Weill Cornell Medicine

Anti-ART1 Monoclonal Antibody for Improved Anticancer Immunotherapy

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Background & Unmet Need

- Standard of care for non-small cell lung cancer (NSCLC) patients is immune checkpoint inhibitors (ICI) alone or with chemotherapy, though most patients fail to achieve a durable response
- In the KEYNOTE-189 trial, treatment-naïve NSCLC patients who received pembrolizumab (anti-PD-1) in addition to standard chemotherapy achieved a 48% objective response, compared to 19% in patients receiving chemotherapy alone
- However, only 0.5% of patients in the KEYNOTE-189 trial achieved a complete response, with only 34% of pembrolizumab-treated patients alive and progression-free at 12 months
- **Unmet Need:** While ICIs have improved outcomes for NSCLC, there remains a persistent unmet need for additional therapies that prolong survival and deliver a durable response

Technology Overview

- **The Technology:** Fully humanized anti-ART1 antibody (22C12 HuLC) for the treatment of NSCLC and other ART1-expressing tumor types
- **The Discovery:** ART1 dampens antitumor immunity by inducing apoptosis of infiltrating $CD8^+$ T cells via ADP-ribosylation of P2X7R
- 22C12 (EC_{50} = ~1 nM, IC_{50} = 4.5 nM) was discovered through immunization of AlivaMab mice with recombinant human ART1 protein, followed by extensive antibody characterization to confirm binding and activity
- A fully humanized derivative (22C12 HuLC) was engineered with equivalent activity *in vitro*
- **PoC Data:** Treatment of mice with 22C12 reduces lung tumor burden in a $CD8^+$ T cell dependent manner and promotes the infiltration of $P2X7R^+$ T cells
- 22C12 was also effective in a mouse model of melanoma, significantly slowing tumor growth

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Patents:
PCT Application Filed

Publications:
Wennerberg et al. *Science Translational Medicine.* 2022.

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Technology Applications

- Treatment of solid tumors (e.g., lung, breast, colon, colorectal, melanoma) that overexpress ART1
- Can be used alone or in combination with other immune checkpoint inhibitor therapies or chemotherapies

Technology Advantages

- Targeting ART1 may overcome the lack of consistent response to immune checkpoint inhibition
- Inhibition of ART1 may overcome failures of CD38 blockade trials through the opposite mechanism, as inhibition of CD38 may upregulate ADP-ribosylation
- The lead mAb candidate 22C12 binds ART1 with high affinity (EC_{50} = ~1 nM) and strong inhibition of enzymatic activity (IC_{50} = 4.5 nM)

Supporting Data / Figures

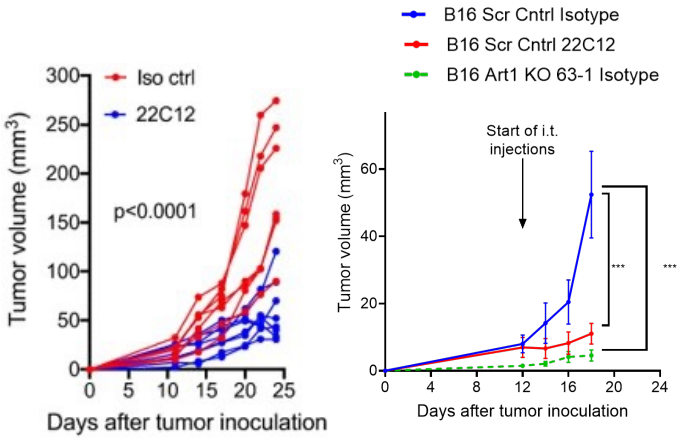

Figure 1: Mice treated with the anti-ART1 mAb 22C12 demonstrated reduced tumor volume in both an orthotopic KP1- $ART1^{OE}$ model of lung cancer ($p<0.0001$) **(Left)** and a subcutaneous B16 model of melanoma ($p<.0001$) **(Right)**.

The Tri-I TDI has produced an extensive preclinical data package that is available under CDA

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KP1 $ART1^{OE}$: Mouse NSCLC line engineered to overexpress murine ART1.
Tri-I TDI: Tri-Institutional Therapeutics Discovery Institute.
Wennerberg et al., *Sci Trans Med.,* 2022.

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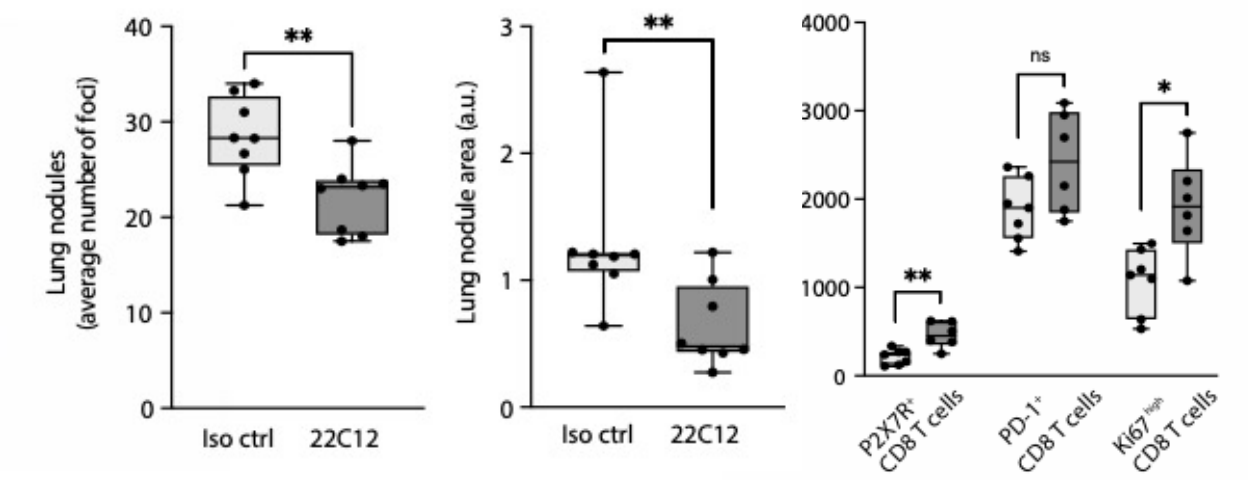

Figure 2: Mice orthotopically inoculated with intravenous injections of KP1- ART1^{OE} tumors were treated with 22C12 or an isotype control. Those receiving the 22C12 demonstrated reduced number of lung tumor nodules **(Left)** and reduced lung surface area occupied by lung tumor nodules **(Middle)**, and increased infiltration of P2X7R^{+}, PD-1^{+}, and Ki67^{high} (proliferative) CD8 T cells **(Right)**.

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