

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

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Background

A recent analysis of 5 studies in solid tumors (not including ESCC) treated with immunotherapy (IO) (Saal *JAMA Oncol* 2024) found patterns of PD (RECIST 1.1) associated with PPOS (=OS–PFS). We hypothesized that the PD pattern in RATIONALE-302 (NCT03430843), a global phase 3 trial showing that tislelizumab (TIS) significantly improved OS vs chemotherapy (CT) as 2L treatment of advanced ESCC, was associated with PPOS and will help identify patients (pts) who may benefit from continued IO.

Methods

Post hoc Kaplan-Meier analysis of PPOS by subgroups defined by PD pattern in pts from RATIONALE-302: PD of existing lesion(s), low-risk (L); PD with new but not existing lesion(s), intermediate-risk (I); and PD of existing and new lesions, high-risk (H).

Results

TIS improved PPOS vs CT regardless of PD pattern (**Table**). In the TIS arm, median (m) PPOS was longest in the I subgroup, which also showed higher PPOS rates at 1 y

and 2 y annual landmarks. In the CT arm, mPPOS was longer in the L subgroup with higher survival rates at annual landmarks.

Post-PD systemic therapy in the TIS arm was received by 71.3%, 75.6%, and 52.7% of pts in the L, I, and H subgroups, respectively; post-PD IO by 6.9%, 24.4%, and 7.3%. A further subgroup was identified within I: mixed PD (n=15) was defined as partial or complete response of existing lesions to TIS with new lesions. The mPPOS of mixed PD was longest compared with L, I without mixed PD, and H subgroups.

Conclusions

The longest OS, and most frequent post-PD IO, in our analysis of pts with ESCC was in the TIS I subgroup, suggesting that patterns of progression may be prognostic. These findings support a potential role for continued IO beyond progression for pts in the I subgroup, especially for pts in the mixed PD population, and warrant further study to determine whether such patterns of PD reflect underlying immune-related response dynamics or delayed therapeutic benefit rather than definitive treatment failure.

	TIS (N=197: L, n=101; I, n=41 [mixed PD, n = 15]; H, n=55)	CT (N=146: L, n=83; I, n=24 [mixed PD, n = 3]; H, n=39)				
mPPOS (95% CI), mo						
L	6.5 (5.1-9.4)	5.6 (3.7-7.5)				
I	7.4 (5.1-12.4)	4.3 (3.4-7.6)				
Mixed PD	9.5 (5.1-13.7)	—				
I without mixed PD	6.6 (3.2-11.6)					
H	4.3 (3.0-6.2)	2.0 (1.3-3.3)				
PPOS rate at landmarks (95% CI), %						
	1 y	2 y	3 y	1 y	2 y	3 y
L	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)
I	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)	—		
I without mixed PD	30.8 (14.6-48.5)	17.9 (6.0-35.1)	4.5 (0.3-18.6)			
H	12.5 (5.3-23.1)	5.6 (1.2-15.1)	0 (NA)	2.7 (0.2-12.1)	0 (NA)	0 (NA)