IMMUNOCERV, an ongoing Phase II trial combining PDS0101, an HPV-specific T cell immunotherapy, with chemotherapy and radiation for treatment of locally advanced cervical cancers (NCT04580771)

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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 affects 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 E6/7 HPV16 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 metastasis or tumors of >5 cm (**Table 1**).

Table 1. Patient Characteristics

Clinical Features	Value
No. patients	9
Mean (range) age at diagnosis, years	42.2 (26-65)
High-risk HPV type (circulating tumor DNA)	
16	6 (66.7 %)
18	2 (22.2 %)
Other	1 (11.1 %)
Number of PDS0101 received	
5	6 (66.7 %)
3	3 (33.3 %)
Histopathological tumor grade	
Well-differentiated	0 (0.0 %)
Moderately-differentiated	3 (33.3 %)
Poor-differentiated	6 (66.7 %)
Lymphovascular space invasion	
Yes	2 (22.2 %)
No	4 (44.4 %)
Unknown	3 (33.3 %)
FIGO stage	
I	1 (11.1 %)
II	1 (11.1 %)
III	5 (55.6 %)
IV	2 (22.2 %)
Clinical node-positive	
Positive	9 (100.0 %)
Negative	0 (0.0 %)
Treatment response at midMRI	
Sub-Optimal	5 (55.6 %)
Optimal	4 (44.4 %)
Treatment efficiency	
CR	8 (88.9 %)
PR	1 (11.1 %)
Survival Status	
Alive	8 (88.9 %)
Dead	1 (11.1 %)

Ethics Approval

All patients were enrolled under a protocol approved by the UT M.D. Anderson Cancer Center Institutional Review Board (MDACC 2019–1260) and written informed consent were obtained from all patients.

Acknowledgements

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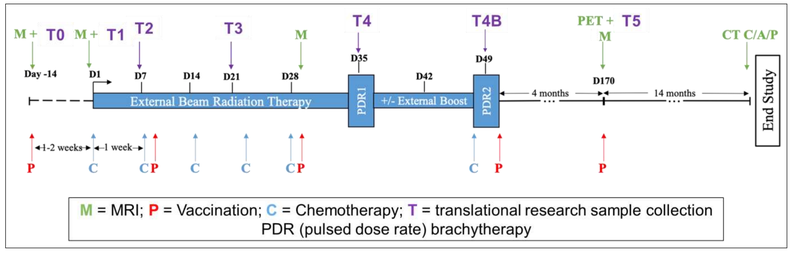
Clinical Trial Schema

Figure 1: Schema for phase II Clinical Trial of PDS0101 with the standard of care treatment for locally advanced cervical cancer



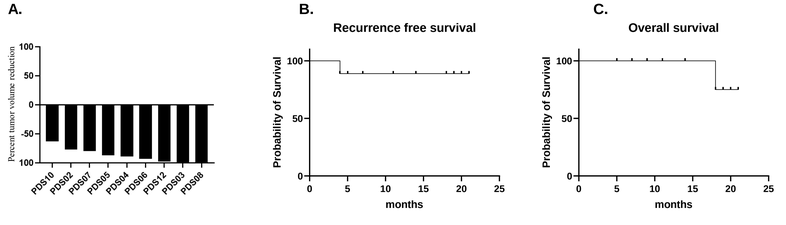
Methods

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

- Given PDS0101 subcutaneously in conjunction with chemoRT on days -14, 7, 28, 49, and 170 for a total of 5 doses (**Figure 1**).
- Evaluated the safety and toxicity profile of delivering PDS0101 in combination with standard-of-care chemoRT in patients with locally advanced cervical cancer.
- Assessed oncologic outcomes in patients with locally advanced cervical cancer treated with PDS0101 in combination with chemoRT.
- Assessed on T0, T1, T2, T3, T4, T4B, T5 for HPV16-specific immune responses by the following methods:
  - Measure CD8+ tumor-infiltrating lymphocytes (TILs) from cervical brush samples using markers of T cell activation (CD69, Granzyme B, IFNg).
  - Circulating tumor HPV DNA (ctDNA) in peripheral blood
  - Compare intratumoral T-cell receptor (TCR) diversities

Results

Figure 2: **A.** Waterfall plot showing reduction in tumor volume from baseline GTV to mid-MRI GTV; **B.** Recurrence-free-survival; **C.** Overall survival.



Results (*cont.*)

Figure 3: The CD69 activation in CD8 T cells increases throughout the treatment (**A**), cytotoxic Granzyme B (CD8) expression peaks at the T4 (**B**), while IFNg is decreased in T3 and increased at T4 and T5 (**C**).

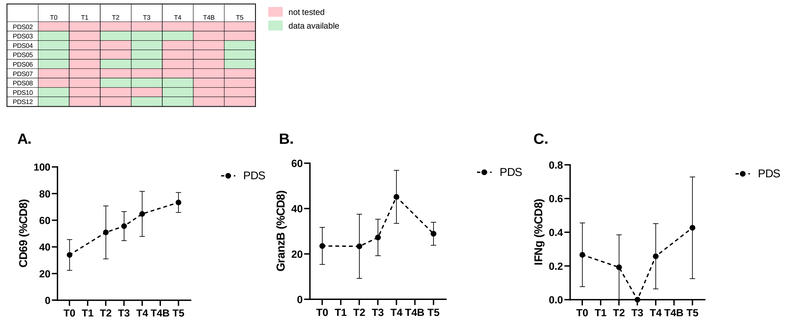


Figure 4: Copies of ctHPV16 DNA in plasma increase in T1 and T2, then dropped at T3

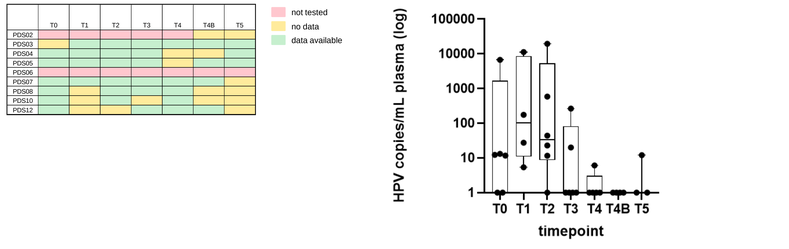
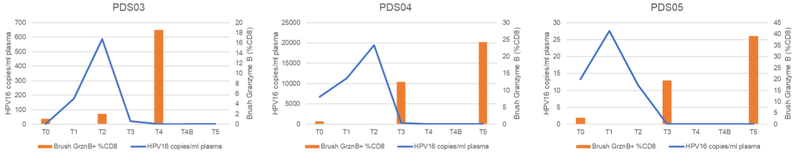
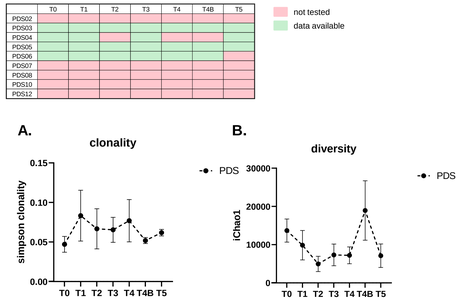


Figure 5: Time course of expansion of cytotoxic CD8 T cells and decline of ctDNA throughout the treatment



Results (*cont.*)

Figure 6: TCR clonality (A) does not change throughout treatment. T cell diversity is highest (B) at the T4B following brachytherapy.



Conclusion

- Seventeen of the planned 35 patients have enrolled in the study. To date, nine patients have completed treatment.
- Toxicity attributable to PDS0101 included self-limited 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 mid-MRI (T4, **Figure 2A**). Four out of 5 patients have more than 90% treatment response.
- Eight of 9 patients enrolled on IMMUNOCERV demonstrated a complete response (CR) on PET at T5 (**Figure 2B**).
- One patient without cancer recurrence died of cardiac event.
- The CD69 expression suggests that CD8 T cells are activated through the treatment (**Figure 3A**), and cytotoxic T cell expression peaks at the T4 (**Figure 3B**). On the other hand, IFNg expression suggests that CD8 T cell contracts in T3 and expands in T4 and T5 (**Figure 3C**).
- Increased ct HPV16 DNA in plasma at T1 and T2 tumor cell death due to PDS0101 (T1) and chemoRT (T2),(**Figure 4**).
- When ctDNA drops at T3, the Grnzyme B expression in CD8 T cells increases (**Figure 5**), suggesting cytotoxic CD8+ T cells are important mediators of antigen-specific immunity.
- The TCR diversity is highest at the T4B, indicating that T cell repertoire is expanding following combination therapy(**Figure 6B**).