ADXS-PSA immunotherapy increases the magnitude and quality of prostate cancer-antigen-specific T cell responses in patients with metastatic castration-resistant prostate cancer

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INTRODUCTION

• Active immunotherapies, such as ADXS-PSA, are designed to generate tumor antigen-specific T cell effectors that reprogram and kill tumor cells.
• ADXS-PSA, a highly attenuated Listeria monocytogenes (Lm)-based immunotherapy that targets prostate-specific antigen (PSA), is currently being evaluated as a treatment for metastatic castration-resistant prostate cancer (mCRPC) in the phase 1/2 KEYNOTE-046 trial as a monotherapy (Part A, presented here) and in combination with KEYTRUDA (Lm [pembrolizumab]) (Part B, ongoing).
• Advaxis’ Lm-based immunotherapies act by stimulating innate immunity through multiple mechanisms including the STING pathway, by reducing the numbers and activities of immunosuppressive cells in the tumor microenvironment, and by inducing the generation of antigen-specific T cells that infiltrate and destroy the tumor.
• Because tumor antigen-specific T cell responses may be linked to the clinical efficacy of active immunotherapies, we quantified the frequency of functional prostate cancer antigen-specific T cells in the peripheral blood of mCRPC patients participating in Part A of the KEYNOTE-046 trial by ELISpot analysis.

OBJECTIVES

• Evaluate the changes in the frequency and functionality of prostate cancer antigen-specific T cells in mCRPC patients undergoing treatment with ADXS-PSA monotherapy (Part A).
• Determine whether any changes in the frequency and functionality of prostate cancer antigen-specific T cells were associated with clinical activity.

MATERIALS AND METHODS

• The KEYNOTE-046 trial (NCT02235557) is a phase 1/2 evaluation of ADXS-PSA alone (Part A), and in combination with KEYTRUDA (pembrolizumab) (Part B), in the treatment of mCRPC. The study design for KEYNOTE-046 trial is summarized in Figure 1.1

RESULTS

• We have taken a comprehensive approach to monitor the frequency and functionality of prostate cancer-antigen-specific T cells in the peripheral blood of ADXS-PSA-treated mCRPC patients.
  - First, we assayed T cell reactivity to peptides derived from multiple prostate cancer antigens to assess the ability of ADXS-PSA to induce or enhance T cell responses to prostate cancer antigens that are not expressed by the Lm-based vector as a measure of antigen spreading.
  - Second, we measured the secretion of multiple T cell effector molecules*
    * to obtain an accurate estimate of the frequency of functional prostate cancer antigen-specific T cells, as a significant proportion of prostate cancer antigen-specific T cells may be overlooked when only one effector molecule is measured.
    * to quantify multifunctional T cells (i.e., T cells with the ability to produce 2 or more effector molecules), T cell multifunctionality, or T cell quality, has been shown to correlate with a protective immune response against various infectious agents and to be associated with favorable outcomes to a number of active and passive immunotherapies.6,8
  - because IFNγ secretion alone has been shown not to correlate with tumor regression.12
  - Quantitative analysis of PSA-specific T cells at baseline detected pre-existing, functional PSA-reactive T cells in 8/9 mCRPC patients prior to ADXS-PSA treatment as well as in 2 age-matched healthy male donors. As predicted, assaying for IFNγ secretion alone underestimated the frequency of pre-existing PSA-specific T cells in mCRPC patients (Figure 3).
  - Changes in the frequency of PSA-specific T cell responses were observed in mCRPC patients during the first 9 weeks of treatment (Figure 4).
  - 78% of patients (7/9) exhibited increases in the PSA-specific T cell response on ADXS-PSA treatment, including the 1 patient with no detectable response at baseline. The 2 patients whose PSA-specific T cell response decreased after treatment had non-stable disease.
  - 56% of patients (5/9) had a >3-fold increase above baseline in the magnitude of the PSA-specific T cell response. Of these 5 patients, 3 had stable disease and 2 had non-stable disease.
  - Changes in the functionality of PSA-specific T cells were observed in mCRPC patients after 3 doses of ADXS-PSA.
  - 78% of the patients (7/9) exhibited increases in the frequency of multifunctional PSA-specific T cells after 3 doses of ADXS-PSA. The 2 patients whose PSA-specific T cell responses decreased after treatment also exhibited decreases in the frequency of multifunctional PSA-specific T cells.
  - 44% of the patients (4/9) exhibited increases in the proportion of multifunctional PSA-specific T cells after 3 doses of ADXS-PSA. Of these 4 patients, 2 had stable disease and 2 had non-stable disease.
  - To determine the extent of antigen spreading after ADXS-PSA treatment, we measured T cell reactivity to peptides derived from PAP, PSA, PSCA, and prostate, all of which are prostate cancer antigens that are not expressed by ADXS-PSA.
  - Pre-existing PAP-, PSA-, PSCA- and prostate-specific T cells were detected in all 9 mCRPC patients prior to ADXS-PSA as well as in 2 age-matched healthy male donors (Figure 5).
  - Changes in the frequency of PAP-, PSA-, PSCA- and prostate-specific T cells were observed in mCRPC patients during the first 9 weeks of treatment (Figure 6).
  - 100% of patients (9/9) exhibited increases in the frequency of T cell reactivity to at least one other well-known prostate cancer antigen, indicative of antigen spreading.

SUMMARY AND CONCLUSIONS

• In Part A patients, ADXS-PSA induced multifunctional T cell responses to a broad range of prostate cancer antigens:
  - 56% of patients (5/9) exhibited a >3-fold increase above baseline in the magnitude of the PSA-reactive T cell response.
  - 100% of patients (9/9) exhibited increases above baseline in the frequency of T cell reactions to at least one other well-known prostate cancer antigen, which is indicative of antigen spreading.
  - 100% of patients (9/9) exhibited increases in T cell multifunctionality to at least 1 of the 3 prostate cancer antigens tested.
  - No significant differences in the magnitude and quality of prostate cancer antigen-specific T cell responses were observed between stable and non-stable disease ADXS-PSA-treated mCRPC patients.
  - Based on the findings in the ADXS-PSA monotherapy arm, further investigation is merited in the ongoing KEYNOTE-combination arm (Part B).

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REFERENCES