

Background

As cancer treatments continue to improve, clinical trials that use overall survival as the primary endpoint often take longer to complete, which can slow access to new safe and effective therapies. To enable earlier access to promising therapies for serious conditions, the FDA's Accelerated Approval pathway allows for approval based on a surrogate or early endpoint that is reasonably likely to predict clinical benefit. One such potential marker is circulating tumor DNA (ctDNA), which are fragments of DNA shed from cancer cells into the bloodstream. Change in ctDNA levels following the start of treatment can be evaluated earlier than current clinical trial endpoints, however, aggregate data analyses are necessary to fully characterize its association with survival. **Validating the use of ctDNA as an endpoint could enable faster identification of effective new cancer therapies and ultimately allow them to reach patients sooner.**

Approach

Developing the necessary evidence to support the use of ctDNA as an early endpoint requires a multiprong approach. *Friends* and colleagues wrote two white papers outlining key considerations for establishing the data that supports the use of ctDNA as an early endpoint.

[“Circulating Tumor DNA in Development of Therapies for Cancer: An Evidentiary Roadmap to an Early Endpoint for Regulatory Decision-Making”](#) demonstrates there are multiple technical and clinical characteristics contributing to variability in ctDNA measurements that should be adequately accounted for when conducting validation studies.



[“Framework for Integrating Change in ctDNA Levels in Advanced Cancer Clinical Trials to Support Meta-analyses for Intermediate Endpoint Validation”](#) builds on these findings and outlines key considerations for future prospectively designed trials for assessing ctDNA as an early endpoint.



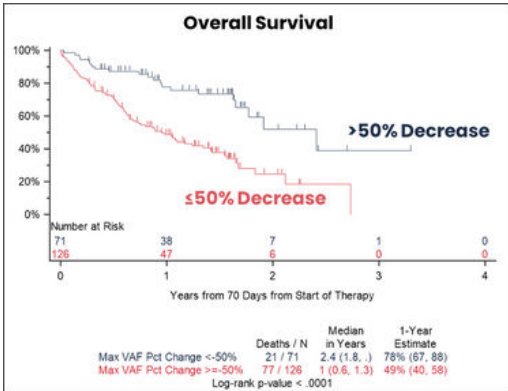
To implement this work, *Friends* leads the ctDNA to Monitor Treatment Response (ctMoniTR) Project, which provides foundation evidence for the use of ctDNA as an early clinical trial endpoint. Key findings from the ctMoniTR Project are summarized on the back.

Findings from our continued work in this space will be consolidated and presented in public meetings and peer-reviewed literature. Our goal is to efficiently evaluate the use of ctDNA as an early endpoint, with the aim of supporting its future role in regulatory decision-making.

Friends leads a multi-stakeholder research project where we aggregate patient-level data from previously completed clinical trials that included ctDNA to track treatment response in advanced cancers. This project brings together data from more than 20 clinical trials totaling over 3000 patients. In collaboration with statisticians at Cancer Research And Biostatistics (CRAB), we evaluate whether changes in ctDNA levels reflect response to treatment for different cancer types and treatments. Through this unique partnership, the ctMoniTR project enables faster and more robust evaluation of ctDNA change, or molecular response (MR), as an early indicator of benefit, advancing the field more efficiently than isolated efforts.

ctMoniTR Step 1

Goal: Assess feasibility and align on methodology to evaluate associations between changes in ctDNA levels and overall survival (OS) in a pilot study.

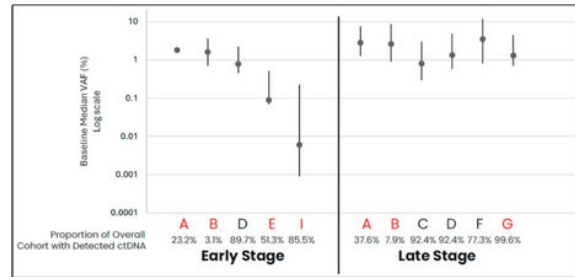


aNSCLC + IO
5 clinical trials
~200 patients

Findings: MR is strongly associated with improved OS (using >50% decrease in ctDNA to define MR).

Baseline ctDNA Project

Goal: Establish evidence regarding baseline (i.e., pre-treatment) sensitivity metrics for ctDNA detection across cancer types, stages, and assays.



Collaboration with diagnostics developers to assess baseline levels in their real-world datasets.

Findings: Variability in ctDNA levels across assays in early-stage NSCLC may be driven by differences in assay performance and methods.

ctMoniTR Step 2

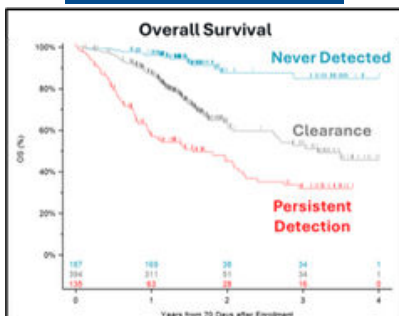
Goal: Expand the scope to study the relationship between changes in ctDNA and clinical outcomes across several clinical settings, drug classes, and cancer types.

Module 1

- Novel treatment
- Expanded dataset



aNSCLC + TKI
8 clinical trials
~1000 patients



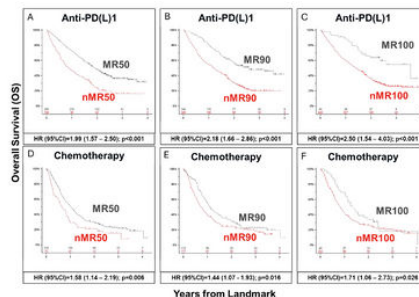
Findings: ctDNA clearance within 10 weeks of treatment initiation was associated with improved OS and PFS.

Module 2

- Assess timing
- Define MR



aNSCLC + IO/ chemotherapy
4 clinical trials
~1000 patients



Findings: ctDNA reductions at early and later timepoints were associated with OS using different MR cutoffs.

Module 3

- Additional cancer types
- Additional treatments

Multiple cancers/ treatments
9 clinical trials
~1000 patients

Consistently show that decreases in ctDNA levels from baseline to on-treatment are associated with improved overall survival.