Title

OS09.6 Long-term follow-up data from 126 patients with recurrent high grade glioma from three Phase 1 trials of Toca 511 and Toca FC: Update and justification for a Phase 2/3 trial

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stem malignant gliomas have one-year progression-free survival rates below 25% and median overall survival of 9 to 10 months with current treatment options and hence represent a significant unmet medical need. Genome-wide sequencing efforts of pediatric gliomas have identified a recurrent and shared missense mutation in the gene encoding the replication-independent variant of histone 3, H3.3. Approximately 70% of diffuse intrinsic pontine gliomas (DIPG) and 50% of thalamic and other midline gliomas harbor the amino-acid substitution from lysine (K) to methionine (M) at the position 27 of H3.3 gene (H3.3.K27M mutation). Tumor-specific missense mutations are not subjected to self-tolerance and can be suitable targets (i.e. neoantigen) for cancer immunotherapy. We evaluated whether the H3.3.K27M mutation can induce specific cytotoxic T lymphocyte (CTL) response in HLA-A2$^+$ human T cells. *In vitro* stimulation of HLA-A2+ donor-derived CD8$^+$ T-cells with a synthetic peptide encompassing the H3.3.K27M mutation (H3.3.K27M epitope) induced CTL lines which recognized not only T2 cells loaded with the synthetic H3.3.K27M epitope peptide but also lysed HLA-A2$^+$ DIPG cell lines which endogenously harbor the H3.3.K27M mutation. On the other hand, the CTL lines did not react to either HLA-A2$^+$ H3.3.K27M -negative DIPG cell lines or H3.3K27M-positive but HLA-A2-negative cells. The H3.3.K27M epitope peptide, but not the non-mutant counterpart, indicated an excellent affinity (Kd 151nM) to HLA-A2 based on competitive binding inhibition assay. From CTL clones with high and specific affinities to HLA-A2-H3.3.K27M-tetramer, cDNAs for T cell receptor (TCR) α- and β-chains were cloned into a retroviral vector. Human HLA-A2$^+$ T-cells transduced with the TCR demonstrated antigen-specific reactivity as well as anti-glioma responses in vitro. Peptide titration assay suggested that the H3.3.K27M-specific TCR had the half-maximal reactivity for peptide recognition of around 100nM. Furthermore, critically important for safety of clinical application, alanine scanning demonstrated that the key amino-acid sequence motif in the epitope for the TCR reactivity is not shared by any known human protein. Finally, intravenous administration of T-cells transduced with the H3.3.K27M-specific TCR significantly inhibited the growth of intracranial HLA-A2$^+$ H3.3.K27M-positive glioma xenografts in immune-deficient mice. These data provide us with a strong basis for developing peptide-based vaccines as well as adoptive transfer therapy using autologous T-cells transduced with the H3.3.K27M-specific TCR.

OS09.5 SYNERGISTIC EFFECT OF REIRRADIATION AND PD-1 INHIBITORS IN RECURRENT HIGH-GRADE GLIOMAS

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BACKGROUND: To date, studies of single agent PD-1 or PDL-1 inhibitors in recurrent high-grade gliomas (HGG) have shown infrequent responses (< 10%) and limited efficacy. Reirradiation is considered one of the standard salvage regimens for selected patients with recurrent gliomas but tumor responses are also infrequent (< 5%). Radiotherapy counteracts the immunosuppressive tumor microenvironment by increasing MHC class I expression and enhancing tumor neoantigen presentation and has a significant synergistic effect with PD-1 inhibition in preclinical models of glioma. METHODS: From December 2014 to June 2016, 20 patients (14 men, 6 women) with recurrent HGG were treated with the combination of reirradiation and PD-1 inhibitors. 18 patients had a glioblastoma, 1 anaplastic astrocytoma and 1 anaplastic oligodendroglioma. The median KPS at the start of this regimen was 70 (50 to 80). The median number of prior treatments for recurrent tumor was 2 (1–4), 100% had prior radaition, 95% prior temozolomide and 55% prior bevacizumab. 8 patients received pembrolizumab (2 mg/Kg every 3 weeks) and 12 patients received nivolumab (3 mg/Kg or 240 mg flat dose every 2 weeks). Median reirradiation dose was 35 Gy (12 Gy to 35 Gy). RESULTS: There were 7 confirmed partial responses (35% objective response rate, ORR), 5 stable disease and 8 progressive disease. The median duration of response was 5 months (2.2 to 10+ months). Median PFS was 4 months and median OS was 10 months. Most common side effects were increased ALT (3 patients) and fatigue (2 patients). There was no obvious case of cerebral edema related to treatment. 5 patients required a mild increase of dexamethasone (2–4 mg) and all other 15 patients had decreased or stable dexamethasone dosage after the reirradiation. CONCLUSIONS: PD-1 inhibitors in combination with re-irradiation can be administered safely to patients with recurrent HGG. The ORR of 35% is an early signal of the potential synergist effect of the combination of PD-1 inhibitors with re-irradiation in HGG. This retrospective analysis of a heavily pre-treated population of recurrent HGG showed significantly higher ORR than either PD-1 inhibitors or re-irradiation alone. A clinical trial under development to test this hypothesis.

OS09.6 LONG-TERM FOLLOW-UP DATA FROM 126 PATIENTS WITH RECURRENT HIGH GRADE GLIOMA FROM THREE PHASE 1 TRIALS OF TOCA 511 AND TOCA FC: UPDATE AND JUSTIFICATION FOR A PHASE 2/3 TRIAL

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Toca 511 (vocimagene amiretrorepvec) is an investigational, conditionally lytic, retroviral replicating vector. The vector infects human cells with selectivity for cancer cells because genome integration is dependent on cell division and viral replication is inhibited by innate and adaptive immune responses, defective in malignant tissues. Toca 511 spreads through cancer cells and stably delivers the gene for an optimized yeast cytosine deaminase that converts courses of the prodrug Toca FC (an investigational, extended-release version of 5-fluorocytosine) into 5-fluorouracil (5-FU). The combined treatment is designed to generate 5-FU in the tumor micro-environment, directly killing cancer cells, leading to activation of antigen presenting cells. 5-FU can also diffuse into nearby immunosuppressive myeloid cells and kill them, leading to further activation of the immune system against the tumor by removing important brakes on the lymphocytes. The safety, viral kinetics, immune response, and preliminary efficacy of Toca 511 and Toca FC have been investigated clinically since 2010 in three, open-label, ascending dose, Phase 1 studies of 126 treated patients with recurrent high grade glioma (rHGG), each evaluating different methods of Toca 511 administration (intratumoral injection, injection into the cavity wall following resection, and intravenous injection followed by resection and injection into the cavity wall). Repeated courses of oral Toca FC follow Toca 511 administration. Results to date include good tolerability; no persistent viremia; successful gene transduction within resected tumors: no evidence for clonality by vector insertion site analysis; and increased median overall survival compared to historical controls with all three methods of vector administration. Partial responses and complete responses with a median duration of initial response of > 26 months start approximately 6–19 months after Toca 511 administration, and are associated with a long term survival. Based on 18Nov2016 data, patients in the resection trial with Toca 5 enrollment criteria and dosing had a clinical benefit rate of 42 % (3CRs, 2PRs, 5 SDs of 24 patients). Examination of IDH1 mutation status shows patients with a response are either wildtype or mutant. Preliminary data from these studies supported initiation of a randomized, Phase 2/3 study in patients with rHGG (NCT02414165) in 2015. Updated pooled safety data, immune response findings, and efficacy data for the Phase 1 studies will be presented.

OS09.7 PHASE III RADOMIZED TRIAL OF AUTOLOGOUS CYTOKINE-INDUCED KILLER CELL IMMUNOTHERAPY FOR NEWLY DIAGNOSED GLIOBLASTOMA IN KOREA

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INTRODUCTION: Adoptive cell immunotherapy involves an ex vivo expansion of autologous cytokine-induced killer (CIK) cells before their reinfusion into the host. We evaluated the efficacy and safety of CIK cell immunotherapy with radiotherapy-temozolomide (TMZ) for the treatment of newly diagnosed glioblastomas. MATERIALS AND METHODS: In this multi-center, open-label, phase 3 study, we randomly assigned patients with newly diagnosed glioblastoma to receive CIK cell immunotherapy combined with standard TMZ chemoradiotherapy (CIK immunotherapy group) or standard TMZ chemoradiotherapy alone (control group). The efficacy endpoints were analyzed in the intention-to-treat set and in the per protocol set. RESULTS: Between December 2008 and October 2012, a total of 180 patients were randomly assigned to the CIK immunotherapy (n = 91) or control group (n = 89). In the intention-to-treat analysis set, median PFS was 8.1 months [95% confidence interval (CI), 5.8 to 8.5 months] in the CIK immunotherapy group, as compared to 5.4 months (95% CI, 3.3 to 7.9 months) in the control group (one-sided log-rank, p = 0.0401). Overall survival did not differ significantly between two groups. Grade 3 or higher adverse events, health-related quality of life and performance status between two groups did not show a significant difference. CONCLUSIONS: The addition of CIK cells immunotherapy to standard chemoradiotherapy with TMZ improved PFS. However, the CIK immunotherapy group did not show evidence of a beneficial effect on overall survival.