FRIENDS of CANCER RESEARCH

Establishing Evidence: New Advancements Using ctDNA

A critical component of oncology clinical trials is evaluating the efficacy of new therapies and identifying which patients respond to therapy. A variety of endpoints are leveraged for measuring treatment efficacy, such as overall survival and progression-free survival. As the magnitude of benefit continues to improve with the advent of new therapies, clinical trials may take longer to assess efficacy based on currently available endpoints. Early endpoints that are reasonably likely to predict clinical benefit, such as response rate based on radiographic imaging, are used to evaluate treatment efficacy earlier than measuring overall survival. There is a need to identify, evaluate, and validate additional novel endpoints to assess efficacy earlier in the course of treatment that are predictive of long-term outcomes.

Circulating tumor DNA (ctDNA) is an emerging, new biomarker that can identify patients who respond to therapies by evaluating the presence and levels of ctDNA in a simple blood draw. Because of emerging data and growing excitement in the field, the U.S. Food and Drug Administration (FDA) released a draft guidance document that highlights the potential use of ctDNA as an early endpoint and emphasizes where additional evidence is needed for validation.[1]

Project Overview

Recognizing the potential value of ctDNA as a novel endpoint in oncology drug development and the need for collaboration, Friends of Cancer Research (*Friends*) launched a unique multi-stakeholder research partnership to generate evidence and determine whether changes in ctDNA associate with long-term outcomes for patients with cancer on treatment. By combining efforts and aggregating data across multiple clinical trials, we will be able to generate the evidence necessary to characterize ctDNA as an indicator of response faster than if any single organization tried to do so alone. The ctDNA for Monitoring Treatment Response (ctMoniTR) Project is designed to answer the important question: Do changes in ctDNA reflect response to treatment? The ctMoniTR Project is taking a stepwise approach to analyze data across multiple trials to evaluate associations between changes in ctDNA and patient outcomes **(Figure 1)**.

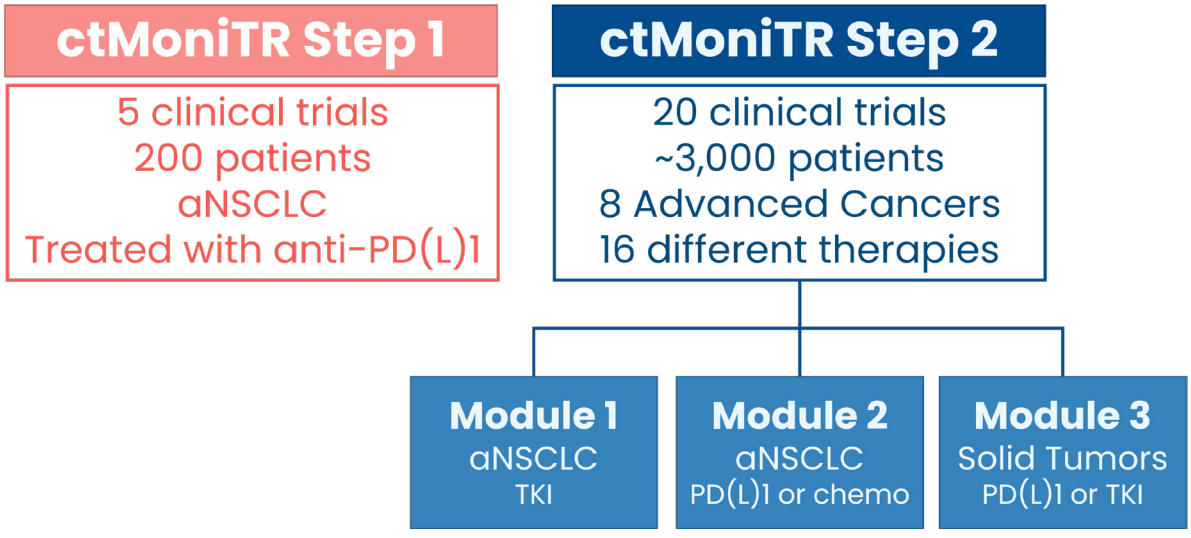

Figure 1. Overview of the ctMoniTR Project.

Findings from Step 1 showed robust and consistent associations between changes in ctDNA and patient outcomes for patients with advanced NSCLC (aNSCLC) receiving immunotherapy.[2] Step 2 of the ctMoniTR Project expands the scope of this research to study the associations between ctDNA and clinical outcomes across several clinical settings, drug classes, and cancer types. Data will be released throughout 2023 and 2024.

In addition to evaluating the use of ctDNA as an early endpoint, it is important to understand the impact assay technology and tumor biology may have on the use of ctDNA in oncology drug development. To establish evidence regarding baseline sensitivity metrics for ctDNA detection across cancer types, stages, and assays, *Friends* initiated a collaborative effort involving multiple diagnostic test developers called the Baseline ctDNA Project. A descriptive meta-analysis will be performed to compare trends in baseline ctDNA levels (ctDNA levels prior to a current cancer treatment) between cancer types and stages **(Figure 2)**. A greater understanding of the biological landscape of baseline ctDNA levels will inform a conceptual framework for the use of ctDNA as an early endpoint predictive of long-term outcomes.

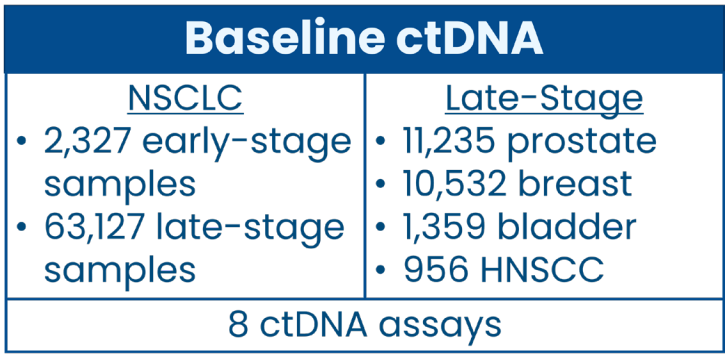

Figure 2. Overview of the Baseline ctDNA Project.

Moving Forward

Both of these projects fill important data gaps outlined in an evidentiary roadmap created by key stakeholders to advance the use of ctDNA as an early endpoint.[3] At the July 11th meeting "Establishing Evidence: New Advancements Using ctDNA" new data and insights will be shared regarding the use of ctDNA in oncology drug development, which will support ongoing research and regulatory discussions around its use as an early endpoint for regulatory processes.

Citations

1. FDA Draft Guidance Document. Use of Circulating Tumor Deoxyribonucleic Acid for Early-Stage Solid Tumor Drug Development. https://www.fda.gov/media/158072/download. (Accessed 6/20/23).
2. Vega D., et al. Changes in Circulating Tumor DNA Reflect Clinical Benefit Across Multiple Studies of Patients With Non–Small-Cell Lung Cancer Treated With Immune Checkpoint Inhibitors. JCO Precis Oncol. 2022 Aug;6:e2100372.
3. Friends of Cancer Research White Paper. Circulating Tumor DNA in Development of Therapies for Cancer: An Evidentiary Roadmap to an Early Endpoint for Regulatory Decision-Making. https://friendsofcancerresearch.org/wp-content/uploads/Circulating_Tumor_DNA_in_Development_of_Therapies_for_Cancer-Evidentiary_Roadmap.pdf