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The influence of harvest method on dendritic cell function and clinical outcomes in a randomized trial of a dendritic cell vaccine to prevent recurrences in high-risk melanoma.

Alexandra Adams, G. Travis Clifton, Timothy J. Vreeland, Anne E. O'Shea, Patrick M. McCarthy, Robert Connor Chick,

Background: A randomized, double-blind, placebo-controlled phase IIb trial of the tumor lysate, particle loaded, dendritic cell (TLPLDC) vaccine was conducted to prevent recurrence in patients (pts) with resected stage III/IV melanoma. Two methods for dendritic cell (DC) harvest were used for vaccine production, including no pretreatment or pretreatment with granulocyte-colony stimulating factor (G-CSF) in an attempt to reduce blood draw volumes. This analysis investigates differences in clinical outcomes and RNA gene expression between these DC harvest methods for TLPLDC vaccine creation. **Methods:** The TLPLDC vaccine is created by loading autologous tumor lysate into yeast cell wall particles (YCWPs) and exposing them to phagocytosis by DCs. By investigator/pt choice, pts had 120mL of blood drawn for DC harvest, or pts received 300µg of G-CSF for pre-DC mobilization and a 50-70 mL blood draw 24-48 hours later. Total vaccine production time was 72 hrs. Pts were randomized 2:1 to receive TLPLDC or placebo (DCs exposed to empty YCWPs). 1-1.5 x10^6 cells/dose were injected intradermally at 0, 1, 2, 6, 12, and 18 months. Differences in disease free survival (DFS) and overall survival (OS) were evaluated by Kaplan Meier analysis between pts who did not receive pretreatment (TLPLDC), pts who did receive pretreatment with G-CSF (TLPLDC+G), and pts receiving placebo. RNA-seq analysis was performed on the total RNA of pts' prepared TLPLDC vaccines to assess gene expression. Relative RNA expression (RRE) was compared between TLPLDC and TLPLDC+G. **Results:** As previously reported, 144 pts were randomized: 102 received TLPLDC (46 TLPLDC, 57 TLPLDC+G)

vs 27.1%, p = 0.027). When compared to TLPLDC+G (n = 3) vaccine, RNA-seq from TLPLDC vaccine (n = 3) showed upregulation of genes associated with DC maturation, including HLA-DMB (RRE: 3.60), IFIT1 (3.38), CD27 (3.26), IFI44L (3.24), MX1 (2.96), HLA-DQA1 (2.67), HLA-DRA (2.40), CD49D (2.34) and CD74 (2.09), while downregulated genes were associated with DC suppression or immaturity including SERPINA1 (RRE:7.8), TLR2 (6.65), CCR1 (5.11), IL10 (4.19), CD93 (3.84) and CD14 (3.25). **Conclusions:** Pts receiving TLPLDC vaccine had significantly improved OS and DFS, while outcomes remained similar between those who received TLPLDC+G vs placebo. Pts who did not receive G-CSF had higher expression of genes linked to DC maturation and antigen processing and presentation, likely explaining the improvement in clinical efficacy. A phase III trial to further assess the TLPLDC vaccine to prevent recurrence is planned. Clinical trial information: NCT02301611.

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