RATIONALE-312: Exploratory Analysis of Tislelizumab Plus Platinum-Etoposide on Brain Disease Progression in First-Line Extensive-Stage Small Cell Lung Cancer

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CONCLUSIONS

- In this exploratory analysis of RATIONALE-312, TIS+CT was associated with a reduced risk of brain PD or RT and improved survival outcomes in patients with brain PD compared with PBO + CT
- Additionally, TIS+CT was associated with a clearly clinically meaningful improvement in quality-adjusted survival in patients with brain PD compared with CT alone
- Taken together, these data suggest that TIS+CT may delay time to brain PD and associated RT and improve the quality-adjusted survival experience of patients who develop brain PD compared with CT alone
- These findings further support TIS+CT as an efficacious first-line treatment of ES-SCLC and highlight its importance in improving patient outcomes in a disease state where brain metastases are common

INTRODUCTION

- RATIONALE-312 (NCT04005716) showed that tislelizumab (TIS) + platinum-etoposide chemotherapy (CT) significantly improved overall survival (OS) and progression-free survival (PFS) compared with placebo (PBO)+CT in first-line extensive-stage small cell lung cancer (ES-SCLC)[1]
- Furthermore, TIS+CT resulted in clinically meaningful improvement in quality of life (QoL) and long-term OS benefit compared with PBO+CT[2,3]
- Brain metastases are present in 10-20% of patients with SCLC at diagnosis and develop in 50-80% during the disease course[4]
- RATIONALE-312 enrolled <1% of patients with baseline brain metastases, which was similar to that observed in CAPSTONE-1 (2%)[5]
- To better understand the impact of TIS on brain metastases in ES-SCLC, an exploratory analysis of RATIONALE-312 was conducted to compare the time to brain progressive disease (PD) in the intent-to-treat (ITT) population and the clinical benefit in patients with brain PD in the TIS+CT and PBO+CT treatment arms

METHODS

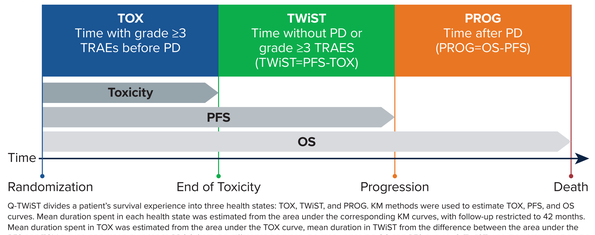
Trial Design

- Data from the final analysis of the multicenter, randomized, double-blind, placebo-controlled phase 3 RATIONALE-312 trial (data cut-off: April 19, 2023) were used[1]
  - Eligible patients with previously untreated ES-SCLC received four cycles of TIS (200 mg) or PBO, with etoposide plus carboplatin or cisplatin intravenously every 3 weeks, followed by TIS (200 mg) or PBO maintenance
  - Patients with previously treated, stable, asymptomatic supratentorial brain metastases were eligible; however, patients with leptomeningeal metastases were excluded
  - Stereotactic radiation or whole-brain radiation was not allowed 14 days before randomization
  - Prophylactic cranial radiation (PCI) was permitted during maintenance treatment
  - MRI or CT imaging of the chest, abdomen, pelvis, and brain was done at baseline, every 6 weeks for the first 48 weeks, and every 9 weeks thereafter
  - Detailed methods were reported previously[1]

Assessments

- Brain PD was defined as time to disease progression in the brain per RECIST v1.1 (including new brain lesions or progression of existing lesions) or receipt of brain radiation therapy (RT)
  - Analysis of time to brain PD included patients with and without brain metastases at baseline
  - Time to brain PD was analyzed by the Kaplan-Meier (KM) method, with patients without brain PD censored at their primary PFS event
  - PFS and OS in patients with brain PD were analyzed by the KM method
- Clinical benefit was determined using a quality-adjusted time without symptoms or toxicity (Q-TWiST) analysis in patients with brain PD (**Figure 1**)
  - Q-TWiST integrates survival, progression, toxicity, and patient-reported QoL into a single, clinically interpretable metric (**Figure 1**)[6]
  - Absolute Q-TWiST gain was defined as the difference in mean Q-TWiST between treatment arms
  - Relative Q-TWiST gain was calculated as the absolute Q-TWiST gain divided by the mean OS in the control arm
  - Relative gains ≥15% are considered clearly clinically meaningful based on commonly accepted thresholds[6,7]

Figure 1. Q-TWiST Analysis Framework



Q-TWiST divides a patient's survival experience into three health states: TOX, TWiST, and PROG. KM methods were used to estimate TOX, PFS, and OS curves. Mean duration spent in each health state was estimated from the area under the corresponding KM curves, with follow-up restricted to 42 months. Mean duration spent in TOX was estimated from the area under the TOX curve, mean duration in TWiST from the difference between the area under the PFS and TOX curves, and mean duration in PROG from the difference between the area under the OS and PFS curves. Q-TWiST was then calculated as the utility-weighted sum of the mean durations: (U_{TOX} × TOX) + (U_{TWiST} × TWiST) + (U_{PROG} × PROG), where U represents the mean QoL utility weight for each health state. Utility weights range from 0 to 1, with 0 representing a health state equivalent to death and 1 representing perfect health. Utility weights were derived from EQ-5D data collected during the RATIONALE-312 trial.

Abbreviations: EQ-5D, EuroQol 5-Dimension questionnaire; KM, Kaplan-Meier; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PROG, time for disease progression to death/censoring; QoL, quality of life; Q-TWiST, quality-adjusted time without symptoms or toxicity; TOX, time with toxicity; TRAE, treatment-related adverse event; TWiST, time without symptoms or toxicity; U, quality-of-life utility weight.

RESULTS

Baseline Characteristics

- Overall, 457 patients (TIS+CT [n=227]; PBO+CT [n=230]) were enrolled in RATIONALE-312
  - Baseline characteristics of patients with or without brain PD were similar in the TIS+CT and PBO + CT arms (**Table 1**)

Table 1. Baseline Characteristics in Patients With or Without Brain PD

Characteristic	Patients With Brain PD		Patients Without Brain PD	
	TIS+CT (n=44)	PBO+CT (n=44)	TIS+CT (n=183)	PBO+CT (n=186)
Age, years				
Median (IQR)	63.5 (56.0-66.5)	59.0 (54.0-63.0)	63.0 (56.0-66.0)	63.0 (55.3-67.8)
<65, n (%)	28 (63.6)	33 (75.0)	110 (60.1)	116 (62.4)
≥65, n (%)	16 (36.4)	11 (25.0)	73 (39.9)	70 (37.6)
Sex, n (%)				
Male	38 (86.4)	34 (77.3)	148 (80.9)	152 (81.7)
Female	6 (13.6)	10 (22.7)	35 (19.1)	34 (18.3)
ECOG PS 0, n (%)				
0	6 (13.6)	4 (9.1)	29 (15.8)	30 (16.1)
1	38 (86.4)	40 (90.9)	154 (84.2)	156 (83.9)
Smoking history, n (%)				
Ever smoker	35 (79.5)	33 (75.0)	139 (76.0)	138 (74.2)
Never smoker	9 (20.5)	11 (25.0)	44 (24.0)	48 (25.8)
AJCC stage, n (%)				
III	2 (4.5)	5 (11.4)	18 (9.8)	24 (12.9)
IV	42 (95.5)	39 (88.6)	165 (90.2)	162 (87.1)
Liver metastasis, n (%)	12 (27.3)	9 (20.5)	52 (28.4)	50 (26.9)

Abbreviations: AJCC, American Joint Committee on Cancer; CT, chemotherapy; IQR, interquartile range; PBO, placebo; PD, progressive disease; TIS, tislelizumab.

Incidence and Time to Brain PD

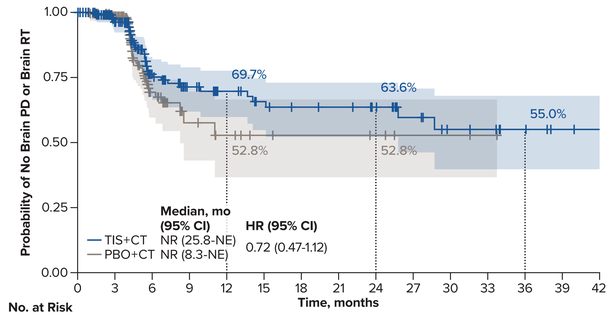
- With a median follow-up of 14.2 months, 44 (19%) patients developed brain PD in each arm of the overall population (**Table 2**)
  - Brain PD was determined by RECIST-defined imaging in 98% of patients in both arms of the overall population (**Table 2**), with most imaging done by MRI (TIS+CT [86%]; PBO+CT [89%]; **Table S1**)
  - Compared with PBO+CT, TIS+CT was associated with a reduced risk for time to brain PD (HR=0.72 [95% CI: 0.47-1.12]; **Figure 2**)

Table 2. Proportion of Patients Developing Brain PD

	Baseline Brain Mets		No Baseline Brain Mets		Overall Population	
	TIS+CT (n=1)	PBO+CT (n=4)	TIS+CT (n=226)	PBO+CT (n=226)	TIS+CT (n=227)	PBO+CT (n=230)
PD, n (%)	1 (100.0)	3 (75.0)	161 (71.2)	198 (87.6)	162 (71.4)	201 (87.4)
Brain PD, n (%)[a]	0 (0.0)	2 (50.0)	44 (19.5)	42 (18.6)	44 (19.4)	44 (19.1)
RECIST-defined brain PD	0 (0.0)	2 (50.0)	43 (19.0)	41 (18.1)	43 (18.9)	43 (18.7)
Receipt of brain RT[b]	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)

[a]Includes both RECIST-defined brain progression and receipt of brain RT; [b]Brain RT without documented RECIST-defined brain PD.
Abbreviations: CT, chemotherapy; Mets, metastasis; PBO, placebo; PD, progressive disease; RT, radiotherapy; TIS, tislelizumab.

Figure 2. Time to Brain PD in Intent-to-Treat Population[a]



[a]Excludes three patients in TIS+CT and one in PBO+CT who received prophylactic cranial irradiation during treatment.
Abbreviations: CI, confidence interval; CT, chemotherapy; mo, month; NE, not estimable; NR, not reached; PBO, placebo; PD, progressive disease; RT, radiotherapy; TIS, tislelizumab.

RT in Patients With PD

- Forty-one patients treated with TIS+CT and 34 patients treated with PBO+CT received brain RT during or after study treatment (**Table S2**)
- Brain RT after study treatment was the most common timing for RT and was delivered in similar proportions in both arms (TIS+CT: 14.5%, PBO+CT: 13.9%; **Table S2**)
- Among patients receiving brain RT during or after study treatment, the cumulative incidence of brain RT over time was numerically lower in the TIS+CT arm, with a 12-month cumulative incidence of 78% versus 92% in the TIS+CT and PBO+CT arms, respectively (**Table 3**)

Table 3. Cumulative Incidence Rate of Brain RT Over Time

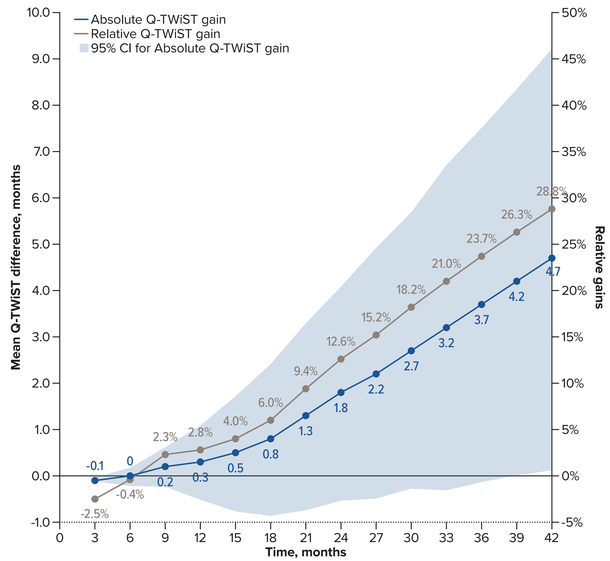
Time From Randomization	TIS+CT (n=41)	PBO+CT (n=34)
6 months, % (95% CI)	31.7 (19.8-48.3)	35.3 (21.8-53.7)
12 months, % (95% CI)	78.0 (64.5-89.1)	91.2 (78.9-97.7)
18 months, % (95% CI)	90.2 (79.0-96.9)	91.2 (78.9-97.7)
24 months, % (95% CI)	92.7 (82.2-98.1)	100.0 (NE-NE)

Abbreviations: CI, confidence interval; CT, chemotherapy; NE, not estimable; PBO, placebo; RT, radiation therapy; TIS, tislelizumab.

Survival Outcomes in Patients with Brain PD

- In patients who developed brain PD, median PFS (4.7 vs 4.4 months) and OS (15.2 vs 14.1 months) were numerically longer with TIS+CT than with PBO+CT (**Figure S1**)

Figure 3. Absolute and Relative Q-TWiST Gain With TIS + CT vs PBO + CT Over Time in Patients With Brain PD



Abbreviations: CT, chemotherapy; PBO, placebo; PD, progressive disease; Q-TWiST, quality-adjusted time without symptoms of disease or toxicity; TIS, tislelizumab.

Q-TWiST in Patients With Brain PD

- Time with toxicity before PD was similar between treatment arms; however, patients in the TIS+CT arm had longer time without symptoms or toxicity and longer time after PD than those in the PBO+CT arm (**Table 3**)
- Among patients with brain PD, TIS+CT was associated with an improved quality-adjusted survival time of 4.7 (95% CI, 0.1-9.2) months at the 42-month follow-up, resulting in a clearly clinically meaningful 28.8% relative gain versus PBO+CT (**Table 3**; **Figure 3**)

Table 4. Mean Health State Duration and Q-TWiST in Patients With Brain PD

Health State	TIS+CT (n=44)	PBO+CT (n=44)	Abs Gain (95% CI)[a]	Nominal *P*-value	Relative Gain
TOX, mo	1.0	1.2	-0.2 (-0.8-0.4)	0.4404	-
TWiST, mo	5.8	3.6	2.2 (0.4-4.1)	0.0193	-
PROG, mo	15.6	11.5	4.0 (-0.6-8.7)	0.0897	-
Q-TWiST, mo	19.1	14.5	4.7 (0.1-9.2)	0.0445	28.8%

[a]The 95% CI was estimated using 1000 bootstrap resamples.
Abbreviations: Abs, absolute; CI, confidence interval; CT, chemotherapy; mo, months; PBO, placebo; PD, progressive disease; PROG, time for disease progression to death/censoring; Q-TWiST, quality-adjusted time without symptoms of disease or toxicity; TIS, tislelizumab; TOX, time with toxicity; TWiST, time without symptoms of disease or toxicity.

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DISCLOSURES

FP: Received speaker and consultant fees from AstraZeneca, Johnson & Johnson, Roche, Amgen, BeOne Medicines, Gilead, PharmaMar, Daiichi Sankyo, and Pfizer, unrelated to the current work.

ACKNOWLEDGMENTS

The authors thank the participants and their families, investigators, co-investigators, and the study teams at each of the participating centers. This study was sponsored by BeOne Medicines, Ltd. Medical writing and editorial assistance were provided by Michael Franklin, Jose Casasnovas Nieves, and Elizabeth Hermans, employees of BeOne Medicines, Ltd.

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Presented at the 2026 European Society for Medical Oncology Annual Meeting; October 23-27, 2026; Madrid, Spain

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Table S1. Brain Imaging Modality in Patients Who Had Brain PD

Imaging Modality	TIS + Chemo (n=44)	PBO + Chemo (n=44)
MRI, n (%)	38 (86.4)	39 (88.6)
CT scan, n (%)	5 (11.4)	5 (11.4)
Contrast-enhanced MRI, n (%)	0 (0.0)	1 (2.3)
Contrast-enhanced CT scan, n (%)	0 (0.0)	1 (2.3)

Abbreviations: Chemo, chemotherapy; CT, computed tomography; PBO, placebo; MRI, magnetic resonance imaging; TIS, tislelizumab.

Table S2. Patients Treated With Brain RT

Brain RT Timing	TIS + CT (n=227)	PBO + CT (n=230)
During study treatment, n (%)	8 (3.5)	2 (0.9)
WBRT study treatment	7 (3.1)	2 (0.9)
SBRT study treatment	4 (1.8)	0 (0.0)
PCI during study treatment	3 (1.3)	1 (0.4)
After study treatment, n (%)	33 (14.5)	32 (13.9)

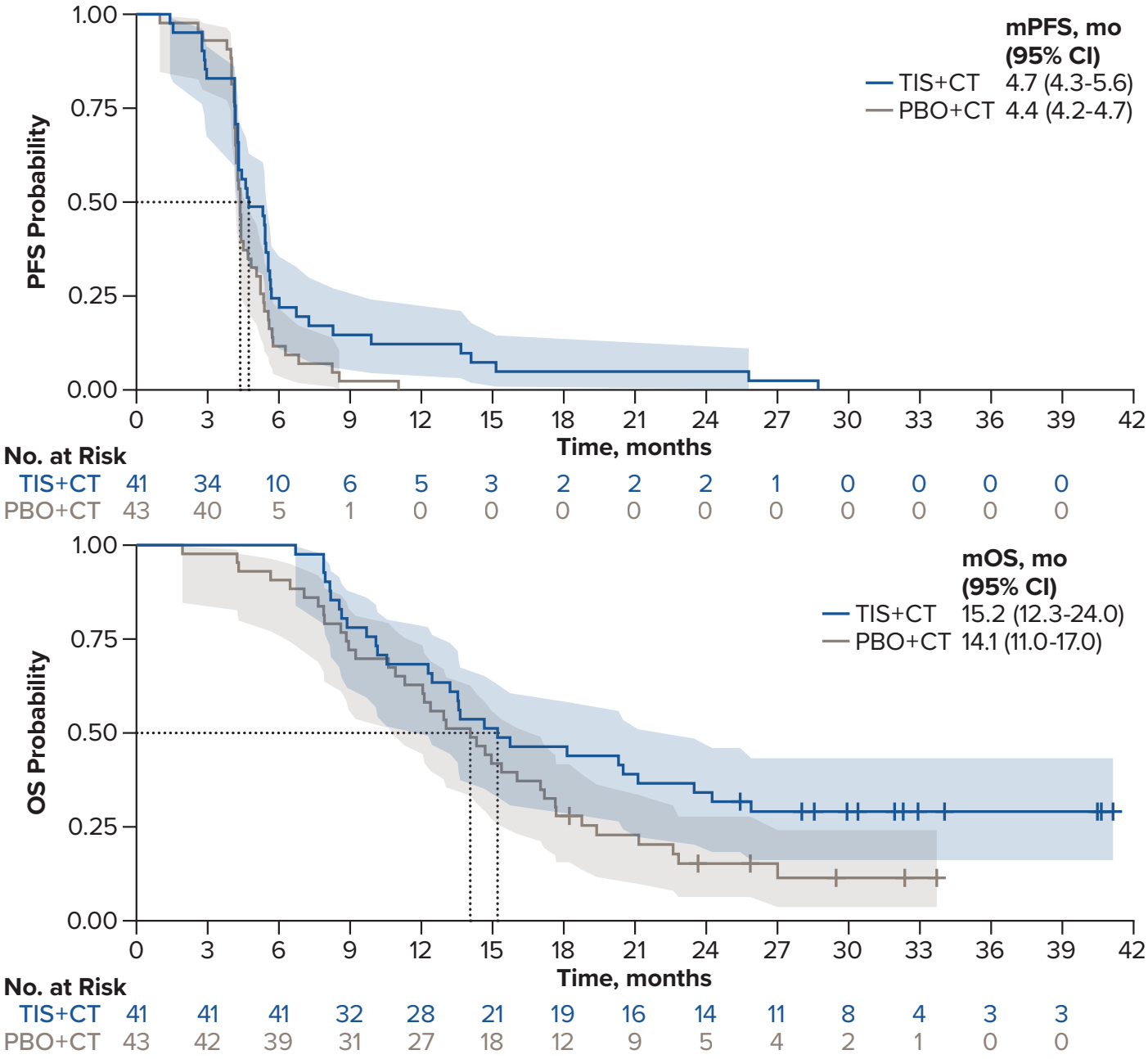
Abbreviations: CT, chemotherapy; PBO, placebo; PCI, prophylactic cranial irradiation; RT, radiotherapy; SBRT, stereotactic body radiotherapy; TIS, tislelizumab; WBRT, whole-brain radiotherapy.

Figure S1 *on next page.*

RATIONALE-312: Exploratory Analysis of Tislelizumab Plus Platinum-Etoposide on Brain Disease Progression in First-Line Extensive-Stage Small Cell Lung Cancer

Supplementary Data

Figure S1. PFS (A) and OS (B) in Patients With Brain PD[a]



[a]Excludes three patients in TIS+CT and one in PBO+CT who received prophylactic cranial irradiation during treatment.

Abbreviations: CI, confidence interval; CT, chemotherapy; mo, months; mOS, median overall survival; mPFS, median progression-free survival; PBO, placebo; PD, progressive disease; TIS, tislelizumab.