equally robust T cell proliferation in both the inguinal and mediastinal lymph nodes (LNs). However, RNA sequencing of adoptively transferred 2C T cells isolated 3-days after transfer from draining LNs identified that T cells activated in the mediastinal LN had reduced levels of IL-2 signaling and blunted effector functions early during priming. Flow cytometry confirmed that T cells primed in the mediastinal LNs did not express CD25, GZMB, or IFN-g, while T cells in inguinal LNs upregulated all three of these effector molecules. Delivery of IL-2 and IL-12 during priming was sufficient to restore effector molecule expression on 2C T cells in mediastinal LNs. Analysis of published patient data identified that a subset of lung cancer patients showed a sizable population of CD8+ TIL with low IL-2 signaling and low expression of effector molecules, including common targets of CBT.

Conclusions Immunotherapy resistance in T cell-inflamed tumors is due to defective CD8+ T cell effector differentiation. IL-2-based therapies could enhance differentiation of functional CD8+ effector T cells and could turn immunotherapy resistant tumors to immunotherapy sensitive tumors. This is the first mechanistic study providing evidence for a distinct type of T cell dysfunction resistant to current CBT.

Ethics Approval This study was approved by MIT’s Committee on Animal Care, protocol number 0220-006-23.

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**184** TWO TYPES OF ANTI-TIGIT ANTIBODIES WITH DISTINCT BINDING EPITOPE AND FUNCTIONAL ACTIVITIES

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Background TIGIT is an inhibitory receptor mainly expressed on natural killer (NK) cells, CD8+ T cells, CD4+ T cells and Treg cells. TIGIT competes with CD226 for binding with CD155. In cancers, CD155 has been reported to up-regulate Treg cells. TIGIT competes with CD226 for binding with PVR. TIGIT with comparative affinity and effectively blocked the AK126 and AK113 could specifically bind to human TIGIT, and competitively bind activity to promote IL-2 secretion was performed in mixed-culture of Jurkat-TIGIT cells and THP-1 cells.

Results AK126 and AK113 could specifically bind to human TIGIT with comparative affinity and effectively blocked the binding of human CD155 and CD112 to human TIGIT. X-ray crystal structure of TIGIT and PVR revealed the C-C’ loop and FG loop regions of TIGIT are the main PVR interaction regions. The only amino acid residue differences in these regions between human and monkey TIGIT are 70C and 73D. AK126 binds to both human and monkey TIGIT, AK113 binds only to monkey TIGIT. This suggests that these residues are required for AK113 binding to human TIGIT, but not required for AK126. Interestingly, results from cell-based assays indicated that AK126 and AK113 showed significantly different activity to induce IL-2 secretion in mixed-culture of Jurkat-TIGIT cells and THP-1 cells (figure 1A and B), in which AK126 had a comparable capacity of activity to 22G2, a leading TIGIT mAb developed by another company, to induce IL-2 secretion, while, AK113 showed a significantly higher capacity than 22G2 and AK126.

Abstract 184 Figure 1 Anti-TIGIT Antibodies Rescues IL-2 Production in Vitro T-Cell Activity Assay in a dose dependent manner. Jurkat-TIGIT cells (Jurkat cells engineered to over-express human TIGIT) were co-cultured with THP-1 cells, and stimulated with plate-bound anti-CD3 mAb in the presence of TIGIT ligand CD155 (A) or CD112 (B) with anti-TIGIT antibodies. After incubated for 48h at 37°C and 5.0% CO2, IL-2 levels were assessed in culture supernatants by ELISA. Data shown as mean with SEM for n = 2.

Conclusions We discovered two distinct types of TIGIT antibodies with differences in both epitope binding and functional activity. The mechanism of action and clinical significance of these antibodies require further investigation.

REFERENCES

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**185** CAMRELIZUMAB MONOTHERAPY OR COMBINATION THERAPY IN PATIENTS WITH RECURRENT OR METASTATIC CERVICAL AND ENDOMETRIAL CARCINOMA: A RETROSPECTIVE STUDY

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Background Patients with recurrent or metastatic cervical and endometrial carcinoma have poor prognosis and few treatment options. Blocking the interaction between PD-1 and its ligands is a promising treatment strategy. Camrelizumab is a humanized anti-programmed death-1 (anti PD-1) antibody. This study aimed to assess the anti-tumour activity and safety of camrelizumab in patients with recurrent or metastatic cervical and endometrial carcinoma.

Methods We performed a retrospective analysis for recurrent or metastatic cervical and endometrial carcinoma patients. Eligible patients were aged 28–73 years with an Eastern Cooporative Oncology Group performance status of 0 or 2. Patients received camrelizumab alone(200 mg iv d1 q2w)or in combination with chemoradiotherapy/chemotherapy. The primary endpoint was objective response (ORR). The secondary endpoints included disease control rate (DCR), median progression-free survival (mPFS) and safety.

Results A total of 21 patients were enrolled between September 20, 2019, and July 8, 2020. 18 patients were evaluated for efficacy and 21 patients were available for safety analysis.
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-HI) 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 HGSOC 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 with 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-PD1 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