NIVOLUMAB COMBINED WITH BRENTUXIMAB VEDOTIN FOR RELAPSED/REFRACTORY PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA: EFFICACY AND SAFETY RESULTS FROM THE PHASE 2 CHECKMATE 436 STUDY

Author(s): Pier Luigi Zinzani , Armando Santoro , Giuseppe Gritti , Pauline Brice , Paul M. Barr , John Kuruvilla , David Cunningham , Justin Kline , Nathalie A. Johnson , Neha A. Mehta-Shah , Thomas Manley , Stephen Francis , Manish Sharma , Alison J. Moskowitz EHA Library. Luigi Zinzani P.

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Background

Primary mediastinal B-cell lymphoma (PMBL) is an infrequent aggressive lymphoma, accounting for < 5% of all non-Hodgkin lymphomas (NHLs). Patients (pts) with relapsed/refractory (R/R) PMBL have poor outcomes. Weak CD30 expression and increased programmed death-1 (PD-1) ligand expression are characteristic features of PMBL, with PD-1 ligand expression potentially contributing to evasion of host immune responses (Green MR et al. *Blood* 2010). Nivolumab, a fully human IgG4 anti−PD-1 immune checkpoint inhibitor monoclonal antibody, augments host antitumor immune responses. Brentuximab vedotin (BV), an anti-CD30 antibody–drug conjugate, induces apoptosis of CD30-expressing cells, and depletes immunosuppressive T regulatory cells, which may potentiate the activity of nivolumab. PD-1 blockade alone and BV monotherapy have been associated with overall response rates (ORRs) of 41% and 13%, respectively, in R/R PMBL (Zinzani PL et al. *Blood* 2017a,b).

Aims

To investigate the efficacy and safety of nivolumab + BV in pts with R/R PMBL from the phase 2 CheckMate 436 study (NCT02581631).

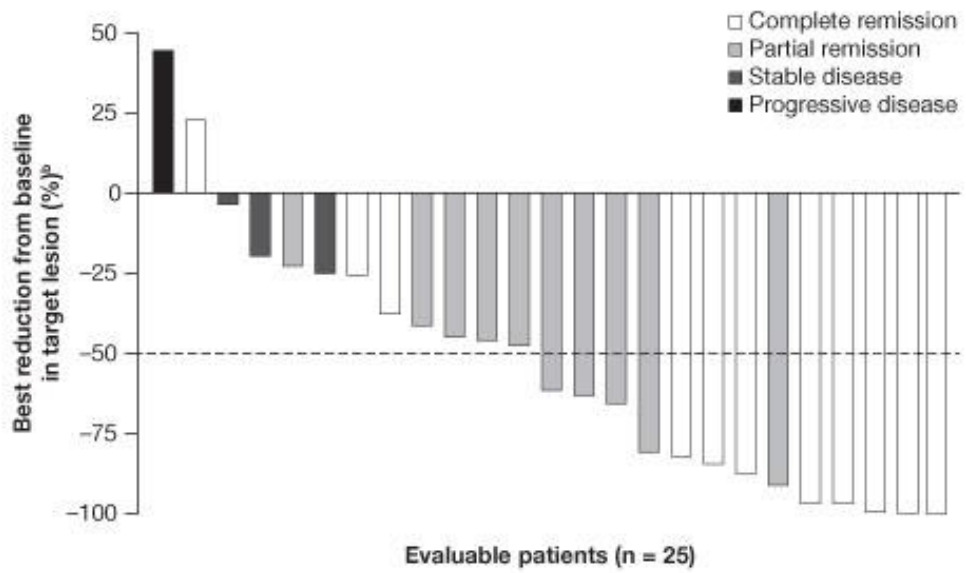
Methods

CheckMate 436 is an international, open-label, phase 1/2 study of nivolumab + BV to treat NHLs with CD30 expression. This expansion cohort enrolled pts with confirmed PMBL and R/R disease after either high-dose conditioning chemotherapy and autologous hematopoietic cell transplantation (auto-HCT) or ≥ 2 prior multi-agent chemotherapy regimens if ineligible for auto-HCT. Pts received nivolumab (240 mg IV) and BV (1.8 mg/kg IV, pre-specified dose modifications allowed) every 3 weeks until disease progression or unacceptable toxicity. Primary endpoints were investigator-assessed ORR per the Lugano 2014 classification and safety. Tumor response was assessed by PET-CT at weeks 6 and 12, every 9 weeks for the following 4 assessments, and every 12 weeks after the first year until disease progression.

Results

30 pts were treated with nivolumab + BV and included in this primary analysis. At baseline, median (min, max) age was 35.5 (19, 83) years, pts had received a median (min, max) of 2 (2, 5) prior systemic therapies, and 4 (13%) had received prior auto-HCT. With a median follow-up of 11.1 months, ORR (95% CI) was 73% (54–88), with 11 pts (37%) achieving complete remission (CR) per Lugano 2014; 13 (52%) of the 25 evaluable pts had a best reduction in target lesion of > 50% (**Figure**). The median duration of response has not been reached. Treatment-related AEs (TRAEs) were reported in 25 (83%) pts. The most frequently reported TRAEs were neutropenia (30%), peripheral neuropathy (27%), peripheral sensory neuropathy, thrombocytopenia, rash, and hyperthyroidism (13% each). Grade 3–4 TRAEs were reported in 16 (53%) pts, including 9 (30%) with neutropenia, 3 (10%) each with thrombocytopenia or peripheral neuropathy, 2 (7%) with decreased neutrophil count, and 1 (3%) each with hypersensitivity, colitis, rash, maculopapular rash, or immune-mediated hepatitis. Four pts (13%) had treatment-related serious AEs, including 2 pts with grade 3–4 colitis, maculopapular rash, or immune-mediated hepatitis.

Figure 1. Best change from baseline in target lesion by best overall response[a]



[a]Per Lugano 2014 criteria incorporating FDG-PET scan;
[b]Sum of the product of the diameters, based on CT scan.

Conclusion

In pts with R/R PMBL, nivolumab + BV demonstrated a high investigator-assessed ORR of 73%, with 37% CR. TRAEs were consistent with the safety profiles of nivolumab and BV treatment alone. The combination of nivolumab + BV may be synergistic and is active in pts with R/R PMBL.