FRIENDS of CANCER RESEARCH

ctDNA Portfolio Development and Milestones

Goal

ctDNA holds promise for measuring treatment efficacy in clinical trials. Friends of Cancer Research (*Friends*) is working to establish an aligned strategy for developing the necessary data to support the use of ctDNA as an early endpoint for treatment response for regulatory decsion-making and leading a multi-stakeholder group to generate this data. Validating the use of ctDNA as an endpoint will accelerate research by enabling rapid identification of effective new cancer therapies and ultimately allow them to reach patients sooner.

Background

The introduction of novel therapeutics, especially targeted therapies, has changed the paradigm for treating solid tumors. While these new therapies provide increased clinical benefit for patients, the concomitant increase in survival time creates a unique challenge in the expedient evaluation of new therapies. Traditional clinical trial designs using long-term clinical outcome endpoints such as progression-free survival (PFS) or overall survival (OS) may not allow for an efficacy determination in a timely manner. The use of ctDNA levels as an early endpoint represents an emerging opportunity to assess efficacy earlier. However, it is critical to obtain robust data to fully qualify and validate ctDNA as an early endpoint for long-term clinical outcomes in solid tumors.

Approach

Establishing the necessary evidence to support the use of ctDNA as an early endpoint requires a multiprong approach:

- **ctDNA Evidentiary Roadmap:** In 2022, *Friends* coordinated a group of stakeholders to develop an aligned strategy for generating data and evidence. Findings demonstrate there are multiple technical and clinical characteristics contributing to variability in ctDNA measurements that should be adequately accounted for when conducting validation studies.
- **The ctDNA to Monitor Treatment Response (ctMoniTR) Project:** This first of its kind partnership seeks to answer the important question: Do changes in ctDNA reflect response to treatment? Step 1 of the project kicked off in early 2019 and included data from 5 clinical trials representing 200 patients with advanced non-small cell lung cancer treated with PD(L)-1 inhibitors. *Friends* worked with stakeholders to establish and implement an analysis approach conducted by Cancer Research And Biostatistics (CRAB). Findings from the study published in the summer of 2022 demonstrate that changes in ctDNA levels associate with treatment outcomes: increases in ctDNA levels associate with poor outcomes while decreases in ctDNA associate with better outcomes. Step 1 showed that harmonizing data across trials with different assays and time points is feasible and set the stage for the ongoing Step 2 project, which expands the approach to rather than into more patients, trials, additional cancer types, and treatments.
- **Baseline ctDNA Levels Project:** Findings from the ctDNA Evidentiary Roadmap highlight a need to evaluate the landscape of ctDNA detection in different cancer types and stages to provide insights into the extent to which findings can be generalized across early- and late-stage cancer settings, as well as across assay technologies. Through a collaborative effort involving multiple diagnostic developers, *Friends* seeks to establish evidence regarding baseline (i.e., pre-treatment) sensitivity metrics for ctDNA detection across cancer types, stages, and assays. This greater understanding of the biological landscape of baseline ctDNA levels will help inform a conceptual framework for the use of ctDNA as an early endpoint predictive of long-term outcomes.

Findings from our continued work in this space will be consolidated and presented in public meetings and peer-reviewed literature in the future. Our hope is that ctDNA will ultimately be used to support regulatory decisions to provide safe and effective treatments to patients faster.