NIVINIHO

A PROSPECTIVE PHASE II STUDY OF NIVOLUMAB ALONE, OR IN COMBINATION WITH VINBLASTIN IN PATIENTS AGED 61 YEARS AND OLDER, WITH CLASSICAL HODGKIN LYMPHOMA AND COEXISTING MEDICAL CONDITIONS

Indication studied:	*Hodgkin Lymphoma*
Developmental phase of study:	*Phase 2*
EudraCT No.	*2017-001939-38*
First subject enrolled:	*30 AUG 2018*
Last subject completed:	*09 AUG 2021*
Data cutoff date:	*12 AUG 2021*
Overall survival update	*09 AUG 2021*
Release date of report:	*22 JUNE 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:  22-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: Nivolumab		
Name of Active Ingredient: Nivolumab		

Title of Study:
A prospective phase II study of nivolumab alone or in combination with Vinblastine in patients aged 61 years and older, with classical Hodgkin lymphoma and coexisting medical conditions.

Coordinating Investigator:

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Study site(s) and countries:
31 study centers in France and Belgium.

Publications (reference):

Studied period (years): Date first subject first visit: 30/08/2018 Date last subject completed: 09/08/2021 Data cutoff date: 12/08/2021	**Phase of development:** Phase II

Trial registry number(s):
ClinicalTrials.gov identifier: NCT03580408
EudraCT number: 2017-001939-38

Objectives:
Primary: To assess the Complete Metabolic Response (CMR) rate by the Lugano classification 2014 (Deauville scale 1-3) based on central review assessed at the end of treatment.

Secondary:

- To assess the feasibility of the protocol, with adequate protocol adherence (adequate dose without excessive delay)
- To assess the safety profile of Nivolumab alone or combined with Vinblastine including immediate toxicities and non-tumor events
- To assess progression-free survival (PFS), event-free survival (EFS), and overall survival (OS)
- To assess Complete Metabolic Response (CMR) rate by the Lugano classification 2014 at the end of induction treatment
- To perform a geriatric assessment program (G8, CIRS-G)

Exploratory:

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- To define the immune contexture of Hodgkin lymphoma in terms of phenotype and activation status of the different subsets of tumor infiltrative immune cells.
- To describe the dynamics of the immune contexture of HL pre and post anti-PD-1 therapy, and the subsequent impact of Vinblastine addition.
- To correlate specific immune contextures and immune dynamics with ant-PD1 efficacy and survival

Methodology:

This study was a multicentric, open-label phase 2 trial, to assess the efficacy and safety of nivolumab alone, or in combination with vinblastine in naive patients aged 61 years and older, with classical Hodgkin Lymphoma and coexisting medical conditions. Treatment consisted in an induction phase of 6 nivolumab injections, delivered at a flat dose of 240 mg every 14 days. Early assessment was done at 12 weeks by PET-CT and CT-scan. Patients who achieved complete metabolic response (CMR) at early assessment completed treatment with nivolumab monotherapy for 18 additional cycles (consolidation phase). Patients who obtained partial metabolic response (PMR) or non-metabolic response (NMR, stable disease) received a combination of 18 cycles of nivolumab plus vinblastine, administered intravenously. In case of progressive disease, according to Lugano Classification (Cheson et al.2014, PET-CT scan-based response) patients were considered in treatment failure.

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

Planned: 56 patients
Enrolled: 64 patients
Analyzed: 64 patients

Diagnosis and main criteria for inclusion:

Eligible patients were first diagnosis of cHL according to WHO criteria excluding nodular lymphocyte predominant subtype; age of 61 years or older; no previous treatment for Hodgkin lymphoma; unfit for poly-chemotherapy because if co-morbidities evaluated by a CIRS score ≥6; Baseline 18-FDG PET scan performed before any treatment with at least one hypermetabolic lesion; Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-3; patients were required to have normal hematological and biochemicals functions unless abnormalities were related to cHL.

Test product, dose, and mode of administration:

All drugs composing the regimens of the study were registered and were available at the hospital pharmacy. Vinblastine was used according to the protocol and Nivolumab was provided by the sponsor for this study.

Duration of treatment:

Patients were recruited for 3 years and followed 6 months after the last patient has completed treatment or prematurely discontinued treatment. The duration of the treatment period was approximately 48 weeks for 24 cycles of immunotherapy +/- chemotherapy. 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:

Nivolumab as reference therapy was used in this study.

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Criteria for evaluation:

Efficacy:

Response was assessed after complete study treatment if patient received all planned cycles or at premature treatment discontinuation according to Lugano Classification (PET-CT-Based 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 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 Full Analysis Set included all patients enrolled in the study and having signed the informed consent, and who received at least one dose of Nivolumab.

The Full Analysis Set was used in a sensitivity analysis to ensure the robustness of the results obtained with the Efficacy Set. It was used to support the primary efficacy analysis.

Patients with missing assessment of CMR at end of treatment or at treatment discontinuation were considered as non-responder.

Safety Set

Safety set included all patients enrolled in the study and having signed the informed consent, and who received at least one dose of Nivolumab. For the purposes of this study, the Full Analysis Set and the Safety Analysis Set were the same.

Efficacy Set

The Efficacy Set included all patients included in the FAS and:

- with an available PET response evaluation at end of treatment or at treatment discontinuation
- or who died from lymphoma before end of treatment or treatment discontinuation
- or who withdrew for progression before end of treatment or treatment discontinuation.

Patients with missing assessment of CMR at end of treatment or at treatment discontinuation, i.e., patients who died from lymphoma or who withdrew for progression, were considered as non-responder.

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This set was used for demographic and baseline characteristics as well as for efficacy analysis.

Per Protocol Set

The PP set included all patients included in the Efficacy Set, with no major protocol deviation. Major protocol deviations were defined during the blind review meeting before the analysis and described in the Data Review Report.

SUMMARY – CONCLUSION

From August 30th, 2018 to April 28th, 2020, 64 patients were included in 31 centers, which composed the full analysis set (FAS), used for safety evaluation. Among these 64 patients, 56 patients were fully evaluable and constituted the efficacy set (ES) used for the efficacy analysis (8 patients progressed early or were not assessed by PET-CT).

The median age at inclusion in the ES was 75 years [range: 62-91]. Patients had a median CIRS-G score of 10 [range: 6-18] at baseline, and a median G8 score of 12.5 [range: 6-17]. Seventy-three percent of patients had a stage III-IV disease and 42.9% of patients had B symptoms. At EOT, 16 patients (28.6%) achieved CMR according to central PET-CT review. Ten patients (17.9%) achieved PMR, 10 patients were in NMR (17.9%) and progressive metabolic disease was observed in 17 patients (30.4%). Three patients were not evaluated. 23 patients received a consolidation with nivolumab and vinblastine. With a median follow-up of 20.1 months, median PFS was 9.8 months [95% CI: 4.2;12].

15/64 patients of the FAS died during treatment (23.4%): 6 patients from lymphoma, 2 patients from toxicity of study treatment, 2 patients from concurrent illness, 1 patient from toxicity of additional treatment after progression, and 4 patients from other causes. The 2-year overall survival was 76.7% [95% CI: 59.6;87.3]. 49/64 patients (76.6%) experienced at least one AE, among which 32 patients experienced grade 3-4 AEs. The 3 more frequent grade 3-4 AEs were neutropenia (8 patients), sepsis (7 patients) and respiratory tract infection (5 patients). Adverse events were related to nivolumab in 36 patients and led to treatment discontinuation in 19 patients (29.7%). Adverse events of special interest i.e., immune-related AEs, were recorded in 22 patients, including 3 pneumonitis, 1 myocarditis, 1 encephalitis and 1 colitis.

Among the 64 patients of the FAS, 34% of patients completed the treatment. The median number of cycles administered was 7 [range: 1-24] for nivolumab and 17 [range: 1-18] for vinblastine.

The NIVINIHO study is the first study to assess the efficacy and safety of an immune checkpoint inhibitor for first line therapy in elderly, frail patients with cHL. The results suggest that in this setting, a nivolumab-based therapy is active in a subset of patients. Further studies and biological analysis are planned to determine which patients may benefit from this approach.

Date of the report: 22 June 2022