#2063

Blood tumor mutational burden (bTMB) and efficacy of immune checkpoint inhibitors (ICIs) in advanced solid tumors: SCRUM-Japan MONSTAR-SCREEN

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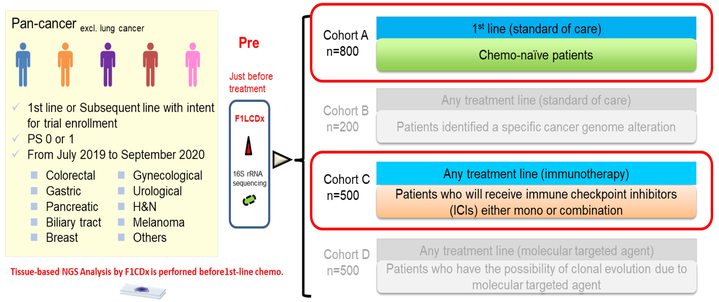
INTRODUCTION

- The dramatic impact of ICIs on treatment outcomes has heightened interest in predictive biomarkers, including genomic markers (i.e. tumor mutational burden (TMB), and microsatellite instability (MSI)).
- Pembrolizumab has been approved by the FDA for previously treated advanced solid tumors with elevated TMB (≥10 mut/Mb on FoundationOne® CDx, F1CDx) .
- Understanding the distribution of TMB by tumor types and between tissue (tTMB) and blood (bTMB) will be clinically important.
- Association between bTMB and efficacy of ICIs in advanced solid tumors has not been fully established.

METHODS

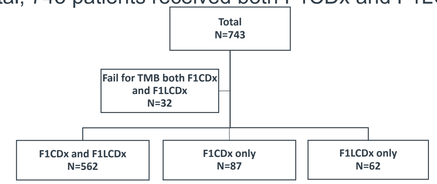


- MONSTAR-SCREEN is an ongoing nationwide profiling and monitoring project of fecal microbiome and circulating tumor DNA (ctDNA) in 2,000 patients with advanced solid tumor at 31 Japanese core cancer institutions.
- This analysis included patients who were enrolled in MONSTAR-SCREEN cohort A (chemo-naïve patients) and C (patients who will receive ICIs) from Jul 2019 to Jun 2021.
- Tissue comprehensive genome profile (CGP) was performed with F1CDx; plasma CGP included FoundationOneLiquid CDx (F1LCDx). Mutational burden was calculated by counting somatic variants (single nucleotide variants and indels, including synonymous variants, excluding germline and driver mutations) with a qualifying variant allele frequency.
- MSI score was assessed using 95 repetitive loci and principal component analysis (tissue) or >1,800 repetitive loci (plasma).
- ctDNA levels were estimated using composite tumor fraction (cTF), a metric that relies on a measure of aneuploidy (TF), or based on maximum VAFs when TF is low.
- The efficacy of anti-PD-1/PD-L1 with or without anti-CTLA4 therapy was evaluated by RECIST v1.1.

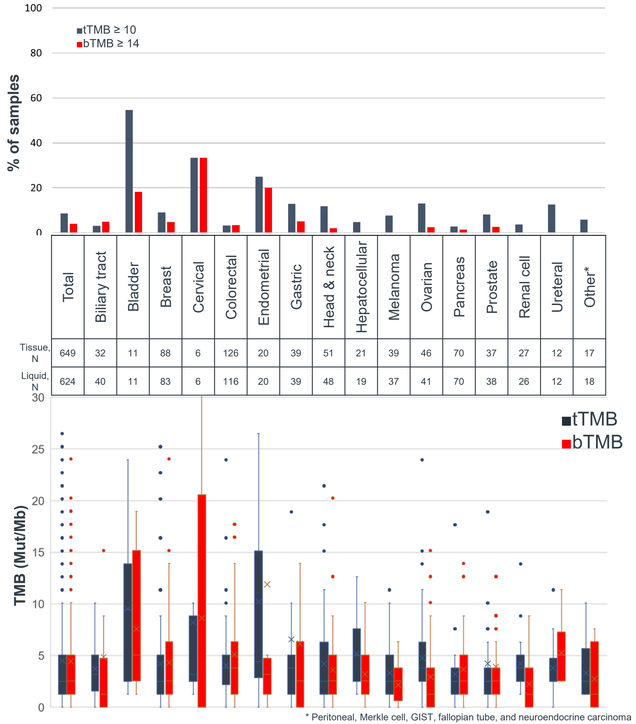
RESULTS

tTMB and bTMB in various cancer types

- In total, 743 patients received both F1CDx and F1LCDx tests.

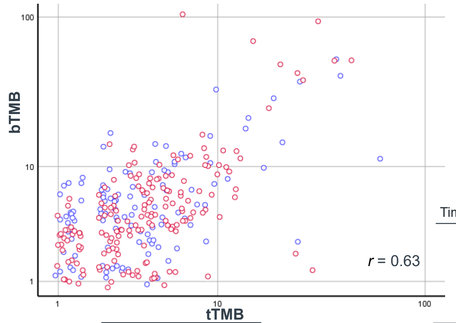


- The results for the cases that were assessable for TMB were as follows;
  - Elevated tTMB ≥ 10 (tTMB-high; tTMB-H) was detected in 8.6% of patients (56/649) and was common in bladder cancer (55%), cervical cancer (33%), and endometrial cancer (25%).
  - Elevated bTMB ≥ 14 (bTMB-high; bTMB-H) was detected in 4.1% of cases (25/624) and was common in cervical cancer (33%), endometrial cancer (20%), and bladder cancer (18%).
- Of 629 patients with known MSI status, MSI-high (MSI-H) was seen in 2.1% of tissue (13/629), and 100% (13/13) were tTMB-H. While MSI-H was detected in 1.7% (11/629) of blood specimens, and 82% (9/11) were bTMB-H.

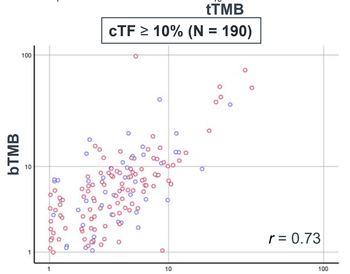


tTMB and bTMB concordance

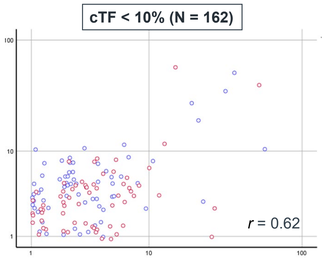
- Among 352 treatment-naïve patients (cohort A) patients with both tissue and liquid CGP results (median interval sample collections, 39 days [range, 0–5280 days] apart), a positive correlation between tTMB and bTMB was shown (r=0.63), especially in patients with interval between tissue and plasma collections less than 90 days and composite tumor fraction (cTF) ≥10 (r=0.75).



Time between collection	N	r
<90 days	212	0.68
≥90 days	140	0.62



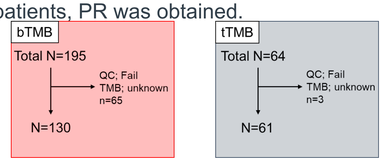
Time between collection	N	r
<90 days	131	0.75
≥90 days	59	0.67



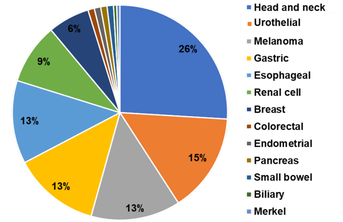
Time between collection	N	r
<90 days	81	0.61
≥90 days	81	0.67

TMB and efficacy of ICIs

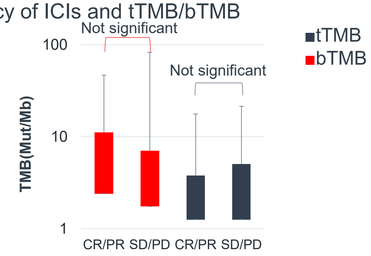
- 195 patients received ICIs therapy in MONSTAR-SCREEN cohort C.
- All patients were analyzed using F1LCDx, and 64 patients were also analyzed using F1CDx.
- Elevated bTMB ≥ 14 was detected in 11 % of patients (14/130).
- ORR was 21% (40/195) overall, with a 43% ORR in bTMB-H patients (6/14).
- MSI-H was detected in 5 patients, all of them were bTMB-H. In two of these patients, PR was obtained.



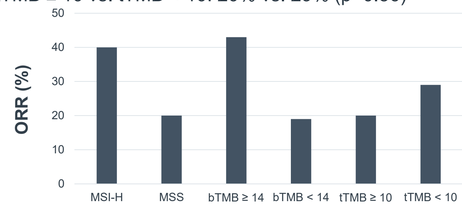
- Cancer type in cohort C



- Efficacy of ICIs and tTMB/bTMB



- Objective response rate by biomarker
  - MSI-H vs. MSS: 40% vs. 20% (p=0.28)
  - bTMB ≥ 14 vs. bTMB < 14: 43% vs. 19% (p=0.05)
  - tTMB ≥ 10 vs. tTMB < 10: 20% vs. 29% (p=0.56)



Conclusion

- Elevated bTMB occurred in approximately 5% of patients with advanced solid tumors.
- There was a positive correlation between bTMB and tTMB, especially in samples collected at a short interval and with cTF ≥ 10.
- The ORR trended higher in bTMB-H patients than in bTMB-low patients, suggesting that bTMB may serve as the potential biomarker for predicting the efficacy of ICIs, particularly when tissue CGP is unavailable.
- Prospective investigation is warranted to clarify clinical utility of bTMB for identifying high TMB tumors that may benefit from ICIs.