administered at Dose Level (DL) 1 = 0.1×10^6, DL2 0.5–1.2×10^6, and DL3/Expansion= 1.2–15×10^6 transduced cells.

**Results**

As of Jan 10, 2020, 11 pts (6 male/5 female) with NSCLC (3 squamous cell, 7 adenocarcinoma, 1 adenosquamous) were treated. Five, 3 and 3 pts received cells at DL1, DL2, and DL3/Expansion, respectively. The most frequently reported adverse events ≥ Grade 3 were lymphopenia (11), leukopenia (9), neutropenia (8), anemia (6), thrombocytopenia (5), and hyponatremia (5). Three pts reported CRS (Grades 1, 2, and 4, respectively). One pt received the highest dose of LD (Flu 30 mg/m^2 Day 1 4 and Cy 1800 mg/m^2 Day 1–2) prior to a second infusion and had a partial response (PR). This pt subsequently developed aplastic anemia and died. Responses included: 1 pt – PR, 3 pts - stable disease, 2 pts – progressive disease, 1 pt - too early to determine, 4 pts - off-study prior to tumor assessment. SPEAR T-cells were detectable in peripheral blood from pts at each dose level, and in tumor tissue from pts at DL1 and DL3.

**Conclusions**

ADP-A2M10 SPEAR T-cells have shown acceptable safety and no evidence of toxicity related to off-target binding or alloreactivity. Given the minimal antitumor activity and the discovery that MAGE-A10 expression frequently overlaps with MAGE-A4 expression, the clinical program has closed. Several trials with SPEAR T-cells targeting MAGE-A4 are ongoing (https://bit.ly/35lnsZK).

**Trial Registration**

NCT02592577

**Ethics Approval**

The trial was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines and was approved by local authorities. An independent ethics committee or institutional review board approved the clinical protocol at each participating center. All the patients provided written informed consent before study entry.

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**DURVALUMAB AFTER CHEMORADIOThERAPY FOR PD-L1 EXPRESSING INOPERABLE STAGE III NSCLC IMPACTS LOCAL-REGIONAL CONTROL AND OVERALL SURVIVAL**

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**Background**

Chemo-radiotherapy (CRT) followed by maintenance treatment with the PD-L1 inhibitor durvalumab is a new standard of care for inoperable stage III NSCLC. The present study aims to evaluate the oncological outcome of patients treated with CRT alone to those treated with CRT and durvalumab (CRT-IO) in the real-world setting.

**Methods**

Retro- and prospectively collected data of 133 consecutive inoperable stage III NSCLC patients treated between 2011–2019 were evaluated. Local-regional-recurrence-free-survival (LRPFS - defined as progression in the mediastinum, hilar and/or supraclavicular region at both sides and the involved lung), progression-free survival (PFS) and overall survival (OS) were evaluated from last day of thoracic radiotherapy (TRT).

**Results**

Median age at diagnosis was 68.5 years; 44 (33%) were female; 58 (44%) were diagnosed with adenocarcinoma. All patients were irradiated to a total dose of at least 60 Gy (EQD2). Median PTV was 709.8 cc (range: 181–1958 cc). 113 (85%) patients were treated with CRT and 20 (15%) PD-L1 expressing patients with CRT-IO. 83% of patients received two cycles of concomitant platinum-based chemotherapy. Median time to initiation of durvalumab after CRT was 0.8 months (range: 0.4–2.1). Median follow-up for entire cohort was 33.3 months (range: 4.8–111.8) and median overall survival (OS) was 24.7 (95% CI: 18.9–30.4) months. In the CRT-IO cohort after a median follow-up of 15.5 (range: 5.1–20.2) months, no deaths were reported at the time of evaluation (August 2020). Improved LRPFS (p = 0.013), PFS (p = 0.033) and OS (p = 0.002) were correlated with CRT-IO compared to the historical cohort of conventional CRT patients. After propensity-score matching (PSM) analysis with age, gender, histology, tumor volume and treatment mode and exact matching for T-and N-stage, 18 CRT-IO patients were matched 1:2 to 36 CRT patients. 12-month LRPFS, PFS and OS rates in the CRT-IO vs CRT cohort were 80% vs 38.8% (p = 0.001), 50% vs 22% (p = 0.013) and 100% vs 75% (p = 0.002), respectively. Also regarding intracranial failure, 6-month brain metastases rates were 0% vs. 6% in the CRT-IO vs CRT cohort (p = 0.290).

**Conclusions**

This real-world analysis demonstrates that durvalumab after CRT has led to significant improvement of local-regional control, PFS and OS in PD-L1 expressing inoperable stage III NSCLC patients compared to a historical cohort.

**Acknowledgements**

The study was partly presented at 2020 Annual Meeting of the American Society of Clinical Oncology (ASCO).

**Trial Registration**

N/A

**Ethics Approval**

The study was approved by Ludwig-Maximilians-University (LMU), Munich, Germany; Institution's Ethics Board, approval number 17-230.

**Consent**

Written informed consent was obtained from the patient for publication of this abstract and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

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**Both Tumor Intrinsic and Extrinsic Factors Contribute to TIL Resistance in Lung Cancer Patients**

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**Background**

Although cancer immunotherapies have achieved great success, many patients either do not respond or initially respond but later relapse. Several resistance mechanisms have been proposed from trials using immune checkpoint inhibitors or CAR-T therapy, but few studies have been conducted on resistance mechanisms to TIL therapy. In our trial, anti-PD1 refractory lung cancer patients were treated using TIL therapy. Several patients responded while others did not. We hypothesize that both tumor intrinsic and extrinsic factors may contribute to TIL resistance in lung cancer patients.

**Methods**

We performed whole exome sequencing on resected baseline tumors and predicted neoantigens using the netMHCpan algorithm. Neoantigen-reactive TIL were screened using IFN-gamma ELISpot assays in a T-DC-neoantigen co-culture system. We also did the same co-culture for TCRVβ sequencing to identify neoantigen-specific TCR clonotypes. Therefore, we have been able to track tumor antigen-specific T cells over time.
time. Combined with single cell RNA sequencing & TCR sequencing, functional features of neoantigen-specific T cells in both baseline and progressive disease (PD) tumors were analyzed.

**Results** Our data show that the presence of neoantigen-specific TIL is associated with durable TIL benefit (p = 0.031). We also identified tumor antigen-specific TCR clonotypes for 3 TIL-treated patients and followed these cells longitudinally in PBMCs. We found that although neoantigen-specific T cells had a dramatic increase after TIL infusion, patients with durable TIL benefit had a longer TIL persistence (p = 0.048, figure 1). RNA sequencing on baseline tumors showed that in patients with no durable TIL benefit, genes contributing to extracellular matrix formation were highly expressed, preventing infused TILs from migrating into tumor sites. In 2 TIL-treated patients, we found that neoantigens which were recognized by infused TILs were missing in PD tumors. In one patient, further investigation of TRM cells from both baseline and PD tumors showed that although T cells in the PD tumor can recognize PD tumor antigens, the T cells highly expressed PD-1, CTLA-4, Lag3 and TIGIT (figure 2), indicating an inability to control tumor progression. Enumeration of immunocyte compositions using CIBERSORT showed that higher M1/M2 ratios were found in patients with durable TIL benefit.

**Conclusions** In summary, higher expression of tumor antigens, longer TIL persistence and more M1 macrophages are associated with durable TIL benefit, while lack of tumor antigens, expression of immune checkpoint molecules, and upregulated formation of extracellular matrix may cause TIL resistance. Therefore, both tumor intrinsic factors and extrinsic factors contribute to TIL resistance in lung cancer patients.

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**Trial Registration** NCT03215810

**Ethics Approval** The study was approved by Chesapeake IRB, approval number Pro00021984.

**REFERENCES**


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**JAVELIN MEDLEY VEGF: PHASE 2 STUDY OF AVELUMAB + AXITINIB IN PATIENTS WITH PREVIOUSLY TREATED NON-CELL LUNG CANCER (NSCLC) OR TREATMENT NAIVE, CISPLATIN-INELIGIBLE UROTHELIAL CANCER (UC)**


**Abstract 280**

**Figure 1** In vivo TIL persistence in patients with durable TIL benefit VS patients with no durable TIL benefit

**Figure 2** PD tumor neoantigen specific T cells (red circled) express immune checkpoint molecules

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**BACKGROUND**

Avelumab, a human anti-PD-L1 monoclonal antibody, has shown a manageable safety profile and antitumor activity in multiple tumor types, including platinum-resistant metastatic or recurrent NSCLC, and is approved...