Phase 1/2a Study of PRL-02, a Long-Acting Intramuscular (IM) Depot Injection of Abiraterone Decanoate in Patients (pts) with Advanced Prostate Cancer

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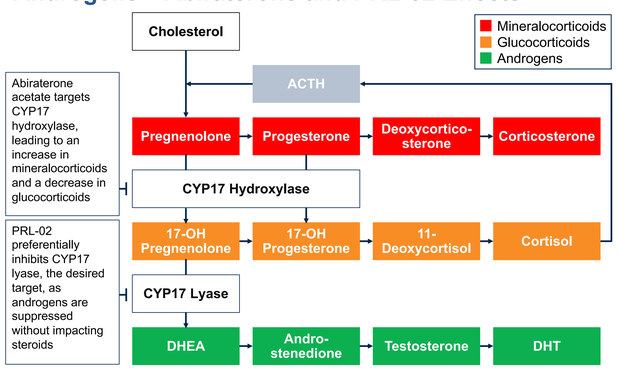
BACKGROUND

- PRL-02 is a long-acting 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 appears to minimally inhibit CYP17 hydroxylase and preferentially inhibit CYP17 lyase, which blocks androgens without harmful increases in mineralocorticoids or depletion of steroids in the glucocorticoid pathway **(Figure 1)**
- Progesterone, in particular, is a known oncogenic driver that activates canonical and non-canonical receptor target genes
- 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[2]

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



OBJECTIVE

The results of an ongoing dose-escalation Phase 1 study evaluating the safety, pharmacokinetics, and efficacy of PRL-02 are presented

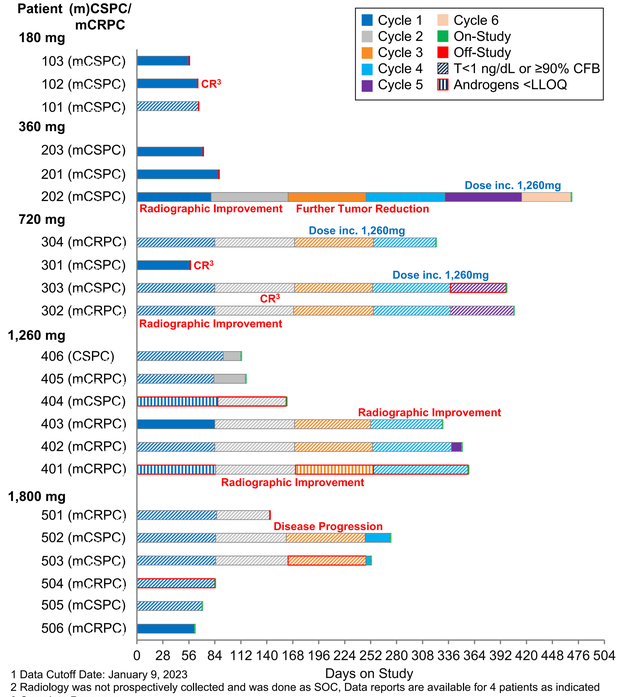
METHODS

- Phase 1 is a standard 3+3 design intended to identify a recommended phase 2 dose (RP2D)
- PRL-02 is administered as an IM injection every 84 days (1 cycle) with daily oral dexamethasone or prednisone
- Patients (pts) with metastatic castrate resistant or sensitive prostate cancer (mCRPC/mCSPC) and a screening T of 2 - 50 ng/dL were included
- Pts with prior treatment with a CYP17 inhibitor and/or concurrent treatment with an AR-blocking agent are excluded
- T levels are assessed at least every 14 days starting from Day 1 of Cycle 1 and every 28 days of all cycles thereafter
- PSA is assessed pre-dose on Day 1 of Cycle 1 and every 28 days of all cycles thereafter

RESULTS

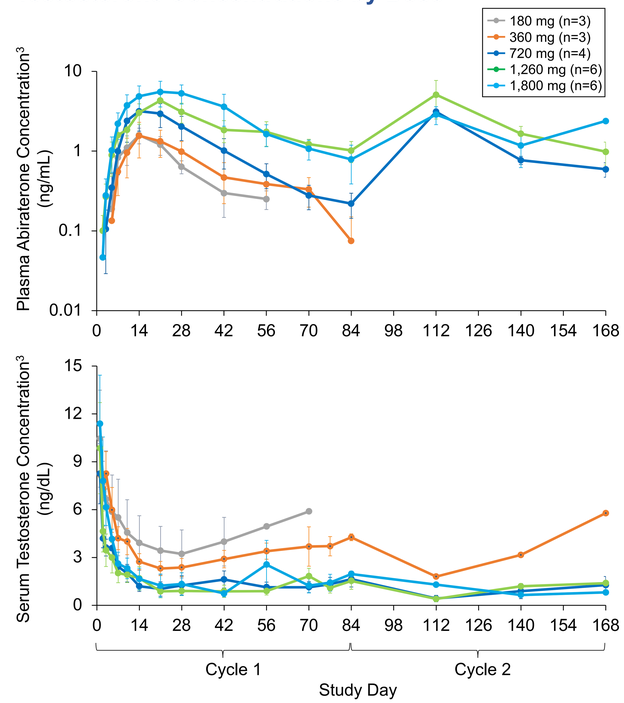
- As of Jan 9, 2023, 22 pts (9 mCRPC, 12 mCSPC, 1 CSPC) were treated across 5 dose cohorts (180, 360, 720, 1,260, 1,800 mg) **(Figure 2)**
- Generally, there was a dose-proportional increase in abiraterone concentrations following a single dose of PRL-02 with a T max of 14 - 28 days and a plasma half-life of 18.3 days **(Figure 3)**
- The median baseline T level, calculated from mean of screening and Day 1 of Cycle 1 pre-dose samples, was 7.45 ng/dL
- Among pts dosed at 720 mg and above:
  - 13 of 16 pts had a 90% reduction in T or values ≤ 1 ng/dL at day 28 **(Figure 2)**
  - The median baseline PSA level was 3.01 ng/mL, and PSA50 was observed in 15 of 16 pts, while PSA90 was observed in 8 of 16 pts post-baseline **(Figure 4)**
- There were no treatment-related serious adverse events (AEs) or dose-limiting toxicities **(Table 1)**
- G2-related AEs were fatigue, decreased appetite, insomnia, hot flush, and peripheral edema
- Dose-response trends in 'up-stream' steroids (e.g., progesterone (P) and corticosterone (C)) were observed **(Table 2)**
- Although serial radiology was not prospectively required, there was a radiographic improvement in 6 pts with data available

Figure 2. Patient Efficacy Over Time – Swim Plot[1,2]



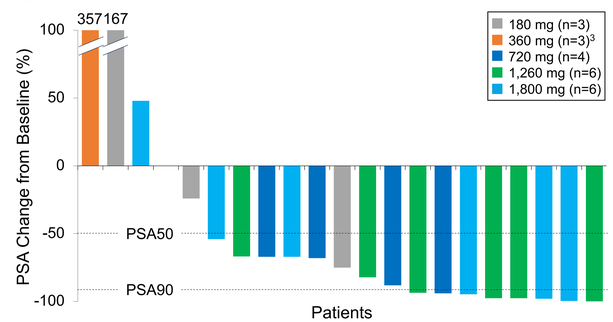
1 Data Cutoff Date: January 9, 2023
2 Radiology was not prospectively collected and was done as SOC, Data reports are available for 4 patients as indicated
3 Complete Response

Figure 3. Plasma Abiraterone and Serum Testosterone Concentrations by Dose[1,2]



1 LLOQ=0.25 ng/mL though Dec 2021; 0.1 from Jan 2022
2 Data Cutoff Date: January 9, 2023
3 Mean (±SE)

Figure 4. Maximum[1] Percent of PSA Change from Baseline[2]



1 Maximum percent is taken from on treatment days, excluding data from end of treatment (EOT)
2 Data Cutoff Date: January 9, 2023
3 Patient 02-1203 did not have an on-treatment PSA value; patient 06-1201 had a PSA reading that was the same as baseline

Table 1. Overall Summary of Adverse Events by Cohort[1]

Adverse Event Category	Dose (mg) 180 (N=3)	360 (N=3)	720 (N=4)	1,260 (N=6)	1,800 (N=6)
Any TEAE[2], n (%)	2 (66.7)	2 (66.7)	4 (100.0)	6 (100.0)	5 (83.3)
Treatment-Related TEAE[2], n (%)	2 (66.7)	1 (33.3)	2 (50.0)	2 (33.3)	3 (50.0)
Serious TEAE[2], n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (16.7)
Treatment-Related Serious AE[3], n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAE[2] that Qualify as a Dose-Limiting Toxicity, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fatal Events, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

1 Data Cutoff Date: January 30, 2023
2 Treatment Emergent Adverse Event
3 Adverse Event

Table 2. Mean Percent Change from Baseline for Up-Stream Steroids for PRL-02[1]

Percent (%)

Dose Group	Up-Stream Steroids	Day 14	28	56	84
720 mg (N=4)	Progesterone	-1	-2	0	0
	Corticosterone	48	27	9	-33
1,260 mg (N=6)	Progesterone	20	35	0	0
	Corticosterone	184	490	19	32
1,800 mg (N=6)	Progesterone	165	86	12	13
	Corticosterone	455	259	54	109

1 Data Cutoff Date: January 9, 2023

CONCLUSIONS

- PRL-02 was well tolerated, with minimal adverse effects observed at all doses
- Dose-dependent T suppression was associated with clinical benefits including PSA responses and radiographic improvement
- Minimal to no increases in P and C were observed in this study
- Based on less P increases with similar T reductions in patients treated with 1,260 mg PRL-02 compared to 1,800 mg, the provisional RP2D is 1,260 mg

IMPLICATIONS

- The available clinical data for PRL-02 confirms the potential for a superior therapeutic index and improved patient convenience compared to daily oral AA + prednisone
- Wright et al. 2020 reported substantial increases in median P (4000%) and C (8593%) in patients treated with oral AA + prednisone[3]
- The lack of rises in P provides a mechanistic basis for the hypothesis that IM PRL-02 may have superior clinical activity over daily oral AA + prednisone
- These hypotheses will be tested in an ongoing Phase 2 study in which the RP2D will be 1,260 mg

References:
1. Moore et al. *J Clin. Oncology*. 2021.
2. Moore et al. *J Clin. Oncology*. 2022.
3. Wright et al. *Eur. J Endocrinol*. 2020.

Acknowledgments:
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