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

1Juraj Adamik*, 2Deena Maurer, 3Paul Munson, 4Alexis Combes, 5Phillippe Pierre, 6Matthew Krummel, 7Rafael Arguello, 8Lisa Butterfield. Parker Institute for Cancer Immunotherapy, University of California, San Francisco, San Francisco, CA, USA; 2University of Pittsburgh, Pittsburgh, PA, USA; 3University of California, San Francisco, San Francisco, CA, USA; 4Centre 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 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.

To further investigate the immuno-metabolic 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 IFNγ+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/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 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 heathy 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

300 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

1Lexy Adams*, 2Robert Chick, 3Guy Clifton, 4Timothy Vreeland, 5Patrick McCarthy, 6Amie O’Shea, 7Phil Kemp Bokhan, 8Amelies Hickeron, 9John Myers, 10Jessica Cindass, 11Diane Hake, 12Mark Faries, 13John Hyngstrom, 14Adam Berger, 15James Jakub, 16Jeffrey Sussman, 17Montaser Shafeen, 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 (YCW) 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 YCW). 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, prespecified analysis by stage, and safety as measured by CTCAE v4.03.
Conclusion This phase IIb trial again demonstrates the safety of the TLPLDC vaccine, and an improved 36-month DFS in patients with resected stage III/IV melanoma who complete the primary vaccine series, particularly in the stage IV subgroup. Next, a phase III trial will evaluate the efficacy of TLPLDC vaccine as adjuvant treatment for resected stage IV melanoma, with patients randomized to receive standard of care PD-1 inhibitors + TLPLDC versus PD-1 inhibitors + placebo.

Trial Registration This is a phase IIb clinical trial registered under NCT02301611

Ethics Approval This study was approved by Western IRB, protocol 20141932.

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Abstract 300 Figure 1 36-month disease free survival for patients receiving TLPLDC vs placebo by PT analysis

Results Overall, 103 patients received TLPLDC and 41 placebo. In PT analysis, 65 patients received TLPLDC and 32 placebo. Total adverse events (AEs), grade 3+ AEs, and serious AEs (SAEs) were similar in placebo vs TLPLDC groups, with one related SAE per treatment arm. By ITT analysis, 36-month OS was 76.2% for TLPLDC vs 70.3% for placebo (HR 0.72, p=0.0437) and 36-month DFS was 35.6% vs 27.1% (HR 0.95, p=0.841). By PT analysis, 36-month DFS was improved with TLPLDC (57.5% vs 35.0%; HR 0.50, p=0.025, figure 1). This effect was even more dramatic in resected stage IV patients (36-month DFS: 60.9% vs 0%; HR 0.12, p=0.001, figure 2).

Abstract 300 Figure 2 36-month disease free survival for subset of stage IV melanoma patients receiving TLPLDC vs placebo by PT analysis

Background The phase 3 IMSPIRE150 study (NCT02908672) demonstrated improved progression-free survival (PFS) with first-line atezolizumab (A) vs placebo (P) combined with vemurafenib (V) + cobimetinib (C) in patients with BRAFV600E mutation–positive advanced melanoma (15.1 vs 10.6 months; hazard ratio [HR] 0.78; 95% confidence interval [CI] 0.63–0.97; P=0.0249). Objective response has been associated with increased survival with chemotherapy and targeted therapies, but it is unclear whether the association holds for immunotherapy.

In this exploratory analysis, we evaluated the impact of response on survival outcomes in patients treated with A+V+C or P+V+C in the IMSPIRE150 study.

Methods 514 patients were randomized 1:1 to A+V+C (n=256) or P+V+C (n=258). Patients received V+C in cycle 1; A or P was added on days 1+15 from cycle 2 onward. The primary endpoints for this exploratory analysis were PFS and overall survival (OS), estimated using the Kaplan-Meier method. Outcomes were analyzed by investigator-assessed best overall response (BOR) per RECIST v1.1 (complete response [CR] vs partial response [PR] vs stable disease [SD]).

Results Median follow-up was 18.9 mo. In the A+V+C arm, BOR was CR (n=41), PR (n=129), and SD (n=58); in the P+V+C arm, BOR was CR (n=46), PR (n=122), and SD (n=58). An imbalance in baseline prognostic factors (eg, lactate dehydrogenase, tumor burden measures) was noted across response categories in both treatment arms, with favorable factors more prevalent in patients with CR and unfavorable factors more prevalent in patients with PR/SD. Improvement in