

ctMoniTR Step 2 Module 1 Findings

Hillary Stires, PhD

Director, Regulatory and Research Partnerships

Friends of Cancer Research

on behalf of the ctMoniTR Step 2 Working Group



FRIENDS
of **CANCER**
RESEARCH

ctMoniTR Overview

Do changes in ctDNA reflect response to treatment?

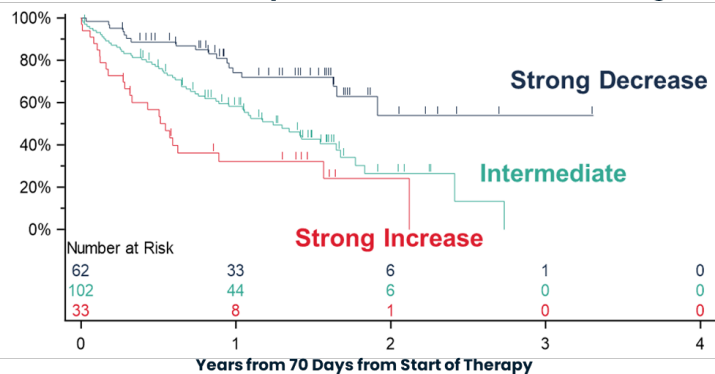
ctMoniTR Step 1

5 clinical trials
200 patients
Advanced NSCLC
Treated with anti-PD(L)1

ctMoniTR Step 2

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

Overall Survival by ctDNA Max VAF 3-Level Change



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

Module 1
aNSCLC
TKI

Module 2
aNSCLC
Anti-PD(L)1 or chemo

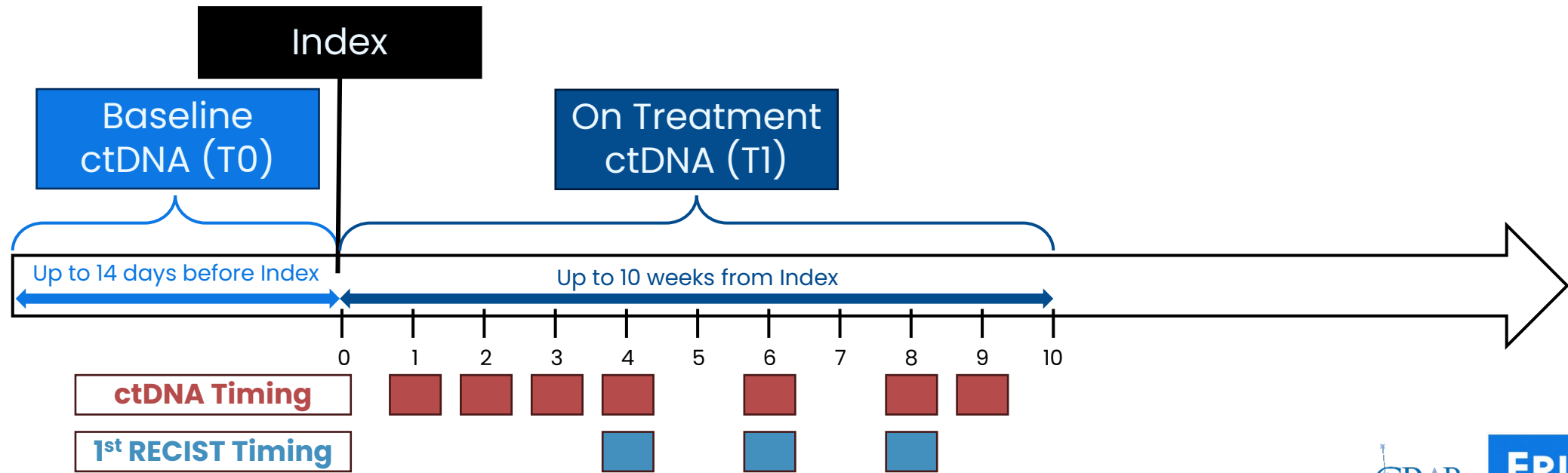
Module 3
Adv. Solid Tumors
Anti-PD(L)1 or TKI

Focus for today



Module 1 Overview

8 Clinical Trials	8 Different TKIs	1015 Patients	5 Assays
----------------------	---------------------	------------------	-------------



Module 1 Overview

Inclusion Criteria

- aNSCLC (93% stage IV)
- Treated with TKI (anti-EGFR, ALK, MET, RET)
- Long-term outcomes – PFS, OS
 - Analyses presented for OS, but results are similar for PFS

Assay Details

- 5 different assays
- ddPCR (n=539 patients) and NGS (n=476 patients)
- Limit of detection for NGS: %VAF 0.1-0.5

Module 1 Approach

RO1

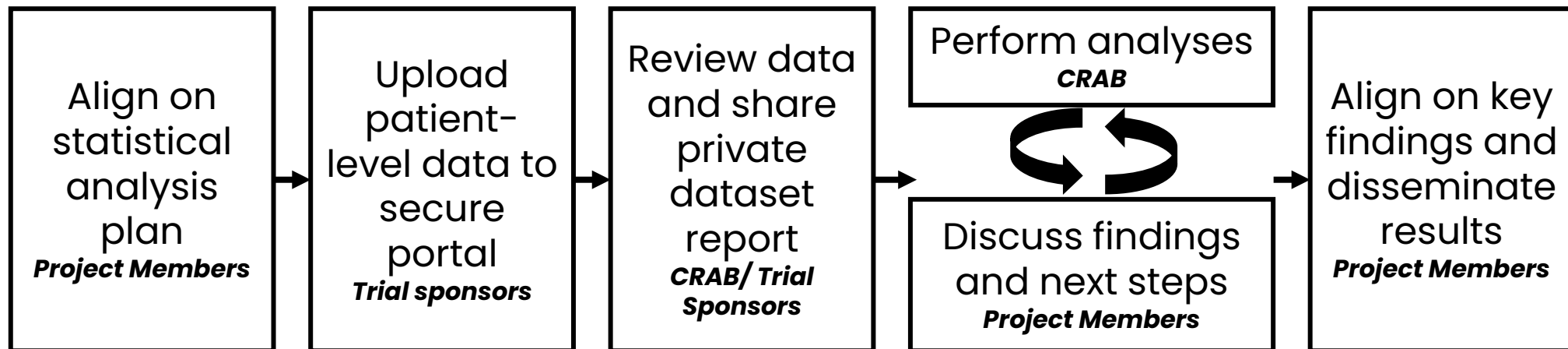
Early Δ ctDNA associations with long-term clinical outcomes

RO2

Δ ctDNA complementing 1st RECIST/ BOR

RO3

Combining Δ ctDNA with 1st RECIST to improve associations with outcomes



Molecular Response as a Percent Change

Δ ctDNA Metrics

- Max VAF
- Calculate as percent change from T0 to T1
 - For those with multiple ctDNA values within the first 10 weeks, use "best" (i.e., lowest) ctDNA for T1

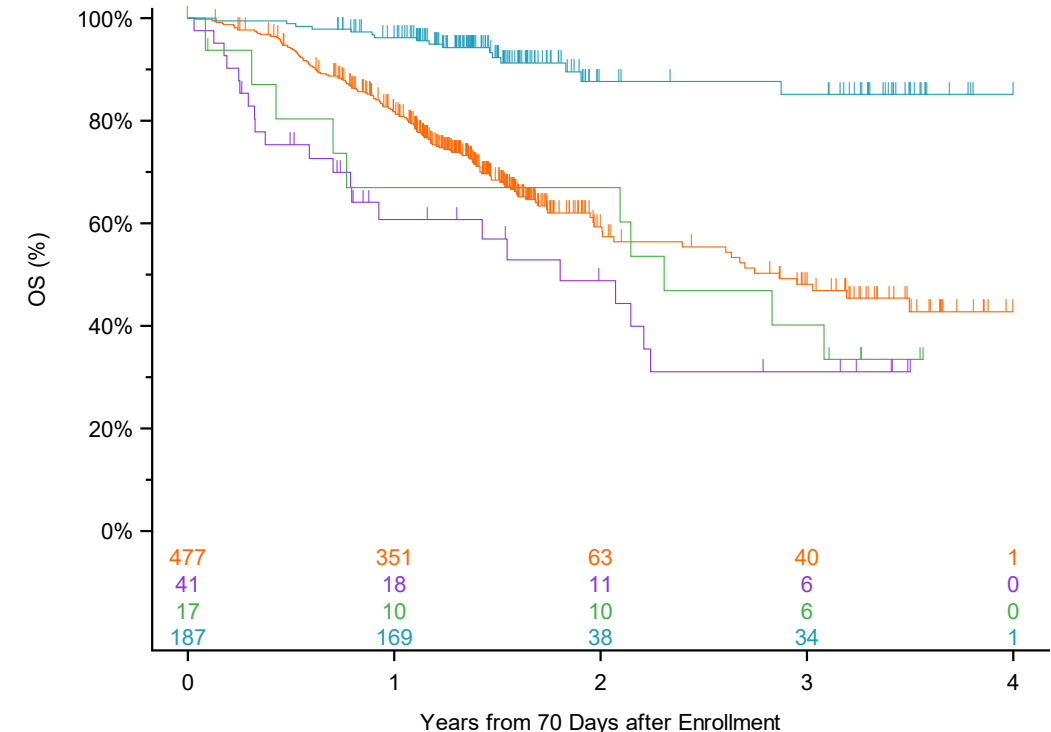
Molecular Response

- **"Decrease"** = >50% decrease
- **"Increase"** = >20% increase
- **"Intermediate"** = 50% decrease to 20% increase
- **"ND/ND"** = not detected

Statistical Analysis

- Kaplan Meier plots
- Multivariable Cox proportional hazards models stratified by cohort, included demographic and clinical confounders

Overall Survival



Categorizing the samples by percent change did not demonstrate separation of Kaplan-Meier Curves

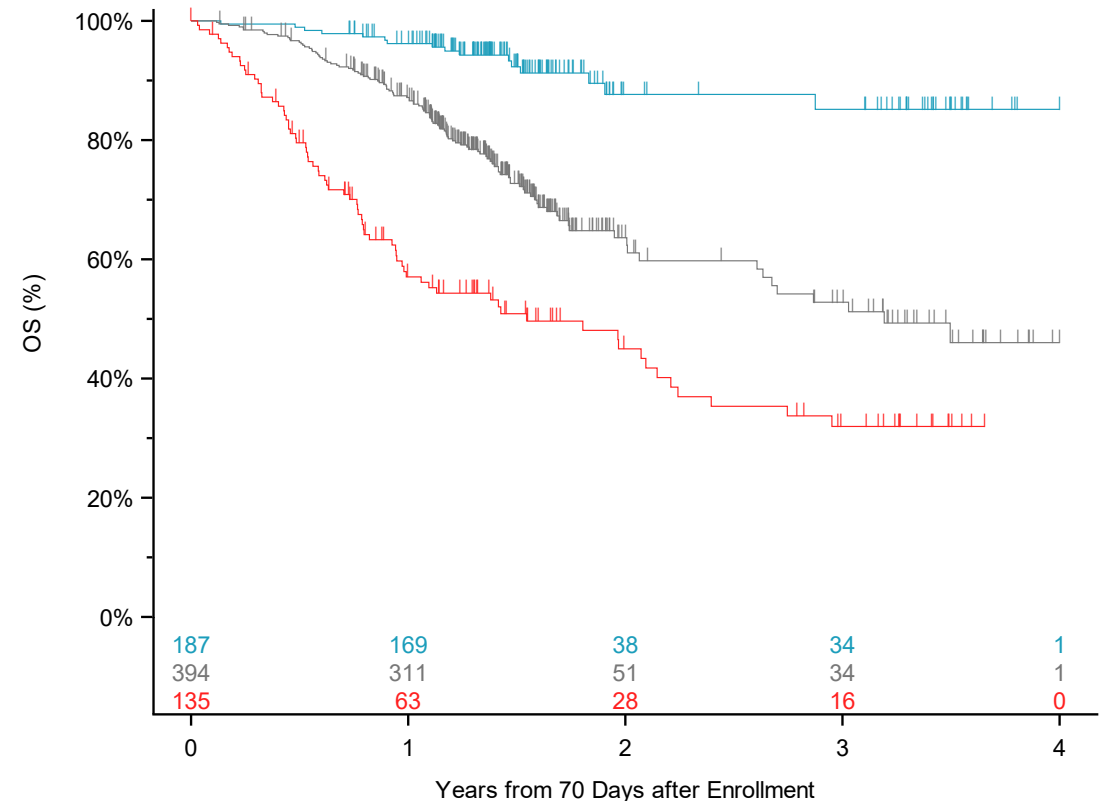
Molecular Response Based on Detection

T0/T1	Definition
ND/ND	Not detected at T0 or T1
D/ND	Detected at T0, not detected at T1
D/D	Detected at T0 and T1

OS multivariable associations, HR (p-value)

		Reference		
		ND/ND	D/ND	D/D
Comparator	ND/ND	-		
	D/ND	2.95 (<0.001)	-	
	D/D	6.25 (<0.001)	2.12 (<0.001)	-

Overall Survival



Patients with non-detected ctDNA on treatment (D/ND) have stronger association with improved survival compared with patients with detected levels of ctDNA on treatment (D/D)

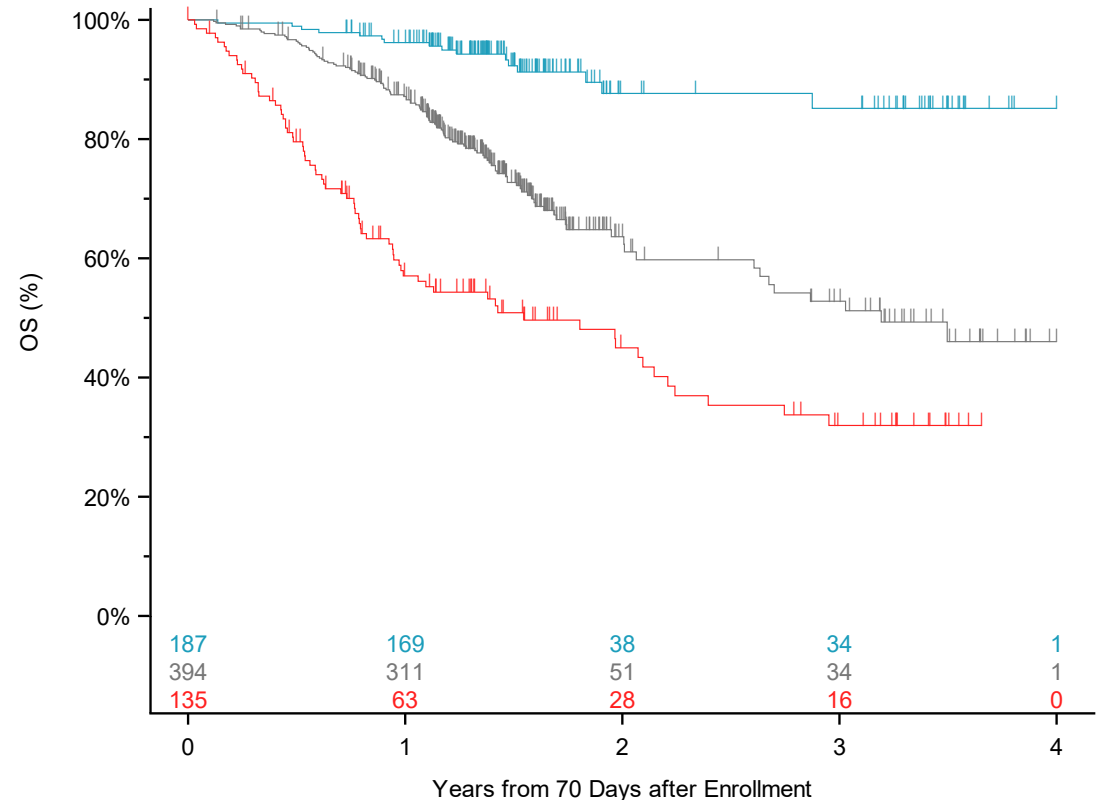


*The ND/D category had very few patients (n=6) so further analyses did not include this category.

Molecular Response Based on Detection

T0/T1	Deaths / N	Median (Yrs)	1-Yr Estimate
ND/ND	16/187	NR	96% (93, 99)
D/ND	114/394	3.2 (2.6, NR)	87% (84, 91)
D/D	72/135	1.5 (1, 2.2)	57% (48, 66)

Overall Survival



OS multivariable associations, HR (p-value)

		Reference		
		ND/ND	D/ND	D/D
Comparator	ND/ND	-		
	D/ND	2.95 (<0.001)	-	
	D/D	6.25 (<0.001)	2.12 (<0.001)	-

Patients with non-detected ctDNA on treatment (D/ND) have stronger association with improved survival compared with patients with detected levels of ctDNA on treatment (D/D)



*The ND/D category had very few patients (n=6) so further analyses did not include this category.

Comparing Molecular and Radiographic Response

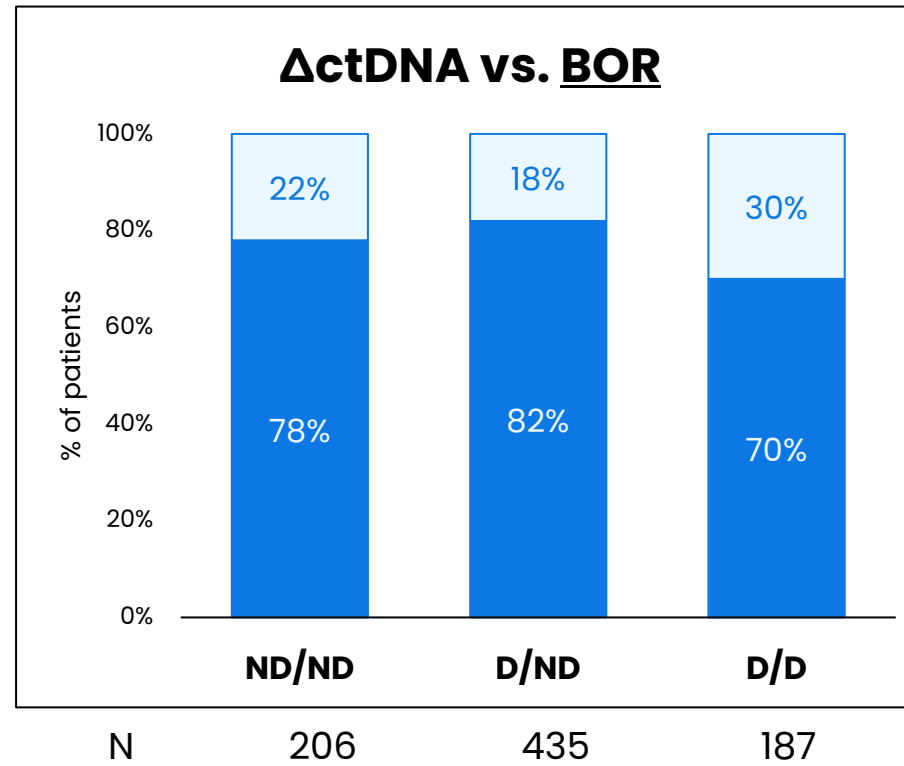
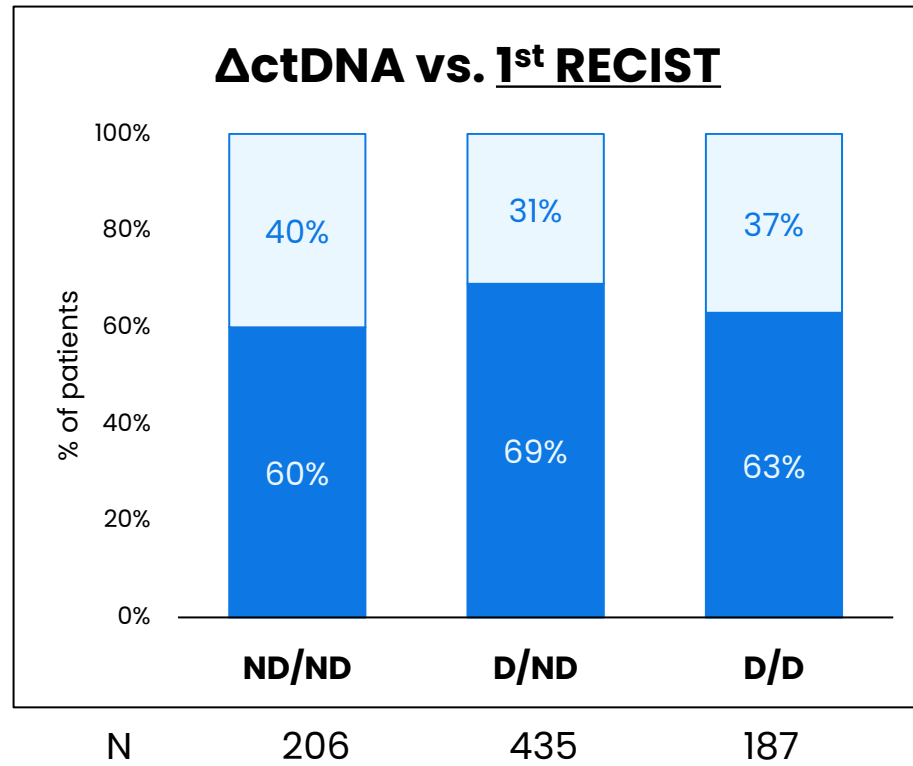
Do patients with ND ctDNA on treatment correlate with responders as defined by 1st RECIST (within the first 10 weeks after index)? Or BOR?

		1 st RECIST				
		CR	PR	SD	PD	Total
BOR	CR	4	28	3	0	35
	PR	0	483	128	0	611
	SD	0	25	132	0	157
	PD	0	0	1	24	25
	Total	4	536	264	24	828

Combine CR and PR into “Responders”

Combine SD and PD into “Non-responders”

Comparing Molecular and Radiographic Response



Distribution of Responders vs. Non-Responders across molecular response categories for 1st RECIST and BOR is similar

Combining Molecular Response and Radiographic Response at 1st RECIST

Analysis 1

Radiographic response + outcomes (no Δ ctDNA)

Kaplan Meier, Cox model

Categories

- Responder
- Non-Responder

Analysis 2

Radiographic response + Δ ctDNA + outcomes

Kaplan Meier, Cox model

Categories

- ND/ND + Responder
- ND/ND + Non-Responder
- D/ND + Responder
- D/ND + Non-Responder
- D/D + Responder
- D/D + Non-Responder

Analysis 3

Compare models

Does combining molecular and radiographic response improve associations with outcomes?

Likelihood Ratio Test

Compare full model to reduced model

- Full model: ctDNA x 1st RECIST
- Reduced model: ctDNA

Analysis 4

PR/ SD + Δ ctDNA + outcomes

Kaplan Meier, Cox model

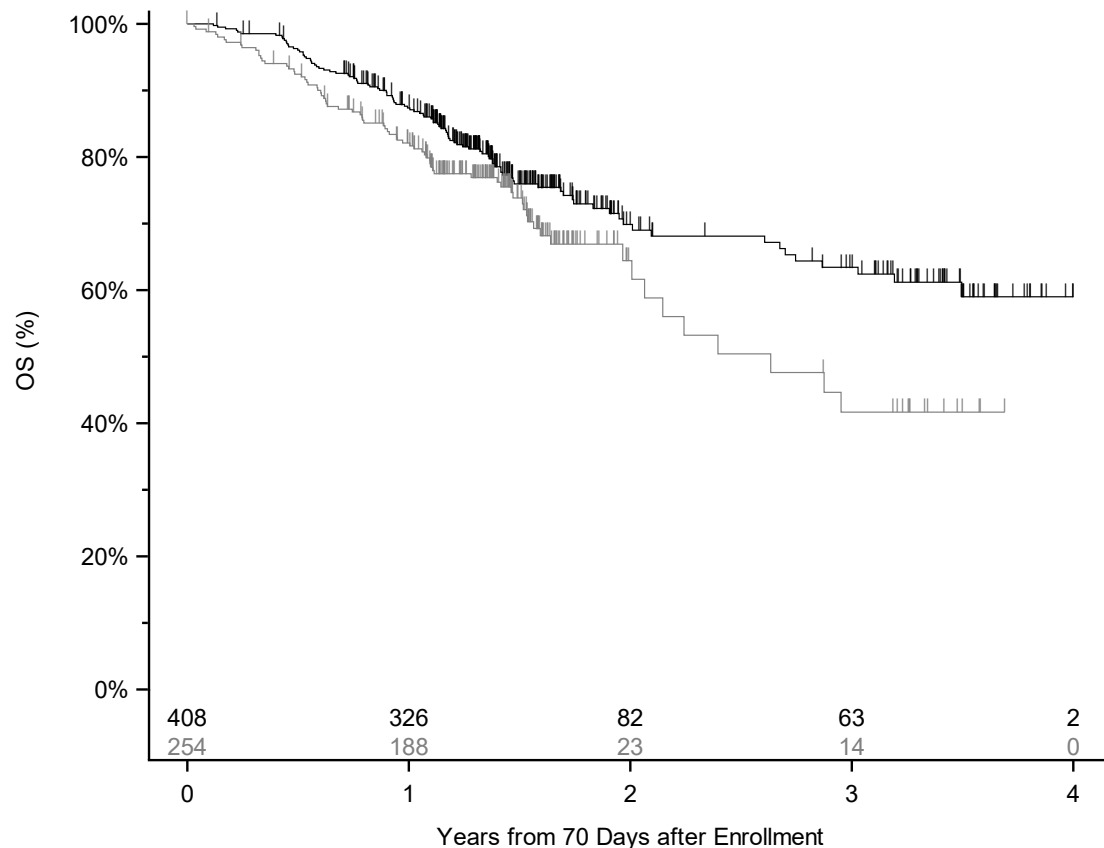
Categories (within PR or SD)

- ND/ND
- D/ND
- D/D

Analysis 1

Radiographic response + outcomes (no Δ ctDNA)

Overall Survival



Radiographic Response Measured at 1st RECIST

	Deaths / N	Median (Yrs)	1-Yr Estimate
Responder	103/408	NR	87% (84,91)
Non-Responder	75/254	2.6 (2.1, NR)	82% (77,87)

OS Multivariable analysis

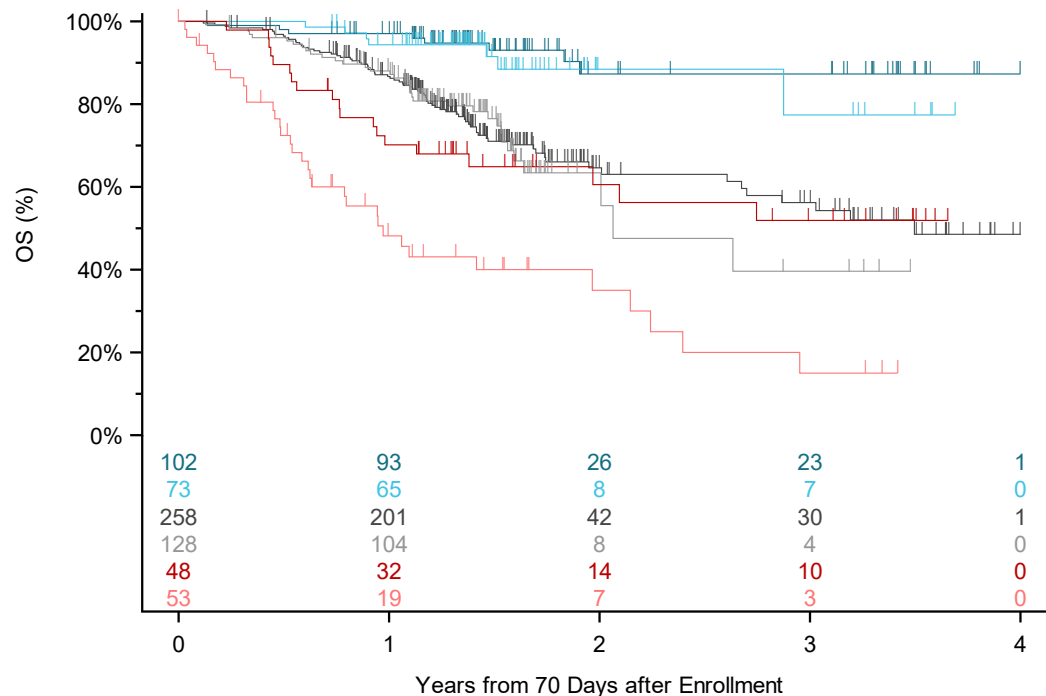
HR= 1.21 (0.87, 1.67) P=0.254

There is no apparent separation between responders and non-responders at 1st RECIST and their association with OS

Analysis 2

Radiographic response + ΔctDNA + Outcomes

Overall Survival



Category	Deaths / N	Median (Yrs)	1-Yr Estimate
ND/ND Responder	8/102	NR	97% (94,100)
ND/ND Non-responder	7/73	NR	94% (89,100)
D/ND Responder	76/258	3.5 (2.7, NR)	87% (82, 91)
D/ND Non-responder	35/128	2.1 (2.0, NR)	88% (82, 94)
D/D Responder	19/48	NR	70% (57, 83)
D/D Non-Responder	33/53	1.0 (0.6, 2.1)	48% (34, 63)

ΔctDNA Category	HR (95% CI)
ND/ND	0.95 (0.34, 2.64); p=0.917
D/ND	0.91 (0.60, 1.39); p=0.675
D/D	1.93 (1.04, 3.58); p=0.037

Incorporating radiographic response at 1st RECIST into molecular response categories does not improve the degree of association with survival for those with ND ctDNA on treatment

Analysis 3

Does combining molecular and radiographic response improve associations with outcomes?

Compare full model to reduced model

- **Full model:** Δ ctDNA x 1st RECIST (+/- covariates)
- **Reduced model:** Δ ctDNA only (+/- covariates)
- Likelihood ratio test for association between OS and 1st RECIST above and beyond Δ ctDNA:
 - ChiSq = 4.7, DF = 3, P=0.195

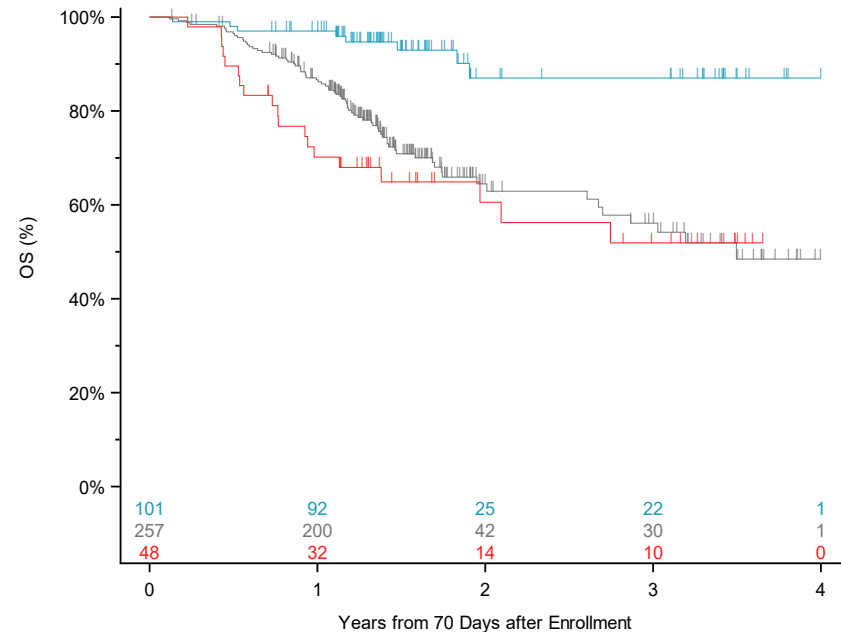
Radiographic response at 1st RECIST does not provide additional value in characterizing the association with OS beyond the contribution of molecular response

Analysis 4

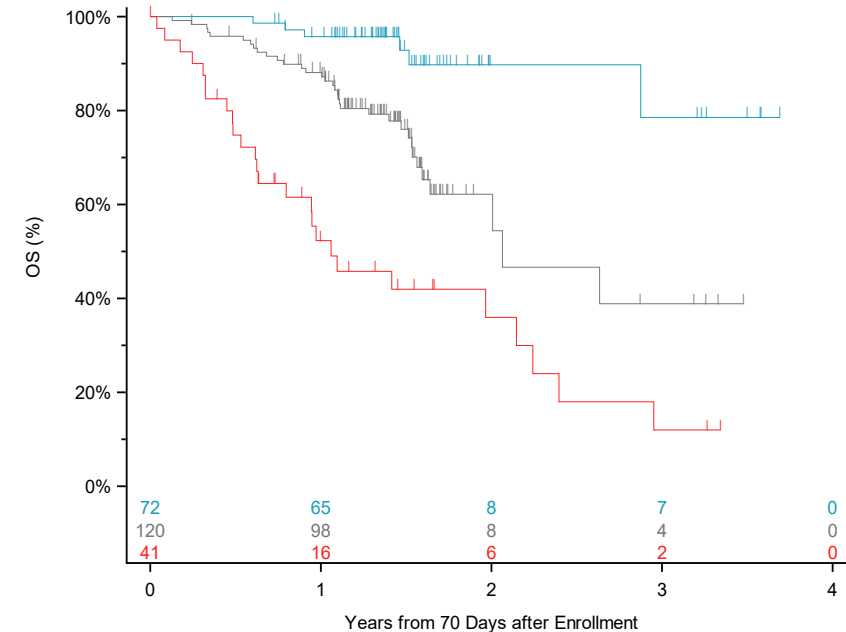
PR/SD + Δ ctDNA + Outcomes

Comparison	PR	SD
	HR (95% CI)	
D/ND vs. ND/ND	2.05 (0.82, 5.13); p=0.124	4.80 (1.78, 12.92); p=0.002
D/D vs. ND/ND	3.32 (1.18, 9.33); p=0.023	19.93 (5.89, 67.44); p<0.001
D/D vs. D/ND	1.62 (0.95, 2.75); p=0.077	4.15 (2.07, 8.33); p<0.001

Overall Survival
PR at 1st RECIST



Overall Survival
SD at 1st RECIST



For patients classified as SD at 1st RECIST, molecular response differentiates associations with overall survival

Module 1 Key Takeaways

- Harmonizing data across 8 clinical trials was feasible
- In aNSCLC treated with TKI:
 - Among patients who had detected ctDNA at baseline, patients with non-detected ctDNA on treatment (D/ND) were associated with improved OS (and PFS) compared to patients with detected levels of ctDNA on treatment (D/D)
 - Molecular response associated with OS (and PFS) while radiographic response at 1st RECIST did not
 - Among patients who were categorized as having SD at 1st RECIST, molecular response identified patients with improved associations with OS (and PFS)

Strengths and Limitations of the Analysis

Strengths

Limitations

Large Dataset

- 8 clinical trials
- 1015 patients
- 8 distinct TKI regimens

- Clear and unifying results across a wide range of features

- Did not have an external validation dataset

Variability

- Assay types
- Sampling timing for ctDNA/ RECIST

- Analyses stratified by cohorts
- Harmonization approaches used

- Potential differential in features due to variability despite sensitivity analyses

Patient-level data

- Multivariable models account for patient-level confounders
- Interrogated ctDNA metrics

- Unable to answer some questions because of anonymization

Retrospective analysis

- Opportunity to analyze multiple datasets with different approaches to data collection

- Prospective analyses would be prespecified



Contextualizing Findings

- Module 1 is not a validation of Step 1 (aNSCLC + anti-PD(L)1)
 - Different treatments (TKI vs. PD(L)1)
 - Different methods of defining change (detection vs. % change)
- However, in both cases, *molecular response associates with improved outcomes*
- Module 2 focuses on aNSCLC + anti-PD(L)1 or chemo
 - Allows us to validate Step 1
 - Consider a different treatment
 - Potential to analyze whether ctDNA can identify a more effective treatment in a randomized controlled trial

THANK YOU TO OUR PROJECT PARTNERS

