Technological advancements over the past decade have given rise to the proliferation of liquid biopsies. Opportunities for using these assays in oncology include to monitor treatment response and identifying minimal residual disease, however, robust evidence development through meta-analytic approaches is needed to sufficiently validate the use of ctDNA as a drug development tool. One example of a collaborative meta-analytical approach is the Friends of Cancer Research (Friends) ctDNA for Monitoring Treatment Response (ctMoniTR) Project. Friends brought together a multi-stakeholder group including statisticians, clinicians, and researchers from academia, industry, and government to perform meta-analyses to determine whether changes in ctDNA levels accurately reflect the therapeutic effect of cancer therapies. Understanding the approach to successfully organizing and performing meta-analyses can support evaluation of other liquid biopsies and validation of intermediate endpoints.

**Overall Approach**

**Background**

At least 2 ctDNA measurements (baseline and follow-up) are collected to define change in ctDNA for monitoring treatment response. The Friends of Cancer Research (Friends) ctDNA for Monitoring Treatment Response (ctMoniTR) Project was comprised of members from collaborating organizations: Cancer Research and Biostatistics (CRAB), Friends of Cancer Research, and clinical trials (CTT). Friends enacted a collaborative study design and analysis plan by selecting independent cancer research groups (CRAB) and formulated a statistical analysis plan. The working group then met and formulated the analysis plan. CRAB worked with diagnostic companies to identify types of ctDNA measurements and approaches to measuring changes in ctDNA. Variant allele frequency (VAF) was the most commonly reported measurement of ctDNA. There was variability across cohorts in the number of variants detected, the magnitude of VAF values, and the range of baseline median, and mean VAF values. Calculation of mean, median, and max VAF for all variants detected in a sample were used to test change in ctDNA.

**Dataset Overview**

**Retrospective Data Inclusion criteria:**
- Advanced NSCLC
- Treated with anti-PD-(L)1 therapy
- Must have RECIST evaluation and OS/PFS data
- At least 2 ctDNA measurements (baseline and follow-up)

**Selecting Independent Cancer Analysis Center (CRAB)**

Selecting independent cancer research groups (CRAB) was a stepwise selection process before selecting Cancer Research and Biostatistics (CRAB) for the project. CRAB approaches to measuring changes in ctDNA included:
- CTCAE-based definitions
- Binary: decrease ≥50% in VAF from baseline to T1
- Ordered categorical: increase, intermediate, and decrease based on VAF from baseline to T1
- Continuous data

**Selecting Timing for Measurements**

- Baseline: ctDNA sample taken within 14 days of starting therapy
- T1: ctDNA sample taken within 70 days of baseline

**Selecting Key Measurements**

The Friends of Cancer Research ctMoniTR Project evaluated the following key questions:

1. *Reductions in ctDNA are strongly associated with better clinical outcomes across multiple measures including OS and PFS.
2. Strength of association remains after accounting for clinical covariates.*

**Test change in VAF from baseline to T1**

**Overall Survival (OS)**

**Progression Free Survival (PFS)**

**Retrospective clinical trials divided into 3 different modules for analysis**

**Collaborative Meta-analytical Approaches to Advance the Use of ctDNA in Clinical Cancer Research: The Friends of Cancer Research ctMoniTR Project**

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