Impact of Progressive Disease Patterns on Post-Progression Overall Survival in Esophageal Squamous Cell Carcinoma: A Post Hoc Analysis of RATIONALE-302

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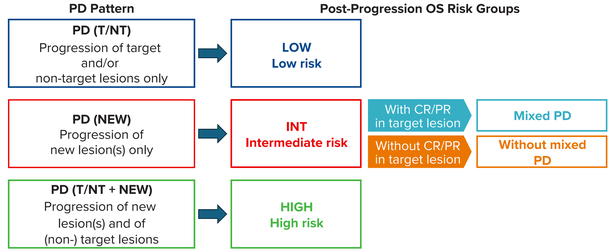
CONCLUSIONS

- Patients in the tislelizumab "intermediate-risk" (INT; progression in new lesions only) subgroup had the longest overall survival (OS) and most frequent use of immunotherapy post progressive disease (PD) per RECIST v1.1, suggesting that patterns of progression may be prognostic
- These findings support a potential role for continued immunotherapy beyond PD for patients in the INT subgroup, especially those who experienced Mixed PD (progression in new lesions but CR/PR in target lesions)
  - Further study is warranted to determine whether such patterns of PD reflect underlying immune-related response dynamics or delayed therapeutic benefit rather than definitive treatment failure

INTRODUCTION

- Globally, esophageal cancer is the 13th most commonly diagnosed cancer and the seventh most common cause of cancer-related death[1]
  - The most common subtype is esophageal squamous cell carcinoma (ESCC; ≈84% of cases)
- Esophageal cancer is most frequently diagnosed at an advanced stage, with poor prognosis[2]
  - The rate of 5-year relative survival in patients diagnosed with metastatic esophageal cancer is 5.3% (US data)
- Tislelizumab is a humanized immunoglobulin G4 monoclonal antibody with high affinity for programmed cell death 1 protein (PD-1)
  - Tislelizumab was designed to minimize binding to FcγR on macrophages, limiting antibody-dependent phagocytosis, a potential anti–PD-1 resistance mechanism[3]
  - In the global phase 3 RATIONALE-302 study (NCT03430843), tislelizumab significantly improved OS vs chemotherapy in second-line treatment of advanced ESCC (median OS of 8.6 months vs 6.3 months)[4]
- A recent post hoc analysis of five studies in solid tumors (not including ESCC) treated with immunotherapy found that patterns of PD (per RECIST v1.1) were associated with post-progression OS (PPOS; OS − progression-free survival) (**Figure 1**)[5]
- We hypothesized that the PD pattern in RATIONALE-302 was associated with PPOS and would help identify patients who may benefit from continued immunotherapy

Figure 1. Proposed Risk Groups for OS Based on Type of Progression per RECIST v1.1[5]



Abbreviations: CR, complete response; NEW, new lesion; NT, non-target lesion; OS, overall survival; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; T, target lesion.

METHODS

- Patients who experienced investigator-assessed progressive disease from RATIONALE-302 (n=197 in tislelizumab vs n=146 in chemo arm) were included in this analysis
- PPOS was analyzed by subgroups defined by PD pattern:
  - PD due to growth of existing lesions was classified as low risk (LOW); PD due to new lesions but not to growth of existing lesions was classified as intermediate risk (INT); and PD due to growth of existing and new lesions was classified as high risk (HIGH)
  - For patients receiving tislelizumab, the INT subgroup was further divided based on the response of target lesions; patients who had partial or complete responses within the target lesions but PD due to new lesions were classified as having Mixed PD (**Figure 1**)

RESULTS

- Median PPOS was longer with tislelizumab vs chemo regardless of PD pattern (**Table 1**, **Figure 2**)
- In the tislelizumab arm, median PPOS was longest in the INT subgroup, which also showed higher PPOS rates at 1-y and 2-y annual landmarks
  - In the tislelizumab INT subgroup, those with Mixed PD had longer PPOS than all other subgroups (**Figure 3**)
- In the chemotherapy arm, median PPOS was longer in the LOW subgroup than in the HIGH or INT subgroups, with higher survival rates at annual landmarks
- Analyses of OS by PD pattern showed trends similar to those observed for PPOS (**Figure 4**)

Table 1. Median PPOS and Landmark Rates of PPOS By PD Pattern

	Tislelizumab (n=197)	Chemotherapy (n=146)
mPPOS (95% CI), mo [n]		
LOW	6.5 (5.1-9.4) [n= 101]	5.6 (3.7-7.5) [n= 83]
INT	7.4 (5.1-12.4) [n= 41]	4.3 (3.4-7.6) [n= 24]
Mixed PD	9.5 (5.1-13.7) [n= 15]	–
Without mixed PD	6.6 (3.2-11.6) [n= 26]	–
HIGH	4.3 (3.0-6.2) [n= 55]	2.0 (1.3-3.3) [n=39]

PPOS rate at landmarks (95% CI), %						
	1 y	**2 y**	**3 y**	**1 y**	**2 y**	**3 y**
LOW	29.5 (20.9-38.6)	10.2 (5.2-17.1)	6.8 (2.9-13.0)	26.8 (17.6-36.8)	9.9 (4.5-17.8)	5.7 (1.9-12.5)
INT	36.6 (22.3-51.0)	16.3 (6.8-29.3)	4.1 (0.4-15.7)	8.7 (1.5-24.2)	4.4 (0.3-18.3)	4.4 (0.3-18.3)
Mixed PD	46.7 (21.2-68.7)	13.3 (2.2-34.6)	6.7 (0.4-26.0)	–	–	–
Without mixed PD	30.8 (14.6-48.5)	17.9 (6.0-35.1)	4.5 (0.3-18.6)	–	–	–
HIGH	12.5 (5.3-23.1)	5.6 (1.2-15.1)	0 (NE, NE)	2.7 (0.2-12.1)	0 (NE, NE)	0 (NE, NE)

Abbreviations: HIGH, high risk; INT, intermediate risk; LOW, low risk; mPPOS, median post-progression overall survival; NE, not estimable; PD, progressive disease; PPOS, post-progression overall survival.

Post-PD Systemic Therapy

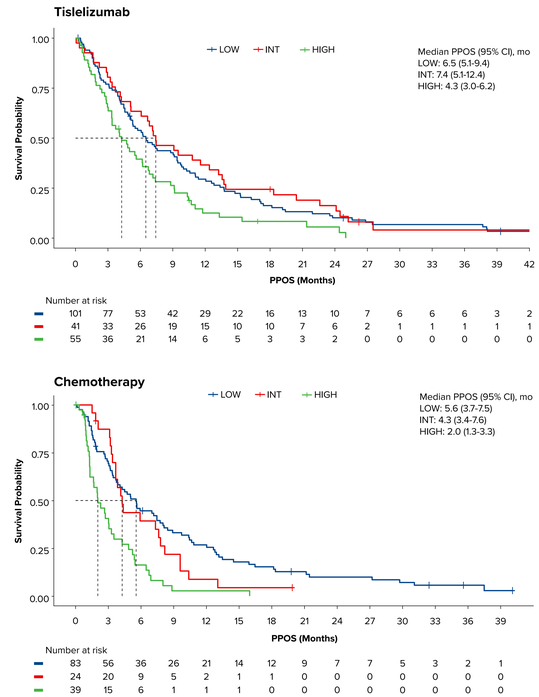
- Across subgroups, approximately 50%-75% of patients received post-PD systemic therapy (**Table 2**)
  - In the tislelizumab arm, patients in the INT subgroup had a much higher rate of immunotherapy after PD compared with the LOW and HIGH subgroups
  - In the chemotherapy arm, the proportion of patients receiving immunotherapy in the INT subgroup was similar to that in the LOW subgroup and about twice that in the HIGH subgroup

Table 2. Post-PD Systemic Therapy

	Tislelizumab (n=197)			Chemotherapy (n=146)		
Therapy, n (%)	**LOW (n=101)**	**INT (n=41)**	**HIGH (n=55)**	**LOW (n=83)**	**INT (n=24)**	**HIGH (n=39)**
Any systemic	72 (71.3)	31 (75.6)	29 (52.7)	52 (62.7)	16 (66.7)	19 (48.7)
Immunotherapy	7 (6.9)	10 (24.4)	4 (7.3)	24 (28.9)	7 (29.2)	5 (12.8)

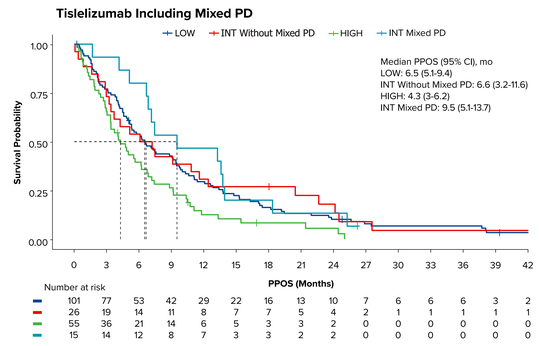
Abbreviations: HIGH, high risk; INT, intermediate risk; LOW, low risk; PD, progressive disease.

Figure 2. KM Analyses of PPOS By PD Pattern



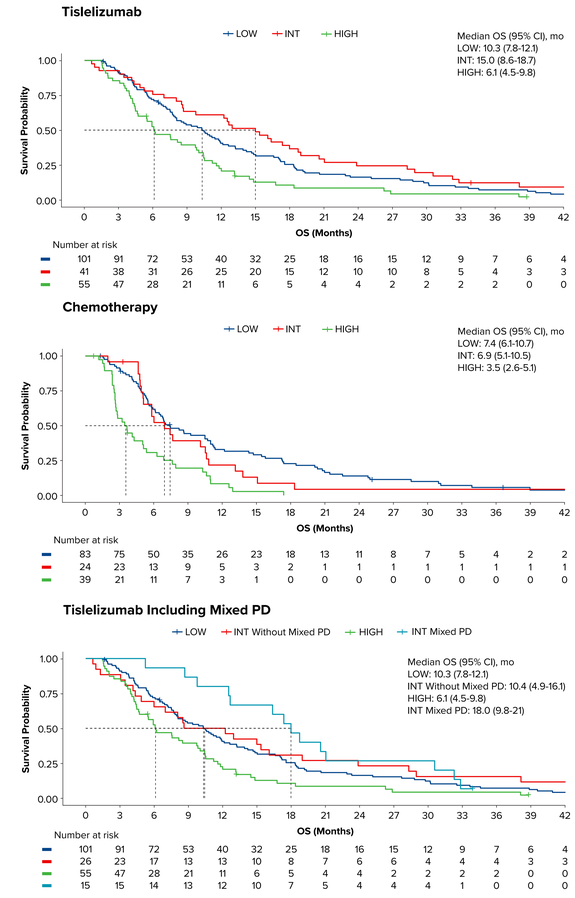
Abbreviations: KM, Kaplan-Meier; PD, progressive disease; PPOS, post-progression overall survival.

Figure 3. KM Analyses of PPOS in the Tislelizumab Arm by PD Pattern, Including Mixed PD



Abbreviations: KM, Kaplan-Meier; PD, progressive disease; PPOS, post-progression overall survival.

Figure 4. KM Analyses of OS By PD Patterns



Abbreviations: KM, Kaplan-Meier; OS, overall survival; PD, progressive disease.

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DISCLOSURES

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