Poster # 140

Phase1/2a Study of PRL-02, a Long-Acting IM Depot Injection of Abiraterone Decanoate in Patients with Prostate Cancer Including Those Previously Treated with Enzalutamide (NCT04729114)

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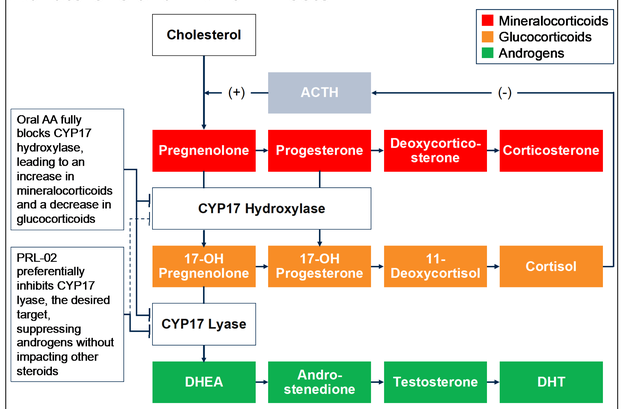
BACKGROUND

- PRL-02 is a long-acting intramuscular (IM) depot injection of abiraterone decanoate, a novel lipophilic prodrug of abiraterone that is delivered through the lymphatic system
- In a castrate monkey model, single-dose PRL-02 suppressed testosterone (T) through 14 weeks to levels comparable to clinical results with oral abiraterone acetate (AA) but with lower and less variable plasma exposures[1]
- PRL-02 minimally inhibits CYP17 hydroxylase and preferentially inhibits CYP17 lyase, and therefore blocks androgens without harmful increases in mineralocorticoids or depletion of steroids in the glucocorticoid pathway **(Fig 1)**
- Progesterone (P), a known oncogenic driver of prostate cancer through the activation of androgen receptor (AR)- and non-AR-driven pathways, is elevated in patients (pts) treated with oral AA[2,3]
- Nonclinical study results show higher abiraterone exposures from PRL-02 compared to oral AA in adrenal, lymph, and bone and lower exposures in liver, brain, and plasma, suggesting that PRL-02 has the potential for a superior therapeutic index and safety profile compared to oral AA[4]

Figure 1. Metabolic Pathway of Cholesterol to Androgens – Abiraterone and PRL-02 Effects



OBJECTIVE

- The results of the dose-escalation Phase 1 study evaluating the safety, pharmacokinetics, pharmacodynamics, and efficacy of PRL-02 are presented
- In addition, this poster includes safety, pharmacokinetics, pharmacodynamics, and efficacy in pts with CRPC whose disease progressed on a prior 2nd-generation androgen receptor-targeting agent [2gAR] (enzalutamide, apalutamide, darolutamide)

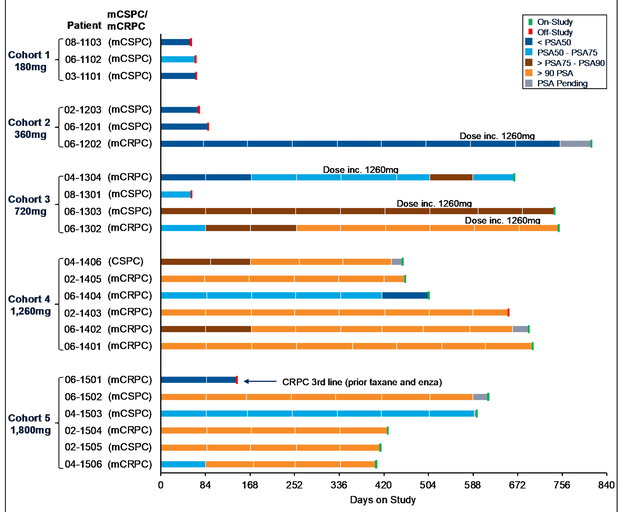
METHODS

- Phase 1 dose escalation was a standard 3+3 design that identified a recommended Phase 2 dose (RP2D) – Cohorts 1-5
- Currently enrolling Phase 1 expansion Cohorts D and E. These include pts who received prior oral AA (Cohort D); or prior enzalutamide, apalutamide, and/or darolutamide (Cohort E) with documented evidence of progression
- PRL-02 is administered as an IM injection every 84 days (1 cycle) along with daily oral dexamethasone (0.5 mg)
- Patients with metastatic castrate resistant or sensitive prostate cancer (mCRPC/mCSPC) ((Cohorts 1-5) or mCRPC only (Cohorts D&E) and a screening T of <50 ng/dL were included
- T and P plasma concentrations were assessed at least every 21 days starting from Day 1 of Cycle 1 through 12 weeks and every 28 days of all cycles thereafter
- Prostate-specific antigen (PSA) is assessed pre-dose on Day 1 of Cycle 1 and every 28 days of all cycles thereafter (exception: at least every 3 weeks in Cycle 1 for Cohorts D and E)

RESULTS

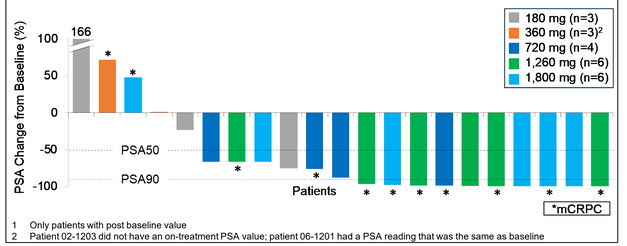
- As of Dec 18, 2023, 41 pts have been dosed as follows:
  - 22 pts (9 mCRPC, 12 mCSPC, 1 CSPC) in dose escalation Cohorts **1-5**: **1**, 180 mg (n=3); **2**, 360 mg (n=3); **3**, 720 mg (n=4); **4**, 1,260 mg (n=6); and **5**, 1,800 mg (n=6)
    - median age 68
    - emerging median time on treatment (TOT) in months per dose level (range) of 2.17 (1.88-2.20+), 2.93 (2.37-26.74+), 23.19 (1.91-24.70+), 19.10 (15.03-23.09+), & 13.88 (4.74-20.33+), respectively **(Fig 2)**
  - 5 pts in Cohort D (mCRPC, oral AA failures) dosed at 1,260 mg
    - median age 74
    - median TOT in months (range) 2.66 (0.63-7.89+)
  - 14 pts in Cohort E (mCRPC, enzalutamide/apalutamide/darolutamide failures) dosed at 1,260 mg
    - median age 77
    - emerging median TOT in months (range) 3.32 (0.07-9.28+) **(Fig 5)**
- Across dose escalation pts, there was generally a dose-proportional increase in plasma abiraterone concentrations following a single dose of PRL-02 with a Tmax of 14-33 days and a mean plasma half-life of 17-23 days. Abiraterone concentrations appeared to be similar between Cohort 4 and 5 pts and Cohort D and E expansion pts **(Fig 4a)**
- The median baseline T level in dose escalation pts was 7.45 ng/dL
- Among dose escalation pts dosed at 1,260 mg and above, 12 of 16 had a 90% reduction in T or values ≤1 ng/dL by day 28, and across all dose escalation pts PSA responses ≥50% and ≥90% were observed in 16 of 21 pts and 10 of 21 pts, respectively **(Fig 3)**
- Evidence that PRL-02 disrupts AR-signaling following 2gAR therapy (e.g., enzalutamide); most patients (8 out of 9) exhibited decreasing or flattening PSA trajectory by the second cycle of PRL-02, including two pts with an unconfirmed PSA50 decline from baseline **(Fig 6)**
- Dose-dependent T and P concentrations were generally similar between Cohort 4 and 5 dose escalation pts and Cohort D and E expansion pts **(Fig 4b and 4c)**, with minimal to no increase in P
- There were no treatment-related serious adverse events (AEs) or dose-limiting toxicities **(Table 1)**
- G2 related AEs included edema peripheral, fatigue, increased bruising, decreased appetite, weight increased, insomnia, and hot flush; symptoms of mineralocorticoid excess were not reported

Figure 2. Swim Plots[1] – Cohorts 1-5 Dose Escalation Patients



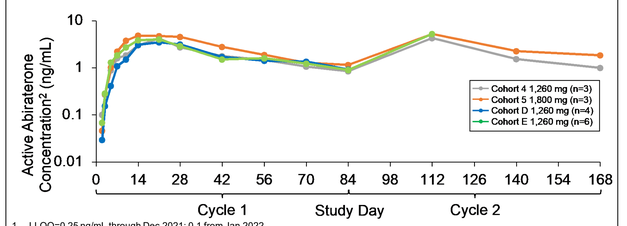
1 A post-baseline PSA value of 0.01 ng/mL was used for response calculation if the post-baseline value was <LLOQ (0.02 ng/mL)

Figure 3. PSA % Change from Baseline – Cohorts 1-5 Dose Escalation Patients[1]



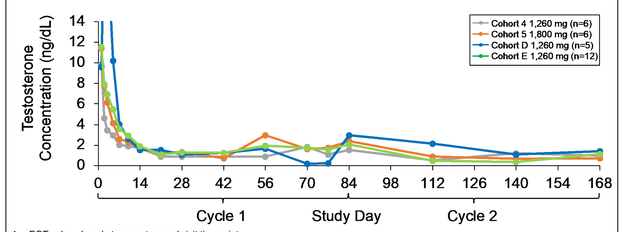
1 Only patients with post baseline value
2 Patient 02-1203 did not have an on-treatment PSA value; patient 06-1201 had a PSA reading that was the same as baseline

Figure 4a. Mean Plasma Abiraterone Concentrations by Dose[1] for Cohorts 4, 5, D, and E



1 LLOQ=0.25 ng/mL through Dec 2021; 0.1 from Jan 2022
2 Mean

Figure 4b. Mean Plasma T Concentrations[1] for Cohorts 4, 5, D, and E



1 EOT value placed at nearest normal visit timepoint

Figure 4c. Mean Plasma P Concentrations for Cohorts 4, 5, D, and E

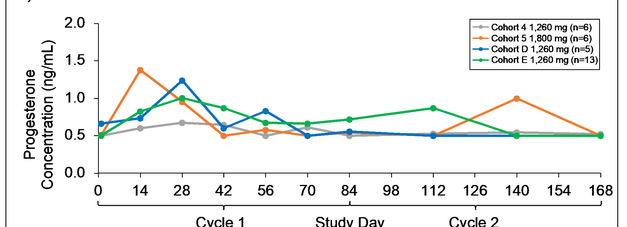
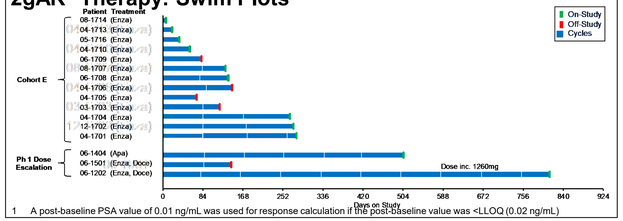
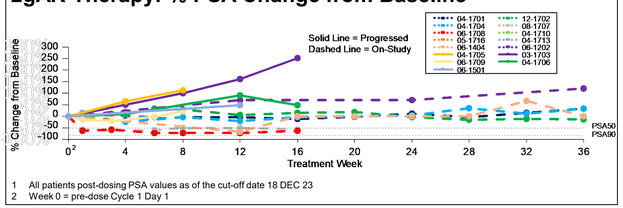


Figure 5. Patients with mCRPC Previously Treated with 2gAR[1] Therapy: Swim Plots



1 A post-baseline PSA value of 0.01 ng/mL was used for response calculation if the post-baseline value was <LLOQ (0.02 ng/mL)

Figure 6. Patients[1] with mCRPC Previously Treated with 2gAR Therapy: % PSA Change from Baseline



1 All patients post-dosing PSA values as of the cut-off date 18 DEC 23
2 Week 0 = pre-dose Cycle 1 Day 1

Table 1. Overall Summary of Adverse Events by Cohort

Adverse Event Category	Cohort 1-3 (180-720 mg) (N=10)	Cohort 4 (1,260 mg) (N=6)	Cohort 5 (1,800 mg) (N=6)	Cohort D and E (1,260 mg) (N=19)
Any TEAE[1], n (%)	8 (80)	6 (100)	6 (100)	15 (79)
Treatment-Related TEAE[1], n (%)	5 (50)	2 (33)	3 (50)	8 (42)
Serious TEAE[1], n (%)	0 (0)	2 (33)	1 (17)	1 (5)
Treatment-Related Serious AE[2], n (%)	0 (0)	0 (0)	0 (0)	0 (0)
TEAE[1] That Qualify as a DLT[3], n (%)	0 (0)	0 (0)	0 (0)	0 (0)
TEAE[1] of Clinical Interest, n (%)	0 (0)	0 (0)	0 (0)	0 (0)
Fatal TEAEs[1], n (%)	0 (0)	0 (0)	0 (0)	0 (0)

1 Treatment Emergent Adverse Event
2 Adverse Event
3 Dose-Limiting Toxicity

CONCLUSIONS

- PRL-02 was well-tolerated, with minimal adverse effects observed at all dose levels explored
- Dose-dependent T suppression was associated with clinical benefits including PSA responses (e.g., PSA50/PSA90)
- Based on profound T suppression, without effect on P concentrations, and initial clinical activity, the provisional recommended Phase 2 dose is 1,260 mg
- At the 1,260 mg PRL-02 dose, PSA responses and/or flattening PSA trajectory was noted in a majority of pts with mCRPC who previously received 2gAR therapy

IMPLICATIONS

- In contrast to a study of oral AA in pts with CRPC that reported substantial increases in median P (0.13 to 5.33 nmol/L)[3], minimal to no increases in P were observed in this study, consistent with high PRL-02 CYP17 lyase selectivity
- The profound and sustained reductions in T without a rise in P provides a mechanistic basis for the hypothesis that PRL-02 may have superior clinical activity over oral AA; these hypotheses are being tested in the ongoing study
- Early results at 1,260 mg following 2gAR therapy (Cohort E) are encouraging
- The clinical activity and safety profile of IM PRL-02, as demonstrated in the Phase 1 dose escalation and expansion cohorts, is encouraging and supports further clinical investigation

References:
1. Moore WR, et al. *J Clin. Oncology*. 2021.
2. Chen EJ, et al. *Clin Cancer Res*. 2015.
3. Wright C, et al. *Eur. J Endocrinol*. 2020.
4. Moore WR, et al. *J Clin. Oncology*. 2022.

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