Abstract # 422730: Molecular Predictors and Immunomodulatory Role of Dual Checkpoint Inhibitor Blockade using Ipilimumab/Nivolumab in Advanced Small Cell Lung Cancer Patients

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Background:

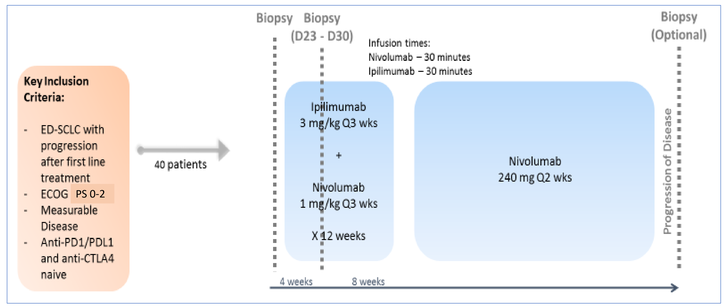
-Small cell lung cancer (SCLC) is an aggressive neuroendocrine carcinoma with poor prognosis. In extensive stage (ES-SCLC) patients, frontline treatment with chemoimmunotherapy shows modest clinical benefit. The biological impact of immunotherapy in SCLC is poorly understood with no clear predictive biomarkers to guide patient selection.

-Recently, molecular subtypes characterized by high expression of transcription factors (Subtypes SCLC-A, SCLC-N, SCLC-P) and an alternative fourth subtype SCLC-Inflammatory (SCLC-I) were used for retrospective stratification of IMpower133 patients treated with platinum doublet alone or with atezolizumab. SCLC-I patients in the Atezo arms derived the most benefit compared to chemotherapy with mOS of 18 mo vs 10 mo (*Gay, et al, 2021 Cancer Cell*).

Methods:

- ES-SCLC patients with relapsed disease were treated with combination nivolumab (nivo) and ipilimumab (ipi) in a single-arm, phase 2 clinical trial (NCT03670056).
- Patients received Nivo 1 mg/kg and ipi 3 mg/kg every 3 weeks for 4 cycles, followed by nivo maintenance until progressive disease (PD) by RECIST 1.1 or treatment-limiting toxicity.
- Biopsies were obtained at baseline, week 4 and progression.
- Whole Exome DNA Sequencing (WES) and RNA-sequencing coupled to Ocean Genomics TxomeAI® data analysis pipeline to extract genomic and transcriptomic features were performed on aired tumor and germline samples.
- Gene set enrichment analysis was performed between timepoints by employing differentially expressed genes and Reactome and Panther pathway databases.

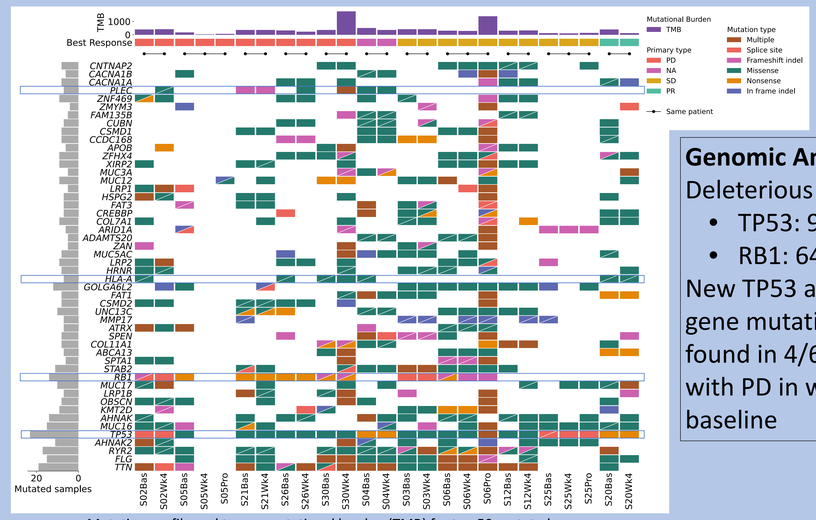
Schema:



Results:

-Genomic analysis showed patients with PD on treatment had more deleterious HLA-A gene mutations in baseline samples than those with clinical activity (PR+ SD).

-Baseline tumor mutational burden (TMB) was comparable in baseline samples from patients with different treatment responses, but prominently increased in week 4 biopsies of PD patients – 42% mean increase for PD; 45% decrease for clinical activity

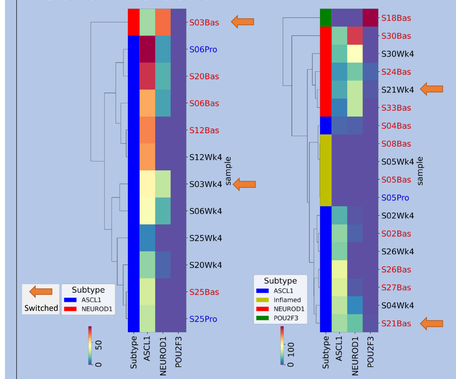


Mutation profile and tumor mutational burden (TMB) for top 50 mutated genes

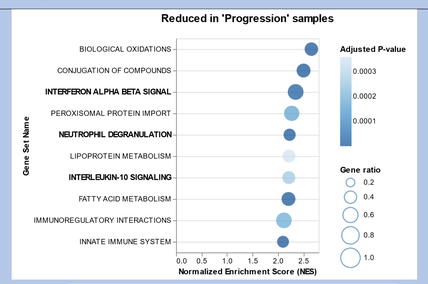
Genomic Analysis:
Deleterious mutations
- TP53: 91%
- RB1: 64%

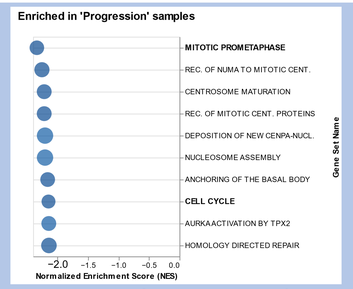
New TP53 and PLEC gene mutations were found in 4/6 patients with PD in week 4 vs baseline

Molecular Subtype Analysis:
- All patients with clinical activity were SCLC-A subtype.
- Subtype switching occurred in 2 cases during treatment (week 4), one from SCLC-A to SCLC-N and another from SCLC-N to SCLC-A.



Subtyping. clinical activity group (on the left) and progressive disease (on the right)





Gene set enrichment analysis of progression vs. week 4. In addition, T-cell activation & PD-1 signalling signatures were enriched in week 4.

Clinical Data:

- 22 patients enrolled and received treatment, with 15 evaluable per RECIST 1.1 criteria.
- 40% patients demonstrated clinical activity (2 PR, 4 SD)
- 60% patients had PD
- Paired biopsies pre- and on-treatment were successfully obtained in 16/22 patients, as well as 3 biopsies at progression.

Major Takeaways:

- Comprehensive clinico-genomic and transcriptomic analysis of prospectively collected paired samples from patients on trial is a useful resource to explore tumor adaptations to treatment and biomarkers.
- Genomic and transcriptomic features associated with treatment sensitivity/resistance to dual checkpoint blockade were identified, including increased local adaptive immune responses such as T-cell activation and PD-1 signaling.
- SCLC-A subtype patients demonstrated clinical activity to immunotherapy using dual checkpoint blockade

Future Directions:

- Further analysis on this SCLC cohort and independent datasets are required to validate findings and uncover additional characteristics of treatment response/resistance.
- The potential genomic and transcriptomic biomarkers presented here must be further validated.

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