Impact of mRNA Vaccines on Anti-PDL1 Immunotherapy Outcomes in Patients with Metastatic Bone Disease

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INTRODUCTION:

Metastatic bone disease is a common and difficult pathology to manage, associated with poor prognosis and low short-term survival rates. Although immune checkpoint inhibitor (ICI) effectiveness has been correlated with intra-tumoral PD-L1 expression and shown to inhibit bone resorption via suppression of osteoclast differentiation (Zuo, Huong, et.al., *Nature Cancer Gene Therapy, 2022)*, there are no clinically available methods to improve sensitivity to ICIs by modulating PD-L1 expression. Personalized mRNA vaccines stimulate robust interferon-dependent innate immune activation in mice including four-fold increases in PD-L1 expression on peripheral and intratumoral myeloid cells and enhanced sensitivity to ICI (Sayour, Grippin, et al., *NanoLetters*, 2019; Mendez-Gomez, et al., *Cell*, *2024*), but the impact of off-the-shelf mRNA vaccines on PD-L1 expression and response to ICI is not known.

METHODS:

We hypothesized that mRNA vaccines targeting SARS-COV-2 would enhance PD-L1 expression and responses to ICI in patients with bone metastases. To test this hypothesis, we utilized institutional databases to identify patients with pathology reports including the term “PD-L1” from August 2020 to November 2023. Clinical, pathological, and molecular data, along with SARS-COV-2 vaccination dates (if applicable), were extracted for each patient. Differences between groups were assessed with Wilcoxon rank-sum tests. To evaluate the impact of mRNA vaccination and PD-L1 immunotherapy on clinical outcomes, we utilized an institutional database to assemble a cohort of patients with Stage IV Non-Small Cell Lung Cancer (NSCLC) treated with immune checkpoint blockade anytime between August 2020 and November 2023. Survival was evaluated with Gehan-Breslow-Wilcoxon tests. The primary objective of this study was to evaluate the impact of COVID mRNA vaccination on PD-L1 expression in bone metastases. The secondary objective of this study was to analyze whether mRNA COVID vaccination provided a survival benefit to patients receiving immune checkpoint inhibition in patients with metastatic bone disease.

RESULTS:

Across the entire cohort of patients with PD-L1 pathology reports (n=5,524), receipt of a SARS-COV-2 mRNA vaccine within 100 days of biopsy was associated with a 55% increase in PD-L1 mean tumor proportion score (TPS) (14% vs 8.9%, p=0.029). However, in patients with osseous tumors (n=94), receipt of a SARS-COV-2 mRNA vaccine within 100 days of biopsy was associated with an even larger increase in TPS (10% vs 1.7%, p<0.005). Of the Stage IV NSCLC patients who were treated with ICI, 296 patients had bone metastases at the initiation of ICI. In this cohort, patients who received a SARS-COV-2 vaccine within 100 days of anti-PDL1 immune checkpoint inhibition (n=57) exhibited improved overall survival compared to those without a SARS-COV-2 mRNA vaccine (n=239) (HR 0.60, 95% CI 0.43-0.85, p= 0.004). 2-year overall survival improved from 37% in patients who received ICI without COVID mRNA vaccination to 56% in patients who received ICI within 100 days of COVID vaccination. Moreover, median overall survival was 446 days among patients without COVID mRNA vaccination, but increased to 910 days when ICI was administered within 100 days of COVID mRNA vaccination. mRNA vaccination without concurrent ICI had no significant impact on overall survival.

DISCUSSION AND CONCLUSION:

Taken together with our previous findings, this data supports further investigation into SARS-COV-2 mRNA vaccines as off-the-shelf adjuvants to stimulate responses to immune checkpoint blockade in patients with metastatic bone disease.