A novel human anti-PD1/IL15 bi-functional protein with robust anti-tumor activity and low systemic toxicity

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BACKGROUND

• Recombinant IL-15 is a key cytokine promoting CD8+ T. NK, and NKT cell proliferation and has demonstrated clinical activity in cancer patients without evidence of Treg activation [1, 2]. However, its short half-life and systemic toxicity limit clinical utility.

• Kadmon has generated an IL-15 fusion protein platform to extend the serum half-life and direct its immune stimulatory activity to fight tumors [3].

• A novel asset of this platform is an anti-PD1/IL-15 bi-functional protein. To test the bi-functional hypothesis of this fusion protein in murine models, four different formats of the surrogate bi-functional proteins were engineered by fusing mouse IL-15 complex to a non-PD1 antibody (m3A7).

• The single IL-15 complex fused to N-terminus of anti-mPD1 antibody (1N-IL-15/m3A7) [figure 1B] showed significant anti-tumor activity primarily due to cis-presentation to PD1 and IL2Rβγ co-expressed on TILs (figure 1A). The cis-presentation potentiates maximizes the bi-functionality of IL15 blockade and stimulation [4].

• Here, we generated a novel therapeutic anti-human PD1 (38B2) antibody fused to the IL-15 complex. Furthermore, a point mutation in IL-15 was introduced to the bi-functional protein to lower its antibody fused to the IL-15 complex. Furthermore, a point mutation in IL-2/-15 dependent CTLL2 (mouse lymphocyte) and M07e (acute human tumors [3]).

METHODS

• 1N-IL-15/38B2, 1N-IL-15/DP47 (non-targeting negative control antibody), IL-15 was introduced to the bi-functional protein. To test the bi-functionality hypothesis of this fusion protein evaluated in competition ELISA and Promega PD1/PD-L1 or PD-L2 single block assays (2D or 2F).

• 1N-IL-15/38B2 and mut-1N-IL-15/38B2 did not change 38B2 CDRs and hence did not impact PD1 blocking activities.

RESULT 1: 1N-IL-15/38B2 and mut-1N-IL-15/38B2 Showed Comparable Binding and Blocking Activities

RESULT 2: mut-1N-IL-15/38B2 Showed Significant Potency Decrease in Proliferating hPBMCs, CTLL2, Mouse Spleen and M07e Cells

RESULTS

RESULT 3: Both 1N-IL-15/38B2 And mut-1N-IL-15/38B2 Exhibited Strong Anti-tumor Activity; mut-1N-IL-15/38B2 Was Safer At High Doses

CONCLUSIONS

• Early data showing robust anti-tumor activity with surrogate 1N-IL-15/m3A7 in a mouse Lewis Lung LL2 model was confirmed with the therapeutic bi-functional antibodies in a pembrolizumab resistant Hpd1-CT26 colorectal model.

• Our experiments demonstrated that mut-1N-IL-15/38B2:
  1. Retained full PD1 blocking activities and exhibited significant potency decrease in proliferating IL2Rβγ expressing cells
  2. Induced tumor regression in a Hpd1-CT26 model at 12 mg/kg highlighting the bi-functionality of this fusion when it bound to PD1 and IL2Rβγ co-expressed on TILs

• Mutated IL-15 lowered potency/stimulation which resulted in lower toxicity and increase therapeutic treatment window.

• These promising results warrant further investigation of this bi-functional in the clinic.


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