Quality-Adjusted Survival Comparison for Tislelizumab + Chemotherapy vs Placebo + Chemotherapy as First-Line Treatment in Gastric/Gastroesophageal Junction Adenocarcinoma Patients With Peritoneal Metastasis: Long-Term Follow-Up From RATIONALE-305

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CONCLUSIONS

- Among advanced GC/GEJC patients with peritoneal metastasis, first-line treatment with TIS + CT demonstrated clinically meaningful improvement in long-term quality-adjusted survival gains (2.6-month absolute/17.7% relative Q-TWiST gain) compared with CT alone
  - Gains were maintained in PD-L1 TAP ≥1% patients and were more pronounced in those with PD-L1 TAP ≥5%
- These Q-TWiST findings, together with the manageable safety profile and sustained and improved health-related QoL previously reported for RATIONALE-305, support TIS + CT as a first-line option for advanced GC/GEJC patients with peritoneal metastasis

INTRODUCTION

- In RATIONALE-305 (NCT03777657), tislelizumab + chemotherapy (TIS + CT) showed superior survival versus placebo + chemotherapy (PBO + CT) in advanced gastric/gastroesophageal junction adenocarcinoma (GC/GEJC)[1,2]
  - TIS + CT versus PBO + CT has also resulted in sustained and improved health-related quality of life (QoL)[3]
- A post hoc analysis further demonstrated survival benefit with TIS + CT in patients with peritoneal metastasis (PM), a poor-prognosis subgroup with a substantial unmet need (**Table 1**)[4]

Table 1. Overall Survival in Patients With PM (3-Year Minimum Follow-Up)[4]

	Overall Survival	
Patients With PM	Median Survival (95% CI), Months	Hazard Ratio (95% CI)
TIS + CT (n=220)	12.3 (10.8-15.0)	0.78 (0.64-0.96)
PBO + CT (n=214)	11.8 (10.6-13.1)	Reference

Abbreviations: CI, confidence interval; CT, chemotherapy; PBO, placebo; PM, peritoneal metastasis; TIS, tislelizumab.

- It is unknown whether the survival benefit of first-line TIS + CT was accompanied by clinically meaningful improvement in quality-adjusted survival in patients with PM from the RATIONALE-305 trial
- The objective of this study was to evaluate quality-adjusted survival benefit with first-line TIS + CT versus PBO + CT using the quality-adjusted time without symptoms or toxicity (Q-TWiST) method (**Figure 1**) in patients with PM

METHODS

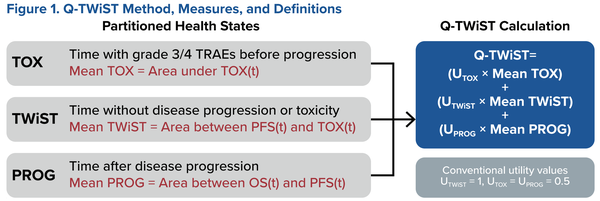
Data Source

- Long-term data were derived from the phase 3 RATIONALE-305 trial with a minimum 3-year follow-up (data cutoff February 28, 2024)

Q-TWiST Methodology

- Q-TWiST integrates survival, toxicity, and patient-reported QoL into a single, clinically interpretable metric[5]
  - Q-TWiST partitions overall survival into three health states: time with grade 3/4 toxicity before progression (TOX), time without progression or toxicity (TWiST), and time after progression (PROG) (**Figure 1**)
  - 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 also 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[5,6]

Figure 1. Q-TWiST Method, 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 of disease progression or toxicity; TOX, time with grade 3/4 toxicity before progression; TOX(t), toxicity at time t; TRAEs, treatment-related adverse events; TWiST, time without progression or toxicity; U, utility weight.

Study Design and Statistical Analyses

Study Populations

- Patients with PM with further stratification by PD-L1 Tumor Area Positivity (TAP) score ≥1% and ≥5%
- Supplemental analysis among the overall RATIONALE-305 intent-to treat population

Base-case Analysis

- Conventional utilities $U_{TWiST}=1$, $U_{TOX}=U_{PROG}=0.5$

Sensitivity Analysiss

- A sensitivity analysis was conducted using patient-reported EQ-5D utility data collected in the RATIONALE-305 trial to provide alternative assumptions for the utility weights. The EQ-5D utility values were computed separately for each treatment arm using the US mapping algorithm

RESULTS

Patients With Peritoneal Metastasis

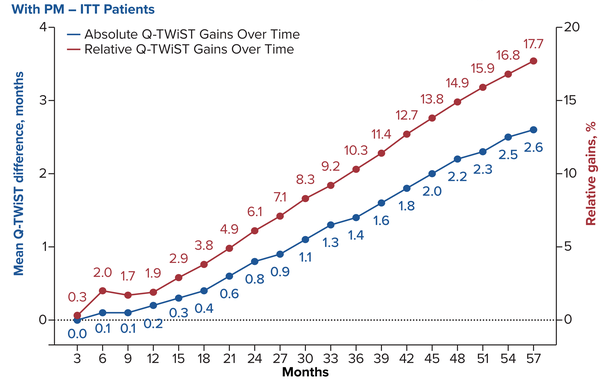
- At the maximum 57-month follow-up, TIS + CT (n=220) showed greater mean Q-TWiST than PBO + CT (n=214) (13.4 vs 10.8 months), corresponding to a clearly clinically important relative gain of 17.7% (absolute gain 2.6 months, 95% CI: 0.1-5.0; *P*=0.04) (**Table 2**)
  - Clearly clinically important relative Q-TWiST gains were also observed in PM subgroups with PD-L1 TAP ≥1% (16.8%) and PD-L1 TAP ≥5% (33.0%)
- Q-TWiST gains increased with longer follow-up in patients with PM (**Figure 2**)
- Sensitivity analyses using trial-derived EQ-5D utilities confirmed and strengthened the main findings, with consistently higher Q-TWiST for TIS + CT versus PBO + CT across all PM cohorts (**Figure 3**)

Table 2. Mean Duration of Each Health State and Q-TWiST Among Patients With PM, Base-Case Analysis

	Mean Duration, Months			
	TIS + CT	PBO + CT	Difference (95% CI), Months	Relative Gain (95% CI), %
Patients with PM – ITT patients (TIS + CT: n=220; PBO + CT: n=214)				
TOX	3.3	2.2	1.2 (-0.2 to 2.6)	
TWiST	8.5	6.9	1.6 (-1.2 to 4.4)	
PROG	6.5	5.7	0.9 (-1.1 to 2.9)	
Q-TWiST	**13.4**	**10.8**	**2.6 (0.1 to 5.0), *P*=0.04**	**17.7 (0.6 to 36.2)**
Patients with PM – PD-L1 TAP ≥1% (TIS + CT: n=190; PBO + CT: n=196)				
TOX	3.4	2.0	1.4 (0.0 to 3.1)	
TWiST	8.6	7.2	1.5 (-1.3 to 4.2)	
PROG	6.3	5.7	0.7 (-1.5 to 2.9)	
Q-TWiST	**13.5**	**11.0**	**2.5 (0.1 to 5.1), *P*<0.05**	**16.8 (0.7 to 36.2)**
Patients with PM – PD-L1 TAP ≥5% (TIS + CT: n=110; PBO +CT: n=107)				
TOX	3.0	1.4	1.6 (0.2 to 3.3)	
TWiST	11.3	7.3	4.0 (-0.2 to 8.5)	
PROG	5.3	5.5	-0.1 (-3.4 to 3.3)	
Q-TWiST	**15.5**	**10.8**	**4.7 (1.1 to 8.6), *P*=0.02**	**33.0 (6.8 to 67.6)**

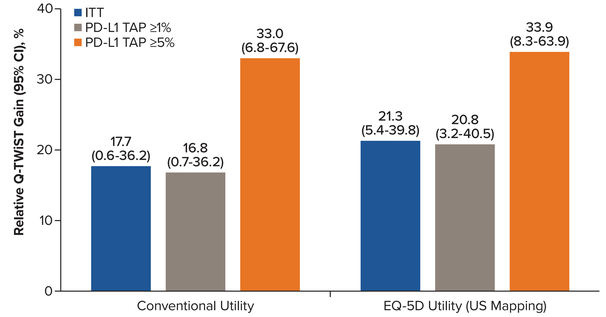
Abbreviations: CI, confidence interval; CT, chemotherapy; ITT, intent-to-treat; PBO, placebo; PM, peritoneal metastasis; PROG, time after progression; Q-TWiST, quality-adjusted time without symptoms of disease progression or toxicity; TAP, Tumor Area Positivity; TIS, tislelizumab; TOX, time with grade 3/4 toxicity before progression; TWiST, time without progression or toxicity.

Figure 2. Q-TWiST Gains for TIS+CT vs PBO+CT Over the Follow-Up Among Patients With PM – ITT Patients



Abbreviations: CT, chemotherapy; ITT, intent-to-treat; PBO, placebo; PM, peritoneal metastasis; Q-TWiST, quality-adjusted time without symptoms of disease progression or toxicity; TIS, tislelizumab.

Figure 3. Relative Q-TWiST Gain for TIS+CT vs PBO+CT in Base-Case and Sensitivity Analysis Among Patients With PM



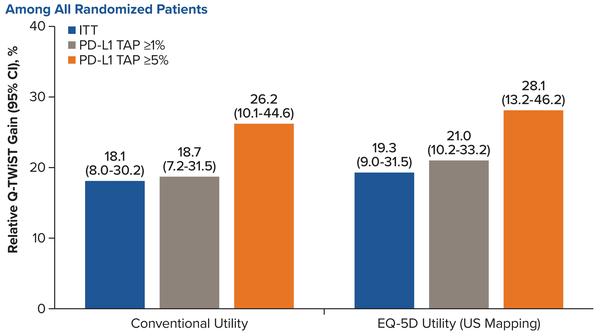
Clearly clinically important relative Q-TWiST gains were observed across all PM cohorts in both base-case and sensitivity analyses.
Abbreviations: CI, confidence interval; CT, chemotherapy; ITT, intent-to-treat; PBO, placebo; PM, peritoneal metastasis; PROG, time after progression; Q-TWiST, quality-adjusted time without symptoms of disease progression or toxicity; TAP, Tumor Area Positivity; TIS, tislelizumab; TOX, time with grade 3/4 toxicity before progression; TWiST, time without progression or toxicity; U, utility weight.

Utilities used in sensitivity analysis	
TIS + CT arm of PM patients: *For ITT patients*, U_{TWiST}=0.870, U_{TOX}=0.863, U_{PROG}=0.817 *For PD-L1 TAP≥1% patients*, U_{TWiST}=0.869, U_{TOX}=0.860, U_{PROG}=0.817 *For PD-L1 TAP≥5% patients*, U_{TWiST}=0.872, U_{TOX}=0.854, U_{PROG}=0.828	PBO + CT arm of PM patients: *For ITT patients*, U_{TWiST}=0.867, U_{TOX}=0.860, U_{PROG}=0.814 *For PD-L1 TAP≥1% patients*, U_{TWiST}=0.865, U_{TOX}=0.856, U_{PROG}=0.813 *For PD-L1 TAP≥5% patients*, U_{TWiST}=0.864, U_{TOX}=0.845, U_{PROG}=0.820

Supplemental Analysis: All Randomized Patients

- TIS + CT (n=501) demonstrated greater mean Q-TWiST than PBO + CT (n=496) (16.3 vs 13.1 months), corresponding to a clearly clinically important relative Q-TWiST gain of 18.1% (absolute gain 3.2 months, 95% CI: 1.5-5.1; *P*<0.01), mirroring the magnitude seen in the PM subgroup (**Figure 4**)
  - Clearly clinically important relative Q-TWiST gains were also observed in the PD-L1 subgroups with TAP ≥1% (18.7%) and TAP ≥5% (26.2%), with statistically significant corresponding absolute Q-TWiST gains of 3.3 months (95% CI: 1.4-5.3; *P*<0.01) and 4.7 months (95% CI: 2.0-7.5; *P*<0.01), respectively (**Figure 4**)
- Sensitivity analyses using trial-derived EQ-5D utilities showed consistently higher relative Q-TWiST gains with TIS + CT (**Figure 4**)
- Gains in favor of TIS + CT were driven predominantly by extended time in the TWiST and TOX health states (**Figure 5**)

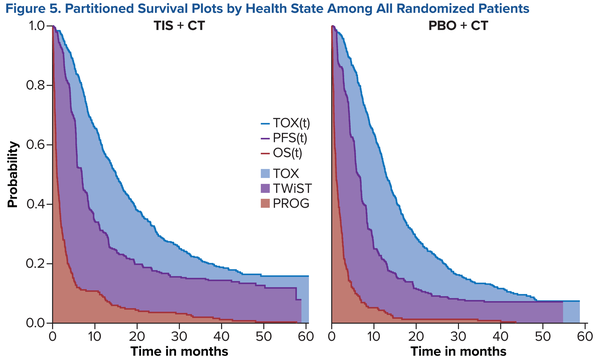
Figure 4. Relative Q-TWiST Gain for TIS+CT vs PBO+CT in Base-Case and Sensitivity Analysis Among All Randomized Patients



Clearly clinically important relative Q-TWiST gains were observed across all randomized patients in both base-case and sensitivity analyses.
Abbreviations: CT, chemotherapy; ITT, intent-to-treat; PBO, placebo; PROG, time after progression; Q-TWiST, quality-adjusted time without symptoms of disease progression or toxicity; TAP, Tumor Area Positivity; TIS, tislelizumab; TOX, time with grade 3/4 toxicity before progression; TWiST, time without progression or toxicity; U, utility weight.

Utilities used in sensitivity analysis	
TIS+CT arm of all randomized patients: *For ITT patients*: U_{TWiST}=0.879, U_{TOX}=0.864, U_{PROG}=0.828 *For PD-L1 TAP≥1% patients*: U_{TWiST}=0.879, U_{TOX}=0.862, U_{PROG}=0.827 *For PD-L1 TAP≥5% patients*:U_{TWiST}=0.886, U_{TOX}=0.862, U_{PROG}=0.838	PBO+CT arm of all randomized patients: *For ITT patients*, U_{TWiST}=0.871, U_{TOX}=0.856, U_{PROG}=0.819 *For PD-L1 TAP≥1% patients*, U_{TWiST}=0.870, U_{TOX}=0.852, U_{PROG}=0.817 *For PD-L1 TAP≥5% patients*, U_{TWiST}=0.872, U_{TOX}=0.848, U_{PROG}=0.824

Figure 5. Partitioned Survival Plots by Health State Among All Randomized Patients



Abbreviations: CT, chemotherapy; OS(t), overall survival at time t; PBO, placebo; PFS(t), progression-free survival at time t; PROG, time after progression; Q-TWiST, quality-adjusted time without symptoms of disease progression or toxicity; TIS, tislelizumab; TOX, time with grade 3/4 toxicity before progression; TOX(t), toxicity at time t; TWiST, time without progression or toxicity.

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DISCLOSURES

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