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# Nivolumab, a promising alternative treatment option to standard-of-care multi-agent chemotherapy in patients with newly-diagnosed, advanced-stage, classical Hodgkin Lymphoma

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The 59th Annual Meeting & Exposition of the American Society of Hematology (ASH) featured the presentation of the primary results of the Phase 2 CheckMate 205 study. In this trial, a treatment regimen consisting of nivolumab followed by a combination of nivolumab and AVD (doxorubicin, vinblastine, and dacarbazine) chemotherapy was shown to be well tolerated in a cohort of newly-diagnosed, advanced-stage classical Hodgkin Lymphoma (cHL) patients.[1] At the end of therapy, N-AVD was associated with an objective response rate (ORR) per IRC (Independent Radiology Review Committee) of 84%, with 67% of patients achieving a complete remission (CR). At 9 months, the modified Progression-Free Survival (mPFS) rate was shown to be 94%. Based on these data, the researchers concluded that nivolumab monotherapy followed by N-AVD may provide a promising alternative treatment option to standard-of-care multi-agent chemo-therapy for patients with newly diagnosed, advanced-stage cHL.[1]

**(BELG J HEMATOL 2018;9(1):12-3)**

ABVD, MOPP/ABV, and BEACOPP are the current standards of care for advanced cHL.[3,4] While all 3 are effective, overall outcomes remain suboptimal for advanced-stage cHL as 12–37% of patients relapse or die within 5 years.[1] In addition to this, outcomes are significantly inferior for older patients, with a greater risk of pulmonary and/or long-term toxicity and a higher incidence of death without progression.[1,3-5]

Alterations of the programmed death ligand-1 (PD-L1) and programmed death ligand-2 (PD-L2) genetic loci are a defining feature of cHL.[6] In the original CheckMate 205 study, nivolumab, an anti-PD-1 monoclonal antibody, was shown to be associated with a favorable efficacy and safety profile as monotherapy in patients with relapsed or refractory cHL after failure of autologous hematopoietic stem cell transplantation (auto-HCT).[1] Greater than 95% of evaluable patients showed a reduction in tumor burden, the ORR was 69% and the median PFS was 15 months. These findings formed the basis to also assess the potential of nivolumab in patients with newly-diagnosed, advanced-stage cHL.

In total, 51 adult patients (63% male) with a median age of 37 years and newly-diagnosed, advanced-stage cHL (stages IIB, III, IV) and an ECOG (Eastern Cooperative Oncology Group) performance status of 0-1 were enrolled in the trial. These patients were first administered monotherapy with 240 mg of nivolumab every 2 weeks for 8 weeks (4 doses). Of these, 49 patients (96%) completed monotherapy. In a next step, 50 patients entered the combination therapy phase and were administered 240 mg of nivolumab in combination with AVD (doxorubicin 25 mg/m$^2$; vinblastine 6 mg/m$^2$; dacarbazine 375 mg/m$^2$) every 2 weeks for 22 weeks (12 doses) (N-AVD). Bleomycin, a cytostatic agent that is routinely used in combination with AVD in the treatment of cHL, was omitted from the treatment due to potential overlapping pulmonary toxicity.[2] In total, 44 patients completed the N-AVD combination therapy, while one completed AVD, for an overall completion rate of 90%. Forty-eight patients entered the follow-up phase (median duration 11.1 months). FDG-PET plus CT/MRI scans were carried out before and after the nivolumab monotherapy and were repeated after 4

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**Conflict of interest:** The selection of the abstracts discussed here is the sole responsibility of the publisher and was not influenced by third parties.

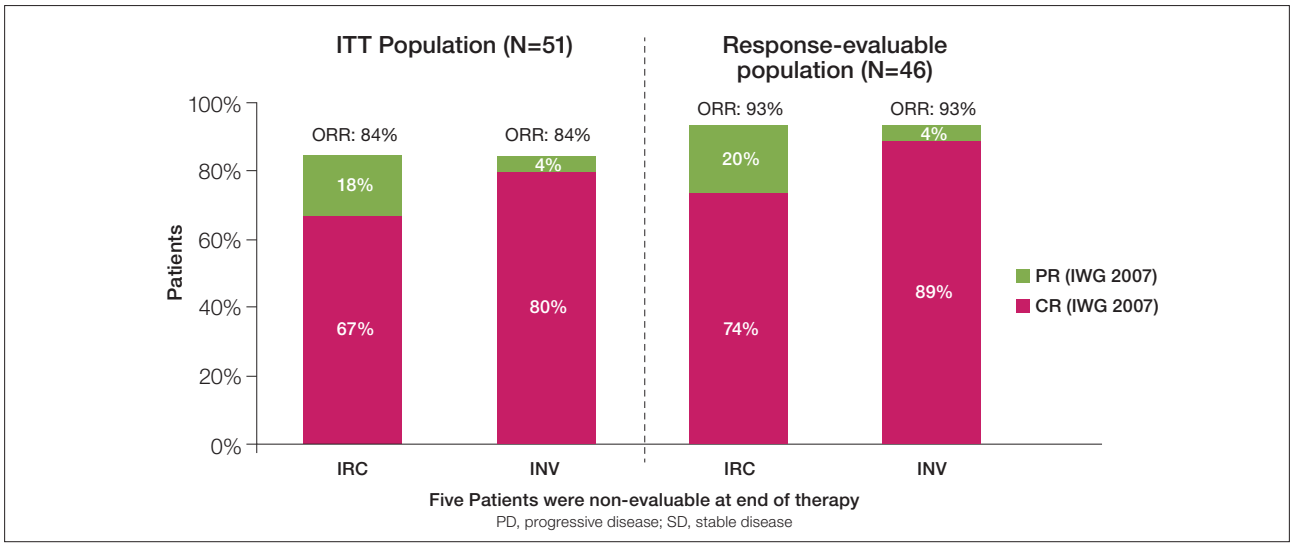


**FIGURE 1.** Response at End of Therapy in Evaluable Patients.

doses of N-AVD and once during the follow-up period. The primary endpoints of this trial were safety and tolerability, while secondary objectives included discontinuation rate, CR and ORR by IRC, CR and ORR by investigator, mPFS, and overall survival (OS).

During ASH 2017, safety and tolerability results were reported for all 51 patients enlisted in this study. In total, 49 patients (96%) reported various treatment-related adverse events (AEs) between the first dose and 30 days after last dose of study therapy, including a reduction in neutrophil count (neutropenia, 55%), nausea (35%), infusion-related reaction (31%), and fatigue (25%). Of these AEs, 59% were grade 3/4 in severity, including neutropenia in 49% of patients. Overall, 8 patients (16%) experienced infections/infestation (grade 3/4 in 2 cases, 4%). Fifty-nine percent of patients received growth factors after starting combination therapy, mostly (90%) as secondary prevention. There were 4 cases (8%) of AEs leading to discontinuation, of which one was classified as grade 3/4. No grade 5 treatment-related AEs occurred within 30 days of the last dose of study therapy. One elderly patient (aged 68 years) died because of study drug toxicity 38 days after the last dose of N-AVD. Pulmonary toxicity compared favorably to historical outcomes with AVD or ABVD and no cases of pneumonitis were reported. Two cases (4%) of grade 3/4 non-endocrine immune-mediated AEs were reported. All non-endocrine immune-mediated AEs were resolved. For endocrine AEs, 7 out of 13 cases were resolved and one patient was discontinued due to hyperthyroidism.

In total, 46 out of the original 51 patients had available response data as assessed by International Working Group Response (IWG) 2007 criteria. In the intent-to-treat (ITT) population, the ORR was 69% per IRC and 67% per investigator at the end of nivolumab monotherapy. At the end of N-AVD, the ORR per IRC was 84%, with 67% achieving a (CR), while the ORR per investigator was 84%, with 80% achieving a CR. In the response-evaluable population, the ORR per IRC was 93%, with 74% achieving a CR, while the ORR per investigator was 93%, with 89% reaching a CR. Five patients were non-evaluable at end of therapy. The probability rate of mPFS was 94% (95% CI 82, 98) at the end of 9 months, with a minimum follow-up of 9.4 months. Of note, mPFS was defined as the time to progression, death, or first subsequent systemic therapy in patients not achieving a CR at end of therapy.

In summary, nivolumab monotherapy followed by N-AVD was well tolerated in patients with newly diagnosed, untreated, advanced-stage cHL. Nearly all patients entered (98%) and completed (90%) the combination phase and the N-AVD safety profile was consistent with historical analyses, with no new safety signals. At the end of therapy, N-AVD was associated with an ORR per IRC of 84%, a CR per IRC in 67% of patients, and a mPFS rate of 94% at 9 months. Overall, these findings indicate that nivolumab followed by N-AVD may provide a promising alternative treatment option to standard-of-care multi-agent chemotherapy for patients with newly-diagnosed, advanced-stage cHL.

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