DEGRADATION OF TYPE III AND IV COLLAGEN ASSOCIATES WITH OUTCOME WHEN MEASURED IN SERUM FROM PATIENTS WITH METASTATIC MELANOMA TREATED WITH IMMUNE CHECKPOINT INHIBITORS

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Background: Predicting immune checkpoint inhibitor (ICI) efficacy is essential for patients with metastatic melanoma. Emerging evidence suggests a key role of collagens and their degradation products in regulating anti-tumor immunity, and response to ICIs. Blood-based collagen biomarkers reflecting tissue turnover is preferred over biopsies, and can be applied as biomarkers for melanoma. In this study, we investigated if degradation products of type III collagen (interstitial matrix) and type IV collagen (basement membrane) were associated with survival outcomes when measured in serum from patients with melanoma treated with ICIs.

Methods: Matrix metalloproteinase (MMP) degraded type III (C3M) and type IV collagen (C4M) were measured by ELISAs in pre-treatment serum from two cohorts of metastatic melanoma patients treated with anti-PD-1 monotherapy (n=35) or with anti-PD-1/anti-CTLA-4 combination therapy (n=22). The association between dichotomized (Q4 vs Q1-Q3) C3M and C4M levels and overall survival (OS) was assessed by Kaplan-Meier analysis.

Results: Metastatic melanoma patients treated with anti-PD-1 monotherapy had significantly shorter OS if they had high (Q4) C3M (p=0.001) or high C4M levels (p=0.0002) compared with low levels. The median overall survival was not reached in biomarker-low patients while it was 509 days and 352 days for C3M and C4M, respectively, in biomarker-high patients. A similar trend was seen in the melanoma patients receiving anti-PD-1/anti-CTLA-4 combination therapy. The median overall survival was 649 days in biomarker-low patients while it was 208 days in biomarker-high patients for C3M and C4M (log-rank, p=0.134).

Conclusions: Blood-based biomarkers of collagen remodeling of the interstitial matrix and basement membrane (C3M and C4M) were associated with poor survival outcomes in two cohorts of metastatic melanoma patients treated with anti-PD-1 monotherapy or with anti-PD-1/anti-CTLA-4 combination therapy. These findings support the link between extracellular matrix remodeling components and poor response to ICIs.

Ethics Approval: Serum samples were collected at Copenhagen University Hospital, Herlev after informed consent and approval by the Ethics Committee for the Capital Region of Denmark in compliance with the Helsinki Declaration of 1975.

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