The Impact of Treatment Modalities on Use of ctDNA as an Early Endpoint in aNSCLC Trials

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1) Friends of Cancer Research 2) NMD Group Inc. 3) Cancer Research And Biostatistics 4) Genentech, Inc. 5) Natera Inc. 6) Foundation Medicine, Inc. 7) Guardant Health, Inc. 8) AstraZeneca 9) Regeneron Pharmaceuticals

Background

Circulating tumor DNA (ctDNA) holds promise as an intermediate endpoint in oncology drug development, particularly in advanced non-small cell lung cancer (aNSCLC) treated with immunotherapy. Friends of Cancer Research established the ctMoniTR Project to aggregate and analyze patient-level data from clinical trials and generate evidence that characterizes the association between change in ctDNA levels on treatment and overall survival (OS). Using patient-level data from 4 randomized controlled trials (RCTs), we assessed change in ctDNA levels and associations with OS among patients treated with anti-PD(L)1 and/or chemotherapy.

Approach

Overall Question

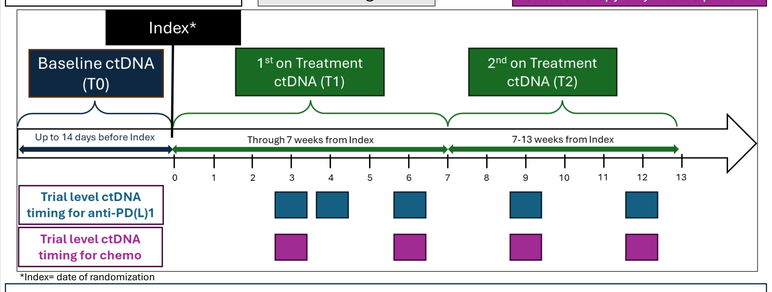
Does change in ctDNA associate with long-term outcomes (i.e., OS)? What ctDNA metrics, timing, and percent change should be used in prospective trials?

4 RCTs comparing an anti-PD(L)1 (with or without chemotherapy) to chemotherapy alone

Inclusion criteria:
- T0 ctDNA
- T1 (&T2) ctDNA
- Covariates
- Landmarking

→ T1= 567 (T1&T2= 425) Anti-PD(L)1 treated patients

→ T1= 330 (T1&T2= 239) Chemotherapy only treated patients



*Index= date of randomization

Research Objective 1 (RO1): Does change in ctDNA associate with OS in patients treated with anti-PD(L)1 (n=567)?

Parameters for Research Objective 1	ctDNA metric	Timing	Percent Change
	Max VAF	Up to 7 weeks post index	>50% decrease >90% decrease

Research Objective 2 (RO2): Does change in ctDNA associate with OS in patients treated with chemotherapy only (n=330)?

Parameters for Research Objective 2	ctDNA metric	Timing	Percent Change
	Max VAF	Up to 7 weeks post index	>50% decrease >90% decrease

Research Objective 3 (RO3): How do ctDNA dynamics interplay with OS in patients treated with anti-PD(L)1 (n=425) or chemotherapy (n=239)?

Parameters for Research Objective 3	ctDNA metric	Timing	Percent Change
	Max VAF	Up to 7 weeks, 7-13 weeks	>50% decrease >90% decrease

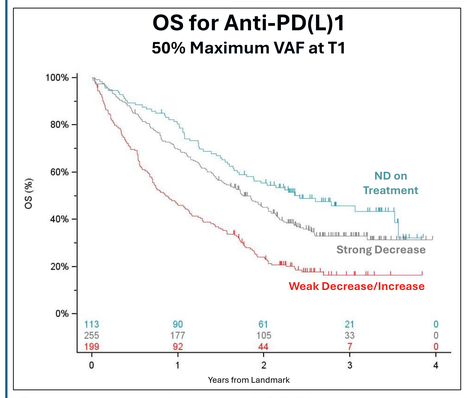
Methods

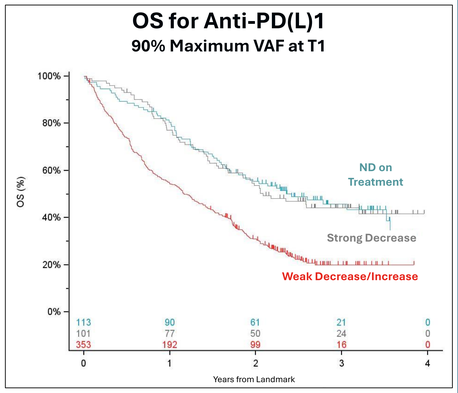
We developed an analysis plan to evaluate change in ctDNA levels by applying cutoffs tailored for anti-PD(L)1 of >50%/>90% decrease in ctDNA (Strong Decrease) compared to <50%/90% decrease/ increase (respectively, Weak Decrease/Increase). A third group with ctDNA that was not detected (ND) on treatment (ND on treatment) was initially assessed as a separate category, was then combined with the patients in the Strong Decrease category to define molecular response (MR50 or MR90). Non-molecular response (nMR) included patients from the Weak Decrease/Increase group. We used landmarked multivariable Cox models adjusted for clinical covariates and stratified by cohorts to assess associations with OS and compared results from T1 to T2.

RO1 Results

ctDNA change up to 7 weeks in anti-PD(L)1

	50% Cutoff HR (95%CI), p-value	90% Cutoff HR (95%CI), p-value
Strong Decrease (vs ND on Treatment)	**1.56 (1.09 - 2.24), 0.015**	1.20 (0.78 - 1.86), 0.400
Weak Decrease/Increase (vs ND on Treatment)	**2.67 (1.90 - 3.75), <0.001**	**2.29 (1.65 - 3.18), <0.001**
Weak Decrease/Increase (vs Strong Decrease)	**1.71 (1.34 - 2.18), <0.001**	**1.90 (1.39 - 2.61), <0.001**



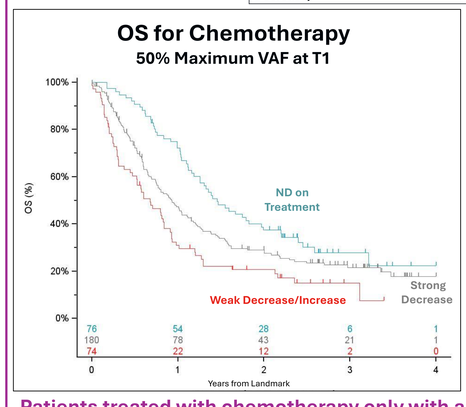


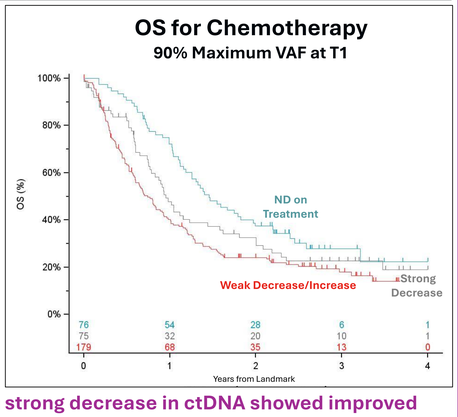
Patients treated with anti-PD(L)1 with a strong decrease in ctDNA showed improved OS compared to patients with a weak decrease/ increase. ND on treatment associated with improved OS compared to a strong decrease for the 50% cutoff but not the 90% cutoff.

RO2 Results

ctDNA change up to 7 weeks in chemo only

	50% Cutoff HR (95%CI), p-value	90% Cutoff HR (95%CI), p-value
Strong Decrease (vs ND on Treatment)	1.22 (0.80 - 1.86), 0.348	1.19 (0.75 - 1.91), 0.460
Weak Decrease/Increase (vs ND on Treatment)	**1.80 (1.19 - 2.71), 0.005**	**1.55 (1.06 - 2.28), 0.025**
Weak Decrease/Increase (vs Strong Decrease)	**1.47 (1.04 - 2.08), 0.028**	1.30 (0.93 - 1.82), 0.125



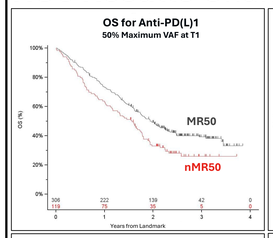


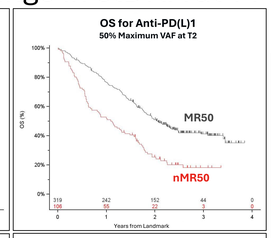
Patients treated with chemotherapy only with a strong decrease in ctDNA showed improved OS compared to patients with a weak decrease/ increase for the 50% cutoff but not the 90% cutoff. ND on treatment associated with improved OS compared to weak decrease/ increase for both cutoffs, however, there were no statistically significant differences between the ND on treatment group and the strong decrease group.

Conclusions

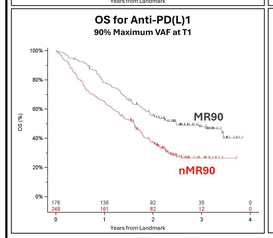
Preliminary data suggest that ctDNA associates with clinical outcomes in immunotherapy- and chemotherapy-treated patients with aNSCLC. MR (i.e., a strong decrease in ctDNA or ND on treatment) is strongly associated with improved OS in patients with aNSCLC treated with anti-PD(L)1 at T1 and T2 using either a 50% or 90% cutoff. For chemotherapy, associations are weaker but MR at T2 is associated with improved OS using either a 50% or 90% cutoff, suggesting later timepoints may be more appropriate to analyze. These data support the growing body of evidence that decreases in ctDNA associate with long-term outcomes, like OS, and set the stage for incorporating ctDNA in an aligned approach in future prospective trials in patients with aNSCLC to support the use of ctDNA as an intermediate endpoint in regulatory decision-making.

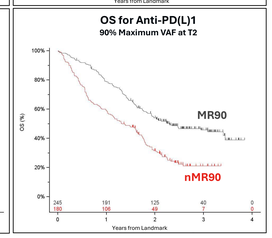
RO3 Results Change in ctDNA at T1 vs. T2





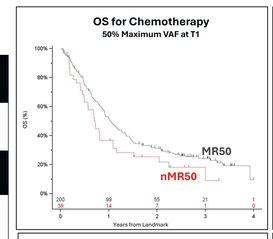
	50% Cutoff T1 HR (95%CI), p-value	50% Cutoff T2 HR (95%CI), p-value
nMR50 (vs MR50)	1.50 (1.13 - 1.98), 0.005	2.20 (1.65 - 2.94), <0.001
	90% Cutoff T1 HR (95%CI), p-value	**90% Cutoff T2** HR (95%CI), p-value
nMR90 (vs MR90)	1.97 (1.49-2.61), <0.001	1.99 (1.54 - 2.58), <0.001

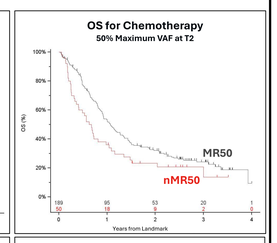




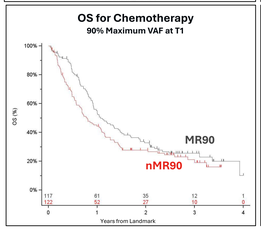
MR50 and MR90 in the anti-PD(L)1 group associated with improved outcomes over nMR at both T1 and T2.

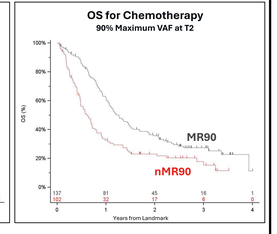
	50% Cutoff T1 HR (95%CI), p-value	50% Cutoff T2 HR (95%CI), p-value
nMR50 (vs MR50)	1.42 (0.92 - 2.19), 0.111	**1.68 (1.12 - 2.52), 0.012**
	90% Cutoff T1 HR (95%CI), p-value	**90% Cutoff T2** HR (95%CI), p-value
nMR90 (vs MR90)	1.26 (0.92 - 1.75), 0.155	**2.01 (1.43 - 2.82), <0.001**



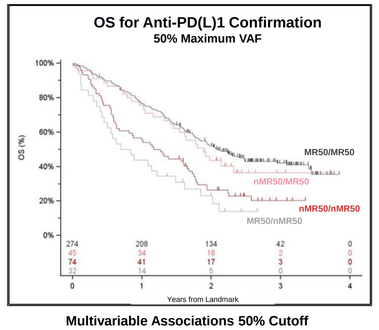


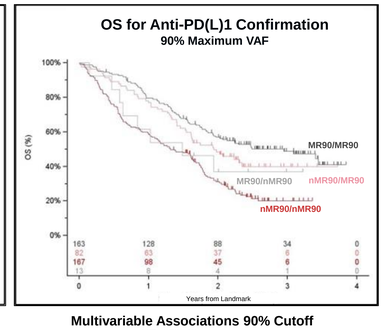
MR50 and MR90 in the chemotherapy group associated with improved outcomes over nMR at T2, but not at T1.





RO3 Results Confirmation analyses





Multivariable Associations 50% Cutoff
HR (95% CI), p-value

Comparator	Reference: MR/MR	nMR/MR	nMR/nMR	MR/nMR
MR/MR	-	-	-	-
nMR/MR	1.38 (0.90 - 2.13) p=0.144	-	-	-
nMR/nMR	**2.09 (1.50 - 2.91) p<0.001**	1.51 (0.94 - 2.44) p=0.088	-	-
MR/nMR	**3.33 (2.06 - 5.38) p<0.001**	**2.41 (1.37 - 4.24) p=0.002**	1.59 (0.97 - 2.63) p=0.067	-

Multivariable Associations 90% Cutoff
HR (95% CI), p-value

Comparator	Reference: MR/MR	nMR/MR	nMR/nMR	MR/nMR
MR/MR	-	-	-	-
nMR/MR	**1.53 (1.04 - 2.25) p=0.032**	-	-	-
nMR/nMR	**2.36 (1.75 - 3.20) p<0.001**	**1.55 (1.09 - 2.19) p=0.013**	-	-
MR/nMR	1.90 (0.90 - 4.01) p=0.093	1.24 (0.58 - 2.67) p=0.579	0.80 (0.39 - 1.67) p=0.555	-

For the anti-PD(L)1 group, approximately 80% of patients fell into the same response category for T1 and T2 (i.e., MR/MR or nMR/nMR). However, when the response categories did not match, it appeared that the T2 timepoint influenced associations with outcomes for pairwise comparisons.