First-Line Tislelizumab Plus Chemotherapy vs Placebo Plus Chemotherapy in Extensive-Stage Small Cell Lung Cancer: Long-Term Follow-Up of RATIONALE-312

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Yun Fan,[1] Yanqiu Zhao,[2] Dingzhi Huang,[3]* Jun Zhao,[4] Tai Qin,[5] Chunyu Wang,[5] Chenqi Chen,[6] Pu Sun,[7] Kirsha Naicker,[8] Yong Song[9]

[1]Department of Thoracic Oncology, Zhejiang Cancer Hospital, Hangzhou, China; [2]Department of Medical Oncology, The Affiliated Cancer Hospital of Zhengzhou University and Henan Cancer Hospital, Zhengzhou, China; [3]Department of Pulmonary Oncology, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China; [4]Department I of Thoracic Oncology, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Peking University Cancer Hospital and Institute, Beijing, China; [5]Clinical Development–Solid Tumors, BeOne Medicines, Ltd., Beijing, China; [6]Statistics, BeOne Medicines, Ltd., New York, NY, USA; [7]Clinical Biomarkers, BeOne Medicines, Ltd., Beijing, China; [8]Clinical Development–Solid Tumors, BeOne Medicines, Ltd., London, UK; [9]Department of Respiratory and Critical Care Medicine, Jinling Hospital, Nanjing Medical University, Nanjing, China. *Presenting author.

CONCLUSIONS

- Long-term follow-up data from RATIONALE-312 showed that patients with extensive-stage small cell lung cancer (ES-SCLC) who were treated with first-line (1L) tislelizumab plus chemotherapy had clinically meaningful and sustained improvements in overall survival (OS) in the intent-to-treat (ITT) and programmed death-ligand 1 (PD-L1)-evaluable populations, and improved investigator-assessed progression-free survival (PFS) in the ITT population vs those treated with placebo plus chemotherapy
- The safety profile of tislelizumab plus chemotherapy was generally well tolerated, with no new safety signals identified
- These data support tislelizumab plus chemotherapy as a 1L treatment option for patients with ES-SCLC

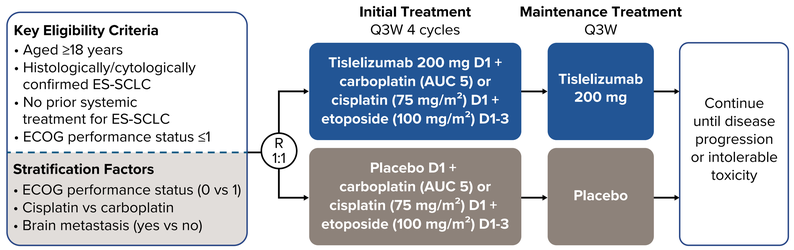
INTRODUCTION

- SCLC constitutes approximately 15% of all lung cancer cases, with more than 80% of patients presenting with ES-SCLC. It is characterised by poor prognosis, and there are limited treatment options[1,2]
- Platinum-based chemotherapy plus etoposide was the standard 1L treatment for ES-SCLC for several decades, until recent advances in anti–programmed cell death protein-1 (PD-1)/PD-L1 immune checkpoint inhibitors combined with platinum-based chemotherapy were found to improve OS in phase 3 trials, thus transforming the 1L treatment landscape for these patients[3-5]
- Tislelizumab, an anti–PD-1 monoclonal antibody, has shown promising clinical benefits in patients with ES-SCLC when combined with chemotherapy in the 1L setting[6]
  - The final analysis of the phase 3 RATIONALE-312 trial (NCT04005716; median study follow-up 14.2 months) demonstrated that tislelizumab plus chemotherapy significantly improved median OS (15.5 vs 13.5 months; hazard ratio [HR]=0.75; 95% confidence interval [CI]: 0.61, 0.93) and median PFS (4.7 vs 4.3 months; HR=0.64; 95% CI: 0.52, 0.78) compared with placebo plus chemotherapy in patients with ES-SCLC[6]
- Here we report long-term data after approximately 4 years of follow-up (an additional 8.3 months of minimum follow-up since the final analysis), including OS with subgroup analyses in both ITT and PD-L1–evaluable populations, and PFS in the ITT population only

METHODS

- RATIONALE-312 was a randomised, double-blind, placebo-controlled, multicentre phase 3 trial evaluating the efficacy and safety of tislelizumab plus chemotherapy (cisplatin or carboplatin + etoposide) vs placebo plus chemotherapy as a 1L treatment in patients with ES-SCLC in China (**Figure 1**)
- PD-L1 expression was assessed centrally using baseline tissue samples stained with the VENTANA PD-L1 (SP263) Assay (Roche) and measured by Tumour Area Positivity (TAP) score, tumour cell (TC) expression score, and immune cell (IC) expression score

Figure 1. Study Design



Statistical Methods
- Planned to enroll 455 patients; 80% power to detect a HR of 0.74 with 355 OS events
- Hierarchical testing on PFS: Only when OS demonstrates significance[a]
- HRs and 95% CIs were estimated using a Cox regression model stratified by ECOG performance status (1 vs 0) and platinum (carboplatin vs cisplatin)

Primary Endpoint
- OS

Key Secondary Endpoints
- PFS, ORR, and DoR (INV-assessed)
- Safety and tolerability

Exploratory Endpoint
- OS analyses in the PD-L1–evaluable population

[a]Under a one-sided *P*-value of .025.
Abbreviations: AUC, area under the curve; D, day; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; INV, investigator; ORR, overall response rate; Q3W, every 3 weeks; R, randomised.

RESULTS

Patient Disposition, Baseline Characteristics, and Subsequent Therapy

- As of the long-term follow-up data cutoff (December 29, 2023), 457 patients were randomised to receive treatment (227 to tislelizumab plus chemotherapy and 230 to placebo plus chemotherapy). The study has completed with no patients remaining in follow-up. Median study follow-up time was 15.4 months (95% CI: 0.2, 53.0) for the tislelizumab plus chemotherapy arm and 13.2 months (95% CI: 0.1, 47.7) for the placebo plus chemotherapy arm
- In the tislelizumab plus chemotherapy arm vs the placebo plus chemotherapy arm, 66.5% vs 79.1% of patients, respectively, received subsequent systemic anticancer therapy, of which the most common was conventional chemotherapy (55.9% vs 68.3%)
- Baseline demographics and disease characteristics were generally well balanced between treatment arms in both the ITT population (**Table 1**) and in the patients with evaluable tumour PD-L1 expression (data not shown). Characteristics were also generally similar between the ITT and the PD-L1–evaluable populations (data not shown), representative of the features of the target patient population

RESULTS

Table 1. Patient Baseline Demographics and Characteristics (ITT Population)

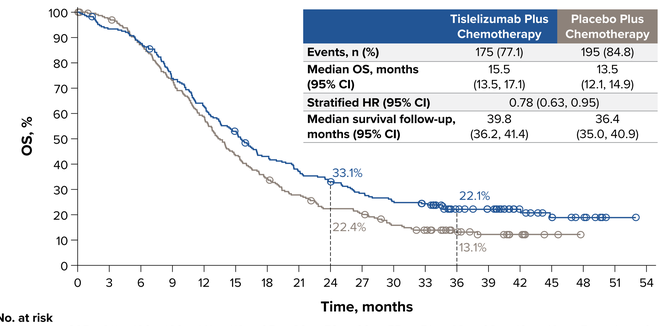
	Tislelizumab Plus Chemotherapy (n=227)	Placebo Plus Chemotherapy (n=230)
Median age (IQR), years	63.0 (56.0-66.0)	62.0 (55.0-67.0)
<65, n (%)	138 (60.8)	149 (64.8)
Sex, n (%)		
Male	186 (81.9)	186 (80.9)
Female	41 (18.1)	44 (19.1)
ECOG performance status, n (%)		
0	35 (15.4)	34 (14.8)
1	192 (84.6)	196 (85.2)
Smoking status, n (%)		
Never	53 (23.3)	59 (25.7)
Current	151 (66.5)	135 (58.7)
Former	23 (10.1)	36 (15.7)
Disease stage, n (%)		
III	20 (8.8)	29 (12.6)
IV	207 (91.2)	201 (87.4)
Confirmed distant metastatic site(s), n (%)		
Liver	64 (28.2)	59 (25.7)
Lung	32 (14.1)	59 (25.7)
Brain	1 (0.4)	4 (1.7)
Lymph nodes	48 (21.1)	45 (19.6)
Presence of brain metastases, n (%)		
Yes	1 (0.4)	4 (1.7)
No	226 (99.6)	226 (98.3)
Choice of platinum, n (%)		
Cisplatin	47 (20.7)	49 (21.3)
Carboplatin	180 (79.3)	181 (78.7)
Baseline LDH, n (%)		
≤ULN	114 (50.2)	109 (47.4)
>ULN	113 (49.8)	121 (52.6)
PD-L1–evaluable population, n (%)	60 (26.4)	65 (28.3)
IC <1%	26 (11.5)	11 (4.8)
IC ≥1%	34 (15.0)	54 (23.5)
TC <1%	56 (24.7)	57 (24.8)
TAP score <1%	37 (16.3)	31 (13.5)
TAP score ≥1%	23 (10.1)	34 (14.8)

Abbreviations: IQR, interquartile range; LDH, lactate dehydrogenase; ULN, upper limit of normal.

Efficacy

- With a median survival follow-up (time from randomization to death or censoring for OS analysis) of 39.8 months in the tislelizumab arm and 36.4 months in the placebo arm (long-term follow-up data cutoff: December 29, 2023), OS benefit was maintained with tislelizumab plus chemotherapy vs placebo plus chemotherapy (15.5 vs 13.5 months; stratified HR=0.78; 95% CI: 0.63, 0.95) in the ITT population, and the 3-year OS rates were 22.1% and 13.1%, respectively (**Figure 2**)
  - The 4-year OS rate in the tislelizumab plus chemotherapy arm was 18.9% with 7 patients still at risk, and no patients remained at risk in the placebo plus chemotherapy arm

Figure 2. OS in the ITT Population



	Tislelizumab Plus Chemotherapy	Placebo Plus Chemotherapy
Events, n (%)	175 (77.1)	195 (84.8)
Median OS, months (95% CI)	15.5 (13.5, 17.1)	13.5 (12.1, 14.9)
Stratified HR (95% CI)	0.78 (0.63, 0.95)	
Median survival follow-up, months (95% CI)	39.8 (36.2, 41.4)	36.4 (35.0, 40.9)

No. at risk																			
Tislelizumab plus chemotherapy	227	211	198	166	141	118	95	82	73	62	55	51	33	28	16	10	7	1	0
Placebo plus chemotherapy	230	221	197	165	132	98	78	62	49	45	33	27	17	12	7	2	0	0	0

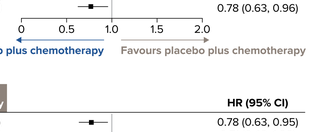
One patient had an unknown death date and was censored at the last known alive date for OS analysis.

- A consistent OS benefit with tislelizumab plus chemotherapy vs placebo plus chemotherapy was observed across several prespecified subgroups based on baseline characteristics, notably those with an ECOG performance status of 1 and presence of liver metastases (**Figure 3A**)
- In an exploratory analysis of patients with evaluable tumour PD-L1 expression, the median OS benefit with tislelizumab plus chemotherapy (n=60) vs placebo plus chemotherapy (n=65) was 20.7 vs 13.5 months, respectively (HR=0.71; 95% CI: 0.48, 1.06). This benefit was consistent with that in the ITT population and was favourable across all PD-L1 subgroups, although wide CIs were observed due to the limited sample sizes (**Figure 3B**)
- Investigator-assessed PFS for the ITT population was improved for patients who were treated with tislelizumab plus chemotherapy compared with those who received placebo plus chemotherapy (4.7 vs 4.3 months; stratified HR=0.65; 95% CI: 0.53, 0.80)

Figure 3. OS by (A) Subgroups Based on Baseline Demographics and Patient Characteristics in the ITT Population and (B) Baseline PD-L1 Expression in the PD-L1–Evaluable Population

A

Subgroup	Events/Total: Tislelizumab Plus Chemotherapy	Events/Total: Placebo Plus Chemotherapy	Median (95% CI): Tislelizumab Plus Chemotherapy	Median (95% CI): Placebo Plus Chemotherapy	HR (95% CI)
Overall	175/227	195/230	15.5 (13.5, 17.1)	13.5 (12.1, 14.9)	0.78 (0.63, 0.95)
Age, years					
<65	103/138	124/149	15.6 (12.8, 18.9)	14.3 (12.4, 15.7)	0.79 (0.61, 1.02)
≥65	72/89	71/81	15.4 (12.2, 20.5)	12.4 (10.9, 14.0)	0.75 (0.54, 1.05)
Sex					
Male	146/186	157/186	15.4 (13.4, 17.1)	13.2 (12.1, 14.7)	0.80 (0.64, 1.00)
Female	29/41	38/44	16.5 (11.0, 24.2)	15.4 (9.4, 18.8)	0.68 (0.42, 1.11)
ECOG performance status					
0	24/35	27/34	17.1 (13.4, 24.2)	15.3 (11.0, 26.2)	0.76 (0.44, 1.33)
1	151/192	168/196	15.2 (12.6, 17.0)	13.3 (12.0, 14.9)	0.78 (0.63, 0.97)
Brain metastasis					
No	174/226	191/226	15.5 (13.4, 17.1)	13.5 (12.1, 14.9)	0.78 (0.64, 0.96)
Choice of platinum					
Cisplatin	38/47	42/49	15.2 (12.3, 17.1)	13.7 (11.4, 18.0)	0.86 (0.55, 1.33)
Carboplatin	137/180	153/181	15.6 (13.2, 19.4)	13.3 (12.0, 15.2)	0.76 (0.60, 0.96)
Liver metastasis at baseline					
Yes	57/64	56/59	11.9 (9.7, 13.6)	10.6 (7.9, 11.3)	0.66 (0.45, 0.96)
No	118/163	139/171	18.2 (15.6, 22.8)	14.9 (13.3, 17.2)	0.78 (0.61, 1.00)
Baseline LDH					
≤ULN	86/114	88/109	18.2 (15.4, 21.3)	15.7 (14.0, 18.4)	0.80 (0.59, 1.07)
>ULN	89/113	107/121	12.2 (10.3, 15.5)	11.8 (10.5, 13.2)	0.78 (0.59, 1.03)
Smoking status					
Never	37/53	48/59	19.7 (12.5, 24.2)	15.4 (11.4, 17.7)	0.72 (0.47, 1.11)
Smoker	138/174	147/171	15.2 (12.8, 17.0)	13.0 (11.8, 14.7)	0.79 (0.63, 1.00)
Disease stage					
III	12/20	23/29	26.7 (15.4, NE)	15.4 (13.2, 26.2)	0.63 (0.31, 1.27)
IV	163/207	172/201	15.1 (12.6, 17.0)	12.8 (11.4, 14.3)	0.78 (0.63, 0.96)



B

Subgroup	Events/Total: Tislelizumab Plus Chemotherapy	Events/Total: Placebo Plus Chemotherapy	Median (95% CI): Tislelizumab Plus Chemotherapy	Median (95% CI): Placebo Plus Chemotherapy	HR (95% CI)
ITT population	175/227	195/230	15.5 (13.5, 17.1)	13.5 (12.1, 14.9)	0.78 (0.63, 0.95)
PD-L1–evaluable population	45/60	53/65	20.7 (12.6, 26.3)	13.5 (10.4, 19.4)	0.71 (0.48, 1.06)
IC <1%	19/26	9/11	18.8 (11.9, 29.8)	13.2 (5.5, 29.3)	0.68 (0.30, 1.51)
IC ≥1%	26/34	44/54	21.0 (11.0, 27.3)	13.5 (9.9, 20.0)	0.73 (0.45, 1.18)
TC <1%	43/56	48/57	19.9 (12.6, 23.8)	12.9 (9.4, 15.7)	0.69 (0.46, 1.05)
TAP score <1%	30/37	28/31	16.2 (10.1, 22.8)	12.9 (9.1, 14.4)	0.70 (0.42, 1.18)
TAP score ≥1%	15/23	25/34	27.2 (17.0, NE)	15.7 (10.0, 23.3)	0.62 (0.33, 1.18)

HRs and 95% CIs were estimated using an unstratified Cox regression model.
Abbreviation: NE, not estimable.

Safety

- The safety profile of tislelizumab plus chemotherapy remained consistent with the known risks of each treatment component, and no new safety signals were identified with long-term follow-up (**Table 2**)
- The most frequently reported any-grade treatment-emergent adverse events (TEAEs) in the tislelizumab plus chemotherapy arm vs the placebo plus chemotherapy arm were anaemia (85.0% vs 84.7%), alopecia (79.3% vs 79.5%), and neutropenia (68.7% vs 70.3%)
- The most frequently reported any-grade treatment-related adverse events (TRAEs) in the tislelizumab plus chemotherapy arm vs the placebo plus chemotherapy arm were alopecia (78.4% vs 79.5%), anaemia (76.7% vs 78.6%), and neutropenia (68.7% vs 70.3%)
- The most frequently reported immune-mediated adverse events (imAEs) in the tislelizumab plus chemotherapy arm vs the placebo plus chemotherapy arm were skin adverse reaction (16.7% vs 8.7%) and hypothyroidism (16.3% vs 4.8%)

Table 2. Safety Summary (Safety Population)

n (%)	Tislelizumab Plus Chemotherapy (n=227)	Placebo Plus Chemotherapy (n=229)
Patients with ≥1 any-grade TEAE	226 (99.6)	228 (99.6)
TRAEs	226 (99.6)	228 (99.6)
Patients with grade ≥3 TEAEs	202 (89.0)	206 (90.0)
TRAEs	194 (85.5)	198 (86.5)
Patients with serious TEAEs	94 (41.4)	70 (30.6)
TRAEs	70 (30.8)	42 (18.3)
TEAEs leading to discontinuation of any treatment component	30 (13.2)	7 (3.1)
TRAEs	24 (10.6)	4 (1.7)
TEAEs leading to modification of any treatment component	155 (68.3)	153 (66.8)
TRAEs	144 (63.4)	145 (63.3)
TEAEs leading to death	14 (6.2)	4 (1.7)
TRAEs	8 (3.5)	0
Patients with ≥1 any-grade imAE	91 (40.1)	42 (18.3)
Patients with grade ≥3 imAEs	25 (11.0)	1 (0.4)

REFERENCES

1. Rudin CM, et al. *Nat Rev Dis Primers*. 2021;7:3.
2. Oronsky B, et al. *J Cancer*. 2022;13:2945-2953.
3. Dingemans AC, et al. *Ann Oncol*. 2021;32:839-853.
4. Paz-Ares L, et al. *ESMO Open*. 2022;7:100408.
5. Liu SV, et al. *J Clin Oncol*. 2021;39:619-630.
6. Cheng Y, et al. *J Thorac Oncol*. 2024;19:1073-1085.

DISCLOSURES

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