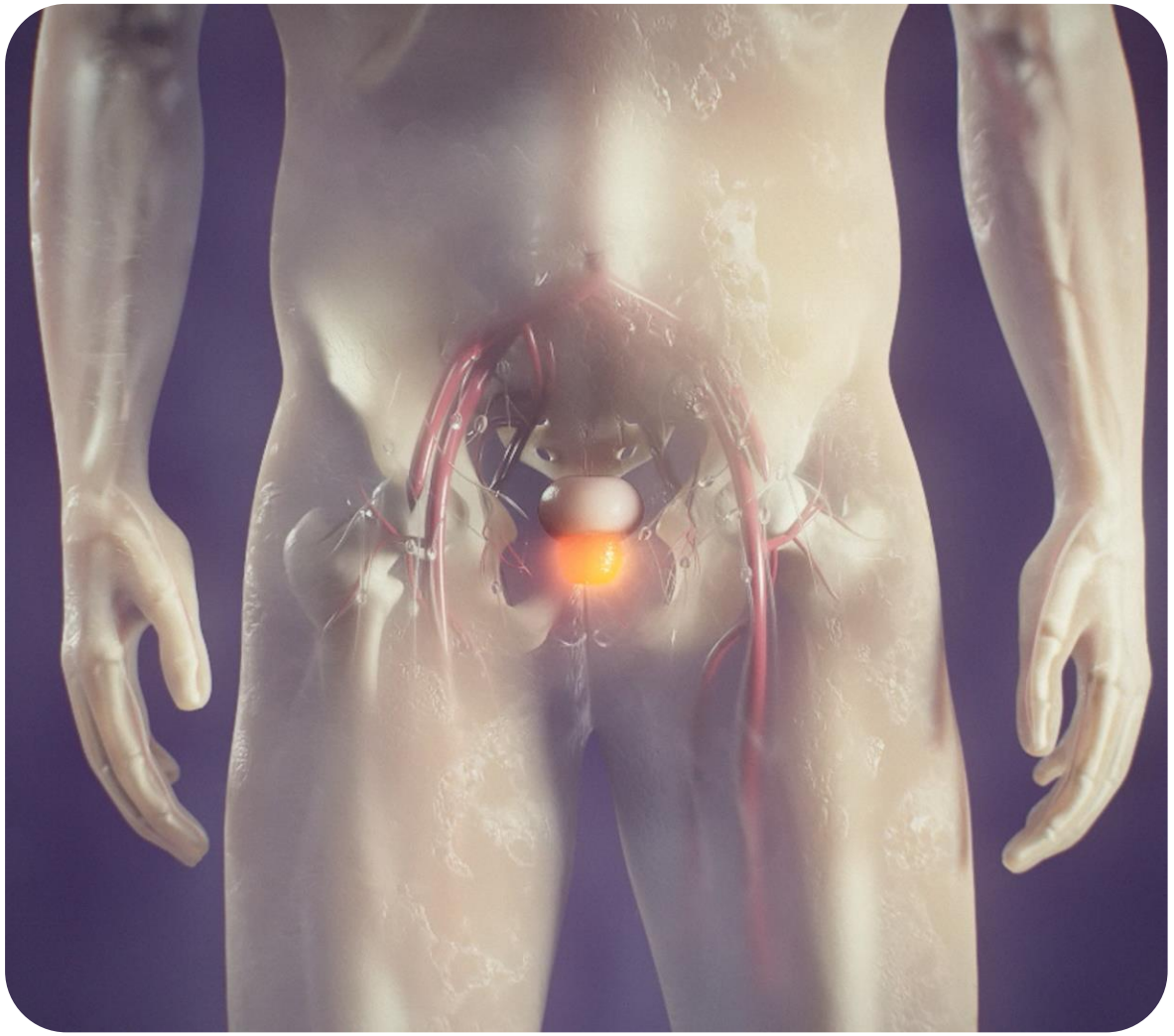
Enhancing AR-Targeted Approaches in Advanced Prostate Cancer

JULY 2023

Learning objectives

- Examine the unmet need in advanced prostate cancer and novel approaches addressing that need
- Describe AR pathway, its associated downstream elements and the interaction between AR, CDK4/6 and cell cycle regulation
- Identify the biological parallels between breast and prostate cancer
- Describe the rationale for clinical trials investigating dual inhibition of AR and CDK4/6 in advanced prostate cancer



AR=androgen receptor; CDK=cyclin-dependent kinase.

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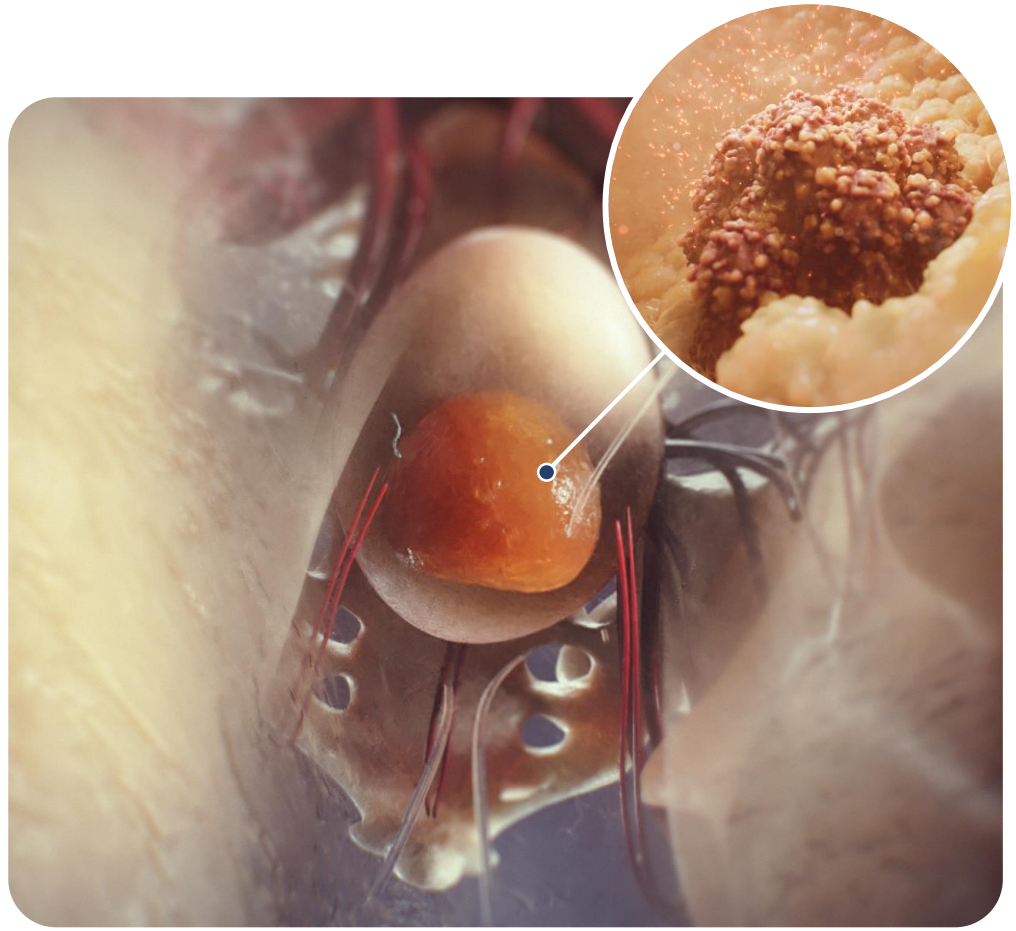
Advanced prostate cancer is associated with cancer-specific mortality

- Prostate cancer (PCa) is the **2nd most common cancer** and **5th leading cause of cancer-related death** among men world-wide[1]
- Most PCa cases are localised and not associated with cancer-specific mortality[2,3]
- However, the **incidence of metastatic advanced PCa is increasing** and remains associated with **cancer-specific mortality**, despite recent advances[3,4]



5-year survival rate, prostate cancer (US)[3]

Nearly 100%	vs.	30%
with local or locally advanced disease		with advanced disease

PCa=prostate cancer.

1. Sung H, Ferlay J, Siegel RL, et al. *CA Cancer J Clin*. 2021;71(3):209-249. 2. Siegel DA, O'Neil ME, Richards TB, et al. *MMWR Morb Mortal Wkly Rep.* 2020;69(41):1473-1480 3. Cancer.net, ASCO. Accessed June 2023. https://www.cancer.net/cancer-types/prostate-cancer/statistics.%20Accessed%20February%2028,%202022. 4. Hamid AA, Sayegh N, Tombal B, et al. *Am Soc Clin Oncol Educ Book.* 2023;43:e390166.

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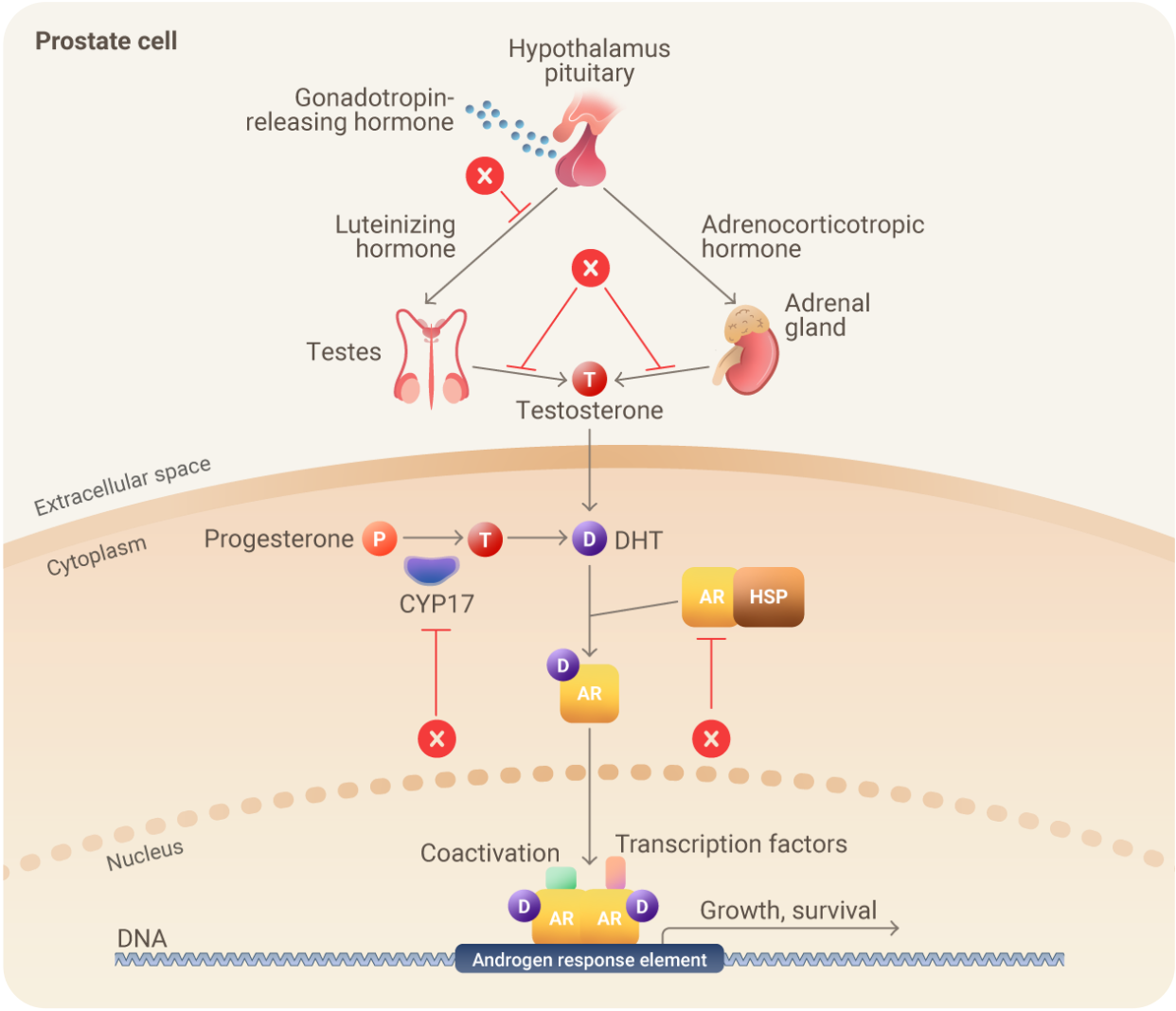
Androgen signaling is a key driver of PCa pathogenesis

- Androgens promote the growth and survival of prostate cells[1]
- In PCa, due to abnormal **androgen signaling**, the androgen receptor drives the expression of target genes, promoting **cancer cell survival and growth**[2,3]
- **Androgen deprivation** is the **mainstay** of advanced prostate cancer management[2,3]



Adapted from He Y et al. *Signal Transduct Target Ther.* 2022;7(1):198 Figure 2, and Tan MH et al. *Acta Pharmacol Sin.* 2015;36(1):3-23 Figure 1; Michmerhuizen AR et al. *NPJ Breast Cancer.* 2020;6:47 Figure 1

AR=androgen receptor; D=dihydrotestosterone; HSP=heat shock protein; P=progesterone; PCa=prostate cancer; T=testosterone.

1. Tan MH, Li J, Xu HE, Melcher K, Yong EL. *Acta Pharmacol Sin.* 2015;36(1):3-23. 2. He Y, Xu W, Xiao YT, Huang H, Gu D, Ren S. *Signal Transduct Target Ther.* 2022;7(1):198. 3. Brighi N, Conteduca V, Lolly C, et al. *Crit Rev Onc/Hem.* 2021;157.

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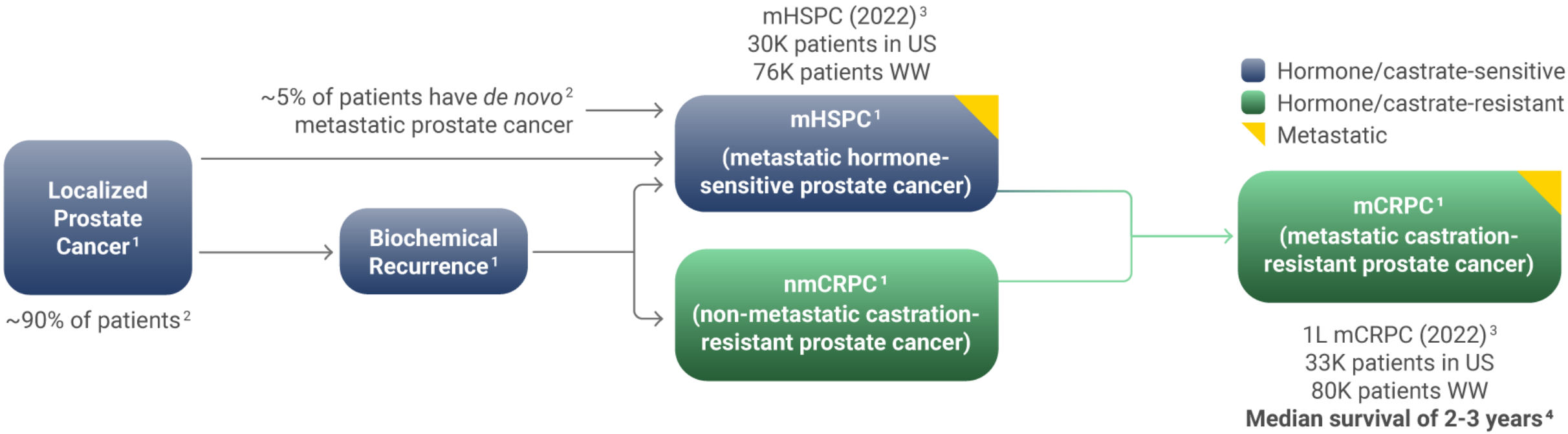
Advanced PCa ultimately progresses to mCRPC due to continued dependence on the AR signaling pathway



Adapted from Saad F, Bögemann M, Suzuki K, Shore N. *Prostate Cancer Prostatic Dis.* 2021;24(2):323-334 Figure 1
AR=androgen receptor; PCa=prostate cancer; US=united states; WW=world-wide.
1. Saad F, Bögemann M, Suzuki K, Shore N. *Prostate Cancer Prostatic Dis.* 2021;24(2):323-334. 2. Siegel DA, O'Neil ME, Richards TB et al. *MMWR Morb Mortal Wkly Rep.* 2020;69(41):1473-1480. 3. Vinuesa L, Parihar N. *Clarivate, DRG.* 2021. 4. Moreira DM, Howard LE, Sourbeer KN, et al. *Clin Genitourin Cancer*. 2017;15(1):60-66.e2.

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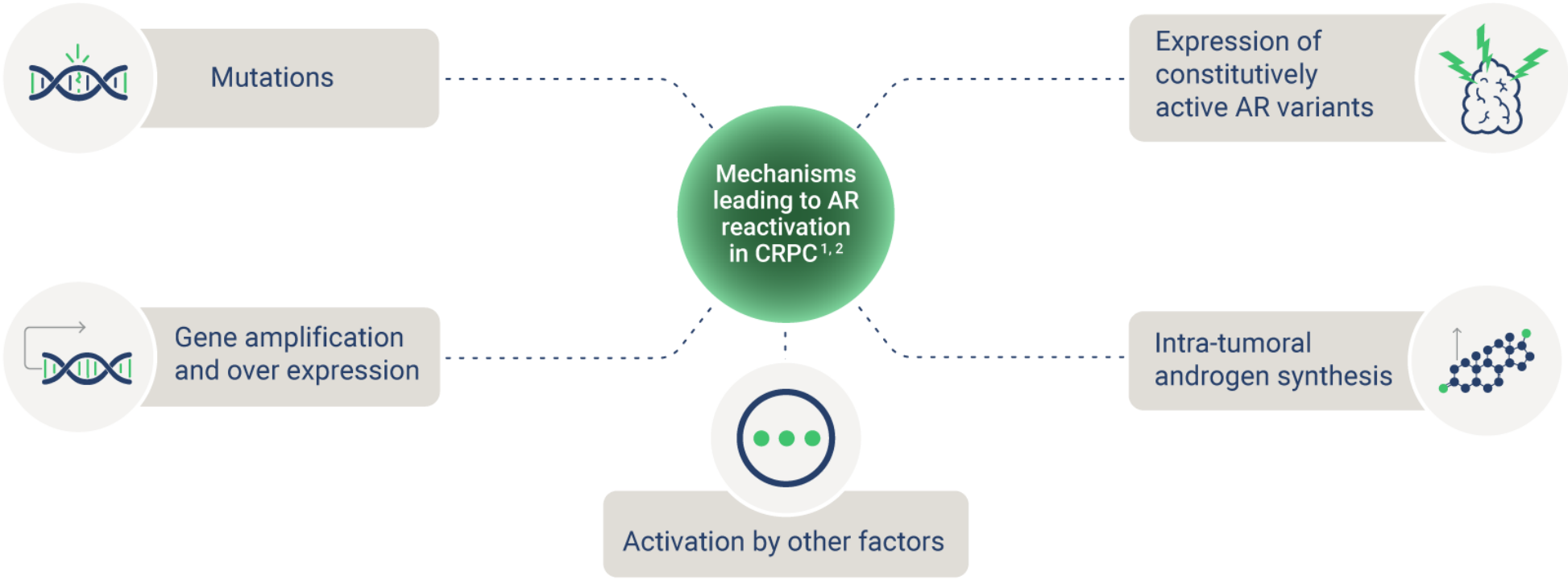
In mCRPC, continued dependence on the AR signaling pathway is driven by AR reactivation



Nearly all patients with **mCRPC** experience **disease progression** and **cancer-specific mortality**[3].

Patients with mCRPC have cancer that is **resistant to androgen deprivation**, highlighting the need for novel approaches to **improve disease control** and further **delay the need for chemotherapy initiation**, currently used to treat advanced disease[2].

AR=androgen receptor; CPRC=castration-resistant prostate cancer; mCPRC=metastatic castration-resistant prostate cancer.

1. He Y, Xu W, Xiao YT et al. *Signal Transduct Target Ther.* 2022;7(1):198. 2. Jernberg E, Bergh A, Wikström P. *Endocr Connect.* 2017;6(8):R146-R161. 3. Verry C, Vincendeau S, Massetti M, et al. *Target Oncol.* 2022;17(4):441-451.

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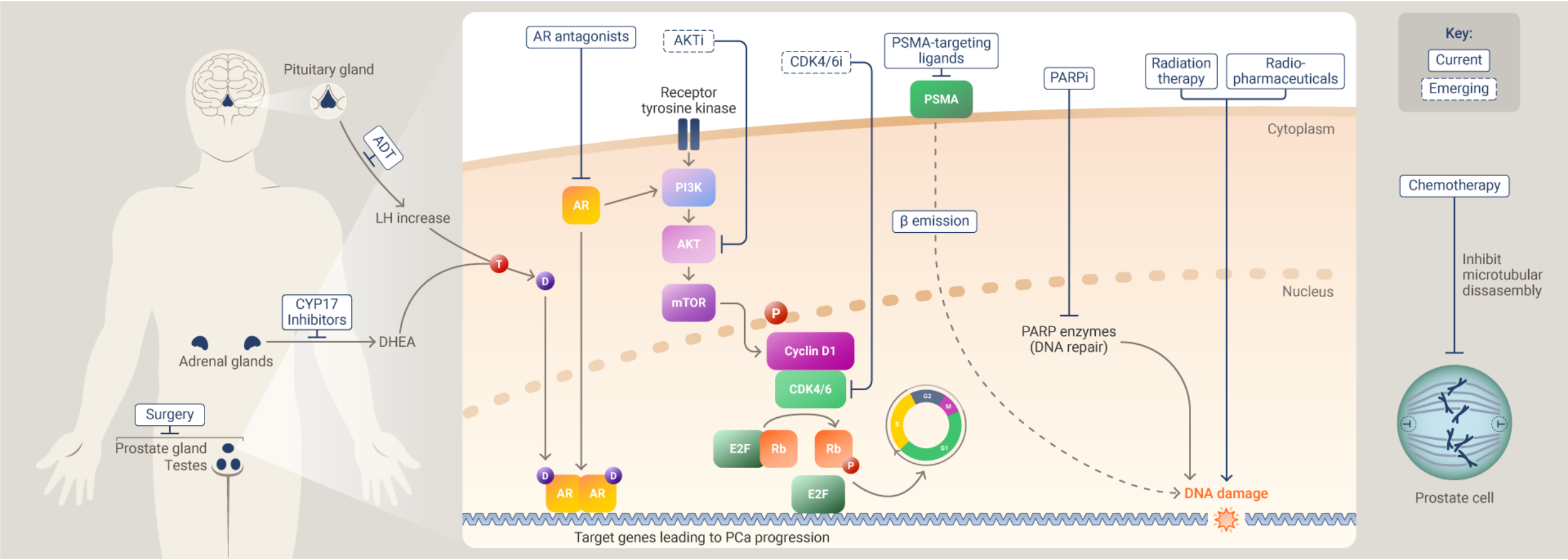
Current and emerging approaches for mCRPC management aim to improve disease control



Not pictured: IO agents, which target the immune system to treat prostate cancer

ADT=androgen deprivation therapy; AR=androgen therapy; CDK=cyclin-dependent kinase; DHEA=dehydroepiandrosterone; D=dihydrotestosterone; HSP=heat shock protein; LH=luteinizing hormone; mCRPC=metastatic castration-resistant prostate cancer; P=phosphorylation; PARP=poly (ADP-ribose) polymerase; PARPi=poly (ADP-ribose) polymerase inhibitor; PCa=prostate cancer; PSMA=prostate specific membrane antigen; T=testosterone.

Adapted from He Y et al. *Signal Transduct Target Ther.* 2022;7(1):198 Figures 1 and 2. Hamid AA et al. *Am Soc Clin Oncol Educ Book*. 2023;43:e390166 Figure 1. Michmerhuizen AR et al. *NPJ Breast Cancer.* 2020;6:47 Figure 1

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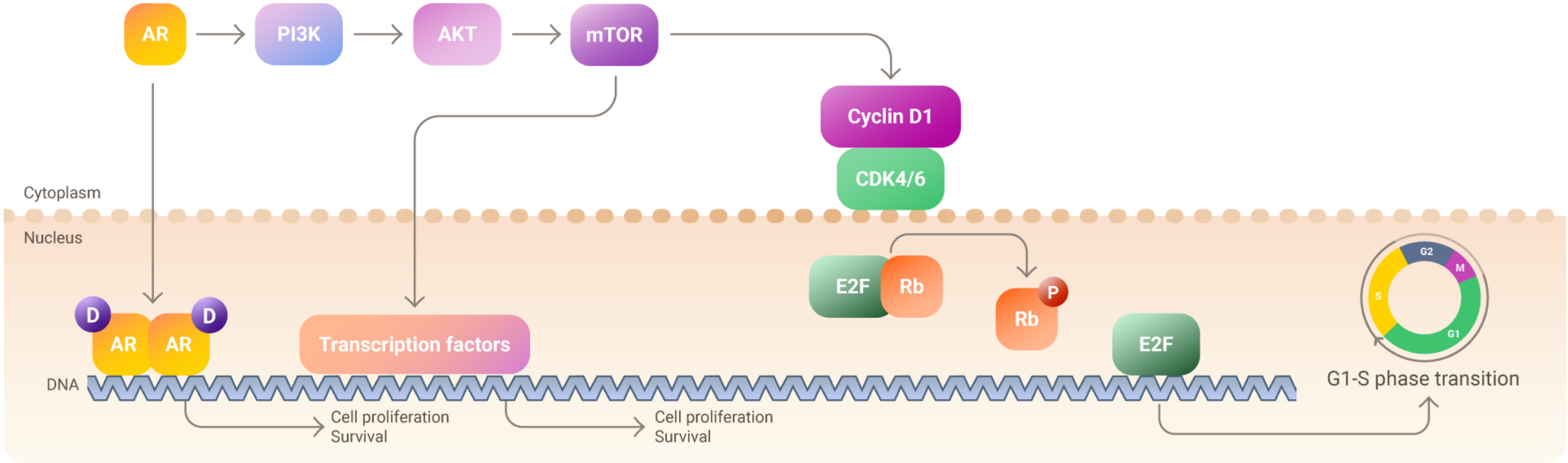
The interaction between AR and other molecular pathways results in PCa cell cycle progression and cancer proliferation

- **The proliferation, survival, differentiation, and motility of cancer cells** are regulated by different intracellular signaling pathways[1]
- Androgens and AR have regulatory roles in these pathways, which ultimately result in **androgen regulation of the cell cycle pathway via AR signaling**[2]



AR=androgen receptor; CDK=cyclin-dependent kinase; D=dihydrotestosterone; P=phosphorylation; PCa=prostate cancer; PI3K=phosphoinositide 3-kinase; Rb=retinoblastoma.

1. De Luca A, Maiello MR, D'Alessio A, et al. *Expert Opin Ther Targets.* 2012;16 Suppl 2:S17-S27. 2. Kase AM, Copland Iii JA, Tan W. *Onco Targets Ther.* 2020;13:10499-10513.

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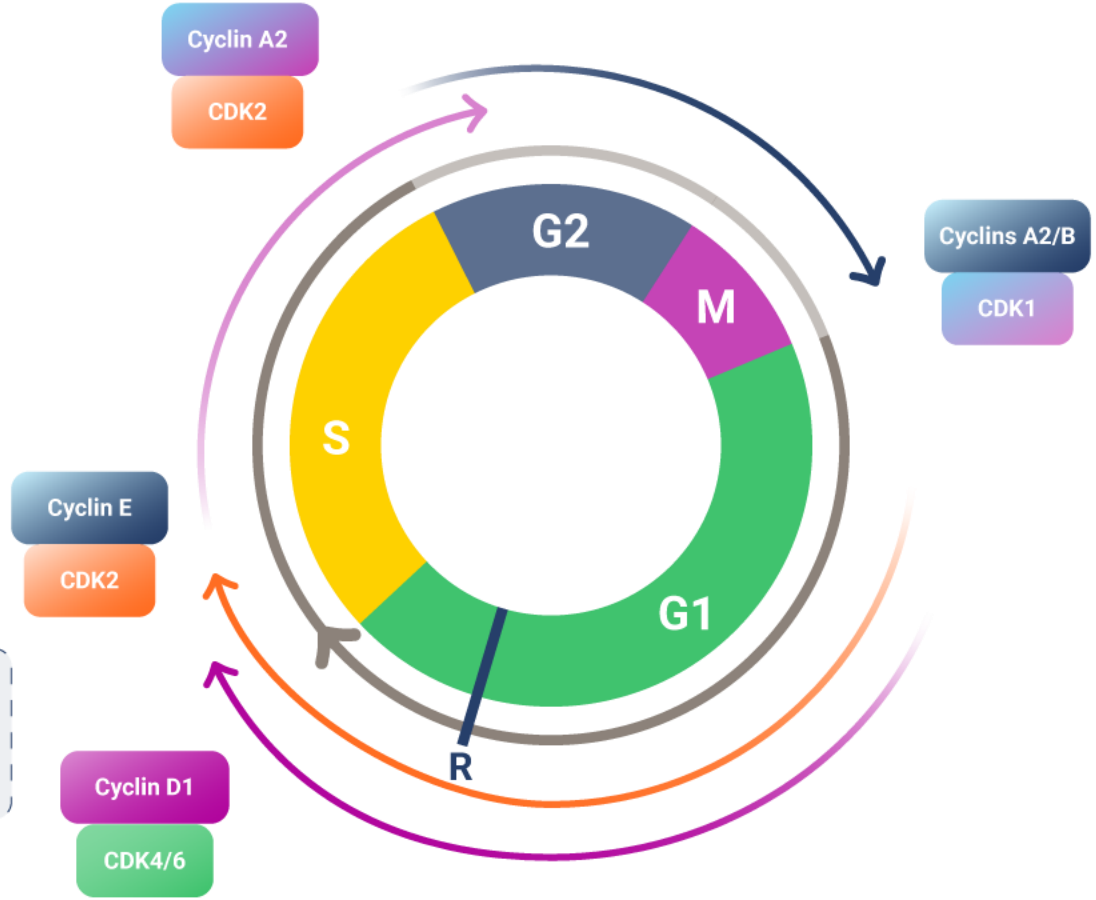
Sustained cellular proliferation is a hallmark of cancer



G1 Growth

S DNA synthesis

G2 Growth

M Mitosis (cell division)

Transition from G1 to S phase is a **key checkpoint** for regulation of the cell cycle[1].

Beyond the restriction (R) point, cells become **"commited" to the cell cycle** and progress autonomously[1,2].

- The cell cycle is controlled by protein kinase complexes consisting of **cyclin-dependent kinases (CDKs)** and their **cyclin** partners[1,2]
- Overexpression of cyclins and CDKs promote **sustained cellular proliferation**, a hallmark of cancer[3]

CDK=cyclin-dependent kinase; R=restriction point.

1. Duronio RJ, Xiong Y. *Cold Spring Harb Perspect Biol.* 2013;5(3):a008904. 2. Mullany LK, White P, Hanse EA, et al. *Cell Cycle.* 2008;7(14):2215-2224. 3. Hanahan D. *Cancer Discov.* 2022;12(1):31-46.

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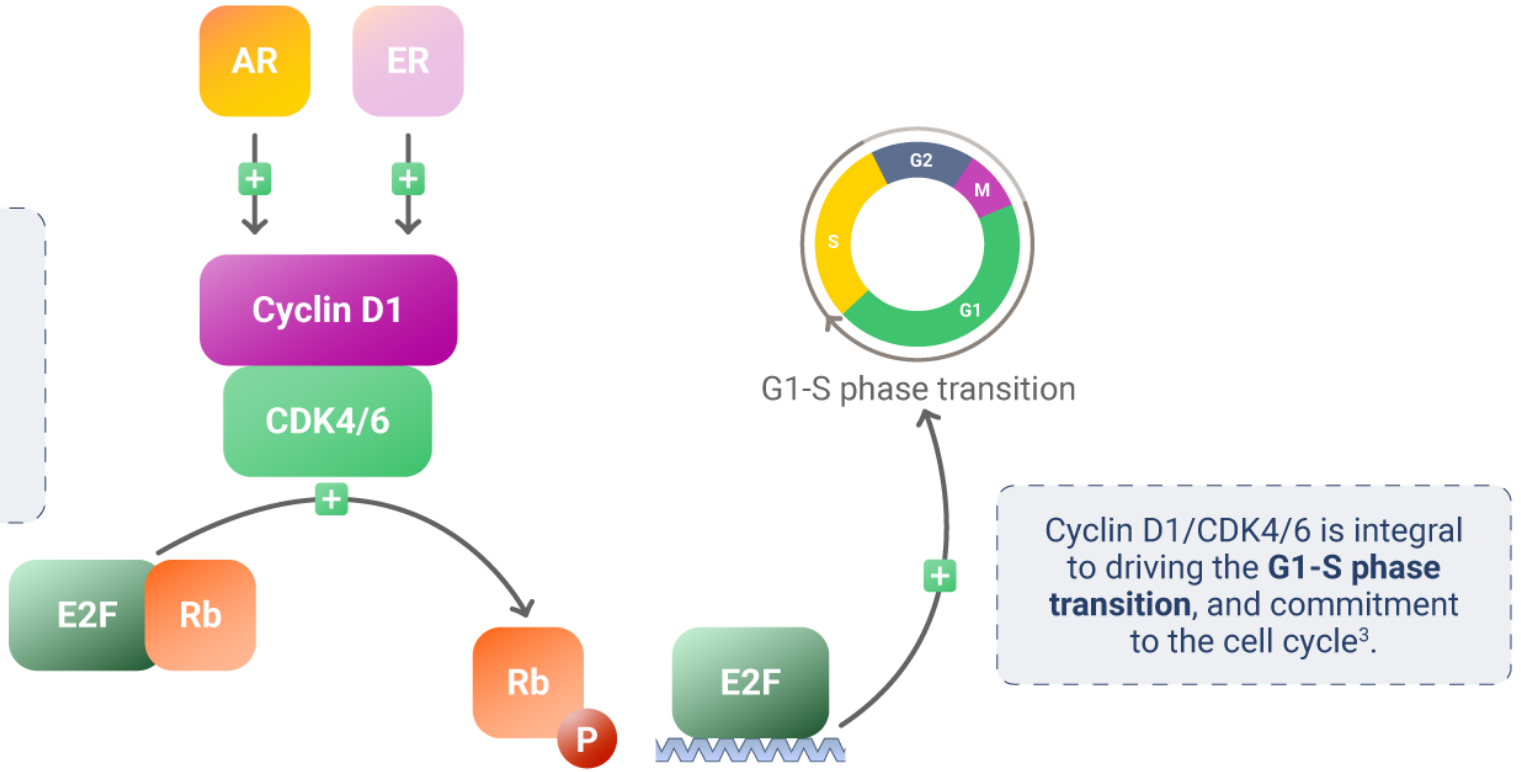
Biological parallels between PCa and HR+ BCa: continued ER and AR signaling drive uncontrolled cellular proliferation by activating CDK4 and 6

Similar to **ER signaling** in **hormone receptor positive (HR+) breast cancer (BCa)**, **AR signaling** in PCa induces over-expression of **Cyclin D1**, which form complexes with CDK4 and CDK6[1,2].



Cyclin D1/CDK4/6 is integral to driving the **G1-S phase transition**, and commitment to the cell cycle[3].

Upregulation of cyclin D1 is a **mechanism of resistance** to hormone-targeted agents, ultimately leading to treatment resistance and cancer cell proliferation and survival[4] .

AR=androgen receptor; Bca=breast cancer; CDK=cyclin-dependent kinase; ER=estrogen receptor; HR+=hormone receptor positive; P=phosphorylation; PCa=prostate cancer; Rb=retinoblastoma protein.

1. Balk SP, Knudsen KE. *Nucl Recept Signal.* 2008;6:e001. 2. Wander SA, O'Brien N, Litchfield L, et al. *Oncologist.* 2022;27:811-821. 3. He Y, Xu W, Xiao YT, Huang H, Gu D, Ren S. *Signal Transduct Target Ther.* 2022;7(1):198. 4. Pal SK, Patel J, He M, et al. *Cancer.* 2018;124(6):1216-1224.

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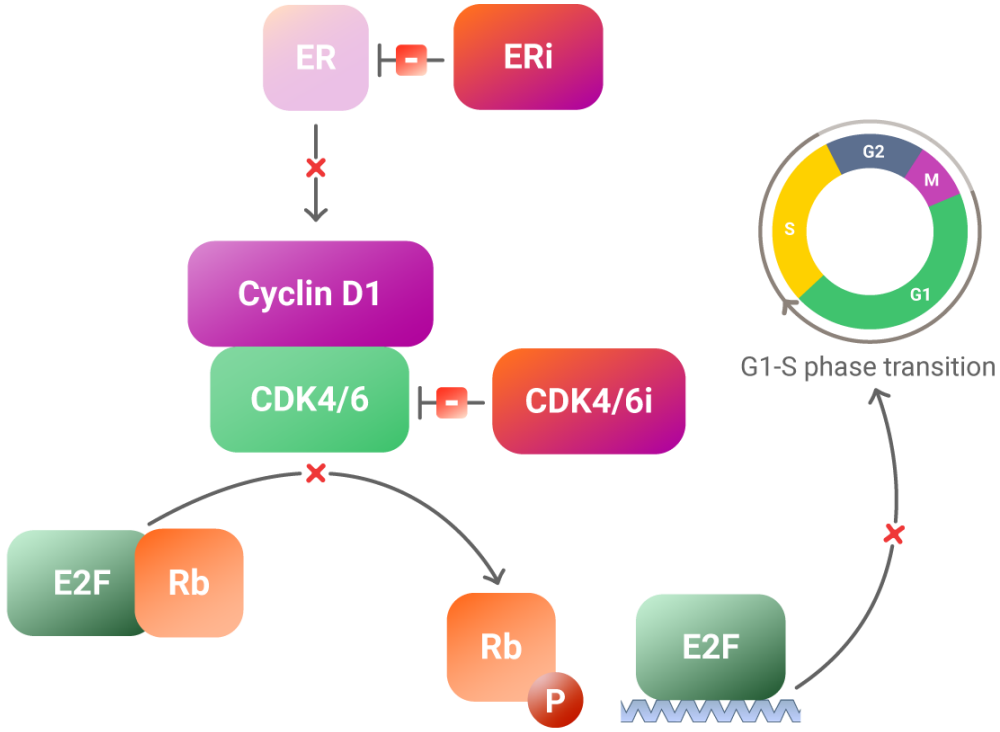
Dysregulation of the cell cycle in HR+ BCa is driven by ER signaling that can be blocked by targeting CDKs

- The ER signaling pathway and CDK4/6 interact **synergistically** to drive tumorigenesis in BCa[1]
- Inhibition of CDK4/6 prevents Rb phosphorylation and G1-S phase cell cycle transition. Therefore, the cancer cell cannot re-enter the cell cycle, resulting in **senescence** and **apoptosis**[2]
- Dual inhibition of ER & CDK4/6 has proven to be a **standard therapy** in hormone receptor-positive breast cancer[1,3]



BCa=breast cancer; CDK=cyclin-dependent kinase; CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; ER=estrogen receptor; ERi=ER inhibitor; HR+=hormone receptor positive; P=phosphorylation; Rb=retinoblastoma protein.

1. Wander SA, O'Brien N, Litchfield L, et al. *Oncologist.* 2022;27:811-821. 2. Scheinberg T, Kench J, Stockler M, et al. *BMJ Open*. 2020;10:e033667. 3. Nabieva N, Fasching PA. *Cancers (Basel).* 2023;15(6):1763.

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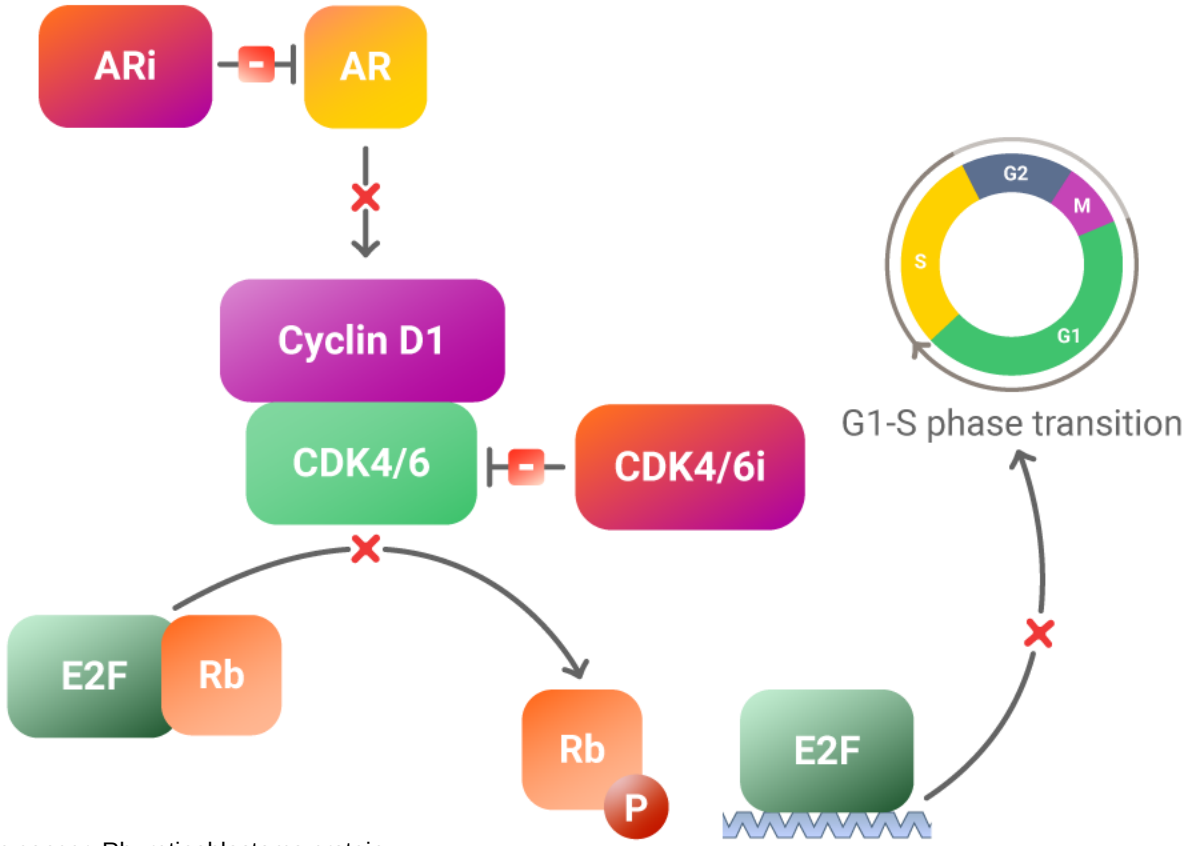
Based on the importance of CDK4 & 6 in BCa, and the biological parallels with prostate cancer, dual inhibition of AR and CDK4/6 is being actively investigated in PCa clinical trials

Hypothesis:
Targeting cell cycle may augment AR inhibition in Advanced Prostate Cancer[1].

CDK4 and 6 play a pivotal role in AR+ PCa cellular proliferation and viability[1].



AR=androgen receptor; ARi=androgen receptor inhibitor;
BCa=breast cancer; CDK=cyclin-dependent kinase; P=phosphorylation; PCa=prostate cancer; Rb=retinoblastoma protein.

1. Brighi N, Conteduca V, Lolly C, et al. *Crit Rev Onc/Hem.* 2021;157.

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Key takeaways

- Prostate cancer (PCa) primarily depends on androgens for growth. Therefore, androgen deprivation is the mainstay of advanced PCa management.
- PCa can become resistant to castration by re-activating AR signaling and continued dependence on the AR signaling pathway, resulting in mCRPC.
- Current and emerging approaches include targeting PSMA expression, co-targeting AR signaling and DNA repair through PARP inhibition, and co-targeting AR and associated downstream elements such as PI3K/AKT/mTOR or the cell cycle, which aim to improve disease control.
- Much like ER signaling in HR+ breast cancer (BCa), signaling through the AR pathway in PCa induces over-expression of D-type cyclins, and subsequent activation of CDK4/6 to sustain cellular proliferation, a hallmark of cancer.
- Dual inhibition of ER and CDK4/6 has proven to be a standard therapy in hormone receptor-positive breast cancer as these pathways interact synergistically to drive tumorigenesis.
- Due to the biological parallels between BCa and PCa, dual inhibition of AR and CDK4/6 is currently being investigated in clinical trials for the treatment of advanced PCa.

AR=androgen receptor; Bca=breast cancer; CDK=cyclin-dependent kinase; ER=estrogen receptor; HR+=hormone receptor positive; mCPRC=metastatic castration-resistant prostate cancer; PCa=prostate cancer; PI3K=phosphoinositide 3-kinase.

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