APR003, an oral liver- and GI-targeted TLR7 agonist, elicits a robust type I interferon response in advanced colorectal cancer patients

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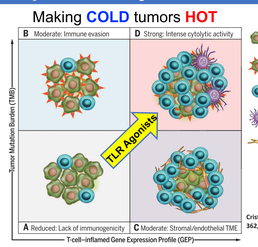
TLR7 Agonists are Complementary to Anti-PD1/PDL1

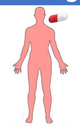
- PD-1/PD-L1 antibodies have limited anti-tumor response likely due to low tumor mutational burden and immune infiltrate
- TLR7 agonists can convert "cold" immune quiescent tumors to "hot" infiltrated tumors – providing a complementary mechanism to checkpoint blockade



- TLR7 functions as a receptor for viral ssRNA; activation elicits IFNα, IP-10 (CXCL10), and other cytokines/chemokines that drive recruitment of T cells
- Level of IP-10 induction by TLR7 agonists has been correlated to anti-tumor efficacy[2]
- Focused activation and decoupling IP-10 from pro-inflammatory IL-6/TNFα responses is predicted to widen the therapeutic window

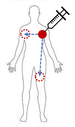
Targeted TLR Agonists Improve Therapeutic Index

Systemic (Oral/I.V.)



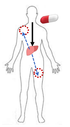
- Non-specific and broad immune activation
- Poor tolerability

Intratumoral (Injection)



- Effective local immune priming of tumor antigens
- Systemic (abscopal) immune
- Clinical Proof-of-Concept achieved with Vidutolimod (CMP-001)
- Limited to cutaneous accessible tumors

GI/Liver-targeted (Oral)



- Oral administration with potential to treat liver and gastrointestinal (GI) tract malignancies and other metastatic tumors via abscopal effect
- Targeted and localized effect with predicted wide therapeutic window

First-In-Class Oral GI/Liver-targeted TLR7 Agonist[1]

- **APR003**: First-in-class orally administered tissue-targeted TLR7 agonist
- **Tissue-Targeting Design:** GI/Liver-targeting via OATP transporters (similar to statins) yielding an increased therapeutic index due to enhanced tissue specificity
- **In Vitro:** selective TLR7 (pDC) over TLR8 (monocyte); active across species
- **PK:** rapid absorption, pulsatile kinetics (weekly administration), high exposure in GI and liver via transporter uptake, low peripheral tissue distribution
- **PD:** robust **IFNα, IP-10** and ***ISG15*** response (desired efficacy correlate), with minimal TNFα, IL-6 (associated with poor tolerability)
- **Efficacy:** preclinical efficacy in multiple orthotopic models of colorectal and liver cancer as single agent and/or in combination with anti-PD1/L1
- **MOA:** increased activated CD103$^+$ DC frequency in GI/Liver draining lymph nodes and tumor-specific infiltrating CD8$^+$ T cells in tumors
- **Toxicity:** no major toxicity identified in non-human primates
- **Clinical Applications:** GI and liver malignancies and potentially other cancers with metastatic disease to the liver

Phase 1a Study Design and Objectives

Study Design

- 3+3 Dose escalation
- Oral administration once weekly in 21-day cycles
- Key Entry Criteria:
  - Unresectable CRC with liver metastases
  - ≥ 2 prior systemic regimens for locally advanced or metastatic disease
  - Must have received irinotecan or oxaliplatin-based therapy, as well as a targeted antibody therapy for metastatic disease
  - MSI-H/dMMR patients must have previously received checkpoint inhibitor therapy

Study Objectives

- Primary – Determine the Maximum Tolerated Dose and/or Recommended Ph2 Dose within the test APR003 dose range
- Secondary – Evaluate antitumor activity
- Exploratory – Assessment of pharmacodynamic biomarkers, including changes in plasma cytokines and interferon-stimulated genes

First-In-Human achieved in Feb 2021 (NCT04645797)

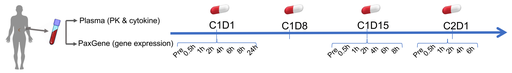
Patient Demographics

	Baseline characteristics		
Dose (mg)	25	50	100
Number of Patients	6	4	1
Mean Age (years)	56	57	52
Gender	4M/2F	4M	1F
MSS status	6 MSS	2 MSS 1 MSI-Low 1 unknown	MSS

Most patients presented with advanced metastatic MSS colorectal cancer, and had progressed on multiple prior lines of therapy

Blood Sampling Schema for PK/PD

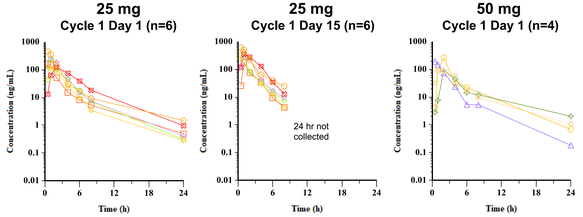
APR003 was administered to patients orally once weekly either at 25 mg or 50 mg in 21-day cycles. Peripheral blood was collected at various time points post-dose on Cycle 1/Day 1 (C1D1), Cycle 1/Day 15 (C1D15), and Cycle 2/Day 1 (C2D1)



Endpoints Analyzed

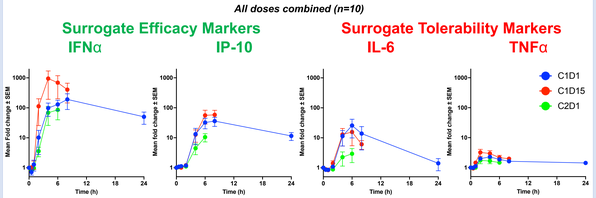
1) Pharmacokinetics: Tmax, Cmax, AUC, T1/2, Vss/F, CL/F
2) Plasma Cytokines (SIMOA®):
   - **IFNα, IP-10** – surrogate efficacy biomarker
   - IFNγ – immune modulation marker associated with anti-tumor response
   - **IL-6, TNFα, IL-1β** – surrogate of poor tolerability biomarker
   - IL-10 – anti-inflammatory, counter regulator for inflammation
3) Gene Expression:
   - ***ISG15*** (*Interferon-stimulated gene 15*) – surrogate efficacy biomarker

APR003 Exhibited a Pulsatile PK Profile



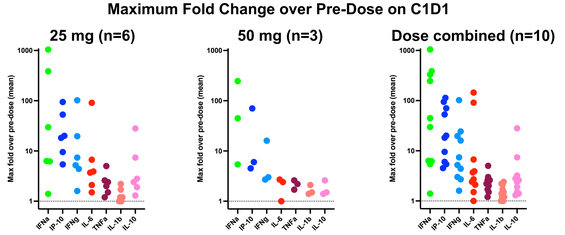
- Rapid oral absorption, Tmax ~1 hour
- Transient exposure, $T_{1/2}$ ~4 hours
- No apparent dose-dependent exposure increase from 25 mg to 50 mg
- No APR003 plasma exposure accumulation or reduction was observed with repeated weekly dosing

APR003 Induced Robust Cytokine Production



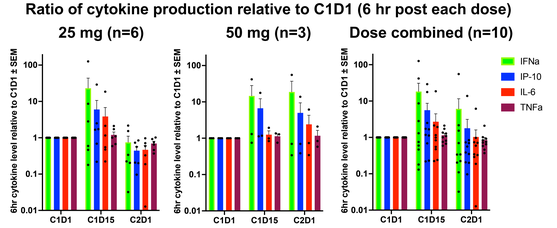
- APR003 induced robust cytokine responses in all patients peaking around 6-8 hours post-dose and declining by 24 hours
- After a week of recovery, all cytokines returned to baseline before the subsequent weekly dose

APR003 Induced Robust IFNα and IP-10 Responses



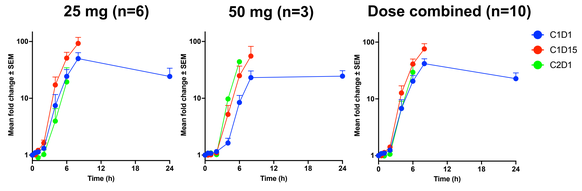
- **IFNα** and **IP-10** (efficacy surrogates) responses were strongly induced in all patients
- IL-6, TNFα, and IL-1β (tolerability surrogates) were mildly induced or induced in less number of patients
- No apparent dose-dependency between 25 and 50 mg doses

Higher IFNα and IP-10 Response on C1D15



- **IFNα** and **IP-10** levels were amplified following the 3rd dose (C1D15) compared to the 1st dose (C1D1)
- Following the 4th dose (C2D1), individual cytokine responses were comparable or slightly diminished relative to the 1st dose (C1D1)

APR003 Induced Robust *ISG15* Response



- ***ISG15*** mRNA, another surrogate of efficacy, was robustly induced by APR003, peaking around 8 hours post dose and declining by 24 hours, consistent with IFNα and IP-10 kinetics
- After a week of recovery, *ISG15* expression returned to baseline before the subsequent weekly dose
- Similar to IFNα and IP-10 responses, *ISG15* expression was higher on C1D15 compared to C1D1

Conclusions

- APR003, a first-in-class oral GI/Liver-targeted TLR7 agonist, was safely administered and rapidly absorbed with a pulsatile PK profile
- APR003 elicited robust **IFNα, IP-10**, and ***ISG15*** responses (surrogate for anti-tumor efficacy), suggesting strong immune priming
- APR003 achieved similar or greater IP-10 responses compared to a reported I.V. administered TLR7/8 agonist that has shown promising anti-tumor responses in combination with anti-PD1[2], and other oral TLR7 agonists that have been investigated in HBV[3,4,5]
- This first-in-human study of APR003 indicates that our tissue-targeted approach may have an increased safety window compared to other (non-targeted) agents of the same class
- Further clinical investigation of APR003 in other GI and Liver malignancies and metastatic disease as a single agent and in combination with checkpoint inhibitor or other complementary therapies is warranted

References

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2. BDB-001: Seven & Eight Biopharma, ASCO 2021
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