RATIONALE-306: Long-Term Quality-Adjusted Survival Comparison of Tislelizumab + Chemotherapy vs Placebo + Chemotherapy as First-Line Treatment for Advanced or Metastatic Esophageal Squamous Cell Carcinoma

565P

Markus Moehler,[1] Mohamad Bassam Sonbol,[2] Sue-Anne McLachlan,[3] Lorenzo Fornaro,[4] Wenxi Tang,[5] Kaijun Wang,[5] Zhang Zhang,[6] Viktor Chirikov,[7] Wenying Quan,[7] Lin Zhan[5]

[1]Department of Medicine, University Medical Center of Johannes Gutenberg-University Clinic, Mainz, Germany; [2]Division of Hematology/Oncology, Mayo Clinic Comprehensive Cancer Center, Phoenix, AZ, USA; [3]Department of Oncology, St Vincent's Hospital Melbourne, Melbourne, VIC, Australia; [4]Unit of Medical Oncology 2, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy; [5]BeOne Medicines, Ltd, San Carlos, CA, USA; [6]BeOne Medicines, Ltd, Beijing, China; [7]OPEN Health, New York, NY, USA

CONCLUSIONS

- First-line treatment with TIS + CT demonstrated clinically meaningful improvement in long-term quality-adjusted survival gains (5.2-month absolute and 29.2% relative Q-TWiST gain at 57 months in the ITT population from RATIONALE-306) compared with PBO + CT in patients with advanced or metastatic ESCC
- Gains were maintained in patients with PD-L1 TAP ≥1% and increased further in those with PD-L1 TAP ≥5%
- Across clinically relevant patient subgroups, TIS + CT consistently demonstrated clinically meaningful Q-TWiST gains vs PBO + CT
- These Q-TWiST benefits, alongside the previously reported manageable safety profile and improved or maintained HRQOL findings from RATIONALE-306, support TIS + CT as a preferred first-line option for patients with advanced or metastatic ESCC

INTRODUCTION

- In RATIONALE-306 (NCT03783442), tislelizumab (TIS) + chemotherapy (CT) showed superior survival vs placebo (PBO) + CT in advanced or metastatic esophageal squamous cell carcinoma (ESCC) regardless of positive programmed cell death 1 ligand 1 (PD-L1) status (**Table 1**)[1-4]
- TIS + CT also improved or maintained health-related quality of life (HRQOL) compared with PBO + CT[5]

Table 1. Overall Survival in Patients With ESCC in RATIONALE-306

	Overall survival	
	Survival, median (95% CI), months	Hazard ratio (95% CI)
Intent to treat		
TIS + CT (n=326)	17.2 (15.8-20.1)	0.70 (0.59-0.83)[2]
PBO + CT (n=323)	10.6 (9.3-12.0)	Reference
PD-L1 TAP ≥1%		
TIS + CT (n=231)	16.8 (15.3-20.8)	0.66 (0.54-0.81)[3]
PBO + CT (n=250)	9.6 (8.9-11.8)	Reference
PD-L1 TAP ≥5%		
TIS + CT (n=172)	19.1 (16.1-24.1)	0.61 (0.48-0.78)[4]
PBO + CT (n=186)	10.0 (8.6-11.9)	Reference

Abbreviations: CT, chemotherapy; ESCC, esophageal squamous cell carcinoma; PBO, placebo; PD-L1, programmed cell death 1 ligand 1; TAP, Tumor Area Positivity; TIS, tislelizumab.

- Whether the survival advantage observed with first-line TIS + CT also translates into a clinically meaningful gain in quality-adjusted survival in patients with ESCC from RATIONALE-306 remains to be established
- This post hoc analysis assessed the quality-adjusted survival benefit of first-line TIS + CT compared with PBO + CT in patients with ESCC using the quality-adjusted time without symptoms or toxicity (Q-TWiST) method

METHODS

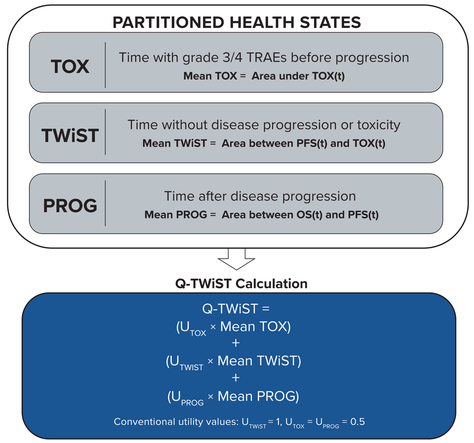
Data Source

- Long-term data were derived from the phase 3 RATIONALE-306 trial with a minimum 3-year follow-up (data cutoff: November 24, 2023)

Q-TWiST Methodology

- Q-TWiST integrates survival, toxicity, and patient-reported quality of life (QOL) into a single, clinically interpretable metric[6]
  - Q-TWiST partitions overall survival into three health states: time with grade 3/4 treatment-related adverse events before progression (TOX), time without progression or toxicity (TWiST), and time after progression (PROG) (**Figure 1**)
    - Restricted mean duration for each health state was estimated from Kaplan-Meier curves for each treatment arm
- Q-TWiST for each treatment arm was calculated as the utility-weighted sum of the three states: (U_{TOX} × TOX) + (U_{TWIST} × TWiST) + (U_{PROG} × PROG), where U represents the QOL utility weight in each respective health state
- 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 overall survival in the control arm
  - Relative gains ≥15% were considered clearly clinically important based on commonly accepted thresholds[6,7]

Figure 1. Q-TWiST Measures and Definitions



Abbreviations: OS(t), overall survival at time t; PFS(t), progression-free survival at time t; PROG, time after progression; Q-TWiST, quality-adjusted time without symptoms or toxicity; TOX, time with grade 3/4 toxicity before progression; TOX(t), toxicity at time t; TRAE, treatment-related adverse event; TWiST, time without progression or toxicity; U, utility weight.

Study Design and Statistical Analyses

- **Study populations**
  - Overall RATIONALE-306 intent-to-treat (ITT) population with further stratification by:
    - PD-L1 Tumor Area Positivity (TAP) score ≥1% and
    - PD-L1 TAP score ≥5%
- **Base-case analysis with conventional utility weights**
  - Q-TWiST gains were estimated at the maximum follow-up of 57 months as well as at different follow-up time points in the ITT, PD-L1 TAP ≥1%, and PD-L1 TAP ≥5% patient populations
  - Subgroup analyses assessed Q-TWiST outcomes at 57 months across clinically relevant patient subgroups examined in RATIONALE-306 within the ITT population
- **Sensitivity analysis**
  - A sensitivity analysis of Q-TWiST outcomes at 57 months was performed using patient-reported EQ-5D utility data collected in RATIONALE-306 to evaluate alternative utility-weight assumptions
    - The EQ-5D utility values were calculated separately for each treatment arm using the US mapping algorithm

RESULTS

Base-case analysis

- At the maximum 57-month follow-up, TIS + CT (n=326) demonstrated greater mean Q-TWiST than PBO + CT (n=323) (17.0 vs 11.8 months, respectively) among ITT patients, corresponding to a clearly clinically important relative gain of 29.2% (absolute gain, 5.2 months; 95% CI, 3.1-7.7; *P*<.001) (**Table 2**)
  - Clearly clinically important relative Q-TWiST gains were also observed in subgroups with PD-L1 TAP ≥1% (33.9% relative gain) and PD-L1 TAP ≥5% (41.3% relative gain) (**Table 2**)
- Q-TWiST gains increased with longer follow-up across the three study cohorts (**Figure 2**)
- Improvement in Q-TWiST observed in the TIS + CT arm across the three study cohorts was primarily driven by a longer duration in the TWiST health state and delayed progression

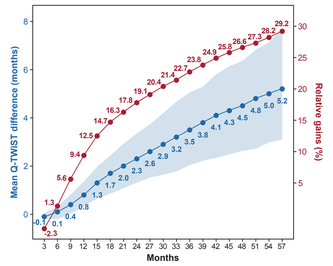
Table 2. Restricted Mean Time in Each Health State and Restricted Mean Q-TWiST in Patients With ESCC, Base-Case Analysis at 57 months

	Restricted mean time, months			
	TIS + CT	PBO + CT	Difference (95% CI), months	Relative gain (95% CI), %
ITT patients (TIS + CT: n=326; PBO + CT: n=323)				
TOX	4.4	2.7	1.6 (0.4 to 2.8)	
TWiST	10.6	5.5	5.0 (2.9 to 7.3)	
PROG	8.6	9.7	−1.2 (−3.6 to 1.1)	
Q-TWiST	**17.0**	**11.8**	**5.2 (3.1 to 7.7); *P*<.001**	**29.2 (16.0 to 45.7)**
PD-L1 TAP ≥1% (TIS + CT: n=231; PBO + CT: n=250)				
TOX	4.6	2.5	2.1 (0.6 to 3.5)	
TWiST	11.1	5.3	5.8 (2.9 to 8.3)	
PROG	8.2	9.8	−1.6 (−4.0 to 1.3)	
Q-TWiST	**17.5**	**11.5**	**6.0 (3.3 to 8.6); *P*<.001**	**33.9 (17.1 to 53.2)**
PD-L1 TAP ≥5% (TIS + CT: n=172; PBO + CT: n=186)				
TOX	4.8	2.8	2.0 (0.1 to 3.9)	
TWiST	12.8	5.3	7.4 (4.1 to 10.5)	
PROG	8.0	9.9	−1.9 (−4.9 to 1.8)	
Q-TWiST	**19.2**	**11.7**	**7.5 (4.1 to 10.6); *P*<.001**	**41.3 (21.4 to 62.8)**

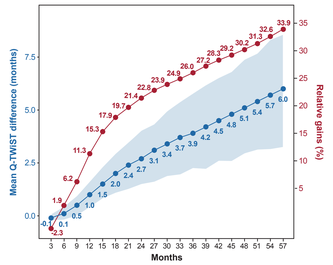
Abbreviations: CT, chemotherapy; ESCC, esophageal squamous cell carcinoma; ITT, intent to treat; PBO, placebo; PD-L1, programmed cell death 1 ligand 1; PROG, time after progression; Q-TWiST, quality-adjusted time without symptoms or toxicity; TAP, Tumor Area Positivity; TIS, tislelizumab; TOX, time with grade 3/4 toxicity before progression; TWiST, time without progression or toxicity.

Figure 2. Q-TWiST Gains with TIS + CT Over Follow-Up Among Patients With ESCC

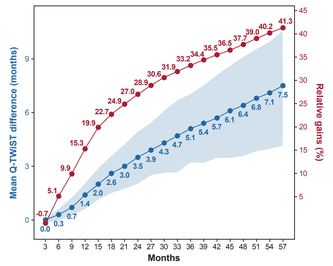
(A) ITT patients



(B) PD-L1 TAP ≥1%



(C) PD-L1 TAP ≥5%

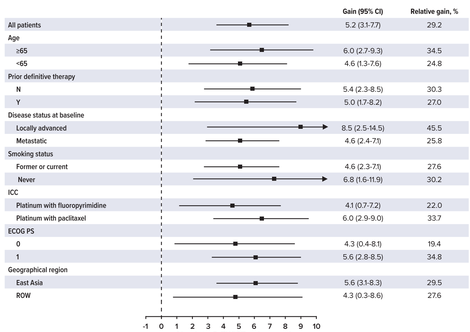


Q-TWiST results over time. (A) ITT patients. (B) Patients with PD-L1 TAP score ≥1%. (C) Patients with PD-L1 TAP score ≥5%. Red line represents relative Q-TWiST gains over time; blue line represents absolute Q-TWiST gains (months) over time; light blue shaded area around the estimates for absolute Q-TWiST gains represents 95% CI band.
Abbreviations: CT, chemotherapy; ESCC, esophageal squamous cell carcinoma; ITT, intent to treat; PD-L1 programmed death ligand-1; Q-TWiST, quality-adjusted time without symptoms or toxicity; TAP, Tumor Area Positivity; TIS, tislelizumab.

Subgroup analysis in ITT patients

- Across clinically relevant patient subgroups of interest, TIS + CT consistently showed Q-TWiST benefit vs PBO + CT, with relative gains in all subgroups exceeding the clearly clinically important threshold (**Figure 3**)
- The largest Q-TWiST benefit was observed in patients with locally advanced disease status, with an 8.5-month absolute gain and 45.5% relative gain at 57 months

Figure 3. Base-Case Q-TWiST Subgroup Analysis Results at 57 Months, ITT Patients



Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; ICC, investigator-chosen chemotherapy; ITT, intent to treat; Q-TWiST quality-adjusted time without symptoms or toxicity; ROW, rest of the world.

Sensitivity analysis

- Sensitivity analyses using trial-derived EQ-5D utilities confirmed and strengthened the main findings, with consistently higher Q-TWiST for TIS + CT vs PBO + CT across all ESCC cohorts (**Table 3**)
  - Clearly clinically important relative Q-TWiST gains were observed across the three study cohorts (**Table 3**)

Table 3. Sensitivity Q-TWiST Analysis at 57 Months With EQ-5D Utility Values by Arm, US Mapping

	Restricted mean Q-TWiST, months			
	TIS + CT	PBO + CT	Difference (95% CI), months	Relative gain (95% CI), %
ITT patients	20.0	15.0	5.0 (2.7 to 7.6); *P*<.001	**27.8 (14.6 to 46.1)**
PD-L1 TAP ≥1%	20.6	14.8	5.8 (2.9 to 8.5); *P*<.001	**32.7 (15.4 to 53.5)**
PD-L1 TAP ≥5%	22.2	15.1	7.1 (3.8 to 10.3); *P*<.001	**39.2 (19.4 to 62.5)**

Utilities used in sensitivity analysis:
TIS + CT arm: for ITT patients, U_{TWIST} = 0.878, U_{TOX} = 0.863, and U_{PROG} = 0.817; for PD-L1 TAP ≥1% patients, U_{TWIST} = 0.884, U_{TOX} = 0.866, and U_{PROG} = 0.828; for PD-L1 TAP ≥5% patients, U_{TWIST} = 0.889, U_{TOX} = 0.873, and U_{PROG} = 0.831.
PBO + CT arm: for ITT patients, U_{TWIST} = 0.870, U_{TOX} = 0.855, and U_{PROG} = 0.809; for PD-L1 TAP ≥1% patients, U_{TWIST} = 0.871, U_{TOX} = 0.853, and U_{PROG} = 0.814; for PD-L1 TAP ≥5% patients, U_{TWIST} = 0.870, U_{TOX} = 0.855, and U_{PROG} = 0.812.
Abbreviations: CT, chemotherapy; ITT, intent to treat; PBO, placebo; PD-L1, programmed cell death 1 ligand 1; Q-TWiST, quality-adjusted time without symptoms or toxicity; TAP, Tumor Area Positivity; TIS, tislelizumab.

REFERENCES

1. Xu J, et al. *Lancet Oncol*. 2023;24(5):483-495.
2. Yoon HH, et al. *J Clin Oncol*. 2024;42(16 suppl):4032-4032.
3. Xu J, et al. *Adv Ther*. 2025;42:2269-2284.
4. Tougeron D, et al. *Ann Oncol*. 2025;36:S154-S155
5. Yoon HH, et al. *J Clin Oncol*. 2025;43:366-366.
6. Revicki DA, et al. *Qual Life Res*. 2006;15(3):411-423.
7. Solem CT, et al. *Expert Rev Pharmacoecon Outcomes Res*. 2018;18:245-253.

ACKNOWLEDGMENTS

The study was sponsored by BeOne Medicines, Ltd. Medical writing support was provided by Hui-Hsuan Liu, PhD, MSc, OPEN Health Communications LLP, and was funded by BeOne Medicines. Editorial support was provided by Nucleus Global, an Inizio company, and supported by BeOne Medicines.

DISCLOSURES

MM: Advisory board: BMS, Servier, Amgen, Lilly, Bayer, BeOne Medicines, Ltd, Novartis, Taiho, Daiichi Sankyo, Amgen, MD; Honoraria: MSD, BMS, Falk Foundation, AIO, BeOne Medicines, Ltd, Amgen; Expert testimony: Sanofi; Other: EORTC Chair.

CORRESPONDENCE: Markus Moehler, markus.moehler@unimedizin-mainz.de

Presented at the ESMO Gastrointestinal Cancers Congress 2026; July 1-4, 2026; Munich, Germany