Combination of a Dipeptidyl Peptidase Inhibitor BXCL701 and Biased CD122 Agonist NKTR-214 with Anti-PD1 Provides Functional Immunomodulatory Immune Response through Inflammatory Cell Therapy

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1. Tumor regression for BXCL701 and NKTR-214 with anti-PD1 in MC38, WEHI 164 mouse model

The mice treated with BXCL701 20 µg qd, in combination with NKTR-214 (0.8 mg/kg: q9d) and anti-PD1 (200 µg; biw) exhibited significant tumor reduction as noted from day 10 (Figure 1 & 2) in the syngeneic mouse models of colorectal adenocarcinoma (MC38) and fibrosarcoma (WEHI-164). Of the mice treated with the triple combination, 100% became tumor-free by day 35. These animals remained tumor free for more than 100 days.

2. BXCL701, NKTR-214 and anti-PD1 induces anti-tumor immunity

The treatment of established tumors (>120 mm³) with the triple combination resulted in 100% tumor-free mice (6/6) in MC38 model by day 35. All the animals remained tumor free for more than 100 days until they were re-challenged. It was found that 6/6 re-challenged mice (only 1 mouse showed slight increase in tumor size) rejected tumor growth unlike naive mice, demonstrating the generation of long-term tumor-specific memory response in the MC38 mouse model (Figure 1).

In case of the WEHI model, out of the 6 mice that received treatment after the establishment of tumors (~110 mm³), 3 mice completed dosing while 3 animals had to be removed from the study due to dosing complications. However, the 3 mice that completed the triple treatment, showed complete tumor regression from day 35 onwards. These 3 mice remained tumor-free for more than 100 days until they were re-challenged. Further, no tumor growth was observed in these mice upon re-challenge, as compared to the naive mice, demonstrating the generation of long term tumor-specific memory response (Figure 2).

3. Macrophage density profiling of responsive and non-responsive tumor models

IHC of Pan02, MC38 and WEHI-164 tumors from untreated animals with anti-mouse Ab (rabbit anti-mouse F4/80, monoclonal antibody, cat. no:70076, Cell signaling) to analyse the macrophage density within the tumors.

These data confirm the development of a CD8+ effector memory T cell response in animals immune to Pan02 cells through the triple combination of BXCL701 + NKTR-214 + anti-PD1 (green shaded) tended to have higher macrophage density in comparison to all other groups.