Project Spotlight: *Friends* TMB Harmonization Project

The TMB Harmonization Project is a collaborative effort that establishes an approach for harmonizing diagnostic tests to provide consistent identification of patients who are likely to respond to certain therapies.

Background

Tumors with a high number of mutations are more sensitive to immunotherapy (IO): the higher the number of tumor mutations, the better the patient's outcome. Therefore, measuring the tumor mutational burden (TMB) helps to identify which patients may benefit from treatment with IO. However, different methods and technologies are used to determine TMB, which can result in variability TMB measurements and reporting. To optimize the use of TMB assays and ensure patients and providers receive accurate and reliable information to make appropriate treatment decisions, identifying sources of discordance and developing best practices to support assay alignment is critical.

Approach

Friends initiated a unique collaboration with key stakeholders including pharmaceutical companies, diagnostics developers, FDA, and academics in September 2017 to discuss variability in how TMB is defined, analyzed, and used in clinical practice, and the need for establishing industry standards. Over the next six months, *Friends* hosted discussions with project participants to develop consensus on a methodological approach to compare TMB assays, to develop a calibration tool to promote reproducibility and comparability across assays, and to provide recommendations for a clinical cutoff to support evaluation of TMB for clinical trial enrollment using a common strategy. Throughout the duration of the project, the group presented findings through public workshops, conferences, and manuscripts.

Findings

Diagnostic developers used data from The Cancer Genome Atlas (TCGA), matched normal-tumor cell lines, and tumor samples to calculate TMB in each sample using their own analysis pipeline. An agreed upon method for estimating TMB was established as the "gold-standard", which enabled comparisons across assays and to the gold standard. The analysis showed that as TMB values increased, so did variability between TMB assays. The group developed a publicly available calibration tool that can assist with assay development, reduce variability, and facilitate interpreting data from across different studies. Additionally, the group agreed on a lower bound cutoff of 10 mutations/megabase should be considered when evaluating TMB for clinical trial enrollment in a pan-tumor indication.

Next Steps

The findings from the TMB Harmonization Project demonstrate the power of a multi-stakeholder project to support assay harmonization. As more complex biomarkers become more routine in oncology care, the non-systematic approach to biomarker development can lead to challenges for regulators, payors, patients, and physicians. This work set the foundation for an ongoing *Friends*' project, the Homologous Recombination Deficiency (HRD) Harmonization Project and provides a foundation to support efforts to modernize diagnostic regulations at the FDA.

TMB Development and Milestones Timeline

KEY

- Clinical Use of TMB
- TMB Harmonization Project

2014

DECEMBER 2014 – First clinical report of TMB effect on response to IO (melanoma) in the literature

2015

APRIL 2015 – Clinical report on TMB effect on response to IO in NSCLC

2016

MAY 2016 – Clinical report on TMB effect on response to IO in bladder cancer

2017

APRIL 2017 – Chalmers report of 100,000 genomes characterizing TMB across tumor types

SEPTEMBER 2017 – *Friends* Hosts Expert Workshop on TMB

SEPTEMBER 2017 – First reports on TMB assay validation in NSCLC

NOVEMBER 2017 – FDA approval of two gene panels to detect genetic cancer mutations (MSK IMPACT and FoundationOne CDx)

2018

FEBRUARY 2018 – Clinical report on TMB effects on response to IO in solid tumors

MAY 2018 – *Friends* TMB Harmonization Project Kickoff

NOVEMBER 2018 – Initial In Silico Data Presented at SITC

2019

JANUARY 2019 – Overview of TMB Harmonization Effort Published

JUNE 2019 – Initial Cell Line Data Presented at ASCO

DECEMBER 2019 – Proposal of a Common Development Strategy for Tissue Agnostic Clinical Trials

2020

FEBRUARY 2020 – TMB Harmonization in Silico Data Published in Journal for ImmunoTherapy of Cancer

APRIL 2020 – Initial Clinical Sample Data Presented at AACR

JUNE 2020 – First FDA Approval of an IO based on TMB, 4th approval based on the presence of a biomarker rather than the primary site of origin

JULY 2020 - Public Meeting Reporting Findings from the Project (Day 1 Overview, Day 2 Overview)

JULY 2020 – TMB Harmonization Project highlighted in NCI release about TMB based FDA approval

2021

SEPTEMBER 2021 – Cell Line and Clinical Sample Data Published in Annals of Oncology