**INTRODUCTION**

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

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

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-IL-2 (AWT020). AWT020 selectively stimulated the expansion of tumor infiltrating T cells while avoiding NK expansion, demonstrating a superior safety profile and excellent antitumor efficacies. It was also shown to be superior to an industrial leading PD-1-IL-2b as tested in multiple tumor models.

**TARGET TUMORAL T CELLS BY DESIGN**

**SUPERIOR T CELL ANTITUMOR IMMUNITY**

- **mAWT020 Is A Superior Antitumor Agent**
  - Superior Antitumor Activity to Single Agents Combined
  - Potent and Selective Tumor Regression
  - No Significant Toxicity

- **mAWT020 Preferentially Expands and Activates T Cells in Tumor**
  - Anewta mAWT020 showed superior tumor suppression
  - Anewta mAWT020 expanded and activated tumor infiltrated CD8+ T cell, but not NK
  - Anewta mAWT020 showed no appreciable toxicity and no lymphocyte expansion in the peripheral blood

- **mAWT020 Avoids NK Driven Toxicity**
  - To understand the roles of NK cell and CD8+ T cell population, an in vivo depletion study was performed
  - mPD1 antibody P1K1526 and gCD2 antibody Lyl.3.2 effectively depleted NK and CD8 T cell population respectively in C57Bl6 mice
  - The antitumor efficacy of IL-2-12 is mainly driven by CD8 T cell
  - The toxicity of competitor’s PD-1-IL-2a is mainly caused by NK cell
  - Analysis of mAWT020 completely avoids NK driven toxicity

**SUPERIOR SAFETY PROFILE**

- **mAWT020 is a Fully Optimized pdP1-IL2 for Superior Efficacy and Safety**
  - In both C57Bl6 and BALB/c 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 has a fully optimized safety profile as compared to competitor’s AWT020 and is a safe and highly potent immunotherapy for cancer.

- **CONCLUSIONS**

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