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POSTER ABSTRACTS

626.AGGRESSIVE LYMPHOMAS: PROSPECTIVE THERAPEUTIC TRIALS

High-Dose Methotrexate Containing Induction Chemotherapy Followed By Nivolumab Consolidation in Older (≥ 65) Patients with Previously Untreated Primary CNS Lymphoma

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Introduction: High-dose methotrexate (HD-MTX)-containing chemotherapy followed by either autologous stem cell transplant (ASCT) or whole-brain irradiation (WBI) is widely considered the standard for primary CNS lymphoma (PCNSL) treatment. However, many older frail patients with PCNSL are unable to undergo ASCT or WBI due to increased risk of treatment-related toxicity, such as infections and neurotoxicity. Without consolidation, survival outcomes are significantly worse, with a 3-year progression free survival (PFS) rate of ~ 30%. Therefore, novel therapeutic approaches are urgently needed for older PCNSL patients. Recently, nivolumab, an anti-PD1 antibody, showed promising clinical activities in relapsed/refractory PCNSL, and we hypothesized that addition of nivolumab in the frontline setting would be safe and improve survival outcomes of older PCNSL patients who are deemed poor candidates for ASCT or WBI.
Methods: In this phase 1/1B single-arm multicenter study, patients ≥ 65, who were deemed poor candidates for ASCT and WBI, with previously untreated PCNSL received at least 3 cycles of HD-MTX-containing chemotherapy followed by nivolumab consolidation for 6 cycles (NCT 04022980). Patients with systemic lymphoma or known ocular involvement were excluded from the study. Stage 1 was designed to evaluate the safety of nivolumab consolidation after HD-MTX-containing induction chemotherapy. A 3+3 design was used as safety run-in, initiating 6 patients on nivolumab at the FDA-approved single-agent dose and monitoring for dose-limiting toxicities (DLTs) during Cycle 1. If less than 2 out of 6 subjects experienced a DLT, then the stage 2 part of study would initiate to evaluate the efficacy of nivolumab consolidation in terms of the 2-year PFS. The patient's neurological function was assessed at baseline and throughout the study follow-up using the Neurologic Assessment in Neuro-Oncology (NANO) scale.
Results: A total of 14 patients enrolled in the study between April 2020 and December 2022 at 4 US sites. In 14 evaluable patients who underwent the study treatment, the median age was 72 years (range, 65-79), 71% patients were female, and 35% patients had ECOG score of 2 or 3. Variations of the following regimens were used for induction: 43% R-MPV (rituximab, methotrexate, procarbazine, and vincristine) (43%), 29% MRT (methotrexate, rituximab, and temozolomide), 21% MR (methotrexate and rituximab), and 7% MATRix (methotrexate, cytarabine, thiotepa, and rituximab). After induction, 58% achieved a complete response (CR), 33% achieved a partial response (PR), and 8% had a stable disease (SD). Patients received a median of 6 cycles of nivolumab consolidation. Patients who received at least 1 cycle of nivolumab consolidation achieved an overall response rate of 83% with a CR rate of 75%. With a median follow-up duration of 18 months, the 1-year overall survival (OS) and PFS rates were 91.7% and 66.1%, respectively. No DLTs were observed during Cycle 1 of nivolumab consolidation in Stage 1. The most common grade ≥ 3 Adverse Events (AEs) associated with nivolumab consolidation included neutropenia (14%) and fatigue (7%). One patient (7%) developed a grade 4 Stevens-Johnson syndrome associated with sepsis and acute kidney injury, requiring discontinuation of nivolumab after Cycle 1.
Conclusion: The current study demonstrates encouraging safety and clinical outcomes of nivolumab consolidation in older PCNSL patients who are deemed poor candidates for ASCT or WBI. No DLT was observed during the safety run-in phase,

and there was no unexpected toxicity associated with nivolumab although 1 patient discontinued the study treatment due to Stevens-Johnson syndrome, a rare but known AE associated with nivolumab, after Cycle 1. Overall, nivolumab consolidation was associated with favorable survival rates in a group of patients with poor-risk PCNSL. We are in the process of identifying various clinical and biological factors, including 9p24.1 copy number alteration, in association with the response to nivolumab consolidation. Furthermore, changes in the neurological function based on the NANO scale assessed before and after the nivolumab consolidation are being analyzed.

Disclosures Park: *BMS:* Research Funding; *Epizyme:* Membership on an entity's Board of Directors or advisory committees; *ADC Therapeutics:* Membership on an entity's Board of Directors or advisory committees; *Seattle Genetics:* Research Funding; *Morphosys:* Membership on an entity's Board of Directors or advisory committees. **Nayak:** *Ono:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Brave Bio:* Consultancy; *Genmab:* Consultancy; *Gilead:* Membership on an entity's Board of Directors or advisory committees; *Walters Kluwer:* Honoraria; *Merck:* Research Funding; *Astra Zeneca:* Research Funding; *Kazia:* Research Funding; *Bristol Myers Squibb:* Research Funding. **Steiner:** *Bristol Myers Squibb:* Research Funding; *Rafael Pharmaceuticals:* Research Funding; *GSK:* Research Funding; *Seattle Genetics:* Research Funding. **Sumrall:** *Bayer:* Consultancy, Speakers Bureau; *Athenex:* Consultancy; *Merck:* Consultancy, Speakers Bureau; *Abbvie:* Consultancy, Speakers Bureau; *Curio Science:* Honoraria; *Exelixis:* Speakers Bureau; *Bristol-Myers Squibb:* Research Funding, Speakers Bureau; *Exelixis:* Consultancy, Research Funding; *Prime Oncology:* Speakers Bureau; *Cardinal Health:* Honoraria; *Gerson Lehrman Group:* Honoraria; *Amgen:* Consultancy; *Novocure:* Consultancy, Research Funding, Speakers Bureau. **Majd:** *Celularity:* Membership on an entity's Board of Directors or advisory committees; *Sumitomo Dainippon Pharma Oncology:* Consultancy. **Dittus:** *Genmab:* Membership on an entity's Board of Directors or advisory committees; *ADC Therapeutics:* Membership on an entity's Board of Directors or advisory committees; *Beigene:* Membership on an entity's Board of Directors or advisory committees; *Seattle Genetics:* Membership on an entity's Board of Directors or advisory committees; *Seattle Genetics:* Research Funding; *Genentech:* Research Funding; *Astrazeneca:* Research Funding.

OffLabel Disclosure: nivolumab in previously untreated primary CNS lymphoma

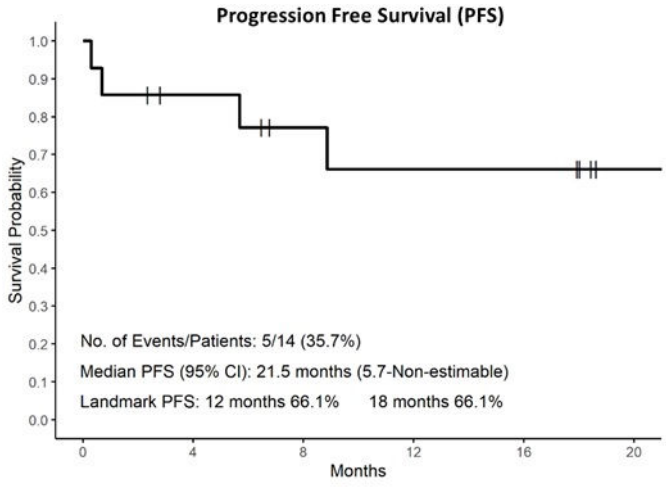

Figure 1

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