Validation of the 31-gene expression profile test to stratify melanoma-specific survival in an unselected, prospectively tested cohort of patients with stage IIB-III cutaneous melanoma

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Background: Given recent FDA extended approval of Pembrolizumab for stage IIB-IIC cutaneous melanoma (CM) patients, it is critical to risk-stratify patients to balance potential benefits versus toxicities of adjuvant therapy. The 31-gene expression profile (31-GEP) is a validated test for CM for risk of recurrence or metastasis prognosis in patients with stage I-III CM. A low-risk (Class 1A) 31-GEP result is associated with lower recurrence risk and higher melanoma-specific survival than an intermediate (Class 1B/2A) or high-risk (Class 2B) result. To validate the 31-GEP's ability to stratify patients' risk in an unselected, prospectively tested cohort of therapy-eligible CM patients, we collaborated with the National Cancer Institute and the Surveillance, Epidemiology, and End Results (SEER) program.

Method: A linkage was conducted between SEER registries' CM cases diagnosed 2012-2018, and 31-GEP tested patients between 2013-2020. A de-identified dataset was used for the analysis. Kaplan-Meier analysis with log-rank test was used to analyze patient melanoma-specific survival (MSS) in the overall cohort and the subset of patients with potential adjuvant therapy access: stage IIB-III melanoma (n=615).

Results: In the overall cohort of patients (N=5,225), those with a 31-GEP Class 1A result had higher 3-year MSS than patients with a Class 2B result (99.7% vs. 90.4%, p<0.001). In multivariable Cox regression analysis, a Class 2B result was an independent significant predictor of MSS (HR=5.71, p=0.01), as were age (HR=1.05, p<0.001), SLN positivity (HR=2.42, p=0.02), and T2b (HR=8.29, p=0.025) and T4b (HR=11.99, p=0.009) tumors. In the subset of patients with stage IIB-III melanoma, those with a 31-GEP Class 1A result had higher 3-year MSS (98.8% vs. 82.4%, p=0.02) than patients with a Class 2B result. Patients with a Class 2B result had a five and a half times higher event rate than those with a Class 1A result for MSS (5.5% [21/382] vs. 1.0% [1/105]).

Conclusion: In a large, unselected, prospectively tested cohort of patients with stage I-III CM, the 31-GEP stratified patient risk of dying from melanoma, validating previous studies. While the 31-GEP identified a subgroup (Class 1A) of traditionally high-risk patients (stage IIB-III CM) who had a >98% MSS over three years, it can also facilitate identifying patients who could warrant earlier adjuvant therapy with a higher 31-GEP class designation.