A PHASE II TRIAL OF MONALIZUMAB PLUS DURVALUMAB PLUS PLATINUM-BASED CHEMOTHERAPY FOR FIRST-LINE TREATMENT OF EXTENSIVE STAGE SMALL CELL LUNG CANCER (MOZART): A HOOSIER CANCER RESEARCH NETWORK STUDY

Background Small-cell lung cancer (SCLC) remains an extremely challenging disease to treat. Systemic chemotherapy with platinum, etoposide, and PD-L1 inhibitor is the standard of care first-line therapy for extensive stage disease. NKG2A/CD94 is an inhibitory receptor, selectively expressed on natural killer (NK) cells and CD8+ T cells in the tumor microenvironment. Its ligand, histocompatibility leucocyte antigen E (HLA-E), is commonly expressed in human cancers. When engaging with HLA-E, the CD94/NKG2A receptor transduces inhibitory signals that suppress immune-mediated cytotoxicity. NKG2A blockade enhances tumor immunity by promoting both, NK and CD8+ T cell, effector functions. Consequently, NKG2A blockade, in the presence of activated T cells, induced by PD-1/PD-L1 blockade, exerts strongly enhanced anti-tumor activity. Monalizumab, a monoclonal antibody targeting NKG2A/CD94, has been shown to enhance NK cell activity against various tumor cells and rescues CD8+ T cell function in combination with PD-(L)1 axis blockade. Pre-clinical data have demonstrated that the absence of NK cells substantially enhances metastatic dissemination of SCLC tumor cells in vivo. Hyperactivation of NK cell activity through augmentation of interleukin-15 or transforming growth factor-β signaling pathways ameliorates SCLC metastases, an effect that is enhanced when combined with anti PD-1 therapy. NK cell function is modulated in response to cytotoxic chemotherapy, especially agents that damage DNA such as platinum. Post-chemotherapy NK cells display an induced expression of NKG2A compared with pre-chemotherapy patients and is associated with a reduced NK cell mediated anti-tumor activity. Altogether, these data suggest that addition of monalizumab to standard of care first-line treatment may be associated with improved efficacy in patients with SCLC.

Methods Patients with extensive-stage SCLC with ECOG performance status of 0–2 and adequate organ function are eligible for enrollment on this single-arm phase II study with an initial safety lead-in cohort. Patients may have received one prior cycle of platinum doublet with or without durvalumab and may have treated or untreated asymptomatic brain metastasis. Patients will receive platinum (cis or carbo), etoposide, durvalumab, and monalizumab every 3 weeks for 4 cycles followed by durvalumab and monalizumab every 4 weeks until disease progression or unacceptable toxicity. Primary endpoints include 1-year progression-free survival, safety, and tolerability. Secondary endpoints include objective response rate, 1-year overall survival, and intracranial progression-free survival. Exploratory objectives include analyzing association of treatment efficacy with minimal residual disease status, blood- and tissue-based genomic and transcriptomic signatures, tumor infiltrating immune cells, and peripheral blood NK cell and CD8+ T cell activity.

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