Longitudinal ctDNA levels and clinical outcomes of first-line (1L) tislelizumab (TIS) + chemotherapy (chemo) treatment for advanced non-small cell lung cancer (NSCLC) in the RATIONALE-304 and 307 studies

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Abstract:

Background: The role of circulating tumor DNA (ctDNA) in monitoring response to immunotherapy in NSCLC is unconfirmed. This is a retrospective analysis of association between longitudinal ctDNA levels and clinical outcomes in 1L TIS (anti-PD-1) + chemo-treated patients (pts) with nonsquamous or squamous NSCLC from RATIONALE-304 (NCT03663205) and 307 (NCT03594747), respectively.

Methods: Blood samples were collected at baseline (BL), first response (FR, complete or partial response assessed by investigators), and progressive disease (PD). ctDNA level was tested by OncoScreen Plus520 (Burning Rock) and the variant allele fraction categorized as undetectable (UD)/detectable (D). Paired ctDNA analysis of BL and post-BL (FR or PD) values was by Wilcoxon sign-rank test. Median PFS and OS was calculated by Kaplan-Meier methodology. PD-L1 expression stratified Cox model was used to evaluate the effect of ctDNA on PFS and OS for BL and FR (adjusted with BL ctDNA) in each study. Impact of other BL characteristics was also assessed.

Results: Of 217 pts treated with TIS + chemo in RATIONALE-304, 76 (35%) at BL, 40 (18%) at FR, and 30 (14%) at PD had ctDNA results. Of 238 pts treated with TIS + chemo in RATIONALE-307, 80 (34%) at BL, 65 (27%) at FR, and 33 (14%) at PD had ctDNA results. Paired ctDNA analysis showed significantly decreased ctDNA levels from BL to FR ($P<0.0001$ in 304 and 307); no obvious change was detected from BL to PD in both studies. Pts with UD ctDNA status at FR had notably longer median PFS and OS compared with pts with D ctDNA; no such association was observed using BL ctDNA status in either study (**Table**).

Conclusions: FR ctDNA level is decreased from BL, and seems to correlate with clinical outcomes of 1L TIS in combination with chemotherapy in NSCLC; ctDNA has potential to be a surrogate biomarker for efficacy. This requires further prospective validation.

Table.Analysis summary of ctDNA and PFS/OS by visit

	Baseline (BL)				First response (FR)			
Study	**RATIONALE-304**		**RATIONALE-307**		**RATIONALE-304**		**RATIONALE-307**	
ctDNA	**UD**	**D**	**UD**	**D**	**UD**	**D**	**UD**	**D**
n	19	57	8	72	32	8	43	22
mPFS, mo (95% CI)[a]	9.23 (5.75, 9.89)	9.69 (7.33, 14.52)	NR (4.93, NR)	9.76 (7.52, 14.55)	17.31 (9.89, NR)	9.20 (3.71, 11.99)	20.01 (9.82, NR)	9.56 (7.39, 13.9)
PFS HR (95% CI), UD/D	1.14 (0.61, 2.21)		0.40 (0.09, 1.73)		0.16 (0.05, 0.5)		0.54 (0.24, 1.21)	
PFS P-value[b]	0.6421		0.2205		0.0019		0.1322	
mOS, mo (95% CI)	NR (9.72, NR)	NR (14,23, NR)	NR (NR, NR)	NR (16.89, NR)	NR (NR, NR)	18.78 (9.92, NR)	NR (NR, NR)	NR (12.85, NR)
OS HR (95% CI), UD/D	1.04 (0.48, 2.25)		NE		0.16 (0.04, 0.69)		0.48 (0.15, 1.51)	
OS P-value[b]	0.9254		NE		0.0147		0.2079	

[a]Primary endpoint assessed by IRC; [b]P-values are reported for descriptive purposes only in this exploratory study.
Abbreviations: CI, confidence interval; D, detectable ctDNA status; HR, hazard ratio; IRC, independent review committee; mo, months; mOS, median overall survival; mPFS, median progression-free survival; NE, not evaluable; NR, not reached; OS, overall survival; PFS, progression-free survival; UD, undetectable ctDNA status