Abstract ID: AB013

A pivotal Phase 2 trial to compare PRTH-101, a monoclonal antibody targeting discoidin domain receptor 1 (DDR1), in combination with an immune checkpoint inhibitor (ICI) to ICI alone, for the treatment of recurrent or metastatic thymic epithelial carcinoma (TEC)

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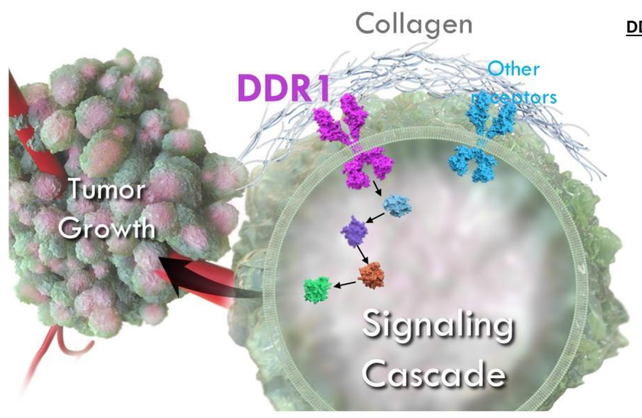
BACKGROUND

PRTH-101 is a humanized monoclonal that binds to the extracellular domain of discoidin domain receptor 1 (DDR1) and blocks its interaction with collagen. DDR1 expression is high in many tumors, including thymic epithelial carcinoma.

PRTH-101 has been studied in a Phase 1, all-comers clinical trial (PRTH-101-0001; NCT05753722). In that trial, patients were treated with PRTH-101 alone or in combination with pembrolizumab. We observed stable disease, two confirmed partial responses (PR), multiple minor RECIST improvements, and improved quality of life in patients across all tumor types.

In thymic tumors, progression-free survival (PFS) of 7.1 months (ongoing) and 1 PR have been observed (please see AB 13). Based on these results, a world-wide registrational trial is planned, to be initiated in 2026, enrolling patients ≥12 years old with recurrent or metastatic thymic epithelial carcinoma (TEC). The trial design has been discussed with FDA, and ex-US Health Authority discussions are planned.

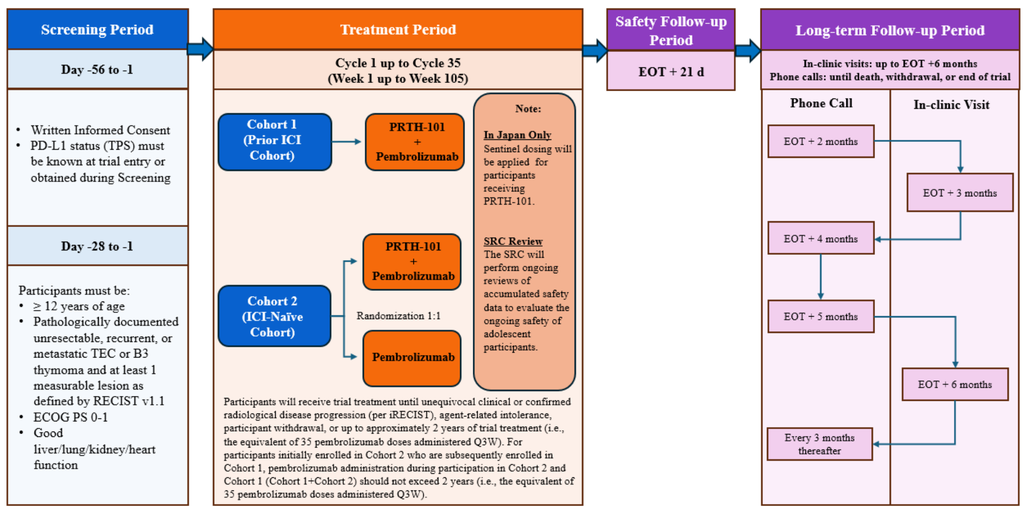


DDR1 role in cancer

- DDR1 is over-expressed in many cancers and fibrosis, and associated with poor survival
- Tumor DDR1 activity is associated with collagen alignment and immune exclusion
- Collagen binding leads to DDR1 receptor clustering, induction of pDDR1, and signaling
- Highly structured collagens are prognostic and predictive in Cancer (Ray *et al.*, Curr. Opin. Cell Biol., 2021; Chen *et al.*, JAMA Netw Open, 2021)
- DDR1 is associated with resistance to PD-L1 inhibitor therapy (Necchi *et al.*, Ann. Onc. 2017; You *et al.*, J. Natl. Cancer Inst. 2022)
- Currently no DDR1 kinase inhibitors in clinical development

STUDY DESIGN and RATIONALE

PRTH-101-2001 Trial Schema



Trial Endpoints

ICI-naïve cohort (n ≅ 88; randomized; stratified by prior pt-based Tx and PD-L1 TPS)
- Primary endpoint: Progression-free survival (PFS) by blinded independent central review (BICR) using RECIST v1.1
- Key secondary endpoints: Overall response rate (ORR) by BICR using RECIST v1.1; OS

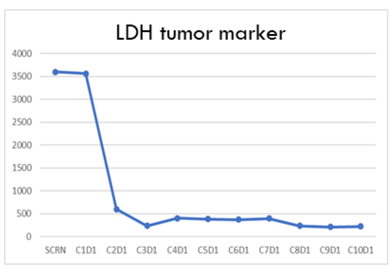
Prior ICI (ICI-refractory) cohort (n ≅ 50; single arm)
- Primary endpoint: ORR by BICR using RECIST v1.1
- Key secondary endpoints: PFS by BICR using RECIST v1.1; OS

Secondary endpoints and objectives
- AEs, clinical laboratory abnormalities, vital signs, and participant-reported symptoms, history and findings
- Further understand population PK of PRTH-101 and effects of co-variates (intrinsic and extrinsic sources of variability) on PK
- Assess the incidence and persistence of ADA, including neutralizing ADA, and the effects of ADA on PK of PRTH-101
- Evaluate pembrolizumab end-of-infusion and pre-dose concentrations in serum

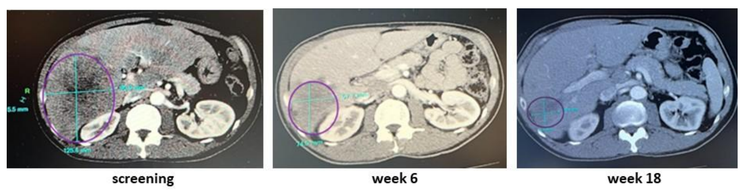
Exploratory objectives and endpoints
- PFS, ORR, and duration of response (DOR) using iRECIST
- O_2 saturation, respiratory rate, heart rate, and Eastern Cooperative Oncology Group Performance Status
- Changes in tumor characteristics (including tumor volume, tumor vascularity, necrosis, and fibrotic changes), from baseline, using standardized imaging criteria
- Change in tumor volume as evaluated by advanced radiological imaging modalities, from baseline
- Change in target lesion avidity, from baseline, by FDG-PET, including but not limited to standardized uptake value $(SUV)_{max}$ and SUV_{mean}
- Change in European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-C30 in participants, from baseline
- Expression of tumor DDR1 at baseline and associate with outcomes

PRTH-101-0001 Trial: Partial Response in thymic epithelial carcinoma: 62-YO male, avid runner, cough and chest tightness, no prior Rx, PD-L1 negative

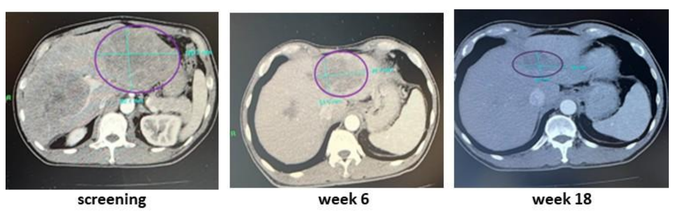
- Explosive tumor growth in 3 months from diagnosis
- 1200 mg PRTH-101 + pembrolizumab
- Has been on study for 8 months
- Normalization of LDH levels
- Publications show that PD-L1-negative thymic cancers do not respond to single-agent pembrolizumab (Giaconne *et al.*, 2017; Cho *et al.*, 2018)



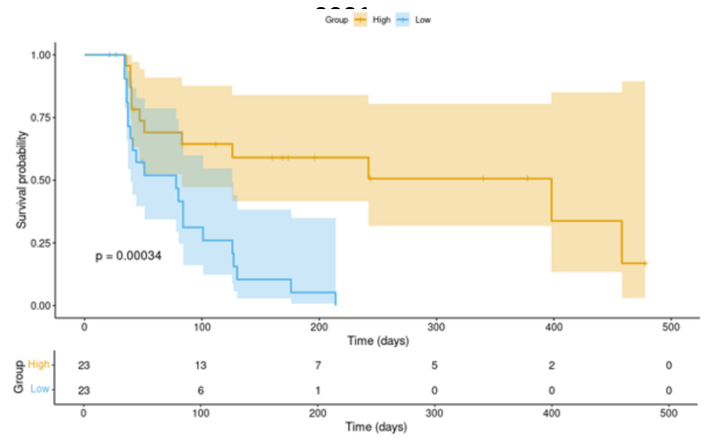
Liver Mass #1



Liver Mass #2



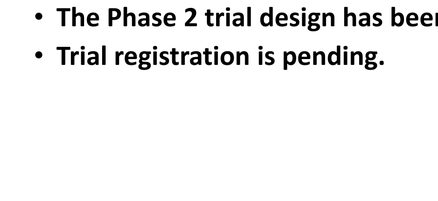
Response to PRTH-101 is correlated with DDR1 expression in PRTH-101-



Baseline DDR1 expression is associated with longer PFS following treatment with PRTH-101, irrespective of co-therapy with pembrolizumab.

Significant reduction in primary tumor and liver metastases (~75% ↓); significant improvements in signs and symptoms

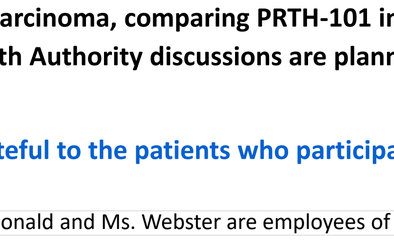
PD-L1 expression correlates with response to pembrolizumab



- Thymic carcinoma
  - 5 (19.2%) PR; 14 (52.8%) SD
  - Median PFS = 6.1 months
- Thymoma
  - 2 (28.6%) PR; 5 (71.6%) SD
  - Median PFS = 6.1 months
- Safety
  - Grade ≥3 irAEs in 71.4% of thymoma patients and 15.4% of thymic carcinoma patients
- Design
  - 26 thymic carcinoma; 7 thymoma; all ICI naive
  - Progression after Pt-based chemotherapy

Cho *et al.*, "Pembrolizumab for Patients With Refractory or Relapsed Thymic Epithelial Tumor: An Open-Label Phase II Trial". Journal of Clinical Oncology, 2019

Response to pembrolizumab in ICI-naïve TEC patients is driven by PD-L1



Patients with low PD-L1 experience progressive disease and shorter survival
- n = 40 patients with TEC, all ICI naïve
- 1 CR (3%); 8 PR (20%); ORR (22.5%)
- Median PFS = 4.2 months
- Median TTR = 6 weeks (6 – 24 weeks)
- Median DOR = 22.4 months from first measurement of response
- SD in 8 (20%) maintained for 6 months

Giaccone *et al.*, Pembrolizumab in patients with thymic carcinoma: a single-arm, single-centre, phase 2 study, Lancet Oncol, 2018

DDR1 is Associated with Resistance to PD-L1 Inhibitor Therapy

- Secondary analyses of DDR1 expression using published data from the IMvigor210 trial (bladder cancer; NCT02108652) were conducted
- Patients with high DDR1 scores who were treated with atezolizumab showed poor overall survival
- DDR1 scores were significantly higher in patients with stable disease or partial disease, compared to patients with complete response for partial response
- DDR1-high patients exhibited a non-T cell-inflamed phenotype
- The data suggest a high DDR1 score may predict lack of response to PD-1/PD-L1-targeted therapy

You, *et al*. J Natl. Cancer Inst. 2022

DISCUSSION

- **PRTH-101 has shown promising results in thymic epithelial tumors, including a partial response and stable disease, and in other tumors in a Phase 1 clinical trial (PRTH-101-0001; please see AB 13).**
  - **Median PFS (ongoing) for TEC patients is 5.7 months (safety dataset) and 7.1 months (event extraction dataset).**
- **PRTH-101 has a novel mechanism of action that may provide a new treatment option for patients with highly fibrotic tumors, such as TEC.**
- **Tumor responses to PRTH-101 and pembrolizumab are correlated with the expression of DDR1, the target of PRTH-101, and PD-L1, respectively.**
- **A world-wide, pivotal Phase 2 trial in recurrent or metastatic thymic carcinoma, comparing PRTH-101 in combination with ICI to ICI alone is planned.**
- **The Phase 2 trial design has been discussed with FDA, and ex-US Health Authority discussions are planned.**
- **Trial registration is pending.**

The Sponsor is grateful to the patients who participated in the Phase 1 trial, and to their families.

Drs. Eder and Macdonald and Ms. Webster are employees of Incendia Therapeutics.

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