Association of tumor mutational burden (TMB) and clinical outcomes with tislelizumab versus chemotherapy in esophageal squamous cell carcinoma (ESCC) from RATIONALE-302.

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Abstract:

Background: Programmed cell death protein 1 (PD-1) inhibitors are approved as second-line (2L) therapy for patients (pts) with ESCC. TMB is a predictive biomarker of response to immune checkpoint blockade in multiple cancers, but its role in ESCC is unclear. Here, we retrospectively investigated the association between TMB and clinical outcomes in the phase 3 RATIONALE-302 study of anti-PD-1 antibody tislelizumab (TIS) vs investigator-chosen chemotherapy (ICC) as 2L treatment for advanced unresectable/metastatic ESCC (NCT03430843).

Methods: Genomic profiling was assessed on tumor tissues collected at baseline using BurningRock OncoScreen Plus 520 NGS panel to determine TMB status. Median progression-free survival (PFS) and overall survival (OS) were calculated using the Kaplan-Meier method. Objective response rate (ORR) was calculated using the binomial exact method. Cox model was applied to assess the effect of TMB on survival outcomes. Hazard ratio (HR) and 95% confidence interval (CI) for OS and PFS in TMB subgroups were estimated.

Results: Of 512 pts enrolled, 209 had evaluable tumor samples (TIS, n=105; ICC, n=104). Using the widely used cutoff of 10 mutations per megabase (mut/Mb), numerically higher ORR and survival benefit with TIS over ICC were observed in the high TMB (TMB-H) vs the low TMB (TMB-L) subgroup (Table). The predictive effect of TMB on survival outcomes was not significant (interaction p-value = 0.0537 for PFS, 0.5374 for OS); however, the effect became significant using the increased cutoff of 12 mut/Mb (TMB-H prevalence = 16.7%; interaction p-value = 0.0267 for PFS, 0.0175 for OS).

Conclusions: TMB status may play a role in predicting clinical outcomes in pts with advanced ESCC treated with TIS versus ICC, especially when a higher TMB cutoff is chosen. These findings need further prospective validation.

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Table. Clinical outcomes by TMB status (cutoff 10 mut/Mb)

TMB status	**TMB-H**		**TMB-L**	
Treatment	**TIS**	**ICC**	**TIS**	**ICC**
n (% in TMB BEP, N=209)	27 (12.9)	31 (14.8)	78 (37.3)	73 (34.9)
ORR, % (95% CI)	33.3 (16.5, 54.0)	6.5 (0.8, 21.4)	16.7 (9.2, 26.8)	17.8 (9.8, 28.5)
Median PFS, months (95% CI)	2.4 (1.4, 5.5)	2.3 (1.3, 2.9)	1.4 (1.3, 2.7)	2.7 (1.5, 3.3)
PFS HR (95% CI)	0.52 (0.28, 0.97)		1.06 (0.73, 1.53)	
Interaction p-value	0.0537			
Median OS, months (95% CI)	6.1 (4.2, 18.6)	4.7 (3.4, 7.0)	8.6 (4.6, 11.8)	7.0 (4.6, 8.6)
OS HR (95% CI)	0.58 (0.32, 1.04)		0.72 (0.50, 1.03)	
Interaction p-value	0.5374			
TMB-adjusted OS HR (95% CI)	0.68 (0.5, 0.92)			

BEP, biomarker evaluable population; CI, confidence interval; HR, hazard ratio; ICC, investigator chosen chemotherapy; OS, overall survival; PFS, progression-free survival; ORR, objective response rate; TIS, tislelizumab; TMB-H, high tumor mutational burden; TMB-L, low tumor mutational burden; TMB-adjusted OS HR, overall HR adjusted for the impact of TMB on OS