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BIOMARKERS

89PD Prognostic and predictive impact of high tumor mutation burden (TMB) in solid tumors: A systematic review and meta-analysis

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Background: Immune checkpoint blockade (ICB) has improved overall survival (OS) in selected patients (pts) with cancers, but predictive biomarkers are required. TMB has been proposed as a potential biomarker, but challenges exist as to its optimal definition, quantification and utility.

Methods: A search of Medline and Embase identified studies reporting association of TMB (high vs low) with survival in pts with solid tumors, irrespective of exposure to ICB. The influence of TMB on OS was explored by meta-analysis, utilizing the generic inverse variance method. Association between baseline factors (age, gender, primary tumor site, stage, smoking history, proportion of pts with squamous histology, receipt of ICB) and survival were assessed with mixed effects meta-regression, weighted by study sample size.

Results: Of 493 studies, 35 were eligible (ICB used in 28); 13 prospective, 22 retrospective; correlation between PD-L1 expression and TMB was not possible due to limited reporting studies. Analysis comprised 10,433 pts; median age: 63 yrs (range 53-73; reported in 18 studies). Median proportion male: 62.5% (range 40-83%), primary tumor site lung: 17 studies (9 squamous histology), melanoma: 5, urothelial: 3, breast: 2, head & neck, biliary and hepatocellular carcinoma: all 1, multiple sites: 5. Eleven different assays for TMB determination were utilized (Foundation One in 15 studies). Amongst 22 studies, where reported, 5 different TMB definitions were used, with only 10 studies reporting a median TMB (Mut/Mb); 11 different TMB "high" thresholds were reported. In the absence of ICB, high TMB was associated with increased risk of death (HR 2.87, 95% CI 1.41-5.82, p=.004). In the presence of ICB, high TMB was associated with improved OS (HR 0.60, 95% CI 0.42-0.86, p=.005), albeit with significant heterogeneity (p=.002). Studies with a higher proportion of male pts had increased hazard of death (β=.75) and those with a higher proportion of pts receiving ICB had a lower hazard of death (β=-.56).

Conclusions: High TMB is a poor prognostic factor in solid tumors, but is predictive of improved OS with ICB. Standardization of TMB analysis/reporting is imperative for reliable clinical application.

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