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Phase 1b Dose Escalation Study of Novel Immunogenic Cell Death (ICD) Inducer PT-112 Plus PD-L1 Inhibitor Avelumab in Solid Tumors

(NCT 03409458)

Abstract 1026MO:

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DISCLOSURE INFORMATION

Scientific advisory board: Phosplatin Therapeutics

Consultant: Black Beret Life Sciences and the Bosarge Foundation

Research funding: United States National Institutes of Health (NIH) Cancer Center Support Grant (CCSG); National Center for Accelerating Translational Sciences (NCATS) Clinical Translational Science Award (CTSA) Grant, Co-Principal Investigator

Sponsor research funding including: Merck & Co. (MSD), Eli Lilly, AstraZeneca, Pfizer, Novartis

Royalties: Wolters Kluwer N.V. publishing

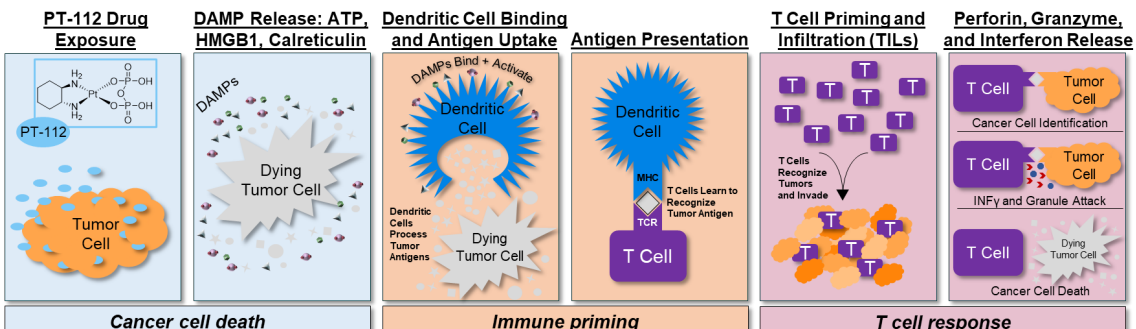
Study sponsored by Phosplatin Therapeutics (New York, NY USA)

PT-112: The first pyrophosphate-platinum conjugate, and potent immunogenic cell death (ICD) inducer

PT-112 mechanism of action / pharmacology:

- DNA damage not primary mechanism / not subject to DNA-repair drug resistance (AACR 2016 / 17)
- Release of damage associated molecular patterns (DAMPs) and immunogenic cell death (ICD) induction (*OncoImmunology* 2020)
- Recruitment of tumor infiltrating lymphocytes (TILs) and synergy with anti-PD-(L)1 (*OncoImmunology* 2020)
- Promotion of bone uptake (osteotropism) via pyrophosphate moiety (ASH 2017)

Immunogenic cell death (ICD)



Source: TDA, DDK

PT-112 clinical background:

- Monotherapy Phase I: well-tolerated in advanced, heavily pre-treated solid tumor patients (N=66)
- No renal damage, no hair loss, low rates of myelosuppression and neurotoxicity
- Single-agent RECIST responses in lung cancers and thymoma, strong signal in prostate cancer (ESMO 2018)

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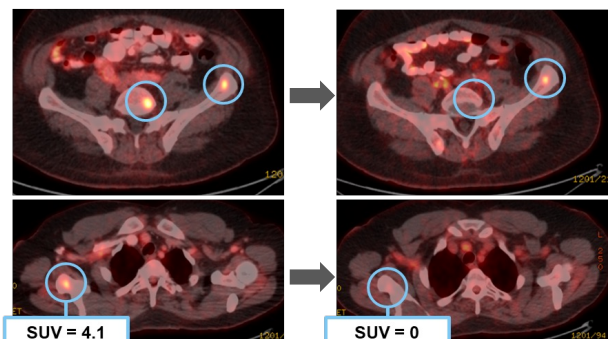
PT-112 dose escalation with fixed-dose avelumab ("PAVE")

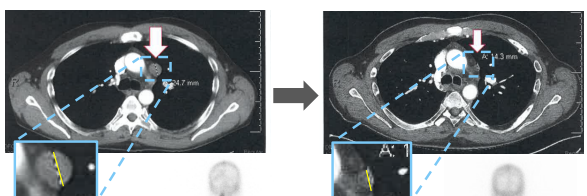
Examples of benefit in two surviving metastatic castration-resistant prostate cancer (mCRPC) patients

PET Baseline (6/06/2018) C3D1

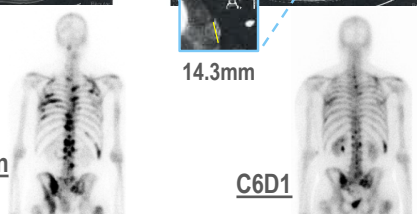


Patient 1: 69-yo male, bone only disease (MSI stable)	
Number of Prior Therapies	7
PT-112 Dose Level	150 mg/m^2
Response	FDG-PET improvement
PSA Reduction	66%
Alk-Phos Reduction	8%
PFS	11.4 months

CT Baseline (6/30/2019) C3D1



Bone scan baseline C6D1



Patient 2: 60-yo male, visceral mets, severe bone pain (PTEN loss)	
Number of Prior Therapies	8
PT-112 Dose Level	200 mg/m^2
RECIST Response	Confirmed PR
PSA Reduction	94%
Alk-Phos Reduction	75%
PFS	8.4 months

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PAVE Study Design and Patient Demographics

Protocol Design

3+3 design to determine combination recommended phase 2 dose (RP2D)

Escalating PT-112, 28-day cycle (IV d1, 8, 15)
Fixed-dose avelumab 800mg (IV d1, 15)

Progressing solid tumor patients who exhausted available therapy; no limit on number of prior treatments

Supplemental enrollment at 200 mg/m^2 PT-112 during escalation for mCRPC patients

Phase 2 dose confirmation to follow on the open protocol

Patient Demographics / Prior Treatment History

	Dose Escalation (n=21)	mCRPC Supplemental (n=15)
PT-112 Dose Levels	150 – 360 mg/m^2	200 mg/m^2
Median Age (Range), Years	62 (48-78)	70 (54-87)
ECOG PS		
0	6	2
1	15	13
Tumor Types		
Breast cancer	4	0
Castration-resistant prostate cancer	3	15
Non-small cell lung cancer	7	0
Sq. cell carcinoma, head and neck	1	0
Urothelial carcinoma	6	0
Prior Systemic Therapy		
Lines of Therapy (Tx) (Range)	4 (1-7)	6 (2-12)
Immune checkpoint Tx, N (%)	14 (67)	9 (60)
Platinum-containing Tx, N (%)	16 (76)	3 (20)
Prior Radiotherapy (%)	17 (81)	9 (60)

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Safety: PT-112 plus avelumab was well tolerated with no DLTs in heavily pre-treated patients

Treatment-Related Adverse Events (TRAEs) occurring in ≥10% of patients

	360 mg/m^2 Escalation Cohort (RP2D), n=4			200 mg/m^2 CRPC Cohort, n=15			All Patients, n=36		
Data shown as: N (%)	Grade 1-2	Grade 3	Grade 4	Grade 1-2	Grade 3	Grade 4	Grade 1-2	Grade 3	Grade 4
Any AE	2 (50)	2 (50)	---	6 (40)	6 (40)	2 (13)	16 (44)	14 (39)	4 (11)
Nausea	1 (25)	1 (25)	---	7 (47)	---	---	17 (47)	1 (3)	---
Fatigue	1 (25)	---	---	5 (33)	---	---	10 (28)	1 (3)	---
Decreased appetite	1 (25)	---	---	6 (40)	1 (7)	---	9 (25)	1 (3)	---
Thrombocytopenia	1 (25)	---	---	1 (7)	1 (7)	1 (7)	4 (11)	4 (11)	2 (6)
Peripheral neuropathy	---	---	---	4 (27)	1 (7)	---	6 (17)	3 (8)	---
Anemia	1 (25)	---	---	---	3 (20)	---	5 (14)	3 (8)	---
Chills	1 (25)	---	---	4 (27)	---	---	7 (19)	---	---
Diarrhea	1 (25)	---	---	2 (13)	1 (7)	---	6 (17)	1 (3)	---
Neutropenia	---	---	---	---	1 (7)	---	2 (6)	2 (6)	1 (3)
Vomiting	---	---	---	3 (20)	---	---	5 (14)	---	---
Leukopenia	---	---	---	---	1 (7)	---	2 (6)	2 (6)	---
Pallor	---	---	---	2 (13)	---	---	4 (11)	---	---

No DLTs or treatment-related deaths. Two cases of immune poly-neuropathy.

The more heavily pre-treated prostate cancer cohort had higher rate of anemia and thrombocytopenia.

360 mg/m^2 PT-112 selected as the recommended phase 2 dose (RP2D). Dose modifications were allowed and effective.

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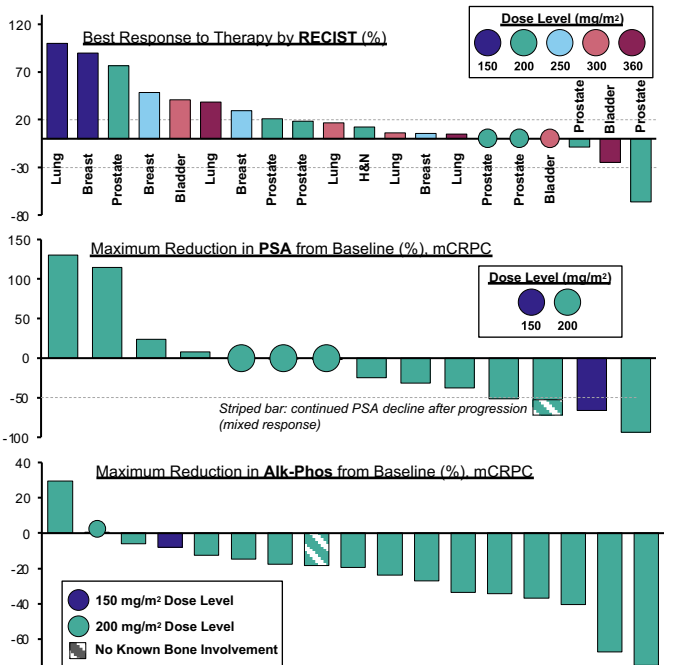
The majority of patients had some level of disease control, with a consistent activity signal in prostate cancer

All patients, n=36	
Evaluable Patients by RECIST	20
PR	1
SD	11
PD	8
mCRPC Patients	18
PSA reduction ≥50% ("PSA_{50}")	4 / 14
Alkaline phosphatase ("Alk-Phos") decreased	15 / 17

Best response of SD or better was achieved in 60% of patients with RECIST-evaluable disease

Strongest efficacy signals to date seen in mCRPC:

- RECIST PR, non-responder to prior immune checkpoint
- 4/14 patients experienced PSA declines of ≥50%
- 15/17 experienced reductions in alkaline phosphatase
- Pain resolution and reduction / cessation of opioid co-medication also reported



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Conclusions

- PT-112 plus avelumab (“PAVE”) was safe and well tolerated in this heavily pre-treated population who have exhausted all standard therapy
- Preliminary evidence of disease control / activity was observed across PT-112 dose levels from 150 to 360mg/m^2
- Objective responses in prostate cancer were noteworthy and possibly due to PT-112’s immunogenic cell death effects and / or its pyrophosphate bone-seeking
- Phase 2 trials are ongoing and include immune correlative studies