# Tislelizumab in Combination with Chemotherapy for First Line Treatment of Esophageal Squamous Cell Carcinoma (ESCC)

**September 26, 2024**

Oncologic Drugs Advisory Committee

BeiGene

# Introduction

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SVP, Chief Medical Officer, Solid Tumors

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# Agenda

**Rationale-306 Results**

**PD-L1 Subgroup Analyses**

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**Clinical Perspective**

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# Additional Experts

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# Tislelizumab Clinical and Regulatory History in ESCC

## Tislelizumab

**May**
FDA EOP2 Consult

**December**
Phase 3 Rationale-306 Initiated

**November**
Completion of enrollment

**February**
IA data cut-off

**July**
BLA submitted for 1L treatment of TIS + C

**November**
3-year follow up data cut-off

**March**
Tislelizumab approved by FDA for 2L treatment of unresectable or metastatic ESCC


## Approvals for other PD-1s

**March**
Pembrolizumab approved by FDA

**May**
Nivolumab approved by FDA

EOP2: End of Phase 2; TIS + C: Tislelizumab plus chemotherapy

# Rationale-306 Overview

First-line treatment with tislelizumab in combination with chemotherapy offers substantial improvement in OS

Statistically significant and clinically meaningful improvement in OS, supported by improvements in PFS, ORR, and DOR in overall population

Acceptable safety profile across broad population of patients with ESCC

Additional analyses across PD-L1 expression levels support the benefit of tislelizumab plus chemotherapy in patients with PD-L1 ≥ 1% in locally advanced or metastatic ESCC

PD-L1: programmed cell death ligand 1
ESCC: esophageal squamous cell carcinoma

# Rationale-306: Efficacy Results

# Rationale-306: Randomized, Double-Blind, Global Phase 3 Study

**Key Eligibility Criteria**

- Histologically-confirmed diagnosis of ESCC
- Stage IV unresectable disease at first diagnosis or unresectable, advanced recurrent, or metastatic disease

**R 1:1**

**Tislelizumab 200 mg IV Q3W +**
(Choice of) platinum [cisplatin or oxaliplatin] + either fluoropyrimidine [5-fluorouracil or capecitabine] or paclitaxel
N = 326

*Maintenance treatment until unacceptable toxicity or disease progression*

**Placebo IV Q3W +**
(Choice of) platinum [cisplatin or oxaliplatin] + either fluoropyrimidine [5-fluorouracil or capecitabine] or paclitaxel
N = 323

# Study Endpoints

| | Endpoints |
|---|---|
| Primary endpoint | OS in ITT |
| Secondary endpoints | PFS<br>ORR<br>OS in PD-L1 ≥ 10%*<br>DOR<br>Safety |

*Requirement for PD-L1 testing added via protocol amendment
ITT: intent-to-treat; PFS: progression-free survival; ORR: objective response rate; DOR: duration of response

# Baseline Demographics Generally Balanced Between Treatment Arms

| | | TIS + C N = 326 | PBO + C N = 323 |
|---|---|---|---|
| Age, median | | 64 | 65 |
| Male | | 87% | 87% |
| Region | China (including Taiwan) | 56% | 58% |
| | Japan | 10% | 10% |
| | South Korea | 9% | 7% |
| | Australia | 0.9% | 0.6% |
| | US | 0.3% | 0.3% |
| | Europe | 24% | 24% |

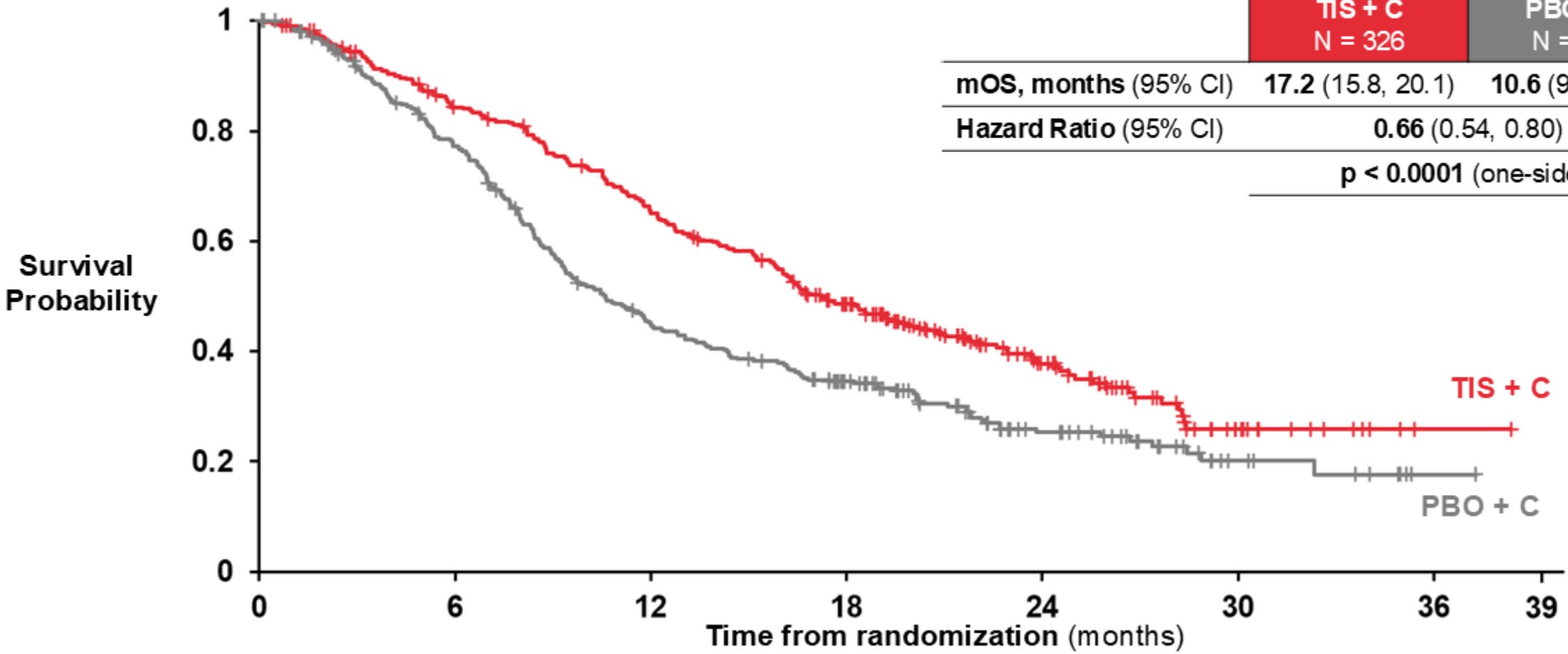
# Baseline Disease Characteristics Balanced and Representative of Target Population

| | | TIS + C N = 326 | PBO + C N = 323 |
|---|---|---|---|
| Time since initial diagnosis, median months | | 2.0 | 2.3 |
| Disease status | Metastatic | 86% | 87% |
| | Locally advanced | 14% | 13% |
| Number of metastatic sites | 0-2 | 83% | 82% |
| | > 2 | 17% | 18% |
| Prior definitive therapy | | 44% | 44% |
| ECOG PS | 0 | 33% | 32% |
| | 1 | 67% | 68% |
| PD-L1 score | ≥ 10% | 36% | 33% |
| | < 10% | 46% | 52% |
| | Unknown | 18% | 15% |

*Requirement for PD-L1 testing added in protocol amendment 2

# Primary Endpoint Met – Clinically Meaningful OS Benefit

| | TIS + C N = 326 | PBO + C N = 323 |
|---|---|---|
| **mOS, months** (95% CI) | **17.2** (15.8, 20.1) | **10.6** (9.3, 12.1) |
| **Hazard Ratio** (95% CI) | **0.66** (0.54, 0.80) | |
| | **p < 0.0001** (one-sided) | |




| | | | | | | | |
|---|---|---|---|---|---|---|---|
| TIS + C | 326 | 264 | 201 | 136 | 58 | 14 | 1 | 0 |
| PBO + C | 323 | 239 | 135 | 91 | 40 | 11 | 1 | 0 |

# Tislelizumab Plus Chemotherapy Provides Improvements in PFS, ORR, and DOR

| Secondary Endpoints | ITT Population TIS + C N = 326 | ITT Population PBO + C N = 323 | Hazard Ratio (95% CI) | p-value (one-sided) |
|---|---|---|---|---|
| **Median PFS, months** (95% CI) | **7.3** (6.9, 8.3) | **5.6** (4.9, 6.0) | **0.62** (0.52, 0.75) | **< 0.0001** |

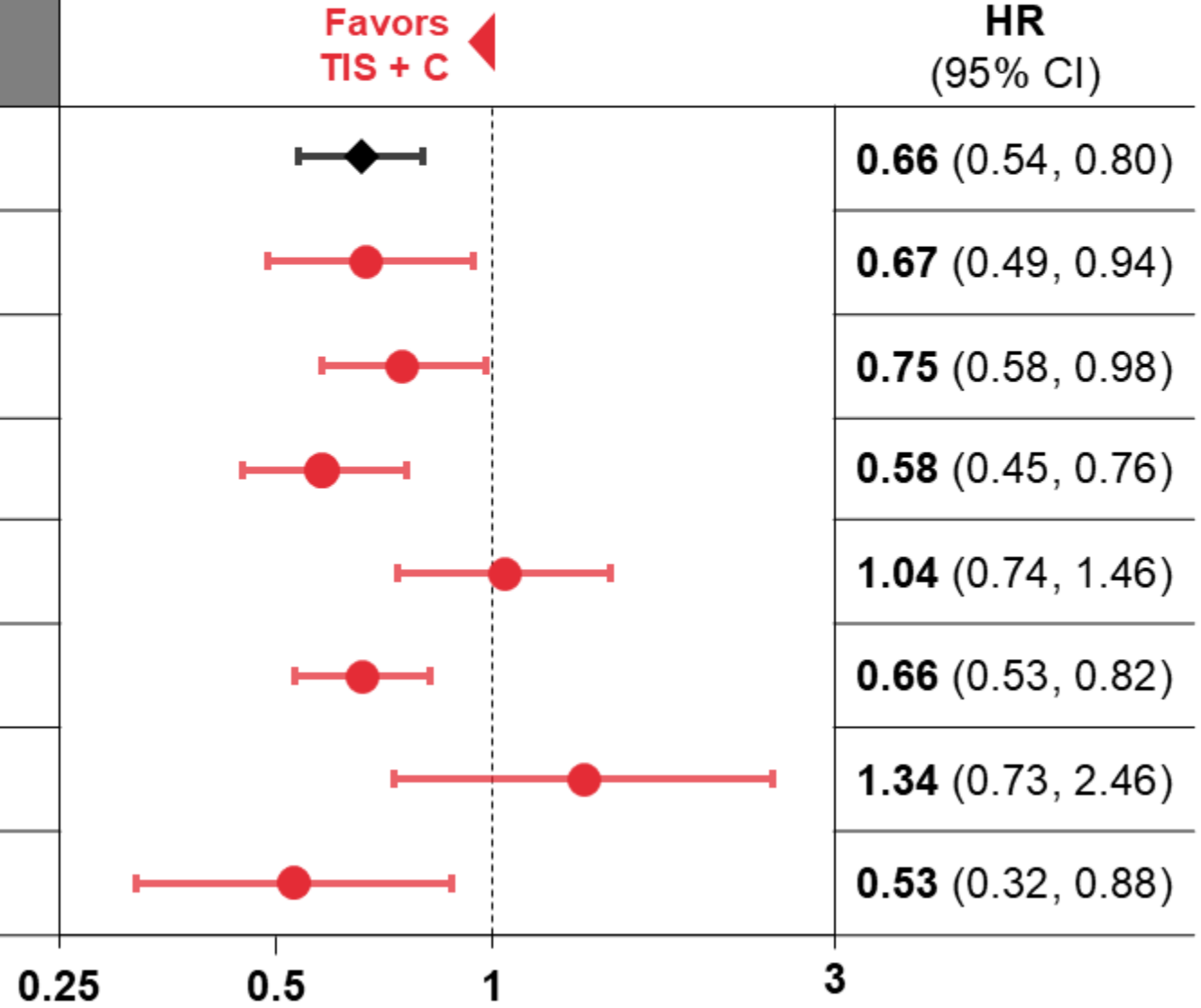
| | | | Odds Ratio (95% CI) |
|---|---|---|---|
| **ORR** (95% CI) | **56.4%** (50.9, 61.9) | **36.2%** (31.0, 41.7) | **2.31** (1.68, 3.17) |

| | | |
|---|---|---|
| **Median DOR, months** (95% CI) | **7.4** (6.9, 8.5) | **6.6** (5.6, 8.3) |

# Rationale-306: PD-L1 Subgroup Analyses

# OS Benefit with Tislelizumab Plus Chemotherapy Across Subgroups with PD-L1 ≥ 1%

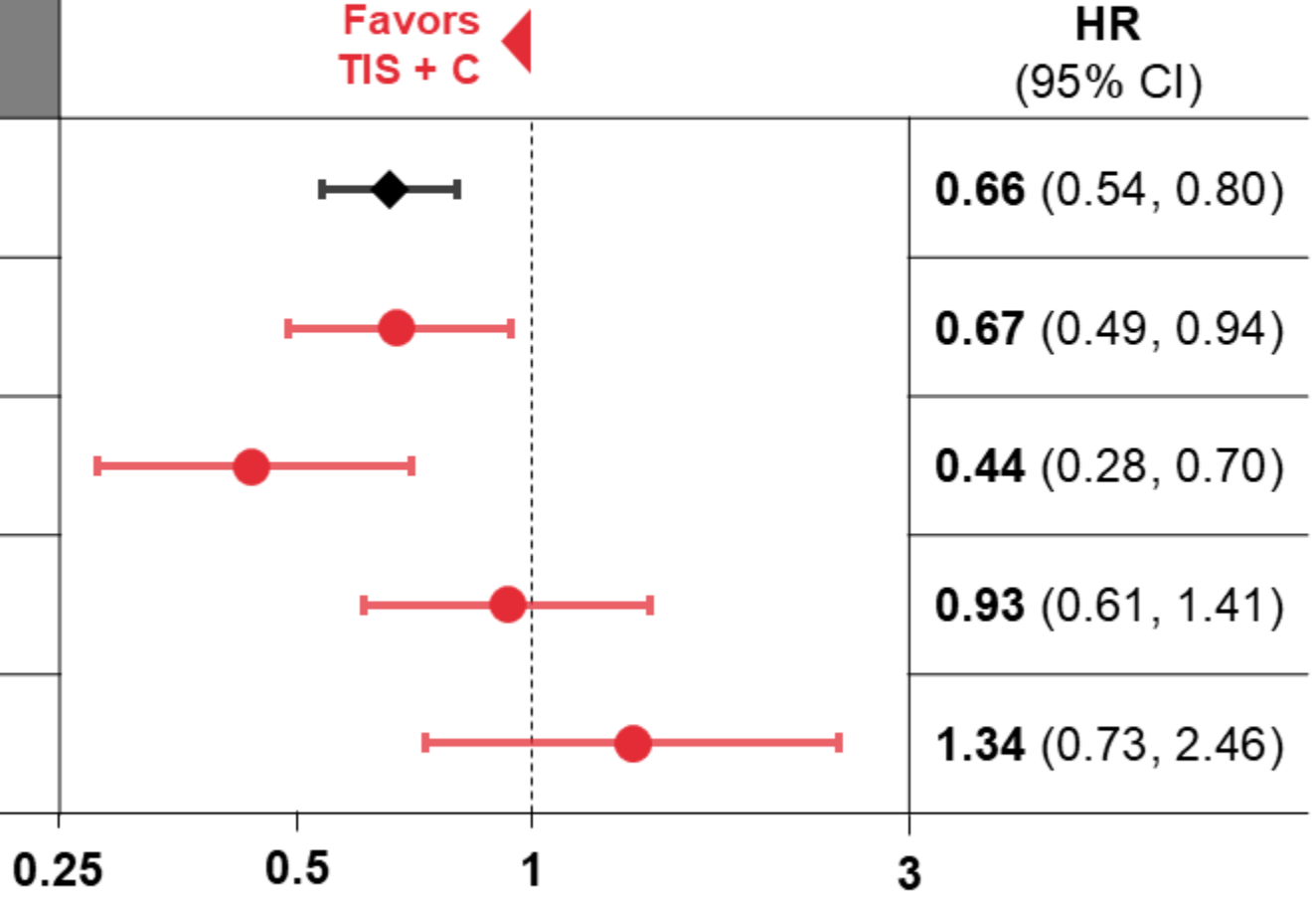
| | TIS + C n / N | PBO + C n / N | HR (95% CI) |
|---|---|---|---|
| **Overall** (ITT) | 197 / 326 | 227 /323 | **0.66** (0.54, 0.80) |
| **≥ 10%** | 70 / 116 | 74 / 107 | **0.67** (0.49, 0.94) |
| **< 10%** | 98 / 151 | 121 /168 | **0.75** (0.58, 0.98) |
| **≥ 5%** | 97 / 172 | 132 / 186 | **0.58** (0.45, 0.76) |
| **< 5%** | 71 / 95 | 63 / 89 | **1.04** (0.74, 1.46) |
| **≥ 1%** | 141 / 231 | 177 / 250 | **0.66** (0.53, 0.82) |
| **< 1%** | 27 / 36 | 18 / 25 | **1.34** (0.73, 2.46) |
| **Unknown** | 29 / 59 | 32 / 48 | **0.53** (0.32, 0.88) |




Data cutoff date: Feb 28, 2022

# OS Analysis Across Subgroups

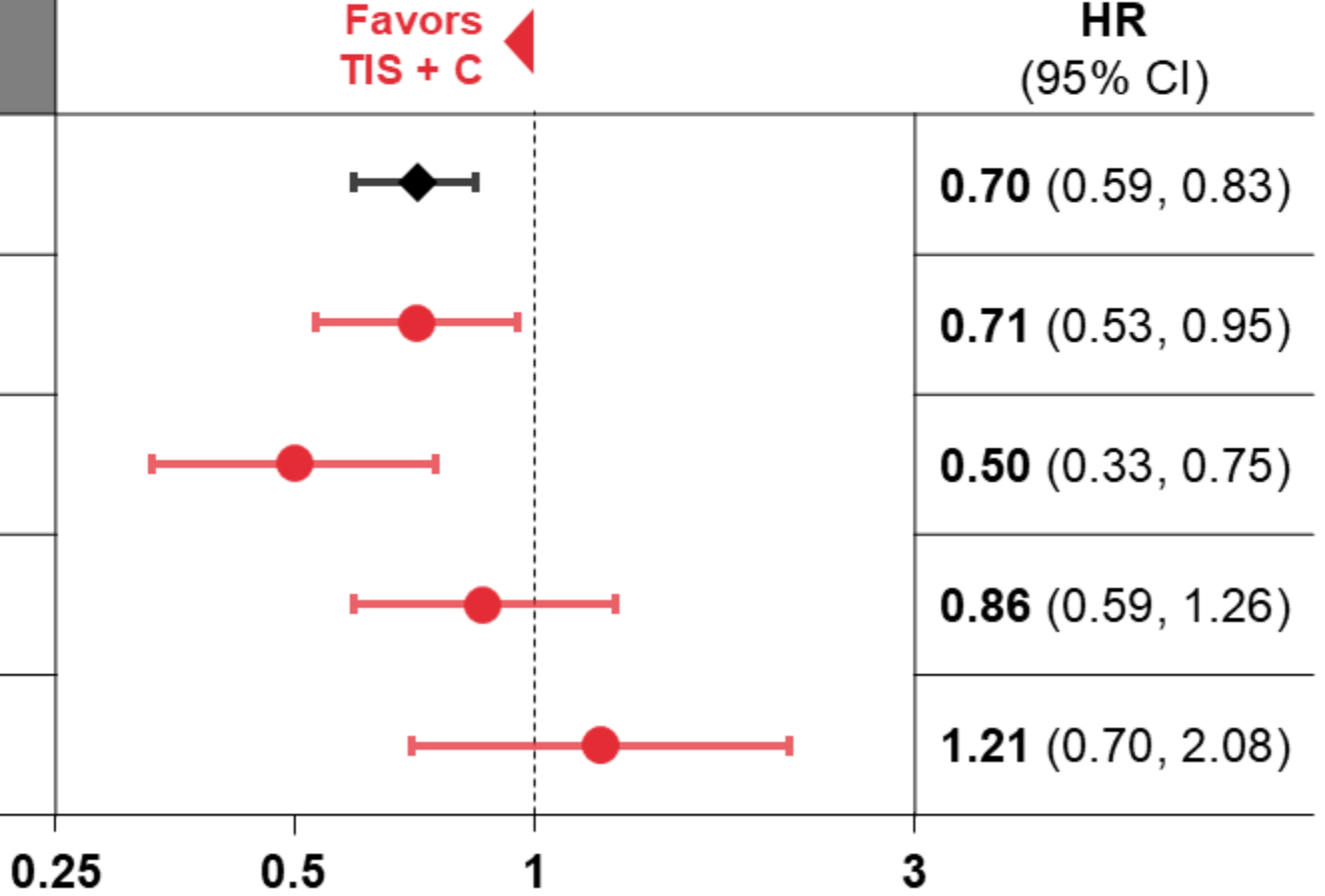
| | TIS + C n / N | PBO + C n / N | HR (95% CI) |
|---|---|---|---|
| **Overall** (ITT) | 197 / 326 | 227 /323 | **0.66** (0.54, 0.80) |
| **≥ 10%** | 70 / 116 | 74 / 107 | **0.67** (0.49, 0.94) |
| **5 – < 10%** | 27 / 56 | 58 / 79 | **0.44** (0.28, 0.70) |
| **1 – < 5%** | 44 / 59 | 45 / 64 | **0.93** (0.61, 1.41) |
| **< 1%** | 27 / 36 | 18 / 25 | **1.34** (0.73, 2.46) |




Data cutoff date: February 28, 2022

# OS Analysis Across Subgroups with 3-Year Follow-Up

| | TIS + C n / N | PBO + C n / N | HR (95% CI) |
|---|---|---|---|
| **Overall** (ITT) | 250 / 326 | 264 / 323 | **0.70** (0.59, 0.83) |
| **≥ 10%** | 90 / 116 | 85 /107 | **0.71** (0.53, 0.95) |
| **5 – < 10%** | 38 / 56 | 66 / 79 | **0.50** (0.33, 0.75) |
| **1 – < 5%** | 50 / 59 | 56 / 64 | **0.86** (0.59, 1.26) |
| **< 1%** | 32 / 36 | 22 / 25 | **1.21** (0.70, 2.08) |




Data cutoff date: Nov 24, 2023

# 3-Year Follow-Up Shows Tislelizumab Plus Chemotherapy Prolongs Survival Among Patients with PD-L1 ≥ 1%

| | **Median OS** (95% CI) | | **Difference** (TIS + C – PBO + C) |
|---|---|---|---|
| | **TIS + C** | **PBO + C** | |
| **Overall** (ITT) | **17.2** (15.8, 20.1) | **10.6** (9.3, 12.0) | **+ 6.6** |
| **≥ 10%** | **16.6** (15.3, 23.4) | **10.0** (8.6, 13.3) | **+ 6.6** |
| **< 10%** | **16.0** (12.3, 19.6) | **10.4** (9.0, 13.4) | **+ 5.6** |
| **≥ 5%** | **19.1** (16.1, 24.1) | **10.0** (8.6, 11.9) | **+ 9.1** |
| **< 5%** | **12.3** (10.8, 16.0) | **10.6** (8.7, 14.4) | **+ 1.7** |
| **≥ 1%** | **16.8** (15.3, 20.8) | **9.6** (8.9, 11.8) | **+ 7.2** |
| **< 1%** | **11.8** (6.2, 16.3) | **16.1** (10.4, 27.1) | **- 4.3** |

**Data cutoff date: Nov 24, 2023**

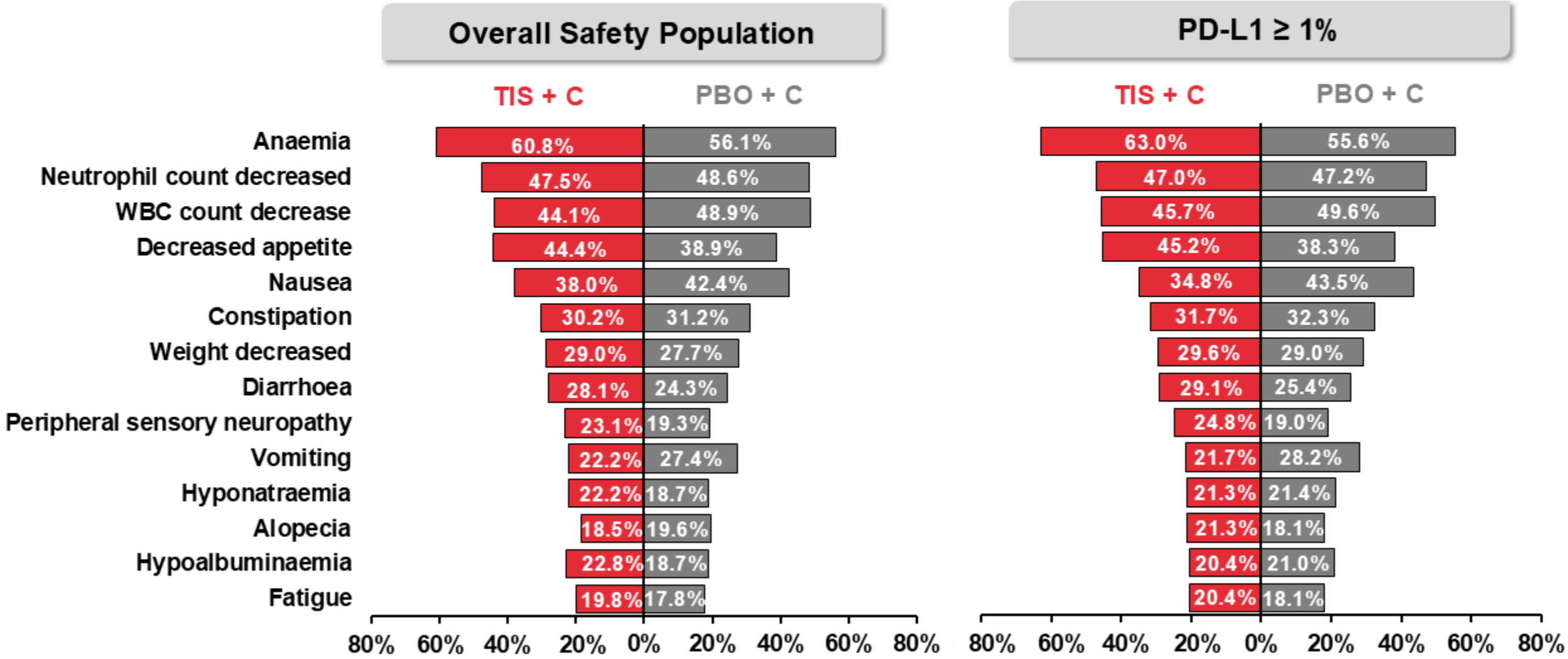
# Rationale-306: Safety Results

# Tislelizumab Plus Chemotherapy Has Manageable Safety Profile

| | Overall Safety Population | | PD-L1 ≥ 1% | |
|---|---|---|---|---|
| | TIS + C N = 324 | PBO + C N = 321 | TIS + C N = 230 | PBO + C N = 248 |
| Any AE | > 99% | > 99% | > 99% | 100% |
| AEs Grade ≥ 3 | 78% | 78% | 78% | 77% |
| Immune-mediated AEs | 35% | 19% | 39% | 20% |
| AEs leading to any dose modification | 76% | 71% | 75% | 72% |
| AEs leading to any treatment discontinuation | 32% | 22% | 35% | 22% |
| SAEs | 48% | 40% | 47% | 39% |
| AEs leading to deaths | 5% | 5% | 6% | 5% |

Data cutoff date: February 28, 2022

# Most Common AEs Similar Between Tislelizumab Plus Chemotherapy vs Placebo Plus Chemotherapy




Data cutoff date: February 28, 2022

# Summary of Tislelizumab Efficacy and Safety

- Rationale-306 showed substantial and significant OS results with tislelizumab plus chemotherapy
- Favorable and clinically meaningful treatment effect observed in patients with low PD-L1 expression
  - Most favorable benefit / risk observed in PD-L1 ≥ 1% population

**Totality of data support use of tislelizumab plus chemotherapy as 1L treatment option for patients with unresectable advanced or metastatic ESCC**

# Clinical Perspective

**Nataliya Uboha, MD, PhD**

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Section of Hematology and Medical Oncology
University of Wisconsin School of Medicine

# Patients with Advanced or Metastatic ESCC Face Poor Prognosis with Limited Treatment Options

**< 1%** of all cancers in US[1,2]

**6%** 5-year survival rate for advanced stage in US[2]; one of lowest rates[3]

debilitating symptoms, including pain, difficulty eating and resultant weight loss

1. Rodriguez et al 2023; 2. American Cancer Society; 3. SEER 2023

# Treatment with Anti-PD-1 Antibodies in Combination with Chemotherapy Can Significantly Prolong OS

- PD-L1 testing done for all patients with advanced gastroesophageal cancers regardless of histology
- > 90% of patients with ESCC have PD-L1 score ≥ 1%

# Clinical Interpretation of Results

- Tislelizumab addition to chemotherapy improved OS
  - OS HR 0.66 in ITT population
  - Maintained at 3 years
- No benefit in patients with PD-L1 < 1 tumors
- My approach: patients with PD-L1 ≥ 1 tumors are treated with immunotherapy in combination with chemotherapy

**PD-L1 score of ≥ 1 is clinically relevant and recommend as appropriate cutoff**

# Tislelizumab in Combination with Chemotherapy for First Line Treatment of Esophageal Squamous Cell Carcinoma (ESCC)

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# NO BACK UP SLIDES SHOWN