Precision oncology-driven real world clinical genomics data mining of *MET* alterations, TMB, and PD-L1 to empower indication agnostic patient enrollment and combination strategies

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INTRODUCTION

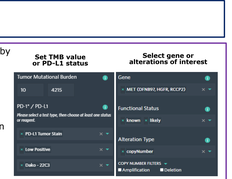
Following MET inhibitor and checkpoint inhibitor approvals, it is essential to identify cancer indications that harbor molecular alterations of interest. A thorough real-world molecular genomics based characterization of those tumors would allow the expansion of cancer specific indications that might benefit from MET and checkpoint inhibitors and shed light on exploring clinically efficacious combination strategies. Importantly, such an approach would provide an end-to-end solution that could significantly contribute to clinical translation and/or back translation strategies for innovative cancer therapies.

METHODS

We systemically interrogated FoundationInsights®[1] (Q1 2021) a dataset of real-world molecular genomic tumor profiling from North American patients with cancer, and investigated the prevalence of *MET* amplifications, *MET exon 14* skipping and *MET* fusions prevalence in 62,110 unique patient samples across five indications (lung adenocarcinoma [LUAD], esophageal/ gastroesophageal-junction/ stomach adenocarcinoma [Eso/GEJ/Sto], papillary renal cell carcinoma, hepatocellular carcinoma [HCC] and glioblastoma). *MET* alteration prevalence was further categorized based on tumor cell PD-L1 IHC status (22C3 pharmDx) and TMB status. For the analysis the following clinical biomarker thresholds were employed.

Interface

Insights allows you to filter data by characteristics like:
- Disease or Disease group
- Demographic details
  - Gender
  - Age
- Biomarker status
  - Tumor mutational burden
  - MSI
  - PD-1/PD-L1
- Alteration characteristics
  - Gene
  - Functional Status
    - Know - Ambiguous
    - Likely - Unknown
  - Alteration type
    - SNVs and InDels
    - Copy number variation
    - Gene rearrangement



Analysis Criteria

***MET* exon 14 skipping[2]**
- **Positive**: Known and likely splicing mutation including D1010x mutations
- **Negative**: No known splicing mutations

MET Amplification
- **High:** Focal amp < 20MB with CN > 5 and Non-focal amp > 20MB with CN>8
- **Low**: 20MB with CN ≤ 8

TMB
- **High:** ≥ 10 mutations/ Mb
- **Low**: < 10 mutations/ Mb

PD-L1 expression

High: PD-L1 (TPS ≥50)
- **Low**: PD-L1 (TPS ≥1 and <50)
- **Negative:** PD-L1 (TPS <1)

Additionally, comprehensive text mining from clinicaltrials.gov[3] were conducted to generate a landscape overview.

RESULTS

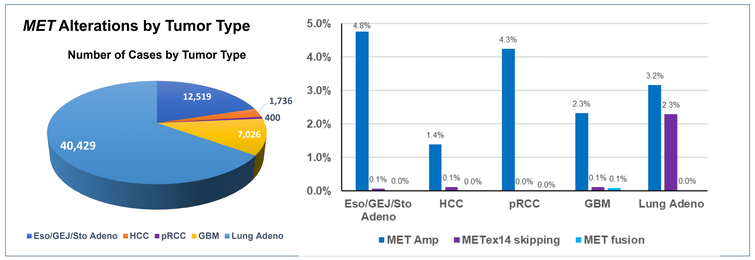


Figure 1. *MET* amplification was the most frequent *MET* alteration in the cancer types examined
- *MET* amplification prevalence ranged from 1.4% in HCC to 4.8% in Eso/GEJ/Sto
- *MET* exon 14 skipping was most frequent in lung adenocarcinoma (2.3%) and rare in other tumors evaluated
- *MET* fusions were rarely observed across indications (≤0.1%) and included: *CAPZA2, HLA-DRB1* and *CD47* (lung adenocarcinoma); *TRIM24, TSPAN12, CAPZA2, PTPRZ1* and *QKI* (glioblastoma); *CAV1* and *SOX30* (gastric cancer) and *SPATS2L* (RCC)

RESULTS

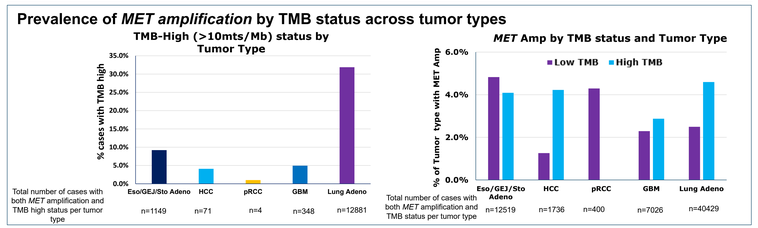


Figure 2. *MET* amplification prevalence was greater in TMB-High tumors (≥10 mutations/megabase, P<0.05)
- In HCC and lung adenocarcinoma *MET* amplification is more frequently observed in tumors with TMB-High
- Only 4 of 400 pRCC were TMB high which might explain the *MET* amplification prevalence of 0% in that subgroup

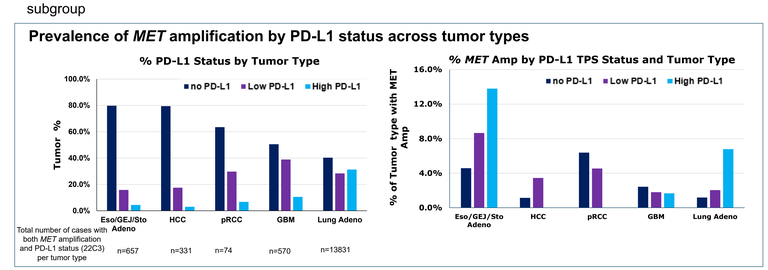


Figure 3. *MET* amplification occurrence was higher in PD-L1 high tumor vs. PD-L1-low or PD-L1-negative tumors (P<0.05)
- *MET* amplification is more common in PD-L1-positive Eso/GEJ/Sto adenocarcinomas and PD-L1-positive lung adenocarcinoma

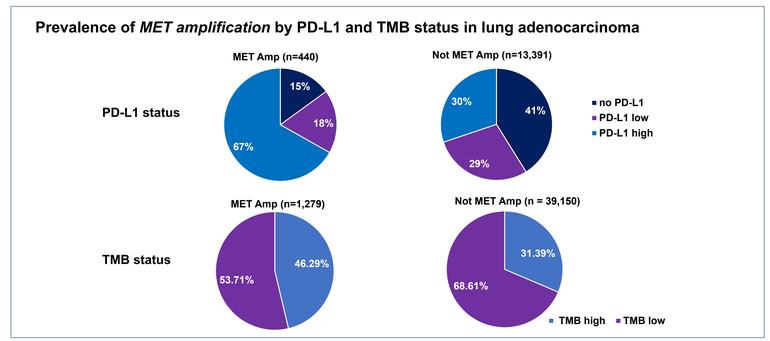


Figure 4. *MET* amplification occurrence was higher in PD-L1-high vs. PD-L1-low or PD-L1-negative lung adenocarcinomas (P<0.05) and was also higher in TMB-high vs TMB-low lung adenocarcinomas
- PD-L1-high expression occurs more frequently in *MET* amplified than not *MET* amplified lung adenocarcinomas
- TMB-high occurs more frequently in *MET* amplified than not *MET* amplified lung adenocarcinomas
- Co-occurrence of *MET* amplification and PD-L1-high/TMB-high supports the rationale for combining MET inhibitors with PD-1/PD-L1 blockade in *MET* amplified selected lung adenocarcinoma patients

RESULTS

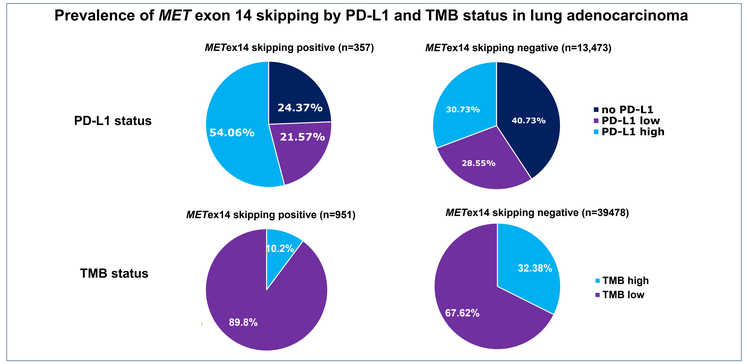


Figure 4 *MET exon 14 skipping occurrence was higher in PD-L1-high vs. PD-L1-low or PD-L1-neg lung adenocarcinomas (P<0.05)*
- PD-L1-high expression occurs more frequently in *MET* exon14 skipping positive than *MET* exon14 skipping negative lung adenocarcinomas
- The proportion of lung adenocarcinomas with TMB-High is lower in the *MET* exon 14 skipping positive group vs. negative group
- Co-occurrence of *MET* exon 14 skipping and PD-L1-high further supports the rationale for combining MET inhibitors with PD-1/PD-L1 blockade in *MET* exon 14 skipping selected lung adenocarcinoma patients

Text Mining
- Text mining results, based on analysis of clinicaltrials.gov[3], indicated that patient selection for MET inhibitors focused primarily on *MET* amplification (95%) before 2016
- From 2016, 56% of trials also include *MET* exon 14 skipping as an eligibility criteria

CONCLUSIONS

- **Real world genomics corroborated *MET* amplification as a predominant *MET* alteration across various indications**
- **The potential clinical benefit to combine MET inhibitors with PD-1/PD-L1 blockades in specific indications and specific subsets of patients is further recognized**
- **Collectively, the comprehensive molecular profiling & text mining approaches will continue to guide application of precision medicine in clinical trial design based on appropriate biomarker selection**

REFERENCES

1. Frampton *et al.,* Nat Biotechnol. 2013 Nov; 31(11): 1023–1031
2. Frampton *et al.,* Cancer Discov (2015) 5 (8): 850–859
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