Longitudinal Circulating Tumor DNA Levels and Clinical Outcomes of First-line Tislelizumab Plus Chemotherapy Treatment for Advanced Non-Small Cell Lung Cancer in the RATIONALE-304 and -307 Studies

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Conclusions

Circulating tumor DNA (ctDNA) level at first response (FR) is decreased from baseline (BL) in both the -304 and -307 studies and appears to correlate with improved clinical outcomes of first-line tislelizumab in combination with chemotherapy (chemo) in non-small cell lung cancer (NSCLC). ctDNA has the potential to be a surrogate biomarker for the efficacy of anti-programmed cell death protein 1 (PD-1) therapy, which requires further prospective validation.

Background

Lung cancer remains the leading cause of cancer mortality.[1] NSCLC accounts for the majority (~85%) of lung cancers, with metastatic disease representing over half of cases (~55%), and long-term prognosis remains poor.[2]

ctDNA enables evaluation of tumor genomics, with potential uses in molecular profiling, treatment response monitoring, and detection of residual disease, but its role in monitoring response to immunotherapy in NSCLC is unconfirmed.[3]

Tislelizumab is a humanized IgG4 anti-PD-1 monoclonal antibody with high affinity and binding specificity for PD-1.[4,5] In the RATIONALE-304 (NCT03663205) and -307 (NCT03594747) studies, tislelizumab plus chemo demonstrated a superior clinical progression-free survival (PFS) benefit compared with chemo alone as first-line treatment of nonsquamous (nsq) and squamous (sq) NSCLC, respectively.[6,7]

Here, we retrospectively analyzed the association between longitudinal ctDNA levels and clinical outcomes among patients with advanced NSCLC treated with tislelizumab plus chemo in RATIONALE-304 and -307. We observed the prognostic and predictive effect of BL ctDNA and further investigated the effect of FR ctDNA on efficacy in the tislelizumab-treated arm.

Methods

The study designs for RATIONALE-304 and -307 have been previously described. For more information, please see the QR codes below.[6,7]

- In RATIONALE-304, patients with nsq-NSCLC were randomized 2:1 to receive either tislelizumab combined with cisplatin or carboplatin plus pemetrexed (Arm A; n=223) or cisplatin or carboplatin plus pemetrexed alone (Arm B; n=111). The primary endpoint was PFS determined by independent review committee (IRC). Overall survival (OS) was a secondary endpoint
- In RATIONALE-307, patients with sq-NSCLC were randomized 1:1:1 to receive tislelizumab combined with carboplatin and either paclitaxel (Arm A; n=120) or *nab*-paclitaxel (Arm B; n=119) vs paclitaxel plus carboplatin alone (Arm C; n=121). The primary endpoint was PFS determined by IRC. OS was a secondary endpoint
- Blood samples were collected at BL, FR (complete or partial response, as assessed by investigators), and progressive disease (PD)
- ctDNA level was tested by BurningRock OncoScreen Plus 520 and the variant allele fraction categorized as undetectable (UD) or detectable (D)
- Paired ctDNA analysis of BL and post-BL (FR or PD) values was by Wilcoxon sign-rank test; median PFS and OS were calculated by Kaplan-Meier methodology
- A programmed death-ligand 1 expression-stratified Cox model was used to evaluate the effect of BL and FR ctDNA level on PFS and OS (adjusted with BL ctDNA) in each study. The impact of other BL characteristics was also assessed

Results

Baseline Characteristics

- Among 217 patients treated with tislelizumab plus chemo in RATIONALE-304, 76 (35%) had ctDNA results at BL, 40 (18%) at FR, and 30 (14%) at PD
- Among 238 patients treated with tislelizumab plus chemo in RATIONALE-307, 80 (34%) had ctDNA results at BL, 65 (27%) at FR, and 33 (14%) at PD
- In the tislelizumab plus chemo treatment arms, the ctDNA-evaluable cohorts were comparable with the overall populations in terms of listed BL characteristics for both studies (**Table 1**)

Table 1. Baseline Characteristics

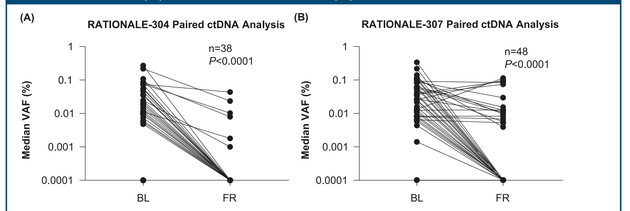
	RATIONALE-304 (Tislelizumab Plus Chemo Arm)		RATIONALE-307 (Tislelizumab Plus Chemo Arms)	
	Overall Population (n=217)[a]	All ctDNA BEP (n=81)[b]	Overall Population (n=238)[a]	All ctDNA BEP (n=101)[b]
Mean (SD) age, years	59.3 (8.5)	58.7 (8.0)	61.1 (7.1)	61.6 (7.7)
Sex, male	165 (76.0)	59 (72.8)	218 (91.6)	88 (87.1)
ECOG PS 1	165 (76.0)	55 (67.9)	185 (77.7)	73 (72.3)
Smoking status				
Current/former	145 (66.8)	54 (66.7)	202 (84.9)	80 (79.2)
Stage IV disease	177 (81.6)	65 (80.2)	160 (67.2)	68 (67.3)
TC PD-L1 expression				
<1%	87 (40.1)	37 (45.7)	95 (39.9)	49 (48.5)
1-49%	53 (24.4)	21 (25.9)	60 (25.2)	25 (24.8)
≥50%	72 (33.2)	23 (28.4)	83 (34.9)	27 (26.7)
Metastases				
Brain	10 (4.6)	2 (2.5)	5 (2.1)	2 (2.0)
Liver	19 (8.8)	3 (3.7)	30 (12.6)	12 (11.9)
Bone	72 (33.2)	26 (32.1)	40 (16.8)	20 (19.8)

Data are n (%), unless otherwise stated. [a]Safety analysis population, defined as all randomized patients who received ≥1 dose of any component of study treatment; in RATIONALE-304, five patients were excluded for having a positive or unknown *EGFR* mutation. [b]ctDNA BEP includes all patients with ctDNA testing at BL/FR/PD. In RATIONALE-304, 76 patients had ctDNA results at BL, two had ctDNA results at FR only, and three at PD only; in RATIONALE-307, 80 patients had ctDNA results at BL, 11 had ctDNA results at FR only, four at PD only, and six had paired ctDNA results at FR and PD but not at BL.
Abbreviations: BEP, biomarker-evaluable population; BL, baseline; ctDNA, circulating tumor DNA; ECOG PS, Eastern Cooperative Oncology Group performance status; FR, first response; PD, progressive disease; PD-L1, programmed death-ligand 1; SD, standard deviation; TC, tumor cell.

Association of ctDNA Levels and Clinical Efficacy of First-line Tislelizumab Plus Chemo in nsq- and sq-NSCLC

- In both studies, changes in ctDNA level from BL were associated with FR (**Figure 1**)
  - Paired ctDNA analysis showed significantly decreased ctDNA levels from BL to FR (*P*<0.0001 in -304 and -307) (**Figure 1**)
  - Paired ctDNA analysis showed no obvious changes from BL to PD (data not shown)
- Patients with UD ctDNA status at FR had notably longer PFS and OS vs patients with D ctDNA at FR (**Table 2, Figure 2**)
- Patients with UD ctDNA status at BL had no obvious differences in PFS and OS vs patients with D ctDNA at BL (**Table 2**)

Figure 1. ctDNA Levels Significantly Decreased at FR Compared With BL in (A) RATIONALE-304 and (B) RATIONALE-307



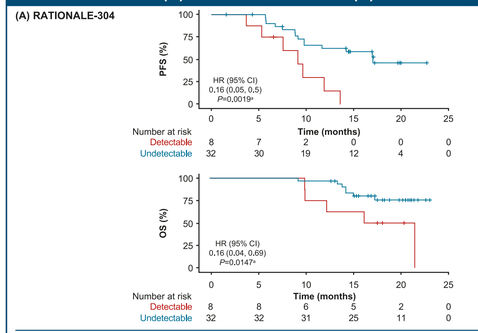
Data shown for patients with matched BL and FR ctDNA samples.
Abbreviations: BL, baseline; ctDNA, circulating tumor DNA; FR, first response; VAF, variant allele frequency.

Table 2. Analysis Summary of ctDNA and PFS/OS by Visit

	RATIONALE-304				RATIONALE-307			
Study	**BL**		**FR**		**BL**		**FR**	
ctDNA status	**UD**	**D**	**UD**	**D**	**UD**	**D**	**UD**	**D**
n	19	57	32	8	8	72	43	22
mPFS, mo (95% CI)[a]	9.23 (5.75, 9.89)	9.69 (7.33, 14.52)	17.31 (9.89, NR)	9.20 (3.71, 11.99)	NR (4.93, NR)	9.76 (7.52, 14.55)	20.01 (9.82, NR)	9.56 (7.39, 13.9)
PFS HR (95% CI)[b]	1.14 (0.61, 2.21) *P*=0.6421[c]		0.16 (0.05, 0.5) *P*=0.0019[c]		0.40 (0.09, 1.73) *P*=0.2205[c]		0.54 (0.24, 1.21) *P*=0.1322[c]	
mOS, mo (95% CI)	NR (9.72, NR)	NR (14.23, NR)	NR (NR, NR)	18.78 (9.92, NR)	NR (NR, NR)	NR (16.89, NR)	NR (NR, NR)	NR (12.85, NR)
OS HR (95% CI)[b]	1.04 (0.48, 2.25) *P*=0.9254[c]		0.16 (0.04, 0.69) *P*=0.0147[c]		NE *P*=NE[c]		0.48 (0.15, 1.51) *P*=0.2079[c]	

[a]Primary endpoint assessed by IRC. [b]PD-L1-stratified Cox model HR presented as D/UD ratio. [c]*P*-values are reported for descriptive purposes only in this exploratory study.
Abbreviations: BL, baseline; CI, confidence interval; ctDNA, circulating tumor DNA; D, detectable; FR, first response; 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; PD-L1, programmed death-ligand 1; PFS, progression-free survival; UD, undetectable.

Figure 2. Patients With Undetectable ctDNA at FR Showed Longer PFS and OS in (A) RATIONALE-304 and (B) RATIONALE-307



For further details please see the corresponding abstract. [a]*P*-values are reported for descriptive purposes only in this exploratory study. **Abbreviations:** CI, confidence interval; ctDNA, circulating tumor DNA; FR, first response; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

Results should be interpreted with caution given the small sample size in study -304 ctDNA subgroups, and nonsignificant differences in -307.

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Disclosures

Disclosure information will be available online with the abstract details.

RATIONALE -304 IA

RATIONALE -307 IA

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