Propella Therapeutics

Bright Ideas Made Brilliant

PROPELLA

Introduction to Propella and PRL-02

Focused on the creation of a pipeline of proprietary oncology therapeutics that utilize lymphatic system delivery the first being PRL-02, a best-in-class therapy for prostate and other androgen-driven cancers

Company

- Spun out of Vizuri Health Sciences in 2020 with technology and products invented and wholly-owned by Propella
- Headquarters in the Research Triangle Park area of North Carolina

Technology & Products

- Best-in-class CYP 17 lyase inhibitor, PRL-02, for androgen-dependent cancers
- PRL-02 Ph 1/2a metastatic prostate cancer (PC) study ongoing; 2023 Ph 2a readout
- Ph 2 localized prostate cancer study to commence in 2023
- Pipeline program to be disclosed in 2H 2022

Experienced Leadership Team

William Moore, PhD
President & CEO

AXYS innocrin precision therapeutics

Brendan Griffin, MBA, MSPPM
Chief Financial Officer

SVBLEERINK

Jackie Walling, MBChB, PhD
Consulting Chief Medical Officer

BIOMARIN
Lilly **Relugolix**

George Cox, PhD, JD
Chief Legal Officer & Corp. Secretary

NIH NATIONAL CANCER INSTITUTE

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Vice President, Product Development

gsk innocrin precision therapeutics

Linda Peterson, MA, CCRA
Vice President, Clinical Operations

Roche Genentech

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University of Washington

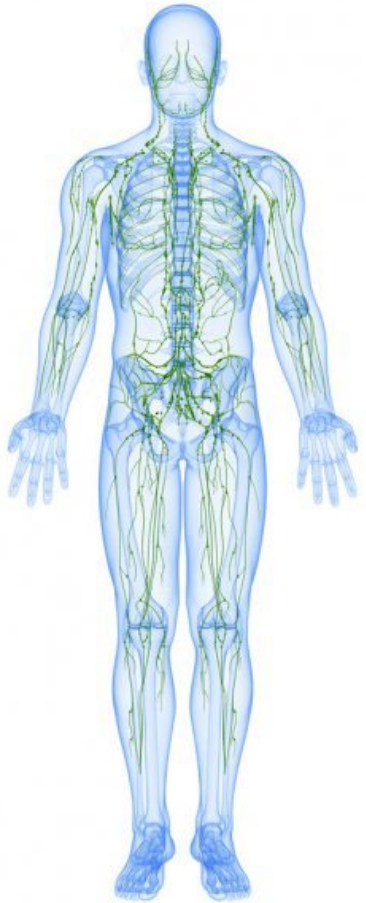
Howard Scher, MD
Memorial Sloan Kettering

Nima Sharifi, MD, PhD
Cleveland Clinic

Neal Shore, MD
Med. Dir., Carolina Urologic Research Center

Advantages of Lymphatic System Targeting

- The lymphatic system is a vast network of vessels, lymph nodes and organs that connects the circulatory and immune systems
- Lymphatic targeting has been successfully used for intramuscular (IM) and oral drug development
- Drugs can be delivered preferentially to target tissues:*
  - Increased exposures in tissues of interest e.g., adrenal gland, testes, lymph nodes, bone metastatic sites
  - Minimal exposures in organs causing toxicity e.g., liver, CNS
  - ***Enhanced activity***
  - ***Improved safety margin***



*Moore, et al. JCO 2022 40:6_suppl, 160-160

PRL-02: Intramuscular (IM) Abiraterone Decanoate

A Long-Acting Depot Injection for Prostate Cancer

PROPELLA

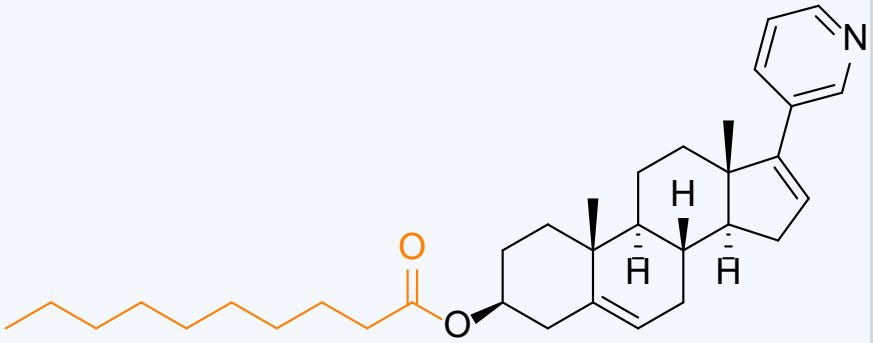
Metastatic Prostate Cancer (PC): The Problem Being Solved

- Chemical castration (e.g., Lupron) is a standard of care for metastatic PC, but androgens produced outside the testes can continue to drive tumor growth through activation of the androgen receptor (AR)
- Treatment goal is to block AR activation by androgens produced in the adrenal glands or tumors
- There are several AR antagonists approved for the treatment of PC including enzalutamide (Astellas/Pfizer), apalutamide (J&J), and darolutamide (Bayer)
- The one approved product (Zytiga®, abiraterone acetate, J&J) that blocks the enzyme (CYP17) that produces androgens is the most prescribed treatment for PC
- Even with these new drugs, the 5-year survival rate is only 30% for men with metastatic disease

> ***Clinicians and FDA will want to see a comparison of PRL-02 to Zytiga because they both block androgen production through the inhibition of CYP17 enzyme. Zytiga's multiple shortcomings include a low safety margin (e.g., liver toxicity) and efficacy limitations due to low bioavailability and profound inhibition of CYP17 hydroxylase while PRL-02 blocks the preferred drug target, CYP17 lyase.***

PRL-02: A Proprietary, Long-acting Intramuscular (IM) Depot

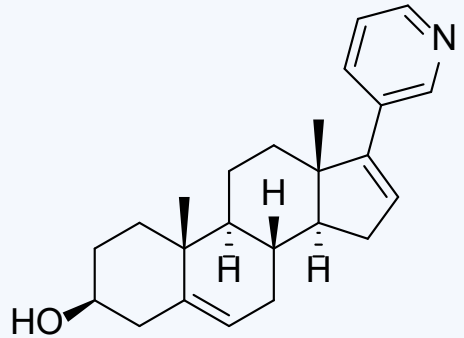
PRL-02, Optimized for Target Tissue Uptake through the Lymphatic System



Abiraterone Decanoate

U.S. Patent No. 10,792,292

Abiraterone: The Active Moiety in Both PRL-02 and ZYTIGA®



A potent inhibitor of CYP17 Lyase and Hydroxylase

PRL-02: Rapid Progression from Concept to Clinical POC

- Product Concept
- Independent Market Research
- Research Activities Commence

2018

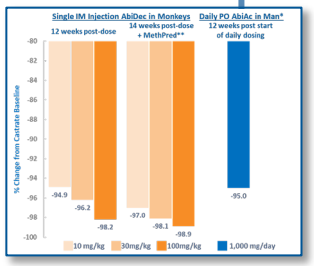
2019

- FDA Pre-IND Meeting
- IND-Enabling Studies Start

2020

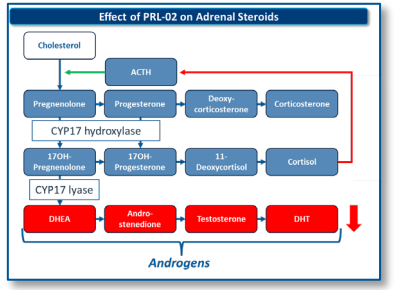
U.S. Patent Issued for Novel Abiraterone Prodrugs


United States Patent
Sharp et al.
US 10,792,292 B2
Oct. 6, 2020



Non-human primate POC achieved

2021



Human POC achieved

2022

- IND Filed
- Phase 1/ 2a Study Start

2023

- FDA EOP1 Meeting
- RP2D Selected

~3 Yrs, $15M, from Product Concept to Human POC

PRL-02: Innovative Advances vs. Zytiga®

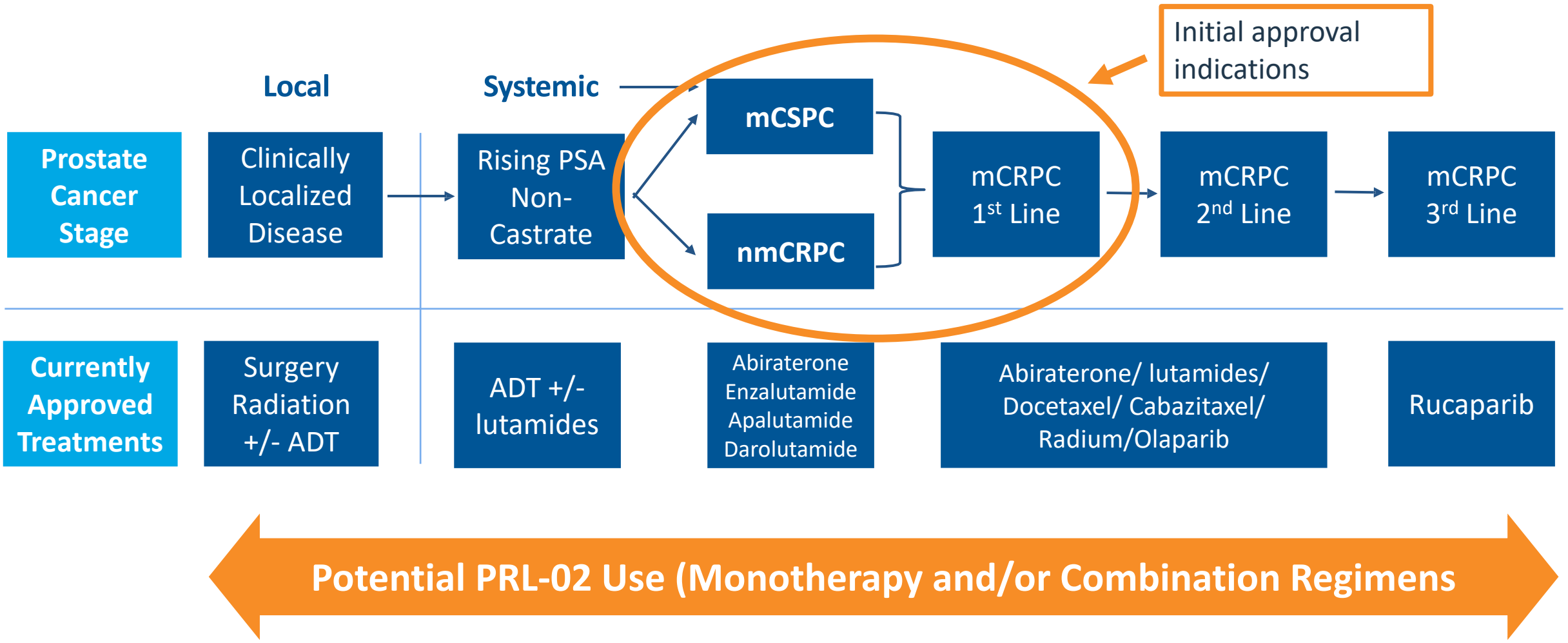
Propella's Unique Product	Validated Mechanism of Action	Patient-Friendly
• PRL-02: Patented abiraterone decanoate for intramuscular (IM) use • Utilizes lymphatic system to deliver drug to target tissues; precise level of abiraterone released to continuously block ***CYP17 lyase*** for 3 months, reducing tumor breakthrough risk	• Abiraterone is the active moiety of Zytiga, the only androgen biosynthesis inhibitor approved for the treatment of PC • Zytiga fully blocks ***CYP17 hydroxylase*** and is approved in combination with prednisone plus a GnRH analog for metastatic castration-resistant PC (mCRPC) and metastatic castration-sensitive PC (mCSPC)	• 3-Month dosing schedule same as many IM GnRH analogs (e.g., Lupron) • Patient reimbursement available in the US through Medicare Part B; physicians will receive a fee • High safety margin demonstrated in the clinic to date; **no liver or safety signals due to CYP17 hydroxylase inhibition (e.g., symptoms of mineralocorticoid excess)**

Competitive Landscape: Marketed AR Pathway Directed Therapies

Company	Therapy	US Price[1] for 1 month	Global Revenue[2]	Type	Indication(s)
Janssen	Zytiga (abiraterone acetate)	$13,064.42	$2,470M	CYP17 inhibitor	• Metastatic castration-resistant prostate cancer (CRPC) • Metastatic high-risk castration-sensitive prostate cancer (CSPC)
Astellas Pfizer	Xtandi (enzalutamide)	$14,730,84	$4,390M	AR Antagonist	• Castration-resistant prostate cancer • Metastatic castration-sensitive prostate cancer.
Janssen	Erleada (apalutamide)	$15,399.91	$760M	AR Antagonist	• Metastatic castration-sensitive prostate cancer (mCSPC) • Non-metastatic castration-resistant prostate cancer (nmCRPC)
Bayer Orion	Nubeqa (darolutamide)	$14,276.16	ND[3]	AR Antagonist	• Non-metastatic castration-resistant prostate cancer

[1]US Price represents average wholesale price ("AWP") as of July 26, 2021; [2]Global revenues for 2020; [3]Nubeqa was approved July 30, 2019. Bayer did not disclose 2020 revenues for Nubeqa.
Sources: Company Filings, Fierce Biotech, UpToDate, FDA Website.

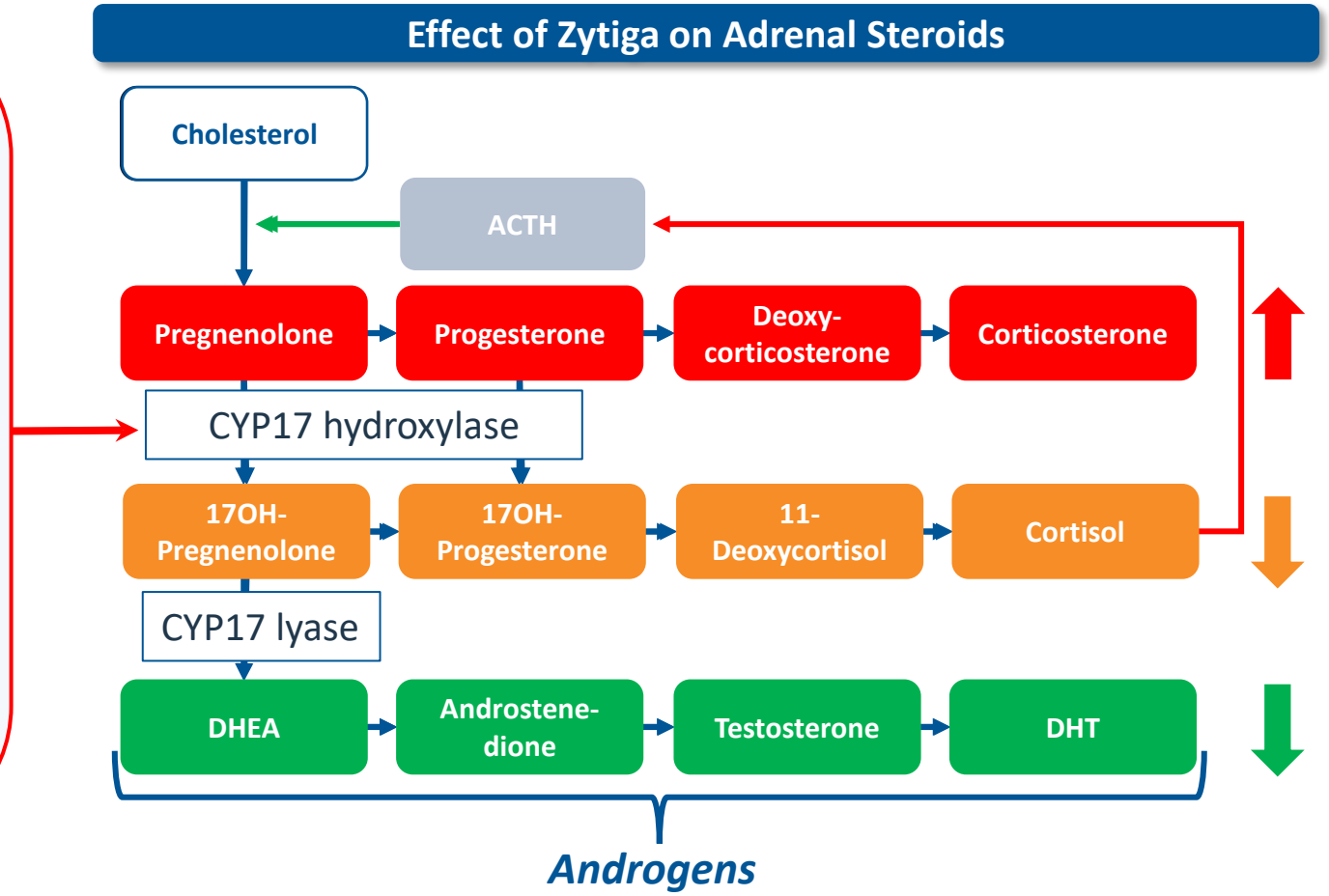
PRL-02: Broad Opportunity Across Entire PC Treatment Spectrum



1. Adopted from Mehlen, Puisieux. Nat Rev Cancer 2006; J Clin Oncol 2016.
2. Sharp, A et al. J Clin Invest 2019.

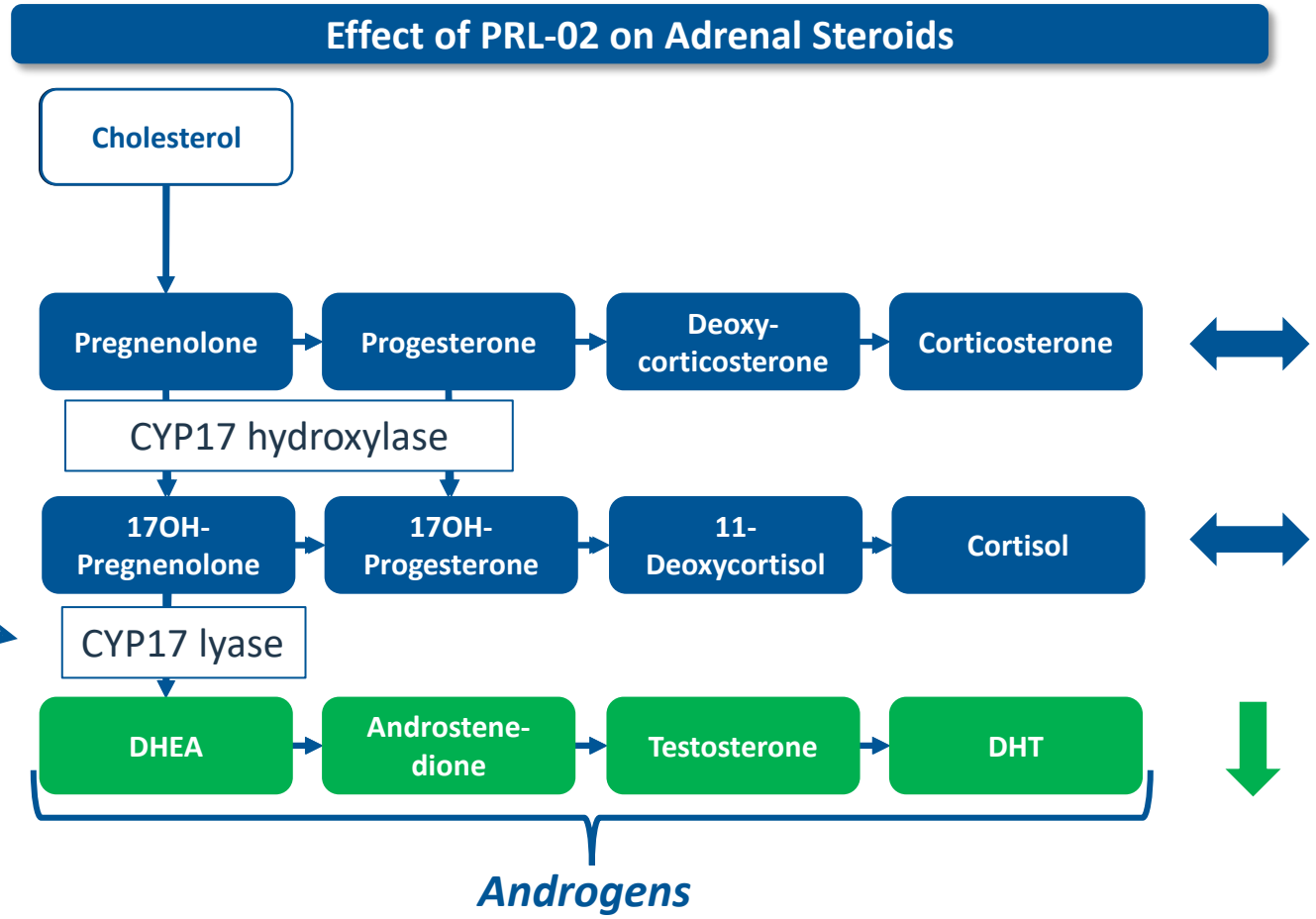
Zytiga: Hydroxylase Inhibition Harms Safety and Efficacy Profile

Zytiga maximally inhibits **CYP17 hydroxylase** which leads a decrease in androgens (**green boxes**) but also to an increase in mineralocorticoids (**red boxes**) and to decreases in glucocorticoids (**orange boxes**). Increased **deoxycorticosterone** and **corticosterone** lead to the symptoms of mineralocorticoid excess (e.g., hypertension, hypokalemia) while increases in **progesterone** and **pregnenolone** adversely impact efficacy. Zytiga must be combined with a **cortisol** replacement (prednisone) to lessen additional safety signals and to prevent a surge in ACTH which will further stimulate mineralocorticoid increases and exacerbate safety signal and efficacy loss.

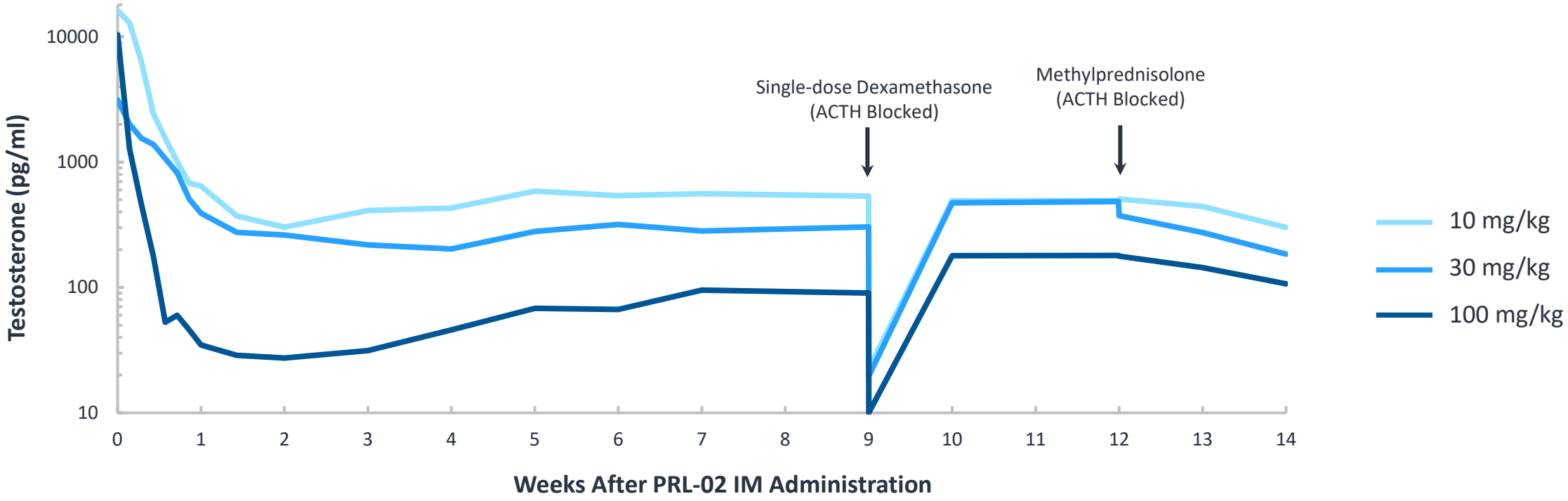


PRL-02: CYP17 lyase Inhibition Improves Safety and Efficacy

Emerging clinical data shows that PRL-02 preferentially inhibits **CYP17 lyase**, the desired target. *PRL-02 delivers identical blockade of androgens as Zytiga without harmful increases in mineralocorticoids or depletion of steroids in the glucocorticoid pathway*

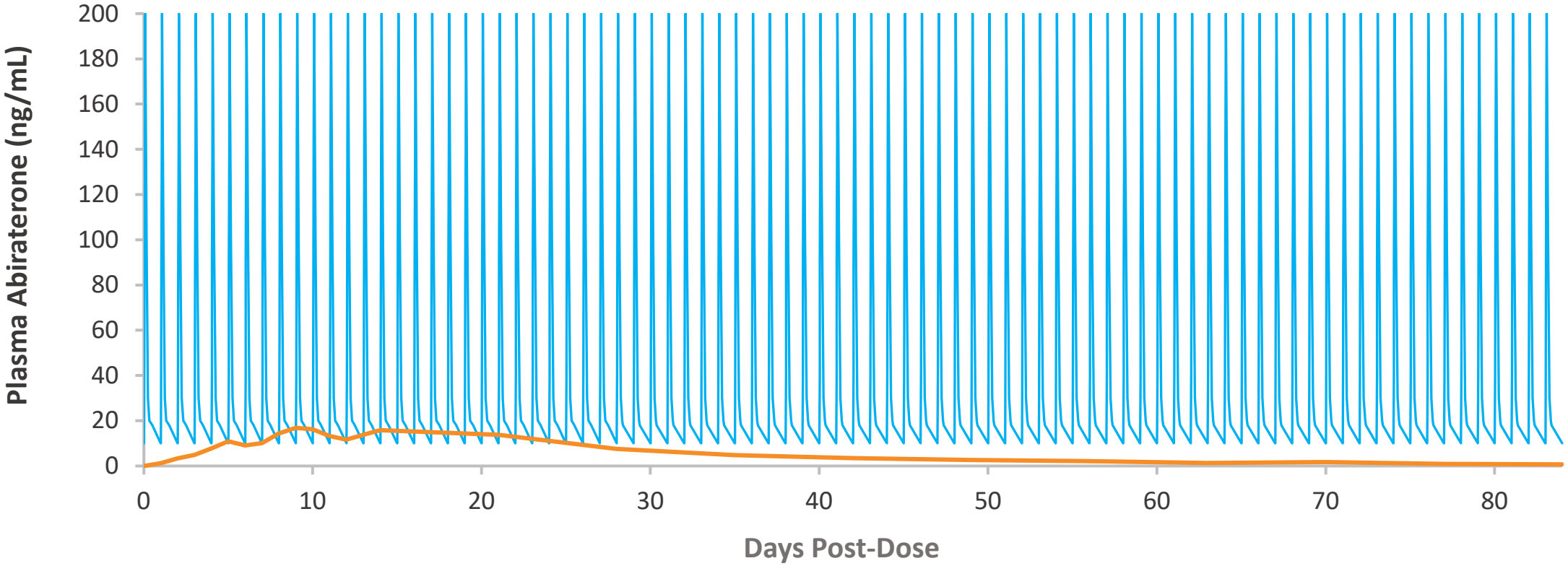


PRL-02: Profound and Durable T Suppression in Castrate Monkeys



T levels following PRL-02 at clinically-relevant doses in monkeys treated with Lupron. Addition of glucocorticoids (the clinical norm) caused further decreases vs. PRL-02 alone.

PRL-02 Primate PK: Low Plasma Exposures Compared to Zytiga

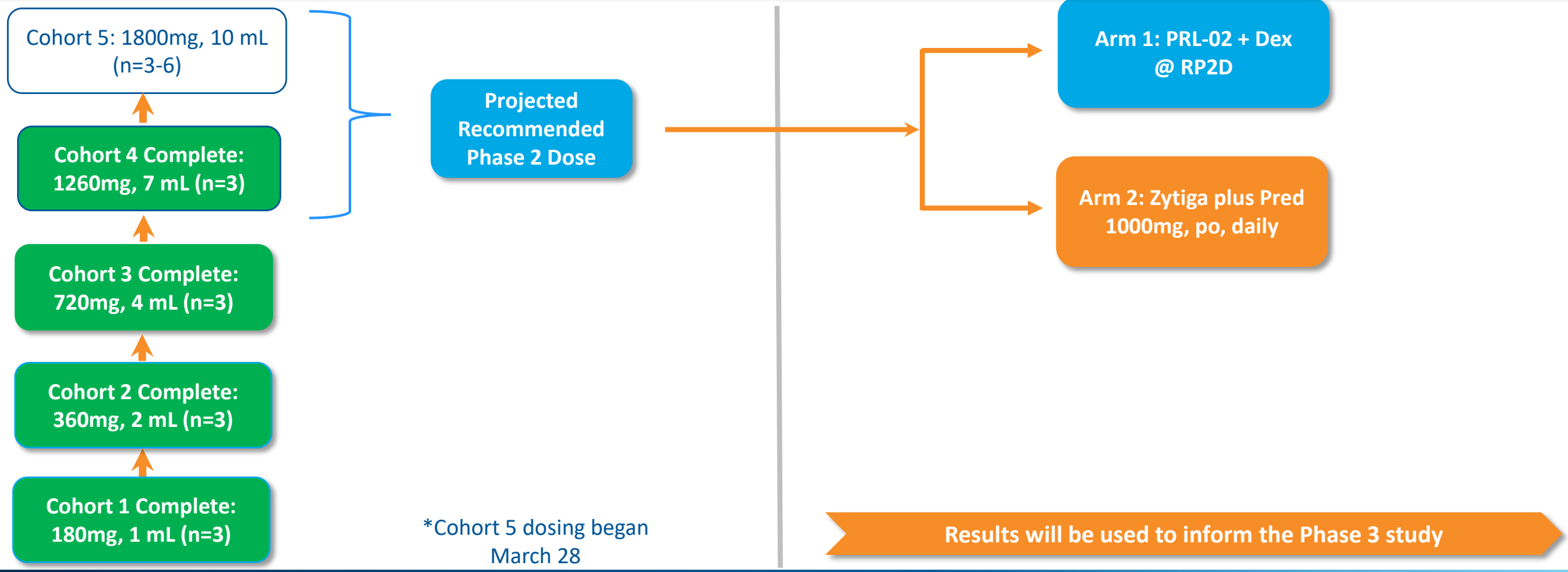


Significantly lower PRL-02 plasma levels (in gold; highly active 30 mg/kg dose in castrate monkey model) vs. Zytiga (in blue; approved human dose), has resulted in improved human safety

Current Status of Phase 1/2a Study in mCRPC/mCSPC Patients

Phase 1: Dose Escalation | **Objective: RP2D (safety, plasma T)**

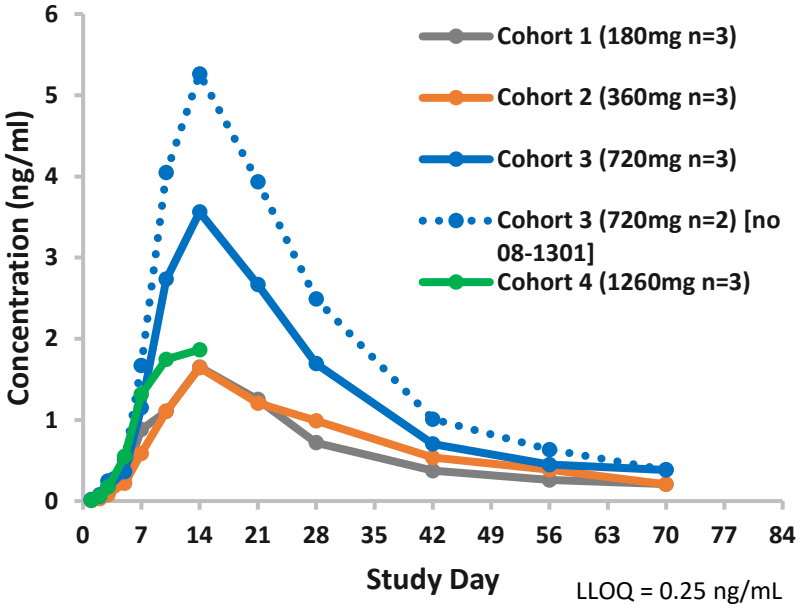
Phase 2a: Expansion ~48-54 patients | **Objective**: Compare plasma T / efficacy of 2 doses of PRL-02 vs. daily Zytiga



Phase 1: Predictable PK, Excellent Safety, Anti-tumor Activity

Plasma PK

- Abiraterone exposures mimic monkey results



Benign Safety Profile

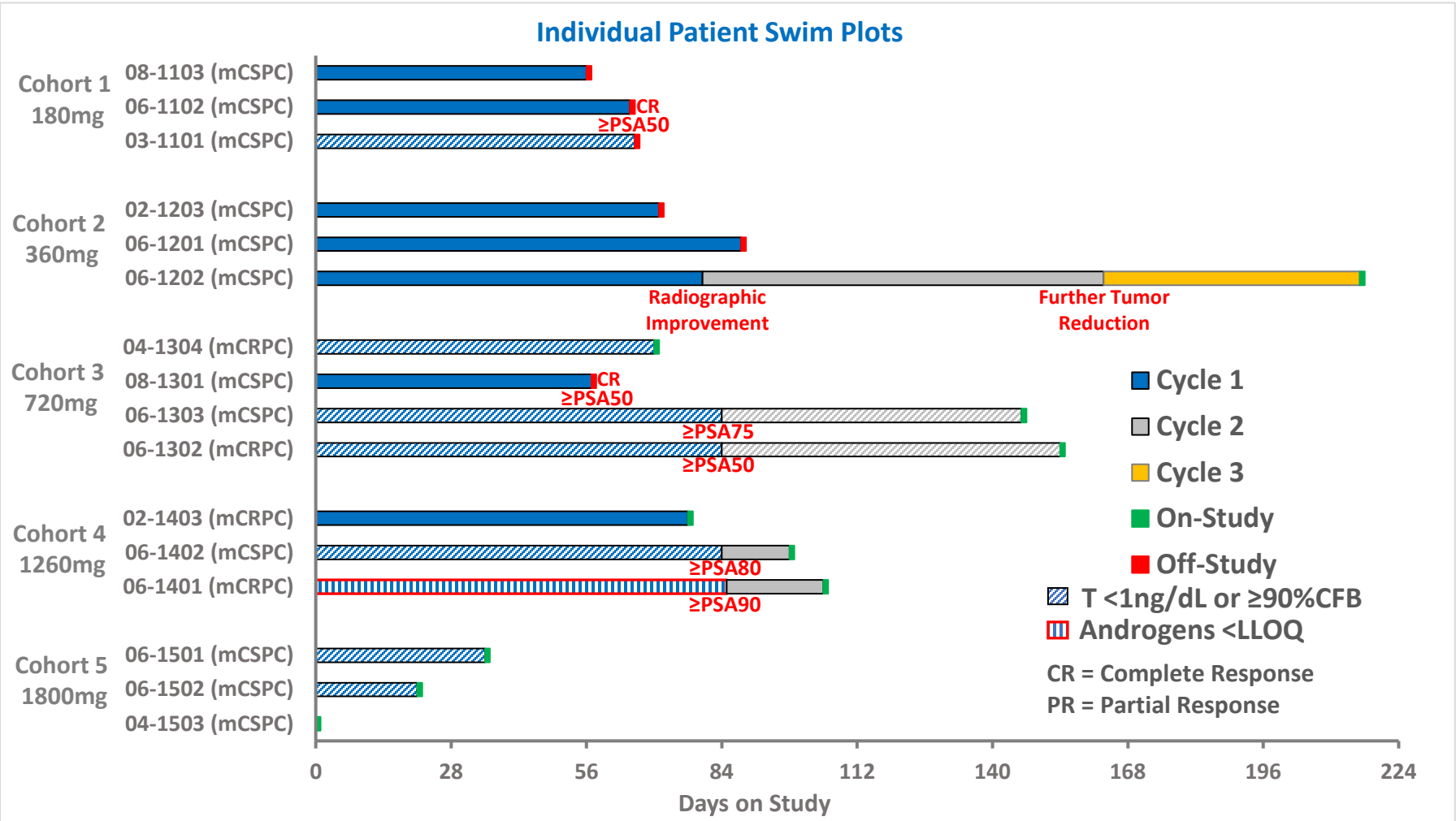
- No DLTs
- No related SAEs
- No signs of mineralocorticoid excess or related liver enzyme elevations
- No treatment discontinuations due to AEs
- Minimum severity of treatment-related adverse events (all G1):
  - flushing
  - hypernatremia
  - insomnia
  - gluteal soreness/bruising

Pharmacology (Efficacy)

- Androgen reductions to goal concentrations achieved for Cohorts 3 & 4 patients
- Lyase selectivity observed
- PSA reductions appear dose-dependent
- Radiographic responses reported for soft-tissue lesions (e.g., lymph) and bone
- Results to-date support broad clinical benefit

Note: Two cohort 3 curves +/- patient 08-1301 who had low/undetectable abiraterone levels as a result of a potential dosing error

COHORTS 1-5: Patient Swim Plots



- Note: Events (PSA and responses) are relative to study day
- Cohort 3
  - PSA responses (≥50% reduction) in all 3 patients with post-baseline measurements
- Cohort 4
  - Treatment Cycle 1 androgens reached LLOQ at multiple timepoints
  - PSA declines of 85% and 99% from baseline at Day 84 for both evaluable patients to date

PRL-02 Profile: Highly Differentiated from Zytiga®

	PRL-02	ZYTIGA
Primary CYP17 Inhibition MOA	**Lyase**	**Hydroxylase**
Route of Administration	**IM Injection**	**Oral**
Define Schedule (Magnitude and Durability of Androgen Reductions)	**Every 3 Months**	**Daily**
Define the Total Dose (90 Days)	**~1g**	**90g**
Establish no Safety or Efficacy Concerns due to Mineralocorticoid Excess	**None to date**	**Label Warnings**
Characterize Safety Profile	**Benign to date**	**Hepatotoxicity, DDIs, Hypertension, Hypokalemia[1]**
Explore Need for Glucocorticoid Supplementation (due to CYP17 lyase selectivity)	**Dexamethasone or NONE[2]**	**Approved only in combination with 5-10 mg daily prednisone**

[2] Opportunity to remove steroid due to lyase selectivity [1] Zytiga Label

PRL-02-1001: Status of RP2D Selection Criteria
An emerging Best-in-class Profile; Proof-of-Concept Achieved

	OBJECTIVE	PRIORITY	STATUS	COMMMENTS
Activity	Dose dependent CYP17 inhibition	1		Dose dependence observed cohorts 1-5
	Magnitude of 4-week androgen reductions at least on par with Zytiga	1		Demonstrated in cohorts 3, 4 and 5
	Durability: 12-week androgen reductions on par with Zytiga	2		Cohorts 3 & 4 results demonstrate 3-month durability
	RP2D is CYP17 lyase-selective	2		Confirmed through cohort 4 and into cohort 5
	PSA or Tumor Responses	3		Not a Ph 1 objective but tumor and PSA responses noted
Safety	Identify the RP2D	1		No DLTs identified in cohorts 1-5; (up to 10 mL)
	No treatment related liver effects or liver enzyme elevations at RP2D	2		Through Day 28 in cohort 4; none to date in cohort 5
	No signs of mineralocorticoid excess (e.g., hypertension, hypokalemia) at RP2D	2		Through Day 28 in cohort 4; none to date in cohort 5
	Safety is not dependent upon glucocorticoid supplementation	3		Not needed for RP2D but a strong advantage if shown

PRIORITY KEY 1=Needed for RP2D, 2=Nice to have, 3=Upside factor

STATUS KEY Complete, On Track, Pending, Will not be achieved

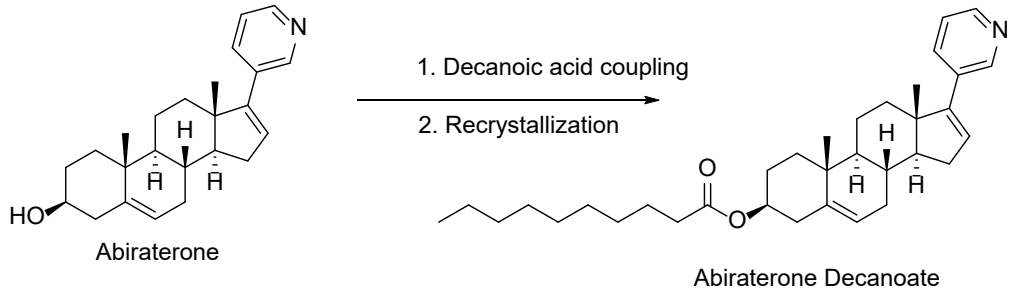
PRL-02 Indications Beyond Zytiga or AR Antagonists

	Localized Prostate Cancer "Neoadjuvant"	Ovarian Cancer	Endometrial Cancer
Known to express CYP17	✓	✓	✓/–
Potential for lymphatic targeting	✓	✓	✓
Tumor growth driven by steroids upstream of CYP17 hydroxylase	✓	✓	✓
Known clinical benefit of androgen-directed therapy	✓	✓/–	✓

Through lymphatic targeting and PRL-02's CYP17 lyase selectivity and excellent safety profile it appears ideally suited for the treatment of additional, high unmet need, hormone driven cancer indications.

PRL-02 CMC Status

- **Drug Substance: Abiraterone Decanoate**
  - Straightforward GMP synthetic process, from abiraterone
  - Abiraterone is widely available and low cost

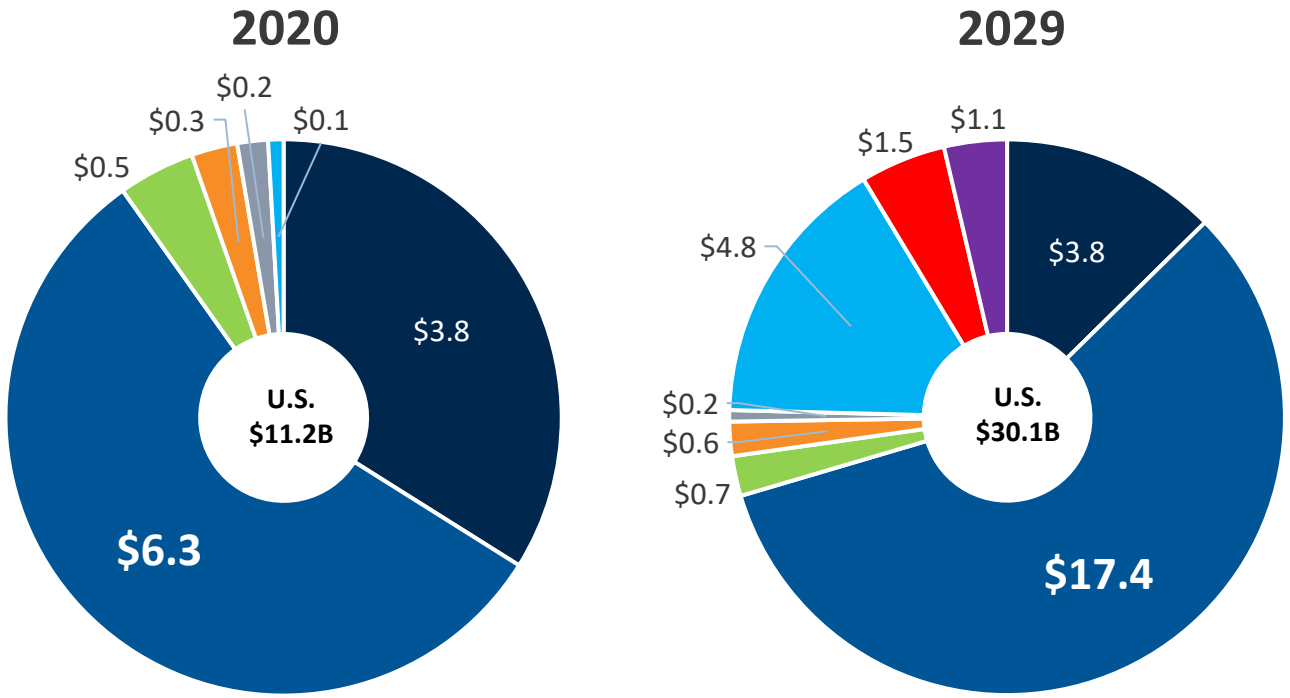


- **Drug Product (IM PRL-02)**
  - Scalable GMP process developed by manufacturer with global capabilities
  - Sufficient API on-hand to support clinical needs into Phase 2

- **Very Low COGS**

PRL-02: Strong US Market Opportunity ($ in Billions)*

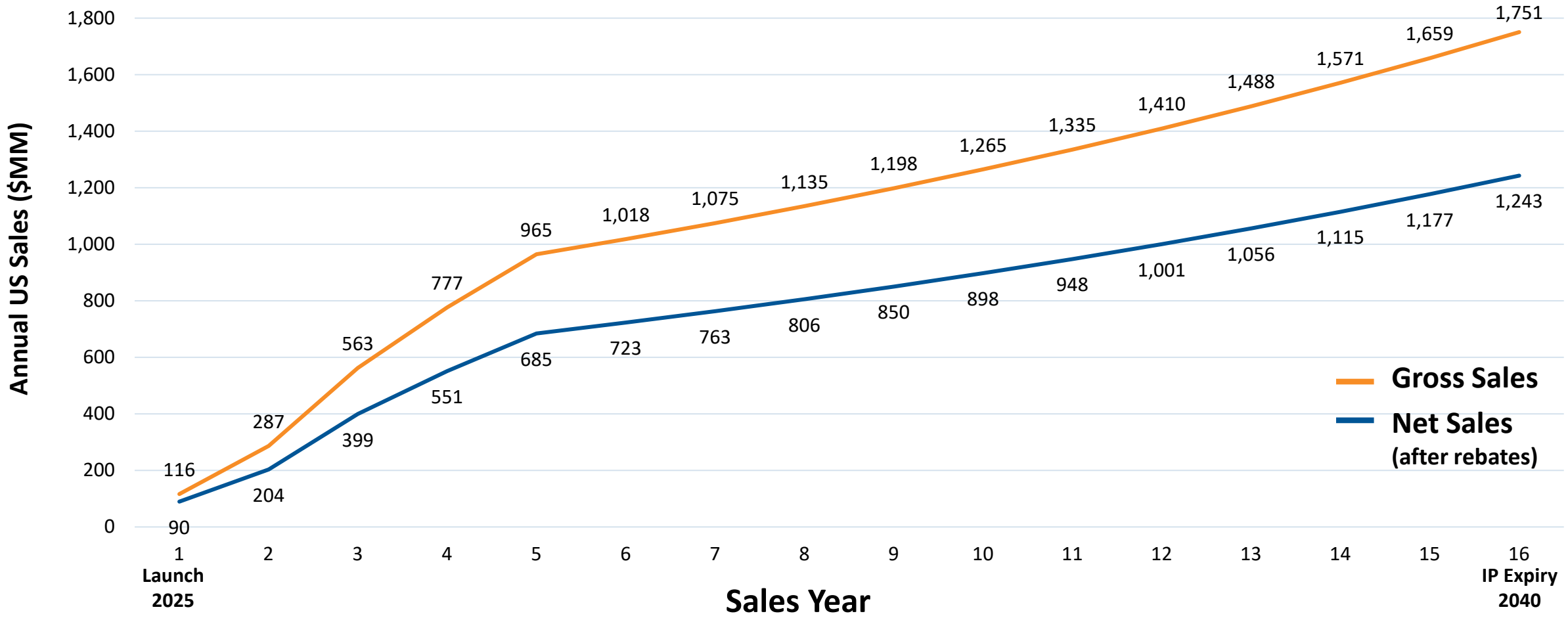
- Hormonal ADT
- **AR-directed therapies (ZYTIGA/XTANDI)**
- Cytotoxic agents
- Bone metastases-targeted agents
- Therapeutic vaccines
- PARP inhibitors
- Kinase inhibitors
- PSMA-targeted radioligands



AR-directed therapies expected to grow from $6.3 billion in 2020 to $17.4 billion in 2029

* "The Prostate Cancer Drug Market", Nature Reviews – Drug Discovery; do Pazo, C., Webster, R.; June 18, 2021

PRL-02: Robust US Sales Forecast



Pharma Deals: Large Players and Terms; Little Recent Innovation

Innovator	Acquirer / Partner	Product	MOA	Stage	Transaction Type	Terms
Cougar	JNJ	Abiraterone Acetate	CYP17 Inhibitor	Phase 2	Acquisition (2009)	$1B
Medivation	1. Astellas 2. Pfizer	Enzalutamide	AR Antagonist	Phase 2	License (2009) Acquisition (2016)	$750M ($110M upfront); $15B
Aragon	JNJ	Apalutamide	AR Antagonist	Phase 2	Acquisition (2013)	$1B ($650M upfront)
Orion	Bayer	Darolutamide	AR Antagonist	Phase 2	Co-development (2014); Bayer paid for all clinical development	$50M upfront plus significant milestones and royalties

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