



The ctMoniTR Project

Nevine Zariffa

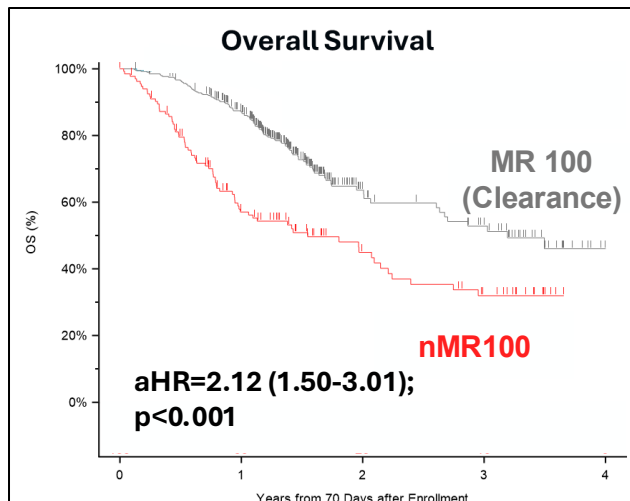
NMD Group

On behalf of the ctMoniTR Project Working Group

General Approach for Endpoint Validation

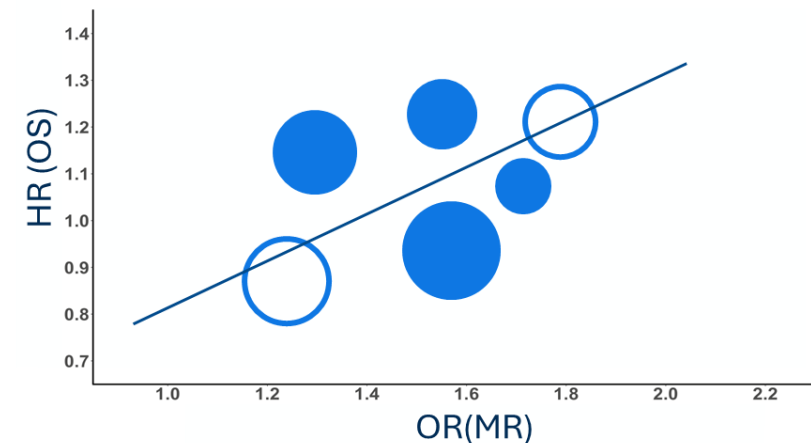
I-association

Individual-level association between the early endpoint (e.g., change in ctDNA levels - MR) and the true endpoint (e.g., OS)



T-association

Trial-level association between *the effect of treatment* on the early endpoint (e.g., OR using ctDNA MR) and *the effect of treatment* on the true endpoint (e.g., HR using OS)



Output

HR of MR vs. nMR

R² comparing OR(MR) to HR(OS)

Interpretation

Magnitude of HR and p-value (<0.05)

Close to 1 (how close is close enough?)

The ctMoniTR Project

The ctDNA for Monitoring Treatment Response Project

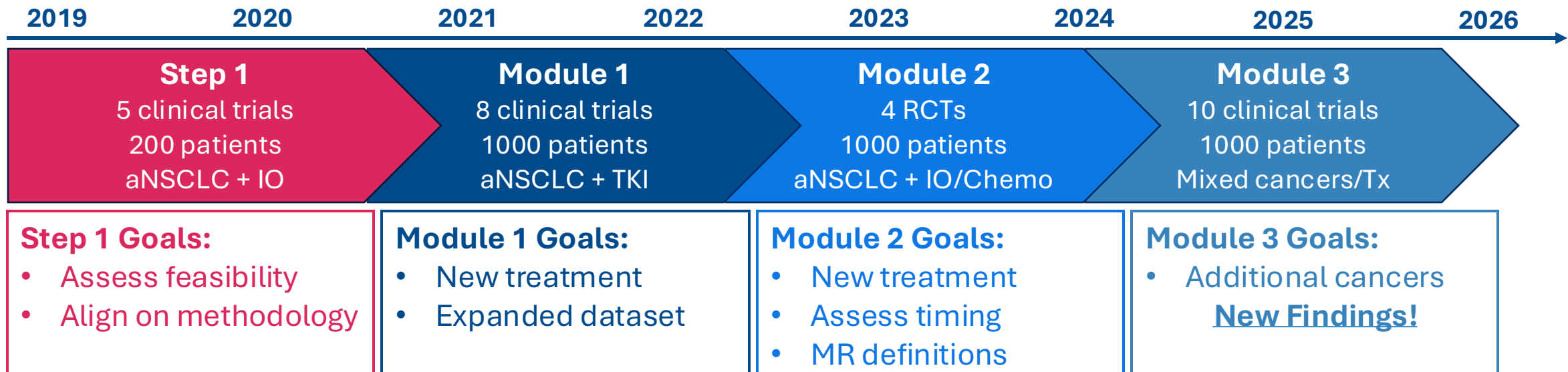
Goals

- Build foundational evidence to support the use of changes in ctDNA levels as an early endpoint for regulatory decision-making
- Aggregate data from >20 previously completed clinical trials in advanced cancer that assess ctDNA and overall survival

The ctMoniTR Project

Friends Aggregates Data Across Clinical Trials

We organized the data into “Steps/Modules” based on disease setting



Decreased ctDNA Levels are Associated with Improved OS

I-associations
Individual-level
analyses

FRIENDS
of CANCER
RESEARCH

Step 1

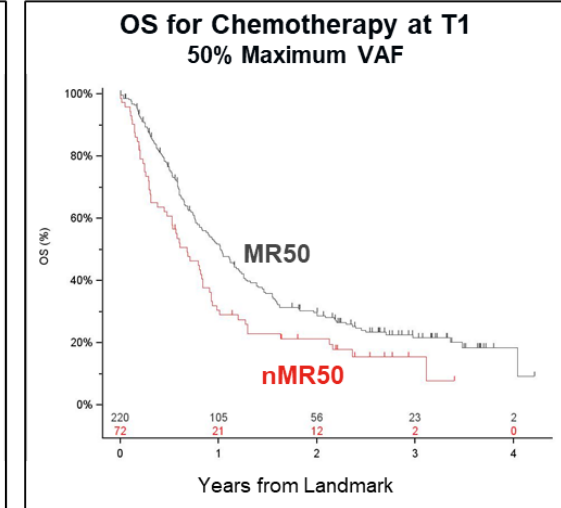
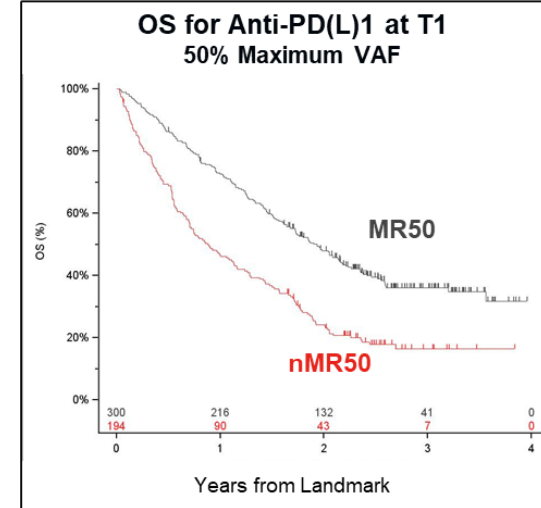
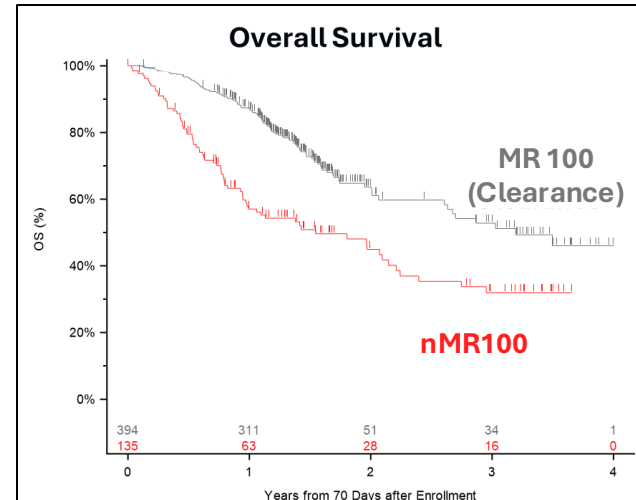
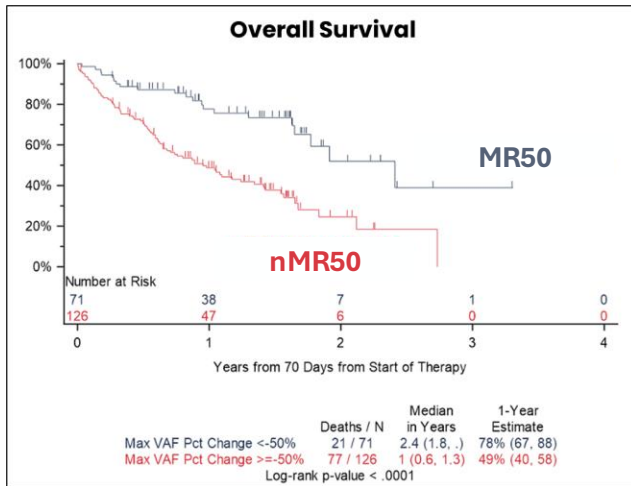
5 clinical trials
200 patients
aNSCLC + IO

Module 1

8 clinical trials
1000 patients
aNSCLC + TKI

Module 2

4 RCTs
1000 patients
aNSCLC + IO/Chemo



Using 50% decrease to define MR, MR is associated with improved OS (aHR=2.98 [1.81-4.90]; p<0.001).
Vega et al. 2022 JCOPO

Using clearance to define MR, MR is associated with improved OS (aHR=2.12 [1.50-3.01]; p<0.001).
Andrews et al. 2025 CCR

Using 50% decrease to define MR, MR is associated with improved OS for IO treated (aHR=1.99 [1.57-2.50]; p<0.001) and chemotherapy treated patients (aHR=1.58 [1.14-2.19]; p=0.006).
Andrews et al. 2025 JITC

Module 3 – Analysis Plan

Goal: Combine non-lung cancer data into a single analysis.

I-associations
Individual-level analyses

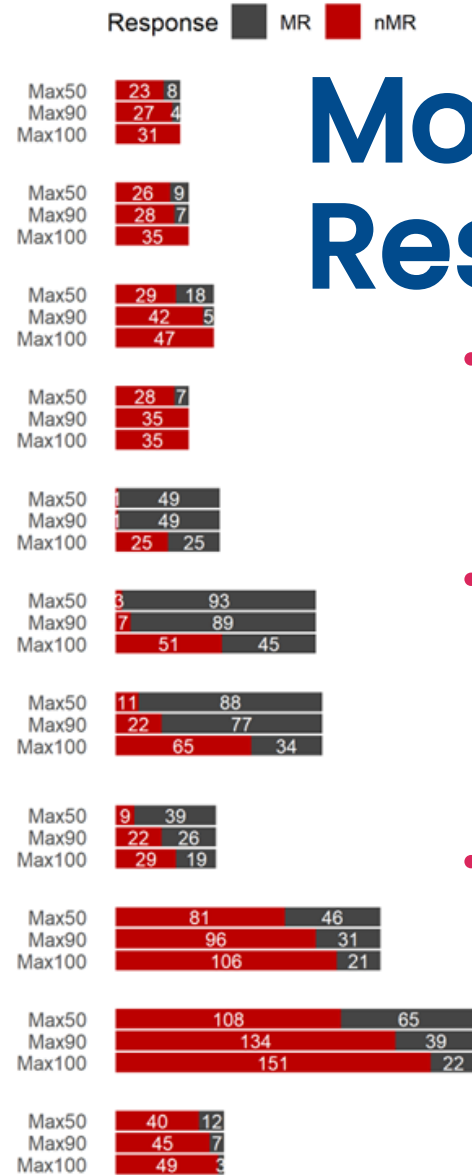
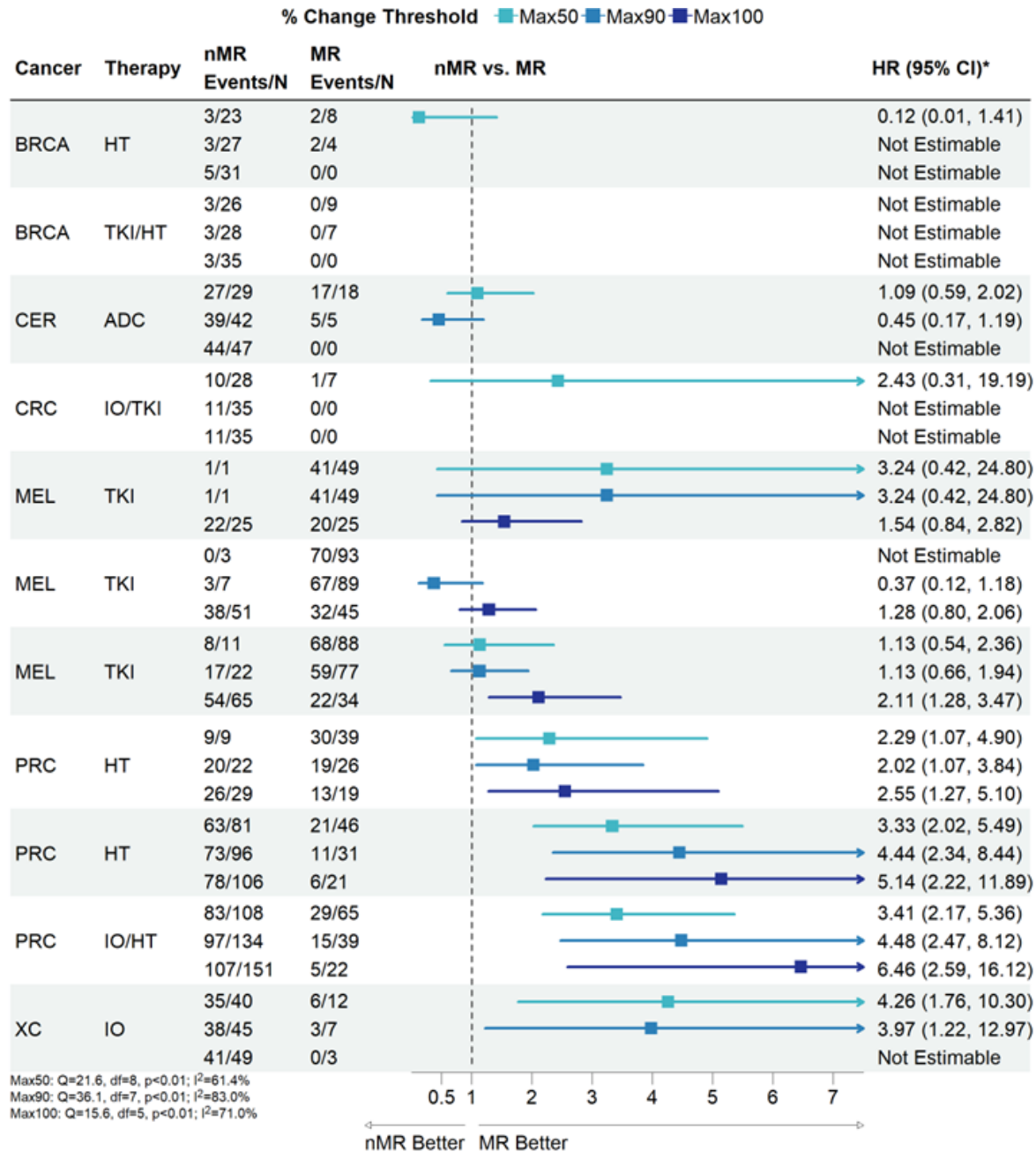
Clinical Trials

Cancer Type	Treatment	Study Design	ctDNA sampling (wks from baseline)	ctDNA Measurement
Breast Cancer	TKI	RCT	0, 8	VAF
Cervical Cancer	Other	Single Arm	0, 3, 9	VAF and ctFE
Colorectal Cancer	TKI / IO	Single Arm	0, 1, 4, 5	VAF
Melanoma	TKI / IO	RCT	0, 4, 8	VAF
Melanoma	TKI	RCT	0, 4	VAF
Melanoma	TKI	Single Arm	0, 4, 8	VAF
Multiple	IO	Single Arm	0, 6	VAF and MTM/ml
Prostate Cancer	Other	Single Arm	0, 4	TF and VAF
Prostate Cancer	IO / Other	RCT	0, 6	TF

Dataset lacks consistency – analyzed all in a Forest Plot rather than by using a Cox model

- For ctDNA: Use Max VAF; T1 = 21-70 days after index; use “best” if multiple measurements
- Assess MR cutoff = 50%, 90%, and 100% clearance

Module 3 – Results



- Tend to see that **decreased ctDNA is associated with improved OS**
- Small sample sizes and lack of replication for treatment and tumor types **make interpretation challenging**
- **We need more analyses** like this – more patients, treatments, and cancers

*Some estimates may be unreliable due to small sample sizes or limited number of events.

Aggregate Analyses on All RCTs

Module	Disease	Treatment Class (n*)	Control Class (n*)	3rd Arm Class (n*)	Assay
M1	NSCLC	TKI (200)	Chemotherapy (50)	N/A	ddPCR
M1	NSCLC	TKI (200)	TKI (200)	N/A	ddPCR
M1	NSCLC	TKI (100)	TKI (100)	N/A	NGS
M2	NSCLC	IO (350)	Chemotherapy (350)	N/A	NGS
M2	NSCLC	IO (250)	Chemotherapy (250)	IO (250)	NGS
M2	NSCLC	IO (50)	Chemotherapy (50)	N/A	NGS
M2	NSCLC	IO (150)	Chemotherapy (150)	IO + Chemo (150)	NGS
M3	Breast Cancer	TKI + Chemo + Other (100)	Chemo + Other (100)	N/A	NGS
M3	Melanoma	TKI (400)	TKI (400)	N/A	ddPCR
M3	Prostate Cancer	IO + Other (400)	Other (400)	N/A	NGS

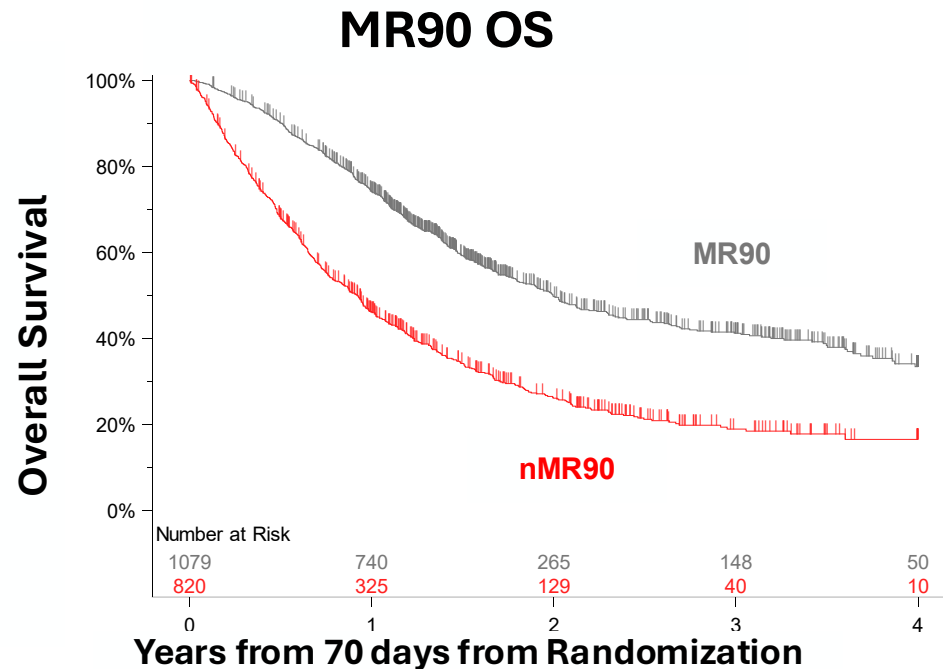
*Sample sizes are approximate.

Select these trials to perform T-association analyses

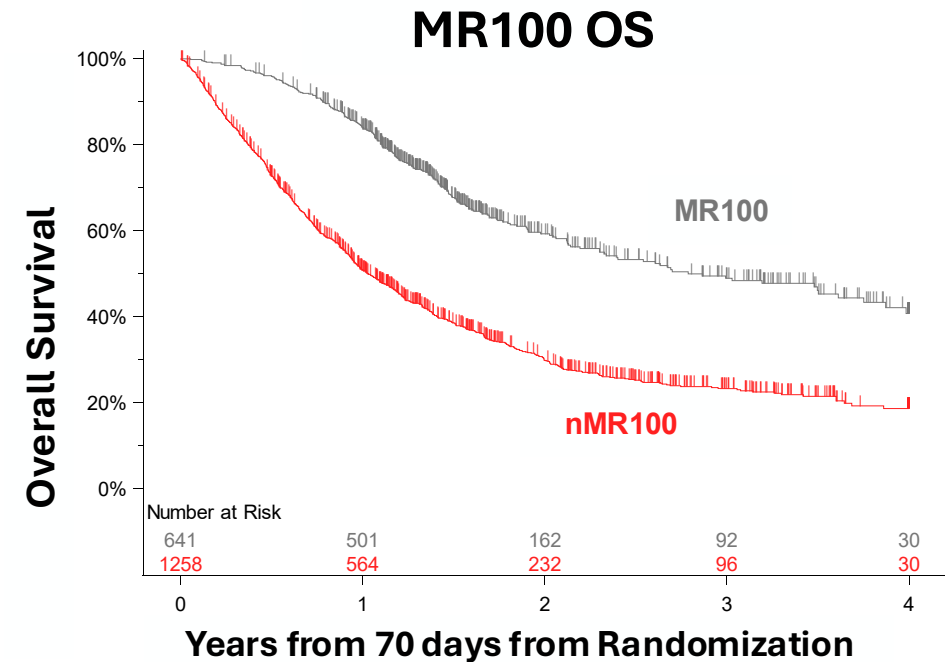
Aggregate Analyses on All RCTs

I-associations
Individual-level analyses

FRIENDS
of CANCER
RESEARCH



aHR (95% CI) = 1.96 (1.71, 2.26), p<0.0001



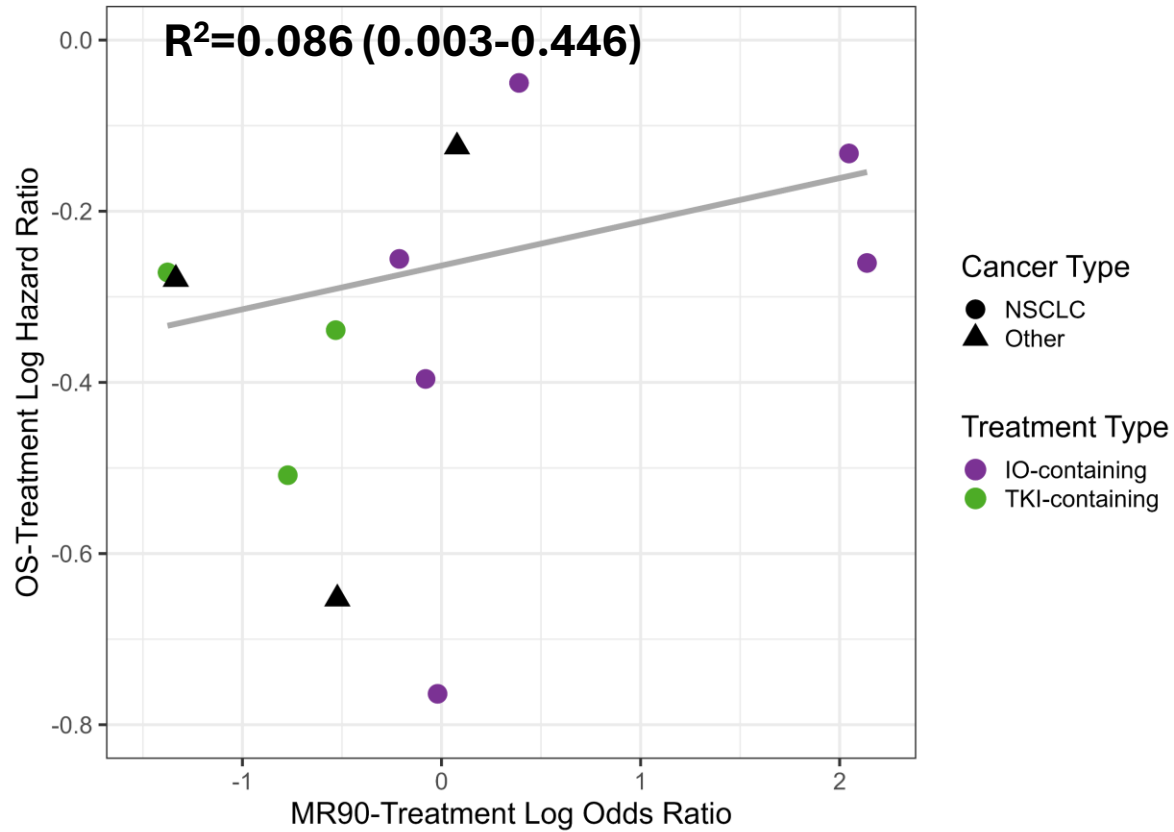
aHR (95% CI) = 2.20 (1.87, 2.59), p<0.0001

Across cancer types and treatments, individual-level analyses demonstrate that decreases in ctDNA levels are associated with improved OS

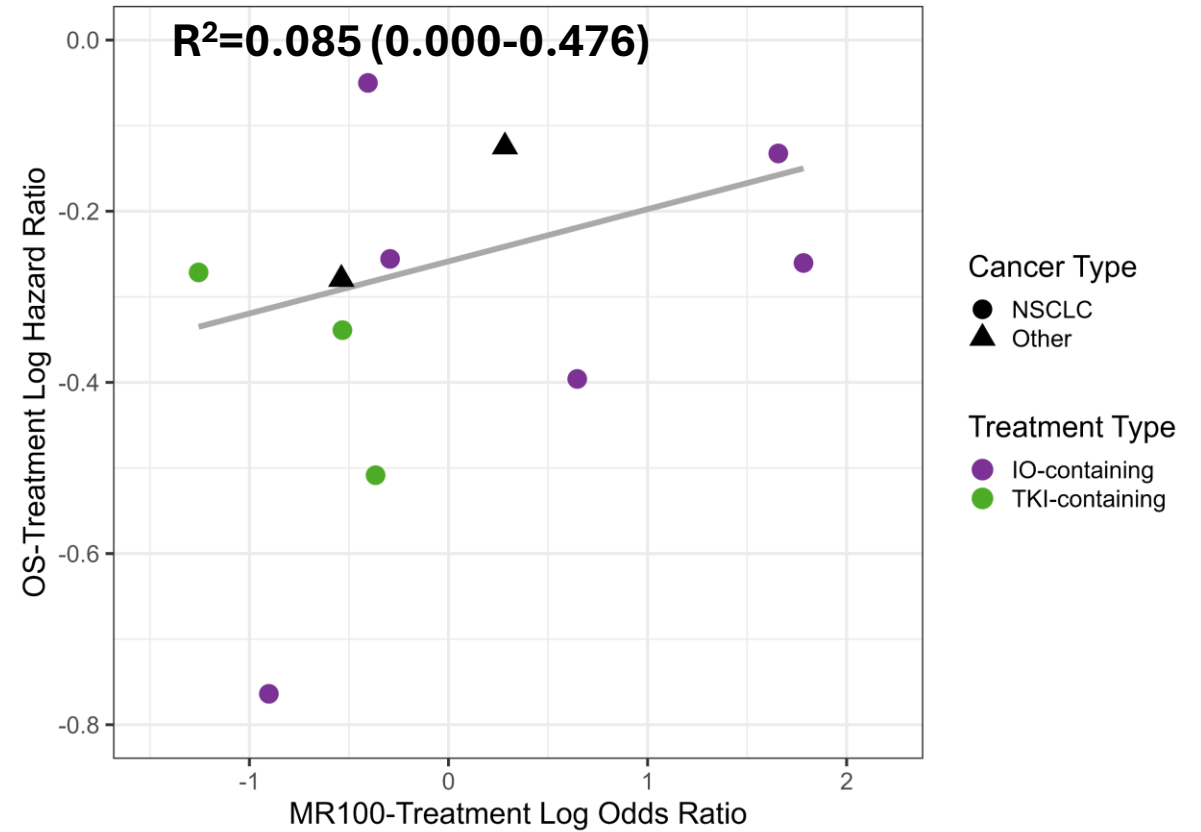
Aggregate Analyses on All RCTs

T-associations
*Trial-level
analyses*

OS vs. MR90



OS vs. MR100



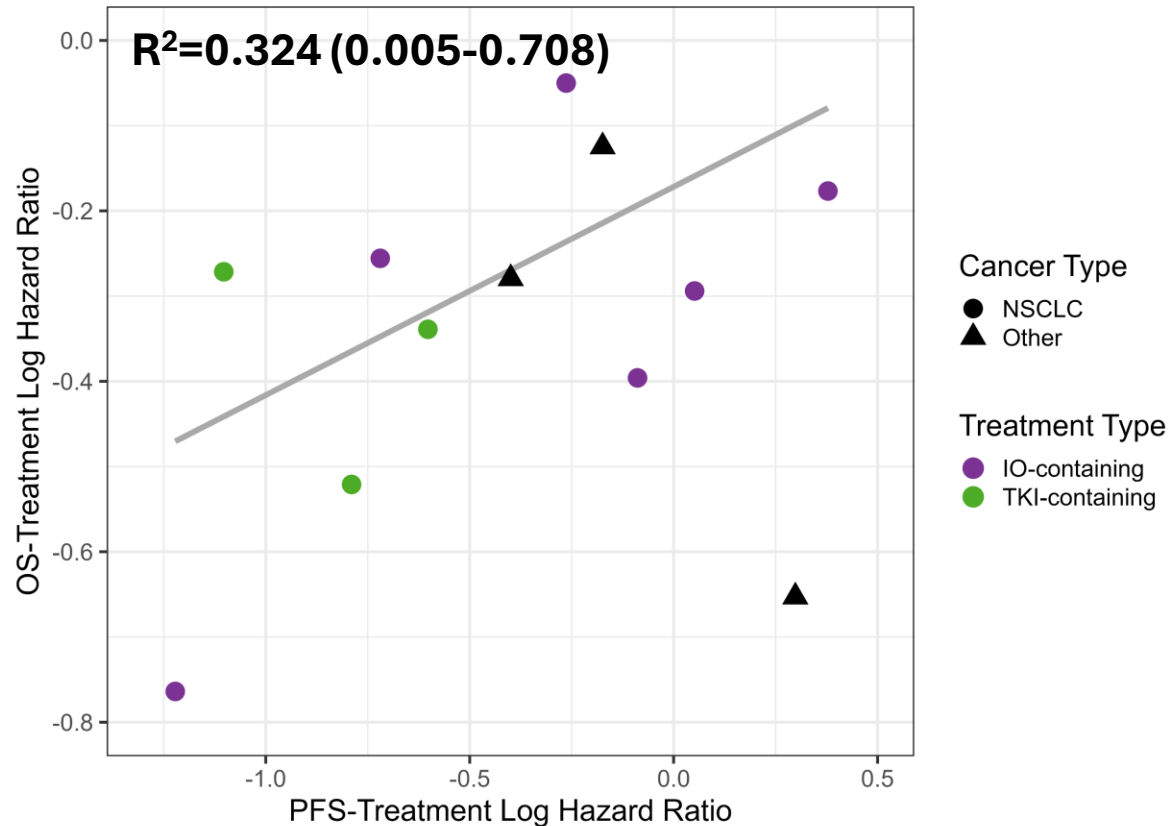
T-associations are low for MR with OS

Aggregate Analyses on All RCTs

T-associations
*Patient-level
analyses*

FRIENDS
of CANCER
RESEARCH

OS vs. PFS



Why might we see low correlations?

Analysis approach:

- Combined treatments and cancer types
- Few studies
- Outliers

Trial design:

- Crossover

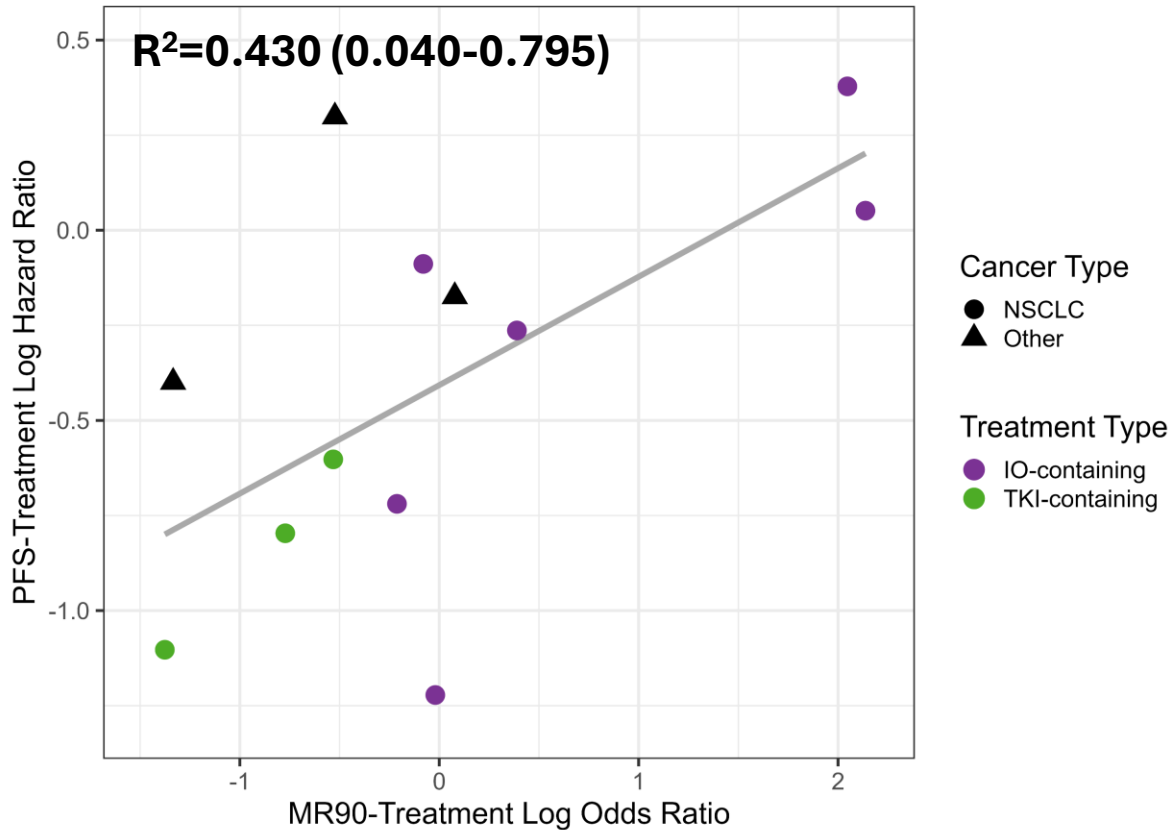
**T-associations are also low for
PFS with OS**

Aggregate Analyses on All RCTs

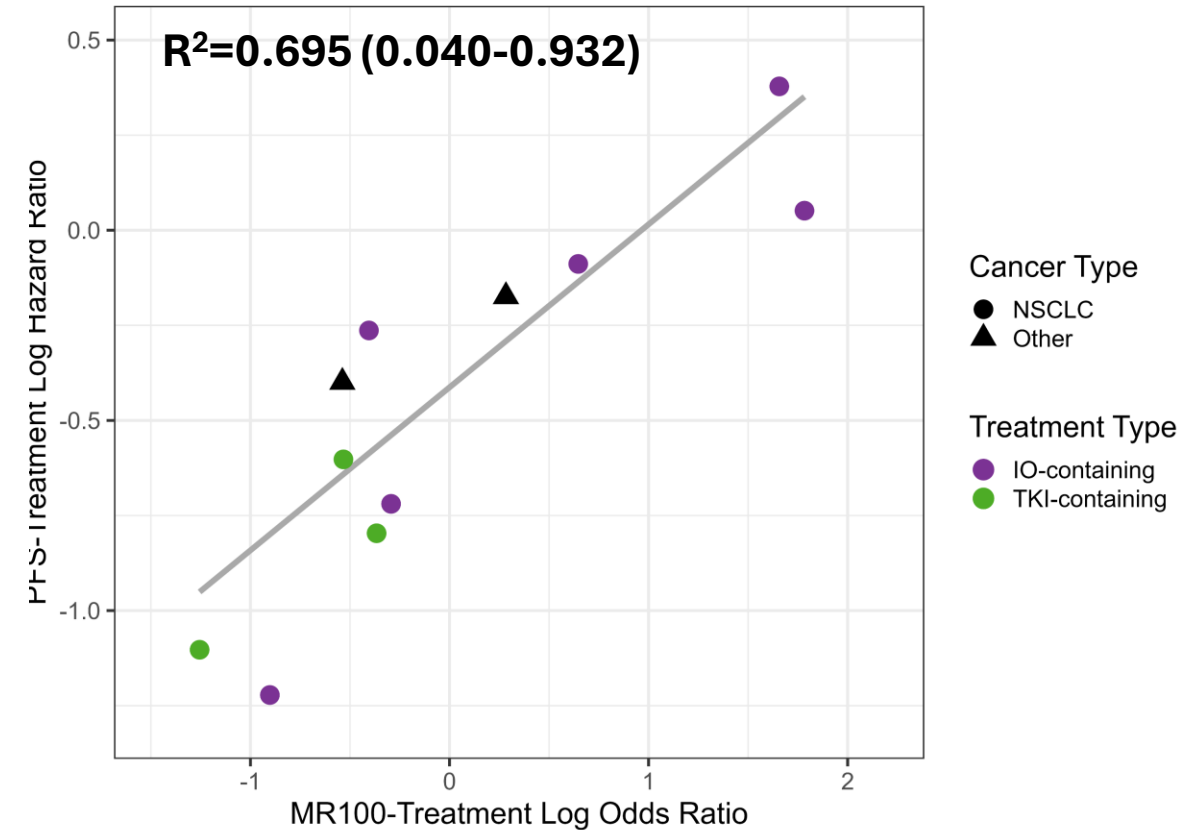
T-associations
*Patient-level
analyses*

FRIENDS
of CANCER
RESEARCH

PFS vs. MR90



PFS vs. MR100



T-associations are stronger for MR with PFS (vs. MR with OS or PFS with OS)

ctMoniTR Takeaways To Date

Consistently observe that decreases in ctDNA levels from baseline through up to 10 weeks on treatment are associated with improved OS for patients with advanced cancer in individual-level analyses

We established an aligned approach for aggregating data to assess associations between decreases in ctDNA levels and OS across multiple clinical trials

Outstanding questions remain regarding the optimal definition of the MR endpoint and the utility of this approach across disease settings

Why are data to date not fit-for-purpose for validating ctDNA as an early endpoint?

ctMoniTR to Date

Focused on settings where RECIST-based assessments work well enough (i.e., advanced NSCLC)

Definition of the endpoint was limited due to data availability: we used a single on-treatment timepoint and timing of ctDNA collection varied

ctDNA not included prospectively leading to data missingness across trials

ctMoniTR in the Future

Consider unmet need settings where ctDNA change is *earlier* or *more functional* than RECIST-based assessments (i.e., early-stage disease, bone-only disease)

Clearly define the endpoint: consider how to assess ctDNA, including when to collect and how this may differ in different settings

Include ctDNA in an aligned, prospective manner to reduce data missingness



**Thank you to CRAB for the statistical
support and the ctMoniTR Project
Working Group for guidance**