Efficacy and safety results from CheckMate 140, a phase 2 study of nivolumab for relapsed/refractory follicular lymphoma

Running head

Nivolumab for R/R follicular lymphoma

Authors

Philippe Armand, Ann Janssens, Giuseppe Gritti, John Radford, John Timmerman, Antonio Pinto, Santiago Mercadal, Peter Johnson, David Cunningham, John P. Leonard, Scott J. Rodig, Patricia Martin-Regueira, Anne Sumbul, Selda Samakoglu, Hao Tang, Stephen M. Ansell

Author affiliations

Philippe Armand, Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA 02215; philippe_armand@dfci.harvard.edu

Ann Janssens, Universitaire Ziekenhuizen Leuven, 3000 Leuven, Belgium; ann.janssens@uzleuven.be

Giuseppe Gritti, Ospedale Papa Giovanni XXIII, Bergamo, BG 24129, Italy; g.gritti@asst-pg23.it

John Radford, University of Manchester and the Christie NHS Foundation Trust, Manchester Academic Health Science Centre, M13 9NT, Manchester, UK; john.radford@manchester.ac.uk

John Timmerman, University of California Los Angeles, Los Angeles, CA, USA, 90095; jtimmerman@mednet.ucla.edu

Antonio Pinto, Istituto Nazionale Tumori, Fondazione Pascale, IRCCS, Naples, NA 80131, Italy; apinto.pascale@gmail.com

Santiago Mercadal, ICO-Duran y Reynals, Hospitalet de Llobregat, Barcelona, Spain, 0890x; smercadal@iconcologia.net

Peter Johnson, University of Southampton and NIHR/CRUK Experimental Cancer Medicine Centre, Southampton, SO16 6YD, UK; johnsonp@soton.ac.uk

David Cunningham, The Royal Marsden Hospital, Surrey, SM2 5PT, UK; david.cunningham@rmh.nhs.uk

John P. Leonard, Weill Cornell Medicine and New York Presbyterian Hospital, New York, NY, USA 10065; jpleonar@med.cornell.edu

Scott J. Rodig, Dana-Farber Cancer Institute and Brigham and Women's Hospital, Boston, MA, USA 02215; srodig@bwh.harvard.edu

Patricia Martin-Regueira, Bristol Myers Squibb, Princeton, NJ, USA, 08648; patricia.martin@bms.com

Anne Sumbul, Bristol Myers Squibb, Princeton, NJ, USA, 08648; anne.sumbul@bms.com

Selda Samakoglu, Bristol Myers Squibb, Princeton, NJ, USA, 08648*; samakoglu@gmail.com

Hao Tang, Bristol Myers Squibb, Princeton, NJ, USA, 08648; tracy.tang@bms.com

Stephen M. Ansell, Mayo Clinic, Rochester, MN, USA, 55905; ansell.stephen@mayo.edu

*Affiliation at time of study

Corresponding author

Philippe Armand

Dana-Farber Cancer Institute, 450 Brookline Ave, Boston, MA, 02215

Telephone: +1 617 632 2305

Fax: + 617 632 4422

Email: philippe_armand@dfci.harvard.edu

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- Nivolumab monotherapy was associated with very limited activity in patients with R/R FL.
- Understanding the tumor microenvironment may be necessary to develop effective checkpoint-based strategies in FL.

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Abstract

(247/250 words)

Nivolumab, an anti–programmed death-1 (PD-1) monoclonal antibody, showed promising activity in relapsed or refractory (R/R) follicular lymphoma (FL) in a phase 1 study. We conducted a phase 2 trial to evaluate further its efficacy and safety in patients with R/R FL and to explore biomarkers of response. Patients with R/R FL and at least two prior lines of therapy, each containing a CD20 antibody or an alkylating agent, were treated with nivolumab 3 mg/kg every 2 weeks. The primary endpoint was objective response rate (ORR) assessed by independent radiologic review committee. Biomarker analyses included gene expression profiling and multiplex immunofluorescence studies of pretreatment tumor samples. A total of 92 patients were treated. After a minimum follow-up of 12 months, ORR was 4% (4/92). Median PFS was 2.2 months (95% confidence interval [CI], 1.9–3.6). Median DOR was 11 months (95% CI, 8–14). Exploratory analyses suggested that responders had significantly higher proportion of CD3+ T cells in the tumor microenvironment than non-responders, but no significant differences in PD-1 or PD-L1 expression were observed. High expression of a set of tumor-associated macrophage genes was associated with reduced PFS (hazard ratio, 3.28; 95% CI, 1.76–6.11; *P* = .001). The safety profile was consistent with previous reports of nivolumab. In conclusion, nivolumab monotherapy was associated with very limited activity in patients with R/R FL. Better understanding of the immune biology of this disease may facilitate the development of effective checkpoint-based strategies. This trial was registered at www.clinicaltrials.gov as #NCT02038946.

Introduction

Follicular lymphoma (FL) typically has an indolent disease course, but is not considered curable with conventional therapies.[1] Most patients experience relapse after frontline therapy, and although newer therapies such as PI3K inhibitors and the immunomodulatory drug lenalidomide may lead to frequent responses in patients with relapsed or refractory (R/R) disease, most patients will subsequently relapse.[2-5] There is therefore a need for novel, effective, and safe therapies for R/R FL.

FL appears to be inherently immunosensitive, as evidenced by the success of allogeneic hematopoietic cell transplantation (HCT),[6,7] as well as occasional responsiveness to other immunotherapeutic agents such as ipilimumab and pidilizumab.[8,9] Nivolumab, a fully human IgG4 monoclonal antibody against programmed death-1 (PD-1), blocks signaling induced by the binding of PD-1 to its ligands PD-L1/L2, which releases inhibition of T cells and restores anti-tumor immune responses.[10] Nivolumab is indicated for the treatment of several tumor types.[10] In CheckMate 039, a phase 1 study targeting several lymphoid malignancies, nivolumab showed promising activity in R/R FL, with an objective response rate (ORR) of 40% (4/10).[11] Responses were durable, with response durations >1.5 years for one patient with complete remission (CR), and ≥6 months for patients with partial remission (PR). This study also suggested a favorable safety profile for nivolumab in R/R FL, similar to that observed in patients with solid tumors and classical Hodgkin lymphoma.[12] Based on these encouraging results, we conducted a phase 2 study to evaluate the efficacy and safety of nivolumab in patients with R/R FL and previous rituximab treatment.

The mechanistic basis of responsiveness to PD-1 blockade in FL has yet to be elucidated. Most FL tumor cells do not express PD-L1/L2,[11,13-15] but PD-L1 has been found on non-malignant tumor-infiltrating immune cells.[11,15] Meanwhile, tumor-infiltrating T cells showed high PD-1 expression and suppressed cytokine signaling.[15] Thus, responses to nivolumab could provide

important insights into the mechanism of PD-1 blockade in FL. Indeed, the host immune response has been recognized as an important determinant of sensitivity of FL to conventional therapy. In one study, two gene expression signatures of non-malignant tumor-infiltrating immune cells, termed 'immune-response 1' (IR-1) and 'immune-response 2' (IR-2), were associated with favorable and poor survival prognoses in FL, respectively.[16] Studies have also found that the degree of infiltrating macrophages and T cells may be prognostic in FL,[17] and progression of disease within 24 months (POD24) was associated with reduced intratumoral immune infiltration.[18] In the present study we therefore examined pretreatment biomarkers as potential predictors of response to nivolumab.

Methods

Study design and patient population

CheckMate 140 (NCT02038946) was a single-arm, open-label, phase 2 trial in patients aged ≥18 years with R/R FL after failure of at least two prior lines of therapy, each of which had to contain a CD-20 antibody or an alkylating agent, and at least one had to include rituximab. Patients were excluded if they had central nervous system involvement, prior treatment with antibodies targeting T-cell co-stimulation or immune checkpoint pathways, prior allogeneic HCT or autologous HCT within 12 weeks prior to receiving study drug. The study was conducted in accordance with Good Clinical Practice, as defined by the International Conference on Harmonization. The study protocol, patient consent forms, and patient recruitment material were approved by the Institutional Review Board/Independent Ethics Committee and conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent before study initiation. The original protocol contained an interim analysis for futility; however,

since further follow-up of the phase 1 CheckMate 039 study showed that many responses were delayed, with half occurring around 9 months,[11] this futility analysis was removed.

Treatment

Patients were treated with nivolumab 3 mg/kg every 2 weeks until disease progression, unacceptable toxicity, or withdrawal of consent. Nivolumab was administered as an intravenous infusion over 60 minutes on day 1 of each treatment cycle. Patients still meeting all other eligibility criteria could continue to receive nivolumab beyond progression if they were deriving apparent clinical benefit from treatment in the opinion of the treating investigator.

Assessments and Endpoints

Tumor responses were assessed by computed tomography or magnetic resonance imaging at baseline, every 8 weeks through the first 8 months, every 12 weeks through months 9–24, and every 6 months thereafter until disease progression. Positron emission tomography scans were required at baseline and to confirm a CR. Bone marrow biopsy or aspirate were required within 90 days prior to consent or during the screening period. For patients with bone marrow involvement at screening, bone marrow biopsy or aspirate were required to confirm a CR. A minimum of 1 formalin-fixed paraffin-embedded (FFPE) tumor tissue block or minimum of 10 FFPE unstained sections were required for biomarker evaluations.

The primary endpoint was ORR assessed by independent radiologic review committee (IRC) according to 2007 International Working Group Response Criteria.[19] The final analysis of the primary endpoint occurred 12 months after the last enrolled patient's first dose of nivolumab. Secondary endpoints included duration of response (DOR), CR rate, PR rate, and progression-free survival (PFS), all assessed by IRC, and ORR by investigator assessment. Exploratory endpoints included safety and tolerability, overall survival (OS), and the association of biomarkers with efficacy measures. Specific biomarkers for evaluation were selected post hoc.

Biomarker assessment

Expression of CD3, CD68, PD-1, and PD-L1 in the tumor microenvironment was analyzed by multispectral immunofluorescence from a subsample of responding and non-responding patients. A pretreatment biopsy was chosen for biomarker studies when possible, and archival tissue was used if pretreatment tissue was insufficient. Staining was performed using BOND RX fully automated stainers (Leica Biosystems, Wetzlar, Germany). Image acquisition was performed using the Mantra multispectral imaging platform (PerkinElmer, Waltham, MA). Areas with non-tumor or residual normal tissue were excluded from the analysis. Representative regions of interest were chosen by the pathologist, and multiple fields of view were acquired at 20× resolution as multispectral images. Cell identification was performed using supervised machine learning algorithms within Inform 2.4 (PerkinElmer, Waltham, MA). Thresholds for staining and the accuracy of phenotypic algorithms were optimized and confirmed by the pathologist for each case.

Gene expression profiling on FFPE pretreatment tumor specimens was performed using the HTG EdgeSeq oncology biomarker panel (OBP; HTG Molecular Diagnostics, Inc., Tucson, AZ). Raw counts for the 2568 genes on the panel were normalized using total counts; a negative binomial was used to model the count distribution using EdgeR software.

RNA sequencing was performed using pretreatment tumor specimens for expression profiling of the complete set of genes in the IR-1 and IR-2 signatures[16] (except for *NDN* and *CEB1* from IR-2) in a select group of responders and non-responders. Data analysis was performed using the Wilcoxon rank-sum test.

Levels of cytokines were measured using Luminex-based technology (HumanMAP panel: Myriad RBM, Austin, TX) from serum collected at baseline and select time points during treatment. Differences in the sum of ranks between groups were compared using Dunn's multiple comparisons test.

Statistical analysis

The desired sample size of 90 patients was chosen to provide 87% power to reject the null hypothesis that the ORR is ≤20%, with a two-sided alpha of 5%. This sample size was also considered sufficient for the safety analysis. All patients who received at least one dose of nivolumab were included in the efficacy and safety analyses. ORR by IRC was summarized by a binomial response rate and its corresponding two-sided 95% exact CI using the Clopper–Pearson method. CR and PR rates by IRC, and ORR by investigator were summarized similarly. DOR by IRC, PFS by IRC and investigator, and OS were summarized based on the Kaplan–Meier product-limit method. Median values of PFS with two-sided 95% CIs (based on the log-log transformation) were calculated. Safety analyses were performed using descriptive statistics using NCI CTCAE version 4.0.

Data sharing statement

The Bristol-Myers Squibb Company policy on data sharing may be found at https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html.

Results

Baseline characteristics and patient disposition

A total of 92 patients were treated with nivolumab. Baseline clinical characteristics of all treated patients are shown in Table 1. Median number of prior therapies was 3 (range, 2–10), with 42% of patients having at least four prior therapies. The percentages of patients with relapsed or refractory disease at baseline were 65% and 35%, respectively, and 45% of patients were POD24. At the clinical cutoff, the minimum follow-up was 12 months. A total of 87 patients (95% of all treated) discontinued study treatment; reasons for discontinuation were disease

progression (76%), study drug toxicity (9%), adverse events (AEs) unrelated to study drug (6%), patient request/withdrawal of consent (7%), lost to follow-up (1%), and no longer meeting study criteria (1%). The median number of doses received was 8 (range, 1–50).

Safety

In total, 95% of patients experienced at least 1 AE and 49% experienced at least one grade 3–4 AE. The most common grade 3–4 AEs were malignant neoplasm progression (5%), neutropenia (5%), abdominal pain (4%), and anemia (4%). Treatment-related AEs (TRAEs) occurred in 54% of patients, most frequently fatigue (13%), diarrhea (11%), and nausea (10%) (Table 2). Most TRAEs were grade 1–2; 15% of patients experienced at least one grade 3–4 TRAE, but no grade 3-4 event occurred in more than 2% of patients (Table 2). Serious AEs (SAEs) were reported in 39% of patients; the most frequent SAEs were malignant neoplasm progression (5%; all were grade 3–4) and pyrexia (4%; all were grade 1–2). Immune-related AEs included rash (9%), diarrhea/colitis (2%), hypersensitivity/infusion reactions (2%), hepatitis (1%), and pneumonitis (1%) (Table S1). Three patients discontinued treatment due to immune-mediated AEs (pneumonitis, rash, and toxic epidermal necrolysis; one patient each).

In all, 30 patients (33%) died during the study, most commonly due to disease progression (17 [18%]). There were three deaths (3%) related to study drug toxicity: 1 patient with toxic epidermal necrolysis, one with acute respiratory failure and septic shock, and one with erythema multiforme.

Efficacy

The ORR based on IRC assessment was 4% (4/92); 1 patient achieved CR and three patients achieved PR (Table 3). The investigator-assessed ORR was 11% (10/92), with 2 CR and 8 PR. More than one third (36%) of evaluable patients experienced reductions in target lesion burden (Figure 1). For patients who responded to treatment, median time to response was 5.0 months (interquartile range, 2.1–10.4), and the median DOR was 10.9 months (95% CI, 8.3–13.6)

(Figure 2A). Median time to next treatment was 5.9 months (95% CI, 4.3–6.6). Median PFS per IRC was 2.2 months (95% CI, 1.9–3.6) (Figure 2B). PFS was similar when stratified by number of prior lines of therapy; median PFS was 3.3 months, 2.1 months, and 2.0 months in patients with 2, 3, or ≥4 prior lines of therapy, respectively. Median PFS was also similar when stratified by best overall response to most recent prior therapy: 2.3 months among patients with CR, 3.7 months with PR, 2.3 months with stable disease (SD), and 1.9 months with progressive disease. The 6-month and 12-month OS rates were 88% (95% CI, 79–93) and 78% (95% CI, 68–85), respectively (Figure 2C). The median OS had not been reached by the clinical cutoff date.

Biomarkers

Selected tumor specimens (n = 10) from four responders and six non-responders (SD or progression) per investigator were evaluated by multispectral immunofluorescence. Significantly more infiltrating CD3+ T cells were observed in FL specimens from responders versus non-responders (*P* = .016; Figure 3A). Most PD-1 was expressed on CD3+ T cells and most PD-L1 on CD68+ macrophages (not shown). More tumor-infiltrating CD3+ PD-1+ T cells and CD68+ PD-L1+ macrophages were observed in responders than non-responders, but these differences were not statistically significant (Figure 3B, C).

In analyses of pretreatment serum levels of 49 cytokines among 78 patients, soluble interleukin 2 receptor α (sIL-2Rα) levels were lower at baseline in responders per investigator versus non-responders (Figure S1) as assessed by rank-sum testing (*P* = .0025), though the absolute differences were small.

A total of 56 patients had evaluable gene expression profile data for HTG EdgeSeq OBP, and 11 for RNASeq. Among an extensive list of published gene signatures involved in immune responses, an IR-2 panel comprising select genes from the IR-2 signature[16] was strongly associated with PFS (Figure S2). We also assessed the association between PFS and the expression of specific tumor-associated macrophage (TAM) genes within the IR-2 signature

(*TLR5*, *C3AR1*, and *FCGR1A*). The risk of disease progression or death was significantly increased in patients with high (above median) levels of baseline *TLR5*, *C3AR1*, and *FCGR1A* versus patients with low (below median) levels, with a hazard ratio of 3.28 (95% CI, 1.76–6.11; *P* = .001) (Figure 4A). Median PFS was 1.9 months (95% CI, 1.7–2.1) and 4.8 months (95% CI, 2.0–5.8) for patients with high and low baseline levels of *TLR5*, *C4AR1*, and *FCGR1A*, respectively. Levels of baseline *TLR5*, *CA4AR1*, and *FCGR1A* (as assessed by signature score) were higher in patients with progressive disease compared with patients who achieved CR or PR per investigator (Figure 4B). The correlation between expression level and best overall response was also significant (*P* = .048) when the complete set of genes in the IR-2 signature was included in the analysis, with a median signature score of −0.63 in patients with CR or PR, and 0.52 in patients with progressive disease (Figure 4C). In contrast, no significant association (*P* = .56) was observed between expression levels of a group of genes within the IR-1 signature[16] expressed in T cells (*TNFSF13B*, *LEF1*, and *STAT4*) and PFS. Median PFS was 2.1 months (95% CI, 1.8–2.3) and 2.3 months (95% CI, 1.9–4.4) for patients with high and low levels of these genes at baseline.

Discussion

The safety profile of nivolumab in patients with R/R FL was similar to that in other settings, although it is notable that two fatal dermatologic complications occurred. While severe dermatologic toxicities have been previously described with PD-1 blockade,[20] these are rare events; future studies with PD-1 blockade in FL could therefore pay close attention to this type of toxicity. Unlike the results in phase 1 study of nivolumab in R/R FL, however, the efficacy of nivolumab monotherapy in this disease was very limited, with an IRC-assessed ORR of 4%, which did not meet the primary endpoint. As in other settings with PD-1 blockade,[12] the investigator-assessed ORR (11%) was higher than IRC-assessed ORR, and the results per

investigator were generally consistent with those per IRC. The difference between the present results and those of the phase 1 study may reflect the larger sample size in the phase 2 study.[11] Our results also differ from interim results of a phase 2 trial evaluating pembrolizumab in combination with rituximab in patients with R/R FL, in which the ORR was 64%.[21,22] In that trial, patients had to be sensitive to rituximab and were less heavily pretreated, with a median of one prior line of therapy. Further analyses will be necessary to determine whether the difference in patient populations explains the difference in efficacy or whether there is indeed synergy between PD-1 blockade and rituximab.

While responses were rare with nivolumab, they appeared durable, consistent with findings from the phase 1 study and prior study of CTLA-4 blockade.[8] To understand the biological basis of such prolonged response, which could yield valuable insights into the immune biology of FL and lead to the rational design of effective combination therapies, we examined potential predictive biomarkers in exploratory post hoc analyses. In previous studies PD-1 was found to be highly expressed on the intratumoral CD4+ follicular T helper cells in the lymph node follicles, and also expressed on exhausted CD4+ cells at lower levels.[15,23] As FL tumors typically lack expression of the PD-1 ligands,[11] it is unlikely that direct disruption of a PD-L1/PD-1 interaction between tumor and T cells underlies responses to PD-1 blockade in FL. In our study PD-L1 was present on CD68+ macrophages, and CD3+ T cells were more abundant in responding patients than non-responders. A slightly higher proportion of CD3+ PD-1+ and CD68+ PD-L1+ cells was found in responders than non-responders, but given the small sample size, the validity of this observation will need to be confirmed. The higher responsiveness of more ‘inflamed’ tumors has been well described with PD-1 blockade.[24,25] Recent work in FL suggested that a population of PD-1+ γδ T lymphocytes may provide a potential source of tumor control that is impaired by PD-1 expression and could therefore be recruited by PD-1 blockade.[26] There is also evidence that other immune checkpoints are expressed in the FL microenvironment including LAG-3,[27] TIM-

3,[28] and TIGIT.[29] Targeting those pathways could be more effective than PD-1 blockade in FL; it is also possible that combination blockade could be synergistic. However, as only a small number of patients were classified as responders (n=4), the number of biopsy samples available for analysis was also low. The associations found between patient response and biomarkers are only hypothesis generating, and their validity will need to be confirmed in subsequent studies.

Our results further strengthen the notion that the tumor microenvironment in FL plays an important role in the course of the disease. The IR-2 signature, comprising genes preferentially expressed in macrophages, dendritic cells, or both, was previously identified as a predictive marker of unfavorable prognosis in FL.[16] In support of this, we found that higher expression of TAM genes (*TLR5*, *C3AR1,* and *FCGR1A*) within IR-2 was associated with an increased risk of disease progression in patients treated with nivolumab. Thus, an immune-related gene signature may be predictive of responsiveness both to conventional therapy and to checkpoint blockade, providing a possible basis for trials combining PD-1/PD-L1 blockade with chemotherapy in FL; one such trial has already reported encouraging preliminary results.[30] Additionally, we found that high serum levels of sIL-2Rα at baseline was associated with poor response to nivolumab, consistent with previous studies that demonstrated poor prognosis in patients with elevated sIL-2R(α) who were treated with rituximab monotherapy or chemotherapy as first-line treatment for FL.[31,32] Levels of sIL-2Rα are likely to reflect the state of the tumor microenvironment, based on a positive correlation between the serum levels of sIL-2Rα and the number of CD68+ macrophages in FL.[33]

Overall, this trial demonstrates that single-agent PD-1 blockade is not effective in R/R FL. This negative finding may be important in several ways. First, it will help in the interpretation of results from trials that use PD-1 blockade in combination with other agents, by providing an estimate of the single-agent contribution of PD-1 blockade. Second, it may provide a note of caution in the design of combination studies that are not supported by biological hypotheses and help to guide

the choice of rational combinations in patients with the appropriate biomarkers. Finally, if confirmed in future studies, the tumor characteristics found here to be associated with responsiveness to PD-1 blockade could form a basis for patient selection in future trials of checkpoint-based therapy.

Authorship

Authors: please provide your authorship form (sent separately)

Conflicts of interest

Authors: please provide your COI information (sent separately)

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Figures captions

Figure 1. Best change in target lesions in response-evaluable patients per independent radiologic review committee. Response-evaluable patients (n = 83) were those with a target lesion(s) assessed at baseline and with at least one on-study time point with all baseline target lesion(s) assessed. Negative values indicate maximum tumor reduction; positive values indicate minimum tumor increase; best change is based on evaluable target lesion measurements up to progression or start of subsequent therapy. Dashed horizontal line indicates the 50% reduction consistent with a response per revised 2007 International Working Group criteria.

Figure 2. Kaplan–Meier estimates of (A) DOR per IRC (B), PFS per IRC, and (C) OS. Symbols represent censored observations. NE, not estimable.

Figure 3. Multispectral immunofluorescence of (A) CD3, (B) CD3 and PD-1, and (C), CD68 and PD-L1 in patients with and without response to nivolumab. ns, not significant.

Figure 4. Outcomes by gene signatures: (A) PFS per IRC by *TLR5*, *C3AR1,* and *FCGR1A* expression; (B) best objective response per investigator by *TLR5*, *C3AR1,* and *GCGR1A* score or by (C) immune-response 2 complete signature score. CR, complete remission; PD, progressive disease; PR, partial remission; SD, stable disease.

Tables

Table 1. Baseline demographic and clinical characteristics (all treated patients)

Characteristic	Patients (N = 92)
Median age (range), years	67 (37–87)
Male sex	48 (52)
Disease stage at diagnosis*	
I	8 (9)
II	12 (13)
III	30 (33)
IV	41 (45)
Bone marrow involvement	
Yes	29 (32)
No	55 (60)
Not reported	8 (9)
FLIPI score at diagnosis	
0–1	8 (9)
2	20 (22)
3–5	38 (41)
Not reported	26 (28)
Number of prior lines of therapy	
Median (range)	3 (2–10)
2	34 (37)
3	19 (21)
≥4	39 (42)
Disease status at baseline	
Relapsed	60 (65)
Refractory	32 (35)
Progression from diagnosis to progression after first-line therapy	
Median (95% CI), years	2.4 (1.7–3.1)
<2 years	41 (45)
≥2 years	50 (55)
Prior radiotherapy	29 (32)
Prior autologous HCT	15 (16)

Data are reported as n (%), unless noted otherwise.
FLIPI, Follicular Lymphoma International Prognostic Index; HCT, hematopoietic cell transplantation.
*Disease stage at diagnosis was not reported for one patient.

Table 2. Summary of treatment-related adverse events (TRAEs) (all treated patients)

Adverse event	Patients, n (%) (N = 92)	
	Any grade	Grade 3–4
Patients with ≥1 TRAE	50 (54)	14 (15)
TRAE occurring in >3% of patients at any grade or in at least one patient at grade 3–4		
Fatigue	12 (13)	0
Diarrhea	10 (11)	2 (2)
Pruritis	5 (5)	0
Myalgia	5 (5)	0
Rash	4 (4)	1 (1)
Cough	4 (4)	0
Pyrexia	4 (4)	0
Neutropenia	3 (3)	2 (2)
Anemia	3 (3)	1 (1)
Vomiting	3 (3)	0
Decreased appetite	3 (3)	0
Colitis	2 (2)	1 (1)
Increased lipase	2 (2)	1 (1)
Mucosal inflammation	2 (2)	1 (1)
Decreased neutrophil count	2 (2)	1 (1)
Autoimmune hemolytic anemia	1 (1)	1 (1)
Herpes zoster	1 (1)	1 (1)
Klebsiella infection	1 (1)	1 (1)
Lung infection	1 (1)	1 (1)
Acute respiratory failure	1 (1)	1 (1)
Pleural effusion	1 (1)	1 (1)
Pneumonia	1 (1)	1 (1)
Pneumonitis	1 (1)	1 (1)
Portal vein thrombosis	1 (1)	1 (1)
Toxic epidermal necrolysis	1 (1)	1 (1)

Includes adverse events reported between first dose and 30 days after last dose of nivolumab.

Table 3. Summary of efficacy

Response	Patients (N = 92)	
	IRC assessment	**Investigator assessment**
Objective response rate, n (%) 95% CI*	4 (4) 1–11	10 (11) 5–19
Best overall response		
Complete remission	1 (1)	2 (2)
Partial remission	3 (3)	8 (9)
Stable disease	35 (38)	39 (42)
Progressive disease	46 (50)	35 (38)
Unable to determine	7 (8)	8 (9)
Median† DOR (95% CI), months	10.9 (8.3–13.6)	12.1 (1.6–NA)
Median† TTR (IQR), months	5.0 (2.1–10.4)	5.3 (2.0–7.6)

Data reported as n (%) unless indicated otherwise. Assessments are based on the 2007 International Working Group criteria.
DOR, duration of response; IQR, interquartile range; IRC, independent radiologic review committee; NA, not available; TTR, time to response.
*Confidence intervals based on the Clopper–Pearson method.
†Computed using Kaplan–Meier method.