

# Final Results of a Phase Ib/IIa Study of Oral Phenoxodiol in Patients with Late-stage, Hormone-Refractory Prostate Cancer

Robert Davies<sup>1</sup>, Mark Frydenberg<sup>2</sup>, Alastair Tulloch<sup>3</sup>, Graham Kelly<sup>4</sup>

*Sir Charles Gairdner Hospital, Perth, Australia<sup>1</sup>; Monash Medical Centre, Melbourne, Australia<sup>2</sup>; St John of God Hospital, Perth, Australia<sup>3</sup>; Marshall Edwards, Inc.<sup>4</sup>*

## RATIONALE

Phenoxodiol (PXD) is an inhibitor of sphingosine-1-phosphate and Akt phosphorylation. Its biological activity is restricted to tumor cells as a result of its primary molecular target being tumor-specific NADH oxidase (t-NOX), a regulator of the plasma membrane quinone-quinol cation pump.

PXD induces cell death within prostate cancer cells both through apoptotic and necrotic mechanisms.

PXD is being developed both as a first-line therapy for early-stage prostate cancer and as a chemo-sensitizer for docetaxel in patients with hormone-refractory, docetaxel-refractory prostate cancer (HRDRPC).

One of the primary purposes of this study was to determine what anti-tumor effect PXD would have as a monotherapy in men with late-stage prostate cancer.

## OBJECTIVES

The primary objectives were:

- to establish the safety and PK profile of oral PXD in men with late-stage prostate cancer
- to confirm an anti-tumor effect of oral PXD in late-stage HRPC
- to identify a suitable dose of PXD to take into the next stage of trialing

## METHODS

**Subjects:** Twenty-six (26) patients with late-stage, hormone-refractory prostate cancer.

**Treatment:** PXD was administered orally, 8-hourly. Three treatment cycles of 21 days of treatment followed by 7 days without treatment. Repeated treatment cycles until disease progression.

Inter-patient dose escalation of PXD (20, 80, 200, and 400 mg per dose), with up to 9 patients per dose stratum.

**Toxicity:** Scored according to NCI criteria.

### **Clinical End-points:**

*PSA response:* PSA  $\geq$  50% below baseline

*PSA doubling time:* Time (weeks) for PSA to double from baseline

*Time to progression:* Time (weeks) between commencement and withdrawal of PXD therapy due to disease progression

## DEMOGRAPHICS

No. of patients: 26

Age: range 56-85 years (mean 72.1)

Gleason Score: range 7-9 (mean 8.1)

Baseline PSA (ng/mL): mean 59.5

Anti-androgen therapy: 24/26 (during study)

## RESULTS - Toxicity

### **Toxicity:**

No drug-associated toxicities or intolerances were observed or reported.

There were 4 serious adverse events, none considered to be associated with PXD therapy.

## RESULTS - Pharmacokinetics

Plasma PXD was almost completely (99.5%) conjugated as the glucuronide and/or sulfate salts.

Steady-state plasma PXD levels were (mean of 3 treatment cycles): 2.0, 6.7, 11.8 and 19.9 ug/mL for the 20, 80, 200 and 400 mg dose strata respectively.

## RESULTS - Efficacy

Data is summarized in Table 1.

The PSA doubling times and time to progression were significantly ( $P < 0.01$ ) greater in the 200 and 400 mg dose strata than in the 20 and 40 mg dose strata.

**Table 1: Efficacy end-points**

Dose	n	PSA response	PSA doubling time (weeks)	Time to progression (weeks)
20	6	0	14	13
80	6	0	22	17
200	5	1	66*	55*
400	9	2	39**	42**

\*One patient remaining on PXD therapy with stable PSA levels at 88 weeks

\*\* Three patients remaining on PXD therapy with stable PSA levels at 40, 72 and 80 weeks.

## CONCLUSIONS

1. PXD is well tolerated and can be administered in continuous treatment cycles at dosages up to 400 mg for up to 80 weeks without side-effects.
2. PXD given on an 8-hourly basis achieves steady-state blood levels with no evidence of accumulation.
3. PXD provides a significant anti-cancer effect as a monotherapy in patients with HRPC at dosages of 200 and 400 mg.