OA02.06
Converting Tumor-Mediated PD-L1 Inhibition into CAR T-Cell Costimulation to Potentiate Thoracic Cancers Immunotherapy

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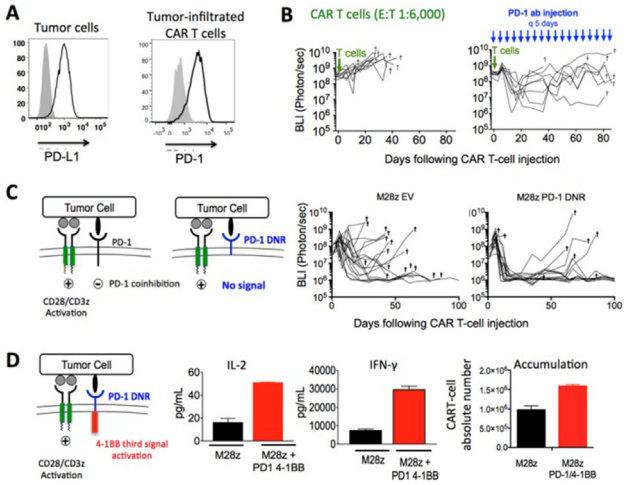
Background: To overcome tumor-mediated inhibition of chimeric antigen receptor (CAR) T cells, we herein investigated the impact of tumor PD-L1 upregulation on CAR T-cell exhaustion and anti-tumor efficacy, and further developed clinically translatable T-cell extrinsic as well as intrinsic strategies to overcome PD-L1 inhibition in models of lung cancer (LC) and malignant pleural mesothelioma (MPM).

Methods: Human T cells were transduced with MSLN-specific CAR with CD28 and CD3zeta domains (M28z) were tested *in vitro* and in clinically-relevant LC and MPM mouse models by bioluminescence imaging, BLI of tumor burden progression. To counteract PD-1/PD-L1 inhibition *in vivo*, we evaluated the efficacy of PD-1 blocking antibody or cell-intrinsic genetic-engineering strategies by cotranducing M28z CAR T cells with a PD-1 dominant negative receptor (PD1-DNR) or with PD-1/4-1BB fusion protein.

Results: A single, low-dose of M28z CAR T cells is able to resist the progression of established tumor for 40 days, but mice eventually died with progressing tumor. Tumor harvest analysis demonstrated the PD-1 and PD-L1 upregulation on CAR T cells and tumor cells (Figure panel A). We then confirmed *in vitro* that PD-L1 inhibits M28z T-cell effector functions (proliferation, cytotoxicity and cytokine secretion). The addition of PD-1 blocking potentiates CAR T-cell therapy *in vivo* but its efficacy requires multiple injections (Panel B). In contrast, a single dose of M28z T cells coexpressing PD1-DNR restore effector functions, enhance tumor burden control (Panel C) and prolong median survival (56 vs 82 days, p=0.001). Converting PD-L1 inhibition into a positive costimulatory signal by PD-1/4-1BB construct cotransduction into M28z CAR T cells enhanced cytokine secretion and T-cell accumulation (Panel D).



Conclusion: Our results demonstrate the therapeutic benefit of providing optimal costimulation and coinhibitory blockade to counteract PD-L1/PD-1 immunosuppression, thus potentiate CAR T-cell therapy for lung cancer and mesothelioma.

Keywords: CAR T-cell immunotherapy, PD-1 and PD-L1, Mesothelioma, lung cancer

OA02.07
Characterization of the Tumor Microenvironment and Investigation of Immune Checkpoint Expression in Malignant Pleural Mesothelioma

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Background: Malignant pleural mesothelioma (MPM) is an aggressive cancer with a poor prognosis and an increasing incidence, for which novel therapeutic strategies are urgently required. Since the immune system has been described to play a role in protection against MPM, characterization of its tumor immune microenvironment (TME) and immune checkpoints might help to identify new immunotherapeutic targets and their predictive and/or prognostic value.

Methods: Immunohistochemistry (IHC) was performed on tissue samples of untreated (n=40) and chemotherapy-pretreated (n=14) MPM patients. Different subsets if immune cells were identified based on staining for CD4, CD8, FoxP3, CD68, CD45RO and granzyme B. The expression of the immune checkpoints TIM-3, LAG-3, PD-1 and its ligand PD-L1 was also investigated. The relationship between the immunological parameters and survival, as well as response to chemotherapy was analyzed using the R statistical software.

Results: All patients had CD8+ tumor infiltrating lymphocytes (TILs), CD68+ histiocytes and macrophages and CD45RO+ T cells in their stroma, with CD8+ TILs being the predominant cell type of the immune infiltrate. Stromal CD4+ TILs were found in 75% of the untreated and 71% of the pretreated samples. A subset of those cells was also FoxP3+ and these CD4+FoxP3+ cells were positively correlated with stromal CD4 expression ($p<0.001$). Less than half of the samples showed positivity for granzyme B. Both, untreated and pretreated patients had PD-1+ TILs, while only 10% of the untreated patients also had PD-1+ tumor cells. PD-L1 positivity on lymphocytes and/or tumor cells was observed for more than half of the patients, with significant differences according to the histological subtype ($p<0.001$). Patients with a sarcomatoid histology showed the most PD-1 expression. TIM-3 was expressed in tumor cells, stromal lymphocytes and plasma cells, less often in pretreated samples compared to untreated samples. All samples were negative for LAG-3. After multivariate analysis stromal CD45RO expression was found to be an independent negative predictive factor for response to chemotherapy ($p=0.017$) and expression of CD4 and TIM-3 in lymphoid aggregates were good prognostic factors ($p=0.008$; $p=0.001$).

Conclusion: Our data reveal the diversity of immune cells present in MPM and point to TIM-3 as a new target in mesothelioma. Administering chemotherapy before or together with PD-1/PD-L1/TIM-3 blocking agents may not be the best combination sequence and further research on the predictive value of CD45RO in the stroma might guide patient selection for chemotherapy.

Keywords: Immune checkpoints, tumor microenvironment, biomarkers

OA03.01
First-Line Nivolumab Monotherapy and Nivolumab plus Ipilimumab in Patients with Advanced NSCLC: Long-Term Outcomes from CheckMate 012

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Background: Nivolumab, a programmed death 1 (PD-1) immune checkpoint inhibitor antibody, has demonstrated improved efficacy and tolerability vs docetaxel in patients with advanced NSCLC that progressed on or after platinum-based chemotherapy and is approved in >50 countries in this patient population. We report efficacy and safety data from a phase 1 study (CheckMate 012; NCT01454102) evaluating first-line nivolumab in patients with advanced NSCLC.

Methods: Patients (N=52) with advanced, chemotherapy-naive NSCLC (any histology) were treated with nivolumab monotherapy at 3 mg/kg IV Q2W until disease progression or unacceptable toxicity. Safety and tolerability was the primary study objective. Efficacy, as measured by objective response rate (ORR) and 24-week progression-free survival (PFS) rate per RECIST v1.1, was the secondary objective. Overall survival (OS) was an exploratory endpoint.

Results: Treatment-related adverse events (TRAEs) were reported in 71% (any grade) and 19% (grade 3–4) of patients. The most frequent select TRAEs (those with potential immunologic causes) by category were skin, endocrine, and gastrointestinal (Table). With a median follow-up of 14.3 months (range, 0.2 to 30.1), the confirmed ORR was 23% (12/52) and 8% (4/52) of patients had complete responses. Of the 12 responses, 8 (67%) were ongoing at the time of database lock; median duration of response was not reached. Median OS was 19.4 months (range, 0.2–35.8+). The 24-week PFS rate was 41% (95% CI: 27–54); 18-month OS rate was 57% (95% CI: 42–70). Updated long-term data will be presented, including 2-year OS and will represent the longest follow-up to date for a PD-1/PD-L1 inhibitor for