Comprehensive genomic profiling to guide immunotherapy in lung cancer

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Background

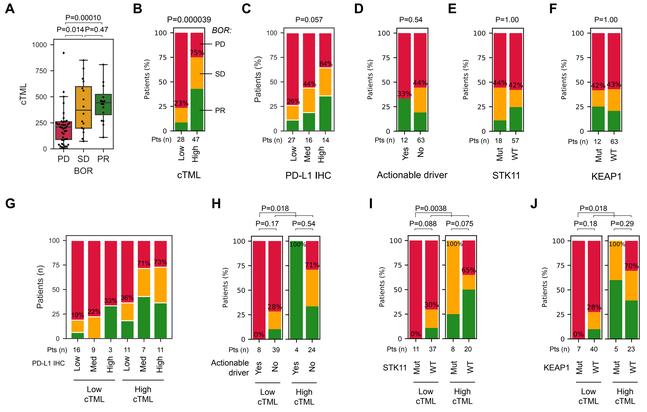
- Most patients with NSCLC are resistant to (standard-of-care) PD-1 blockade immunotherapy and suffer from overtreatment.
- Recent studies have suggested that tumors of non-responsive patients carry:
  - Actionable drivers for TKI treatment (in EGFR, MET, ALK, RET, or BRAF);
  - Genomic alterations in STK11/LKB1;
  - And/or genomic alterations in KEAP1.
- We investigated the effects of actionable/STK11/KEAP1 alterations in contexts of low vs high clonal tumor mutational load (cTML; the total number of clonal, non-synonymous mutations)

Methods

- TANGO study: prospective, real-world data collection of 75 NSCLC patients treated with PD-1 blockade monotherapy:
  - Whole genome tumor/normal sequencing (WGS)
  - RNA-sequencing
  - PD-L1 immunohistochemistry (IHC)
- Primary outcome measure:
  - Primary resistance (best overall response [BOR] = progressive disease [PD; RECIST1.1])
- Secondary outcome measures:
  - Progression-free survival (PFS)
  - Overall survival (OS)
- We tested associations of actionable drivers or (clonal, bi-allelic) STK11/KEAP1 alterations with outcomes in contexts of a low (<300; pre-defined threshold) vs high (≥300) cTML.

Results: cTML-specific associations with primary resistance

Primary resistance: best overal response (BOR) = PD (according to RECIST v1.1)

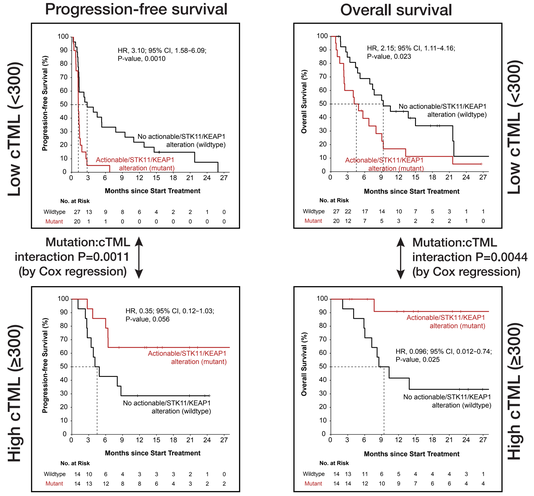


Conclusion: Actionable/STK11/KEAP1 alterations only marked primary resistance to PD-1 blockade in patients with a low cTML.
(Actionable/STK11/KEAP1 alterations were not associated with cTML of PD-L1 status)

TAKE HOME MESSAGES

1. High cTML overwhelms resistance pathways for PD-1 blockade in NSCLC.
2. This drives clinical benefit of PD-1 blockade despite the presence of known resistance mutations (actionable drivers, STK11/KEAP1 alterations).
3. In the context of a low cTML, actionable/STK11/KEAP1 alterations resulted in primary resistance to PD-1 blockade in 20/20 (100%) patients.
4. PD-1 blockade may only be safely withheld from NSCLC patients with actionable/STK11/KEAP1 alterations if their tumors also have a low cTML.

Results: cTML-specific associations with survival



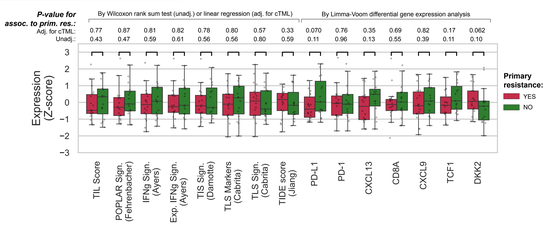
Conclusion: Actionable/STK11/KEAP1 alterations were only associated with poor survival in the context of a low cTML.

Baseline characteristics of TANGO study population

Overall (n)	75
Age (mean (SD))	62.55 (9.93)
Gender (%)	
Male	39 (52.0)
Female	36 (48.0)
Smoking status (n (%))	
Current	15 (20.0)
Former	42 (56.0)
Never	7 (9.3)
Unknown	11 (14.7)
Pack years (mean (SD))	29.11 (19.28)
ECOG (n (%))	
0	18 (24.0)
1	40 (53.3)
2	9 (12.0)
>2	1 (1.3)
Unknown	7 (9.3)
Previous cancer therapy (n (%))	
Chemotherapy	49 (65.3)
Chemo-RT	1 (1.3)
None	12 (16.0)
Other	2 (2.7)
TKI	9 (12.0)
Unknown	2 (2.7)
Treatment (n (%))	
Atezolizumab	1 (1.3)
Durvalumab	2 (2.7)
Nivolumab	48 (64.0)
Pembrolizumab	24 (32.0)

Treatment line (n (%))	
1	13 (17.6)
2	54 (73.0)
3	5 (6.8)
4	2 (2.7)
No. Of IO cycles (mean (SD))	11.66 (12.23)
Biopsy location (n (%))	
Metastasis	52 (69.3)
Primary tumor	21 (28.0)
Unknown	2 (2.7)
Histology (n (%))	
Adenocarcinoma	45 (60.0)
Squamous cell carcinoma	13 (17.3)
NOS	11 (14.7)
Other	2 (2.7)
Unknown	4 (5.3)
PD-L1 expression status (n (%))	
<1%	27 (36.0)
1-50%	16 (21.3)
>50%	14 (18.7)
unknown	18 (24.0)
BOR (n (%))	
PD	43 (57.3)
PR	16 (21.3)
SD	16 (21.3)

Results: RNA-seq analysis



Conclusion: Bulk RNA-seq immune marker gene(set) analysis did not further improve the identification of resistant patients.

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The authors declare no conflicts of interest

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