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Tumor mutational burden in clinical routine practice: Identifying the right threshold?

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BACKGROUND

Immunotherapy has revolutionized the management of several types of cancers. Recently, pembrolizumab was granted FDA approval for patients with recurrent and/or metastatic cancers with TMB exceeding 10 mutations/Mb assessed by the FoundationOneCDx assay. One major challenge is to reproduce the TMB results obtained by **FoundationOne (FO)** using other sequencing panels. Based on the experience of **Institut Curie (IC)** Molecular Tumor Board, we assessed and compared TMB according to both IC and FO algorithms.

METHODS

Using an in-house 571 genes NGS panel spanning 1.6 Mb of coding sequence, we assessed TMB in 328 FFPE solid tumor samples from 34 different cancer types applying both in-house IC and FO algorithms (**Fig 1**).

TMB calculations were performed using a new in-house bioinformatics tool, highly flexible and that can be applied to any sequencing panels (*https://github.com/bioinfo-pf-curie/TMB*).

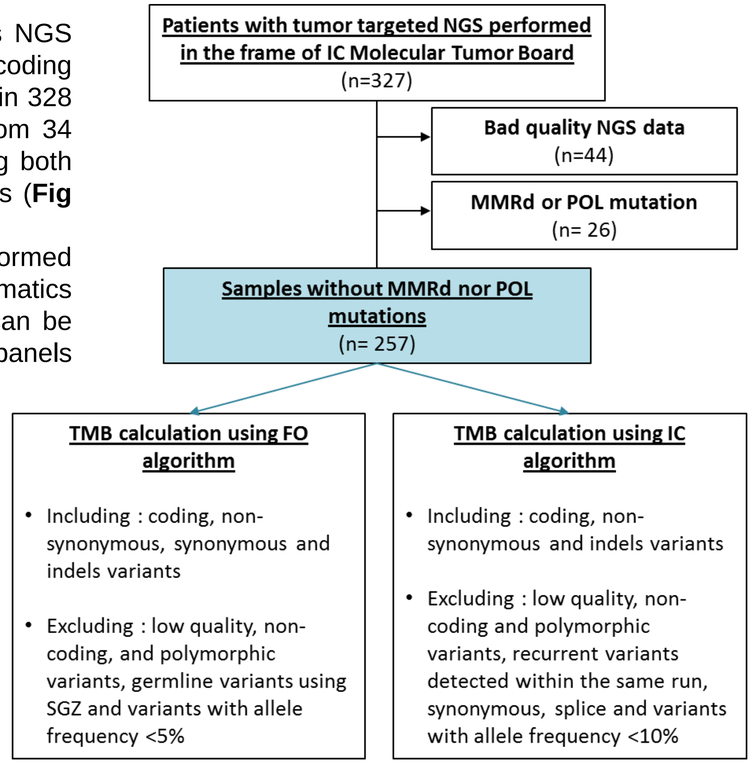

Figure 1. Methods

IC: Institut Curie
FO: FoundationOne
SGZ: Somatic Germline Zygosity algorithm

RESULTS

Main cancer types were breast (19%), sarcoma (17%), ovarian (10%) and colorectal cancers (9%) (**Fig 2**). Median TMB values obtained with the FO algorithm were significantly higher compared to the ones obtained with IC algorithm (median of 41.6 mutations/Mb versus 8.2 mutations/Mb respectively; p<0.0001 using paired Wilcoxon nonparametric test, **Fig 3**).

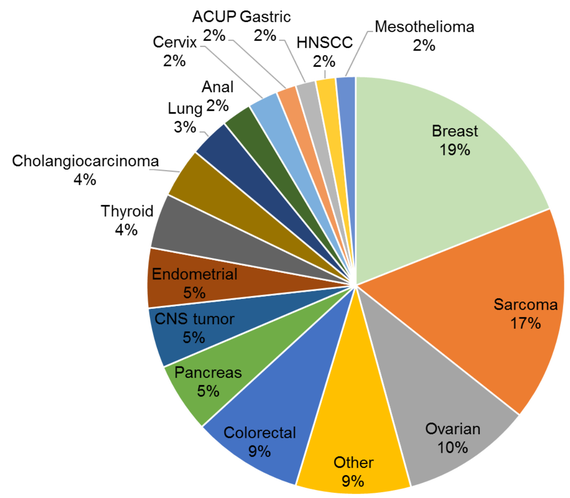

Figure 2. Repartition of tumor types analyzed

ACUP: Adenocarcinoma of Unknown Primary
CNS: Central nervous system
HNSCC: Head and neck squamous cell carcinoma

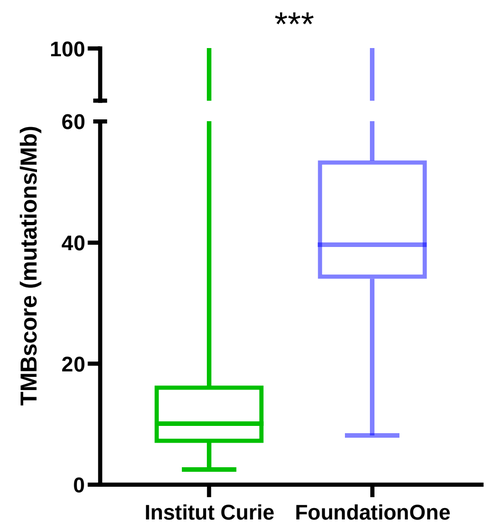

Figure 3. Repartition of TMB scores across samples according to Institut Curie or FoundationOne® algorithms.
*** p<0.0005 using paired Wilcoxon nonparametric test.

CONCLUSIONS

- The application of FO algorithm for the assessment of TMB using IC large panel gave significantly higher TMB values, suggesting that the FO threshold (10 mut/Mb) cannot be transposed to all panels.
- Further studies are required to validate these results in cohorts treated by immunotherapy.
- A collective effort to standardize and make TMB calculation methods accessible for different stakeholders is key.