miRs involved in this process, we identified miRs that were consistently up-regulated in HUVEC 6 hours after 20 Gy exposure to ionizing irradiation or hydrogen peroxide treatment. miR-103 emerged as the top candidate. Importantly, irradiation of a brain tumor xenograft resulted in rapid upregulation of miR-103 in the tumor vasculature but not in the tumor cells. Transfection of endothelial cells (EC) with miR-103 mimics increased accumulation of DNA strand breaks and apoptosis in ECs. Moreover, inhibition of radiation induced miR-103 expression suppressed EC apoptosis in vitro and in vivo, suggesting that induction miR-103 expression is a key mediator of the cytotoxic effects of radiation on EC. Using substractive expression and RISC-trap assay, we identified and confirmed that the radiation sensitizing effects of miR-103 on EC is mediated through 1) suppression of key DNA repair genes (TREX1 and FANCF) as well as 2) increased release of anti-angiogenic cytokines, including IP10. Local and systemic delivery of miR-103 in vivousing a patient derived, orthotopic glioblastoma xenograft model caused DNA damage accumulation in ECs, increased anti-angiogenic cytokine release form ECs, and suppressed glioblastoma growth. CONCLUSION: Our findings reveal miR-103 play critical roles in modulation endothelial DNA repair through regulation of EC DNA repair capacity and cytokine release. Disruption of the crosstalk between vasculature and tumor cells that can be exploited as a glioblastoma therapeutic strategy.

ANGI-10. GENETIC DOWN REGULATION OF CXCR4 IN GLIOMA CELLS REDUCES INVASION, REDUCES TUMOR PROGRESSION, AND INCREASES SENSITIVITY TO RADIATION

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Glioblastoma multiforme (GBM) is a lethal brain tumor. Radiation therapy has been an essential part of treatment for glioma patients. Despite high radiation therapy along with anticancer drugs, GBMs invariably recur. Glioma Stem Cells (GSCs) resistant to chemo and radiation therapies are mainly responsible for GBM recurrence. Therefore, increase sensitivity of GBM cells to radiation and/chemo therapies could be of therapeutic value. We have recently described that GBM derived glioma stem cells grow along blood vessels (Baker et al, 2014). In this study we observed that different primary human glioma stem cell lines, HF2303, MSP-12, IN859 and IN2045, and a mouse glioma Gl26-cit cell line, showed significant directional migration towards human and mouse brain-derived endothelial (MBVE) cells. To uncover the mechanism of GBM cell migration, we tested the role of various chemokines and inhibitors utilizing in vitromigration assays. Notably, migration of Gl26-cit and HF2303 towards MBVE was significantly inhibited by AMD3100 (CXCR4 inhibitor). We further confirmed these findings by knocking down of CXCR4 in GL26-cit cells using shRNA. The migration of CXCR4 knock-down in GL26-cit-shCXCR4 cells towards MBVE was significantly reduced compared to control shRNA treated Gl26-cit cells (Gl26-cit-NT). We next established an orthotopic brain tumor in mice using GL26-cit-shCXCR4 and Gl26-cit-NT cells. Mice implanted with down regulated CXCR4 GL26-cit-shCXCR4 cells exhibited prolonged survival compared to Gl26-cit-NT mice. Brain section analysis showed that GL26-cit-shCXCR4 cells are less invasive. Lastly, we tested the effect of radiation on mice implanted with GL26-cit-shCXCR4 or Gl26-cit-NTcells. Mice implanted with GL26-cit-shCXCR4 cells showed further improvement in survival compared to Gl26-cit-NT tumor-bearing mice upon radiation. In summary, CXCR4-CXCL12 signaling is critical for the perivascular invasion of GBM cells and targeting this axis makes tumors less invasive and more sensitive to radiation therapy. Targeting CXCR4-CXCL12 signaling could be a potential therapeutic strategy for treatment of GBM.

ANGI-11. BONE MARROW-DERIVED MESENCHYMAL STEM CELLS-MEDIATED RADIORESISTANCE IN GLIOBLASTOMA ANGIOGENESIS

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As the central component of heightened vascularization in glioblastoma (GBM), endothelial cells (EC) are arguably the most responsive stromal cells in the tumor microenvironment (TME) during conventional treatment using ionizing radiation (IR) and have important implication in cancer progression as well as therapy-resistance. Although the inherent tumor tropism and angiogenic property of mesenchymal stem cells (MSC) has been documented in GBM, little is known about the function of MSC that are recruited to the GBM Tumor microenvironment. To elucidate the effect of MSC on irradiated EC, we studied the influence of IR, MSC or MSC condition media (CM) on human umbilical vein endothelial cells (HUVECs). IR decreased HUVEC cell proliferation at 24 and 48 hours whilst MSCCM increased cell proliferation at 48 hours. MSCCM doubled the viable number of non-irradiated HUVECs at 48 hours. IR caused phosphorylation of p53 in HUVECs regardless of MSC presence. While 2Gy of radiation was able to transiently increase p-ATM level at 4 hours post IR, MSCCM prolonged this process up to 8 hours. IR preferentially increased p-Akt levels (but not p-ERK1/2) at 8 hours post IR while MSCCM advanced this event to 4 hours and amplified it by two folds when given 15Gy. IR was found to up-regulate mRNA levels of CXCL5, CXCL10, ICAM1, VCAM1 and tissue factor in a dose-dependent manner whereas MSC co-culture boosted the expression of above angiogenic factors. Interestingly, up-regulation of the same set of IR-driven genes in GBM was positively correlated with poor survival in the TCGA GBM database, a strong correlation that was absent if using gene list that was obtained from IR and MSC combine treatment in HUVEC. These findings suggest that MSC promotes angiogenesis in GBM by facilitating the IR-induced active state as well as the effectiveness of DNA damage repair in endothelial cells.

ADULT CLINICAL TRIALS (IMMUNOLOGICAL)

ATIM-02. SUCCESSFUL CANCER-SELECTIVE GENE DELIVERY FOLLOWING INTRAVENOUS TOCA 511 DELIVERY IN PATIENTS WITH RECURRENT HIGH GRADE GLIOMA (HGG)

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Recurrent HGG remains resistant to therapy with survival ranging from 7.2–9.2 months. An ongoing clinical study (NCT01985256) using a retroviral replicating vector (RRV), Toca 511, in combination with oral Toca FC (extended-release 5-fluorocytosine [5-FC]) is evaluating the highest tolerated doses and viral pharmacokinetics in patients with recurrent HGG. Toca 511 (vocimagene amiretrorepvec) encodes a yeast-derived, codon-optimized, heat-stabilized cytosine deaminase (CD) that converts 5-FC to the anti-cancer drug 5-FU in infected tumors. Toca 511 was intravenously administered over 1, 3, or 5 days with subsequent tumor resection and injection of Toca 511 into resection cavity walls. Six weeks later Toca FC was administered for 7 days every 6 weeks. Resected tumor was evaluated for presence of virus and transgene. Tumor samples have demonstrated presence of viral DNA signal in a dose dependent manner with 14/17 (82%) detectable overall of which 7/9 (78%) were in subjects treated with 3-day delivery and 100% (3/3) with 5-day delivery. Quantifiable viral DNA was found in 8/17 (47%) overall of which 5/9 (56%) was in the 3-day and 2/3 (67%) in the 5-day IV cohorts. Expression of the transgene was detectable by IHC. Five weeks after Toca 511 injection, viral RNA could not be detected in blood above the lower quantification limit. Median overall survival for efficacy evaluable population is 13.6 months (95% CI 7.2, NR). Based on 11 subjects evaluated by independent radiology review, 1 was reported to have a radiologic CR (with an unrelated stroke) and 2 to have stable disease. Safety data to date shows good tolerability with low grade pyrexia (n=2, 18.2%) and related SAEs of cerebral cyst and vasogenic edema. This study demonstrates successful gene transduction following IV delivery of Toca 511 and shows encouraging survival data. Updated safety and efficacy data will be presented.

ATIM-03. ACT IV: AN INTERNATIONAL, DOUBLE-BLIND, PHASE 3 TRIAL OF RINDOPEPIMUT IN NEWLY DIAGNOSED, EGFRvIII-EXPRESSING GLIOBLASTOMA

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BACKGROUND: The EGFR deletion mutation, EGFRvIII, is expressed in ~30% of glioblastomas (GBM). The EGFRvIII-targeted vaccine rindopepimut consists of EGFRvIII peptide conjugated to keyhole limpet hemocyanin (KLH). A survival benefit was observed in a randomized phase 2 trial of recurrent GBM (ReACT; n=73). In three phase 2 studies of 105 total patients with newly diagnosed, EGFRvIII+ GBM and minimal residual disease (MRD), the median overall survival (mOS) was 20–22 months, as compared to ~16 months for two matched contemporary datasets (n=16, n=29). METHODS: Patients with newly diagnosed, resected, EGFRvIII+ GBM were, after standard chemoradiation, stratified by RPA class, MGMT promoter methylation, and geographic region, and randomized (1:1) to double-blind rindopepimut or control (KLH) concurrent with standard maintenance temozolomide. Primary endpoint is OS for MRD patients (enhancing tumor <2 cm2 post-chemoradiation by central review) aiming to detect hazard ratio (HR) ≤0.71 with 80% power and alpha=0.05 (log-rank test). Interim analyses were preplanned at 50% and 75% of events. Secondary analyses included patients with ≥2 cm2 of residual tumor (non-MRD). RESULTS: 745 patients (405 MRD) were enrolled at 165 centers. The study was terminated for futility after the 2nd interim analysis (MRD OS HR=0.99). At final analysis, mOS for rindopepimut vs. control was 20.1 vs. 20.0 (HR=1.01; p=0.93) in the MRD cohort, and 14.8 vs. 14.1 (HR=0.79; p=0.066) with 2-year OS 30% vs. 19% in the non-MRD cohort. There were no substantial differences in progression-free survival. Rindopepimut was well tolerated (chief toxicity: injection site reaction) with robust anti-EGFRvIII immune response. CONCLUSIONS: The study failed to demonstrate a survival benefit for patients treated with rindopepimut and standard chemotherapy. Rindopepimut OS is comparable to prior studies, however, patients in the control arm fared better than historical controls. A trend for long-term survival benefit in non-MRD patients suggests a preferential effect in bulkier disease.

ATIM-04. PHASE 2 STUDY TO EVALUATE THE CLINICAL EFFICACY AND SAFETY OF MEDI4736 (DURVALUMAB [DUR]) IN PATIENTS WITH GLIOBLASTOMA (GBM): RESULTS FOR COHORT B (DUR MONOTHERAPY), BEVACIZUMAB (BEV) NAÏVE PATIENTS WITH RECURRENT GBM

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BACKGROUND: DUR is a human IgG1 mAb against PD-L1. Blockade of PD-1/PD-L1 has shown benefit among solid tumors; data implicate PD-1/PD-L1 signaling as a significant contributor to immunosuppression in GBM. BEV is an approved angiogenesis inhibitor for recurrent GBM; angiogenesis inhibition may promote antitumor benefit of immunotherapies. METHODS: This ongoing Phase 2 open-label study (NCT02336165) evaluates the safety and efficacy of DUR (10 mg/kg Q2W) in 5 GBM cohorts. This report presents safety and efficacy for Cohort B (BEV-naïve recurrent GBM; DUR monotherapy). The primary efficacy endpoint for Cohort B is progression-free survival at 6 months (PFS-6), based on modified RANO by investigator assessment; secondary endpoints include safety/tolerability. A PFS-6 of 10% is the comparative historical benchmark (pre-BEV). The null hypothesis (PFS-6 ≤ 10%) was tested in the Intent-to-Treat (ITT) population against the alternative hypothesis (α=0.05, 90% confidence interval [CI]). ITT includes patients receiving any dose of DUR and having at least baseline and 1 post-baseline tumor assessment. RESULTS: First patient dosed: 05Mar2015; data cutoff: 05Feb2016. Cohort B completed enrollment of 31 patients (male: 83.9%; mean age: 54.0 [24-77] years; baseline ECOG PS0: 51.6%, PS1: 48.4%; baseline measurable lesions: 77.4%). Incidences of treatment-related adverse events (TRAEs) by maximum CTCAE grade (Gr) were Gr1: 35.5%; Gr2: 41.9%; Gr3: 9.7%; and Gr4/5: 0%. Most common TRAEs (≥3 (9.7%) patients): fatigue, headache, hemiparesis, increased AST, and decreased platelets, WBCs and lymphocytes. Thirty patients were evaluable for efficacy (PFS, objective response rate [ORR]); 6 were progression free at 6 months. Kaplan-Meier estimate for PFS-6 was 20.0% (90% CI: 9.7, 33.0). ORR: partial response, 5 (16.7%) patients; stable disease, 13 (43.3%). CONCLUSIONS: DUR monotherapy appears to be well tolerated and shows activity in BEV-naïve recurrent GBM. Further studies are warranted.

ATIM-05. COMPLEMENTARY CLINICAL AND ANCILLARY DATA FROM 123 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 5-FU directly kills cancer cells likely leading to activation of antigen presenting cells in the tumor microenvironment. 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 an important inflammatory brake. The safety, viral kinetics, immune response, and preliminary efficacy of Toca 511 and Toca FC have been investigated since 2010 in three, open-label, ascending dose, Phase 1 studies of 123 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 resection cavity wall) followed by multiple courses of oral Toca FC. Results to date include good tolerability; no persistent viremia; successful gene transduction within resected tumors; and median overall survival with stereotactic biopsy needle, resection cavity wall, and intravenous/cavity wall vector injection ranging from 12.1–13.6 months. Analysis of pretreatment resected tumor samples for mRNA expression patterns showed a survival-related signature that otherwise does not correlate with survival in publically available databases. Preliminary data from these studies supported initiation of a randomized, Phase 2/3 study in patients with rHGG (NCT02414165) in 2015. Updated and pooled safety data, immune response findings, and updated efficacy data for the Phase 1 studies will be presented.

ATIM-06. DOES THE OCCURRENCE OF A RASH CORRELATE WITH RESPONSE IN GLIOBLASTOMA PATIENTS TREATED WITH IPILIMUMAB?

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BACKGROUND: There is emerging evidence for the use of immune checkpoint inhibitors in glioblastoma. These drugs are associated with significant immune-mediated toxicities including skin rash. There remains no established method of identifying those patients most likely to respond but treatment related adverse events have been associated with improved outcomes with other anti-cancer therapies. METHODS: 37 patients with glioblastoma were consented for treatment with ipilimumab in combination with bevacizumab, along with G-CSF or GM-CSF. Occurrence of a rash and best radiological responses were analyzed and compared for all patients