patients with ECOG ≥2, elevated LDH, and treated with I-O and other therapies. For a subgroup of index therapy patients with a BOR assessment to baseline anti-PD-1 therapy (n=237), there was a significant association (p<0.01) of OS with BOR to baseline therapy, with higher median OS for those with an initial response (12 months) or stable disease (14 months) compared to a BOR of disease progression (6 months). There was also a significant OS association with BOR to baseline anti-PD-1 therapy for the subgroups receiving I-O therapy (n=119/237, p<0.01) and other therapies (n=37/237, p=0.01).

Conclusions Suboptimal OS in patients who progress on anti-PD-1 therapy in a real-world clinical setting, with predictors of enhanced survival, highlights the need for further research to inform optimal treatment strategies.

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NOVEL ANTI-SIRPALPHA ANTIBODIES WITH DIFFERENTIATED CHARACTERISTICS AS PROMISING CANCER THERAPEUTICS

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Background Therapeutically targeting tumor myeloid cells has emerged as a novel and complementary strategy to existing cancer immunotherapy approaches. The interaction of tumor expressed CD47 with SIRP alpha (signal regulatory protein-alpha, SIRPA) on macrophages, dendritic cells and neutrophils inhibits key immune effector mechanisms. Targeting SIRPA-CD47 represents a novel approach to enhance anti-tumor immunity by augmenting or reactivating critical tumor clearance mechanisms.

H5F9, an antibody against CD47, has shown promising therapeutic activities in patients with MSD, AML and NHL. However, agents targeting CD47 present hematological toxicities and present a huge antigen sink leading to not achieving an optimum therapeutic window. Our approach is to target SIRP alpha, the receptor of CD47 and focus therapeutic targeting to relevant mechanisms related to phagocytosis and myeloid cell activation and at the same time avoid undesired effects of blocking CD47. SIRP gamma, a very close relative of SIRP alpha is expressed on T cells and also binds to CD47. It has been shown that blockade of SIRP gamma-CD47 interaction inhibits T cell proliferation and blocks trans-endothelial T cell migration. Hence, our aim is to generate SIRP alpha selective antibodies that do not cross-react with SIRP gamma and have minimal impact on T cell functions.

Methods Using Apexigen’s APXiMAB™ proprietary antibody discovery platform, we have generated two novel anti-SIRP alpha antibodies (APX701 & APX702) with differentiated properties as compared to other approaches targeting the CD47/SIRP alpha axis. We have used ELISA, FACS based cell binding and blocking assays, and functional assays including in vitro phagocytosis and antibody-dependent cell phagocytosis (ADCP) in combination with tumor-opsonizing antibody to select APX701 & APX702.

Results Our novel preclinical-stage APX701 & APX702 antibodies have demonstrated the following attributes: high binding affinity to human SIRP alpha (APX701 Kd = 0.95nM, APX702 Kd = 0.88nM), no binding to SIRP gamma, efficient blockade of SIRP alpha binding to CD47 (APX701 IC50 = 1.04nM, APX702 IC50 = 0.80nM), potent macrophage mediated phagocytosis, enhancement of ADCP mediated by tumor-opsonizing antibody and favorable developability CMC profiles. In comparison with the benchmark antibody OSE-172, APX701 & APX702 showed potent phagocytosis activity and ADCP enhancement in all donors tested while OSE-172 induced phagocytosis in only 50% of the donors. This may result from the fact that APX701 and APX702 bind to all major SIRP alpha variants (V1, V2 & V8; covering ~92% population) while OSE 172 only binds to SIRPaV1 (~50% population).

Conclusions APX701 and APX702 demonstrate differentiated anti-SIRPaV alpha activities by enhancing myeloid cell-mediated anti-tumor immunity and reactivating critical tumor clearance mechanisms within the tumor microenvironment.

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A CLEAR INCREASE IN TILS AND MODEST TUMOR GROWTH INHIBITION BY PEMBROLIZUMAB IN PROSTATE CANCER TUMORS GROWING IN BONE OF CD34+ ENGRAFTED NOG MICE

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Background The recent KEYNOTE-199 trial raises hope for new treatment options for prostate cancer patients with the encouraging results of checkpoint inhibitor activity in a subset of prostate cancer patients, also including patients with bone-predominant disease. However, the patient subset that benefited from the treatment was small, needing identification predictive biomarkers. Proper preclinical models can help in the biomarker quest as well as in the search and selection of the best possible combination partners for further clinical trials.

Methods In this study the bone-metastatic disease was modeled by intratibial inoculation of LNCaP human prostate cancer cells to male CIEA NOG® (NOG) mice and NOG mice engrafted with human CD34+ hematopoietic stem cells (huNOG, Taconic Biosciences). Tumor growth was followed by serum PSA measurements and tumor-induced bone changes by X-ray images. At study week 4, the PSA positive mice were stratified to two groups (n=10) treated with IgG4 isotype control or pembrolizumab (5 mg/kg, i.p., Q5D) until the end of the study. Tumor-induced bone changes were followed by X-ray 4, 8 and 10 weeks after inoculation. The study was terminated 10 weeks after inoculation and tumors were processed for histological and immunohistochemical (IHC) analysis of tumor infiltrating lymphocytes (TILs). Changes in blood cell counts were assessed by flow cytometry and hematology (n=5/group).

Results At sacrifice, tumor-induced bone changes were observed in all mice, and there was no difference between the groups. Even though the PSA was not significantly lower in the pembrolizumab-treated group, the average histological tumorous surface was lower. In flow cytometry of peripheral blood, increases in the portions of CD3+ leukocytes and double positive CD4+CD8+ cells were observed, but no differences were found in CD4+ nor CD8+ T-cells. However, CD8+ T-cells were radically increased within the tumor as analyzed by IHC.