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Letter
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# Nivolumab in Relapsed/Refractory Classical Hodgkin Lymphoma – Extended Follow-up of 30 Patients Treated Within the CheckMate 205 Trial in a Single-Center

Jesko Momotow[1,2], Helen Goergen[1,2], Karolin Behringer[1,2], Paul J. Bröckelmann[1,2], Sven Borchmann[1,2,3,4], Bastian v. Tresckow[1,2], Carsten Kobe[2,5], Andreas Engert[1,2], Stephanie Sasse[1,2]

**Correspondence:** Stephanie Sasse (e-mail: stephanie.sasse@uk-koeln.de).

The introduction of anti-PD1 (programmed death receptor 1) antibodies provides a new treatment option for relapsed/refractory (r/r) classical Hodgkin lymphoma (cHL) patients with excellent response rates in the nivolumab and pembrolizumab pivotal trials. So far, only limited data on long-term disease control and survival with PD1-blockade in r/r cHL exist. To address this important issue, we analyzed 30 patients treated with nivolumab in the CheckMate205 trial in Cologne with the longest observation time reported so far (median follow-up 43 months). Despite a higher percentage of patients with stage IV disease and B symptoms compared to the entire patient population of trial cohorts A to C, similar overall response rates (ORR) and median progression-free survival (PFS) were observed in our cohort. Within the extended follow-up period the majority of patients relapsed while on PD1-blockade, but overall survival (OS) is still excellent.

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*[1]Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf, University of Cologne*
*[2]German Hodgkin Study Group (GHSG)*
*[3]Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf, Center for Molecular Medicine, University of Cologne*
*[4]Faculty of Medicine, Else Kröner Forschungskolleg Clonal Evolution in Cancer, University of Cologne*
*[5]Department of Nuclear Medicine, University Hospital of Cologne, Cologne, Germany.*

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The introduction of anti-PD1 (programmed death receptor 1) antibodies provides a new treatment option for relapsed/refractory (r/r) classical Hodgkin lymphoma (cHL) patients with excellent response rates in the nivolumab and pembrolizumab pivotal trials. So far, only limited data on long-term disease control and survival with PD1-blockade in r/r cHL exist. To address this important issue, we analyzed 30 patients treated with nivolumab in the CheckMate205 trial in Cologne with the longest observation time reported so far (median follow-up 43 months). Despite a higher percentage of patients with stage IV disease and B symptoms compared to the entire patient population of trial cohorts A to C, similar overall response rates (ORR) and median progression-free survival (PFS) were observed in our cohort. Within the extended follow-up period the majority of patients relapsed while on PD1-blockade, but overall survival (OS) is still excellent.

Before application of the immunomodulatory approach of PD1-blockade the outcome of patients with disease recurrence after high-dose chemotherapy and autologous stem cell transplant (ASCT) was poor with a median OS of only 2 years.[1] In those patients achieving a remission with salvage treatment consolidating allogeneic stem cell transplantation (aSCT) as potentially curative treatment option might be discussed; in highly-selected patients, 3-year relapse free and overall survival rates of up to 40% and 78% after aSCT have been documented.[2]

By targeting the PD 1/PD-ligand (PD-L) pathway a promising new therapeutic option for patients in a - so far - palliative setting was assessed.[3–5] Based on pooled data of a phase I and II trial (CheckMate 039 and 205) nivolumab received approval by the US Food and Drug administration (FDA) and by the European Medicines Agency (EMA) for r/r cHL patients after ASCT and treatment with brentuximab vedotin (BV) or after at least 3 lines of systemic therapies including ASCT.[3,4,6]

The recently published follow-up analyses of CheckMate 205 confirmed the initial safety profile and efficacy of nivolumab in r/r cHL with no relevant impact of prior BV treatment. As shown after a median follow up of 18 months, duration of response differed dependent on the depth of response, but even in those patients achieving stable disease (SD) as best response a median PFS of 11 months and a 12-months OS rate of 98% were documented.[7] The most current analysis with a minimum follow-up of 31 months reported a median PFS of 15 months and 24-months OS rates of 86% to 90% in the different treatment cohorts.[8]

A total of 30 r/r cHL patients have been treated at the University Hospital of Cologne within the CheckMate 205 trial: 8 patients in cohort A (BV naïve), 16 in cohort B (BV after ASCT), and 6 in cohort C (BV before and/or after ASCT; Fig. 1). The majority of our patients were enrolled at the beginning of the trial enabling us to report the longest follow-up period thus far with a median of 43 months. Details of the trial design (CA209205; clinicaltrials.gov NCT02181738), eligibility criteria, statistics, the initial assessment of cohort B, the current assessment of cohort A, B, and C of the CheckMate 205 trial have already been reported.[4,7] Patient characteristics, outcomes and treatment-related adverse events (AEs) documented between September

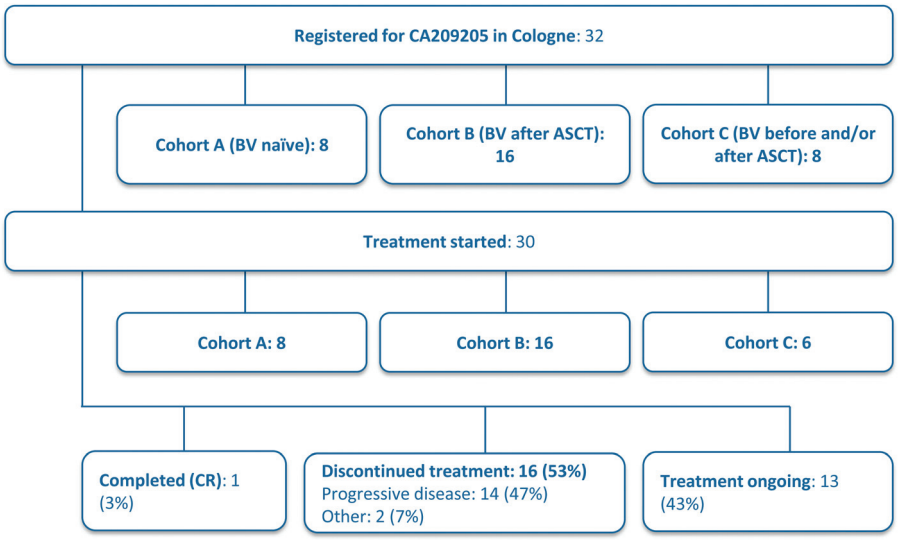


**Figure 1. Trial flowchart of the single-center cohort analysis of patients registered for the CA209205 trial in Cologne.** ASCT = autologous stem cell transplantation; BV = brentuximab vedotin; CR = complete response.

2014 and January 2019 were assessed for all patients treated in Cologne and analyzed by means of descriptive statistics. PFS and OS were analyzed according to Kaplan–Meier. PFS was defined as the time from the first day of nivolumab treatment until the date of first progression on PD1-blockade, relapse, or until death from any cause. OS was calculated from the same starting date until death from any cause. If none of the events had occurred, PFS and OS were censored at the date of the last documented follow-up in Cologne. Analyses were done using SAS version 9.4 (SAS Institute, Cary, NC).

Patient characteristics of our single-center cohort did not differ relevantly from the entire trial cohorts A to C except for a higher percentage of patients with stage IV disease (73% vs 57%) and B symptoms (60% vs 22%) (supplementary Table 1, Supplemental Digital Content, http://links.lww.com/HS/A45).

Based on local radiology assessment, ORR in our cohort was 84% (25/30) with best response being complete response (CR) and partial response (PR) in 8 (27%) and 17 (57%) patients, respectively. SD was documented in 4 (13%) patients and 1 patient (3%) had progressive disease as best response (supplementary Table 2, Supplemental Digital Content, http://links.lww.com/HS/A45).

Independent review committee (IRC) response assessment in our patient cohort resulted in an ORR of 70% (21/30) including 4 (13%) CRs and 17 (57%) PRs. According to IRC assessment, SD was documented in 6 (20%) and progressive disease in 3 (10%) patients as best response (supplementary Table 2, Supplemental Digital Content, http://links.lww.com/HS/A45).

As already discussed by Armand et al, 2018, the response criteria applied in the CheckMate 205 trial might not properly reflect atypical response patterns observed with immune checkpoint inhibitors.[7,9] These atypical response patterns are even more difficult to be quantified in advanced-stage disease including organ or bone marrow involvement and might explain the discrepancies between local and IRC response assessment in our patient cohort.[10,11]

With a median observation time of 43 months, a median PFS of 18.6 months and 12-, 24- and 48-months PFS estimates of 59.4% [95% CI 41.6%–77.1%], 41.9% [95% CI 23.9%–59.9%] and 24.4% [95% CI 5.1%–43.8%], respectively, were assessed (Fig. 2A).

15/19 patients who developed progressive disease had persistent clinical benefit and therefore continued treatment within the trial beyond documented tumor progression (TBP). TBP resulted in PR in 2, SD in 3 and progressive disease in 10 patients as best response with a median treatment duration beyond progression of 25.1 weeks (range 6–177 weeks) (supplementary Table 3, Supplemental Digital Content, http://links.lww.com/HS/A45).

2/19 patients with progressive disease on nivolumab proceeded to aSCT after achieving remission with salvage chemotherapy and nivolumab combined with radiotherapy, respectively. In 1 patient severe acute graft vs host disease had to be treated. Both patients are still in remission.

The 12-, 24- and 48-months OS estimates were 96.7% [95% CI 90.2%–100.0%], 86.3% [95% CI 73.8%–98.8%] and 82.9% [95% CI 69.2%–96.5%], respectively (Fig. 2B).

Response rates, median PFS, 12- and 24-months OS in our cohort were similar to results of the overall trial population of cohorts A to C of CheckMate 205 and to the results of Keynote-087, the phase II approval trial with the anti-PD1 antibody pembrolizumab. In accordance with the recently reported update of these trials the majority of patients in our cohort relapsed or developed progressive disease.[7,8,12]

However, also in line with the available follow-up analyses of cohorts A to C, our single-center analysis indicates that, at least in a subset of patients, further disease control might be achieved by continuing anti-PD1 TBP.[7] Of note, nine patients enrolled in our center continued to receive nivolumab as single agent or as part of a multimodal therapy approach after discontinuation of treatment within CheckMate 205 because of disease progression. As of January 2019, 5 of those patients receiving nivolumab as monotherapy beyond progression had SD more than one year after first documentation of progressive disease.

Retrospective analyses of Rossi et al, 2018, and of Carreau et al, 2018 suggest that in patients with a former aggressive and

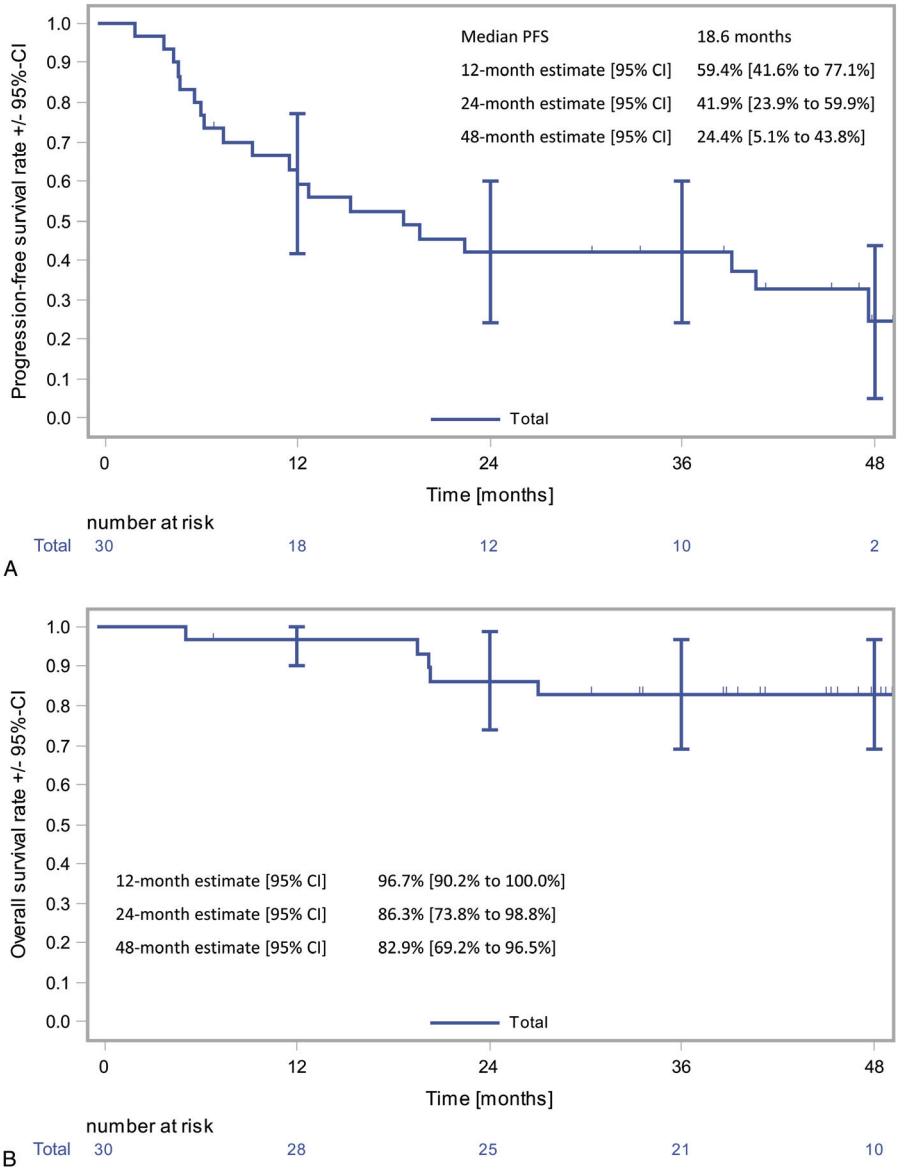


Figure 2. **Kaplan–Meier survival plots showing 95% confidence intervals (CI) for (A) progression-free survival (PFS) and (B) overall survival (OS).**

chemotherapy-refractory disease who develop relapsed or progressive disease on anti-PD1 treatment, this immunomodulatory treatment approach might result in a more indolent disease at relapse and might re-sensitize it to subsequent chemotherapy.[13,14] However, this hypothesis has to be confirmed by evaluation of a larger patient cohort.

The current assessment of nivolumab-related AEs in our single-center cohort confirmed the recently reported safety data of the CheckMate 205 trial and are in line with the safety profile reported for PD1-blockade with pembrolizumab.[5,7,8,10] Twenty-four patients of our single-center cohort (80%) developed at least 1 drug-related AE. The majority of these AEs was mild or moderate. All infusion- and the majority of autoimmune reactions (irAEs) completely resolved with the appropriate management. In 20 patients the manifestation of an irAE required the application of corticosteroids. Only 1 patient discontinued nivolumab due to a drug-related AE. No relevant treatment-related cytopenia and no treatment-related infections were documented (supplementary Tables 4 and 5, Supplemental Digital Content, http://links.lww.com/HS/A45).

In conclusion, with the longest follow-up reported so far, our single-center analysis of patients treated within the CheckMate 205 trial confirms the existing favorable efficacy and safety profile of PD1-blockade in r/r cHL. Neither the response nor the survival rates were impaired by the high proportion of patients with stage IV disease and B symptoms in our cohort. However, our analysis showed that despite a favorable initial response the majority of patients relapse on anti-PD1 monotherapy. A durable response - as indicated by results of small case series - might be achieved by consolidating aSCT. It is not clear yet if the reduced relapse rate after aSCT translates in an improved OS.[15] Furthermore, application of current response criteria might not properly reflect clinical benefit as well as overall survival on checkpoint blockade. These questions need to be addressed and mechanisms of resistance to PD1-blockade to be explored in order to optimize checkpoint blockade in r/r cHL.

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