A Phase 2 study of immunogenic cell death inducer PT-112 in metastatic castration-resistant prostate cancer patients

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Abstract TPS292

Background and Rationale

- PT-112 is a novel immunogenic small molecule currently in development for several cancers.
- PT-112 causes cancer cell organelle stress and induces immunogenic cell death, leading to an anti-cancer adaptive immune response across *in vitro* and *in vivo* human and murine models[1-3].
- PT-112 has demonstrated osteotropism in biodistribution experiments in mice[4].
- Preliminary evidence of safety, efficacy, and clinical benefit in mCRPC was seen in monotherapy and in combination with anti-PD-L1 in two prior dose escalation trials with PT-112[5-8].
- Together, this evidence represents the opportunity and strong rationale to further explore PT-112 in mCRPC, an immunologically "cold" disease to checkpoint inhibition, with a high prevalence of bone metastases[9].

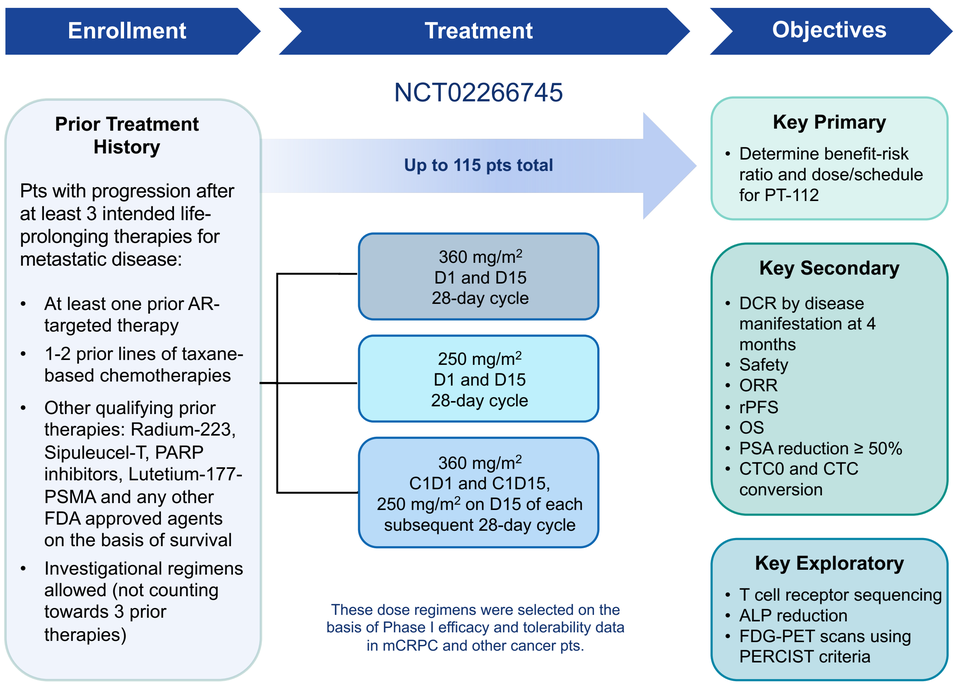
Aims

- To characterize the risk/benefit ratio and select the optimal dose and schedule of PT-112 in line with FDA's Project Optimus.
- To assess the efficacy of PT-112 with respect to clinical, radiographic, PSA, and circulating tumor cell (CTC) responses.
- To utilize blood-based T cell receptor sequencing for elucidating the underlying immune mechanism of PT-112 in humans.

Trial Progress

As of February 1, 2023, 41 patients (pts) have been enrolled.

Trial Design



These dose regimens were selected on the basis of Phase I efficacy and tolerability data in mCRPC and other cancer pts.

Statistical Analysis

Benefit-risk ratio of each dosing arm will be judged in part by comparative safety assessments and a Fleming Two-Stage design for assessing disease control at 4 months.

Correlative Research

This trial incorporates advanced correlative research programs to:

- Assess CTC changes as an efficacy measure
- Investigate immunogenicity in humans
- Understand the above with respect to selection of a dose regimen

Circulating Tumor Cell Monitoring

In an analysis of > 6,000 mCRPC pts, CTC declines (CTC0 and CTC conversions) were correlated with improvements in survival to a greater extent than PSA declines (PSA_{50})[10], prompting incorporation of CTC changes as a secondary endpoint. The use of Epic's next-generation platform also allows for CTC subtyping (*e.g.* AR+, small cell).

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T Cell Receptor Sequencing

Higher baseline T cell fractions in the blood have been associated with longer OS[11] and PFS[12] in clinical studies using checkpoint inhibitors, prompting incorporation of the T cell receptor sequencing platform immunoSEQ® as an exploratory objective. This technology allows for monitoring of T cell fraction as well as changes in immune cell populations in response to treatment. Treatment-induced changes in the T cell repertoire may provide supportive clinical evidence of ICD induction by PT-112.

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Significance

Effective and durable therapeutic options for mCRPC pts are still limited. Prior nonclinical and clinical data suggest PT-112 may be a promising option for these pts, due to its immunogenicity and osteotropism. This is a proof-of-concept study with the goal of optimizing the dosing regimen of PT-112. Extensive biomarker analyses were incorporated to generate meaningful evidence on efficacy and elucidate PT-112's immunogenicity in humans.

References

1. Yamazaki T, Buqué A, Ames TD, et al: PT-112 induces immunogenic cell death and synergizes with immune checkpoint blockers in mouse tumor models. OncoImmunology 9:1721810, 2020
2. Soler R, Ames T, Marco Brualla J, et al: PT-112, a first-in-class pyrophosphate-platinum conjugate, selectively targets highly glycolytic tumor cells. European Journal of Cancer 138:S53–S54, 2020
3. Soler-Agesta R, Ames TD, Price M, et al: Abstract 1115: PT-112 induces potent mitochondrial stress and immunogenic cell death in human prostate cancer cell lines. Cancer Research 82:1115, 2022
4. Ames TD, Sharik ME, Rather GM, et al: Translational Research of PT-112, a Clinical Agent in Advanced Phase I Development: Evident Bone Tropism, Synergy In Vitro with Bortezomib and Lenalidomide , and Potent Efficacy in the Vk*MYC Mouse Model of Multiple Myeloma. Blood 130:1797–1797, 2017
5. Karp DD, Dronca RS, Camidge R, et al: 1026MO Phase Ib dose escalation study of novel immunogenic cell death (ICD) inducer PT-112 plus PD-L1 inhibitor avelumab in solid tumours. Annals of Oncology 31:S708, 2020
6. Bryce AH, Dronca RS, Costello BA, et al: PT-112 in advanced metastatic castrate-resistant prostate cancer (mCRPC), as monotherapy or in combination with PD-L1 inhibitor avelumab: Findings from two phase I studies. JCO 38:83–83, 2020
7. Bryce AH, Dronca RS, Costello BA, et al: A phase 1b study of novel immunogenic cell death inducer PT-112 plus PD-L1 inhibitor avelumab in metastatic castrate-resistant prostate cancer (mCRPC) patients. JCO 39:e17025–e17025, 2021
8. Karp DD, Camidge DR, Infante JR, et al: Phase I study of PT-112, a novel pyrophosphate-platinum immunogenic cell death inducer, in advanced solid tumours. eClinicalMedicine 49:101430, 2022
9. Vitkin N, Nersesian S, Siemens DR, et al: The Tumor Immune Contexture of Prostate Cancer. Front Immunol 10:603, 2019
10. Heller G, McCormack R, Kheoh T, et al: Circulating Tumor Cell Number as a Response Measure of Prolonged Survival for Metastatic Castration-Resistant Prostate Cancer: A Comparison With Prostate-Specific Antigen Across Five Randomized Phase III Clinical Trials. JCO 36:572–580, 2017
11. Reuben A, Zhang J, Chiou S-H, et al: Comprehensive T cell repertoire characterization of non-small cell lung cancer. Nat Commun 11:603, 2020
12. Pruessmann W, Rytlewski J, Wilmott J, et al: Molecular analysis of primary melanoma T cells identifies patients at risk for metastatic recurrence. Nat Cancer 1:197–209, 2020

Study Population

Key Inclusion Criteria	Key Exclusion Criteria
• Histologically or cytologically confirmed adenocarcinoma of the prostate. • mCRPC, where metastatic status is defined as having documented metastatic lesion(s) on either bone scan or CT/MRI scan. • Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-1. • Progressive disease, either measurable on physical examination or imaging by Response Evaluation Criteria in Solid Tumors (RECIST v1.1), Prostate Cancer Working Group 3 (PCWG3) or by informative tumor marker(s). • Adequate organ function based on laboratory values. • If there is a known history of brain metastases, either treated or untreated, that site of disease must be stable.	• Any cytotoxic chemotherapy within 21 days prior to initiation of study drug. • Any immunomodulatory drug therapy, anti-neoplastic hormonal therapy, immunosuppressive therapy, corticosteroids, or growth factor treatment within 14 days prior to initiation of study drug. • Bone marrow reserve which is not adequate for participation in this trial. • Radiotherapy within 28 days prior to baseline. • Fraction of radiotherapy to > 25% of bone marrow. • Major surgery within 28 days prior to initiation of study drug.

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