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

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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. 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-1 inhibition. PRTH-101 is a humanized IgG1 antibody that binds to the extracellular domain of both membrane-bound and soluble DDR1. 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. 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.

Methods

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 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 dose cohorts to aid biomarker correlation with dose and response. The second part 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 design. A third part 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. Safety, efficacy, pharmacokinetic, and pharmacodynamic endpoints will be monitored and reported. DDR1 expression levels on tumors, circulating DDR1, molecular and cellular changes in the TME, and changes on CD8 PET imaging will also be assessed.