A phase 1 first-in-human study of PRTH-101, an IgG1 monoclonal antibody targeting DDR1, as a monotherapy and combined with pembrolizumab in patients with advanced solid malignancies

Shiraj Sen[1], Alex Spira[2], David Sommerhalder[3], Funda Meric-Bernstam[4], Vivek Subbiah[4], Jordan D. Berlin[5], Aparna Parikh[6], Michael Cecchini[7], Rachel E. Sanborn[8], Priyanka Chablani[9], George E. Peoples[10], Thomas Schürpf[11], Laura A. Dillon[11], G. Travis Clifton[11], J. Paul Eder[11], Anthony Tolcher[3]

[1]Next Oncology, Dallas, TX, USA; [2]Next Oncology, Alexandria, VA, USA; [3]Next Oncology, San Antonio, TX, USA; [4]MD Anderson Cancer Center, Houston, TX, USA; [5]Vanderbilt University Medical Center, Nashville, TN, USA; [6]Massachusetts General Hospital, Boston, MA, USA; [7]Yale University School of Medicine, New Haven, CT, USA; Earle A. Chiles Research Institute, Providence Cancer Institute, Oregon, USA [9]University of Pittsburgh Medical Center, Pittsburgh, PA, USA; [10]Lumabridge, San Antonio, TX, USA; [11]Incendia Therapeutics, Boston, MA, USA

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Background

- Discoidin domain receptor 1 (DDR1) is a collagen receptor that represents a promising therapeutic target due to its role in excluding lymphocytes from the tumor microenvironment (TME) by aligning collagen fibers (**Figure 1**).
- DDR1 expression is high in multiple cancer types and associated with worse survival. DDR1 activity-driven RNA signatures are associated with poor responses to PD-L1 inhibition. (1)
- PRTH-101 is a humanized IgG1 antibody that binds to the extracellular domain of both membrane-bound and soluble DDR1.
- PRTH-101 inhibits DDR1-collagen interaction, effectively blocks kinase activation of DDR1, and blocks the shedding of the DDR1 extracellular domain (ECD) with high potency (**Figure 2**) (2).
- In preclinical models, PRTH-101 monotherapy resulted in disruption of aligned collagen fibers in the tumor stroma, increased infiltration of lymphocytes, and tumor growth inhibition (3).
- When PRTH-101 is combined with PD-1 inhibition, activated T cell infiltration is increased compared to PRTH-101 alone. These data provide a strong rationale for evaluating PRTH-101 as monotherapy and in combination with PD-1 blockade in multiple indications.

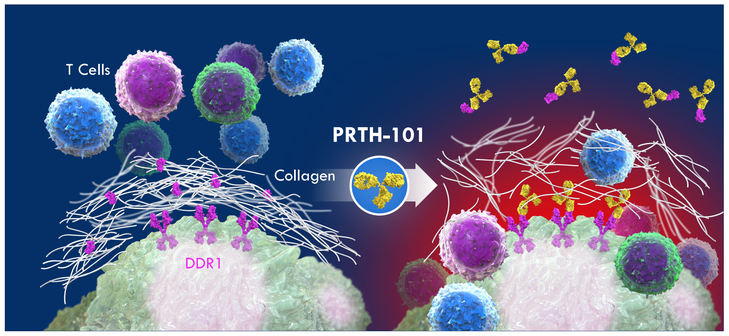

Figure 1. *Schematic of the mechanism of action of PRTH-101.*
DDR1 is expressed on tumor cells. It binds to collagen fibers in the extracellular matrix, resulting in the formation of long, aligned collagen fibers that prevent effective T cell infiltration into the tumor parenchyma. Upon binding by PRTH-101, DDR1 can no longer bind collagen, resulting in disorganized collagen, increased T cell penetration in tumors, and anti-tumor effects.

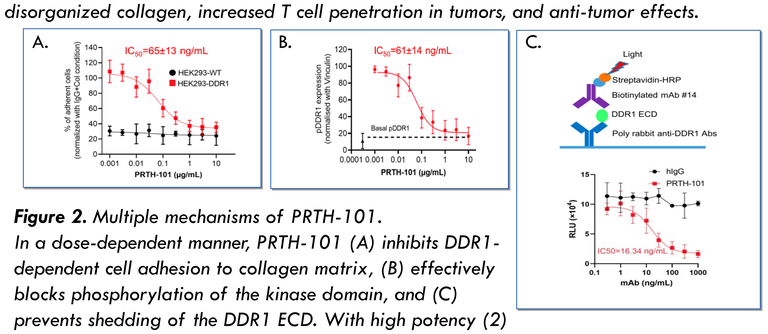

Figure 2. *Multiple mechanisms of PRTH-101.*
In a dose-dependent manner, PRTH-101 (A) inhibits DDR1-dependent cell adhesion to collagen matrix, (B) effectively blocks phosphorylation of the kinase domain, and (C) prevents shedding of the DDR1 ECD. With high potency (2)

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Study Design

- This is a Phase 1, first-in-human study that will evaluate intravenous PRTH-101 +/- pembrolizumab in patients with advanced solid tumors.
- The first part (Ph1a) seeks to identify the maximum tolerated dose (MTD) or optimal biologic dose (OBD), of PRTH-101 to determine the recommended phase 2 dose (RP2D).
- Biomarker backfill cohorts of 10 additional patients each are planned for the two highest monotherapy dose cohorts to aid biomarker correlation with dose and response.
- The second part (Ph1b) seeks to identify the MTD or OBD of PRTH-101 in combination with pembrolizumab to determine the PRTH-101 combination RP2D.
- Both parts will use a Bayesian Optimal Interval (BOIN) design.
- A third part (Ph1c) consists of dose expansion in disease-directed cohorts to assess the anti-tumor efficacy of PRTH-101 monotherapy and/or combination therapy in up to 40 patients per cohort in a Bayesian Optimal Phase 2 design with prespecified stopping boundaries based on objective response rates.

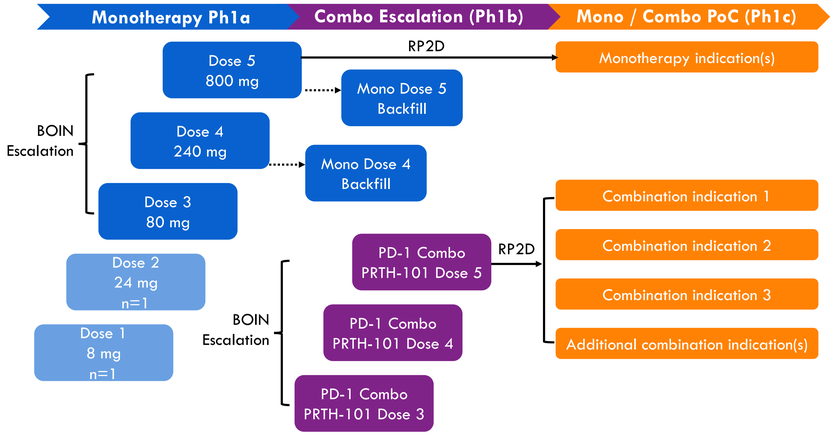

Figure 2 *PRTH-101 first-in-human trial design. BOIN: Bayesian Optimal Interval Design*

Key Eligibility Criteria

All patients:

- Metastatic or advanced, unresectable malignancy and measurable disease per RECIST v1.1, excluding hepatocellular carcinoma, sarcomas, and gliomas.
- Refractory to or intolerable of or the subject is unwilling or ineligible to receive standard treatment known to confer benefit.
- Subject must have a site of disease amenable to and be a candidate for tumor biopsy or have archival tissue available at enrollment.
- Eastern Cooperative Oncology Group performance status (PS) 0-1.

Phase 1b and Phase 1c when receiving combination with pembrolizumab:

- No history of immune-related adverse events to immune CPIs ≥ grade 3, myocarditis grade ≥ 2, or recurrent grade 2 pneumonitis and/or have not discontinued prior therapy with immune CPIs because of adverse reactions.

Primary Endpoints

Phase 1a/b

- To evaluate the safety and tolerability of PRTH-101 with and without pembrolizumab.
- To determine the recommended Phase 2 dose (RP2D) of PRTH-101 with and without pembrolizumab.
- To define the PK profile of PRTH-101 with and without pembrolizumab.

Phase 1c

- To evaluate anti-tumor activity of PRTH-101 as monotherapy and in combination with pembrolizumab in selected indications.
- To evaluate the safety and tolerability of PRTH-101 in combination with pembrolizumab in selected indications.

Biomarker Plan

A robust biomarker plan will inform patient selection for ongoing clinical development. Target occupancy and pharmacodynamic measurements will help inform the RP2D. Tumor, serum, skin, and non-invasive biomarkers will be evaluated as exploratory endpoints (**Table 1**)

* Utilize to guide dose selection	Sample	Analyte	Assay
Patient selection	Tumor	DDR1	IHC, mIF
	Serum	DDR1 sECD	ELISA
Target occupancy	Serum	PRTH-101-bound DDR1 sECD*	ELISA
Signaling pharmacodynamic (PD) effect	Skin	pDDR1*	JESS
Tumor microenvironment (TME) PD effect	Tumor	CD8*	mIF
	Tumor	Immune cell/stroma spatial features	mIF, H&E AI
	Tumor	Collagen orientation*	Polarized light microscopy
	Tumor	Gene expression	RNA-seq
	Serum	Collagen peptides*	ELISA
	Non-invasive	CD8*	CD8 PET/CT

Table 1. *Biomarker plan for PRTH-101 first-in-human clinical trial.*
AI: artificial intelligence; IHC: immunohistochemistry; mIF: multiplex immunofluorescence; pDDR1: phosphorylated DDR1; sECD: soluble extracellular domain

References

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Disclosures

- This trial is sponsored by Incendia Therapeutics.
- Drs. Schürpf, Dillon, Clifton, and Eder are employees of Incendia Therapeutics.