



Advanced Prostate Cancer

November 4 2017

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- In 2017 161,000 new cases of prostate cancer diagnosed in US, mostly with elevated PSA
- 5-10% will present with metastatic disease
- In 2017: 26,000 men will die of prostate cancer
- Not everyone with advanced prostate cancer will die of their disease

Management of men with advanced prostate cancer

Goals:

- Prolonging survival (Live longer)
- Minimizing complications
- Maintaining quality of life

Presentation

- Recurrence following definitive therapy
 - Majority of cases are bony lesions in skeleton
 - Signs of disseminated disease is an rising serum PSA after definitive therap



Figure 1

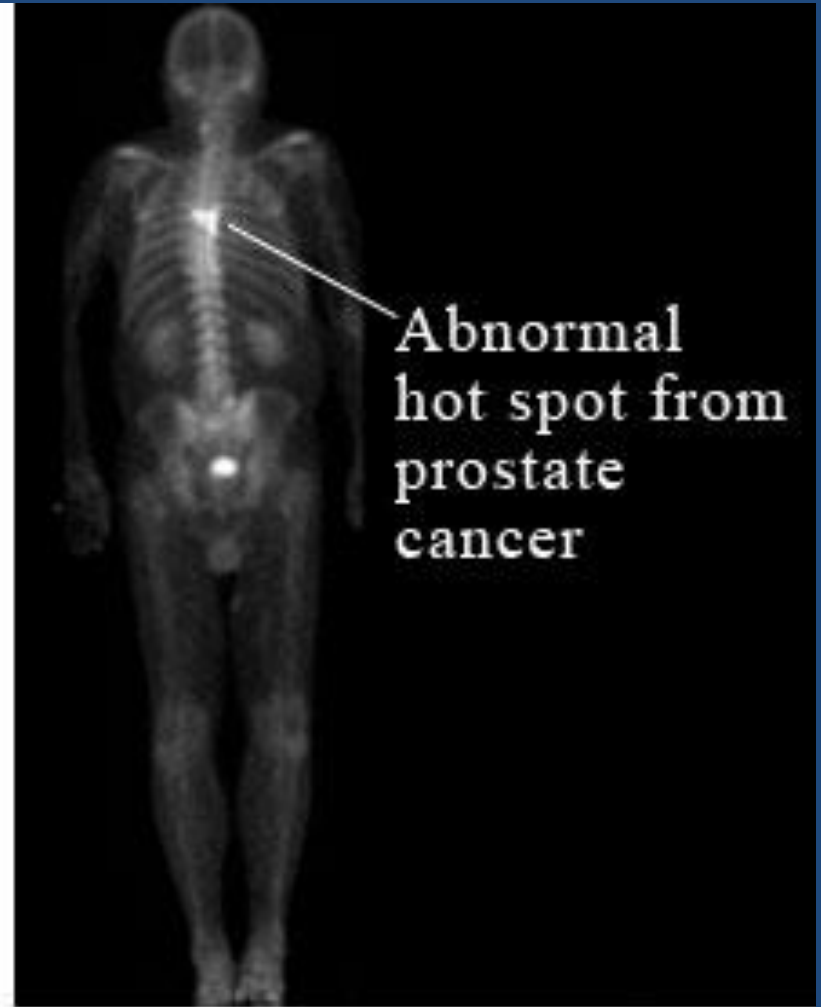
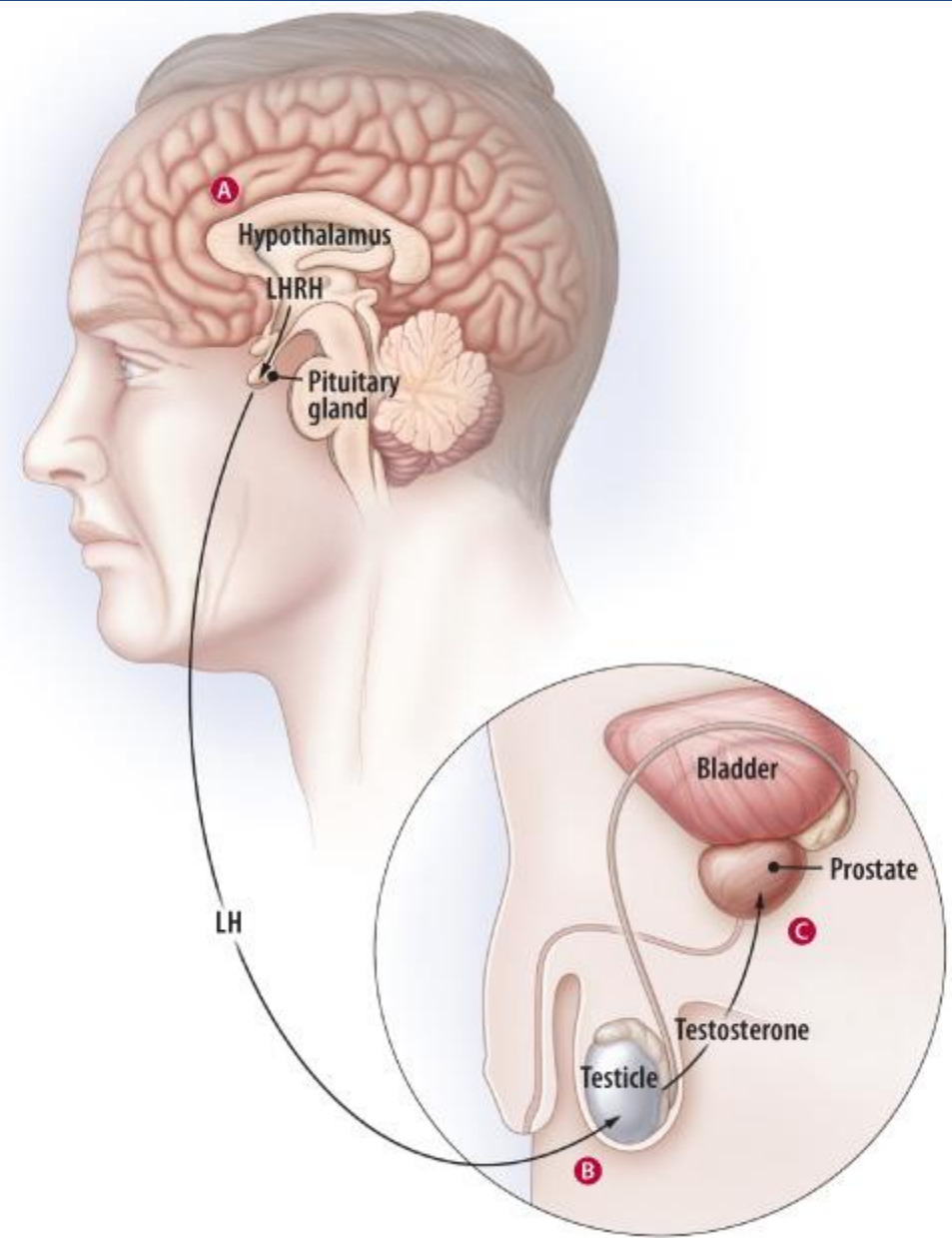


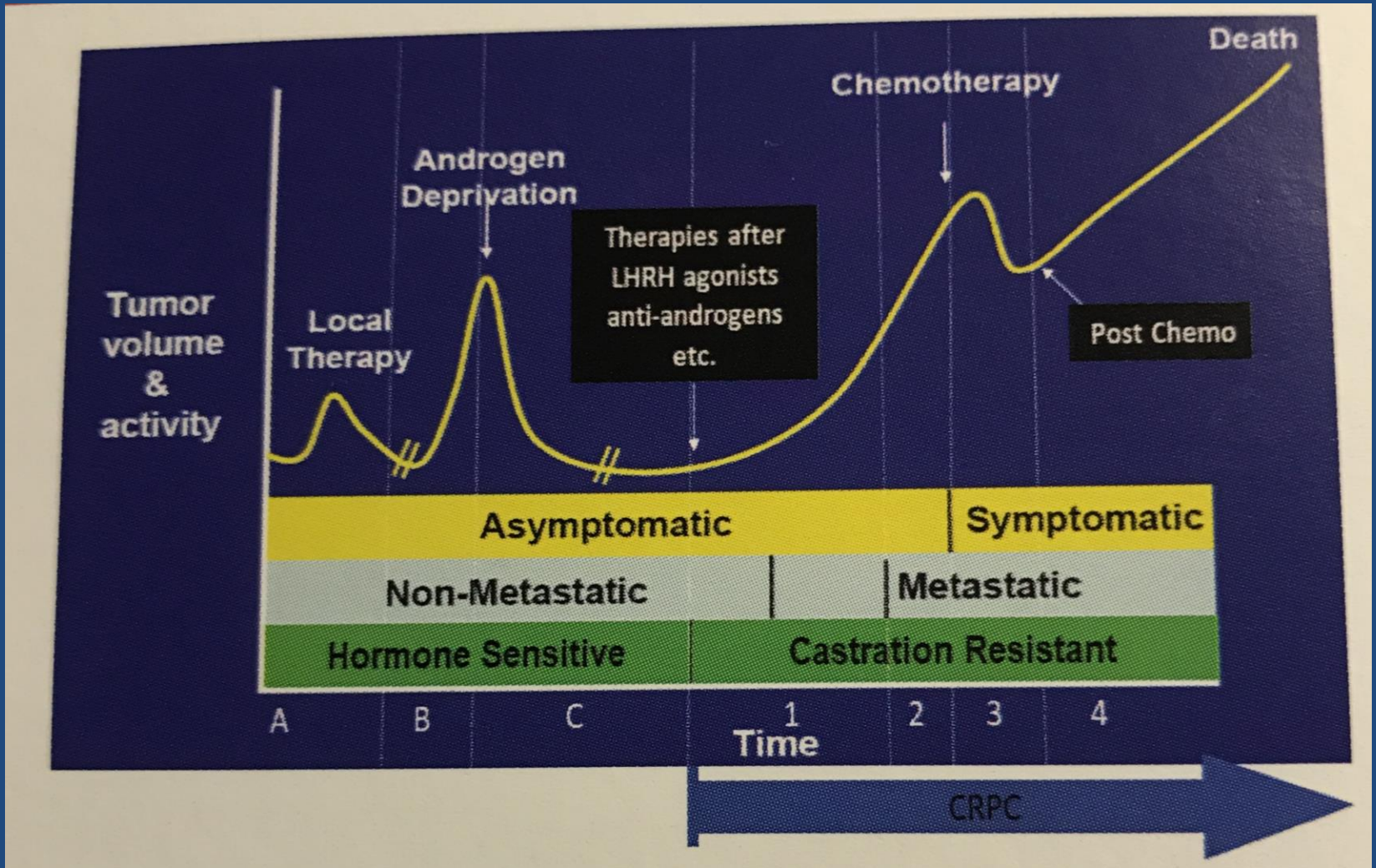
Figure 2

Mechanism of prostate cancer

- Prostate cancer is dependent upon androgen for continued growth
- **Androgen= hormone or testosterone**, that stimulates or controls the development and maintenance of males
 - Testicle/Sperm formation
 - Sex characteristics
 - Muscle
 - Inhibit fat
 - Protect bones



OLD TREATMENT MODEL



TREATMENT IN 2017

Castration-Sensitive		Castration-Resistant	
Nonmetastatic	Metastatic, asymptomatic	Metastatic, symptomatic	Metastatic advanced
<ul style="list-style-type: none"> • ADT 	<ul style="list-style-type: none"> • ADT +/- Docetaxel or Abiraterone • Radiation for oligometastatic disease ? 	<ul style="list-style-type: none"> • Clinical Trials • 2^o hormonal therapy • Sipuleucel-T • Enzalutamide • Abiraterone 	<ul style="list-style-type: none"> • Clinical Trials • Radium-223 • Enzalutamide • Abiraterone • Docetaxel
			<ul style="list-style-type: none"> • Clinical Trials • Radium-223 • Docetaxel • Cabazitaxel • Carboplatin ? • PARP inhibitors ? • Checkpoint blockade ?

Referral Point

- Androgen deprivation therapy (ADT) is the standard initial approach for patients when systemic therapy is indicated for metastatic prostate cancer or evidence of disseminated disease based upon PSA
 - Bilateral orchiectomy (surgical castration)
 - Medical orchiectomy.

- **Bilateral orchiectomy** — simple, cost-effective procedure
 - serum testosterone levels rapidly decrease to castrate levels.
- **Medical orchiectomy** — Medical orchiectomy decreases testicular production of testosterone by its effects on the hypothalamic pituitary axis.
- **GnRH agonists**
 - Eligard (leuprolide)
 - Zoladex (goserelin)

E-907

NDC 0024 0793 75

Eligard[®] 7.5 mg

leuprolide acetate for
injectable suspension

7.5 mg Every month

Sterile
For subcutaneous injection
Must be constituted before use

Store refrigerated 2 to 8°C
(36 to 46°F)

Rx Only

sanofi aventis

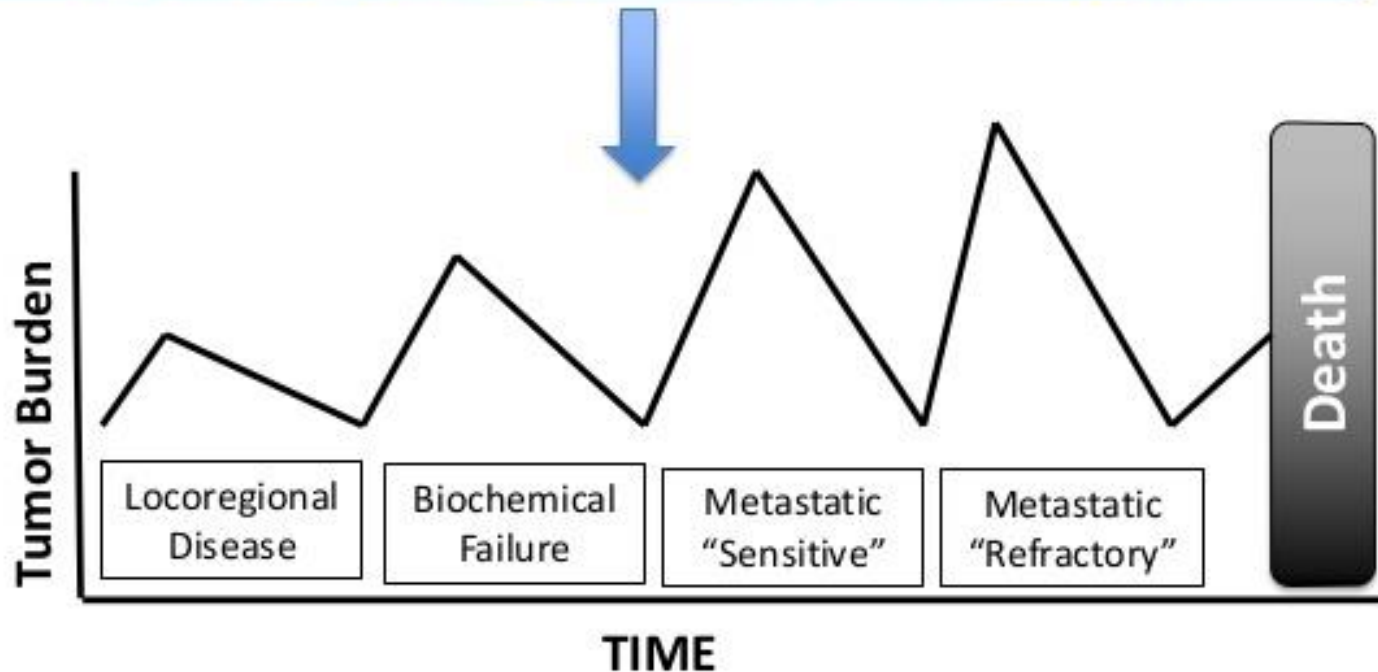


Side effects of ADT

- Sexual dysfunction
- Osteoporosis and risk of bone fractures
- Cardiovascular disease and diabetes:
- Decreased muscle and increased fat
- Hot flashes
- Lack of energy
- Changes in body image, including gynecomastia, decreased penile and testicular size, and thinning of body hair.
- Decreased cognitive performance or depression, although these changes may be related to aging and disease rather than ADT

Prostate Cancer: Natural History:

Effective Castration & AR Blocking
Serum Testosterone < 0.2 – 0.5 ng/ml



Androgen synthesis inhibitors

- **ABIRATERONE: Zytiga**
 - blocks the synthesis of androgens in the tumor as well as in the testes and adrenal glands.



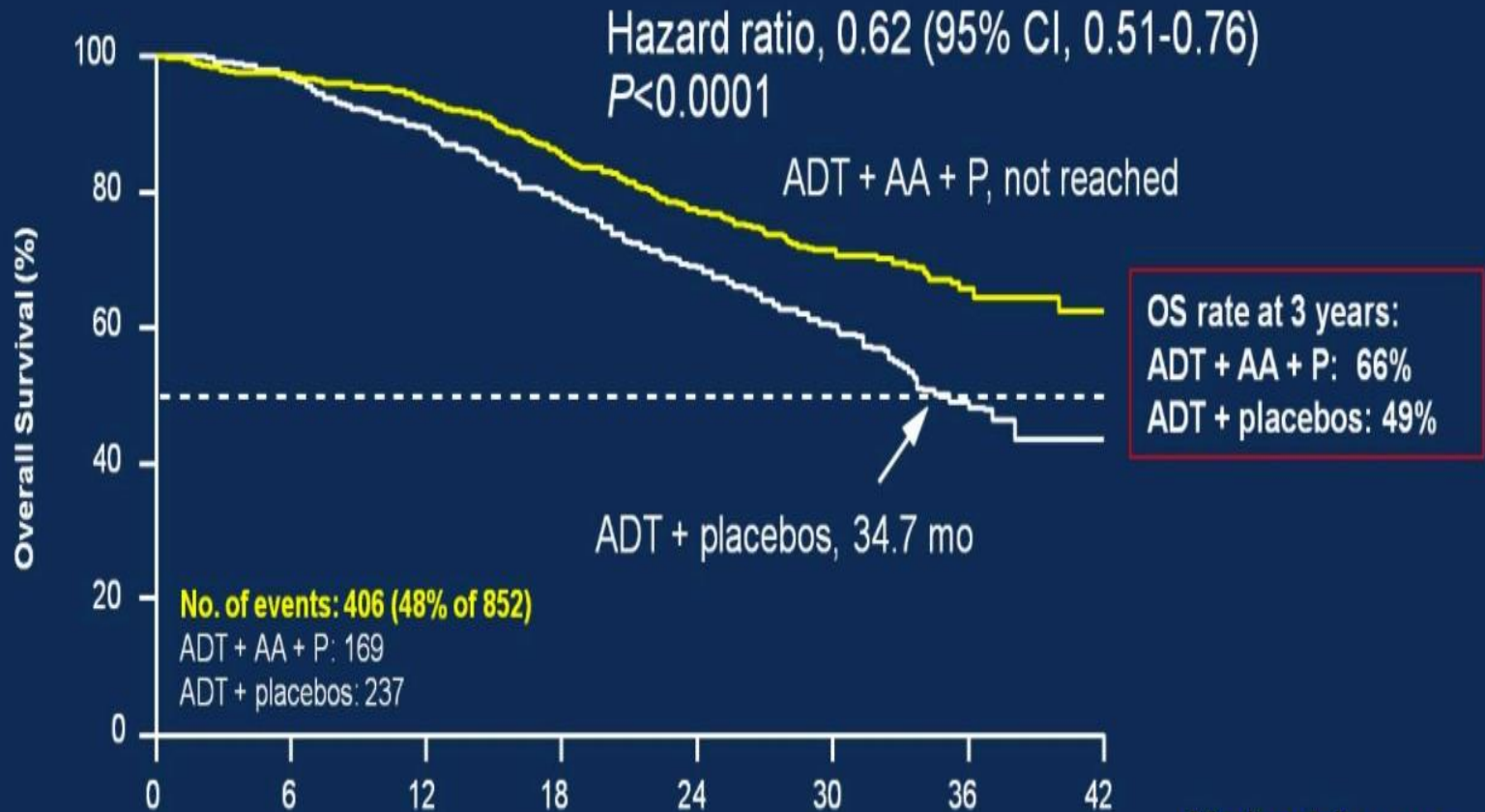
CASTRATION SENSITIVE DISEASE



Abiraterone in Castrate Sensitive disease

- **LATITUDE trial** —1199 men with newly diagnosed castration-sensitive metastatic prostate cancer were randomly assigned either to ADT plus abiraterone and prednisone or to AD
- High-risk disease at least two of three high-risk parameters
 - Gleason score 8 or higher
 - At least three bone lesions
 - Presence of measurable visceral metastasis.
- Improved Overall survival

Statistically significant **38%** risk reduction of death



No. at risk	Months							
	0	6	12	18	24	30	36	42
ADT + AA + P	597	565	529	479	388	233	93	9
ADT + placebos	602	564	504	432	332	172	57	2

STAMPEDE TRIAL

- STAMPEDE trial, 1917 men were randomly assigned to ADT plus abiraterone and prednisone or to ADT alone
- High-risk prostate cancer
 - stage T3-T4N0M0 disease with either PSA ≥ 40 ng/mL or Gleason sum 8 to 10
 - node-positive nonmetastatic disease (N1M0)
 - metastatic disease (M1)
- Overall survival was significantly increased with the addition of abiraterone (three-year survival 83 versus 76 percent with ADT alone, HR 0.63, 95% CI 0.52-0.76). Results were similar for those with nonmetastatic and metastatic disease (HR 0.75 and 0.61, respectively).

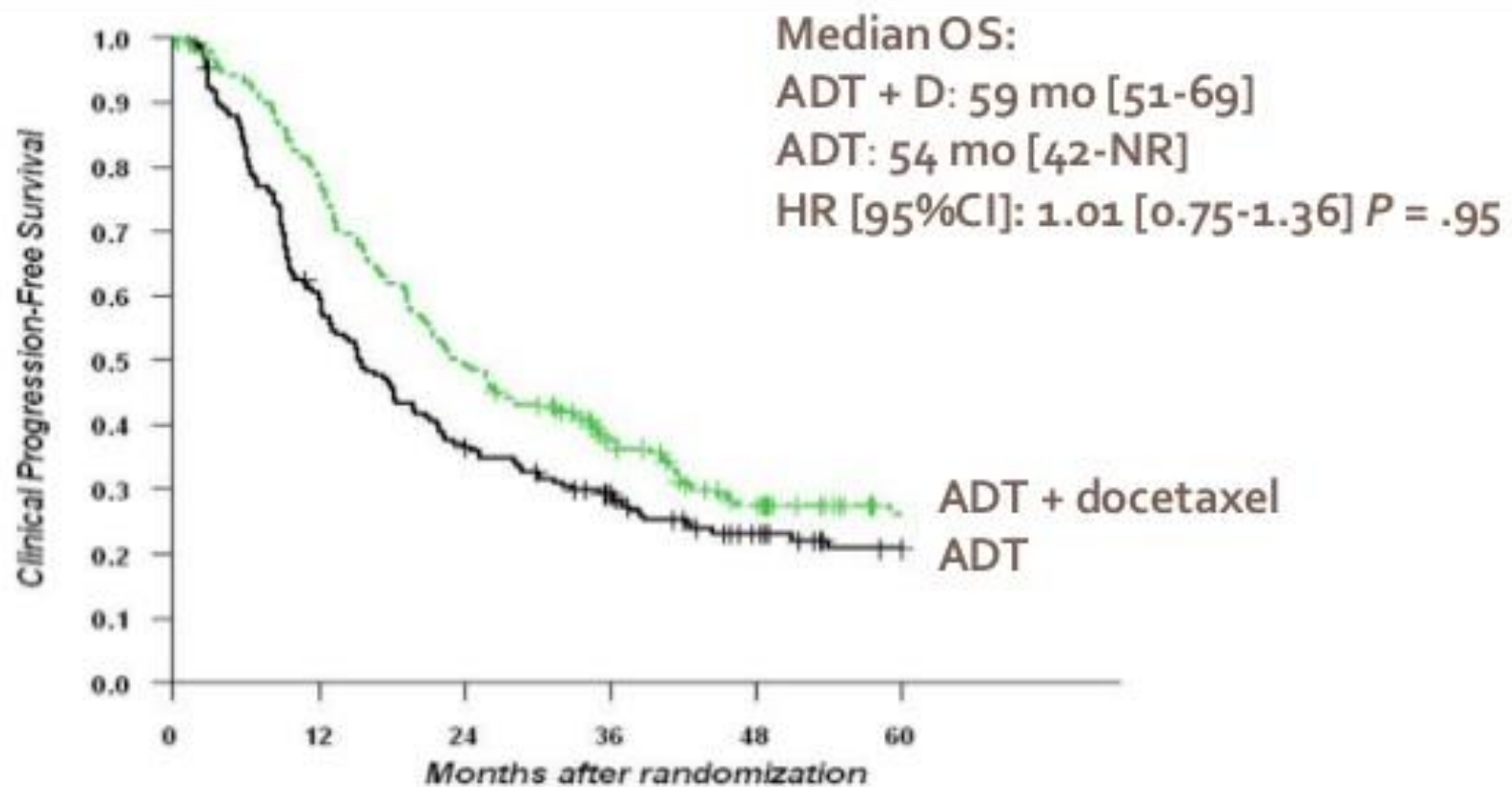
CHEMOHORMONAL THERAPY

- CHAARTED trial, in which 790 men with previously untreated, castration sensitive metastatic prostate cancer
 - 65 percent of patients had high volume disease
 - defined by visceral metastases or four or more bone metastases

ADT plus docetaxel (six cycles given every three weeks) vs to ADT alone

- Benefit:
- Increased overall survival median 58 versus 44 months
- Achieving a serum PSA <0.2 ng/mL was significantly more frequent at both 6 and 12 months with chemohormonal therapy compared with ADT alone
- Clinical progression was also significantly longer with chemohormonal therapy

Overall Survival

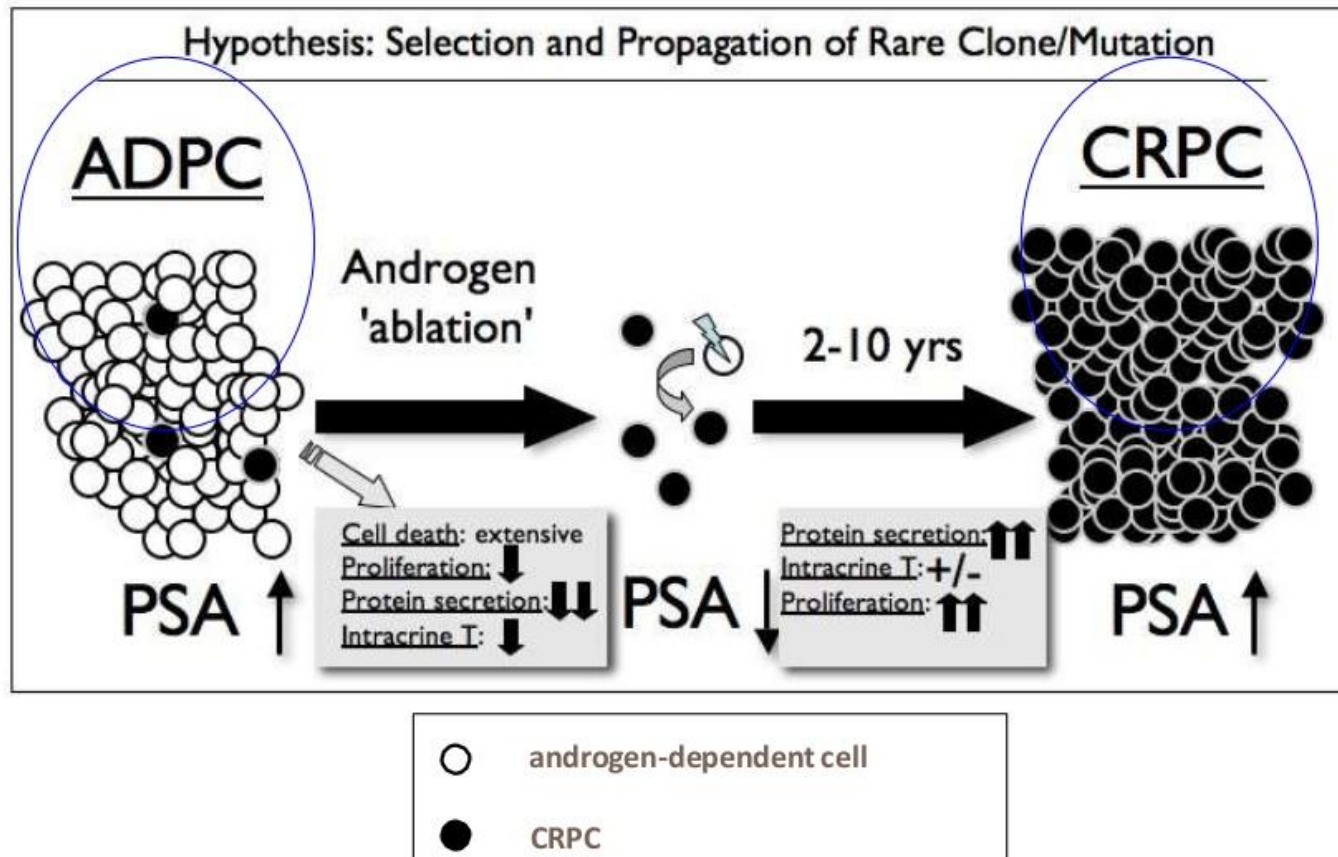


Patients	193	113	69	46	26	14	ADT
at risk :	192	146	92	57	34	16	ADT + docetaxel

CASTRATION RESISTANT DISEASE

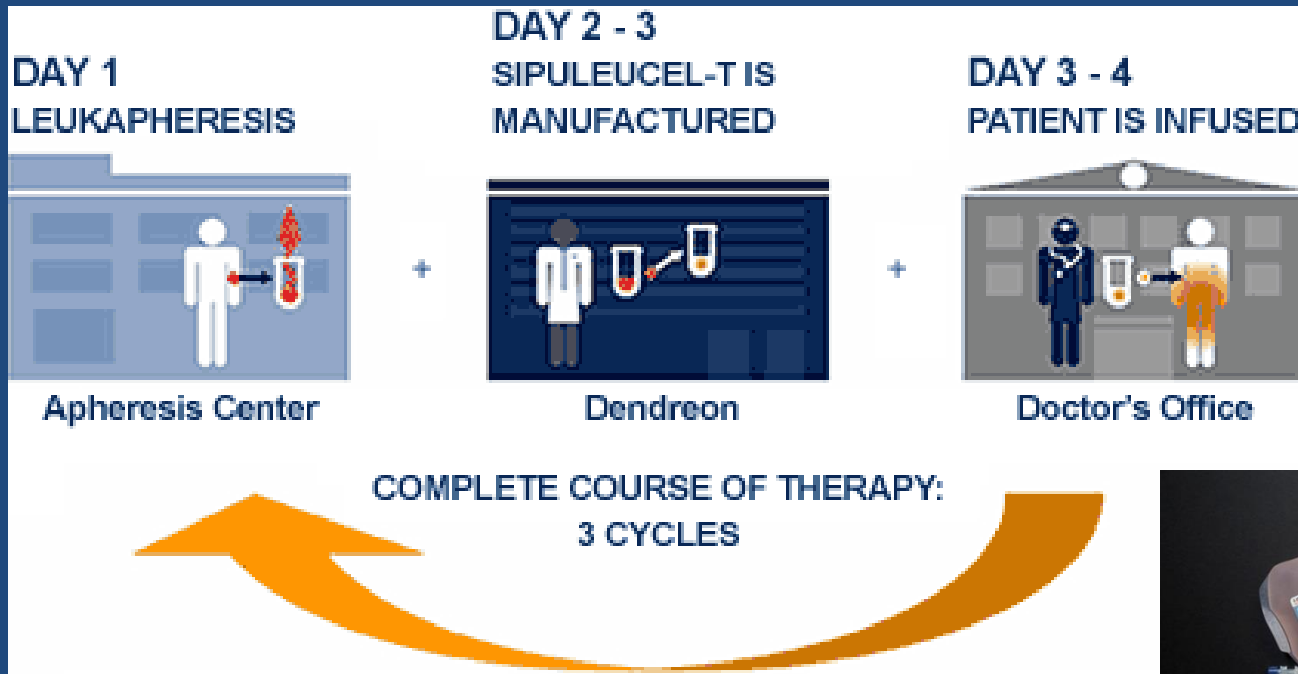
- Despite initial response rates of 90 %, nearly all men eventually develop progressive disease following ADT
 - This is referred to as castrate-resistant prostate cancer.
- Signs of resistant disease
 - Increase in serum PSA
 - New metastases
 - Progression of existing metastases

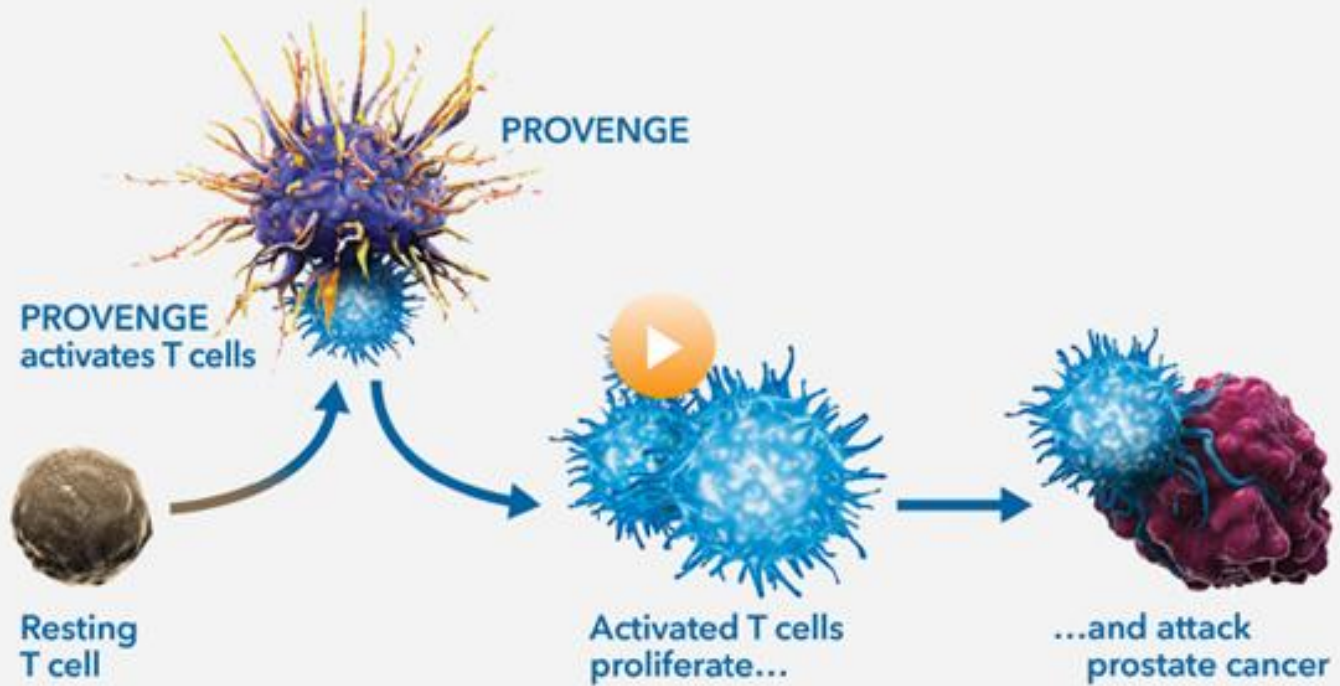
Intrinsic Resistance to ADT



Immunotherapy

- Provenge: Vaccine designed to enhance the immune T cell response to prostate cancer





- Who is eligible for provenge?
 - Castration-resistant metastatic prostate cancer
 - Radiologic evidence of metastasis
 - Serum testosterone <50 ng/dL
 - Good performance status
 - Excluded patients: visceral metastases or requiring opioid analgesic
- IMPACT trial that enrolled 512 men
 - Improved overall survival with (median 25.8 versus 21.7 months)
 - Adverse events more common with provenge
 - Chills, fatigue, fever, nausea, and headache
 - Cerebrovascular events were reported in 3.5 percent

Questions of Provenge

- Few PSA declines
- Controversial MOA: Does it work the way we thought
- Cost

Androgen synthesis inhibitors

- **ABIRATERONE: Zytiga**
 - blocks the synthesis of androgens in the tumor as well as in the testes and adrenal glands.



Patients previously treated with chemotherapy

- Phase III trial, 1195 men who had previously been treated with a chemotherapy
 - Abiraterone (1000 mg/day) plus prednisone (5 mg twice a day) vs placebo plus prednisone
- Benefits:
 - Overall survival: 15.8 versus 11.2 months
 - Improvements in time to PSA progression, radiologic progression-free survival, and PSA response rate
 - Improvement with palliation of pain intensity due to bone metastases
 - Improvement in the time to first skeletal-related event

Patients with no previous chemo

- Phase III trial, 1088 men with metastatic, asymptomatic or minimal symptomatic castration resistant prostate cancer
 - Abiraterone plus prednisone vs placebo plus prednisone
- Benefits
 - Overall survival: median 35.3 versus 30.1 months
 - Delay initiation of cytotoxic chemotherapy, opiate use for cancer-related pain, PSA progression, and decline in performance status.

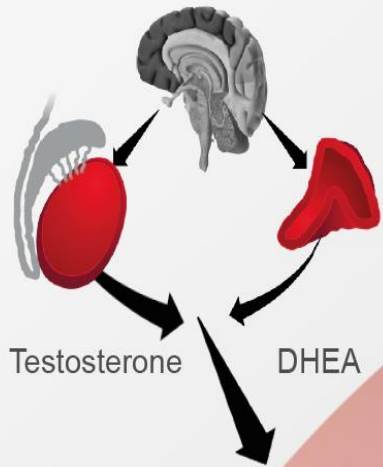
Side effects

- Fluid retention
- Low potassium: Hypokalemia
- Non-specific cardiac abnormalities, abnormal liver function tests, and hypertension
- Monthly potassium and blood pressure monitoring are essential to the proper management of patients on abiraterone.

Enzalutamide: Xtandi

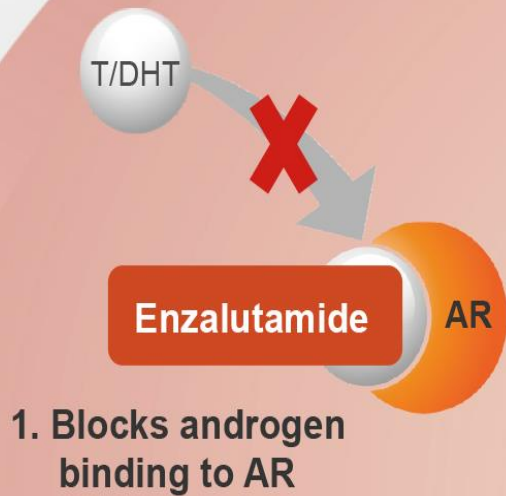
- Enzalutamide binds to the androgen binding site in the androgen receptor





CYTOPLASM

2. Prevents nuclear translocation of AR



3. Impairs AR binding to DNA preventing modulation of gene expression



Prior chemotherapy patients

- AFFIRM trial, 1199 men with castrate-resistant prostate cancer who had received prior chemotherapy
 - Enzalutamide(160 mg as a single dose once daily)
- Benefits:
 - Overall survival (median 18.4 versus 13.6 months)
 - Improvement PSA
 - Soft tissue response
 - Quality of life
 - Time to PSA progression
 - Radiographic progression-free survival
 - Time to first skeletal related event

No previous chemotherapy

- Phase III PREVAIL trial, 1717 men who had not received prior chemotherapy
- Benefit:
 - Overall survival increased (estimated median 32.4 versus 30.2 months).
 - Delay time to initiation of chemotherapy, time to first skeletal related event, and time to PSA progression

Side effects

- Fatigue
- Diarrhea
- Hot flashes
- Musculoskeletal pain
- Headache
- Development of seizures, which occurred in seven patients

COMBINING ABIRATERONE AND ENZALUTAMIDE

- Both androgen synthesis inhibitors and androgen receptor antagonists target androgen-based pathways.
- Preliminary results found that the combination was well tolerated and there were no unanticipated toxicities
- Studies on going

Chemotherapy



Chemotherapy: Docetaxel

- TAX-327 trial, 1006 men with chemotherapy-naive metastatic castrate-resistant prostate cancer
 - Docetaxel (75 mg/m² every three weeks) vs Mitoxantrone
 - All patients received prednisone 5 mg orally twice a day
- Benefit:
 - Overall survival (median 19.2 versus 16.3 months)
 - Higher PSA response rate
 - Higher pain response rate
 - Toxicity
 - Fatigue
 - Fluid retention
 - Neutropenic infection (3percent)
 - Neuropathy
 - Hypersensitivity reactions
 - Hair loss

Chemotherapy: Cabazitaxel

- Phase III TROPIC trial, 755 men, all of whom had progressed on docetaxel
- Cabazitaxel (every three weeks) vs mitoxantrone .
 - All received oral prednisone (10 mg/day)
- Benefit
 - Overall survival median survival 15.1 versus 12.7 months

Radium-223



Mechanism and handling



Radium-223 Handling and Administration

- The radiologic half-life of radium-223 (11.4 days) allows sufficient time for its preparation, distribution (including long-distance shipment), and administration to patients
- Radium-223 is a ready-to-use intravenous injection product administered using standard equipment and requiring minimal radiation shielding during handling, and minimal radiation protection after treatment
- Patients are treated on an outpatient basis and have no restrictions on family contact afterwards

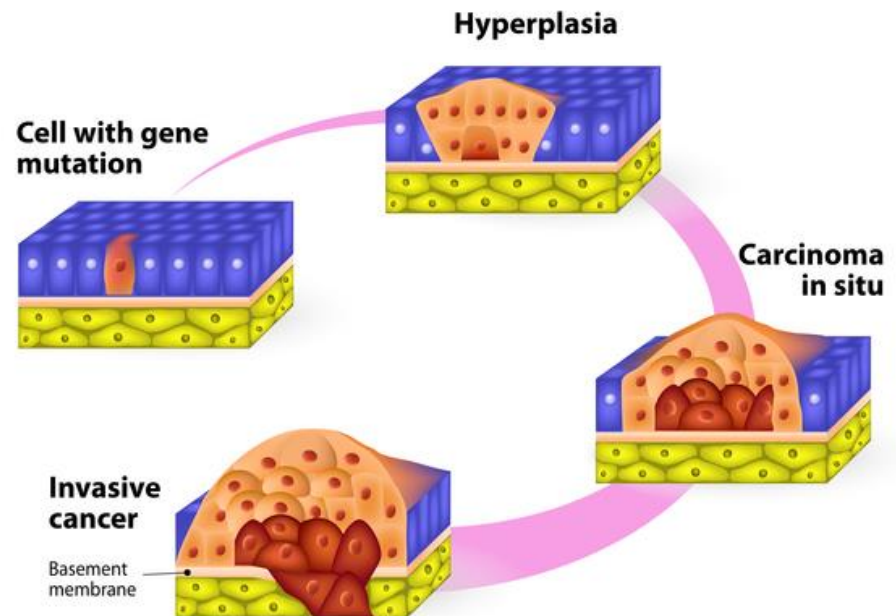
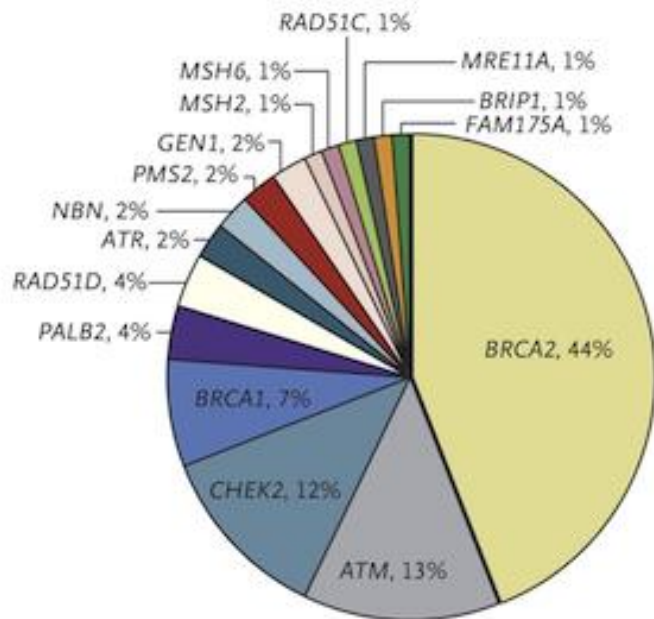


Fig. 1: Overall survival (OS) in ALSYMPCA trial. Courtesy of Chris Parker, MD.[†]

Radium 223

- Prolong OS
- Improve SRE
- Benefit in pre and post chemotherapy patients
- Rare decline in PSA
- Given over 6 months
- Well tolerated
 - Bone marrow suppression
 - Dehydration: Due to GI events

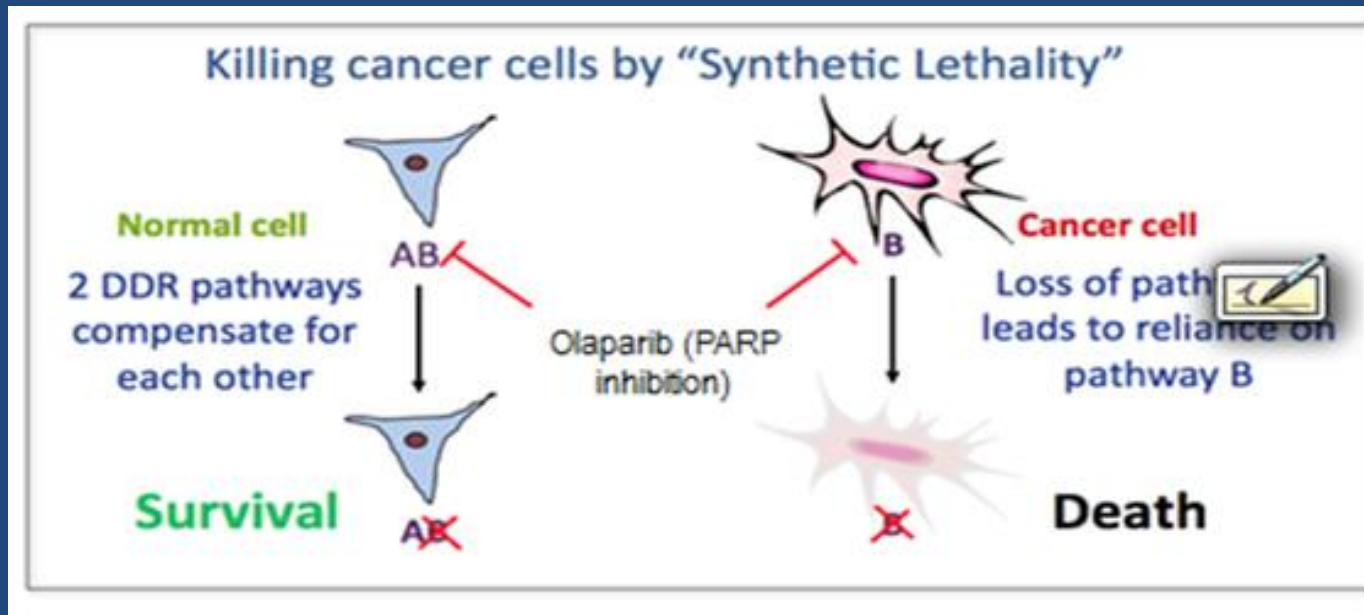
Inherited Mutations in DNA-Repair Genes Found in Advanced Prostate Cancers



Inherited Mutations in DNA-Repair Genes Found in Advanced Prostate Cancers

- Nearly 12% of men with advanced prostate cancer have inherited mutations in genes that play a role in repairing damaged DNA

Olaparib



Olaparib

- FDA breakthrough therapy designation as treatment for patients with BRCA1/2 or ATM mutation mCRPC in those received taxane based chemotherapy and either xtandi or zytiga.

TREATMENT OF PATIENTS WITH SYMPTOMATIC BONE METASTASES

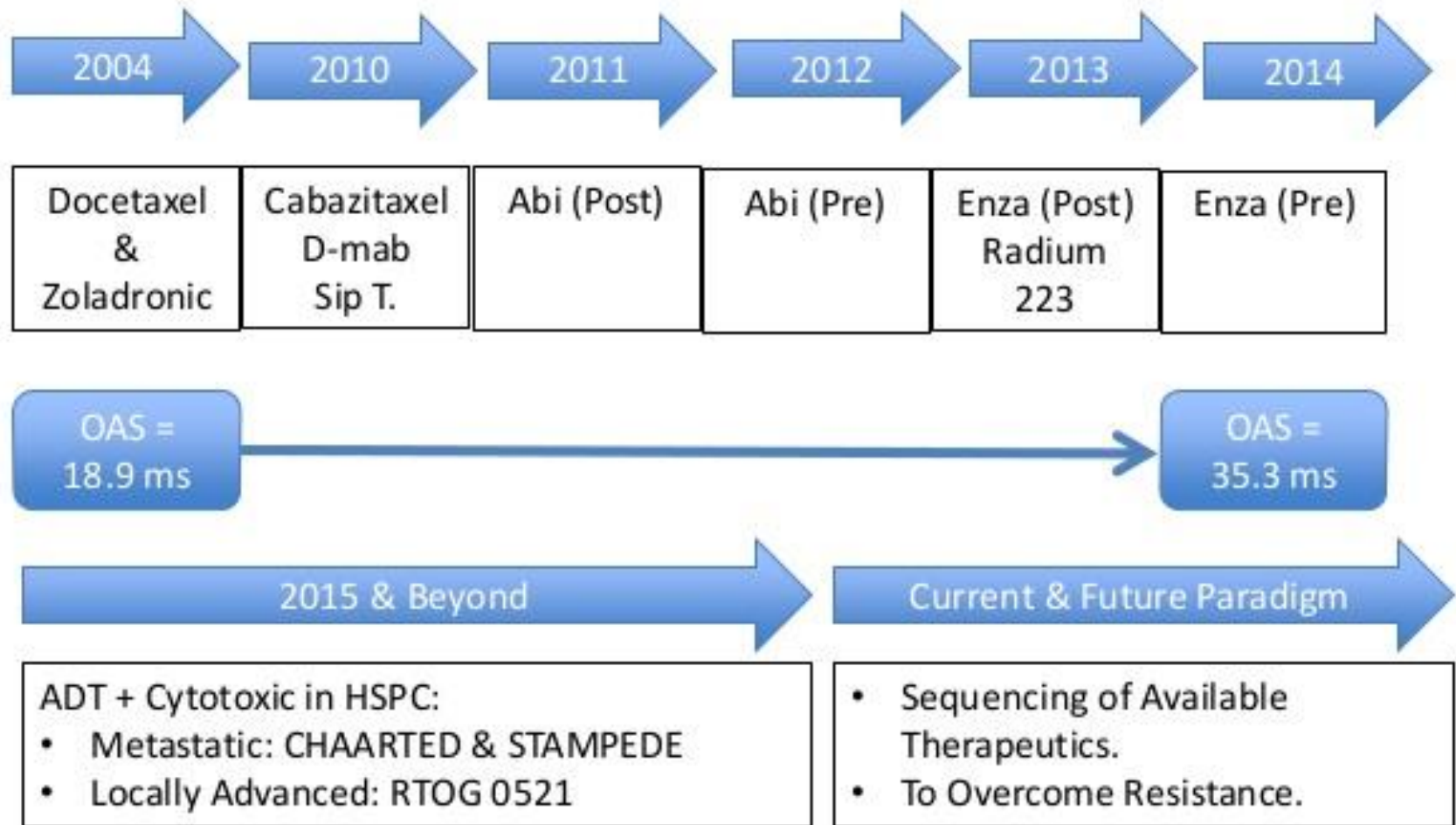
- External beam radiation therapy
- Bone-targeted radiopharmaceuticals
 - Radium-223: alpha particle emitting agent
 - Prolongs overall survival and decreases symptomatic skeletal events due to bone metastases
 - Decrease the incidence of symptomatic skeletal events
 - first use of external beam RT
 - new pathologic fracture
 - spinal cord compression
 - tumor related orthopedic surgery intervention
 - Beta particle (strontium-89) emitting radiopharmaceuticals may yield some symptomatic benefit they do not significantly prolong overall survival

Prevention of skeletal related events due to bone metastases

- **Zometa** : prevent the loss of bone
- —Delay the development of skeletal-related events
 - pathologic fractures
 - radiation therapy to bone
 - surgery to bone
 - spinal cord compression
- **Denosumab**: monoclonal antibody prevents bone loss
 - Prevention of skeletal related events
- Denosumab is more effective than zoledronic acid in preventing skeletal related events in men with established bone metastatic castration resistant prostate cancer
 - Does not improve overall survival or time to disease progression.
- **Side effects**
 - Osteonecrosis of the jaw (ONJ)
 - Hypocalcemia
 - Renal impairment is a concern with bisphosphonates but not denosumab



Prostate Cancer: The Story: New Chapters:



DO YOU WANT MORE
TREATMENT OPTIONS?!

Thank you!!!

- Questions
- 505-842-8171

