2024 ESMO GASTROINTESTINAL CANCERS
Annual Congress

TISLELIZUMAB (TIS) + CHEMOTHERAPY (CT) VS PLACEBO (PBO) + CT IN HER2-NEGATIVE ADVANCED OR METASTATIC GASTRIC OR GASTRO-OESOPHAGEAL JUNCTION ADENOCARCINOMA (GC/GEJC)

PD-L1 Biomarker Analysis from RATIONALE-305

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

DECLARATION OF INTERESTS

Prof. Markus Moehler reports

- Consultancy/advisory role for Bayer, Merck Sharp & Dohme (MSD), Merck Serono, Amgen, Taiho Pharmaceutical, Pfizer, Roche, Lilly, Servier Laboratories, BeiGene, Bristol Myers Squibb (BMS), AstraZeneca, Astellas, 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
- Other remuneration from Amgen, Merck Serono, Roche, Bayer, American Society for Clinical Oncology (ASCO), German Cancer Society, MSD, European Society for Medical Oncology (ESMO), BeiGene, and European Organisation for Research and Treatment (EORTC)

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PD-L1 Biomarker Analysis from RATIONALE-305

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BACKGROUND

- The PD-L1 **Tumor Area Positivity (TAP)** score is a newly developed scoring system evaluating both immune and tumour cells. The TAP score has been analytically developed and validated for advanced GC/GEJC in the RATIONALE-305 study
  - In **RATIONALE-305**, tislelizumab (TIS) + chemotherapy (CT) demonstrated significant overall survival (OS) benefit vs CT as first-line therapy, in all randomised patients (HR=0.80; 95% CI: 0.70, 0.92; P=0.001) and patients with **TAP score** ≥5% (HR=0.71; 95% CI: 0.58, 0.86)[1,2]
- In advanced GC/GEJC, PD-L1 score based on combined positive score (CPS) using a mixture of immune and tumour cell expression has shown predictive value to checkpoint inhibitors
  - In **CheckMate 649**, nivolumab demonstrated OS benefit in CPS ≥10, ≥5, and ≥1, and all randomised patients[3]
  - In **KEYNOTE-859**, pembrolizumab showed OS benefit in CPS ≥10 and ≥1, and all randomised patients[4]
- In this **exploratory post hoc analysis**, we report OS and progression-free survival (PFS) results in PD-L1 subgroups defined by TAP score and CPS, as well as concordance of TAP score and CPS at multiple thresholds (1% vs 1, 5% vs 5, and 10% vs 10) in RATIONALE-305

1. Moehler M, et al. Presented at ASCO GI 2023; Abstract #286. 2. Qiu MZ, et al. *BMJ*. 2024;385:e078876. 3. Shitara K, et al. *Nature*. 2022;603:942-948. 4. Rha SY, et al. *Lancet Oncol*. 2023;24:1181-1195.
Abbreviations: GC/GEJC, gastric or gastro-oesophageal junction adenocarcinoma; HR, hazard ratio; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

STUDY DESIGN

Randomised, Double-blind, Global Phase 3 Study

Key Eligibility Criteria

- Histologically confirmed GC/GEJC
- Excluded patients with HER2-positive tumours
- No previous therapy for unresectable, locally advanced or metastatic GC/GEJC

Stratification Factors

- Regions of enrolment: China (including Taiwan) vs Japan and South Korea vs US and Europe and other regions
- PD-L1 expression (PD-L1 score ≥5% vs PD-L1 score <5%)
- Presence of peritoneal metastasis (yes vs no)
- Investigator-chosen chemotherapy (oxaliplatin + capecitabine or cisplatin + 5-fluorouracil)

R 1:1

TIS 200 mg IV Q3W + CT (oxaliplatin + capecitabine or cisplatin + 5-fluorouracil)[a]

Maintenance treatment until unacceptable toxicity or disease progression

PBO IV Q3W + CT (oxaliplatin + capecitabine or cisplatin + 5-fluorouracil)[a]

Primary Endpoints

OS in PD-L1–positive (PD-L1 TAP score ≥5%) and ITT analysis set

Post Hoc Analysis

- Subgroup analysis of OS and PFS using exploratory PD-L1 TAP score and CPS cutoffs
- TAP score vs CPS concordance

- PD-L1 expression was assessed prospectively by central laboratory using the TAP score, stained by the VENTANA PD-L1 (SP263) assay
- For exploratory purposes, pathologists in the central laboratory scored the same stained samples according to CPS[b]

TAP Score (%)

Score Formula $\frac{\text{Area occupied by PD-L1 staining tumour cells and immune cells}}{\text{Tumour area}} \times 100\%$

Cell Types Included in PD-L1 Score: Tumour cells, immune cells[c]
Scoring Method: Visual-based estimation on tumour area

CPS

Score Formula $\frac{\text{\# PD-L1 staining tumour cells and immune cells}}{\text{Total \# viable tumour cells}} \times 100$

Cell Types Included in PD-L1 Score: Tumour cells, immune cells[d]
Scoring Method: Cell count (time consuming)

[a] CT: oxaliplatin 130 mg/m^2 day 1 + capecitabine 1000 mg/m^2 BID, days 1-14, Q3W; cisplatin 80 mg/m^2 day 1 + 5-fluorouracil 800 mg/m^2/day, days 1-5, Q3W. [b] Off-label for the VENTANA PD-L1 (SP263) assay [c] Including lymphocytes, macrophages, histiocytes, reticular dendritic cells, plasma cells, and neutrophils. [d] Including lymphocytes and macrophages. **Abbreviations:** BID, twice daily; CPS, combined positive score; CT, chemotherapy; GC/GEJC, gastric or gastro-oesophageal junction adenocarcinoma; HER2, human epidermal growth factor receptor 2; IV, intravenous; ITT, intent-to-treat; OS, overall survival; PBO, placebo; PD-L1, programmed death-ligand 1; PFS, progression-free survival; Q3W, once every 3 weeks; R, randomised; TAP, Tumor Area Positivity; TIS, tislelizumab.

PREVALENCE OF PD-L1 SUBGROUPS BY TAP SCORE OR CPS

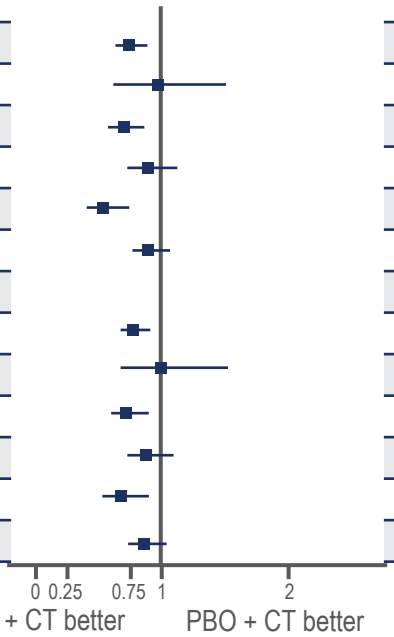
- Of 997 patients randomised, 997 had evaluable TAP scores and 974 had evaluable post-hoc CPS results
- **Prevalence** was comparable across arms by TAP score or CPS under different thresholds

PD-L1 Status TAP Score/CPS	TAP Score, n (%) N=997		CPS, n (%) N=974	
	TIS + CT N=501	PBO + CT N=496	TIS + CT N=491	PBO + CT N=483
≥1%/≥1	432 (86.2)	453 (91.3)	420 (85.5)	434 (89.9)
<1%/<1	69 (13.8)	43 (8.7)	71 (14.5)	49 (10.1)
≥5%/≥5	274 (54.7)	272 (54.8)	254 (51.7)	269 (55.7)
<5%/<5	227 (45.3)	224 (45.2)	237 (48.3)	214 (44.3)
≥10%/≥10	136 (27.1)	145 (29.2)	151 (30.8)	138 (28.6)
<10%/<10	365 (72.9)	351 (70.8)	340 (69.2)	345 (71.4)

Abbreviations: CPS, combined positive score; CT, chemotherapy; PBO, placebo; PD-L1, programmed death-ligand 1; TAP, Tumor Area Positivity; TIS, tislelizumab.

OS IMPROVEMENT FOR TIS + CT VS PBO + CT IN PD-L1 SUBGROUPS BY TAP SCORE AND CPS

PD-L1 Status	Event/Total		HR for Death (95% CI)	OS, Unstratified HR (95% CI)
	TIS + CT	PBO + CT		
TAP score				
≥1%	318/432	370/453		0.78 (0.67, 0.90)
<1%	52/69	36/43		0.98 (0.64, 1.50)
≥5%	192/274	219/272		0.72 (0.59, 0.88)
<5%	178/227	187/224		0.91 (0.74, 1.12)
≥10%	84/136	118/145		0.57 (0.43, 0.76)
<10%	286/365	288/351		0.91 (0.77, 1.07)
CPS				
≥1	308/420	356/434		0.78 (0.67, 0.91)
<1	53/71	39/49		1.01 (0.66, 1.52)
≥5	175/254	211/269		0.73 (0.60, 0.89)
<5	186/237	184/214		0.89 (0.72, 1.09)
≥10	100/151	111/138		0.68 (0.52, 0.90)
<10	261/340	284/345		0.87 (0.73, 1.03)

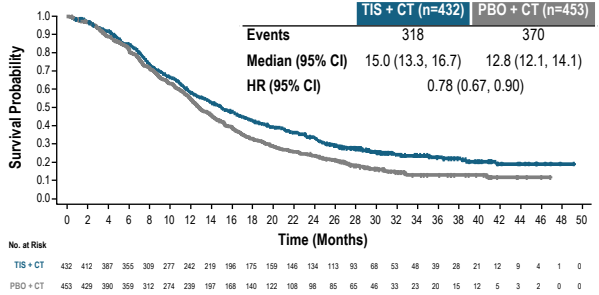


- Similar to previously reported results in patients with PD-L1 TAP score ≥5%, addition of TIS to CT as first-line treatment for GC/GEJC improved OS in patients with PD-L1 TAP scores of ≥10% and ≥1%
- OS results defined by TAP scores and CPS were similar

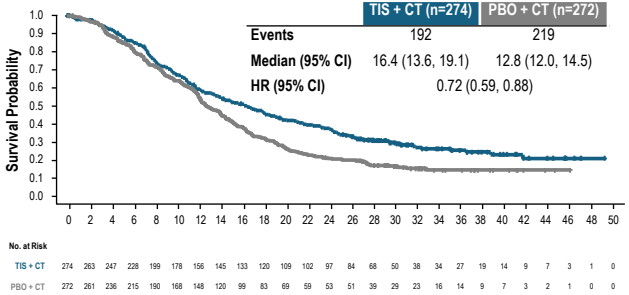
Abbreviations: CI, confidence interval; CPS, combined positive score; CT, chemotherapy; GC/GEJC, gastric or gastro-oesophageal junction adenocarcinoma; HR, hazard ratio; OS, overall survival; PBO, placebo; PD-L1, programmed death-ligand 1; TAP, Tumor Area Positivity; TIS, tislelizumab.

SIMILAR OS BENEFIT IN PD-L1–POSITIVE SUBGROUPS WITH CUTOFF AT 1%, 5%, AND 10% THRESHOLDS FOR EACH SCORE

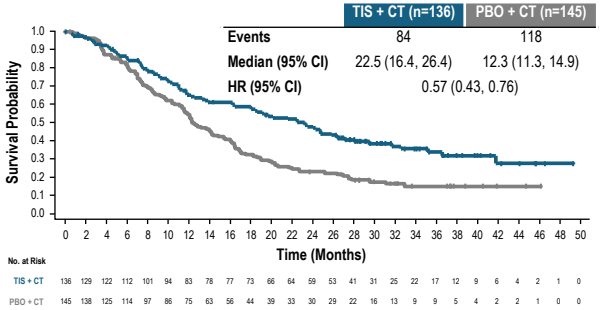
TAP ≥1%



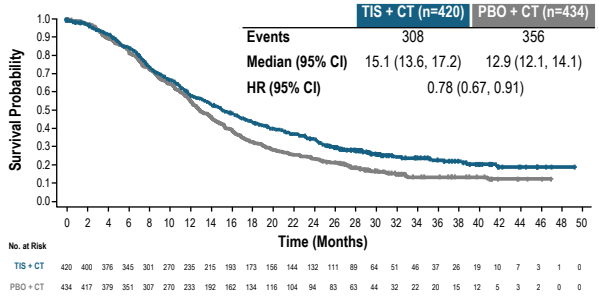
TAP ≥5%



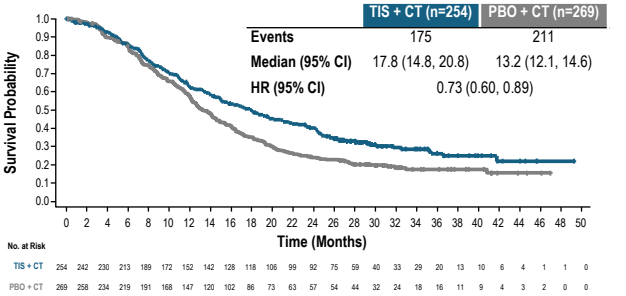
TAP ≥10%



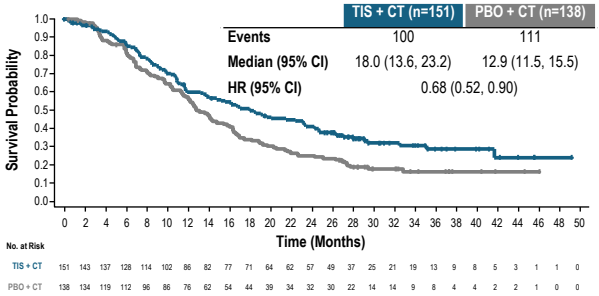
CPS ≥1



CPS ≥5



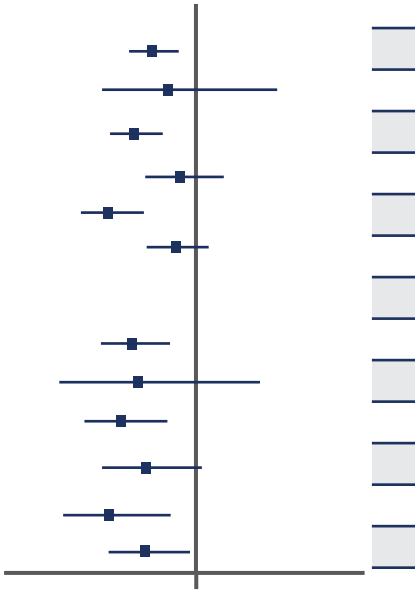
CPS ≥10



Abbreviations: CI, confidence interval; CPS, combined positive score; CT, chemotherapy; HR, hazard ratio; OS, overall survival; PBO, placebo; PD-L1, programmed death-ligand 1; TAP, Tumor Area Positivity; TIS, tislelizumab.

PFS IMPROVEMENT FOR TIS + CT VS PBO + CT IN PD-L1 SUBGROUPS BY TAP SCORE AND CPS

PD-L1 Status	Event/Total		HR for Death (95% CI)	PFS, Unstratified HR (95% CI)
	TIS + CT	PBO + CT		
TAP score				
≥1%	316/432	364/453		0.78 (0.67, 0.91)
<1%	45/69	27/43		0.87 (0.54, 1.41)
≥5%	189/274	216/272		0.69 (0.57, 0.84)
<5%	172/227	175/224		0.92 (0.75, 1.14)
≥10%	88/136	119/145		0.56 (0.42, 0.74)
<10%	273/365	272/351		0.90 (0.76, 1.06)
CPS				
≥1	303/420	348/434		0.77 (0.66, 0.90)
<1	49/71	36/49		0.80 (0.52, 1.23)
≥5	179/254	212/269		0.73 (0.60, 0.90)
<5	173/237	172/214		0.82 (0.67, 1.02)
≥10	102/151	107/138		0.69 (0.53, 0.91)
<10	250/340	277/345		0.82 (0.69, 0.97)

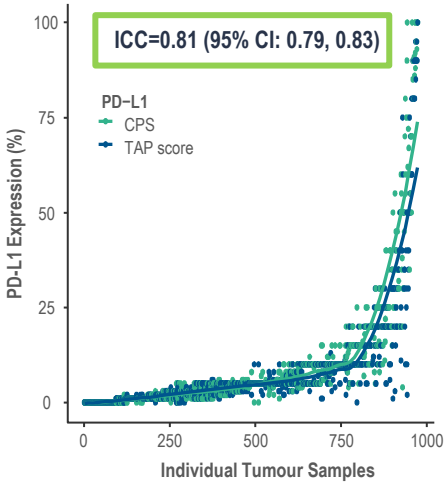


- Similar to previously reported results in patients with PD-L1 TAP score ≥5%, addition of TIS to CT as first-line treatment for GC/GEJC improved PFS in patients with PD-L1 TAP scores of ≥10% and ≥1%
- PFS results defined by TAP scores and CPS were similar

Abbreviations: CI, confidence interval; CPS, combined positive score; CT, chemotherapy; GC/GEJC, gastric or gastro-oesophageal junction adenocarcinoma; HR, hazard ratio; PBO, placebo; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TAP, Tumor Area Positivity; TIS, tislelizumab.

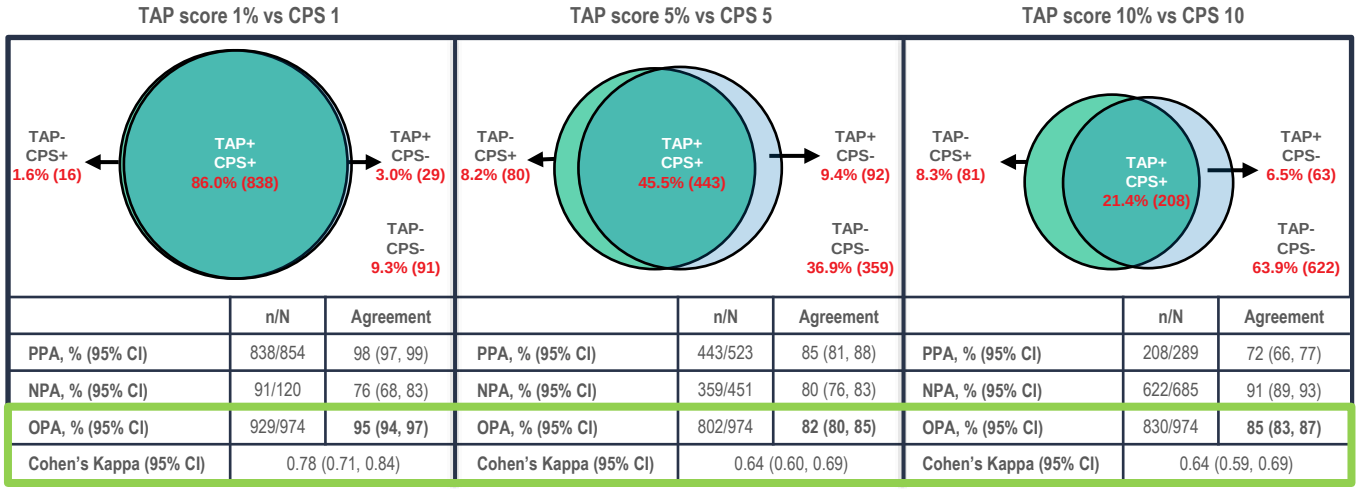
SUBSTANTIAL CONCORDANCE FOR TAP SCORE AND CPS IN GC/GEJC

- Good correlation was observed between TAP score and CPS based on interclass correlation coefficient (ICC=0.81 [0.79, 0.83])
- TAP score and CPS showed substantial concordance in terms of overall percent agreement (OPA) and Cohen's Kappa at matched thresholds for each score (OPA [95% CI]: 95% [94, 97], 82% [80, 85], and 85% [83, 87] at 1%, 5%, and 10% thresholds of each score, respectively)



Strength of Reliability (ICC)

Poor	Moderate	Good	Excellent
<0.50	(0.50-0.75)	(0.75-0.90)	(≥0.90)



	n/N	Agreement
PPA, % (95% CI)	838/854	98 (97, 99)
NPA, % (95% CI)	91/120	76 (68, 83)
OPA, % (95% CI)	929/974	**95 (94, 97)**
Cohen's Kappa (95% CI)	0.78 (0.71, 0.84)	

	n/N	Agreement
PPA, % (95% CI)	443/523	85 (81, 88)
NPA, % (95% CI)	359/451	80 (76, 83)
OPA, % (95% CI)	802/974	**82 (80, 85)**
Cohen's Kappa (95% CI)	0.64 (0.60, 0.69)	

	n/N	Agreement
PPA, % (95% CI)	208/289	72 (66, 77)
NPA, % (95% CI)	622/685	91 (89, 93)
OPA, % (95% CI)	830/974	**85 (83, 87)**
Cohen's Kappa (95% CI)	0.64 (0.59, 0.69)	

Strength of Agreement (Kappa)

Slight	Fair	Moderate	Substantial	Almost perfect
(0.01-0.20)	(0.21-0.40)	(0.41-0.60)	(0.61-0.80)	(0.81-1.0)

Abbreviations: CI, confidence interval; CPS, combined positive score; GC/GEJC, gastric or gastro-oesophageal junction adenocarcinoma; NPA, negative percent agreement; PPA, positive percent agreement; PD-L1, programmed death-ligand 1; TAP, Tumor Area Positivity.

CONCLUSIONS

- Both TAP score and CPS are viable for PD-L1 expression measurement in patients with GC/GEJC
  - TAP score and CPS at matched thresholds (1% vs 1, 5% vs 5, 10% vs 10) exhibited substantial concordance in GC/GEJC among patients enrolled
- TIS + CT improved OS and PFS in patients with PD-L1 TAP scores of ≥10% and ≥1%, as well as the prespecified population with TAP score ≥5%
  - Comparable OS and PFS results were observed in PD-L1 subgroups by TAP score at a prespecified cutoff of 5% and by CPS at cutoff of 5, TAP score 10% vs CPS 10, and TAP score 1% vs CPS 1
- These PD-L1 subgroup results, along with previous results from the RATIONALE-305 primary analysis in all randomised patients, support TIS + CT as a new first-line treatment option for advanced HER2-negative GC/GEJC

Abbreviations: CPS, combined positive score; CT, chemotherapy; GC/GEJC, gastric or gastro-oesophageal junction adenocarcinoma; HER2, human epidermal growth factor receptor 2; OS, overall survival; PBO, placebo; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TAP, Tumor Area Positivity; TIS, tislelizumab.

ACKNOWLEDGEMENTS

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- This study was sponsored by BeiGene
- Medical writing support was provided by Nitya Venkataraman, PhD, of Parexel, with funding provided by BeiGene

THANK YOU

APPENDIX

SCORING METHODS COMPARISON BETWEEN TAP SCORE AND CPS

- PD-L1 expression was assessed prospectively by central laboratory using the TAP score, stained by the VENTANA PD-L1 (SP263) assay
- For exploratory purposes, pathologists in the central laboratory scored the same stained samples according to CPS[a]

	TAP Score (%)	CPS
Score Formula	$\frac{\text{Area occupied by PD-L1 staining tumour cells and immune cells}}{\text{Tumour area}} \times 100\%$	$\frac{\text{\# PD-L1 staining tumour cells and immune cells}}{\text{Total \# viable tumour cells}} \times 100$
Cell Types Included in PD-L1 Score	• Tumour cells • Immune cells (including lymphocytes, macrophages, histiocytes, reticular dendritic cells, plasma cells, and neutrophils)	• Tumour cells • Immune cells (including lymphocytes and macrophages)
Scoring Method	• Visual-based estimation on tumour area	• Cell count (time consuming)

[a] Off-label for the VENTANA PD-L1 (SP263) assay.
Abbreviations: CPS, combined positive score; PD-L1, programmed death-ligand 1; TAP, Tumor Area Positivity.