Combinations: Immunotherapy/Immunotherapy

The effects of combination treatment of IMM-101, a heat-killed whole cell preparation of *Mycobacterium obuense* (NCTC 13365) with Check Point Inhibitors in pre-clinical models.

James Crooks[1], Sheila Brown[1], Audrey Gauthier[2], Marc Hillairet de Boisferon[2], Andrew MacDonald[1] and Laura Rosa Brunet[3]
[1]*University of Manchester, Manchester, UK*
[2]*Oncodesign, Dijon, France*
[2]*Immodulon Therapeutics LTD, London, UK*

While harnessing the power of the immune system to control cancer is becoming established as an effective way of treating patients, it has become increasingly clear that transformed cells exploit a number of mechanisms to escape such control. Hence, while the clinical use of check point inhibitors (CPI) has yielded significant success, there is mounting evidence to suggest that combination treatment of CPI with immunomodulating therapies may further benefit cancer patients. Immodulon Therapeutics is developing IMM-101, an immunotherapeutic agent based on a heat-killed whole cell preparation of *Mycobacterium obuense* (NCTC 13365), which modulates systemic immune responses, as an adjunctive immunotherapy for cancer. Based on exposure data in over 300 patients, alone and in combination, IMM-101 is well-tolerated. Additionally, extended overall survival and progression-free survival were observed in IMAGE-1, a randomised open-label, phase II, first-line, proof of concept study (NCT01303172), in combination with gemcitabine in advanced pancreatic ductal adenocarcinoma.

We found that *in vitro* exposure of IMM-101 primes *in vitro* generated murine Dendritic Cells (DC) and human monocyte derived DC in a dose dependent manner and functionally affect DC by enhancing their ability to process and present antigen. Moreover, IMM-101 activated DC promote T cell secretion of IFN-γ following re-stimulation of draining lymph node cell preparations, 7 days after adoptive transfer of IMM-101 primed DCs into naïve recipient mice. We also investigated whether the effects of IMM-101 on innate and adaptive immune responses indeed improve on the therapeutic benefit of CPI treatment (anti-CTLA-4 or anti-PD-1) in two murine xenograft models using B16-F10, a mouse melanoma cell line, and EMT6, a mouse breast cell line.

We assessed effects on tumour burden and local and systemic immunological bias in treated mice. We report a significant benefit from combination treatment of CPI and IMM-101 on tumour burden. We also observed significant change to the $CD8^+$/Treg ratio at the tumour site. We performed *in vitro* stimulation (antigenic as well as polyclonal) of immune cells present at the tumour site, in the draining lymph nodes and in the spleen. We report results at different time points over the course of the disease.

On the basis of these promising results, formal clinical evaluation of IMM-101 in combination treatment with anti-PD-1 treatment is being undertaken (EudraCT Number: 2016-001459-28).