Characterization of Tumor Mutation Load (TML) in Solid Tumors

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Abstract

Background: Rapid advances in immunotherapy have created a need for biomarkers to improve patient treatment selection. TML is proposed as a potential predictive biomarker due to its association with tumor immunogenicity.

Methods: TML was assessed in 7,748 solid tumors from 14 different origins using somatic nonsynonymous missense mutations sequenced with a 592-gene panel. High TML was set at ≥ 17 mutations per megabase (mt/MB) based on an established concordance (> 99%) with MSI-High status in colorectal cancer (CRC).

Results: Mean TML was highest in melanoma (Mel, 21 mt/MB), non-small cell lung cancer (NSCLC, 11 mt/MB), and bladder cancer (BLC; 11 mt/MB), whereas prostate cancer (PC), pancreas adenocarcinoma (PA), and renal cell carcinoma (RCC) had the lowest levels (all 6 mt/MB). High TML was seen most frequently in Mel (36%), NSCLC (15%), BLC (15%), and anal cancer (SCCA; 9%), whereas it was seen least frequently in PA (1.6%) and RCC (0.5%). Primary NSCLC carried lower TML than its brain metastases (11 vs. 16 mt/MB, p < 0.001). Older age was associated with higher TML in Mel (p = 0.001), CRC (p = 0.009), breast cancer (BC; p = 0.01), and NSCLC (p = 0.02). Higher TML was seen in males than in females for Mel (p = 0.002) and NSCLC (p < 0.001). Presence of mutations in oncogenic driver genes such as EGFR, ALK, ROS1 and RET fusions, as well as cMET exon 14 skipping mutations correlated with lower TML in NSCLC (6.9 vs. 12 mt/MB, p < 0.001), as did BRAF and NRAS mutations in Mel (17 vs. 26, p = 0.003). Conversely, mutations in tumor suppressor genes such as ARID1A (CRC, NSCLC, and BLC) and NF1 (BC, CRC, Mel, BLC, and NSCLC) were associated with higher TML (p < 0.05). MSI-high was correlated with high TML in CRC and gastric cancers (p < 0.05).

Conclusions: TML varied significantly among different cancers. High TML was associated with older age, presence of tumor suppressor gene mutations, and absence of other oncogenic mutations. Future studies will assess the impact of TML on clinical outcome and establish the role of TML in selecting patients for immunotherapy.

Methods

- Multi-platform profiling was performed at a CLIA-certified lab (Caris Life Sciences)
- TML was assessed in 7,748 tumors from 14 different cancers using somatic nonsynonymous missense mutations sequenced with a 592gene panel .
- High TML was set at ≥ 17 mutations per megabase (mt/MB) based on an established concordance (> 99%) with MSIHigh status in CRC.
- Primary antibodies used for PD-L1 analysis were SP142 (non-NSCLC) and 22c3 (NSCLC).
- Universal cutoff of 2+, 5% was used as the cutoff
- PD-L1 expression on the membrane of tumor cells was evaluated.
- Correlation of TML with biomarkers, gender and age were assessed using student's t test and linear regression, respectively (R software http://www.R-project.org/.)

Cancer Type	N
Anal Cancer	47
Biliary Tract	256
Bladder Cancer	173
Breast Cancer (BC)	1143
TNBC	401
NON-TNBC	702
CRC (Colorectal Cancer)	1768
Left	611
Right	390
GE (Gastroesophageal cancer)	454
HCC (Hepatocellular cancer)	92
Kidney Cancer	192
Melanoma	399
NSCLC	2185
Pancreatic Cancer	611
Prostate Cancer (PC)	234
SBA (Small Bowel Adenocarcinoma)	95
SCLC (Small Cell Lung Cancer)	99
Total	7748

Results

Figure 1: Landscape of tumor mutational load across 14 cancer types. Top: TML-high was defined as TML >= 17 mutations/megabase. Bottom: The green lines indicate the average TML observed. The horizontal red line within each read box represents the median value and the bottom and top ends of each box represent the 1st and 3rd quartile.

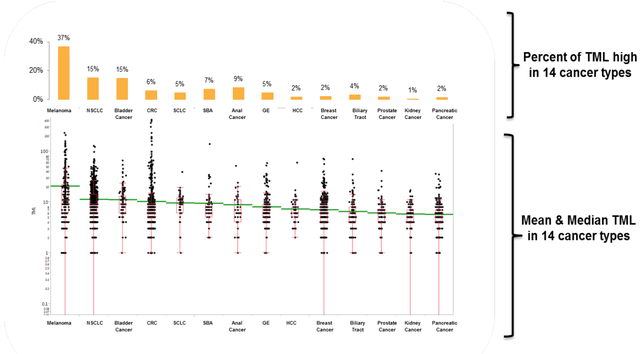


Figure 2: The proportion of samples that are TML-high and/or PD-L1 high.

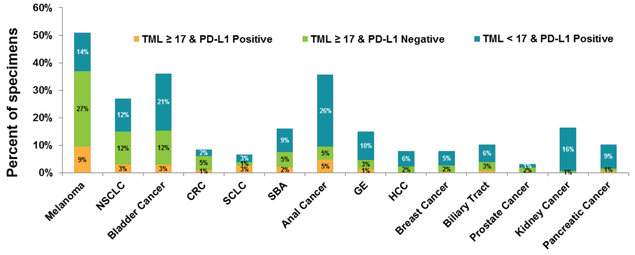
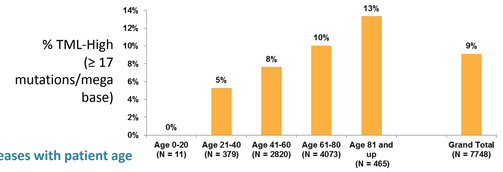


Figure 3: The proportion of TML-high tumors (in all cancer types combined) by age group.



% TML-High increases with patient age

Results, continued

Figure 4: Impact of gender on TML. Top: Percent of TML-high. Bottom: mean TML. In the complete cohort, male gender is significantly associated with higher TML. When cancer types were investigated individually, 3 cancer types showed significant gender differences in TML.

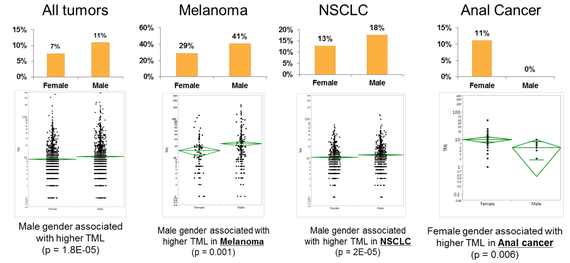
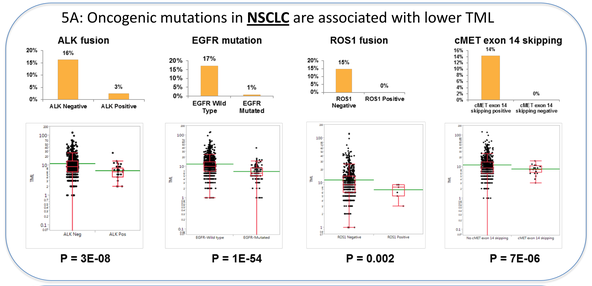
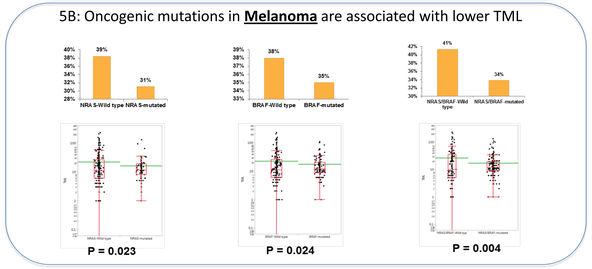
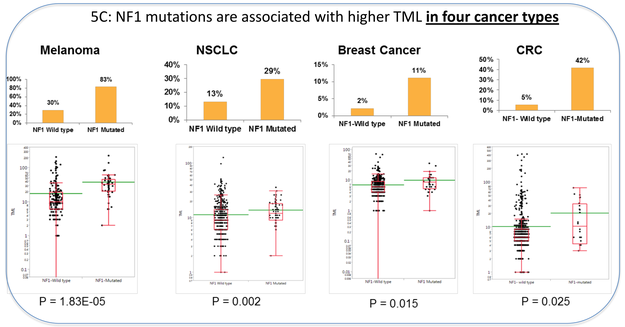


Figure 5: Relationship of genetic mutations and TML. In addition to the observed high correlation of TML with MSI-H in CRC and gastric cancer (Salem 2017, ASCO GI), other TML-associated molecular alterations are shown below.





Results, continued



Conclusions

- TML, assessed by NextGen sequencing on a 592-gene panel, revealed significant variation among different cancers
- Assessment of both TML and PD-L1 may identify potential responders to immune checkpoint inhibitors
- Cancer types that carry the highest proportion of favorable molecular profile to immune checkpoint inhibitors include melanoma, bladder cancer, anal cancer, NSCLC, kidney cancer and small bowel adenocarcinoma.
- Overall, male gender is associated with high TML, likely due to etiological factors including UV, smoking and viral infection.
- In addition to a known correlation with MSI, high TML was associated with older age, presence of tumor suppressor gene mutations, and an absence of other oncogenic mutations.
- Future studies will assess the impact of TML on clinical outcome and establish its role in selecting patients for immunotherapy

References

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