

For 18 evaluated patients, the ORR and DCR was 50% (9/18) and 83.3% (15/18), respectively. In addition, 4 patients received camrelizumab monotherapy with the ORR of 0% (0/4) and DCR of 25% (1/4), and 14 patients received camrelizumab combination therapy with the ORR of 64.3% (9/14) and DCR of 100% (14/14). 16 of 21 patients were still receiving the treatment, the median PFS was not yet achieved. Exploratory analysis showed that patients with reactive cutaneous capillary endothelial proliferation (RCCEP) had the higher objective response rate than those without RCCEP (57.1% vs 45.5%). Treatment-related adverse events occurred in 47.6% (10/21) of patients, and the most common adverse events were RCCEP (33.3%), rash (14.3%), dry skin (9.5%). Treatment-related grade 3 adverse events occurred in 4.8% (1/21) of patients.

Conclusions Camrelizumab showed antitumour activity in recurrent or metastatic cervical and endometrial carcinoma with manageable toxicities. Camrelizumab combination therapy had better efficacy compared with monotherapy. RCCEP occurrence was positively associated with outcomes of camrelizumab. Further studies are needed to verify this data.

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186

DISTINCT IMMUNE SIGNATURES PREDICTING CLINICAL RESPONSE TO PD-1 BLOCKADE THERAPY IN GYNECOLOGICAL CANCERS REVEALED BY HIGH-DIMENSIONAL IMMUNE PROFILING

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Background Although immune checkpoint blockade revolutionized cancer therapy, response rates have been mixed in gynecological malignancies. While uterine endometrial cancer with high microsatellite instability (MSI-H) and high tumor mutational burden (TMB) respond robustly to checkpoint blockade, high-grade serous ovarian cancer (HGSOC) with low TMB respond modestly. Currently, there has been no known immune signature or T cell phenotype that predicts clinical response in gynecological tumors.

Methods To dissect the immune landscape and T cell phenotypes in gynecological cancer patients receiving PD-1 blockade, we used high-dimensional cytometry (flow cytometry and mass cytometry (CyTOF)). We performed longitudinal deep immune profiling of PBMC from patients with recurrent uterine endometrial cancer receiving single-arm nivolumab, and HSGOC patients receiving neoadjuvant nivolumab plus platinum-based chemotherapy prior to debulking surgery.

Results Chemotherapy-resistant MSI-H uterine cancer patients treated with nivolumab had a proliferative T cell response 2–4 weeks post PD-1 blockade, consistent with responses seen in high TMB melanoma and lung cancer. The responding Ki67+ CD8 T cell population was largely CD45RAloCD27hi or CD45RAloCD27lo and highly expressed PD1, CTLA-4, and CD39, consistent with the phenotype of exhausted T cells (TEX). These exhausted-like cells are enriched in responders, whereas early expansion Tregs are enriched in non-responders. Unlike patients with uterine endometrial cancer, patients with TMBlo ovarian cancer did not have a clear proliferative CD8 T cell response after neoadjuvant nivolumab plus chemotherapy treatment, suggesting systemic immune suppression. At

baseline, ovarian cancer without recurrence have more terminally differentiated effector-like CD8 T cells, and patients with recurrence have more naive-like cells. Thus, both high and low TMB gynecological tumors have distinct immune landscapes associated with clinical response. Additionally, in MSI-H uterine endometrial cancer patients, the length of time between the prior chemotherapy and the initiation of immunotherapy was negatively correlated with T cell reinvigoration post immunotherapy and clinical response. This suggests the importance of optimize therapeutic timing to maximize the therapeutic efficacy when combining immunotherapy and chemotherapy.

Conclusions Collectively, our immune profiling revealed the distinct immune signatures associated with clinical response to PD-1 blockade in gynecological cancers. Our results also suggest that TMBhi inflamed versus TMBlo cold tumor microenvironment, and timing of chemo/immunotherapy could impact differentiation and functions of T cells.

Ethics Approval The study was approved by MSKCC Ethics Board, approval number 17–180 and 17–182.

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187

REAL-WORLD TREATMENT PATTERNS AND CLINICAL PREDICTORS OF OVERALL SURVIVAL AMONG ANTI-PD-1 EXPOSED ADVANCED MELANOMA PATIENTS WITH DOCUMENTED EVIDENCE OF DISEASE PROGRESSION

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Background Immuno-oncology (I-O) plays a major role in the treatment of advanced melanoma (aMel); however, resistance to therapy remains an important clinical problem. This study examined treatment patterns and overall survival (OS) for aMel patients who progressed on anti-programmed death ligand 1 (anti-PD-1) therapy in a real-world clinical setting.

Methods A retrospective database study of Flatiron electronic medical records (EMR) was conducted with 304 aMel patients who progressed on first or second line anti-PD1 (baseline) therapy with pembrolizumab or nivolumab and received subsequent (index) therapy with ≥ 3 months of potential follow-up. Patients who discontinued treatment for reasons other than progression (primarily toxicity) were excluded. The primary outcome was OS, defined using EMR data linked to external mortality sources (e.g. Social Security Death Index). OS analysis was stratified by several factors (e.g. age, ECOG, BRAF, LDH, type of index therapy, and best overall response [BOR] to baseline anti-PD-1 therapy). BOR defined as response, stable disease, or disease progression was based on clinician assessment following radiographic imaging. Descriptive and log-rank test statistics for OS were used.

Results Among patients receiving index therapy (n=304), 50% received I-O (n=91/151 combination therapy), 36% received BRAFi/MEKi (n=102/109 combination therapy) and 14% received other therapies (n=34/44 chemotherapy). Median (range) age was 67 (23–85) years, with 65% male, 62% ECOG ≤ 1 , 33% elevated LDH, and 51% with BRAF mutations. Most patients received baseline anti-PD1 monotherapy (77%) as first line therapy. Median OS (95%CI) was 7.2 (6.4, 8.8) months, with a significant OS association with ECOG ≤ 1 (p<0.001), normal LDH (p<0.001), and BRAFi/MEKi (p=0.02), with higher median OS of 9 vs 5 months, 11 vs 6 months, and 11 vs 7 and 6 months, respectively, compared to

patients with ECOG \geq 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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188

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 SIRP-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 SIRPalph V1 (~50% population).

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

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189

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 biomarkers¹. 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.