Exploratory biomarker analysis of the phase 3 RATIONALE 305 trial: First-line (1L) tislelizumab (TIS) + chemotherapy (CT) vs placebo (PBO) + CT for advanced gastric cancer/gastro-oesophageal junction adenocarcinoma (GC/GEJC)

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Introduction: In the randomised phase 3 RATIONALE 305 trial (NCT03777657), patients (pts) with advanced GC/GEJC treated with 1L TIS + CT had significantly improved overall survival (OS) vs PBO + CT. We present exploratory biomarker and molecular subtyping results from RATIONALE 305 derived using RNA sequencing (RNAseq) and whole exome sequencing (WES) data.

Patients and Methods: RNAseq (507/997, 50.9%) of baseline (BL) tumor tissue was used to assess gene expression signatures (GES); GES subgroups were defined by median cutoff. WES (235/997, 23.6%) of BL tumor tissue and matching blood samples was performed to assess tumor mutational burden (TMB), human leukocyte antigen (HLA) genotyping, significantly mutated genes, and cytoband amplifications (amp). Multicolour immunohistochemistry was employed as a validation assay. Associations between biomarker status and OS were evaluated. All *P* values are descriptive.

Results: BL characteristics in the GES- or WES-evaluable pts were similar to the ITT population. High inflammation (eg, cytotoxic T cells [CTL]) and low immunosuppression (eg, neutrophils) GES were associated with improved OS for TIS + CT vs PBO + CT (**Table**). High clonal TMB was linked to improved OS with TIS + CT vs PBO + CT **(Table),** while total TMB showed no clear association. Non-HLA B27 supertype or *TP53* wildtype or 20q13.13 non- amp were associated with improved OS benefit with TIS + CT vs PBO + CT (**Table**). A novel molecular scoring system incorporating WES-derived biomarkers (favourable: cTMB-

high, ARID1A mutation, B62 supertype; risk-associated: TP53 mutation, 20q13/11q13 amplifications, B27 supertype) was used to stratify patients into molecular subtypes (MS1-MS4), with varying treatment benefit **(Table).** Immunofluorescence validation confirmed that patients with higher baseline intratumoural IFN γ +CD8+ T-cells correlated with a trend towards improved OS compared with those with lower IFN γ +CD8+ T-cells.

Conclusion: This exploratory biomarker analysis found that high CTL GES and low neutrophil GES, as well as clonal TMB, certain HLA genotypes, TP53 wildtype, and cytoband non-amp were all associated with OS benefit in 1L TIS + CT vs PBO + CT treated pts with advanced GC/GEJC. These findings lay the foundation for the development of clinically meaningful biomarkers that can facilitate identification of patients with a higher likelihood of achieving benefit from immunotherapy in advanced GC/GEJC

Table

Population	Subpopulation	TIS + CT vs PBO + CT			
		N	**OS HR (95% CI)**	***P* value**	**Interaction *P value***
GES evaluable		507			
	CTL high	254	0.69 (0.52, 0.91)	0.009	0.063
	CTL low	253	1.00 (0.76, 1.32)	0.999	
	Neutrophil high	254	1.01 (0.76, 1.33)	0.970	0.044
	Neutrophil low	253	0.67 (0.50, 0.89)	0.005	
WES evaluable		235			
	High cTMB (90th percentile)	24	0.37 (0.14, 0.95)	0.038	0.125
	Low cTMB (90th percentile)	211	0.80 (0.59, 1.08)	0.144	
	HLA B27	52	1.30 (0.70, 2.41)	0.401	0.045
	HLA non-B27	183	0.64 (0.46, 0.89)	0.007	
	TP53 mutation[a]	148	0.96 (0.67, 1.38)	0.825	0.025

	TP53 wildtype	84	0.48 (0.29, 0.78)	0.003	
	20q13.13 non-amp	205	0.64 (0.47, 0.88)	0.005	0.002
	20q13.13 amp	30	2.58 (1.15, 5.79)	0.021	
	MS1	59	2.32 (1.26, 4.27)	0.007	
	MS2	59	0.90 (0.52, 1.56)	0.712	
	MS3	71	0.53 (0.32, 0.89)	0.017	
	MS4	46	0.27 (0.13, 0.53)	<0.001	

[a]Pts with TP53 amplification not included