HIJAK

CLINICAL STUDY REPORT

Investigational Product:	Ruxolitinib
Protocol No./Study No.:	HIJAK
EudraCT No.:	2012-004246-15
Study Title:	Phase II study of oral JAK1/JAK2 inhibitor INC424 in adult patients with relapsed/refractory classical Hodgkin's lymphoma

Development Phase:	II
Indication:	Relapsed/refractory classical Hodgkin's lymphoma

Date First Patient enrolled:	10-Jul-2013
Date Last Patient Last Visit:	12-Jun-2018
Report Date:	19-Sep-2018
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1. SYNOPSIS

Name of Sponsor/Company:	LYSARC	
Name of Finished Product:	Ruxolitinib	

Title of Study:
Phase II study of oral JAK1/JAK2 inhibitor INC424 in adult patients with relapsed/refractory classical Hodgkin's lymphoma

Coordinating Investigators:
Prof. Eric Van den Neste (Coordinating Investigator) and Prof. Franck Morschhauser (Co-coordinating Investigator),

Study Centers:
Eight LYSA centers in France and two LYSA centers in Belgium.
Coordinating center: LYSARC (The Lymphoma Academic Research Organisation), Centre Hospitalier Lyon Sud, Secteur Sainte Eugénie (Pavillon 6D), 69495 Pierre Bénite cedex, France.

Publications:
Haematologica. 2018 May;103(5):840-848

Study Dates:		**Phase of Development:**
Date of first patient enrolled:	10-Jul-2013	II
Date of last patient last visit :	13-Sep-2017	
Date of protocol end of study:	12-Jun-2018	
Median study duration (per patient):	17.6 months	

Primary Objective:
To assess the efficacy of oral JAK1/2 inhibitor ruxolitinib measured by overall response rate (ORR) by IWG criteria (Cheson 2007) occurring after 6 cycles of oral JAK1/2 inhibitor ruxolitinib treatment in patients with advanced HL for whom no curative option is available.

Secondary Objectives:

- To assess the safety of oral JAK1/2 inhibitor ruxolitinib treatment in Hodgkin Lymphoma
- To assess the efficacy of oral JAK1/2 inhibitor ruxolitinib measured by overall response rate (ORR) by IWG criteria (Cheson 2007) occurring after 2 and 4 cycles of oral JAK1/2 inhibitor ruxolitinib treatment
- To assess the efficacy of oral JAK1/2 inhibitor ruxolitinib measured by overall response rate (ORR) by IWG criteria (Cheson 1999) occurring after 2, 4 and 6 cycles of oral JAK1/2 inhibitor ruxolitinib treatment
- To assess the efficacy of oral JAK1/2 inhibitor ruxolitinib measured by the time to response, the duration of response, progression free survival rates after 6 and 12 months, overall survival according to IWG criteria (Cheson 1999)
- To assess the efficacy of oral JAK1/2 inhibitor ruxolitinib on systemic symptoms such as fever, sweating, fatigue, itching

Methodology:
Multicenter, single arm and opened label phase II study in patients with relapsed/refractory classical Hodgkin's lymphoma. Patients have been recruited over 18 months and followed until 2 years after the end of treatment.

The duration of the screening period for each patient is approximately 4 weeks

The duration of the treatment period is 2.5 years : patients will receive oral ruxolitinib during 6 cycles of 28 days for the induction period.

Patients who achieve at least a SD (according Cheson 2007) at the end of cycle 6 and for whose a clinical benefit is observed according to the Investigator's opinion will be eligible for maintenance treatment by ruxolitinib (at the same posology for the induction period) twice daily every day of 28-day cycles. Treatment should be continued up to 2 years or until disease progression, intolerability and/or the investigator determine that further therapy is not in the patient's best interest (e.g., due to noncompliance, toxicity etc.)

Each patient will then go into follow-up. Individual participation ends upon death or until 2 years after the end of treatment, whichever comes first. After disease progression patients will be followed for survival only.

Number of Patients: 33
A total of 33 patients were planned in the study in order to obtain 28 evaluable patients.

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Inclusion criteria:

- Patients ≥ 18 years with classical HL relapsing or refractory after at least 1 prior systemic therapy. Patients must have relapsed after high-dose therapy with ASCT, or have been deemed ineligible for high-dose therapy with ASCT
- ECOG performance status < 3
- Measurable nodal disease: 1 cm in the longest transverse diameter and clearly measurable in at least two perpendicular dimensions, as determined by CT scan (MRI is allowed only if CT scan cannot be performed).
- Patient has the following laboratory values:
  - Absolute neutrophil count (ANC) ≥ 1.0 x 10^9/L [SI units 1.0 x 10^9/L]
  - Platelet count ≥ 75 x 10^9/L
  - Serum creatinine ≤ 1.5 x upper limit of normal (ULN)
  - Serum bilirubin ≤ 1.5 x ULN (or ≤ 3.0 x ULN, if patient has Gilbert syndrome)
  - AST/SGOT and/or ALT/SGPT ≤ 2.5 x ULN or ≤ 5.0 x ULN if the transaminase elevation is due to liver disease involvement
- Signed written informed consent
- Life expectancy ≥ 3 months
- Corrected QT interval < 450 mSec
- Men and women of childbearing potential must agree to use an adequate method of contraception during the study treatment and for at least 1 week after the last study drug administration
- The patient must be covered by a social security system (for inclusions in France)

Exclusion criteria:

- Previous treatment with ruxolitinib or another JAK inhibitor
- Contraindication to ruxolitinib
- Patient received chemotherapy or radiotherapy or any investigational drug within 14 days prior to starting study drug or whose side effects of such therapy have not resolved to ≤ grade 1
- Patient treated with allogeneic hematopoietic stem cell transplant who is currently on, or has received immunosuppressive therapy within 90 days prior to start of screening and/or have ≥ Grade 2 graft versus host disease (GvHD).
- Patient with prior history of another active primary malignancy ≤ 2 years before study entry, with the exception of non-melanoma skin cancer, and carcinoma in situ of uterine cervix
- Any serious active disease or co-morbid medical condition that, according to the investigator's decision, will substantially increase the risk associated with the subject's participation in the study.
- Uncontrolled infectious disease, including active HBV infection defined by either detection of HBs Antigen or presence of anti HBc antibody without detectable anti HBs antibody.
- HIV, HCV or HTLV serology positivity and/or documented infection with active hepatitis B- Prior history of CNS involvement with lymphoma
- Pregnant or lactating woman
- Adult patient unable to provide informed consent because of intellectual impairment, any serious medical condition, laboratory abnormality or psychiatric illness.

Investigational Product:

Ruxolitinib: provided by Novartis Pharma SAS in bottles of 60 tablets or in boxes containing 56 tablets distributed into 4 blisters of 14 tablets each.

Lot numbers: H005KI, H963EI, H999KI, S0002, S0010, S0011

Criteria for Evaluation:

Clinical examinations (including vital signs, ECOG [performance status]) and laboratory safety tests (including complete blood counts, serum chemistries and haemostasis) were to be obtained prior to drug administration, before each 28 day cycle of treatment, and up to 30 days after the last study treatment administration. In addition, laboratory safety tests were performed every week during first 2 cycles, then every 2 weeks

Some blood samples were also collected for biomarkers evaluation at screening, cycle 2 day 1 and cycle 4 day 1.

Tumor assessment was to include clinical examination, vital signs, laboratory tests, systemic symptoms questionnaire, neck, chest, abdomen and pelvis CT scan, PET scan, bone marrow examination at baseline, at the end of cycle 2, cycle 4 and at the end of cycle 6 and every 6 cycles thereafter in maintenance period and at the end of treatment evaluation which was planned within 30 days +/- 7 days after the last drug

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administration or in case of ruxolitinib discontinuation. Bone marrow examination was only be repeated to confirm a CR if it was positive at diagnosis. To ensure comparability, baseline and on-study methods for response assessment were to be performed using the same techniques.
Adverse event type, intensity (according to the NCI CTCAE v. 4.0), duration, seriousness, and relationship to study treatment were recorded in eCRF and were to be assessed up to 30 days after last drug administration. Laboratory abnormalities were be assessed according to the NCI-CTCAE v. 4.0.

Statistical Methodology:
The primary endpoint is the Overall Response Rate (ORR) using the IWG criteria (Cheson 2007) as assessed by the Investigator at the end of induction treatment (6 cycles if patient received all planned cycles otherwise at withdrawal). Patient without response assessment (due to whatever reason) have been considered as non-responder.
Secondary endpoints included response rates throughout the study according to Cheson 99 criteria, complete response rates, best response rates time to response, duration of response, evaluation of systemic symptoms, safety and tolerability assessments.
Overall Response Rate is described as counts and percentages (including missing data). Response is expressed as percentages with 90% confidence limits (to be consistent with one sided 5% level of significance) according to Pearson-Clopper method.
Response rates are expressed as counts and percentages (including missing data) with their 95% confidence limits according to Exact Pearson-Clopper method.
Time to event variables are described in Kaplan-Meier plots of time to first event and summary tables of Kaplan-Meier estimates for criterion rates at fixed time points, with 95% confidence intervals (CIs). The median time to event was calculated (if reached) with 95% CIs.
Follow-up throughout the study is presented as reverse Kaplan-Meier plots of time to death and summary tables of reverse Kaplan-Meier estimates for criterion rates at fixed time points with 95% CIs. The median follow-up is calculated with 95% CIs.
Quantitative variables: sample size, mean, standard deviation, median, range; quartiles are presented when considered relevant. Qualitative variables are described in terms of frequency of each response category and frequencies converted into percentages of the number of patients with available data.

Sample Size Determination:
For the sample size evaluation, the following hypothesis has been taken:
- Ineffective treatment will be considered if the ORR $\leq$ 15% (P0)
- effective treatment will be considered if the ORR $\geq$ 35% (P1)

Sample size calculation was performed with East 5.4 using an exact single-stage phase II design (A'Hern RP. Sample size tables for exact single-stage phase II designs. Stat Med. 2001. 20(6):859-66).
Assuming an α risk of 0.05 and β of 0.20 with a one-sided test, 28 evaluable patients are needed with a cut-off number of 8 patients.
If 8 patients or more presented an overall responses (CR or PR according to Cheson 2007 criteria), the hypothesis that ORR $\leq$ 15% is rejected with a target error rate of 0.05 and an actual error rate of 0.05. If the number of responses is 7 or less, the hypothesis that ORR $\geq$ 35% is rejected with a target error rate of 0.2 and an actual error rate of 0.187

RESULTS:
Disposition and demography
A total of 33 patients were enrolled in the study. 31 patients discontinued prematurely. This was mainly due to disease progression (30 patients) and one patient discontinued due to concurrent illness.
Median age at baseline was 37 years (range: 19-80) with a preponderance of male patients (63.6%).
The performance status (ECOG) was 0, 1, 2 and 3 for 6 (18.2%), 10 (30.3%), 1 (3%) and 2 (6.1%) patients , respectively. The median number of previous treatment lines received was 5 (range: 4-7); 27 (81.8%) patients were refractory to the last line of treatment.

Exposure
The duration of exposure to the treatment was lower than planned since 31 patients discontinued the study prematurely, mostly due to disease progression. The median number of cycles was 4.0, and the median duration of treatment being 3.65 months. The duration of cycle was as expected with a median of 28 days. Nine patients (27.3%) received at least six cycles of ruxolitinib and six (18.2%) received more than six cycles.

Efficacy
Primary endpoint:
The ORR at the end of treatment after 6 cycles of ruxolitinib during induction phase was 9.4% (3/32 patients).

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30 patients (93.8%) showed progressive disease. The remainder showed stable disease; another 11 patients had transient stable disease.

Secondary endpoints:

Response rates in each cohort were poor; the median PFS was 3.5 (95% CL: 1.9-4.6) months and the median OS was 27.1 (95% CL: 17.2-NA) months. Best overall response rate (CR/PR) was 18.8% (6/32 patients).

Biomarker analysis

Using bead-based immunoassays, plasma levels of 27 cytokines related to the immune system were measured atbaseline and after the first cycle of treatment. At baseline, there was no difference in cytokine levels between responders and non-responders. In responders, the only cytokine that decreased significantly was CX-CL10 (P=0.01). In patients presenting with pruritus (n=11), the levels of platelet-derived growth factor-BB (PDGF-BB), interleukin (IL)-5, IL-10, IL-12, IL-13, IL-17, eotaxin, fibroblast growth factor basic (FGF basic), macrophage inflammatory protein 1b (MIP1b), regulated on activation, normal T-cell expressed and secreted (RANTES), and vascular endothelial growth factor (VEGF) were significantly increased. In the latter patients, ruxolitinib treatment significantly decreased the levels of PDGF-BB, IL-10, IL-12, IL-13, IL-17, FGF basic and VEGF. Among the patients who could be analyzed for JAK2 amplification in HRS cells (n=12), polysomy (suggesting hyperdiploidy) was detected in all of them, and specific JAK2 amplification in only one. This latter patient achieved a partial response as determined by computed tomography criteria and also a positron emission tomography-determined response lasting 4 months. It is noteworthy that the PDL1 and PDL2 loci (which are in the vicinity of the JAK2 locus at 9p24), analyzed by fluorescent in situ hybridization with bacterial artificial chromosome probes, showed the same pattern of gains as for the JAK2 locus.

Safety

Adverse events

Overall, 45.5% of patients experienced an AE (reported from grade 3 and grade 2 for infections), but only 21.2% experienced an AE that was considered to be related to ruxolitinib, and only 30.3% experienced an AE that was ≥ Grade 3 in intensity. Of the AEs considered to be related to ruxolitinib, anaemia was the most common, reported by 5 (15.2%) patients. A total of 5 (15.2%) patients overall experienced a SAE; 3 (9.1%) of these patients had at least one SAE related to ruxolitinib. No SAE that was considered to be related to ruxolitinib had a fatal outcome.

Deaths

A total of 14 patients died (42.4%). All deaths except two (toxicity of additional treatment and multiorgan failure) were due to hematological malignancy, which would not be unexpected in this patient population, and all occurred after the treatment period.

Second primary malignancies

Two patients experienced a second primary malignancy (intestine adenocarcinoma and Bowen's disesase).

Hematology, serum biochemistry, vital signs, clinical examination

There were no clinically important or unexpected findings in this patient population for hematology, serum biochemistry, vital signs, or clinical examination data at baseline, during the study, or at follow-up.

CONCLUSIONS:

Based on a strong biological rationale for clinical evaluation of JAK2 blockade in HL, we initiated a phase II study of ruxolitinib in R/R HL patients. The study failed to fulfill the efficacy criteria for further development of the drug as monotherapy as overall response rate (ORR) measured by IWG criteria (Cheson 2007) occurring after 6 cycles of oral JAK1/2 inhibitor ruxolitinib treatment patients with advanced HL was 9.4%. Nonetheless, in patients with very advanced disease ruxolitinib showed hints of activity that surpassed solely an anti-inflammatory effect. This may suggest that further improvements will come from a more complete inhibition of signaling pathways involved in HRS cell survival or from combination with chemotherapy, such as BV.

Report Date: *19-Sep-2018*