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Preliminary efficacy, safety, and immunomodulatory effects of PT-112 from a phase 2 proof of concept study in patients (pts) with thymic epithelial tumors (TETs).

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Background: Immune checkpoint inhibitors (ICIs) are associated with a high risk of immune-related adverse events (irAEs) in pts with TETs (thymoma and thymic carcinoma). PT-112, a novel inducer of immunogenic cell death, has demonstrated safety and efficacy in phase I trials. We present results of an unplanned interim analysis of a phase 2, NIH IRB-approved clinical trial to evaluate the clinical activity, tolerability, and correlative immunology of PT-112 in TETs (NCT05104736). **Methods:** Eligible pts with TETs with progression after prior platinum therapy were treated with PT-112 360 mg/m^2 iv on days 1, 8 and 15 of a 28-day cycle until progression or development of intolerable toxicity. Prior history of autoimmunity (AI) or treatment with ICI was permitted. Primary objective is to determine the objective response rate. Immune activation was assessed by flow cytometry and multiplex immunofluorescence. **Results:** Ten pts have received treatment (median age 54, 3 females, 5 thymic carcinomas, 3 with prior TET-associated AI disease). Median number of prior systemic therapies is 2.5 (range, 1-4) and all pts have received cisplatin, paclitaxel, or both previously. Nine pts are evaluable for response, with stable disease in 8 (89%) and progressive disease in 1 (11%) pt. After a median potential follow-up of 7.4 months (mo) median progression-free survival is not reached in pts with thymoma and is 6.2 mo (95% CI: 1.8- 7.9 mo) in thymic carcinoma. All pts are evaluable for toxicity. The most common (all grades) treatment-related adverse events (TRAEs) are peripheral neuropathy (60%), anemia, fatigue and myalgias (each in 50%). Grade $\geq$ 3 TRAEs in more than one patient include anemia (30%) and neutropenia (20%). Two (20%) pts experienced relapse of AI: ocular myasthenia and immune cytopenias. The most common reason for treatment hold is peripheral neuropathy (40%). Treatment was discontinued due to TRAE (peripheral neuropathy) in 1 (10%) pt. There are no treatment related deaths. Treatment was associated with an increase in CD8+ T cells, activated CD4+ T cells and NK cells in peripheral blood. There was an increase in pro-inflammatory serum analytes (IFNg, TNFa, sCD27:sCD40L and sCD73) and a decrease in immunosuppressive analytes (VEGF, sCD40L and TGFb) compared with baseline. Paired tumor biopsies are being analyzed by multiplex immunofluorescence and results will be presented. **Conclusions:** PT-112 is safe and clinically active in pts with recurrent TETs. In contrast to ICIs, no new irAEs were observed. Immune analyses show evidence of early treatment-related immune activation and support the rationale underlying this novel treatment approach for TETs. Enrollment is ongoing with an accrual ceiling of 53. These initial results support further evaluation of PT-112 in TETs as monotherapy and in combination with other immunomodulatory interventions. Clinical trial information: NCT05104736. Research Sponsor: U.S. National Institutes of Health; This research was supported in part by the Intramural Research Program of the Center for Cancer Research, National Cancer Institute (NCI), National Institutes of Health, and via a Cooperative Research and Development Agreement (CRADA) between the NCI and Promontory Therapeutics Inc.