Background

Human Papillomavirus (HPV) cancers are uniquely antigenic with a ubiquitous and essential expression of the viral proteins E6 and E7. Radiation therapy (RT) is essential in treating locally advanced HPV-associated cancers, including cervical cancers. Radiation therapy may synergize with immunotherapy to stimulate T-cell-mediated anti-tumor effects by increasing T-cell flux in tumors and promoting pathways that result in increased antigen presentation. To evaluate this, we are conducting a single-arm phase II trial combining PDS0101, an E6/E7 HPV6E T cell activating immunotherapy delivered subcutaneously, combined with the standard of care chemoradiation for patients with locally advanced squamous cell cervical cancer with either lymph node metastases or tumors of ≥5 cm. (Table 1).

Clinical Trial Schema

Methods

Eligible patients had high-risk locally advanced cervical cancer with squamous cells with positive nodes and/or tumors of ≥5 cm or larger.

• Given PDS0101 subcutaneously in conjunction with chemorRT on days 14, 28, 42, and 56 for a total of 5 doses (Figure 1).

• Evaluated the safety and toxicity profile of delivering PDS0101 in combination with standard-of-care chemorRT in patients with locally advanced cervical cancer.

• Assessed oncologic outcomes in patients with locally advanced cervical cancer treated with PDS0101 in combination with chemorRT.

• Assessed T1T, T4T, T2T, and T4B T cells for HPV6E-specific immune responses by the following methods:
  - Measure CD8+ tumor-infiltrating lymphocytes (TILs) from cervical brush samples using markers of T-cell activation (CD25, Granzyme B, IFNγ).
  - Circulating tumor HPV DNA (ctDNA) in peripheral blood.
  - Capture intratumoral T-cell receptor (TCR) diversities

Results

Results (cont.)

Figure 6: TCR clonality (A) does not change throughout treatment. TCR diversity is highest (B) at the 710 day follow-up brachytherapy.

Conclusions

• Seventeen of the planned 35 patients have enrolled in the study. To date, nine patients have completed treatment.

• Toxicity attributable to PDS0101 included cell-limit grade 1 and 2 local injection site reactions in 7 patients (3 Grade 1 and 4 Grade 2).

• All patients have more than 60% of shrinkage of tumor size at midRT (Table 2).

• Four out of five patients have more than 90% treatment response.

• Eight of 9 patients enrolled on IMMUNOCERV demonstrated a complete response (CR) on PET at T1 (Figure 2B).

• One patient without cancer recurrence died of cardiac event.

• The CD8+ expression suggests that CD8+ T cells are activated through the treatment (Figure 3A, B) and cytotoxic T-cell expression peaks at the T4 (Figure 3B).

• When ctDNA drops at T3, the Granzyme B-expressing peak T cells increases (Figure 5), suggesting cytotoxic CD8+ T cells are important mediators of antigen-specific responses.

• The TCR diversity is highest at the T490, indicating that T cell repertoire is expanding following combination therapy (Figure 6B).

Table 1. Patient Characteristics

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Ethics Approval

All patients were enrolled under a protocol approved by the UT M.D. Anderson Cancer Center Institutional Review Board (MDACC 2019-1200) and written informed consent was obtained from all patients.

Acknowledgements

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