haematologica
Journal of the Ferrata Storti Foundation

Nivolumab with or without vinblastine for first-line treatment of elderly patients with Hodgkin lymphoma and coexisting medical conditions: the Niviniho phase II Lysa study

by Julien Lazarovici, Sandy Amorim, Krimo Bouabdallah, Marguerite Fournier, Stéphanie Guidez, Lysiane Molina, Franck Morschhauser, Baptiste Delapierre, Thomas Gastinne, Kamel Laribi, Vincent Launay, Bohrane Slama, Nawel Belmecheri, René-Olivier Casasnovas, Anne Corby, Eric Durot, Pierre Feugier, Emmanuelle Nicolas-Virelizier, David Sibon, Alina Berriolo-Riedinger, Véronique Edeline, Thierry Vander Borght, Diane Damotte, Alexandra Traverse-Glehen, Vincent Ribrag and Marc André

Received: November 6, 2025.
Accepted: May 20, 2026.

Citation: Julien Lazarovici, Sandy Amorim, Krimo Bouabdallah, Marguerite Fournier, Stéphanie Guidez, Lysiane Molina, Franck Morschhauser, Baptiste Delapierre, Thomas Gastinne, Kamel Laribi, Vincent Launay, Bohrane Slama, Nawel Belmecheri, René-Olivier Casasnovas, Anne Corby, Eric Durot, Pierre Feugier, Emmanuelle Nicolas-Virelizier, David Sibon, Alina Berriolo-Riedinger, Véronique Edeline, Thierry Vander Borght, Diane Damotte, Alexandra Traverse-Glehen, Vincent Ribrag and Marc André. Nivolumab with or without vinblastine for first-line treatment of elderly patients with Hodgkin lymphoma and coexisting medical conditions: the Niviniho phase II Lysa study. Haematologica. 2026 May 28. doi: 10.3324/haematol.2025.300166 [Epub ahead of print]

Nivolumab with or without vinblastine for first-line treatment of elderly patients with Hodgkin lymphoma and coexisting medical conditions: the Niviniho phase II Lysa study

Authors: Julien Lazarovici[1]; Sandy Amorim[2;]; Krimo Bouabdallah[3]; Marguerite Fournier[4]; Stéphanie Guidez[5]; Lysiane Molina[6]; Franck Morschhauser[7]; Baptiste Delapierre[8]; Thomas Gastinne[9]; Kamel Laribi[10]; Vincent Launay[11]; Bohrane Slama[12]; Nawel Belmecheri[13]; René-Olivier Casasnovas[14]; Anne Corby[15]; Eric Durot[16]; Pierre Feugier[17]; Emmanuelle Nicolas-Virelizie[18]; David Sibon[19]; Alina Berriolo-Riedinger[20]; Véronique Edeline[21]; Thierry Vander Borght[22]; Diane Damotte[23]; Alexandra Traverse-Glehen[24]; Vincent Ribrag[1*]; and Marc André[25*] for the Lymphoma Study Association (LYSA)

[1]Département d'Hématologie, Gustave Roussy Cancer Campus, Grand Paris, Villejuif, France

[2]Service d'Hématologie, Hôpital Saint-Vincent de Paul, Lille, France

[3]Service d'Hématologie, CHU de Bordeaux, Hôpital Haut-Lévêque, Bordeaux, France

[4] Biostatistics Department, LYSARC, Hôpital Lyon-Sud, Pierre-Bénite, France

[5] Service d'Hématologie, CHU de Poitiers, Poitiers, France

[6]Service d'Hématologie, CHU de Grenoble, Grenoble, France

[7]Service d'Hématologie, CHU de Lille, Hôpital Claude Huriez, Lille, France

[8]Institut d'Hématologie de Basse Normandie, Caen, France

[9]Service d'Hématologie, CHU de Nantes, Nantes, France

[10]Département d'hématologie, CH Le Mans, Le Mans, France

[11]Service d'Hématologie, CH de Saint Brieuc, Hôpital Yves Le Foll, Saint Brieuc, France

[12]Service d'Hématologie, CHU d'Avignon, Hôpital Henri Duffaut, Avignon, France

[13]Service d'Hématologie, Institut Paoli Calmettes, Marseille, France

[14]Service d'Hématologie, CHU de Dijon, Hôpital du Bocage, Dijon, France

[15]Service d'Hématologie, CH de la Rochelle, La Rochelle, France

[16]Service d'Hématologie, CHU de Reims, Reims, France

[17]Service d'Hématologie, CHU de Brabois, Nancy, France

[18]Service d'Hématologie et de Cancérologie Médicale, Centre Léon Bérard, Lyon, France

[19]Service d'Hématologie, APHP Hôpital Necker, Paris, France

[20]Service de Médecine Nucléaire, Centre Georges-François Leclerc, Dijon, France

[21]Département d'Imagerie Médicale, Gustave Roussy Cancer Campus Grand Paris, Villejuif, France

[22]Service de Médecine Nucléaire, CHU Mont Godinne, UC Louvain, Louvain-la-Neuve, Belgium

[23]service de pathologie GHU paris centre, Université Paris Cité, Paris, France

[24]Service d'Anatomie et Cytologie Pathologiques, CH Lyon-Sud, Hospices Civils, Pierre-Bénite, France

[25]Service d'Hématologie, CHU UCL Namur, Yvoir, Belgium

EQUAL CONTRIBUTION

*V.R. and M.A. contributed equally to this work.

CORRESPONDING AUTHOR

Vincent Ribrag, M.D, Gustave Roussy Cancer Campus. Villejuif , France

Vincent.ribrag@gustaveroussy.fr

Short title : First line treatment with nivolumab in elderly patients with hodgkin lymphoma

KEY POINTS

Elderly patients with Hodgkin lymphoma who are unfit for chemotherapy have a very poor prognosis.

Nivolumab, with or without vinblastine, is active in this population; however, the response rate was lower than expected, despite and overall survival exceeding 70% at two years.

Treatment was tolerable in this population.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the first author, VR (vincent.ribrag@gustaveroussy.fr) upon reasonable request.

CLINICAL TRIAL REGISTRATION: NCT03580408

Authors' contribution

JL, VR and MA wrote the manuscript; G.G.R. collected the data; JL, VR, MF and MA analyzed the data ; VE, A B-R and TVB provided PET-CT support ; DD provided pathology support K.S., SA, KB, SG, LM, FM, BD, TG ; KL, VL, BS, NB, R-O C, AC, ED,

PF, E N V, DS, A T-G provided clinical care to the patient ; and, VR, JL, MA and VE conceived and supervised the study.

All authors approved the final version of the manuscript.

Disclosure statement

No potential conflict of interest was reported by the authors.

FUNDING: LYSARC

VR. has received consulting fundings from abbvie, lilly, ipsen, beigene, astra zeneca, research funding from ASTEX and GSK, TG. has received consulting fundings from Roche, BMS, Takeda, Novartis, Gilead, MA. Has received consulting fundings from takeda, BMS, gilead, incyte and beigene, FM. has received consulting fundings from roche, BMS, abbvie, takeda, janssen, chugai, astra zeneca, kite gilead, miltenyi. LM. has received consulting fundings from Jansen, Novartis , gilead, abbvie, astra zeneca, takeda. SG. has received consulting fundings from Abbvie, Incyte, Astra Zeneca, Novartis, BMS. DS has received consulting fundings from abbvie, beigene, gilead, J&J, takeda ; KL has received consulting fundings from novartis, takeda, jansen, abbvie, BMS, sanofi, kite, beigene, pfizer, astra zeneca.

ACKNOWLEDGMENT

Medical editorial support was provided by Peter Todd of Tajut Ltd. (Kaiapoi, New Zealand) and funded by CHU UCL, Namur, Yvoir, Belgium and Tina Zaarour at Gustave Roussy

ABSTRACT

The prognosis of elderly patients with Hodgkin lymphoma (HL) unfit for conventional chemotherapy remains poor. We report the results of the LYSA phase II NIVINIHO trial in treatment-naive HL patients aged ≥ 61 years with comorbidities contraindicating standard chemotherapy. Treatment included an induction phase with nivolumab alone, followed by a consolidation phase: either nivolumab monotherapy for patients with early complete metabolic response or nivolumab plus vinblastine for patients with stable disease or partial response. The primary objective of the study was the complete metabolic response (CMR) rate at the end of treatment.

From August 2018 to April 2020, 64 patients were enrolled. Median age was 75.0 (range, 62 to 91) years, Ann Arbor stage was advanced (stage III-IV) in 75.0% of patients. At end of nivolumab induction, 11 patients (17.2%) achieved CMR and were consolidated with nivolumab alone, 23 (35.9%) patients obtained PMR or SD and received vinblastine plus nivolumab. Among the 56 evaluable patients, 16 (28.6%) achieved CMR at the end of treatment. With a median follow-up of 24.4 months (range, 0.9 to 35.2), median progression-free survival (PFS) was 9.8 months (95% confidence interval [CI], 4.2 to 12) while the 2-year overall survival (OS) rate was 74.1% (95%CI, 58.9% to 84.4%). Thirty-two patients (50%) experienced grade ≥ 3 adverse events (AEs). Nivolumab-related adverse events led to treatment discontinuation in 19 patients (29.7%).

Our results show that nivolumab can be administrated to elderly, frail patients unfit for classical chemotherapy; however, the objective response rate with monotherapy remains low. Trial registration number: NCT03580408.

INTRODUCTION

Elderly patients, commonly defined as those >60 years of age, represent approximately 20% of all adults with Hodgkin lymphoma (HL).[1] Several studies have shown that, despite therapeutic advances, these patients have poorer prognosis than their younger counterparts.[2-7] In addition to more aggressive disease presentation at diagnosis and inferior response to treatment, this may be due to the high incidence of comorbidities in this population, resulting in increased toxicity from standard therapies.[8-10]

Few therapeutic options are available in the subgroup of patients unfit for polychemotherapy because of comorbidities (assessed by a CRIS score $\geq$ 6).

Nivolumab is a human IgG4 anti-PD1 antibody that has shown a favorable safety profile and high response rates in heavily pre-treated patients with relapsed and refractory HL.[11-12] However, most patients treated with nivolumab monotherapy do not achieve a complete response (CR) and eventually relapse. Given the strong rationale for combining nivolumab and other immune checkpoint inhibitors with chemotherapy,[13] several groups have explored sequential or concomitant strategies of nivolumab or other immune checkpoint inhibitors with chemotherapy in both relapsed/refractory HL[14-15] and, more recently, as first-line therapy.[16-19] However, most of these trials included young and fit patients, and there remains a lack of data and an unmet therapeutic need in elderly, unfit populations.

This led us to design a phase II trial, on behalf of the Lymphoma Study Association (LYSA), to evaluate the safety and efficacy of nivolumab alone or in combination with vinblastine in patients with suboptimal response, in elderly patients unfit for classical

chemotherapy (the NIVINIHO study).

METHODS (see Supplementary File 1)

Study Design and Participants

This prospective, multicenter, open-label, phase II trial evaluated the safety and efficacy of an induction phase of nivolumab monotherapy, followed by a consolidation phase of nivolumab alone or, in patients with suboptimal response assessed early in the treatment, combined with vinblastine in first-line treatment for elderly, unfit patients with HL. Patient's ≥61 years, untreated, with a diagnosis of HL (WHO 2016 criteria), and considered unfit for polychemotherapy due to a Cumulative Illness Rating Scale-Geriatric (CIRS-G) score ≥6.[20] All Ann Arbor stages were allowed. Full inclusion and exclusion criteria are available in the study protocol (available online).

The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines and the ethical principles outlined in the Declaration of Helsinki. The protocol and amendments were reviewed and approved by the Independent Ethics Committees of the participating centers prior to study initiation. All patients provided written informed consent prior to study enrollment.

Procedures

Treatment comprised of an induction phase with six cycles of fixed-dose nivolumab (240 mg administered intravenously every 2 weeks), followed by a consolidation phase based

on early response assessment at week 12 using fluorodeoxyglucose positron emission tomography (FDG-PET)/computed tomography (CT) and CT scan.

Patients achieving complete metabolic response (CMR) at 12 weeks continued with nivolumab monotherapy alone on the same schedule. Those with partial response (PMR) or stable disease (SD) received a combination of nivolumab plus vinblastine at 6 mg/m^2 (maximum total dose 12 mg) every two weeks for 18 cycles. (Fig 1). Disease response was re-assessed after 12 consolidation cycles by CT scan (FDG-PET/CT optional) and again at the end of treatment (after 24 total cycles) or upon treatment discontinuation. Disease response was evaluated by FDG-PET/CT and CT-scan. Responding patients entered a 6-month follow-up phase after completing or prematurely discontinuing treatment.

Adverse events (AEs) were recorded from the first drug administration and up to 100 days after the last drug administration. Serious AEs (SAEs) were recorded from consent signature until 100 days after last drug administration of the study.

Objectives

The primary endpoint was the complete metabolic response (CMR) rate at the end of treatment, assessed centrally using the 2014 Lugano classification (Deauville score 1-3). Secondary endpoints included the CMR rate at the end of induction; progression-free survival (PFS), defined as the time from first dose of nivolumab to the first documented disease progression, relapse, or death from any cause; event-free survival (EFS), defined

as the time from first nivolumab dose to the first documented progression, relapse, initiation of new anti-lymphoma therapy, or death from any cause; and overall survival (OS), defined as the time from first nivolumab administered to the date of death from any cause.

Additional secondary endpoints included the feasibility of the treatment protocol, the safety profile of nivolumab alone or in combined with vinblastine, and the results of a geriatric assessment program using the Geriatric-8 [G-8] and CIRS-G scoring system.

Statistical analysis

The primary endpoint was centralized complete metabolic response rate (CMR rate) at end of treatment or at permanent treatment discontinuation, according to PET-CT-based Lugano 2014 criteria. Sample size was performed with East 6.3 using an exact single-stage phase II design. The trial was powered to detect an increase of CMR from 50% to 70% with 90% power and an one-sided alpha of 5%. Assuming these hypotheses, 56 evaluable patients were needed. A patient was considered as evaluable if he was included in the efficacy set.

The Full analysis Set (FAS) included patients enrolled in NIVINIHO study who have received at least one dose of study treatment. 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.

RESULTS

Patients

Between August 30, 2018 and April 28, 2020, 64 patients were enrolled across 31 centers and received at least one dose of nivolumab, which comprised the full analysis set used for safety evaluation. The efficacy set (ES), used for both demographic and baseline characteristics as well as efficacy analyses included 56 patients who were assessed for efficacy. Eight patients from the Full Analysis Set (FAS) were excluded from the ES (stop treatment before any evaluation) for the following reasons: 1 patient died from toxicity before tumor assessment; 3 patients discontinued treatment due to adverse events prior to tumor assessment; 1 patient withdrew consent; 1 patient was excluded due to a protocol deviation; and 2 patients were withdrawn from the study at the discretion of the investigator without undergoing tumor assessment.

Baseline demographics and disease characteristics of the 64 patients are shown in Table 1: median age at inclusion was 75 years (range 62 to 91) with most patients (79.7%) aged 65 to 85 years. Seven patients (10.9%) were ≥85 years. Disease was advanced in most cases: 75.0% of patients had Ann Arbor stage III-IV disease and 45.3% had B symptoms at diagnosis. Nodular sclerosis was the predominant histologic subtype (59.4%) followed by mixed cellularity (20.3%). Five patients had a diagnosis of lymphocyte-rich HL. Median G-8 score was 12.5 (range, 6 to 17) and median CIRS-G score was 10 (range, 6 to 18). Most patients had at least one severe (level 3 or 4) comorbidity. The median severity

index calculated as the total CIRS-G score divided by the number of categories endorsed was 2.2.

Efficacy

Of the 56 evaluable patients (ES set), 24 permanently discontinued treatment during induction due to disease progression (n = 16), treatment toxicity (n = 7), and one patient was withdrawn from the study after incidental discovery of a neuroendocrine tumor (Fig 2). Thirty-two patients entered the consolidation phase, of whom nine received nivolumab monotherapy (due to CMR at week 12), and 23 received combination therapy with nivolumab and vinblastine.

During consolidation, 13 patients permanently discontinued treatment, 4 in the nivolumab monotherapy arm (2 due to Hodgkin lymphoma progression, 1 due to toxicity, and 1 for personal decision) and 9 in the combination arm (4 due to progression and 5 due to toxicity).

At the end of treatment 16 of 56 patients (28.6%; 90% confidence interval [CI], 18.8% to 40.1%) achieved CMR at the end of the study treatment on central review according to the Lugano classification (Table 2). Ten patients (17.9%) achieved PMR, no metabolic response (NMR) in 10 (17.9%), and progressive metabolic disease in 17 (30.4%). Three were not evaluated.

These results were confirmed by a sensitivity analysis performed on all 64 patients using Full Analysis Set. Patients who relapsed or died during treatment were considered as non-responders: 16 (25%; 90% CI, 16.3 to 35.5) of the 64 patients achieved CMR at end

of study treatment, and 10 more patients (15.6%) achieved PMR, which resulted in an ORR of 40.6% at end of study treatment. Ten patients (17.9%) achieved CMR at end of induction (EOI) on central review, and 25 patients (44.6%) obtained PMR. The remaining patients had NMR (n = 8, 14.3%) or progressed at EOI (n = 11, 19.6%). Two patients had not been evaluated at EOI.

Survival duration outcomes are provided in Figure 3. With a median follow-up of 24.4 months (range, 0.9 to 35.2), the median PFS was 9.8 months (95% CI, 4.2 to 12). Forty-five patients (80.4%) experienced a PFS event, including 43 progressions or relapses (95.6%) and two deaths (4.4%). Among the 43 patients who progressed or relapsed, 38 (88.4%) received subsequent treatments, which included (but were not limited to) chemotherapy in 31 patients (81.6%), brentuximab vedotin in 15 (39.5%), and radiotherapy in seven (18.4%). Notably, 18 of these patients received anthracycline-based therapy at relapse or progression. The overall response rate after additional treatment was 52.6%, with 16 patients (42.1%) achieving CMR. Event-free survival events were observed in 46 patients (82.1%), defined as further treatment for HL and/or progression and/or death. The 2-year progression-free survival rate was 21.2% (95% CI, 11.6% to 32.7%). The 2-year overall survival rate was 74.1% (95% CI, 58.9% to 84.4%). A total of 18 out of the 64 patients (28.1%) died during the study, including two patients who died during induction, and 16 during the follow-up period. No deaths occurred during consolidation. The primary cause of death was HL in nine patients, including one during induction. Two patients died from treatment-related toxicity (meningitis and pneumonitis): one during induction and one during the follow-up period. Other causes of death included

concurrent illness (n = 2), and one each due to toxicity of additional treatment, acute respiratory failure, intestinal obstruction, septic shock, and subdural hematoma (Appendix Table S1, online only).

Safety

Among the 64 patients evaluated for safety, 34% completed the full course of treatment. The mean percentage of planned dose was 99% for nivolumab and 100% for vinblastine during study. The median interval between two cycles was 14 days (interquartile range [IQR], 14-14) during both the induction and consolidation phases, regardless of the consolidation arm. The median number of cycles administered was 6 cycles (IQR, 5 to 6) during induction (nivolumab) (n = 56), 16 cycles (8 to 18) of nivolumab in the consolidation (n = 34), and 17 (12 to 18) of vinblastin (+ nivolumab) (n = 23).

Forty-nine (76.6%) of 64 patients experienced at least one AE during the treatment period, with a median of three AEs per patient, and a maximum of 11 (Table 3). Thirty-two patients (50%) experienced AEs grade ≥ 3 (Table 3). SAEs occurred in 28 patients (43.8%) (Table 3), including sepsis in seven patients (10.9%) and pneumonitis in four patients ~~with pneumonitis~~ (6.2%). AEs related to nivolumab occurred in 36 patients and led to treatment discontinuation in 19 patients (29.7%) (Table 3). The most commonly reported AEs included respiratory tract infections (n = 10, 15.6%), urinary tract infections (n = 9, 14.1%), neutropenia (n = 8, 12.5%), and sepsis (n = 7,10.9%) (Appendix Table S2, online only). The three most frequent AEs ≥ grade 3 were neutropenia (n = 8 patients,

12.5%), sepsis (n = 7, 10.9%), and respiratory tract infection (n = 5, 7.8%) (Appendix Table S2, online only). Adverse events of special interest (AESIs) were reported in 24 patients (37.5%), with a total of 36 AESIs (Appendix Table S3, online only). Twelve AESIs led to nivolumab discontinuation and one fatal AESI (pneumonitis) occurred after a single nivolumab injection. Additionally, four patients (6.3%) were diagnosed with a second primary malignancy, occurring at a median of 9.0 months after treatment initiation. These included one case each with basal cell carcinoma, Bowen's disease, lung adenocarcinoma, and neuroendocrine tumor.

DISCUSSION

There are few published reports on patients with HL who are unfit for first-line standard chemotherapy. One Norwegian study reported survival outcomes in patients either ineligible for classical HL chemotherapy or treated with a palliative intent, the median OS of 0.8 and 0.5 years, respectively. These findings strongly suggest a need for alternative treatment options beyond conventional anticancer drugs in the population[21]. The NIVINIHO study evaluated the efficacy and safety of nivolumab alone or combined with vinblastine as the first-line therapy for elderly patients with Hodgkin lymphoma who had coexisting medical conditions and considered unfit for standard chemotherapy. With a complete CMR rate of 28.6% (95% CI, 17.3% to 42.2%) at the end of treatment, the study did not meet its pre-specified endpoint. We first assessed nivolumab monotherapy, but only 9/56 (16%) of the patients reached a CMR at week 12 (early assessment) suggesting that nivolumab alone is not very effective in these elderly population. These results are

comparable to those of another study in elderly patients with Hodgkin's lymphoma unfit for standard chemotherapy, which evaluated a first-line combination of nivolumab and bretuximab vedotin. That study reported an overall response rate of 64%, with 52% achieving complete remission, a median progression-free survival of 18.3 months, and a median OS that was not reach at a median follow-up of 21.2 months. A new update of this study confirm, with a median follow-up of 58.5 months, a prolonged median OS which is still not reached in these patients. [19]

Neither our study nor the study reported by Cheson et al. met the pre-specified response criteria. However, the 2-year overall survival rate was 74.1%, while it remained unreached in the Cheson study with a follow-up of at 21 months of follow-up[18-19].

However, these outcomes remain inferior to the 73% CR rate reported by Forero-Torres et al. who used brentuximab vedotin as a frontline therapy in a population of patients aged 60 years and older. [22] Notably, in this study, 52% of the 27 patients were considered ineligible for or declined conventional anthracycline-based chemotherapy. Therefore, 48% of the study cohort remained eligible for conventional chemotherapy, making the population different from that of our cohort, in which approximately all the patients were unable to receive classical anticancer drugs.

Despite the lower response rates in our cohort, the 2-year overall survival rate of 74.1% compares favorably with the historical cohorts of elderly patients with classical HL treated with conventional therapy.[4-9] Many patients who experienced relapse or progression in our study received and responded to subsequent treatments, including non-classical chemotherapy, antibody-drug conjugates, and radiotherapy. Although the NIVINIHO study was not designed to assess time to second progression or relapse, it is likely that

several of these patients achieved durable responses, contributing to the favorable survival.

The toxicity observed in our study was higher than anticipated, based on data from phase I and II studies of immune checkpoint inhibitors.[11,12,23,24] AEs related to nivolumab occurred in 36 patients (56.3%), leading to treatment discontinuation in 19 patients. This rate of toxicity exceeds that reported in aforementioned studies of anti-PD1 antibodies, combined with chemotherapy.[14,15,17,18,25] Of note, the only treatment-related death reported in arm D of the Checkmate 205 study (first-line therapy) occurred in a 68-year-old patient who experienced four serious SAEs attributed to nivolumab plus AVD treatment. Other patients of that subgroup (three out of five aged > 60 years) also experienced grade 3-4 treatment-related AEs;[16] however, the number of patients involved limits firm conclusions. Several studies in older patients receiving immune checkpoint inhibitors for solid tumors;[26,27]have shown higher rates of AEs, including immune-related events however, this data remains controversial and does not appear to compromise efficacy.[28]

The role of nivolumab in fit elderly patients (60 years and older) who are able to receive standard AVD chemotherapy has been recently reported.[29] The S1826 compared BV-AVD regimen versus nivolumab – AVD regimen and found that, among the subgroup of elderly patients, nivolumab-AVD was superior in term of PFS and OS, with a favorable safety profile. These data suggest that nivolumab-AVD could be considered a standard treatment option in this subgroup of patients.[29]

Our study has several limitations. For practical reasons, geriatric assessment was limited

to the G-8 and CIRS-G scores, which may not sufficiently capture frailty in elderly patients with cancer, including HL.[30] It is therefore possible that with a more comprehensive geriatric assessment may have identified some of the patients included in our study as too frail to participate in a curative-intent prospective study. Conversely, the relatively low CIRS-G score (≥ 6) might have allowed inclusion of patients in the NIVINIHO study who were in fact eligible for frontline anthracycline-based therapy. Although detailed outcome data for the 18 patients who received anthracycline-based therapy as second-line treatment are lacking, one could hypothesize that the response rates contributed to the discrepancy between poor response rates and relatively favorable overall survival in our study.

The choice of vinblastine in combination with nivolumab in the consolidation phase of the study, for patients with partial response represents another limitation. Similarly, safety data were also lacking on the association of anthracyclines with nivolumab and raised concerns on the potential toxicity in this vulnerable population. That underlines the importance of implementing complete geriatric evaluation including and developing prognostic scores that may help to better identify patients who can benefit from anthracycline-based chemotherapies.

Lastly, the PET-guided design of our study might not be appropriate for immune checkpoint inhibitors, as repeat biopsy or imaging at 12 weeks, as recommended by the LYmphoma Response to Immunomodulatory Therapy Criteria (LYRIC) was not possible in this setting.

In conclusion, while nivolumab-based therapy may demonstrate activity in a subset of

elderly patients, unfit patients with HL, the results of our study do not support this approach as a first-line treatment in this population. The toxicity observed in our study was higher than anticipated. Nonetheless, the results of the NIVINIHO study provides important data and demonstrates the feasibility of conducting prospective trials in this rarely studied group, which represents a significant unmet medical need. Furthermore, our findings underscore the importance of geriatric assessment for guiding treatment decisions for elderly patients with HL.

REFERENCES

1. Stark GL, Wood KM, Jack F, et al. Hodgkin's disease in the elderly: a population-based study. Br J Haematol. 2002;119(2):432-440.
2. Sjöberg J, Halthur C, Kristinsson SY, et al. Progress in Hodgkin lymphoma: a population-based study on patients diagnosed in Sweden from 1973-2009. Blood. 2012;119(4):990-996.
3. Brenner H, Gondos A, Pulte D. Ongoing improvement in long-term survival of patients with Hodgkin disease at all ages and recent catch-up of older patients. Blood. 2008;111(6):2977-2983.
4. Engert A, Ballova V, Haverkamp H, et al. Hodgkin’s lymphoma in elderly patients: a comprehensive retrospective analysis from the German Hodgkin's Study Group. J Clin Oncol. 2005;23(22):5052-5060.
5. Proctor SJ, Wilkinson J, Jones G, et al. Evaluation of treatment outcome in 175 patients with Hodgkin lymphoma aged 60 years or over: the SHIELD study. Blood. 2012;119(25):6005-6015.
6. Evens AM, Hong F, Gordon LI, et al. The efficacy and tolerability of adriamycin, bleomycin, vinblastine, dacarbazine and Stanford V in older Hodgkin lymphoma patients: a comprehensive analysis from the North American intergroup trial E2496. Br J Haematol. 2013;161(1):76-86.
7. Böll B, Görgen H, Fuchs M, et al. ABVD in Older patients with early-stage Hodgkin lymphoma treated within the German Hodgkin Study Group HD10 and HD11 trials. J Clin Oncol. 2013;31(12):1522-1529.

8. Ballova V, Rüffer JU, Haverkamp H, et al. A prospectively randomized trial carried out by the German Hodgkin Study Group (GHSG) for elderly patients with advanced Hodgkin's disease comparing BEACOPP baseline and COPP-ABVD (study HD9 elderly). Ann Oncol. 2005;16(1):124-131.
9. Evens AM, Helenowski I, Ramsdale E, et al. A retrospective multicenter analysis of elderly Hodgkin lymphoma: outcomes and prognostic factors in the modern era. Blood. 2012;119(3):692-695.
10. Böll B, Goergen H, Behringer K, et al. Bleomycin in older early-stage favorable Hodgkin lymphoma patients: analysis of the German Hodgkin Study Group (GHSG) HD10 and HD13 trials. Blood. 2016;127(18):2189-2192.
11. Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. New Engl J Med. 2015;372(4):311-319.
12. Younes A, Santoro A, Shipp M, et al. Nivolumab for classical Hodgkin’s lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: a multicentre, multicohort, single-arm phase 2 trial. Lancet Oncol. 2016;17(9):1283-1294.
13. Nowak AK, Robinson BW, Lake RA. Synergy between chemotherapy and immunotherapy in the treatment of established murine solid tumors. Cancer Res. 2003;63(15):4490-4496.
14. Advani RH, Moskowitz AJ, Bartlett NL, et al. Brentuximab vedotin in combination with nivolumab in relapsed or refractory Hodgkin lymphoma: 3-year study results. Blood. 2021;138(6):427-438.

15. Moskowitz AJ, Shah G, Schöder H, et al. Phase II trial of pembrolizumab plus gemcitabine, vinorelbine, and liposomal doxorubicin as second-line therapy for relapsed or refractory classical Hodgkin lymphoma. J Clin Oncol. 2021;39(28):3109-3117.
16. Ramchandren R, Domingo-Domènech E, Rueda A, et al. Nivolumab for newly diagnosed advanced-stage classic Hodgkin lymphoma: safety and efficacy in the Phase II CheckMate 205 Study. J Clin Oncol. 2019;37(23):1997-2007.
17. Bröckelmann PJ, Goergen H, Keller U, et al. Efficacy of nivolumab and AVD in early-stage unfavorable classic Hodgkin lymphoma: the randomized phase 2 German Hodgkin Study Group NIVAHL Trial. JAMA Oncol. 2020;6(6):872-880.
18. Cheson BD, Bartlett NL, LaPlant B, et al. Brentuximab vedotin plus nivolumab as first-line therapy in older or chemotherapy-ineligible patients with Hodgkin lymphoma (ACCRU): a multicentre, single-arm, phase 2 trial. Lancet Haematol. 2020;7(11):e808-e815.
19. Cheson BD, Bartlett NL, Knopf B, et al. Brentuximab vedotin and nivolumab for untreated patients with Hodgkin lymphoma: long-term results. Blood Adv. 2025;9(15):3750-3753.
20. Soubeyran P, Bellera C, Goyard J, et al. Screening for vulnerability in older cancer patients: the ONCODAGE prospective multicenter cohort ptudy. PLoS One. 2014;9(12):e115060.
21. Lia K, Jørgensen RRK, L Wold B, et al. Overall survival and causes of death in elderly patients with Hodgkin lymphoma: a norwegian population-based case-control study. Haematologica. 2024;109(5):1403-1412.

22. Forero-Torres A, Holkova B, Goldschmidt J, et al. Phase 2 study of frontline brentuximab vedotin monotherapy in Hodgkin lymphoma patients aged 60 years and older. Blood. 2015;126(26): 2798-2804.
23. Armand P, Shipp MA, Ribrag V, et al. Programmed death-1 blockade with pembrolizumab in patients with classical Hodgkin lymphoma after brentuximab vedotin failure. J Clin Oncol. 2016;34(31):3733-3739.
24. Chen R, Zinzani PL, Fanale MA, et al. Phase II Study of the efficacy and safety of pembrolizumab for relapsed/refractory classic Hodgkin lymphoma. J Clin Oncol. 2017;35(19):2125-2132.
25. Allen PB, Savas H, Evens AM, et al. Pembrolizumab followed by AVD in untreated early unfavorable and advanced-stage classical Hodgkin lymphoma. Blood. 2021;137(10):1318-1326.
26. Baldini C, Martin Romano P, Voisin A-L, et al. Impact of aging on immune-related adverse events generated by anti-programmed death (ligand)PD-(L)1 therapies. Eur J Cancer. 2020;129:71-79.
27. Huang X, Tian T, Zhang Y, et al. Age-associated changes in adverse events arising from anti-PD-(L)1 therapy. Front Oncol. 2021;11:619385.
28. Kim CM, Lee JB, Shin SJ, et al. The efficacy of immune checkpoint inhibitors in elderly patients: a meta-analysis and meta-regression. ESMO Open. 2022;7(5):100577.
29. Rutherford SC, Li H, Herrera AF, et al. Nivolumab-AVD versus Brentuximab Vedotin-AVD in older patients with advanced-stage classic Hodgkin lymphoma enrolled on S1826. J Clin Oncol. 2025;43(27):2968-2973.

30. Evens AM, Carter J, Loh KP, et al. Management of older Hodgkin lymphoma patients. Hematology. 2019;2019(1):233-242.

TABLES

TABLE 1. Baseline Demographic and Disease Characteristics

Characteristic	Efficacy set (n = 56)	Full analysis set (n = 64)
Sex		
Female	24 (42.9)	25 (39.1)
Male	32 (57.1)	39 (60.9)
Median age, years (range)	75.0 (62-91)	75.0 (62-91)
Age group		
≤ 65 years	5 (8.9)	6 (9.4)
65-85 years	45 (80.4)	51 (79.7)
≥ 85 years	6 (10.7)	7 (10.9)
ECOG performance status		
0-1	43 (76.8)	48 (75.0)
2-3	13 (23.2)	16 (25.0)
Ann Arbor stage		
I-II	15 (26.8)	16 (25.0)
III-IV	41 (73.2)	48 (75.0)
B symptoms		
No	32 (57.1)	35 (54.7)
Yes	24 (42.9)	29 (45.3)
Histological local diagnosis		
Nodular sclerosis	33 (58.9)	38 (59.4)
Mixed cellularity	11 (19.6)	13 (20.3)
Unclassifiable	7 (12.5)	8 (12.5)
Lymphocyte-rich	5 (8.9)	5 (7.8)
Diagnosis according to central review		
Classical Hodgkin lymphoma	49 (94.2)	53 (91.4)
Unclassifiable lymphoma	2 (3.8)	2 (3.4)
Gray zone lymphoma between Hodgkin and EBV lymphoproliferative disorders	1 (1.9)	1 (1.7)
Histiocyte/T-cell rich DLBCL	0	1 (1.7)
Peripheral T-cell lymphoma, not otherwise specified	0	1 (1.7%)
Missing	4	6
Median G-8 score (range)	12.5 (6-17)	12.0 (5-17)*
Median CIRS-G score (range)		
Total score	10.0 (6-18)	10.0 (6-18)
Total number categories endorsed	5.0 (2-8)	5.0 (2-8)

Severity index	2.2 (2-4)	2.2 (2-4)
No of categories at level 3 severity		
1	37 (66.1)	44 (68.8)
2	15 (26.8)	16 (25)
3	4 (7.1)	4 (6.3)
No. of categories at level 4 severity		
1	54 (96.4)	62 (96.9)
2	2 (3.6)	2 (3.1)

Data are presented as n (%) unless otherwise specified.

Abbreviations: CIRS-G, Cumulative Illness Rating Scale-Geriatric; DLBCL, diffuse large B-cell lymphoma; EBV, Epstein-Barr virus; ECOG, Eastern Cooperative Oncology Group; G-8, Geriatric-8 score.

*Only 63 patients evaluated.

TABLE 2. Metabolic Response Rate on Central Review

	Efficacy set (n = 56)
Metabolic response according to Lugano classification*	
Complete metabolic response	16 (28.6)
Partial metabolic response	10 (17.9)
No metabolic response	10 (17.9)
Progressive metabolic disease	17 (30.4)
Not evaluated	3 (5.4)
Complete metabolic response rate	
~~CMR rate (90% CI)~~	~~28.6 (18.8-40.1)~~
CMR rate (95% CI)	28.6 (17.3-42.2)

Data are presented as n (%) unless otherwise specified.

Abbreviations: CI, confidence interval; CMR, complete metabolic response; CT, computed tomography; PET, positron emission tomography.

*Based on PET/CT.

TABLE 3. Adverse Events

	Safety set (n = 64)				
	Before treatment (n = 64)	**Induction phase (n = 64)**	**Consolidation phase (n = 34)**	**Follow-up (n = 26)**	**Total (n = 64)**
Patients with at least one AE	2 (3.1)	37 (57.8)	27 (79.4)	9 (34.6)	49 (76.6)
Median no. of AEs per patient (range)	1.0 (1-1)	1.0 (1-6)	2.0 (1-8)	1.0 (1-6)	3.0 (1-11)
Patients with at least one AE grade ≥ 3	2 (3.1)	14 (21.9)	16 (47.1)	6 (23.1)	32 (50.0)
Patients with at least one SAE	2 (3.1)	14 (21.9)	11 (32.4)	5 (19.2)	28 (43.8)
Patients with at least one fatal AE	0	2 (3.1)	0	2 (7.7)	3 (4.7)
Patients with AEs related to nivolumab	0	24 (37.5)	18 (52.9)	3 (11.5)	36 (56.3)
Patients with AEs related to vinblastine	0	0	13 (38.2)	0	13 (20.3)
AEs leading to nivolumab discontinuation	0	11 (17.2)	8 (23.5)	0	19 (29.7)
AEs leading to vinblastine discontinuation	0	1 (1.6)	5 (14.7)	0	6 (9.4)
AESIs	0	18 (28.1)	7 (20.6)	2 (7.7)	24 (37.5)
Patients with at least one respiratory tract infection	0	5 (7.8)	6 (17.6)	2 (7.7)	10 (15.6)
Patients with at least one urinary tract infection	0	3 (4.7)	7 (20.6)	0	9 (14.1)
Patients with at least one neutropenia	0	0	8 (23.5)	0	8 (12.5)
Patients with at least one sepsis	1 (1.6)	3 (4.7)	1 (2.9)	2 (7.7)	7 (10.9)

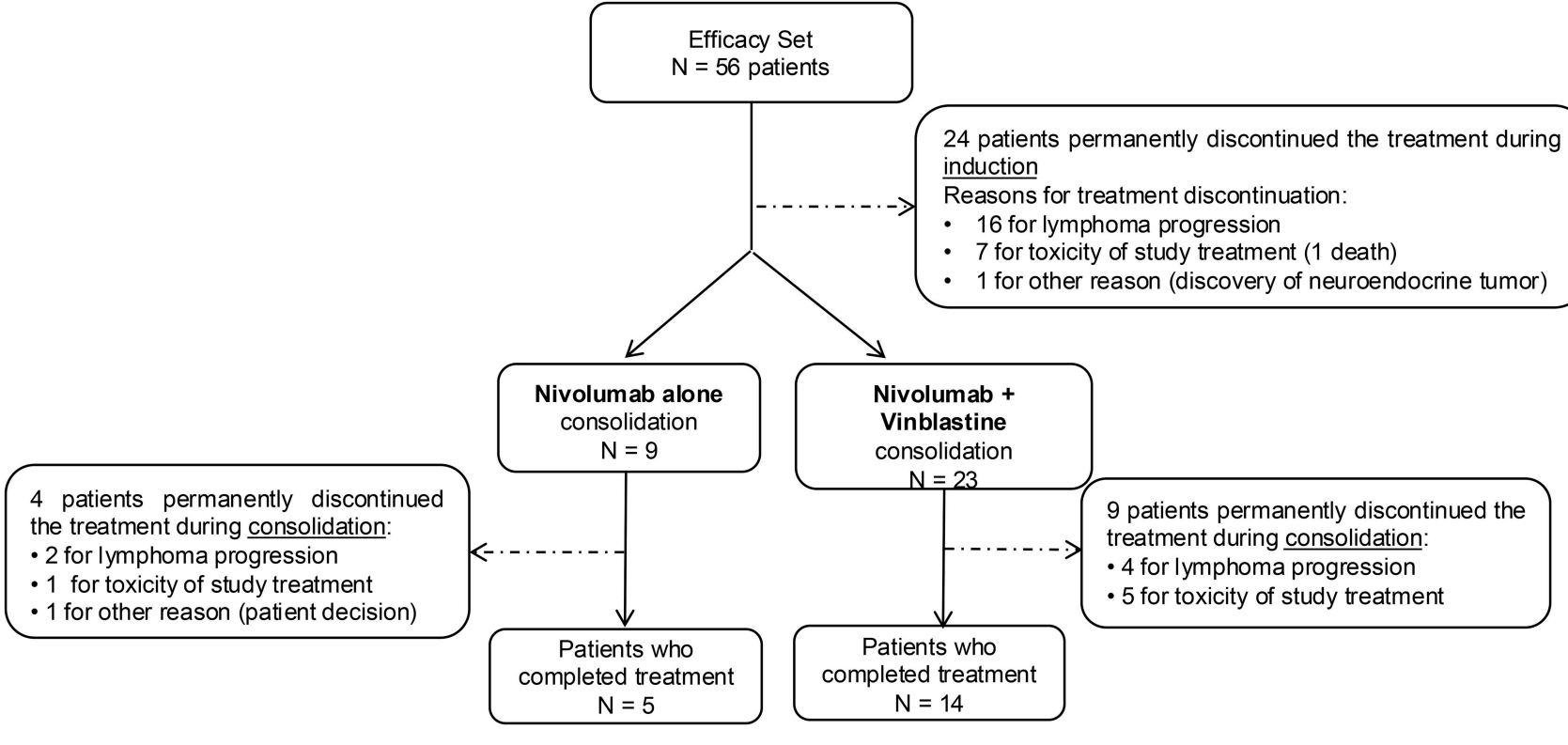
Data are presented as n (%) unless otherwise specified.
Abbreviations: AE, adverse event; AESI, adverse event of special interest; SAE, serious adverse event.

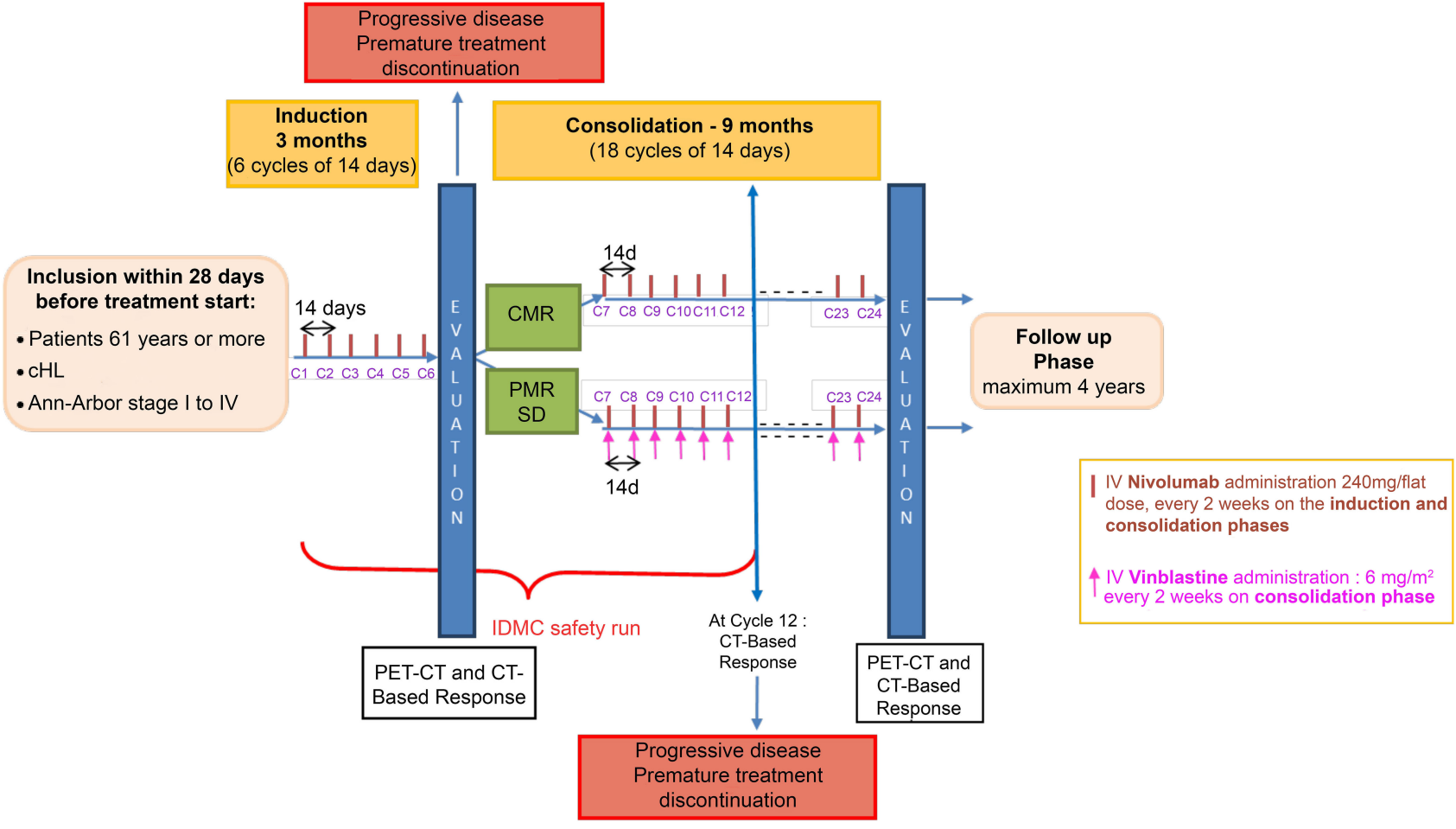
Figure 1. Overall study design. Abbreviations: CMR, complete metabolic response; C, cycle; CT, computed tomography; d, days; IV, intravenous; PET, positron emission tomography; PMR, partial metabolic response; SD, stable disease.

Figure 2. Patients' flowchart.

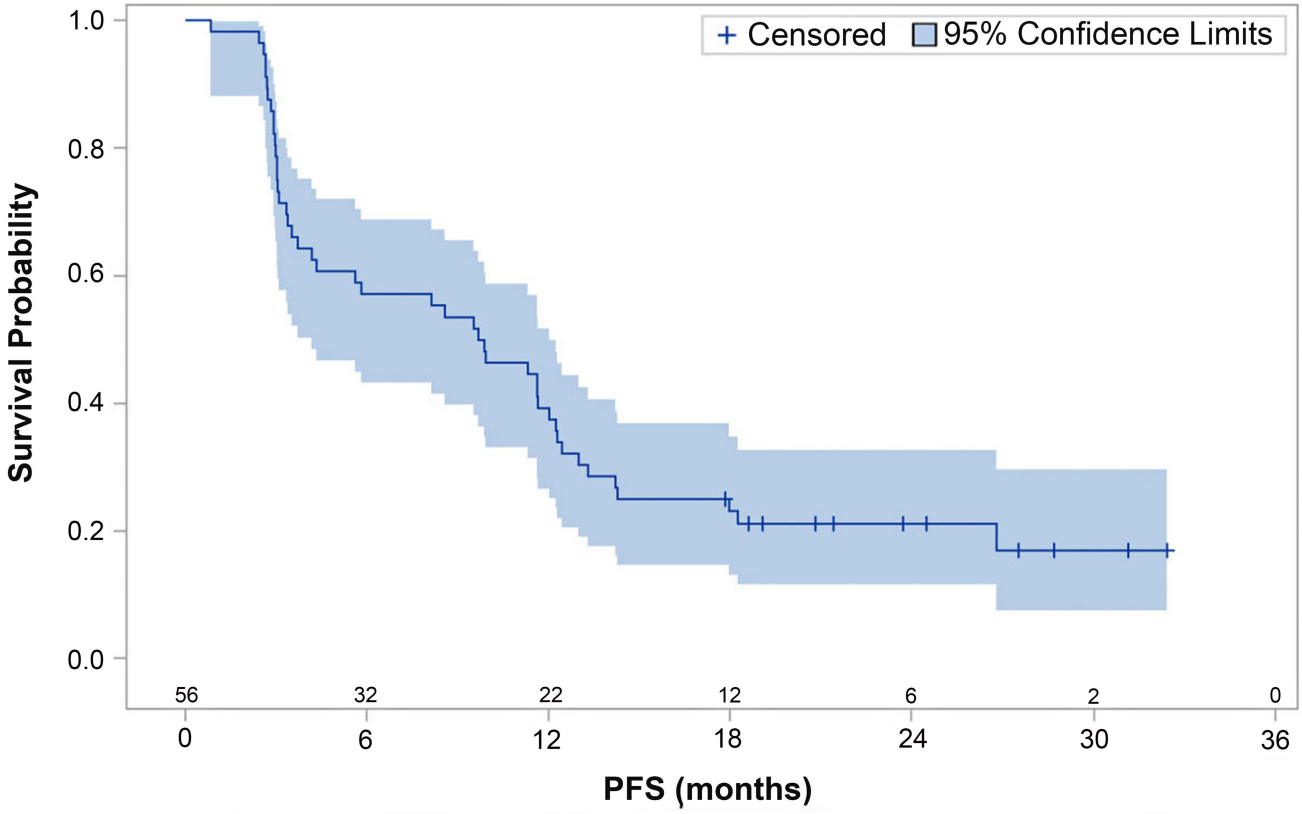
Figure 3. Kaplan-Meier survival plots (PFS and OS).

Abbreviations: CL, confidence limits; OS, overall survival and PFS, progression-free survival.


Efficacy Set
N = 56 patients
24 patients permanently discontinued the treatment during induction
Reasons for treatment discontinuation:
• 16 for lymphoma progression
• 7 for toxicity of study treatment (1 death)
• 1 for other reason (discovery of neuroendocrine tumor)
Nivolumab alone consolidation
N = 9
Nivolumab + Vinblastine consolidation
N = 23
4 patients permanently discontinued the treatment during consolidation:
• 2 for lymphoma progression
• 1 for toxicity of study treatment
• 1 for other reason (patient decision)
9 patients permanently discontinued the treatment during consolidation:
• 4 for lymphoma progression
• 5 for toxicity of study treatment
Patients who completed treatment
N = 5
Patients who completed treatment
N = 14

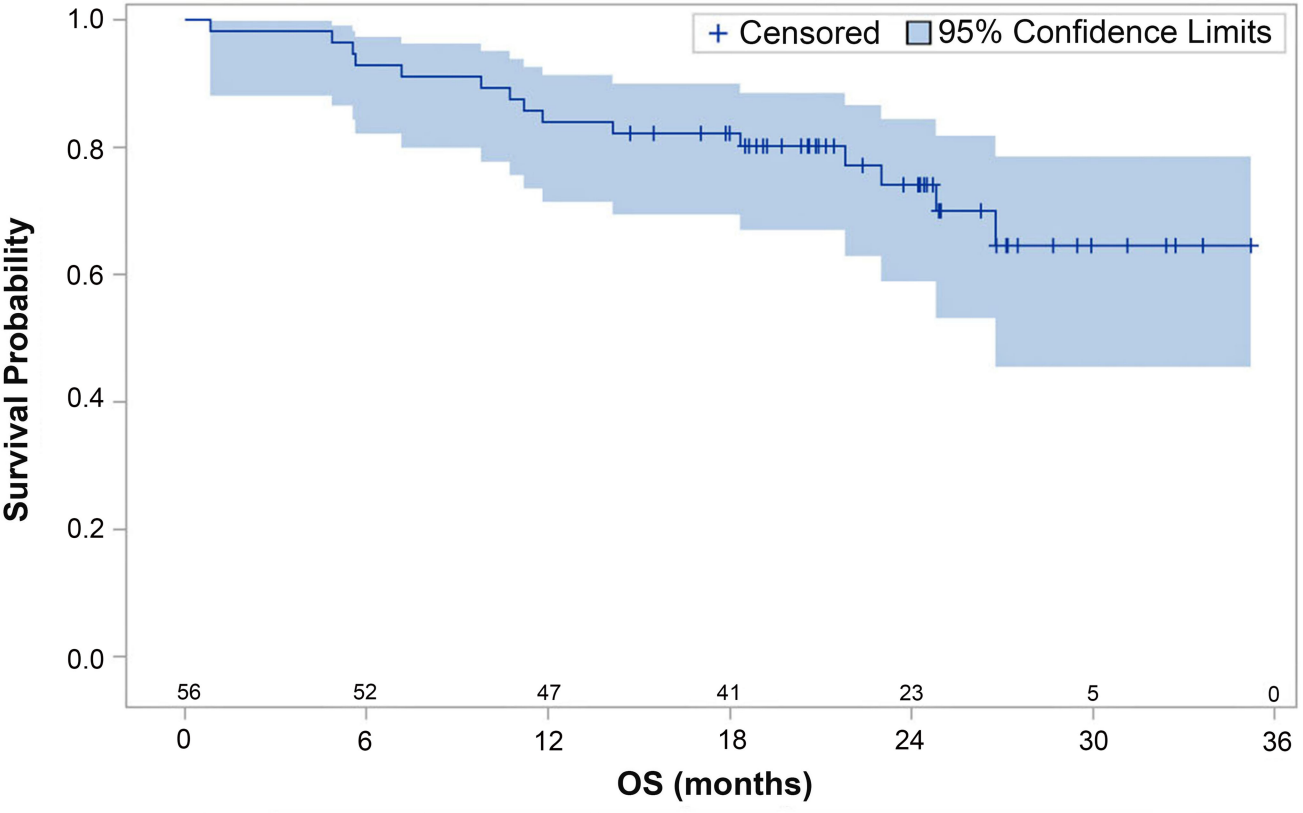

Progressive disease
Premature treatment discontinuation
Induction
3 months
(6 cycles of 14 days)
Consolidation - 9 months
(18 cycles of 14 days)
Inclusion within 28 days before treatment start:
• Patients 61 years or more
• cHL
• Ann-Arbor stage I to IV
14 days
C1 C2 C3 C4 C5 C6
EVALUATION
CMR
PMR
SD
14d
C7 C8 C9 C10 C11 C12
C23 C24
14d
EVALUATION
Follow up
Phase
maximum 4 years
IV Nivolumab administration 240mg/flat dose, every 2 weeks on the induction and consolidation phases
IV Vinblastine administration : 6 mg/m² every 2 weeks on consolidation phase
IDMC safety run
PET-CT and CT-Based Response
At Cycle 12 : CT-Based Response
PET-CT and CT-Based Response
Progressive disease
Premature treatment discontinuation

PFS - Efficacy Set
with Number of Subjects at Risk



No. of Subjects	Event	Censored	Median Survival (95%CL)
56	80.4 % (45)	19.6 % (11)	Not reached (4.2 ; 12)

OS - Efficacy Set
with Number of Subjects at Risk



No. of Subjects	Event	Censored	Median Survival (95%CL)
56	26.8 % (15)	73.2 % (41)	Not reached (26.8 ; NA)

Supplementary File 1: Methods

Study Design and Participants

This prospective, multicenter, open-label, phase II trial evaluated the safety and efficacy of an induction phase of nivolumab monotherapy, followed by a consolidation phase of nivolumab alone or, in patients with suboptimal response assessed early in the treatment, combined with vinblastine in first-line treatment for elderly, unfit patients with HL. Patient's ≥61 years, untreated, with a diagnosis of HL (WHO 2016 criteria), and considered unfit for polychemotherapy due to a Cumulative Illness Rating Scale-Geriatric (CIRS-G) score ≥6.[20] All Ann Arbor stages were allowed. Full inclusion and exclusion criteria are available in the study protocol (available online).

The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines and the ethical principles of the Declaration of Helsinki. The protocol and all amendments were reviewed and approved by the Independent Ethics Committees of participating centers. Written informed consent was obtained from all participants.

Procedures

Treatment comprised of an induction phase with six cycles of fixed-dose nivolumab (240 mg administered intravenously every 2 weeks), followed by a consolidation phase based on early response assessment at week 12 using fluorodeoxyglucose positron emission tomography (FDG-PET)/computed tomography (CT) and CT scan.

Patients achieving complete metabolic response (CMR) at 12 weeks continued with

nivolumab monotherapy alone on the same schedule. Those with partial response (PMR) received a combination of nivolumab plus vinblastine at 6 mg/m^2 (maximum total dose 12 mg) every two weeks for 18 cycles. (Fig 1). Disease response was re-assessed after 12 consolidation cycles by CT scan (FDG-PET/CT optional) and again at the end of treatment (after 24 total cycles) or upon treatment discontinuation. Disease response was evaluated by FDG-PET/CT and CT-scan. Responding patients entered a 6-month follow-up phase after completing or prematurely discontinuing treatment.

Adverse events (AEs) were recorded from the first drug administration and up to 100 days after the last drug administration and were graded according to the Common Terminology Criteria for Adverse Events grading system v4.0, regardless of their relationship to investigational products. Serious AEs (SAEs) were recorded from consent signature until 100 days after last drug administration of the study. SAEs occurring after this time were also reported if considered related to study medications. Immune-related AEs, classified as AEs of special interest (AESIs), were reported separately, regardless of severity or seriousness.

Due to limited published safety data on nivolumab and vinblastine combination therapy at trial initiation, an Independent Data Monitoring Committee (IDMC) of at least three independent members (two HL experts and one statistician). The IDMC reviewed safety data after the first six patients had been treated with the combination of nivolumab and vinblastine, and had completed 6 cycles, or received at least 1 cycle and discontinued treatment thereafter.

A pathological review was performed by two expert hematopathologists (D.D., A.T.-G.) at the LYSA Pathology Institute, Hôpital Henri Mondor, Créteil, France. PET/CT were

centrally reviewed (A.B.-R., V.E., T.V.B.), treatment decisions were based on local interpretations.

Objectives

The primary endpoint was the complete metabolic response (CMR) rate at the end of treatment, assessed centrally using the 2014 Lugano classification (Deauville score 1-3).

Secondary endpoints included the CMR rate at the end of induction; progression-free survival (PFS), defined as the time from first dose of nivolumab to the first documented disease progression, relapse, or death from any cause; event-free survival (EFS), defined as the time from first nivolumab dose to the first documented progression, relapse, initiation of new anti-lymphoma therapy, or death from any cause; and overall survival (OS), defined as the time from first nivolumab administered to the date of death from any cause.

Additional secondary endpoints included the feasibility of the treatment protocol, the safety profile of nivolumab alone or in combined with vinblastine, and the results of a geriatric assessment program using the Geriatric-8 [G-8] and CIRS-G scoring system.

Statistical Analysis

Based on historical data available in literature,[5-9] we estimated that, using conventional treatments, and in patients able to receive a classical chemotherapy, 50% of these patients would obtain a CMR at the end of treatment and we hypothesized a CMR rate ≥70% for patients with the experimental treatment approach. Sample size calculation

was performed with East 6.3 using an exact single-stage phase II design. Assuming an α risk of 0.05 and β risk of 0.10 with a one-sided test, 56 evaluable patients were needed. Accounting for a 15% drop out rate, an overall sample size of 64 patients needed to be enrolled in the study. Time to event analyses (PFS, EFS, and OS) were performed using the Kaplan-Meier method.

The protocol prespecified the Full Analysis Set (FAS) defined as all patients included in the study after signing the informed consent and the Efficacy Set (ES) defined as 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.

All statistical analyses were performed using SAS v9.3 3 and AdClin v3.1.0.

APPENDIX

TABLE S1. Summary of Deaths

Safety set (n = 64)	
Cause of Death	**No. of pts**
HL	9*
Treatment toxicity	2**
Concurrent illness	2 pts
Toxicity of additional treatment	1 pt
Acute respiratory failure	1
Intestinal obstruction	1
Septic shock, and	1
Subdural hematoma	1

* 1 pt during induction, 8 pts during FU
** 1 pts during induction, 2 pts during FU

TABLE S2. Adverse Events

	Safety set (n = 64)									
	Before treatment		**Induction phase**		**Consolidation phase**		**Follow-up**		**Total**	
	No. of pts (%)	**No. of events**	**No. of pts (%)**	**No. of events**	**No. of pts (%)**	**No. of events**	**No. of pts (%)**	**No. of events**	**No. of pts (%)**	**No. of events**
Most common any grade AEs*										
Respiratory tract infection	0	0	6 (9.4)	6	6 (9.4)	6	1 (1.6)	1	10 (15.6)	13
Urinary tract infection	0	0	3 (4.7)	3	7 (10.9)	8	0	0	9 (14.1)	11
Sepsis	1 (1.6)	1	3 (4.7)	3	1 (1.6)	1	2 (3.1)	2	7 (10.9)	7
Neutropenia	0	0	0	0	8 (12.5)	17	0	0	8 (12.5)	17
Diarrhea	0	0	2 (3.1)	3	2 (3.1)	2	2 (3.1)	2	6 (9.4)	7
Thyroid disorder	0	0	4 (6.2)	4	1 (1.6)	1	1 (1.6)	1	6 (9.4)	6
Toxic skin eruption	0	0	4 (6.2)	5	1 (1.6)	1	0	0	5 (7.8)	6
Pneumonitis	0	0	2 (3.1)	2	1 (1.6)	1	1 (1.6)	1	4 (6.2)	4

Infusion-related reaction	0	0	4 (6.2)	4	0	0	0	0	4 (6.2)	4
AEs grade ≥ 3										
Neutropenia	0	0	0	0	8 (12.5)	17	1 (1.6)	17	8 (12.5)	17
Sepsis	1 (1.6)	1	3 (4.7)	3	1 (1.6)	1	2 (3.1)	2	7 (10.9)	7
Respiratory tract infection	0	0	3 (4.7)	3	1 (1.6)	1	1 (1.6)	1	5 (7.8)	5

Abbreviations: AE, adverse event; pts, patients.

TABLE S3. Adverse Events of Special Interest

AESIs	No. of events (%)
Immune-related endocrinopathies	8 (22.2)
Immune-related rash	7 (19.4)
Immune-related pneumonitis	4 (11.1)
Immune-related nephritis or renal dysfunction	2 (5.6)
Immune-related colitis	1 (2.8)
Immune-related hepatitis	1 (2.8)
Other immune-related adverse reactions*	9 (25.0)
Infusion reactions	4 (11.1)
TOTAL	36 (100)

Abbreviations: AESI, adverse event of special interest.

*Non-pre-specified AESIs, including for one patient five events (1 pericarditis, 2 cardio-respiratory arrests, 1 sepsis, and 1 paralysis, which were all considered as immune-related) and for the other four patients immune-mediated myocarditis, auto-immune encephalitis, stomatitis, and neuromuscular toxicity, each as single events.