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FACE-TO-FACE AND LIVE STREAMING



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Espacio Maldonado, Madrid

New Targeted Therapies for Prostate Cancer

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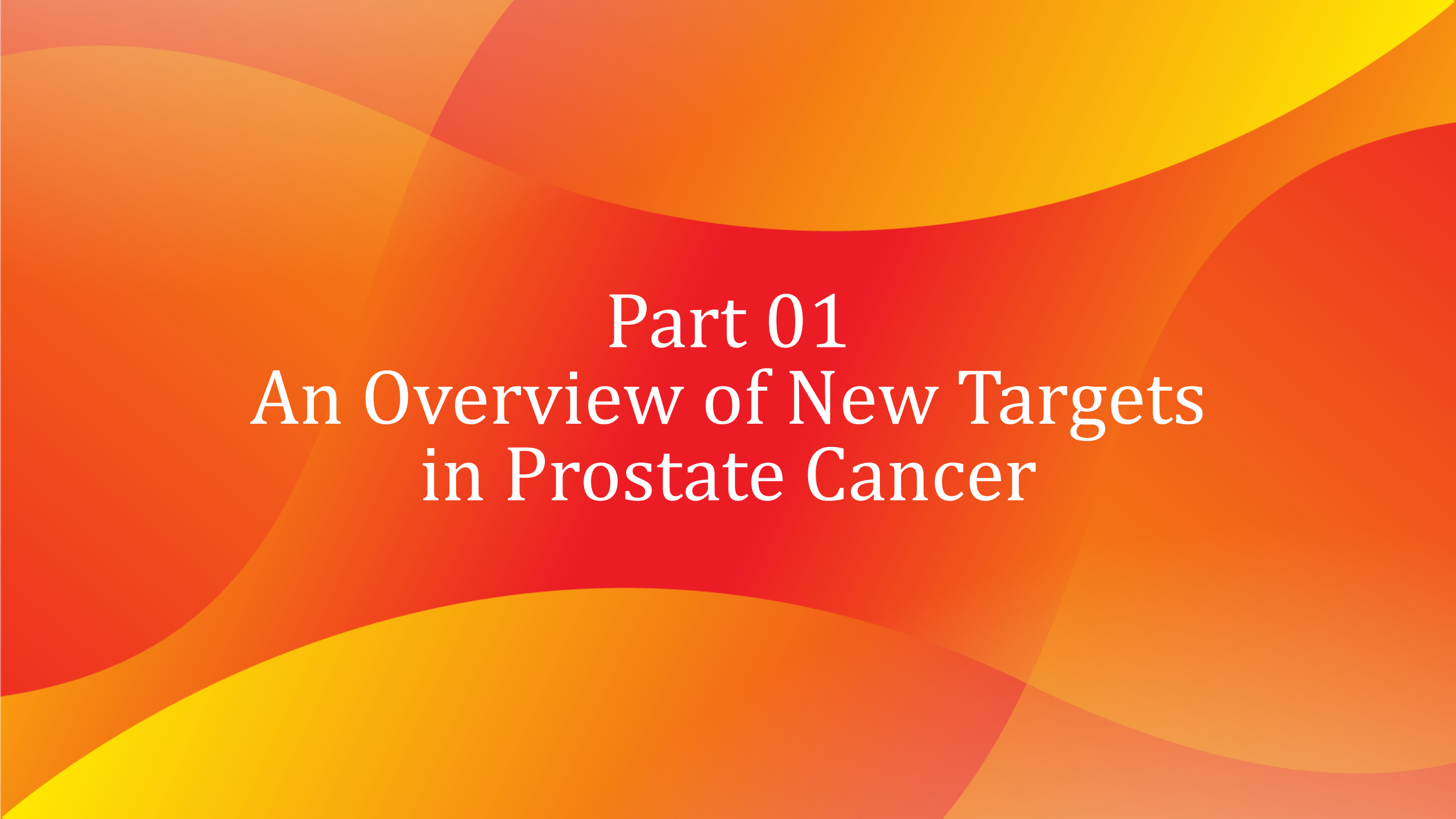
Fudan University Prostate Cancer Institute · Shanghai Genitourinary Cancer Institute

Outline

01 An Overview of New **Targets** in Prstate Cancer

02 Progress, Target by Target B7-H3 · PSMA · STEAP1, KLK2, DLL3 · AR · EZH2 · PARP and AKT

03 From Target to Praticice Pace map, selection, and what comes next



Part 01

An Overview of New Targets in Prostate Cancer

Why do we need new targets now?

Gap 1

Beyond standard treatment

- With ARPI and 177 Lu-PSMA moving into earlier lines, **no standard option remains** after ARPI, taxane and radioligand therapy.

Gap 2

Loss of target expression

- ~20% of mCRPC show low / absent PSMA expression and are ineligible for radioligand therapy.
- Visceral and liver metastases respond poorly to available therapies.

Gap 3

Lineage plasticity

- 15~20% of late CRPC turn NEPC with loss of AR and PSMA expression under treatment.

Re-sequencing existing agents will not close these gaps.

New targets are required.

Axis A — Refining proven mechanisms

ARPI — AR antagonism



AR degradation or redirection

BMS BMS-986365 AR Degradar PROTAC Phase I/II	Hengrui SHR-5041 AR PROTAC Phase I/II
CSPC Zhengda TQB3201 AR PROTAC Phase I/II	Halda HLD-0915 First-in-class AR RIPTAC Phase I

^{177}Lu -PSMA RLT — beta radiation



Alpha emitters / Beyond PSMA

Novartis ^{225}Ac -PSMA-617 Target & Mechanism: α particles induce complex, irreparable DNA double-strand breaks, leading to potent cell death independent of cell cycle or hypoxia Clinical Phase: PSMAcTION II/III AcTFIRST III	Lannacheng ^{225}Ac -LNC1011 ^{177}Lu -LNC1011 Target & Mechanism: α/β particles induce complex, irreparable DNA double-strand breaks, leading to potent cell death independent of cell cycle or hypoxia Clinical Phase: Phase I/II First-in-Human
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Docetaxel — untargeted chemotherapy



ADCs — antibody-guided chemotherapy

B7-H3 ADCs:
cORR 33–39%, mrPFS ~10–11 months.

YL201 MediLink Therapeutics Phase II	DB-1311 / BNT324 DualityBio / BioNTech Phase III
I-DXd / DS-7300a Daiichi Sankyo / Merck Phase III	HS-20093 / GSK5764227 Hansoh Pharma / GSK Phase II

ASCO GU 2026, ESMO 2024 / 2023 and other latest international conferences

New targets: hK2 and ACP3

ACP3 is on >95% of PCa including PSMA-low/ NEPC with minimal salivary and renal uptake.

FIH PET, Eur Urol 2026.

Axis B — New mechanisms

T-cell Engagers

Bispecific antibodies simultaneously bind tumor surface antigens and CD3 on T cells.

J&J / Janssen Phase III

Pasritamig

(JNJ-78278343)

Target: **KLK2 × CD3**

Amgen Phase III

Xaluritamig

(AMG 509)

Target: **STEAP1 × CD3**

Epigenetic Targets Reverse Drug Resistance

Jiang Su Heng Rui KAT6 Inhibitor

HRS-2189 + HRS-5041 (remains)

Dual KAT6A/B inhibition, combination regimen for Metastatic Castration-Resistant Prostate Cancer (mCRPC)

Phase II

Heng Yi Therapeutics BET Inhibitor

ZEN003694 (remains)

BRD2/3/4 bromodomain inhibition, disrupts reading of ZEN003694 combined with enzalutamide as monotherapy for mCRPC

Phase 2b

Pfizer

EZH2 Inhibitor

Mevrometostat (remains)

Selective EZH2 inhibition, H3K27me3 demethylation
Mevrometostat combined with enzalutamide for mCRPC after failing novel

Phase III

Daiichi Sankyo Dual EZH1/2 Inhibitor

Valemetostat (remains)

Dual EZH1/2 inhibition, comprehensive epigenetic blockade
Valemetostat combined with darolutamide for chemotherapy-naïve mCRPC

Phase I/II

PI3K-AKT

AstraZeneca Approved

Capivasertib

(AZD 5363)

Approved 2026 in PTEN-deficient mHSPC

PARP1

Cleaner PARP1-selective for BRCA-altered disease

Merck Approved

Niraparib

(MK-4827)

AstraZeneca Phase III

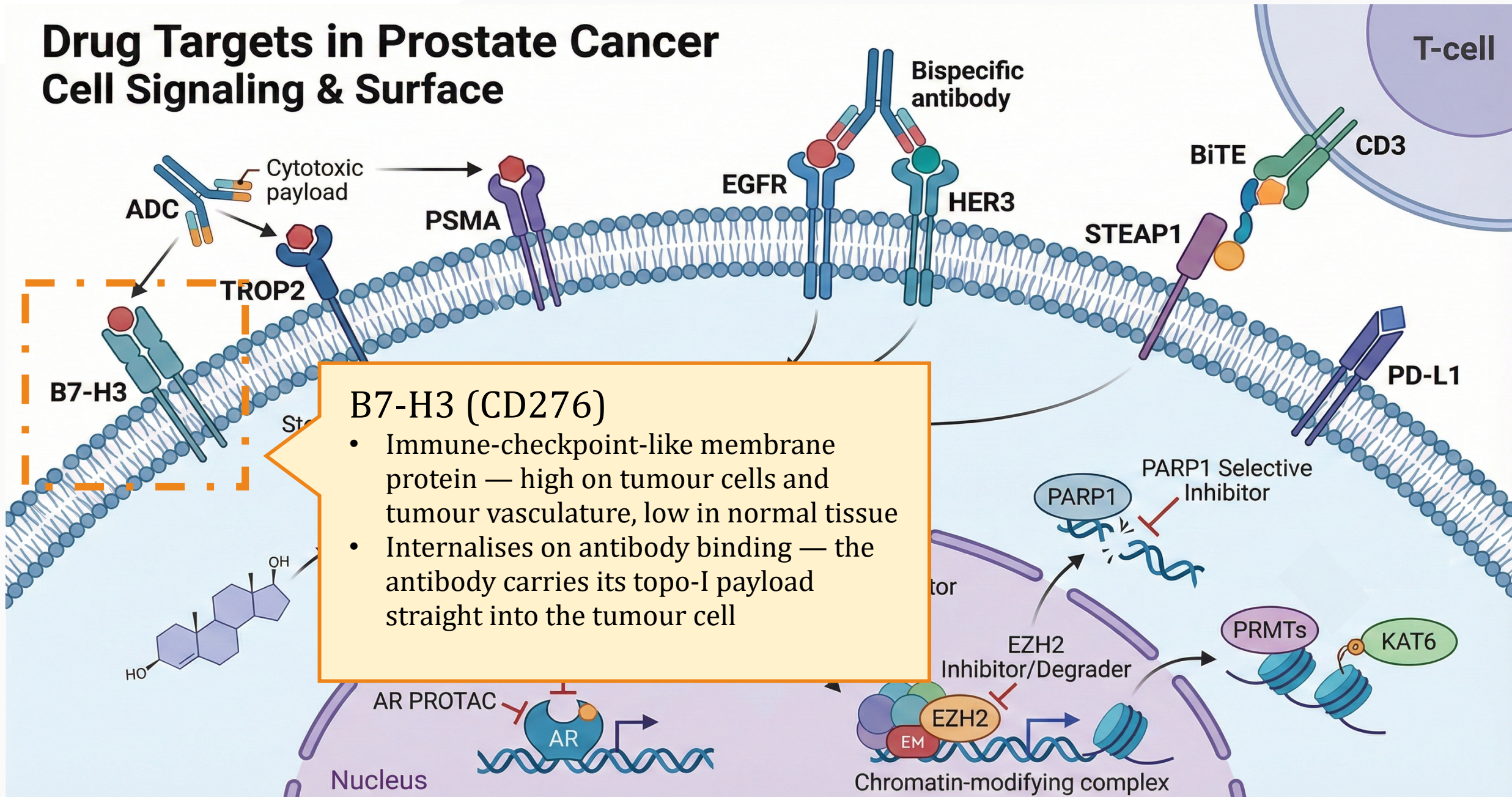
Saruparib

(AZD 5305)

Both Axes: Matching the Patients, the Target and the Test.

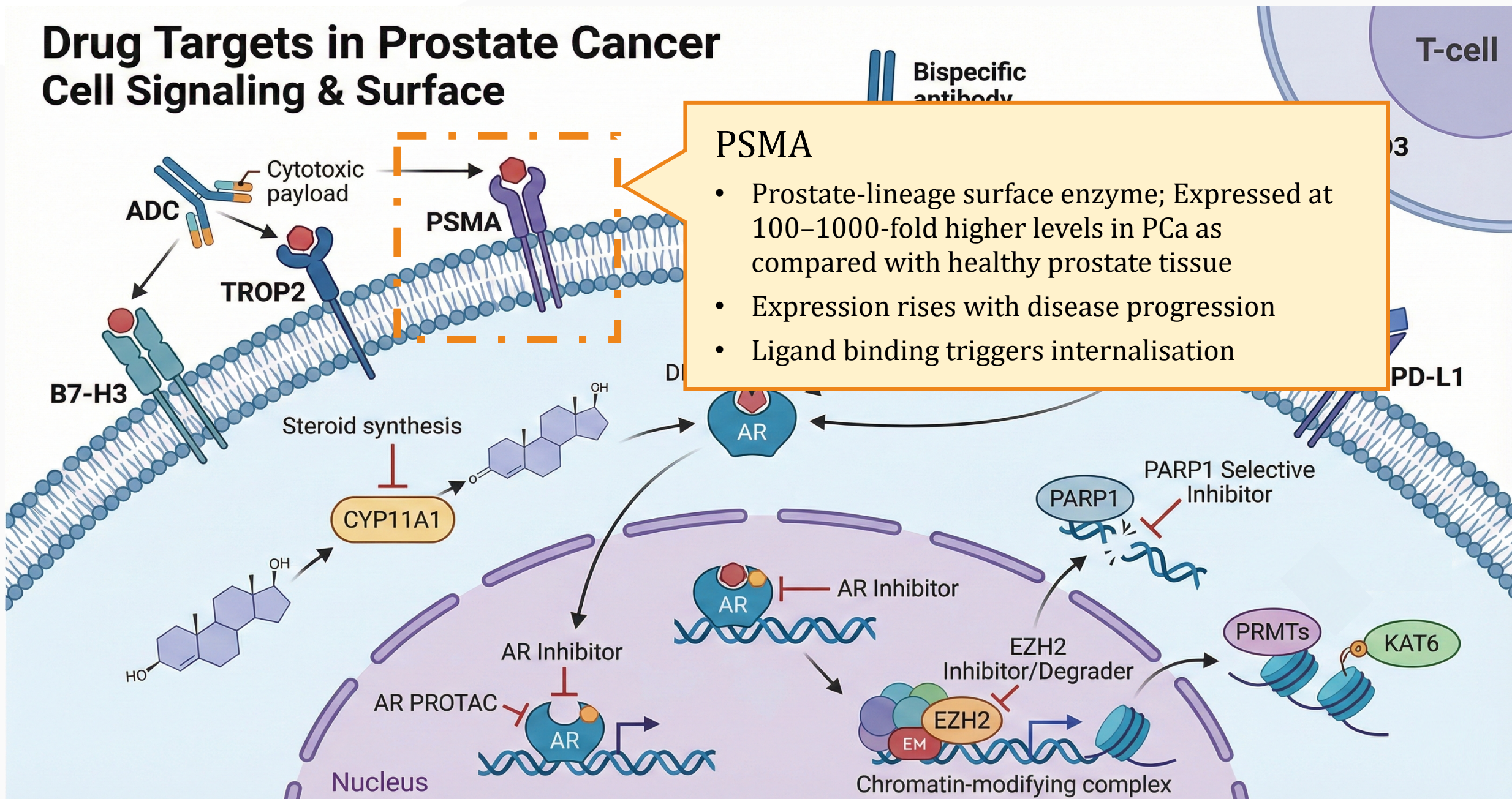
Drug Targets in Prostate Cancer

Cell Signaling & Surface



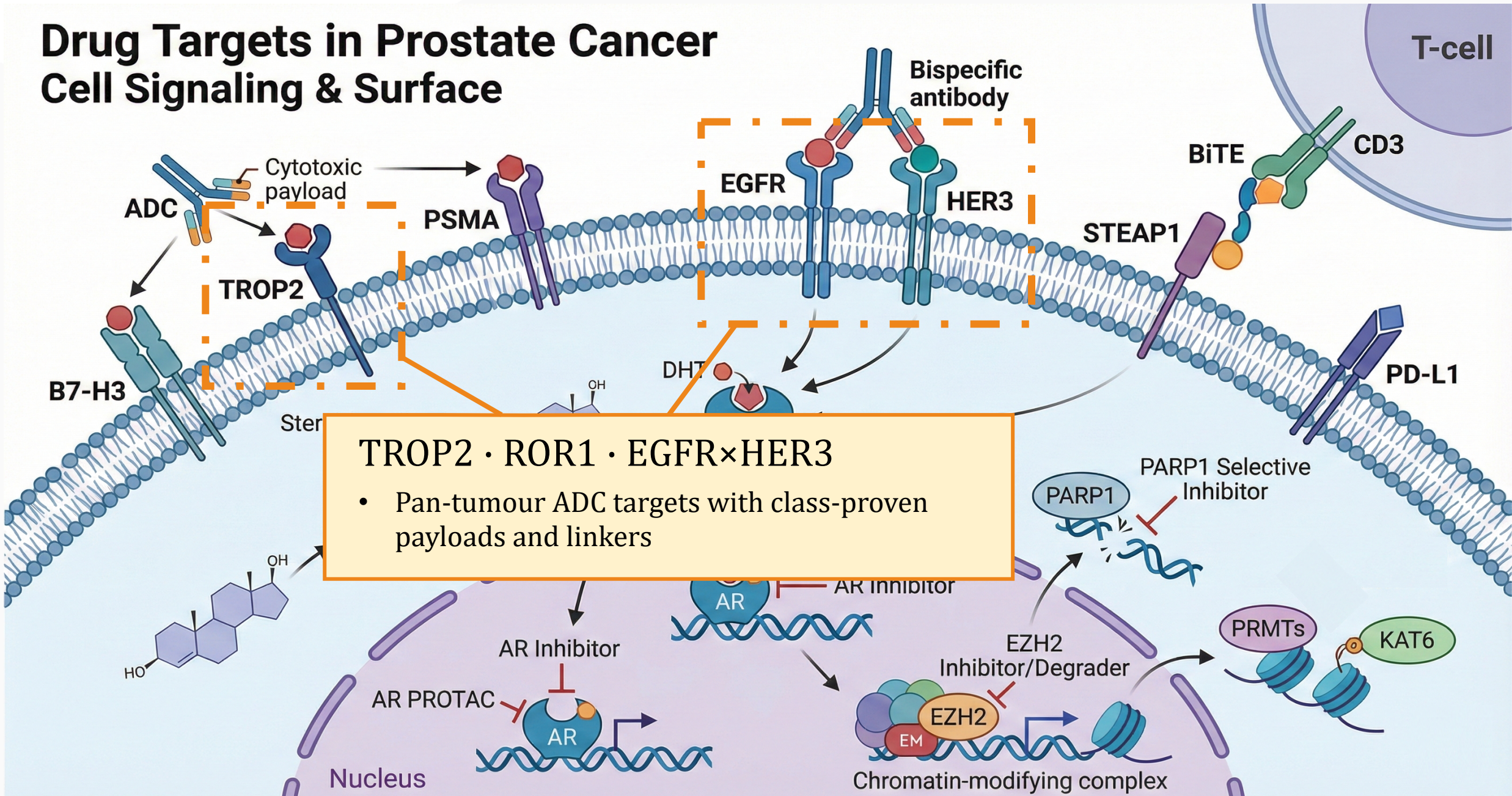
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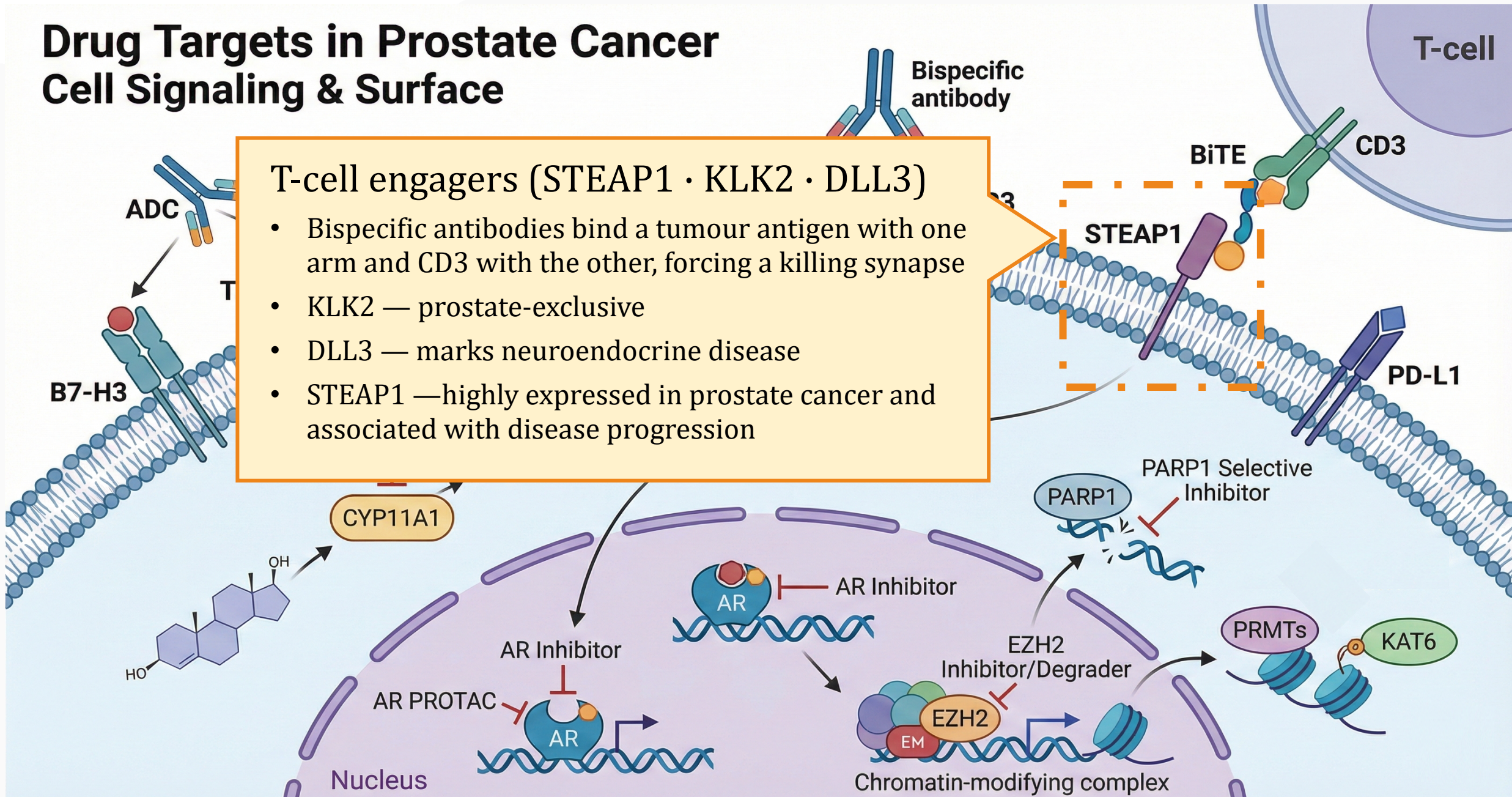


Drug Targets in Prostate Cancer

Cell Signaling & Surface

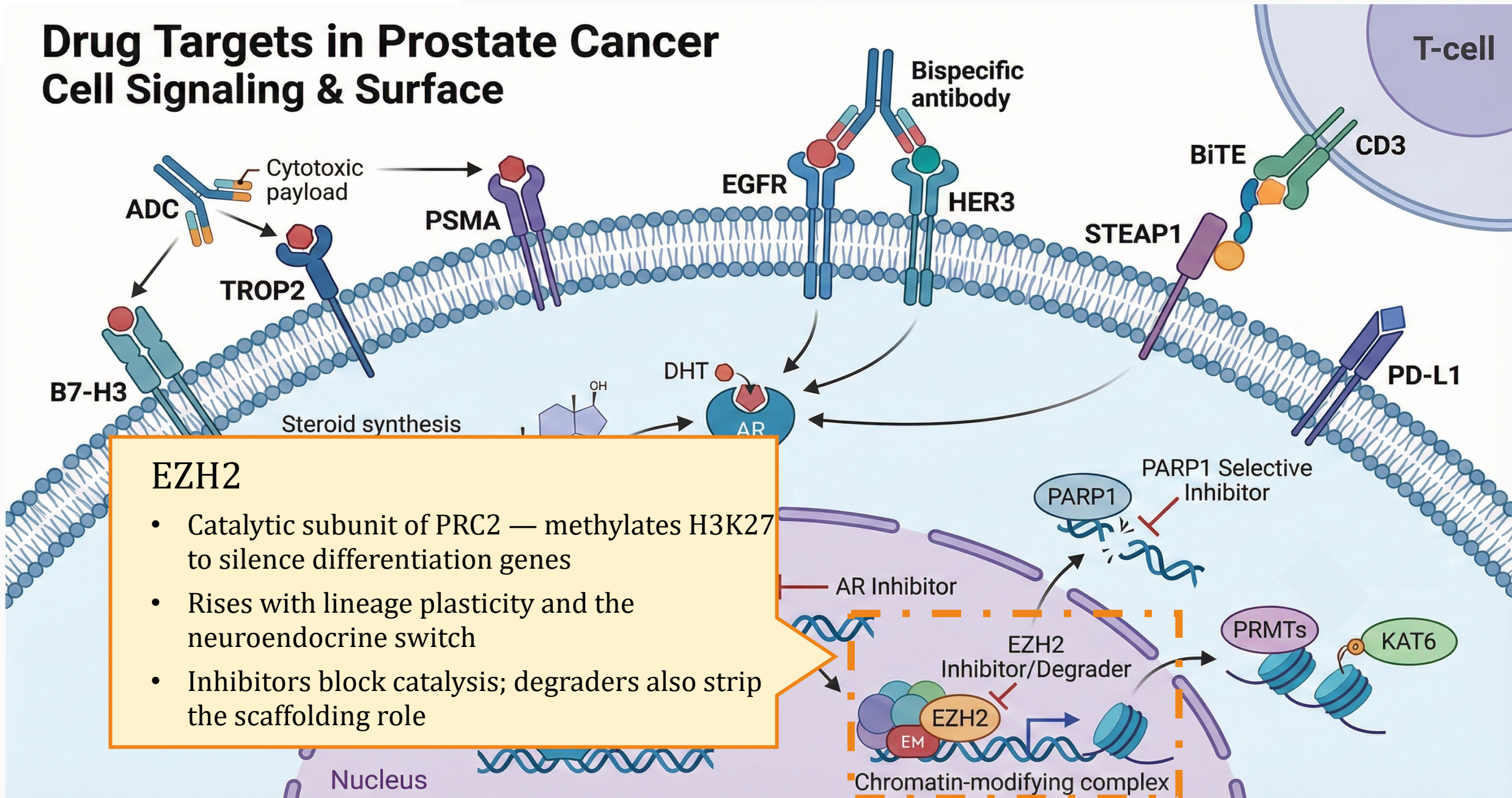
T-cell engagers (STEAP1 · KLK2 · DLL3)

- Bispecific antibodies bind a tumour antigen with one arm and CD3 with the other, forcing a killing synapse
- KLK2 — prostate-exclusive
- DLL3 — marks neuroendocrine disease
- STEAP1 — highly expressed in prostate cancer and associated with disease progression



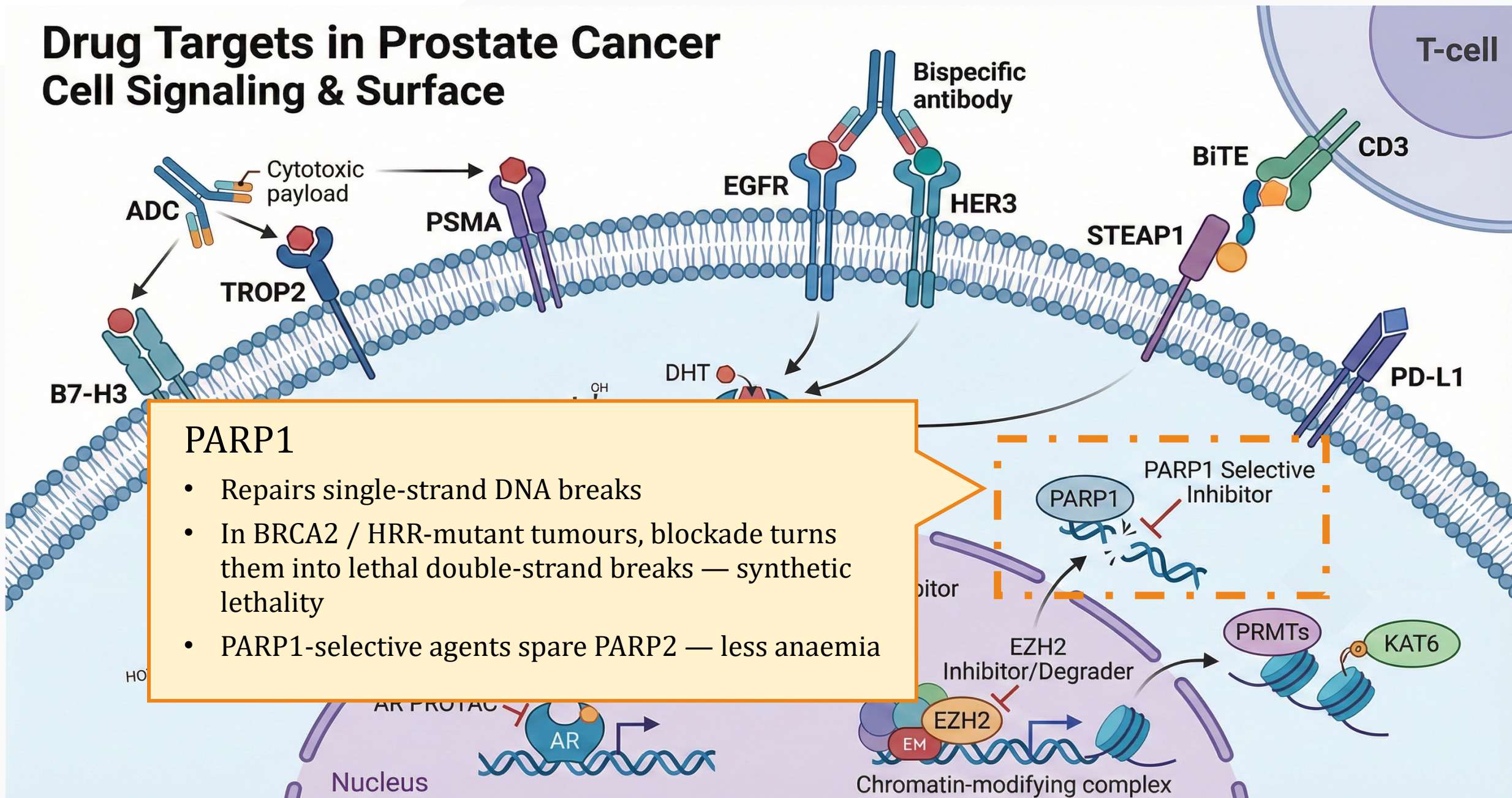
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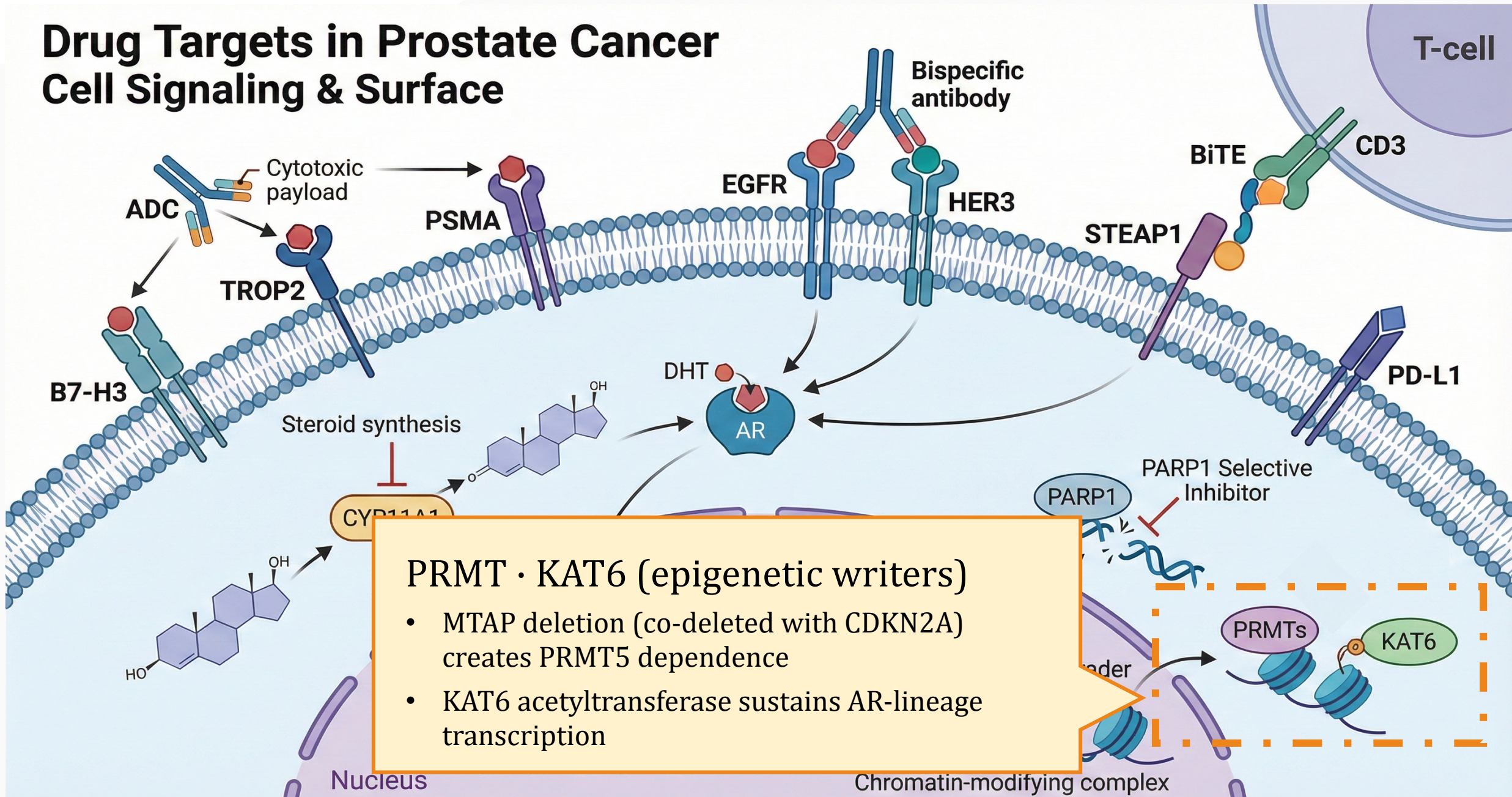
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Drug Targets in Prostate Cancer

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Part 02

Progress, Target by Target

--B7-H3 · PSMA · STEAP1, KLK2 · EZH2, PARP, AKT · AR

B7-H3 ADCs

Feature / Drug	YL201 MediLink Therapeutics Phase II	DB-1311 / BNT324 DualityBio / BioNTech Phase III	HS-20093 / GSK5764227 Hansoh Pharma / GSK Phase II	I-DXd / DS-7300a Daiichi Sankyo / Merck Phase III
Target & Antibody	B7-H3 (Humanized IgG1)	B7-H3 (Monoclonal Antibody)	B7-H3 (Fully Humanized IgG1)	B7-H3 (Humanized IgG1)
Payload	TOP1 Inhibitor	TOP1 Inhibitor	TOP1 Inhibitor	TOP1 Inhibitor
Linker	Tumor Microenv.-Activated Cleavable (TMALIN®)	Cleavable Linker	Cleavable Linker	Cleavable Linker
DAR Value	8	~6	~4	~4
Objective Response	Pending (SCLC ORR 54.2%)	34.5%	38.9% Taxane-pretreated / 41.7% Taxane-naïve	25%
PSA50 Response	Pending	35.4%	40.7% pretreated / 23.8% naïve	Not Disclosed
rPFS / DOR	Pending	Median rPFS: 11.3 mo · DOR: 10.2 mo	Follow-up Ongoing	Median DOR: 6.4 mo
Safety — grade ≥3 focus	Neutropenia 31.7% · leukopenia 29.5% · anaemia 25.0% · ILD only 1.3% · discontinuation 5.4%	Mostly grade 1–2 nausea + haematologic events; no new signals	Mainly neutropenia and anaemia — manageable	DXd class — ILD: 12% any grade, ~4% grade ≥3 (SCLC programme)

Summary: B7-H3 ADCs demonstrate ~30–40% ORR in heavily pretreated mCRPC, indicating breakthrough potential in late-line treatment.

PSMA — from approved beta RLT to alpha emitters

① APPROVED — MOVING EARLIER

^{177}Lu -PSMA-617 · Pluvicto — Novartis

- VISION — OS benefit after ARPI and taxane; the practice-changing approval
- PSMAfore — rPFS benefit pre-taxane, ARPI-failure mCRPC
- PSMAAddition — moves RLT into mHSPC, on top of ARPI

APPROVED — mCRPC · mHSPC ph 3 positive

② A BETTER BETA

^{177}Lu -PNT2002 · Lantheus / POINT
SPLASH ph 3 — rPFS HR 0.71 post-ARPI;
filing under way

PHASE 3 POSITIVE

^{177}Lu -PSMA-I&T · Curium

Alternative beta ligand, long academic
record — ECLIPSE ph 3

PHASE 3 — ECLIPSE

TLX591 · Telix

Antibody-based ^{177}Lu RLT — long
tumour retention, two-dose regimen

PHASE 3 — ProstACT GLOBAL

③ ALPHA EMITTERS — POST- ^{177}Lu

^{225}Ac -AAA817 · Novartis

PSMA-617 ligand armed with an alpha
emitter — PSA50 ~40–70% after ^{177}Lu
failure; xerostomia ~50% is the price

PHASE 3 — AcTFirst · AcTION ph 2/3

FPI-2265 · Bristol Myers Squibb

^{225}Ac -PSMA-I&T — alpha RLT studied in
both ^{177}Lu -naive and -refractory mCRPC;
dose optimisation ongoing

PHASE 2/3 — AlphaBreak

PSMA — the China wave

Programme	Differentiating feature	Evidence and design	Stage
177Lu-LNC1011 LNCYT	Albumin-binding dansylamide core — longer blood half-life, higher tumour uptake and retention	ORR 50% · DCR 100% (ph 1); IIT (Peking Union): PR/SD at 75–100 mCi	Phase 1/2
177Lu-JH020002 Bivision	Higher PSMA affinity than PSMA-617	Ph 1: 1.85 → 8.88 GBq, accelerated titration; ph 2 at RP2D; US–China dual IND	Phase 2
HRS-4357 Hengrui	strong preclinical activity in bone- metastasis models	Ph 1 dose escalation; ph 2 cohort expansion — cohort A: monotherapy in mCRPC; cohort B: + SOC in mHSPC	Phase 3 ongoing
MHB048C Minghui Pharma	PSMA-targeted ADC	First-in-human dose escalation in PSMA- positive advanced PCa	Phase 1
GenSci143 GeneScience Pharma	B7-H3 × PSMA bispecific ADC	First-in-human dose escalation in advanced PCa	Phase 1

ADCs: Targets Beyond B7H3 and PSMA

Drug	Target	Phase	Rationale
sac-TMT (SKB264) Kelun-Biotech	TROP2	Ph 1/2	Already approved in China (TNBC, EGFR-mutant NSCLC); TROP2 class proven in breast/bladder — prostate cohorts open
BL-B01D1 (iza-bren) Biokin	EGFR × HER3	Ph 1/2	First-in-class bispecific ADC — ph 3 in NPC: ORR 54.6% vs 27.0% (PFS HR 0.44), approved in China; prostate cohort open
HDM2005 Huadong Medicine	ROR1	Ph 1	MMAE payload; ROR1 marks aggressive, stem-like tumour cells

TCE Programmes

Pasritamig · KLK2 × CD3 (J&J) — phase 3 running

- **PSA50 42.4%** · rPFS 7.9 months · n = 174, median 4 prior lines
- **The cleanest TCE** to date
- **CRS 8.9%, all grade 1** · no ICANS · grade ≥3 TRAEs only 9.8% · infusion reactions 24.4%, all grade 1–2.
- One infusion **every 6 weeks** — suitable for routine outpatient practice.

Lesson 1: a target without expression in normal organs largely mitigates the safety problem.

Xaluritamig · STEAP1 × CD3 (Amgen)
— phase 3 vs cabazitaxel

- **PSA50 49%** · PSA90 30% · **ORR 24%** · OS 17.7 months (phase 1)
- STEAP1 expressed in **~80%** of advanced PCa — **no IHC selection required**.
- **CRS 72–78%, mostly grade 1–2**, cycle 1 only. Unique signal: myalgia 61% (30% grade ≥3), arthralgia 22%.
- mHSPC combination studies ongoing — TCEs are moving into **earlier lines** of therapy.

Lesson 2: a less restricted target remains viable when dosing is engineered (step-up, longer intervals) and CRS is managed early.

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Sources: pasritamig ph 1 (Baldini C et al., JCO / ASCO 2025 abstr 5017); xaluritamig FIH, Cancer Discov 2024 & updates (NCT04221542).

The Intracellular Front — PARP, AKT, and EZH2

Programme	Target	Efficacy	Safety — watch for	Status 2026
Niraparib + abiraterone GSK · Janssen	PARP inhibitor + ARPI	AMPLITUDE: rPFS HR 0.63 (0.49–0.80) overall HRRm; 0.52 in BRCA1/2, 0.46 in BRCA2 — median NE vs 26.0 mo	Blood counts, blood pressure	Approved Dec 2025 — BRCA2-mutated mCSPC
Capivasertib + abiraterone AstraZeneca	AKT inhibitor + ARPI	CAPItello-281: rPFS 33.2 vs 25.7m, HR 0.81 (0.66–0.98), P = 0.034 — first proven AKT benefit in prostate cancer	Rash, diarrhoea, hyperglycaemia	Approved 2026 — PTEN-deficient mHSPC
Saruparib (AZD5305) AstraZeneca	PARP1-selective inhibitor	Phase 2: greater PARP1 selectivity with less marrow toxicity	Anaemia	Phase 3 running
Mevrometostat + enzalutamide Pfizer	EZH2 inhibitor + ARPI	Phase 2: rPFS benefit after abiraterone failure	Class effects mild to date	Phase 3 running

AR remains the target

AR degraders (PROTAC and beyond)

Programme	Mechanism · class	Efficacy — early data	Safety — watch for	Status
ARV-766 Arvinas · Pfizer	AR degrader — PROTAC	PSA50 50% in AR-LBD-mutant mCRPC	Better tolerated than ARV-110 — less fatigue, nausea, diarrhoea	Phase 3 planned
BMS-986365 Bristol Myers Squibb	Degrader + AR antagonist	PSA50 32% overall · 50% at 900 mg BID · rPFS 16.5m chemo-naïve	QTc 47% (9% grade 3) · bradycardia 34% — no grade 4–5 events	Phase 1/2
HLD-0915 — RIPTAC Halda	AR as docking site — suppresses BRD4	Active after ARPI, taxanes, ¹⁷⁷ Lu, even after AR degraders	—	Phase 1 · FDA fast-track
HRS-5041 · TQB3201 Hengrui · CSPC Zhengda	AR degraders — China	—	—	Phase 1/2

AR remains the target

CYP11A1 — upstream blockade of androgen synthesis

Programme	Mechanism · class	Efficacy — early data	Safety — watch for	Status
MK-5684 / ODM-208 Merck	CYP11A1 inhibitor — upstream synthesis blockade	PSA50 53.3% in AR- mutated mCRPC (CYPIDES ph 2)	Cortisol blockade — low-dose steroid replacement incorporated	Phase 2/3
INV-9956 Yuanli Bio	CYP11A1 inhibitor — China-origin	—	—	Phase 1/2
Abiraterone nanocrystal	Improved ARPI formulation	Exposure independent of meals	—	Phase 3

Candidates for the next phase-3 landscape

Target	Characteristic	Drug and stage	Early signal
DLL3	Marks the neuroendocrine lineage	Tarlatamab (TCE, ph2) · DLL3 radioligands (ph1)	ORR 10.5% → 22.2% in DLL3-high · CRS 75% but only 1 case grade ≥3
hK2 (KLK2)	Prostate-restricted like PSMA, with a cleaner normal-tissue profile	²²⁵ Ac-JNJ-69086420 (alpha RLT, ph1/2)	PSA50 responses after ¹⁷⁷ Lu failure · cytopenias are the expected on-target toxicity
ACP3 (PAP)	On >95% of prostate cancers — including PSMA-low and NEPC; nearly absent from salivary glands and kidney	⁶⁸ Ga-OncoACP3 PET (FIH 2026) · ¹⁷⁷ Lu / ²²⁵ Ac-OncoACP3 · RYZ701/711 (RayzeBio/BMS)	FIH PET outperformed matched PSMA scans in 11/25 pairs; first ¹⁷⁷ Lu patients treated safely
ROR1	Oncofetal antigen — tumour-restricted	HDM2005 ADC (ph1)	Dose escalation; lymphoma experience supports the target
EZH1/2	Epigenetic driver of lineage plasticity and switching	Valemetostat (ph1/2) · mevrometostat (ph3)	Combinations with ARPI designed to slow lineage escape
≠ Double targets	B7-H3×PSMA / EGFR×HER3	GenSci143 · BL-B01D1 (ph1)	First-in-human dose escalation — monitor expression pairing

Part 03

From Target to Praticice

--Pace map, selection, and what comes next

The state of play — where each target stands

Target	Lead modality	Lead programmes	Furthest stage — pace
PSMA - beta	Radioligand therapy	¹⁷⁷ Lu-PSMA-617	Approved — VISION, PSMAfore; moving earlier
PARP	PARP inhibitor + ARPI	Niraparib + abiraterone	Approved — AMPLITUDE, BRCA2-mutated
AKT	AKT inhibitor + ARPI	Capivasertib + abiraterone	Approved — CAPItello-281, PTEN-loss
PSMA- alpha	Alpha RLT	²²⁵ Ac-AAA817	Phase 3 — AcTFirst, AcTION
B7-H3	ADC	I-DXd · YL201 · HS-20093 · DB-1311	Phase 3 — IDEate-Prostate01; a four-ADC race
EZH2	Inhibitor / degrader + ARPI	Mevrometostat · XNW5004 · AXT-1003	Phase 3 — MEVPRO-3
AR	Degraders · CYP11A1 inhibitors	BMS-986365 · MK-5684 · ARV-766	Phase 3 — rechARge; MK-5684 vs ARPI
STEAP1 · KLK2 · DLL3	T-cell engagers	Xaluritamig · pasritamig · tarlatamab	Phase 1/2 — proof of mechanism
TROP2 · ROR1 · EGFR×HER3 · PRMT · KAT6	ADCs · small molecules	Sac-TMT · BL-B01D1 · HDM2005 · CTS2190 · HRS-2189	Phase 1/2 — early

From one resistance to many: how escape biology is shifting

	Yesterday — ~2019	Today — 2026	Tomorrow — 2028+
Prior therapy at mCRPC entry	ADT, maybe one ARPI	ADT + ARPI ± docetaxel ± PARPi / AKTi	Triplets and quadruplets as standard
Dominant escape biology	AR-addicted — re-challenge effective	AR mutation / amplification enriched; AR re-wiring	Lineage plasticity; AR-low and AR-null states
Rising clinical features	Bone-dominant, PSMA-high	More visceral disease, PSMA-low, t-NEPC	Intra-patient heterogeneity as the rule
Target opportunities	PSMA, AR	Lineage-stable antigens: B7-H3, STEAP1, KLK2 · AR degraders	DLL3, EZH2, ROR1 · dual-target ADCs · lineage-agnostic payloads
Trial design	"Post-ARPI" treated as a single population	Stratify by prior exposure and ctDNA	ctDNA- and IHC-defined cohorts; re-biopsy built in

A framework for selection -- Test First, then Treat.

At progression → reassess disease biology

PSMA-high, bone-dominant	➡ PSMA radioligand therapy — ^{177}Lu → ^{225}Ac if needed
PSMA-low or liver metastases	➡ B7-H3 ADC — YL201, DB-1311, HS-20093 or I-DXd trials
AR-LBD mutation on ctDNA	➡ AR degrader — ARV-766, BMS-986365, HRS-5041; CYP11A1 options
Good performance status — fit for synergy	➡ T-cell engager — pasritamig (Q6W, outpatient) or xaluritamig
Neuroendocrine transformation	➡ Platinum backbone now; DLL3 / B7-H3 / SEZ6-directed trials next
BRCA2 or PTEN loss (at mHSPC)	➡ Niraparib + abiraterone · capivasertib + abiraterone (approved 2025–26)

Key message: the right trial begins with the right test —

repeated at every progression (ctDNA, PET, re-biopsy). Monitoring is part of treatment.

Take-home Messages

01

Advanced platforms — ADCs, alpha-RLT, T-cell engagers and AR degraders — have entered pivotal trials and are beginning to reshape the therapeutic landscape of mCRPC.

02

For disease escaping the AR-PSMA axis — PSMA-low, visceral or lineage-shifted — antibody-guided and alpha-emitting modalities offer the most promising paths forward.

03

Frontline intensification accelerates AR-independent escape; durable control will require targeting non-AR lineage drivers and the epigenetic machinery of plasticity.

04

Precision therapy means moving from fixed line-based sequencing to continuous biological stratification — PET, ctDNA and tissue re-profiling at every progression.

Thanks for watching!

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