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Patient-Reported Outcome-Based Deterioration Predicts Overall Survival in Patients with Advanced Gastric Adenocarcinoma with PD-L1 Score of ≥5%: Post Hoc Analysis from the RATIONALE-305 Trial

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Declaration of Interests

Markus Moehler reports consultancy or advisory roles for Bayer, Merck Sharp & Dohme (MSD), Merck Serono, Amgen, Taiho Pharmaceutical, Pfizer, Roche, Lilly, Servier Laboratories, BeOne Medicines, Bristol Myers Squibb (BMS), AstraZeneca, Astellas Pharma, Dragonfly, and Novartis; honoraria from Amgen, Roche/Genentech, Merck Serono, MSD Oncology, BMS, AstraZeneca/MedImmune, Servier Laboratories, Pierre Fabre, Sanofi, Falk foundation, Transcenta Holding, Daiichi Sankyo, Astellas Pharma, and Nordic Pharma; grant/research funding from Amgen, Leap Therapeutics, Merck Serono, and MSD; and other remuneration from Amgen, Merck Serono, Roche, Bayer, American Society for Clinical Oncology (ASCO), German Cancer Society, MSD, European Society for Medical Oncology (ESMO), BeOne Medicines, and European Organisation for Research and Treatment (EORTC)

Background

The RATIONALE-305 trial (NCT03777657) demonstrated statistically significant and clinically meaningful improvements in OS (HR, 0.80 [95% CI, 0.70-0.92]) with T+C compared to P+C in patients with a PD-L1 score of ≥5% (final analysis)[1]

PROs were maintained or improved in the T+C arm compared with the P+C arm

Associations between PROs and clinical outcomes (e.g., OS) in GC/GEJC remain inadequately understood. Joint modeling may offer a robust framework for clinicians/oncologist to potentially identify at-risk patients earlier, enabling more personalized, anticipatory care strategies that support timely intervention before clinical deterioration becomes outwardly apparent

Here, the objective of the current analysis was to develop a joint survival model to evaluate the predictive and prognostic value of PROs for OS in patients with PD-L1 score of ≥5% within the RATIONALE-305 trial population

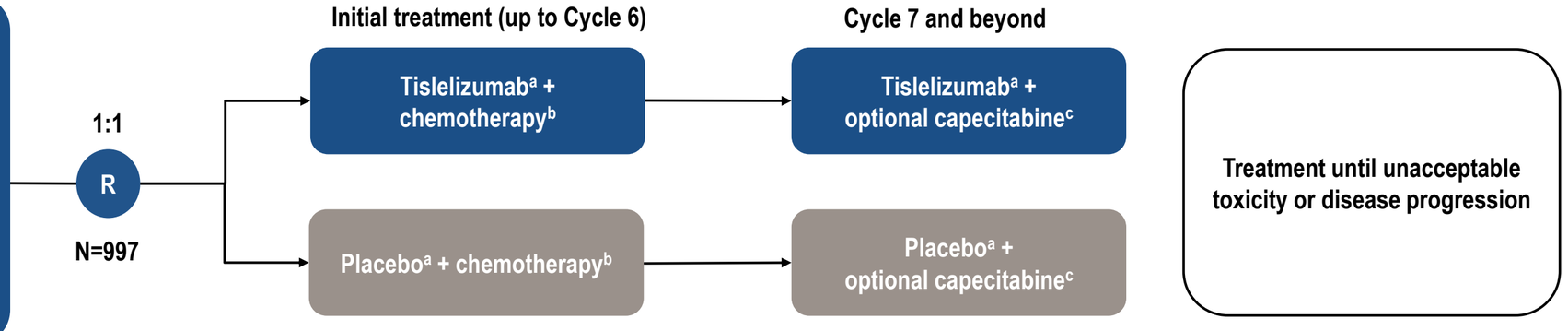
[1]Qiu MZ et al. *BMJ* 2024;385:e078876; **ClinicalTrials.gov: NCT03777657.**
Abbreviations: GEJC=gastroesophageal junction adenocarcinoma; GI=gastrointestinal; OS=overall survival; P+C=placebo + chemotherapy; PD-L1=programmed death-ligand 1; PRO=patient-reported outcome; RS-D=recurrent symptomatic deterioration; T+C=tislelizumab + chemotherapy

Dr Markus Moehler

Study Design and Methods

Key Eligibility Criteria

- Locally advanced unresectable or metastatic GC histologically confirmed adenocarcinoma
- No HER2-positive disease
- No prior systemic therapy for advanced disease
- At least one measurable or non-measurable lesion (RECIST v1.1)
- ECOG PS 0 or 1



Stratification Factors

- Regions of enrollment
- Peritoneal metastasis
- PD-L1 expression score (≥5% vs <5%)[d]
- Investigator-chosen chemotherapy (XELOX or FP)

Endpoints

- **Primary endpoint:** OS in PD-L1 score ≥5% and ITT populations
- **Secondary endpoints:** PROs, PFS, ORR, DoR, and safety

- **PRO Endpoints:**
  - **Secondary endpoints included** the most **disease-and treatment relevant PRO symptoms/functions from the core EORTC QLQ-C30** (GHS/QoL, physical functioning, and fatigue) and **gastric cancer-specific module EORTC QLQ-STO22** (dysphagia/odynophagia, pain/discomfort, upper gastrointestinal [GI] symptoms, and dietary restrictions)
- **Statistical Analyses:**
  - The analytic cohort included a total of 475 patients in the PD-L1 expression ≥5% subgroup (n=238, T+C vs n=237, P+C)
  - A joint survival model was specified for: (1) a LMM for PRO Δ_{BL}[e], (2) a Cox survival model for RS-D events, and (3) a Cox survival model for OS, with all components linked to account for their interdependence
  - RS-D event was defined as any Δ_{BL}[e] score ≥10[2] for both the QLQ-C30 and QLQ-STO22
    - For a deterioration event to qualify as a recurrent event, it had to be a unique event (e.g., 2 events had to be separated by non-events to qualify as recurrent)
  - Model and parameter convergence were evaluated using trace and density plots, survival model HRs, and the $\hat{R}$ statistic

[a]Tislelizumab 200 mg or placebo Q3W (Day 1). [b]Oxaliplatin 130 mg/m² IV (Day 1) and oral capecitabine 1000 mg/m² twice daily (14 consecutive days from Day 1) Q3W (XELOX), or cisplatin 80 mg/m² IV (Day 1) and 5-fluorouracil 800 mg/m²/day IV (Days 1-5) Q3W (FP). [c]Capecitabine as maintenance therapy was optional and only for XELOX-treated patients. [d]PD-L1 score was determined using the VENTANA PD-L1 (SP263) assay by tumor area positivity score. [eb]Δ_{BL} represents the change from baseline in patient-reported outcome scores. [1]Osoba D et al. J Clin Oncol. 1998;16(1):139-44.

Abbreviations: C=chemotherapy; DoR=duration of response; ECOG PS=Eastern Cooperative Oncology Group Performance Status; EORTC=European Organisation for Research and Treatment of Cancer; FP=5-fluorouracil and cisplatin; GI=gastrointestinal; HER2=human epidermal growth factor receptor 2; ITT=intent-to-treat; IV=intravenous; LMM=linear mixed model; ORR=objective response rate; OS=overall survival; P=placebo; PD-L1=programmed death-ligand 1; PFS=progression-free survival; PRO=patient-reported outcome; Q3W=once every 3 weeks; QLQ-C30=Quality of Life Questionnaire Core-30; QLQ-STO22= Quality of Life Questionnaire-Gastric Cancer Module; R=randomized; RECIST v1.1=Response Evaluation Criteria in Solid Tumors version 1.1; T=tislelizumab; XELOX=capecitabine and oxaliplatin.

Joint Survival Model for RS-D and OS Adjusting for QLQ-C30 PRO CFBL, Treatment Arm, and Stratification Factors in Patients with PD-L1 Score ≥5%

Parameter	P-value	$\hat{R}$[a]	HR (95% CI)
GHS/QoL			
Δ_{BL}[b] – T+C effect[c] (linear mixed model)	**0.01**	1.00	NA
Recurrent symptomatic deterioration – longitudinal effect (Cox model)	0.91	1.03	1.00 (1.00, 1,01)
OS – T+C effect[c] (Cox model)	**0.01**	1.00	0.72 (0.57, 0.91)
OS – longitudinal effect (Cox model)	**<0.01**	1.00	0.99 (0.98, 0.99)
OS – recurrent symptomatic deterioration (frailty) (Cox model)	0.99	1.10	1.02 (0.02, 62.23)[d]
Physical Functioning			
Δ_{BL}[b] – T+C effect[c] (linear mixed model)	0.23	1.00	N/A
Recurrent symptomatic deterioration – longitudinal effect (Cox model)	**0.01**	1.00	1.01 (1.01, 1.02)
OS – T+C effect[c] (Cox model)	**0.01**	1.00	0.73 (0.57, 0.93)
OS – longitudinal effect (Cox model)	**<0.01**	1.07	0.98 (0.98, 0.99)
OS – recurrent symptomatic deterioration (frailty) (Cox model)	0.98	1.01	1.07 (0.01, 257.79)[d]
Fatigue			
Δ_{BL}[b] – T+C effect[c] (linear mixed model)	0.14	1.00	NA
Recurrent symptomatic deterioration – longitudinal effect (Cox model)	**<0.01**	1.11	1.03 (1.02, 1.03)
OS – T+C effect[c] (Cox model)	**0.01**	1.00	0.69 (0.54, 0.87)
OS – longitudinal effect (Cox model)	**<0.01**	1.01	1.01 (1.01, 1.02)
OS – recurrent symptomatic deterioration (frailty) (Cox model)	0.84	1.01	0.57 (0.01, 42.30)[d]

[a]An $\hat{R}$ statistic with a value of 1.0 indicated acceptable convergence. [b]Δ_{BL} represents the change from baseline in patient-reported outcome scores. [c]Treatment effect was coded as tislelizumab plus chemotherapy versus placebo plus chemotherapy with the former as the effect group. [d]Association parameter and not HR.

Notes: Each model was adjusted for the following RATIONALE-305 stratification factors: geographic region (Asia versus non-Asia) and presence of peritoneal metastasis (yes versus no). Highlighted values in blue are statistically significant at the nominal 0.05 significance level. For the GHS/QoL and Physical functioning scales, higher scores indicated better health or functioning; thus, a positive Δ_{BL} reflected improvement. For symptom scales, higher scores indicated worse symptoms; therefore, a negative Δ_{BL} reflected symptom improvement

Abbreviations: CI=confidence interval; GHS/QoL=global health status/quality of life; GI=gastrointestinal; HR=hazard ratio, N/A=not applicable; OS=overall survival; PD-L1=programmed death-ligand 1; T+C=tislelizumab + chemotherapy.

Joint Survival Model: Description of Results

- Significant improvement in GHS/QoL (Δ_{BL} – T+C effect) was observed with T+C compared to P+C
- Declining physical functioning and worsening fatigue (RS-D – longitudinal effect) was significantly associated with an increased risk for future RS-D events (HRs: 1.01–1.03; P < 0.01)
- T+C significantly reduced the hazard of OS events in all PRO domains (OS – T+C effect) compared to P+C with HRs ranging from 0.69–0.73, reflecting a 27%–31% lower likelihood of death
- Longitudinal improvements in GHS/QoL and physical functioning (OS – longitudinal effect) were significantly associated with a reduced risk of death (HRs: 0.98-0.99; P < 0.01), while worsening fatigue was significantly associated with an increased risk of death (HR: 1.01; P < 0.01)

Joint Survival Model for RS-D and OS Adjusting for QLQ-STO22 PRO CFBL, Treatment Arm, and Stratification Factors in Patients with PD-L1 Score ≥5%

Parameter	P-value	$\hat{R}$[a]	HR (95% CI)
Dysphagia/Odynophagia			
Δ_{BL}[b] – T+C effect[c] (linear mixed model)	0.12	1.00	NA
Recurrent symptomatic deterioration – longitudinal effect (Cox model)	**<0.01**	1.03	1.03 (1.02, 1.04)
OS – T+C effect[c] (Cox model)	**0.01**	1.01	0.65 (0.47, 0.84)
OS – longitudinal effect (Cox model)	**0.01**	1.02	1.01 (1.00, 1.02)
OS – Recurrent symptomatic deterioration event (frailty) (Cox model)	0.34	1.04	3.80 (0.09, 116.36)[d]
Pain/Discomfort			
Δ_{BL}[b] – T+C effect[c] (linear mixed model)	0.12	1.00	NA
Recurrent symptomatic deterioration – longitudinal effect (Cox model)	**<0.01**	1.13	1.05 (1.04, 1.07)
OS – T+C effect[c] (Cox model)	**0.01**	1.03	0.67 (0.52, 0.86)
OS – longitudinal effect (Cox model)	**0.04**	1.03	1.01 (1.00, 1.02)
OS – Recurrent symptomatic deterioration event (frailty) (Cox model)	0.76	1.06	2.33 (0.03, 195.46)[d]
Upper GI Symptoms			
Δ_{BL}[b] – T+C effect[c] (linear mixed model)	**0.01**	1.00	NA
Recurrent symptomatic deterioration – longitudinal effect (Cox model)	**<0.01**	1.04	1.06 (1.05, 1.07)
OS – T+C effect[c] (Cox model)	**0.01**	1.00	0.67 (0.53, 0.85)
OS – longitudinal effect (Cox model)	**0.02**	1.00	1.01 (1.00, 1.02)
OS – Recurrent symptomatic deterioration event (frailty) (Cox model)	0.85	1.01	1.49 (0.03, 85.12)[d]
Dietary Restrictions			
Δ_{BL}[b] – T+C effect[c] (linear mixed model)	**0.02**	1.00	NA
Recurrent symptomatic deterioration – longitudinal effect (Cox model)	**<0.01**	1.03	1.03 (1.02, 1.03)
OS – T+C effect[c] (Cox model)	**0.01**	1.02	0.67 (0.48, 0.87)
OS – longitudinal effect (Cox model)	**<0.01**	1.08	1.02 (1.01, 1.03)
OS – RS-D event (frailty) (Cox model)	0.47	1.02	5.12 (0.05, 288.01)[d]

[a]An $\hat{R}$ statistic with a value of 1.0 indicated acceptable convergence. [b]Δ_{BL} represents the change from baseline in patient-reported outcome scores. [c]Treatment effect was coded as tislelizumab plus chemotherapy versus placebo plus chemotherapy with the former as the effect group. [d]Association parameter and not HR.

Notes: Each model was adjusted for the following RATIONALE-305 stratification factors: geographic region (Asia versus non-Asia) and presence of peritoneal metastasis (yes versus no). Highlighted values in blue are statistically significant at the nominal 0.05 significance level. For the GHS/QoL and Physical functioning scales, higher scores indicated better health or functioning; thus, a positive Δ_{BL} reflected improvement. For symptom scales, higher scores indicated worse symptoms; therefore, a negative Δ_{BL} reflected symptom improvement

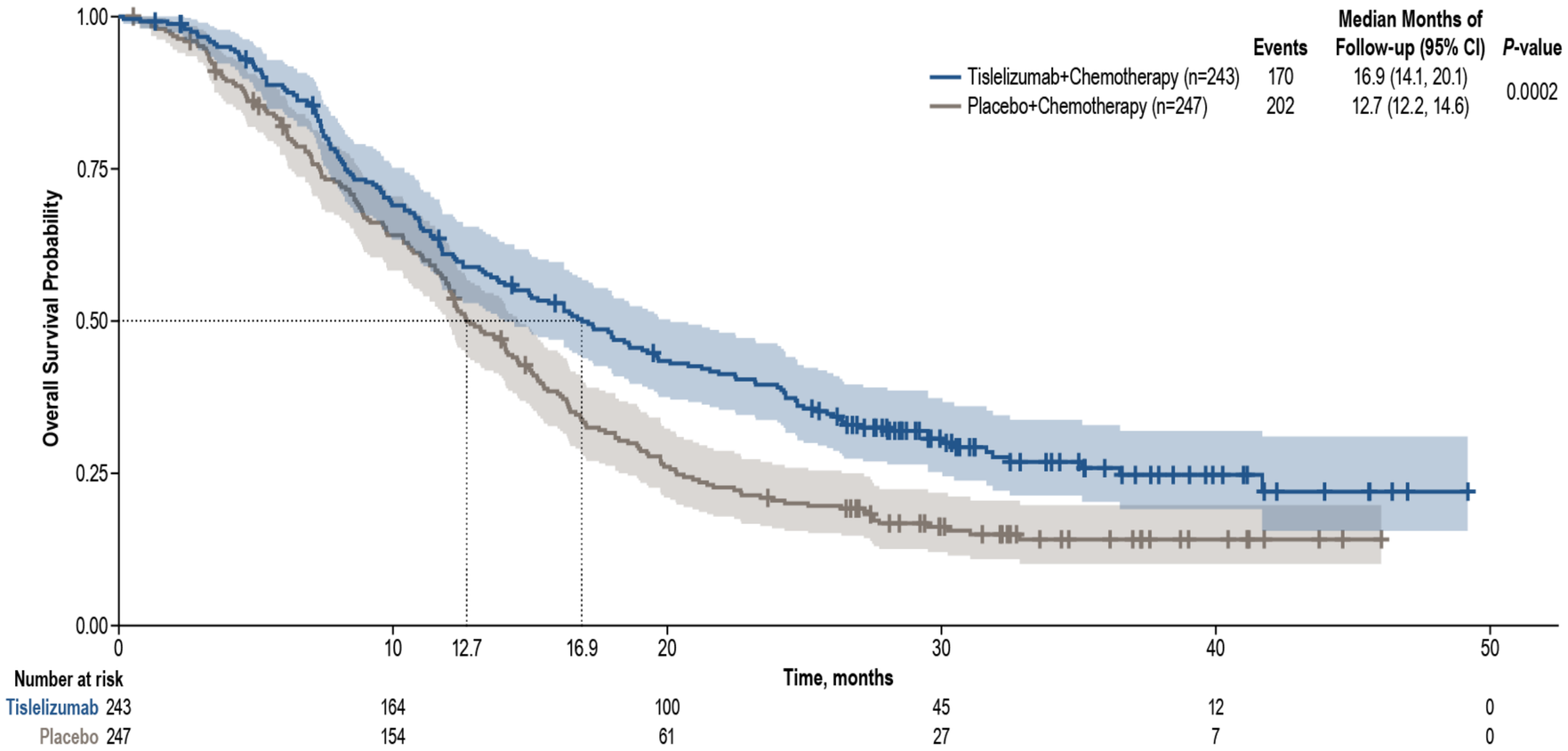
Abbreviations: CFBL=change from baseline; CI=confidence interval; GHS/QoL=global health status/quality of life; GI=gastrointestinal; HR=hazard ratio; N/A=not applicable; OS=overall survival; PD-L1=programmed death-ligand 1; T+C=tislelizumab + chemotherapy.

Joint Survival Model: Description of Results

- Significant improvement in upper GI symptoms and dietary restrictions (Δ_{BL} – T+C effect) was observed with T+C compared to P+C
- For all domains, worsening symptoms (RS-D – longitudinal effect) was significantly associated with an increased risk of future RS-D events (HRs: 1.03–1.06; all P < 0.01)
- T+C significantly reduced the hazard of OS events in all PRO domains (OS – T+C effect) compared to P+C with HRs ranging from 0.65–0.67, reflecting a 33%–35% lower likelihood of death
- Worsening symptom burden over time (OS – longitudinal effect) was significantly associated with increased risk of death across all PRO domains (HR: 1.01–1.02; all P ≤ 0.04)

KM Plot of OS Adjusted for QLQ-C30 GHS/QoL in Joint Survival Model (PD-L1 ≥5%)

Example of GHS/QoL Scores from Post Hoc Analysis; Not Primary OS Analysis Derived from ITT Population[1]



+4.2 Months OS

T+C led to a median OS of 16.9 months; P+C led to a median OS of 12.7 months

Log-rank *P*-value: **0.0002**

Notes: The dashed lines represent the median time-to-event for each treatment arm. Time was defined as months since baseline. KM plots were generated for all domains, as one example GHS/QoL is presented.

[1]The KM plot is derived from a post hoc joint survival model and reflects OS for the sub-population with patient-reported GHS/QoL scores in the PD-L1 ≥5% subgroup. It is not the prespecified primary OS analysis from the ITT population.

Abbreviations: CI=confidence interval; GHS/QoL: global health status/quality of life; ITT=intent-to-treat; KMM=Kaplan Meier; OS=overall survival; P+C=placebo + chemotherapy; QLQ-C30: Quality of Life Questionnaire – Core 30; T+C=tislelizumab + chemotherapy.

Author Conclusions

- From the joint survival model, the addition of T+C resulted in improvements in QLQ-C30 GHS/QoL, STO22 upper GI symptoms, and dietary restrictions compared to the P+C arm, representing a meaningful benefit for patients with GC/GEJC
- Worsening patient-reported symptoms was significantly associated with an increased risk of future RS-D events, underscoring the prognostic value of longitudinal symptom trajectories in identifying clinical deterioration
- After adjusting for the risk of RS-D events, T+C demonstrated a 27%–35% lower risk of death compared to P+C, indicating a predictive survival benefit across all PRO domains, highlighting that patients who survive longer may also maintain better QoL
- Longitudinal improvements in GHS/QoL and physical functioning were significantly associated with reduced mortality risk, while worsening symptom burden increased the risk of death across all domains, independent of treatment assignment
- These findings highlight the utility of joint survival modeling as a robust framework for analyzing PRO data in oncology trials−optimizing PRO endpoint selection and trial design, while also supporting earlier symptom detection, more informed clinical decision-making, and improved patient–clinician dialogue

Evidence derived from this study demonstrates that PRO data can provide prognostic and predictive insights into OS, further supporting the benefit of T+C as a first-line option for patients with PD-L1 score ≥5%

Abbreviations: CI=confidence interval; EORTC=European Organisation for Research and Treatment of Cancer; GC=Gastric cancer; GEJC=gastroesophageal junction adenocarcinom; GI=gastrointestinal; GHS/QoL: global health status/quality of life; QLQ-C30: Quality of Life Questionnaire – Core 30; ITT=intent-to-treat; QLQ-STO22= Quality of Life Questionnaire-Gastric Cancer Module; P+C=placebo + chemotherapy; PD-L1=programmed death-ligand 1; PRO=patient-reported outcome; RS-D=recurrent symptomatic deterioration; T+C=tislelizumab + chemotherapy.

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Thank you!

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