MA04.11
Neoantigen Targeting and T Cell Reshaping in Resectable NSCLC Patients Treated with Neoadjuvant PD-1 Blockade

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Background: PD-1 blockade is now standard treatment for advanced non-small cell lung cancer (NSCLC) and has recently shown impressive efficacy in promoting major pathologic response (MPR) and delaying relapse in the neoadjuvant setting. The role of tumor mutational burden, and specifically T cells targeting neoantigens derived from these mutations, in facilitating tumor clearance has been demonstrated in advanced NSCLC. However, it is unknown how neoadjuvant PD-1 blockade impacts the frequency and function of tumor specific T cells and their ability to promote major pathologic response, or how these factors may synergize to prevent or delay relapse after surgical resection. **Method:** Whole exome sequencing and neoantigen prediction was performed on pre-treatment tumor biopsies and matched normal tissue from 11 patients with resectable NSCLC treated with neoadjuvant nivolumab as part of a clinical trial (NCT02259621). T cell recognition of peptides representing candidate neoantigens was evaluated using the MANAFEST assay, which identifies T cell receptor clonotypes corresponding to antigen specificities. T cell receptor sequencing was additionally performed on serial peripheral blood T cells, pre-treatment tumor biopsies, and resected post-treatment tissues. A bioinformatic platform was developed to evaluate the dynamics of intratumoral T cell clonotypes, and more specifically neoantigen-specific clonotypes detected before, during, and after treatment and during long-term follow-up. **Result:** High-magnitude, polyclonal neoantigen-specific T cell responses were detected in the peripheral blood and persisted for many months after surgical resection and cessation of treatment. Binding to and stability with cognate HLA I molecules was validated for reactive neoantigens. Significant treatment-induced systemic perturbations in the tumor-specific T cell repertoire and an influx of peripheral T cell clonotypes into tumor tissue and lymph nodes was observed in patients regardless of pathologic response, whereas peripheral clonotypic reshaping of the anti-tumor repertoire and intratumoral T cell clonality were associated with MPR status. **Conclusion:** We show significant and systemic alterations in the peripheral anti-tumor T cell repertoire in NSCLC patients treated with neoadjuvant anti-PD-1 regardless of MPR status. Notwithstanding, the impaired restructuring of the anti-tumor T cell repertoire in patients without MPR highlights a potential immunological deficiency to overcome in future therapeutic approaches aiming to increase the MPR rate in NSCLC patients treated with neoadjuvant PD-1 blockade. **Keywords:** neoantigen recognition, T cell dynamics during checkpoint blockade, Neoadjuvant checkpoint blockade in NSCLC

MA05.01
E6508: Phase II Study of Immunotherapy with Tecemotide and Bevacizumab after Chemoradiation in Unresectable Stage III NS-NSCLC

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Background: Chemoradiation (CRT) is standard of care for unresectable stage III NSCLC. Tecemotide is a MUC1 antigen-specific cancer immunotherapy. Bevacizumab is considered to have a significant role in immune modulation. Immunotherapy in combination with VEGF blockade was tested in this phase II trial combining tecemotide and bevacizumab in patients with stage III NS- NSCLC. **Method:** Subjects with stage III NS-NSCLC suitable for definitive CRT received carboplatin(C) AUC 2 + paclitaxel(P) 45 mg/m2 weekly + 66 Gy/33fx/6.5wk and consolidation C AUC 6 + P 225 mg/m2 q21 days x 2. Patients with CR/PR/SD were then registered onto Step 2 (S2). S2 was 6 weekly tecemotide injections followed by q6 weekly injections and bevacizumab 15 mg/kg q3 weeks for up to 34 doses. The primary endpoint was safety of tecemotide and bevacizumab after CRT and consolidation. The proportion of circulating dendritic cells and their expression of CD40, HLA-DR and CD123 (IL-3R) were analyzed by flow cytometry at various time points. **Result:** 70 patients were enrolled from Dec 2010 to Oct 2014; 68 started therapy, and 39 completed CRT and consolidation therapy. Reasons for discontinuation included progression (11) and toxicity (10). 33 patients were registered to S2. The median number of S2 cycles was 12 (range 2-34). S2 toxicity: gr 3 N=9 (6 hypertension), gr 4 N=1, gr 5 N=1. Among the treated and eligible patients (n=31), from study entry, the median PFS was 14.3 (95% CI 11.0-22.2), OS was 40.1 (95% CI 21.7-NA) months. A correlative trend of increased expression of CD40 and HLA-DR on CD11c+ cells was observed at cycle 7 (week 21) of S2. **Conclusion:** This cooperative group trial met its endpoint, demonstrating tolerability of tecemotide and bevacizumab after CRT and consolidation in NS-NSCLC pts. In this select group of patients, therapy with tecemotide and bevacizumab was associated with encouraging PFS and OS. **Keywords:** Immunotherapy, Stage III NSCLC, chemoradiation

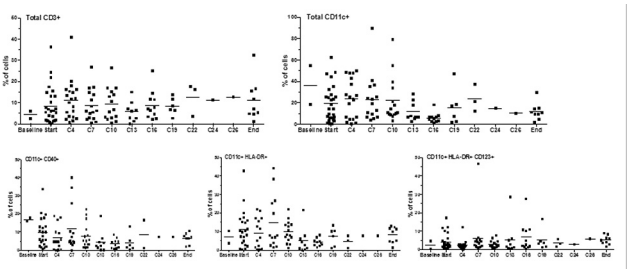


Figure 1. Trend of lymphoid and dendritic cell populations during the course of therapy. Data shown are from the flow analysis of CD3, CD11c, CD40, HLADR and CD123 (IL-3R). A trend of increased expression of CD40 and HLA-DR on CD11c+ cells was observed at Cycle 7.

MA05.02
PACIFIC Subgroup Analysis: Pneumonitis in Stage III, Unresectable NSCLC Patients Treated with Durvalumab vs. Placebo After CRT

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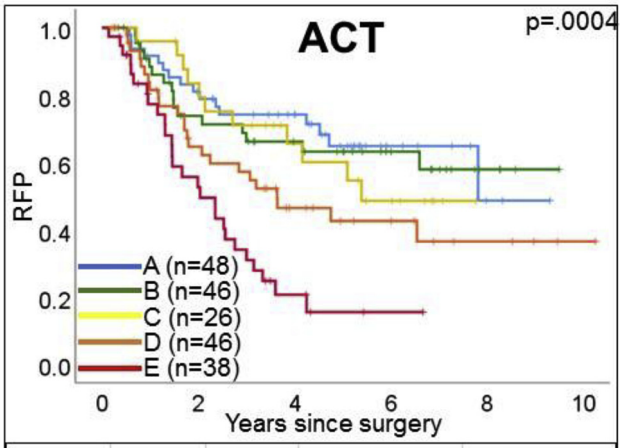
Background: In the Phase 3 PACIFIC study of durvalumab versus placebo in patients with stage III, unresectable non-small cell lung cancer (NSCLC) after concurrent chemoradiotherapy (cCRT), on-treatment pneumonitis or radiation pneumonitis ('pneumonitis') occurred in both arms with similar rates of grade 3/4 pneumonitis (durvalumab, 3.4%; placebo, 2.6%). We performed exploratory analyses to further characterize time to onset and duration of pneumonitis and examine its relationship with underlying risk factors, including patient characteristics and prior CRT. **Method:** PACIFIC (NCT02125461) was a randomized, double-blind study of patients with WHO PS 0/1 without progression after ≥2 cycles of platinum-based cCRT. Patients were stratified by age, sex, and smoking history and randomized (2:1) 1–42 days after completing cCRT to durvalumab 10 mg/kg IV Q2W or placebo up to 12 months. Potential associations between the presence of the AE pneumonitis (investigator assessed with review/adjudication by study sponsor) and baseline characteristics or patient disposition were investigated. **Result:** As of Feb 13, 2017, 709 patients had received treatment; 33.6% on durvalumab and 24.9% on placebo had any-grade pneumonitis. Treatment exposure was similar in patients with or without pneumonitis across both arms. Median time to onset of pneumonitis from treatment start was the same for both durvalumab and placebo, 55.0 days (73.0 and 76.5 days from RT completion). Pneumonitis was self-limited, with median durations of 64.0 and 57.0 days, respectively. Patients with pneumonitis were more likely to be Asian (47.9% vs 17.6%) or have EGFR mutations (11.0% vs 3.8%); however, the proportions of patients with pneumonitis and these risk factors were numerically lower with durvalumab than with placebo (Asian: 44.4% [71/160] vs 57.6% [34/59]; EGFRm: 10.6% [17/160] vs 11.9% [7/59]), suggesting no apparent interaction with treatment. There were no apparent associations of pneumonitis with baseline respiratory disorders, prior RT dose, or prior cisplatin or carboplatin use. Previous induction CT was more commonly associated with the absence of pneumonitis in both treatment arms (durvalumab: 30.1% vs 17.5%; placebo: 31.5% vs 20.3%). The presence of pneumonitis was associated with greater discontinuation due to AEs (durvalumab: 25.6% vs 10.2%; placebo: 18.6% vs 6.8%) regardless of treatment. **Conclusion:** Rates of pneumonitis were higher in Asian patients and those with EGFRm, as previously reported. Durvalumab did not increase pneumonitis in patients with these risk factors. There were no differences in treatment exposure in patients based on the presence/absence of pneumonitis. Multivariate analyses may further assist in the discernment of etiologic risks. **Keywords:** PACIFIC, durvalumab, pneumonitis

MA05.03

Immune Microenvironment and its Association with Adjuvant Chemotherapy Benefit in Locoregionally Advanced Lung Adenocarcinoma

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Background: The impact of the tumor immune microenvironment on the effectiveness of platinum-based adjuvant chemotherapy (ACT) in locoregionally advanced (stage II-III) lung adenocarcinoma (ADC) is unknown. We performed an analysis of the cellular components of the tumoral and tumor-associated stromal immune environment in stage II-III lung ADC and examined their association with ACT benefit. **Method:** Tissue microarrays (6 tumor and 3 stromal cores from each tumor) were constructed using resected tissue from patients with pT2-T4N1 lung ADC (n=500, 2000-2012) who did (n=225) and did not (n=214) receive ACT. Multiplex immunofluorescence was used to determine the quantity, localization, and colocalization of 21 types of immune cells and markers (including PD-1, PD-L1, CD3, CD20, CD68, CD163, MPO, and PanCK). The association between immune cell infiltration and recurrence free probability (RFP) was compared using Kaplan-Meier methods, and benefit from ACT by unsupervised hierarchical cluster modeling. **Result:** Overall, increased tumoral infiltration of $CD20^+$ B-cells and $CD3^+$ and $CD4^+$ T-cells was associated with an improvement in 5-yr RFP ($CD20^+$ low vs high: 37% vs 49%, p=.03; $CD3^+$: 39% vs 48%, p=.003; and $CD4^+$: 39% vs 47%, p=.02, respectively) whereas increased stromal MPO^+ neutrophil infiltration was associated with a worse 5-yr RFP (low vs high: 50% vs 38%, p=.003). Among patients who received ACT, cluster modeling revealed 5 risk groups (Groups A-E; Figure) with immune signatures including tumoral B-cells and $CD163^+PD\text{-}1^+$ macrophages as well as stromal $CD57^+$ NK-cells and $CD163^+PD\text{-}L1^+$ macrophages that provided a progressive stratification of RFP following adjuvant treatment. **Conclusion:** Immune infiltration analysis can predict benefit from ACT and thereby provide a rationale to select patients for either chemotherapy, immunotherapy, or combination therapy following surgical resection. **Keywords:** Immune-cells, chemotherapy, NSCLC



Group	Str-CD57$^+$	Tu-CD20$^+$	Str-CD163$^+$PDL1$^+$	Tu-CD163$^+$PD1$^+$
A	Low	-	-	-
B	High	High	-	-
C	High	Low	Low	-
D	High	Low	High	High
E	High	Low	High	Low

Top: RFP stratification by group following ACT
Bottom: Group definitions based on immune infiltration signature
Tu-Tumor, Str-Stroma

MA05.05

Photon-Based Cardiac Sparing Via Volumetric Modulated Arc Therapy in Thoracic Radiation Therapy for Locally Advanced Non-Small Cell Lung Cancer

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