Management of Incurable Prostate Cancer in 2014

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Knight Cancer Institute, OHSU

2014: Cancer Estimates

Estimated New Cases*

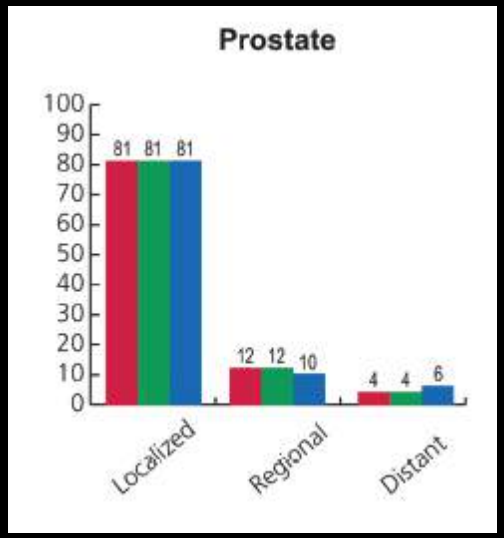
Males		
Prostate	233,000	27%
Lung & bronchus	116,000	14%
Colorectum	71,830	8%
Urinary bladder	56,390	7%
Melanoma of the skin	43,890	5%
Kidney & renal pelvis	39,140	5%
Non-Hodgkin lymphoma	38,270	4%
Oral cavity & pharynx	30,220	4%
Leukemia	30,100	4%
Liver & intrahepatic bile duct	24,600	3%
All Sites	**855,220**	**100%**

Estimated Deaths

Males		
Lung & bronchus	86,930	28%
Prostate	29,480	10%
Colorectum	26,270	8%
Pancreas	20,170	7%
Liver & intrahepatic bile duct	15,870	5%
Leukemia	14,040	5%
Esophagus	12,450	4%
Urinary bladder	11,170	4%
Non-Hodgkin lymphoma	10,470	3%
Kidney & renal pelvis	8,900	3%
All Sites	**310,010**	**100%**

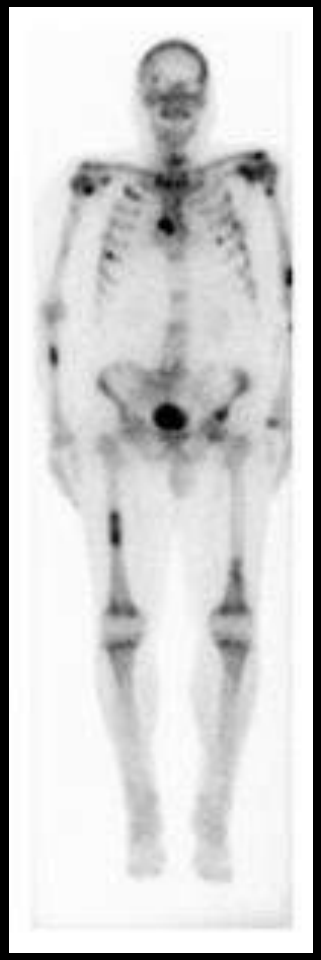
CA Cancer J Clin 2014;64:9-29.

Stage at Diagnosis



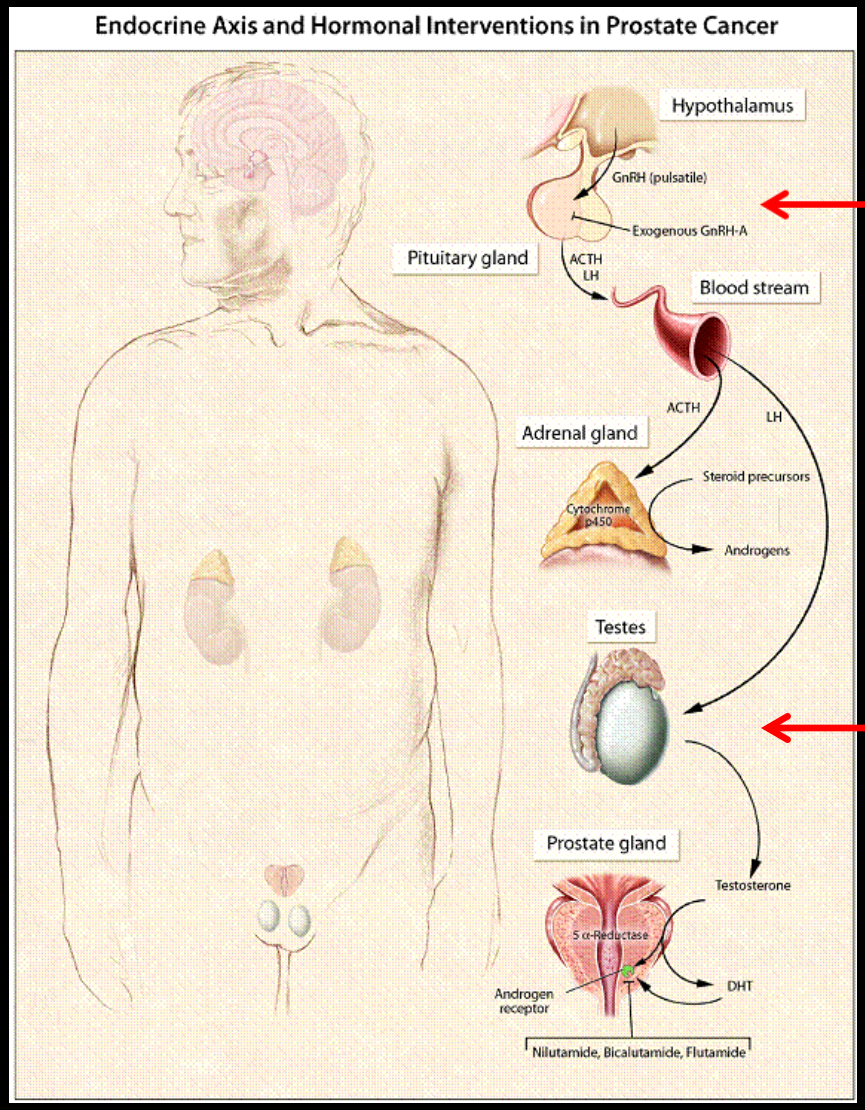
- 4% of men present with metastatic disease
- Many more men develop metastatic cancer after presenting with localized cancer

Metastatic Prostate Cancer



- Definition
- Sites of metastases:
  - bone (90%)
  - lymph nodes (60%)
  - liver/lungs (25-45%)
- Initial Therapy: Androgen Suppression

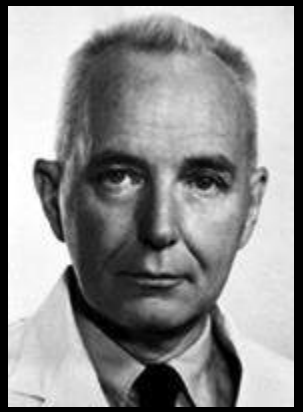
Decreasing Androgens



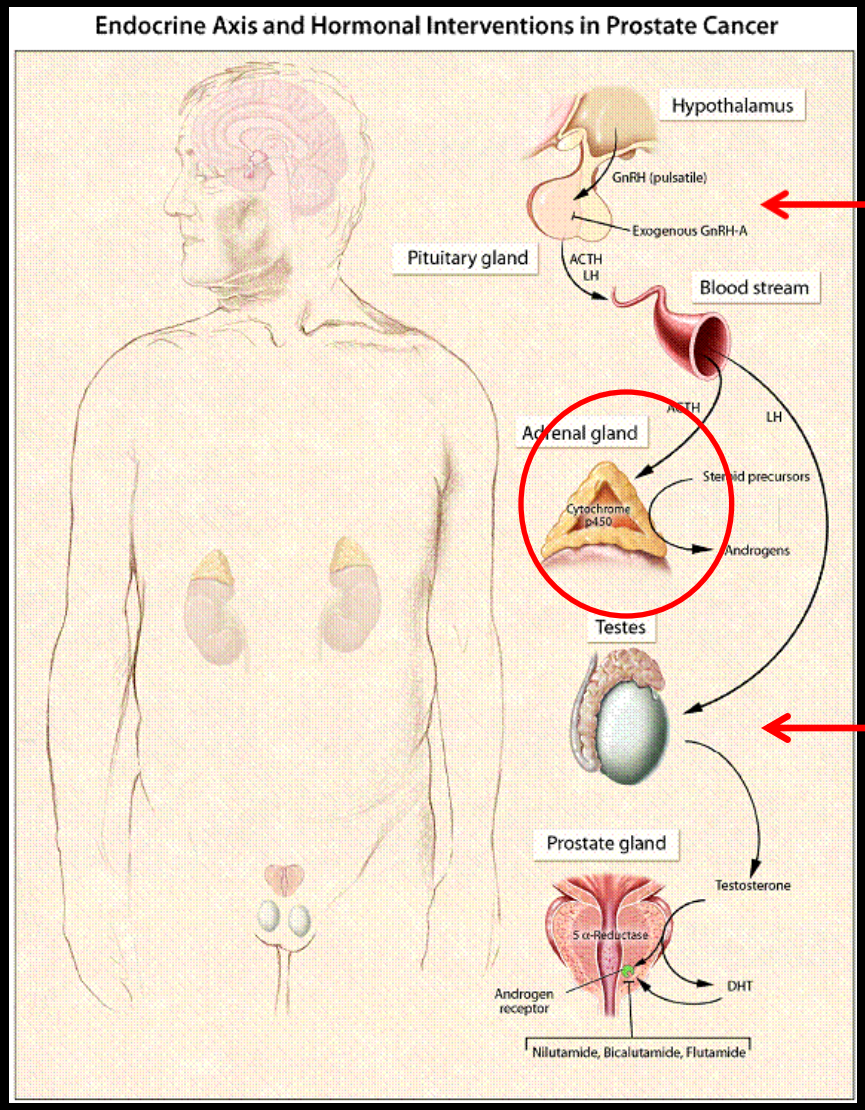
LHRH Agonist Therapy (1980s)

Testosterone < 50 ng/dl

Surgical Castration 1940s



Decreasing Androgens



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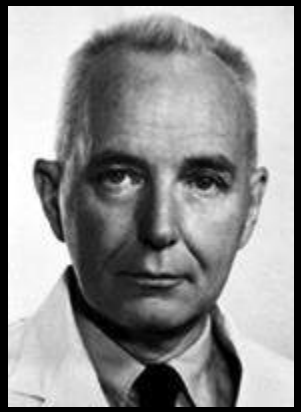
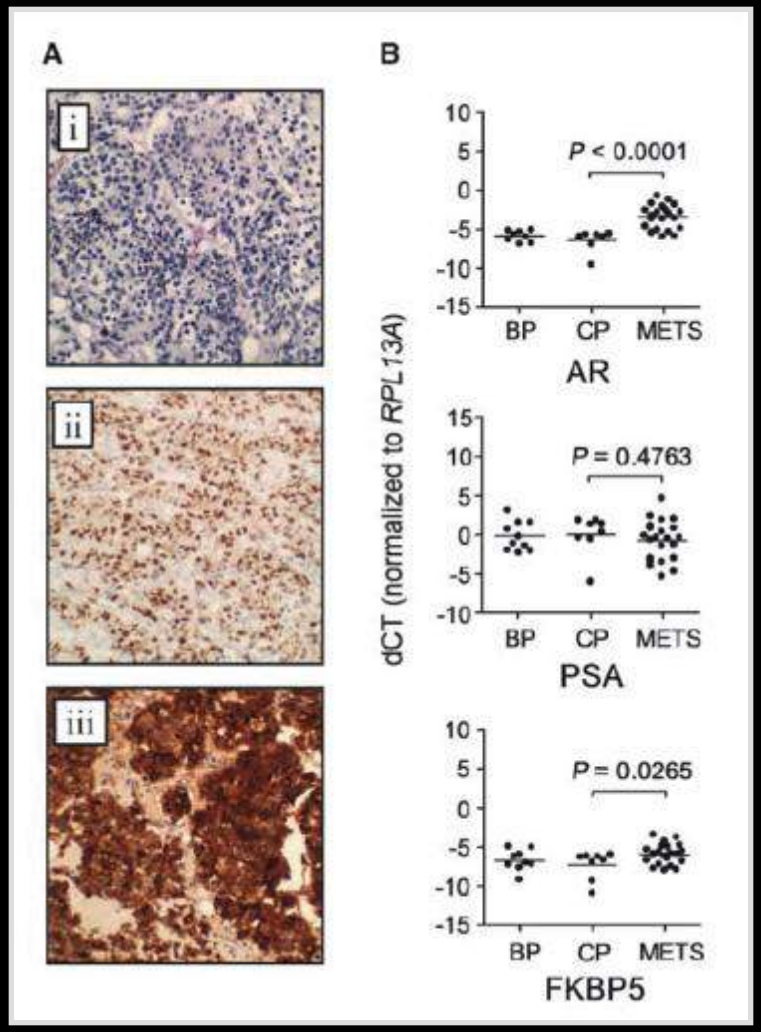


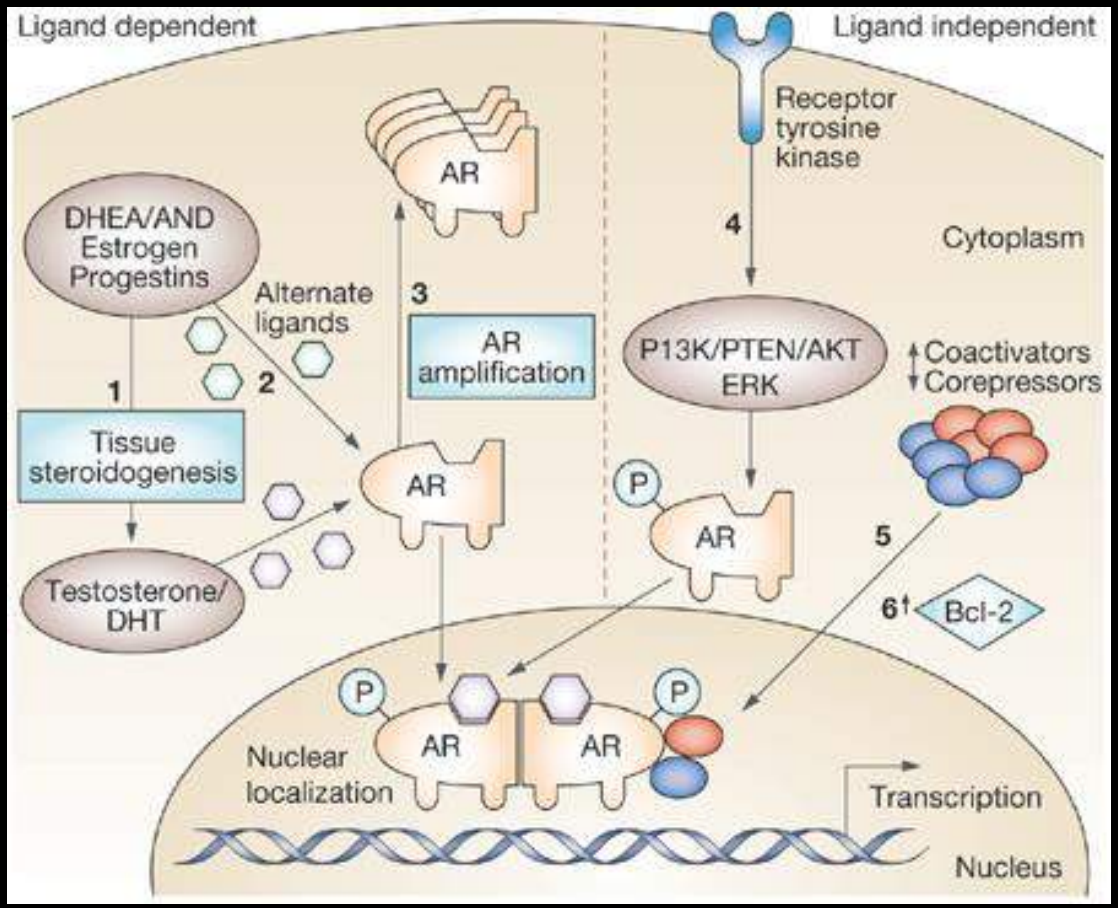
Androgen Insensitive → **Castration Resistant**



- In a metastatic lymph node from a hormone-refractory patient
  - ✓ Androgen receptor expressed
  - ✓ PSA expressed
  - ✓ Androgen responsive genes expressed

Montgomery RB, Cancer Res 68:4457-54, 2008

Mechanisms of Castration Resistance in Prostate Cancer



Nature Clinical Practice Urology (2009) **6**, 76-85

Metastatic, Castration Resistant Prostate Cancer

+Nuclear Medicine Bone scan

OR

+CT Scan

+

Testosterone < 50 ng/dl

Timeline for FDA Approval

2009	Julie Completes Training
2010	**Sipuleucel-T**
	Cabazitaxel
2011	**Abiraterone** post-chemotherapy
2012	**Enzalutamide** post-chemotherapy
	Abiraterone pre-chemotherapy
2013	**Radium-223**
2014	(Enzalutamide pre-chemotherapy)

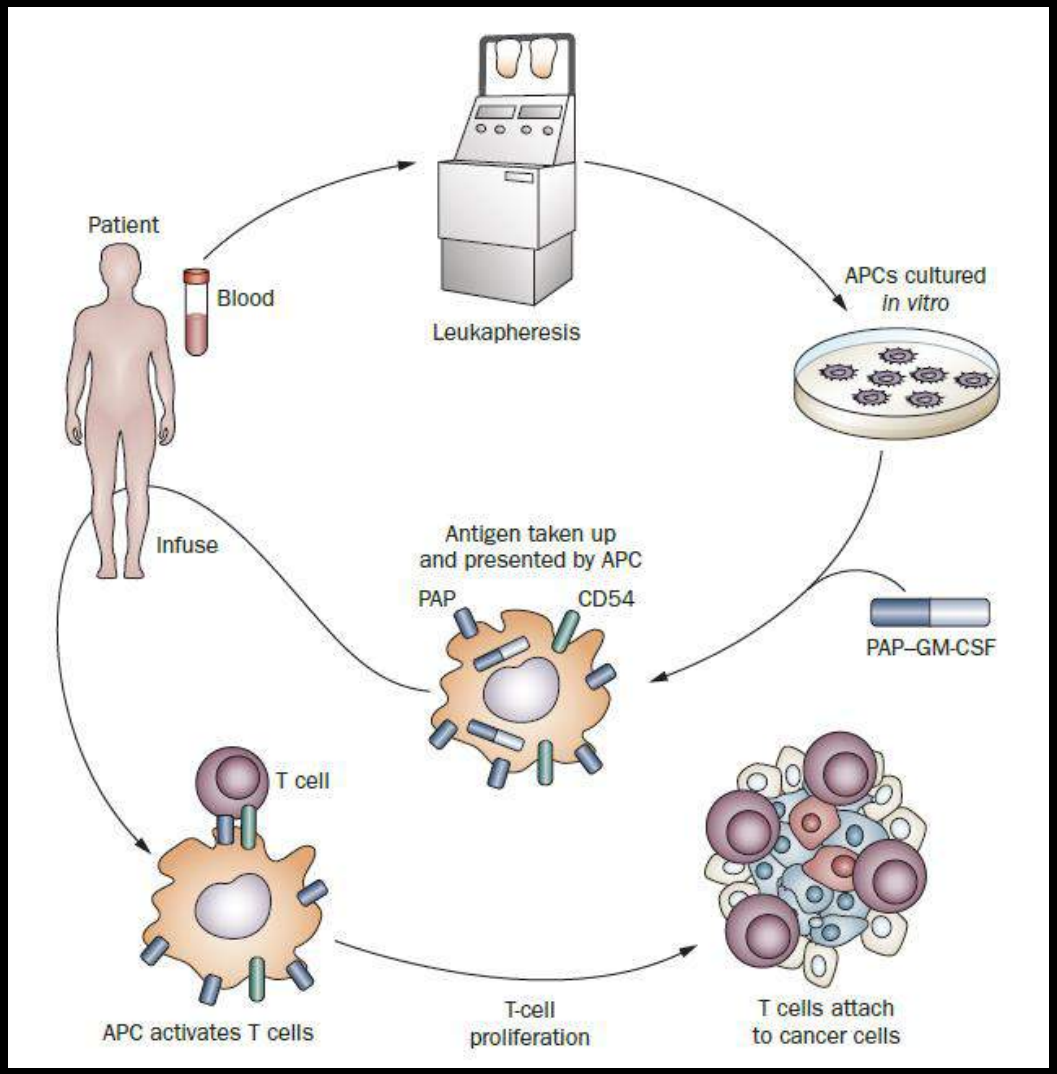
IMMUNOTHERAPY

CHEMOTHERAPY

HORMONE THERAPY

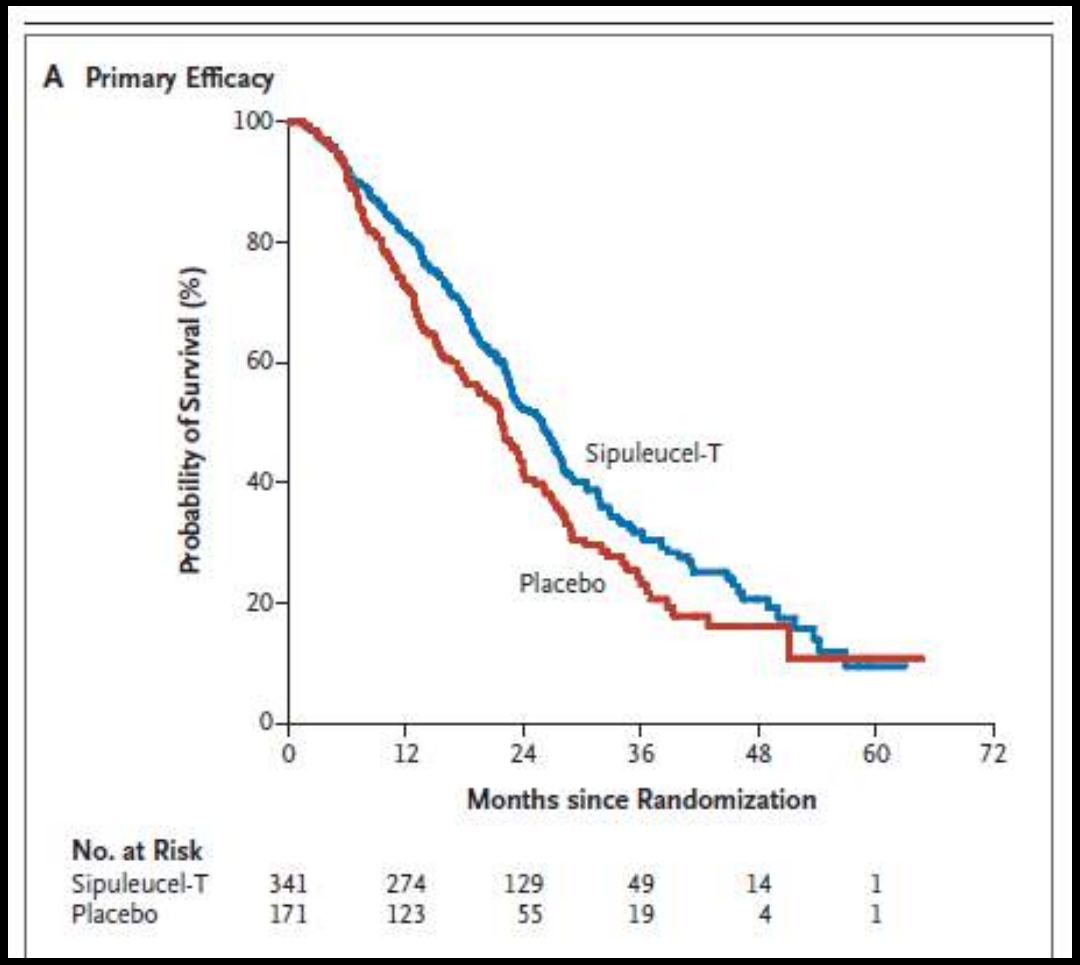
RADIATION THERAPY

Immunotherapy: Sipuleucel-T (aka Provenge)



Nature Review Clinical Oncology 2011; 8: 551-561.

Improved Survival



- Overall survival: 25.8 versus 21.7 months
- No significant PSA decreases, tumor size decreases
- Used in minimally symptomatic patients

NEJM 2010; 363: 411-422

Side Effects of Sipuleucel-T

- Related to cytokine release
- Risk of receiving someone else's cells
- Risk of receiving infected cells

Sipuleucel-T: Maximizing Effect (still learning to use this therapy)

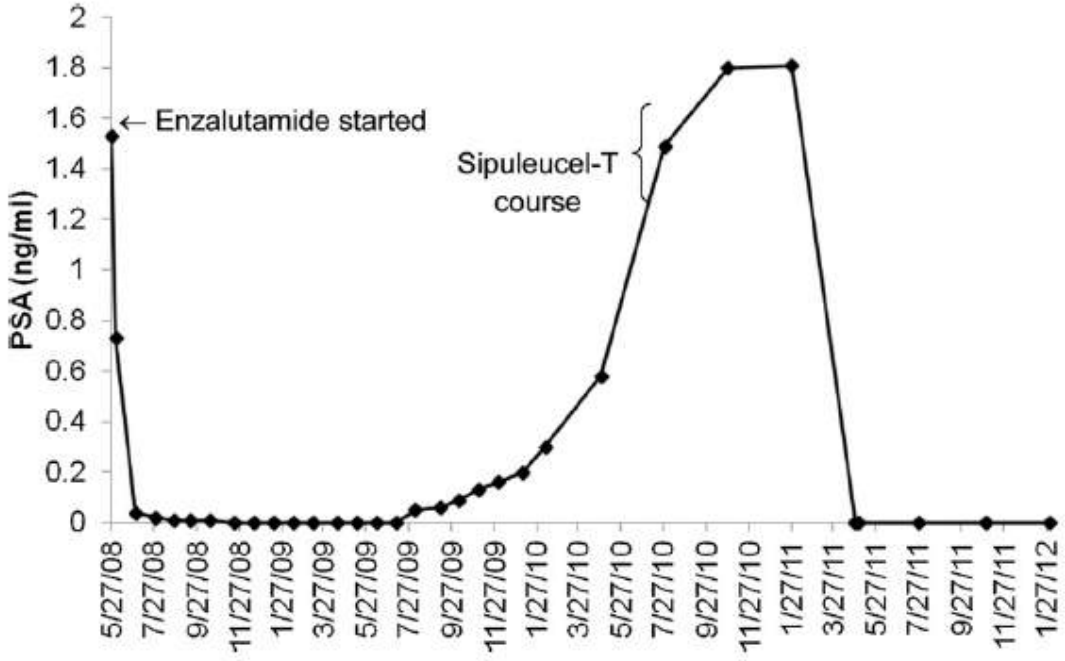
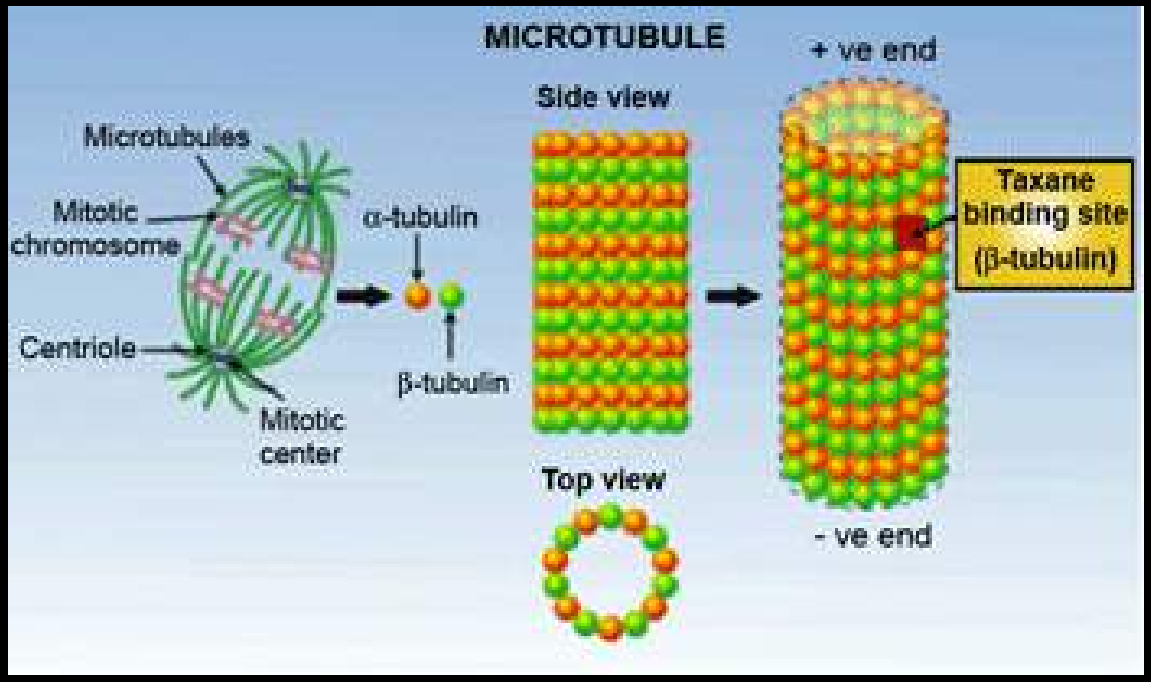


Figure 1. Patient's prostate-specific antigen (PSA) levels graphed by time. He started enzalutamide on May 27, 2008 and received a course of sipuleucel-T from August 30, 2010 to September 27, 2010. His PSA level remained undetectable since April 28, 2011.

Urology 2013; 81: 381-383.

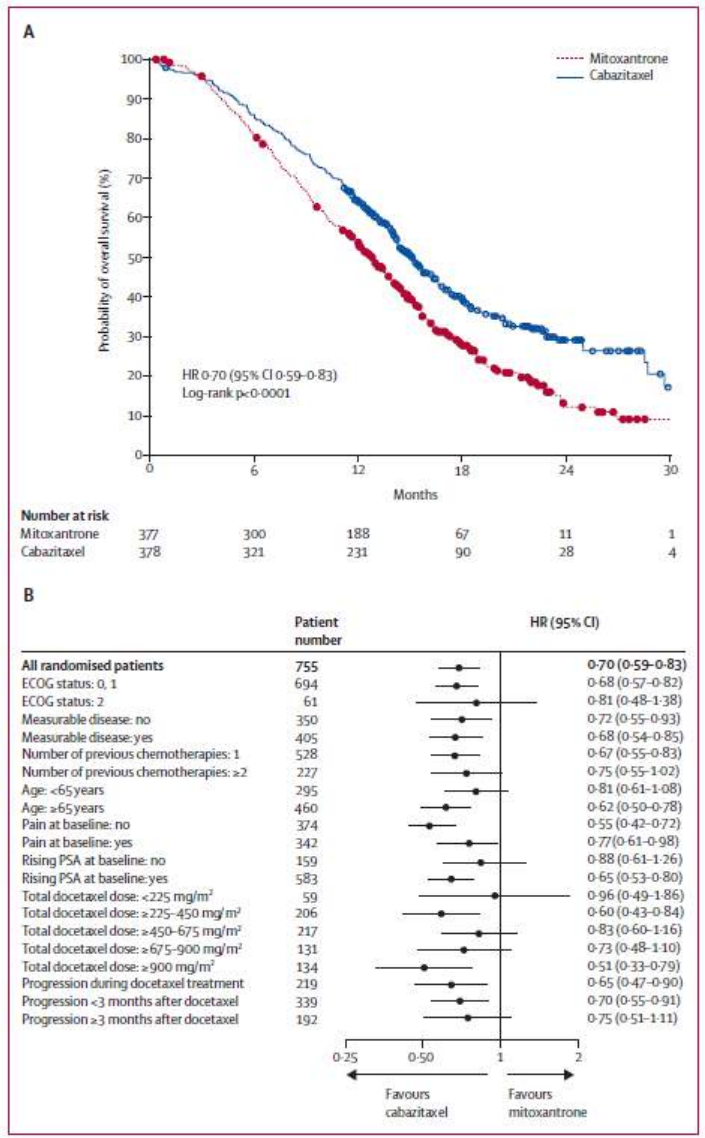
Chemotherapy

- Taxanes
  - First line: Docetaxel + prednisone 5 mg bid
  - Second line: Cabazitaxel + prednisone 5 mg bid



Clin Cancer Res. 2008;14:7167-7172.

Chemotherapy: Cabazitaxel + Prednisone (aka Jevtana)



Overall survival: 15.1 months versus 12.7 months

Pain control

Lancet Oncology 2010; 376: 1147-54.

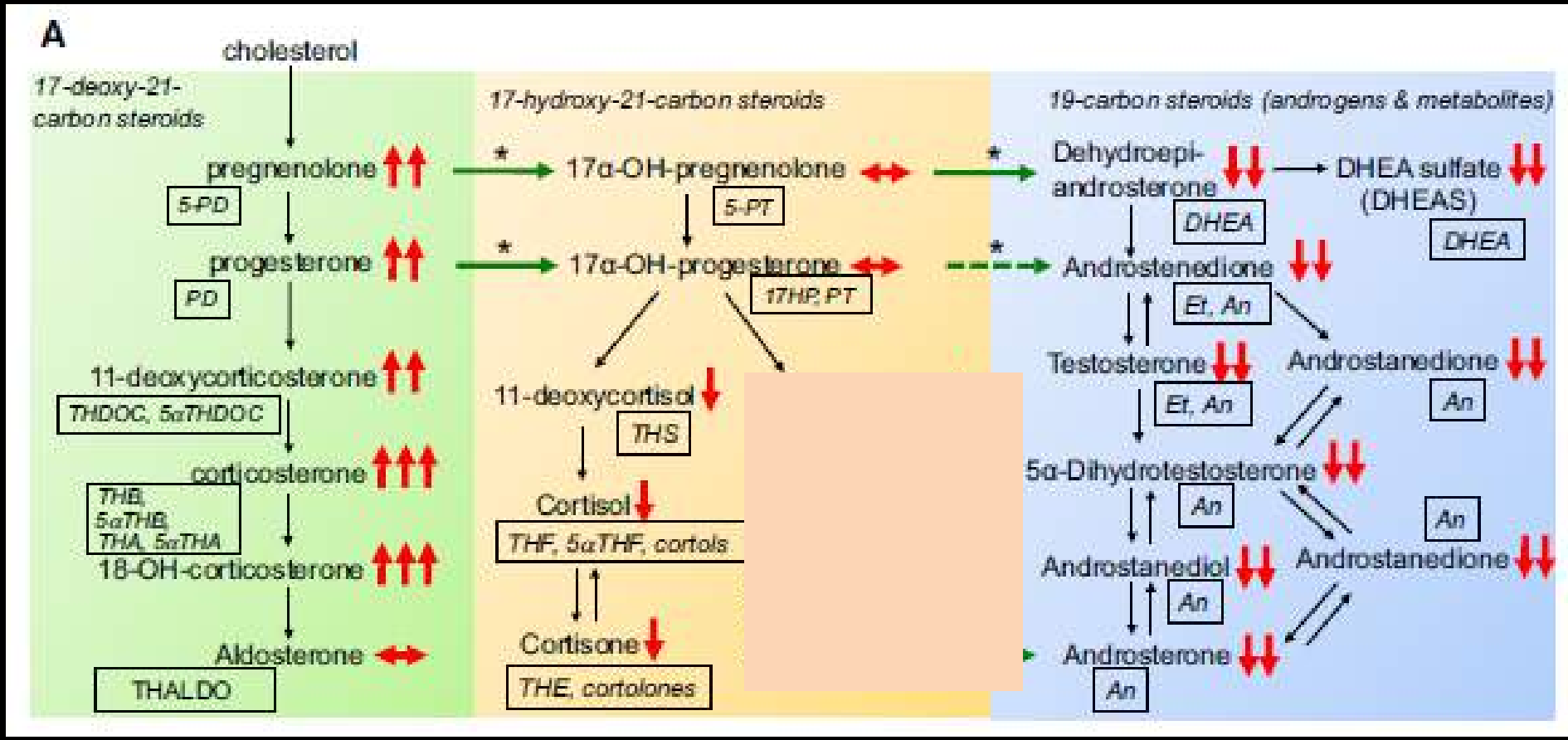
Cabazitaxel + Prednisone Toxicity

- Significant myelosuppression
- Rate of neutropenia and neutropenic fever
- Fatigue

Hormone Therapy

- More complete suppression of androgen production
  - Abiraterone
- More complete blockade of androgen receptor signaling
  - Enzalutamide

Hormone Therapy: Abiraterone (+ Prednisone) (aka Zytiga)



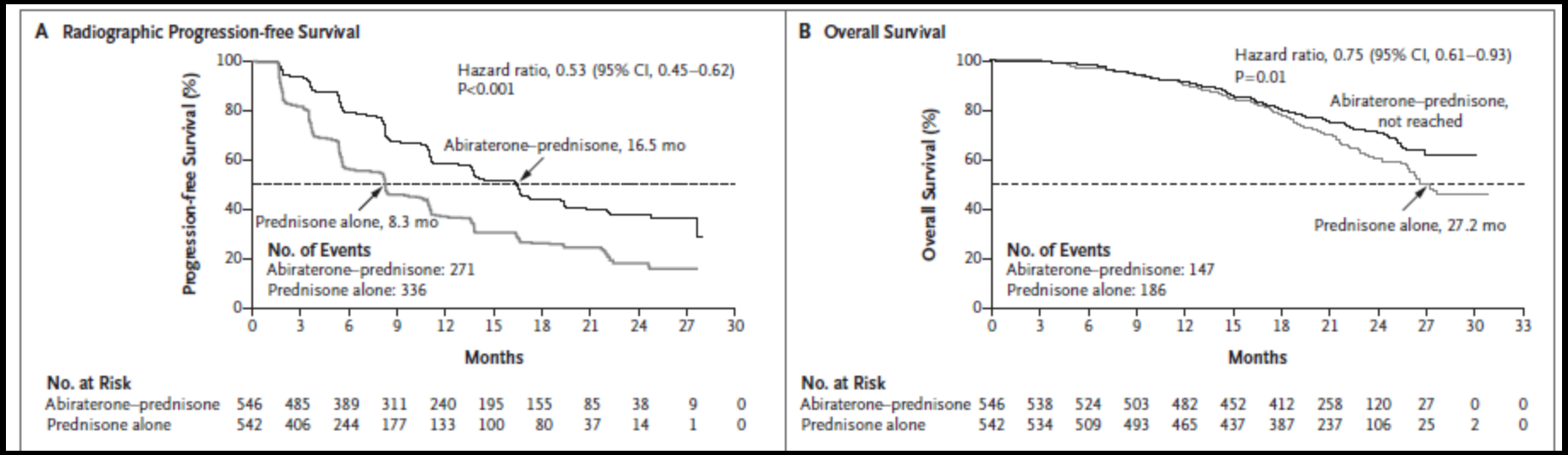
Mineralocorticoids **Glucocorticoids** **Androgen hormones**

Inhibits 17 hydroxylase and 17,20 lyase enzymes (green arrows)

J Clin Endocrinol Metab, February 2012, 97(2):507–516

Randomized comparison of abiraterone + prednisone vs. placebo + prednisone in chemotherapy-naïve mCRPC

Radiographic Progression-free Survival, Overall Survival



Ryan CJ et al. N Engl J Med 2013;368:138-148.

Adverse Events

Table 2. Adverse Events.*

Adverse Event	Abiraterone–Prednisone (N=542)	Prednisone Alone (N=540)
	no. of patients (%)	
Any adverse event	537 (99)	524 (97)
Grade 3 or 4 adverse event	258 (48)	225 (42)
Any serious adverse event	178 (33)	142 (26)
Adverse event leading to treatment discontinuation	55 (10)	49 (9)
Adverse event leading to death*	20 (4)	12 (2)
Adverse event of grade 1–4 in ≥15% of patients in either group		
Fatigue	212 (39)	185 (34)
Back pain	173 (32)	173 (32)
Arthralgia	154 (28)	129 (24)
Nausea	120 (22)	118 (22)
Constipation	125 (23)	103 (19)
Hot flush	121 (22)	98 (18)
Diarrhea	117 (22)	96 (18)
Bone pain	106 (20)	103 (19)
Muscle spasm	75 (14)	110 (20)
Pain in extremity	90 (17)	85 (16)
Cough	94 (17)	73 (14)

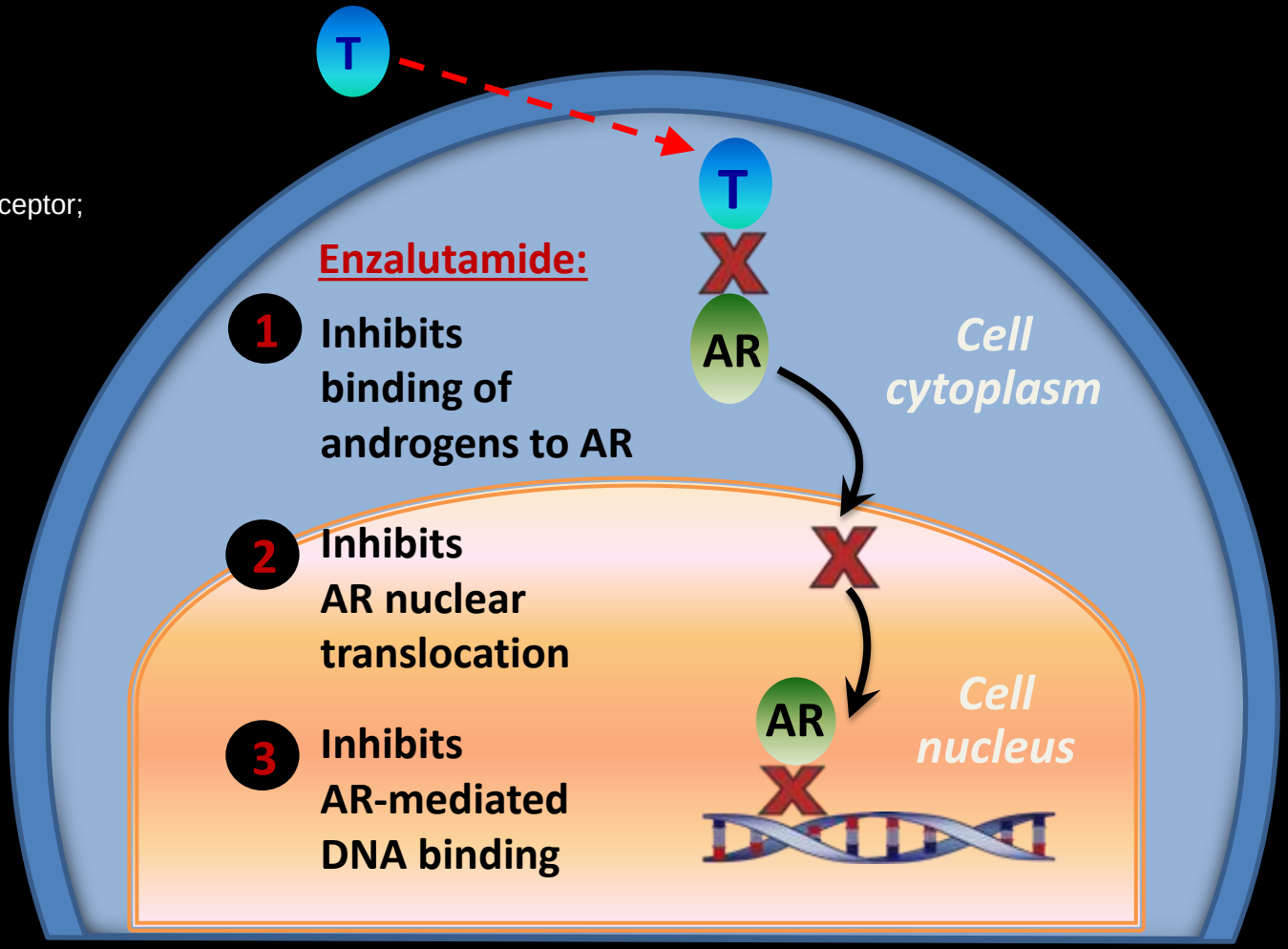
* The most common adverse events leading to death were general disorders, including disease progression, a decline in physical health, and infections including pneumonia and respiratory tract infection.

- Hepatotoxicities: Elevated AST/ALT
- Cardiac toxicities: 5 discontinuations related to abiraterone plus 2 cardiac deaths
- Mineralocorticoid excess

Ryan CJ et al. N Engl J Med 2013;368:138-148

Enzalutamide: An Androgen Receptor Inhibitor

AR=androgen receptor;
T=testosterone.

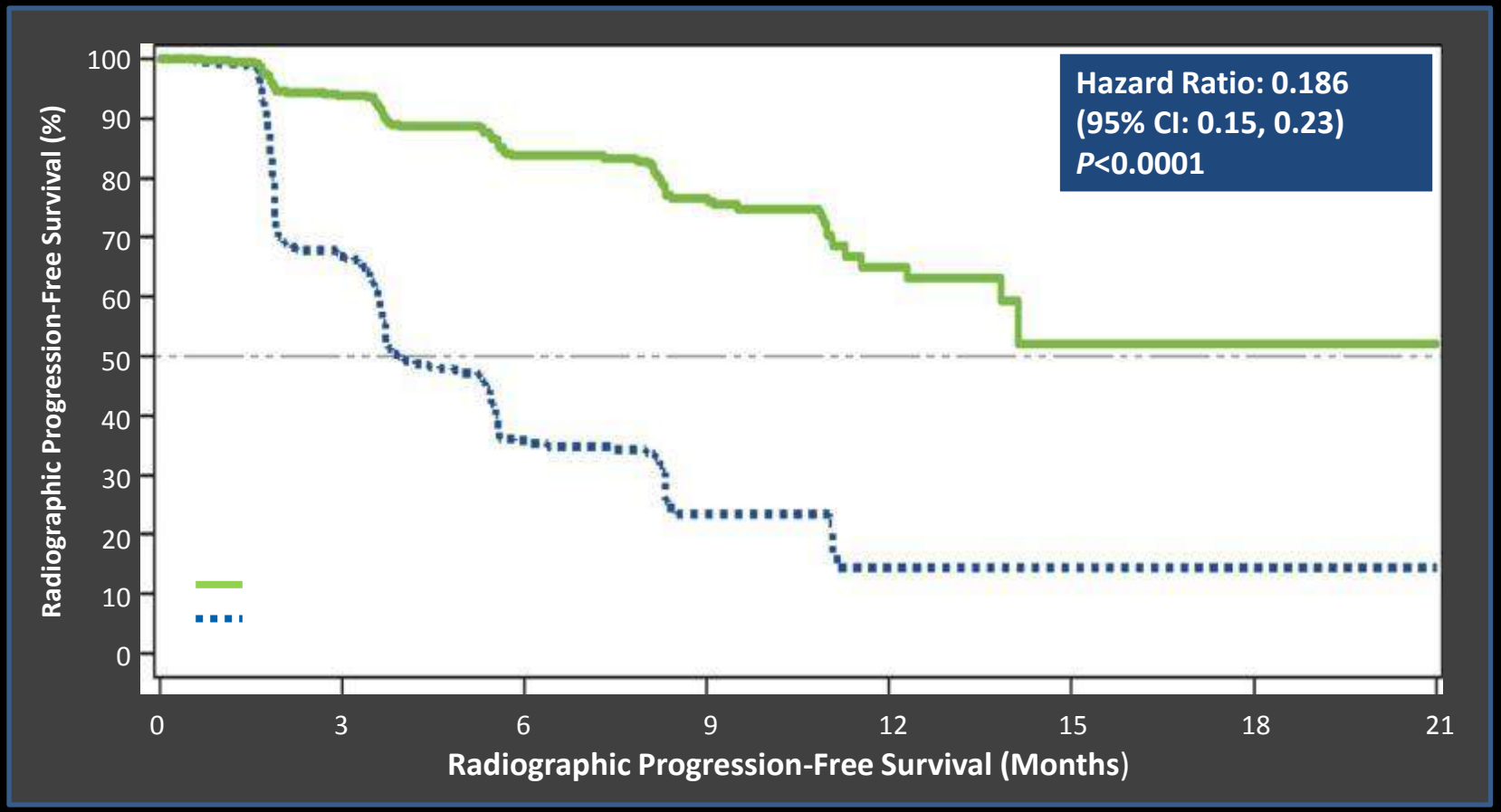


Enzalutamide improved overall survival and radiographic progression-free survival in patients with metastatic castration-resistant prostate cancer post-docetaxel[1]

1. Scher et al. N Engl J Med 2012; 367:1187-97.

OHSU “PREVAIL”s Hormone Therapy: Enzalutamide (aka Xtandi)

Enzalutamide Prolonged Radiographic Progression-Free Survival



Patients at Risk

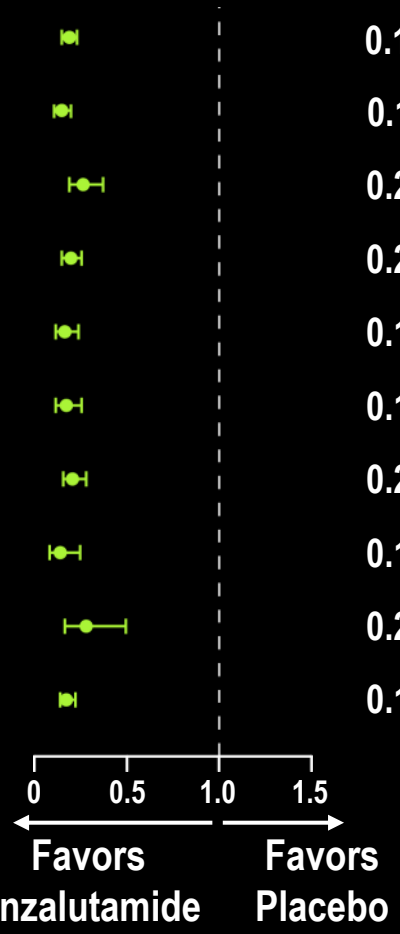
Enzalutamide	832	514	256	128	34	5	1	0
Placebo	801	305	79	20	5	0	0	0

Estimated median rPFS, months (95% CI): Enzalutamide: NYR (13.8, NYR); Placebo: 3.9 (3.7, 5.4)

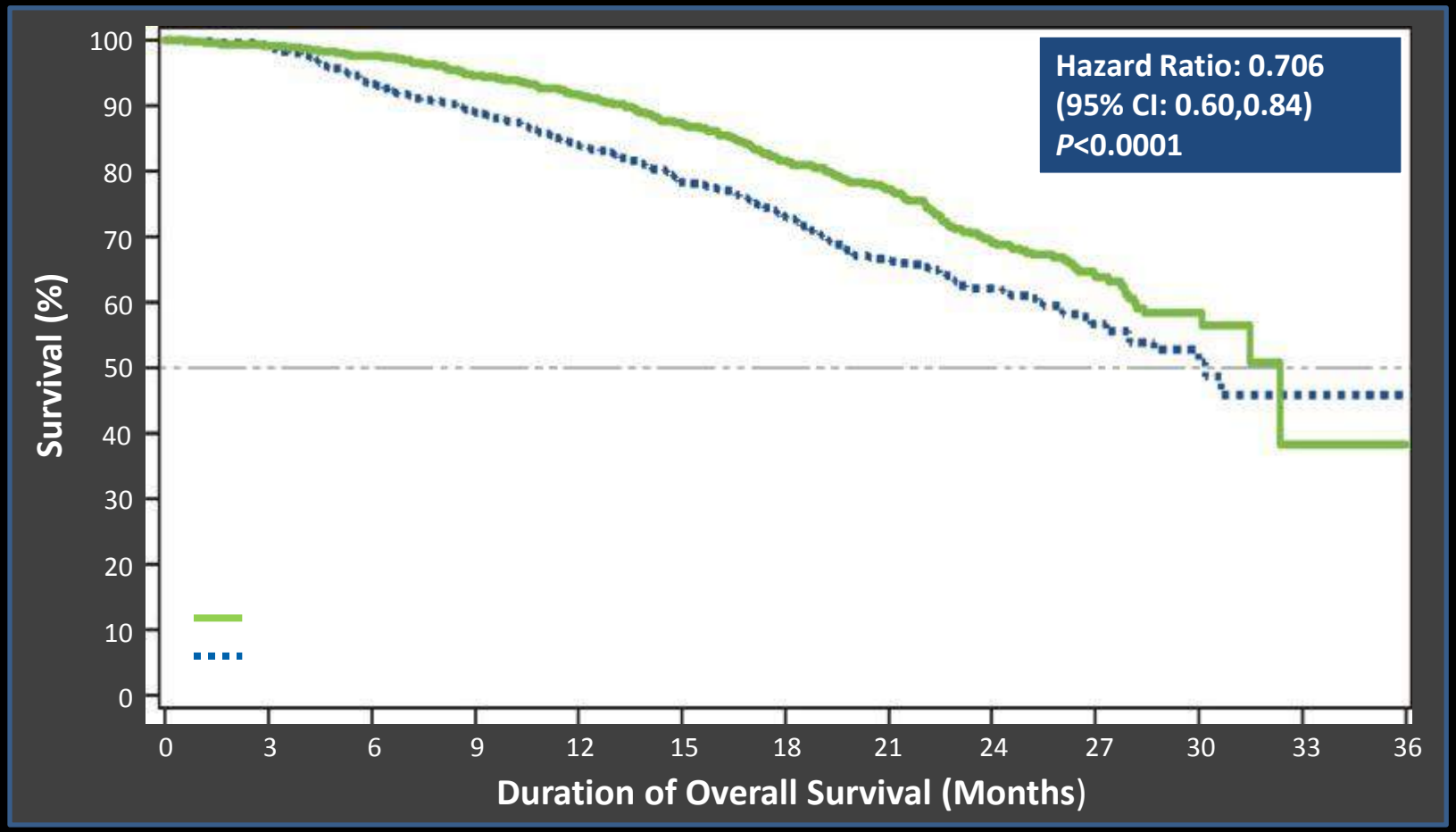
NYR = Not Yet Reached

Radiographic Progression-Free Survival Benefit was Consistent Across Subgroups

Subgroup	Number of Patients Enzalutamide / Placebo	Hazard Ratio (95% CI)
All patients	832 / 801	0.19 (0.15, 0.23)
ECOG performance status at baseline=0	557 / 549	0.15 (0.11, 0.20)
ECOG performance status at baseline=1	275 / 252	0.27 (0.19, 0.37)
Age <75	529 / 517	0.20 (0.15, 0.26)
Age ≥75	303 / 284	0.17 (0.12, 0.24)
Geographic region – North America	214 / 204	0.17 (0.12, 0.25)
Geographic region – Europe	456 / 435	0.21 (0.15, 0.28)
Geographic region – Rest of world	162 / 162	0.14 (0.08, 0.25)
Visceral disease (lung and/or liver) at screening – Yes	97 / 101	0.28 (0.16, 0.49)
Visceral disease (lung and/or liver) at screening – No	735 / 700	0.17 (0.14, 0.22)



Enzalutamide Reduced Risk of Death by 29%



Patients at Risk

Enzalutamide	872	863	850	824	797	745	566	395	244	128	33	2	0
Placebo	845	835	781	744	701	644	484	328	213	102	27	2	0

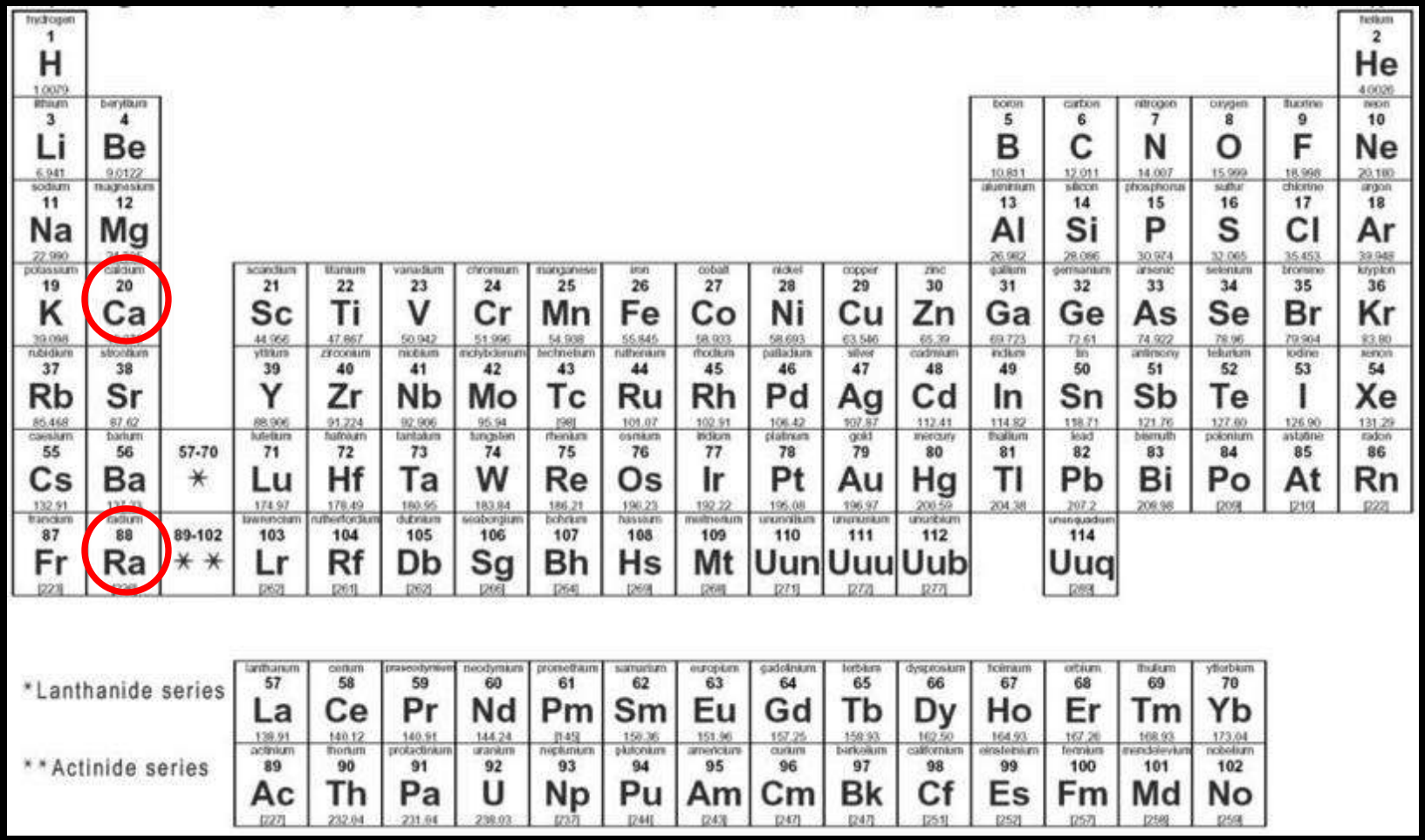
Estimated median OS, months (95% CI): Enzalutamide: 32.4 (30.1, NYR); Placebo: 30.2 (28.0, NYR)

NYR = Not Yet Reached

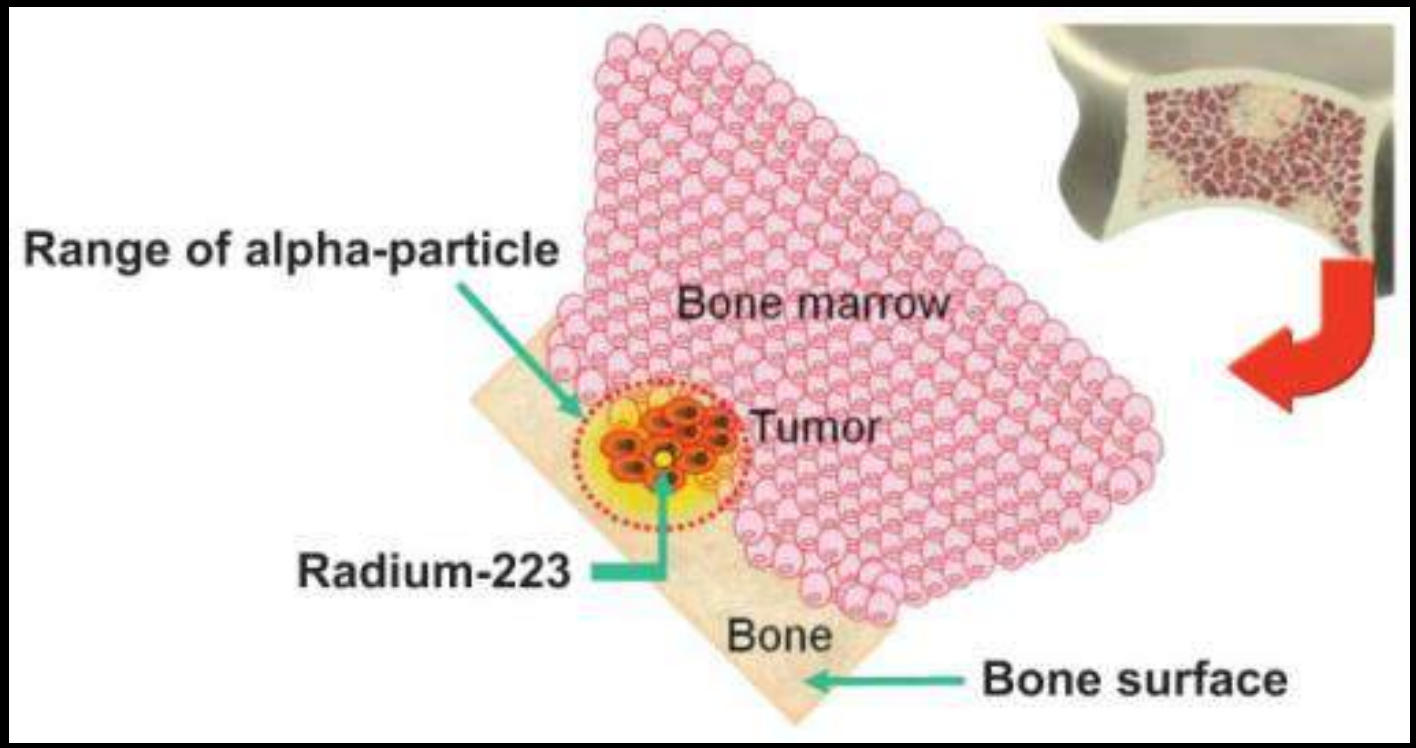
Enzalutamide Toxicity

- Special concern Seizure
  - Dose limiting toxicity in phase I study (360 mg/day, 600 mg/day and questionable 480 mg/day)
  - Six in the post-chemotherapy study
  - Two In the pre-chemotherapy study

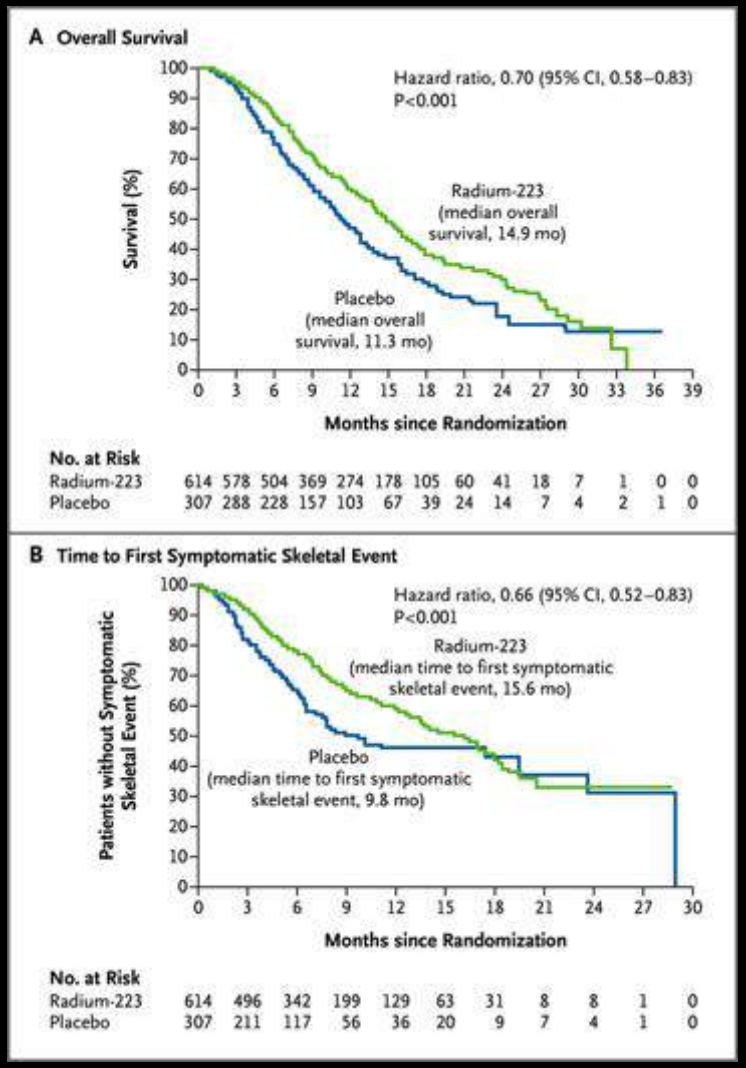
Radiation Therapy: Radium-223 (aka Xofigo)



Radium-223


Range of alpha-particle
Bone marrow
Tumor
Radium-223
Bone
Bone surface

Radium-223



Clinical trial required painful bone metastatic disease without visceral disease.

- Improved survival
- **Pain relief**
- Fewer fractures and other skeletal related events

NEJM 2013; 369(3): 213-223

Radium-223 Toxicity

- Flare in bone pain
- Myelosuppression: requires good marrow function prior to treatment (platelet count > 100,000/mm^3 and leukocyte count > 3000/mm^3)

Elderly

Estimated New Cases*

		Males
Prostate	233,000	27%
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All Sites	**310,010**	**100%**

15,188 will be men ≥ 80 years

CA Cancer J Clin 2014;64:9-29.

Considerations for the Elderly

Agent	Analysis	Conclusion
Sipuleucel-T	Survival: > 71 years vs ≤ 71 years Product integrity: ≥ 80 vs < 80 years old	No difference
Cabazitaxel/Prednisone	19% in study were ≥ 75 years	No analysis
Abiraterone/Prednisone	Adverse events ≥ 75 years vs. < 75 years	Similar
Enzalutamide	Post-chemotherapy, survival: < 75 years and men ≥ 75 years	No difference in survival More fatigue, edema, diarrhea men ≥ 75 years
Radium-223	Survival < 67 years, 67-74 years, and ≥ 75 years	Good in all groups

Name Confusion

Table 1. New Drugs for the Treatment of Prostate Cancer.

Generic Name	Trade Name	Intended Use
Zoledronic acid	Zometa	Reduction of skeletal-related events due to metastatic prostate cancer
Denosumab	Xgeva	Reduction of skeletal-related events due to metastatic prostate cancer
Abiraterone	Zytiga	Treatment of metastatic castration-resistant prostate cancer
Enzalutamide	Xtandi	Treatment of metastatic castration-resistant prostate cancer
Cabazitaxel	Jevtana	Treatment of metastatic castration-resistant prostate cancer

N ENGL J MED 368;2 NEJM.ORG JANUARY 10, 2013

Radium-223
Goserelin

Xofigo
Zoladex

FDA Response

Manufacturers do not have an "insatiable proclivity to include the letters X and Z" in proprietary names; approximately 2% of the more than 6000 approved drug names begin with X or Z.[2] Also, a review of recently approved and pending proprietary names did not find a disproportionate number of names commencing with X or Z. The relative

N ENGL J MED 368;20 NEJM.ORG MAY 16, 2013

Timeline for FDA Approval

2009	Julie Completes Training
2010	**Sipuleucel-T**
	Cabazitaxel
2011	**Abiraterone** post-chemotherapy
2012	**Enzalutamide** post-chemotherapy
	Abiraterone pre-chemotherapy
2013	**Radium-223**
2014	(Enzalutamide pre-chemotherapy)

IMMUNOTHERAPY

CHEMOTHERAPY

HORMONE THERAPY

RADIATION THERAPY

Unanswered Questions

- Ordering of the agents
- Combination of agents
- Effects of longer term androgen suppression therapy on the body
- Tumor characteristics after multiple treatments

Graff's Research Projects

- Clinical Trials
  1. Pembrolizumab study (more details to come)
  2. Early ipilimumab study
  3. Cabazitaxel/Enzalutamide combo study
  4. (ARN-509 + chemotherapy + LHRH agonist in newly diagnosed metastatic disease)
  5. Pembrolizumab + Enzalutamide + Degarelix in Neoadjuvant Setting

Addition of Pembrolizumab Upon Progression of mCRPC on Enzalutamide

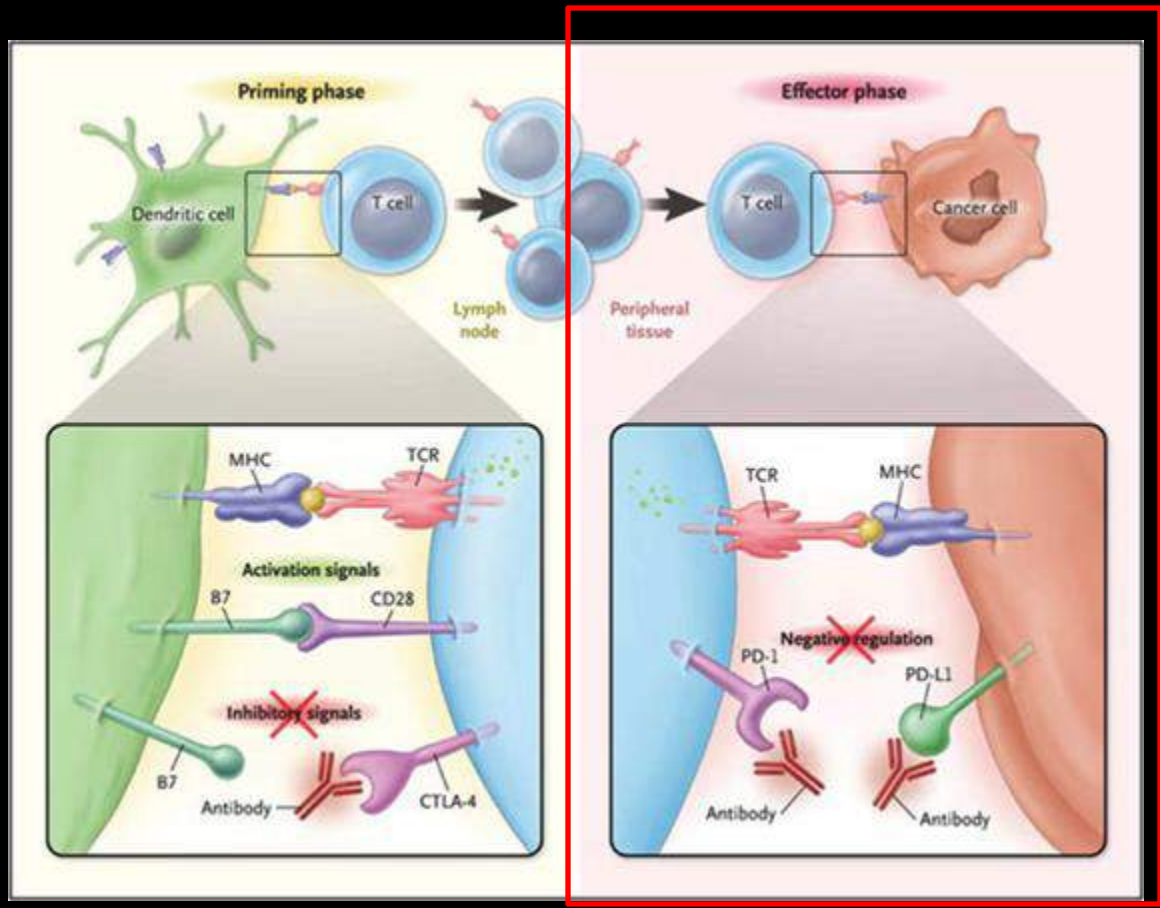
(NCT02312557)

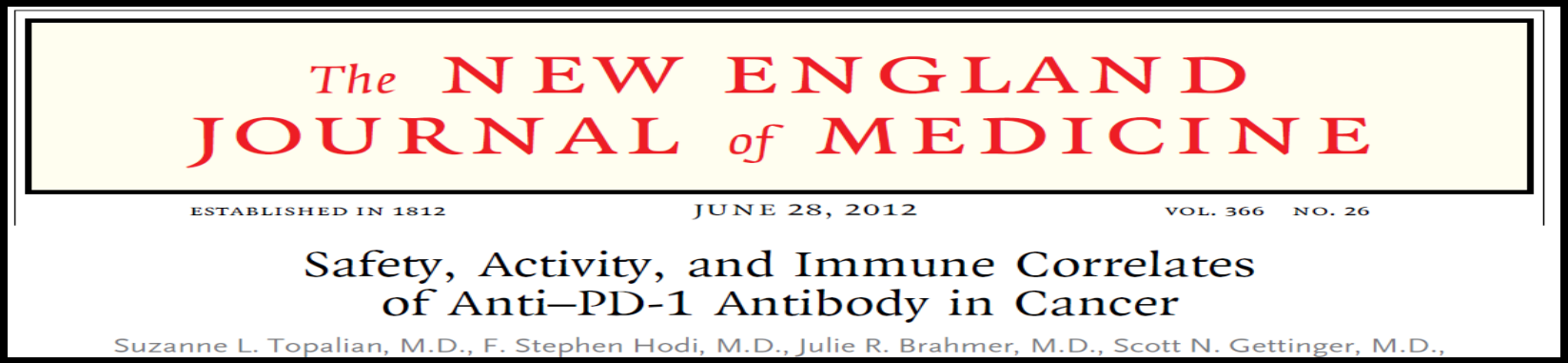
PI: Julie Graff

Lead Site: OHSU

Pembrolizumab

- PD-1 Antibody
- FDA approved for advanced melanoma
- What is the activity of this agent in CRPC?





The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 28, 2012 VOL. 366 NO. 26

Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer

Suzanne L. Topalian, M.D., F. Stephen Hodi, M.D., Julie R. Brahmer, M.D., Scott N. Gettinger, M.D.,

- Phase I study of “nivolumab” multiple cancer types that included **17 CRPC patients**
- None of them had an “objective response”
- Only 2 patients with mCRPC had tumors analyzed for PD-L1 expression. Both stained negative
- Overall, there was a 36% OR in PD-L1+ tumors and 0% in PD-L1- tumors

PD-L1 is highly expressed in Enzalutamide resistant prostate cancer

Jennifer L. Bishop[1], Alexander Sio[1], Arkhjamil Angeles[1], Morgan E. Roberts[2], Arun A. Azad[3], Kim N. Chi[3] and Amina Zoubeidi[1,4]

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[3] Department of Medicine, Division of Medical Oncology, BC Cancer Agency, University of British Columbia, Vancouver, BC, Canada

[4] Department of Urologic Sciences, University of British Columbia, Vancouver, BC, Canada

Correspondence to: *Amina Zoubeidi,* ***email:*** *azoubeidi@prostatecentre.com*

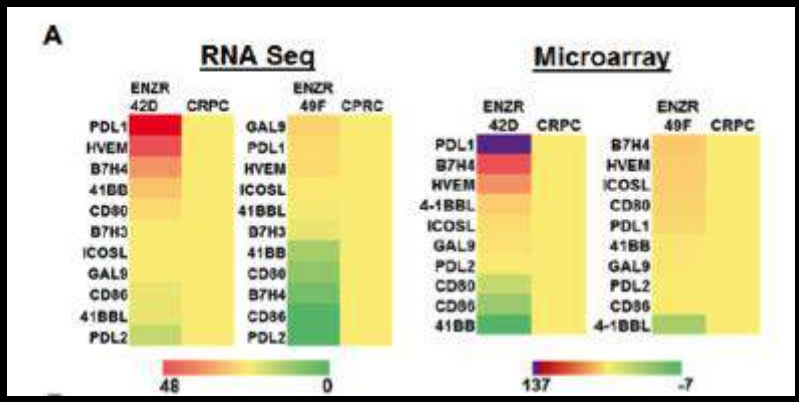
Keywords:Enzalutamide resistant CRPC, Immunotherapy, PD-L1

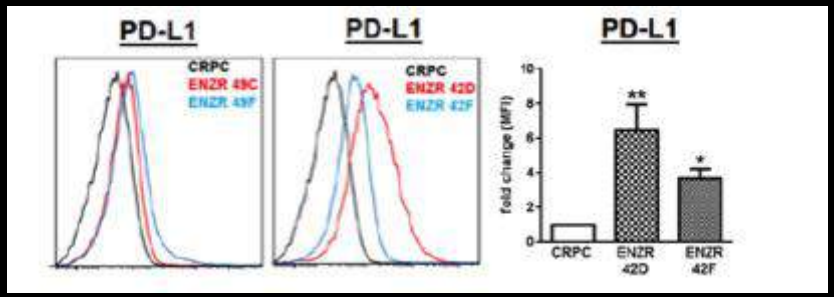
Received: *October 30, 2014* ***Accepted:*** *November 06, 2014* ***Published:*** *November 06, 2014*

Oncotarget 2014; 6(1): 234

Findings

- PD-L1 is upregulated in enzalutamide-resistant cell lines and xenografts
- In PBMCs of patients with mCRPC progressing on enzalutamide, PD-L1 is upregulated relative to men with mCRPC prior to enzalutamide.





Complete Response in a Patient with Enzalutamide-Resistant CRPC with Sipuleucel-T

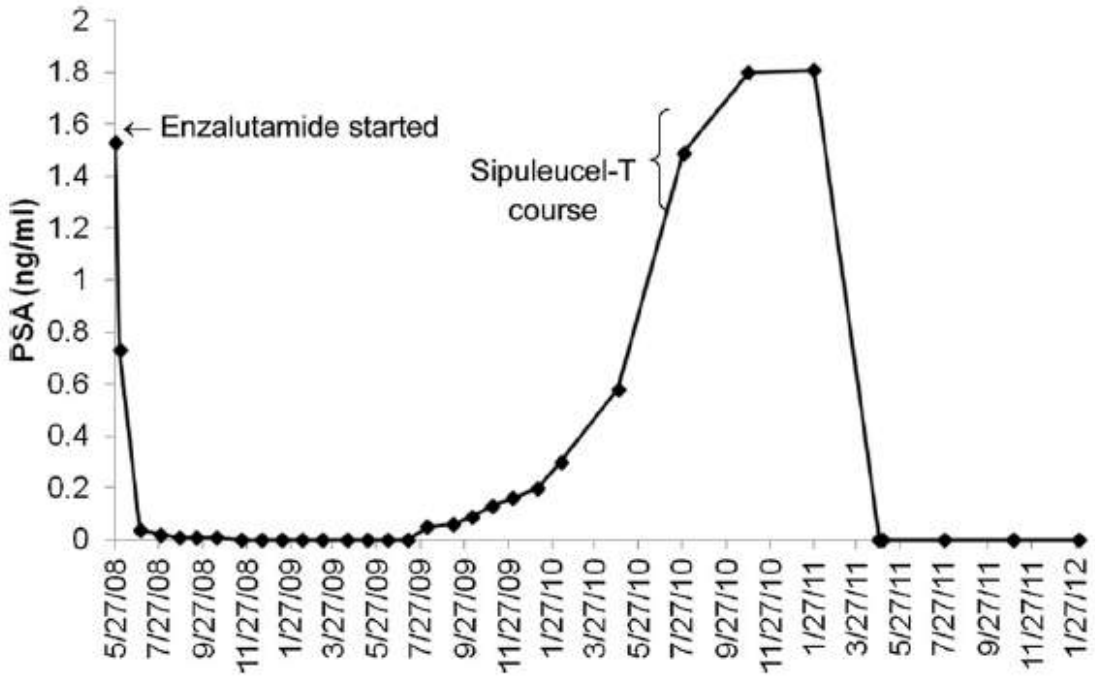


Figure 1. Patient's prostate-specific antigen (PSA) levels graphed by time. He started enzalutamide on May 27, 2008 and received a course of sipuleucel-T from August 30, 2010 to September 27, 2010. His PSA level remained undetectable since April 28, 2011.

Urology. 2013 Feb;81(2):381-3

General Study Information

- Phase II
- Investigator initiated: OHSU sponsor, supported by Merck
- Total: 28 Subjects

Objectives

- Primary: PSA response by ≥ 50%

Using a null hypothesis of 5% and alternate hypothesis of 25%, 25 evaluable patients are needed with 90% power and a one-sided alpha of 0.05. To account for potential drop-out, we will enroll 28 subjects.

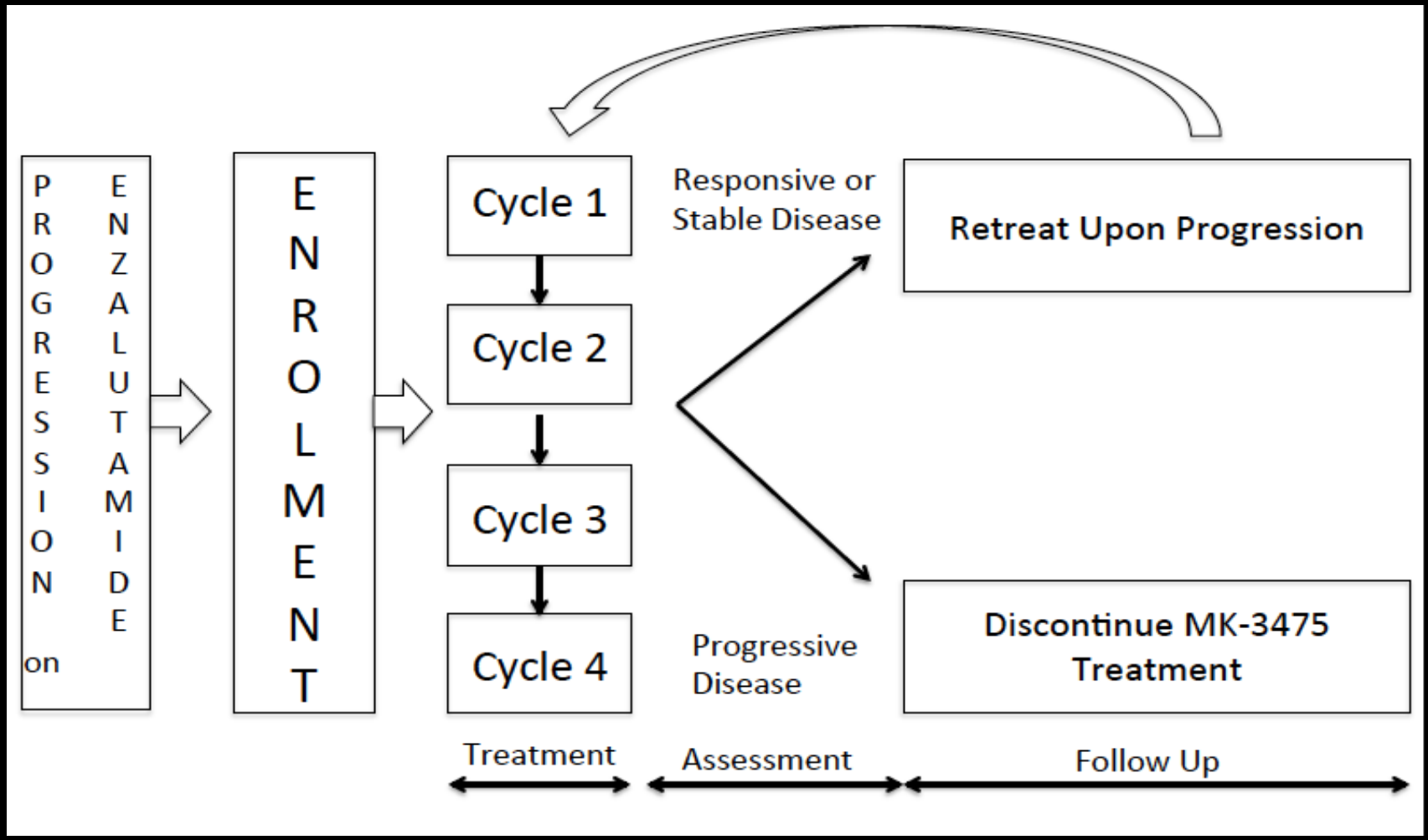
- Secondary: PSA PFS, Radiographic PFS, OS

Correlative Work

- Study Specific Tissue Biopsy
  - IHC for PD-1, PD-L1 and PD-L2
  - IHC for total CD45+ cells (leukocytes), lymphocytes (CD8+, CD4+, and B cells), and macrophages
- Peripheral blood mononuclear cells
  - T effector/memory panel (CD45, CD3, CD8, CCR7, CD45RA,CD45RO, CD69, CD44, CD62L)
  - T regulatory panel (CD45, CD3, CD4, FoxP3, CD25, CD127, CD69, CD44)
  - T help panel (CD45, CD3, CD4, CD45RA, CD45RO, CD69, CD44, CD62L)
  - Cytokine propensity of the above T cell subsets (IFN-γ, IL-2, IL-4, IL-12, IL-13, IL-10, IL-18, TNF-α, TGF-β, IL-17)
- Archived Tissue
  - IHC for PD-1, PD-L1 and PD-L2
- Circulating Tumor Cells
- Systemic inflammatory markers: Serum IL-8, IL-6, IL-1, TNF and TGF-beta

Eligibility Criteria

- Must have had a 50% decrease in PSA on enzalutamide and be progressing by PSA or scans
- Biopsy is required, *if there is a spot amenable to biopsy*
- Prior chemo for castration-resistant disease is excluded
- Prior Provenge (sipuleucel-T) and abiraterone are permitted
- Prior Ipilimumab is excluded, as is anti PD-1
- No active autoimmune diseases or symptom requiring systemic steroids



Imaging Every 12 weeks
No discontinuation for PSA only progression

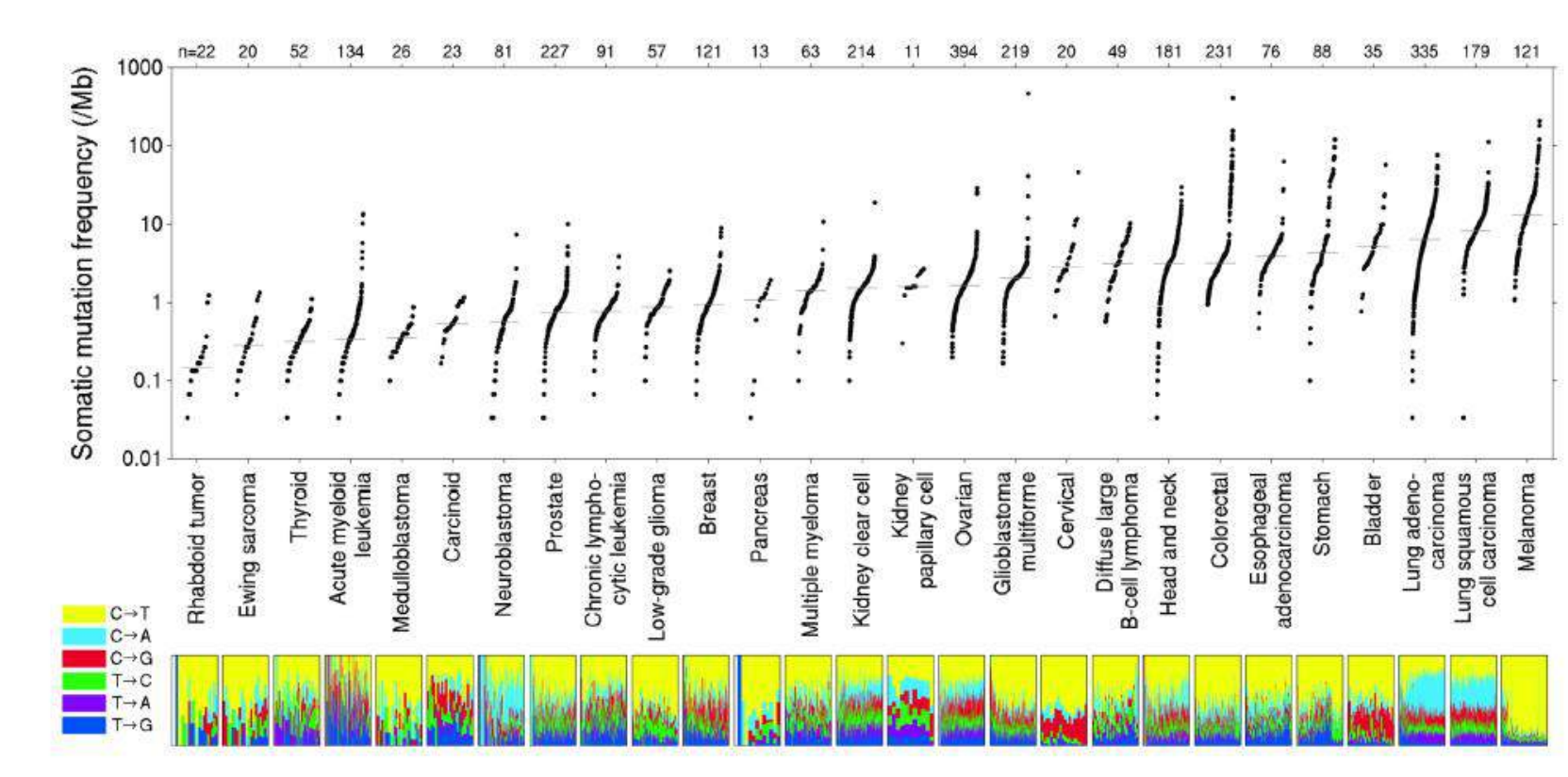
Study Summary

- Enzalutamide continued daily
- IV infusion of Pembro Q3Weeks for 4 cycles
- Monitoring phase
- If response or stable, Re-treatment 4 cycles
- Follow for survival

Leveraging the Pembrolizumab Study

- Submitted a grant to Prostate Cancer Foundation with the following aims.
  - Measurement of T cell quantity in the tumor pre and post-pembrolizumab therapy
  - Measure function of T cells in the tumor pre and post-pembrolizumab therapy
  - Determine mutational status of tumor pre and post-pembrolizumab

Mutational heterogeneity in cancer and the search for new cancer genes



Nature. 2013 July 11; 499(7457): 214-218.

Other ongoing projects

- “Safety and Efficacy of Enzalutamide in Veterans with Prostate Cancer” Co-investigator Nina Lamble. 94 Veterans consented to date.
- “Mechanism of falls in men on enzalutamide” with Max Gordon and Kerri Winters-Stone

OHSU Prostate Cancer Team