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

Hillary Stires, Brittany McKelvey, Mark Stewart, Jeff Allen
Friends of Cancer Research, Washington, DC, USA

Background

Technologic 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

Key Question: Do changes in ctDNA reflect response to treatment?

2018 | 2019 | 2020 | 2021 | 2022 | 2023 and beyond

ctDNA Discussion at *Friends* Annual Meeting
- Focus on the state of ctDNA as a monitoring tool to evaluate response
- Proposed a pilot study to operationalize the use of ctDNA in drug development

ctMoniTR Step 1 Kickoff → **ctMoniTR Step 1 Data Analysis** → **ctMoniTR Step 2 Kickoff** → **ctMoniTR Step 2 Data Analysis**

← **Step 1 publication:** Vega, D. M. *et al. JCO Precis Oncol* **6**, e2100372 (2022).

Key Decisions for ctMoniTR Step 1

Consideration	Key Decision
Explicit Analysis Plan	Expert Statistician created the statistical analysis plan with concrete goals and opportunities for additional discussions as data were analyzed
Level of Data Sharing	Scenario analysis (simple study level data results are shared, sharing individual patient level data (IPLD) with analysis center, federated IPLD), ultimately led to sharing IPLD with analysis center
Select Independent Analysis Center	Curated options and conspired 12 groups in a stepwise selection process before selecting Cancer Research And Biostatistics (CRAB)
Project Organization	Key stakeholders from collaborating organizations (e.g., statistical, clinical, regulatory) participated in discussions regarding study design and analysis

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)

→ **5 clinical trials of aNSCLC treated with PD-(L)1**

Investigators determined approach to ctDNA collection (timing, volume, assay, etc.)

Key Steps to Data Analysis

The working group discussed the approach and developed an analysis plan

Drug sponsors uploaded patient level data from clinical trials

CRAB performed the analyses based on the analysis plan

The working group reviewed and formulated findings

Approach to ctMoniTR Step 1 Analysis

Define ctDNA Metrics

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 mean, median, and maximum VAF values

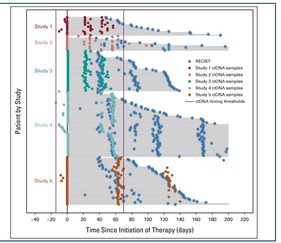
Calculate mean, median, and max VAF for all variants detected in a sample

Calculate percent change in mean, med, or max VAF from baseline to each on-treatment timepoint

Test change in mean, med, and max VAF to test association with outcomes

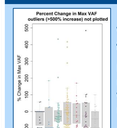
Select Timing for Measurements

- Performed descriptive analyses across cohorts
- Timing and frequency of ctDNA samples varied between cohorts
- ctDNA Definitions:
  - **Baseline ctDNA sample:** Collected within 14 days prior to the start of therapy
  - **T1 ctDNA sample:** The first on treatment ctDNA sample taken within 70 days of baseline
  - **Change in ctDNA:** T1/baseline



Model Change in ctDNA

Continuous

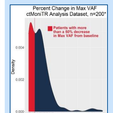


Percent change of VAF from baseline to T1

Distribution of data made the raw variable difficult to model.

Continuous: % change in [mean, median, or max] VAF from baseline to T1, with outliers capped at 500%

2-Level

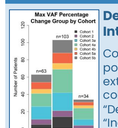


Y/N decrease in VAF more than 50%

Optimal cut-point analysis used to select the ~50% cut (the value that maximized differences in Overall Survival).

Binary: % change in [mean, median, or max] VAF from baseline to T1, categorized in ≥ ~50% change yes/no groups

3-Level



Decrease, Increase, Intermediate

Cohort-specific cut-points, 50% most extreme within each cohort defined as "Decrease" and "Increase", accounted for different spread of cohort's data.

Ordered categorical: % change in VAF from baseline to T1, categorized into Increase, Intermediate, and Decrease groups

ctMoniTR Step 1 Findings

200 patients with NSCLC treated with immunotherapy

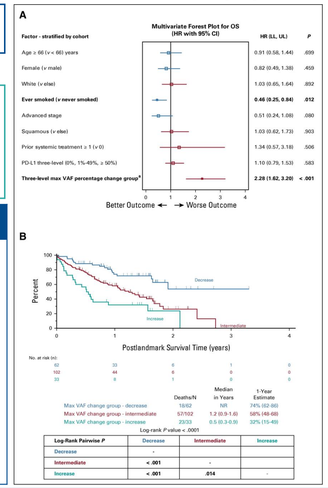
- **63** patients had a **decrease** in ctDNA levels from baseline
- **103** patients had an **intermediate change** in ctDNA levels from baseline
- **34** patients had an **increase** in ctDNA levels from baseline

Key Findings

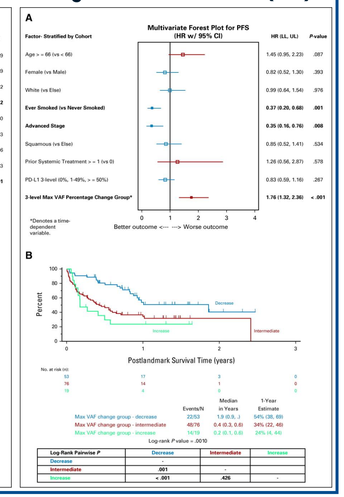
We harmonized disparate datasets through statistical methods and other approaches.

This enabled aggregate data analysis which revealed that:
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
3. Baseline ctDNA levels alone were not predictive of clinical outcomes

Overall Survival (OS)



Progression Free Survival (PFS)



ctMoniTR Step 2 Approach

Retrospective clinical trials divided into 3 different modules for analysis

18	3,000	8	16
clinical trials	patients	tumor types	therapies

- **Module 1** NSCLC TKI
- **Module 2** NSCLC IO and Chemo
- **Module 3** Solid Tumors IO or TKI

Opportunities New to ctMoniTR Step 2

Repeat measures
Create models of repeat measures for measuring ctDNA levels for individual patients over multiple timepoints when available

ctDNA and RECIST
Consider differences in the timing and frequency of ctDNA and RECIST measurements across sponsors and impact on analyses

Meta-analysis
Perform meta-analysis to evaluate ctDNA changes as a potential indicator of response for different treatments and tumor types

Timeline for 2023 and Beyond

Jan | Feb | Mar | Apr | May | Jun | Jul | Aug | Sep | Oct | Nov | Dec

- **Module 1 Analysis**
- **Finalize M2 Data** → **Module 2 Analysis**
- **Finalize M3 Data** → **Module 3 Analysis**