cfRNA and PD-L1 with clinical response to therapy (chemotherapy, immunotherapy (IMMUNO) or targeted therapy) in stage IV NSCLC pts. Our group has been the first one to use cfRNA to detect PD-L1. **Method:** Blood was drawn from 31 pts under various treatments (tx) every 6-8 weeks, at the same time that CT scans were done. CfRNA was extracted from the resulting plasma and reverse transcribed with random hexamers to cDNA. Levels of cfRNA were quantitated by RT-qPCR and correlated with pts clinical response (CR/PR/SD/PD), as determined by CT scans. **Result:** A total of 31 lung cancer pts were enrolled in a 2-year clinical study. 25 of 31 pts completed already the first two cycles of tx and had CT scans done. Of these, 6/8 pts with progressive disease (PD) showed increased (INC) levels of cfRNA, 9/13 pts with stable disease (SD) showed either no change (NC) or decreased (DEC) cfRNA, and 4/4 pts with partial response (PR) had NC or DEC cfRNA, corresponding to 76% concordance between cfRNA and clinical responses. PD-L1 expression measured in plasma cfRNA matched the tissue expression in 7/10 pts. In the one pt where PD-L1 was (-) in blood and (+) in tissue there was PD on IMMUNO. Among 8 pts treated with IMMUNO: 3/3 pts with PD showed INC PD-L1 cfRNA expression, 3/3 pts with SD had NC in negative PD-L1 status, and 2 pts with PR showed DEC PD-L1 cfRNA, corresponding to 100% correlation between PD-L1 expression levels and pt response. Of the 31 pts, 32% (10/31) harbored KRAS mutations in cfDNA. Of those with KRAS+ status by tissue-based testing, 83% matched with cfDNA results. Among KRAS+ pts, 80% (8/10) showed PD-L1 cfRNA expression in same blood draws with KRAS+ cfDNA, suggesting correlation between these cfDNA and cfRNA analyses. **Conclusion:** Significant association was observed between clinical response and changes in plasma cfRNA levels in NSCLC pts (76%). There was concordance between tissue- and blood-based testing in both DNA (KRAS mutations, 83%) and RNA (PD-L1 expression, 70%). While on IMMUNO levels of PD-L1 expression could be used to monitor response to immunotherapy. **Keywords:** PDL-1, cfRNA, NSCLC

MA19.08
Detection of Primary Immunotherapy Resistance to PD-1 Checkpoint Inhibitors (PD1CI) in 2nd Line NSCLC

J. Aerts,[1] E. Smit,[2] M. Muller,[2] A. Niemeijer,[3] C. Oliveira,[4] H. Roder,[4] J. Roder[4] *[1]Erasmus MC, Rotterdam/NL, [2]Nki, Amsterdam/NL, [3]VU Medical Centre, Amsterdam/NL, [4]Biodesix, Boulder/US*

Background: PD1CI are capable of restoring immunity, but some patients do not benefit. While molecular tests like PD-L1 expression and TMB help in enriching response in respective subsets, a test identifying patients showing primary resistance to PD1CI which does not require tissue samples could help in optimizing treatment regimens. **Method:** Sophisticated mass spectrometry profiling data from a development set (S) of pre-treatment serum from 116 2nd line NSCLC patients treated with nivolumab were correlated with outcome data (PFS/OS)using multivariate machine learning techniques related to deep learning. The resulting test stratified patients into three groups: group A having very poor outcomes, group B having intermediate outcomes, and group C having very good outcomes. Development results were obtained using out-of-bag estimators. Two additional patient cohorts treated with nivolumab, V1(N=58) and V2(N=75), were used for validation. **Result:** The proportions of patients in A, B, and C were 41:43:32 in S, 23:18:17 in V1, and 32:19:24 in V2. Median PFS/OS in the poor prognosis group A was 43/132 days in S, 105/189 days in V1, 90/278 days in V2, and in the good prognosis group C 276/528 days in S, 192/459 days in V1, and 155/not reached days in V2. In a comparison with historical controls treated with single agent chemotherapy and analyzed with the same technique, nivolumab appeared substantially superior in the good prognosis group C, while there was no evidence of superiority in the poor prognosis group A. In multivariate analysis including performance status, smoking history, and histology, the test remained an independent predictor of outcome. The patterns of protein expression related to poor prognosis in group A patients were associated with elevated complement, wound healing, and acute phase reactants. **Conclusion:** We developed and validated a test stratifying patients into three groups with significantly different outcomes on nivolumab. The poor prognosis group showed little benefit from nivolumab, and other treatments may be needed, while in the good prognosis group outcomes were very good for a 2nd line population. Our results emphasize the important role of the host immune response in the prediction of PD1CI efficacy. Data on PD-L1 IHC from these cohorts will be included in the multivariate analysis and presented at the meeting. **Keywords:** Immunotherapy, advanced NSCLC, Checkpoint Inhibitor

MA19.09
Concurrent Mutations in STK11 and KEAP1 is Associated with Resistance to PD-(L)1 Blockade in Patients with NSCLC Despite High TMB

K. Arbour, R. Shen, A. Plodkowski, H. Rizvi, A. Ni, N. Long, D. Halpenny, F. Sanchez-Vega, C. Rudin, G. Riely, M. Hellmann *Memorial Sloan Kettering Cancer Center, New York, NY/US*

Background: Targeted next generation sequencing (NGS) testing for lung cancer patients identifies recurrent patterns of co-mutations. STK11 is known to be associated with poor outcomes with immunotherapy. We have identified that STK11 is commonly co-mutated with KEAP1, but the impact of this pattern of co-mutation on response to immunotherapy is not known. **Method:** We identified 308 patients with advanced lung cancer treated at Memorial Sloan Kettering Cancer Center who underwent NGS testing with MSK-IMPACT and received at least one dose of PD-(L)1 inhibitor. Progression free survival (PFS) and overall survival (OS) from treatment initiation of PD-(L)1 blockade were calculated using Kaplan-Meier methodology and compared using logrank method and t-test for continuous variables. **Result:** In a cohort of 308 patients with NSCLC treated with PD-(L)1 blockade, STK11 or KEAP1 mutations occurred frequently (23% and 22% respectively) and concurrent STK11 and KEAP1 mutations (STK11mut/KEAP1mut) were common (56% of all STK11 mutant patients and 13% of all lung cancers, Fisher's test of association $p<0.0001$). Other common co-mutations with STK11 included KRAS (50%) and TP53 (48%). STK11mut/KEAP1mut patients had higher TMB than STK11wt/KEAP1wt patients (median 9.4 vs 6.1, Mann-Whitney p= 0.0002). STK11mut/KEAP1mut (n=39) patients had diminished PFS and OS compared to patients with STK11wt/KEAP1wt (n=210) (PFS HR 1.5, p=0.02; OS HR 2.3, p=0.001). As context, outcomes in STK11mut/KEAP1mut patients were similarly poor to EGFR mutant patients (n=28) treated with PD-(L)1 blockade (PFS p=0.7) despite substantially different tumor mutation burden (9.4 vs 4.9 mut/Mb, $p<0.0001$). Among STK11mut/KEAP1mut patients, poor outcomes were unchanged irrespective of KRAS status (PFS p=0.8, OS p=0.5). Patients with mutations in STK11 alone (n=31) or KEAP1 alone (n=28) had outcomes that more closely mirrored STK11wt/KEAP1wt patients (PFS p=0.9 and 0.1 respectively, OS p=0.1 and 0.2 respectively). **Conclusion:** KEAP1 plus STK11 co-mutation is a common event in NSCLC that is distinctly associated with poor outcomes with PD-(L)1 blockade despite otherwise favor molecular features. **Keywords:** Immune checkpoint blockade, non-small cell lung cancer, STK11

MA19.10
Impact of STK11/LKB1 Genomic Alterations on Clinical Outcomes with Chemo-Immunotherapy in Non-Squamous NSCLC

F. Skoulidis,[1] Y. Elamin,[1] V. Lam,[1] J. Zhang,[1] J. Lewis,[2] W. Rinsurongkawong,[2] J. Lee,[3] J. Roth,[4] S. Swisher,[5] V. Papadimitrakopoulou,[1] J. Heymach[1] *[1]Thoracic, Head and Neck Medical Oncology, The University of Texas M. D Anderson Cancer Center, Houston, TX/US, [2]Quantitative Reasearch Computing, The University of*