

ACTIVATING CD73 ON B CELLS AS A TARGET FOR IMMUNOTHERAPY OF COVID-19 AND VIRAL ASSOCIATED CANCERS: CLINICAL ACTIVITY IN HUMAN PAPILLOMA VIRUS POSITIVE (HPV) HEAD AND NECK SQUAMOUS CELL CANCERS (HNSCC)

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Background Mupadolimab (mupa) is a humanized FcγR binding-deficient IgG1 anti-CD73 antibody that has agonistic properties.¹ CD73 is involved in production of adenosine and in cellular trafficking. Mupa reacts with the majority of circulating B cells leading to activation and expression of differentiation markers CD69, CD138 and CD38, and transformation into plasmablasts with secretion of IgM and IgG. B cell activation provided the rationale to develop mupa for immunotherapy of cancer and Covid-19. Intratumor HPV specific B cells have been reported in HNSCC.² This report describes properties of mupa and the early signs of clinical activity in HPV+ HNSCC.

Methods ELISA and flow cytometry were used to measure binding of anti-CD73. Humanized NSG-SGM3 mice were used to evaluate effects of Mupa on human anti-SARS CoV2 spike protein (SP) response. CD73 expression in biopsies was measured by immunohistochemistry. Mupa (IV q 3 weeks) with or without pembrolizumab is being evaluated in an ongoing phase 1 trial in patients with refractory cancers.

Results Mupa binding to CD73 was blocked by APCP, an analog of adenosine diphosphate that locks CD73 in the closed conformation, indicating mupa binding to the open conformation. Cross blocking and cellular internalization studies showed that mupa is distinct from other anti-CD73 antibodies such as MEDI9447 and AD2. NSG-SGM3 mice were immunized with 50 μg SP subcutaneously and treated with mupa 10mg/kg or control IgG IP. Mupa treated animals mounted an antigen specific human anti-SP response; no antibody responses were seen in controls (P=0.02). In the dose-escalation portion of the phase 1 trial, mupa doses of ≥12 mg/kg saturated CD73 sites on circulating B cells. High stromal CD73 expression was observed in HPV+ HNSCC biopsies from 5 evaluable patients with chemotherapy and anti-PD1 refractory disease, and tumor regression was seen in 2 of these patients receiving 7 and 16 cycles of ≥12 mg/kg mupa without pembrolizumab. Safety of mupa+pembrolizumab was evaluated in 16 patients with no MTD reached and no changes in serum immunoglobulins. Transient reductions in circulating CD73 B cells were observed consistent with redistribution to lymphoid tissues.

Conclusions CD73 plays a role in B cell activation and differentiation. Mupa is an antibody with agonistic activity that stimulates B cells and enhances antigen specific antibody production. This activity supports a strategy to combine mupa with pembrolizumab to enhance both humoral and cellular immunity in the treatment of viral associated cancers such as HPV+HNSCC, and viral infections.

Trial Registration NCT03454451

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Ethics Approval The study was approved by Western IRB, approval number 1-1066703-1. Participants gave informed consent before taking part.

<http://dx.doi.org/10.1136/jitc-2021-SITC2021.701>