/6 experienced first cycle DLT, the next cohort had to start one dose level higher.

If $\geq$ 2/3 or $\geq$ 2/6 patients experience DLTs in the first cycle of treatment, then the MTD is considered to have been exceeded. Three more patients had to be entered at the previous dose level (if only 3 patients were previously treated at that prior dose) or 6 patients had to be entered at an intermediate dose level (not yet tested), for the definition of the MTD. Evaluation of safety profile and exposure in patients treated up to then in the study would have guided the selection of the intermediate dose level. 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 have been enrolled at any time. In presence of 1st cycle DLT in the first patient, the third patient could be enrolled only after the second patient had completed the first cycle without DLT. In case a cohort needs to be expanded to more than 3 patients, the additional patients could be enrolled simultaneously. The third or the sixth evaluable patient of each cohort

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had to be observed for one cycle before subsequent patients were enrolled at the next higher dose level. If a patient discontinued treatment before completing Cycle 1 for reasons other than treatment-related toxicities, an additional patient must be enrolled at the same dose level. After the characterization of dose level 2, in absence of first cycle DLTs or significant toxicities related to combination regimen, administration of an additional dose of romidepsin (day 15) was considered. After characterization of dose level 2, in absence of first cycle DLTs or relevant toxicities related to combination regimen, dose escalation with danusertib continued until the definition of the MTD with 33% dose increments. In addition, after the definition of the RP2D as per original schedule, if recovery of toxicities allows it, reduction of cycle duration to 3 weeks instead of 4 weeks, was also considered.
Before activation of the Phase II part, Phase I results (safety and efficacy) were scheduled to be reviewed in order to define or not the activation of the Phase II part. The Phase II part, was not activated because the pharmacokinetics parameters of romidepsin could not be evaluated..

Danusertib was administered by 3-hour IV infusion after completion of romidepsin administration on Days 1 and 8 in a 28-day cycle (4 weeks). The starting dose was 200 mg/m^2 and, as stated in study protocol, it was expected that at least two different doses of danusertib (i.e., 200 mg/m^2, 300 mg/m^2) would have been tested, but due to dose limiting toxicities in 2/6 patients treated at the first dose level of danusertib (200 mg/m^2) with romidepsin (12 mg/m^2) the following 6 patients were treated at 160 mg/m^2 of danusertib plus romidepsin at 12 mg/m^2. No DLTs occurred among the 6 patients of the dose level -1 who completed the first cycle of treatment. . Danusertib, provided free of charge by Nerviano Medical Sciences S.r.l., was supplied in vials of 10 mg/mL in 5% dextrose solution (150 mg in a 15 mL solution). The hydrochloride salt of danusertib is formed in situ during sterile aqueous solution manufacture. The supplied solution had to be diluted in 500 mL 5% dextrose prior to administration. The drug product had to be stored at 2-8°C (refrigerated conditions), protected from light and then equilibrated at RT shortly before use

Romidepsin was administered first, IV over a 4-hour period on Days 1 and 8 of a 28-day cycle (4 weeks), at a fixed dose of 12 mg/m^2 . Romidepsin was supplied by Celgene International free of charge as a kit containing two vials in a single carton, one vial of romidepsin for injection and one vial of diluent. The drug vial contained a lyophilized powder of 10 mg of romidepsin and 20 mg of povidone, USP (used as a bulking agent). The diluent vial contained 2 mL (deliverable volume) of a 4:1 mixture of propylene glycol and ethanol. The carton had to be stored at 20° to 25°C.

Danusertib batches: N1301231, N1402164, N1501879

Romidepsin batches: 14F0059, 13F0563

Reference Therapy, Dose and Mode of Administration, Batch Number: Not applicable**.**

Duration of Treatment: Each cycle was scheduled to last 4 weeks; disease response had to be assessed every 2 cycles.
Patients experiencing complete remission (CR) at Cycle 4, 5 or 6 of treatment either received 2 cycles more prior to interrupt the study treatment administration or underwent other therapeutic procedures (e.g., bone marrow transplantation according to Investigator's judgment). All other patients received study treatment until disease progression, patient refusal to continue study treatment, withdrawal of patient consent, or the occurrence of unacceptable toxicity.

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Endpoints and Criteria for Evaluation:

Efficacy:

Phase I Part:
Primary End-Point: MTD/RP2D and First cycle DLTs.
Secondary End-Point: Objective tumor response defined by Cheson's Criteria.

Phase II Part:
Primary End-Point • Objective Response Rate (ORR) (complete and partial response) as per Cheson's Criteria.
Secondary End-Points: Time to Response (TTR), Duration of Response (DoR), Time to Progression (TTP), Overall Survival (OS).

Safety:

Phase I Part
Secondary End Points: Overall safety profile characterized by type, frequency, severity (graded using the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] Version 4.03), timing of adverse events and laboratory abnormalities and Romidepsin and danusertib maximal plasma concentration (Cmax).

Phase II Part
Secondary End Points: Overall safety profile characterized by type, frequency, severity (graded using the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] Version 4.03), timing of adverse events and laboratory abnormalities.

Evaluation was performed on Enrolled patients or treated patients or Per-Protocol patients according the below statements.

Enrolled Patients: This population included all subjects who gave written informed consent to participate in the study and was accounted for in the analysis of patient disposition.

Treated Patients: The treated patient population consisted of all enrolled subjects who actually received at least one study drug administration. This was the patient population for the primary efficacy analysis of ORR. This population was evaluated in the analysis of patient disposition, baseline and tumor characteristics, safety and treatment exposure and was the primary population for the efficacy analyses.

Per-Protocol Patients (PP): it consisted of all treated patients who received at least 2 complete cycles of the study combination and with at least 1 post-treatment disease assessment. Patients presenting at baseline laboratory values (both hematological and biochemical) not fulfilling requirements as per inclusion criteria no. 9 as well as patients who did not receive any prior systemic therapies were excluded from the per-protocol population. The PP population was used only for the phase II part of study. The primary and all secondary efficacy endpoints of the phase II part of the study were confirmed in the PP population.

Statistical Methods:
Efficacy Analyses

Phase I part
For patients treated in the phase I part of the study, efficacy data was presented in individual patients' data listings, by dose level. The objective tumor response was measured according to Cheson's Criteria. Response of Non Target Lesions was defined according to RECIST criteria.

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Phase II part

The primary efficacy analysis was performed by calculating the Objective Response Rate (CR and PR) as per Cheson's Criteria in the treated patient population of the Phase II of the study. The ORR was calculated as the proportion of patients with complete and partial response out of the total number of treated patients. Decision rules applied in the analysis of the phase II primary efficacy endpoint were at least 4/9 out of 19/39 treated patients with CR+PR are required to reject the null hypothesis of a ORR rate as low as 15.0%, at the α-level = 0.10. Exact 95% confidence intervals were reported. Estimate of the rate of unconfirmed tumor objective response was considered as supportive.

Other Efficacy Endpoints Follow-up time and time interval among assessments was summarized by descriptive statistics. Time to response (TTR) was defined as the time from start of treatment to the first confirmed objective tumor response (CR+PR). The analysis was carried out through the competing risk method, considering progressions or deaths before achieving an objective response as competing events. Duration of response (RD) was defined as the time from the first date of confirmed tumor response to the date of tumor progression or death due to underlying cancer, whichever came first. Alive patients who did not progress at the time of analysis were censored at their last tumor assessment. Time to Progression (TTP) was defined as the period from the time when criteria for response (i.e., CR or PR) are first met to the date of tumor progression or death due to underlying cancer, whichever came first. Alive patients who did not progress at the time of analysis were censored at their last tumor assessment. Overall Survival was defined as the time for start of treatment to death due to any cause. Alive patients were censored at their last follow-up date. Patients lost to follow up were censored to the last contact date. All time-to-event endpoints but time to response were analyzed by the Kaplan-Meier method; quartiles estimates together with 95% CI were provided. Estimates at fixed time point (e.g. 6, 12 and 18 months) were reported. All endpoints are graphically displayed. With regard to RD and TTP, in presence of patients who died without evidence of progression the analysis was switch to the more appropriate competing risk method using death as competing event. All collected efficacy data are presented in individual patients' data listings, by study phase, dose level (phase I part only)

Safety Analyses

Adverse events (AEs) were coded using MedDRA 16.1, they are presented by Preferred Term) and graded according to NCI CTCAE version 4.03. The analysis addressed all events that occurred on treatment and whose onset date is posterior to the date of first treatment administration. For each sign and symptom, frequency, distribution of patients according to the worst CTC grade reported during the whole study period were provided by dose level. AEs with a relationship to study treatment assessed as possible/probable/definite by the investigator were described in the same way. Specific subsets of adverse events such as SAEs, AEs with CTC grade 3-5, AEs causing withdrawal from study treatment, are also displayed.

Laboratory data, graded according to the NCI CTCAE version 4.03; each hematological and biochemical parameter included in the NCI CTCAE system, were analyzed by means of shift tables, selecting the worst CTC grade reported on-treatment vs. the grade recorded at baseline, within each treatment cohort. Analysis by time window (Cycle 1 vs. Cycles > 1) were performed as well, to investigate the potential cumulative toxic effects. Summary statistics (median, minimum, maximum) of nadir/zenith values, along with time to nadir/zenith of grade 3-4 and time to recovery from grade 3-4 nadir/zenith were carried out, by dose level and time window, for selected laboratory tests as clinically indicated. Laboratory parameters not graded by the NCI CTCAE system were categorized in 'normal' and 'abnormal' values according to the worst value on-treatment (within or out the normal range respectively) and tabulated vs. baseline finding. All deaths occurred during the study reporting period are presented in individual data listings. Deaths are described in terms of relationship to the study treatment and according to the time from last dosing. LVEF worst value on treatment

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was categorized as above 50%, 50%-45%,<45% and tabulated showing the number and percentage of patients within the above categories. Summary statistics will be provided for the maximum LVEF decrease from baseline, whenever applicable.

SUMMARY OF RESULTS:

The study was closed on 15 December 2016 at the end of the Phase I part for Sponsor decision. In the Phase II part, the study objective was the further evaluation of the efficacy and the characterization of the safety profile of the combination. To this aim the pharmacokinetics parameters of both drugs should have been calculated, but due to lack of agreement with Celgene Company, the pharmacokinetics parameters of romidepsin could not be evaluated. As consequence, the study continuation with the same schedule of treatment without pharmacokinetics data was judged not justified by the Sponsor.

Disposition of Subjects and Baseline Characteristics:

Between 11 December 2013 and 04 February 2016, 12 patients, coming from 2 different investigational sited in Italy were enrolled. All patients received study medications. At the time of data base lock (xx-Jul-2017) all patients were off study. The most frequent reason for study discontinuation was the start of a new therapy (83 % in danusertib160 mg/m^2 group and 50 % in danusertib 200 mg/m^2). Reason for treatment discontinuation was progression (50.0 % in both groups), Investigator's decision (33.3 % in danusertib 160 mg/m^2 and 50.0 % in danusertib 200 mg/m^2), and adverse event (16.7 % in danusertib 160 mg/m^2). The mean age at study entry was 48.9 years (50.3 years in danusertib 160 mg/m^2 and 47.5 years in danusertib 200 mg/m^2). In either group, male gender was predominant (83.3 % in danusertib 160 mg/m^2 and 50 % in danusertib 200 mg/m^2). 100 % and 83.3 % of patients were of white race in the two groups. One patient in danusertib 200 mg/m^2 belonged to the black race. ECOG performance status scored either 0 (66.7 % in danusertib 160 mg/m^2 and 33.3 % in danusertib 200 mg/m^2) or 1 (33.3% in danusertib 160 mg/m^2 and 50.0% in danusertib 200 mg/m^2). Only one patient had ECOG scored 2, in danusertib 200 mg/m^2 group. In danusertib 160 mg/m^2 group, patients' weight, height, and BSA averaged 78.8 kg, 168.3 cm, and 1.8 m^2. in danusertib 200 group, patients' weight, height, and BSA averaged 66.9 kg, 171.3 cm, and 1.8 m^2. All patients had confirmed diagnosis of Hodgkin or non-Hodgkin lymphomas. In danusertib 160 mg/m^2 group 2 patients were affected by Diffuse Large B-Cell Lymphoma (DLBCL), 2 from Peripheral T-Cell lymphoma, and 2 from Anaplastic Large Cell Lymphoma (ALCL) ALK-. In danusertib 200 group, 1 patient was affected by Diffuse Large B-Cell Lymphoma (DLBCL), 1 from Primary Mediastinal Large B-Cell Lymphoma, 1 from Nodular Sclerosis classical Hodgkin Lymphoma, 1 from peripheral T-Cell Lymphoma and 2 from Angioimmunoblastic T-Cell Lymphoma. At study entry most of the patients were on stage IV (4 in danusertib 160 mg/m^2 group and 5 in danusertib 200 mg/m^2 group). Time from primary diagnosis to treatment start was 92.7 months (min – max: 3.6 – 478.6) in danusertib160 mg/m^2 group and 56.8 months (min – max: 8.7 – 270.7) in danusertib 200 group.

Treatment Exposure

Twelve patients were treated: 6 with danusertib 160 mg/m^2 and 6 with danusertib 200 mg/m^2 given in association with romidepsin at 12 mg/m^2. The 12 patients received a total of 30 4-week-cycles. The median number of cycles per patient was 2 (min-max: 1-6). The median treatment duration was 8.1 weeks (min-max: 4.0 – 25.0). The median relative dose intensity achieved were slightly below 100% for the lower danusertib dose tested, while around 80 % was reached with the highest dose.

Efficacy Results:

Responses were observed in two patients (one in each treatment group) and three further patients achieved SD (2 treated with danusertib 160 mg/m^2 and 1 with danusertib 200 mg/m^2).

The results were observed only in Phase I part of the study, which had MTD/RP2D as primary objective. Peripheral Blood Mononuclated Cells (PBMC), were to be collected for the determination of Histone H3

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acetylation and phosphorylation and also analysis of additional biomarkers related to the mechanism of action of the combination or of the single agent currently under study, were to be also considered. Since the collected samples were considered not adequate from the qualitative and quantitative point of view, no exploratory analyses were conducted.

Safety Results:
All twelve treated patients were evaluated for safety. According to protocol definition, 2 first Cycle dose limiting toxicities were reported at the dose level of danusertib 200 mg/m^2 and consisted in Grade 3 febrile neutropenia and a Grade 4 neutropenia lasting > 7 days. Both considered as definitively related to the study treatment.
Due to the first DLT, the cohort was expanded to 6 cases. Afterwards, after the second DLT, the dose was reduced to danusertib 160 mg/m^2. At this dose level no DLTs were observed. All patients experienced at least 1 treatment emergent adverse event in the first or subsequent cycles. Drug-related events were reported in 9 (75.0 %) patients receiving any dose level. The most frequent (≥15.0%) drug-related events were Nausea (5 patients, 41.7 %), Diarrhea (4 patients, 33.3 %), Neutropenia (4 patients, 33.3 %), Pyrexia (3 patients, 25.0 %), Asthenia (3 patients, 25.0 %), Thrombocytopenia (3 patients, 25.0 %), Vomiting (2 patients, 16.7 %), Decreased Appetite (2 patients, 16.7 %), Leukopenia (2 patients, 16.7 %). CTC Grade 3-4 drug-related events were reported in 4 patients (33.3%). The most frequent was Neutropenia (4 patients, 33.3%) reported in Patient No. 0002 (Cycle 1), Patient No. 0003 (Cycles 1 and twice during Cycle 2), Patient No. 0006 (twice at Cycle 1 and three times at Cycles 2 and 3), Patient No. 0011 (Cycles 1, 2, 3, and twice at Cycle 5). No Grade 5 drug-related events were reported during the study. The more frequent treatment emergent hematologic abnormality was Neutropenia (33.3 %). Treatment emergent abnormalities of blood chemistry parameters were of Grade 1 or 2 except for three cases of Grade 3 Sodium increase (2 with danusertib 200 mg/m^2), one Grade 3 Calcium increase (danusertib160 mg/m^2), one Grade 4 of Potassium increase and one Grade 4 of total bilirubin increase, both receiving danusertib 200 mg/m^2. Occasional hypertensive episode (defined as on treatment systolic blood pressure > 150 mm Hg or diastolic blood pressure > 100 mm Hg) were observed in 3 (25 %) treated patients: Patient No. 0008 at Cycle 1, Patient 0011 at Cycle 3 (twice), and Patient 0010 at Cycle 10. No treatment emergent abnormalities were reported in ECG tracing.
No treatment emergent abnormality was reported in LVEF. Only one drug-related adverse event (nausea Grade 3) led to treatment discontinuation in one patient (Patient No. 0011) treated with danusertib at 160 mg/m^2.
The only three reported SAEs occurred in one patient (Patient No. 0002) who experienced, not drug-related nausea (Grade 3), febrile neutropenia (grade 3) drug-related and death not drug-related since due to disease progression.. This death occurred during the reporting period specified in the study protocol. All the study drugs toxicities were considered as unexpected due to the first-in-human association study. The MTD was reached at danusertib dose level of 160 mg/m^2 given in association with romidepsin at 12 mg/m^2 in a 28-day cycle.

CONCLUSIONS: The primary end point of Phase I of the study was reached and the recommended Phase II dose defined as 160 mg/m^2 given in association with romidepsin at 12 mg/m^2 in a 28-Day cycle. The study drug was well tolerated at this dose. Some signs of activity (two PR, one in each dose level and 3 SD) were observed. The Phase II part, was not activated because it was not possible to evaluate the activity of romidepsin in combination with danusertib

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