RATIONALE-303 Phase 3 Tislelizumab vs Docetaxel in Previously Treated Advanced NSCLC: China Subgroup Analysis

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Introduction

Tislelizumab is an anti-PD-1 antibody engineered to minimize FcγR binding on macrophages in order to abrogate antibody-dependent phagocytosis, a potential mechanism of resistance to anti-PD-1 therapy. RATIONALE-303 (NCT03358875) demonstrated improved overall survival (OS) for tislelizumab vs docetaxel in the intention-to-treat (ITT) and PD-L1 ≥25% analysis sets with a manageable safety profile.

Methods

Patients with squamous/non-squamous NSCLC who progressed during/after platinum-based doublet chemotherapy were randomized 2:1 to receive tislelizumab (200 mg) or docetaxel (75 mg/m^2) Q3W. Stratification factors included histology (squamous vs non-squamous), lines of therapy (2L vs 3L) and PD-L1 expression (≥25% vs <25% tumor cells). The primary endpoint was OS (ITT and PD-L1). Secondary endpoints were objective response rate (ORR), duration of response (DoR), progression-free survival (PFS) and safety. Here, efficacy and safety of tislelizumab vs docetaxel are assessed in Chinese patients.

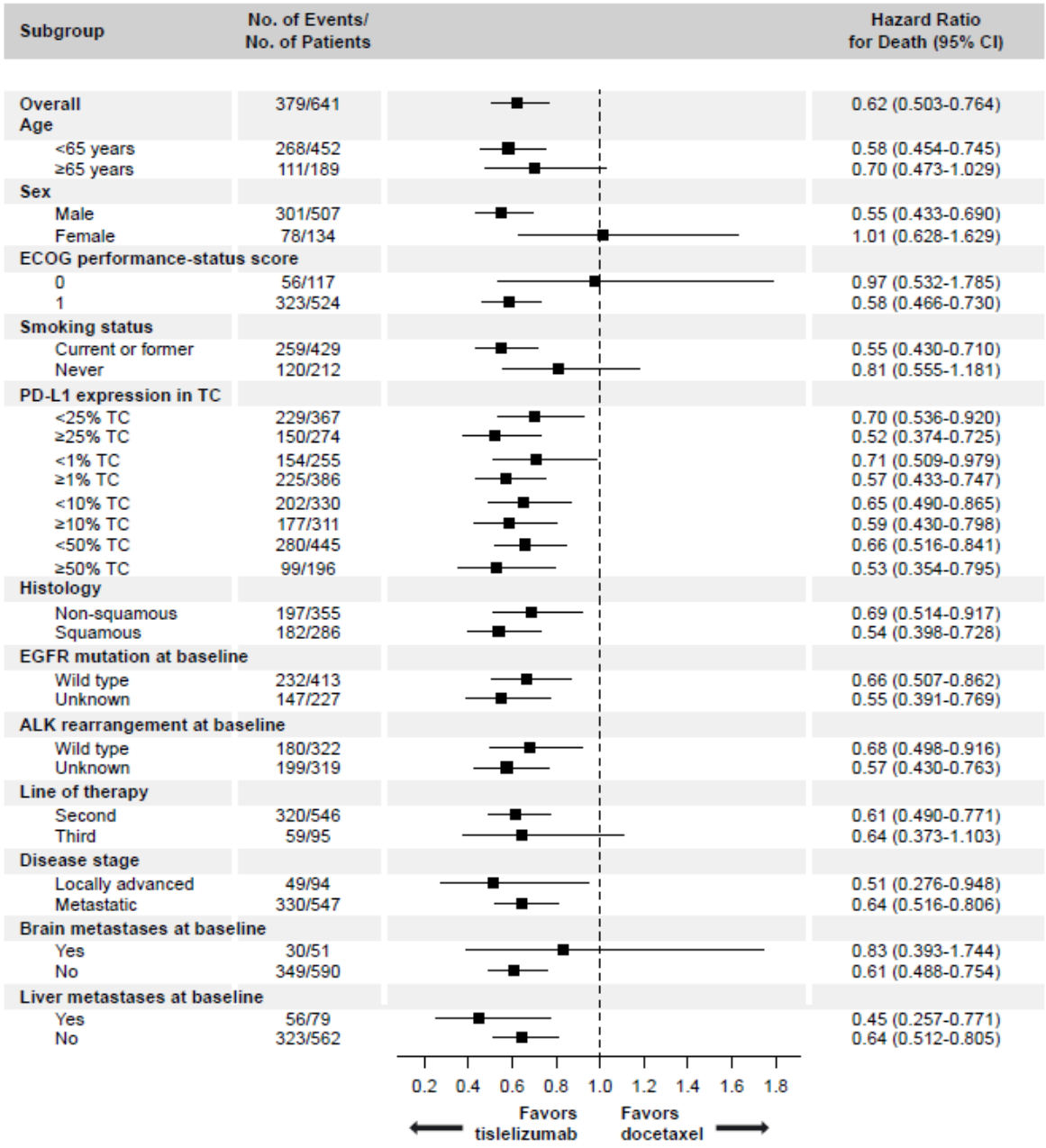
Results

641 Chinese patients were randomized. Median age was 61.0 years and 79.1% were male. Baseline characteristics were similar to the ITT population. 87.7% had discontinued treatment and 11.9% received subsequent immunotherapy. At a median follow-up of 20.7 months, OS was significantly longer for tislelizumab vs docetaxel (median OS: 17.8 vs 11.5 months; HR=0.62; P<0.0001). OS improvement with tislelizumab was observed in most subgroups (**Figure**). PFS, ORR and DoR were also improved for tislelizumab vs docetaxel (**Table**). 96.7% (tislelizumab) and 98.6% (docetaxel) of patients experienced ≥1 TEAE and 39.0% (tislelizumab) and 75.1% (docetaxel) of patients experienced a ≥grade 3 TEAE. 1.7% (tislelizumab) and 1.4% (docetaxel) experienced treatment-related TEAEs leading to death. The top three most common TEAEs were anemia, ALT increase and cough in the tislelizumab group and alopecia, anemia and neutrophil count decrease in the docetaxel group (**Table**).

Conclusions

Consistent with the ITT analysis, clinical improvement was shown with tislelizumab in Chinese patients with advanced NSCLC and tislelizumab had a tolerable and manageable safety profile.

Figure: Overall survival (Efficacy analysis set – China)



Abbreviations: ALK, anaplastic lymphoma kinase; CI, confidence interval; PD-L1, programmed death ligand-1; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; TC, tumor cell. Hazard ratio and its 95% CI was estimated from unstratified Cox model with docetaxel group as reference group.

Table: Efficacy and safety

Efficacy[a]	**Tislelizumab (n=423)**		**Docetaxel (n=218)**	
Median OS, mo (95% CI)	17.8 (15.44, 20.90)		11.5 (9.43, 13.93)	
HR (95% CI)[b]	0.62 (0.500, 0.761)			
P-value[c]	<0.0001			
Median PFS, mo (95% CI)	4.1 (3.42, 4.34)		2.3 (2.14, 3.58)	
HR (95% CI)[b]	0.61 (0.501, 0.741)			
P-value[c]	<0.0001			
ORR, n (%)	91 (21.5)		12 (5.5)	
Median DoR, mo (95% CI)	13.5 (8.54, 21.78)		4.2 (0.56, 6.24)	
Safety[d]	**Tislelizumab (n=423)**		**Docetaxel (n=209)**	
TEAEs ≥15% of patients in either arm, n (%)	**All grade**	**≥Grade 3**	**All grade**	**≥Grade 3**
Anemia	132 (31.2)	17 (4.0)	98 (46.9)	14 (6.7)
ALT increased	98 (23.2)	3 (0.7)	38 (18.2)	0 (0.0)
Cough	93 (22.0)	5 (1.2)	36 (17.2)	1 (0.5)
AST increased	92 (21.7)	4 (0.9)	30 (14.4)	1 (0.5)
Weight decreased	77 (18.2)	4 (0.9)	21 (10.0)	0 (0.0)
Decreased appetite	69 (16.3)	5 (1.2)	46 (22.0)	2 (1.0)
Hypoalbuminemia	66 (15.6)	0 (0.0)	37 (17.7)	0 (0.0)
Constipation	55 (13.0)	0 (0.0)	38 (18.2)	0 (0.0)
Asthenia	54 (12.8)	3 (0.7)	45 (21.5)	9 (4.3)
White blood cell count decreased	20 (4.7)	1 (0.2)	72 (34.4)	46 (22.0)
Neutrophil count decreased	15 (3.5)	3 (0.7)	91 (43.5)	68 (32.5)
Leukopenia	14 (3.3)	1 (0.2)	59 (28.2)	36 (17.2)
Neutropenia	7 (1.7)	2 (0.5)	56 (26.8)	51 (24.4)
Alopecia	4 (0.9)	0 (0.0)	106 (50.7)	1 (0.5)

[a]Efficacy analysis set – China; [b]Stratified; [c]One-sided stratified log-rank test; [d]Safety analysis set - China.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; DoR, duration of response; HR, hazard ratio; mo, months; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TEAE, treatment-emergent adverse event.