Detection of Primary Immunotherapy Resistance to PD-1 Checkpoint Inhibitors in 2nd Line NSCLC  
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Background

- Anti-PD-1 therapy, while capable of restoring immunity, does not benefit all patients.
- While molecular tests like PD-L1 expression and TMB help in enriching response in respective subsets, a test identifying patients showing primary resistance to anti-PD-1 therapy could help in optimizing treatment regimens. Such a test would be particularly useful if it did not require tissue.
- We present results on the development and validation of a pre-treatment serum test with potential utility to identify patients with very poor outcomes on anti-PD-1 therapy.

Methods

- Test developed using methods similar to those used in recent work in melanoma (J Weber et al, Cancer Immunol Res. 2018 6(12):70-86).
- Deep MALBIR method of mass spectrometry used to probe circulatory proteins, exploring 5 orders of magnitude in abundance.
- Spectra processed to make them comparable across samples; mass spectral features (peaks) defined.
- Modern machine-learning used to correlate clinical and MS data to create a hierarchy of classifiers to stratify patients into 3 groups with the better, intermediate and poorer outcomes.
- Reliable results obtained from development set data using cross-validation-type approach ("out-of-bag" estimate).

Patient Cohorts

1. NSCLC patients treated at NKI with nivolumab validated
2. Validation Set 1, VS (N=116); 59 2nd line, 31 3rd line, 8 4th line and 15 5th line NSCLC patients treated at NKI with nivolumab
3. Validation Set 2, VS (N=179); 75 NSCLC patients treated at Erasmus MC with nivolumab
4. Chemotherapy Controls, D (N=68): 2 second line NSCLC patients treated with docetaxel

Results: Development Cohort

- FRR test stratifies patients as A (15% A (poor outcome), 43 (17%) B (intermediate outcome), 52 (21%) C (good outcomes))
- Development Set: A vs B vs C
- Development Set: resistant (A) vs sensitive (B+C)

Results: Validation Cohorts

- Validation Set 1: resistant (A) vs sensitive (B+C)
- Validation Set 2: resistant (A) vs sensitive (B+C)

Conclusions

- From retrospective samples we developed and validated a pre-treatment serum test that stratifies NSCLC patients by degree of benefit from immunotherapy.
- The resistant (poor performance) group had very poor outcomes
- The good performance group contained ~40% of patients with durable benefit
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- The resistant group was characterized by pre-existing increased activation in resistant cells
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