2024 ESMO GASTROINTESTINAL CANCERS
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TISLELIZUMAB (TIS) + CHEMOTHERAPY (CT) VS PLACEBO (PBO) + CT IN LOCALLY ADVANCED UNRESECTABLE OR METASTATIC ESOPHAGEAL SQUAMOUS CELL CARCINOMA (ESCC)

PD-L1 Biomarker Analysis from RATIONALE-306

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DECLARATION OF INTERESTS

Eric Raymond reports no conflicts of interest

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BACKGROUND

- The PD-L1 **Tumor Area Positivity (TAP)** score is a newly developed area scoring system evaluating both immune and tumour cells. The TAP score has been analytically developed and validated for advanced ESCC in the RATIONALE-306 study
  - In **RATIONALE-306**, tislelizumab (TIS) + chemotherapy (CT) demonstrated a significant improvement in overall survival (OS) in all randomised patients (HR=0.70; 95% CI: 0.59, 0.83) and patients with PD-L1 **TAP score** ≥10% (HR=0.70; 95% CI: 0.52, 0.95) compared with placebo (PBO) + CT, with a sustained survival benefit observed after a minimum 3-year follow-up
- In advanced ESCC, combined positive score (CPS) as mixed PD-L1 expression in immune and tumour single cells was able to predict responses to checkpoint inhibitors
  - In KEYNOTE-590, pembrolizumab showed significant OS benefit in all randomised patients and patients with CPS ≥10[1]
  - In CheckMate 648, nivolumab showed significant OS benefit in all randomised patients and enhanced OS benefit in patients with CPS ≥1, ≥5, and ≥10[2]
- In these **exploratory post-hoc analyses** from a minimum 3-year follow-up, 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 in RATIONALE-306

1. Sun JM, et al. *Lancet*. 2021;398(10302):759-771. 2. Kato K, et al. *Cancer Med*. 2024;13(9):e7235.
Abbreviations: CI, confidence interval; ESCC, esophageal squamous cell carcinoma; HR, hazard ratio; PD-L1, programmed death-ligand 1.

STUDY DESIGN

Randomised, Double-blind, Global Phase 3 Study

Key Eligibility Criteria

- Unresectable locally advanced or metastatic ESCC
- No prior systemic treatment for advanced disease
- ECOG PS 0 or 1
- Measurable or evaluable disease per RECIST v1.1

R 1:1

TIS 200 mg IV Q3W + CT (platinum + fluoropyrimidine or platinum + paclitaxel)[a]

Maintenance treatment until unacceptable toxicity or disease progression

PBO IV Q3W + CT (platinum + fluoropyrimidine or platinum + paclitaxel)[a]

Primary Endpoints
OS in ITT analysis set
Secondary Endpoints
OS in TAP score ≥10%, PFS, ORR, DoR, HRQoL, safety

Post Hoc Analysis

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

Stratification Factors

- Geographic region (Asia [excluding Japan] vs Japan vs Rest of World)
- Prior definitive therapy (yes vs no)
- Investigator-chosen chemotherapy (platinum/fluoropyrimidine vs platinum/paclitaxel paclitaxel)

[a]The platinum agent may be cisplatin 60-80 mg/m^2 day 1 or oxaliplatin 130 mg/m^2 day 1 (except in China, Taiwan, Japan, and countries where oxaliplatin substitution is not permitted) according to site or investigator preference, or standard practice as determined prior to randomisation. The fluoropyrimidine may be 5-fluorouracil 750-800 mg/m^2 days 1-5 or capecitabine 1000 mg/m^2 days 1-14 twice a day. Paclitaxel 175 mg/m^2 day 1.
Abbreviations: CPS, combined positive score; CT, chemotherapy; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Score performance status; ESCC, esophageal squamous cell carcinoma; HRQoL, health-related quality of life; ITT, intent-to-treat; IV, intravenous; ORR, objective response rate; OS, overall survival; PBO, placebo; PD-L1, programmed death-ligand 1; PFS, progression-free survival; Q3W, once every 3 weeks; R, randomised; RECIST, Response Evaluation Criteria in Solid Tumors; TAP, Tumor Area Positivity; TIS, tislelizumab.

SCORING METHODS COMPARISON BETWEEN TAP SCORE AND CPS

- PD-L1 expression was stained using VENTANA PD-L1 (SP263) assay (Roche) and determined by TAP in RATIONALE-306
- 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.

PREVALENCE OF PD-L1 SUBGROUPS BY TAP SCORE OR CPS

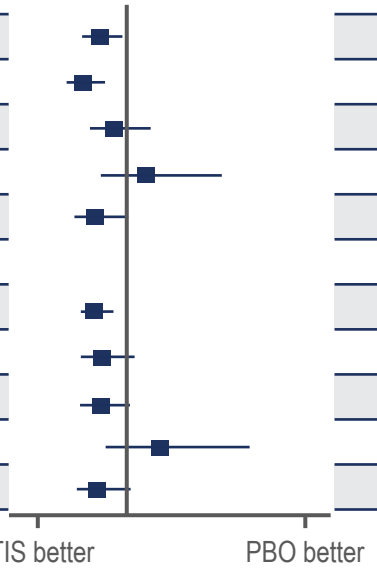
- Of 649 patients randomised, 542 had evaluable TAP scores and 537 had evaluable post hoc CPS
- Prevalence was comparable across arms by TAP score or CPS at different thresholds

PD-L1 Status TAP Score/CPS	TAP Score, n (%) N=542		CPS, n (%) N=537	
	TIS + CT N=267	PBO + CT N=275	TIS + CT N=264	PBO + CT N=273
≥10%/≥10	116 (43.4)	107 (38.9)	115 (43.6)	113 (41.4)
5% to <10%/5 to <10	56 (21.0)	79 (28.7)	54 (20.5)	61 (22.3)
1% to <5%/1 to <5	59 (22.1)	64 (23.3)	64 (24.2)	73 (26.7)
<1%/<1	36 (13.5)	25 (9.1)	31 (11.7)	26 (9.5)

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

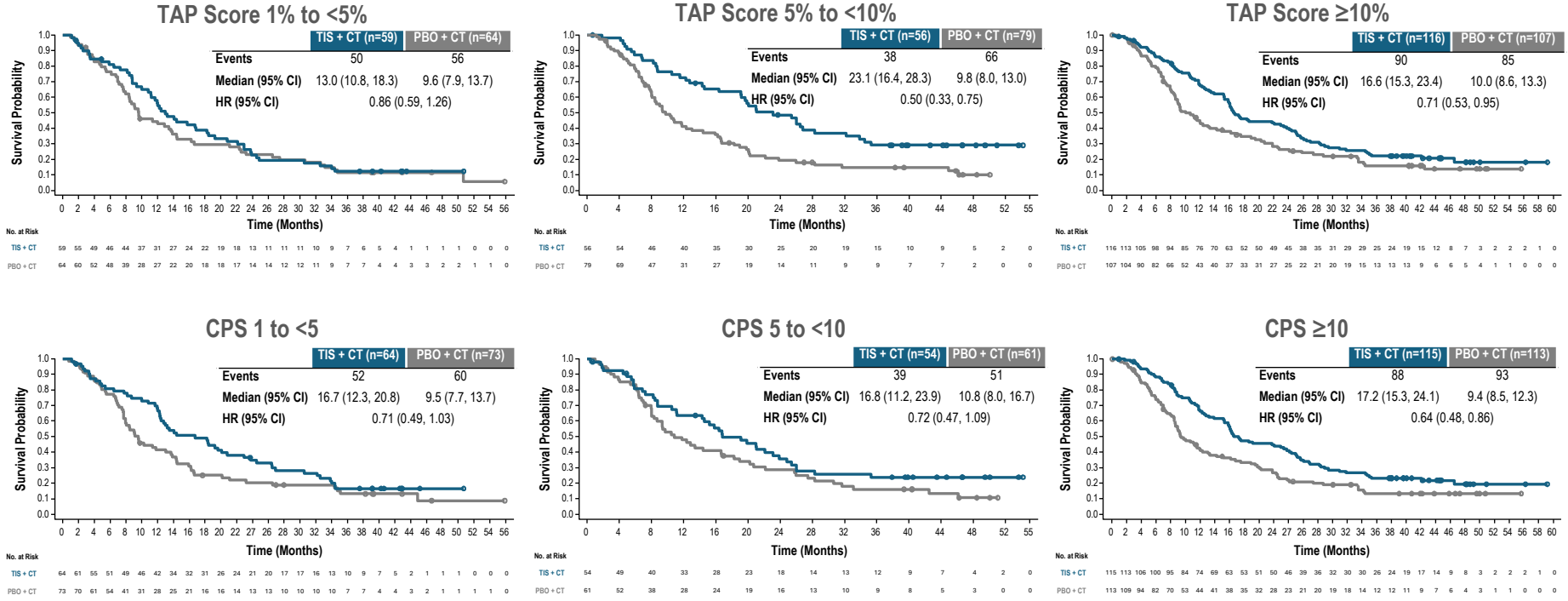
PD-L1 Status	Event/Total		HR for Death (95% CI)	OS, Unstratified HR (95% CI)
	TIS + CT	PBO + CT		
TAP score				
≥10%	90/116	85/107		0.71 (0.53, 0.95)
5% to <10%	38/56	66/79		0.50 (0.33, 0.75)
1% to <5%	50/59	56/64		0.86 (0.59, 1.26)
<1%	32/36	22/25		1.21 (0.70, 2.08)
Unknown	40/59	35/48		0.65 (0.41, 1.02)
CPS				
≥10	88/115	93/113		0.64 (0.48, 0.86)
5 to <10	39/54	51/61		0.72 (0.47, 1.09)
1 to <5	52/64	60/73		0.71 (0.49, 1.03)
<1	28/31	23/26		1.36 (0.78, 2.38)
Unknown	43/62	37/50		0.66 (0.42, 1.02)



- After a minimum 3-year follow-up, OS improvement with TIS + CT vs PBO + CT was seen in PD-L1 subgroups with TAP score ≥1% or CPS ≥1
- The small subgroup size with TAP score <1% or CPS <1 limited interpretation of efficacy data
- OS results defined by TAP scores and CPS were similar

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.

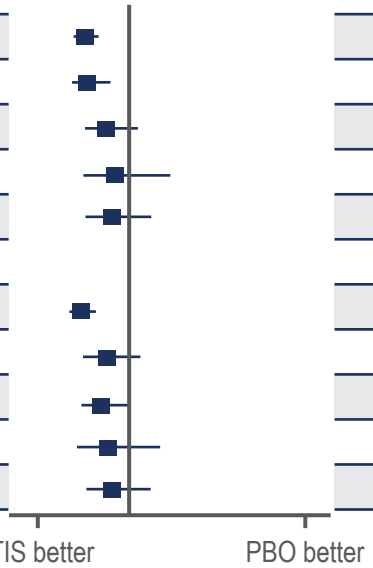
SIMILAR OS TREND IN PD-L1–POSITIVE SUBGROUPS BASED ON ASSOCIATED CLINICAL CUTOFFS



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				
≥10%	81/116	93/107		0.49 (0.36, 0.67)
5% to <10%	38/56	60/79		0.52 (0.34, 0.79)
1% to <5%	45/59	52/64		0.74 (0.49, 1.11)
<1%	27/36	22/25		0.83 (0.47, 1.46)
Unknown	42/59	34/48		0.79 (0.50, 1.25)
CPS				
≥10	80/115	97/113		0.45 (0.33, 0.61)
5 to <10	41/54	49/61		0.74 (0.48, 1.12)
1 to <5	44/64	56/73		0.66 (0.44, 0.98)
<1	23/31	23/26		0.76 (0.42, 1.35)
Unknown	45/62	36/50		0.79 (0.51, 1.23)

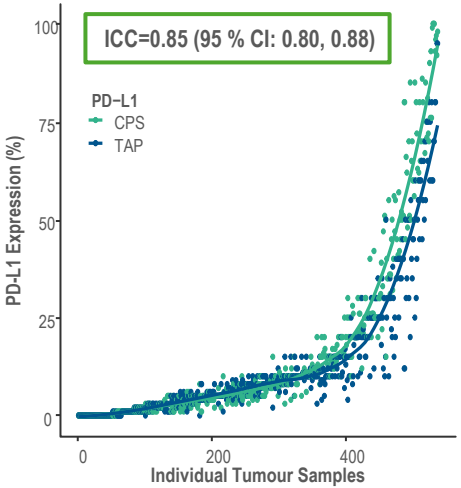


- After a minimum 3-year follow-up, PFS improvement with TIS + CT vs PBO + CT was seen in all PD-L1 subgroups
- PFS results defined by TAP scores and CPS were similar

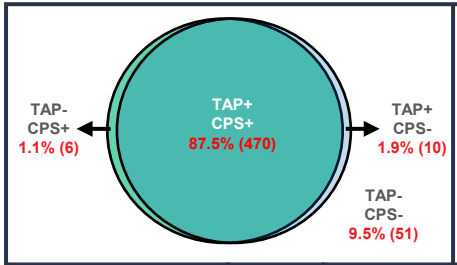
Abbreviations: CI, confidence interval; CPS, combined positive score; CT, chemotherapy; HR, hazard ratio; PBO, placebo; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TAP, Tumor Area Positivity; TIS, tislelizumab.

SUBSTANTIAL CONCORDANCE AND GOOD CORRELATION BETWEEN TAP AND CPS SCORING IN ESCC

- Good correlation was observed between TAP score and CPS, as shown by the interclass correlation coefficient (ICC=0.85 [0.80, 0.88])
- TAP score and CPS showed substantial concordance at multiple cutoffs in terms of overall percent agreement (OPA) and Cohen's Kappa (OPA [95% CI]: 97% [96, 98], 85% [82, 88], 89% [87, 92] at 1%, 5%, and 10% thresholds of each score, respectively)

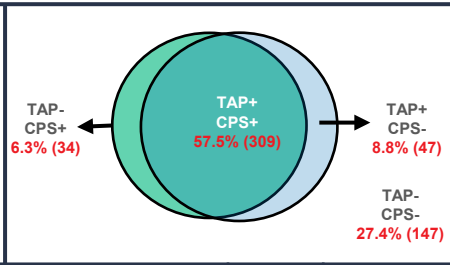


TAP Score 1% vs CPS 1



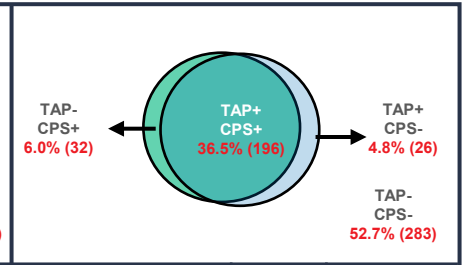
	n/N	Agreement
PPA, % (95% CI)	470/480	98 (97, 99)
NPA, % (95% CI)	51/57	89 (81, 96)
OPA, % (95% CI)	521/537	**97 (96, 98)**
Cohen's Kappa (95% CI)	0.85 (0.77, 0.92)	

TAP Score 5% vs CPS 5



	n/N	Agreement
PPA, % (95% CI)	309/343	90 (87, 93)
NPA, % (95% CI)	147/194	76 (70, 82)
OPA, % (95% CI)	456/537	**85 (82, 88)**
Cohen's Kappa (95% CI)	0.67 (0.60, 0.73)	

TAP Score 10% vs CPS 10



	n/N	Agreement
PPA, % (95% CI)	196/228	86 (82, 90)
NPA, % (95% CI)	283/309	92 (88, 94)
OPA, % (95% CI)	479/537	**89 (87, 92)**
Cohen's Kappa (95% CI)	0.78 (0.72, 0.83)	

Strength of Reliability (ICC)

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

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)

Eric Raymond

Abbreviations: CI, confidence interval; CPS, combined positive score; ESCC, esophageal squamous cell carcinoma; NPA, negative percent agreement; PD-L1, programmed death-ligand 1; PPA, positive percent agreement; TAP, Tumor Area Positivity.

CONCLUSIONS

- Both TAP score and CPS are viable for PD-L1 expression measurement in patients with ESCC
  - TIS + CT improved OS in patients with PD-L1 TAP scores of 1 to <5%, 5 to <10%, as well as the prespecified TAP score ≥10%, and improved PFS regardless of PD-L1 expression
  - Comparable OS and PFS benefit was observed in PD-L1 subgroups by CPS
  - TAP score and CPS at matched thresholds (1% vs 1, 5% vs 5, 10% vs 10) exhibited substantial concordance in ESCC
- These findings from the 3-year follow-up provide further support for the therapeutic advantages of TIS + CT over PBO + CT as first-line treatment of ESCC, as well as the interchangeability of TAP score and CPS in measuring PD-L1 expression in ESCC

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

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THANK YOU