A Safe and Highly Potent αPD1-IL2 Fusion (AWT020) that Decouples the Efficacy and Toxicity of IL-2 Therapy

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INTRODUCTION

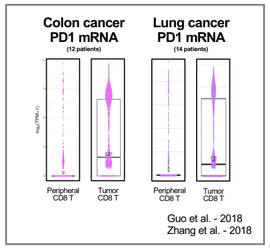
Interleukin 2 (IL-2) is one of the most important cytokines for cancer immunotherapy[1]. The clinical efficacy of IL-2 had been proven in the treatment of metastatic renal cell carcinoma and metastatic melanoma with overall response rate of 15-25% and the response is generally dose dependent[2,3]. However, high dose IL-2 treatment is associated with severe adverse effects such as vascular leak syndrome (VLS), which affects multiple organs and greatly limits the therapeutic potential of IL-2[4].

The toxicity of IL-2, over many years of scientific research, has been attributed to its binding to CD25, or IL-2Rα[5,6]. Recently, a number of commonly named No-α-IL2 variants with abolished IL-2Rα binding, were demonstrated to have an improved safety profile in the early phase of clinical studies. Compared to WT IL-2, No-α-IL2 has less stimulation to eosinophils and regulatory T cells (Treg), while it still universally activates all the IL-2Rβγ expressing immune cells, including T cells and NK cells[7].

To further enhance the specificity of IL-2, we engineered a fusion protein comprised of an anti-PD-1 antibody and a potency optimized No-α-IL2 (AWT020). AWT020 selectively stimulated the expansion of tumor infiltrating T cells while avoiding NK expansion, demonstrating a superb safety profile and excellent antitumor efficacies. It was also shown to be superior to an industrial leading αPD1-IL-2x as tested in multiple tumor models.

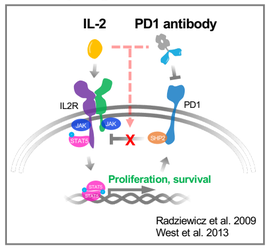
TARGET TUMORAL T CELLS BY DESIGN

PD1 Expression is Highly Specific to TIL



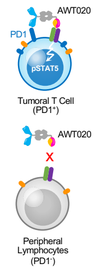
Guo et al. - 2018
Zhang et al. - 2018

PD1 Blockade Synergizes with IL-2



Radziewicz et al. 2009
West et al. 2013

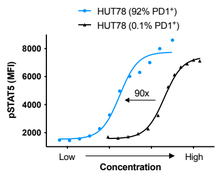
PD1 Dependent TIL Activation



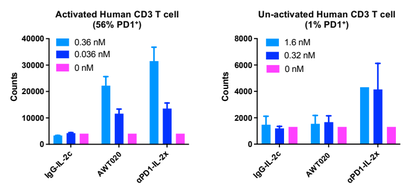
Toxicity ↓ **Efficacy ↑**

AWT020 Selectively Activates PD-1+ T Cells

Potent and Selective Activator of STAT5 signaling



Potent and Selective Expander of PD1high Human CD3+ T Cells



- AWT020 potently induced pSTAT5 signaling in PD1+ T cell lymphoma cells (HUT78)
- αPD1-IL-2x robustly enhanced the proliferation of both PD1high and PD1low human CD3+ T cells.
- AWT020 only induced the proliferation of PD1high human CD3+ T cells.
- Non-targeting IgG-IL-2c control showed no obvious induction of T cell proliferation.

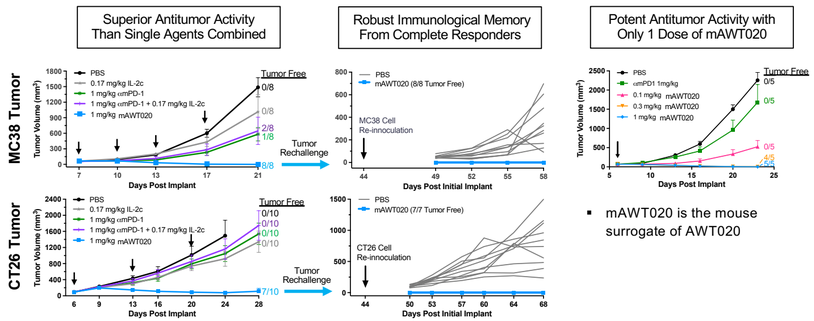
SUPERIOR T CELL ANTITUMOR IMMUNITY

mAWT020 Is A Superior Antitumor Agent

Superior Antitumor Activity Than Single Agents Combined

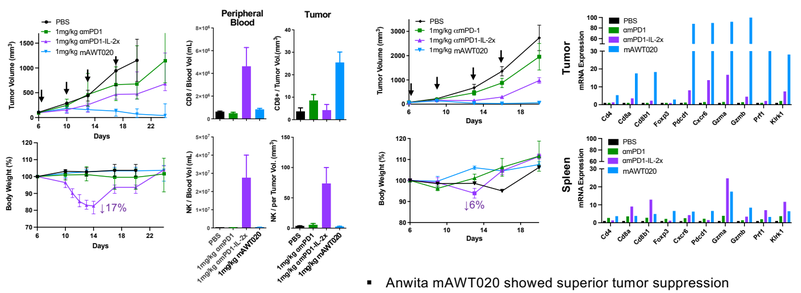
Robust Immunological Memory From Complete Responders

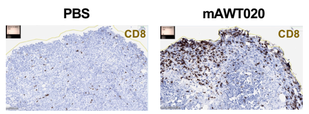
Potent Antitumor Activity with Only 1 Dose of mAWT020



- mAWT020 is the mouse surrogate of AWT020

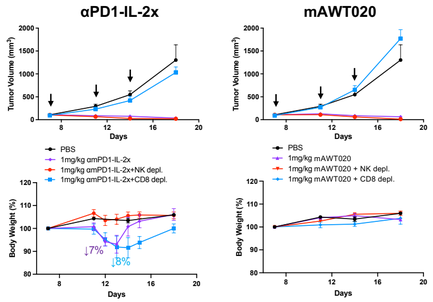
mAWT020 Preferentially Expands and Activates T Cells in Tumor





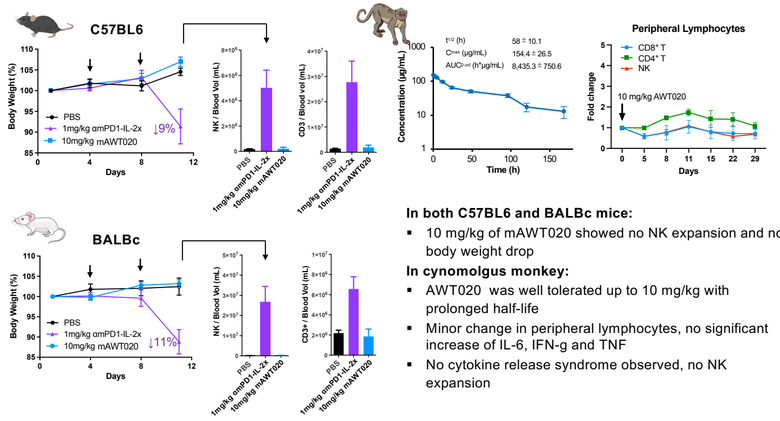
- Anwita mAWT020 showed superior tumor suppression
- Anwita mAWT020 expanded and activated tumor infiltrated CD8+ T cell, but not NK
- Anwita mAWT020 showed no appreciable toxicity and no lymphocyte expansion in the peripheral blood
- Competitor's αPD1-IL-2x primarily expanded NK in PB and tumor and showed significantly higher toxicity

mAWT020 Avoids NK Driven Toxicity



- To understand the roles of NK cell and CD8 T cell population, an in vivo depletion study was performed
- αNK antibody PK136 and αCD8 antibody Lyt 3.2 effectively depleted NK and CD8 T cell population respectively in C57/BL6 mice
- The antitumor efficacy of αPD1-IL-2 is mainly driven by CD8 T cell
- The toxicity of competitor's αPD1-IL-2x is mainly caused by NK cell
- Anwita's mAWT020 completely avoids NK driven toxicity

SUPERIOR SAFETY PROFILE



In both C57BL6 and BALBc mice:

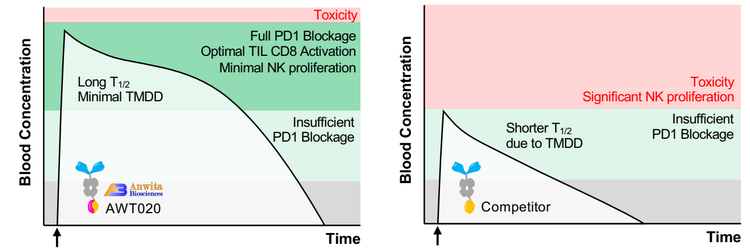
- 10 mg/kg of mAWT020 showed no NK expansion and no body weight drop

In cynomolgus monkey:

- AWT020 was well tolerated up to 10 mg/kg with prolonged half-life
- Minor change in peripheral lymphocytes, no significant increase of IL-6, IFN-g and TNF
- No cytokine release syndrome observed, no NK expansion

CONCLUSIONS

AWT020 is a Fully Optimized αPD1-IL2 for Superior Efficacy and Safety



		AWT020 Anwita	αPD1-IL2x Leading competitor
Activity and Efficacy	CD8 T expansion in PB	<2x	~4x
	CD8 T expansion in Tumor	>5x	<2x
	NK expansion in PB	<2x	>20x
	NK expansion in Tumor	<2x	>10x
	Anti-Tumor Efficacy (TGI)	Superior	Good
Toxicity and PK	MTD (Mouse)	>10 mg/kg	~1 mg/kg
	MTD (Monkey)	>10 mg/kg	est. ~1 mg/kg
	PK (Monkey)	Superior, minimal TMDD	Strong TMDD
	Therapeutic Window	>100	est. ~3-10

In summary, the preclinical observations support the development of AWT020 as revolutionary IL-2 immunotherapy for cancer. An Investigational New Drug (IND) application is planned for AWT020 by 1H 2023.

References

1. Jiang et al. 2016
2. Clark et al. 2021
3. Rosenberg et al. 2014
4. Dutcher et al. 2014
5. Krieg et al. 2010
6. Hu et al. 2003
7. Ptacin et al. 2021

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