ABSTRACT

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Circulating Immune Cell and Outcome Analysis from the Phase 2 Study of PD-L1 Blockade with Durvalumab for Newly Diagnosed and Recurrent Glioblastoma.

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BACKGROUND: Programmed death-ligand 1 (PD-L1) is upregulated in glioblastoma and supports immunosuppression. We evaluated PD-L1 blockade with durvalumab among glioblastoma cohorts and investigated potential biomarkers.

METHODS: MGMT unmethylated newly diagnosed patients received radiotherapy plus durvalumab (cohort A; n=40). Bevacizumab-naïve, recurrent patients received durvalumab alone (cohort B; n=31), or in combination with standard bevacizumab (cohort B2; n=33), or low-dose bevacizumab (cohort B3; n=33). Bevacizumab-refractory patients received durvalumab plus bevacizumab (cohort C; n=22). Primary endpoints were: OS-12 (A); PFS-6 (B, B2, B3); and OS-6 (C). Exploratory biomarkers included: a systematic, quantitative and phenotypic evaluation of circulating immune cells; tumor mutational burden (TMB); and tumor immune activation signature (IAS).

RESULTS: No cohort achieved the primary efficacy endpoint. Outcome was comparable among recurrent, bevacizumab-naive cohorts. No unexpected toxicities were observed. A widespread reduction of effector immune cell subsets was noted among recurrent patients compared to newly diagnosed that was partially due to dexamethasone use. A trend of increased CD8+Ki67+ T cells at day 15 was noted among patients who achieved the primary endpoint and were not on dexamethasone. Neither TMB nor IAS predicted outcome.

CONCLUSION: Recurrent glioblastoma patients have markedly lower baseline levels of multiple circulating immune cell subsets compared to newly diagnosed patients. An early increase in systemic Ki67+CD8+ cells may warrant further

evaluation as a potential biomarker of therapeutic benefit among glioblastoma patients undergoing checkpoint therapy. Dexamethasone decreased immune cell subsets. PD-L1 blockade and combination with standard or reduced dose bevacizumab was ineffective.

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