Title

CTIM-26. PATIENT-SPECIFIC DENDRITIC CELL VACCINE (DC-ATA) PULSED WITH ANTIGENS FROM SELF-RENEWING AUTOLOGOUS TUMOR CELLS IN THE TREATMENT OF NEWLY-DIAGNOSED GLIOBLASTOMA: A PHASE II TRIAL

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Authors

Bota, Daniela
Piccioni, David
LaRocca, R
et al.

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metastases, we hypothesize that the combination of Osimertinib and SRS will lead to better long term control of brain metastases as well as the systemic disease. METHODS: This is an open label, single arm, phase I multi-institution study. It will employ a 3 + 3 design. After enrollment onto the study, patients will be started on Osimertinib at the predetermined level daily for 0–7 days, after which all patients will undergo radiosurgery and then receive Osimertinib daily concurrently until disease progression, withdrawal or until unacceptable toxicity. SRS will be given in single fraction as determined by the treating radiation oncologist and neurosurgeon. RESULTS: Primary endpoint include Safety, tolerability and maximum tolerated dose (MTD) of Osimertinib, when administered in combination with SRS in patients with EGFR positive NSCLC with brain metastases. Secondary endpoints include Six-month intra-cranial and extra-cranial progression-free survival (PFS-6), overall survival, overall response rate, both intracranial and extra cranial in patients with EGFR positive NSCLC brain metastases. CONCLUSION: This is an ongoing clinical trial.

CTIM-23. A PHASE 1 TRIAL OF D2C7-IT IN COMBINATION WITH ATEZOLIZUMAB IN RECURRENT WHO GRADE IV MALIGNANT GLIOMA (MG)

Annick Desjardins[1], Dina Randazzo[1], Vidya Chandramohan[1], Katherine Peters[1], Margaret Johnson[1], Daniel Landi[2], Mustafa Khasraw[3], Stevie Threatt[1], Chevelle Bullock[1], James Herndon, II[2], Eric Lipp[1], John Sampson[3], Allan Friedman[1], Henry Friedman[1], David Ashley[1], and Darell Bigner[1]; [1]Duke University Medical Center, Durham, NC, USA, [2]Duke University School of Medicine, Durham, NC, USA, [3]Duke University, Durham, NC, USA

BACKGROUND: D2C7 immunotoxin (D2C7-IT) is a dual-specific recombinant immunotoxin comprising an EGFR-wt and mutant-specific (EGFRvIII) monoclonal antibody fragment and a genetically engineered form of the pseudomonas exotoxin. When injected directly into the tumor mass by convection enhanced delivery (CED), in addition to direct tumor cell killing, immunotoxins induce secondary immune responses by the activation of CD4+ and CD8+ T-cells. We completed a phase 1 dose escalation study of D2C7-IT injected by CED into recurrent WHO grade III-IV MG and identified the phase 2 dose (6,920 ng/mL). Three patients remain in partial response more than 58, 38, and 32 months after a single D2C7-IT intratumoral infusion. As optimal induction of anti-tumor immune responses by immunotoxins is impeded by potent MG-mediated immunosuppression, we are assessing the toxicity of the combination of D2C7-IT with atezolizumab in patients with recurrent WHO grade IV MG. METHODS: Eligibility includes adult patients with recurrence of a solitary supratentorial WHO grade IV MG; ≥4 weeks after chemotherapy, bevacizumab or study drug; adequate organ function; and KPS >70%. Patient receives an intratumoral infusion of D2C7-IT and initiates two weeks later atezolizumab at 1200mg, followed by atezolizumab every 3 weeks for up to 2 years. Two cohorts of 3 patients are initially accrued to assess the toxicity of the combination. Assuming accrual continues after the initial two cohorts of 3 patients, an additional 12 patients will be accrued to the study. RESULT: The first enrolled patient experienced a grade 3 DLT (grade III ALT elevation) after the first infusion of atezolizumab, but showed a more extensive immunotherapeutic effect by imaging than observed with patients on the D2C7-IT monotherapy trial. Enrollment is ongoing. CONCLUSION: D2C7-IT monotherapy has shown prolonged survival and disease control in some patients. We are now evaluating the combination of D2C7-IT with checkpoint inhibition.

CTIM-24. AUTOLOGOUS CD34+ ENRICHED HEMATOPOIETIC PROGENITOR CELLS GENETICALLY MODIFIED FOR HUMAN INTERFERON-A2, ARE WELL TOLERATED & RAPIDLY ENGRAFT IN PATIENTS WITH GLIOBLASTOMA MULTIFORME (TEM-GBM_001 STUDY)

Gaetano Finocchiaro[1], Bernhard Gentner[2], Marica Eoli[3], Farina Francesca[2], Elena Anghileri[3], Stefania Girlanda[2], Matteo Carrabba[2], Valeria Cuccarini[1], Francesco DiMeco[4], Federico Legnani[1], Bianca Pollo[1], Maria Grazia Bruzzone[1], Marco Saini[1], Paolo Ferroli[1], Alessia Capotondo[2], Rosina Paterra[1], Mariagrazia Garramone[2], Stefania Mazzoleni[5], Andrew Zambanini[5], Carlo Russo[5], Luigi Naldini[6], and Fabio Ciceri[2]; [1]Istituto Neurologico Carlo Besta, Milan, Italy, [2]IRCSS Ospedale San Raffaele, Milan, Italy, [3]Unit of Molecular Neuro-Oncology, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy, [4]Istituto Neurologico Carlo Besta, Milan, USA, [5]Genenta Science, Milan, Italy, [6]San Raffaele Vita-Salute University, Milan, Italy

GBM with an unmethylated MGMT gene promoter is associated with very poor prognosis. A subset of tumor associated macrophages expressing the angiopoietin receptor Tie2 (TEMs) can be genetically modified for local & tumor restricted release of interferon-α2 (IFN). IFN has antitumor effects, inhibits angiogenesis & modulates the immune system. Temferon consists of autologous HSPCs transduced ex-vivo with an LVV encoding an IFN gene & expression control sequences for TEMs. TEM-GBM is an open-label, Phase I/IIa study (Part A: 3x3x3 dose escalation; Part B: n=12), & Temferon (single dose) is given to patients with first diagnosis of GBM & unmethylated MGMT promoter. Part A 3rd cohort is ongoing & completes dosing in September 2020. Eight patients completed screening; one patient died (disease progression) before Temferon was administered. Six patients received Temferon (3 women, 3 men, mean age 52.3 years). Cohort 1 received Temferon $0.5x10^6$ cells/kg & Cohort 2, $1x10^6$ cells/kg. Neutropenia & thrombocytopenia occurred as expected following conditioning & hematologic recovery (HR) occurred median D+13. Transduced PBMCs were identified by vector copy number (VCN) on myeloid cells at HR & at later timepoints. In general, a dose-ordered increase in VCN was observed (mean VCN D+30 CD14+ Cohort 1: 0.094, cohort 2: 0.125); 1 patient in each cohort had low VCNs. VCN remained detectable up to recent follow up visits (≤ D+180). No dose-limiting toxicities have been reported. Four SAEs occurred in 3 patients who received Temferon (pneumonia, pulmonary embolism, febrile neutropenia, fatigue) but these events were not attributed to Temferon, resolved, & may have been related to the conditioning regimen (carmustine & thiotepa). Disease progression has been confirmed in 3 patients who received Temferon. These preliminary results indicate feasibility of engrafting a pre-determined fraction of Temferon cells in the bone marrow of GBM patients without, so far, causing dose-limiting toxicity.

CTIM-25. ONCOLYTIC VIRUS FOR DIPG: THE CLINICAL EXPERIENCE WITH DNX-2401

Marta M Alonso[1], Ignacio Iñigo-Marco[1], Marc Garcia-Moure[1], Marisol González-Huarriz[2], Chris Jones[3], Alan MACKAY[3], Esther Hulleman[4], Jasper Van der Lugt[5], Carlos De Andrea[1], Maria Villalba[1], Ruben Hernandez[1], Sandra Hervás[1], Ibon Tamayo[6], Frederick Lang[7], Candelaria Gomez-Manzano[7], Juan Fueyo[7], Ricardo Diez-Valle[8], Jaime Gállego-pérez de Larraya[10], and Sonia Tejada[2]; [1]Clinica Universidad de Navarra, Pamplona, Spain, [2]Clínica Universidad de Navarra, Pamplona, Spain, [3]The Institute of Cancer Research, London, United Kingdom, [4]Emma Children's Hospital, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, Netherlands, [5]Princess Maxima, Rotterdam, Netherlands, [6]c, Pamplona, Spain, [7]MD Anderson Cancer Center, Houston, TX, USA, [8]Quiron Salud, Madrid, Spain

Despite our increased understanding of Diffuse Intrinsic Pontine Glioma (DIPG) the outcome remains dismal. Recently we showed that the virus Delta-24-RGD (DNX-2401 in the clinic) was effective in preclinical models of DIPG and had the ability to trigger an antitumor immune response. These data allowed us to propel a phase I clinical trial for newly diagnosed DIPGs (NCT03178032) where the patients received an intratumoral viral injection followed by standard radiotherapy. The main objective is to determine the safety, tolerability, and toxicity of DNX-2401. Secondary endpoints are overall survival at 12 months, percentage of responses and induced immune response against tumor. Tumor biopsy was performed through the cerebellar peduncle, followed by intratumoral injection of DNX-2401 (N=12). Three patients were treated with the $D1=1x10^{10}$vp and because the lack of toxicity we escalated to the $D2= 5x10^{10}$vp. The procedure was well tolerated and safe. All patients displayed a reduced tumor volume after combined treatment. We performed molecular studies in 9 out of the 12 patients. The immune cell composition of the biopsies was assessed using multiplexed quantitative immunofluorescence. T cells were hardly noticeable in these tumors while macrophages were abundant. We detected increased clonal T cell diversity following treatment with virus in peripheral blood lymphocytes when compared paired pre- and post-treatment samples from the trial. In addition, we measure pre and post treatment neutralizing antibodies and its relationship with survival. Finally, we performed functional studies using 2 cell lines isolated from patients included in this trial to assess the response to the virus (infectivity, viability, T-cell recognition). Overall, the administration of DNX2401 was safe, feasible and therapeutically beneficial in a subgroup of patients. This trial constitutes a proof of principle that aids to understand the response of DIPGs to viral therapies allowing to set the bases to improve this strategy for DIPG.

CTIM-26. PATIENT-SPECIFIC DENDRITIC CELL VACCINE (DC-ATA) PULSED WITH ANTIGENS FROM SELF-RENEWING AUTOLOGOUS TUMOR CELLS IN THE TREATMENT OF NEWLY-DIAGNOSED GLIOBLASTOMA: A PHASE II TRIAL

Daniela Bota[1], David Piccioni[2], R. LaRocca[3], Christopher Duma[4], Santosh Kesari[5], Jose Carrillo[5], Robert T. O'Donnell[6], Robert Aiken[7], Frank Hsu[8], Xiao-Tang Kong[8], Candace Hsieh[9], Chris Langford[9], Krystal Carta[9], Adrienne Wang[9], James Langford[9], Thomas Taylor[10], Gabriel Nistor[9], and Robert Dillman[9]; [1]Department of Neurology, UC Irvine, Irvine, CA, USA, [2]UCSD, San Diego, CA, USA, [3]Norton Cancer Institute, Louisville, KY, USA, [4]Hoag Hospital and Hoag Neuroscience Institute, Newport Beach, CA, USA, [5]John Wayne Cancer Institute and Pacific Neuroscience Institute, Santa Monica, CA, USA, [6]Univ California Davis, Davis, CA, USA, [7]UMDNJ, New Brunswick, NJ, USA, [8]UC Irvine,

Orange, CA, USA, [9]AIVITA Biomedical, Inc., Irvine, CA, USA, [10]UCI, Irvine, CA, USA

GBM standard treatment is associated with poor survival. Adjunctive therapy with patient-specific vaccines may improve outcomes by enhancing anti-GBM immune responses. A multi-institutional phase II clinical trial was designed with a primary objective of 75% survival 15 months after intent-to-treat enrollment. IL-4 and GM-CSF were used to generate dendritic cells (DC) from monocytes. DC were incubated with autologous tumor antigens (ATA) from the lysate of cultured GBM cells to produce each patient-specific DC-ATA vaccine. Each dose was admixed with 500 mcg GM-CSF at the time of subcutaneous injections at weeks 1, 2, 3, 8, 12, 16, 20 and 24. Enrollment has been completed in April 2020 (n=60). Three patients withdrew from the study prior to starting treatment leaving 57 patients for whom data is available. So far 57 patients have received 344 doses; 27 have completed all 8 doses, 11 received fewer than 8 doses at the time they discontinued treatment, 19 are currently in treatment. No patient has discontinued treatment because of toxicity. 9 pt had died and the preliminary 12 months overall survival is 74%. In a preliminary serologic analysis 12 of 16 patients (75%) had an increase in markers associated with Th1/NK, Th2/immunoglobulins, and Th2 hypersensitivity (eotaxins, IgE and IL17F) by week-3; 9 of 15 (60%) had a decrease in angiogenesis factors, growth factors, and tumor markers by week-8. Immunologic data for all 55 patients who received at least two injections will be available November 2020. This patient-specific DC-ATA immunotherapy approach is feasible, is associated with changes in serologic markers, and may be increasing intratumor inflammation that may be associated with on-target toxicity and efficacy. A interim survival analysis will be conducted in mid-October 2020, 15 months after the 28th patient was enrolled; results will be available November 2020 [Clinicaltrials.gov NCT03400917].

CTIM-27. PHASE I/II STUDY OF CONTROLLED IL-12 AS IMMUNOTHERAPY FOR DIFFUSE INTRINSIC PONTINE GLIOMA (DIPG)

Stewart Goldman[1], Sabine Mueller[2], Susan Chi[3], Amanda Saratsis[1], Rudy Allen[1], Jill Buck[4], Nathan Demars[4], Nira Hadar[4], Taylor Estupinan[4], John Miao[4], Erin Walsh[4], Arnold Gelb[4], and Laurence Cooper[4]; [1]Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA, [2]University of California, San Francisco, San Francisco, CA, USA, [3]Dana-Farber Cancer Institute/Boston Children's Hospital, Boston, MA, USA, [4]Ziopharm Oncology, Inc., Boston, MA, USA

DIPG, which is the leading cause of pediatric brain cancer death with no effective treatment, has neither a highly immunosuppressive nor inflammatory tumor microenvironment (TME). Therefore, eliciting a pro-inflammatory TME may provide therapeutic benefit. We previously demonstrated in adults with recurrent glioblastoma that loco-regional delivery of interleukin 12 administered under the control of the proprietary transcriptional switch RheoSwitch Therapeutic System® (RTS®) delivered via a replication-incompetent adenovirus ("Controlled IL-12") turned "cold" tumors "hot" for up to 5.8 months (Sci Transl Med. 2019;11(505)) and seemed to improve median overall survival as compared with historical controls (SNO 2020). A multicenter, phase I/II, open-label study (NCT03330197) is determining the safety and tolerability of Ad (2 x 10^{11} viral particles) administered by stereotactic intratumoral injection (Day 0) and 14 daily (Days 1 to 14) V doses (10 or 20 mg, body surface area adjusted). The first DIPG subject enrolled was in April 2020 with completion of the first cohort (arm 1, n=3) enrollment anticipated by September 2020. The first subject has tolerated treatment well with no SAEs during the evaluation period. Endogenous serum cytokines increased (including IFN-g 11.4 pg/mL, Day 3), consistent with V crossing the blood-brain barrier and activating the RTS® switch to conditionally produce recombinant IL-12. Other biomarkers include plasma PK and circulating DNA. Follow-up is ongoing and enrollment is proceeding. Since development of effective immunotherapy for DIPG likely depends on eliciting a tumor-specific effector immune response, Controlled IL-12 is a promising immunotherapy candidate. The first DIPG subject shows encouraging data on safety, tolerability, serum cytokines and early signs consistent with a clinical response. After completion of dose-escalation, the study may be expanded up to 30 patients, which will be considered the phase II component of the study.

CTIM-28. PHASE 2 TRIAL OF CONTROLLED IL-12 IN COMBINATION WITH PD-1 INHIBITOR IN ADULT SUBJECTS WITH RECURRENT GLIOBLASTOMA (RGBM)

Rimas Lukas[1], E. Antonio Chiocca[2], Nancy Ann Oberheim Bush[3], Joseph Landolfi[4], Robert Cavaliere[5], John Yu[6], Sylvia Kurz[7], Nathan Demars[8], Jill Buck[8], Nira Hadar[8], John Miao[8], John Loewy[8], Yunxia Wang[8], Arnold Gelb[8], and Laurence Cooper[8]; [1]Northwestern Memorial Hospital, Chicago, IL, USA, [2]Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA, [3]University of California San Francisco, San Francisco, CA, USA, [4]JFK Medical Center, Edison, NJ, USA, [5]Baptist MD Anderson Cancer Center, Jacksonville, FL, USA, [6]Cedars-Sinai Medical Center, Los Angeles, CA, USA, [7]NYU Langone Health, New York, NY, USA, [8]Ziopharm Oncology, Inc., Boston, MA, USA

Ad-RTS-hIL-12 (Ad) is a gene therapy candidate for intratumoral (IT) delivery that conditionally expresses IL-12 (IL-12) under the transcriptional control of orally administered veledimex (V) acting via the RheoSwitch Therapeutic System® gene switch. Increased PD-1 expression in samples of rGBM following Ad+V (ASCO 2020) supports combination immunotherapy with a PD-1 inhibitor. Phase 1 trials in rGBM of Ad+V as monotherapy and in combination with PD-1 inhibitor revealed encouraging safety and survival data. This phase 2 trial (NCT04006119) in adults with rGBM is evaluating safety and efficacy (overall survival) of Ad + V with pre/post-operative cemiplimab-rwlc (cemi) 350 mg IV, Days -7, 15, then Q3W; Ad single IT injection (2 x 10^{11} viral particles, day of resection (Day 0) /craniotomy); and V (20 mg PO, Days 0–14). Longitudinal sampling of serum assessed IL-12 and endogenous cytokines production. Anti-tumor effects were described upon preliminary review. Serial MRI evaluated tumor response. Follow-up described overall survival. Initial safety data (51 unique adverse reactions in 28 subjects) appeared similar to Ad+V and the cemi label, respectively, being manageable without synergistic toxicities and generally reversible. Of 35 SAEs reported in 18 subjects, 10 SAEs in 7 subjects were related to Ad+V. IL-12 and IFN-g levels increased after Ad+V administration peaking on Day 3 at 34 ± 11 pg/mL and 13 ± 5 pg/mL (mean ± SEM), respectively. Immune-mediated anti-tumor effects were noted, including a post-treatment biopsy to rule out progression which demonstrated an immune infiltrate consistent with pseudoprogression and loss of tumor cell heterogeneity suggesting immunoediting. Enrollment is anticipated to be completed in 2Q2020 with follow-up ongoing and initial survival data will be presented. V crossed the blood-brain barrier to produce functional IL-12. Controlled IL-12 therapy and cemi is a rational combination with initial data consistent with immune-mediated anti-tumor effects with a favorable safety profile.

CTIM-29. CRUCIAL APPLICATION OF SINGLE CELL GENE EXPRESSION FOR MONITORING CHANGES IN GLIOBLASTOMA PATIENTS WITH SUSTAINED RADIOGRAPHIC RESPONSE TO CMV PP65-LAMP RNA-PULSED DENDRITIC CELL-BASED VACCINES

Oleg Yegorov[1], Changlin Yang[2], Anjelika Dechkovskaia[2], Maryam Rahman[1], Ashley Ghiaseddin[1], and Duane Mitchell[2]; [1]University of Florida, Gainesville, FL, USA, [2]University of Florida, Department of Neurosurgery, Gainesville, FL, USA

BACKGROUND: The application of single cell sequencing as a novel immune monitoring platform can be used to identify the molecular mechanisms of immune response to dendritic cell- based vaccines, trace the cell types and states involved, and uncover novel biomarkers for immunotherapy. We applied single-cell RNA Seq analysis of longitudinal peripheral blood mononuclear cells (PBMCs) in patients with newly-diagnosed GBM enrolled on the ATTAC II clinical trial (FDA IND BB-16530; Clinicaltrials.gov # NCT02465268) who experienced a sustained radiographic response to autologous CMV pp65-LAMP RNA-pulsed DC vaccines plus GM-CSF and tetanus-diphtheria booster administered during adjuvant cycles of dose-intensified temozolomide. METHODS: We constructed 5' gene expression libraries and T cell receptor enriched libraries for 10x Genomics single-cell 5' and VDJ sequencing, generated from PBMCs collected prior to and during patient immunization using dendritic cells loaded with messenger ribonucleic acid encoding the human cytomegalovirus (CMV) matrix protein pp65 conjugated with the lysosomal associated membrane protein (LAMP) sequence. RESULTS: Overall, we sequenced a total of 189,808 single-cell transcriptomes from 5 patients. We leveraged these transcriptome-wide features to distinguish 15 peripheral immune cell subtypes in tested PBMCs. Analysis revealed dynamic changes in immune cell subsets over the course of first three vaccines, including increases in cytotoxic CD8 T cells, CD4 T cells, and NK cell subsets. Increased markers of T cell activation were observed during vaccination. Surprisingly, we observed a very high-level frequency of natural killer T (NKT) cells in the patient with a complete durable response compared to other patients. After three DC vaccines, the level of NKT cells in PBMC of this patient increased up to 10%. CONCLUSIONS: These results emphasize the importance of subset specific profiling to achieve higher resolution in monitoring immune responses compared with bulk expression profiling in patients receiving immunotherapeutic treatment.

CTIM-30. EFFICACY OF PEMBROLIZUMAB IN PATIENTS WITH PITUITARY CARCINOMA: RESULTS FROM A PHASE II STUDY

Nazanin Majd[1], Steven Waguespack[1], Janku Filip[1], Siqing Fu[1], Marta Penas-Prado[2], Mingxuan Xu[1], Anas Alshawa[3], Carlos Kamiya-Matsuoka[1], Shaan Raza[1], Ian McCutcheon[1], and Naing Aung[1]; [1]MD Anderson Cancer Center, Houston, TX, USA, [2]NIH/NCI, Washington DC, USA, [3]University of Arizona, Tucson, AZ, USA

Pituitary carcinoma is an aggressive tumor characterized by metastatic spread beyond the sellar region that leads to debilitating symptoms and poor