

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

Authors: Francesco Passiglia,¹ William N. William Jr.,² Riyaz Shah,³ Steven Kao,⁴ Justin Gainor,⁵ Julian Kretz,⁶ Kirsha Naicker,⁷ Wenxi Tang,⁸ Mike Shetka,⁸ Mesha Austin Taylor,⁸ Sandip Patel⁹

Affiliations: ¹University of Turin, Turin, Italy; ²Grupo Oncoclínicas, São Paulo, Brazil; ³Maidstone Hospital, Maidstone, UK; ⁴Chris O'Brien Lifehouse, Camperdown, Australia; ⁵Harvard Medical School, Boston, MA, US; ⁶BeOne Medicines GmbH, Basel, Switzerland; ⁷BeOne Medicines Ltd, London, United Kingdom; ⁸BeOne Medicines Ltd, San Carlos, CA, United States; ⁹University of California, San Diego, CA, United States

Background: Brain metastases in SCLC occur in about 20% of patients (pts) at diagnosis and up to 80% after 2 years, leading to poor prognosis. In RATIONALE-312 (NCT04005716), tislelizumab (TIS) + chemotherapy (CT) demonstrated overall survival (OS) benefit compared with placebo (PBO) + CT in first-line extensive-stage (ES) SCLC. An exploratory analysis of RATIONALE-312 evaluating time to progressive disease (PD) in the brain and quality-adjusted time without symptoms or toxicity (Q-TWiST) in pts with brain PD is reported here.

Methods: This RATIONALE-312 exploratory analysis included pts with brain metastases (stable, treated or asymptomatic) or without brain metastases at baseline. Per protocol specification, brain imaging (CT or MRI) was done at baseline, Q6W for the first 48 weeks, and Q9W thereafter. Brain PD was defined as time to PD in brain per RECIST v1.1 or radiation therapy (RT) to the brain during treatment. Time-to-brain PD was analyzed by Kaplan-Meier method. Q-TWiST method was used for quality-adjusted survival incorporating EQ-5D utility data.

Results: By April 19, 2023, 457 pts (227 TIS+CT, 230 PBO+CT) were evaluated with a median follow-up of 14.2 months. One pt (<1%) in the TIS+CT arm and 4 (2%) in the PBO+CT arm had brain metastases at baseline. 44 pts (19%) in each arm had brain PD during the trial; 41 (18%) in TIS+CT and 34 (15%) in PBO+CT received brain RT; 3 (1%) and 1 (<1%), respectively, received prophylactic cranial irradiation. TIS+CT was associated with risk reduction in brain PD compared with PBO+CT (Table); Q-TWiST showed a 28.8% improvement (absolute gain of 4.7 months, $P<0.05$) for TIS+CT.

Conclusions: Compared with PBO+CT, TIS+CT reduced the risk of brain PD. In addition to longer PFS and OS in pts with brain PD, TIS+CT was associated with a clearly clinically important benefit in Q-TWiST. These findings further support TIS+CT as an efficacious therapy for 1L ES-SCLC.

Table		
	TIS+CT	PBO+CT
Overall Population^a		
	N=224	N=229
Median time-to-brain PD, mo (95%CI)	NR (25.8-NE)	NR (8.3-NE)
	Hazard ratio, =0.72 (0.47-1.12)	
Median time-to-brain RT, mo	7.06	6.41
Patients who Received Brain RT During/Subsequent to Treatment		
	n=41	n=34
Cumulative incidence rate of brain RT at 1 year, %	78.0	91.2
Patients with Brain PD		
	n=44	n=44
Median PFS, mo (95%CI)	5.4 (4.3-5.6)	4.4 (4.2-5.7)
Median OS, mo (95%CI)	15.5 (12.3-23.5)	13.6 (10.6-17.0)
Q-TWiST ^b , mo	19.1	14.5
^a Excludes 3 patients in TIS+CT and 1 in PBO+CT that received PCI. ^b At 42-months follow-up. CT, chemotherapy; mo, months; NE, not evaluable; PBO, placebo; PD, progressive disease; RT, radiation therapy; TIS, tislelizumab.		