Early plasma circulating tumor DNA (ctDNA) changes predict response to first-line pembrolizumab +/- chemotherapy in non-small cell lung cancer (NSCLC)

Biagio Ricciuti[1], Greg Jones[2], Mariano Severgnini[3], Tadd Lazarus[2], Gonzalo Recondo[1], Christine A. Champagne[1], Mizuki Nishino[4], Michael L. Cheng[1], Geoffrey R. Oxnard[1], Mark M. Awad[1]

[1]Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; [2]Inivata Inc., Research Triangle Park, NC, USA;
[3]Center for Immuno-Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; [4]Department of Radiology, Brigham and Women's Hospital and Dana-Farber Cancer Institute, Boston, MA, USA

Introduction

The PD-1 inhibitor pembrolizumab represents 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 [1-2].

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 from immune checkpoint inhibitors (ICIs). Detection of plasma circulating tumor DNA (ctDNA) is an emerging tool that may permit real-time assessment of response to ICI.

In this study we hypothesized that early changes in plasma ctDNA changes by next generation sequencing (NGS) would enable early detection of response to first-line pembrolizumab +/- chemotherapy in treatment naïve NSCLCs prior to radiological assessment.

Methods

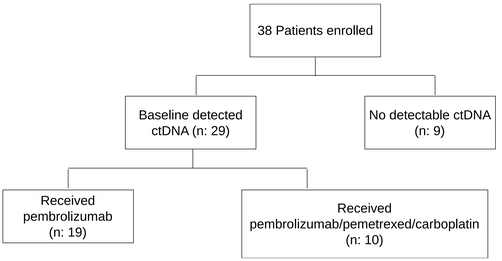
Patients with advanced NSCLC who received first-line treatment with pembrolizumab alone or in combination with platinum doublet chemotherapy at the Dana-Farber Cancer Institute, and had consented to a correlative research study (DF/HCC protocol #02–180), were enrolled in this study.

Blood samples were collected from each lung cancer patient on the first day of treatment (prior to the start of therapy), and at each subsequent cycle prior to therapy administration. Upon collection, blood samples were transferred to EDTA-coated tubes and processed to plasma by centrifugation. After plasma extraction, 2ml of plasma were stored at −80°C according to validated specifications and shipped to the Inivata Clinical Laboratory Improvement Amendments–accredited laboratory (Research Triangle Park, NC) for InVisionFirst® ctDNA analysis [4] .

For longitudinal monitoring and assessment of changes in AF, if more than one mutation was identified in a baseline sample, the mutation having the highest allelic fraction was used to track ctDNA levels over time compared to baseline.

Results

Study flow chart



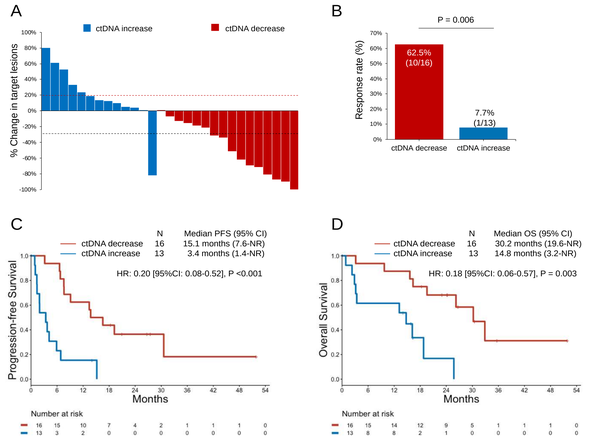
Results

Clinical outcomes to pembrolizumab +/-chemotherapy according to early ctDNA change

Patient characteristics

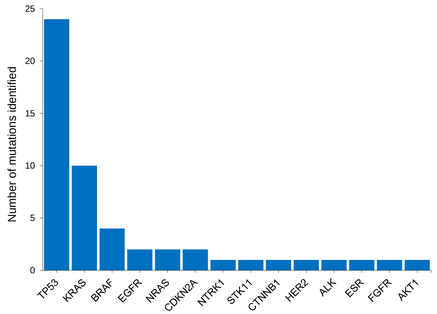
	Plasma AF decrease	Plasma AF increase	P
Age, median (range)	61 (39-89)	66 (43-80)	0.31
Sex:			
- Male	3 (18.8)	3 (23.1)	1.0
- Female	13 (81.2)	10 (76.9)	
Histology:			
- Adenocarcinoma	14 (87.5)	11 (84.6)	1.0
- Squamous	2 (12.5)	2 (15.4)	
PS ECOG:			
- 0-1	15 (93.7)	9 (69.2)	0.14
- ≥1	1 (6.2)	4 (30.8)	
Smoking status			
- Current/Former	16 (100.0)	11 (84.6)	0.19
- Never	0 (0.0)	2 (15.4)	
Driver mutation by tissue NGS:			
- KRAS	8 (57.1)	2 (16.7)	
- EGFR	0 (0.0)	2 (16.7)	
- BRAF	2 (14.3)	2 (16.7)	0.11
- ERBB2	1 (7.1)	0 (0.0)	
- None identified	3 (21.4)	6 (50.0)	
- Not assessed	2	1	
Treatment received:			
- Pembrolizumab	8 (50.0)	11 (84.6)	0.11
- Carboplatin/Pemetrexed/Pembrolizumab	8 (50.0)	2 (15.4)	
PD-L1 expression			
- <50%	4 (33.3)	1 (8.3)	0.32
- ≥50%	8 (66.7)	11 (91.7)	
- Not assessed	4	1	
TMB, median (range)	8.4 (3.8-26.6)	12.9 (3.8-16.7)	0.71

ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed death ligand 1; TMB, tumor mutational burden.



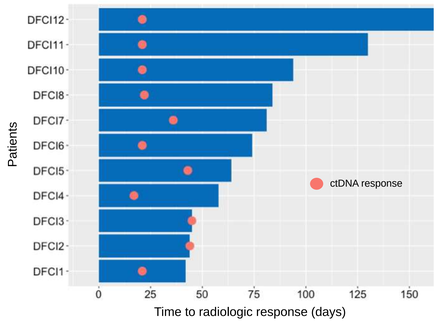
(A) Percentage change in target lesions from baseline and (B) histograms showing the overall response rate to pembrolizumab +/- chemotherapy in patients with decrease versus increase in plasma ctDNA at the first-follow-up. (C) Progression-free and (D) overall survival to pembrolizumab +/- chemotherapy in patients with decrease versus increase in plasma ctDNA at the first-follow-up.

Distribution of baseline mutations detected by plasma NGS

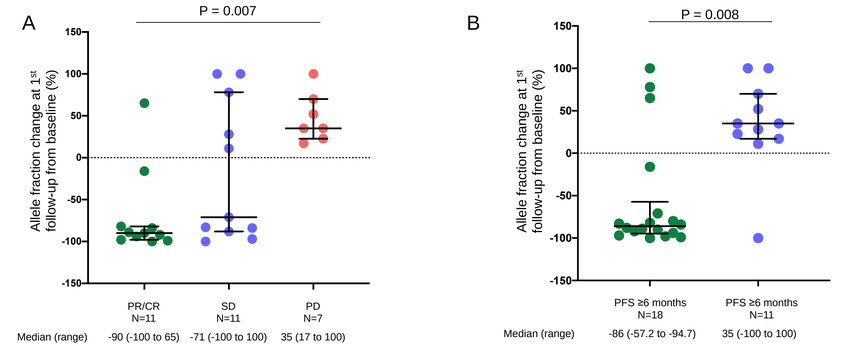


Distribution of the 52 mutations detected by plasma NGS prior to the start of pembrolizumab +/- chemotherapy among the 29 patients with detectable alterations at baseline

ctDNA response anticipates radiologic response

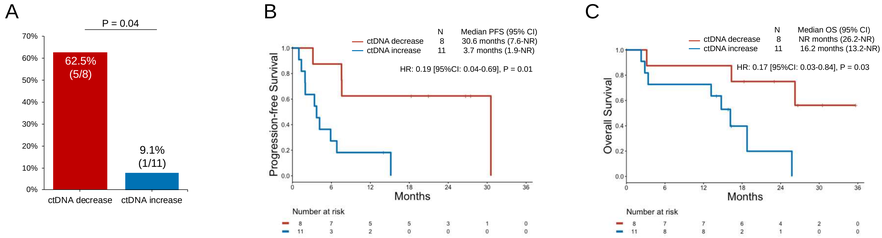


Early ctDNA change and response to pembrolizumab +/-chemotherapy



(A) Plasma ctDNA change at the first follow-up according to the response to pembrolizumab +/- chemotherapy. (B) Plasma ctDNA change at the first follow-up according to the achievement of a PFS of ≥6 months vs <6 months to pembrolizumab +/- chemotherapy.

Clinical outcomes to pembrolizumab monotherapy according to early ctDNA change



(A) Overall response rate to pembrolizumab monotherapy in patients with decrease versus increase in plasma ctDNA at the first-follow-up. (B) Progression-free and (C) overall survival to first-line pembrolizumab monotherapy in patients with decrease versus increase in plasma ctDNA at the first-follow-up.

Conclusions

- The amplicon-based plasma NGS platform, InVisionFirst®, 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 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

1.ReckM, Rodríguez-Abreu D, Robinson AG, et al: New England Journal of Medicine 375:1823-1833, 2016
2.Gandhi L, Rodríguez-Abreu D, GadgeelS, et al: New England Journal of Medicine 378:2078-2092, 2018
3.Paz-Ares LG, LuftA, TafreshiA, et al: Journal of Clinical Oncology 36:105-105, 2018
4.Plagnol V, Woodhouse S, Howarth K, et al:LensingS, Smith M, et al. PLOS ONE 13(3): e0193802.