BV-ICE

Phase I/II feasibility study of Brentuximab Vedotin in refractory / relapsed Hodgkin lymphoma patients who are treated by chemotherapy (ICE) in second line and eligible for autologous transplantation

Indication studied:	*Hodgkin Lymphoma*
Developmental phase of study:	*Phase 2*
EudraCT No.	*2014-002722-13*
First subject enrolled:	*09 March 2016*
Last subject completed:	*14 May 2021*
Data cutoff date:	*12 July 2021*
Overall survival update	*12 July 2021*
Release date of report:	*27 July 2022*

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This trial was conducted in accordance with the ethical principles of Good Clinical Practice, according to the ICH Harmonized Tripartite Guideline.

Sponsor's Responsible Medical Officer:  28-JUL-2022

Pascale Cony-Makhoul, MD Date

1. SYNOPSIS

Name of Sponsor/Company: LYSARC	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Brentuximab Vedotin		
Name of Active Ingredient: Brentuximab Vedotin		

Title of Study:

Phase I/II feasibility study of Brentuximab Vedotin in refractory / relapsed Hodgkin lymphoma patients who are treated by chemotherapy (ICE) in second line and eligible for autologous transplantation.

Coordinating Investigator:

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Study site(s) and countries:

18 study centers in France and Belgium.

Publications (reference):

Studied period (years): Date first subject first visit: 09 March 2016 Date last subject completed: 04 June 2021 Data cutoff date: 12 July 2021	**Phase of development:** Phase I/II

Trial registry number(s):

ClinicalTrials.gov identifier: NCT02686346

EudraCT number: 2014-002722-13

Objectives:

PHASE I:

Primary objective:

- To determine the MTD and/or RP2D (Recommended Phase II dose) of BV when administered to adult patients treated with ICE in refractory or relapsed Hodgkin's lymphomas.

Secondary objectives:

- To characterize the safety and tolerability of BV in patient treated with ICE.

- To assess preliminary anti-tumor activity of BV in patient treated with ICE.

PHASE II

Primary objective:

- To evaluate the efficacy of BV in patient treated with ICE as first salvage treatment (establish the fraction of responding patients – Complete Metabolic Response (CMR)) as judged by the center by Lugano classification after the second cycle.

Secondary objective:

- To assess the OMR rate (CMR and PMR) after 3 cycles of BV and ICE and one cycle of BV

- To assess the toxicity profile of BV in patient treated with ICE

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- To assess hematological recovery after each cycle of BV and ICE

- To assess the feasibility of harvesting an autologous peripheral blood stem cell graft after BV in patient treated with ICE

- To assess the fraction of patients (CMR/PMR) eligible for auto-PBSCT who actually undergo one or two auto-PBSCT

- To evaluate PFS and OS with this treatment regimen

Exploratory objective:

- To identify predictive factors for response, PFS and OS (for phase II only)

Methodology:

This study was a phase I/II prospective multicenter study. This study was designed as a phase IB/II trial.

The first part (phase IB) was a dose escalation design to explore the safety and assess the recommended phase II dose of Brentuximab Vedotin in Hodgkin lymphoma patients treated with ICE regimen.

The second part (phase II), depending on the selected dose after the completion of phase IB part of the study, explored safety in addition to efficacy of the recommended dose of Brentuximab Vedotin in a selected population of patients treated with ICE with Hodgkin lymphoma.

Patients received 3 cycles of 21 days of BV (1.2 mg/kg or 1.8 mg/kg IV capped at 100 kg) on Day 1 combined with the ICE regimen (etoposide 100 mg/m² on Days 1 to 3, carboplatin AUC (5) max 800 mg and ifosfamide + mesna 5 g/m² on Day 2). A fourth injection of BV 1.8 mg/kg was performed on Day 21 from cycle 3. Patients with no CMR at PET C2 were considered out of study treatment and should receive other salvage chemotherapy. Local and central assessments of PET-CT at baseline, after 2 cycles of BV-ICE and before ASCT (PET0, PETC2, and PETC4) were performed according to the Lugano criteria classification. A central review of PET-Scan was performed.

Number of subjects (planned, enrolled, and analyzed):

Planned: Phase I: up to 12 patients / Phase II: 43 patients
Enrolled: Phase I: 10 patients / Phase II: 43 patients
Analyzed: Phase I: 10 patients / Phase II: 42 patients

Diagnosis and main criteria for inclusion:

Eligible patients were first R/R CD30-positive cHL patients, aged 18-65 years, eligible for ASCT with PET-positive disease at relapse. Patients with peripheral neuropathy grade 2 or more or treated with BV in first-line therapy were excluded.

Test product, dose, and mode of administration:

Drugs composing the ICE regimen are registered and are available at the hospital pharmacy. Chemotherapy products are to be used according to summary of product characteristics.

Brentuximab vedotin was provided by the sponsor for this study and used according to the protocol and the Investigator Brochure.

Duration of treatment:

Phase I: patients were recruited for 11 months and followed 3 years after the last patient has completed

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treatment or prematurely discontinued treatment.

Phase II: Patients were recruited for 10 months and followed 3 years after the last patient has completed treatment or prematurely discontinued treatment. The duration of the treatment period was approximately 3 months. End of study was defined as the last visit of the last patient in follow-up planned by the protocol.

Reference therapy, dose, and mode of administration:
Brentuximab vedotin as reference therapy was used in this study.

Criteria for evaluation:
Efficacy:

The primary endpoint for the phase II part of the study was the Complete Metabolic Response Rate (CMR) after 2 cycles of treatment or at permanent treatment discontinuation, according to Lugano classification for assessment of response.

The categorization of the patients according to response results at the end of study treatment or at premature treatment discontinuation was performed as follows:

- CMR → responder
- PMR → non responder
- NMR → non responder
- PMD → non responder
- Not Evaluated / Missing (for any reason) → non responder

Safety:
This trial was designed to allow early termination or modification of the protocol for efficacy and safety concerns (serious adverse event, adverse event leading to treatment discontinuation or dose modifications, death) based on the advice of an independent IDMC.

Statistical methods:

Full Analysis Set

The FAS included all patients having signed the informed consent and who received at least one dose of Brentuximab Vedotin. This set was used for demographic data, medical history, baseline diagnosis, patient disposition summaries, safety analyses (including extent of exposure to trial medication, adverse events and laboratory data summaries) and efficacy parameters.

DLT Set

The DLT Set included all patients from phase I who received full dose of Brentuximab Vedotin and ICE regimen during the cycle 1 unless the missed doses were due to study drug related AE(s),. This set was used for phase I part of the study.

Efficacy Set

The efficacy set included all patients included in the FAS, with an available response assessment at 2 cycles and no major protocol violation. Major protocol violations were defined during the data cleaning review meetings which occurred before each analysis. The Efficacy Set was used to ensure the robustness

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of the results obtained with the Full Analysis Set. It was used to support the primary efficacy analysis.

SUMMARY – CONCLUSION

This phase I/II study assessed the combination of brentuximab vedotin (BV) with ifosfamide-carboplatin-etoposide (ICE) as a second-line therapy in refractory/relapsed (R/R) classical Hodgkin lymphoma (cHL) patients. Phase I study was designed to determine the recommended phase II dose (RP2D) of BV (10 patients) and phase II evaluated the rate of complete metabolic response (CMR) after 2 cycles of BV-ICE (42 patients).

There were no DLT during phase I recommending BV 1.8 mg/kg for phase II. Twenty-six patients (61.9%) achieved (CMR) after 2 BV-ICE and 37 patients (88%) were transplanted.

With a median follow-up of 42 months, the 3-year progression free survival (PFS) and overall survival (OS) rate were 64.3% and 100%, respectively. In exploratory analyses to identify predictive factors of response PFS and OS, more than 2 prior cycles of BEACOPP was associated with poorer response at EOT, and response at the end of treatment according to central review was the only significant prognostic factor of PFS. For phase II patients, hematological toxicities (81%) and infections (28.6%) were the most frequent adverse event encountered

BV-ICE regimen is feasible with manageable toxicities and could be an alternative to other salvage treatments.

Date of the report: 27 July 2022