

Tislelizumab for the Treatment of Gastric or Gastroesophageal Junction (G/GEJ) Adenocarcinoma

September 26, 2024

Oncologic Drugs Advisory Committee

BeiGene



Introduction

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SVP, Chief Medical Officer, Solid Tumors
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Agenda

Tislelizumab Background

Rationale-305 Results

PD-L1 Subgroup Analyses

Clinical Perspective

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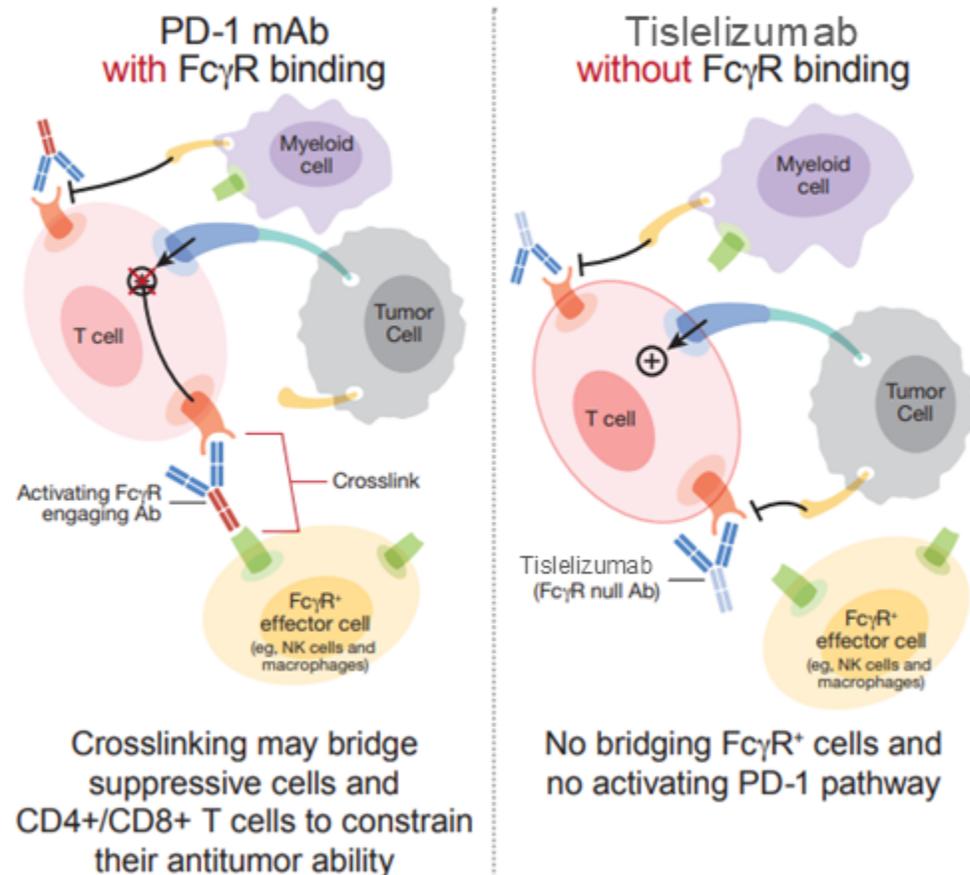
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Tislelizumab: Design and Mechanism

- Uniquely designed IgG4 for potent PD-1 binding and robust CD8+ T-cell activation
- Competitively blocks the interaction of PD-1 with both PD-L1 and PD-L2
- Specifically engineered to avoid binding to Fc gamma receptors and C1q
 - Avoids antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity



Clinical and Regulatory History in G/GEJ

Tislelizumab

June
FDA EOP2
Consultation

December
Phase 3
Rationale-305
Initiated

February
Completion
of
enrollment

October
IA data cut-off

February
FA data cut-off

December
BLA Submitted
to FDA

2018

2019

2020

2021

2022

2023

2024

April
Nivolumab approved
by FDA

November
Pembrolizumab
approved by FDA

**Approvals for
other PD-1s**

Rationale-305 Overview

Treatment with tislelizumab plus chemotherapy improved OS in locally advanced or metastatic G/GEJ cancer and can provide an important treatment option



Benefit/risk profile of tislelizumab plus chemotherapy as 1L treatment is most favorable when PD-L1 \geq 5% and consistent with approved PD-1 inhibitors



Tislelizumab plus chemotherapy has tolerable and acceptable safety profile



Rationale-305: Efficacy

Rationale-305: Randomized, Double-Blind, Global Phase 3 Study

Key Eligibility Criteria

- Histologically confirmed G/GEJ cancer
- Excluded patients with HER2-positive tumors
- No previous therapy for unresectable, locally advanced or metastatic G/GEJ cancer

R
1:1

Tislelizumab 200 mg IV Q3W + chemotherapy
(oxaliplatin + capecitabine
or cisplatin + 5-fluorouracil)
N = 501

*Maintenance treatment until unacceptable
toxicity or disease progression*

Placebo IV Q3W + chemotherapy
(oxaliplatin + capecitabine
or cisplatin + 5-fluorouracil)
N = 496

Study Endpoints

	Endpoints
Primary endpoint	OS in PD-L1 \geq 5% OS in ITT
Secondary endpoints	PFS ORR DOR Safety

All analyses prespecified scoring method for PD-L1 expression using TAP

ITT: intent-to-treat; PFS: progression-free survival; ORR: objective response rate; DOR: duration of response

Rationale for Analysis Based Upon PD-L1 $\geq 5\%$

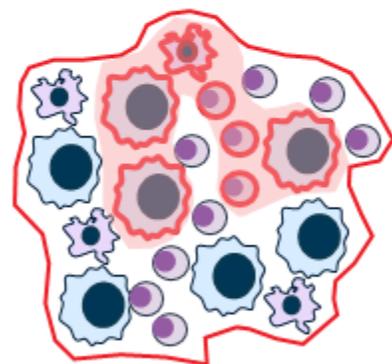
- Post-hoc analysis of patients with 2L+ gastric and esophageal adenocarcinoma
- Initial analysis of 46 patients treated with tislelizumab
- Confirmatory analysis of 77 patients:
 - 50 patients with GC
 - 27 patients with EAC
- Receiver operating characteristic analysis based on ORR identified PD-L1 $\geq 5\%$

	PD-L1 < 5% n = 39	PD-L1 $\geq 5\%$ n = 38
ORR (95%CI)	2.6% (0.1, 13.5)	15.8% (6.0, 31.3)
Sensitivity / Specificity	85.7% / 54.3%	
PPV / NPV	15.8% / 97.4%	

TAP and CPS Designed to Measure Same Biology

Tumor Area Positivity (TAP)

$$\frac{\text{Area occupied by PD-L1 stained TCs and ICs}}{\text{Tumor area}} \times 100\%$$

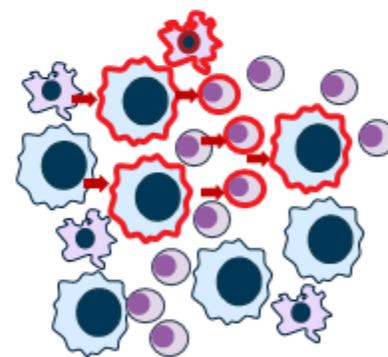


Visual estimation

Include PD-L1 positive tumor cells and all tumor associated immune cells

Combined Positive Score (CPS)

$$\frac{\text{Number of PD-L1 stained TCs and ICs}}{\text{Total number of viable TCs}} \times 100$$



Cell counting

Include PD-L1 positive tumor cells, lymphocytes and macrophages

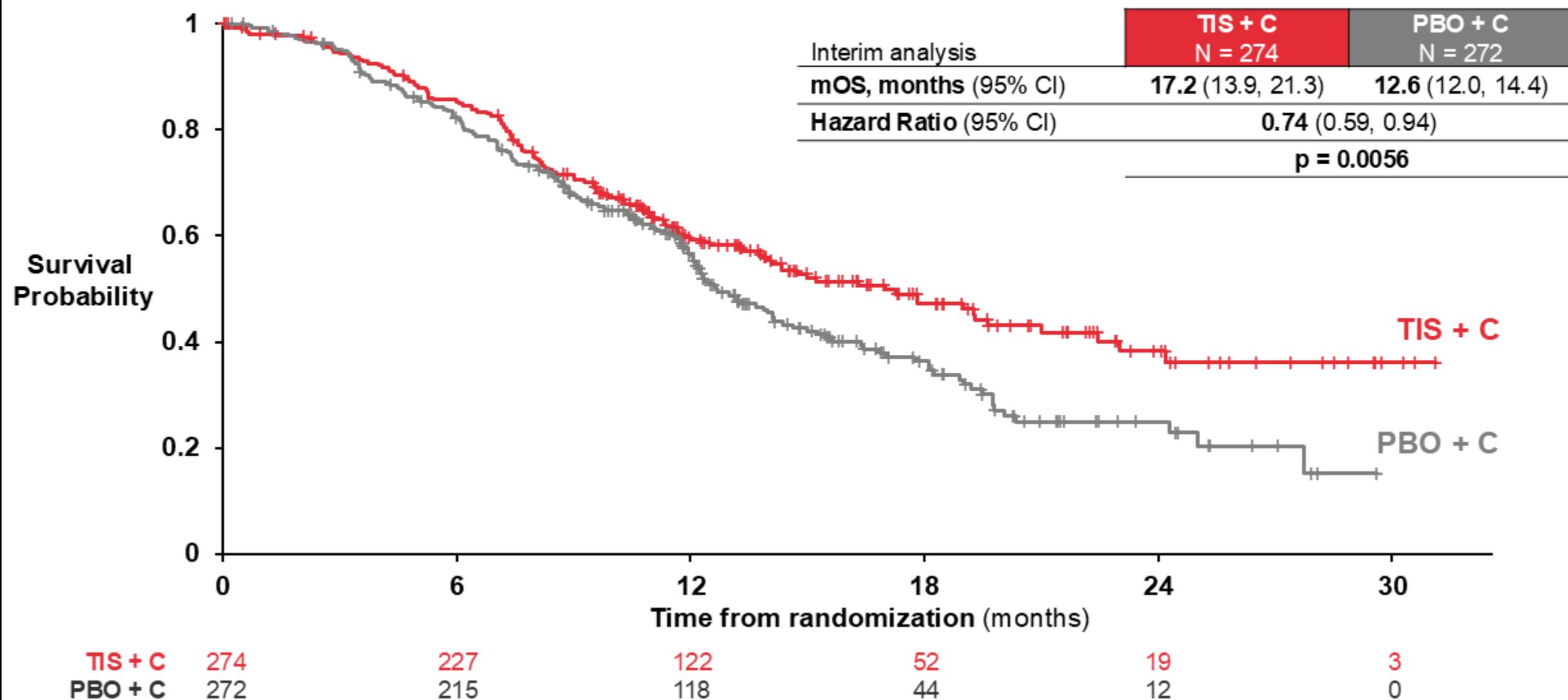
Baseline Demographics Generally Balanced Between Treatment Arms

		TIS + C N = 501	PBO + C N = 496
Age, median		60	61
Male		69%	70%
Region	China (including Taiwan)	52%	52%
	Japan	10%	10%
	South Korea	13%	13%
	US	2%	3%
	Europe	23%	22%

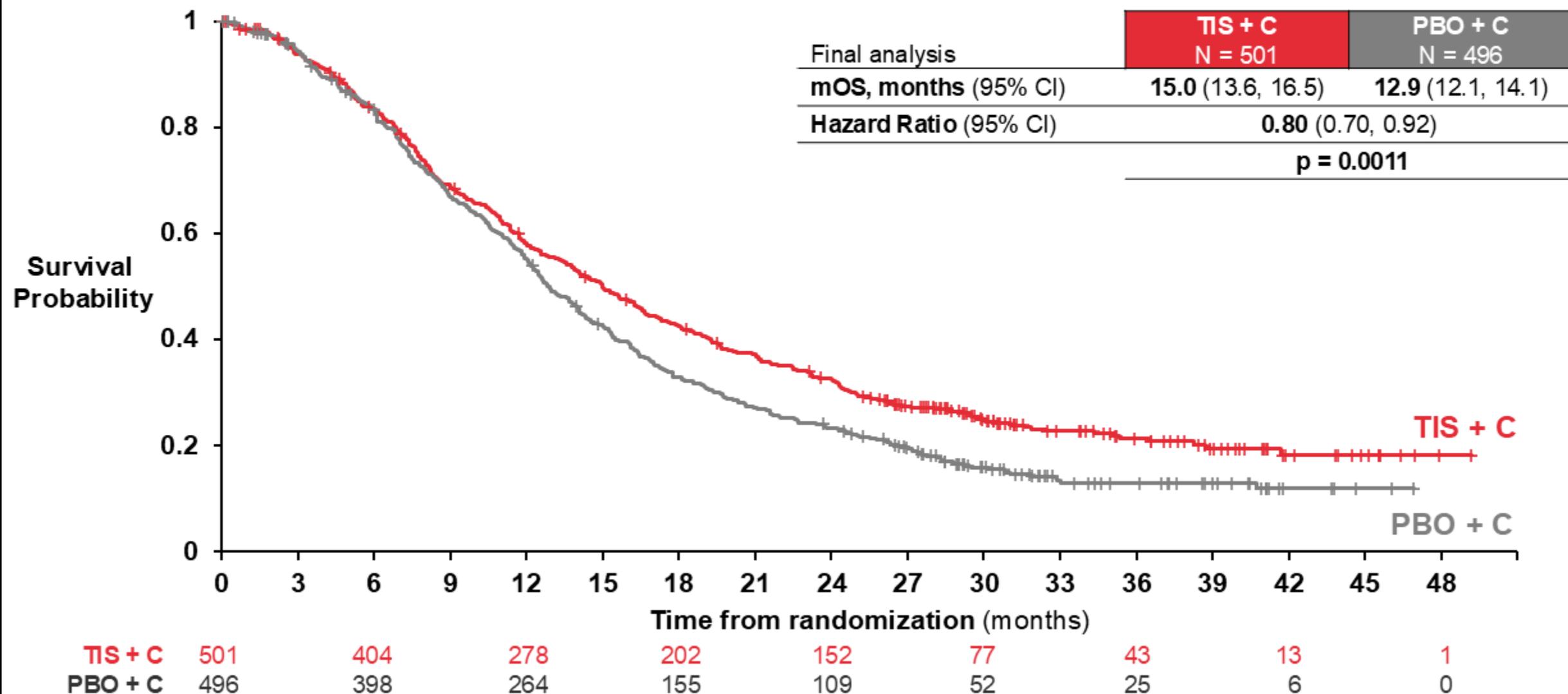
Baseline Disease Characteristics Balanced and Representative of Target Patient Population

		TIS + C N = 501	PBO + C N = 496
Time since initial diagnosis, median months		1.5	1.6
Disease status	Metastatic	99%	99%
	Locally advanced	1%	1%
Number of metastatic sites	0-2	67%	68%
	≥ 3	33%	32%
Prior gastrectomy / esophagectomy		27%	28%
ECOG PS	0	34%	31%
	1	66%	69%
PD-L1 score	≥ 5 %	55%	55%
	< 5%	45%	45%

Primary Endpoint Met – Clinically Meaningful OS Benefit in PD-L1 $\geq 5\%$ (Interim Analysis)



Primary Endpoint Met – Clinically Meaningful OS Benefit in ITT (Final Analysis)



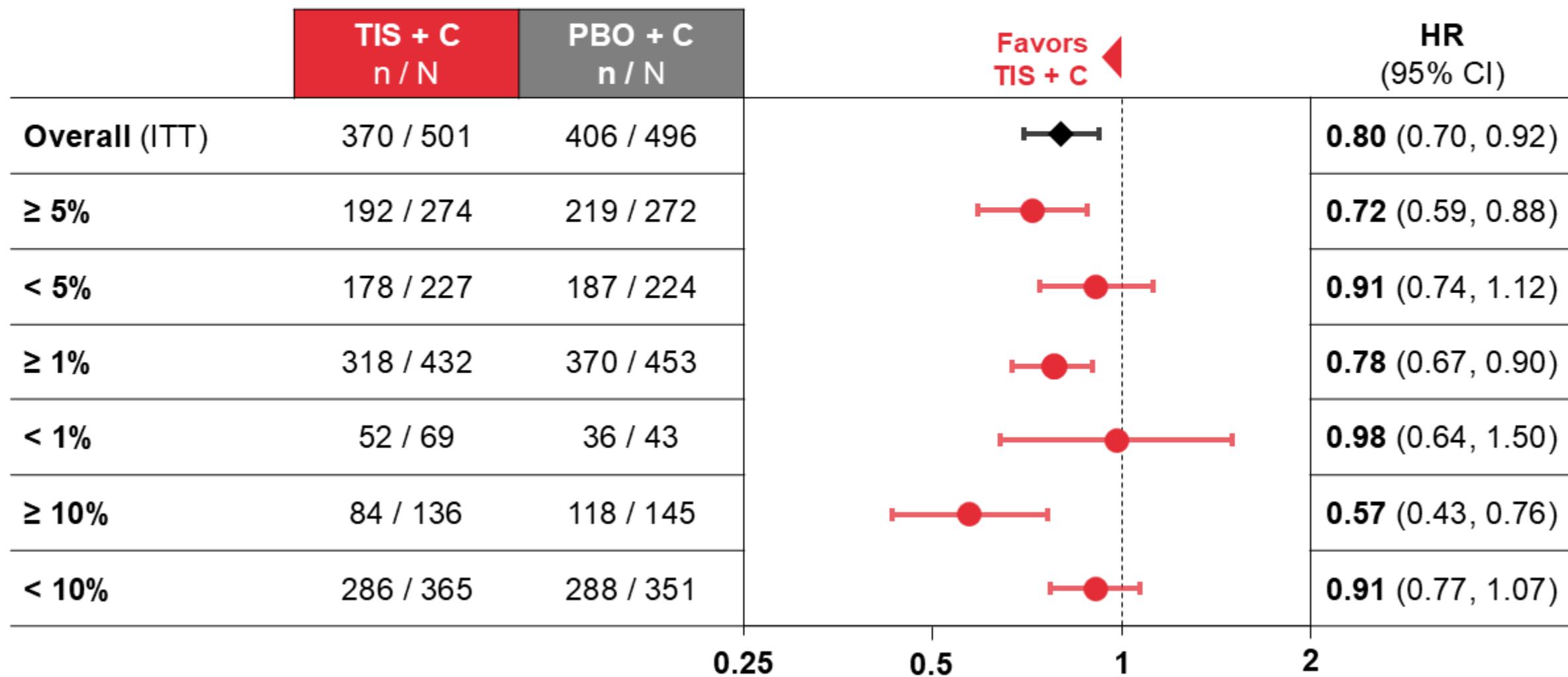
OS Benefit with Tislelizumab Plus Chemotherapy Supported by Improvements in PFS, ORR, and DOR

Secondary Endpoints	PD-L1 \geq 5%		Hazard Ratio (95% CI)	p-value (one-sided)
	TIS + C N = 274	PBO + C N = 272		
Median PFS, months (95% CI)	7.2 (5.8, 8.4)	5.9 (5.6, 7.0)	0.67 (0.55, 0.83)	< 0.0001
ORR (95% CI)	50.4% (44.3, 56.4)	43.0% (37.1, 49.1)	1.36 (0.97, 1.92)	NS
Median DOR, months (95% CI)	9.0 (8.2, 19.4)	7.1 (5.7, 8.3)		

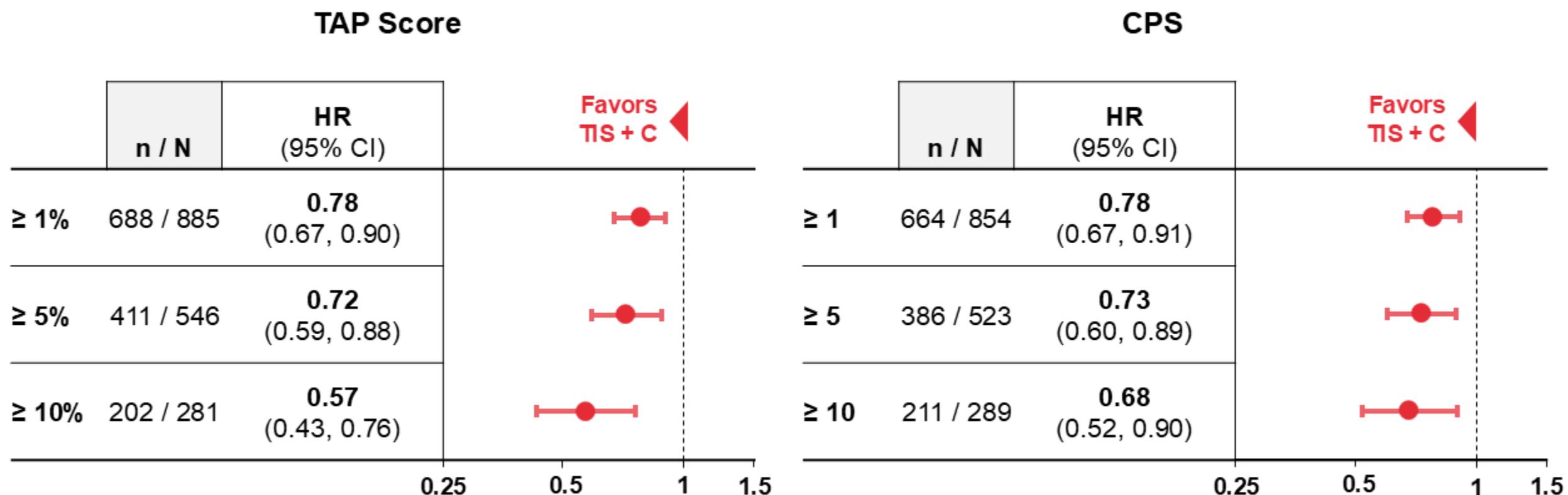


Rationale-305: PD-L1 Subgroup Analyses

Favorable OS Benefit with Tislelizumab Plus Chemotherapy Across PD-L1 Subgroups



Comparable OS Improvement in PD-L1 Subgroups by TAP Score and CPS





Rationale-305: Safety

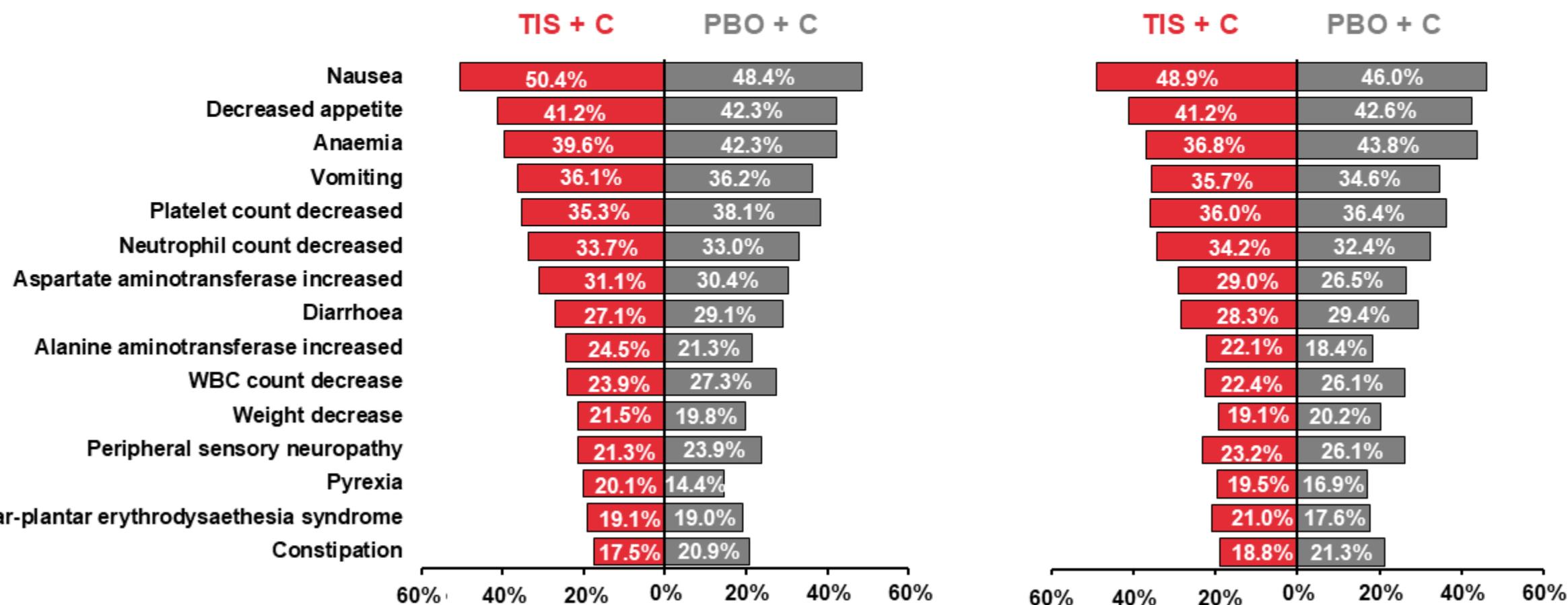
Tislelizumab Plus Chemotherapy Has Manageable Safety Profile

	Overall Safety Population		PD-L1 \geq 5%	
	TIS + C N = 498	PBO + C N = 494	TIS + C N = 272	PBO + C N = 272
Any AE	99%	98%	> 99%	98%
AEs Grade \geq 3	69%	66%	68%	65%
Immune-mediated AEs	31%	12%	29%	13%
AEs leading to any dose modification	77%	76%	78%	74%
AEs leading to any treatment discontinuation	23%	14%	24%	13%
SAEs	42%	36%	46%	37%
AEs leading to death	4%	4%	4%	3%

Most Common AEs Similar Between Tislelizumab Plus Chemotherapy and Placebo Plus Chemotherapy

Overall Safety Population

PD-L1 $\geq 5\%$



Tislelizumab Conclusion

- Tislelizumab demonstrated statistically significant and clinically meaningful improvement in overall survival
- Benefit / risk is most favorable among patients in prespecified PD-L1 $\geq 5\%$ group
 - OS benefit accompanied by improvements in PFS, ORR, and DOR
 - Consistent and manageable safety profile across PD-L1 subgroups

Totally of data support use of tislelizumab plus chemotherapy as 1L treatment option for patients with advanced G/GEJ



Clinical Perspective

Nataliya Uboha, MD, PhD

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Section of Hematology and Medical Oncology

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Gastric Cancer – Aggressive Solid Tumor with Poor Prognosis

Population

- Majority of diagnoses occur in advanced stage due to challenges in early detection

Incidence

- ~ 26,000 new cases and 10,000 deaths in US¹

Survival

- 5-year survival only 7% for patients with advanced or metastatic disease²

Treatment Landscape

Front-line treatments are critical for treatment of patients with advanced disease

Many patients decline clinically and not candidate for subsequent therapies



Addition of PD-1 inhibitors to chemotherapy prolongs OS in GC patients

PD-L1 Cut-Offs and Clinical Use

- Data across studies show that patients with PD-L1 positive tumors benefit from anti-PD1 agents
- Tislelizumab with chemotherapy significantly improved OS
 - OS HR 0.72 in PD-L1 $\geq 5\%$ and HR 0.80 in ITT population
 - OS HR 0.78 in patients with PD-L1 $\geq 1\%$
- No benefit in patients with PD-L1 < 1 tumors across studies
- Recommend PD-L1 threshold of ≥ 1
 - Unified across class

PD-L1 ≥ 1 allows appropriate access to therapy and will preclude offering suboptimal treatments to patients

Tislelizumab for the Treatment of Gastric or Gastroesophageal Junction (G/GEJ) Adenocarcinoma

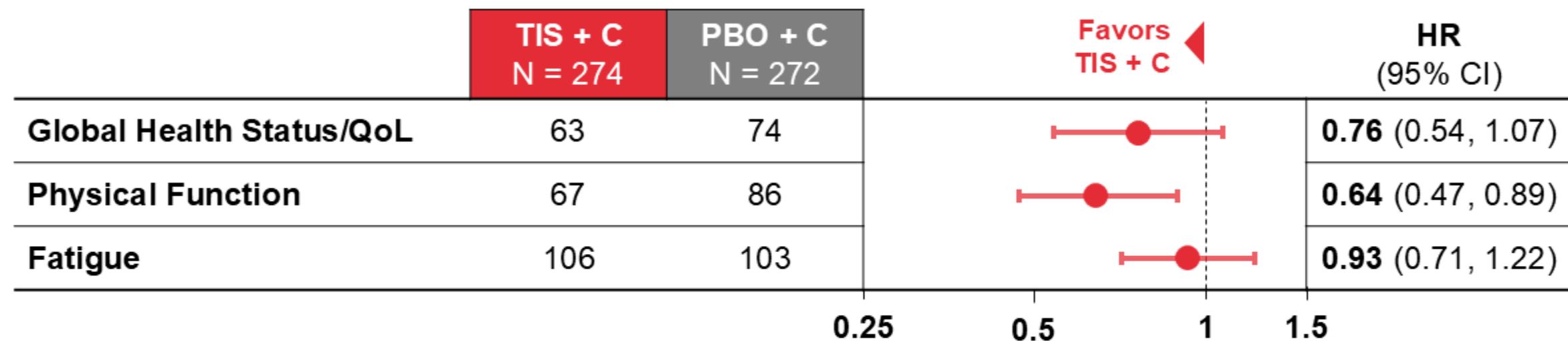
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**BACK UP SLIDES
SHOWN**

EORTC QLQ-C30 Scores for PD-L1 TAP Cutoff $\geq 5\%$



Time to deterioration analysis, defined by ≥ 10 -point difference from baseline

Increases in scores for global health status/QoL and physical function are improvements; increases in score for fatigue is deterioration

DCO: 28FEB2023

Numerically Higher ORR in All PD-L1 Subgroups

