The combination of hyper-amplification and tumor mutational burden as a pan-cancer biomarker in patients treated with tislelizumab

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Abstract:

Background

High tumor mutational burden (TMB-H) is associated with elevated neoantigen expression across tumors, linked with an improved response to PD-(L)1 inhibitors. Here we report data from the final analysis of a Phase 1 trial that enrolled patients (pts) with various solid tumors treated with tislelizumab (NCT02407990). We evaluated the association of TMB with clinical outcomes, integrative biomarker analysis of genomic alterations and gene expression profiling by TMB status.

Methods

451 pts were enrolled and treated with different doses of tislelizumab. Baseline tumor tissue was evaluated for gene expression (HTG EdgeSeq Precision Immuno-Oncology Panel) and genomic profiling (FoundationOne CDx). TMB-H and gene hyperamplification (HA) were defined as ≥ 10 mutations/Mb and a minimum of copy number gain > 5, respectively. Associations with progression-free survival (PFS) and overall survival (OS) were examined using Cox proportional hazards models.

Results

The overall objective response rate was 13.3% (95% CI: 10.3, 16.8), median (m) PFS 2.1 months (95% CI: 2.1, 2.7), and

mOS 10.3 months (95% CI: 8.5, 11.6). Improved clinical outcomes were observed in pts with TMB-H tumors (n=43, 16.2% of TMB evaluable pts), and response was further enriched in pts without gene HA (TMB-H/HA-) (**Table**). This population showed elevated cytotoxic T-cell activity and interferon signaling in the TME, along with fewer hyper-amplified genes in RTK-RAS-PI3K pathway. This was validated in an independent PD-(L)1 inhibitor treated pan-cancer cohort (n=837): TMB-H/HA-(n=139) had longer OS than TMB-H/HA+ (n=89) (mOS: 34 vs 15 months, P=0.07).

Conclusions

The combination of TMB and HA was found to be predictive of clinical benefit across various solid tumor types, treated with tislelizumab. This joint algorithm, as reported by one clinically approved assay, may provide new insights to the identification of pts who are most likely to gain benefit from PD-(L)1 blockade.

Table: Clinical outcomes in pts subgroups by TMB and HA status

	TMB-H			**TMB-L**		
	Overall	HA-	HA+	Overall	HA-	HA+
n (% in TMB BEP [N =266])	43 (16.2)	20 (7.5)	23 (8.6)	223 (83.8)	103 (38.7)	120 (45.1)
ORR, % (95% CI)	32.6 (19.1, 48.5)	50.0 (27.2, 72.8)	17.4 (5.0, 38.8)	10.3 (6.7, 15.1)	11.7 (6.2, 19.5)	9.2 (4.7, 15.8)
mPFS, months (95% CI)	8.3 (2.0, 11.5)	15.1 (8.1, NR)	2.0 (1.2, 8.3)	2.1 (2.0, 2.1)	2.1 (2.1, 4.0)	2.0 (2.0, 2.1)
mOS, months (95% CI)	20.1 (10.3, 37.4)	30.9 (11.1, NR)	9.7 (2.8, 23.8)	11.1 (7.7, 11.9)	13.9 (11.1, 18.2)	6.7 (5.6, 8.1)

BEP, biomarker evaluable population; CI, confidence interval; HA, hyperamplification; NR, not reached; ORR, objective response rate; mOS, median overall survival; mPFS, median progression-free survival; TMB-H, high tumor mutational burden; TMB-L, low tumor mutational burden