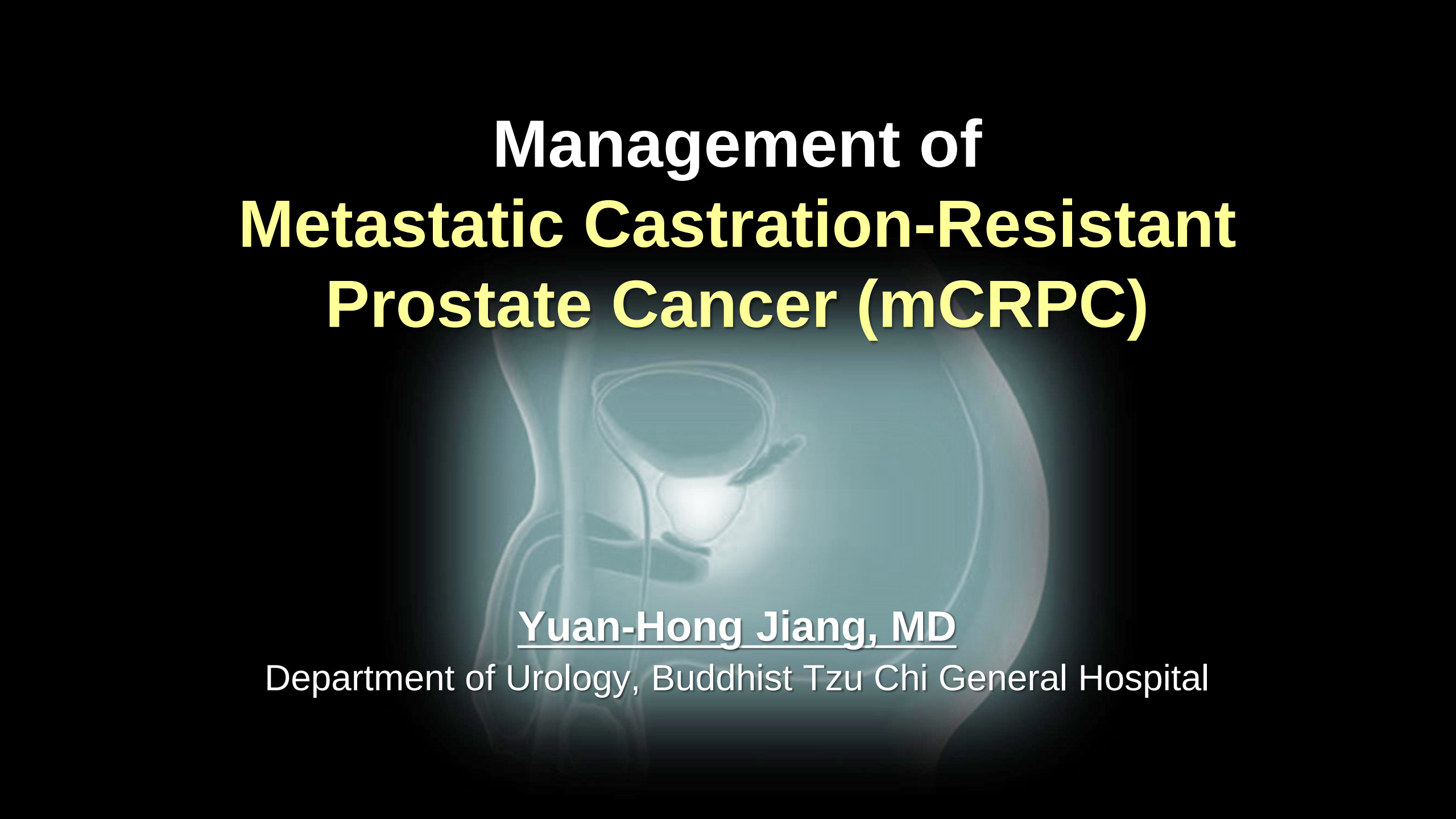
Management of Metastatic Castration-Resistant Prostate Cancer (mCRPC)



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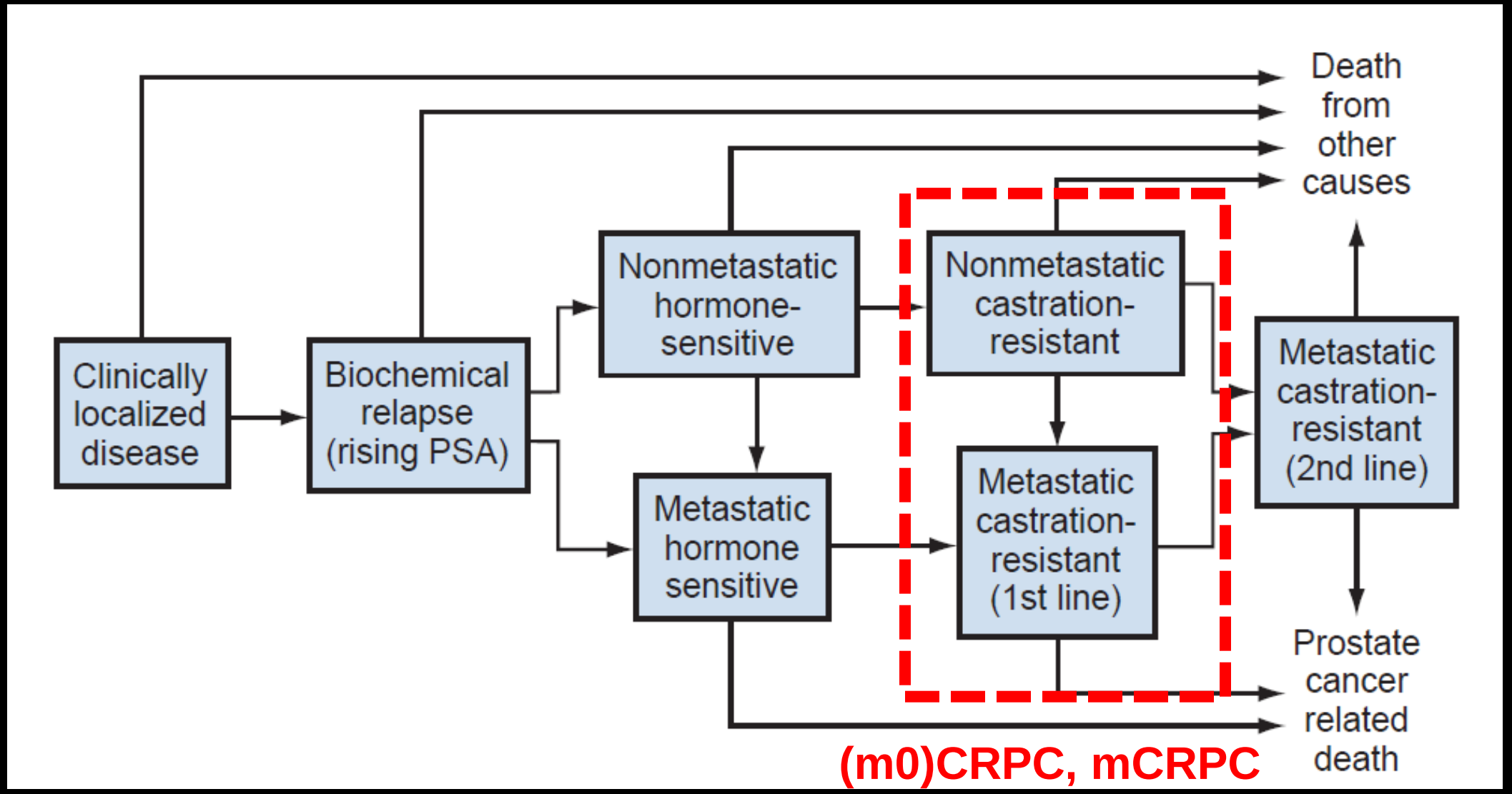
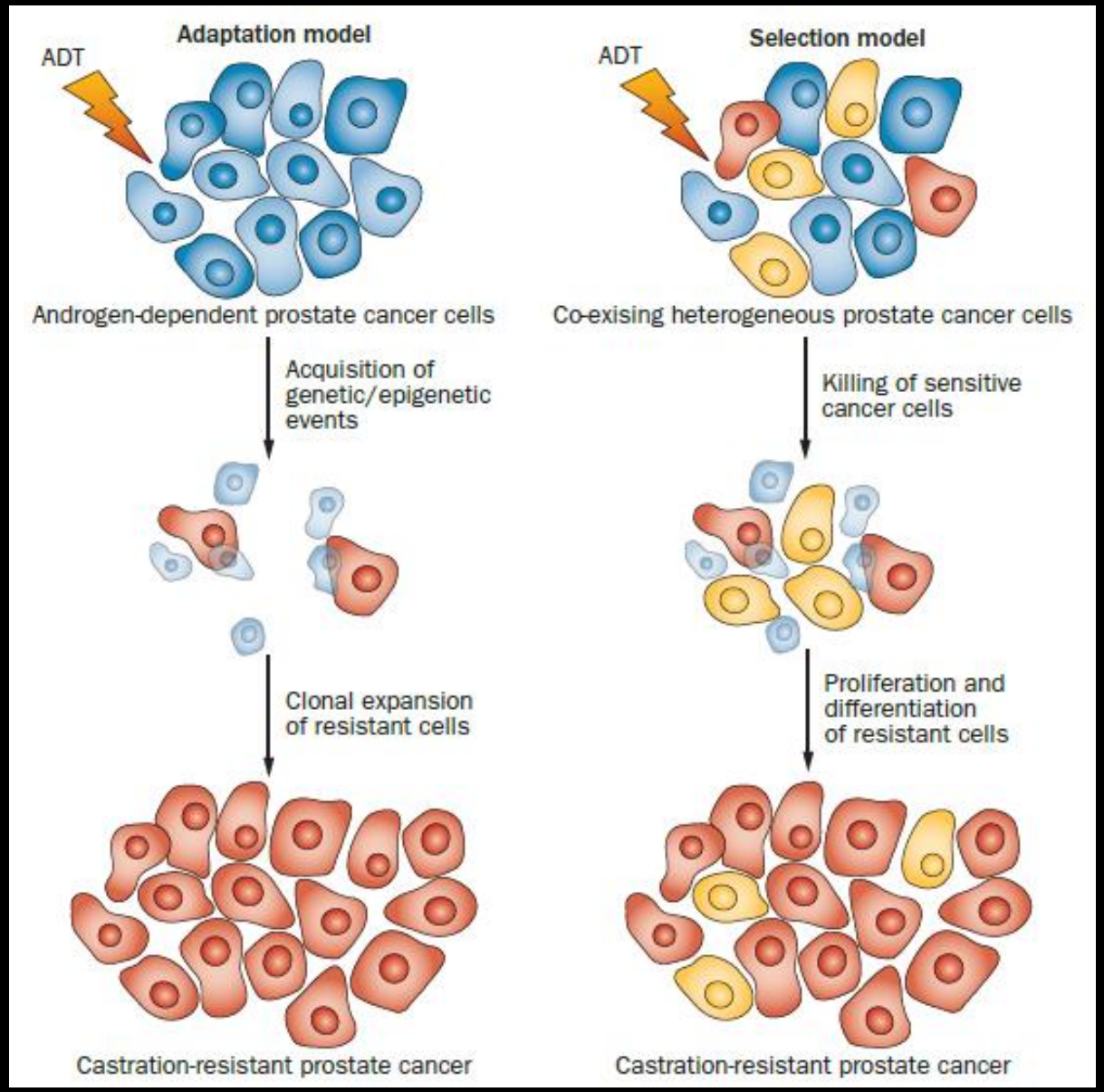
Clinical Stage of Prostate Cancer



Adaptation and Selection models of CRPC



Nat Rev Urol. 2013 Feb;10(2):90

Definition of CRPC

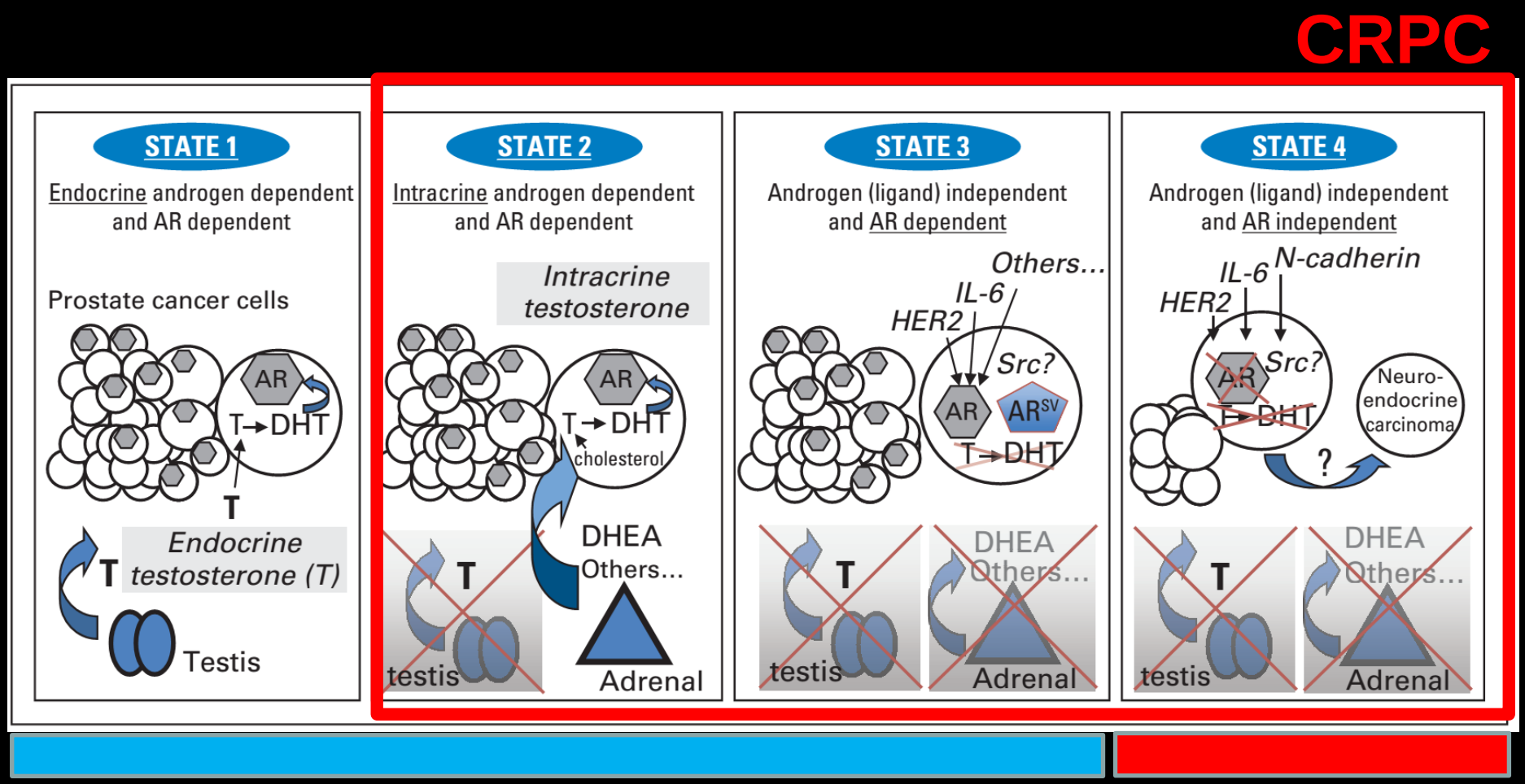
- **Castrate serum testosterone < 50 ng/dL** or 1.7 nmol/L **+** either

a. Biochemical progression: 3 consecutive rises in PSA one week apart resulting in two 50% increases over the nadir, and a PSA > 2 ng/mL or

b. Radiological progression: The appearance of new lesions: ≥ 2 new bone lesions on bone scan or a soft tissue lesion using RECIST (Response Evaluation Criteria in Solid Tumors)

*** Symptomatic progression alone: not sufficient** to diagnose CRPC

Four States of Prostate Cancer



* Intracrine: (synthesis) inside tumor cells

J Clin Oncol. 2012 Feb 20;30(6):644

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2022
Prostate Cancer

NCCN Guidelines Index
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Discussion

SYSTEMIC THERAPY FOR M1 CRPC[aaa]

CRPC, imaging studies positive for metastases

- Metastatic lesion biopsy[bbb]
- Tumor testing for MSI-H or dMMR and for homologous recombination gene mutations (HRRm), if not previously performed[c,ccc]
- Consider tumor mutational burden (TMB) testing[c]

- Continue ADT[t] to maintain castrate levels of serum testosterone (<50 ng/dL)
- Additional treatment options:
  - Bone antiresorptive therapy with denosumab (category 1, preferred) or zoledronic acid if bone metastases present
  - Palliative RT[o] for painful bone metastases
  - Best supportive care

Adenocarcinoma[bbb] → See PROS-15

Small cell/ neuroendocrine prostate cancer (NEPC)[bbb] →

First-line and subsequent treatment options[ddd]:
- Chemotherapy[yy,eee]
  - Cisplatin/etoposide
  - Carboplatin/etoposide
  - Docetaxel/carboplatin
  - Cabazitaxel/carboplatin[fff]
- Best supportive care

SYSTEMIC THERAPY FOR M1 CRPC: ADENOCARCINOMA[ddd,ggg,hhh]

No prior docetaxel/no prior novel hormone therapy[iii]

- Preferred regimens
  - Abiraterone[t,jjj] (category 1[kkk])
  - Docetaxel[yy,lll] (category 1)
  - Enzalutamide[t] (category 1)
- Useful in certain circumstances
  - Sipuleucel-T[yy,mmm] (category 1)
  - Radium-223[nnn] for symptomatic bone metastases (category 1)
- Other recommended regimens
  - Other secondary hormone therapy[t]

Prior novel hormone therapy/No prior docetaxel[iii,ooo]

- Preferred regimens
  - Docetaxel (category 1)[yy]
  - Sipuleucel-T[yy,mmm]
- Useful in certain circumstances
  - Olaparib for HRRm (category 1)[ppp]
  - Cabazitaxel/carboplatin[yy,fff]
  - Pembrolizumab for MSI-H, dMMR, or TMB ≥10 mut/Mb[yy]
  - Radium-223[nnn] for symptomatic bone metastases (category 1)
  - Rucaparib for BRCAm[qqq]
- Other recommended regimens
  - Abiraterone[t,jjj]
  - Abiraterone + dexamethasone[jjj,qqq]
  - Enzalutamide[t]
  - Other secondary hormone therapy[t]

Prior docetaxel/no prior novel hormone therapy[iii]

- Preferred regimens
  - Abiraterone[t,jjj] (category 1)
  - Cabazitaxel[yy]
  - Enzalutamide[t] (category 1)
- Useful in certain circumstances
  - Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies[yy]
  - Cabazitaxel/carboplatin[yy,fff]
  - Pembrolizumab for MSI-H, dMMR, or TMB ≥10 mut/Mb[yy]
  - Radium-223[nnn] for symptomatic bone metastases (category 1)
- Other recommended regimens
  - Sipuleucel-T[yy,mmm]
  - Other secondary hormone therapy[t]

Prior docetaxel and prior novel hormone therapy[iii,ooo]

(All systemic therapies are category 2B if visceral metastases are present)

- Preferred regimens
  - Cabazitaxel[yy] (category 1[kkk])
  - Docetaxel rechallenge[yy]
- Useful in certain circumstances
  - Olaparib for HRRm (category 1[kkk])[ppp]
  - Cabazitaxel/carboplatin[yy,fff]
  - Pembrolizumab for MSI-H, dMMR, or TMB ≥10 mut/Mb[yy]
  - Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies[yy]
  - Radium-223[nnn] for symptomatic bone metastases (category 1[kkk])
  - Rucaparib for BRCAm[qqq]
- Other recommended regimens
  - Abiraterone[t,jjj]
  - Enzalutamide[t]
  - Other secondary hormone therapy[t]

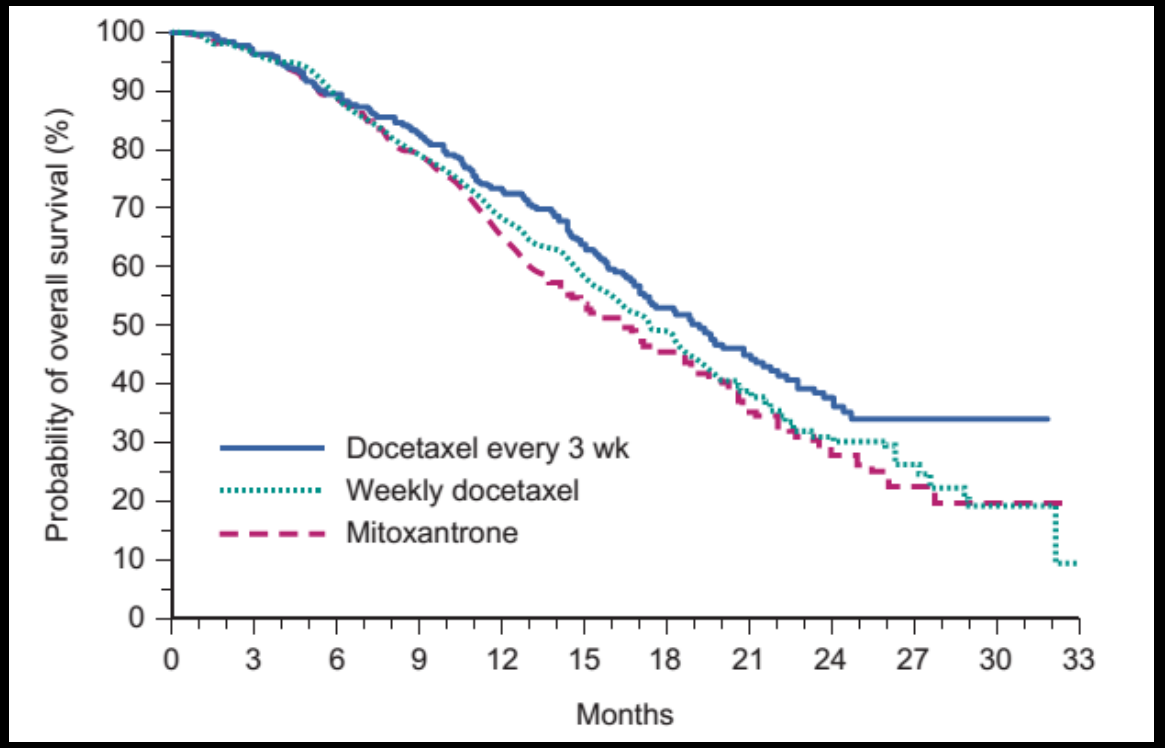
FDA-Approved Agents for mCRPC

- **Androgen receptor "targeting"**
  - Abiraterone (2011), enzalutamide (2012)
- **Cytotoxics**
  - Docetaxel (2004), cabazitaxel (2010), mitoxantrone (1996), estramustine (1981)
- **Immunotherapy**
  - Sipuleucel-T (2010)
  - Pembrolizumab (2017)
- **Radiopharmaceuticals**
  - Radium-223 (2013)
- **PARP inhibitors**
  - Olaparib (2020), rucaparib (2020)

1st line treatmenet for mCRPC

- **Docetaxel:** chemotherapy, cytotoxic agent,
  conventional standard treatment
- **Abiraterone** (pre-chemotherapy): inhibition of androgen synthesis
- **Enzalutamide** (pre-chemotherapy): 2nd Anti-androgen agent
- **Sipuleucel-T**

Docetaxel to treat mCRPC



- TAX 327 study: **Docetaxel 75mg/m2 Q3W x 6 cycles**
  - ↑ median OS 2-2.9 mo; ↓pain ; ↑ QoL
  - Pain/ PSA responder rate: 35% / 45%
  - **AE: myelosuppression (neutropenia),** fatigue, peripheral edema, neurotoxicity, hyperlacrimation, and nail dystrophy

Docetaxel to treat mCRPC

- **Independent prognostic factors** to stratify response to docetaxel:
  - Visceral metastases / pain
  - Anaemia (Hb < 13 g/dL)
  - Bone scan progression
  - Prior estramustine therapy

→ low risk (0 or 1 factor), median OS **25.7mo**

→ intermediate (2 factors), median OS **18.7mo**

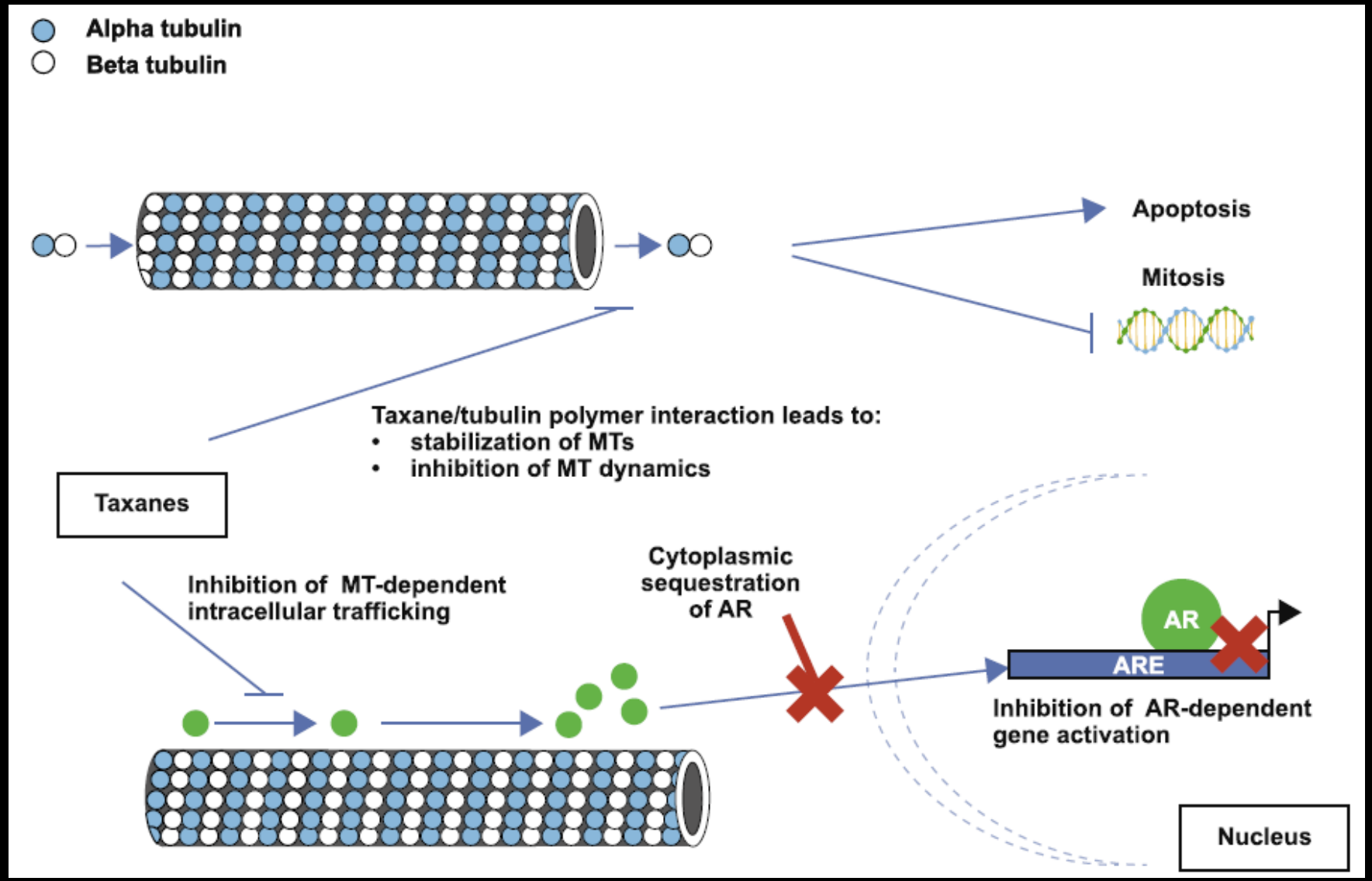
→ high risk (3 or 4 factors), median OS **12.8 mo**

→ If unable to tolerate,

changed regimen: **50mg/m2 Q2W x 9 cycles** (60mg/m2 Q3W x 6 cycles)

(similar efficacy, less Gr3-4 AE)

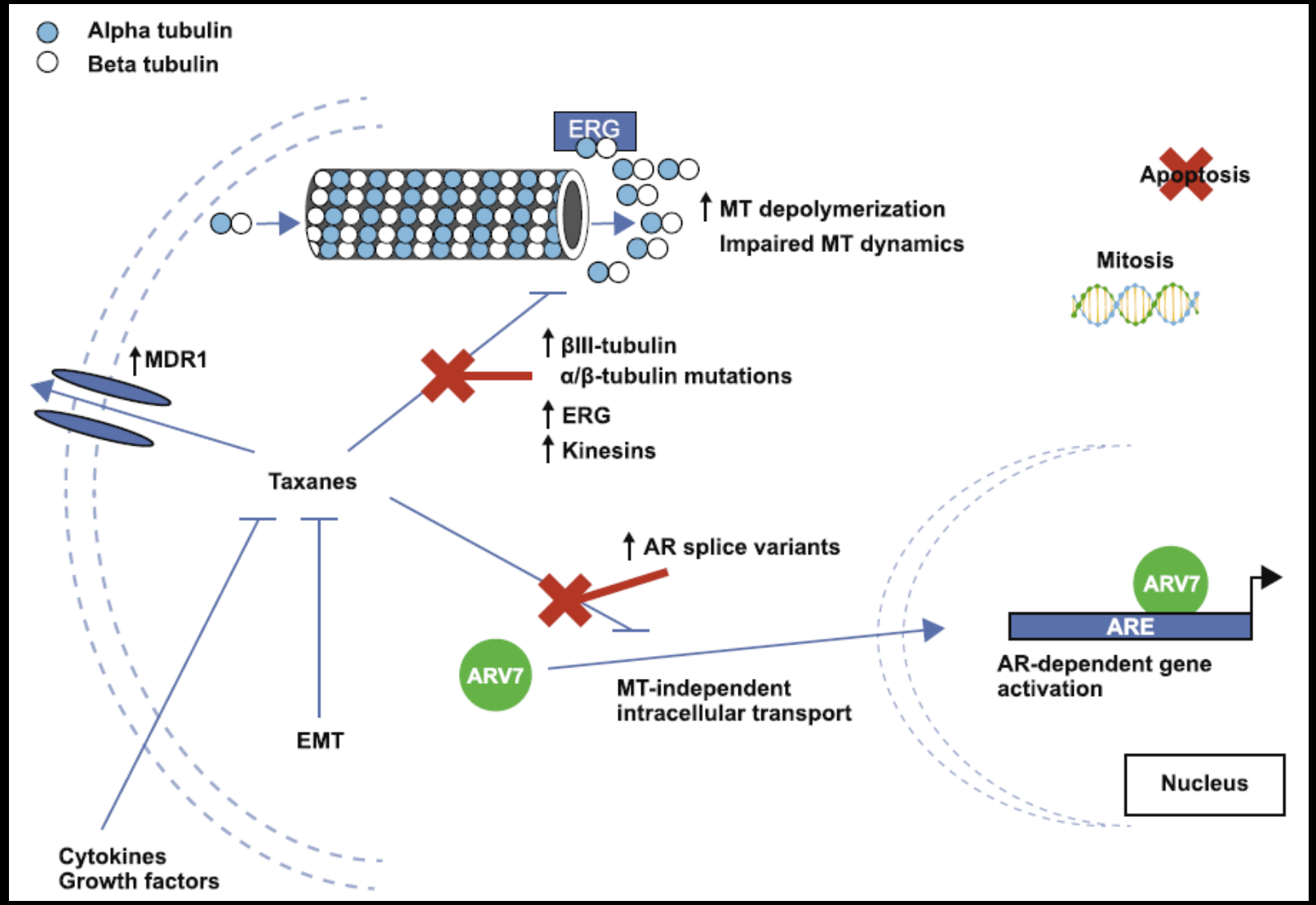
Taxane chemotherapy in mCRPC



Cancer Treat Rev. 2017 Jun;57:16

Taxane chemotherapy in mCRPC

Resistance mechanisms



Cancer Treat Rev. 2017 Jun;57:16

Mechanisms of resistance to chemotherapy in prostate cancer.

1. Multidrug resistance (MDR) phenotype [98,101–103]

MDR genes are overexpressed in prostate cancer. These molecular pumps lower intracellular taxane concentrations. Cabazitaxel is less sensitive to the MDR resistance phenotype versus docetaxel. ABCB1 expression is correlated with tumor grade, stage and PSA levels.

2. Tubulin alterations [106–110]

Elevated expression of βIII-tubulin leads to taxane resistance; βIII-tubulin-containing microtubules are less stable and exhibit aberrant dynamicity. Docetaxel-treated CRPC patients who are positive for βIII-tubulin expression have a worse prognosis compared with βIII-tubulin-negative patients. Mutations in α-tubulin and β-tubulin can impair docetaxel-induced polymerization of tubulin.

3. ERG rearrangements [42,111]

As a result of gene fusions with the 5′ promoter of AR-driven genes, the ERG transcription factor is overexpressed in over 50% of prostate cancers. ERG interacts with tubulin, suggesting an extra-nuclear function. An ERG-tubulin interaction affects microtubule dynamics, leading to increased cellular catastrophe and resistance to taxane treatment.

4. Kinesins [115–117]

The kinesin family of motor proteins (e.g. MCAK) interact with microtubules, and have been associated with resistance to taxanes.

5. AR splice variants (AR-Vs) [15,19,20,119,120]

AR-Vs are overexpressed in prostate cancer. ARv567 requires dynamic microtubules for nuclear transportation. Docetaxel treatment is highly efficacious in ARv567-expressing tumor xenografts. AR-V7 can function independently of microtubules, but there are conflicting data regarding AR-V7 as a biomarker for taxane resistance.

6. Cytokines/inflammation [123,124]

Docetaxel treatment has been associated with inflammation and increased cytokine expression in prostate cancer cell lines. Resistance to docetaxel may develop as a consequence of increased CCL2 expression, which activates the PI3K/AKT signaling pathway and promotes cell survival.

7. Growth factors and intracellular pathways [127–129]

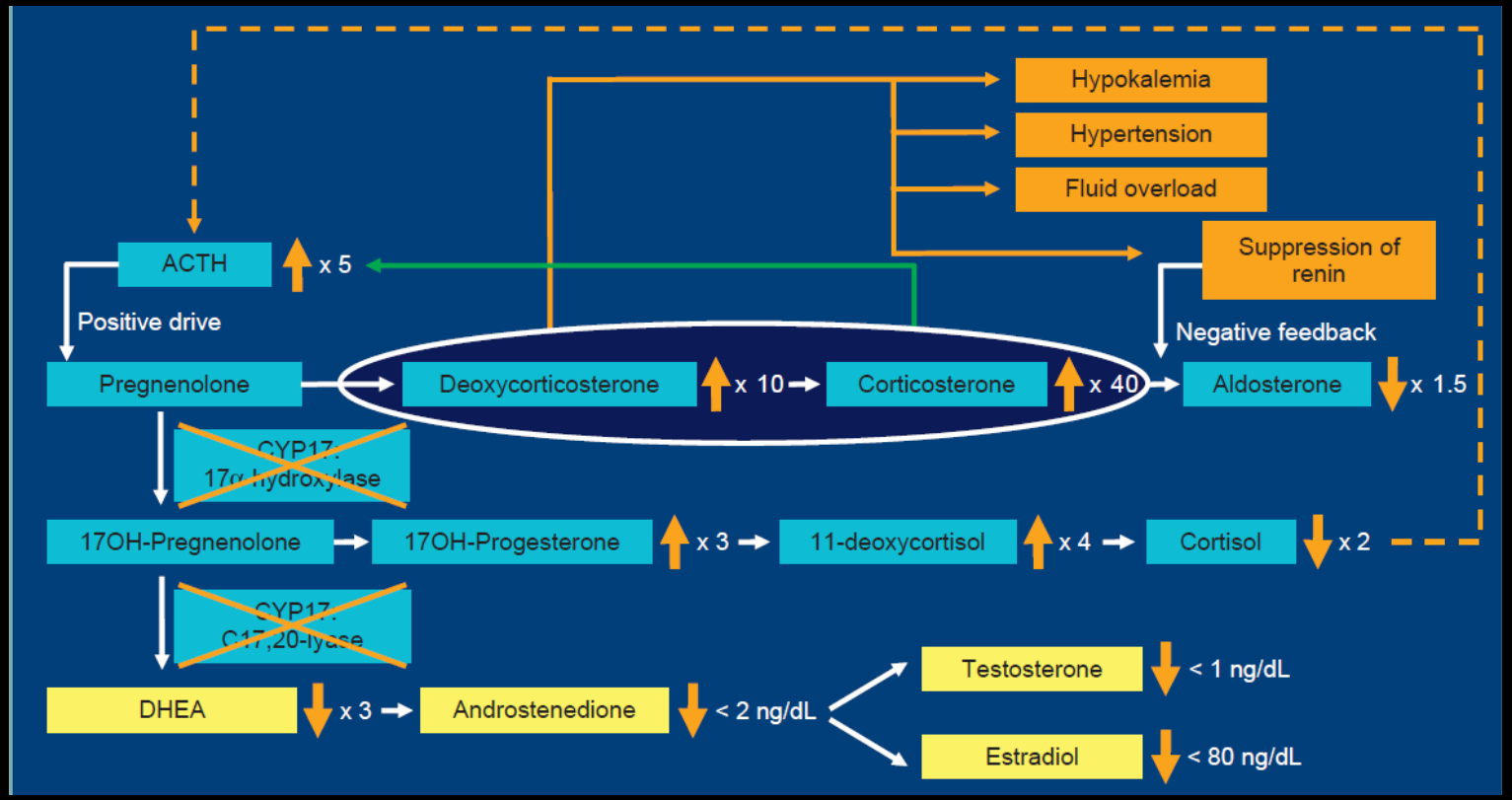
Deregulation of growth factors and downstream intracellular pathways has been associated with resistance to chemotherapy in solid tumors. The growth factor IGF-2 is upregulated by GATA2, which in turn activates the PI3K/AKT and ERK1/2 pathways and induction of cell survival and resistance to chemotherapy. The Notch and Hedgehog pathways may also have a role in the development of resistance to taxanes.

8. Epithelial-mesenchymal transition [130,131]

Epithelial-mesenchymal transition contributes to docetaxel resistance in prostate cancer cells. The resistance mechanism might involve reduced expression of the microRNAs miR-200c and miR-205.

AR, androgen receptor; ERG, ETS-related gene; PSA, prostate specific antigen; CRPC, castration-resistant prostate cancer; MCAK, mitotic centromere-associated kinesin.

Mechanism actions of **Abiraterone**



* Abiraterone acetate (AA):
a CYP17 inhibitor (17α-hydrolase and 17,20-lyase inhibition)
→ secondary mineralocorticoid excess: hypokalemia, hypertension, pedal edema

* Sites of Actions:
- Adrenal gland
- Intra-tumor: overexpression of CYP17 has been demonstrated in tumors of men with CRPC (intracrine)

Abiraterone to treat mCRPC

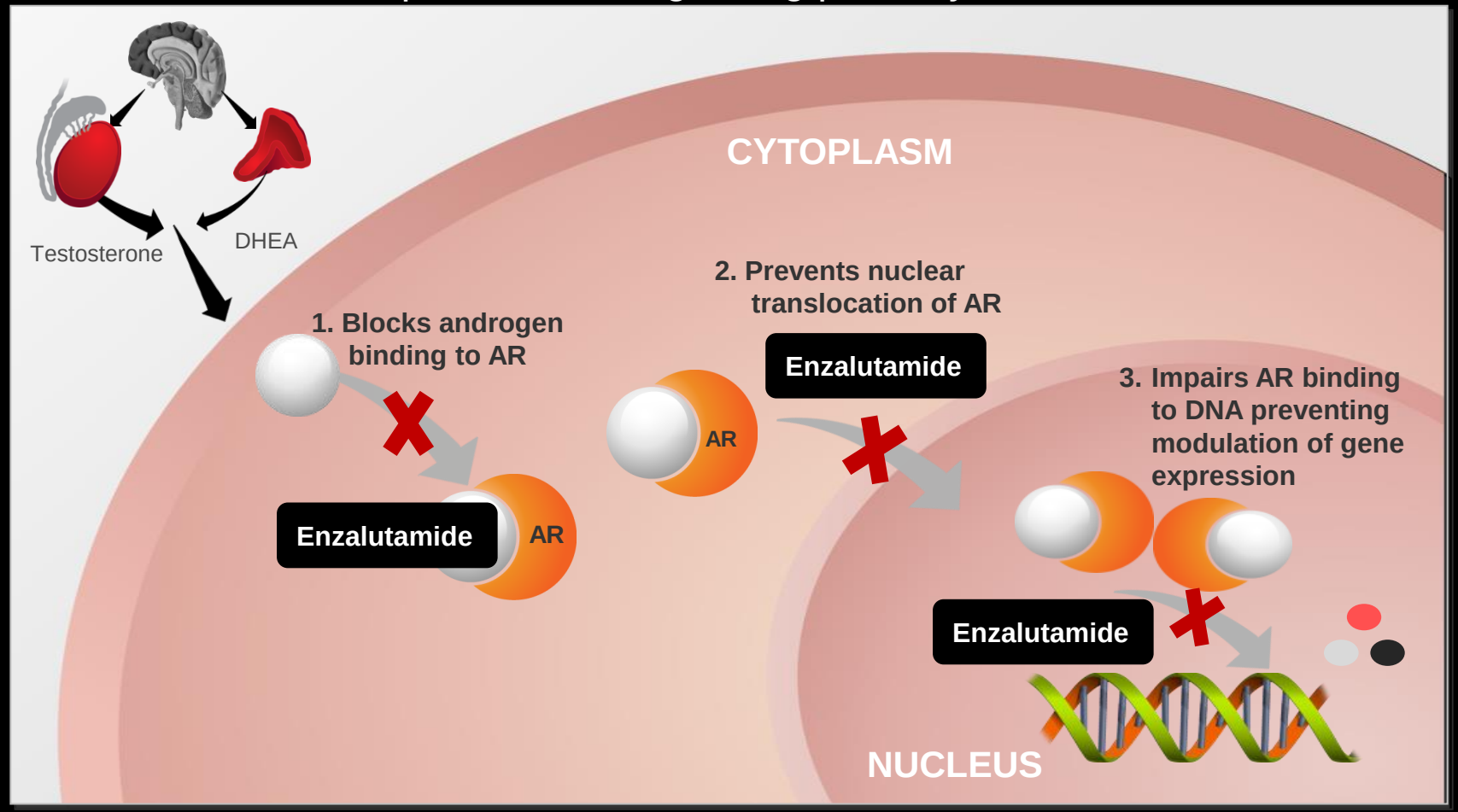
- To treat **chemo-naïve mCRPC** (COU-AA-302 study)
  - OS: 34.7 vs. 30.3 mo (HR: 0.81 p =0.0033).
  - radiologic PFS: 16.5 vs. 8.3 mo ($p < 0.0001$)
  - AE: mineralocorticoid excess and liver function abnormalities (mostly Gr.1-2)

- To treat **post-chemotherapy mCRPC** (COU-AA-301 study)
  - OS: 14.8 vs. 10.9 mo (HR: 0.65, $p<0.001$)
  - radiologic PFS: 5.6 vs. 3.6 mo
  - AE: mineralocorticoid excess and liver function abnormalities (mostly Gr.1-2)

Mechanism actions of **Enzalutamide**

Androgen Receptor Signaling Inhibitor

- Enzalutamide directly targets the AR and exerts its effects on three essential steps in the AR signalling pathway[1,2]



AR=androgen receptor; DHEA=dehydroepiandrosterone; DHT=dihydrotestosterone.

1. Tran C, *et al. Science* 2009;324:787–90; 2. Hu R, *et al. Expert Rev Endocrinol Metab* 2010;5:753–64

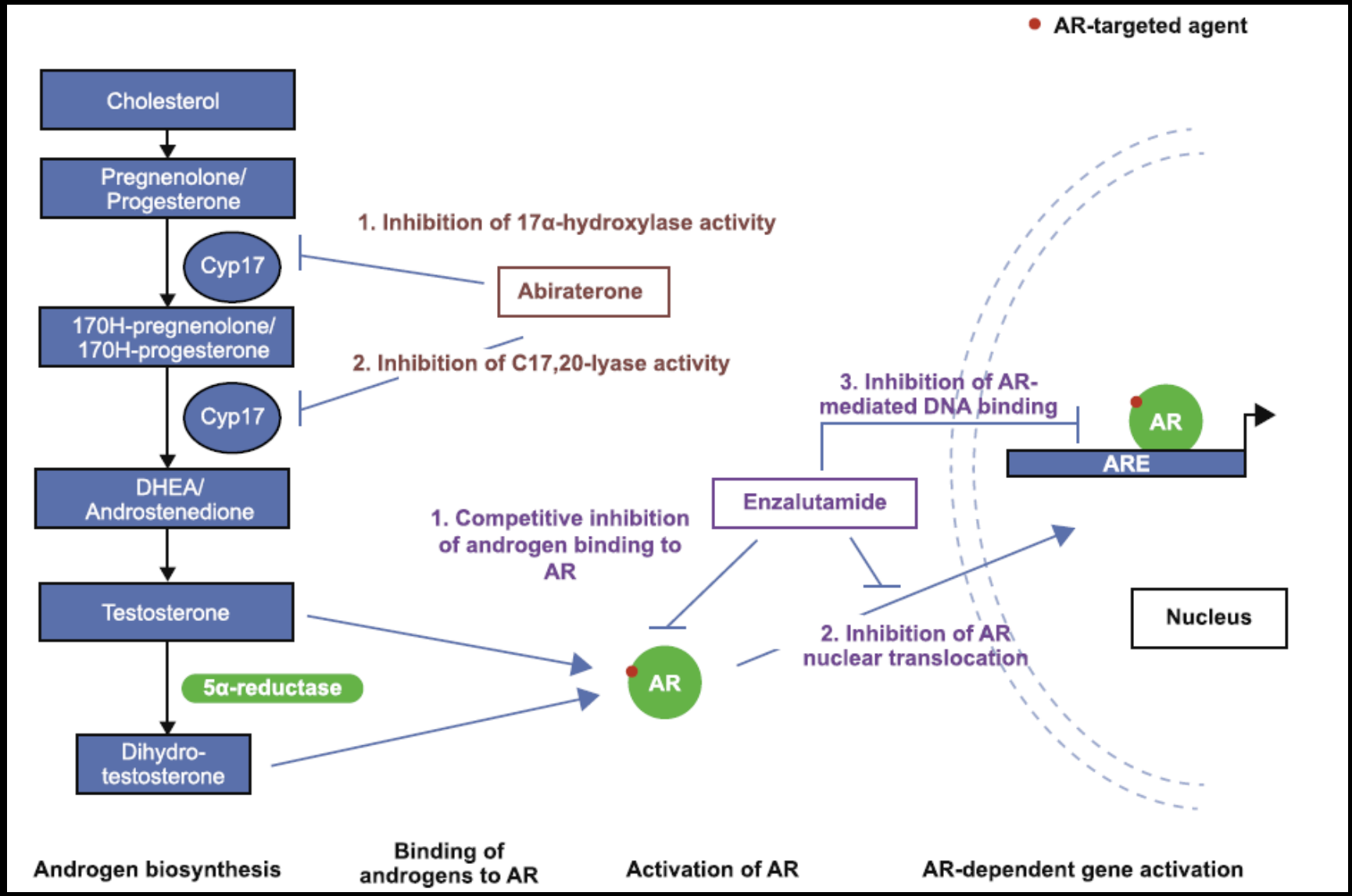
Enzalutamide to treat mCRPC

- To treat **chemo-naïve mCRPC** (PREVAIL study)
  - OS: 32.4 vs. 30.2 mo (HR: 0.71, p<0.001)
  - rPFS: 20.0 vs. 5.4 mo (HR: 0.186, p < 0.0001)
  - ≥ 50% decrease in PSA: 78% pts
  - **Well-tolerated & effective in elderly(>75yr) and visceral meta!**
  - AE: fatigue and hypertension

- To treat **post-chemotherapy mCRPC** (AFFIRM study)
  - OS: 18.4 vs. 13.6 mo. (HR: 0.63, p<0.001)
  - radiologic PFS: 8.3 vs. 2.9 mo (HR: 0.40, p<0.001)
  - AE: fatigue and hypertension, lower incidence of Gr.3-4AE;

    0.6% incidence of seizure

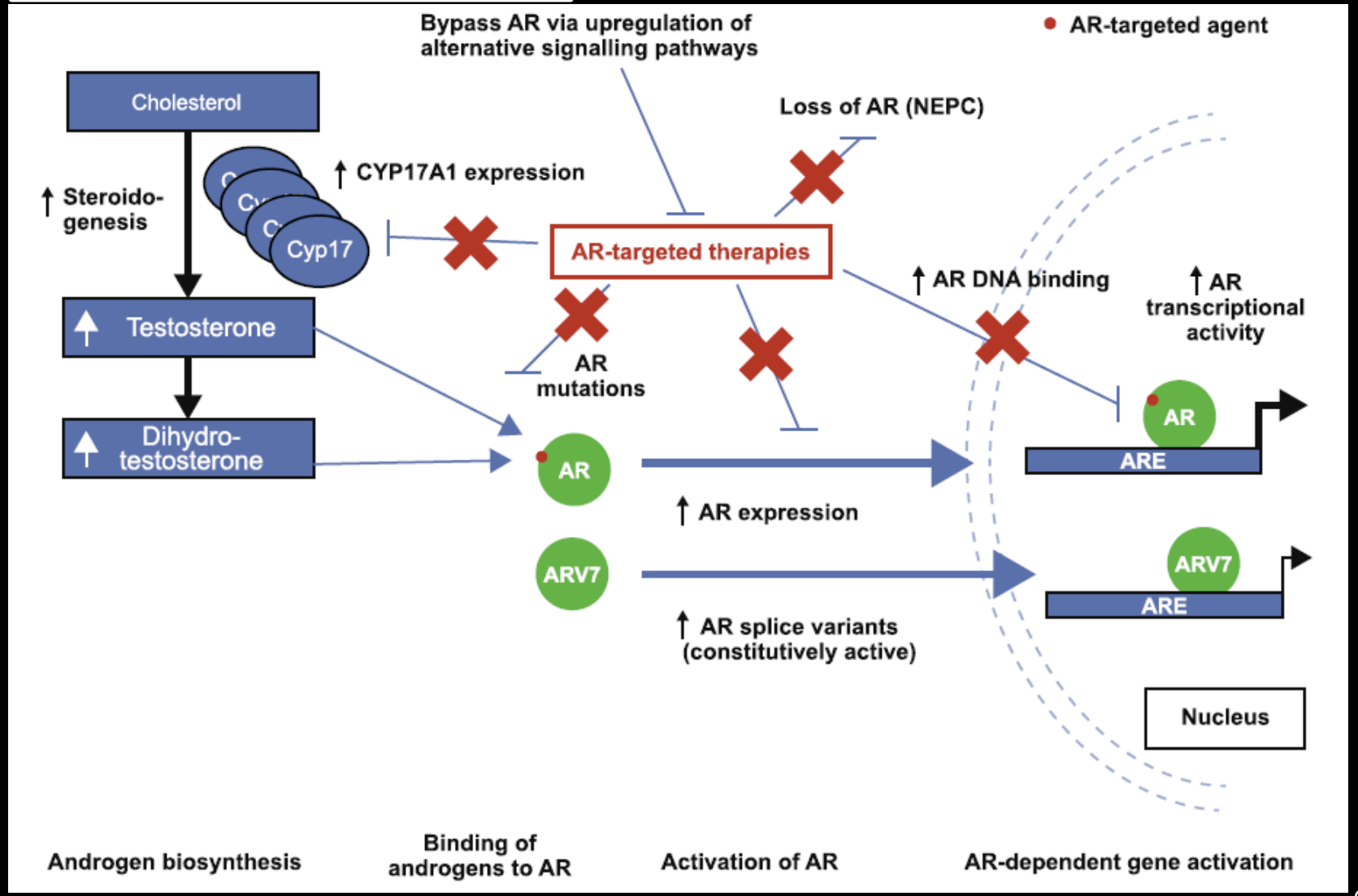
AR-targeted therapies in mCRPC



Cancer Treat Rev. 2017 Jun;57:16

AR-targeted therapies in mCRPC

Resistance mechanisms



Cancer Treat Rev. 2017 Jun;57:16

Mechanisms of resistance to AR-targeted therapy in prostate cancer.

1. AR splice variants (AR-Vs) [12,13,18,21,22,24–26]

AR-Vs lack a ligand binding domain leading to constitutive activity in the absence of ligands and ligand-independent AR signaling. AR-V7 or ARv567es form dimers with full-length AR, facilitating AR nuclear localization, and decreasing the ability of therapies to inhibit nuclear trafficking. ARv567es confers resistance to enzalutamide, and AR-V7 confers resistance to abiraterone and enzalutamide.

2. AR overexpression [27–30]

AR overexpression increases AR responses to the low androgen level in the CRPC state, and can be caused by AR gain or amplification. Common in CRPC: 80% of patients have an elevated gene copy number and approx. 30% have high-level amplification. May play more of a role in resistance to enzalutamide versus abiraterone.

3. Increased AR transcriptional activity [31–34,36,37]

Phosphorylation, ubiquitylation, and methylation of the AR can enhance AR transcriptional activity. May mediate resistance to both enzalutamide and abiraterone.

4. Stabilization of the AR [38–41]

AR antagonists work, in part, by preventing stabilization of the AR-DNA complex. Some proteins mediating stabilization of the AR may be overexpressed at low androgen levels. HER2 and HER3 have been implicated in the stabilization of the AR and increasing AR-DNA binding, and low androgen levels increase HER2 expression. May mediate resistance to enzalutamide and abiraterone.

5. ERG gene rearrangements [43,47]

Up to 70% of mCRPCs overexpress ERG, and TMPRSS2-ERG is a marker of advanced disease. ERG gene rearrangements may confer resistance via upregulation of AKR1C3 which mediates increased androgen synthesis. Implicated in resistance to abiraterone.

6. AR mutations [48,50–52,54,56]

Mutations in exon 8 alter the steroid binding pockets of the AR, allowing AR antagonists to take on an agonist confirmation. F876L mutation confers resistance to enzalutamide and ARN-509 by converting these agents into partial agonists. T877A mutation has been associated with resistance to abiraterone.

7. Increased steroidogenesis [13,55,58,59]

After ADT, increased intratumoral synthesis of testosterone and DHT from weak androgens produced by the adrenal glands, and possible *de novo* synthesis from cholesterol, can cause AR reactivation. mCRPC shifts from being endocrine-driven to paracrine-driven. Abiraterone treatment selects for cells that have increased intratumoral expression of CYP17A1, and are therefore able to synthesize androgens *de novo*.

8. Alternate signal transduction pathways [25,63,64,68]

Resistance to AR-targeted agents in prostate cancer cells may be mediated by activation of alternative signaling pathways that trigger cell survival and proliferation, such as NF-kB, PI3K-AKT, and glucocorticoid receptor.

9. Loss of AR: small cell and neuroendocrine carcinoma of the prostate [70–72]

NEPC may be linked with resistance to AR inhibition. Neuroendocrine cells normally regulate growth, differentiation and secretion in the prostate and these cells lack expression of the AR. A subset of patients with loss of AR expression may be resistant to AR-targeted therapy.

ADT, androgen deprivation therapy; AR, androgen receptor; CRPC, castration-resistant prostate cancer; DHT, dihydrotestosterone; ERG, ETS-related gene; mCRPC, metastatic castration-resistant prostate cancer; NEPC, neuroendocrine carcinoma of the prostate.

Sipuleucel-T to treat mCRPC

- **Immunotherapy**
- Sipuleucel-T (Provenge):

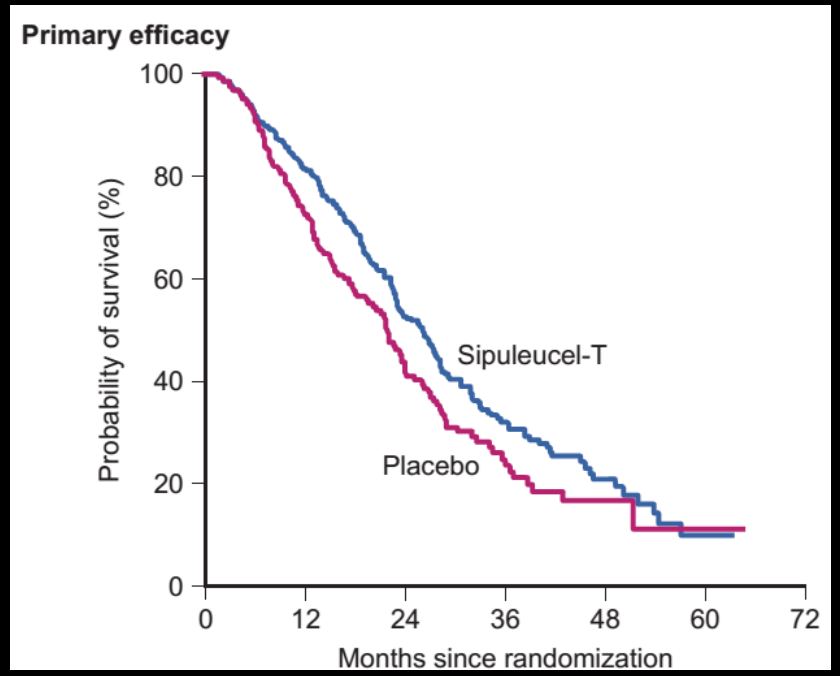
a personalized vaccine that is derived from autologous CD54+dendritic cells, the major class of antigen-presenting cells, which are apheresed from individuals and processed with a recombinant fusion protein composed of PAP (Prostatic acid phosphatase) and GM-CSF.

- **Limitations:**
  - asymptomatic/ minimal symptomatic
  - **NO** liver metastasis
  - Life expectancy >6mo
  - ECOG: 0-1

Sipuleucel-T to treat mCRPC

- IMPACT study (NEJM 2010; 363:411)
  - OS: **25.8** vs. 21.7 mo (HR: 0.78, p=0.03)
  - PFS: 3.7 vs. 3.6 mo. (no difference)
  - Good tolerance
  - **More Gr. 1-2 AE: cytokine-reated**
    - milld-to moderate chills 57.1%
    - Pyrexia 29.3%
    - Headache 16.0%

  (similar Gr. 3-4 AE to control)

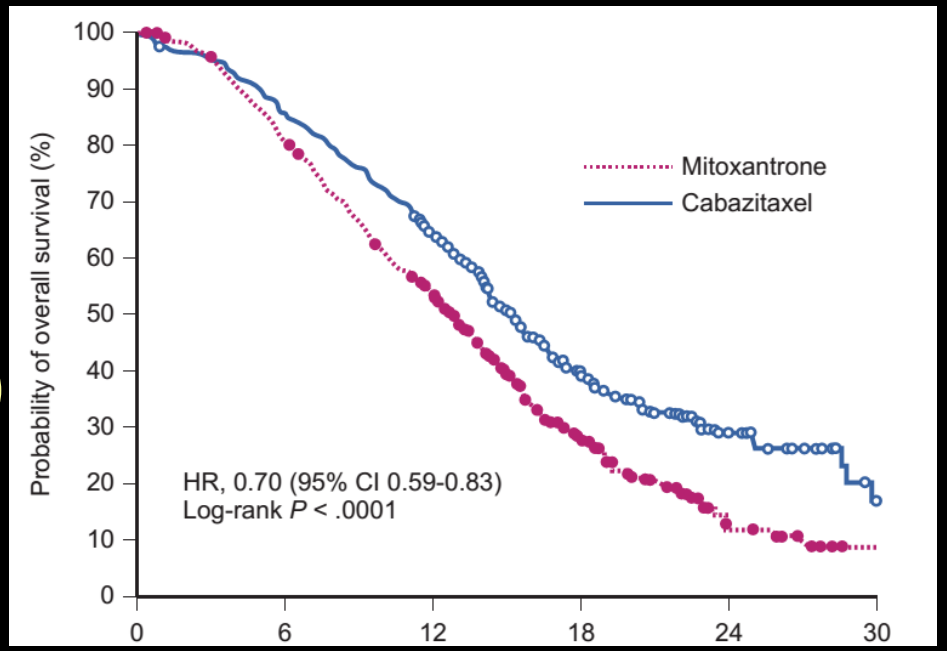


Cabazitaxel to treat mCRPC

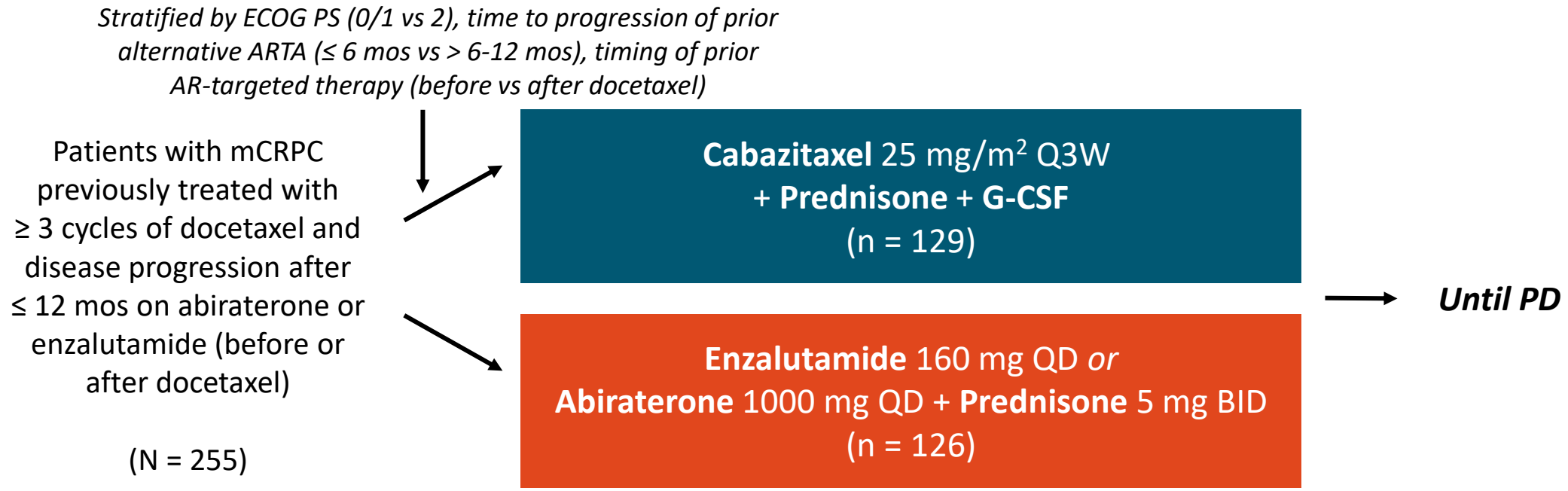
- A semi-synthetic **taxane** derivative
- International phase 3 RCT (TROPIC) to treat
  progressive mCRPC after docetaxel treatment
  - 25mg/m2 Q3W x 10 cycles
  - OS: **15.1** VS 12.7 mo (p<0.0001)
  - PFS: 2.8 VS 1.4 mo (p<0.0001)
  - PSA response rate:

  39.2% VS 17.8% (p<0.0002)
  - **Gr.3-4 AE:**

  haematological (68.2%),
  non-haematological (57.4%)
  → Prophylactic G-CSF



CARD Trial: Phase IV Trial of Cabazitaxel vs Abiraterone or Enzalutamide in Previously Treated mCRPC

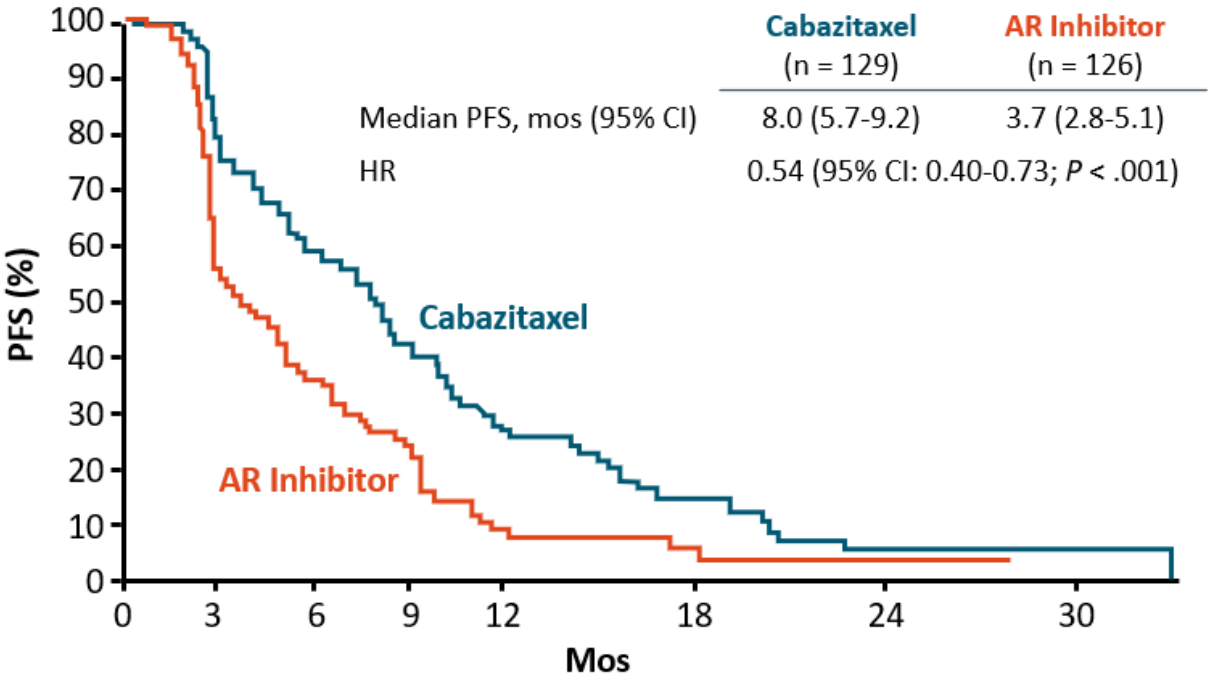


- Primary endpoint: imaging-based PFS
- Secondary endpoint: OS, PFS, PSA response, tumor response, time to SSE, pain response, and safety

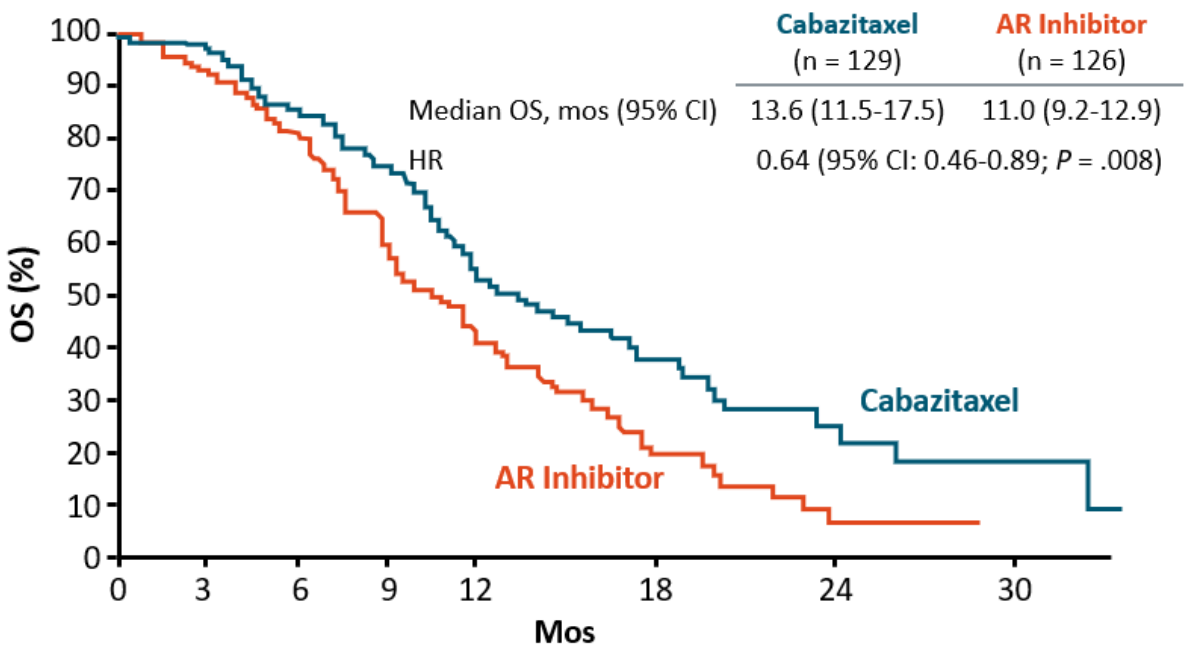
de Wit. NEJM. 2019;381:2506.

CARD trial

Imaging-Based PFS

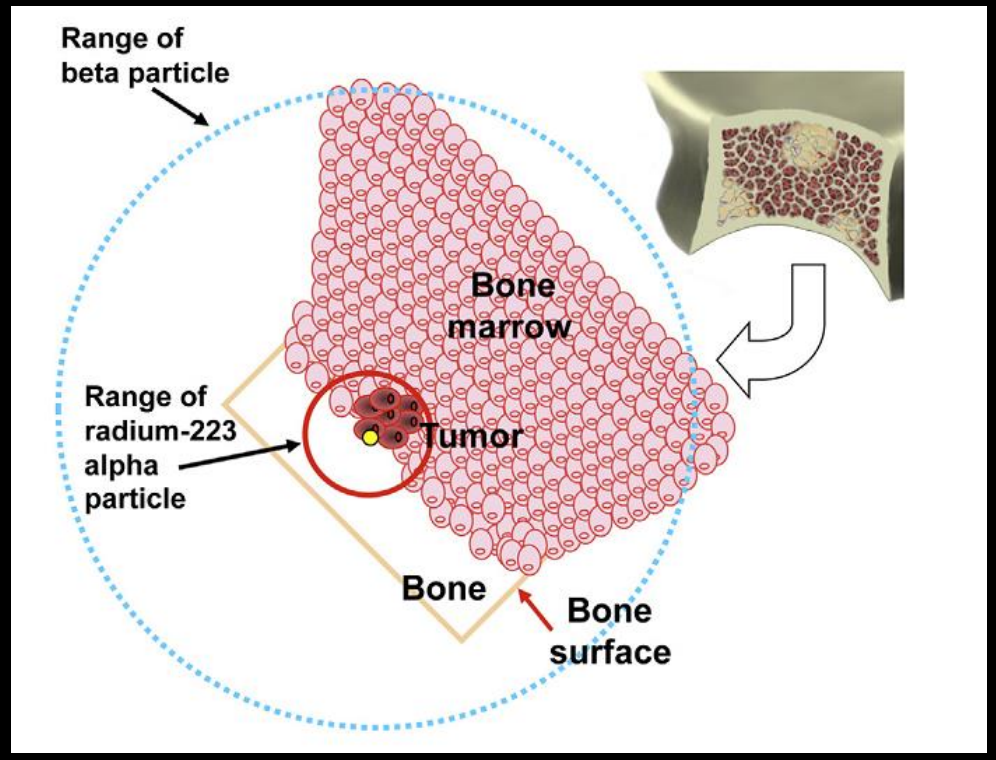


OS



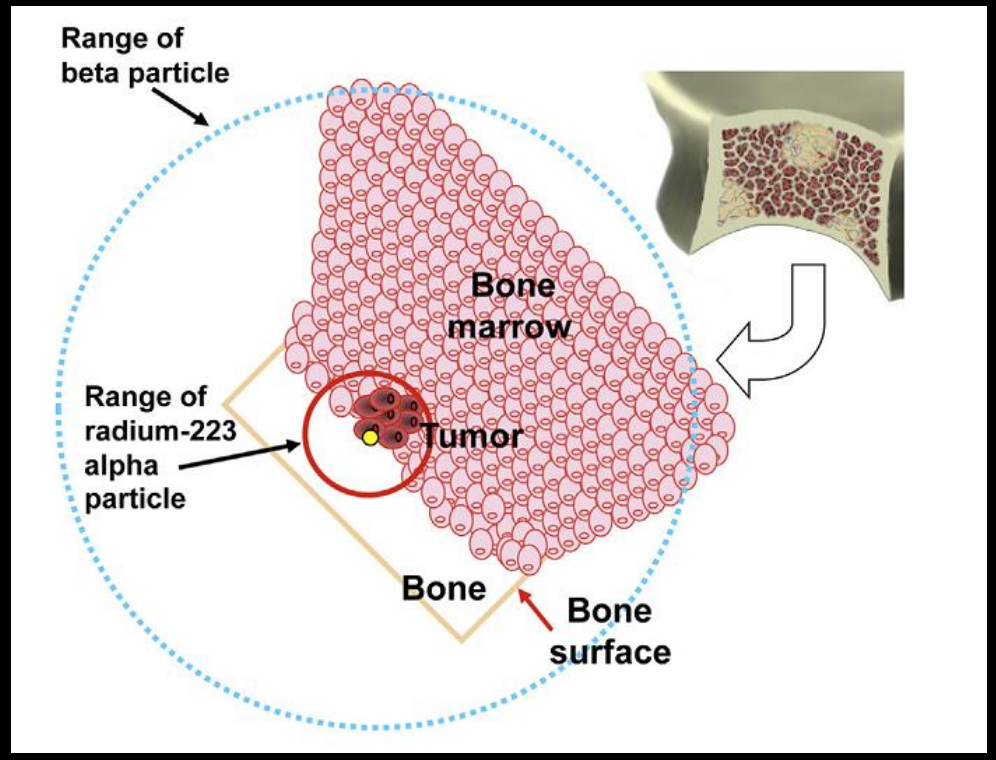
de Wit. NEJM. 2019;381:2506.

Mechanism actions of **Radium-223**



- Radium-223: **an alpha-emitting radiopharmaceutical**, mimics calcium in forming complexes with the bone mineral hydroxyapatite, which specifically targets bone metastases

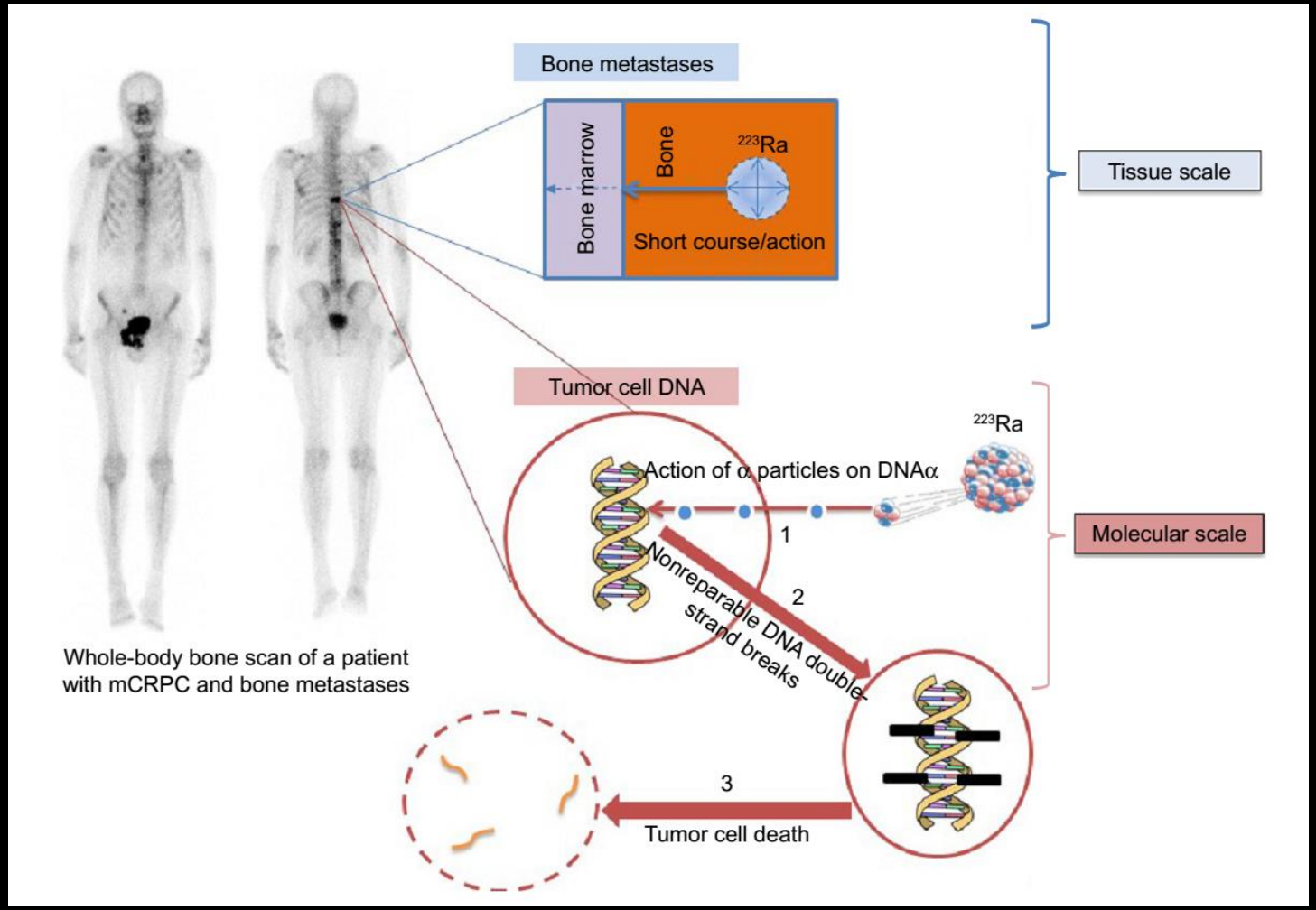
Mechanism actions of **Radium-223**



→ emitting alpha particles within the tumor microenvironment
effective range of <100 mm (2-10 cell diameters)

→ **low impact on myeloproliferative tissue**, thereby minimizing myelosuppression-associated AEs
(Gr.3-4: neutropenia 2%, thrombocytopenia 3%, anemia 6%)

Mechanism actions of **Radium-223**



- Current role: **mCRPC** with **symptomatic bone** metastasis,
  without visceral meta ! (chemo-naïve or post-chemotherapy)

Ra-223 to treat mCRPC

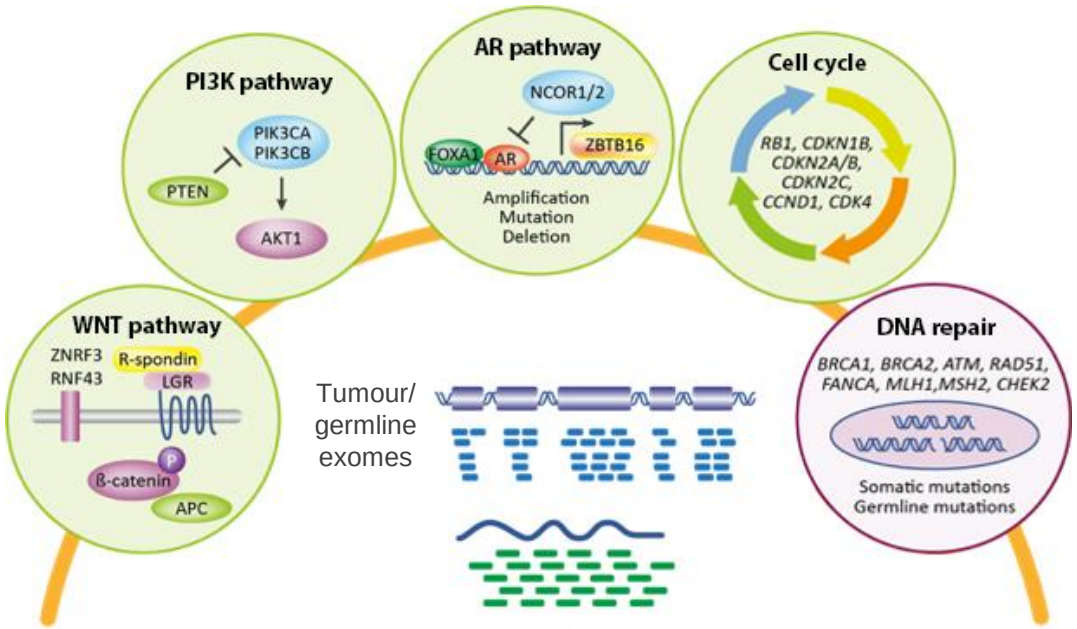
Table 1 ^{223}Ra efficacy in metastatic castration-resistant prostate cancer

Trial type	Design	Population	Previous treatment (% of patients)	PSA response	ALP response	OS
Phase II[35] N=100	Four arms: 5 kBq/kg 25 kBq/kg/6 w 50 kBq/kg/6 w 100 kBq/kg/6 w (single injection)	mCRPC with symptomatic bone metastases	Docetaxel (36) Bicalutamide (63) Estramustine (17)	NR	NR	NR
Phase II[28] N=122	Three arms: 25 kBq/kg/6 w 50 kBq/kg/6 w 80 kBq/kg/6 w (up to six injections)	mCRPC with bone metastases	Docetaxel (20) Anti-androgens (>92)	Decrease >30% at 24 w: 16%	Decrease >50% at 24 w: 50%	NR
Phase III[29] N=921	Placebo vs 50 kBq/kg/6 w ^{223}Ra (up to six injections)	mCRPC with symptomatic bone metastases, without visceral metastases	Docetaxel (57)	Decrease >30% at 12 w:16% vs 6%, $P<0.001$ Median time to PSA progression: HR =0.64; 95% CI 0.54–0.77; $P<0.001$	Decrease >30% at 4 w: 47% vs 3%, $P<0.001$ Median time to ALP progression: HR =0.17; 95% CI 0.13–0.22; $P<0.001$	14.9 mo vs 11.6 mo HR =0.70; 95% CI 0.58–0.83 $P<0.001$
Phase III-b[32] N=696	50 or 55 kBq/kg/6 w ^{223}Ra (up to six injections) 27% received concomitantly AA/Enza	mCRPC with asymptomatic or symptomatic bone metastases, without visceral metastases	Docetaxel (60) AA (40) Enza (8)	Decrease >30% at 12 w: 14%	Decrease >30%: 47%	16 mo
Retrospective study[33] N=144	^{223}Ra up to six injections	mCRPC with bone metastases	Chemotherapy (55) AA and/or Enza (46.5)	Decrease >50% from baseline: 14% (n=18/128)	Decrease >50% from baseline: 23% (n=16/70)	15.7 mo
Retrospective study[33] N=58	^{223}Ra up to six injections	mCRPC with bone metastases	Docetaxel (52)	Median PSA increase from baseline: (225 vs 418)	Median ALP decrease from baseline: (292 vs 138)	8.33 mo

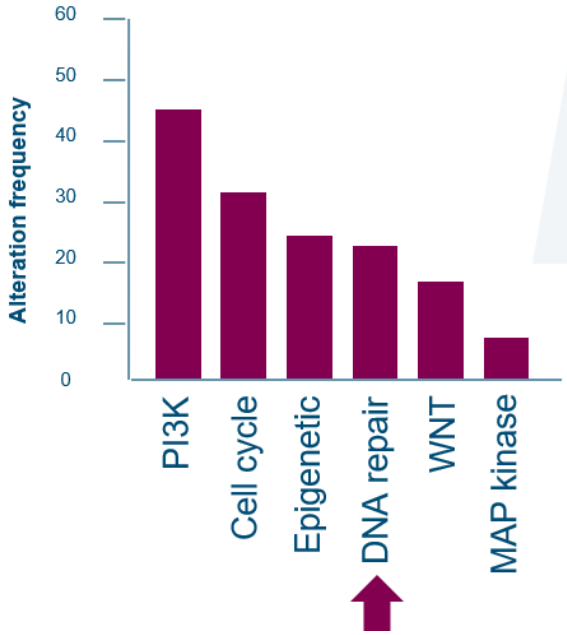
Abbreviations: AA, abiraterone acetate; ALP, alkaline phosphatase; Enza, enzalutamide; mCRPC, metastatic castration-resistant prostate cancer; mo, months; NR, not reported; ^{233}Ra, radium-223; OS, overall survival; PSA, prostate-specific antigen; w, weeks.

Metastatic prostate cancer is biologically heterogeneous

- Multiple pathways have been identified with genomic alterations in association with advanced prostate cancer[1]



- Approximately 25% of patients with mCRPC have alterations associated with DNA repair pathways*[2]



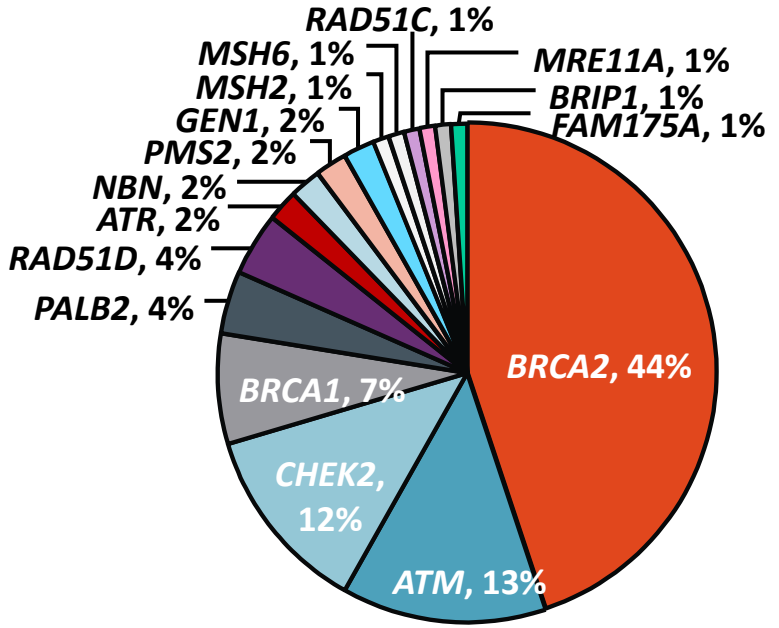
Homologous recombination repair (HRR) is a key mechanism for DNA repair[3,4]

1. Robinson D et al. Cell. 2015;161:1215–1228; 2. Abida W et al. PNAS. 2019;116:11428-436; 3. Lord CJ and Ashworth A. Nature. 2012;481:287–293; 4. O'Connor MJ. Mol Cell. 2015;60:547–560

DNA Repair Gene Alterations Are Common in Metastatic Prostate Cancer

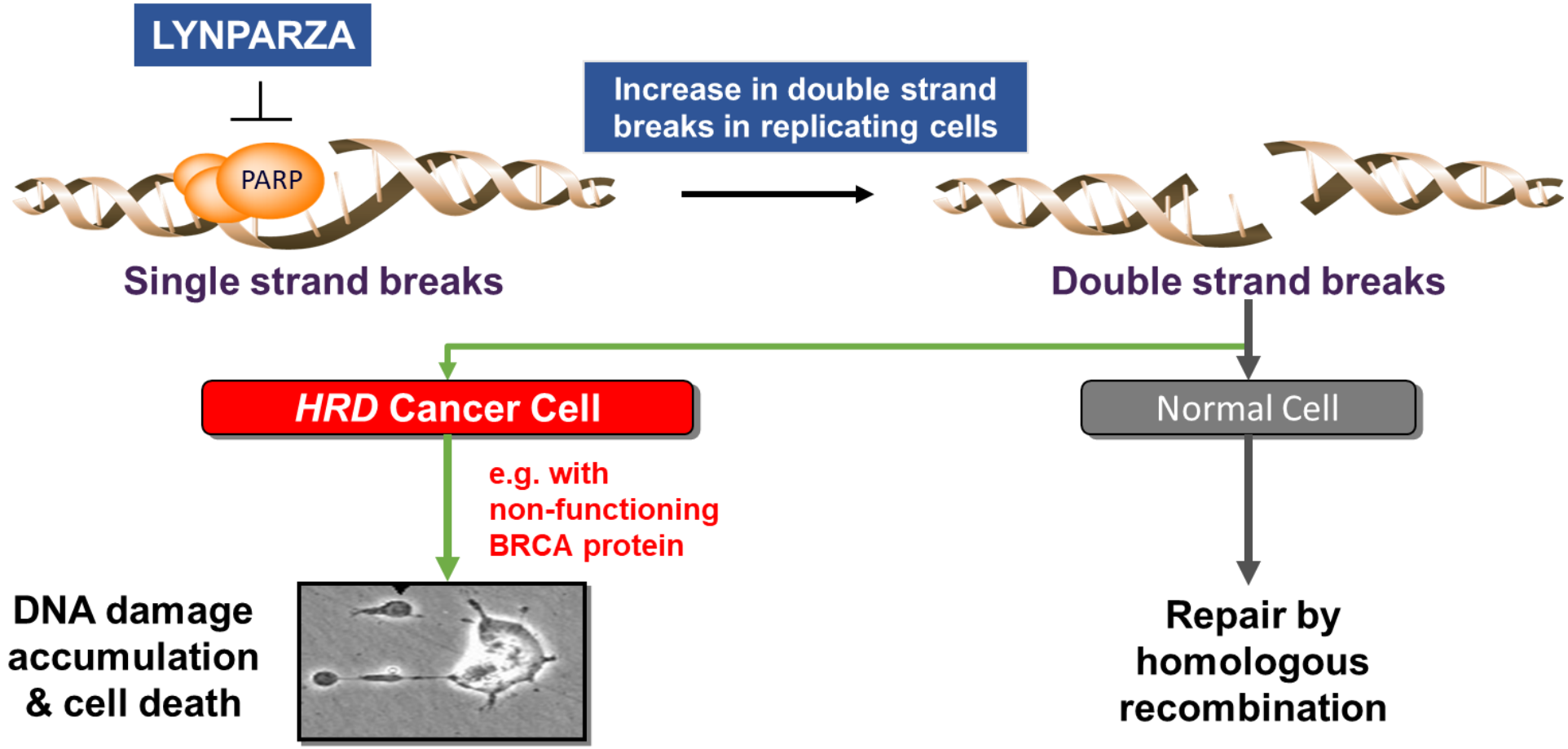
- **23%** of metastatic castration-resistant prostate cancers have DNA repair alterations[1]
- Frequency of DNA repair alterations increases with disease progression
- 11.8% of 692 men with metastatic prostate cancer had germline DNA repair defects[2]
- Not all men with germline mutations had a family history of cancer

Distribution of Presumed Pathogenic Germline Mutations[2]



1. Robinson. Cell. 2015;161:1215. 2. Pritchard. NEJM. 2016;375:443.

Olaparib (LYNPARZA) targets PARP, causing a synthetic lethal interaction in tumours with BRCA gene alterations*[1–3]



1. LYNPARZA (olaparib) 100 mg and 150 mg film-coated tablets. Summary of Product Characteristics; 2. O'Connor MJ. Mol Cell. 2015; 60(4):547–560; 3. Lord CJ and Ashworth A. Science 2017;355(6330):1152–1158;

PROfound: 1st Phase III RCTof a PARPi in mCRPC[1,2]

mCRPC post NHA

mCRPC with disease progression on prior NHA, for metastatic or non-metastatic CRPC or for mHSPC (e.g. abiraterone, enzalutamide)

HRR mutation

Alterations in ≥1 of 15 qualifying genes with a direct or indirect role in HRR*

Pre and post chemotherapy

PROfound enrolled both taxane-naïve and taxane-treated patients

Cohort A: BRCA1/2 or ATM

n=245

BRCA n=158
ATM n=90†

Open label

Cohort B:

n=142

12 other HRRm**

2:1

LYNPARZA
(300 mg BID tablets) n=162
(BRCA n=101; ATM n=64)

NHA retreatment‡ n=83
(BRCA n=57; ATM n=26)

Optional crossover to LYNPARZA following progression on NHA retreatment

2:1

LYNPARZA
(300 mg BID tablets) n=94

NHA retreatment‡ n=48

Primary endpoint

- rPFS BICR (Cohort A)¶

Key secondary endpoints§

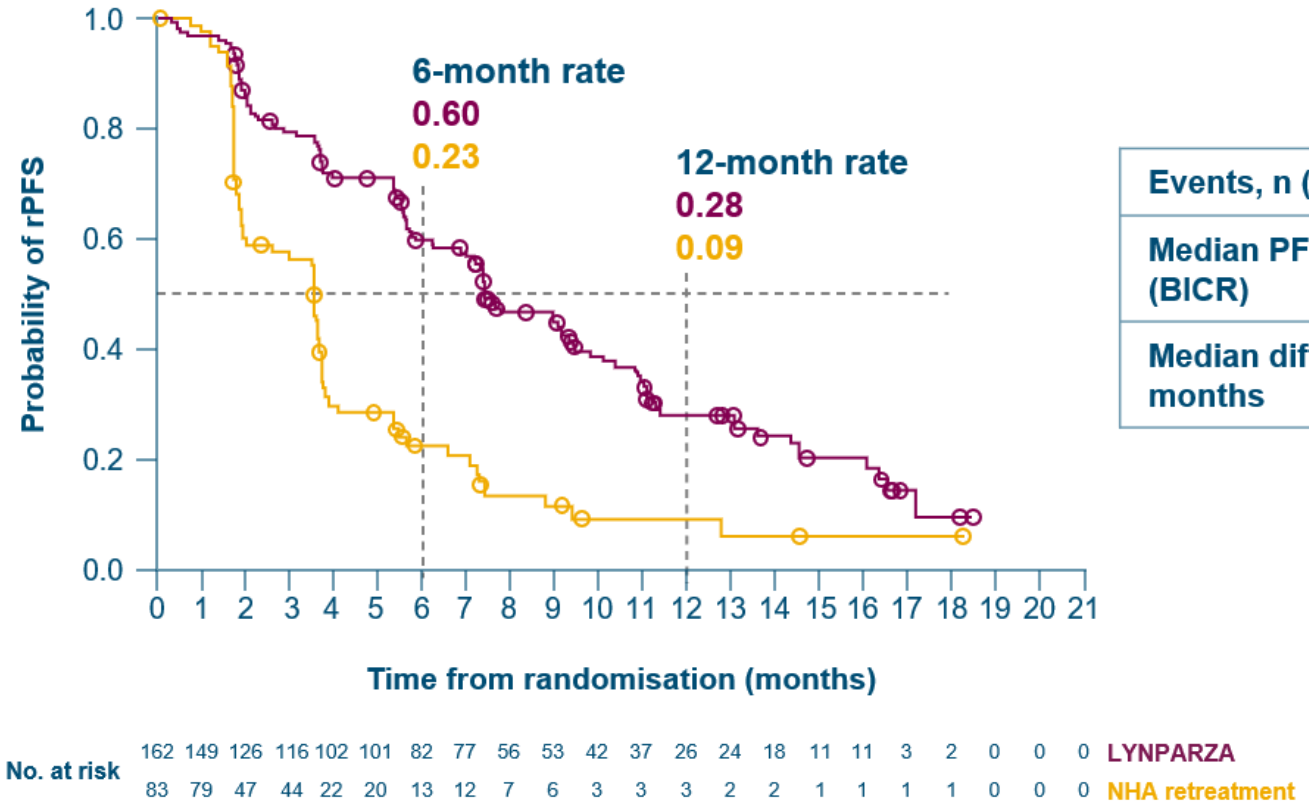
- ORR (Cohort A)¶
- rPFS BICR (Cohort A + B)¶
- Time to pain progression (Cohort A)
- OS (Cohort A)

Patient randomisation was stratified by: Prior taxane therapy (yes/no) and measurable disease at baseline (yes/no)

1. de Bono J et al. N Engl J Med. 2020;382(22):2091–2102;
2. de Bono J et al. Presented at ESMO 2019, 27th September – 1st October, Barcelona. Abstract 847PD;

PROfound: Primary endpoint
Olaparib reduced the risk of progression or death by 66%[1]

rPFS in patients with **BRCA or ATM mutations (Cohort A)**[1]



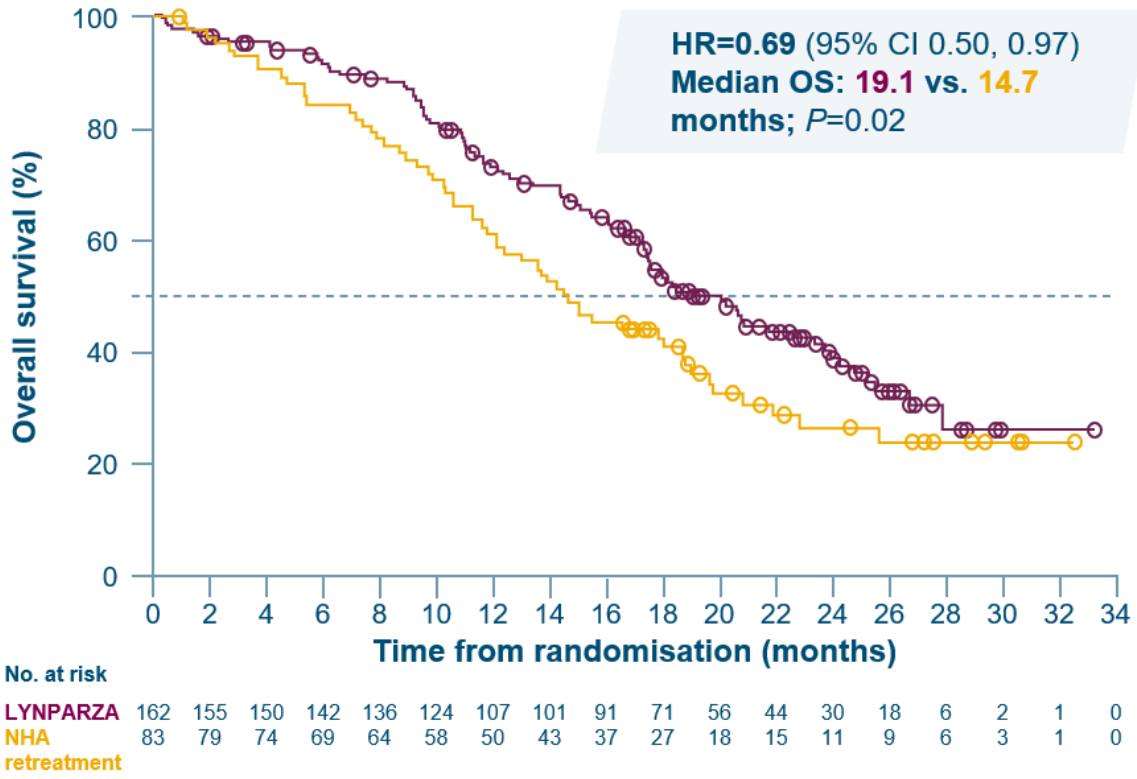
	LYNPARZA (n=162)	NHA retreatment (n=83)
Events, n (%)	106 (65.4)	68 (81.9)
Median PFS, months (BICR)	7.4	3.6
Median difference, months	+3.8	
	HR=0.34 95% CI (0.25, 0.47) *P*<0.001	

1. de Bono J et al. N Engl J Med. 2020;382(22):2091–2102.

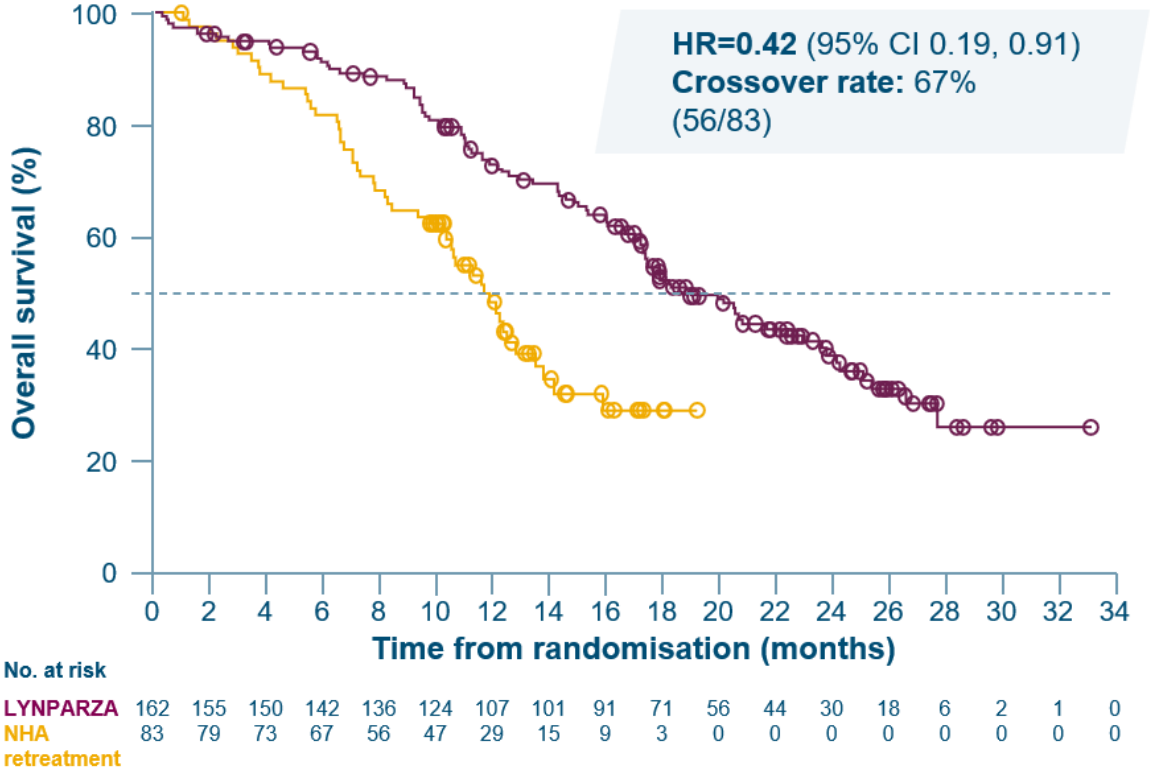
PROfound: Survival benefits

Adjusting for crossover suggested greater benefit with Olaparib vs. NHA retreatment

Cohort A



Cohort A with adjustment for crossover*



* Hussain M, et al. New Engl J Med. 2020 [Epub ahead of print] DOI: 10.1056/NEJMoa2022485.