Exploring the use of ctDNA for Monitoring Treatment Response:

The Friends of Cancer Research ctMoniTR Project

Jeff Allen, PhD
President & CEO

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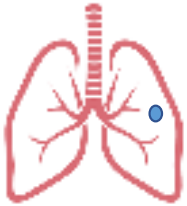
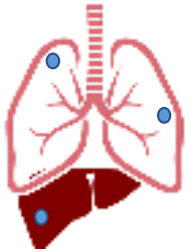
Potential applications of ctDNA assays and regulatory considerations

LOW BURDEN OF DISEASE



Early Detection/ Screening	Molecular Profiling/ Prognostication	Residual Disease Detection	Assess Response	Monitoring tumor evolution
• Differentiate normal/ pathogenic in healthy people • Detection thresholds must be sensitive to find low levels of tumor DNA • Identify tumor of origin • Detect favorable tumors with more benign course from aggressive tumors	• Detection of prognostic biomarkers to reliably identify high risk patients • Detection of targetable variants if tissue limited/difficult to access	• Detect low amount of residual ctDNA that is specific to tumor • Enrichment clinical trials • Potential to correlate with long term outcome	• Follow levels of ctDNA over time that correlate with early PD prior to detection by traditional imaging modalities • Consider qualitative or quantitative assays • Potential to correlate with long term outcome	• Concordance ctDNA levels with increasing burden of disease • Monitoring clonal evolution for drug targets

HIGH BURDEN OF DISEASE



Adapted from Narayan et al., Oncologist 2020

ctDNA as a monitoring tool for early treatment response

- Use of ctDNA to monitor response provides new opportunities and a timely area of investigation
  - Rapid turn-around time, less-invasive method
  - Allow for earlier identification of response – support for go/no-go decisions, patient selection, regulatory use as an intermediate/surrogate endpoint
- Challenges
  - Variability in the way ctDNA assessment has been designed into clinical trials
  - Different collection methods
  - Difference on how ctDNA changes are reported by different ctDNA assays
- What evidence needs to be established to answer the question:

Do changes in ctDNA levels accurately reflect the therapeutic effect of cancer therapies?

ctMoniTR Project
Step 1 Objectives and Milestones

1. Investigate the feasibility of harmonizing ctDNA data measured from different assays using different collection schedules
2. Align on a methodology to combine clinical data from multiple trials in lung cancer
3. Characterize associations between ctDNA values and tumor response

Can trends observed in smaller independent datasets be replicated in a larger combined dataset?

ctMoniTR Project

Workflow	Step 1	Step 2	Early-Stage Disease
Goals	• Aligned on a methodology to combine data from multiple trials in lung cancer • Harmonized ctDNA data measured from different assays using different collection schedules • Manuscript forthcoming	• Update Step 1 methodology for combining data to account for additional treatment settings and tumor types • Harmonize ctDNA data from various uniformly collected datasets • Validate Step 1 findings	• 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
Approach	• Advanced stage NSCLC treated with PD-(L)1 inhibitors • Previously collected data from clinical trial and observational cohort studies	• Advanced solid tumors treated with PD-(L)1 inhibitors or TKI • Previously collected data from clinical trial and observational cohort studies	• Next Steps: Inventory of data availability in solid tumors • Previously collected data from clinical trial and observational cohort studies

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ctMoniTR Step 1 Project Participants

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- Diana Merino Vega
- Mark Stewart
- Jeff Allen
- Hillary Stires

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- Margi Sheth
- Lingmin Zeng

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- George Green
- Anthony Jarkowski
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- Mark Sausen
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- Rob Scharpf
- James White

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- Julie Kobie
- Carol Pena
- Eric Rubin
- Alex Snyder

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- Alex Lovejoy
- Maximilian Schmid

GRAIL
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GUARDANT
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- Katie Quinn

CRAB
- Antje Hoering
- Katie Nishimura
- Vanessa Cilento
- Adam Rosenthal
- Matt Scott

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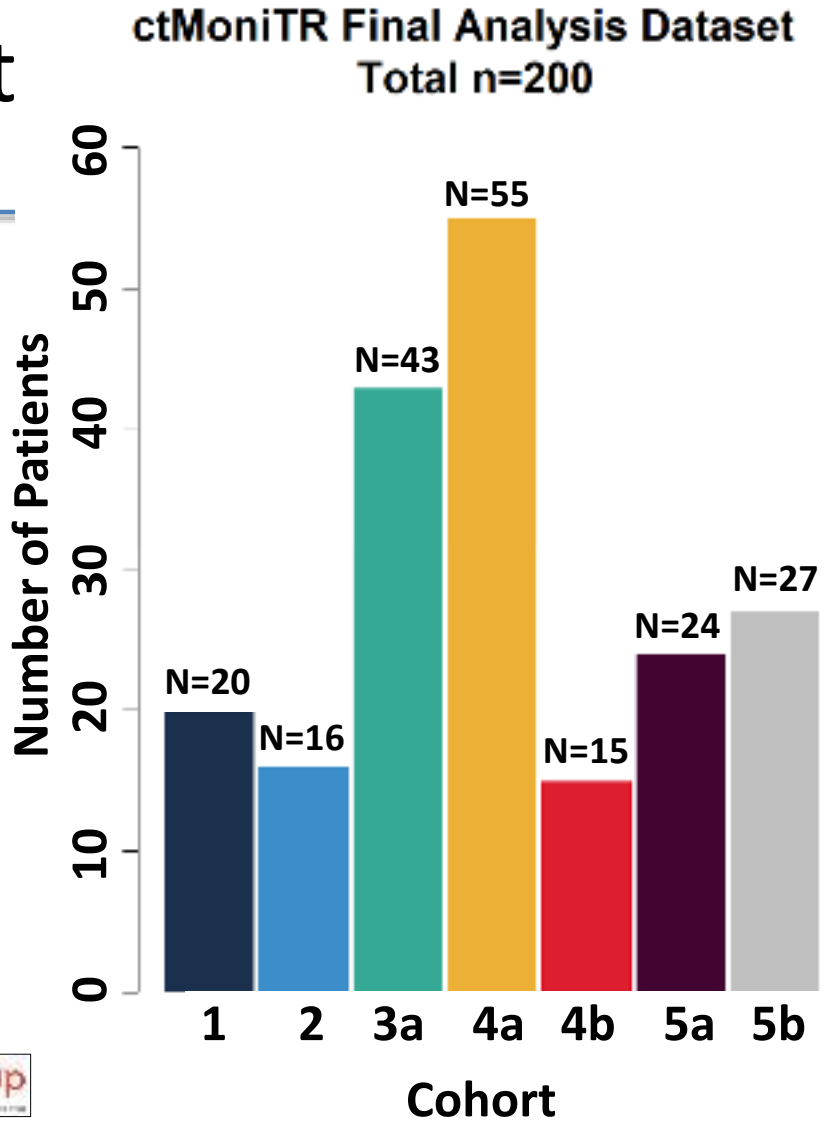
Analysis Dataset

Study population:

- Available data (previously published, already collected)
- Patients with advanced NSCLC
- Treated with anti-PD-(L)1 therapy (plus control arm, if Randomized Controlled Trial "RCT")
- Must have tumor response evaluation, and OS/PFS data
- ctDNA measurements (VAF) at baseline, plus 1 or more follow-up samples



ctMoniTR Project Step 1 Objectives and Milestones

Study population:

- Available data (previously published, already collected, individual level)
- Patients with advanced NSCLC
- Treated with anti-PD-(L)1 therapy (plus control arm, if trial was randomized)
- Must have tumor response evaluation, and OS/PFS data
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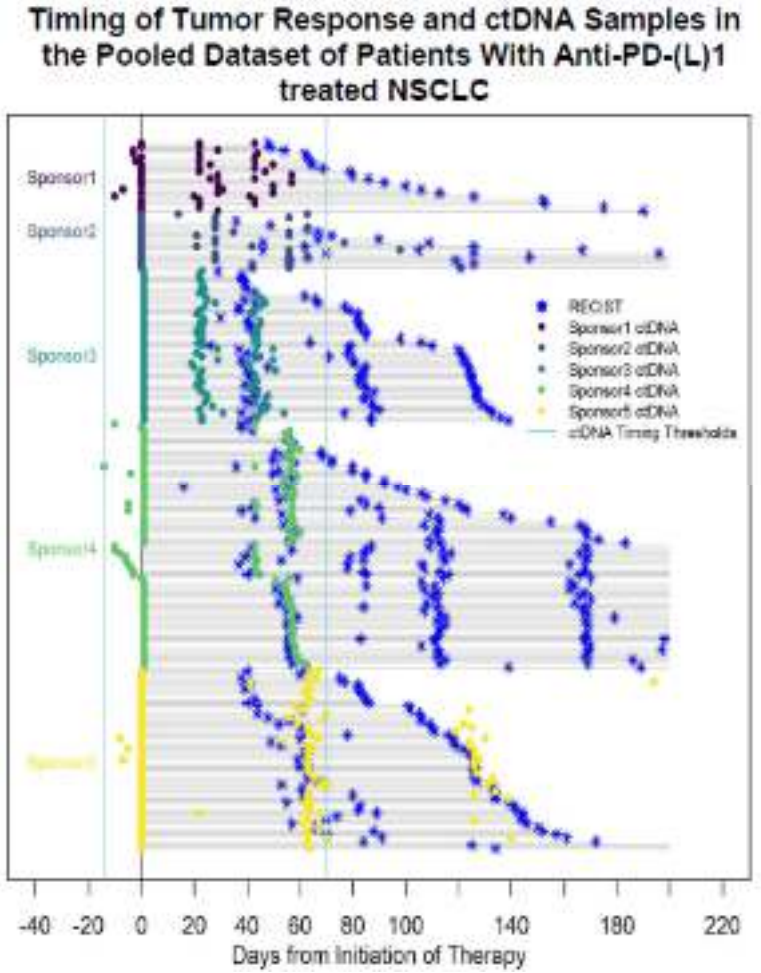
Can trends observed in smaller independent datasets be replicated in a larger combined dataset?

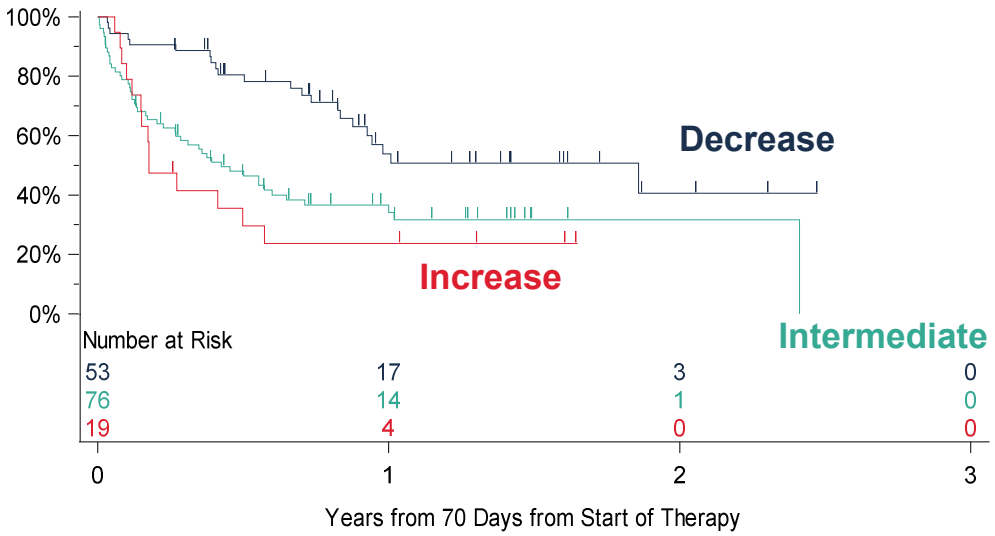


Inconsistent Timing of ctDNA Sampling

Different Number of ctDNA Samples per Patient

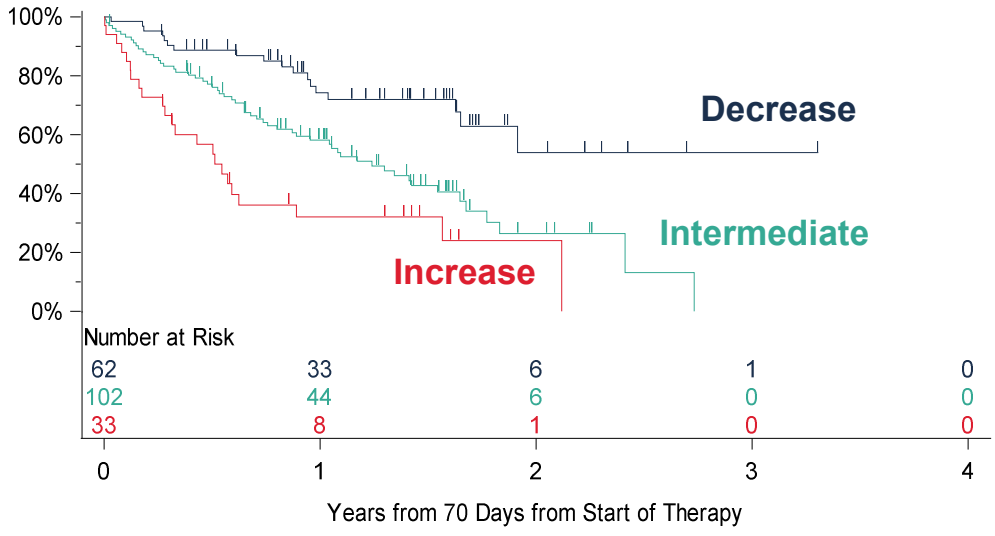
Robust Association Observed Between Strong Decreases in ctDNA and Patient Survival

Progression-Free Survival by Max VAF*



Log-rank Pairwise p-value	Decrease	Intermediate	Increase
Decrease	-		
Intermediate	**0.001**	-	
Increase	**<0.001**	0.426	-

Overall Survival by Max VAF



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

Survival Outcomes (3-Level)

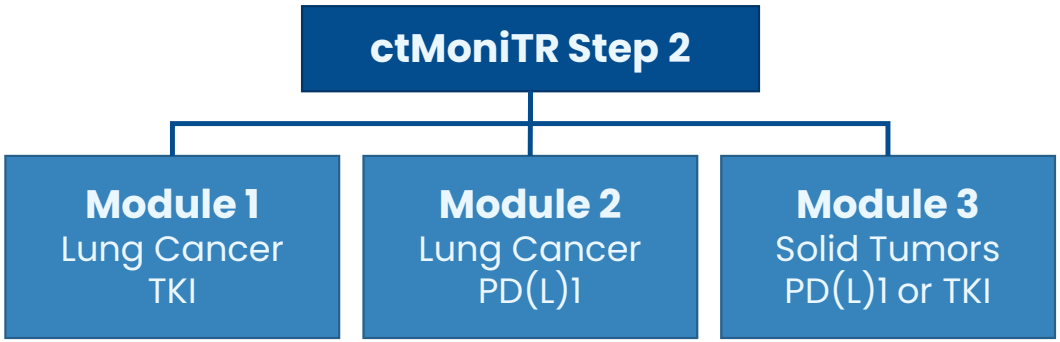
Kaplan-Meier Curves

*Note: patients with progression within 70 days were excluded from the PFS plots.

ctMoniTR Step 2 Project Overview

Objectives:

- Determine how long after treatment initiation can we detect an association between changes in ctDNA and clinical response
- Explore the extent to which ctDNA can complement RECIST
- Characterize whether changes in ctDNA are a prognostic indicator
- Examine ctDNA as a potential drug development tool or intermediate endpoint



22 clinical trials
3,000 patients
8 tumor types
16 different therapies

Provides an opportunity for generalizability but also represents a challenge in terms of complexity

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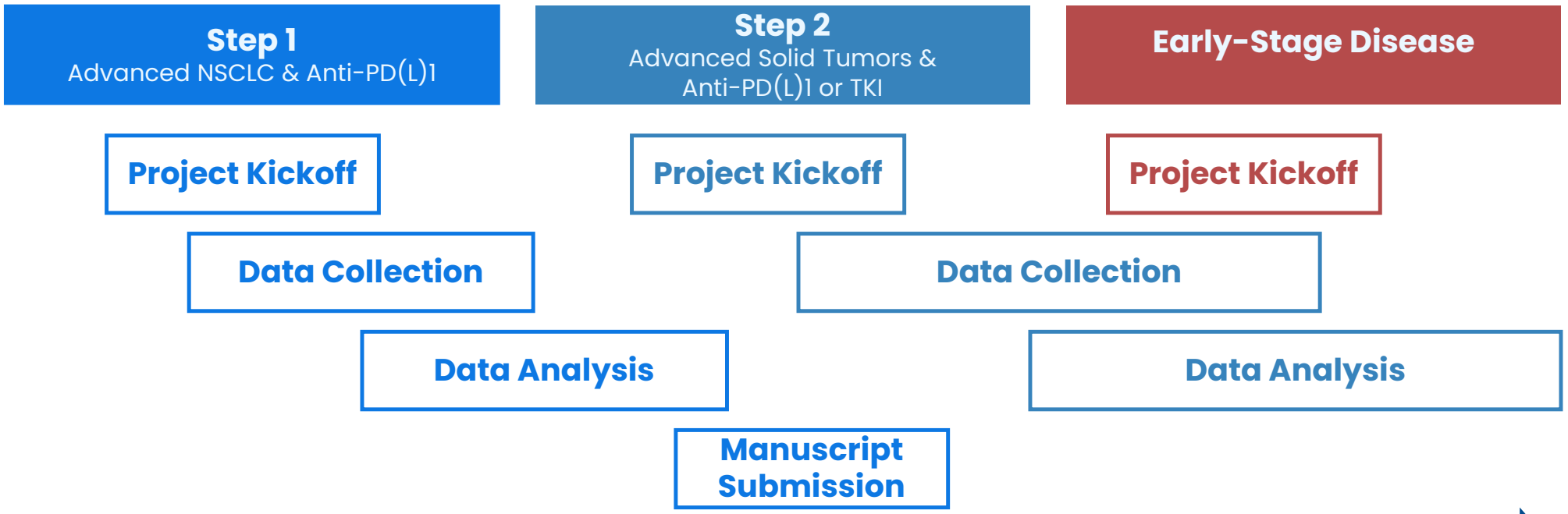
ctMoniTR Project Timeline



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- Pfizer, Inc.,
- Princess Margaret Cancer Centre
- Regeneron Pharmaceuticals Inc.
- Resolution Bioscience, Inc.
- Takeda Pharmaceutical Company