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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.

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

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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 transcriptomic 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.¹ To further investigate the immuno-metabolic features of monocyte-derived DC vaccines, we are employing a novel flow cytometry-based method, called SCENITH² 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 γ +LPS for additional 24 hrs. Tolerogenic DC (Tol DC) were generated using vitamin-D3 and dexamethasone. Seahorse[®] was used to measure DC metabolic profile. Cytex/Aurora spectral flow cytometry was used for multiparametric phenotypic and metabolic analysis by SCENITHTM.

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/OXPHOS and exogenous FAO. Interestingly, while the glycolytic rate of non-responding patient DC was the lowest, overall, 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 HIF1 α 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 immunosuppressed 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.

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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

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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 (YCWP) 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 YCWP). 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 intention-to-treat (IT) analysis and per-treatment (PT) analysis, with secondary endpoints including 36-month DFS and OS by ITT and PT analysis, pre-specified analysis by stage, and safety as measured by CTCAE v4.03.