Background TARP is expressed in >90% of prostate cancer throughout Gleason score and stages. Two TARP-targeting vaccines were developed at the NCI (figure 1). HLA-A*0201-restricted epitopes Wild Type 27-35 (TARP27-35WT) and Epitope-Enhanced 29-37(9V) (TARP29-37(9V)EE) of TARP were injected with an adjuvant or on autologous dendritic cells (DCs). Previously, the first-in-human clinical trial studying TARP-targeting vaccines in biochemically recurrent prostate cancer was reported.1, 2 This is a follow-up report focused on immunogenicity.

Methods TARP-specific T cell responses were assessed on study weeks 0, 12, 18, and 24 with vaccinations at weeks 3, 6, 9, 12, and 15 (Peptide vaccine =21, DC vaccine =20). PBMCs to assess the T cell response were collected and cryopreserved for batch testing. PSA was tested every 3 weeks. PSA-slope log was calculated using the MSKCC nomogram. Decreased PSA-slope log following vaccination at week 24 or week 48 was defined as the study-specific response as previously reported.

Thawed PBMCs were in vitro stimulated (IVS) with either TARP27-35WT, TARP29-37EE, or TARP29-37WT-pulsed monocytes in the presence of IL-7.[1] After 7 days of IVS, the cells were tested for tetramer-specific T cells by flow cytometry and for peptide-specific IFN-gamma response by ELISPOT.

Results Peptide-pulsed DC immunization induced tetramer-positive T cells at weeks 12, 18, and 24 post-immunization. The TARP29-37EE peptide performed as intended to induce specific T cells, the vast majority of which reacted equally well to the WT version of the EE sequence by 2-color flow cytometry. Only a small proportion reacted uniquely to EE, but not WT. This shows proof of the principle that EE-peptide can induce WT-specific T cells (figure 2).

In addition, all six patients who had the strongest IFN-gamma ELISPOT response to TARP27-35WT, TARP29-37EE, and TARP29-37WT peptides had decreased PSA-slope log at week 24 and/or 48 which corresponds to the study defined responses among 40 patients tested (figure 3). ELISPOT responses were more frequent in patients immunized with DC vaccines than in those with peptide/adjuvant vaccines.

Conclusions This first-in-human TARP vaccine study of peptide versus peptide-loaded DC platforms showed immunogenicity by peptide-HLA-tetramer assay and ELISPOT to detect IFN-gamma-producing cells. Importantly for proof-of-principle, the T cells recognizing the EE peptide immunogen recognized equally well the WT counterpart present in the tumor, as required for epitope-enhancement to be effective. The ability of high IFN-gamma ELISPOT response to the vaccine peptides to predict clinical responsiveness as measured by decreased PSA-slope log supports a protective role of antigen-specific T cells.

Acknowledgements The authors thank the patients and their families/caregivers for participating. This study was supported by the Center for Cancer Research/NCI intramural program. The authors appreciate the contributions of Dr. Anatoli Malyguine and Dr. Michael Davies who previously served at the Frederick National Laboratory for Cancer Research, and the members of NIH Clinical Center Pharmacy IDMRS (Investigational Drug Management and Research Section).

REFERENCES
Abstract 557 Figure 3  The highest IFN-gamma ELISPOT responses against TARP peptide
Six patients with the highest IFN-gamma ELISPOT responses of PBMCs to one or both vaccine peptides at serial time points were all among the responders based on decrease in PSA-slope log at week 24 or 48. Patient’s study number and stimulating peptides are indicated at the bottom. Colored bars represent different time points. Vertical axis is IFN-gamma ELISPOTs per 100,000 cells.