1373 STC-15, AN ORAL SMALL MOLECULE INHIBITOR OF THE RNA METHYLTRANSFERASE METTL3, INHIBITS TUMOUR GROWTH THROUGH ACTIVATION OF ANTI-CANCER IMMUNE RESPONSES AND SYNERGISES WITH IMMUNE CHECKPOINT BLOCKADE

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Background METTL3 is an RNA methyltransferase responsible for the deposition of N-6-methyladenosine (m^6A) modification on mRNA and long non-coding RNA (lncRNA) transcripts, to regulate their stability, splicing, transport and translation. Small molecule inhibitors of METTL3 catalytic activity have previously demonstrated direct anti-tumour efficacy in models of acute myeloid leukemia (AML). Here we present pre-clinical data showing that STC-15, an orally bioavailable small molecule inhibitor of METTL3, restrains cancer growth and induces anti-cancer immunity

Methods To characterise transcriptomic changes following METTL3 inhibition, RNA sequencing studies were performed on several cancer cell lines treated with STC-15. Induction of specific genes was validated by qPCR and Western Blots. The functional consequence of the upregulation of innate immune pathways was investigated in vitro using a co-culture system of SKOV3 ovarian cancer cells and human peripheral blood mononuclear cells (PBMC) or purified primary CD8+ T-cells, and animal studies using subcutaneous A20 and MC38 mouse syngeneic tumour models

Results Inhibition of METTL3 by STC-15 in cancer cell lines leads to prominent upregulation of genes associated with innate immunity, including type-I and type-III IFNs, as well as many interferon stimulated genes. Cells treated with STC-15 accumulated double-stranded RNA suggesting that activation of IFN signalling is triggered by innate pattern recognition sensors.

In an in vitro co-culture system, STC-15 demonstrated strong and dose-dependent enhancement of PBMC-mediated killing of cancer cells. Similar results were obtained when replacing PBMC with purified CD8+ T-cells.

In MC38 colorectal and A20 lymphoma syngeneic models, oral treatment of immune-competent tumour bearing mice with STC-15 significantly inhibited tumour growth. In vivo depletion of CD8+ T-cells abrogated the response to STC-15.

Combination of STC-15 with anti-PD1 antibody resulted in tumour regression in both models, with mice remaining tumour-free long after treatment ceased. When regressed mice from the A20 model were re-challenged with a new batch of A20 cells, no new tumour growth was observed, further demonstrating the induction of durable anti-tumour immunity

Conclusions In pre-clinical cancer models, STC-15 treatment results in activation of innate immune pathways, inhibits tumour growth via activation of CD8+ T-cell mediated tumour cell killing, and enhances the anti-tumour properties of anti-PD1 therapy to generate a durable anti-tumour immune response. These data provide the rationale for the development of STC-15 both as monotherapy and in combination with checkpoint inhibition for the treatment of solid tumour malignancies. A Phase I, First-in-Human clinical trial is planned to begin in 2022

Ethics Approval Animal welfare for this study complies with the UK Animals Scientific Procedures Act 1986 (ASPA) in line with Directive 2010/63/EU of the European Parliament and the Council of 22 September 2010 on the protection of animals used for scientific purposes.

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