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

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ABSTRACT

Phenoxodiol (PXD) is a novel anti-cancer agent that is being developed as a therapy for hormone-refractory prostate cancer (HRPC), in particular those that are refractory to docetaxel.

The primary biochemical target of phenoxodiol is the sphingosine kinase-Akt signaling pathway, resulting in induction of apoptosis in prostate cancer cells through blockage of the phosphorylation of the anti-apoptotic factors, XIAP and $FLIP_s$.

A Phase Ib/IIa study was conducted in 19 men with HRPC, all of whom had metastatic disease and rapidly rising PSA levels. The objectives were safety, pharmacokinetics, and efficacy based on ability to give a PSA response (> 50% fall) and time to disease progression (TTP). PXD was given 8-hourly for 3 consecutive weeks each month for 6 months. There were 4 dose strata (4-6 subjects per stratum) – 20, 80, 200 and 400 mg. The age of the subjects was mean 72.1 years, the Gleason score was mean 8, and the baseline PSA level was mean 60 ng/mL.

There was a dose-response effect on PSA response, with the 400 mg dose producing a response in 3 of 4 patients. There also was a dose-response effect on TTP, rising from mean 10.4 weeks (20 mg) to mean 80.0 weeks (400 mg).

No drug-associated toxicities or intolerances were found with PXD. The 8-hourly treatment schedule at each dosage produced steady-state plasma levels of PXD.

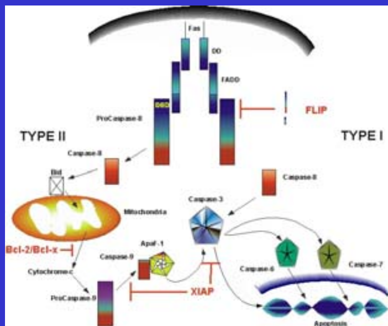

Fig. 1. Mechanism of action of PXD. PXD prevents phosphorylation of the anti-apoptotic proteins, XIAP and $FLIP_{short}$, thereby facilitating the activation of executioner caspases in prostate cancer cells via both intrinsic and extrinsic apoptotic pathways.

DEMOGRAPHICS

No. of patients: 19

Age: range 56-85 years (mean 72.1)

Gleason Score: range 7-9 (mean 8.1)

Baseline PSA (ng/mL): range 5 - 118 (mean 59.5)

Anti-androgen therapy: 22/24

METHODS

Toxicity: Scored according to NCI criteria.
Pharmacokinetics: Steady-state plasma levels.
Time to disease progression (TTP): PSA >25% higher than baseline and/or clinical progression (↑metastases, ↓clinical status).
PSA response: >50% decline from baseline for ≥ 1 month

OUTCOME #1 - Safety/Tolerability

No drug-associated toxicities or intolerances were found in the study at any dosage of PXD including patients treated with 400 mg tid for 6 months.

OUTCOME #2 - Pharmacokinetics

PXD in plasma was 99.9% conjugated as glucuronide-glucuronide, sulfate-sulfate, and glucuronide-sulfate forms.

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.

OUTCOMES #3 & #4 – Time to disease progression and PSA response

Dose	n	TTP (weeks)	PSA response
20	6	10.4	0
80	5	16.5	0
200	4	38.0	0
400	4	80.0	3*

* Two patients having stabilized PSA levels at 24 weeks equivalent to baseline levels; 1 patient with a PSA level < 1 ng/mL

CONCLUSIONS

1. PXD (oral dosage formulation) was well tolerated by patients with late-stage prostate cancer, with no evidence of toxicity or intolerances when dosages up to 400 mg were given t.i.d. for periods up to 24 weeks.
2. PXD given on an 8-hourly basis achieved steady-state blood levels with no evidence of accumulation over periods up to 24 weeks.
3. A dose-response effect of PXD on PSA levels was evidenced in this small study, with 3 of 4 patients treated with 400 mg PXD showing a >50% decline in PSA levels for > 1 month, with all three of those patients having normalized or stabilized PSA levels and clinical status at 24 weeks.
4. There was a dose-response effect of PXD on time to progression of disease with the 400 mg dose producing an 8-fold increase compared to the 20 mg dose.
5. These results justify conducting a larger study in which PXD (400 mg dose) will be used as a monotherapy in men with late-stage, hormone-refractory prostate cancer.