PRTX007, an Optimized TLR7 Agonist for Systemic Immunotherapy of Cancers: Interim Analysis of Phase I Study in Healthy Volunteers

Charlotte R. Lemech[1], Christopher Argent[1], Curtis L. Scribner[2], Richard Daniels[3], James R. Appleman[3]

[1]Scientia Clinical Research, LTD, Randwick, NSW, Australia; [2]Curtis L. Scribner, Oakland, CA, USA; [3]Primmune Therapeutics Inc., Carlsbad, CA, USA

8165

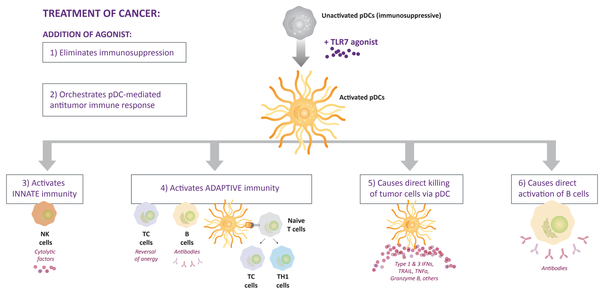
primmune Therapeutics

scientia CLINICAL RESEARCH

Background

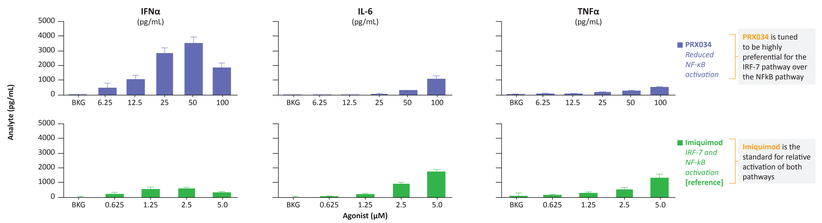
- The TLR7 (toll-like receptor 7) pathway to stimulate innate and adaptive immunity for treatment of cancer and multiple viral diseases, has been well characterized
- Systemically administered TLR7 agonists present a variety of challenges as clinical drug candidates to provide therapeutic benefit
- Primmune Therapeutics has designed and developed an orally administered, systemically distributed TLR7 agonist that elicits a robust, well-tolerated immune response involving activation of plasmacytoid dendritic cells (pDCs) throughout the body[1]; it is expected to also activate pDCs resident in the tumor microenvironment in cancer patients
- PRTX007 (oral prodrug) and the corresponding well-tolerated TLR7 agonist, PRX034, achieve acceptable potency with dose- dependent control of immune induction without driving a pro-inflammatory response

Activation of Plasmacytoid Dendritic Cells (pDCs) by TLR7 Agonists Elicits Effective Anti-tumor Response



IFN=interferon; NK=natural killer; TC=cytotoxic T cell; TH1= Type 1 T helper cells; TLR7=toll-like receptor 7; TNFα=tumor necrosis factor alpha; TRAIL=tumor necrosis factor–related apoptosis-inducing ligand.

PRX034 is Highly Preferential for pDC-mediated Interferon Induction While Minimizing Inflammatory Cytokine Production When Compared to Traditional TLR7 Agonists

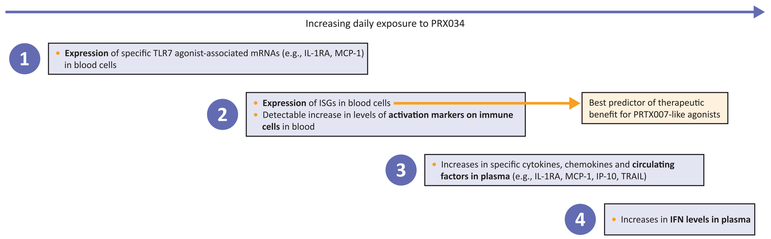


PRX034 is tuned to be highly preferential for the IRF-7 pathway over the NFκB pathway

Imiquimod is the standard for relative activation of both pathways

TLR7-specific agonists elicit biased cellular pharmacology. Human peripheral blood mononuclear cells (hPBMCs) cytokine release profiles of PRX034 (blue bars) and imiquimod (green bars) are shown for 49 donors. hPBMC incubation with agonist was for 24 hours. Error bars are standard error of the mean.

Overview of Pharmacodynamic Markers and Relative Sensitivity to PRTX007 Dose in the Phase 1a Clinical Study

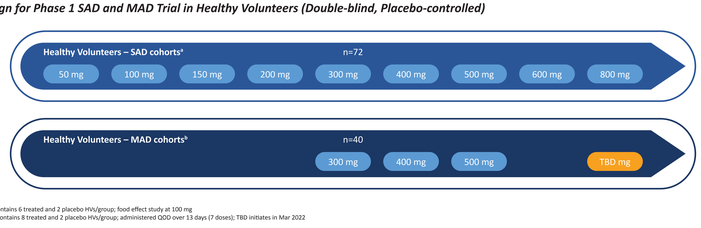


ISG=interferon-stimulated gene

Methods

- This is a first-in-human, phase 1, single-center, prospective, randomized, double-blind, placebo-controlled study of 9 single-ascending dose (SAD) cohorts and 4 multiple-ascending dose (MAD) cohorts of PRTX007 administered orally to adult healthy volunteers (HVs) that is ongoing in Sydney, Australia
  - 500 mg MAD cohort truncated after 5th dose because of COVID
- Primary objective is to assess clinical safety and tolerability of PRTX007 in HVs
- Secondary objectives are to (1) assess the pharmacokinetic (PK) characteristics of both PRTX007 and PRX034, and (2) assess the pharmacodynamic (PD) responses of PRX034 over single and multiple doses in normal HVs

Study Design for Phase 1 SAD and MAD Trial in Healthy Volunteers (Double-blind, Placebo-controlled)



[a]: Each SAD cohort contains 6 treated and 2 placebo HVs/group; food effect study at 100 mg
[b]: Each MAD cohort contains 8 treated and 2 placebo HVs/group; administered QDD over 13 days (7 doses); TBD initiates in Mar 2022

Results

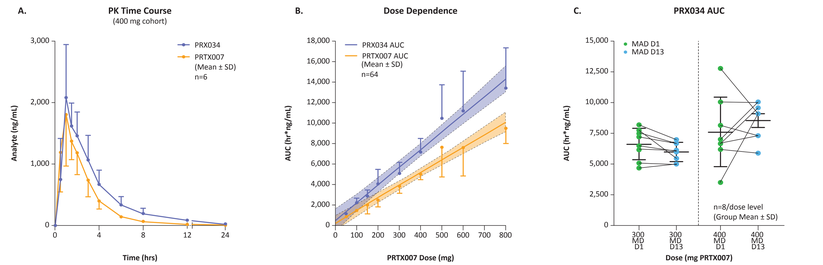
Favorable Safety Profile and Tolerability

Safety and adverse event (AE) data for 102 subjects across nine SAD and three MAD cohorts

- Most AEs are incidental and not dose related. No moderate or severe AEs; no serious AEs (SAEs)
- Most common drug-related AE is headache, which is seen in 11.8% of subjects
  - Mild (9.8%, n=10), Moderate (2.0%, n=2)
  - Transient in nature and resolved either without intervention or with use of OTC meds
  - These occur in both treated and placebo groups (n=10 vs n=20) with no dose dependence
- Elevated ALT noted in two subjects at both the 300 mg MAD and 400 mg MAD dose cohorts
  - Not seen in the 500 mg MAD cohort
  - No associated changes in AST, bilirubin or alkaline phosphatase
  - No stopping or dose modifications required, and ALT levels resolved to within normal range post-dosing
- Three mild to moderate fevers recorded at the 500 mg MAD dose

Well-behaved PK of PRX034 Following Oral Administration of PRTX007

Human pharmacokinetics (SAD cohorts 50-800 mg; MAD cohorts 300-500 mg PRTX007)



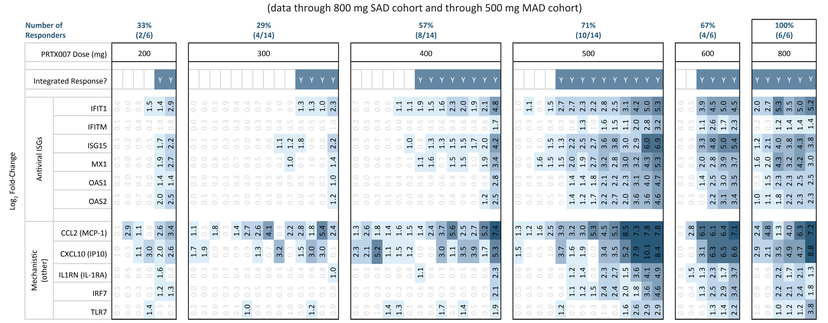
- Rapid absorption and conversion of prodrug PRTX007 to agonist PRX034 following oral administration
- Targeted short duration of pulsatile exposure to PRX034
  - Duration of systemic exposure to PRX034 at pharmacologically active levels is consistent with activation of innate immune response without counter-regulation

- Dose-proportional increase in exposure to prodrug and active agonist
- Agonist/Prodrug AUC~ 1.7 for all subjects

- Exposure unchanged between 1st (D1) and 7th (D13) doses

Induction of IFN-Stimulated Gene Products (ISG) and Other TLR7-Associated Cytokines Without NF-κB-Mediated Inflammatory Cytokines (IL-1β, IL-6, TNFα)

Heat map of selected transcripts demonstrates coordinated response following first dose
(data through 800 mg SAD cohort and through 500 mg MAD cohort)



Values are Log2 $R_{max12hr}$ (Log2 maximal fold-change from pretreatment baseline during 24 hr period following administration of PRTX007).
All HVs receiving PRTX007 in the SAD 200 mg through 800 mg cohorts, and the 300 through 500 mg MAD cohorts (n=60) are shown. Color intensity is as shown in scale.
ISG=interferon-stimulated gene product.

Antiviral ISGs	IFIT1	interferon-induced protein with tetratricopeptide repeats 1
	IFITM	interferon-induced transmembrane protein 1
	ISG15	ISG15 ubiquitin-like modifier
	MX1	MX dynamin like GTPase 1
	OAS1	2'-5'-oligoadenylate synthetase 1
	OAS2	2'-5'-oligoadenylate synthetase 2

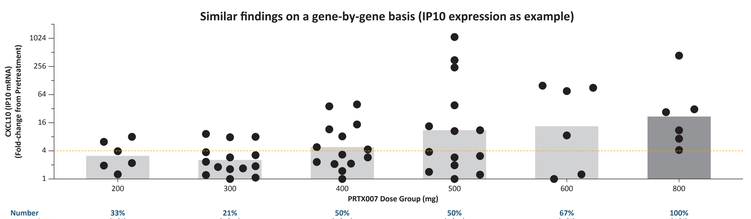
Mechanistic (other)	CCL2 (MCP-1)	C-C motif chemokine ligand 2; MCP-1
	CXCL10 (IP10)	C-X-C motif chemokine ligand 10; IP-10
	IL1RN (IL-1RA)	interleukin 1 receptor antagonist; IL-1RA
	IRF7	interferon regulatory factor 7
	TLR7	toll-like receptor 7

Color Scale

Min	Max	Color
0.0	1.0	
1.0	2.0	
2.0	3.0	
3.0	4.0	
4.0	5.0	
5.0	6.0	
6.0	7.0	
7.0	10.5	

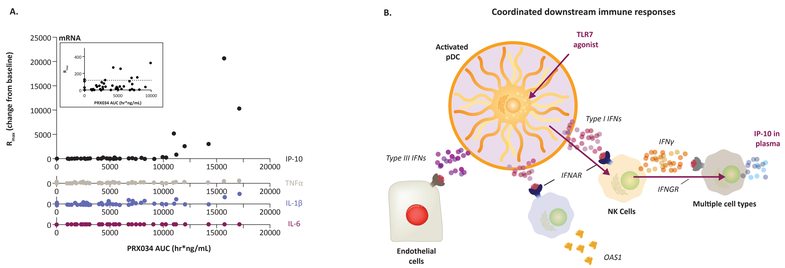
- Pharmacodynamic response increases with dose as measured by:
  - Proportion of HVs responding to first- or single-dose administration
  - Magnitude of induction within responders
- The integrated response rate at 800 mg in the SAD cohort is 100%
- These ISG transcript increases are observed in the absence of a corresponding increase in circulating interferons (data not shown)

Similar findings on a gene-by-gene basis (IP10 expression as example)



*Gold dashed line represents threshold of response for this gene

IP-10 (CXCL10): Breadth of immune induction without induction of NF-κB pathway products

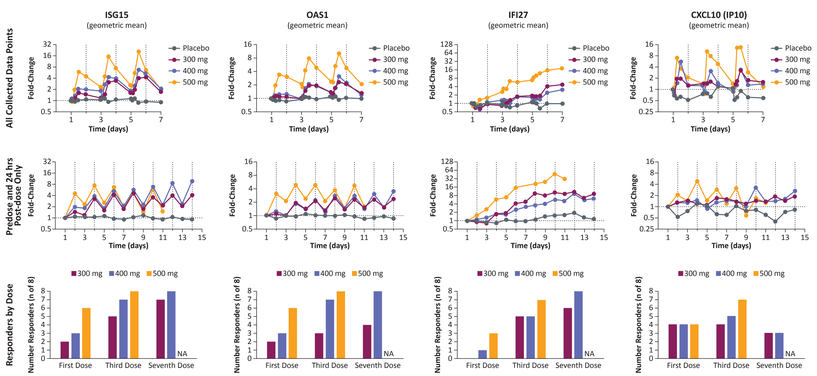


- Increased IP-10 in plasma indicates action through extended cellular network
- Not accompanied by increased inflammatory factors

AUC=area under the plasma drug concentration-time curve; IFNAR=IFN alpha receptor; IFNGR=IFN gamma receptor; IP-10=interferon gamma-induced protein 10; OAS1=2'-5'-oligoadenylate synthetase 1; Rmax=maximum response.
A. mRNA expression of markers after a SAD of PRTX007 at 50 to 600 mg (n = 64; includes placebo-treated HVs). The inset shows that some statistically significant responses (values above dashed line) of lower magnitudes also occur at lower exposures to PRX034. The threshold for significance is set from the placebo group (n = 16) as the geometric mean (GM) of IP10 mRNA + 2*SD of the GM; values above this line represent true responders. **B.** Coordinated downstream immune response.

- Selected circulating markers induced by PRX034 exposure in 50 to 600 mg SAD in HVs
  - IP-10, IL-1RA, monocyte chemoattractant protein 1 (MCP1), and tumor necrosis factor–related apoptosis-inducing ligand (TRAIL) are expressed at high levels in plasma (data not shown for IL-1RA, MCP1, or TRAIL)
  - IP-10 protein levels and mRNA levels increase in response to drug exposure (**A**)
- Increased IP-10 in plasma indicates activation of multiple cell types downstream from activated pDCs (see cell types in, **B**)
- Inflammatory factor production (IL-6, TNFα, IL-1β) is not observed even in the face of this profound immune stimulation (**B**)

When PRTX007 is Administered Repeatedly on a QOD (Every Other Day) Dosing Schedule, the Magnitude of ISG Induction Increases Until a Steady State is Reached



AUC = area under the plasma drug concentration-time curve.

Population pharmacodynamic responses to repeated doses at 300, 400 and 500 mg/dose are shown. Detailed daily kinetics are available following administration of the first three doses (Day 1-6, top row). Sparse kinetics are available on subsequent days (sparse kinetics depicted for D1-14 for 300 and 400 mg dose groups and D1-10 for 500 mg dose group, middle row).

- No induction is observed for classic inflammatory factors IL-6, TNFα and IL-1β (data not shown)
- In general, the magnitude of response increases with each dose until a steady-state is achieved (typically by dose 3-4, see middle row)
  - For ISG15, OAS1 and CXCL10 (IP-10), expression peaks at 12-24 hours followed by a decline until the next dose of PRTX007 is administered (top row)
  - For IFI27 (interferon alpha inducible protein 27), accumulation is observed throughout the entire time course until steady state is achieved (top and middle rows)
- For the classical ISGs (ISG15, OAS1, IFI27), the number of responders (HVs achieving a defined threshold for increase in mRNA level versus baseline) increases with repeated dosing until steady state is achieved (bottom row)
  - For CXCL10 (IP-10) which is not directly linked to type I interferons, this pattern is less obvious (bottom row)

Conclusions & Discussion

- At the interim analysis, PRTX007 demonstrated a favorable safety profile when administered orally to all 9 SAD and 3 MAD cohorts tested
  - No SAEs; lack of AEs historically associated with TLR7 agonists
- Stable systemic immune induction without evidence of counter-regulation is achieved upon QOD dosing
  - Induction of ISGs without significant increases in circulating IFNs
  - No increase in expression or circulating levels of proinflammatory cytokines (eg, TNFα, IL-6, IL-1β)
- Both the clinical characteristics and unique pattern of immune induction by PRTX007 support its use in combination with immune checkpoint inhibitors (ICPIs)
  - Local antitumor activity of intratumorally administered pDC-activating agents in combination with systemic ICPIs is well recognized but overall clinical benefit has been limited
  - We believe the proposed combinations will increase therapeutic benefit in cancer immunotherapy by maintaining sustained, systemic immune pressure involving both innate and adaptive immunity

Reference

1. Appleman JA, et al. Abstract 582: Selection of a novel toll-like receptor 7 (TLR7) agonist PRX034 for immunotherapy of cancer. *Cancer Res*. 2020; 80 (16S): 582.

Disclosures & Acknowledgements

This study was funded by Primmune Therapeutics, Inc.
Medical writing services were provided by SCIENT Healthcare Communications and funded by Primmune Therapeutics, Inc., (Carlsbad, CA).

Presented at AACR Annual Meeting 2022 | April 8–13, 2022 | New Orleans, LA