Results of a Phase I/II prospective dose escalation trial evaluating safety and efficacy of combination ^{177}Lu PSMA 617 and idronoxil (NOX66) in men with mCRPC: LuPIN trial

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Introduction

Despite treatment advances, metastatic castrate resistant prostate cancer (mCRPC) remains a lethal disease. Trials in ^{177}LuPSMA-617 have demonstrated good efficacy and safety, but synergistic combinations may further improve treatment responses. Idronoxil (NOX66) inhibits external NADH oxidase type 2 with downstream pro-apoptotic actions including radio-sensitization. We present results of a prospective single arm phase 1/2 dose escalation/expansion trial of ^{177}Lu PSMA-617 and NOX66 in end-stage mCRPC.

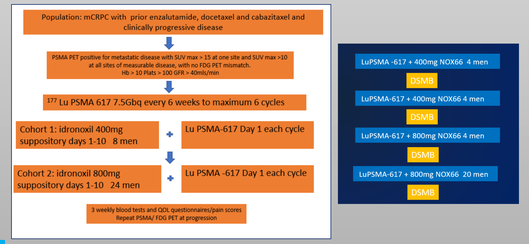
Hypothesis

Combined cancer targeted treatments using ^{177} Lu PSMA-617 and NOX66 will be safe with improved efficacy over single agent therapy in end-stage mCRPC.

Methods

- Men with progressive mCRPC post androgen signalling inhibition (ASI) and taxane chemotherapy (docetaxel and cabazitaxel) were considered eligible. Additional key inclusion criteria included:
  - PSMA PET/CT intensity SUV max > 15 in at least one site and SUV max > 10 at all measurable sites with no discordant disease on FDG PET/CT
  - Hb >10, Platelets >100 and GFR >40mls/min
- Patients received up to 6 doses of ^{177} Lu-PSMA 617 (7.5Gbq) +NOX66 administered day 1 of a 42 day cycle in combination with NOX66 suppositories days 1-10
- Data safety monitoring board meetings were taken regularly (Figure 1) The first 8 men received 400mg NOX66 (Cohort 1). NOX66 dose was then escalated to 800mg dose (Cohort 2).
- Safety, efficacy, pain scores, and QOL data were collected.

Figure 1:Study Schema and Data Safety Schedule



Results

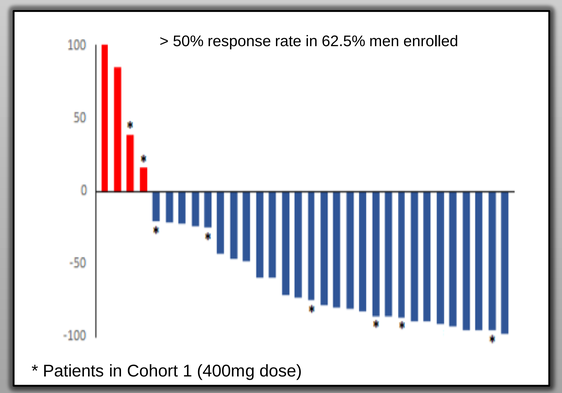
Table 1. Patient characteristics

Characteristics	Cohort 1 (8 men)	Cohort 2 (24 men)	Overall (32 men)
Age	68 (65-73)	69.5 (64-73)	69 (64-73)
PSA (ng/mL)	176 (107-316)	114 (62-460)	115 (62-439)
> 20 metastases	5/8	16/24	21/32 (65%)
ECOG			
0	2/8	10/24	12/32 (38%)
1	3/8	10/24	13/32 (40%)
2	3/8	4/24	7/32 (22%)
Prior Treatment			
Docetaxel	8/8	24/24	32/32 (100%)
Abi/enza	8/8	24/24	32/32 (100%)
Cabazitaxel	5/8	24/24	29/32 (91%)
Sites of disease			
Bone only	5/8	9/24	14/32 (44%)
Bone + Lymph nodes	2/8	8/24	10/32 (31%
Lymph nodes	0/8	2/24	2/32 (6%)
Bone + Viscera	1/8	5/24	6/32 (19%)

Median age and PSA reported with interquartile ranges

Results

Figure 2. Waterfall Plot for PSA response



* Patients in Cohort 1 (400mg dose)

- 32 men enrolled between November 2017 and June 2019
  - Baseline characteristics are summarized in **Table 1**
  - 9/41 (22%) failed screening based on imaging with low PSMA expression or FDG discordance.
- 31/32 (97%) received ≥ 2 cycles, 15/32 (47%) completed the maximum allowed 6 cycles.
- PSA responses are summarized in **Figures 2 and 3**
  - Any fall in PSA occurred in 28/32 (87%)
  - PSA response > 50% occurred in 20/32 (62.5%)
  - Median PSA PFS 6.1 months (95% CI 2.9 - 9.3)
  - 5/32 (16%) have not yet progressed (PSA or radiographically)
- Overall survival is summarized in **Figure 4**
  - Median overall survival 17.1 months (95% CI 6.2 - 27.9)
- Adverse events are summarized in **Table 2**:
  - Grade 1 Xerostomia, fatigue and anaemia were common
- 24/32 (50%) had baseline pain scores ≥3, of which 50% (12/24) had a significant reduction in pain indicators

Figure 3. PSA progression free survival

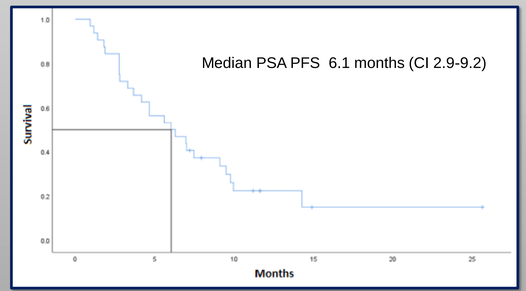


Figure 4. Overall survival

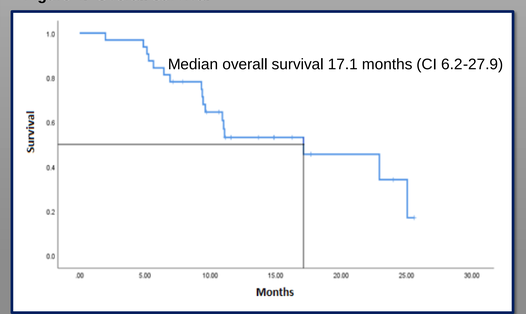


Table 2: Toxicity

Toxicity	Grade 1	Grade 2	Grade 3	All Grades
Xerostomia	17/32	2/32	0/32	19/32 (59%)
Fatigue	15/32	2/32	1/32	18/32 (56%)
Thrombocytopenia	2/32	0/32	0/32	2/32 (6%)
Anemia	14/32	6/32	0/32	20/32 (63%)
Neutropenia	0/32	0/32	0/32	0/32
Nausea	8/32	0/32	0/32	8/32 (25%)
Anal inflammation	7/32	2/32	0/32	9/32 (28%)
pneumonitis	0/32	1/32	0/32	1/32 (3%)

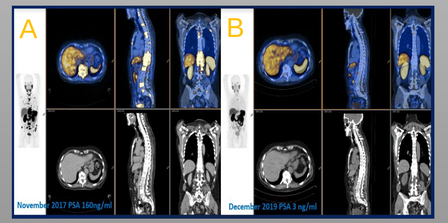


Figure 5. A 76 year old male was enrolled with progressive symptomatic bone metastases post abiraterone and both docetaxel and cabazitaxel. Scan (A) is the prescreening PSMA PET scan and scan (B) the 6 week post treatment PSMA PET. No PSA progression documented to date with no subsequent prostate treatments administered. PSA 3 ng/mL.

Conclusions

Combination Lu PSMA 617 + idronoxil (NOX66) is a safe treatment in men with heavily pre-treated metastatic castrate-resistant prostate cancer. The efficacy endpoints, including overall survival, are encouraging and further evaluation in larger phase II trials is warranted.

References

1. Hofman, M.S., et al., *[(177)Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study.* Lancet Oncol. 2018 Jun;19(6):825-833.
2. Emmett,L et al, *Results of a Prospective Phase 2 Pilot Trial of 177Lu-PSMA-617 Therapy for Metastatic Castration-Resistant Prostate Cancer Including Imaging Predictors of Treatment Response and Patterns of Progression*. Clin Genitourin Cancer. 2019 Feb;17(1):15-22

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