Abstract #83

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

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Introduction

Background: PT-112, the first pyrophosphate conjugate in Phase I/II clinical development, induces robust immunogenic cell death and is osteotropic, prompting study in mCRPC during Phase I. We report safety and efficacy findings in the mCRPC sub-population given PT-112 monotherapy (NCT02266745) or in combination with avelumab ("PAVE") (NCT03409458, ongoing).

Methods: Patients (pts) received PT-112 days 1, 8, 15 of a 28d cycle; pts on the PAVE combination also received 800 mg avelumab days 1 and 15; all enrolled during dose escalation or at PT-112 doses previously deemed safe. Pts on therapy (Tx) for ≥2 cycles or who stopped Tx due to progressive disease or treatment-related adverse events (TRAEs) were evaluated for exploratory efficacy. Additionally, an investigator-assessed retrospective analysis of survival among PT-112 monotherapy patients was conducted.

Results: Results cited in abstract #83 are shown here in tables and figures. Additionally, retrospective analysis for PT-112 monotherapy patients assessed median survival of 15.1 months from study entry.

Figure 1: PT-112 Chemical Structure

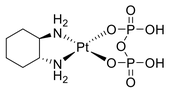


Table 1: Demographics

	PT-112 Monotherapy	PT-112 + Avelumab
Total Number of Patients	10	18
Median Age (Range), Years	70 (56-83)	69 (54-87)
Ethnicity		
Caucasian	9	15
African American	1	3
ECOG PS		
0	2	2
1	8	16
Site of Disease		
Lung	1	6
Liver	2	2
Lymph Node	5	13
Bone	8	16
Number of Disease Sites		
Single	5	4
Multiple	5	14
Median PSA at Baseline (Range), ng/mL	110 (9.7-299)	166.4 (0.1-2114)
Anemia at Baseline		
Grade 1	8	15
Grade 2	1	2
Median Prior Lines of Systemic Therapy (Range)	6.5 (2-13)	6 (2-12)

Table 2: Treatment-Related AEs

	PT-112 Monotherapy (200-420 mg/m²)					PT-112 (150-200 mg/m²) + Avelumab				
	G1	G2	G3	G4	All (%)	G1	G2	G3	G4	All (%)
Bone Marrow Toxicities										
Anemia	---	2	1	---	3 (30)	---	2	3	---	5 (28)
Leukopenia	---	---	1	---	1 (10)	1	---	1	---	2 (11)
Neutropenia	---	---	3	---	3 (30)	---	1	1	---	2 (11)
Thrombocytopenia	3	1	3	---	7 (70)	2	---	1	2	5 (28)
Constitutional Toxicities										
Chills	---	---	---	---	---	3	---	---	---	3 (17)
Dehydration	---	---	---	---	---	---	---	1	---	1 (6)
Fatigue	1	3	---	---	4 (40)	2	5	---	---	7 (39)
Gastrointestinal Disorders										
Diarrhea	---	---	---	---	---	3	---	1	---	4 (22)
Nausea	1	1	---	---	2 (20)	5	4	---	---	9 (50)
Vomiting	2	1	---	---	3 (30)	1	2	---	---	3 (17)
Investigations										
Amylase increased	---	---	---	---	---	1	1	---	---	2 (11)
Creatinine increased	---	---	---	---	---	2	---	---	---	2 (11)
Hypocalcemia	---	---	1	---	1 (10)	---	---	---	---	---
Hypokalemia	---	---	---	---	---	1	---	1	---	2 (11)
Hypomagnesemia	1	---	---	---	1 (10)	1	---	---	---	1 (6)
Hyponatremia	---	---	---	---	---	---	---	---	1	1 (6)
Hypophosphatemia	---	---	---	---	---	---	---	1	---	1 (6)
Metabolism & Nutrition Disorders										
Anorexia	2	---	---	---	2 (20)	3	4	1	---	8 (44)
Weight loss	---	1	---	---	1 (10)	1	---	---	---	1 (6)
Neurological Disorders										
Dizziness	1	1	---	---	2 (20)	1	---	---	---	1 (6)
Headache	---	---	---	---	---	2	---	---	---	2 (11)
Peripheral neuropathy	2	---	---	---	2 (20)	2	1	2	---	5 (28)
Tremor	1	---	---	---	1 (10)	1	---	---	---	1 (6)
Renal & Urinary Disorders										
Acute Kidney Injury	---	---	---	---	---	---	---	1	---	1 (6)
Resp., Thoracic & Mediastinal Disorders										
Bilateral Vocal Cord Paralysis	---	---	---	---	---	---	---	1	---	1 (6)
Dyspnea	---	---	---	---	---	---	1	1	---	2 (11)
Respiratory Depression	---	---	---	---	---	---	---	1	---	1 (6)
Skin & Subcutaneous Tissue Disorders										
Dyschromia	---	---	---	---	---	1	2	---	---	3 (17)

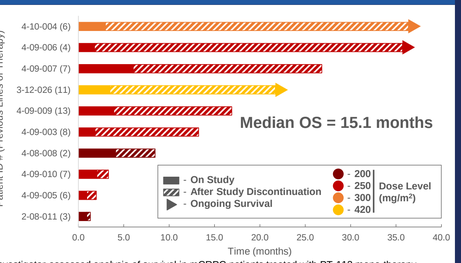
Note: No grade 5 TRAEs occurred. AEs < grade 3 occurring in a single patient across both studies were not included.

Table 3: Exploratory Efficacy Parameters

	PT-112 Monotherapy	PT-112 + Avelumab
RECIST		
# of Patients with Reduction	2/7	2/9
# of Patients with ≥30% Reduction	1/7	1/9
PSA		
# of Patients with Reduction	3/10	7/14
# of Patients with ≥50% Reduction	1/10	4/14
Alkaline Phosphatase (ALP)		
# of Patients with Reduction	9/10	15/16
PFS		
# of Patients with ≥4 months	3/10	9/17
# of Patients with ≥6 months	1/10	4/17
Median (Range), months	2.6 (0.9-6.1)	4.0 (0-11.3)

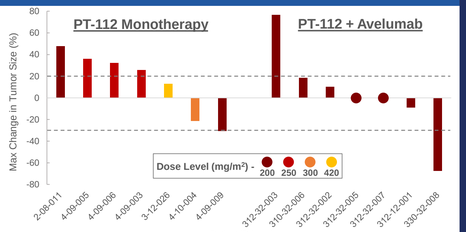
Notes: PFS values are lower bound estimates, due to cases of ongoing PFS and patients leaving study for reasons other than PD and lacking follow-up information. 1 patient was not included in the PFS analysis due to leaving the study after <2 cycles and for reasons other than PD or TRAEs. Patients were eligible for RECIST, PSA, and ALP analysis if they had both baseline and ≥1 follow-up measurement. Only patients with measurable disease were candidates for RECIST analysis.

Figure 2: Survival on Monotherapy



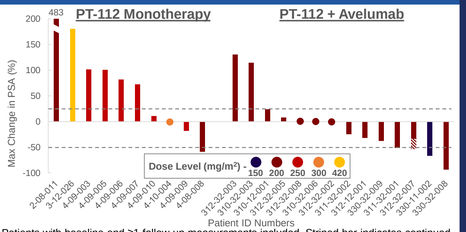
Investigator-assessed analysis of survival in mCRPC patients treated with PT-112 mono-therapy

Figure 3: Change in Tumor Size by RECIST



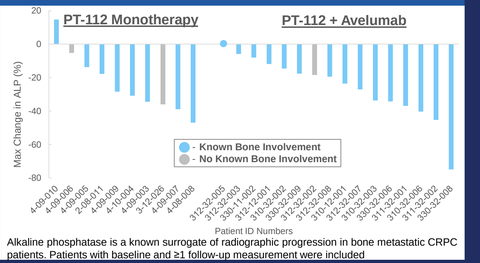
Patients with measurable disease, in addition to baseline and ≥1 follow-up measurements included

Figure 4: Change in PSA



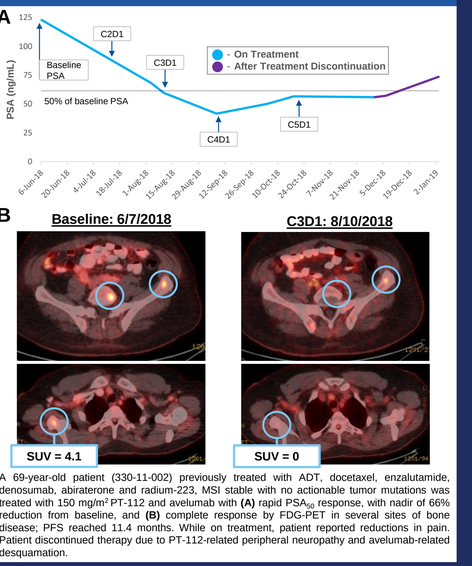
Patients with baseline and ≥1 follow-up measurements included. Striped bar indicates continued PSA decline in a patient after progressing on the basis of medical imaging (mixed response).

Figure 5: Change in Alkaline Phosphatase



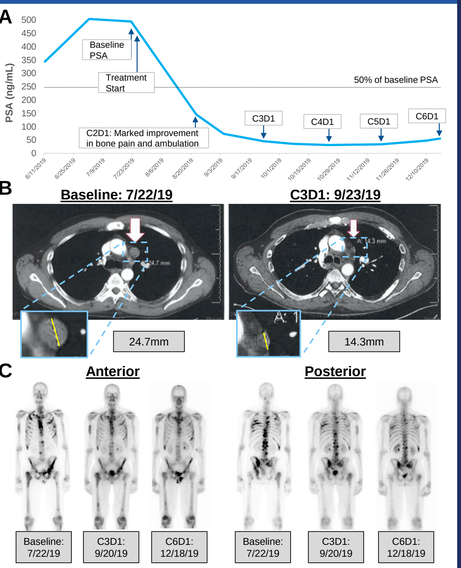
Alkaline phosphatase is a known surrogate of radiographic progression in bone metastatic CRPC patients. Patients with baseline and ≥1 follow-up measurement were included

Figure 6: PAVE Durable Responder, 150mg/m²



A 69-year-old patient (330-11-002) previously treated with ADT, docetaxel, enzalutamide, denosumab, abiraterone and radium-223, MSI stable with no actionable tumor mutations was treated with 150 mg/m² PT-112 and avelumab with **(A)** rapid PSA_{50} response, with nadir of 66% reduction from baseline, and **(B)** complete response by FDG-PET in several sites of bone disease; PFS reached 11.4 months. While on treatment, patient reported reductions in pain. Patient discontinued therapy due to PT-112-related peripheral neuropathy and avelumab-related desquamation.

Figure 7: PAVE Ongoing Responder, 200mg/m²



A 60 year old pt (330-32-008) previously treated with ADT, docetaxel, abiraterone, apalutamide, ipilimumab, radium-223, and copanlisib, with PIKCBmut and PTEN loss, was treated with 200 mg/m² PT-112 and avelumab with **(A)** rapid PSA_{50} response, with nadir of 94% reduction from baseline; **(B)** RECIST PR, with 68% reduction from baseline; and **(C)** an acute reduction in bone scan signal at multiple metastatic sites. PFS is ongoing at 6.5 months. The patient remains on study.

Conclusions

PT-112 was well-tolerated with evidence of efficacy in mCRPC as mono-Tx and in combination with avelumab in heavily pre-treated pts. Bone pain improvement and nearly universal observation of ALP reduction suggest marked therapeutic activity of PT-112 in bone metastases. While limited in number, the monotherapy cohort had evidence of unexpected, prolonged overall survival. Serologic, RECIST and clinical responses, as well as prolonged disease control in multiple pts substantiate further development of PT-112 in mCRPC.

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