


The evolving landscape of advanced prostate cancer treatment

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Objectives

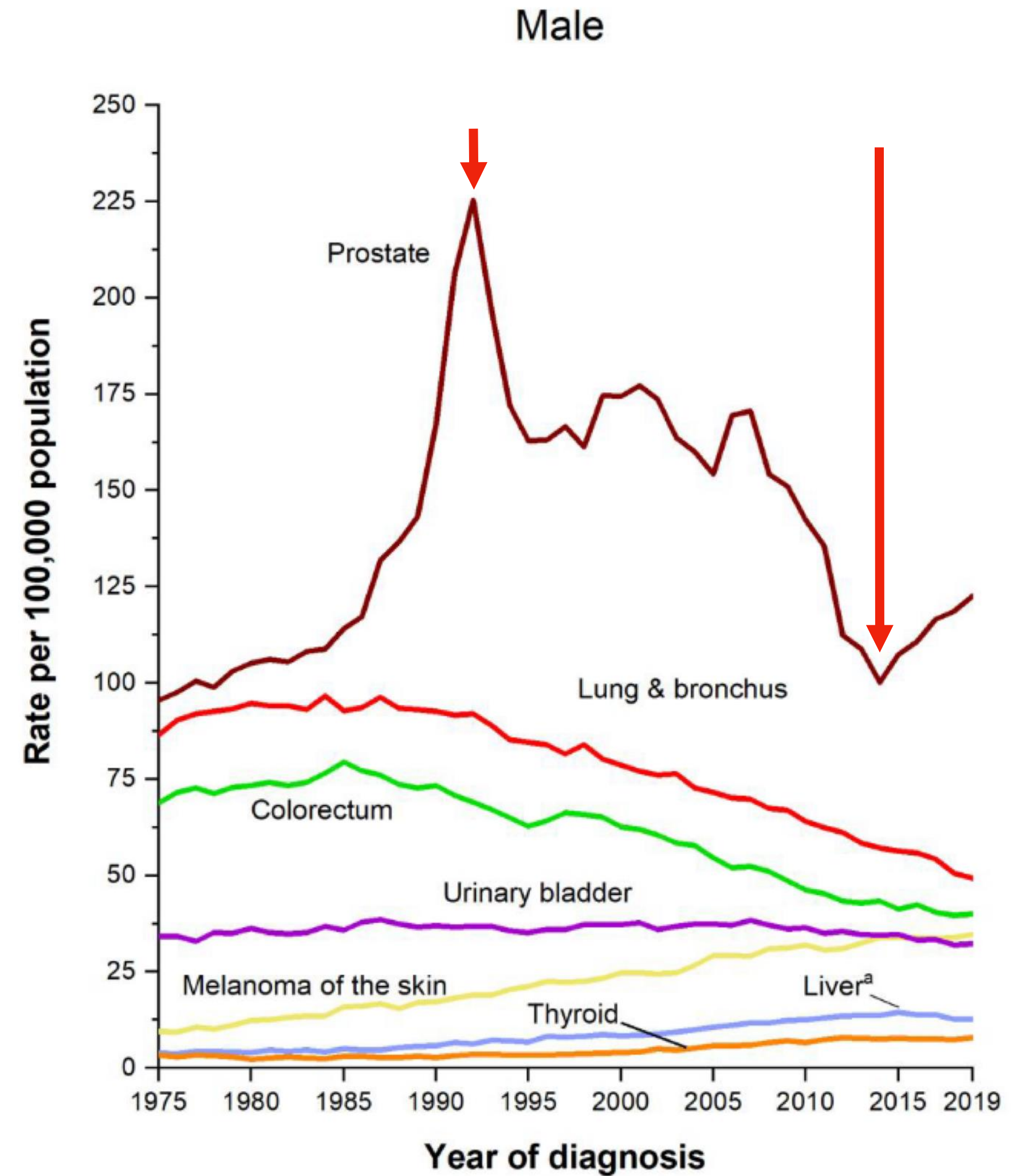
- **introduction**
- stages of prostate cancer
- classes of treatment
- genetic testing
- supportive care
- the future

Estimated New Cases

			Males
Prostate	288,300	29%	
Lung & bronchus	117,550	12%	
Colon & rectum	81,860	8%	
Urinary bladder	62,420	6%	
Melanoma of the skin	58,120	6%	
Kidney & renal pelvis	52,360	5%	
Non-Hodgkin lymphoma	44,880	4%	
Oral cavity & pharynx	39,290	4%	
Leukemia	35,670	4%	
Pancreas	33,130	3%	
All Sites	1,010,310	100%	

Estimated Deaths

			Males
Lung & bronchus	67,160	21%	
Prostate	34,700	11%	
Colon & rectum	28,470	9%	
Pancreas	26,620	8%	
Liver & intrahepatic bile duct	19,000	6%	
Leukemia	13,900	4%	
Esophagus	12,920	4%	
Urinary bladder	12,160	4%	
Non-Hodgkin lymphoma	11,780	4%	
Brain & other nervous system	11,020	3%	
All Sites	322,080	100%	



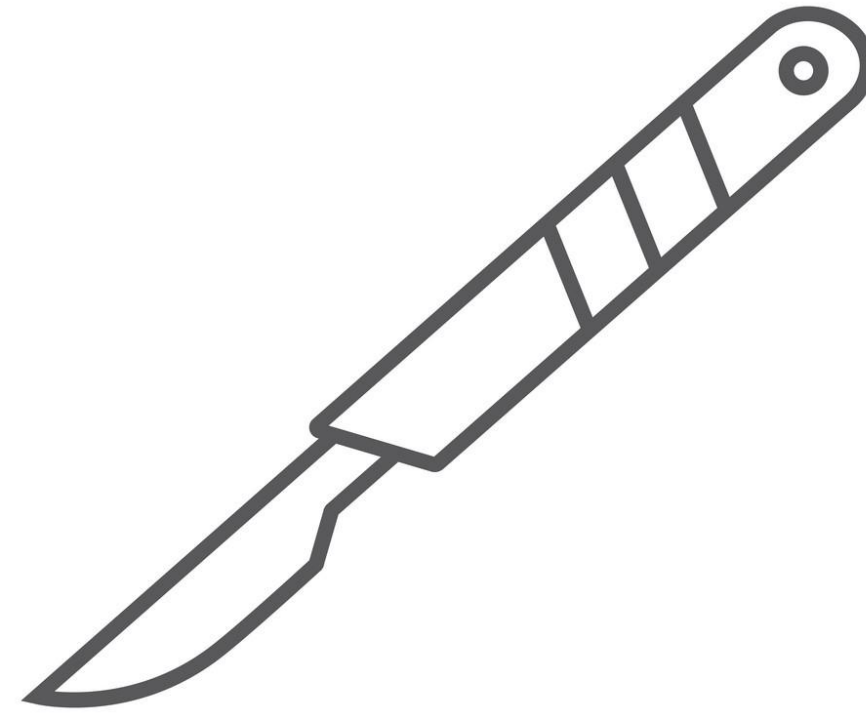
Risk Factors

- Age
- Ethnicity
- Family history/genetic predisposition
- Diet

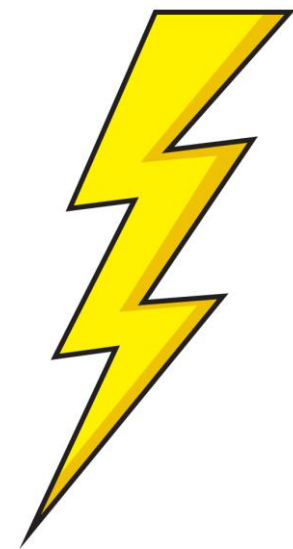
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Localized prostate cancer

- **Surgery (radical prostatectomy)**



- **Radiation therapy**



- **Active surveillance**



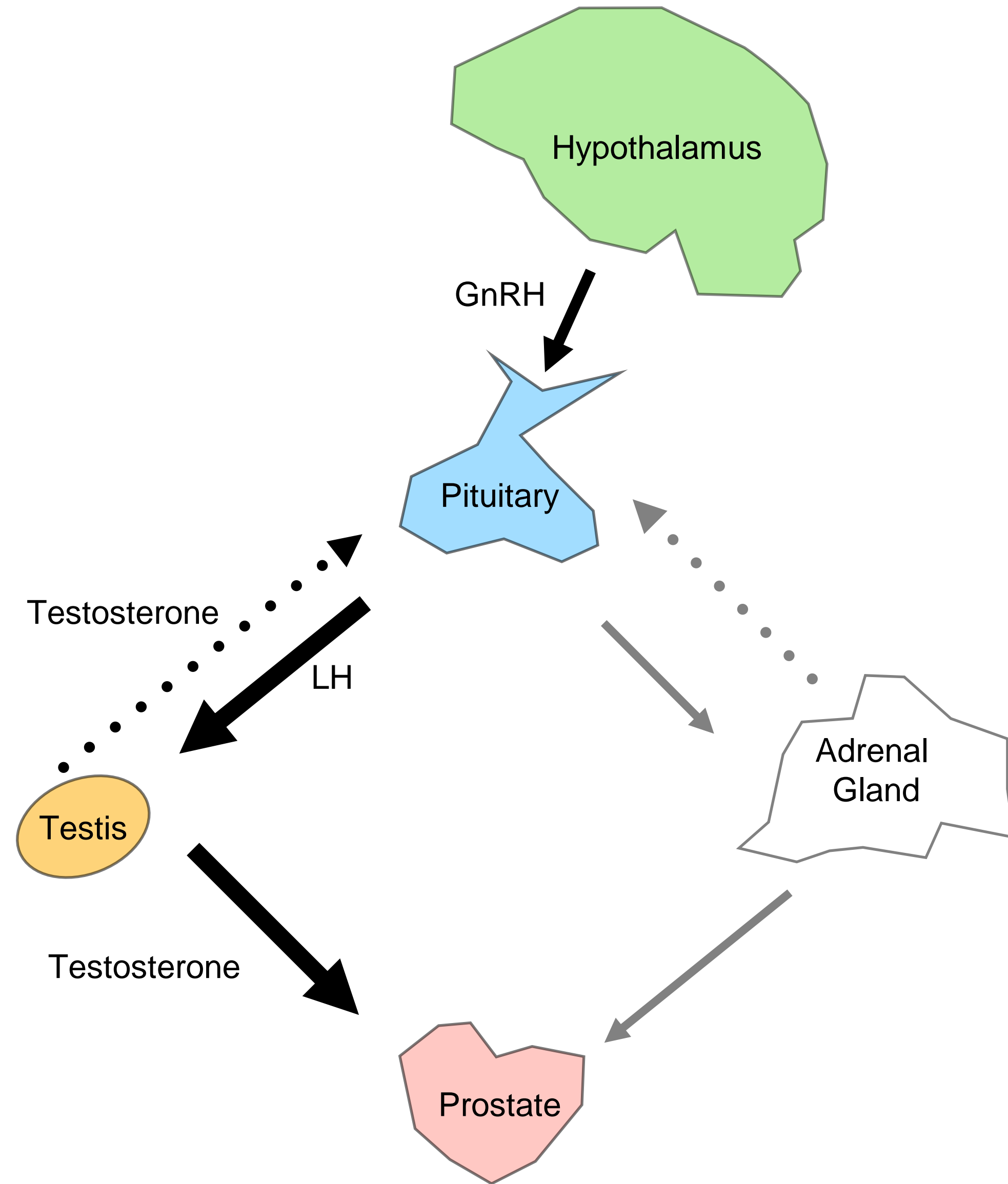
What is advanced prostate cancer?

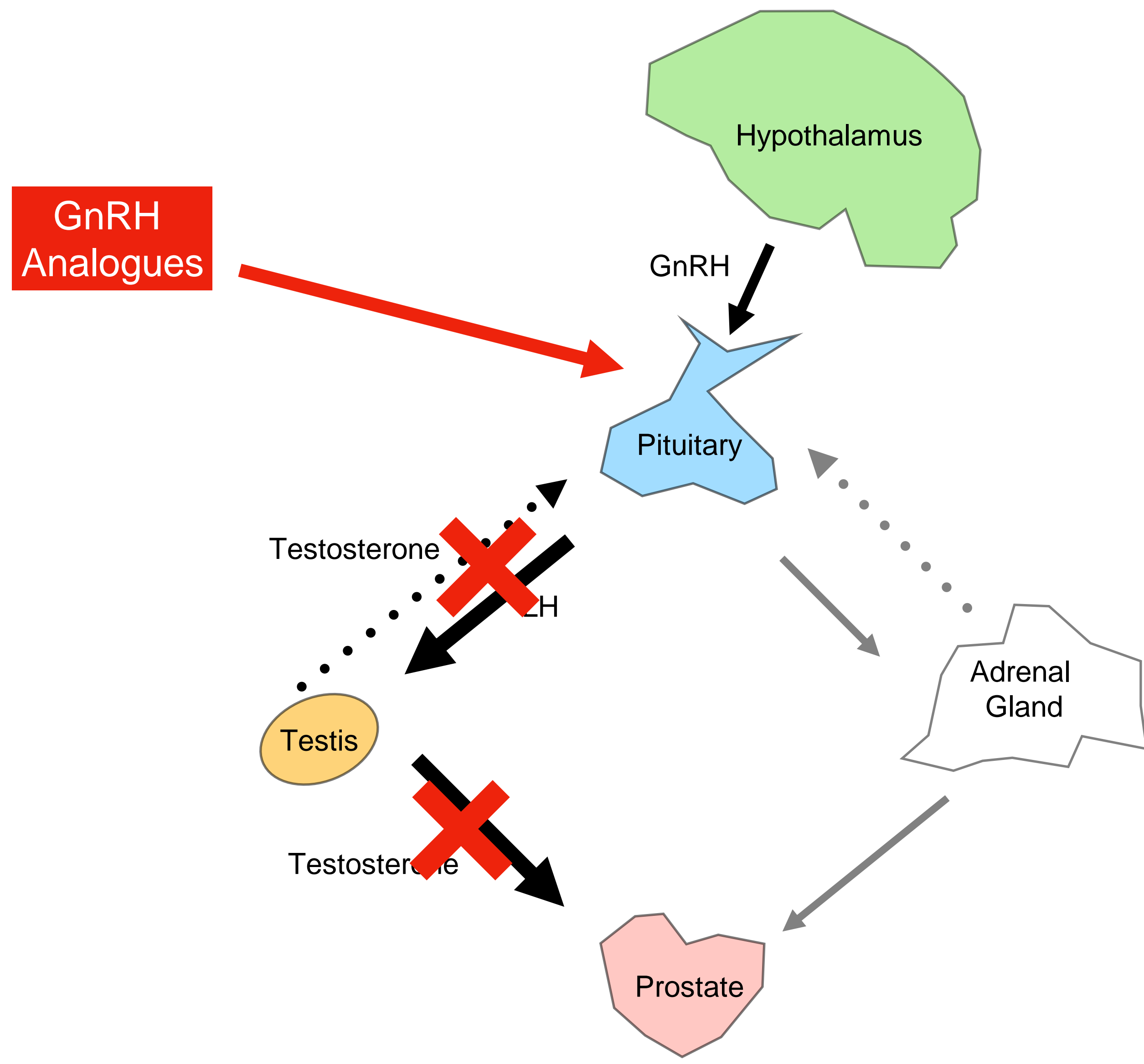
- Defined as prostate cancer spreads outside the prostate
- Stage IV or metastatic disease
- Most common sites of prostate cancer spread are to: lymph nodes, bones, liver, lung
- No specific symptoms, sometimes detect only rise in PSA (biochemical recurrence)

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Treatment

- Prostate cancer is very sensitive to testosterone (androgen)
 - 95% of testosterone comes from the testicle (~5% from adrenal gland, other tissue)
- “Hormone therapy” = shutting down production of testosterone (Androgen Deprivation Therapy or ADT)





Androgen Deprivation Therapy (ADT)

- **GnRH agonists** - leuprolide (eligard, lupron), goserelin (zoladex), triptorelin (treistar)
- **GnRH antagonists** - degarelix (firmagon), ***relugolix (orgovyx)***

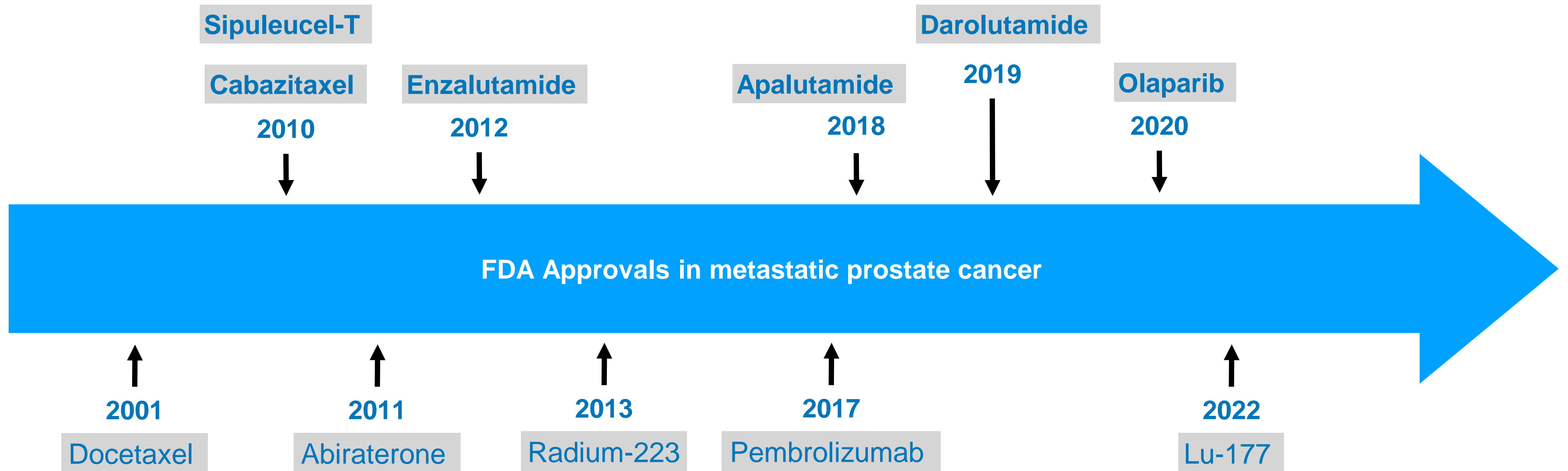
Side effects:

- >> hot flashes, mood changes, loss of libido, fatigue/decreased strength
- >> decreased bone density, increased risk of diabetes/heart disease

When ADT stops working

- Deprivation works on average for 1-1.5 yrs
- Defined as “castration-resistant” prostate cancer
- **ADD** therapy to target testosterone produced by (a) adrenal glands and (b) prostate cancer cells

Timeline



Chemotherapy

Mitoxantrone

- IV administration
- 1st FDA approval (1996), improved quality of life but **NOT** survival

Docetaxel (Taxotere)

- IV administration
- **1st treatment to improve survival with advanced castrate-resistant prostate cancer**

Cabazitaxel (Jevtana)

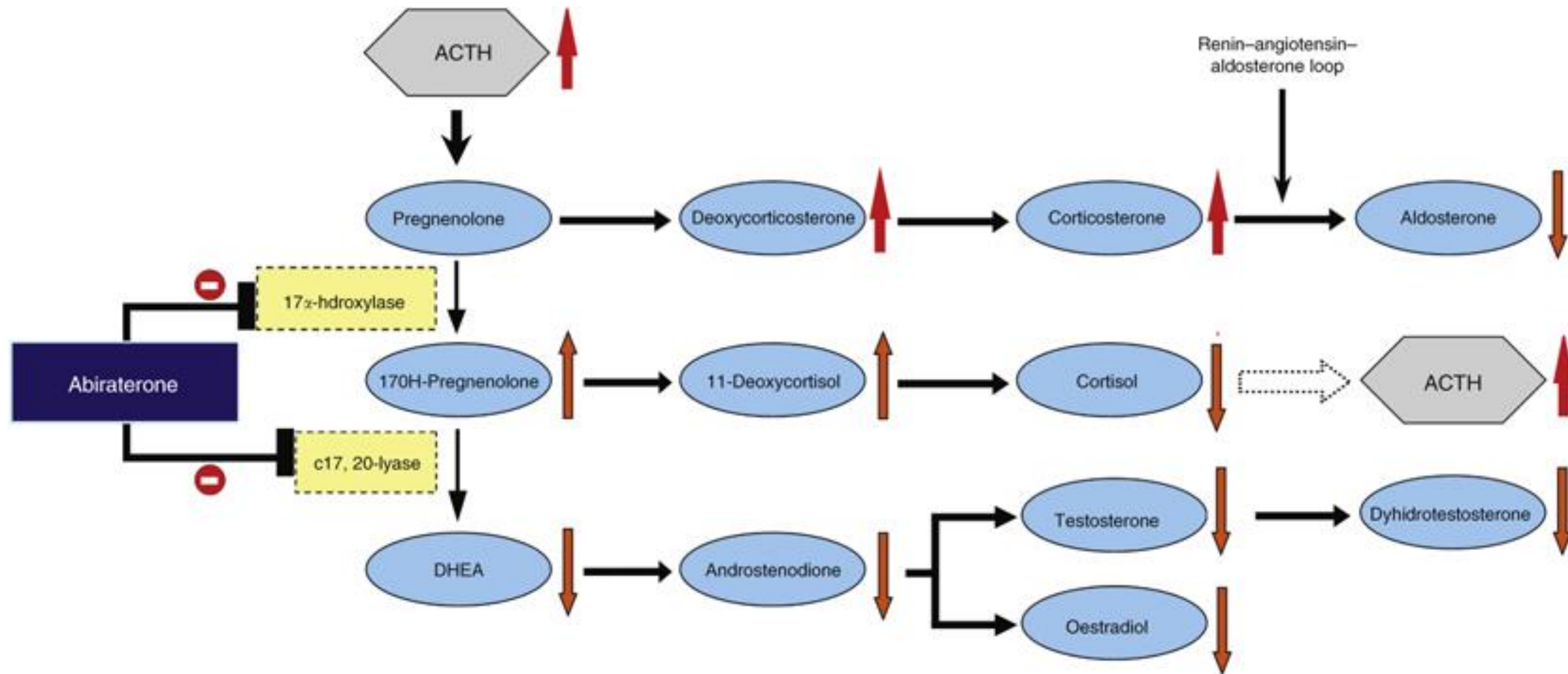
- IV administration
- Indicated in patients whose cancer is growing despite docetaxel therapy

Next-generation oral hormones

Abiraterone (Zytiga)

- blocks synthesis in tumor, testes, and adrenal glands
- must be taken with low dose prednisone (insufficient cortisol production)
- 1,000 mg once daily (in combination with prednisone)
- **250 mg once daily administered with or within 30 minutes of low-fat breakfast**

Next-generation oral hormones



Next-generation oral hormones

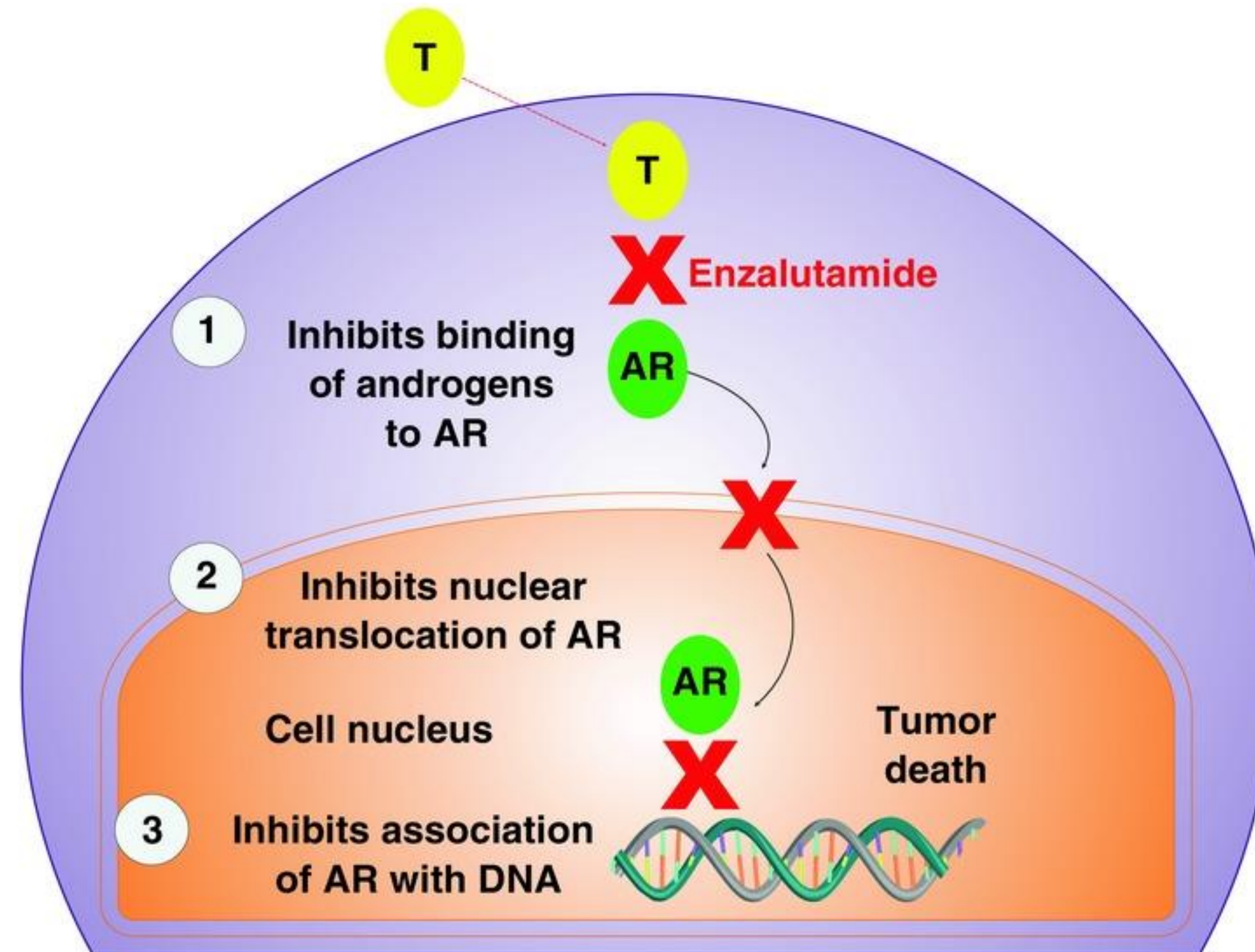
Enzalutamide (Xtandi)*

Apalutamide (Erleada)

Darolutamide (Nubeqa)

- block (a) binding of androgen to androgen receptor, (b) nuclear translocation of androgen receptor, (c) association of androgen receptor with DNA
- concurrent treatment with steroids not required
- risk of falls, seizures

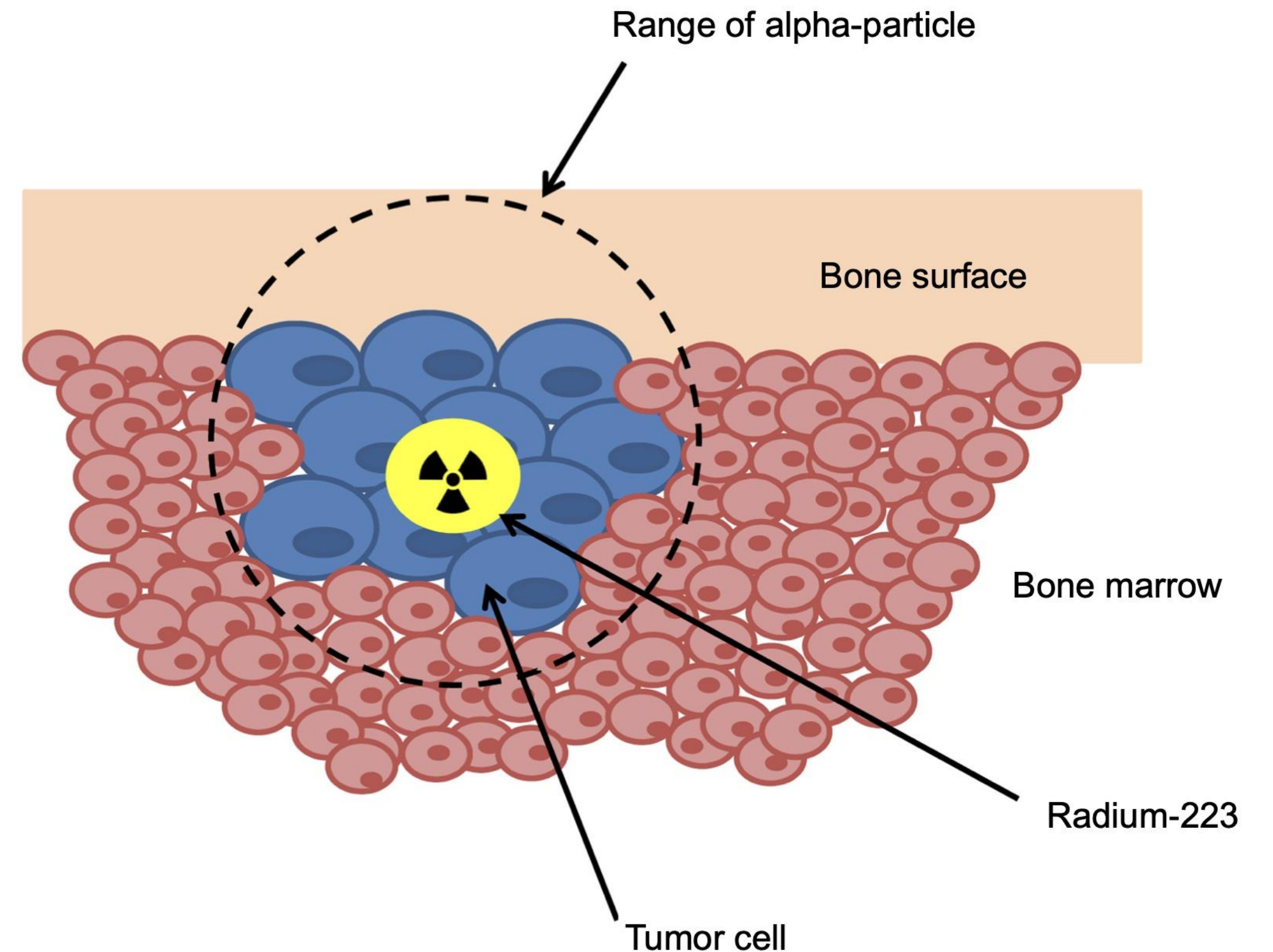
Next-generation oral hormones



Radiopharmaceutical

Radium-223 (Xofigo)

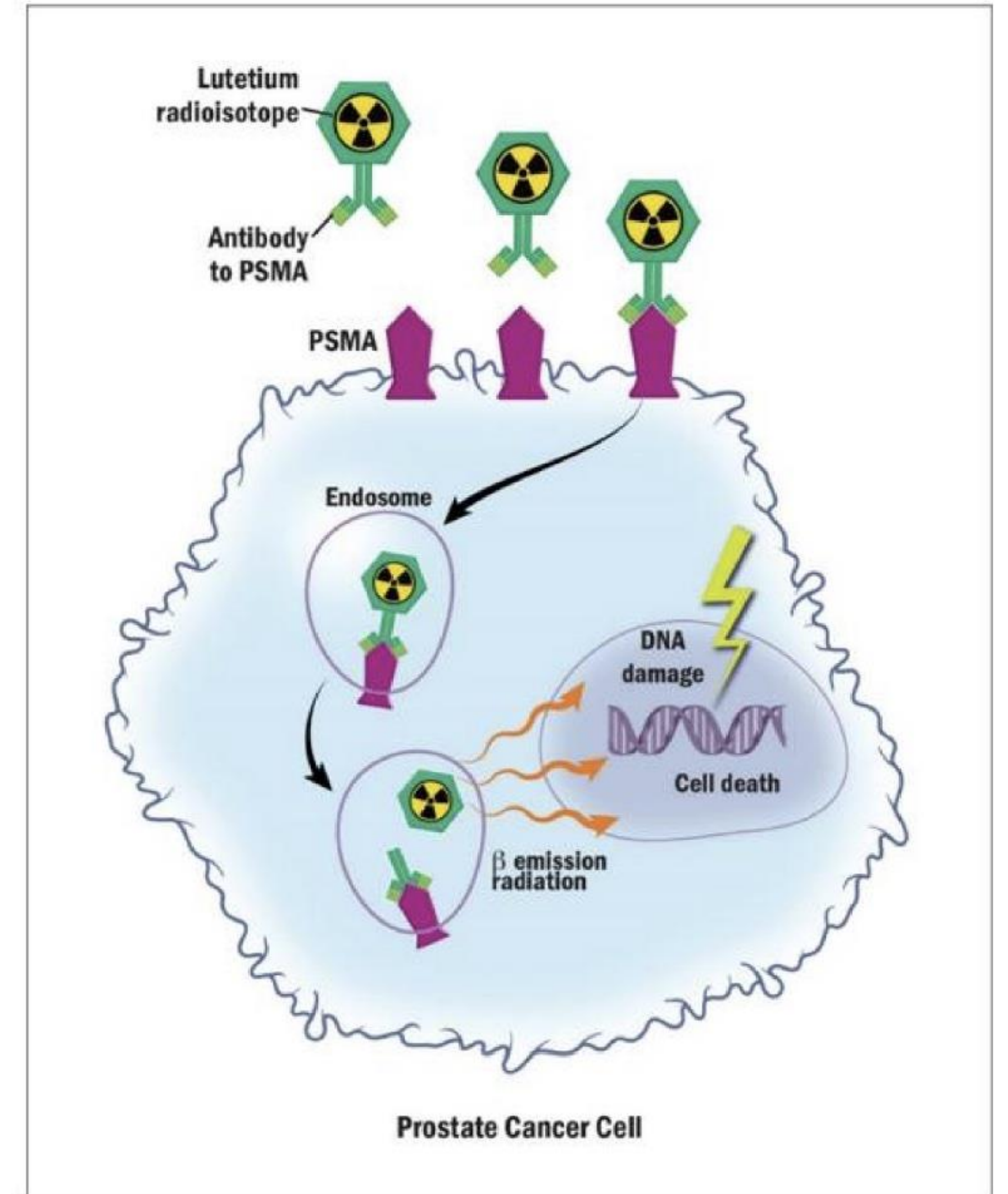
- bone-seeking element
- limited to men with symptomatic bone metastasis without other sites of disease
- IV administration every 4 wks for 6 doses
- effective in reducing bone pain
- improves survival



Radiopharmaceutical

Lutetium-177 vipivotide tetraxetan (Pluvicto)

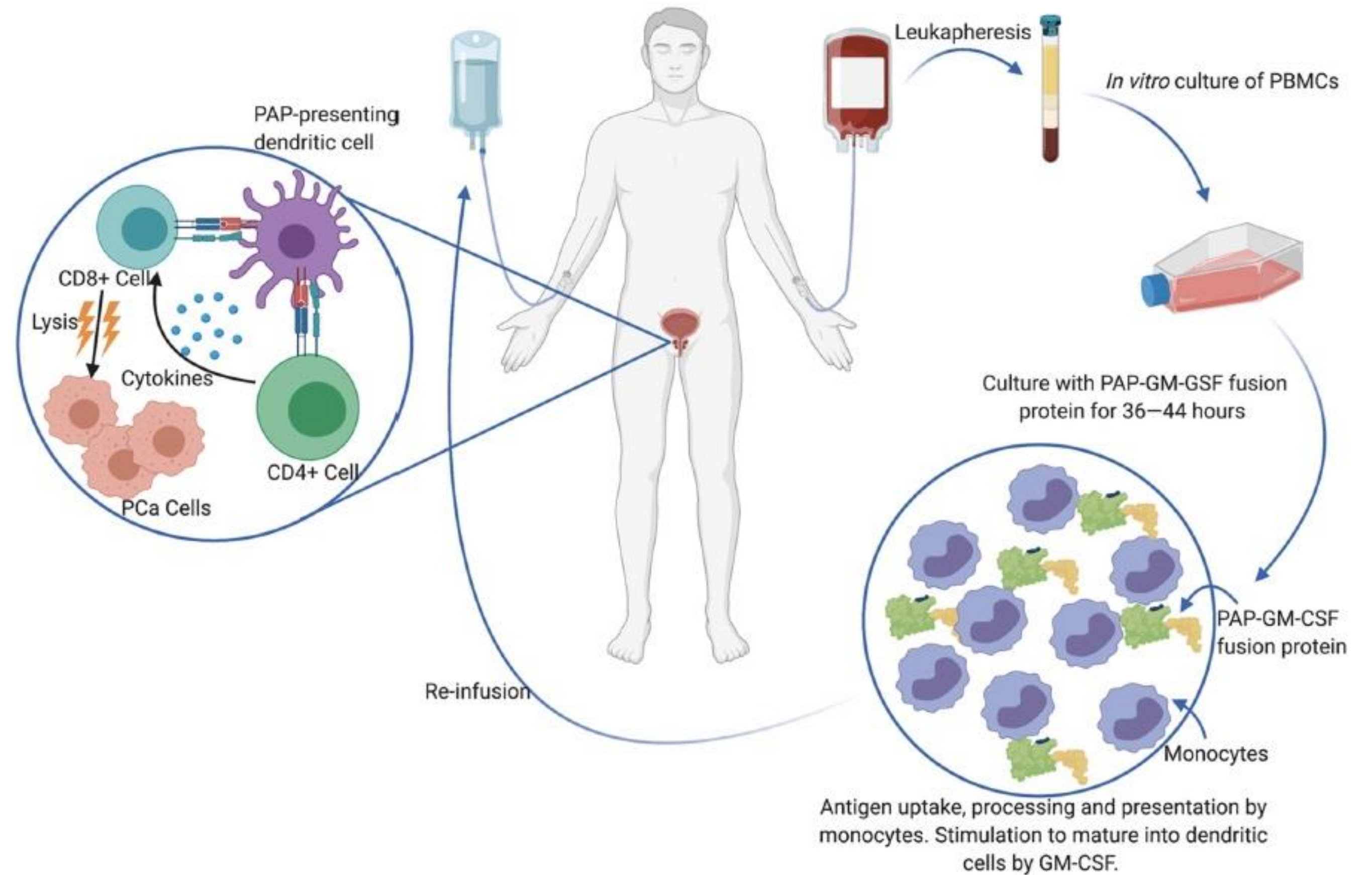
- FDA approved 03/2022
- for patients with taxane and oral androgen-refractory PSMA (prostate-specific membrane antigen) positive metastatic, castrate-resistant prostate cancer
- side effects include low WBC, kidney toxicity, and salivary gland symptoms (pain, swelling, dry mouth)



Cellular immunotherapy

Sipuleucel-T (Provenge)

- therapeutic vaccination
- immune cells (dendritic cells) harvested, stimulated to target prostate cancer cells
- typically used for patients with slowly progressive disease, asymptomatic



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- **genetic testing, targeted treatment**
- supportive care
- the future

Genetics

- 2 types of genetic testing:
 - **(A) Germline**
 - hereditary, present in all cells from birth
 - **(B) Somatic**
 - acquired, gene mutations found in the tumor cells



https://www.cdc.gov/genomics/gtesting/genetic_testing.htm

Targeted therapies

PARP inhibitors

- Olaparib (lynparza)
- Rucaparib (rubraca)
- block repair of cancer cell DNA strand breaks
- approved for castrate-resistant prostate cancer with certain germline or somatic mutations (including BRCA1/2)
- side effects include GI distress and low blood counts

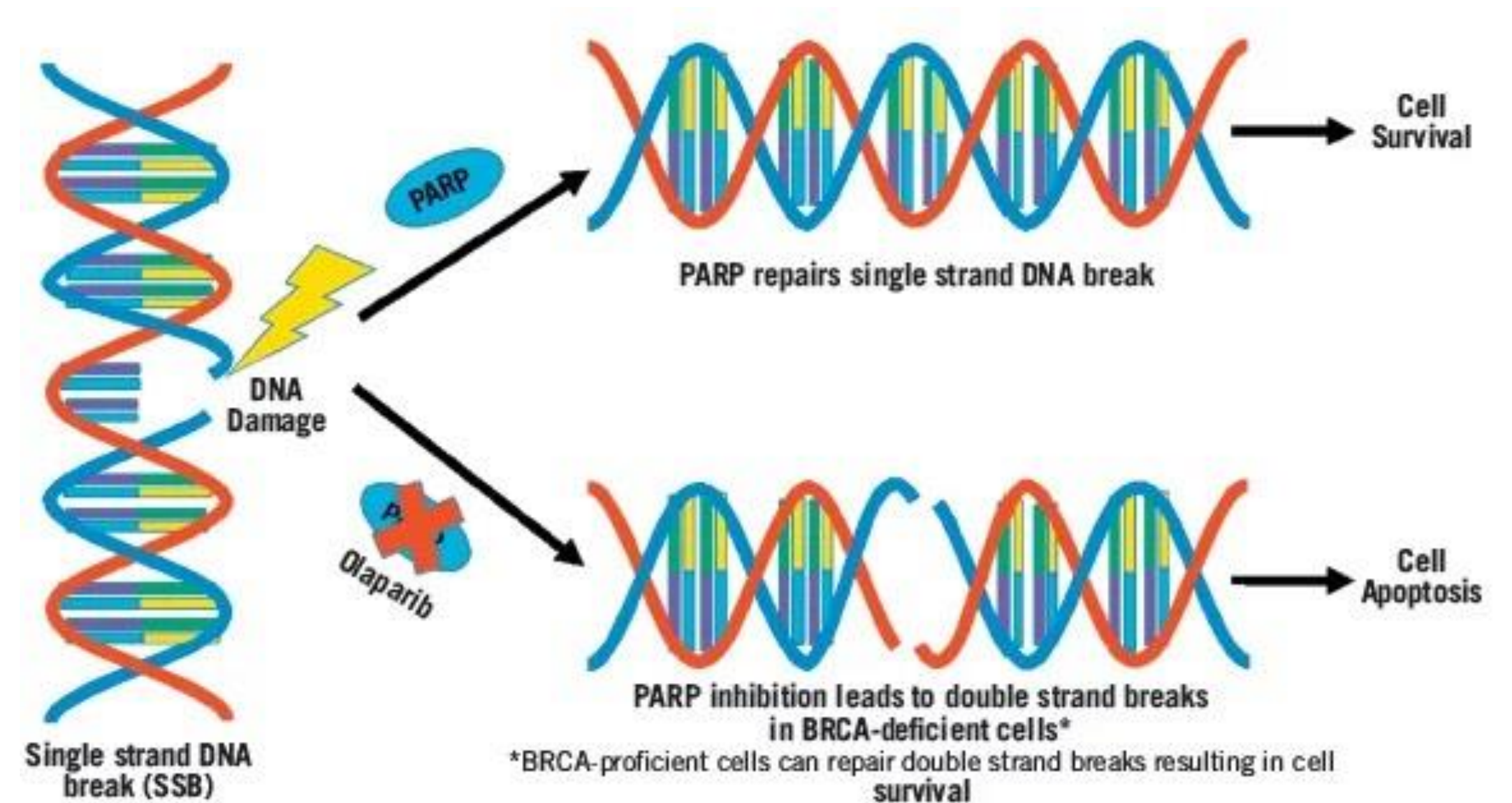


FIGURE Illustration of Olaparib Mechanism Specifically in *BRCA*-Deficient Cells Compared With Normal Cells[1]

PARP = poly (ADP-ribose) polymerase.

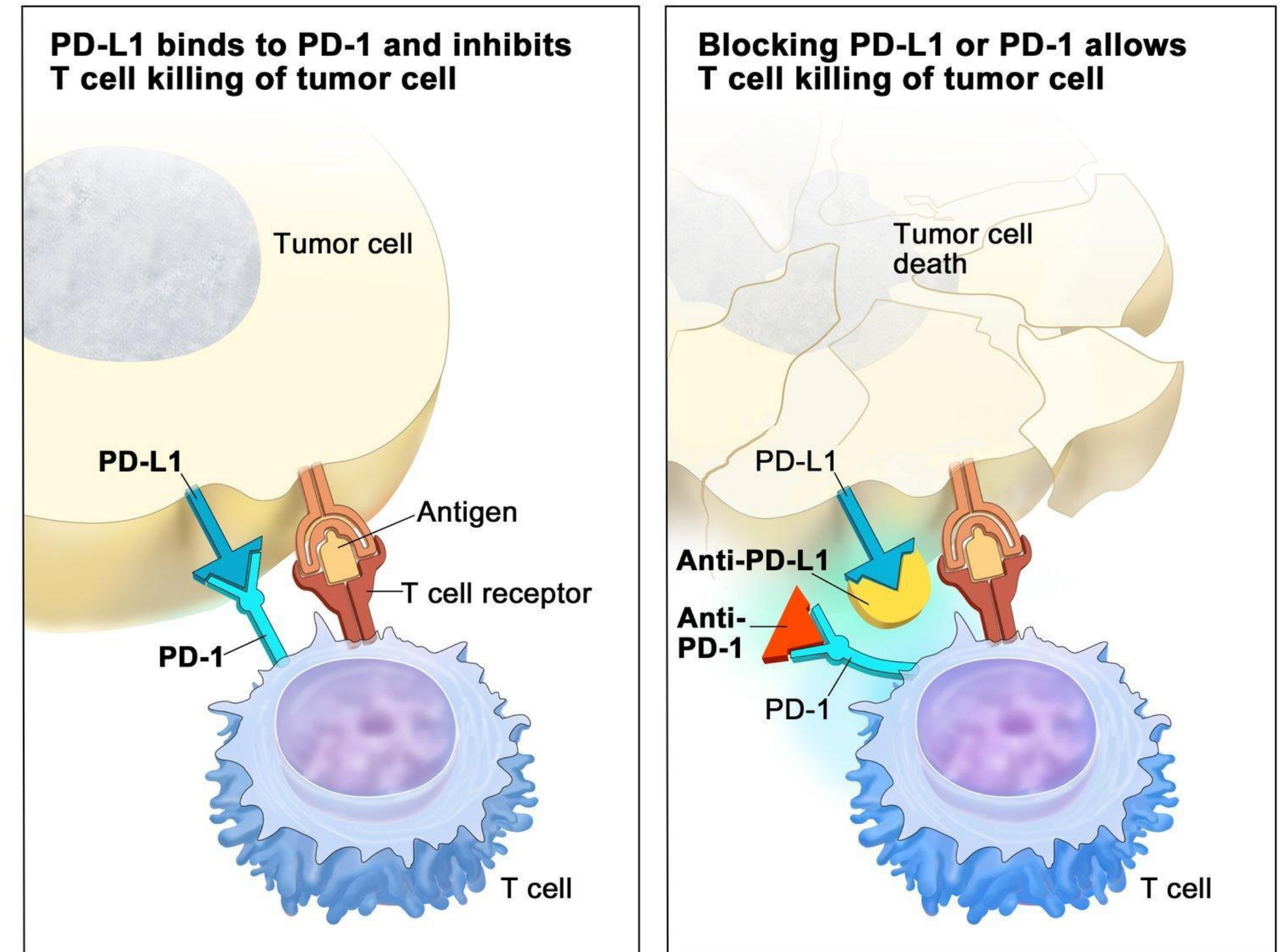
Checkpoint immunotherapy

Pembrolizumab (Keytruda)

Nivolumab (Opdivo)

Dostarlimab (Jemperli)

- immune cells have checkpoints (“brakes”) to prevent over-activation
- Inhibitors work by blocking checkpoint proteins from binding, preventing transmission of the “off” signal and allowing T-cells to kill cancer cells
- approved in uncommon subtype of prostate cancers (dMMR/MSI-H or high TMB)



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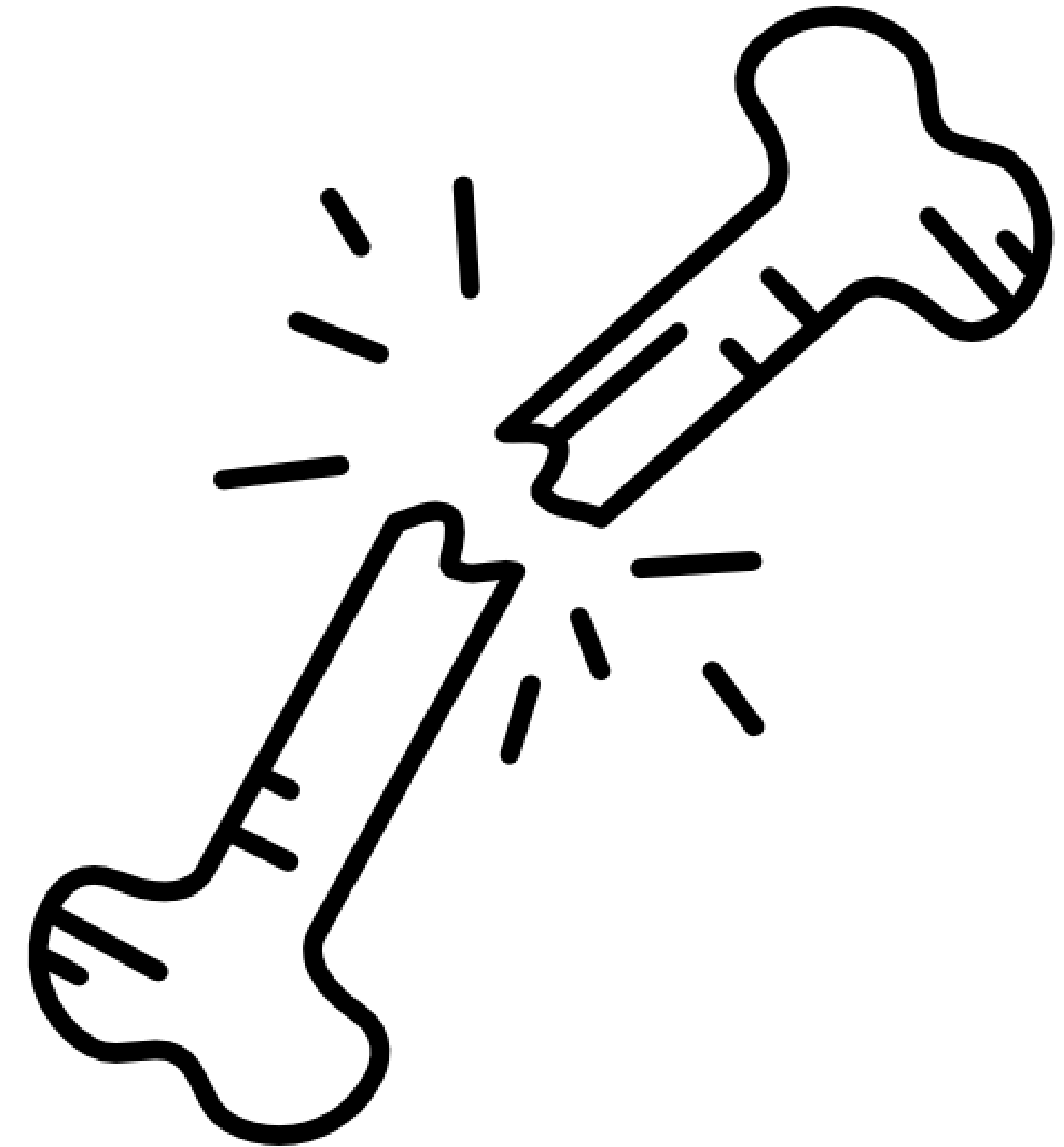
<https://www.cancer.gov/about-cancer/treatment/types/immunotherapy/checkpoint-inhibitors>

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Supportive care

Bone Health

- Loss of bone mineral density due to:
 - aging
 - androgen deprivation
 - presence of cancer
- leads to major risk of fractures



Supportive care

Bone Health

- **Zoledronic acid (Zometa, Reclast)**
 - in a class of drugs called bisphosphonates
 - blocks breakdown of bone mineral calcium
- **Denosumab (Xgeva, Prolia)**
 - monoclonal antibody against RANKL (receptor on osteoclasts)
- associated with risk of **osteonecrosis of jaw** and can cause **low calcium levels**
- very to important to complete **dental evaluation** prior to treatment

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Future directions, ongoing questions

- Role of triplet therapy (ADT + oral anti-androgen + chemotherapy)
- Exploring other immunotherapy agents (Bispecific antibodies, CAR-T cells)
- Identifying, developing targeted therapies, ways to combat hormone therapy resistance
- Best sequence of treatment?
- PARPi use in patients without genetic repair abnormalities

Thank you!

Questions? matthew.kotlove@stelizabeth.com