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First-line Chemotherapy With or Without Tislelizumab for Extensive-stage Small Cell Lung Cancer: RATIONALE-312 Phase 3 Study

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Background

- The prognosis for ES-SCLC is exceptionally poor, with limited treatment options[1-3]
- Platinum-based chemotherapy (etoposide plus platinum) has been the standard of care for three decades[3,4]
- Anti-PD-L1 antibodies in combination with chemotherapy have emerged as the new standard of care for 1L ES-SCLC in recent years[5-7]; however, the flexibility to select a treatment regimen based on efficacy, safety, and accessibility in clinical practice is still limited
- Tislelizumab, a monoclonal antibody with high affinity and binding specificity for PD-1,[8] in combination with chemotherapy showed promising antitumor activity in patients with untreated ES-SCLC in a phase 2 study[9]
- The phase 3 RATIONALE-312 trial aimed to compare the efficacy and safety of tislelizumab versus placebo in combination with etoposide plus platinum as 1L treatment for patients with ES-SCLC in China

1. Rudin CM, et al. *Nat Rev Dis Primers.* 2021;7:3; 2. Oronsky B, et al. *J Cancer.* 2022;13:2945-2953; 3. Sathiyapalan A, et al. *Curr Oncol.* 2022;29:9046-9065; 4. Paz-Ares L, et al. *Lancet.* 2019;394:1929-1939; 5. Paz-Ares L, et al. *ESMO Open.* 2022:7:100408; 6. Liu SV, et al. *J Clin Oncol.* 2021;39:619-630; 7. Mathieu L, et al. *Oncologist.* 2021;26:433-438; 8. Hong Y, et al. *FEBS Open Bio.* 2021;11:782-792; 9. Wang Z, et al. *Lung Cancer.* 2020;147:259-268.
Abbreviations: 1L, first-line; ES-SCLC, extensive-stage small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

Study Design

Randomized, double-blind, placebo-controlled, multicenter, phase 3 study (NCT04005716)

Key eligibility criteria
- Patients aged ≥18 years with histologically/cytologically confirmed ES-SCLC
- No prior systemic treatment for ES-SCLC
- ECOG PS ≤1

R 1:1

Induction treatment (Q3W, four cycles)

- Tislelizumab 200 mg D1 + carboplatin (AUC 5) or cisplatin (75 mg/m^2), D1 + etoposide (100 mg/m^2), D1-3
- Placebo D1 + carboplatin (AUC 5) or cisplatin (75 mg/m^2), D1 + etoposide (100 mg/m^2), D1-3

Maintenance treatment

- Tislelizumab 200 mg Q3W
- Placebo Q3W

Continue until disease progression or intolerable toxicity

Stratification factors
- ECOG PS (0 vs 1)
- Cisplatin vs carboplatin
- Brain metastasis (yes vs no)

Primary endpoint: OS

Key secondary endpoints:
- PFS, ORR, and DoR (INV-assessed)
- Safety and tolerability

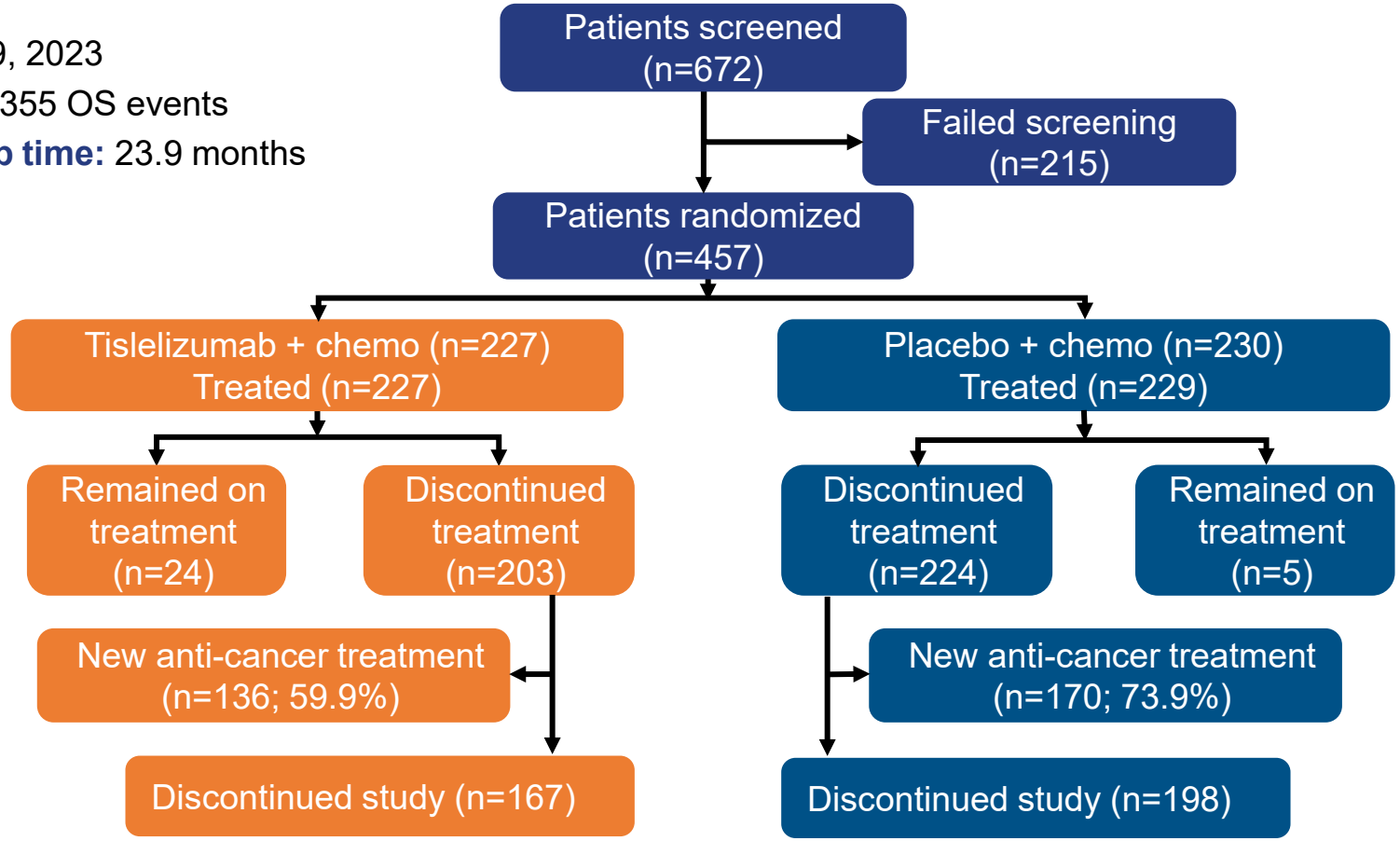
Statistical methods
- Planned to enroll 455 pts; 80% power to detect HR 0.74 with 353 OS events
- Hierarchical testing on PFS: only when OS demonstrates significance[a]

[a]Under 1-sided *P*-value of 0.025.

Abbreviations: AUC, area under the curve; D, day; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ES-SCLC, extensive-stage small cell lung cancer; HR, hazard ratio; INV, investigator; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomized.

Patient Disposition

Data cut-off date: April 19, 2023
Final analysis: Based on 355 OS events
Minimum study follow-up time: 23.9 months



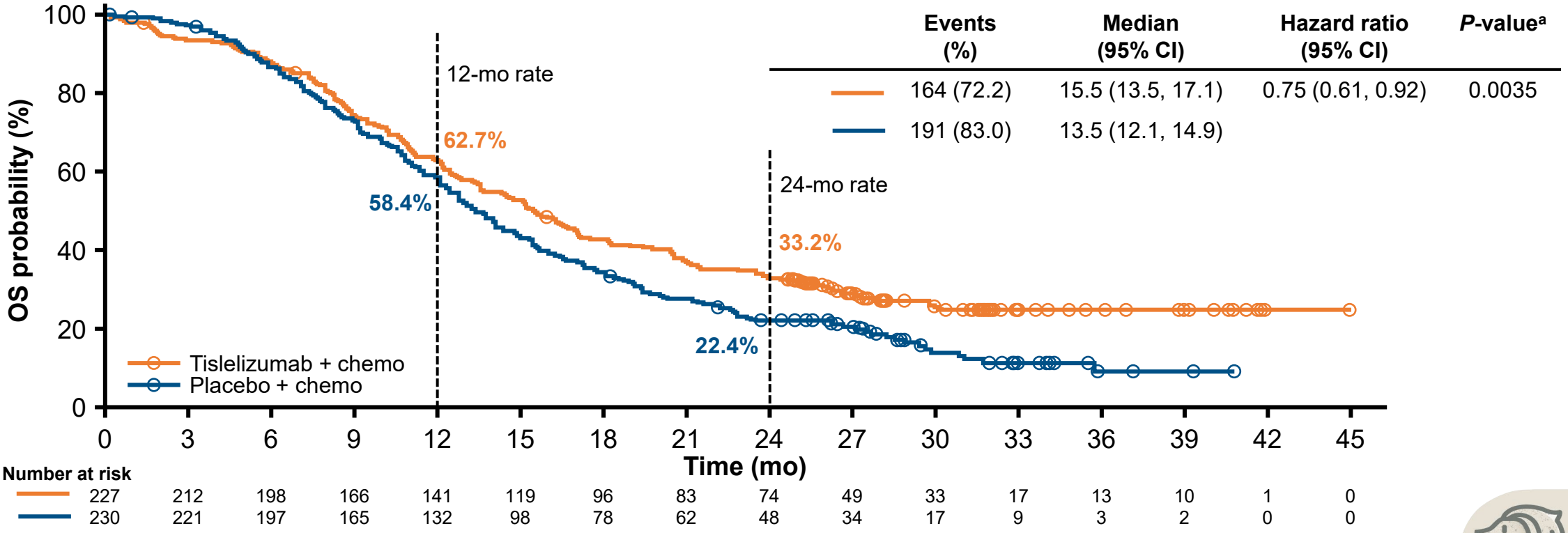
Abbreviation: chemo, chemotherapy.

Baseline Characteristics

		Tislelizumab + chemo (n=227)	Placebo + chemo (n=230)
Age (years), median (range)		63 (31-78)	62 (34-78)
≥65 years, n (%)		89 (39.2)	81 (35.2)
Male, n (%)		186 (81.9)	186 (80.9)
ECOG PS, 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)
AJCC staging at study entry, n (%)	III	20 (8.8)	29 (12.6)
	IV	207 (91.2)	201 (87.4)
Distant metastatic site(s), n (%)	Liver	64 (28.2)	59 (25.7)
	Brain	1 (0.4)	4 (1.7)
≥3 metastatic sites, n (%)		183 (80.6)	164 (71.3)
Baseline LDH, n (%)	≤ULN	114 (50.2)	109 (47.4)
	>ULN	113 (49.8)	121 (52.6)
Choice of platinum, n (%)	Cisplatin	47 (20.7)	49 (21.3)
	Carboplatin	180 (79.3)	181 (78.7)

Abbreviations: AJCC, American Joint Committee on Cancer; chemo, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; ULN, upper limit of normal.

Overall Survival (OS)



	Events (%)	Median (95% CI)	Hazard ratio (95% CI)	*P*-value[a]
Tislelizumab + chemo	164 (72.2)	15.5 (13.5, 17.1)	0.75 (0.61, 0.92)	0.0035
Placebo + chemo	191 (83.0)	13.5 (12.1, 14.9)		

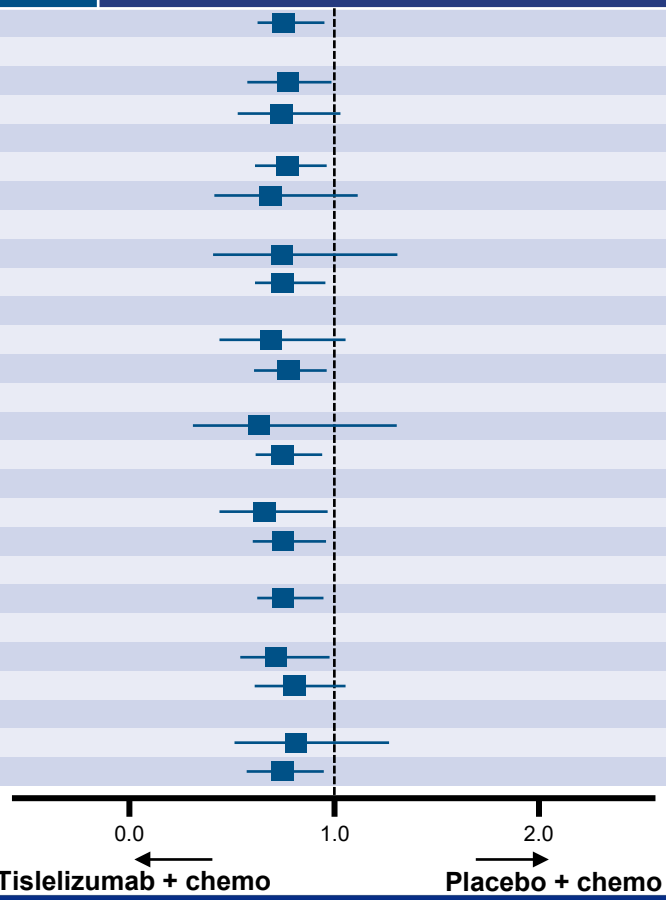
Number at risk

Tislelizumab + chemo	227	212	198	166	141	119	96	83	74	49	33	17	13	10	1	0
Placebo + chemo	230	221	197	165	132	98	78	62	48	34	17	9	3	2	0	0

[a]One-sided p-value from stratified log-rank test; superiority threshold: 0.0211. **Abbreviations:** chemo, chemotherapy; CI, confidence interval; mo, months; OS, overall survival.

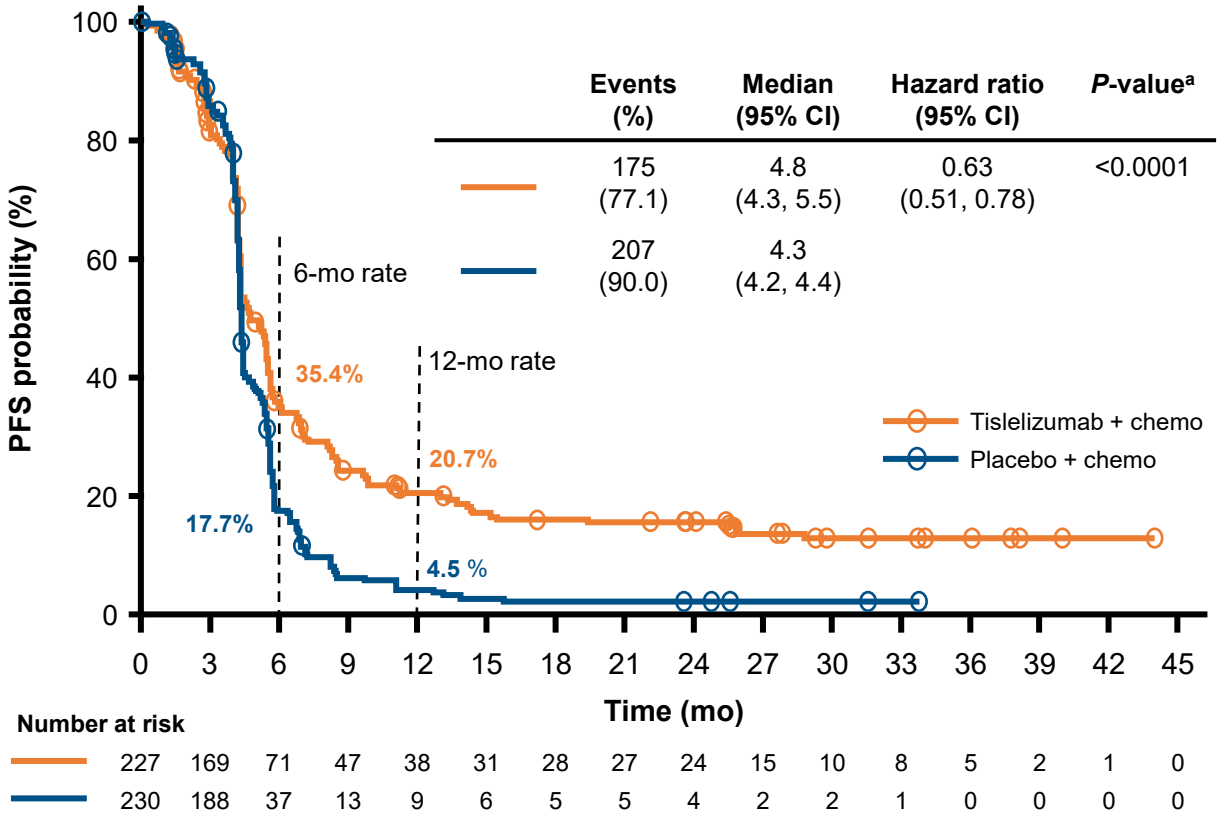
OS Subgroup Analyses

Subgroup	Tislelizumab + chemo Event/total	Placebo + chemo Event/total	Hazard ratio (95% CI)[a]
Overall	164/227	191/230	0.75 (0.61, 0.93)
Age group			
<65 years	98/138	122/149	0.76 (0.58, 0.99)
≥65 years	66/89	69/81	0.73 (0.52, 1.02)
Sex			
Male	135/186	153/186	0.76 (0.60, 0.96)
Female	29/41	38/44	0.69 (0.42, 1.12)
ECOG performance status			
0	23/35	27/34	0.74 (0.42, 1.29)
1	141/192	164/196	0.75 (0.60, 0.94)
Smoking status			
Never	35/53	48/59	0.69 (0.44, 1.06)
Smoker	129/174	143/171	0.77 (0.60, 0.97)
AJCC staging at study entry			
III	11/20	21/29	0.62 (0.30, 1.29)
IV	153/207	170/201	0.74 (0.60, 0.93)
Liver metastases at baseline			
Yes	54/64	56/59	0.65 (0.44, 0.95)
No	110/163	135/171	0.75 (0.59, 0.97)
Brain metastasis			
No	163/226	187/226	0.75 (0.61, 0.93)
Baseline LDH			
≤ULN	78/114	88/109	0.72 (0.53, 0.98)
>ULN	86/113	103/121	0.80 (0.60, 1.06)
Choice of platinum			
Cisplatin	35/47	42/49	0.81 (0.51, 1.26)
Carboplatin	129/180	149/181	0.74 (0.58, 0.93)

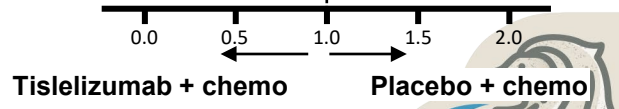


[a]Unstratified hazard ratios.
Abbreviations: AJCC, American Joint Committee on Cancer; chemo, chemotherapy; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; OS, overall survival; ULN, upper limit of normal.

Progression-free Survival (PFS)



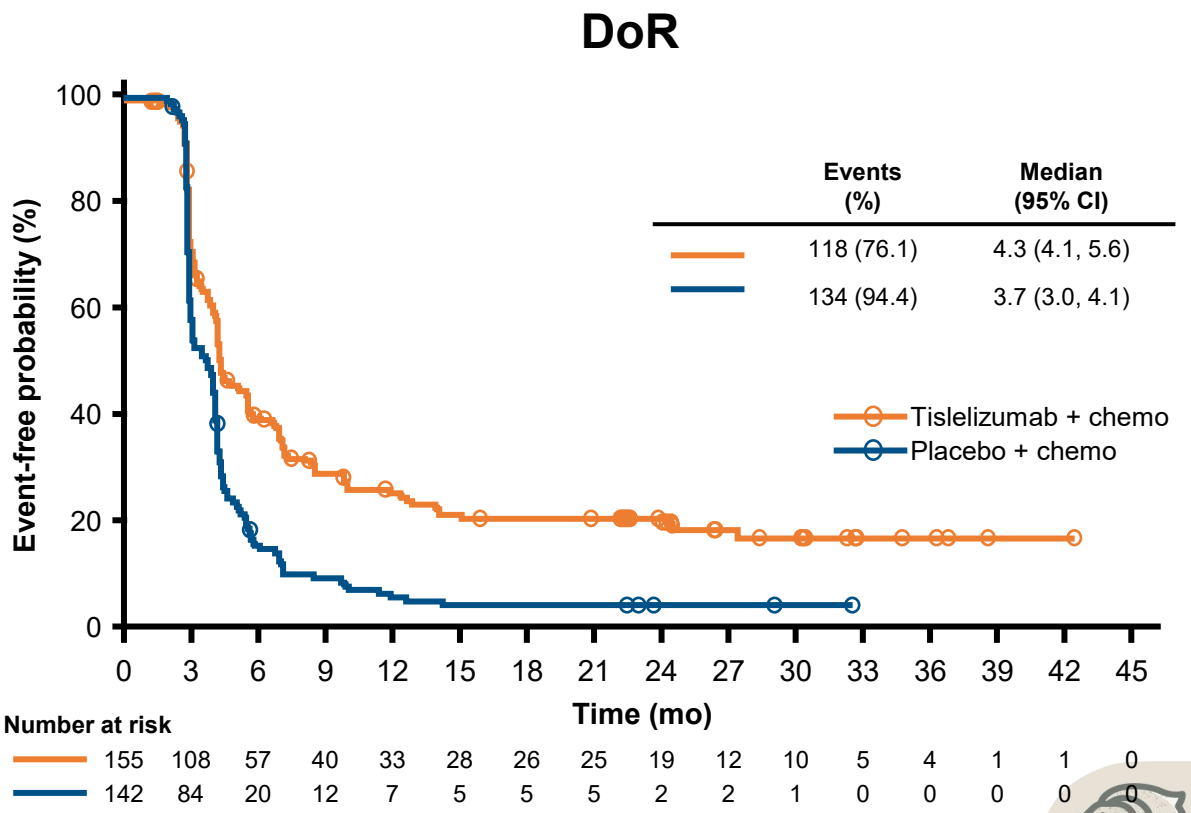
Subgroup	Tislelizumab + chemo Event/total	Placebo + chemo Event/total	Hazard ratio (95% CI)[b]
Overall	175/227	207/230	0.63 (0.51, 0.77)
Age group			
<65 years	105/138	138/149	0.58 (0.45, 0.76)
≥65 years	70/89	69/81	0.74 (0.53, 1.05)
Sex			
Male	143/186	165/186	0.69 (0.55, 0.87)
Female	32/41	42/44	0.38 (0.23, 0.63)
ECOG performance status			
0	28/35	29/34	0.65 (0.39, 1.10)
1	147/192	178/196	0.63 (0.50, 0.79)
Smoking status			
Never	41/53	55/59	0.50 (0.32, 0.77)
Smoker	134/174	152/171	0.67 (0.53, 0.85)
AJCC staging at study entry			
III	14/20	25/29	0.50 (0.25, 1.00)
IV	161/207	182/201	0.62 (0.50, 0.77)
Liver metastases at baseline			
Yes	51/64	56/59	0.70 (0.47, 1.03)
No	124/163	151/171	0.60 (0.47, 0.77)
Brain metastasis			
No	174/226	204/226	0.63 (0.51, 0.77)
Baseline LDH			
≤ULN	91/114	97/109	0.63 (0.47, 0.84)
>ULN	84/113	110/121	0.64 (0.48, 0.86)
Choice of platinum			
Cisplatin	38/47	43/49	0.75 (0.48, 1.18)
Carboplatin	137/180	164/181	0.60 (0.48, 0.76)



[a]One-sided p-value from stratified log-rank test. [b]Unstratified hazard ratios.
Abbreviations: AJCC, American Joint Committee on Cancer; chemo, chemotherapy; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; mo, months; PFS, progression-free survival; ULN, upper limit of normal.

Confirmed Antitumor Response

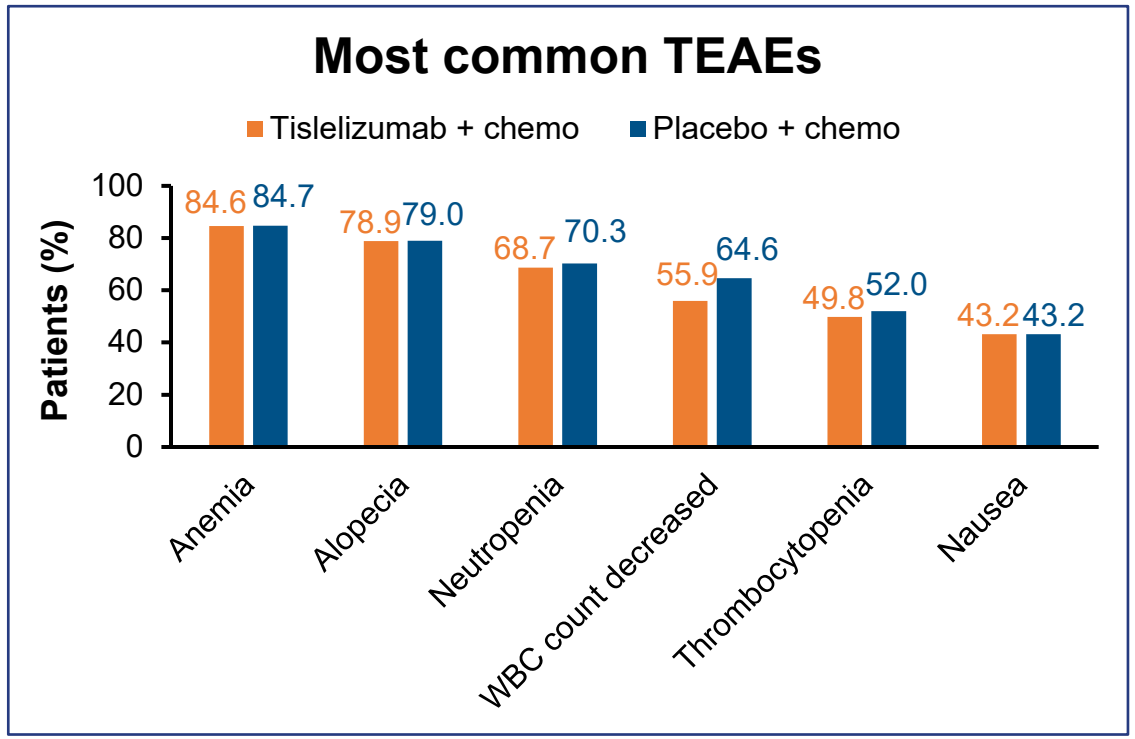
	Tislelizumab + chemo (n=227)	Placebo + chemo (n=230)
ORR, % (95% CI)	68.3 (61.8, 74.3)	61.7 (55.1, 68.0)
Best overall response, n (%)		
CR	1 (0.4)	0 (0.0)
PR	154 (67.8)	142 (61.7)
SD	46 (20.3)	60 (26.1)
Non-CR/non-PD	0 (0.0)	1 (0.4)
PD	11 (4.8)	15 (6.5)
NE or NA	15 (6.6)	12 (5.2)



Abbreviations: chemo, chemotherapy; CI, confidence interval; CR, complete response; DoR, duration of response; mo, months; NA, not assessable; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria In Solid Tumours version 1.1; SD, stable disease.

Safety Summary

	Tislelizumab + chemo (n=227)	Placebo + chemo (n=229)
Tislelizumab/placebo cycles		
Mean	11.8	7.3
Median (range)	6.0 (1-59)	6.0 (1-48)
>16 cycles, n (%)	44 (19.4%)	10 (4.4%)
Chemotherapy cycles, median, n (range)	4 (1-4)	4 (1-4)
TEAEs, n (%)	226 (99.6)	228 (99.6)
Treatment-related[a]	226 (99.6)	228 (99.6)
Grade ≥3	201 (88.5)	206 (90.0)
Serious	94 (41.4)	69 (30.1)
Leading to discontinuation[b]	30 (13.2)	7 (3.1)
Leading to death[c]	14 (6.2)	4 (1.7)
Tislelizumab/placebo-related	7 (3.1)	0 (0.0)
Chemotherapy-related	6 (2.6)	0 (0.0)
Immune-mediated AEs, n (%)	87 (38.3)	41 (17.9)
Leading to death	1 (0.4)	0 (0.0)
Infusion-related reactions, n (%)	8 (3.5)	5 (2.2)



The most common immune-mediated AEs in the tislelizumab plus chemo arm were hypothyroidism (13.7%), rash (13.2%), hyperthyroidism (5.7%)

[a]Related to any study drug. [b]Led to discontinuation of any component. [c]Tislelizumab/placebo related AE leading to death were respiratory failure, thrombocytopenia, gastrointestinal hemorrhage, autoimmune myocarditis, cardiac failure acute, depressed level of consciousness, and death. **Abbreviations:** AE, adverse event; chemo, chemotherapy, TEAE, treatment-emergent adverse event; WBC, white blood cell.

Conclusions

- RATIONALE-312 met its primary endpoint, demonstrating a statistically significant and clinically meaningful improvement in OS with tislelizumab plus chemotherapy compared with placebo plus chemotherapy in 1L ES-SCLC
  - Median OS 15.5 vs 13.5 months (HR 0.75 [95% CI: 0.61, 0.92]; *P*=0.0035)
  - Survival benefit was consistently observed across all the pre-defined subgroups, accompanied by significant improvement in PFS, increase in ORR, and more durable responses compared with placebo plus chemotherapy
- Tislelizumab plus chemotherapy showed a manageable safety profile

The results from this study confirm that the PD-1 inhibitor tislelizumab, in combination with chemotherapy, can improve OS in ES-SCLC, adding supporting evidence for the use of PD-1 inhibitors in 1L treatment of ES-SCLC

Abbreviations: IL, first-line; CI, confidence intervals; ES-SCLC, extensive-stage small cell lung cancer; HR, hazard ratio; OS, overall survival; PD-1, programmed cell death protein 1; PFS, progression-free survival.

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