

Using PSA Dynamics to Optimize Docetaxel Scheduling in Metastatic Prostate Cancer

Renee Brady-Nicholls, Ph.D.

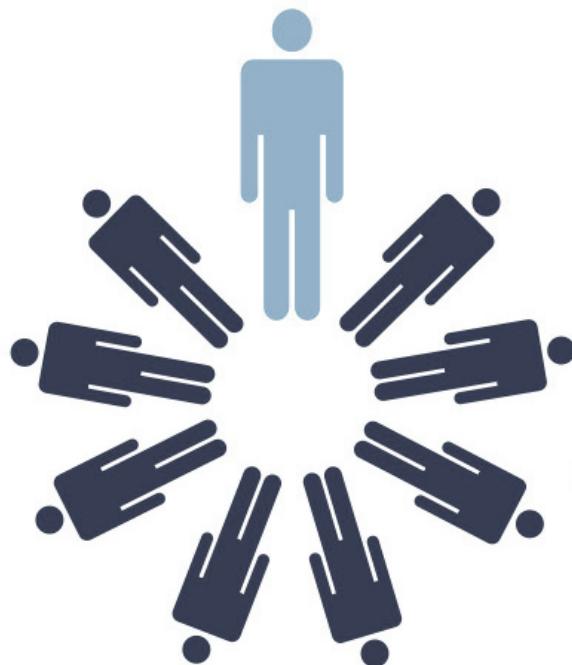
Research Instructor

Integrated Mathematical Oncology

H. Lee Moffitt Cancer & Research Institute

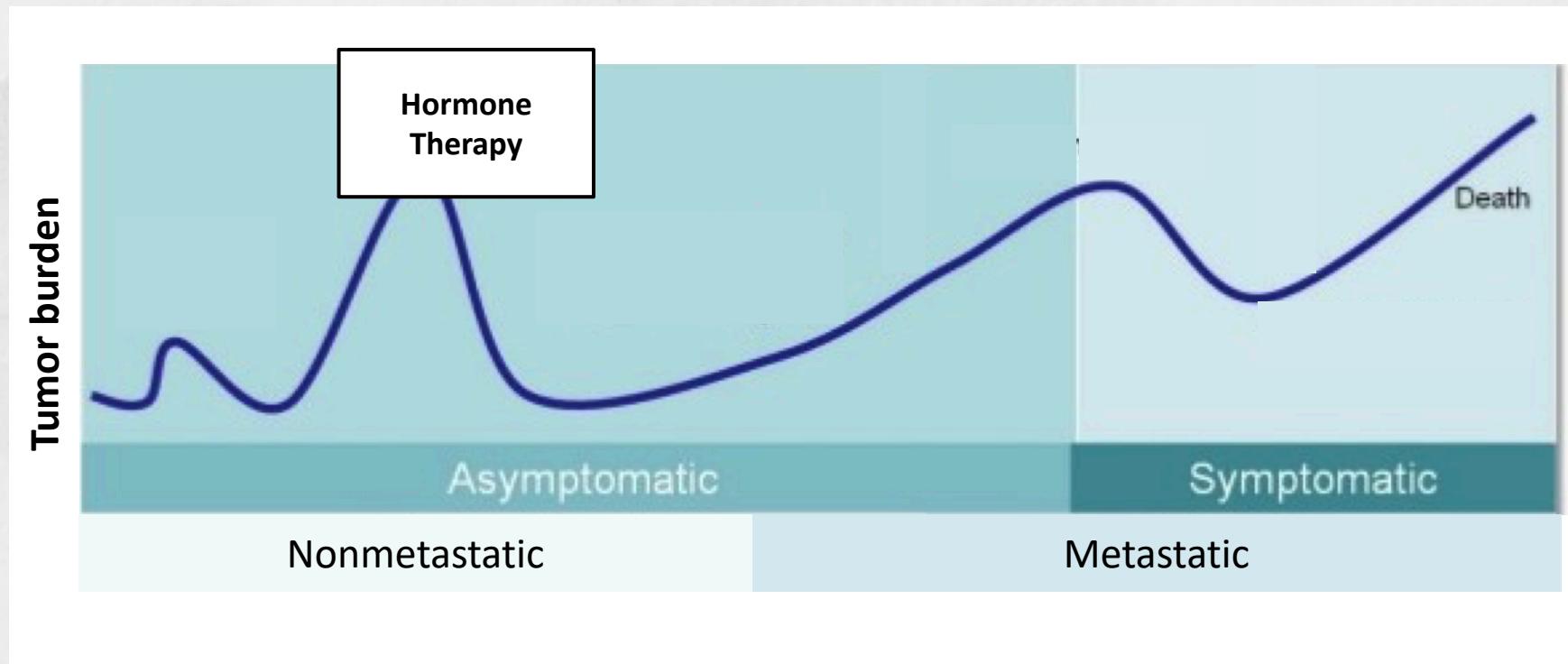
renee.brady@moffitt.org

PROSTATE CANCER



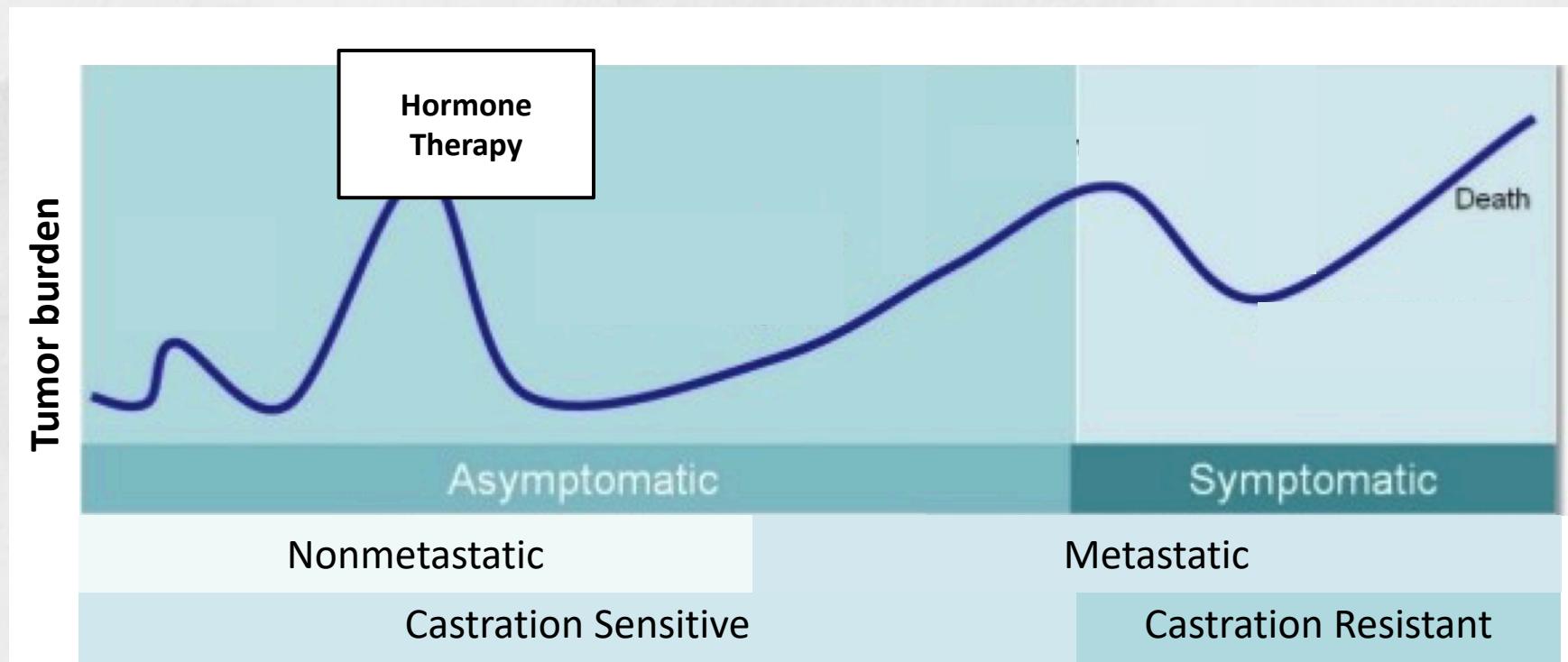
1 in 9
AMERICAN MEN WILL
GET PROSTATE CANCER
DURING HIS LIFETIME

TREATING PROSTATE CANCER



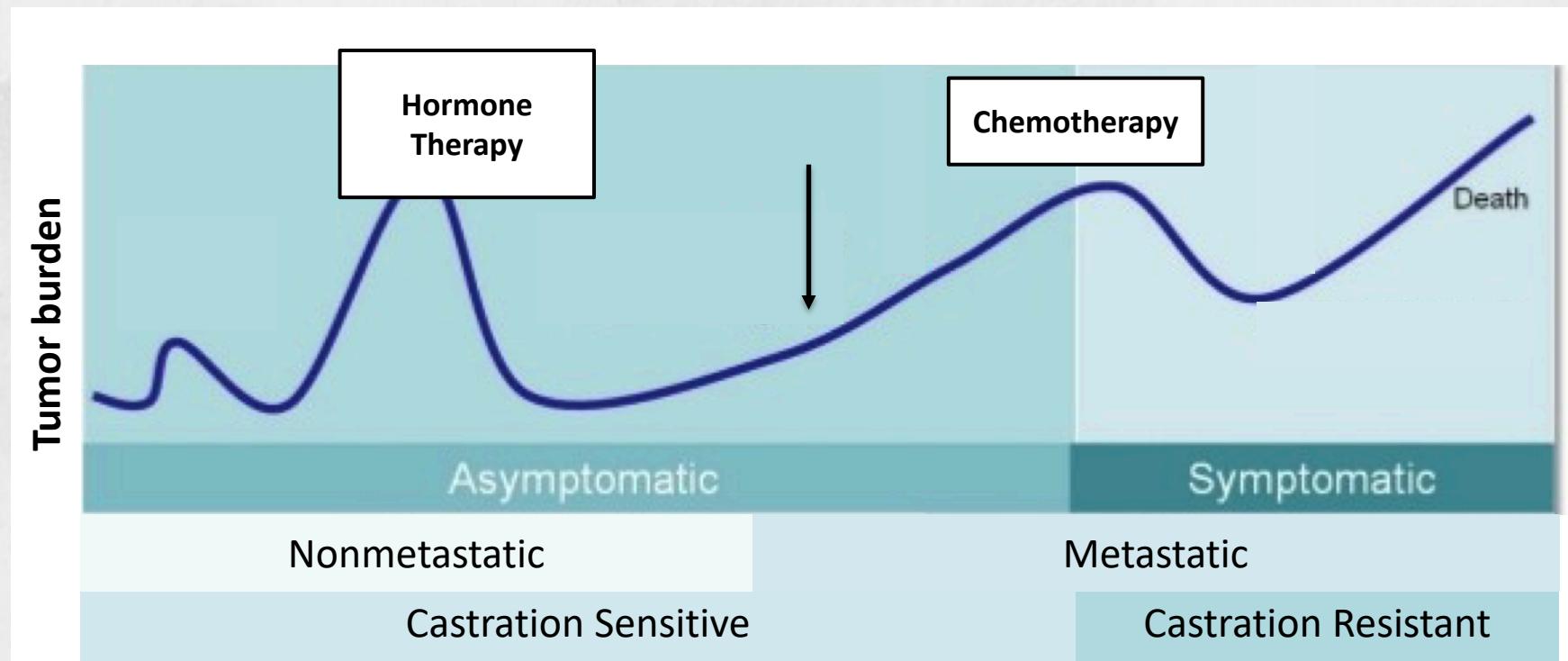
Androgen deprivation therapy has been the mainstay treatment for over 70 years!

TREATING PROSTATE CANCER



Median survival in metastatic prostate cancer patients receiving ADT is ~3 years

TREATING PROSTATE CANCER



Is it more beneficial to give chemotherapy prior to the development of castration resistant disease?

CASTRATION SENSITIVE

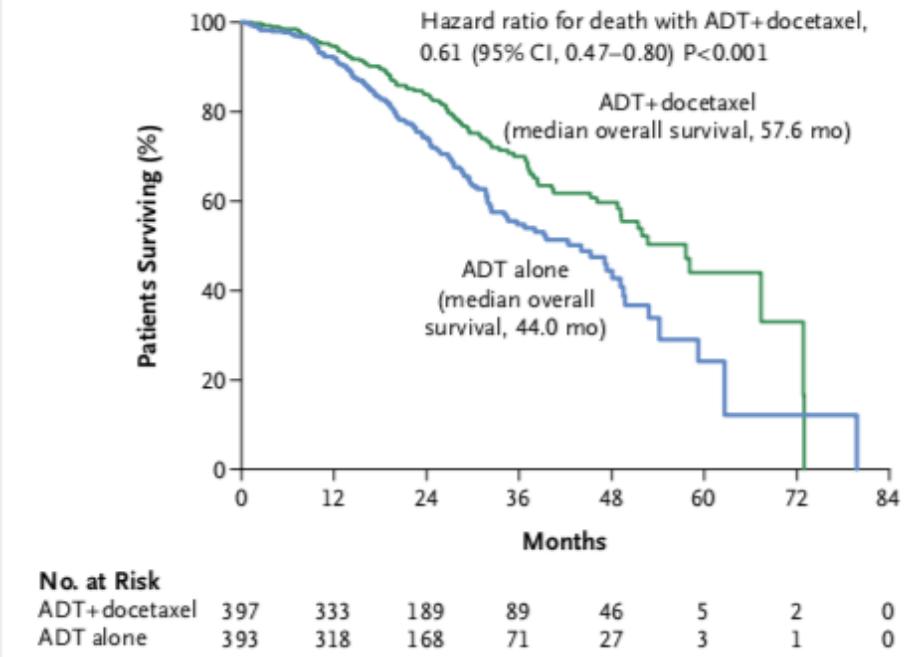
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer

Christopher J. Sweeney, M.B., B.S., Yu-Hui Chen, M.S., M.P.H., Michael Carducci, M.D., Glenn Liu, M.D., David F. Jarrard, M.D., Mario Eisenberger, M.D., Yu-Ning Wong, M.D., M.S.C.E., Noah Hahn, M.D., Manish Kohli, M.D., Matthew M. Cooney, M.D., Robert Dreicer, M.D., Nicholas J. Vogelzang, M.D., Joel Picus, M.D., Daniel Shevrin, M.D., Maha Hussain, M.B., Ch.B., Jorge A. Garcia, M.D., and Robert S. DiPaola, M.D.

A All Patients



Early chemotherapy extended overall survival by 13 months in castration sensitive metastatic patients when compared to ADT alone

CASTRATION RESISTANT

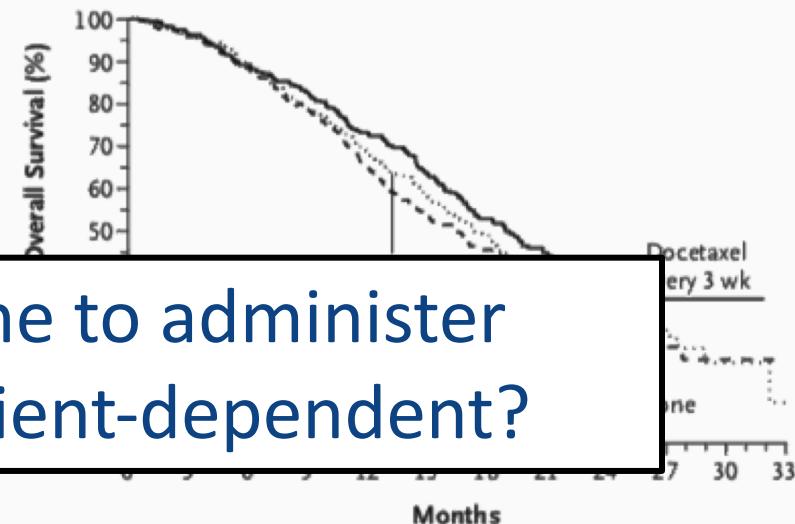
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

D
plus
lat

What is the optimal time to administer chemotherapy? Is it patient-dependent?

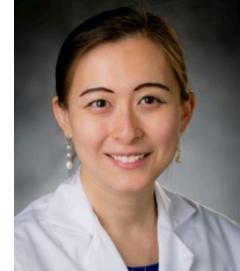
Nicholas D. James, M.D., Ph.D., Ingela Turesson, M.D., Ph.D.,
Mark A. Rosenthal, M.D., Ph.D., and Mario A. Eisenberger, M.D.,
for the TAX 327 Investigators



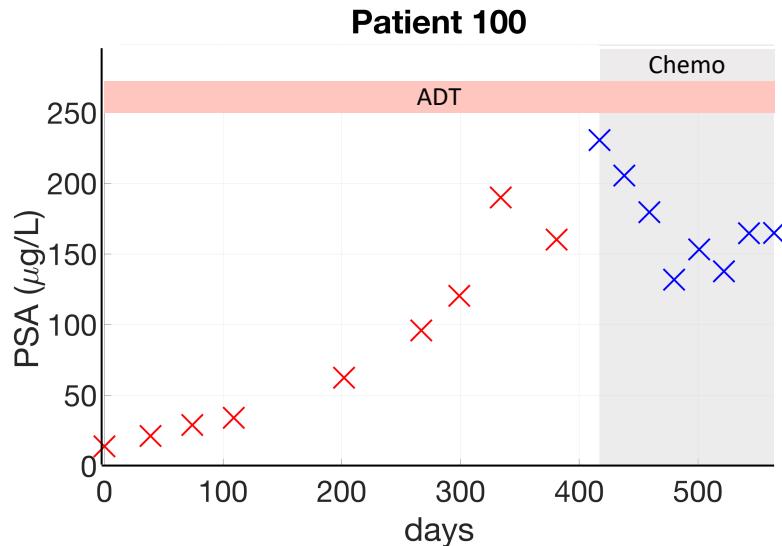
No. at Risk	0	12	24	33	48	60	72
Docetaxel every 3 wk	335	296	217	104	37	5	
Weekly docetaxel	334	297	200	105	29	4	
Mitoxantrone	337	297	192	95	29	3	

Administering chemotherapy after castration resistant PCa development extended overall survival by just 2.4 months

Biomarker

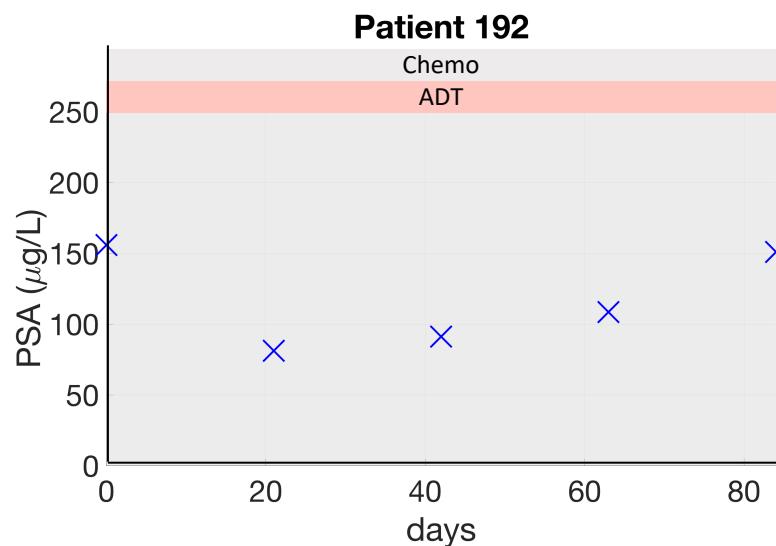


Castration Resistant



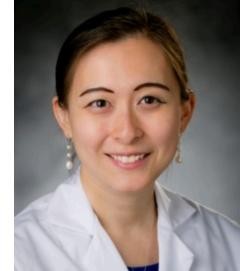
- 38 patients
- ADT alone followed by up to 10 cycles of chemotherapy

Castration Naïve

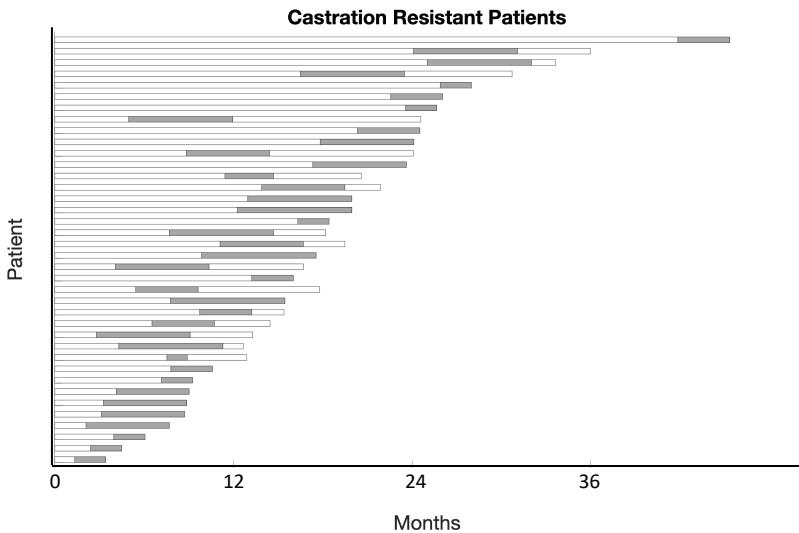


- 56 patients
- ADT with up to 6 cycles of chemotherapy concurrently

Biomarker

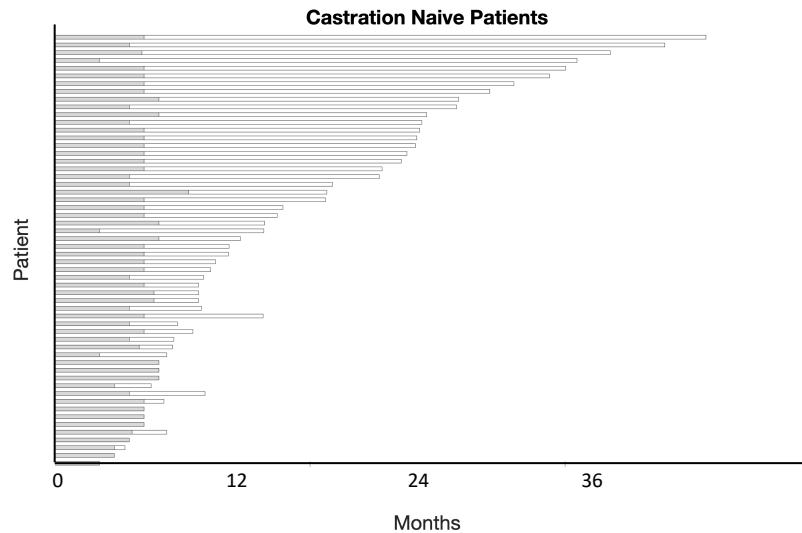


Castration Resistant



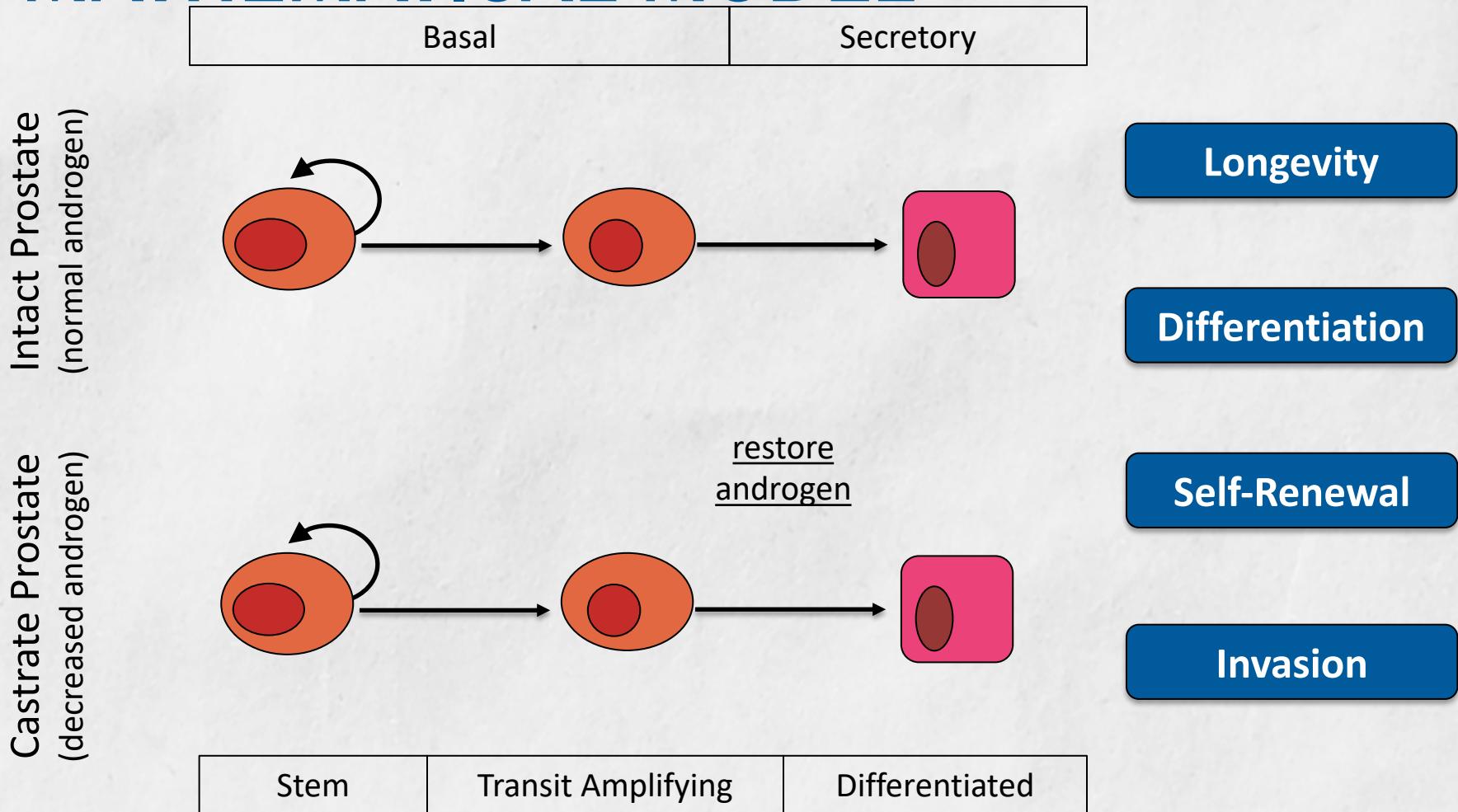
- 38 patients
- ADT alone followed by up to 10 cycles of chemotherapy

Castration Naïve

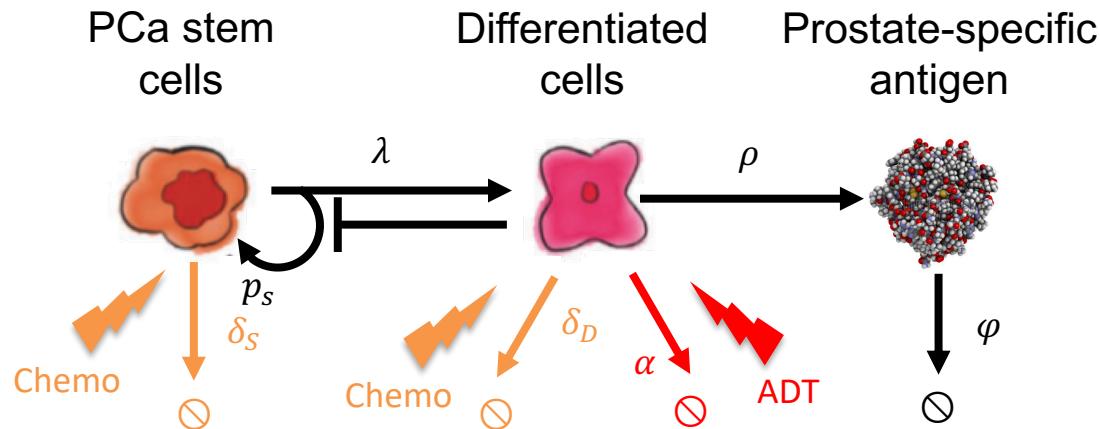


- 56 patients
- ADT with up to 6 cycles of chemotherapy concurrently

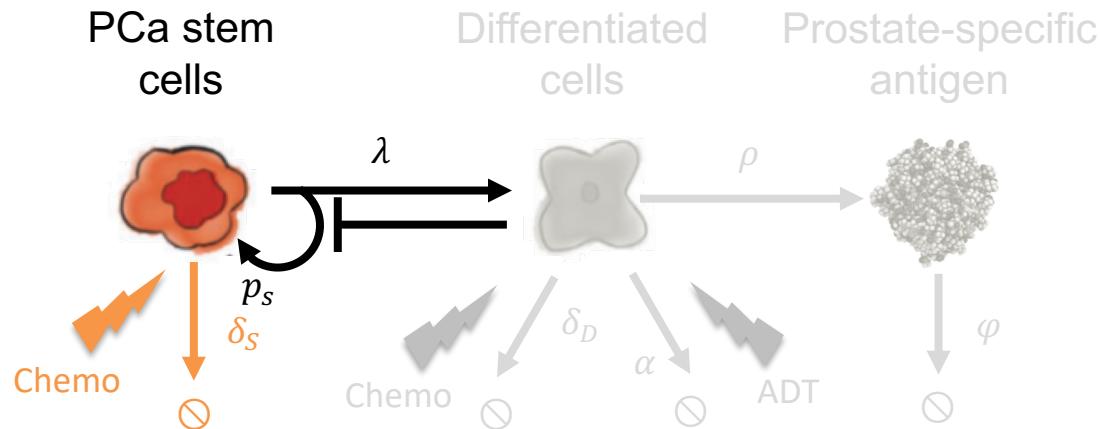
MATHEMATICAL MODEL



MATHEMATICAL MODEL

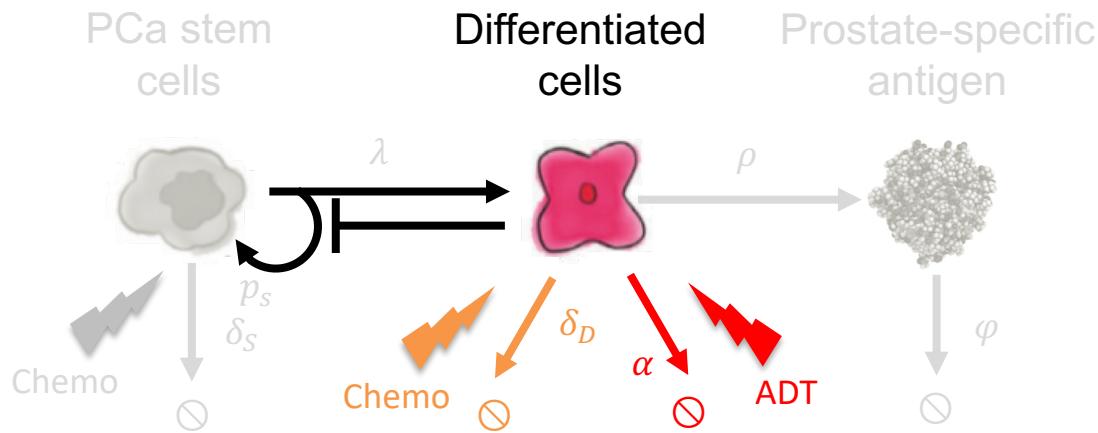


MATHEMATICAL MODEL



$$\frac{dS}{dt} = \left(\frac{S}{S + D} \right) p_s \lambda S - \delta_S T_{xD} S$$

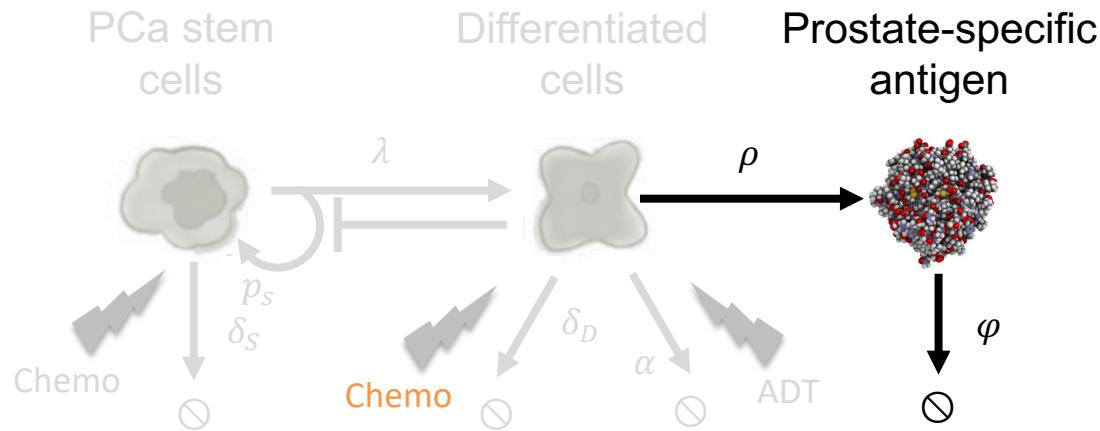
MATHEMATICAL MODEL



$$\frac{dS}{dt} = \left(\frac{S}{S + D} \right) p_s \lambda S - \delta_S T_{xS} S$$

$$\frac{dD}{dt} = \left(1 - \left(\frac{S}{S + D} \right) p_s \right) \lambda S - \alpha T_x D - \delta_D T_{xD} D$$

MATHEMATICAL MODEL



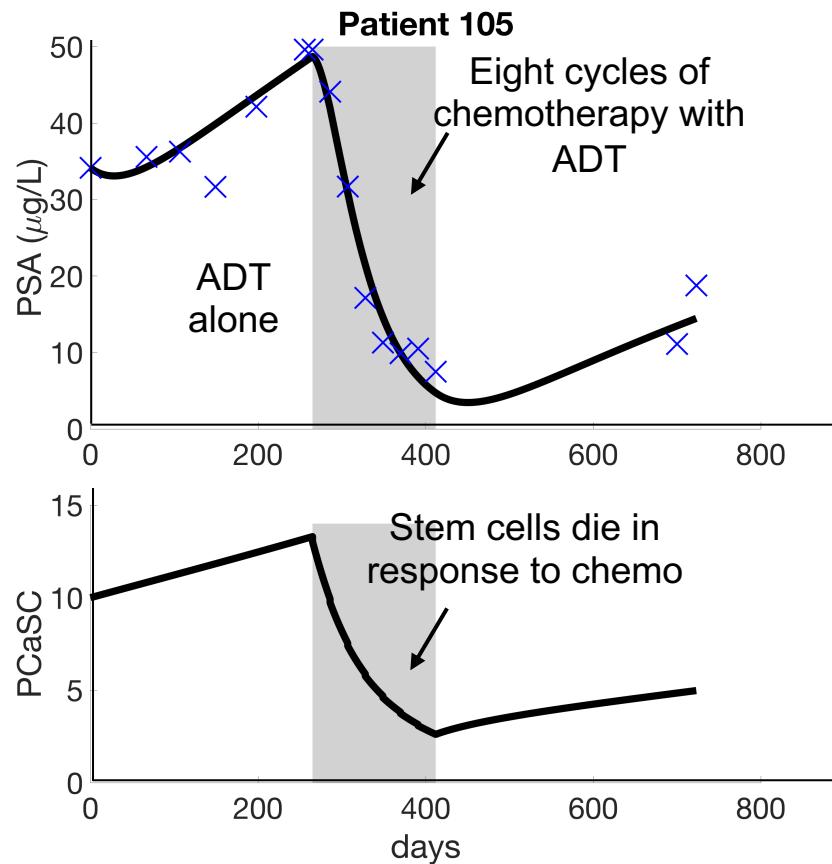
$$\frac{dS}{dt} = \left(\frac{S}{S + D} \right) p_s \lambda S - \delta_S T_{xS} S$$

$$\frac{dD}{dt} = \left(1 - \left(\frac{S}{S + D} \right) p_s \right) \lambda S - \alpha T_x D - \delta_D T_{xD} D$$

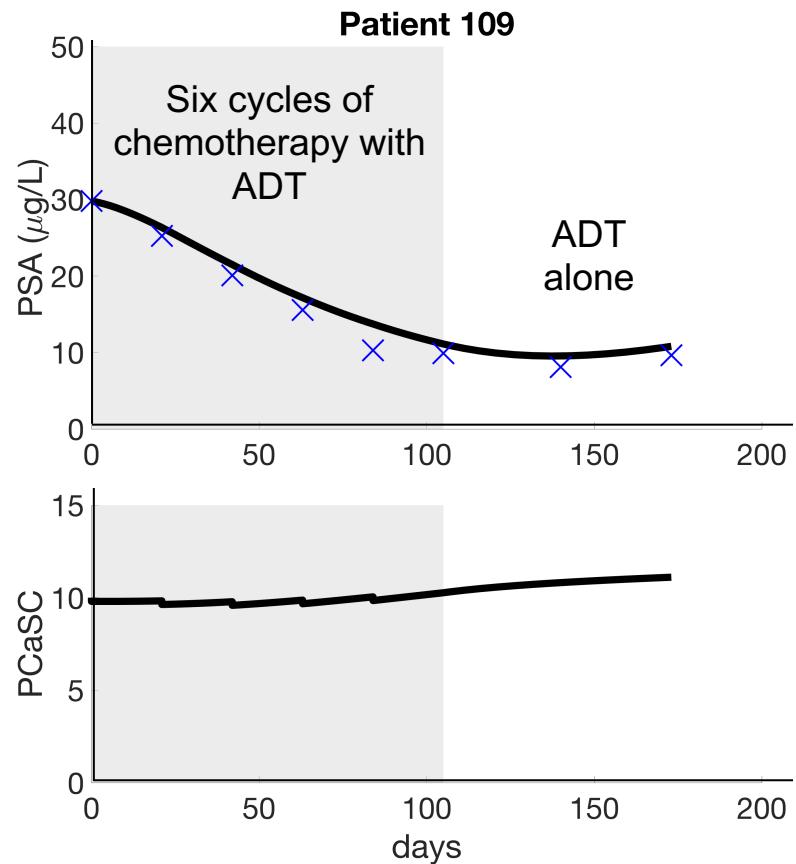
$$\frac{dP}{dt} = \rho D - \varphi P$$

MODEL CALIBRATION

Castration Resistant

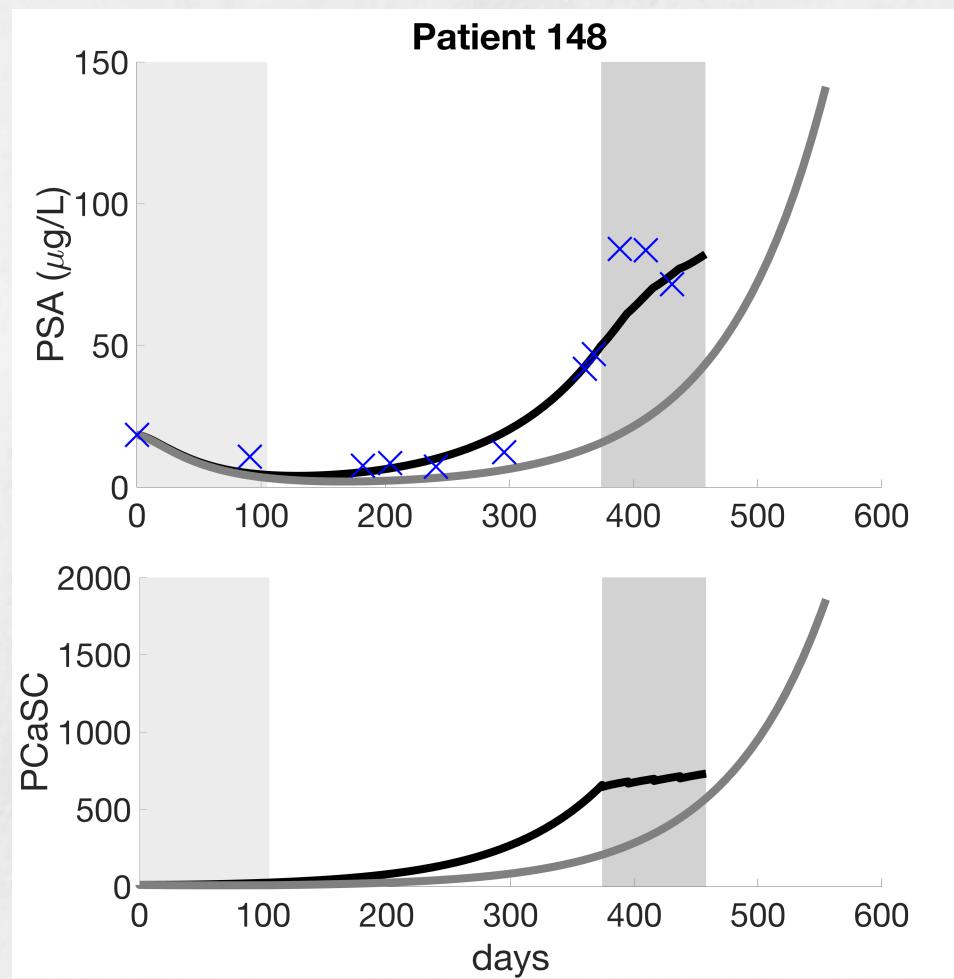


Castration Naïve



EARLY VS. LATE

Castration
Resistant

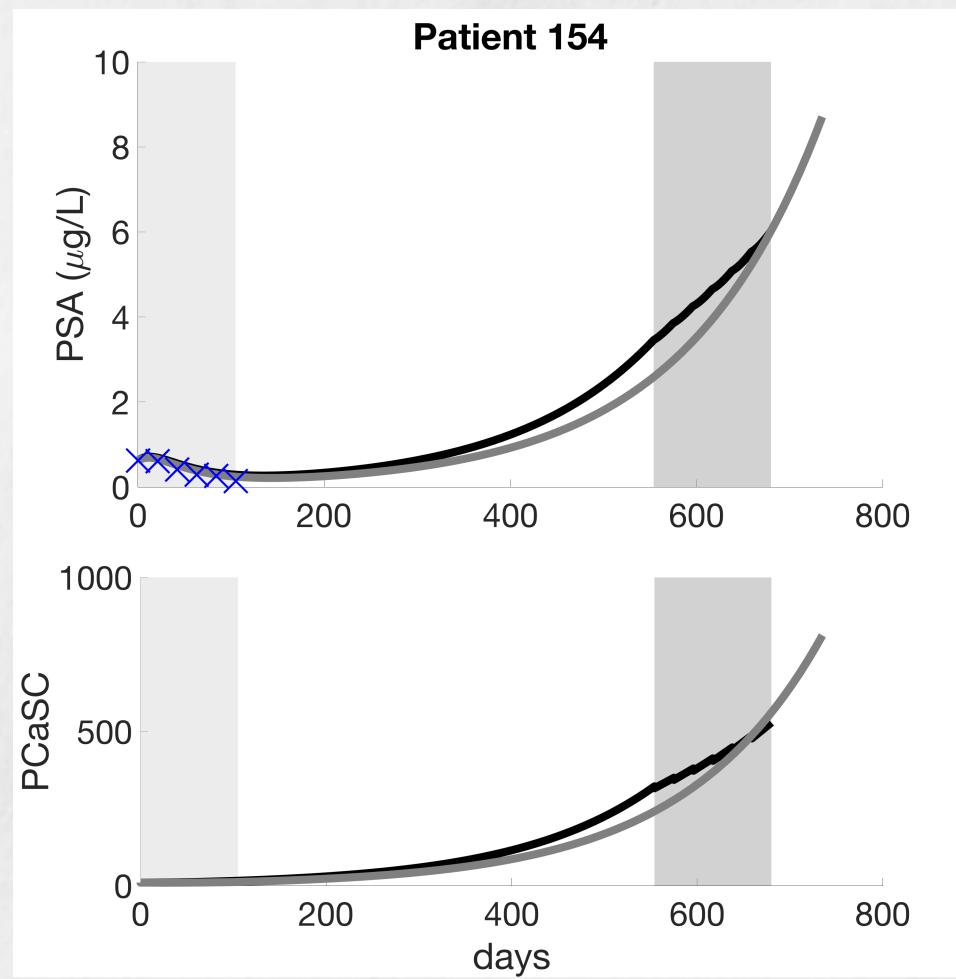


Early > Late

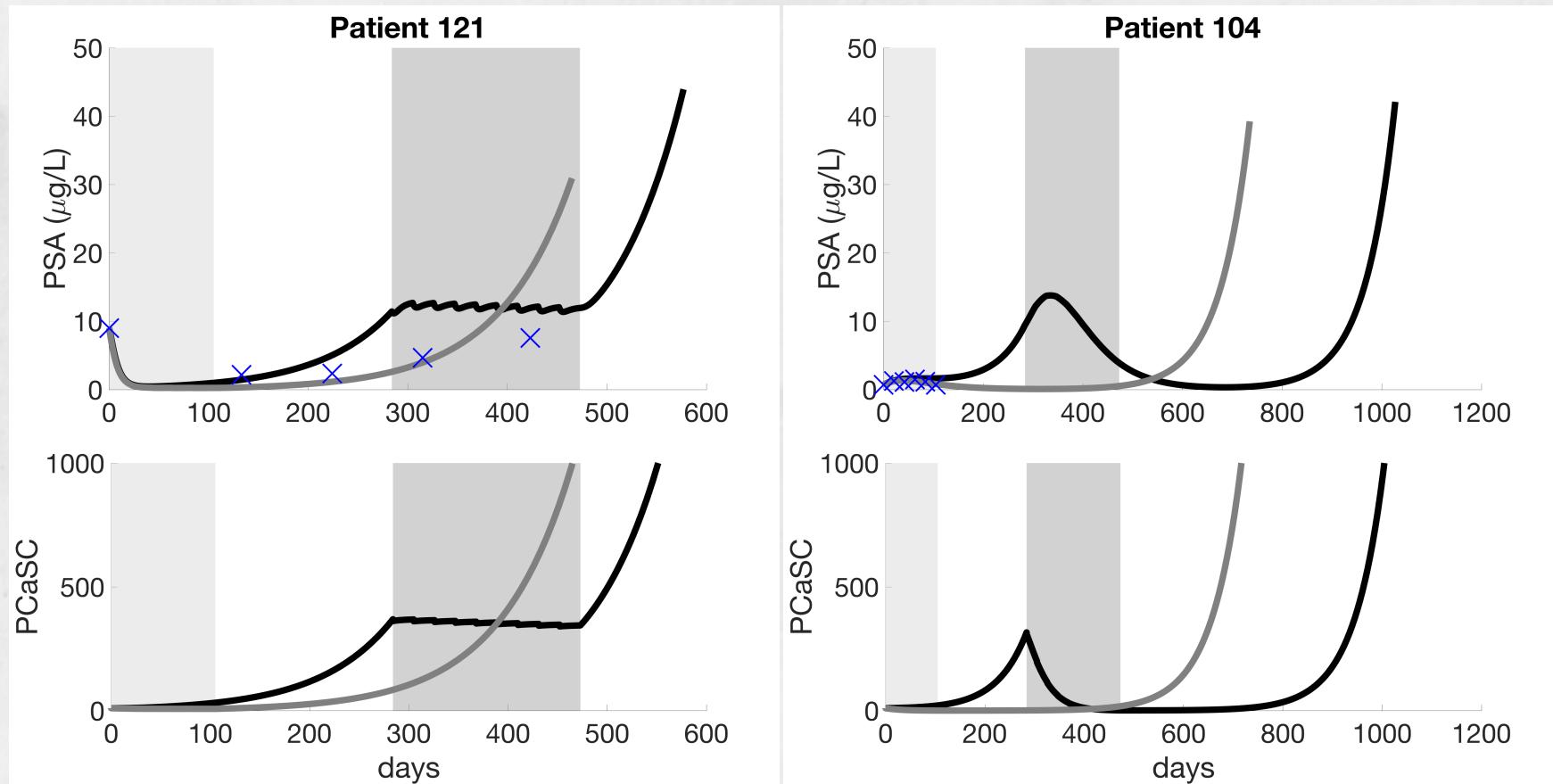
EARLY VS. LATE

Castration
Naïve

Early > Late



EARLY VS. LATE

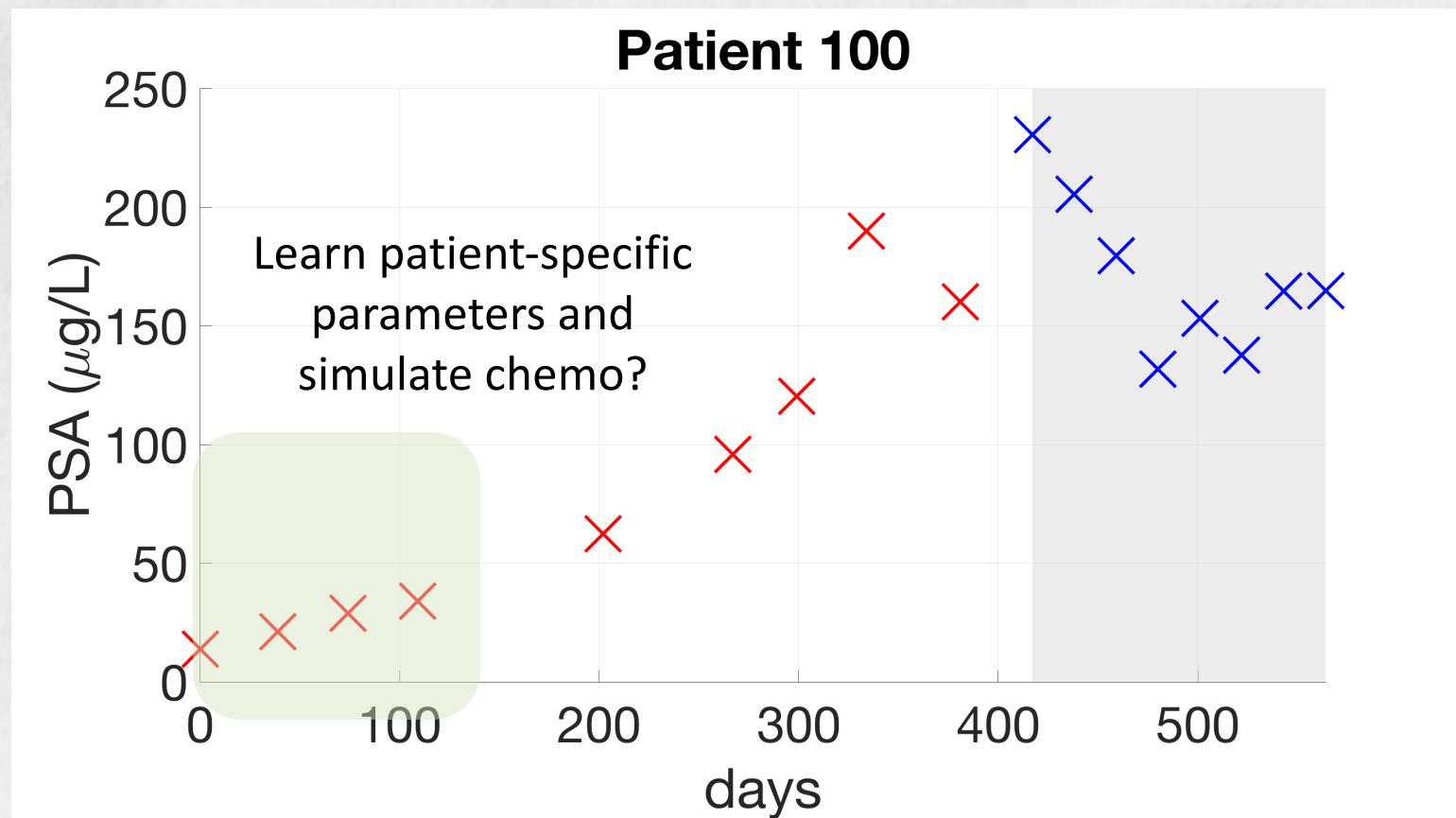


Early < Late

TAKEAWAYS

- Optimal chemotherapy timing is patient-specific
- Stem cell self-renewal was primary driver of resistance in intermittent hormone therapy study
 - Does this separate patients who need chemo early vs late?

CAN WE LEARN THIS EARLY?



SUMMARY

- Extended stem cell model to investigate optimal time to administer chemotherapy after hormone therapy
- Model can accurately describe PSA dynamics in both early and late chemotherapy settings
- Model simulations imply that timing may be patient-specific, but may be best to give prior to mCRPC development

ACKNOWLEDGEMENTS

@EnderlingLab



MOFFITT
CANCER CENTER



Robert A.
Gatenby



Jingsong
Zhang



Travis A.
Gerke



Tian
Zhang



Andrew Z.
Wang



John D.
Nagy