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Title: NIVOLUMAB-BASED THERAPY OF RELAPSED OR REFRACTORY PRIMARY LARGE B-CELL LYMPHOMA OF IMMUNE-PRIVILEGED SITES AND DLBCL WITH SECONDARY CNS INVOLVEMENT

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Background:

Primary large B-cell lymphoma of immune-privileged sites (PLBLIPS) encompass primary central nervous system lymphoma (PLCNS) and primary testicular lymphoma (PTL) which are characterized by alterations of the 9p24 locus leading to increased PD-L1 expression on tumor cells. Chapuy et al. demonstrated that systemic diffuse large B-cell lymphoma (DLBCL) with involvement of CNS (SLCNS) or testis is generally belonged to the C5 subtype and has mutational profile similar to PLCNS and PTL. In all mentioned diseases types, patients (pts) with relapsed/refractory (r/r) disease after intensive chemotherapy have dismal prognosis, defining the need for novel treatment approaches. In such cases, anti-PD1 antibody nivolumab (Nivo) may represent an attractive and feasible biology-driven therapeutic option. However, published data have shown controversial information about the efficacy of Nivo in PLCNS. In one case series of 5 pts objective response (OR) in pts with r/r PLBLIPS was 100%, after mono-Nivo, in contrast in CheckMate 647 study, enrolled 47 pts with PLCNS, OR was only reached in 6,4% (L. Nayak et al., Blood, 2017; L. Nayak et al., NCT02857426).

Aims:

To evaluate the efficacy of Nivo-based therapy in pts with r/r PLBLIPS and SLCNS.

Methods:

Since 2017 in RM Gorbacheva Research Institute 14 pts with PLBLIPS and 9 pts with SLCNS have received Nivo-based treatment. PLBLIPS cohort included 13 pts with PLCNS, 1 with PTL and CNS involvement. In SLCNS tumors were presented by DLBCL in 8 pts (89%) and primary mediastinal large B-cell lymphoma in 1 (11%). All patients had active disease at the moment of Nivo treatment. Patients characteristics are summarized in Table 1. Expression of PD-L1 was studied in 8 pts with PLCNS and 4 with SLCNS. Among PLCNS positive (more then 1 %) PD-L1 expression was observed in 7 cases (88%), among SLCNS - in 4 (100%). Response was evaluated according to International Primary CNS Lymphoma Collaborative Group criteria (Abrey et al 2005).

Results:

Nivo in monotherapy and combined therapy was used in 12 pts (86%) and 2 pts (14%) with PLBLIPS and 5 pts (56%) and 4 pts (44%) with SLCNS respectively (Table 1). OR after therapy was reached in 10 pts (71%) from PLBLIPS group and in 6 pts (67%) from SLCNS group ($p>0.05$). Complete response was achieved in 7 pts (50%) and in 4 pts (44%) with PLBLIPS and SLCNS respectively. At the moment of data cut off the median follow-up of alive pts was 32 months (mo) for PLBLIPS and 33 mo for SLCNS. Two-year overall survival (OS) in pts with PLBLIPS was 53% and the median OS was not reached (10,9 mo - NR). Two-year OS in pts with SLCNS was 44%, the median OS was 7 mo (4,5 mo - NR). There was no difference in OS between groups ($p=0.39$). Two-year progression free survival (PFS) in PLBLIPS and SLCNS groups was 31% and 44% respectively ($p=0.93$). The median PFS was 11,6 mo (2,2 mo - NR) in pts with PLBLIPS and 5,6 mo (0,7 mo - NR) in pts with SLCNS. After Nivo-based treatment 3 pts with PLCNS received consolidation by radiation therapy (RT), 2 pts underwent autologous hematopoietic stem cell transplantation (auto-HSCT), 1 pt got maintenance by ibrutinib. 2 pts with SLCNS 2 were consolidated by RT, 1 pt underwent auto-HSCT and 1 pt received maintenance by lenalidomide

Summary/Conclusion: While data of published reports regarding efficacy of Nivolumab in lymphoma pts with CNS involvement is discordant, our analysis demonstrate its promising activity as monotherapy or as part of

combination treatment in pts with r/r PLCNS and SLNCS.

Keywords: Immunotherapy, Relapsed lymphoma, CNS lymphoma