TPS9592 Poster Session

Phase I/Ib study of concurrent intravenous (IV) and intrathecal (IT) nivolumab (N) and relatlimab (R) for metastatic melanoma (MM) patients (pts) with leptomeningeal disease (LMD).

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Background: Pts with LMD face dismal prognosis, with median overall survival (OS) measured in months. We previously reported the safety and efficacy data from an open label, single arm and center phase I/IB trial for MM pts with LMD, using IT/IV N (*Nature Medicine*, Glitza et al.). 50 pts were treated. Median OS was 7.5 months and the toxicity was minimal. This approach was adopted into the NCCN guidelines, as these data suggest a subset of pts benefit from IT/IV N without high toxicity. N (anti-PD1) and R (anti-LAG3) represents a fixed- dose combination (FDC) approved by the FDA in 2022 for the treatment of unresectable MM. IV N/R has shown improved outcomes vs N in MM pts, and we identified LAG3 expression on CD8 T cells in the cerebrospinal fluid (CSF) of MM pts with LMD, in a pattern very similar to the expression of PD1. Subsequent work on C57BL/6 murine models with B16 and YUMM3 established LMD confirmed that combined treatment with IT/systemic anti-PD1/anti-LAG3 was the only treatment to significantly improve OS versus IT/systemic control treatment. We therefore added a non-randomized arm of concurrent IT/IV N/R to the previous study. Based on the prior tolerated dose of IT N 50mg, and the approved FDC ratio for IV N/R, we chose a FDC of IT N/R 50mg/16.7mg with concurrent with IV N/R at 480mg/160mg. We hypothesize that IT/IV N/R will be safe and an effective treatment for MM pts with LMD. **Methods:** This is a Phase Ib, non-randomized, single center trial of concurrent IT/IV N/R in adult (≥18 years) MM pts with LMD (NCT03025256). Up to 20 pts will receive IT N/R every 28 days, and Cycle 1 (C1) will consist of IT N/R only. In subsequent cycles the IT dose will be followed by an IV dose of N/R. Most pertinent inclusion criteria are radiographic and/or CSF cytological evidence of LMD, ECOG PS of ≤ 2, ≤ 4 mg per 24 hours of dexamethasone (or the equivalent), with adequate organ function. Prior radiation and treatment with immunotherapy is allowed, as is the use of concurrent BRAF/MEK inhibitors. Primary endpoint is safety, and Bayesian toxicity monitoring rule will be used. Secondary endpoints are OS, survival rates at 3,6 and 12 months, and median duration of treatment. CSF, blood and microbiome samples will be collected at various time points. The first patient was enrolled in October 2024 and accrual of patients is ongoing (NCT03025256). Clinical trial information: NCT03025256. Research Sponsor: Bristol Myers Squibb.