1430 - 1510 ORAL SESSION III ~ GLIOMA

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Combination Immunotherapy for Glioma: Beyond PD 1 Inhibition

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Programmed Cell Death – 1 (PD1) inhibition activates tumor-specific T-lymphocytes and is an effective clinical therapy against some cancers. Preclinical data regarding immune checkpoint inhibitors against malignant glioma is scant, and interim analyses of clinical trials suggest modest effect in patients as single agents. We examined PD-1 inhibition in murine glioblastoma models in combination with other immunomodulatory agents. Methods – Syngeneic glioma tumors (GL261 and CT2A) were implanted intracranially in C57/Bl6 mice. In separate experiments, PD-1 inhibition was combined with antibody blockade of t-cell immunoglobulin and mucin protein (TIM3), ligation of OX40 on T-lymphocytes, or vaccination with irradiated GM-CSF expressing tumor cells. Systemic antitumor immunity and tumor infiltrating lymphocytes were analyzed by ELISPOT assay and flow cytometry, respectively. Results - In both syngeneic glioma models, day 3,6, and 9 systemic delivery of a monoclonal antibody against PD-1 led to increased survival vs. controls. In animals with GL261 intracranial tumors, survival was improved by combination of PD-1 blockade with subcutaneous injection of irradiated GM-CSF expressing GL261 tumor cells, with antibody blockade of t-cell immunoglobulin and mucin protein 3 (TIM3), or binding of OX40 on T-lymphocytes by an activating antibody. In most cases, ELISPOT analyses demonstrated enhanced Th1 immunity by combination immunotherapies. Vaccination was associated with an increased intratumoral CD8+ T lymphocyte / FoxP3+ T lymphocyte ratio. Conclusion –Blockade of PD-1 on T lymphocytes in glioma-bearing mice is active. Both antitumor immunity and survival can be enhanced by combination of PD-1 inhibition with agents that activate antitumor immunity by complementary mechanisms.

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Encouraging Survival with Toca 511 and Toca FC Compared to External Lomustine Control

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Recurrent glioblastoma (GBM) has an unmet need for effective therapies. Toca 511 (vocimagene amiretrorepvec), a retroviral replicating vector with the transgene cytosine deaminase, selectively infects, persists and spreads in tumor. Subsequent oral administration of 5-fluorocytosine (Toca FC) produces 5-fluorouracil (5-FU) within infected cells. 5-FU kills cancer cells and myeloid derived suppressor cells, inducing robust antitumor immune responses in animal models. In 2 Phase 1 studies, Toca 511 was administered into the cavity wall after surgical resection (NCT01470794) or intratumoral injection by biopsy needle (NCT01156584). To provide context to the results observed, subjects were compared to an external lomustine treated control (Courtesy Denovo Biopharma; Wick 2010). Treatment with Toca 511/Toca FC from 2 Phase I studies showed significant improvement in OS HR equals to 0.48, p less than 0.001, with similar effect in the surgical resection (OS HR 0.45, p equals to 0.003) and intratumoral injection (OS HR 0.56, p equals to 0.060). Fewer related greater or equal to Grade 3 adverse events (AEs) were reported for Toca 511/Toca FC (2.5 percent) vs. lomustine (36.9 percent). There was a virtual absence of hematologic toxicity for Toca 511/Toca FC vs. lomustine (Grade greater or equal to 3 thrombocytopenia 23.8 percent). Discontinuations for AEs occurred in 0percent for Toca 511/Toca FC vs. 4.8 percent for lomustine. Toca 511 is surgically delivered and treatment-emergent AEs regardless of attribution included incision site pain (20 percent), procedural pain (12.5 percent), and wound infection (5 percent) vs. 0percent, 1.2 percent, 1.2 percent respectively for lomustine. Toca 511/Toca FC significantly improved survival and safety relative to lomustine. A Phase 2/3 trial has launched (NCT02414165).

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Tumor-Associated Astrocytes Promote Glioma Invasion via Cx43

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Although genetic mutations are usually responsible for the initial tumor formation and progression, changes in the microenvironment also have a critical role in facilitating this process. Many "untransformed" cells infiltrate the tumors, and recent evidence suggests cancer cells can ‘reprogram’ normal cells by miRNAs, which are small, non-coding RNA molecules that regulate several protein targets. One prominent feature of glioma pathology is massive gliosis, an inflammatory response consisting of reactive astrocytes, in and around the tumor. We show that expression of Cx43, a major gap junction protein in astrocytes, is significantly enhanced in astrocytes at the tumor border. Using a mouse model consisting of syngeneic intracranial implantation of GL261 glioma cells into Nestin-Cre:Cx43fl/fl mice in which Cx43 is selectively eliminated in astrocytes, we demonstrate that reduction of astrocytic Cx43 decreases the dissemination of glioma cells from the tumor core. Similarly, knocking down Cx43 in astrocytes also reduces glioma invasion in a co-culture of glioma cells and astrocytes. By comparing the microRNA profiles of the astrocytes before and after co-culture with human glioma cells, we have identified a miR-5096 that appears to reprogram astrocytes to enhance the invasiveness of glioma cells. We are now examining whether we can prevent glioma cells from invading the brain and establishing recurrent secondary tumors by stopping the exchange of materials between glioma cells and astrocytes through eliminating Cx43 channel activity.