541 DIABETES AND GLUCOSE LEVEL AS METABOLIC DETERMINANTS OF IMMUNE CHECKPOINT INHIBITORS RESPONSE IN MELANOMA

[1,2]Yu Jen A Jan*, [1,3]Soravis Osataphan, [1,4]Cho Han Chiang, [1,2]Kerry Reynolds, [1,2]Ryan Sullivan. [1]*Harvard Medical School, Boston, MA, USA*; [2]*Massachusetts General Hospital, Boston, MA, USA*; [3]*Beth Israel Deaconess Medical Center, Boston, MA, USA*; [4]*Mount Auburn Hospital, Cambridge, MA, USA*

Background The current guideline-recommended treatment for melanoma at stage IIb or above involves immune checkpoint inhibitors (ICIs). Recent studies have explored the correlations between metabolic derangements and the efficacy of ICIs, considering their impact on T-cell-mediated immune response and interactions with other immunologic compartments in the tumor micro-environments. In this study, we aim to investigate the effect of metabolic abnormalities on treatment outcomes by analyzing real-world data from melanoma patients receiving ICIs.

Methods We performed a retrospective multicenter cohort study in patients with melanoma treated with ICIs including pembrolizumab, nivolumab, ipilimumab, atezolizumab across the ten hospitals in the Mass General Brigham health care system between January 2014 to December 2022. Type 2 diabetes and hyperlipidemia were defined by ICD-9 and 10 diagnostic codes. Laboratory data and body mass index (BMI) at the time of starting ICI therapy were collected. Overall survival was evaluated with Kaplan-Meier survival analysis and cox proportional hazards model.

Results A total of 2082 patients with melanoma treated with ICIs were included. Among all patients, 43% received pembrolizumab, 16% received nivolumab, 9.4% received ipilimumab, 30.5% received ipilimumab and nivolumab and 0.9% received atezolizumab. At the start of ICI therapy, 13.3% of the patients had type II diabetes, 36.8% had hyperlipidemia, 34.8% were overweight and 33.1% of patients were obese based on BMI. The study found that having a diagnosis of type II diabetes at the time of starting ICI therapy was associated with worse overall survival (Unadjusted HR:1.32, 95% CI:1.09–1.61, p=0.005; Adjusted for age and sex- HR:1.24, 95%CI:1.02–1.51, p=0.03). However, the presence of dyslipidemia showed no significant difference in overall survival. When using 126 mg/dL as the glucose cutoff, patients with glucose $\geq$ 126 mg/dL pre-ICI treatment had worse overall survival (Unadjusted HR:1.64, 95%CI:1.41–1.91, p<0.001; Adjusted for age and sex- HR:1.52, 95%CI:1.30–1.78, p<0.001). Being overweight or obese was associated with better survival compared to normal BMI (Unadjusted HR:0.71, 95%CI:0.60–0.84, p<0.001, HR:0.67, 95%CI:0.56–0.79, p<0.001 respectively; Adjusted for age and sex- HR:0.71, 95%CI:0.60–0.85, p<0.001, HR:0.70, 95%CI:0.59–0.83, p<0.001 respectively).

Conclusions Overall, these findings indicate that type II diabetes and higher glucose levels before ICI treatment are associated with worse survival in patients with melanoma. However, being overweight or obese is associated with better survival, as was observed in other studies. Further studies are needed to explore the underlying molecular mechanisms that drive worse outcomes in patients with diabetes and hyperglycemia and better outcomes in overweight/obese patients treated with ICIs.

Ethics Approval The study was approved by Mass General Brigham IRB Protocol #: 2023P000244 as an exempt study.

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