Hormone Therapy Resistance Historical Perspective

November 21, 2024

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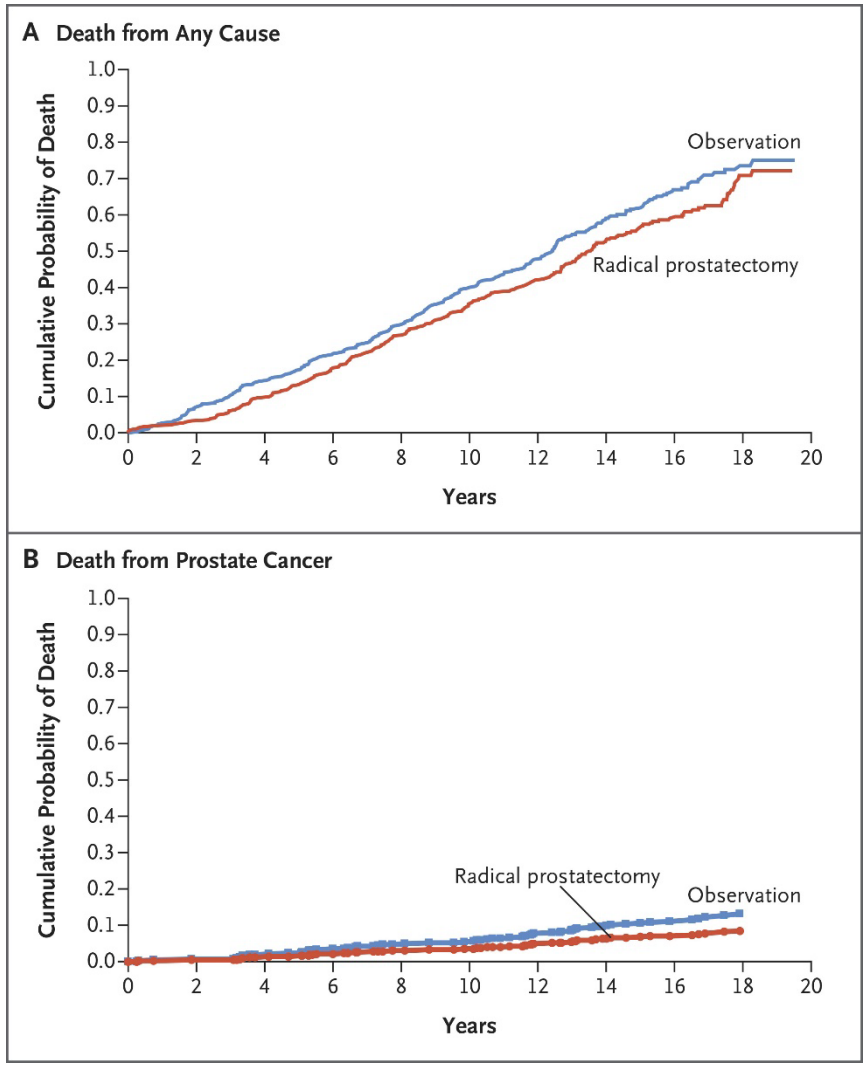
Human Oncology and Pathogenesis Program

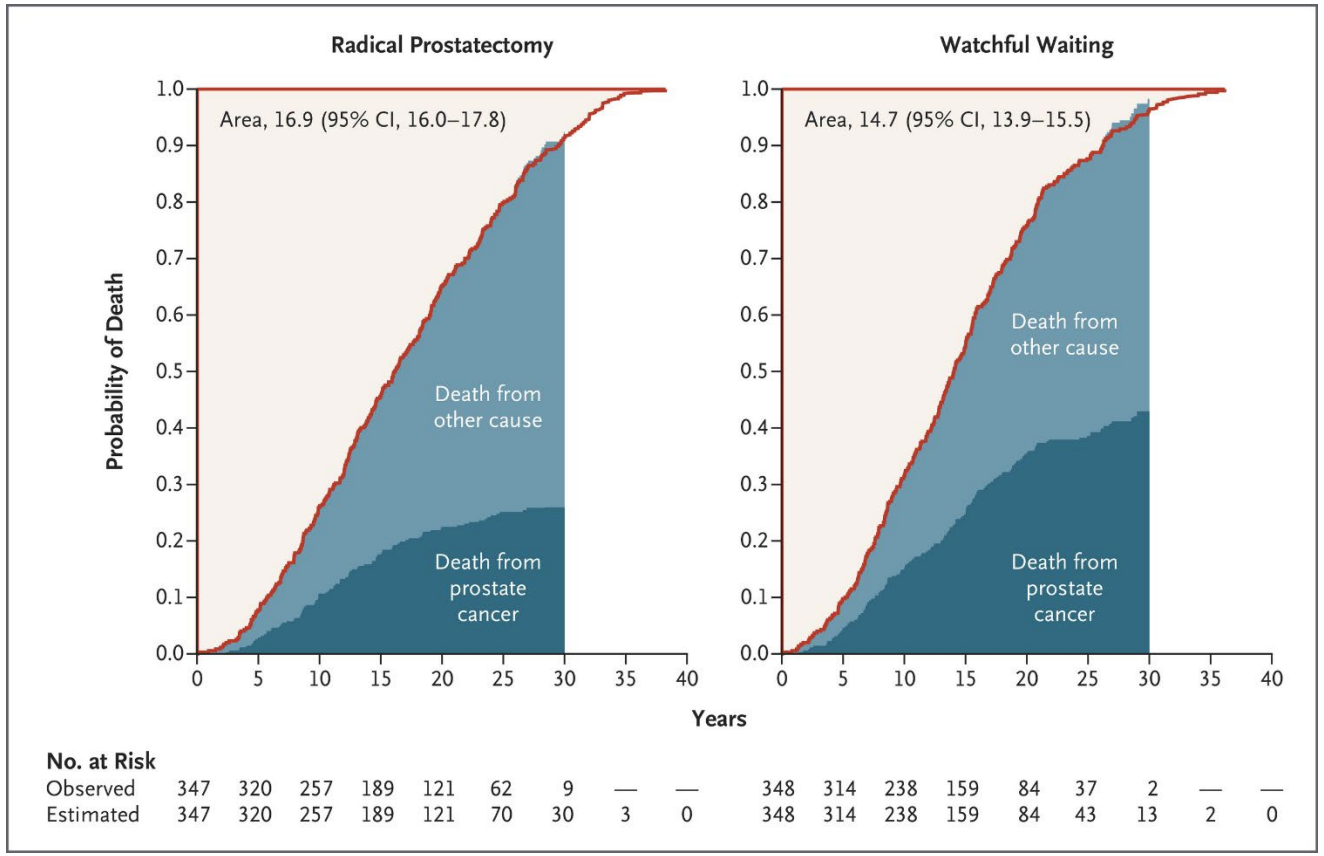
Department of Medicine

Prostate Cancer Intervention versus Observation Trial (PIVOT). (1994 – 2002, PSA Era)



Wilt, TJ et. al. NEJM 2017

Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) (1989 – 1999, Pre-PSA)



Holmberg, L et. al. NEJM 2024

Lineage therapy in prostate cancer

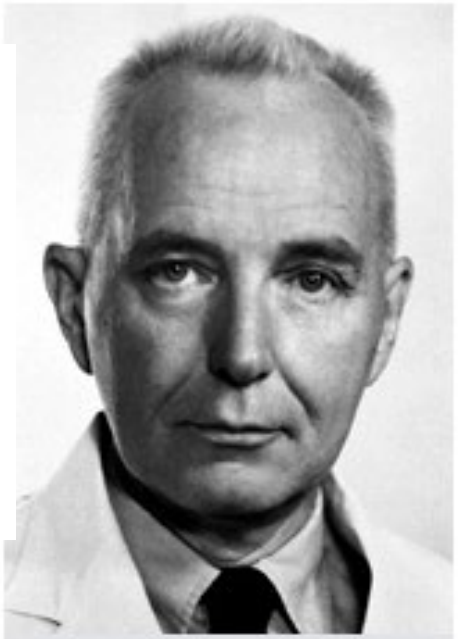
Studies on Prostatic Cancer

I. The Effect of Castration, of Estrogen and of Androgen Injection on Serum Phosphatases in Metastatic Carcinoma of the Prostate*

Charles Huggins, M.D., and Clarence V. Hodges, M.D.

(From the Department of Surgery, the University of Chicago, Chicago, Illinois)

(Received for publication March 22, 1941)



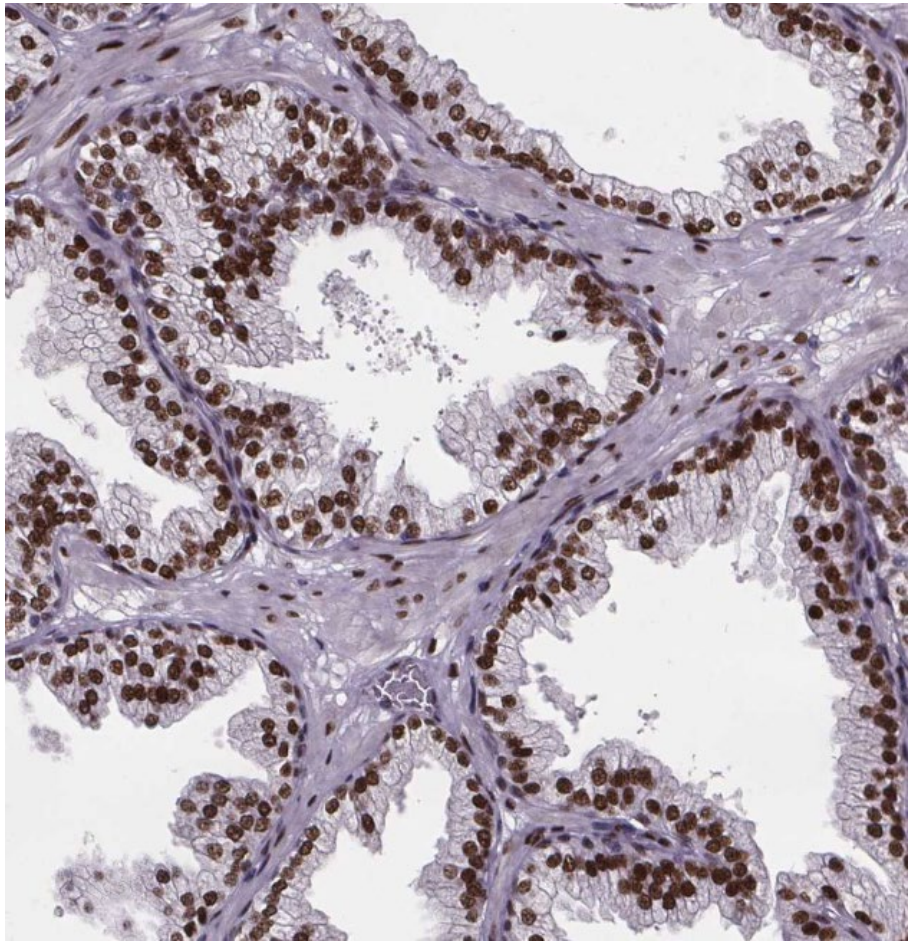
Charles Brenton Huggins

1966 Nobel Lecture

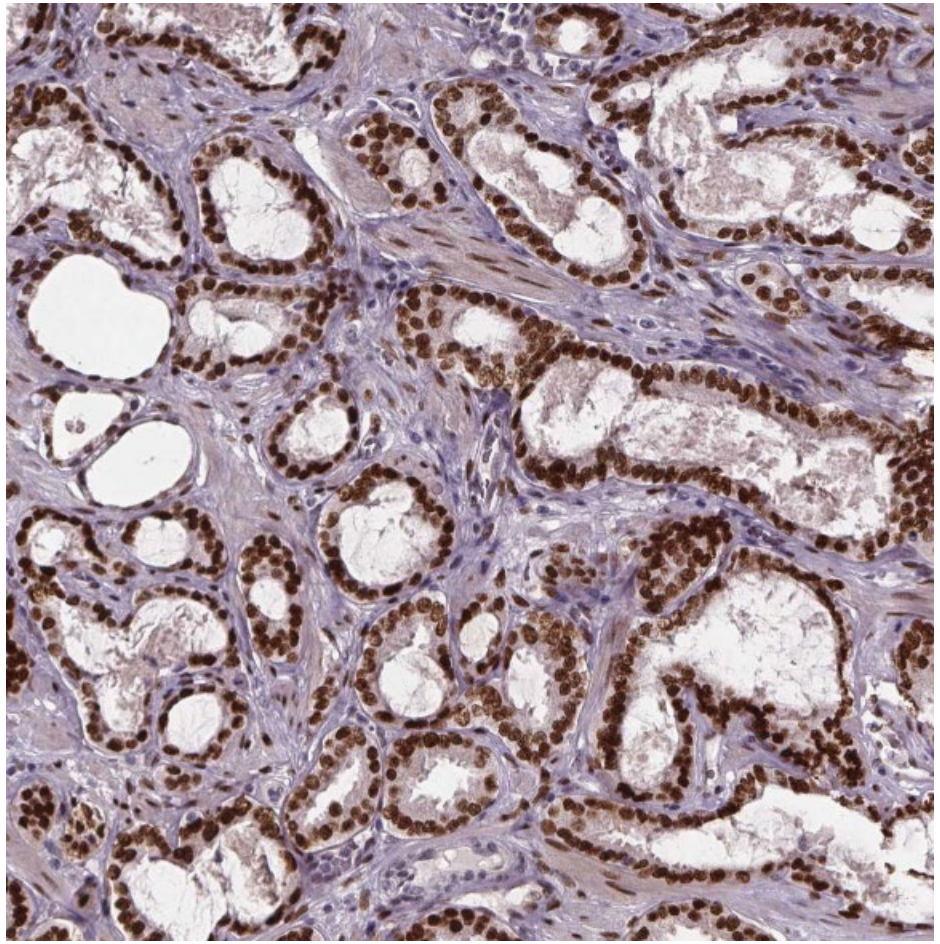
The first series of patients with prostatic cancer treated by orchiectomy [16] comprised 21 patients with far advanced metastases; only 4 of them survived for more than 12 years. Despite regressions of great magnitude, it is obvious that there were many failures of endocrine therapy to control the disease but; on the whole, the life span had been extended by the novel treatments and there had been a decrease of man-pain hours.

The androgen receptor (AR) is the target of androgen deprivation therapy

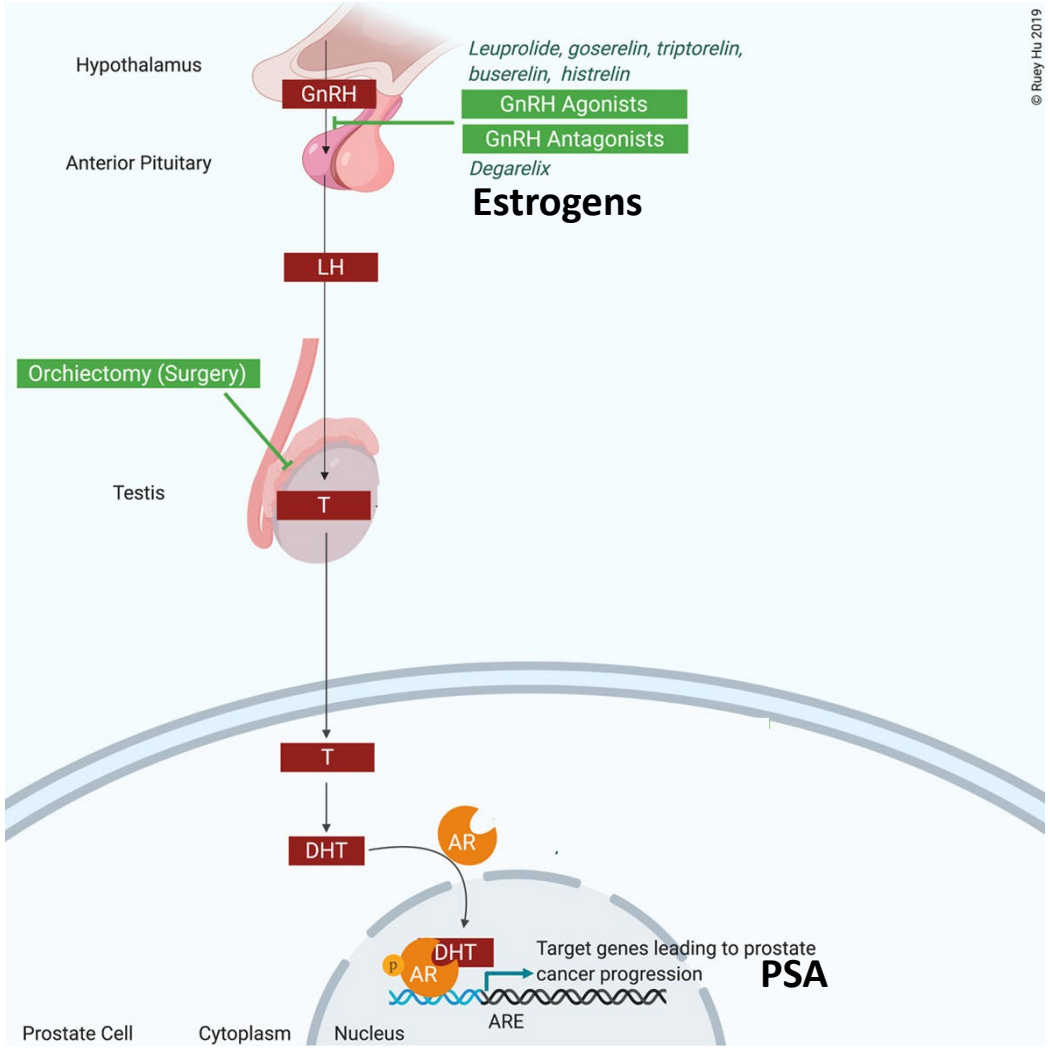
Benign Prostate



Prostate Cancer

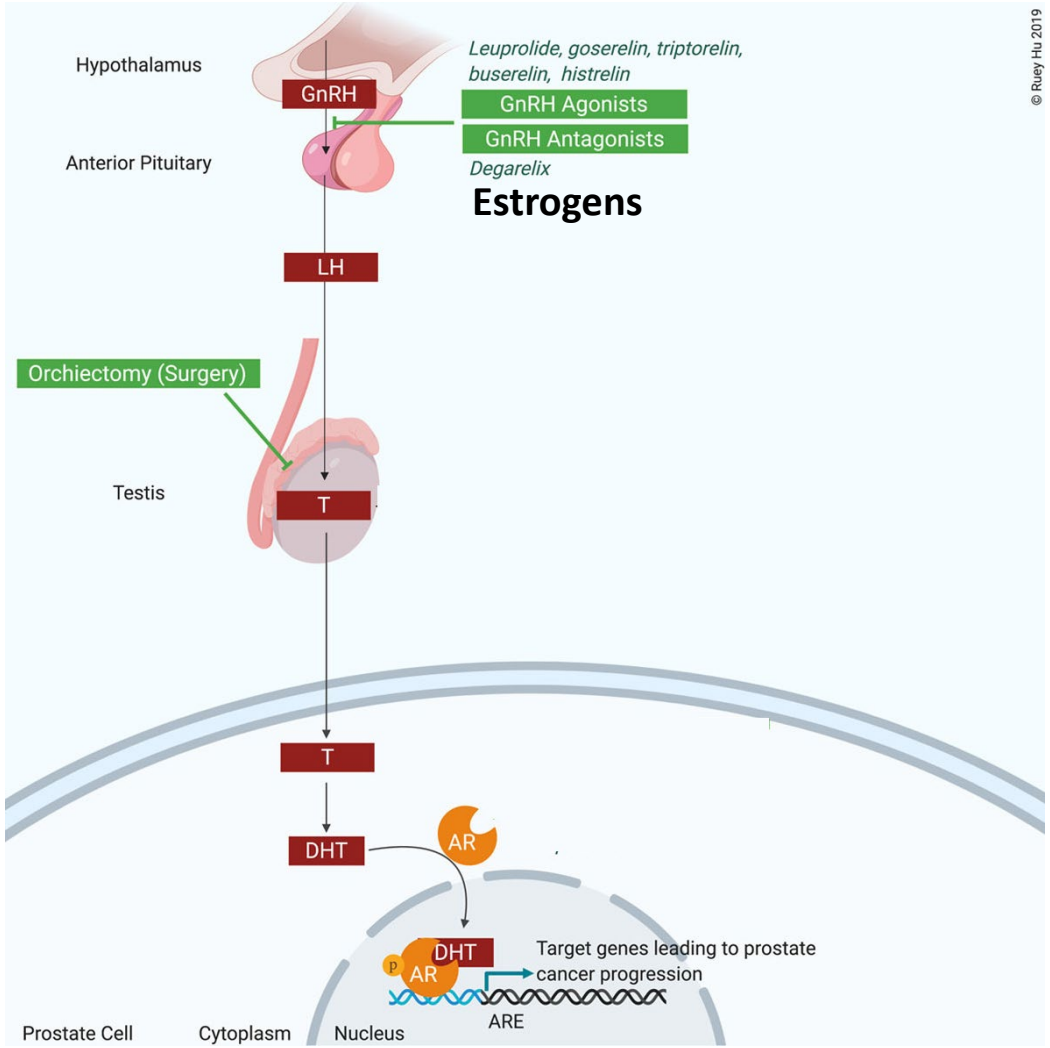


GnRH Antagonists leads to more rapid testosterone decline

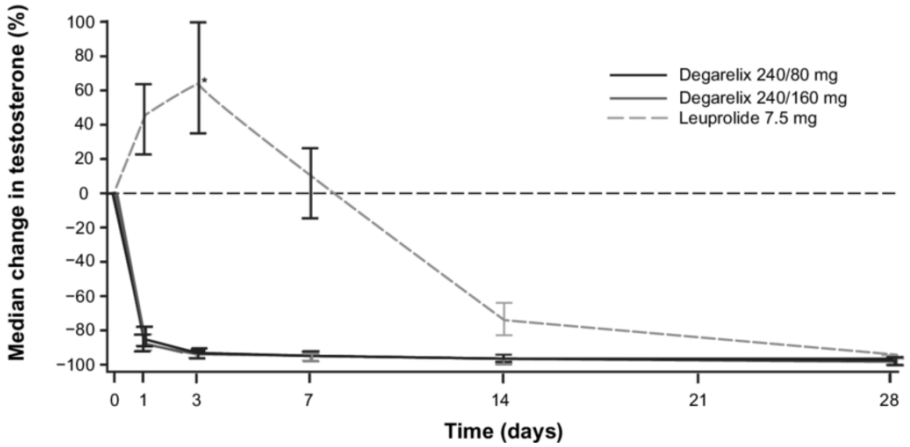


Hu JR, et. al. Arterioscler Thromb Vasc Biol. 2020

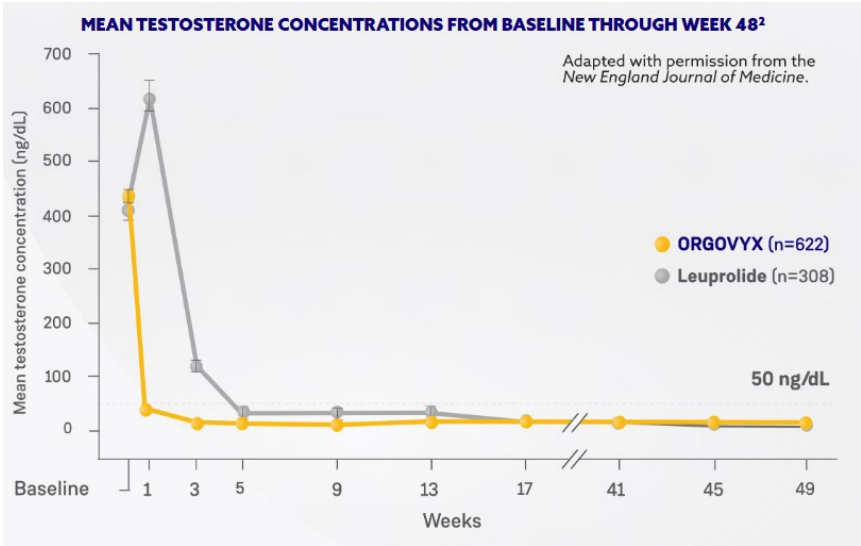
GnRH Antagonists leads to more rapid testosterone decline



Hu JR, et. al. Arterioscler Thromb Vasc Biol. 2020

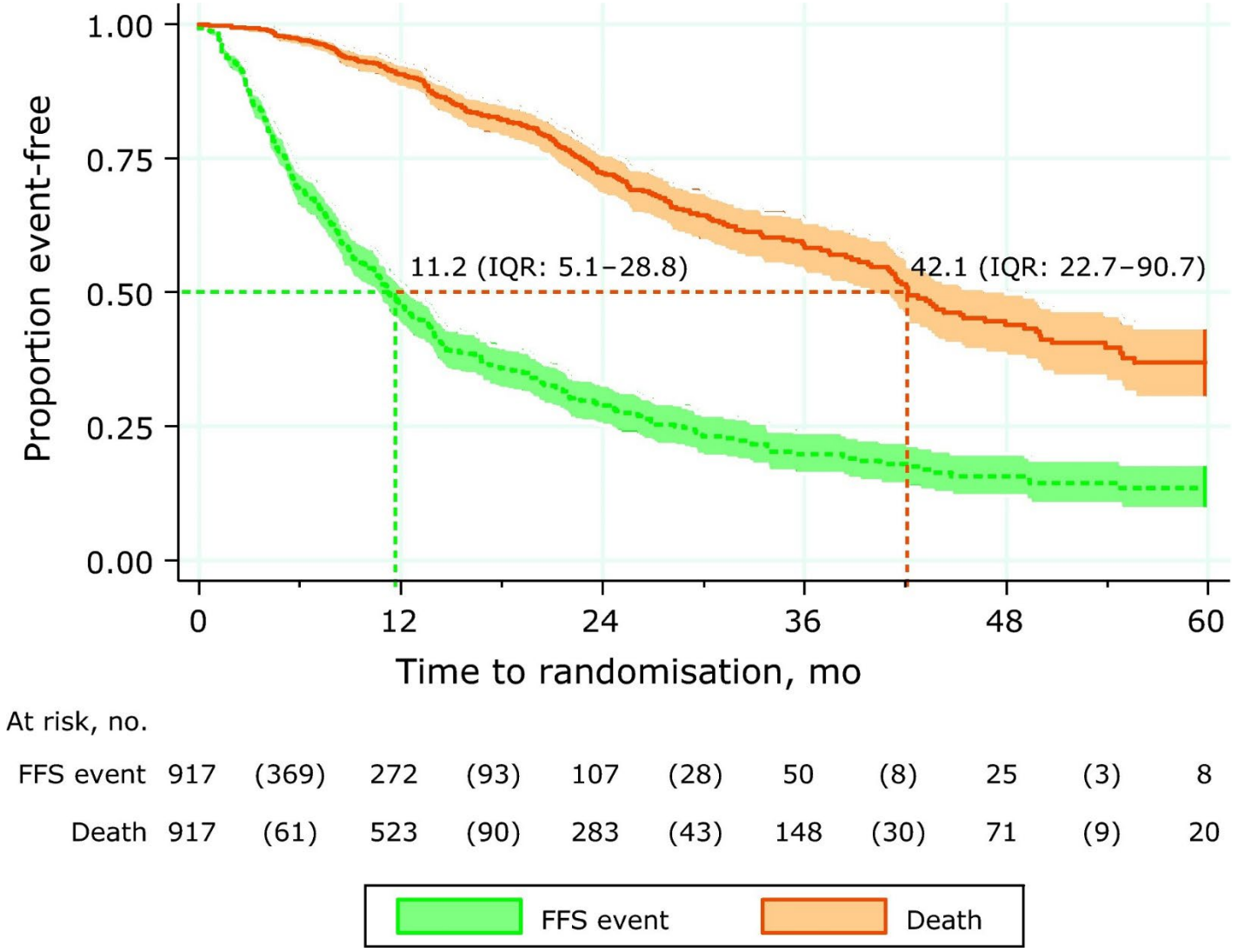


Klotz L, et al. BJU Int. 2008



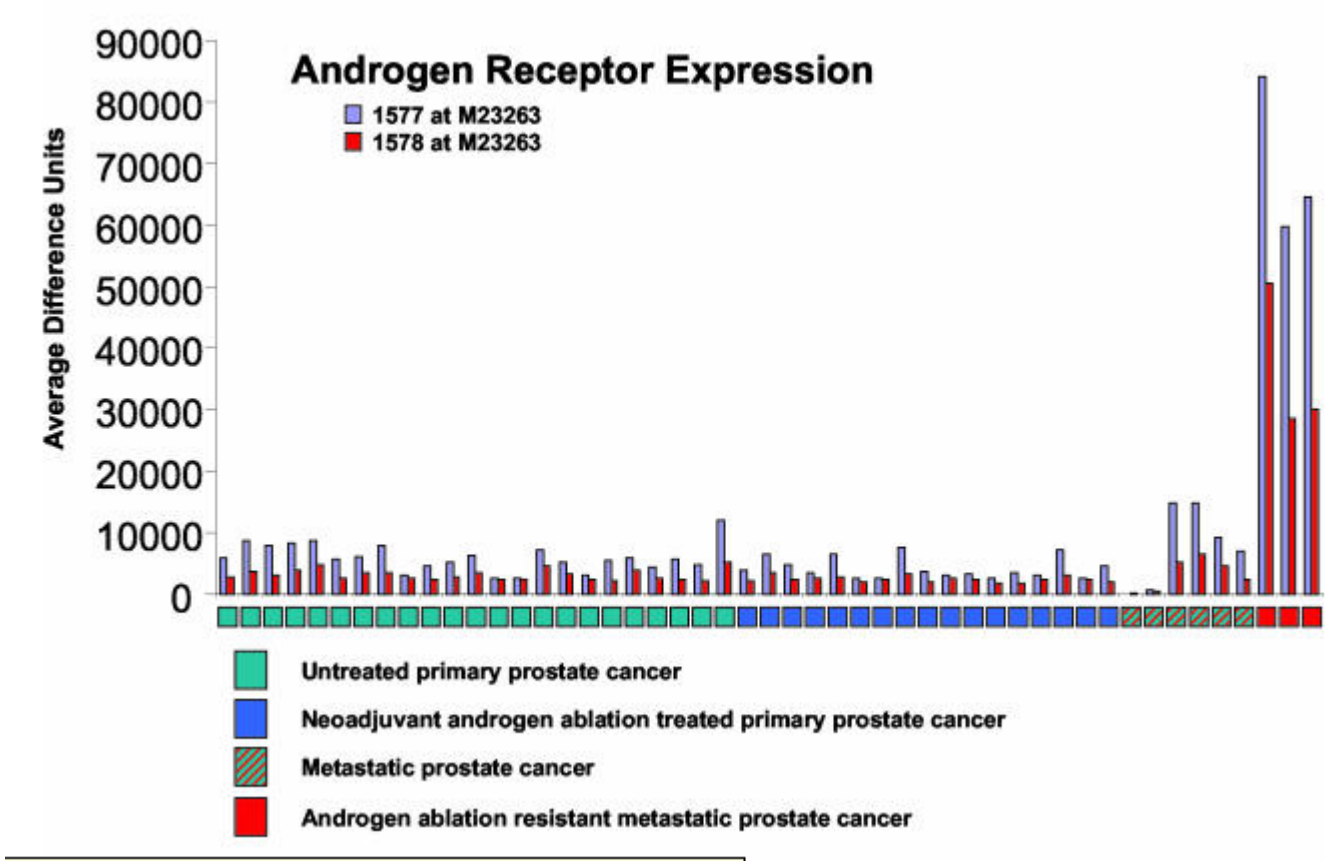
https://www.orgovyxhcp.com/efficacy/

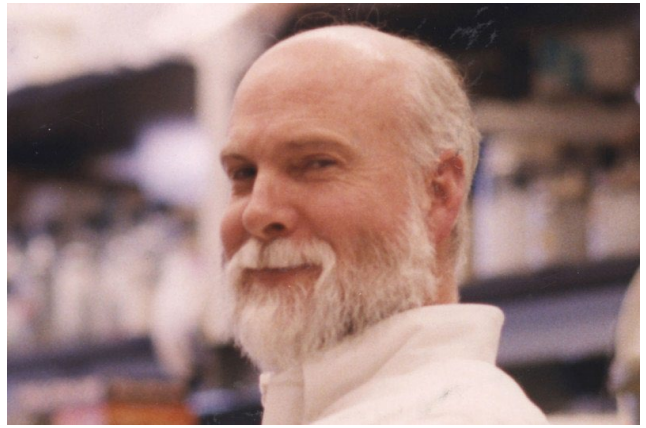
Durability of response to ADT in metastatic PCa



James et. al. European Urology **2015 67, 1028-1038DOI: (10.1016/j.eururo.2014.09.032)**

Castrate-resistant prostate cancer frequently overexpress AR



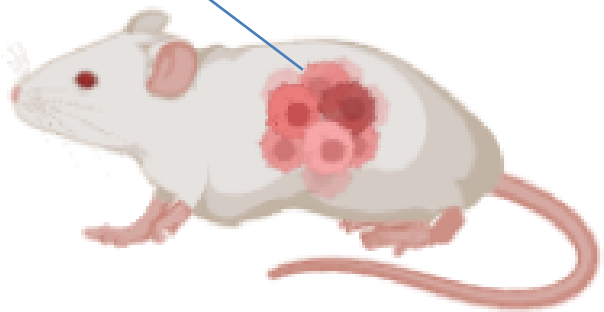


Holzbeierlein et al. Am J. Path (2004) 164:217

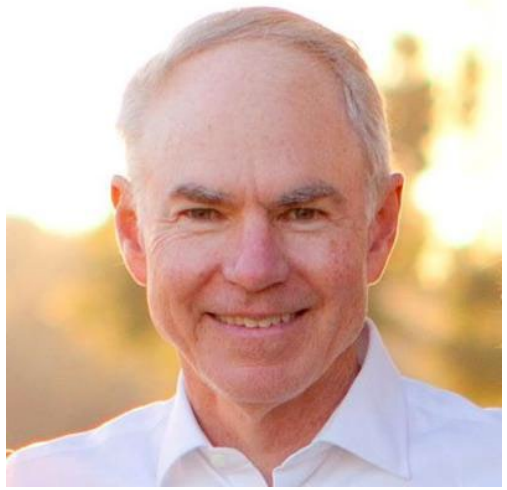
Differential Expression

Hormone Sensitive Xenograft

Castration

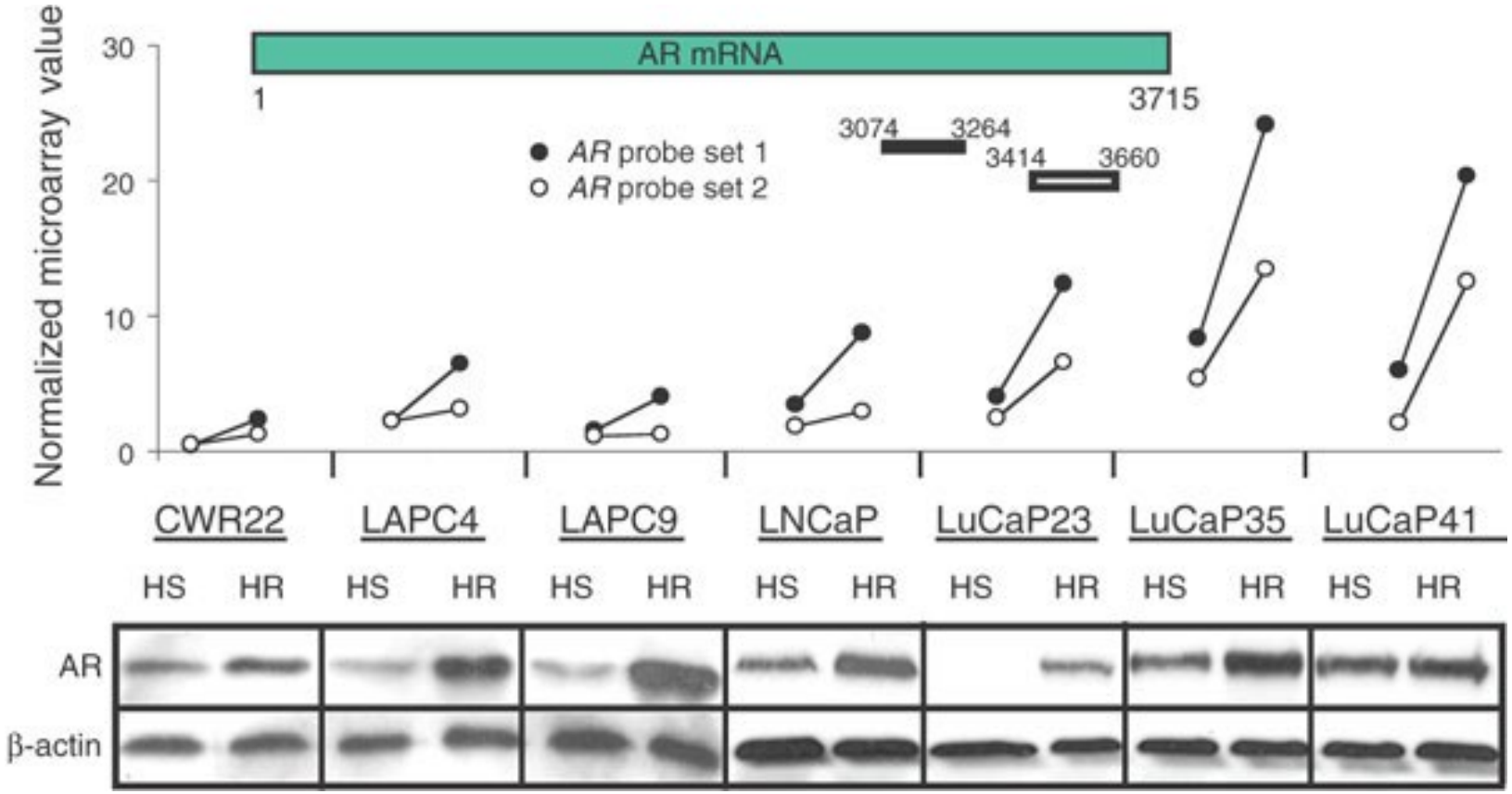


Hormone Sensitive Xenograft



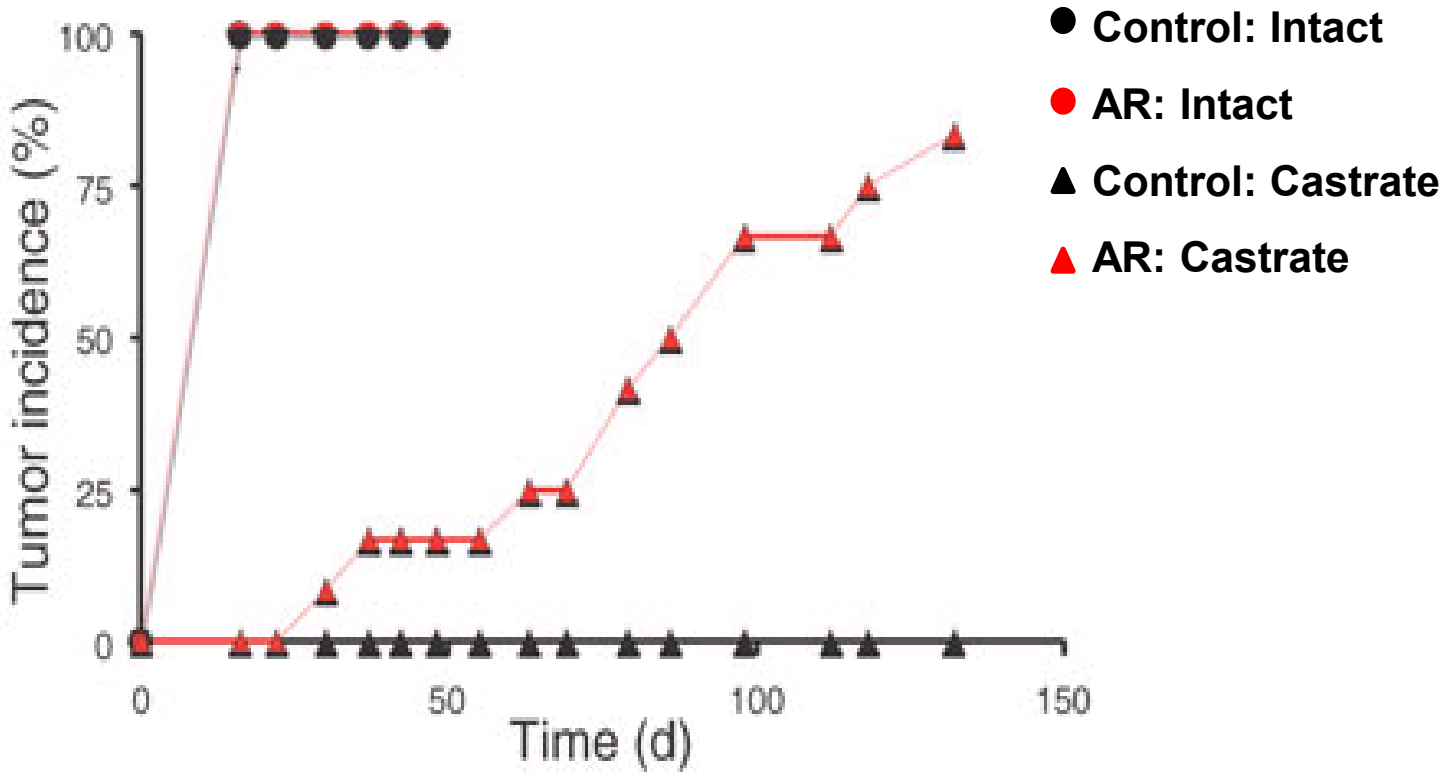
Chen et. Al. Nat Med (2005)

AR is only consistently upregulated gene in HR



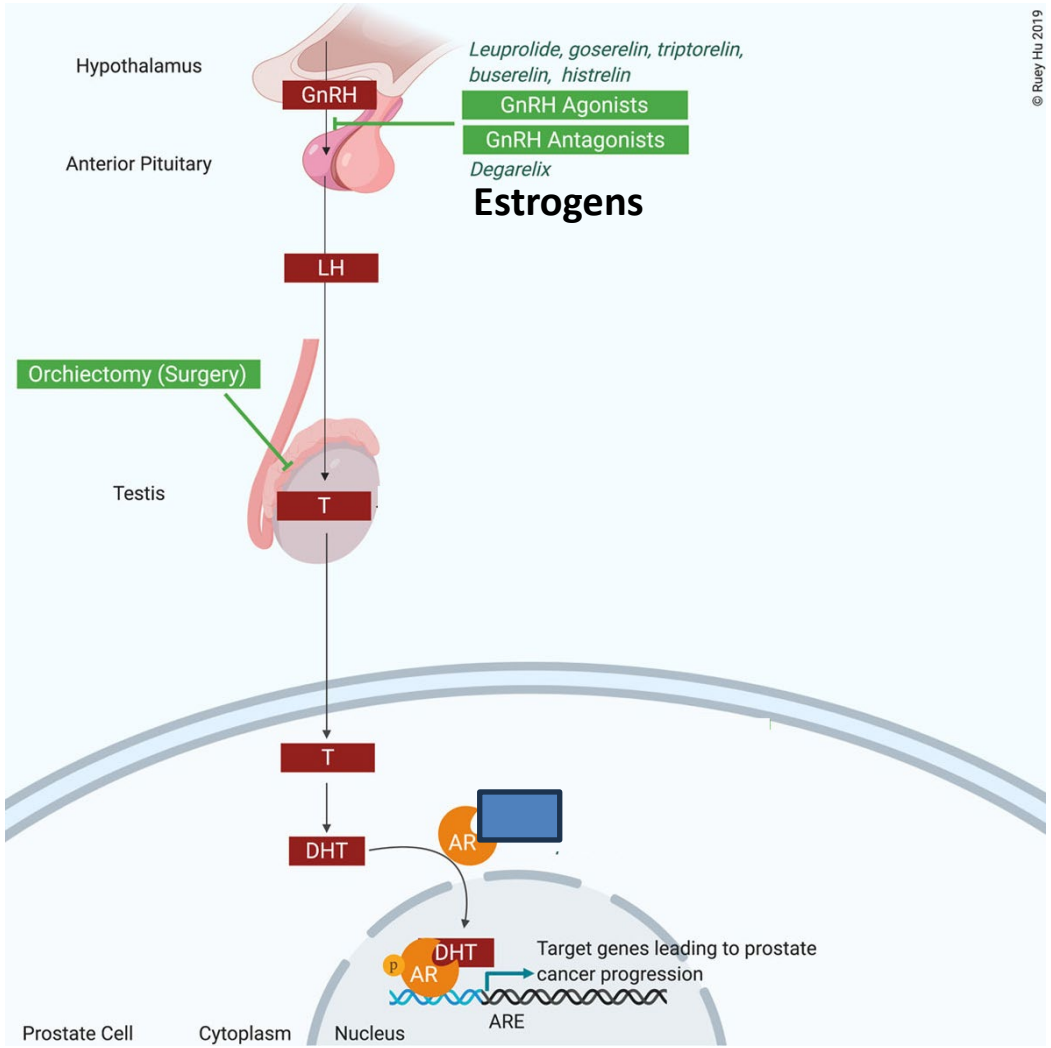
Chen et. Al. Nat Med (2005)

AR overexpression is sufficient for castration resistance



Chen et. al. Nature Med 2005

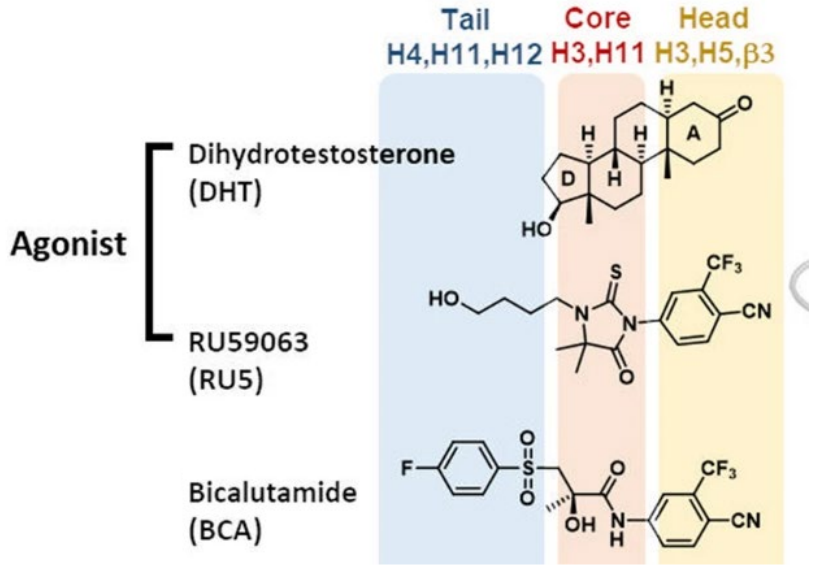
Antiandrogen to inhibit AR activity

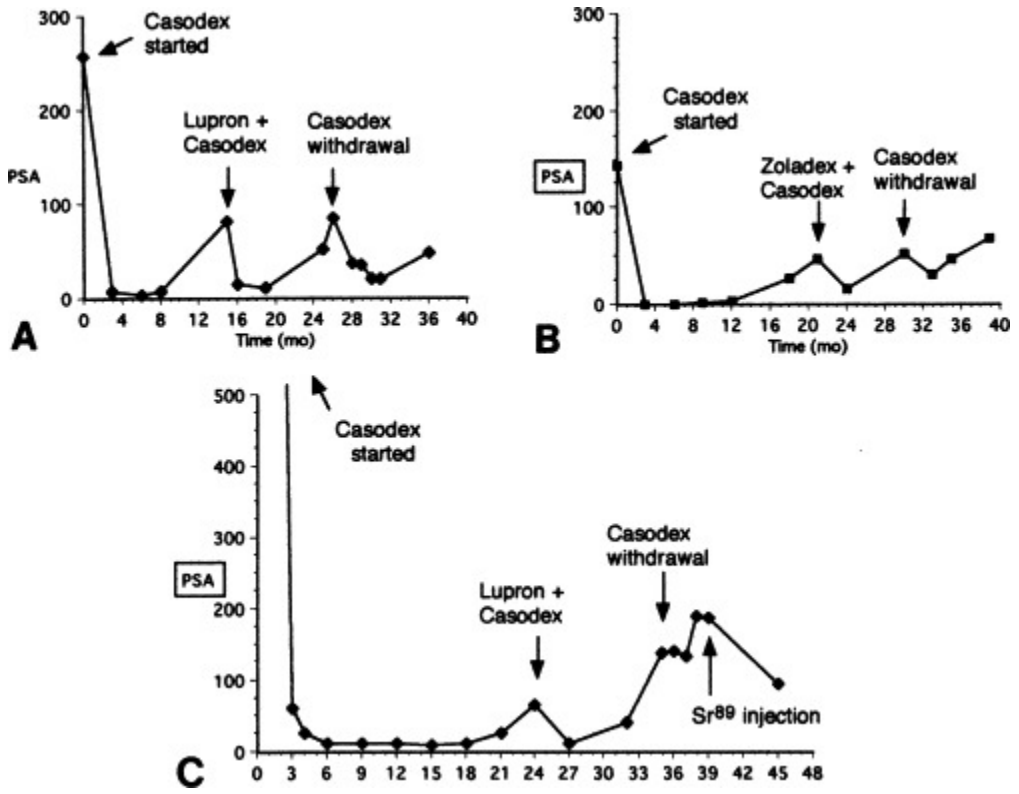


Antiandrogen

Hu JR, et. al. Arterioscler Thromb Vasc Biol. 2020

Bicalutamide and antiandrogen withdrawal response

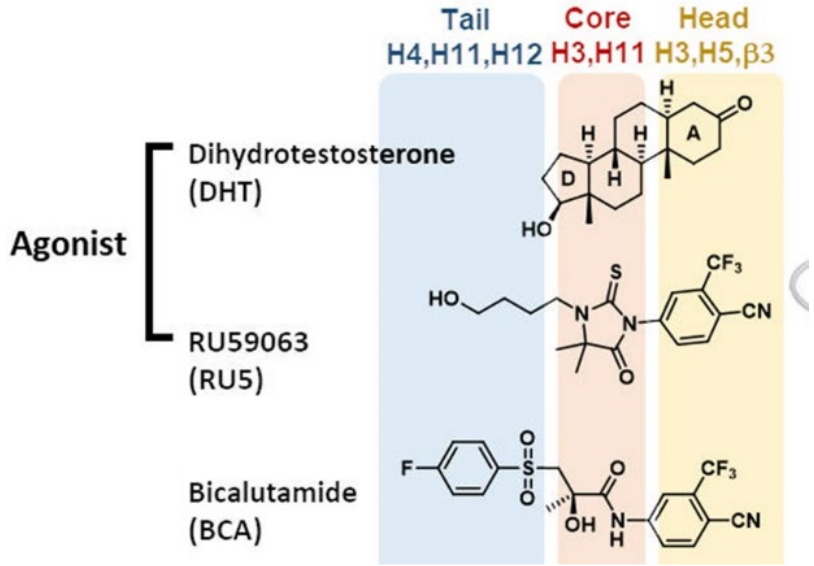


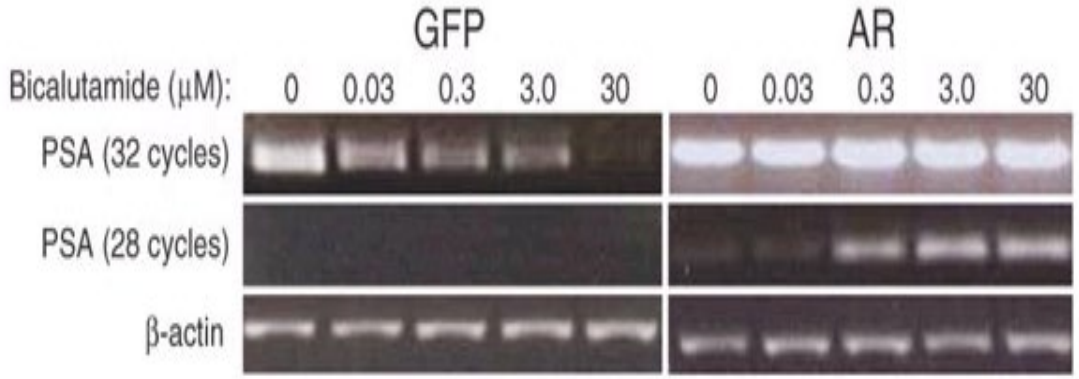


Gim et. al. Scientific Reports (2021)

Nieh et. al. J Urol (1995)

Bicalutamide is an agonist when AR is high

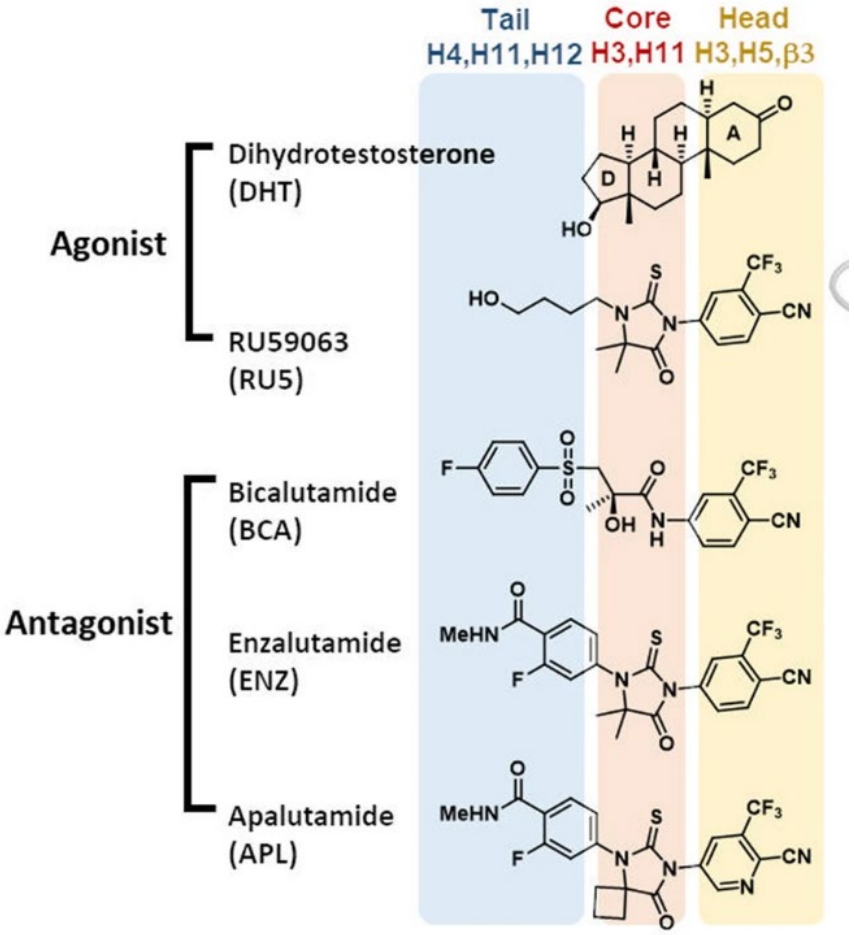




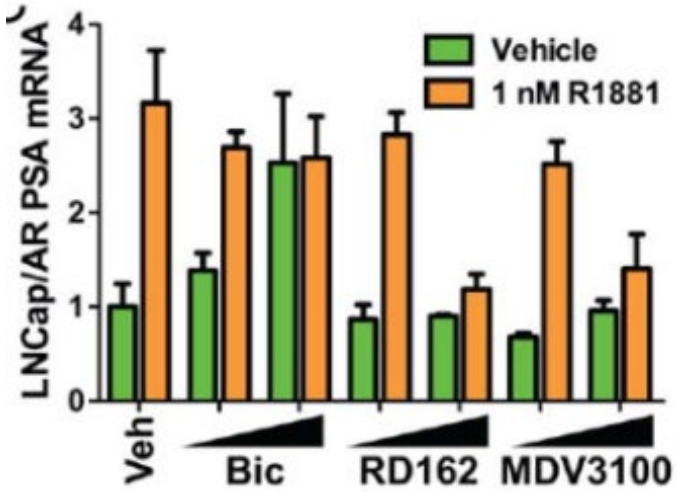
Gim et. al. Scientific Reports (2021)

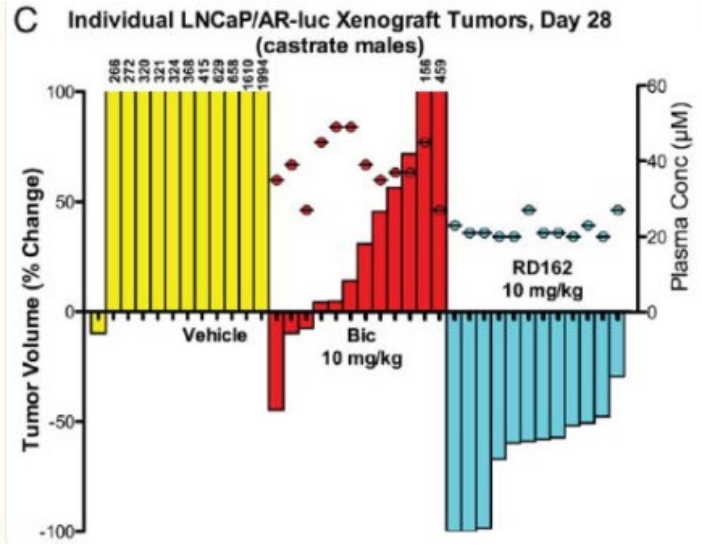
Chen et. al. Nature Med 2005

Enzalutamide and apalutamide are pure AR antagonists



Gim et. al. Scientific Reports (2021)

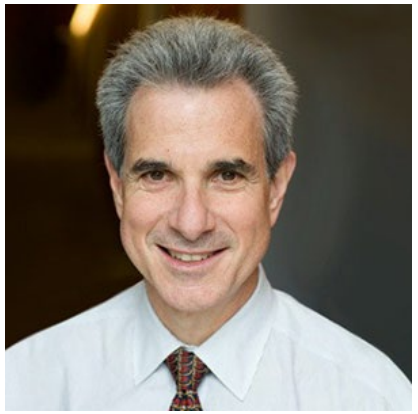


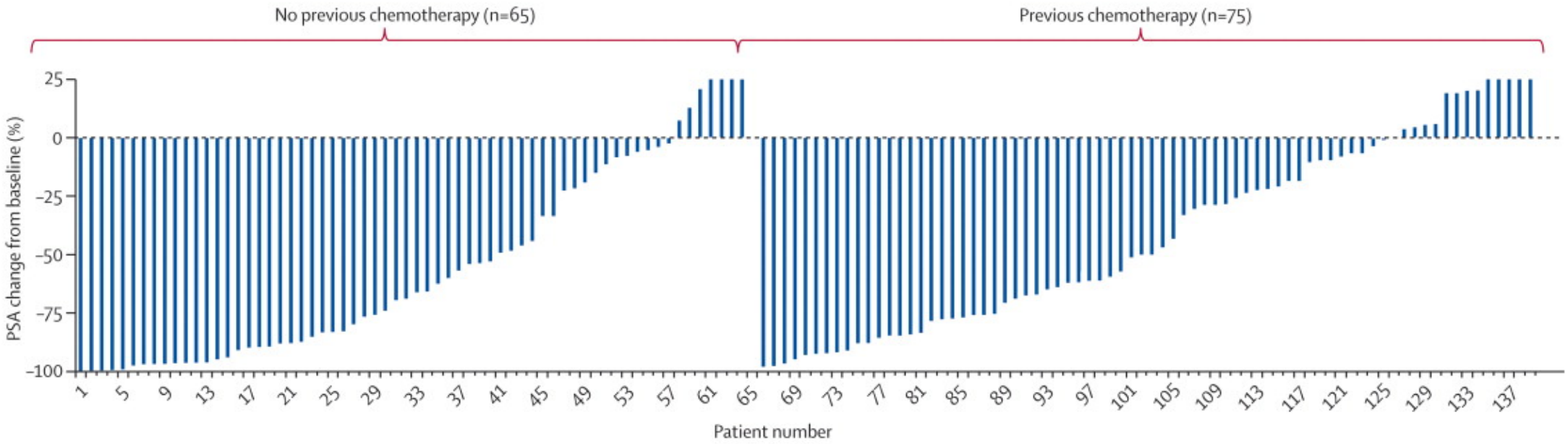


Tran C et. al. Science 2010

Antitumour activity of MDV3100 in castration-resistant prostate cancer: a phase 1–2 study

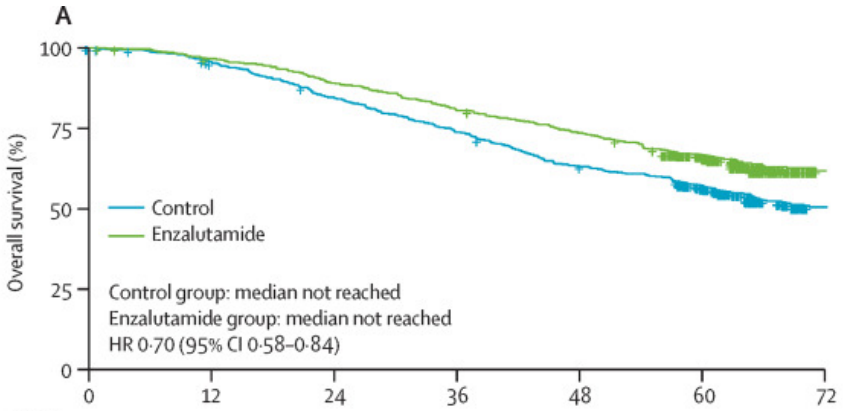
Howard I Scher, Tomasz M Beer, Celestia S Higano, Aseem Anand, Mary-Ellen Taplin, Eleni Efstathiou, Dana Rathkopf, Julia Shelkey, Evan Y Yu, Joshi Alumkal, David Hung, Mohammad Hirmand, Lynn Seely, Michael J Morris, Daniel C Danila, John Humm, Steve Larson, Martin Fleisher, Charles L Sawyers, the Prostate Cancer Foundation/Department of Defense Prostate Cancer Clinical Trials Consortium



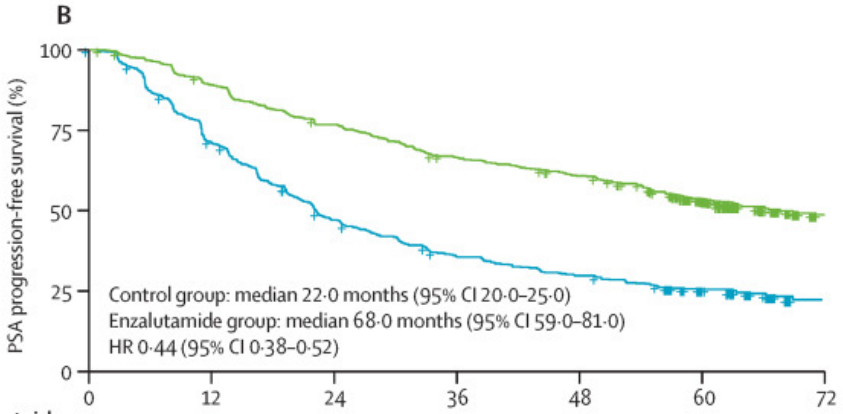


Scher HI C et. al. Lancet 2010

ENZAMET Trial



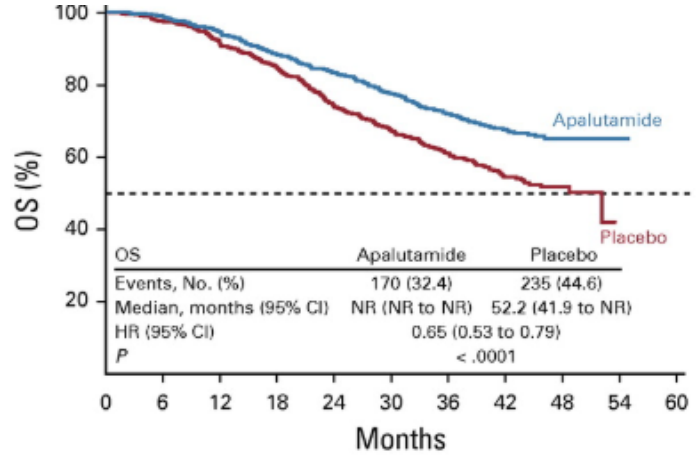
Number at risk (number censored)							
Control group	562	531 (7)	468 (9)	408 (9)	347 (11)	280 (46)	106 (195)
Enzalutamide group	563	541 (3)	499 (3)	451 (3)	410 (5)	336 (41)	133 (226)



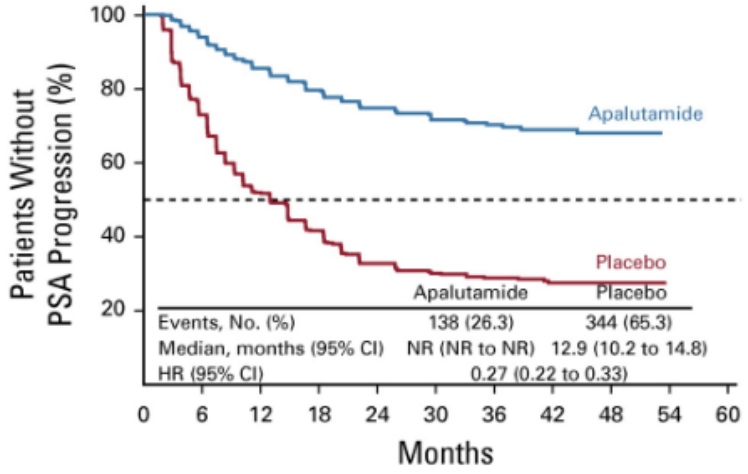
Number at risk (number censored)							
Control group	562	395 (7)	258 (11)	193 (14)	161 (14)	119 (33)	48 (93)
Enzalutamide group	563	499 (3)	429 (4)	370 (6)	335 (9)	262 (44)	100 (189)

ID Davis et al. N Engl J Med 2019;381:121-131.
Sweeney, CJ Lancet Oncology 2023

TITAN Trial



No. at risk:											
Apalutamide	525	513	489	452	425	394	362	227	52	3	0
Placebo	527	510	474	436	374	339	301	181	43	0	0

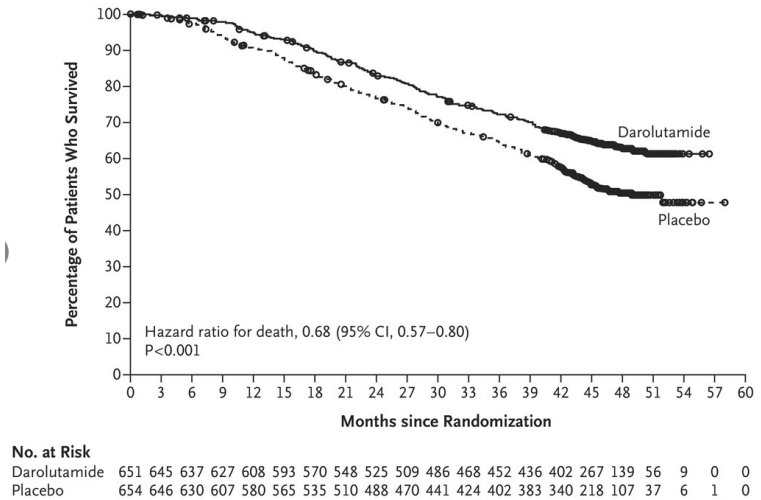


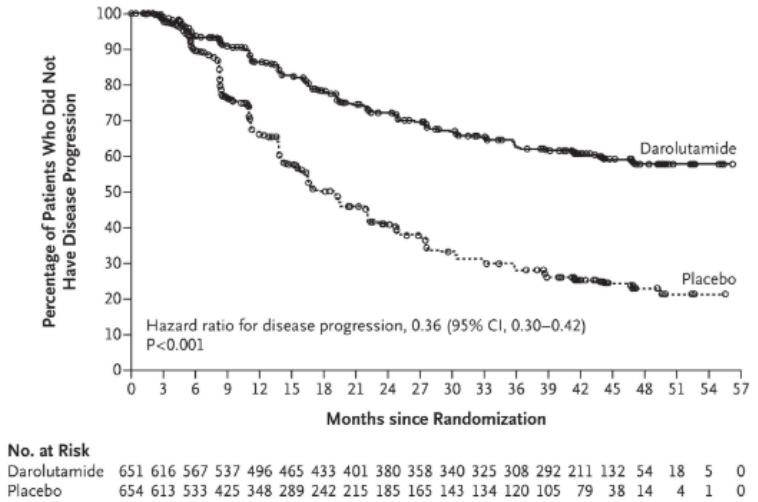
No. at risk:											
Apalutamide	525	450	384	341	303	277	253	123	19	0	0
Placebo	527	356	244	190	140	125	105	52	13	0	0

KN Chi et al. N Engl J Med 2019;381:13-24
KN Chi et al. JCO 2021

darolutamide (Nubeqa)

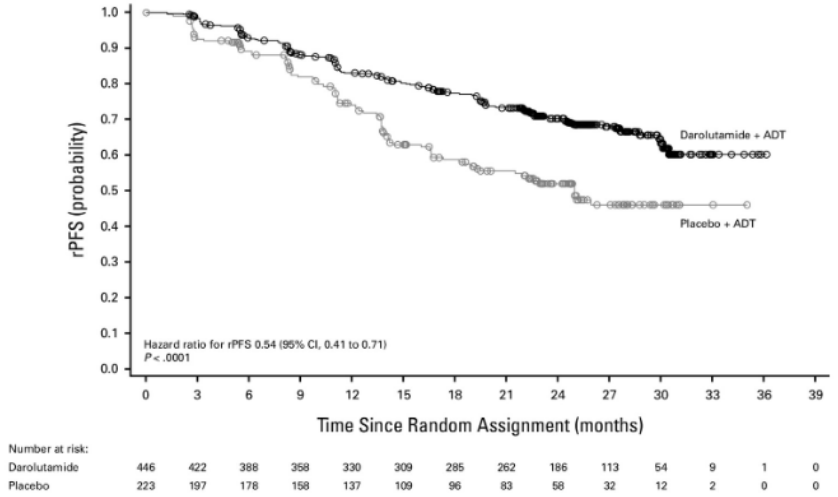
ARASENS Trial (control is ADT + docetaxel)

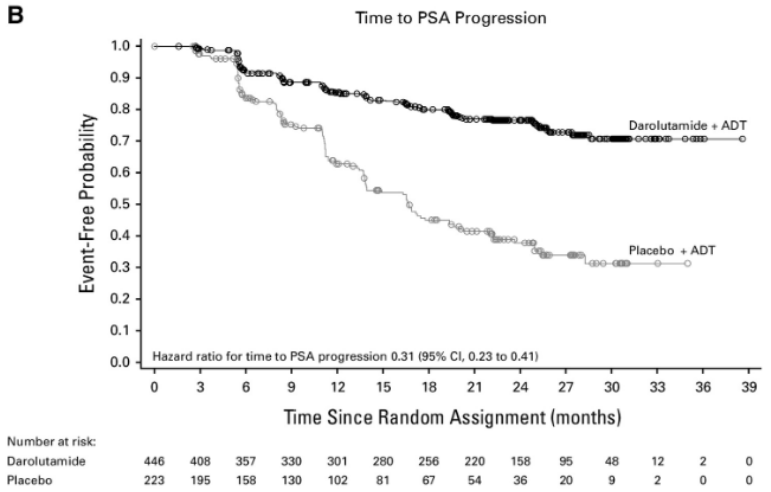




Smith MR et al. NEJM 2022

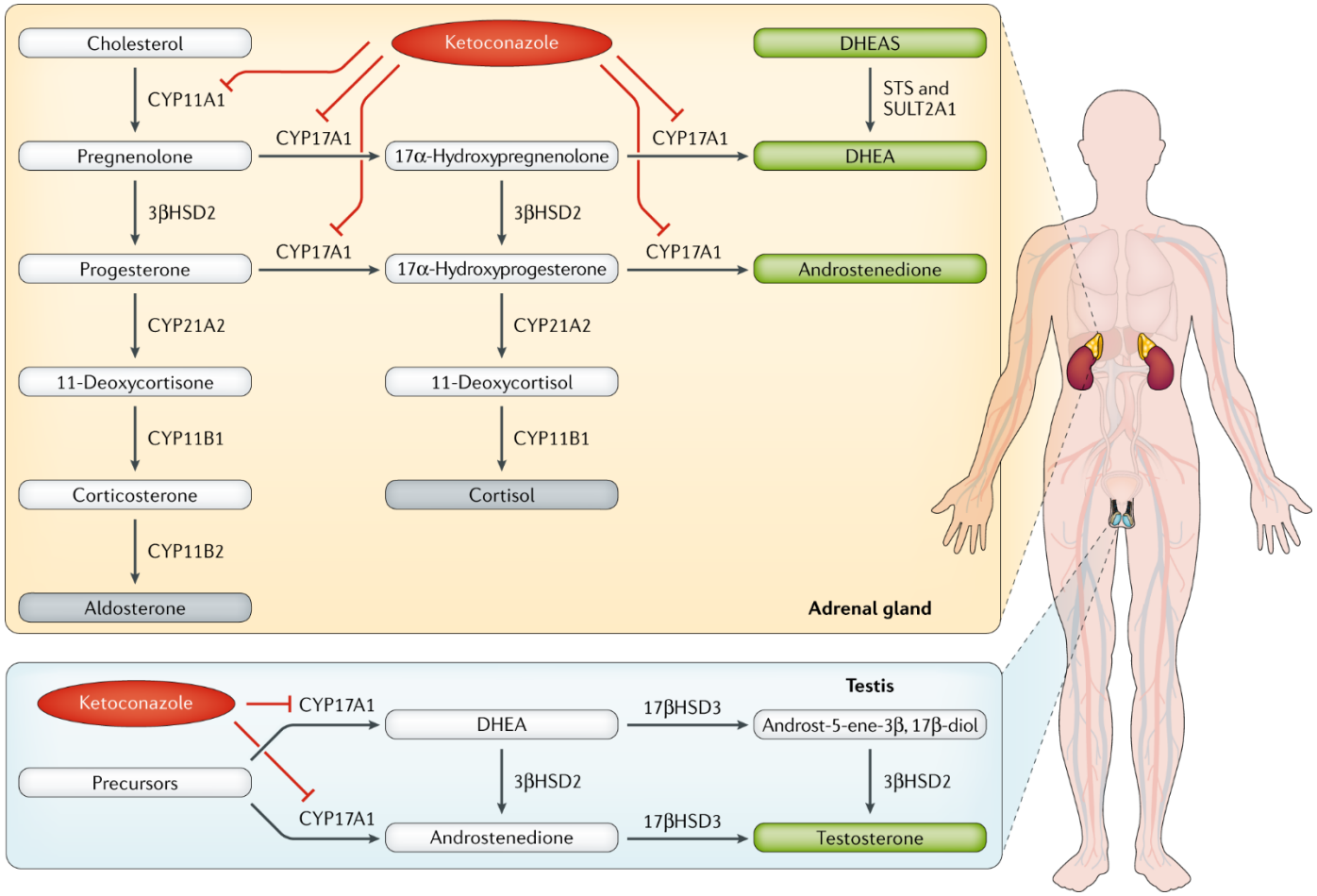
ARANOTE Trial (control is ADT)

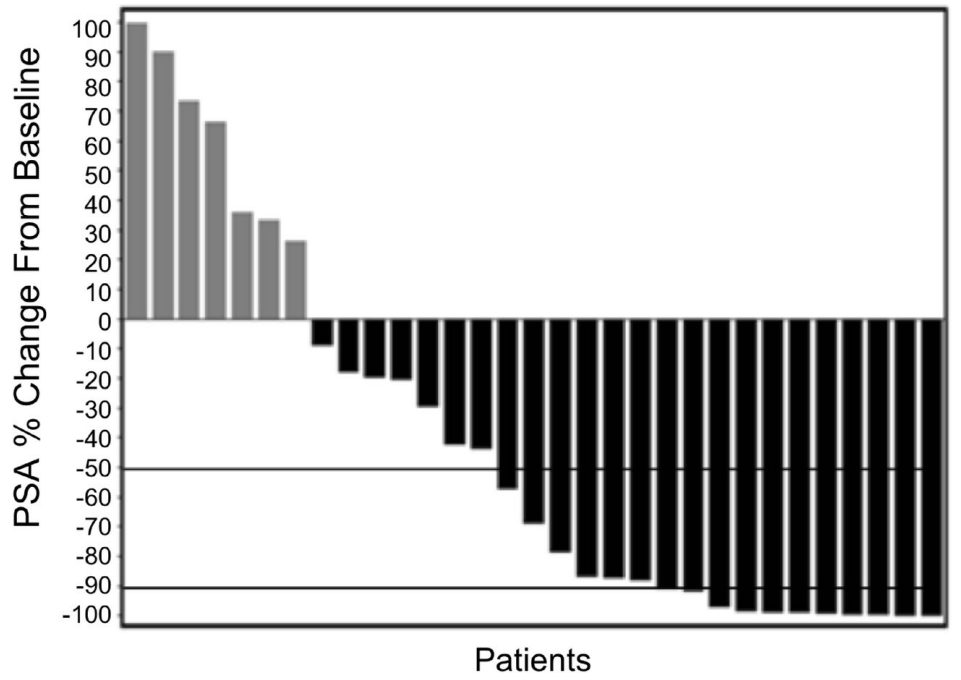




Saad F et al. JCO 2024

Ketoconazole a (toxic) treatment for CRPC

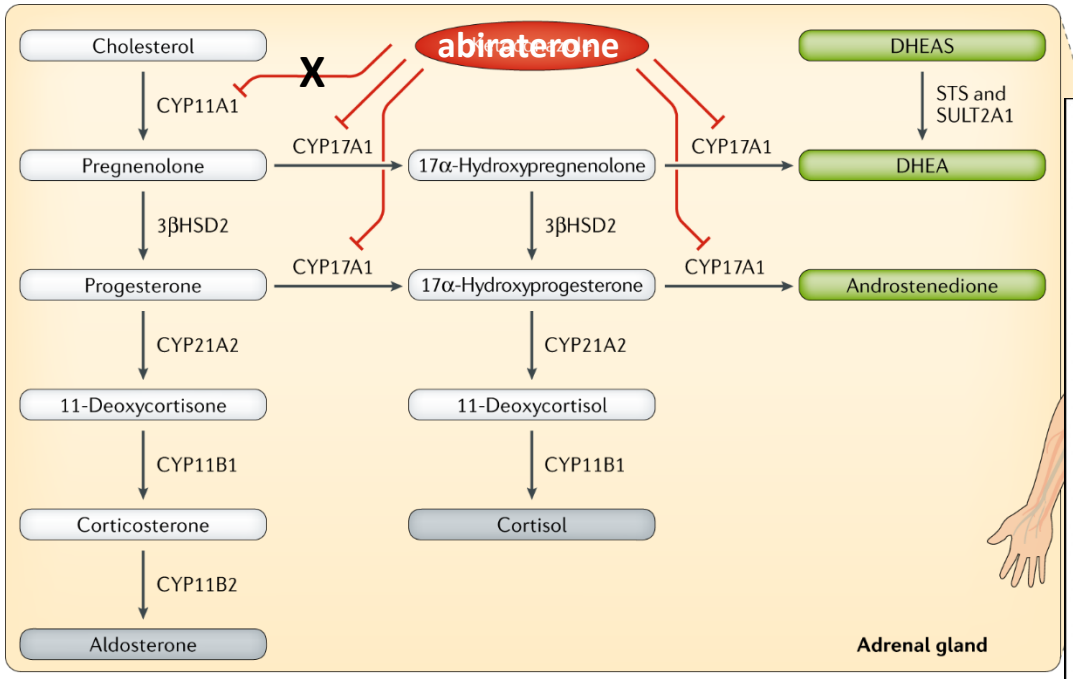


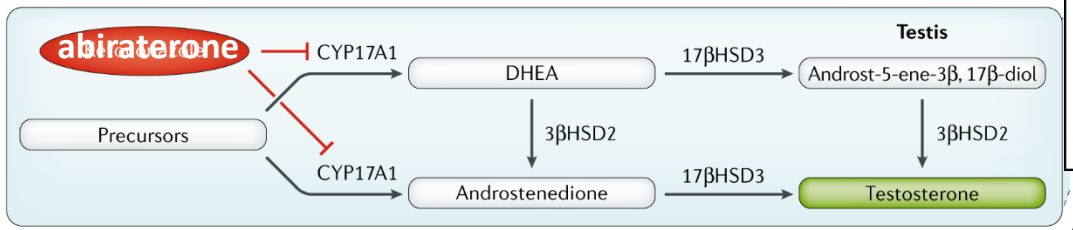


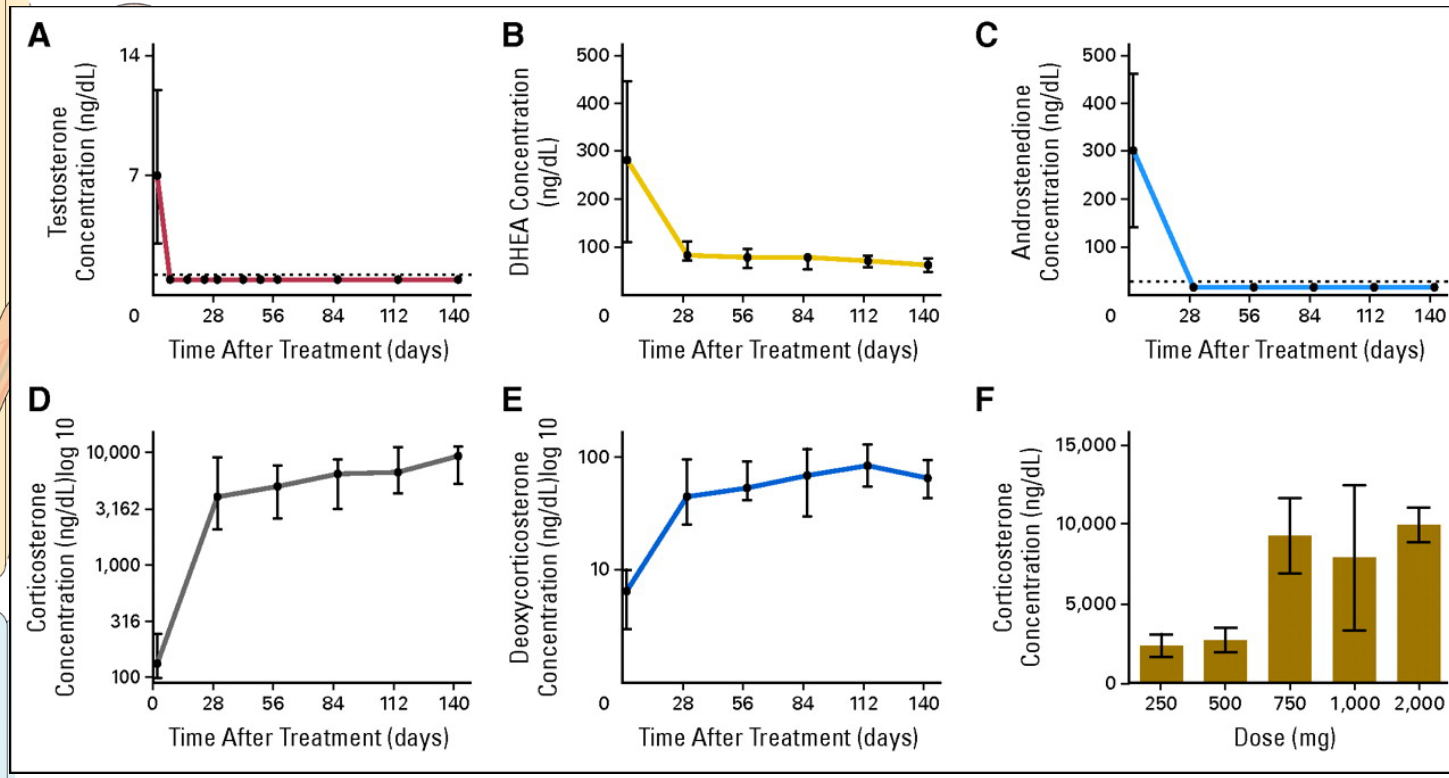
Patel et al. Nature Rev Urol 2018

Pedro C. Barata et. al. Inv New Drugs 2018

abiraterone a (less toxic) treatment for CRPC





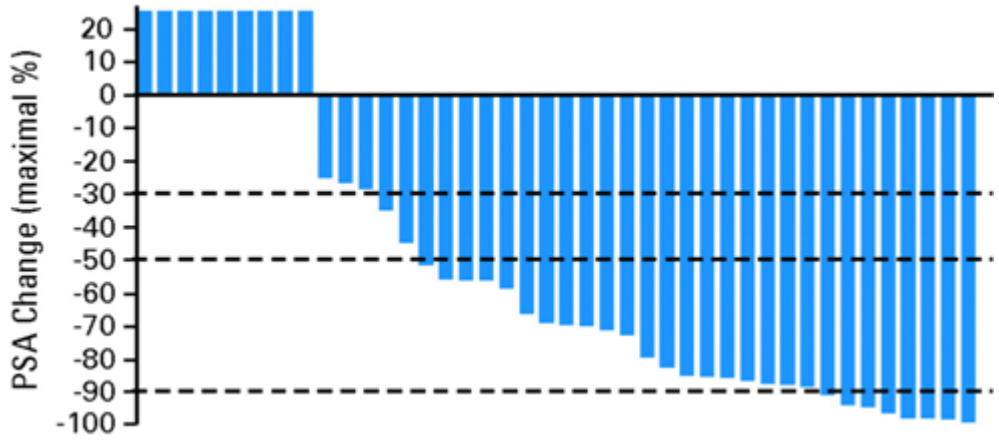


Attard G et al. JCO 2008;26:4563-4571

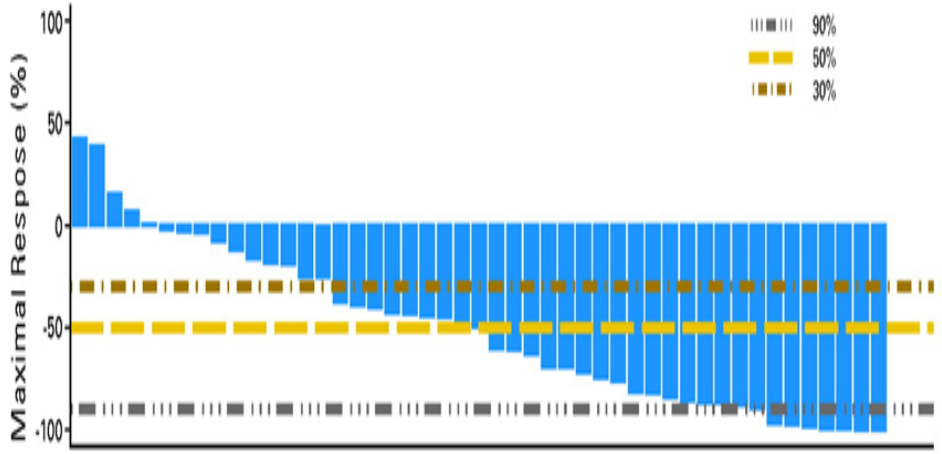
Patel et al. Nature Rev Urol 2018

Changes in prostate-specific antigen (PSA) with abiraterone acetate.

Pre-Chemo



Post-Chemo



Attard G et al. JCO 2009;27:3742-3748

Reid A H et al. JCO 2010;28:1489-1495

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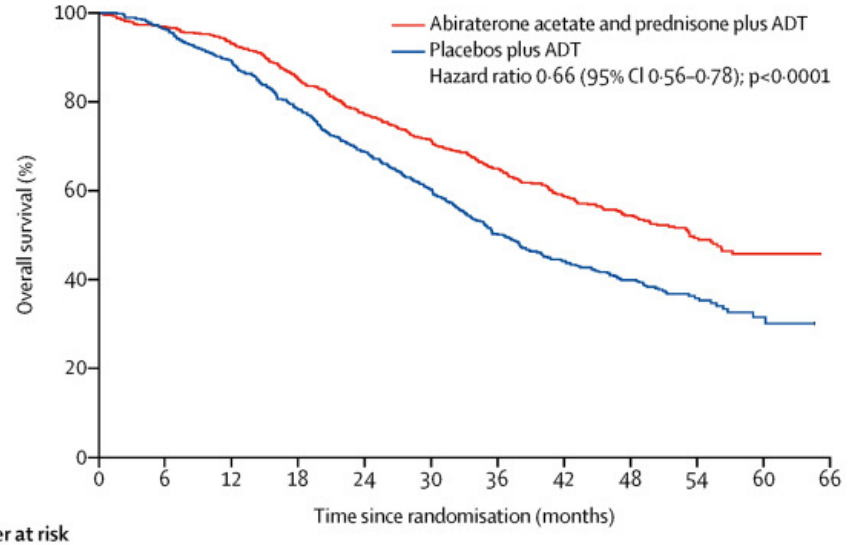
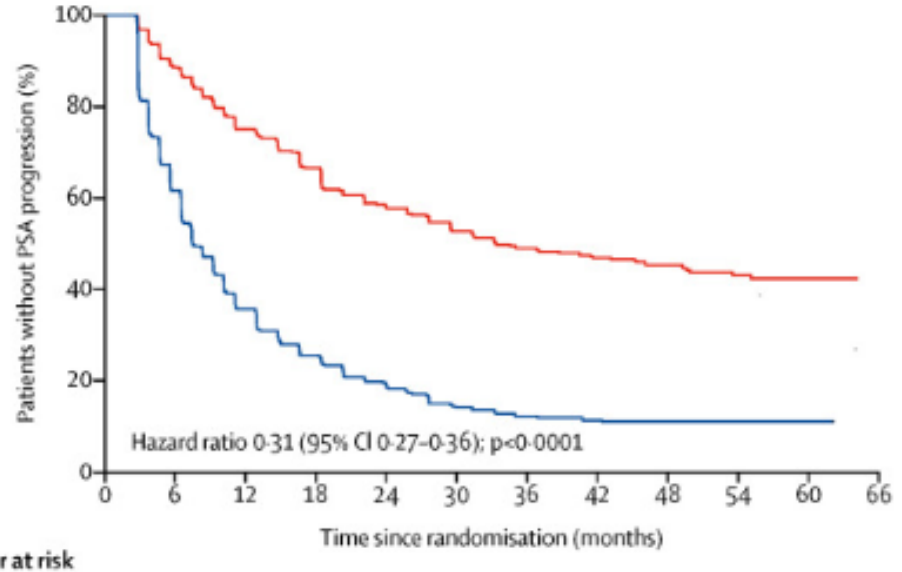
LATITUDE Trial of upfront abiraterone



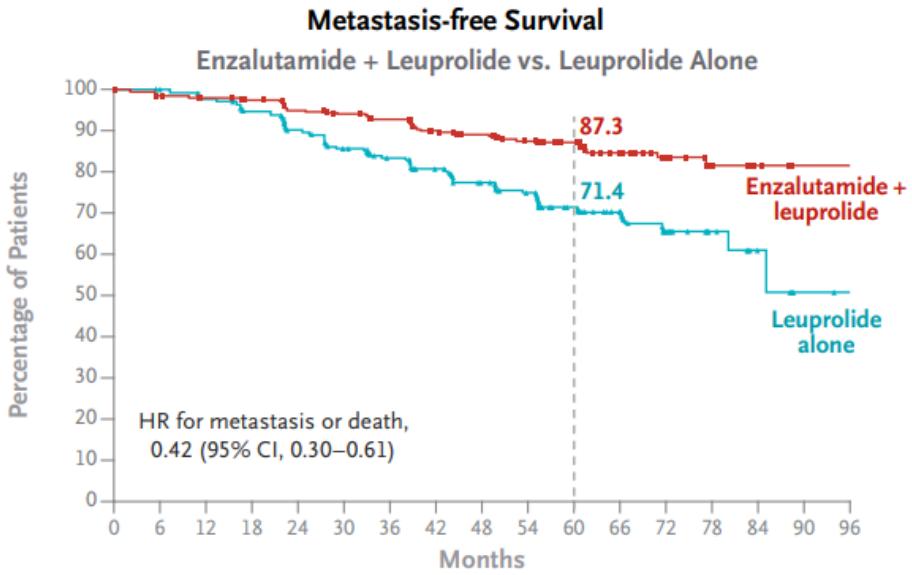
Number at risk (number censored)												
Abiraterone acetate and prednisone plus ADT	597	565 (14)	529 (28)	479 (34)	425 (42)	389 (46)	351 (50)	311 (57)	240 (106)	124 (205)	40 (282)	0 (322)
Placebos plus ADT	602	564 (17)	505 (34)	432 (47)	368 (58)	315 (37)	256 (74)	220 (79)	165 (114)	69 (197)	23 (237)	0 (259)

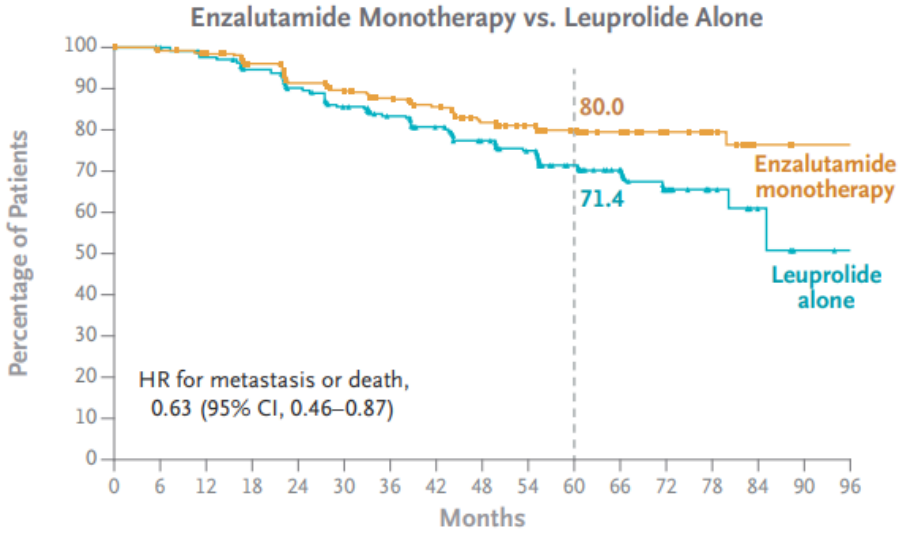


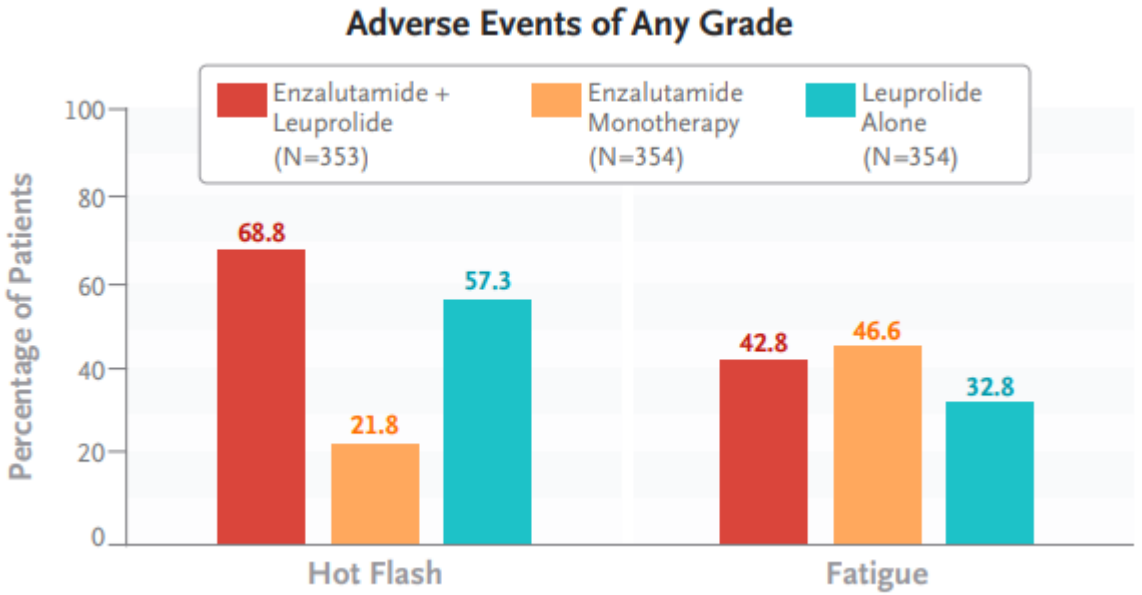
Number at risk (number censored)												
Abiraterone acetate and prednisone plus ADT	597 (0)	482 (51)	379 (83)	316 (104)	249 (130)	215 (143)	191 (152)	171 (164)	128 (202)	62 (263)	20 (304)	0 (324)
Placebos plus ADT	602 (0)	320 (72)	172 (88)	116 (96)	74 (108)	51 (114)	41 (117)	38 (117)	20 (134)	7 (147)	1 (153)	0 (154)

Fizazi K et al. N Engl J Med 2017;377:352-360.
Fizazi K et al. Lancet Oncol 2019

Do you need ADT?







Freedland, SJ NEJM 2023

Toxicities of ARSIs

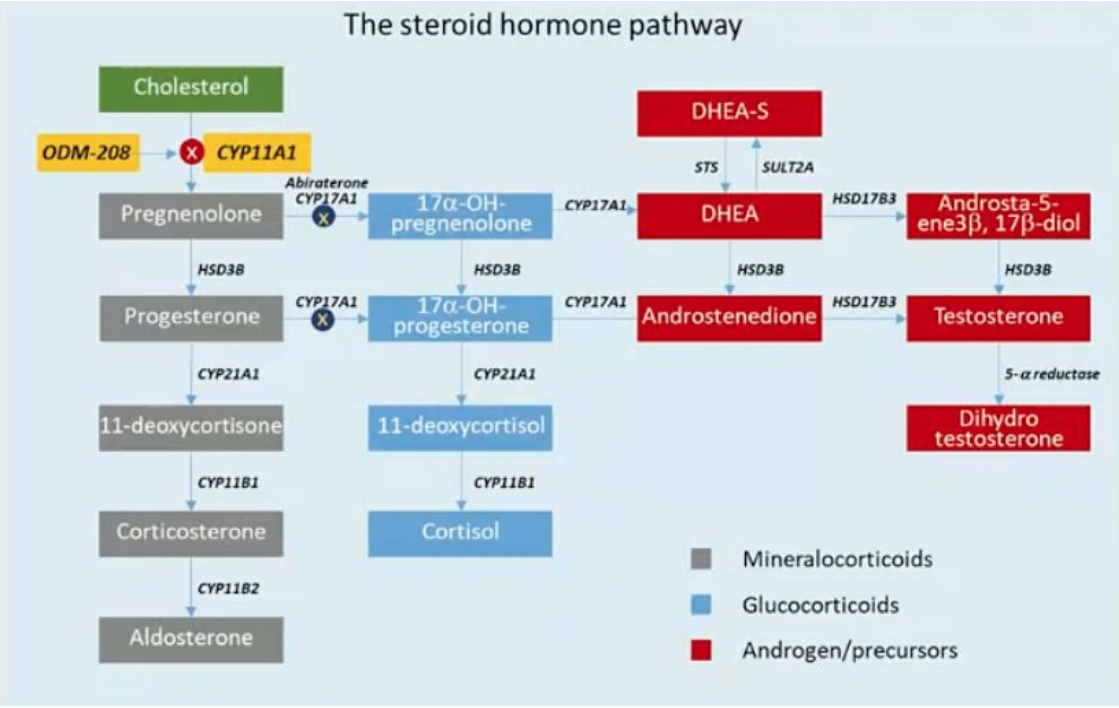
Type of Toxicity	Toxicity Grade	Abiraterone				Enzalutamide		
		Exp. Arm, %	Ctr. Arm, %	RR (95% CI); *P* Value	Heterogeneity	Exp. Arm, %	Ctr. Arm, %	RR (95% CI); *P* Value
Cardiac	All	13.7	9.5	1.41 (1.21-1.64); <.001	χ^2 = 0.96, *P*= .81; I^2 = 0%	8.6	7.1	1.41 (0.75-2.63); .28
	High	4.5	2.9	2.22 (1.60-3.27); <.001	χ^2 = 1.09, *P*= .8; I^2 = 0%	2.5	2.1	1.32 (0.85–2.06); .2
Hypertension	All	26.2	14.8	1.79 (1.45-2.21); <.001	χ^2 = 9.47, *P*= .02; I^2 = 68%	10.5	4.2	2.74 (2.07–3.63); <.001
	High	6.9	3.6	2.19 (1.73-2.78); <.001	χ^2 = 4.52, *P*= .21; I^2 = 34%	4.8	2.2	2.44 (1.64–3.63); <.001

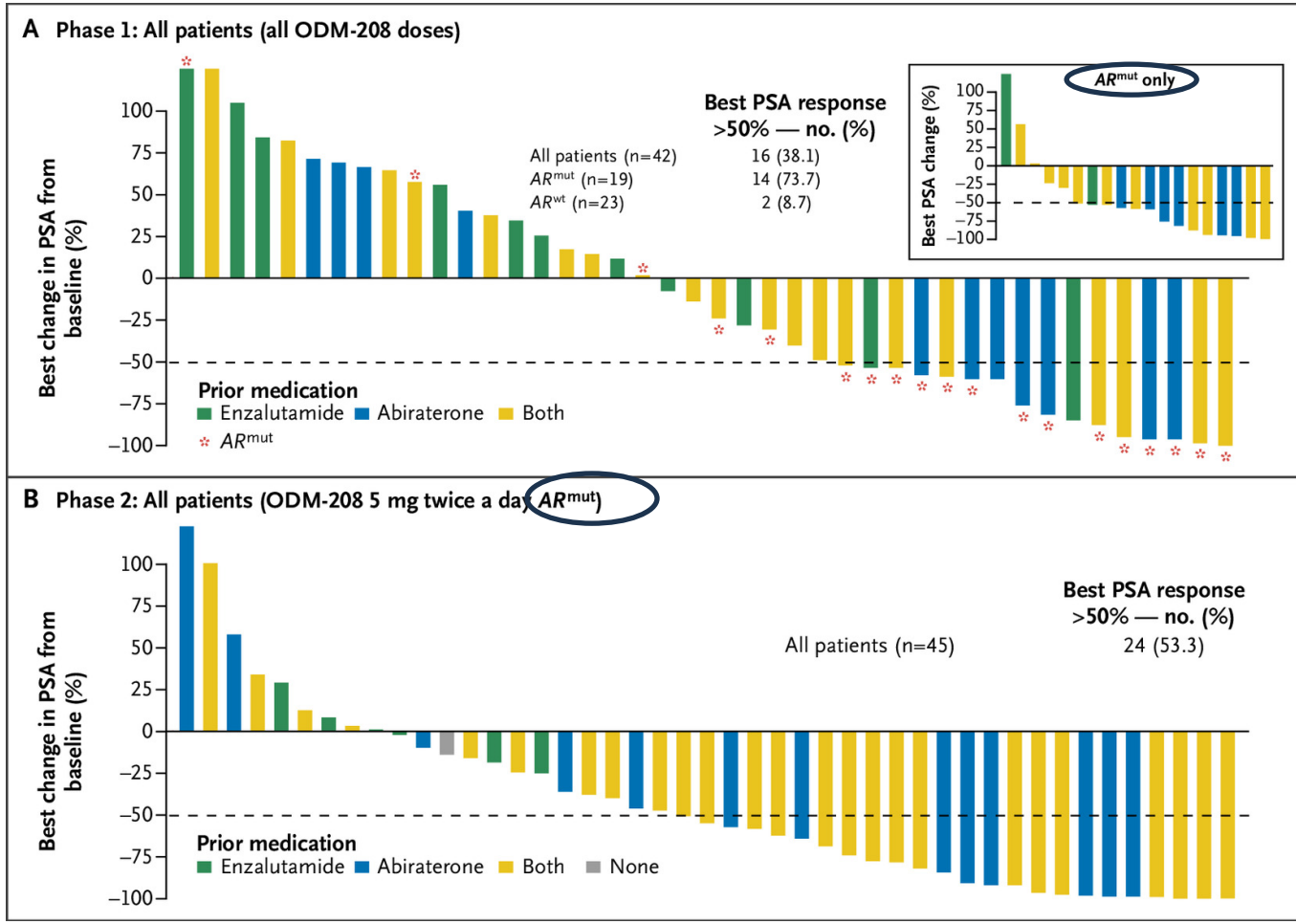
Iacovelli R, et al Clin Genitourinary Cancer 2018

	Darolutamide	Apalutamide	Enzalutamide
AE (% vs placebo)	ARAMIS	SPARTAN	PROSPER
Fatigue	13.2 vs 8.3	33.0 vs 21.0	45.6 vs 22.2
Fall	5.2 vs 4.9	22.0 vs 9.5	18.1 vs 6.2
Fracture	5.5 vs 3.6	18.0 vs 7.5	17.6 vs 5.4
Rash	3.1 vs 1.1	26.0 vs 6.3	4.1 vs 2.8
Hypertension	7.8 vs 6.5	28.0 vs 21.0	18.0 vs 6.0
Seizure	0.2 vs 0.2	0.6 vs 0.0	0.3 vs 0.0
Mental/cognitive impairment	2.0 vs 1.8		7.8 vs 2.2
Treatment discontinuation due to any AE	8.9 vs 8.7	15.0 vs 7.3	17.0 vs 9.0

Yang CK et al. J Formos Med Assoc . 2023

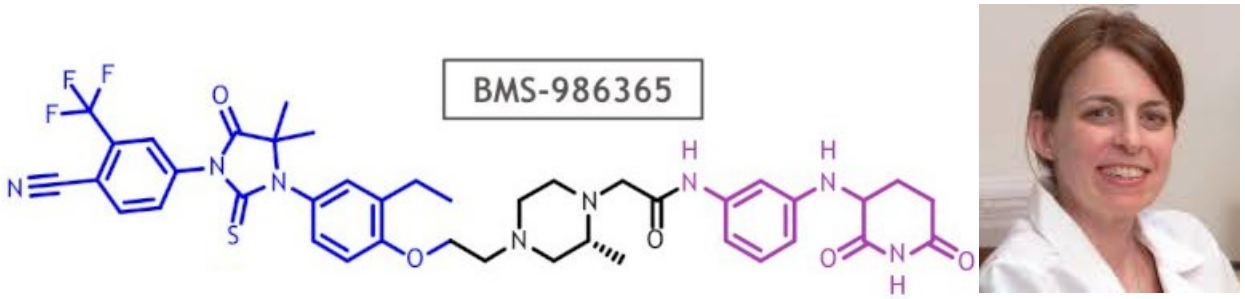
What's Next in AR targeting

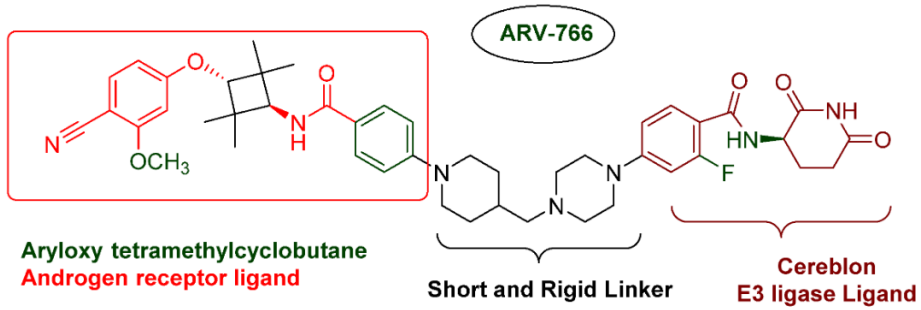


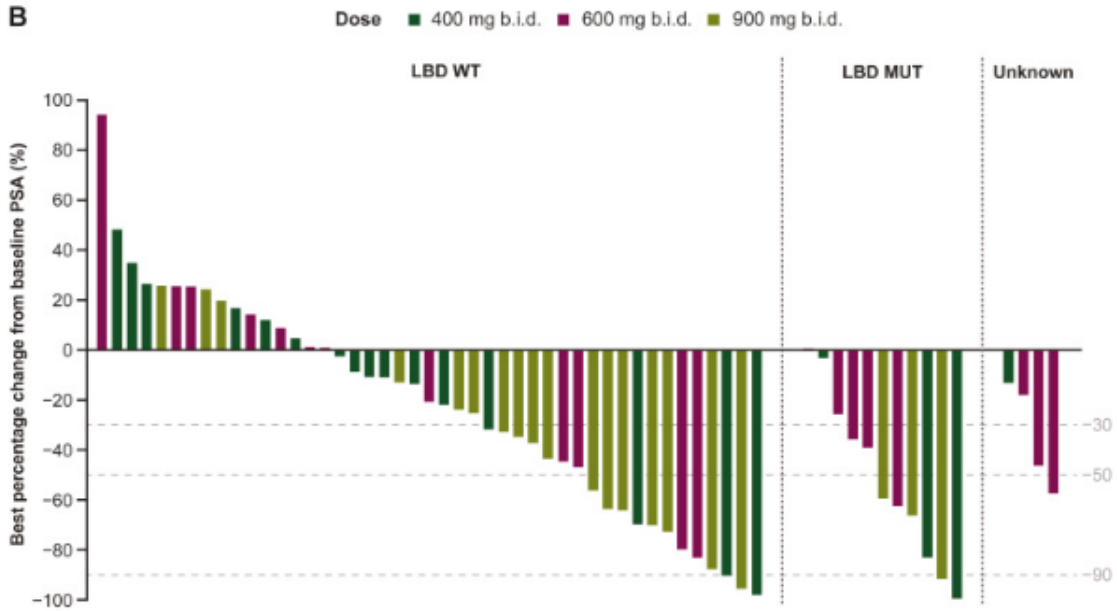


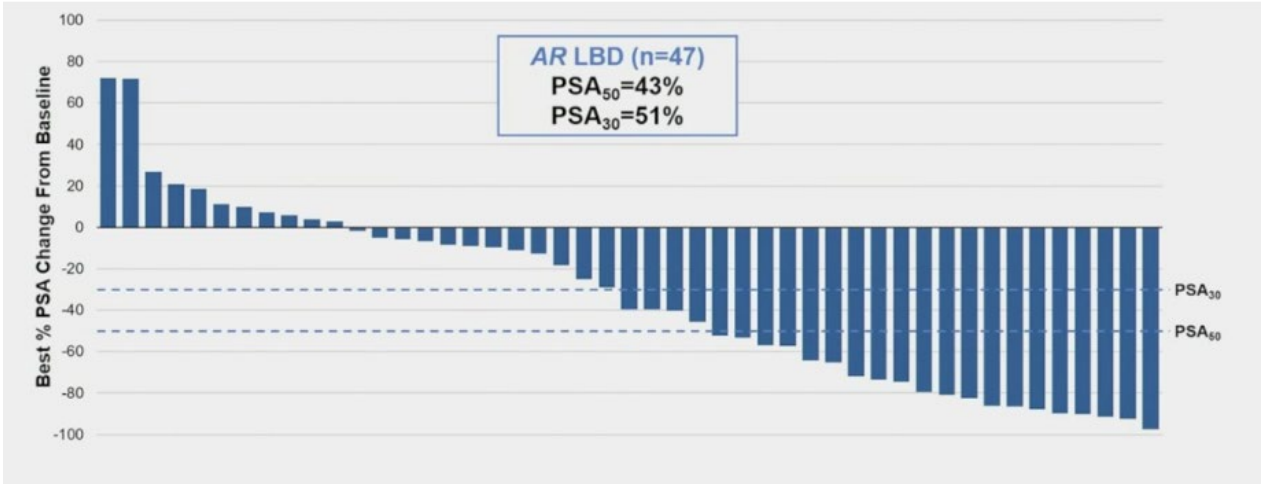
Fizazi, K et al. NEJM Evidence 2023

What's Next in AR targeting







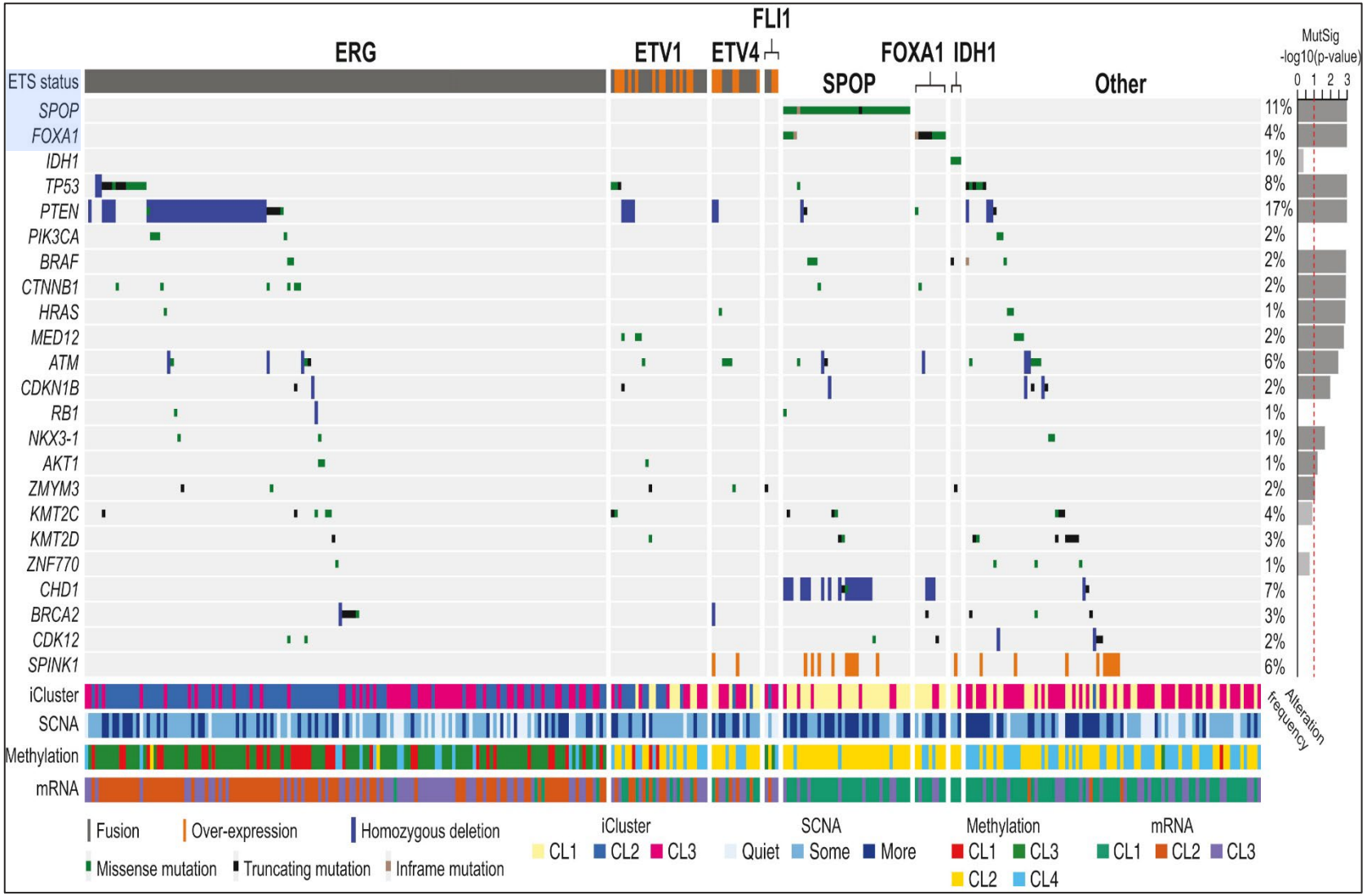


Petrylak, DP, K et al. ASCO Annual Meeting 2024

Rathkopf DE, et al Ann Oncol 2024

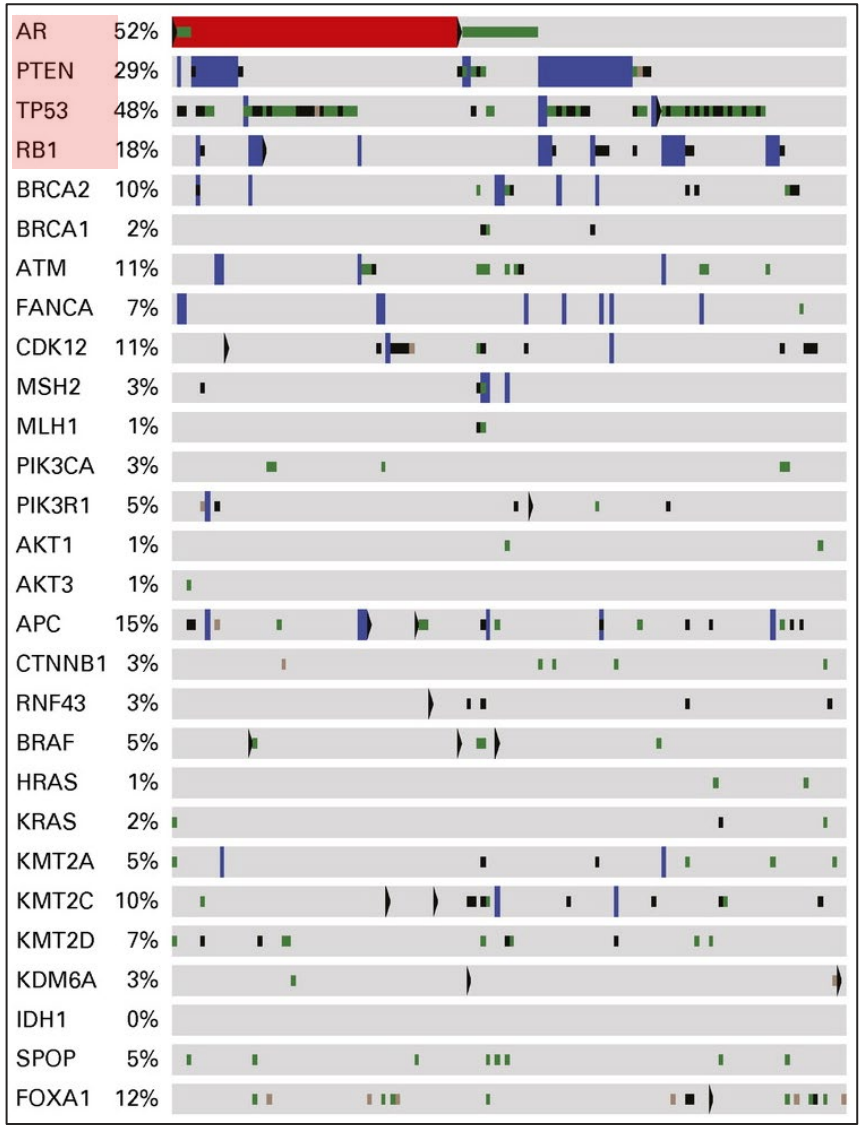
Why are AR^{MUT} samples most sensitive

Primary Prostate Cancer (TCGA)



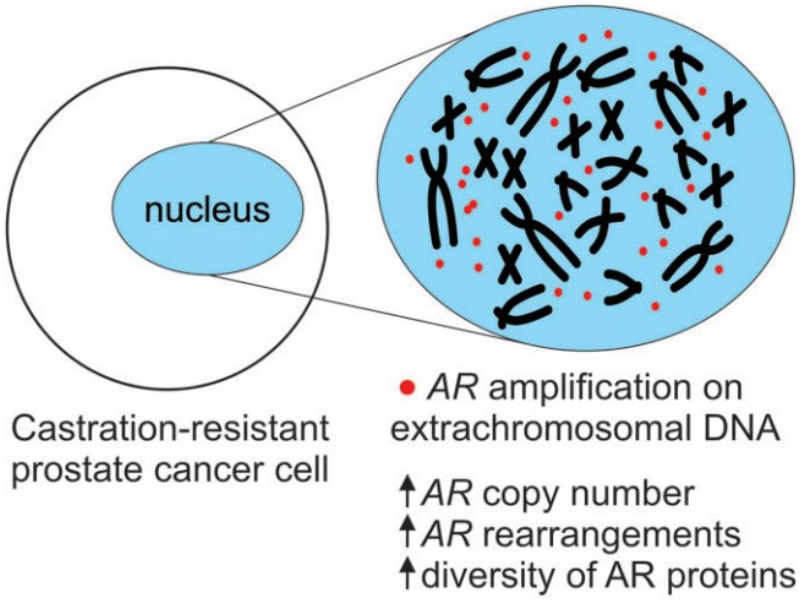
Schultz, N et al. Cell 2015

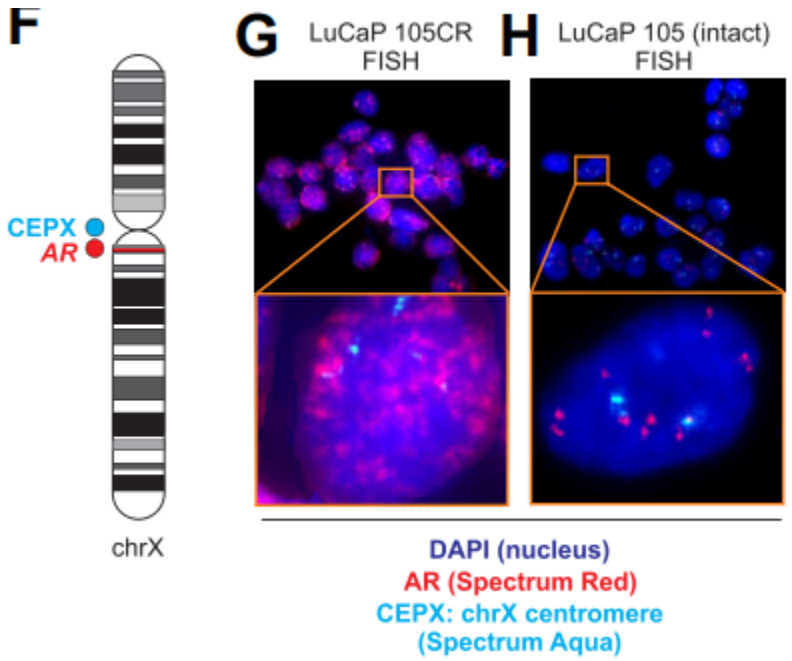
Metastatic CRPC (MSK)



Abida W et. al. *JCO Precision Oncology* 2017v

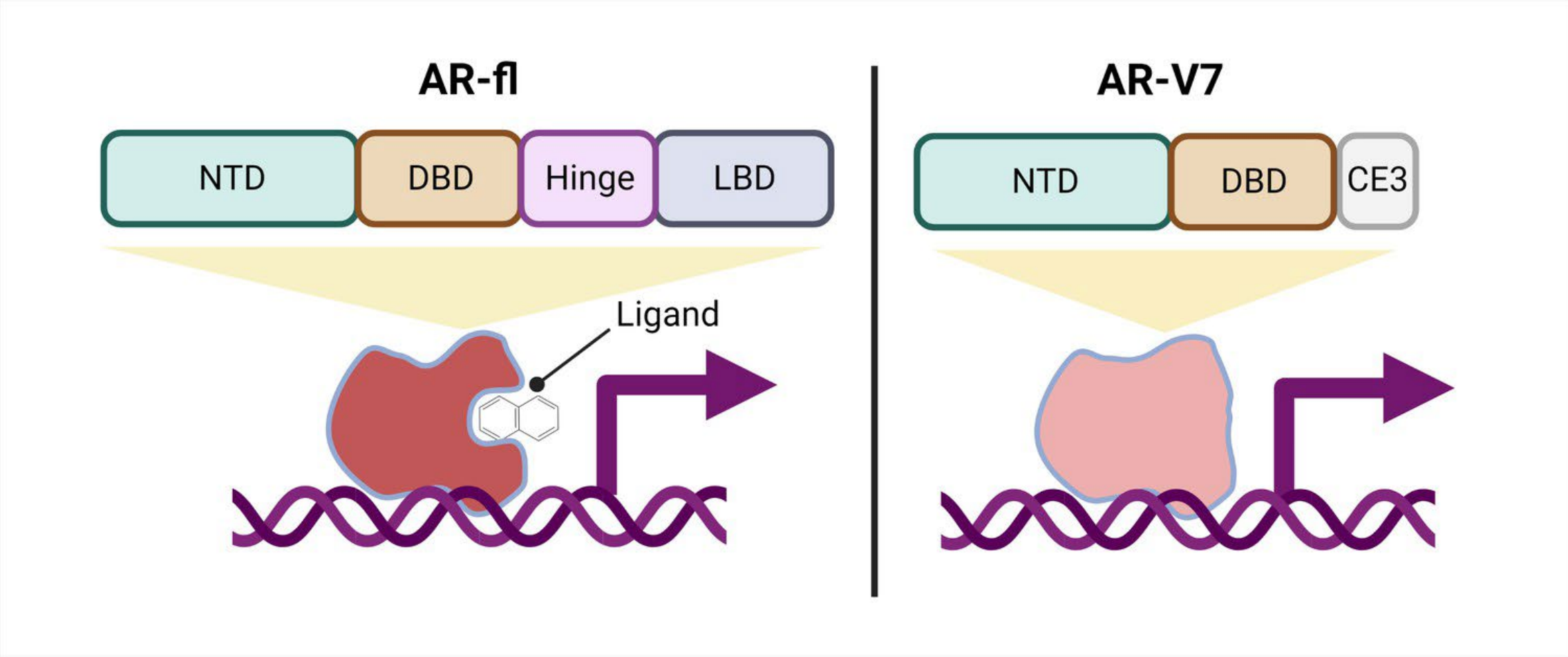
AR amplification through extrachromosomal DNA





Zivanovic A, et al., NAR Cancer 2023

AR-V7 is resistant to ligand targeted therapy



Article

Enhancing transcription–replication conflict targets ecDNA-positive cancers

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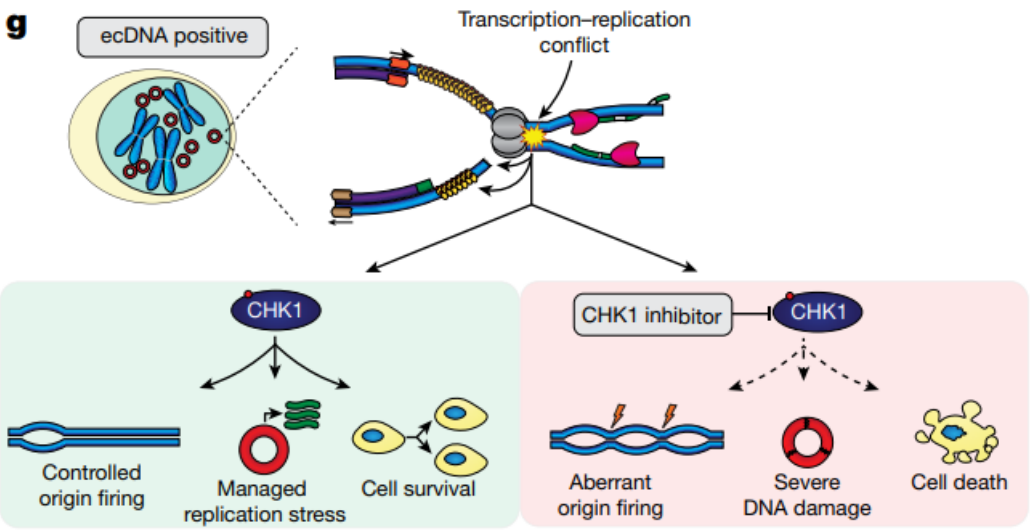
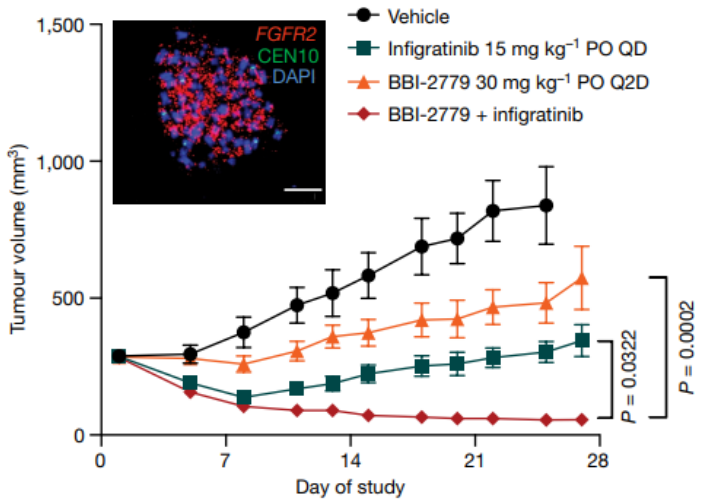
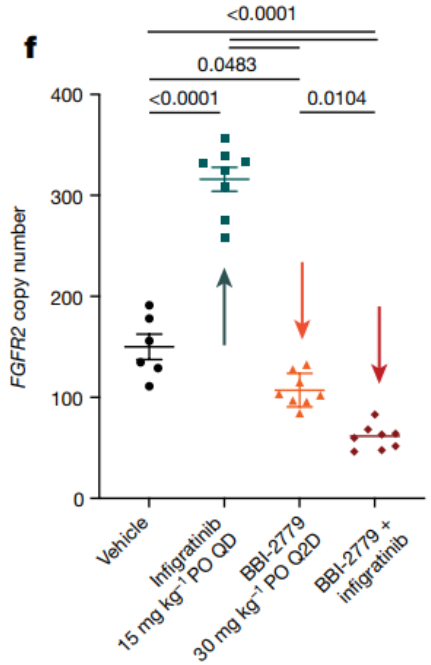
Jun Tang[1,2,13], Natasha E. Weiser[1,3,13], Guiping Wang[3,4,13], Sudhir Chowdhry[5], Ellis J. Curtis[1,2,6], Yanding Zhao[3,4,7], Ivy Tsz-Lo Wong[1,2], Georgi K. Marinov[4], Rui Li[3], Philip Hanoian[8], Edison Tse[5], Salvador Garcia Mojica[5], Ryan Hansen[5], Joshua Plum[5], Auzon Steffy[5], Snezana Milutinovic[5], S. Todd Meyer[5], Jens Luebeck[9], Yanbo Wang[1,2,3], Shu Zhang[1,2,3], Nicolas Altemose[4], Christina Curtis[4,10,11], William J. Greenleaf[4], Vineet Bafna[9], Stephen J. Benkovic[8], Anthony B. Pinkerton[5], Shailaja Kasibhatla[5], Christian A. Hassig[5,14]✉, Paul S. Mischel[1,2,14]✉ & Howard Y. Chang[3,4,7,12,14]✉

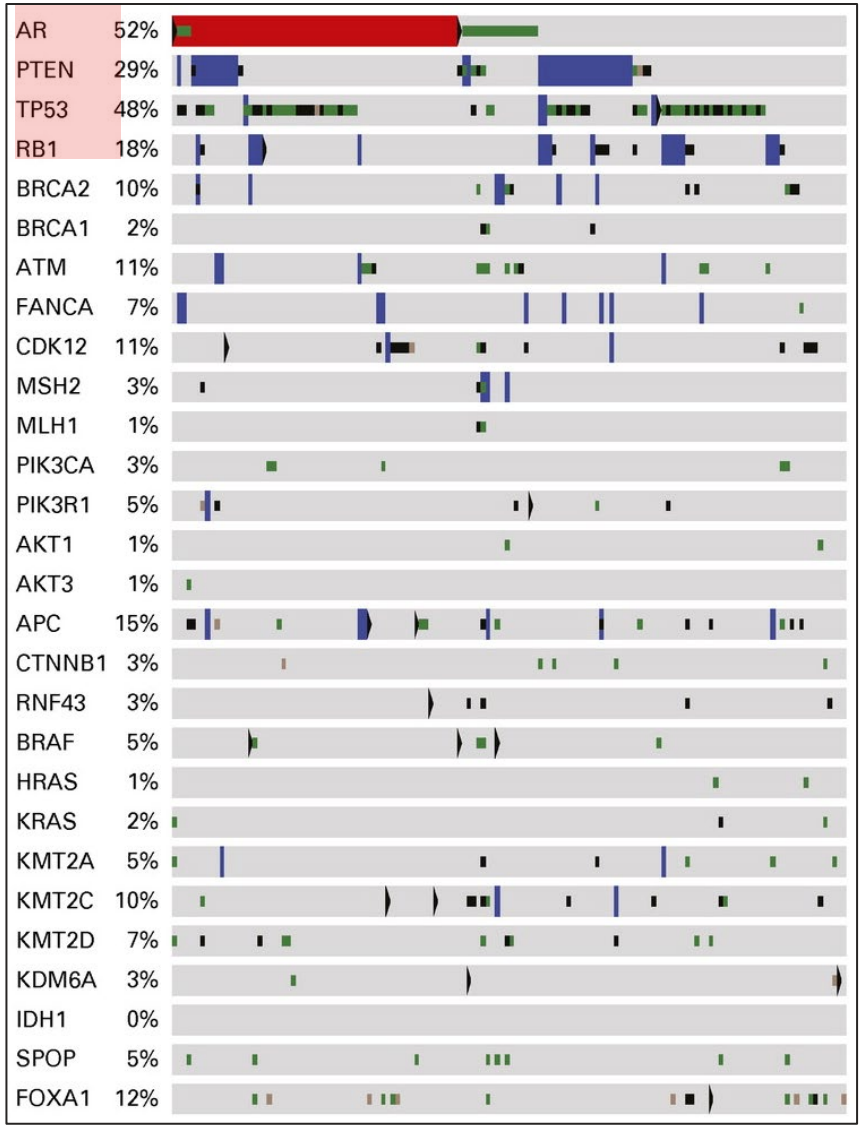




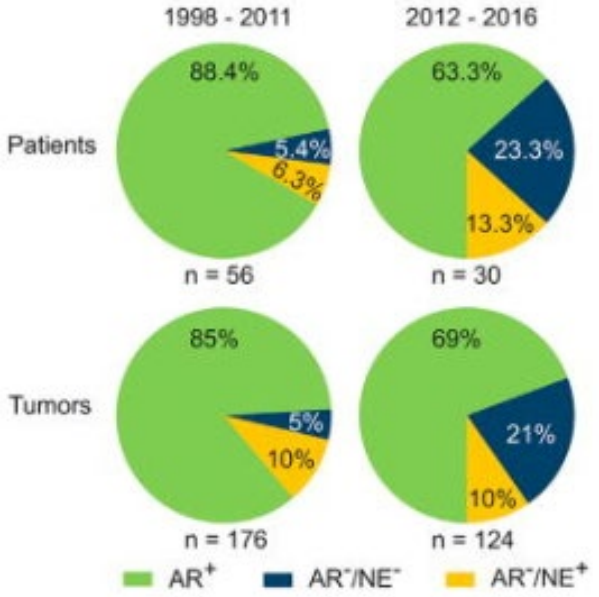


AR independence is more common

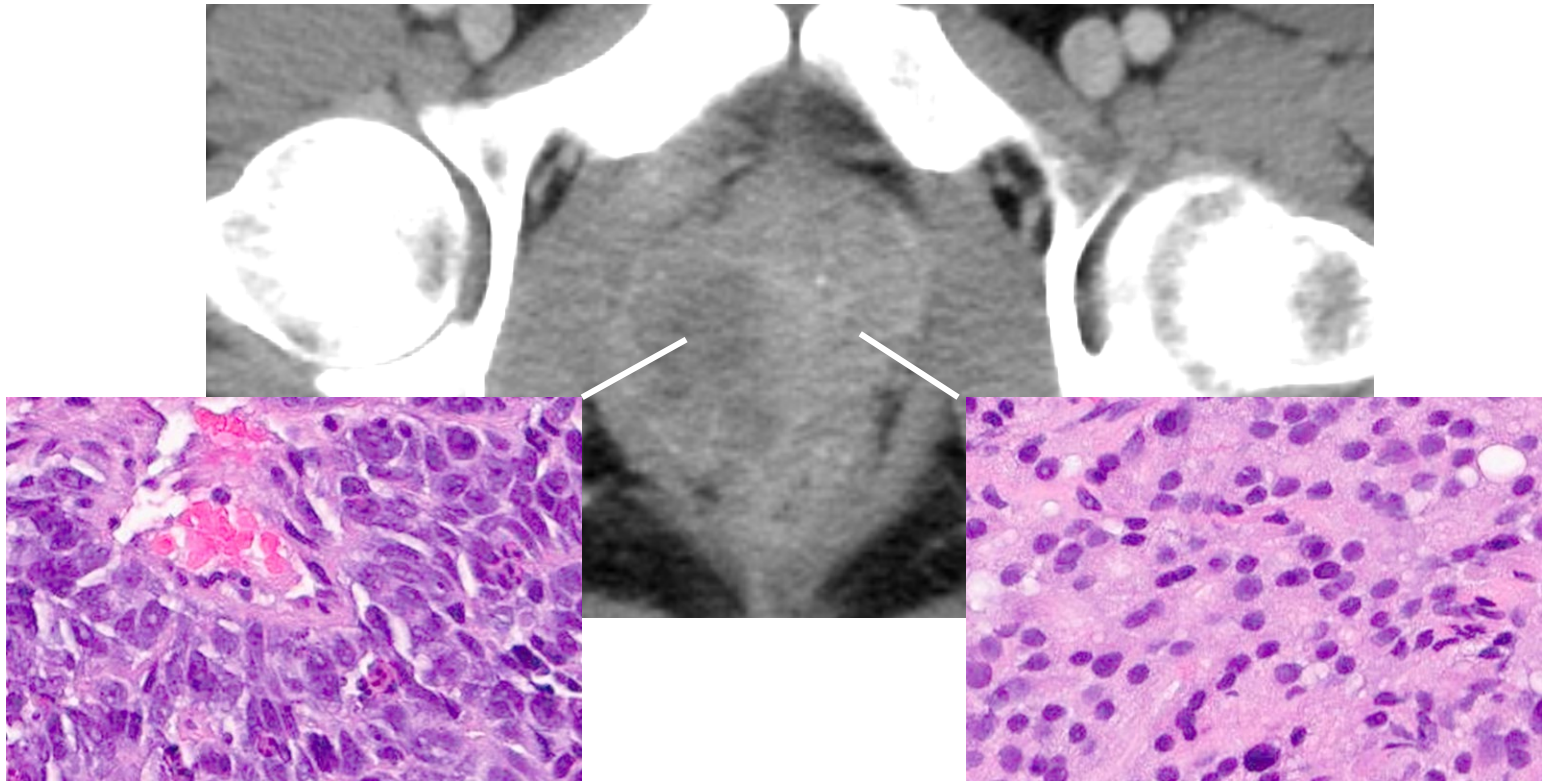
Metastatic CRPC (MSK)



Abida W et. al. *JCO Precision Oncology* 2017



Evidence of lineage plasticity driven by RB1 loss

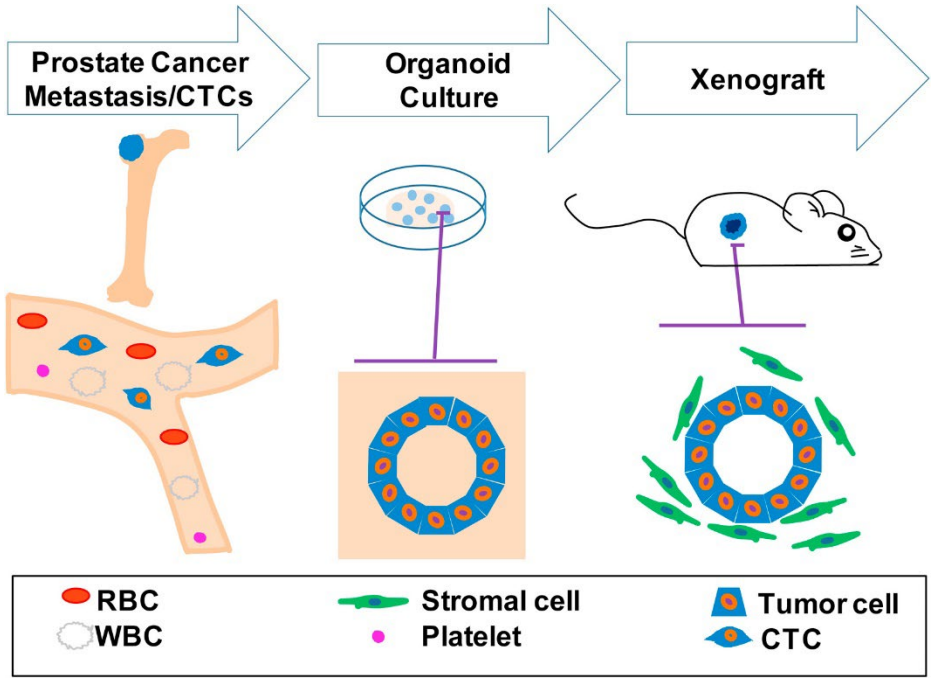


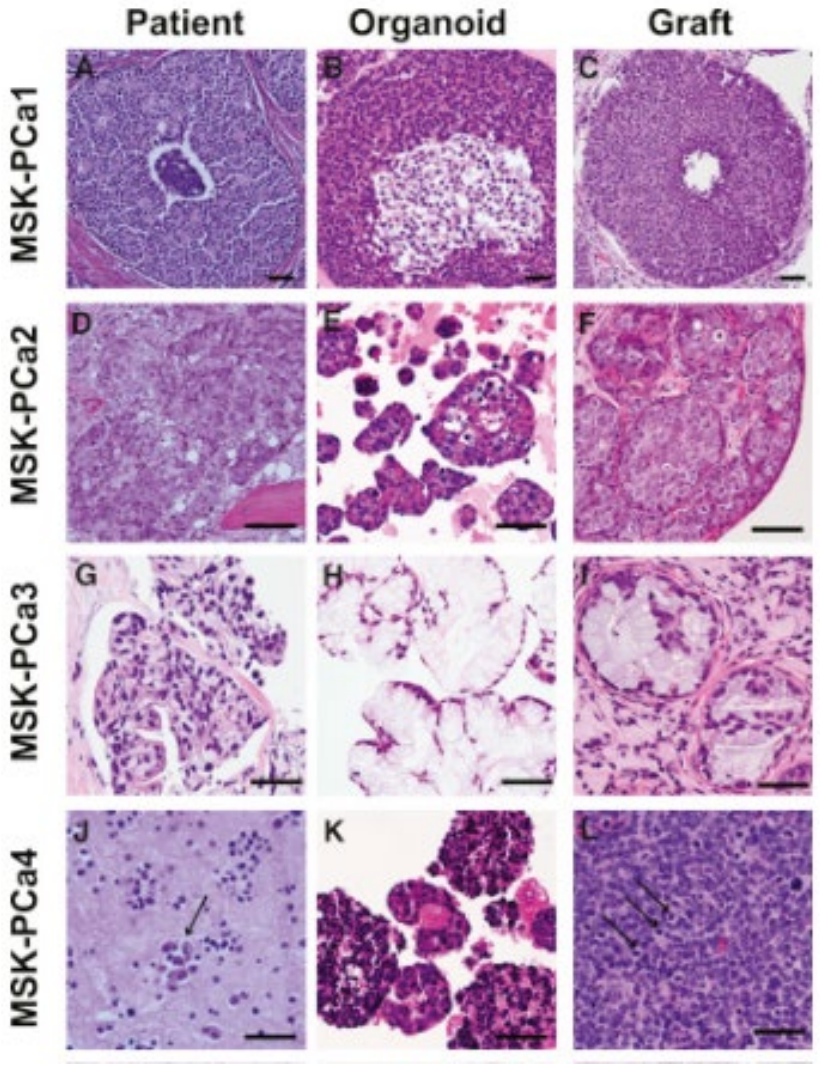
Lesion 2: Small Cell Histology
1. TP53 p.Y163C
2. PTEN Deletion
3. CTNNB1 exon3 p.D32A
4. PIK3CG exon6 splicing variant p.X798_splice
5. TMPRSS2 rearrangement
6. RB1 Intragenic deletion
7. RAD51D Deletion (Fold Change: -2.6)
8. KMT2C exon44 p.K3847E

Lesion 1: Adenocarcinoma Histology
1. TP53 p.Y163C
2. PTEN Deletion
3. CTNNB1 exon3 p.D32A
4. PIK3CG exon6 splicing variant p.X798_splice
5. TMPRSS2 rearrangement

Anuradha Gopalan

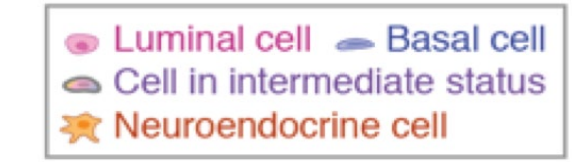
Patient derived organoids of prostate cancer

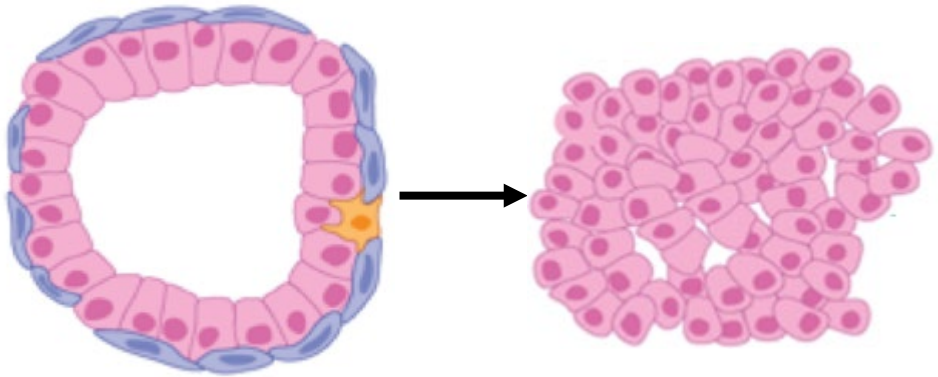




Gao D et. al. *Cell 2014*

How many subtypes of CRPC are there





AR dependent
- AR mutation
- AR Amplification
- AR Splice Variant

Neuroendocrine

?

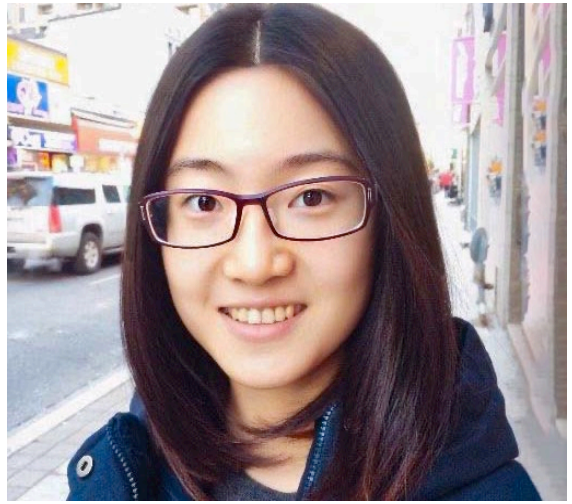
CRPC

Normal

Hormone sensitive Prostate Cancer

Ekta Khurana

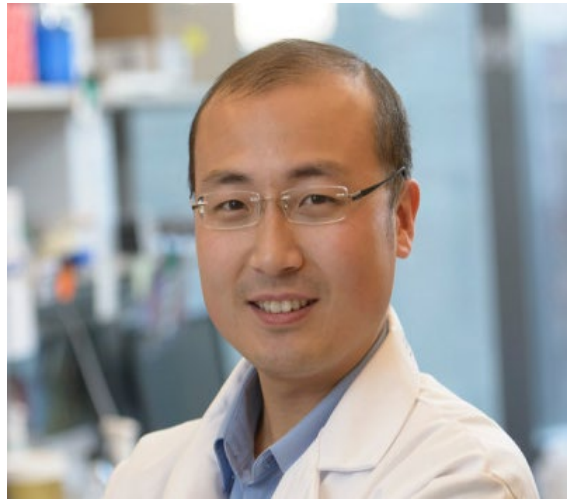
Cindy Lee



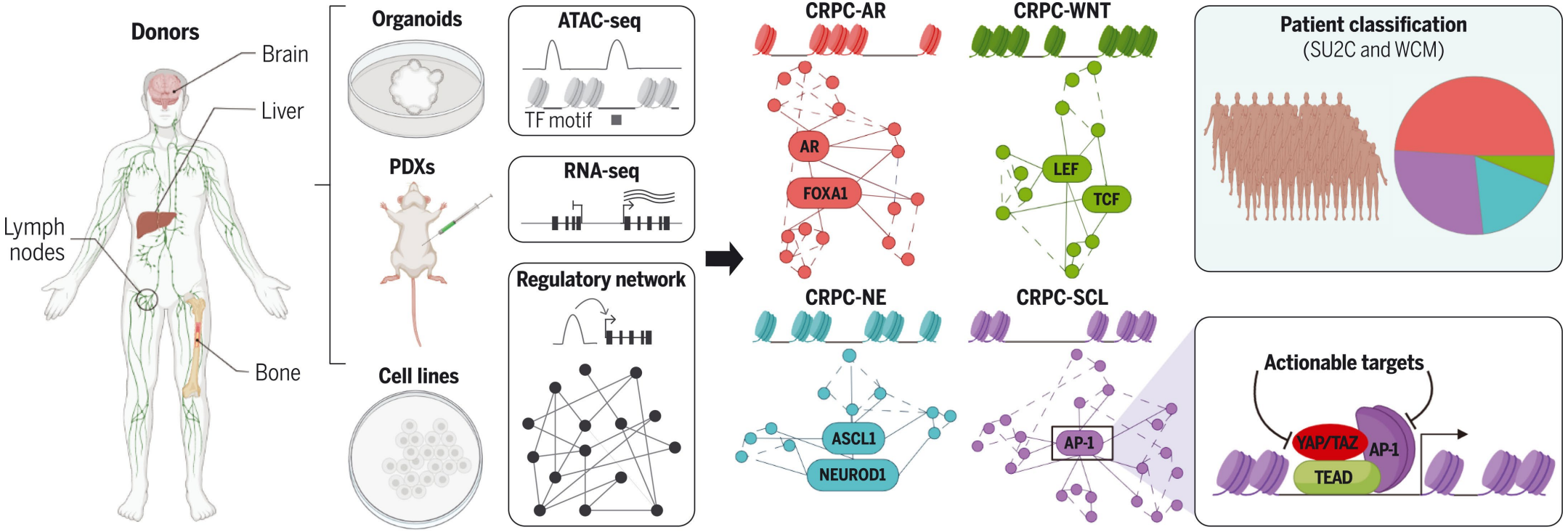
Erica Xu

Chen Khuan Wong

Fanying Tang



Shangqian Wang



Ekta Khurana

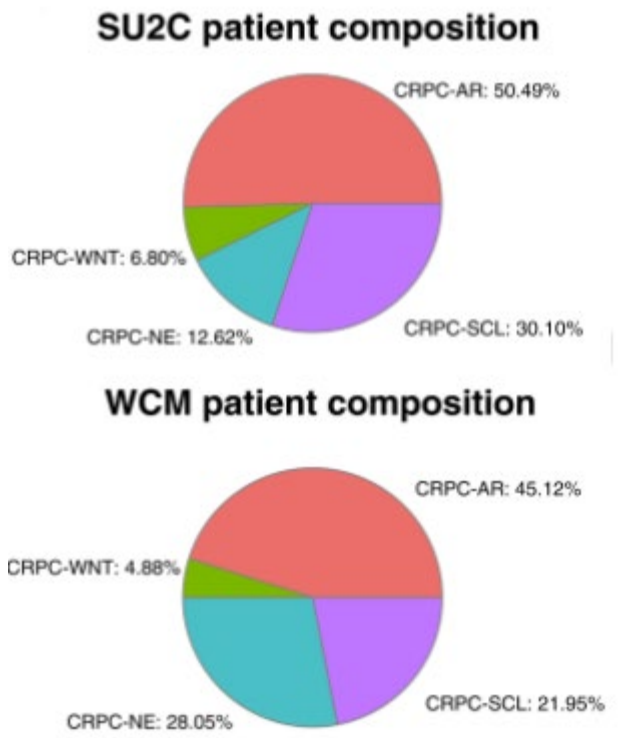
Chen Khuan Wong

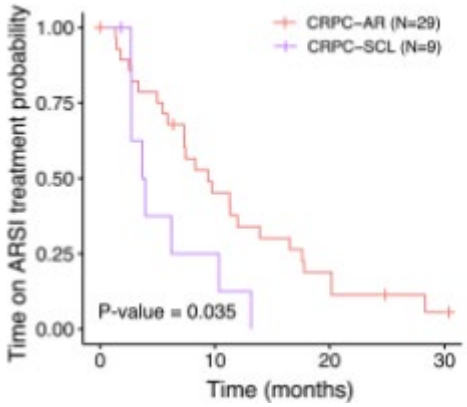
Fanying Tang

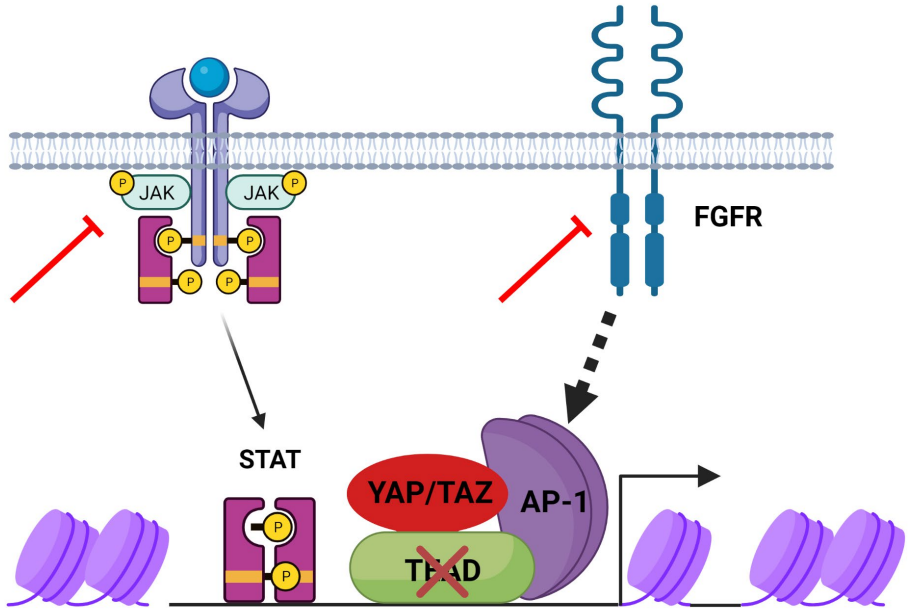
Cindy Lee

Tang et. al Chromatin profiles classify castration-resistant prostate cancers suggesting therapeutic targets, Science 2022

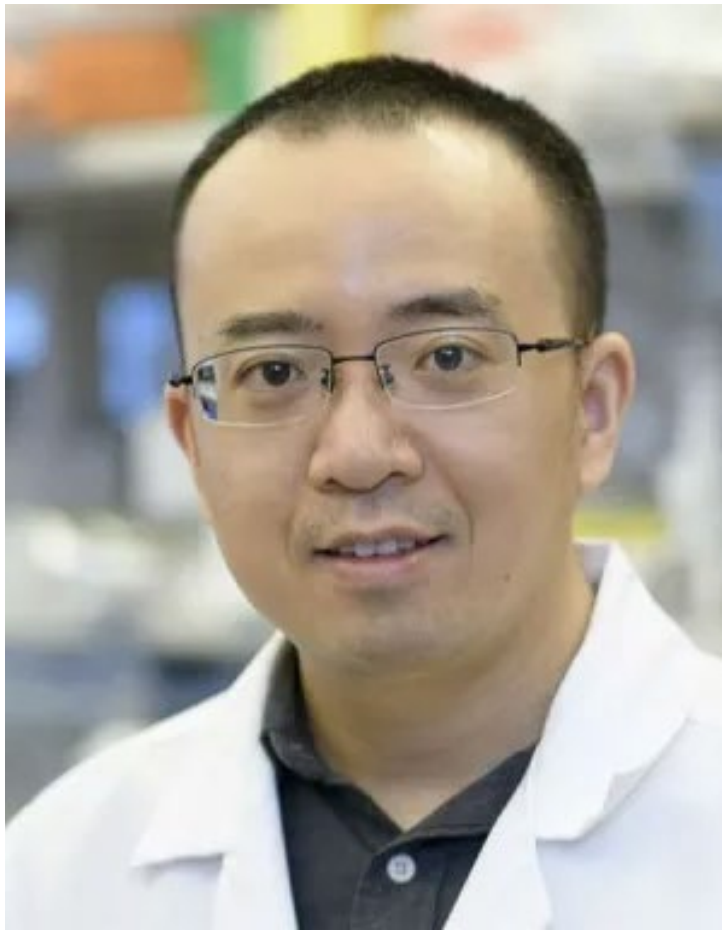
CRPC-SCL are common and less responsive to ARSI







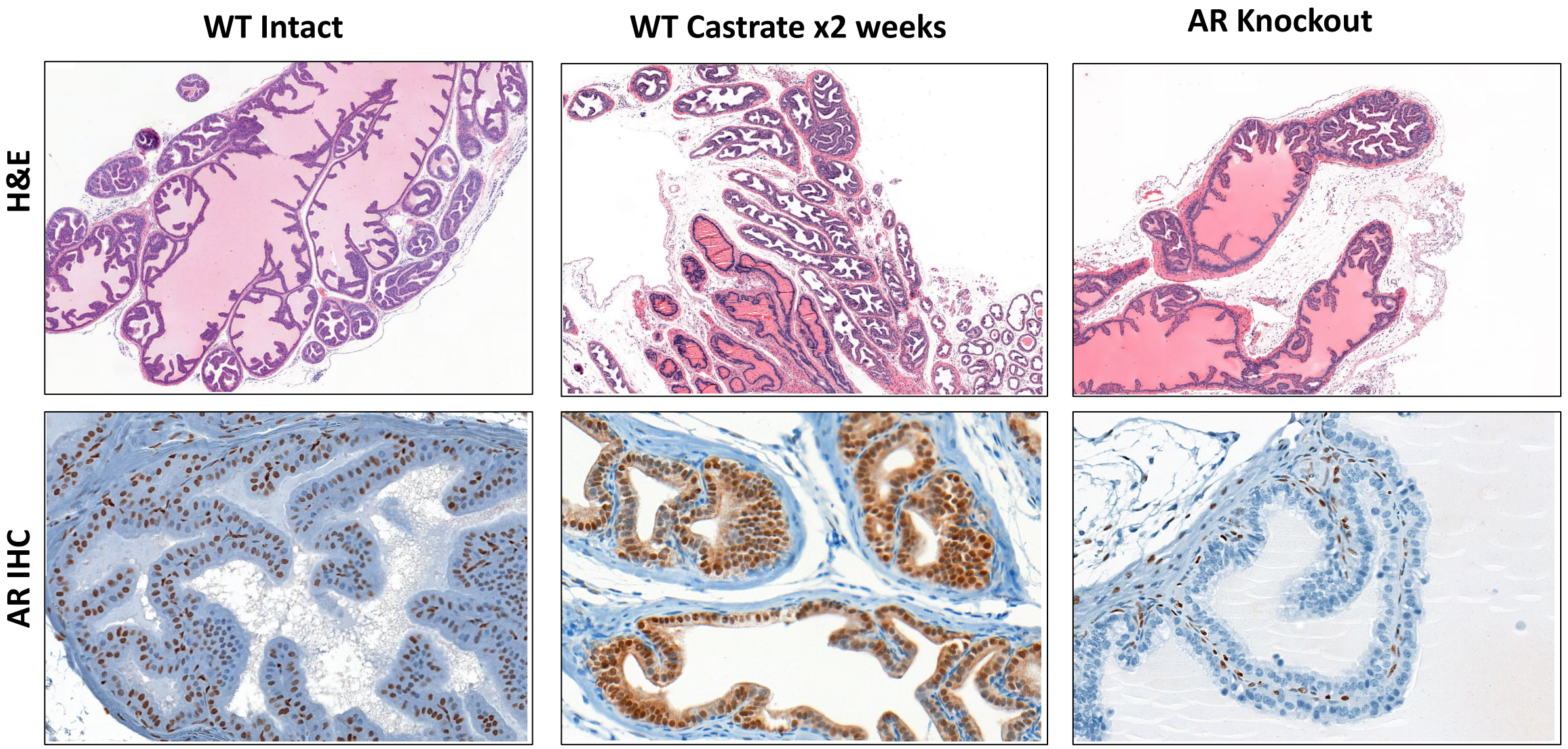
Take a step back—Why is untreated prostate cancer AR dependent



Dan Li

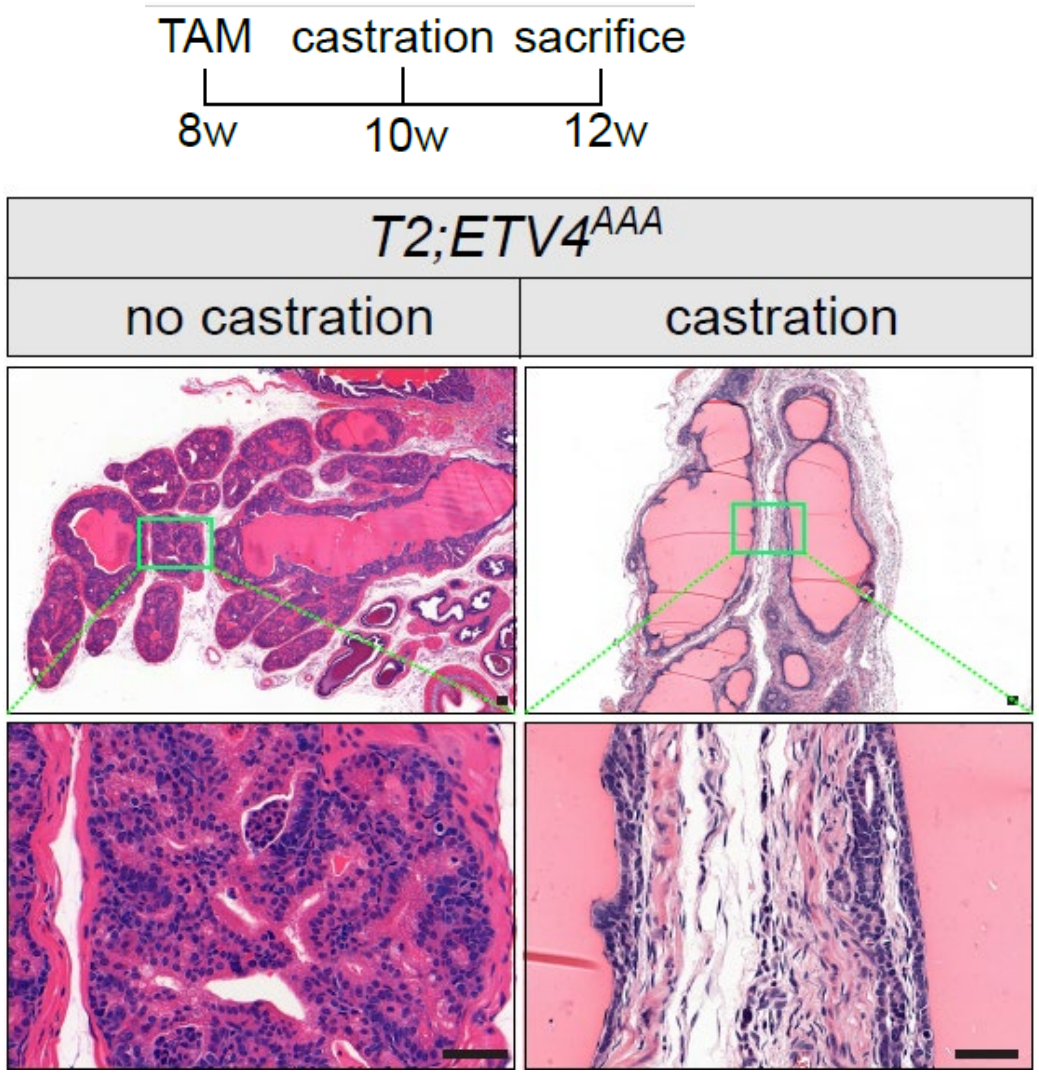
Aaron Wang

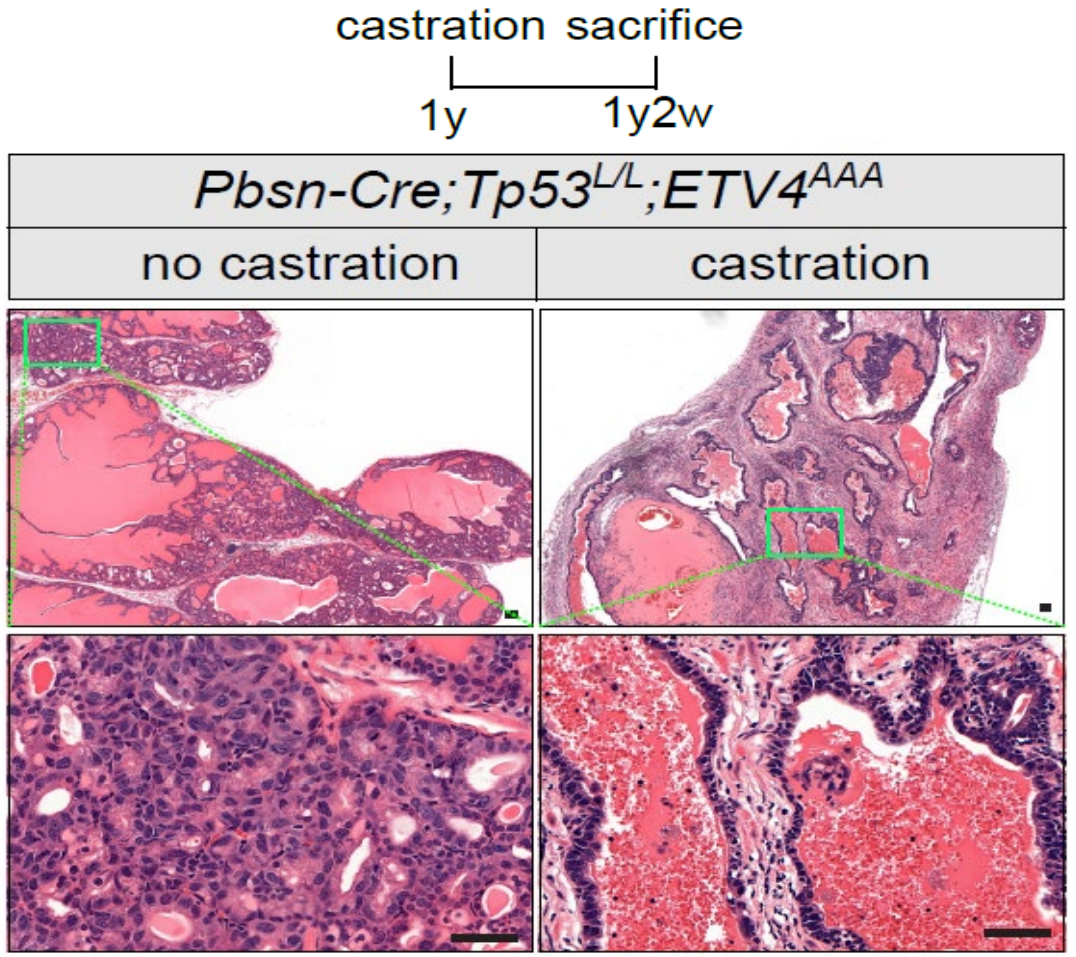
No epithelial regression with Lumianl AR knockout



Li et al **In Preparation**

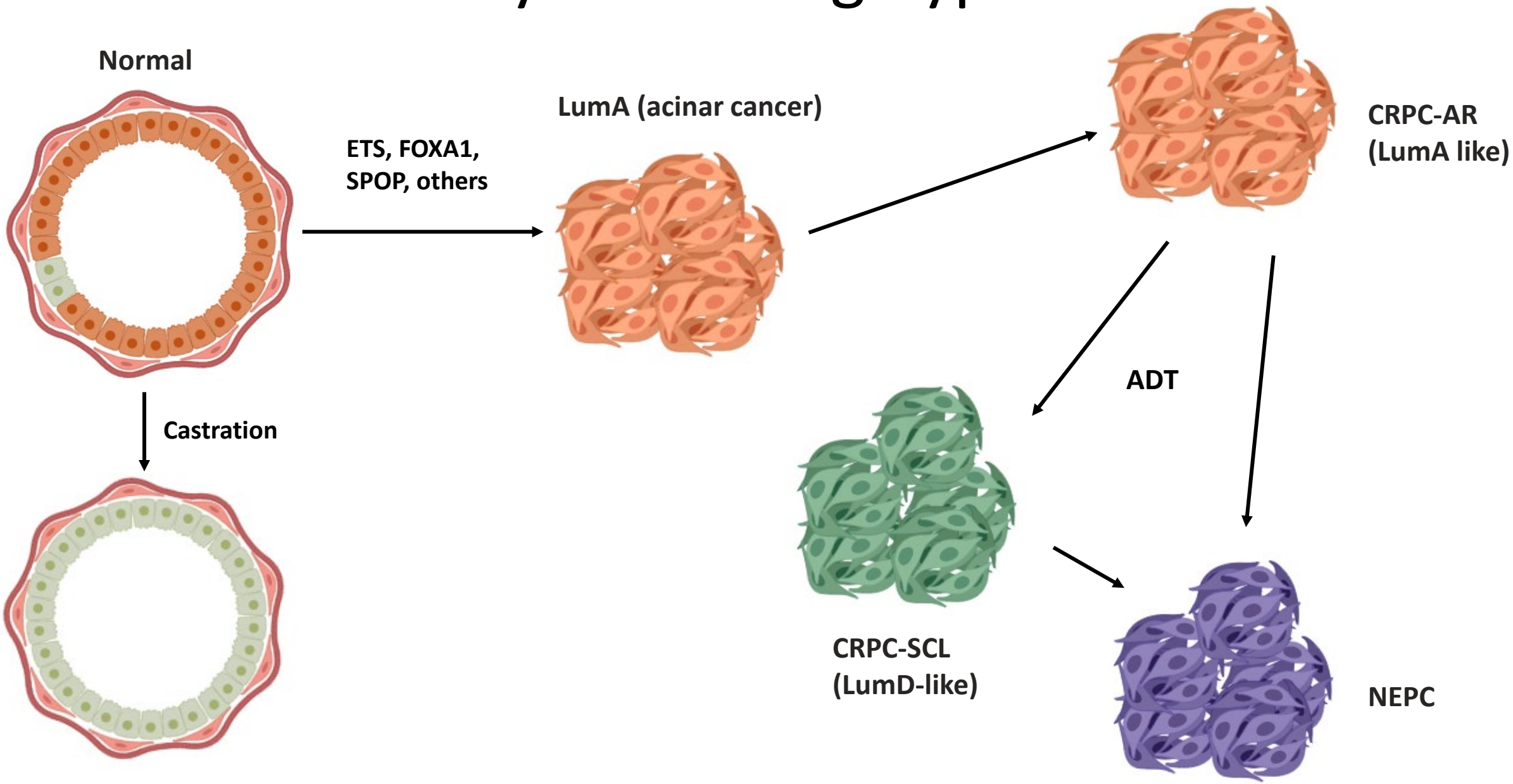
ETV4-driven prostate cancer highly AR dependent





Li et al **In Preparation**

Summary – Working hypothesis



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