Gastrointestinal/liver-targeted TLR7 agonist for treatment of colorectal and liver cancers

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1. Introduction

- Checkpoint inhibitors (PD-1/PD-L1 antibodies) have become the backbone of IO therapies, however, only a fraction of patients respond
- Current data suggest response rates are influenced by a myriad of mechanisms affecting the tumor microenvironment, including mutational burden and level of immune infiltration
- Intra-tumor immune infiltrates have the capacity to convert "cold" immune incompetent tumors into "hot" inflammatory tumors, thus providing a complementary mechanism to the traditional antitumoral strategies
- As clinical proof-of-concept, intratumoral TLR7 agonists have shown promising anti-tumor responses in combination with checkpoint inhibitors; however, successful clinical applications have been limited to cutaneous-accessible tumor types

2. Toll-Like Receptor 7

- Expression: Human TLR7 expressed mainly in plasmacytoid dendritic cells
- Function: TLR7 activation elicits Th1-type immune responses through the induction of pro-inflammatory cytokines (IFN-α, IFN-β), increased antigen processing/ presentation (MHC-I), and direct tumor cell killing
- Drugability: One of the few innate immune receptors that can be activated by small molecule, which allows for fine tuning of TLR7 agonist properties using proven medicinal design principles
- Examples: Intratumoral TLR7 agonists have demonstrated pre-clinical and early clinical efficacy in solid tumors (KOMET-202, NCT01917, LG-165)

3. APR003 is a Gl/Liver-Targeted Oral TLR7 agonist

LOCAL IMMUNE PRIMING LEADS TO SYSTEMIC ANTI-TUMOR IMMUNITY

- Systemic administration leads to poor tolerability and potential immune tolerance induction
- Intratumoral administration biases local immune priming of tumor antigens leading to systemic (albeit limited) but durable anti-tumor activity in cutaneous accessible tumors
- Oral/Gl Liver targeted TLR7 agonist can circumvent the limitations of both systemic and intratumoral approaches to treat colorectal and liver cancers, and potentially other cancers with liver metastases

4. Gl/Liver Targeting Through OATP

- OATP1B1/KO mice showed no difference in tumor growth of TLR7 agonist APR003 vs. control

5. In vitro Activity

- Target selectivity: APR003 is >10-fold selective for TLR7 over TLR8
- Cellular activity: Active in plasmacytoid dendritic cells, but not in THP-1 monocytes
- Species cross-reactivity: Active across mouse, monkey, and human cells

6. Pharmacokinetics

- Pulsatil kinetics (ideal for in vivo vaccination): High clearance, short elimination half-life and low volume of distribution
- Tissue-restricted distribution: Concentrates in the Gl, liver, and kidney (consistent with transport mechanism)

7. Pharmacodynamics

- Primary response (transient): IFNα expression elicited in Gl, liver, mesenteric lymph node
- Secondary response (amplified): interferon-stimulated genes (ISGs) in the target tissue and interferon-inducible protein 10 (IFN-10) in serum
- Dose dependency: no bell-shaped response observed over 1000-fold range

8. IP-10 Induction Over TNFa

- APR003 induced stronger IP-10 response over TNFa compared to GS-920 (oral TLR7 agonist, Phase IIb in HBV)
- GS-920 caused more body weight loss at doses that produced similar IP-10 levels as APR003

9. Orthotopic Syngeneic Liver Tumor Model

- In an orthotopic CT26 liver cancer model, APR003 (30 mg/kg) decreased tumor burden and increased survival as single agent and effects were augmented in combination with anti-PDL1
- BIoluminescence imaging allows non-invasive monitoring of tumor growth on internal organs
- Cross-validation by gross examination, liver weights, and survival

10. CT26 Liver Tumor Model

- APR003 exhibited anti-tumor efficacy over a wide dose range (10 – 300 mg/kg) in A221 (liver PD vs serum PD)
- Systemic administration of APR003 on top of anti-PD-L1 further increased tumor-specific immunity

11. CT26 Liver Tumor Model (Dose Response)

- APR003 exhibited anti-tumor efficacy over a wide dose range (10 – 300 mg/kg) in A221 (liver PD vs serum PD)
- Systemic administration of APR003 on top of anti-PD-L1 further increased tumor-specific immunity

12. CT26 Colorectal Tumor Model

- APR003 exhibited anti-tumor efficacy over a wide dose range (10 – 300 mg/kg) in A221 (liver PD vs serum PD)
- Systemic administration of APR003 on top of anti-PD-L1 further increased tumor-specific immunity

13. Local Immune Priming Inhibiting C6D T Cells

- APR003 induced a greater frequency of activated CD103+ dendritic cells in liver draining lymph nodes, but not in distal non-draining lymph nodes

14. Increased Tumor-Infiltrating C6D T Cells

- Combination treatment APR003 on top of anti-PD-L1 further increased tumor-specific (A14) in CD6 T cells in the liver tumor

15. Tissue-Specific vs Systemic Administration

- Systemic administration (via subcutaneous injection) of APR003 is less efficacious compared to tissue-specific oral administration at comparable liver exposure
- However, oral/Gl liver targeted APR003 administration (higher serum exposure) induced more severe IL-6 and TNFa, which were not essential for anti-tumor efficacy and can lead to poor tolerability
- Therefore, Gl Liver targeted oral administration is a more optimal way to deliver TLR7 agonist to colorectal and liver cancers over systemic administration

16. Summary

- Drug Design: using medicinal chemistry of liver-targeting drugs, including transport mechanism properties
- APR003 was designed using medicinal chemistry principles of liver-targeting drugs, including transport mechanism properties
- APR003 exhibits a novel mode of action beyond typical TLR7 agonist
- APR003-induced liver-specific efficacy can target both liver primary tumors and metastases
- APR003 displayed a tissue-restricted profile with high exposure in the Gl, liver, and kidney, consistent with transport mechanism