TPS8667 **Poster Session**

A phase 2 safety and efficacy study of PRT3789 in combination with pembrolizumab in patients with advanced or metastatic solid tumors and a *SMARCA4* mutation.

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Background: Genes encoding subunits of the switch/sucrose non-fermentable (SWI/SNF) chromatin remodeling complex are often mutated in cancer (~20% of all human cancers). The SWI/SNF complex contains either SMARCA2 or SMARCA4 enzymatic subunits for ATP-dependent chromatin remodeling. Since SMARCA2 and SMARCA4 function as mutually exclusive catalytic subunits of the SWI/SNF complex, cells exhibiting SMARCA4 loss rely on its paralog, SMARCA2, making SMARCA2 an attractive therapeutic target. In NSCLC, *SMARCA4* mutations are associated with aggressive and invasive disease. PRT3789 has been shown to increase antigen processing and presentation of unique MHC class I peptides, and increase T-cell activity and IFN-γ production in *SMARCA4*-mutated cancer cells. SMARCA2 degradation by PRT3789 promoted the effects of anti-PD1 therapy in SMARCA4-deficient mouse models, and PRT3789 combined with pembrolizumab (pembro), a humanized immunoglobulin G4 monoclonal antibody, promoted cell death of SMARCA4-deficient NSCLC cells. While inhibitors targeting the PD-1/PD-L1 axis have shown remarkable clinical activity across a broad range of tumor types, some patients demonstrate an inadequate response and disease progression consistent with the natural disease course that may be tied to innate resistance mechanisms. Other patients progressed after a period of disease control, which may be associated with acquired resistance mechanisms. PRT3789 + pembro may re-sensitize resistant cancers to subsequent anti–PD(L)-1 therapy. **Methods:** This is an open-label, 2-part, multicenter study to evaluate the safety, tolerability, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of PRT3789 + pembro in patients who are resistant to prior anti–PD(L)-1 therapy. Adults with any advanced, recurrent, or metastatic solid tumor and any *SMARCA4* mutation are eligible to enroll into part 1, a safety run-in to establish the initial safety of PRT3789 376 mg intravenous (IV) once weekly + pembro 200 mg IV every 3 weeks. Part 2 will target adults with advanced, recurrent, metastatic NSCLC or upper gastrointestinal cancer with a *SMARCA4* loss-of-function mutation. Other key eligibility criteria include documented prior or acquired resistance to anti–PD(L)-1 therapy, or received prior standard-of-care therapy, but naive to anti–PD(L)-1 therapy due to PD-L1 negative expression. A safety review committee will evaluate dose-limiting toxicities (DLTs) in part 1 and advise on opening part 2 and regularly review accumulated safety data during the study. The primary endpoints are safety, tolerability, and incidence of DLTs in part 1, and overall response rate and duration of response in part 2. Secondary endpoints include progression-free survival, clinical benefit rate, PK, and PD of PRT3789. This study is actively recruiting. Clinical trial information: NCT06682806. Research Sponsor: Prelude Therapeutics Incorporated.