

A Phase 2 Study of Nivolumab Using a Fixed Dose of 40 mg (Nivo40) in Patients With Relapsed/Refractory Hodgkin Lymphoma

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Abstract

The introduction of nivolumab has changed the landscape of relapsed/refractory classical Hodgkin lymphoma (r/r cHL) treatment. Despite its clinical importance, this therapy may remain inaccessible for a significant number of patients worldwide, especially in low-income countries, due to its high cost. The results of pharmacokinetic analysis and clinical observations suggest the potential efficacy of low dose nivolumab in r/r cHL patients. The aim of this trial was to assess the efficacy and safety of nivolumab at a fixed dose of 40 mg in patients with r/r cHL. The study included 30 patients with r/r cHL, treated with 40 mg nivolumab every 2 weeks. The median dose of nivolumab per kilogram bodyweight was 0.59 mg/kg (0.4–1 mg/kg). Median follow up was 19.2 months (range 12.7–25.4). The objective response rate was 70%, with 13 (43.3%) patients achieving a complete response. Median PFS was 18.4 months (95% CI, 11.3 to 18.5 months) with 18-month PFS of 53.6% (95% CI, 32%–71%). At the time of analysis, 96.7% of patients were alive with a median OS not reached. Severe (grade 3–5) adverse events were observed in 4 patients (13.3%). Nivolumab in a fixed dose of 40 mg was efficient in patients with r/r cHL, independent from dose per kg bodyweight. The results of this study are in good agreement with previously reported data and create a rationale for further studies aimed to define the optimal dosing regimen of nivolumab for the treatment of r/r cHL. Registered at www.clinicaltrials.gov (NCT03343665)

Introduction

Up to a quarter of patients with classical Hodgkin lymphoma (cHL) are resistant or have disease relapse after the first-line chemotherapy.¹ For such patients with relapsed or refractory (r/r) disease, a second-line chemotherapy and autologous hematopoietic stem cell transplantation (ASCT) may lead to a sustained remission in about half of the cases.² Historically, patients who failed ASCT had a dismal prognosis with a life expectancy less than 2 years.^{3–5} Brentuximab vedotin (BV), an anti-CD 30 immunoconjugate, has demonstrated activity after ASCT failure, with overall (ORR) and complete response (CR) rates of 72% and 33% respectively. Despite high ORR, most patients

eventually progress or relapse, with a median progression-free survival (PFS) of 9.3 months, while up to 15% may remain in the sustained CR without further medical interventions.⁶ With a novel data about the genetics and tumor microenvironment of cHL, specifically the demonstration of a high level of programmed death 1 (PD-1) ligand expression on the surface of Reed-Stenberg cells, there has been much interest in immunotherapy approaches, particularly PD-1 inhibitors. The results of clinical trials of the anti-PD-1 antibodies nivolumab and pembrolizumab demonstrated 1-year overall survival (OS) of 92% and 2-year OS 91.1% respectively.^{7,8} This apparent improvement in OS compared to historical cohorts was confirmed in real-world clinical practice.^{9–11} At the same time, this novel treatment raises new questions such as the optimal method of response assessment during immune checkpoint inhibitors (ICI) treatment, the optimal treatment duration and salvage treatment approaches for ICI-resistant cases. Another important problem is the optimal dosing regimen of PD-1 inhibitors. Due to its unique mechanism of action, the efficacy and toxicity profiles of ICI are different from those of chemotherapy and immunoconjugates. Nivolumab pharmacokinetics studies demonstrated that median PD-1 receptor occupancy on peripheral blood CD3 + T cells from 69 patients with melanoma treated at a dose of 0.1 to 10.0 mg/kg every 2 weeks averaged around 65% for every dose level over 0.3 mg/kg, independent of nivolumab concentrations.¹² Moreover, no

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This study was supported by AdVita charity foundation.

The authors have indicated they have no potential conflicts of interest to disclose.

Supplemental digital content is available for this article.

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HemaSphere (2020) 4:5(e480). <http://dx.doi.org/10.1097/HS9.0000000000000480>.

HS9.0000000000000480.

Received: 25 April 2020 / Accepted: 4 August 2020

correlation between the dose, adverse events and efficacy were observed in clinical trials of anti-PD-1 antibodies across a range of solid malignancies.^{13–15} The dosing regimen question is especially important in the case of Hodgkin lymphoma because of its unique biology, high rate of PD-L1 overexpression defined by the prevalence of chromosomal alterations of 9p24.1 locus, and profound sensitivity to PD-1 blockade.¹⁶ The results of pharmacokinetic analysis and early clinical observations in solid malignancies¹⁷ were followed by several case reports showing dramatic responses to low dose nivolumab and pembrolizumab in r/r cHL patients that had either previously undergone or had not undergone allogeneic stem cells transplantation.^{18,19} Such observations were also described for other types of malignant lymphomas.²⁰ With the accumulation of data regarding the efficiency of low dose of PD-1 inhibitors, there has been interest in prospective trials assessing the optimal dosing regimens.^{21–23} The importance of such trials is defined by the current annual cost for nivolumab treatment in Europe, estimated ~90,000 euro²⁴ and representing a significant financial burden for healthcare systems and patients' families. Therefore, the reduction of dose, provided that the effect of such treatment would be comparable to standard, may become an important milestone that would help to expand the access to this life-saving treatment for patients with r/r cHL, especially in low-income regions. To date, there are no prospective trials reporting the outcomes of the low dose nivolumab treatment in r/r Hodgkin lymphoma patients. The aim of this single-center prospective clinical trial was to assess the efficacy and safety of nivolumab in a fixed dose of 40 mg in patients with resistant and relapsed classical Hodgkin lymphoma.

Methods

Study design and population

This was a phase 2 single-arm, open-label study. The inclusion criteria were histologically confirmed diagnosis of classical Hodgkin lymphoma, relapsed or refractory after at least 2 previous lines of therapy, age 18 to 70 years old, no uncontrolled bacterial or fungal infection at the time of enrolment, no requirement for intensive care, pregnancy, active or prior documented autoimmune diseases requiring systemic treatment. Patients who had received previous therapy with nivolumab or other PD-1 inhibitor were excluded from the study. This study was performed in accordance with the Declaration of Helsinki and approved by the institutional review board. All enrolled patients gave written informed consent. The patients received IV nivolumab infusions at a fixed dose of 40 mg on day 1 of a 14-day cycle up to 24 cycles in the absence of tumor progression or treatment intolerance. The dose was chosen because it is a minimal pharmaceutical form currently produced, exceeding the dose of 0.3 mg/kg that was shown to saturate peripheral PD-1 receptors in PK studies.¹² The study design did not restrict the therapy of patients after the end of study treatment or after disease progression at discretion of treating physician. The disease status was assessed every 3 months during the first 2 years, then every 6 months, or earlier in special circumstances (alloH SCT, or initiation of another treatment regimens). The response was assessed by investigators, using PET/CT scans and according to the Lymphoma Response to Immunomodulatory therapy Criteria (LYRIC). Adverse events (AEs) were monitored from baseline through the End-of-Treatment visit and graded according to Common Terminology Criteria for Adverse Events (CTCAE) v 4.03.

Primary chemoresistance was defined either by progression at any time during first-line therapy and up to 3 months after the end of treatment, and/or by persistence of a PET positive residual mass, using the quantitative 5-point scale Deauville score. Early relapse was defined as time to treatment failure more than three months but less than 12 months after end of first-line therapy.

Statistical analysis

Based on the results of the multicentre studies assessing the efficacy of PD-1 inhibitors in cHL patients, the 40% estimate of progression-free survival was used to calculate the sample size. The sample size was selected to provide 10% standard deviation of progression-free survival at the end of the follow-up. The 10% deviation corresponded to the sample size of 24 patients. The number was increased to 30 for the situation when participants may drop-out before the end of follow up. The primary efficacy endpoint was the overall response rate during nivolumab therapy, defined as the proportion of patients with complete response (CR) or partial response (PR) in measurable lesions by LYRIC criteria within a timeframe of 12 months. The efficacy and safety evaluable population included those patients who received at least 1 cycle of therapy. To evaluate the best response, all assessments during therapy were analysed up to the treatment discontinuation or initiation of other therapy. Secondary endpoints included frequency of grade 3 or higher treatment-related adverse events by NCI CTCAE 4.03, duration of response (DOR), progression-free survival (PFS) and overall survival (OS). Duration of response was defined as the time from initial objective response to documented disease progression or death; PFS was defined as the time from the first nivolumab infusion to disease progression, relapse or death; overall survival (OS) defined as the time from the first nivolumab infusion to death from any reason. In each survival outcome, data were censored at the date of last contact for patients who have not experienced the events of interest during their follow-up. Difference in OS and PFS between groups were tested with a log-rank test. DOR, PFS and OS were estimated using the Kaplan-Meier method with 95% CIs estimates. The impact of clinical factors on response was tested with Chi-square and Kruskal-Wallis tests. Data analysis was performed using SAS and SPSS software. This study was registered at www.clinicaltrials.gov (NCT03343665)

Results

Patient characteristics and treatment

A total of 30 patients with r/r cHL were enrolled in the study between July 2017 and July 2018. The median age was 33 years (range 21–52), 9 were male, 21 were female. All (100%) patients had active disease status with measurable lesions at the study entry. Most patients (26, 86.6%) patients had satisfactory ECOG (0–2) status at the study start. Sixteen (53.3%) of patients presented with B-symptoms at study entry. Twenty-four (80%) patients had a primary refractory disease. The median number of previous therapy lines was 4 (2–7). Prior therapy included ASCT and BV treatment in 7 (23.3%) and 10 (30%) cases, respectively. Among required patients, 17 (56.6%) were refractory for previous treatment regimen. Detailed demographic characteristics and clinical data are presented in Table 1.

Table 1
Demographic and Clinical Characteristics of the Study Population

Characteristic	N (%)
Median age, years (range)	33 (21–52)
Gender male/female	21/9
Body mass index, median (range)	1.79 (1.35–2.15)
Histological type	
Nodular sclerosis	24 (80)
Mixed cellularity	6 (20)
Primary chemoresistant	24 (80)
Early relapse	3 (10)
ECOG at the study entry	
0	2 (6.7)
1	15 (50)
2	9 (30)
3	3 (10)
4	1 (3.3)
Disease stage at study entry	
II	5 (16.6)
III	2 (6.6)
IV	23 (76.6)
B-symptoms at the study entry	16 (53.3)
Median number of prior therapy lines (range)	4 (2–7)
Prior radiotherapy	19 (63.3)
Prior ASCT	7 (23.3)
Prior BV treatment	10 (33.3)
Refractory to previous treatment regimen	17 (56.6)
Median time from diagnosis to nivolumab treatment, years (range)	3,5 (0.8–18.8)

Efficacy

All patients were included in the efficacy analysis. At the time of analysis, the median follow up was 19.2 months (range 12.7–25.4). The overall response rate during nivolumab 40 mg treatment was 70%. The best response to treatment (shown in Fig. 1A) was CR in 13 (43.3%) patients, PR in 8 (26.7%), stable disease in 1 (3.3%), progression of disease in 1 (3.3%), indeterminate response in 7 (23.3%): 4 (13.3%) IR type 2, and 3 (10%) IR type 3. The median time to best response was 3.3 months (range 2.6–12.3). There was no difference in the BOR regarding previous treatment: number of previous therapy lines ($p=0.28$) prior ASCT ($p=0.43$) or BV ($p=0.36$) treatment. The median weight of patients at the moment of study initiation was 67.5 kilogram (40–100 kg), and therefore the median dose of nivolumab was 0.59 mg/kg (range 0.4–1 mg/kg). There was no association between the dose of nivolumab per kilogram bodyweight and response ($p=0.73$). Figure 1B shows the patient's BOR and outcomes. One notable case, demonstrating the potential of this therapy was that of a patient with a severely impaired functional status (ECOG 4), massive tumor burden and bulky lesions who achieved a complete response by PET/CT scan with low dose nivolumab (Supplementary Digital Content, Fig. 1, <http://links.lww.com/HS/A99>).

At the time of analysis, 96.7% were alive with median overall survival not reached (Fig. 1C), 18-months PFS was 53.6% (95% CI, 32%–71%) with median of 18.4 months (95% CI, 16.3–20.6 months) from initiation of nivolumab therapy (Fig. 1C). Among 21 patients with objective response to nivo treatment, the median duration of response was 18.6 months (95% CI 13.4–23.9 months). At the moment of analysis 6 patients were continuing the treatment with low dose nivolumab, in 24 patients treatment was discontinued. Among them, in 2 patients treatment was permanently discontinued due to toxicity, in 9 patients due to disease

progression, in 7 patients with CR therapy was discontinued after the end of the planned study treatment, in 6 patients due other reasons including treatment change at discretion of treating physician and informed consent withdrawal.

Toxicity

Adverse events observed during nivolumab treatment are summarized in Table 2. A total of 28 (93.3%) patients had adverse events of any grade. There were no cases of fatal toxicities. The most common adverse events were fever and pruritus (12, 40.0%) followed by headache (11, 36.7%), fatigue (8, 26.7%) and arthralgia (8, 26.7%). Grade ≥ 3 adverse events were observed in 4 patients (13.3%), and included increased ALT/AST, arthralgia, anemia, pneumonia, pneumonitis, myelodysplastic syndrome (MDS) (grade 5) each occurring in one patient. The MDS was considered as a consequence of prior chemotherapy in a heavily pretreated patient and not related to nivolumab therapy. Grade ≥ 3 immune-related adverse events were observed in 3 (10%) of patients and included arthralgia (gr 3), pneumonitis (gr 4) and increased ALT/AST (gr 4). Hypothyroidism was observed in 6 (20%) of patients. In mentioned 3 (10%) cases of grade ≥ 3 immune-related adverse events, nivolumab treatment was discontinued, treatment with 1 mg/kg methylprednisolone was initiated with complete resolution of observed irAE's. In one patient (with gr 3 arthralgia), the therapy was subsequently reinitiated with no recurrence of irAE. At the moment of follow up, 29 patients remain alive. One death in a patient with IR as BOR after the treatment was associated with MDS RAEB-1 and was not attributed to nivolumab toxicity.

Factors influencing the prognosis and biomarkers assessment

At the time of analysis, only one patient had died, and therefore an adequate statistical analysis of factors influencing OS was not possible. The influence of several clinical factors on PFS was analyzed (Supplementary Digital Content, Table 1, <http://links.lww.com/HS/A99>). The PFS was not statistically different regarding the prior treatment—number of therapy lines ($p=0.766$), BV treatment ($p=0.408$), ASCT ($p=0.184$), as well as key clinical factors—age ($p=0.463$), disease status at the study start ($p=0.251$), or bulky disease before nivolumab treatment ($p=0.234$). Importantly, nivolumab dose per kilogram bodyweight did not affect the PFS ($p=0.701$). Patients PFS according to dose quartile is presented in Figure 2S, <http://links.lww.com/HS/A99>. Patients with CR during nivolumab therapy had a tendency ($p=0.08$) for a better PFS compared to other patients: median PFS in patients with CR was 20.9 (95% CI 13.8 months—NR) months versus 17.5 months (95% CI 14.4 months—NR) in patients with other types of response. There was no significant difference regarding PFS in patients with CR when compared with patients with PR ($p=0.379$). Among the factors which significantly affected PFS in the analysed population were B-symptoms at the time of nivolumab initiation ($p=0.024$) as well as achievement of PET-negative CR at first restaging at 3 months after the start of the treatment ($p=0.046$). Patients that had B symptoms at study inclusion had significantly worse 18-month PFS of 40.9% (95% CI, 13.3%–67.3%) with a median of 17.4 months (95% CI 12.5–19.2 months) versus 67.7% (95% CI, 34.9%–86.5%) with a median PFS not reached in patients without B-symptoms (Fig. 2A). Patients that achieved PET

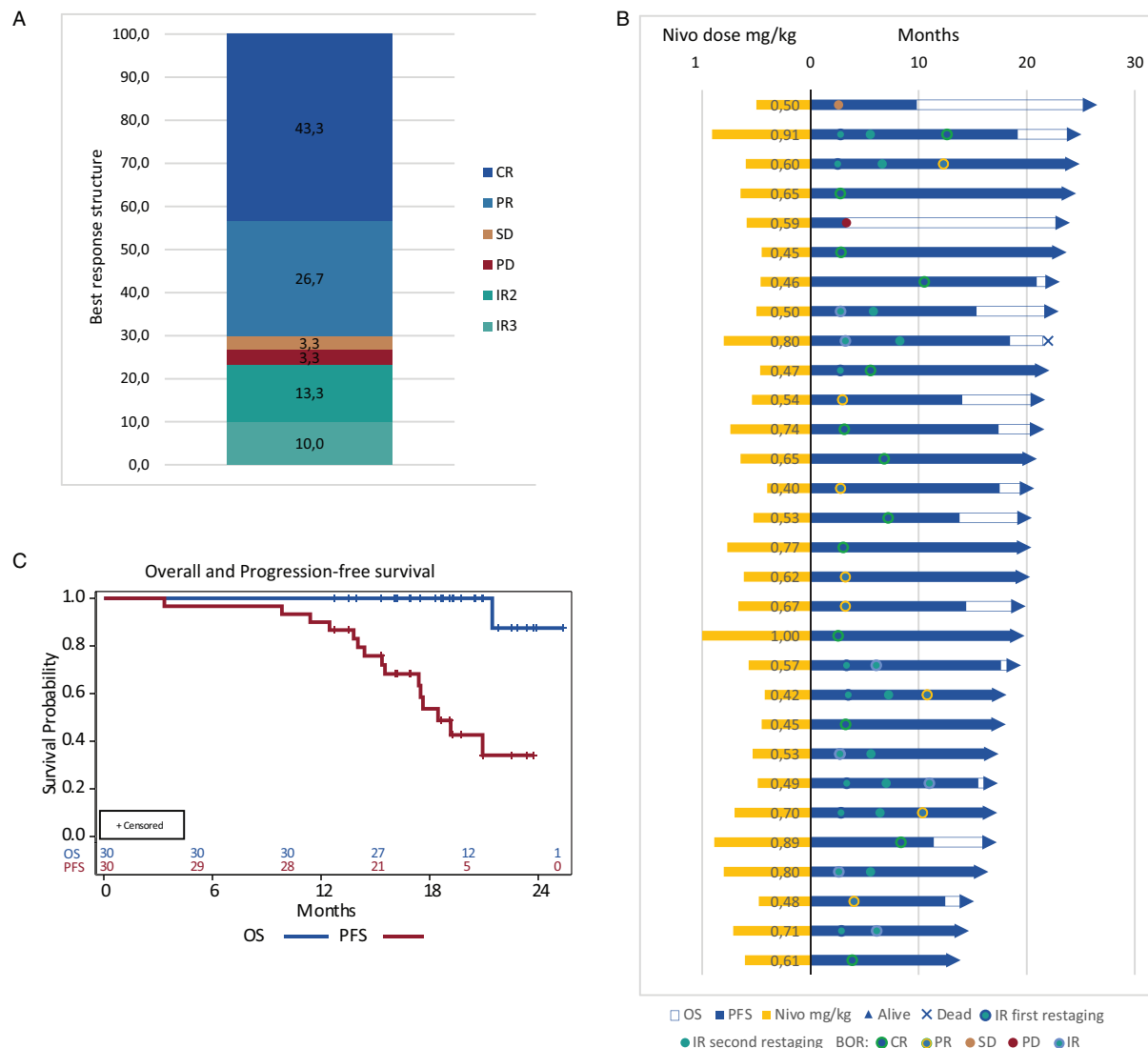


Figure 1. Response characteristics among all patients and treatment outcomes. (A) Structure of best overall response (BOR) during nivolumab treatment. The colors represent the BOR during nivolumab treatment: blue complete response (CR), light blue partial response (PR), brown stable disease (SD), red progression (PD), tial indeterminate response type 2 (IR2), light tial indeterminate response type 2 (IR2). Numbers represent the percent of patients with particular response type. Response characteristics and outcomes in all patients. (B) Overall survival for the whole patient group according to nivolumab dosage. (C) Overall (blue) and progression-free survival (PFS) in whole patient group.

negative CR at 3 months after the start of the treatment had significantly better prognosis: in PET(-) patients at first restaging, the 18-mo PFS was 80.0% (95% CI 20.4%–96.9%) with median not reached, versus 45.9% (95% CI 23.0%–66.2%) with median 17.6 months (95% CI 14.4–20.9 months) in other patients (Fig. 2B).

In one patient with persistent IR2 the biopsy of the involved lymph node was performed, confirming the presence of a viable tumor. The number of PD1+CD3+ cells in the peripheral blood samples of 7 patients before and after the first infusion of low dose nivolumab by flow cytometry analysis. The median proportion of PD1+CD3+ T-cells in peripheral blood was 33% (range 15.7–80.1). There was a significant reduction in the PD1+CD3+ cells proportion of peripheral blood T-lymphocytes after the first infusion of the nivolumab with median 0.7% (range 0%–1.7%) ($p=0.02$) (Fig. 3)

Discussion

The results of this study demonstrate that nivolumab in a fixed dosing regimen of 40 mg was effective for the treatment of patients with relapsed and refractory classical Hodgkin lymphoma, which was comparable to the efficacy of nivolumab at the labelled dose (3 mg/kg / 240 mg every 2 weeks or 480 mg every 4 weeks). With a median follow up of 19 months, the overall survival was 96.6% which is considerably better according to the prognosis of patients treated with chemotherapy and brentuximab vedotin.^{3–6} The overall survival rate observed in this trial is in a good agreement with the results of clinical trials assessing the efficacy of the standard dose nivolumab (1 year OS 90%–93% in different cohorts) and pembrolizumab (2 year OS 89.4%–92.5% in different cohorts) as well as a real-life experience.^{7–10} The response and restaging in current trial were based on the LYRIC

Table 2

Structure of AE During Nivolumab 40mg Dosing Regimen Therapy

Type of AE	AE overall		AE Gr 1-2		AE Gr 3-4	
Any	28	93.3%	28	93.3%	4	13.3%
Fever	12	40.0%	12	40.0%	0	0.0%
Pruritus	12	40.0%	12	40.0%	0	0.0%
Headache	11	36.7%	11	36.7%	0	0.0%
Fatigue	8	26.7%	8	26.7%	0	0.0%
Arthralgia	8	26.7%	7	23.3%	1	3.3%
Xerostomia	8	26.7%	8	26.7%	0	0.0%
AKI	7	23.3%	7	23.3%	0	0.0%
ALT/AST increased	7	23.3%	6	20.0%	1	3.3%
Anemia	7	23.3%	6	20.0%	1	3.3%
Dyspnea	6	20.0%	6	20.0%	0	0.0%
Maculopapular rash	6	20.0%	6	20.0%	0	0.0%
Hypothyroidism	6	20.0%	6	20.0%	0	0.0%
Blurred vision	6	20.0%	6	20.0%	0	0.0%
Cough	5	16.7%	5	16.7%	0	0.0%
Vomiting	5	16.7%	5	16.7%	0	0.0%
Abdominal pain	5	16.7%	5	16.7%	0	0.0%
Platelet count decreased	5	16.7%	5	16.7%	0	0.0%
Palpitations	4	13.3%	4	13.3%	0	0.0%
Upper respiratory infection	3	10.0%	3	10.0%	0	0.0%
Herpetic infection	3	10.0%	3	10.0%	0	0.0%
Leukopenia	3	10.0%	3	10.0%	0	0.0%
Constipation	2	6.7%	2	6.7%	0	0.0%
Pneumonia	1	3.3%	0	0.0%	1	3.3%
Pneumonitis	1	3.3%	0	0.0%	1	3.3%
Myelodysplastic syndrome	0	0.0%	0	0.0%	1	3.3%

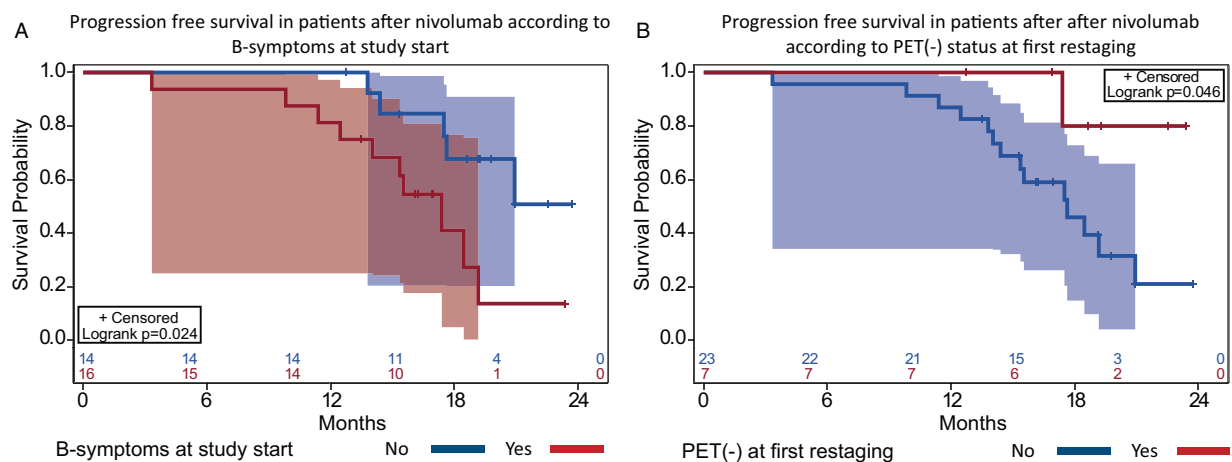


Figure 2. Progression-free survival regarding the presence of B-symptoms and PET(-) status at first restaging. A. Progression-free survival (PFS) in patients without B-symptoms vs. patients with B-symptoms at study start. B. Progression-free survival (PFS) in patients with early PET negative complete response at 3 months after the treatment initiation versus other patients.

criteria. One of the main aims of the LYRIC criteria is the prevention of the premature discontinuation of the therapy in patients with unconventional tumor response patterns. Our group was the first to report the application of these criteria in a prospective setting,⁹ demonstrating that patients with IR have the outcomes comparable to patients with PR and SD. In the current study, among treated patients, 13 (43.3%) had an IR at the first restaging at 3 months after treatment initiation: IR type 1 (IR1) in 2 patients, IR type 2 (IR2) in 8 patients, IR type 3 (IR3) in 3 patients. In all of these cases, nivolumab treatment was continued. Upon subsequent restaging at six months, 1 patient

had disease progression as defined by LYRIC, therefore his best response was reconsidered as a PD at 3 months, 3 patients achieved a conventional response (1 CR, 2 PR) (Fig. 1B). Overall, during the first year of treatment 5 patients achieved a conventional response and 1 patient was reconsidered as having a PD at first restaging. In 7 patients with IR that were included in BOR structure, 3 received additional treatment before the PD, and 4 had IR within primary endpoint timeframe of 12 months (NCT03343665). All of the patients with IR had clear clinical benefit with resolution of disease symptoms if they were present before the treatment initiation. Based on these observations, the

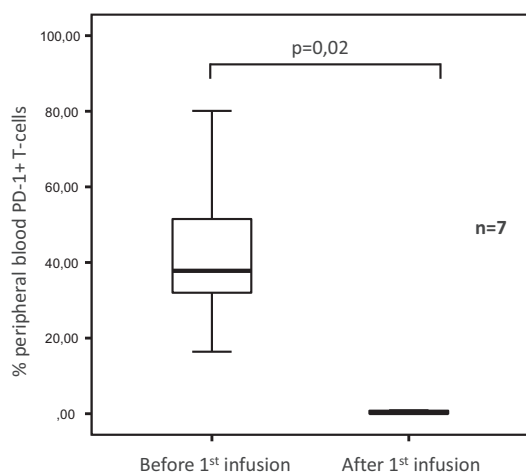


Figure 3. Dynamics of CD3+PD1+ T cells proportion from peripheral blood lymphocytes. Box plots represent median values and ranges, p - significance level (Wilcoxon matched pair test).

IR was also considered as a best response type in the current analysis, representing BOR in 23.3% of patients, which is similar to our previous experience (20%).⁹ To better correlate the efficacy of 40 mg nivolumab therapy with responses reported in clinical trials, the responses were also reassessed according to CT-based Lugano criteria (Supplementary Digital Content, Figure 3, <http://links.lww.com/HS/A99>). In the present study, the overall response rate was 70%, and median PFS was 18.4 (95% CI, 16.3–20.6) months which are comparable to results observed during treatment with standard dosing regimen: 65% to 73% ORR, median PFS of 11.9 to 18.3 months in cohorts A-C of nivolumab pivotal study, and 64% ORR, 19.4 months median PFS previously reported by our group.^{7,9} The safety profile was also similar to adverse events structure observed for standard dose nivolumab treatment with 93.3% of patients experiencing adverse events during 40 mg nivolumab therapy.^{7–10} The analysis also revealed the prognostic factors influencing the PFS of patients during nivolumab treatment: the presence of B-symptoms at the moment of nivolumab initiation and early response to therapy which is also in agreement with data reported from other groups.²⁵

Dose selection for ICI presents a challenge due to the failure to identify a maximum tolerated dose of nivolumab, which showed similar safety profile across various tumor types and dose levels (0.1–10 mg/kg) in early clinical trials.¹² Moreover, the efficacy analysis suggested that nivolumab at 1 mg/kg Q2W may be active for high-immunogenic tumor types of melanoma and RCC, however, a dose of 3 mg/kg Q2W may be required for the less-immunogenic tumor type of NSCLC. Based on these findings, the dose of nivolumab at 3 mg/kg Q2W was selected as a monotherapy dose across tumor types.¹² This dose was later translated into the clinical studies of nivolumab for r/r cHL. Approved PD-1 antibodies were initially developed and approved by the FDA as bodyweight-based dosing regimens. However, with the accumulation of population pharmacokinetic analysis data during anti-PD-1 antibodies development, it was revealed that bodyweight contributes only marginally to pharmacokinetic parameters. This led to the introduction and approval of flat dosing regimens of nivolumab 480 mg Q4W instead of 3 mg/kg Q2W and pembrolizumab 200 mg Q3W instead of 2 mg/kg Q3W, which were chosen for patient convenience and improved

efficiency for pharmacy and cancer care units.²³ Despite this optimization, the current treatment regimens are possibly excessive for cHL, while representing a significant financial burden for the healthcare system. In the current study, the median dose of nivolumab was 0.59 mg/kg (0.4–1 mg/kg), which is 3 to 7.5 fold lower than the standard bodyweight dosing regimens for this drug, with a corresponding reduction in treatment costs. In all patients the infused dose was higher than the plateau level of 0.3 mg/kg for PD-1 receptor occupancy, showed in pharmacokinetics studies. Also, the treatment biomarkers performed for a limited number of patients in this trial showed a dramatic decrease in the proportion of CD3+PD-1+ in T-cells population from initial level with median 33% (range 15.7–80.1) to a minimal level with median 0.7% (range 0%–1.7%) after the first infusion. This observation should be interpreted with caution, as it may not reflect the receptor occupancy, especially in tissue compartments and tumor lesions. Nevertheless, importantly, the response structure and PFS were not associated with nivolumab dose per kg bodyweight. These promising results provide a basis for future randomized trials aimed to define the optimal dosing regimen of PD-1 inhibitors for the treatment of r/r cHL, with potentially important financial implications.

Conclusion

Nivolumab administered at a fixed dose of 40 mg appears to be an effective treatment for relapsed and refractory classical Hodgkin lymphoma. The response structure, overall and progression-free survival observed in this study were independent from dose per kg bodyweight and were in good agreement with data from registrational clinical trials. This data creates a rationale for the initiation of a randomized prospective clinical trial aimed to confirm the non-inferiority of 40 mg dose to standard bodyweight or flat dosing regimens. Achievement of this goal will allow to decrease the financial burden of nivolumab treatment and expand the access of r/r cHL patients to this life-saving therapy.

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