

The ctMoniTR Project

ctDNA for Monitoring Treatment Response

The Definition: **circulating tumor DNA (ctDNA)** is genetic material shed from cancer cells and found in the bloodstream, or plasma. Assessing ctDNA is sometimes referred to as a “**liquid biopsy**.” Scientists are investigating whether measuring ctDNA could be used as a reliable, non-invasive, and rapid approach for numerous clinical applications, such as monitoring a patient’s response to treatment.

The Problem: Various small-scale studies have investigated the use of ctDNA as a biomarker of treatment response over time using different ctDNA assays and collection schedules. An initial positive trend was observed, linking a reduction in ctDNA in plasma and a tumor’s response to treatment; however, whether these trends hold across larger studies is not fully understood. Transitioning ctDNA from a research tool into clinical use will require rigorous and comprehensive studies to fully assess and determine its ability to accurately predict clinical outcomes.

The Solution: **Friends of Cancer Research (Friends)** convened stakeholders from academia, government, industry, and patient advocacy groups to establish an approach to evaluate ctDNA levels and conduct key analytical and clinical validation studies. These analyses will develop the necessary evidence to establish ctDNA as a reliable monitoring tool for treatment response and set solid foundations for the development of ctDNA as a potential surrogate biomarker.

The Research Question: Do changes in ctDNA reflect response to treatment?

Workflow	Step 1	Step 2	Early-Stage Disease
Approach	<ul style="list-style-type: none"> Aligned on a methodology to combine data from multiple trials in NSCLC Harmonized ctDNA data measured from different assays using different collection schedules <i>Manuscript forthcoming</i> 	<ul style="list-style-type: none"> Update Step 1 methodology for combining data to account for additional treatment settings and tumor types Validate Step 1 findings in a bigger cohort with more treatment classes and cancer types 	<ul style="list-style-type: none"> Identify and prioritize clinical questions supporting use of ctDNA as an early endpoint to support regulatory approval Define areas of needed data alignment to combine data from multiple clinical trials
Data	Advanced stage NSCLC treated with PD-(L)1 inhibitors	Advanced solid tumors treated with PD-(L)1 inhibitors or TKI	<i>Next Steps:</i> Inventory of data availability in solid tumors

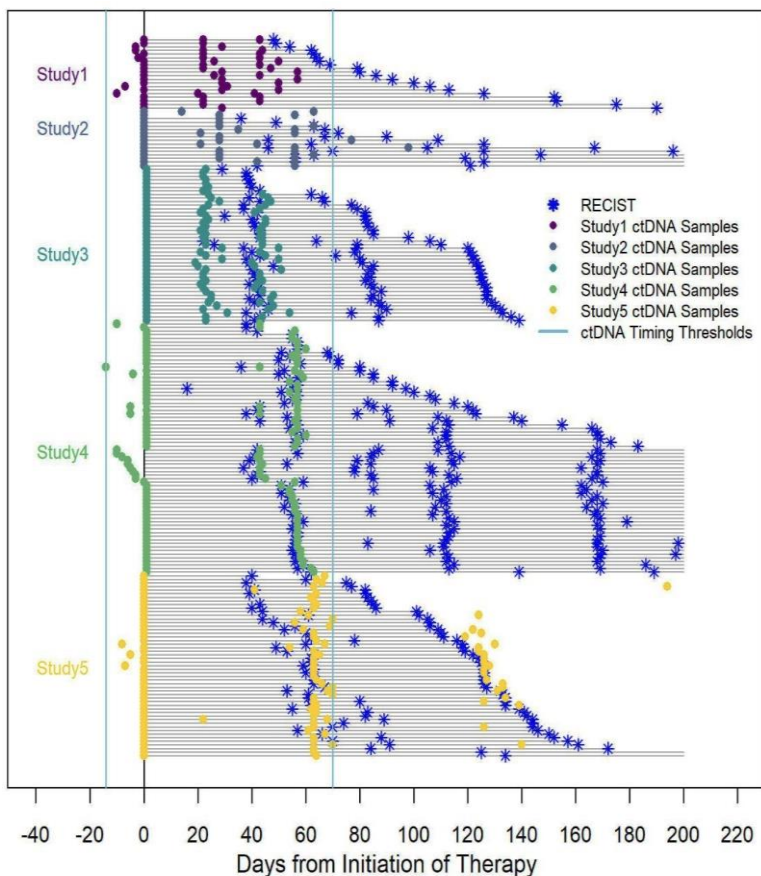
Why Is This Important? The ctMoniTR Project will validate whether ctDNA can be used as a biomarker to easily and more rapidly determine whether a drug is working. By getting this information quickly and in a less invasive way, physicians and patients will understand if the treatment is working or if they should change treatments. This will accelerate research by enabling quicker identification of new treatments that show a rapid anti-tumor effect and generate needed evidence for determining the role of ctDNA as a potential surrogate biomarker.

Who Is Involved? Friends is proud to partner with Agilent Technologies, Inc., AstraZeneca, Bayer, Biodesix, Boehringer Ingelheim, Bristol Myers Squibb, Cancer Research And Biostatistics (CRAB), EMD Serono, Inc., US Food and Drug Administration (FDA), Foundation Medicine, Inc., Genentech, Inc., Guardant Health, Inc., Illumina, Inc., Johns Hopkins University, Lilly Oncology, Merck & Co., Inc., Molecular Characterization Laboratory (MoCha) at Frederick National Laboratory, Memorial Sloan Kettering Cancer Center, Natera, Inc., NMD Group LLC., Novartis AG, Penn Medicine, Pfizer, Inc., Princess Margaret Cancer Centre, Regeneron Pharmaceuticals, Inc., Resolution Bioscience, Inc., Roche Diagnostics, Takeda Pharmaceutical Company.

Disparate Datasets Can Be Harmonized Through Statistical Methods

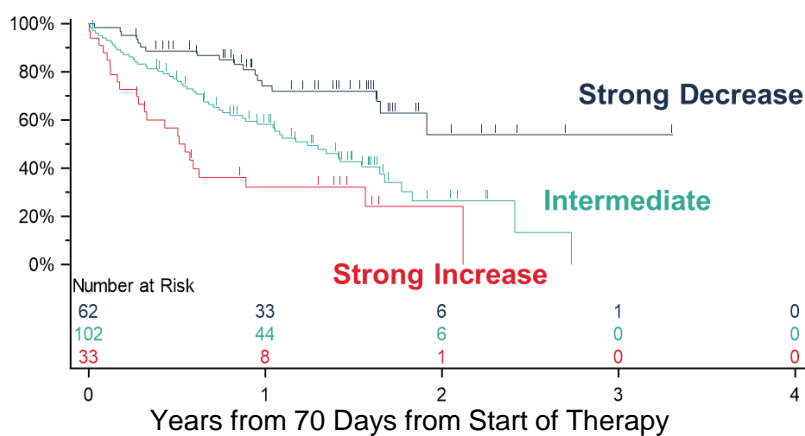
- Created tools and protocols for streamlining the evaluation of compatibility across patient-level ctDNA datasets
- Designed harmonization strategies to overcome challenges inherent to ctDNA datasets, including variability in data stratification and definitions, study-specific thresholds, and data transformation
- Successfully demonstrated the feasibility of aggregating clinical datasets from disparate sources

Timing of Tumor Response and ctDNA Samples in the Pooled Dataset of Patients with NSCLC treated with Anti-PD-(L)1



Consistent Association Between Reductions in ctDNA and Improved Treatment Outcomes

Overall Survival by ctDNA Max VAF 3-Level Change Groups in Patients With Anti-PD-(L)1 treated NSCLC



Log-rank Pairwise p-value	Decrease	Intermediate	Increase
Decrease	-		
Intermediate	<0.001	-	
Increase	<0.001	0.014	-

- Reductions in ctDNA are strongly associated with better clinical outcomes across multiple measures, including:
 - Overall Survival
 - Progression-Free Survival (PFS)
 - Durable Clinical Benefit (PFS ≥ 6 months)
 - Patient Response defined as partial response or better
- Baseline ctDNA levels alone were not predictive of clinical outcomes

Strength of Association Remains After Accounting for Clinical Covariates

- Associations remained even after accounting for cohort-specific differences and other clinical covariates, such as:
 - Demographics (age, sex & race)
 - Clinical (disease stage, histology, prior therapies, PD-L1 levels)
 - Smoking status

Step 2 and Beyond: Step 2 will generate evidence that will demonstrate whether the association between changes in ctDNA and treatment outcomes is observed in additional treatment settings and explore how early changes in ctDNA could predict response to treatment. *Friends* is also actively exploring the possibility of a harmonization effort in early-stage disease.

For more information about this exciting collaboration, please visit www.focr.org/ctDNA.