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Spatial distribution of CD8+ and FoxP3+ in a window of opportunity for durvalumab (MEDI4736) plus metformin trial in squamous cell carcinoma of the head and neck (HNSCC)

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Background

Anti-PD-L1 Immune checkpoint inhibition shows promise. Durvalumab (D) is an anti-PD-L1 monoclonal antibody with effect in solid tumors. Metformin (M) alters immunity in the tumor microenvironment, but clinical benefit has yet to demonstrated. Multiplex immune profiling has shown utility in predicting outcomes in HNSCC. We examine the distribution of CD8+ and FoxP3+ tumor-infiltrating T-cells and digital spatial genomic profiling (DSP) in response to therapy with D ± M.

Methods

In a single-center phase I, 4-week window of opportunity trial of resectable HNSCC, patients were randomized 3:1 to a single dose of D +/- daily M (up to 1000 mg BID). We analyzed CD8+ and FoxP3+ T-cell composition at the primary site pre- and post-therapy in the tumor and stromal interface. Whole slide images (WSI) were digitally analyzed (Aperio Technologies, Vista, CA). Image analysis algorithms were employed for CD8+ & FoxP3+ T cell counts (CC) and respective distances. A subset of samples were analyzed by NanoString GeoMX^{TM} DSP for CD8+, FoxP3+, and cytotoxic T-cell gene set transcripts.

Results

Of 32 evaluable patients, 37.5% (n = 12) had primary site pathologic response. Pre-treatment mean CD8-FoxP3 distance was greater in responders (20.5 µm vs 15.5 µm; $p < 0.001$). Mean CD8-FoxP3 distance showed a 15.4% decrease in responders ($p < 0.001$) and a 28.8% increase in non-responders ($p < 0.001$). Mean CD8-FoxP3 distances increased by 4.54% with D+M ($p < 0.001$) and 29.6% with D alone ($p < 0.001$). Relative CD8+ CC/µm^2 decreased within the tumor by 21.4% in responders ($p = 0.003$) and 14.9% with D+M ($p = 0.004$). DSP analysis of a subset of patients suggested an increase in cytotoxic T-cell signatures with therapy. Pre-treatment samples from responders showed higher cytotoxic T-cell signatures.

Conclusions

Greater pre-treatment mean CD8-FoxP3 distance and decreases in mean CD8-FoxP3 distances post-treatment were associated with pathologic response. Increased cytotoxic T-cell activity as determined by DSP were observed with therapy. This preliminary data suggests spatial analysis of T-cell subsets may be a biomarker for treatment response.

Clinical trial identification

NCT03618654.

Legal entity responsible for the study

J.M. Curry.

Funding

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Disclosure

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