797 A NOVEL ANTI-PD-1/IL15 BI-FUNCTIONAL ANTIBODY WITH ROBUST ANTI-TUMOR ACTIVITY IN MULTIPLE SOLID TUMORS

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Background Immune checkpoint inhibitors (ICI) such as PD-1/PD-L1 have revolutionized cancer therapy, but only a fraction of patients responded to approved ICIs; the majority are either resistant or quickly become refractory. IL-15 is a key cytokine promoting CD8+ T, NK, and NKT cell proliferation and has demonstrated clinical activity. Kadmon has established a cytokine fusion protein platform to extend the IL-15 serum half-life and direct its action to tumors and/or T cells in tumor microenvironment (TME).[1–3] An important asset of this platform is KD050, an anti-PD1/IL15 bi-functional antibody with a novel mutation on the IL15 to lower the systemic toxicity of IL-15. Previous studies showed that KD050[1] and its mouse surrogate[2] were cis-presented to PD-1 and IL2/15Rß? co-expressed TILs. The simultaneous binding to both PD-1 and IL2Rß potentially maximized KD050 bi-functionality of PD-1 blockade and IL-15 stimulation, resulting in robust anti-tumor activity in a PD-1/PD-L1 resistant human PD-1/PD-L1 transgenic colon carcinoma model (hPD-1/PD-L1 CT26) and murine lung cancer model (LL/2), respectively. Here, we continue to evaluate KD050 surrogate anti-tumor activity in multiple murine solid tumor models.

Methods KD050 mouse surrogate, mPD-1 antibody m3A7 and anti-PD-1/ non-mutated IL15 fusion (wtKD050) were generated and characterized in vitro as done previously.[1 2] Single-dose efficacy of KD050 mouse surrogate was evaluated in 12 syngeneic murine models (MC38, CT26, H22, LL/2, Pan02, A20, B16-F10, B16-BL6, Renca, Hepa1-6, RM-1 and EMT6), and anti-tumor efficacy was further evaluated in Pan02 model in different dose levels and frequencies. Briefly, tumor cells were subcutaneously transplanted to the mice and the treatment was started when tumors reached 100 mm^3.

Results KD050 surrogate showed similar potencies as the mPD-1 antibody m3A7 in binding to the soluble and cell expressed human PD-1 and blocking of the PD-L1 binding to PD-1. Comparing to wtKD050 (anti-PD-1/ non-mutated IL15 fusion), mutated IL15 fusion KD050 surrogate showed lower CD8 T cell stimulation in the CTLL2 and mouse spleen cell proliferation. In vivo, different levels of tumor regression were observed in all 12 models with no significant systemic toxicity. Furthermore, tumor rejection in some mice was achieved in the MC38, CT26, A20, H22, Pan02 and EMT6 models, and dose response anti-tumor efficacy was observed in Pan02 model.

Conclusions We demonstrated that KD050 surrogate had very robust anti-tumor activity and low systemic toxicity in mice bearing multiple solid tumors. These findings suggest that the bi-functional antibody KD050 has encouraging therapeutic potential.

REFERENCES

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3. Polonskaya Z. etc. SITC 2020 #573

Ethics Approval All studies were conducted following an approved IACUC protocol. Although this study was not conducted in accordance with the FDA Good Laboratory Practice regulations, 21 CFR Part 58, all experimental data management and reporting procedures were in strict accordance with applicable Crown Bioscience, Inc. Guidelines and Standard Operating Procedures. The methods and results in the Final Study Report accurately reflect the raw data generated during the execution of the study.

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