cell dose and LDR via Pmax. Biomarker correlation analysis indicates that LDR impacts the level of IL-15 pre-infusion, which correlates with response directly. IFNγ, IL-6, and IL-2RA levels appear to be promising pharmacodynamic markers. Optimizing dose and LDR may offer opportunities to maximize antitumor efficacy.

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Trial Registration Clinicaltrials.gov NCT01343043

Ethics Approval This study was approved by the appropriate institutional review boards and independent ethics committees.

Background NY-ESO-1–specific T cells (letetresgene autoleucel [lete-cel]; GSK3377794) are autologous T cells transduced with a self-inactivating lentiviral vector to express an engineered NY-ESO-1–specific TCR that recognizes HLA-A*02–presented peptides derived from NY-ESO-1, a cancer/testis antigen expressed in 70%–80% of SS. NCT01343043 was a Phase I, open-label trial assessing safety, efficacy, and pharmacokinetics of lete-cel in patients with SS; activity was evaluated after different lymphodepletion conditioning regimens and in patients with differing levels of NY-ESO-1 expression.

Methods Patients with unresectable, metastatic, or recurrent SS who were intolerant/nonresponsive to standard first-line chemotherapy enrolled in 4 cohorts based on NY-ESO-1 tumor expression and more intensive lymphodepletion regimen in Cohorts 1–4, efficacy, and peak persistence in the mITT population (table 1). Primary endpoint was investigator-assessed overall response rate (ORR) per RECIST v1.1; secondary endpoints included duration of response (DoR), progression-free survival (PFS), overall survival (OS), and safety. Transduced cell persistence was measured by qPCR of transgene vector copies in DNA extracted from PBMCs. Study was not designed/powered to compare cohorts.

Results Overall, 50 patients enrolled; 45 received lete-cel infusion (modified intent-to-treat population). Demographics were similar between cohorts. Median time in study was 480/278/321/16.4 weeks; median PFS was 15.4/13.1/8.6/22.4 weeks (table 1). As of 27Jan2020, median OS for Cohorts 1/2/3/4, respectively, median DoR was 31.0/8.6/24.3/9.9/19.9 months; Cohort 4 median OS was immature (table 1). Complete (lasting 34 weeks) and 14 partial responses occurred in all cohorts, but patients with high NY-ESO-1 expression and more intensive lymphodepletion regimen received greatest benefit.

Conclusions In patients with advanced SS who need effective treatment, lete-cel had a manageable safety profile; responses occurred in all cohorts, but patients with high NY-ESO-1 expression and more intensive lymphodepletion regimen received greatest benefit.

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**IMMUNO-METABOLIC SIGNATURES OF DENDRITIC CELL ASSOCIATE WITH T-CELL RESPONSES IN MELANOMA PATIENTS**

1Juraj Adamik*, 2Deena Maurer, 3Paul Munson, 4Alexis Combes, 5Philippe Pierre, 6Matthew Krummel, 7Rafael Argüello, 8Lisa Butterfield, 9Parker Institute for Cancer Immunotherapy, University of California, San Francisco, San Francisco, CA, USA; 10University of Pittsburgh, Pittsburgh, PA, USA; 11University of California, San Francisco, San Francisco, CA, USA; 12Centre d’Immunologie de Marseille-Luminy, Marseille, France

**Background** The therapeutic efficacy of Dendritic cells (DC) vaccines remains low and there is an unmet need for more effective vaccine design to achieve durable clinical outcomes. Our study analyzed the transcriptional and energetic metabolism profile of an adenoviral-based DC vaccine targeted against three commonly shared melanoma antigens: Tyrosinase, MART-1 and MAGE-A6 from 35 subjects enrolled in a Phase I study of autologous DC vaccines in late-stage melanoma. To further investigate the immunometabolic features of monocyte-derived DC vaccines, we are employing a novel flow cytometry-based method, called SCENITH to integrate functional metabolic states with multiparametric DC immune phenotypes.

Methods iDC were generated from HD and patient monocytes using GM-CSF+IL-4 for 5d. DC were matured (mDC) using IFN?+LPS for additional 24 hrs. Tolerogenic DC (Tol DC) were generated using vitamin-D3 and dexamethasone. Seahorse® was used to measure DC metabolic profile. Cytek/Aurora spectral flow cytometry was used for multiparametric-phenotypic and metabolic analysis by SCENITH.

**Results** Melanoma patient mDC used for autologous vaccine generation showed significantly altered metabolic gene signatures associated with enhanced oxidative phosphorylation (OXPHOS) and lipid metabolism pathways as compared to HD mDC. Furthermore, increased enrichment for mitochondrial respiration genes involved in the TCA cycle, electron transport chain and fatty acid oxidation (FAO) correlated with inferior tumor antigen-specific T cell responses and clinical outcome in patients. Seahorse analyses confirmed that HD and good outcome patient DC demonstrated the highest maturation-induced reduction in maximal oxygen consumption rate (OCR)/ OXPHOS and exogenous FAO. Interestingly, while the glycolytic rate of non-responding patient DC was the lowest, over all, we observe only a moderate increase in glycolytic capacity during DC maturation. SCENITH analysis showed that unlike monocytes, which are primarily glycolytic, differentiated mono-derived iDC and mDC utilize both glycolysis and mitochondrial respiration. Interestingly, under tolerogenic (Tol) differentiation conditions Tol iDC shift from glucose dependence into FAO and/ or glutaminolysis while Tol mDC strongly depend on OXPHOS. Consistent with dependence on mitochondrial respiration, Tol mDC exhibit reduced HIF1a levels together with enhanced p-AMPK:p-mTOR ratio. Additionally, we show that the altered metabolism of Tol mDC is linked to retention of CD14-monocyte antigen with reduced DC markers HLA-DR, CD86, CD206, CD11c, CD33, with increased PD-L1 and ILT3 expression. Furthermore, we show that unlike HD mDC, tolerogenic and melanoma patient-derived mDC populations exhibit similar metabolic and immune characteristics.

**Conclusions** We demonstrate that metabolic profile of DCs is tightly associated to the immuno-stimulatory potential of DC vaccines from cancer patients. Using SCENITH, we linked phenotypic and functional metabolic changes associated to immune signatures that correspond to healthy and immuno-suppressed DC differentiation.

**Ethics Approval** The clinical trial reported was fully approved by the Univ. Pittsburgh PRC and IRB (PRO12010416, #09–021) and had FDA IND #15044 and NCT01622933.

**REFERENCES**


**FINAL ANALYSIS OF A PROSPECTIVE, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE IIB TRIAL OF TUMOR LYSATE, PARTICLE-LOADED, DENDRITIC CELL VACCINE IN STAGE III/IV MELANOMA: 36-MONTH ANALYSIS**

1Larry Adams*, 2Robert Chick, 3Guy Clifton, 4Timothy Vreeland, 5Patrick McCarthy, 6Anne O’Shea, 7Phil Kemp Bohan, 8Amelies Hickeron, 9John Myers, 10Jessica Cindasso, 11Diane Hale, 12Mark Faries, 13John Hyngstrom, 14Adam Berger, 15James Jakub, 16Jeffrey Sussman, 17Montaser Shabean, 18Thomas Wagner, 19George Peoples, 20Brooke Army Medical Center, San Antonio, TX, USA; 21John Wayne Cancer Institute, Los Angeles, CA, USA; 22University of Utah, Salt Lake City, UT, USA; 23Rutgers Cancer Institute of New Jersey, Philadelphia, PA, USA; 24Mayo Clinic, Rochester, MN, USA; 25University of Cincinnati, Cincinnati, OH, USA; 26University of Arizona, Phoenix, AZ, USA; 27Orbis Health Solutions, Greenville, SC, USA; 28Cancer Vaccine Development Program, San Antonio, TX, USA

**Background** The tumor lysate, particle-loaded, dendritic cell (TLPLDC) vaccine is created ex vivo by loading autologous dendritic cells (DC) with yeast cell wall particles (YCWPs) containing autologous tumor lysate, thus delivering tumor antigens to the DC cytoplasm via phagocytosis. TLPLDC then activates a robust T cell response against the unique antigens for each patient. The primary analysis of the prospective, randomized, multi-center, double-blind, placebo-controlled phase IIb trial in patients with resected stage III/IV melanoma showed TLPLDC improved 24-month disease-free survival (DFS) in the per-treatment (PT) analysis (patients completing the 6-month primary vaccine series). Here, we examine the secondary endpoint of 36-month DFS and overall survival (OS).

**Methods** Patients with resected stage III/IV melanoma were randomized 2:1 to TLPLDC vaccine or placebo (autologous DC loaded with empty YCWPs). Treatments were given at 0, 1, 2, 6, 12 and 18 months. The protocol was amended to include patients receiving concurrent checkpoint inhibitors (CPIs) to follow changes in standard of care. The co-primary endpoints were 24-month DFS by intent-to-treat (IT) analysis and per-treatment (PT) analysis, with secondary endpoints including 36-month DFS and OS by ITT and PT analysis, prespecified analysis by stage, and safety as measured by CTCAE v4.03.