Early Plasma ctDNA Response Anticipates Clinical Response to First-Line Immunotherapy

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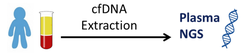
Background

- Immune checkpoint inhibitors (ICI) that target PD-1/PD-L1 are emerging as an important component of front-line treatment of metastatic non-small cell lung cancer (NSCLC) patients, either as monotherapy or in combination with doublet chemotherapy.
- Pembrolizumab has FDA approval as a single agent for non-squamous NSCLC patients with high PD-L1 expression (TPS 50%)[1] and in combination with doublet chemotherapy, regardless of PD-L1 expression[2].
- Thus in the near future, selecting between immunotherapy alone versus combination chemoimmunotherapy may become a critical question in the front-line setting for many patients.
- However, current biomarkers are insufficient to optimally guide decision-making for individual patients with PD-L1 expression and tumor mutational burden (TMB), limited in their ability to distinguish between patients who will benefit.
- Longitudinal monitoring of plasma circulating tumor DNA (ctDNA) is an emerging tool that may permit real-time assessment of response to ICI, in advance of radiologic or clinical assessment.
- We hypothesized that serial assessment of plasma ctDNA using the clinically validated next generation sequencing (NGS) ctDNA assay, InVision™, demonstrating high sensitivity and specificity, would enable early detection of response to ICI in NSCLC.

Methods

- Patients with advanced NSCLC who received first-line treatment with pembrolizumab alone or in combination with platinum doublet chemotherapy at the Dana-Farber Cancer Institute were enrolled in this study.
- Plasma collected from patients prior to starting therapy and again at 3 weeks after starting therapy was analyzed by NGS
- Plasma NGS was performed using the Inivata Liquid Biopsy Platform, Invision®, which uses a combination of enhanced tagged amplicon sequencing and statistically-based analysis algorithms. 36 cancer-related genes are examined using gene specific primers designed to hotspots and entire coding regions of interest[4]



- Plasma NGS results were analyzed and detected gene alterations and allele frequency (AF) were reported **blinded** to patients characteristics, treatment and outcomes.
- For longitudinal monitoring and assessment of changes in AF, if more than one mutation was identified in a baseline sample, we used the mutation having the highest allelic fraction to track ctDNA levels over time compared to baseline

Results

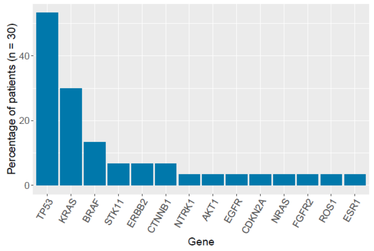
I. Population

Baseline Characteristics	N=30 (%)
Sex, female	22 (73%)
Age, median (years, range)	64 (47-89)
Smoking	
Non smoker	4 (13%)
Smoker	26 (87%)
ECOG Performance Status-Score	
0	8 (27%)
1	4 (63%)
2	3 (10%)
Histology	
Adenocarcinoma	24 (80%)
Squamous	4 (13%)
Other	2 (7%)
PD-L1 Tumor Proportion Score	
1-49%	7 (23%)
≥ 50%	19 (63%)
Not Evaluated	4 (13%)
Therapy	
Pembrozilumab	22 (73%)
Carboplatin/Pemetrexed/Pembrolizumab	8 (27%)
Best Response Rate	
Complete/partial response	12 (40%)
Stable disease	12 (40%)
Progressive disease	6 (20%)

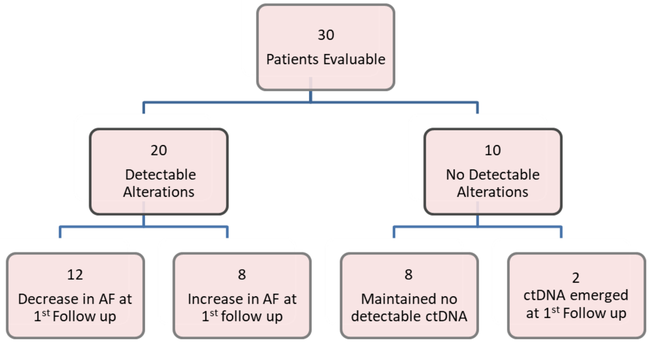
II. Plasma NGS Profiling

- 126 plasma samples (~1.5 mL) from 30 patients were studied.
- For each case, a minimum of 2 specimens and up to maximum of 6 were profiled:
  - Prior to the first infusion of therapy (baseline)
  - Initial follow-up draws (Day 21-60)
  - Subsequent follow-up draws (Day 38-392)
- Baseline alterations were detected in 20/30 (67%) samples with 50% of samples having <1% AF.

Distribution of Detected Baseline Alterations

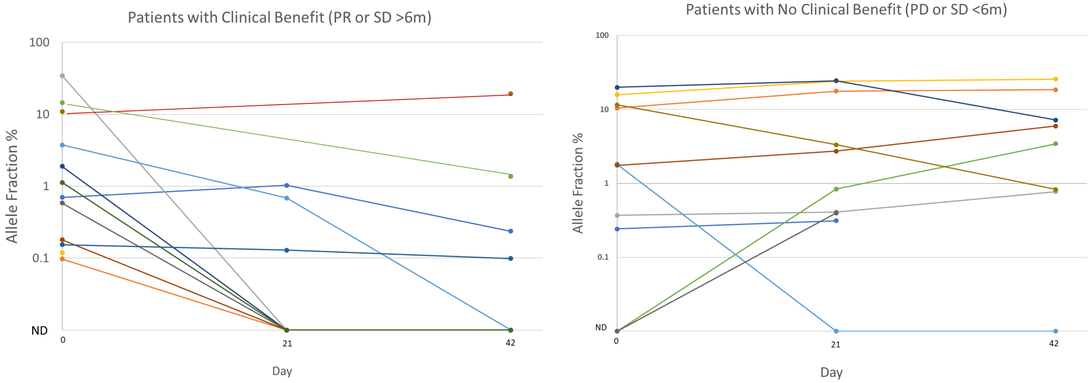


III. Serial Assessment of Plasma ctDNA in PD-1 Treated NSCLC Patients From Baseline to 1st Time Point



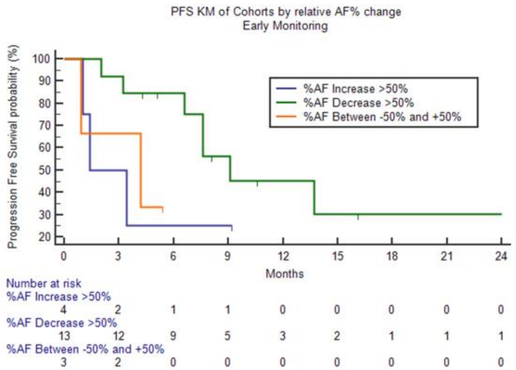
- Among the 30 patients who underwent plasma profiling, 10 (30%) had no detectable ctDNA at baseline while 20 patients had detectable alterations in ctDNA (range 1-4 alterations).
- 7/8 patients maintained no detectable ctDNA during serial analyses and responded to treatment,(4 PR, 3 SD, 1 PD) and 2 patients with emergence of ctDNA within the first 6 weeks of treatment initiation experienced progressive disease
- 12/20 (60%) patients exhibited decreases in AF at the 1st follow up while 8 patients showed AF increases.

IV. Correlation Between Changes in Baseline ctDNA AF to Clinical Benefit



Radiographic responses were preceded by earlier changes in ctDNA AF. Among 12 pts with clinical benefit (8 with partial response (PR); 4 with stable disease (SD) > 6 months), 10 patients had >50% decrease in AF% at 6 weeks with 7 patients achieving total clearance by day 21. Among 10 patients with no clinical benefit (5 progressive disease; 5 with SD < 6 months) 7 patients had an increase in AF% at 6 weeks.

V. PFS in Early Kinetics Cohorts



Observation of the early kinetics were grouped into 3 cohorts for PFS analysis. Patients were grouped into: a) those with AF% decrease of >50%; b) those with AF% increase of >50%; and c) those whose AF% change was between +50% and -50%.

Median PFS (95% CI)	>50% AF Increase	1.4 months (0.98-4.2)
	>50% AF Decrease	9.1 months (7.56-13.74)
	-50%<AF%<+50%	4.2 monthhs (0.85-4.18)

Conclusion

- The amplicon-based plasma NGS platform, InVision, demonstrated the ability to detect early quantitative changes across a wide range of variants in samples from patients with advanced NSCLC treated with first-line immunotherapy.
- Rapid decreases and clearance of ctDNA in advance of radiological and clinical assessment correlated with clinical benefit, while increasing or newly detectable ctDNA was a harbinger of progressive disease.
- These results suggest a potential role for longitudinal plasma ctDNA NGS analysis as a new efficacy metric to rapidly assess response or resistance to immunotherapies

References

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