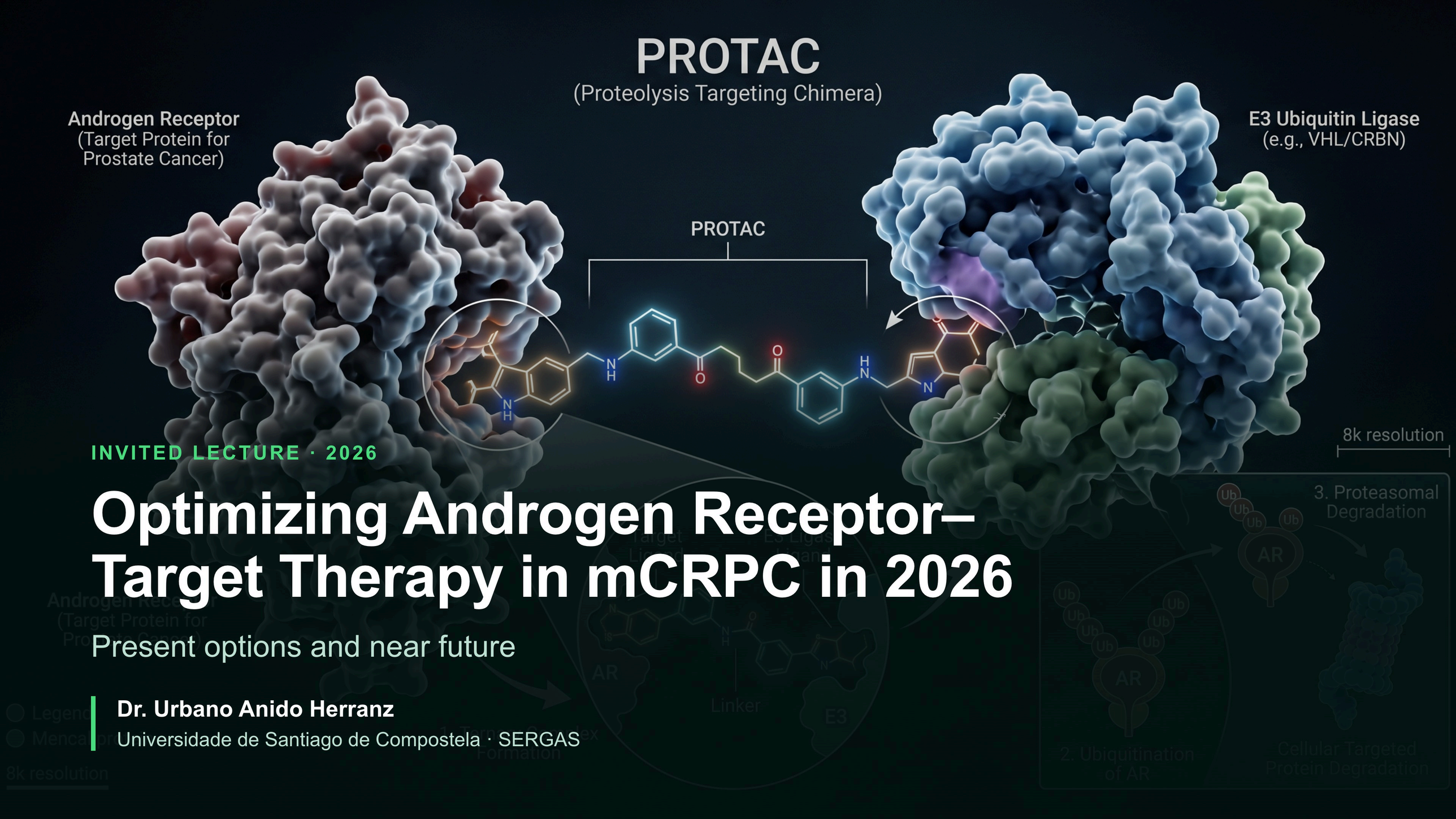


INVITED LECTURE · 2026

Optimizing Androgen Receptor–Target Therapy in mCRPC in 2026

Present options and near future

Dr. Urbano Anido Herranz
Universidade de Santiago de Compostela · SERGAS

Conflicts of interest

Stocks	Novavax · Biomea Fusion · Candel Therapeutics · Personalis · Telix
Consulting or advisory board	Novartis · Ipsen · AstraZeneca · Merck · Pfizer · Astellas · Bayer · Janssen · Recordati · MSD
Travel support	Ipsen · Bayer · Merck · Pfizer · Novartis · AstraZeneca
Honoraria	Novartis · Ipsen · Astellas · Bayer · BMS · Pfizer · Roche · AstraZeneca · Merck · Eisai · Rovi · Priothera*
Participation in clinical trials / institutional support	Pfizer · AstraZeneca · Janssen · BMS · Roche · Ipsen · Bayer · Novartis · MSD · Astellas · ITM · Gilead · Bicycle

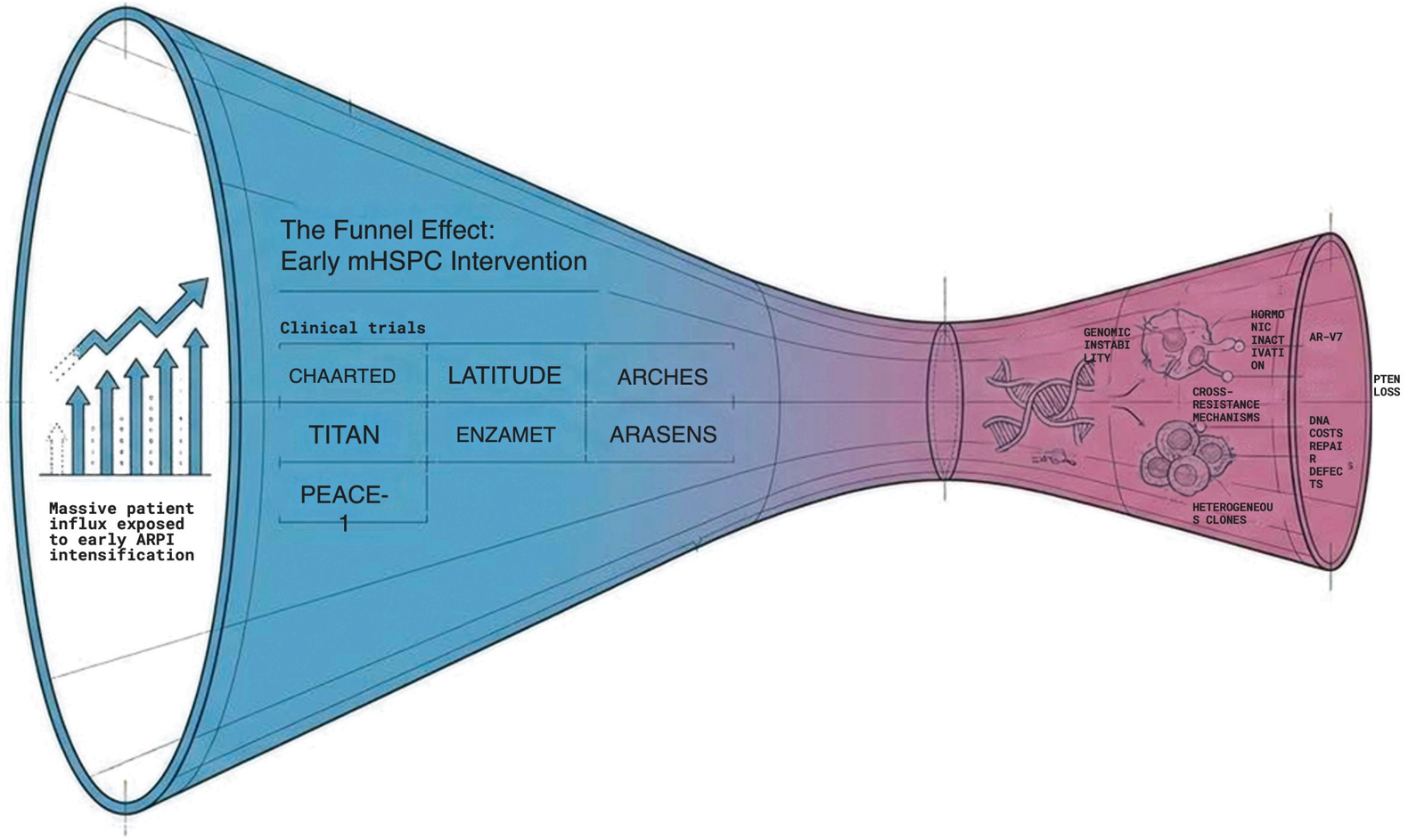
* Immediate family member

The patient has changed

And the evidence base did not follow him

PIVOTAL TRIALS VS THE CLINIC

The patient in this room has changed



FLATIRON COHORT · N = 5,361 · 2016–2023

Prior ARPI before mCRPC: 10% → 35% in five years

10.3%

prior ARPI in 2018

34.8%

prior ARPI in 2023

24.6 mo

median OS from start of first-line mCRPC

73.9% still received no treatment intensification at all before mCRPC. The migration is real but incomplete, and the trend line has years left to run.

Comparing a contemporary cohort against pivotal-trial medians is not comparing treatments. It is comparing populations.

CURRENT PROTOCOLS, NOT HISTORICAL ONES

And we are still excluding him

ARANOTE	Excluded men pretreated with second-generation antiandrogens
ARV-766 Part C	Requires patients naïve to novel hormonal agents
EPI-7386 + enzalutamide	The only randomized test of an N-terminal domain inhibitor ever conducted, run in men naïve to second-generation antiandrogens

We are still generating evidence about a vanishing patient while the real one waits.

What resistance actually looks like

Ranked by what it changes, not by biology

DECISIONAL RELEVANCE

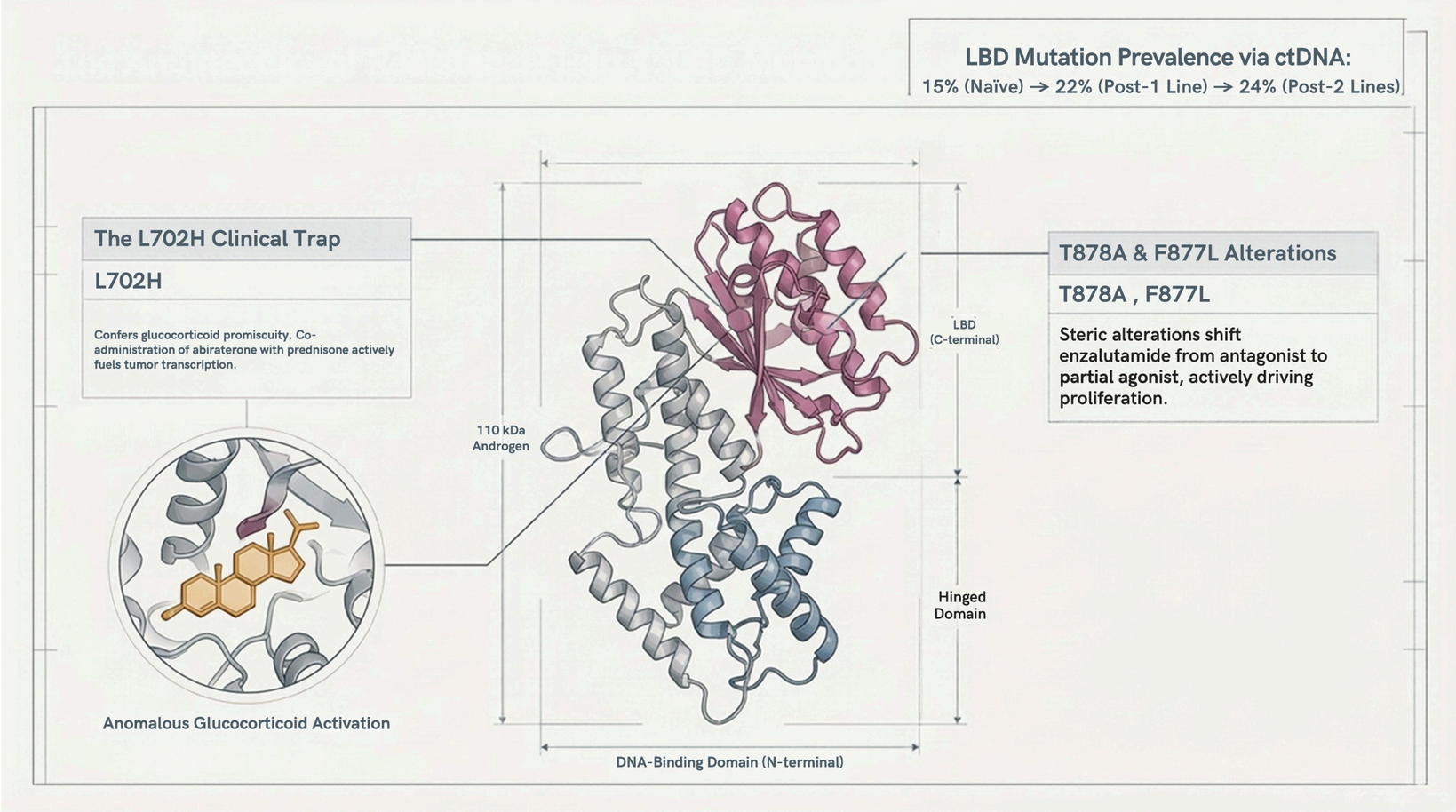
Resistance, ranked by what it changes

Level 1	Measurable and actionable	AR-LBD mutations
Level 2	Measurable, not actionable	AR amplification
Level 3	Not routinely measurable	Lineage plasticity
Level 4	Mechanistic hypothesis	CYP51A1 bypass

GUARDANT INFORM · 678 PAIRED SAMPLES

What ctDNA actually shows before and after ARPI

Alteration	Pre	Post
AR amplification	10.8%	**25.6%**
AR L702H	1.3%	**7.9%**
AR T878A	2.9%	**7.1%**



THE MOST FREQUENT POST-ARPI ALTERATION

The amplification problem

10.8%

before ARPI

25.6%

AR amplification after ARPI

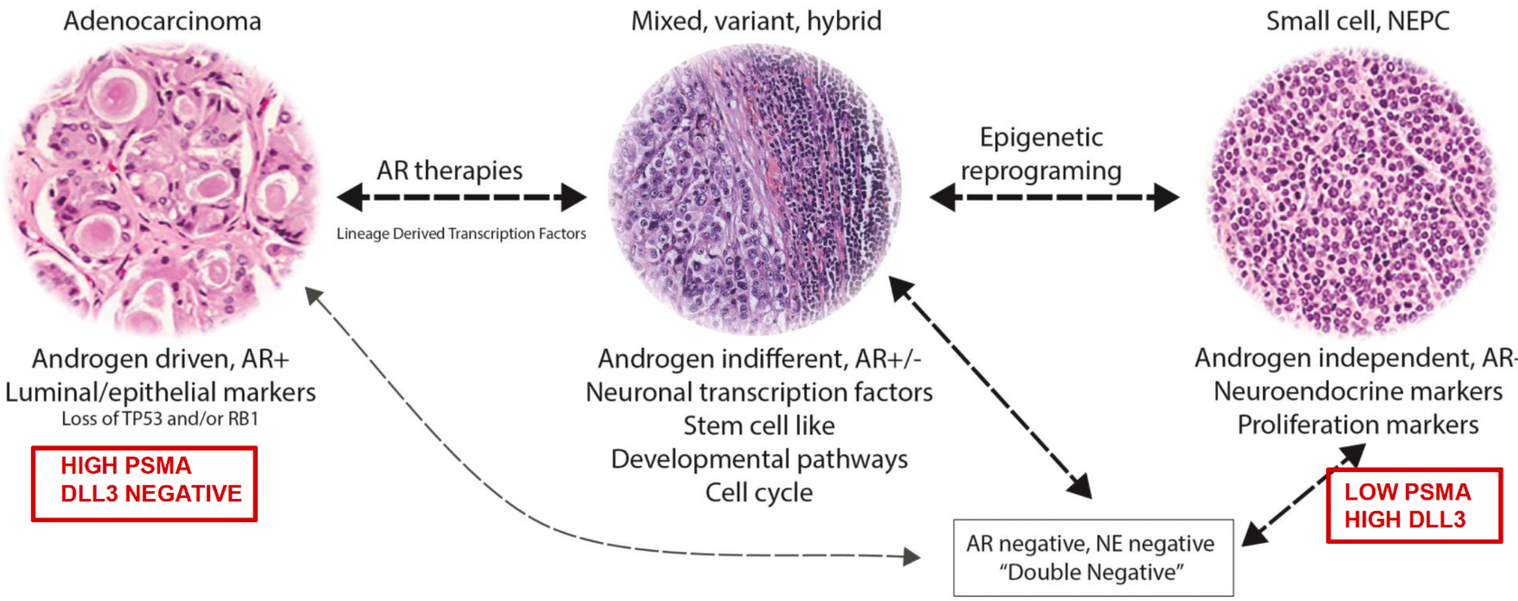
The most frequent alteration is the one nobody is targeting.

More receptor is not corrected by inhibiting the ligand better. Not one class in development specifically addresses it.

Its value today is prognostic, not predictive.

LEVEL 3 · THE CEILING ON THIS TALK

Lineage plasticity is intrapatient



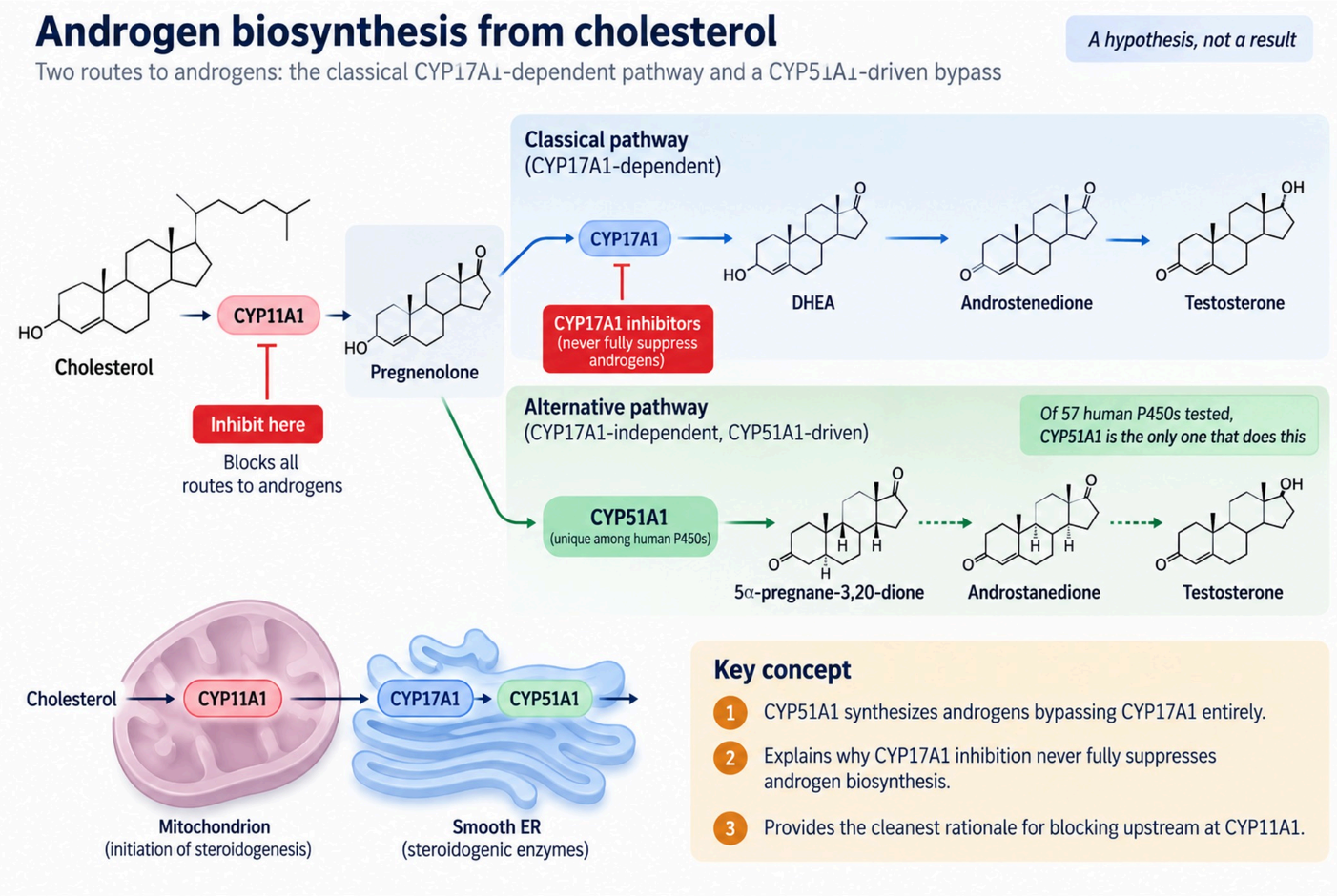
Adapted from Beltran H. et al. Clin Cancer Res 2019

Suspect it on clinical–analytical discordance: rapid visceral progression with a flat or falling PSA, liver metastases, hypercalcaemia. Confirm it only by biopsy.

No refinement of AR targeting has an answer to this — worth remembering when we discuss the next generation as though the ceiling were removable.

LEVEL 4 · MECHANISTIC HYPOTHESIS

A bypass around CYP17A1





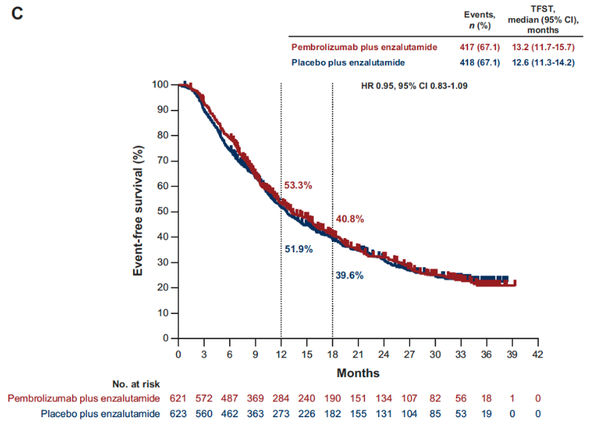
Does a second ARPI make sense?

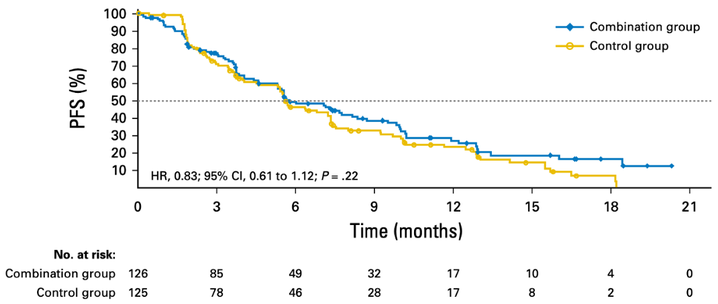
KHALAF · PHASE 2 CROSSOVER · 202 PATIENTS

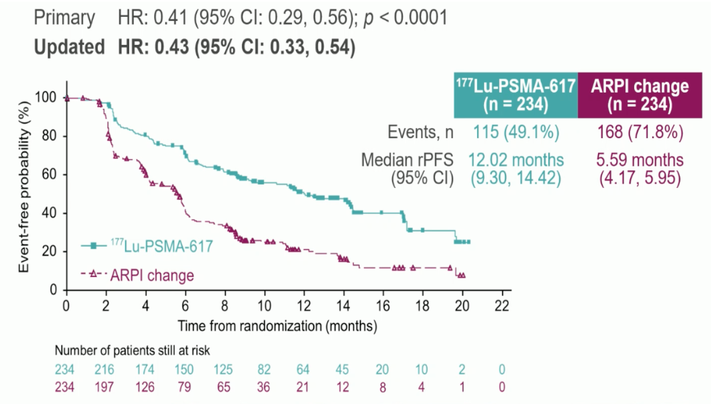
Second-line PSA response: 36% versus 4%

36% Enzalutamide after abiraterone · 26 of 73

4% Abiraterone after enzalutamide · 3 of 75







Attard G JCO 2018; Graff JN Ann Oncol 2025; Fizazi K Ann Oncol 2025

Abiraterone lowers ligand; enzalutamide blocks the receptor. A tumour that has learned to function on minimal ligand has learned nothing about receptor blockade. **If you are going to switch, there is only one direction.**

CONTACT-02 CONTROL ARM · ARPI SWITCH

4.2

months median progression-free survival

95% CI 3.7–5.7; median overall survival 15.0 months. The best documented performance of ARPI switch in a modern phase 3 trial.

Selected trial population, protocol-mandated imaging.

EAU 2026

The guidelines

"Avoid sequencing of androgen receptor targeted agents"

WEAK RECOMMENDATION

"Offer chemotherapy to patients previously treated with an ARPI"

STRONG RECOMMENDATION

AT THE POINT OF ARPI FAILURE

A decision algorithm

Step 1

ctDNA at mCRPC entry if possible

Step 2

Actionable alteration?

HRR, MSI → trial or PARP inhibitor

Step 3

Change mechanism

Taxane · ^{177}Lu-PSMA · Ra-223

Step 4

Second ARPI as exception

Frail, or declines chemotherapy

12-week gate Enzalutamide after abiraterone, never the reverse, with a pre-agreed stopping rule. If PSA has not fallen, you stop. The common error is not choosing the switch — it is continuing an inactive switch for six months.

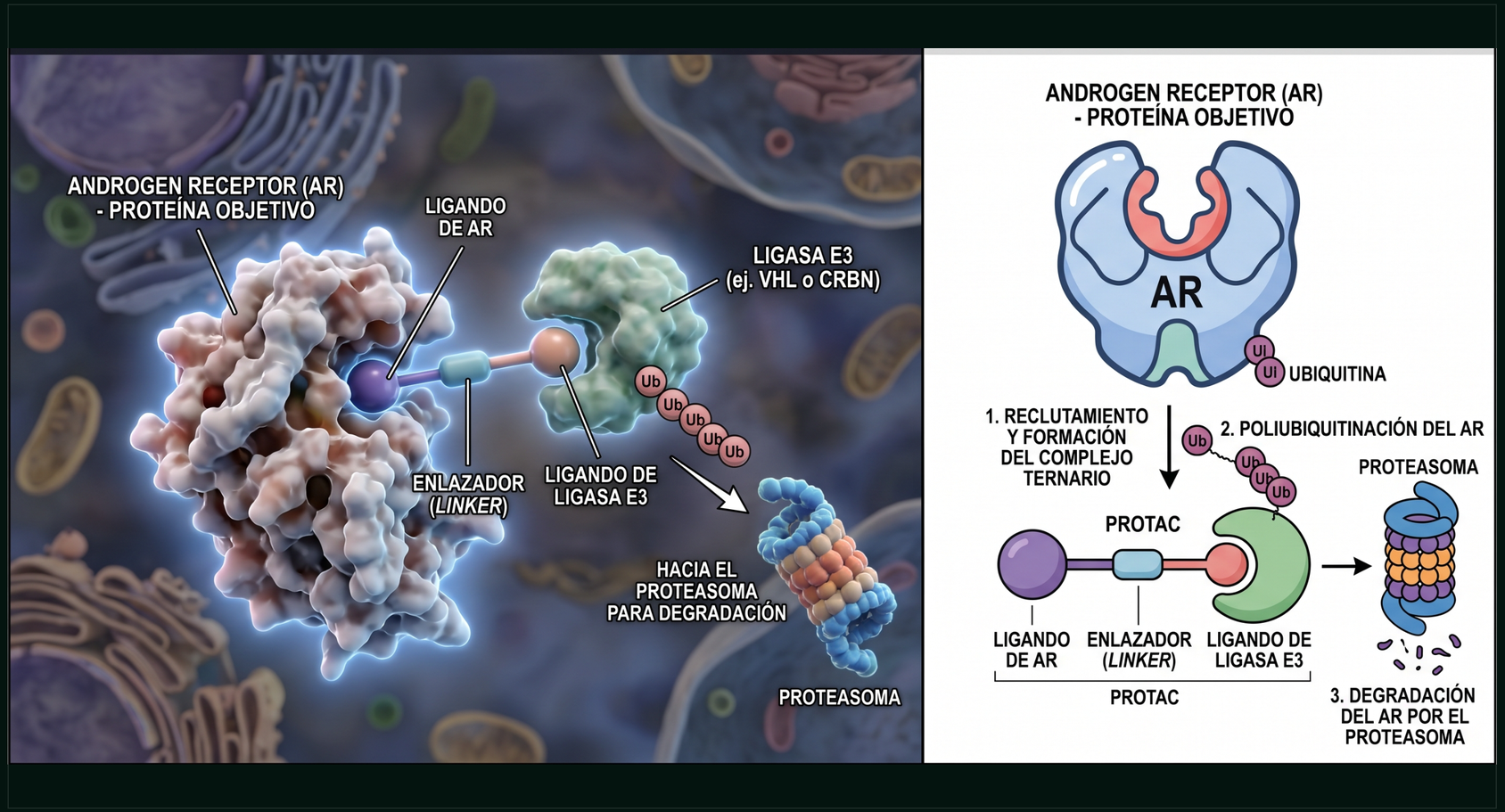
IV

Designing around resistance

Degraders, N-terminal inhibitors and upstream blockade

How a PROTAC removes the androgen receptor

PROTEOLYSIS-TARGETING CHIMERA



1 · Ternary complex. One end binds AR, the other an E3 ubiquitin ligase — VHL or cereblon

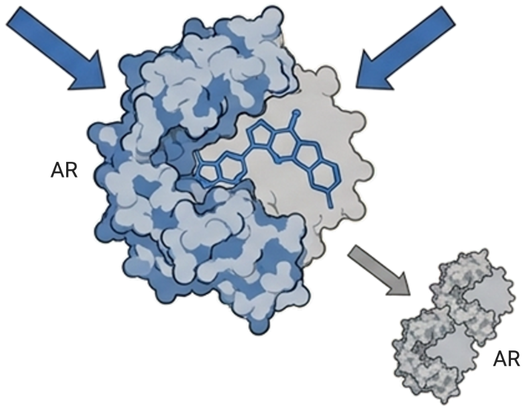
2 · Polyubiquitination. The induced complex catalyses iterative ubiquitin transfer onto the receptor

3 · Degradation. The proteasome destroys AR; the degrader dissociates and acts again

THE DESIGN SHIFT

Occupancy pharmacology versus event-driven pharmacology

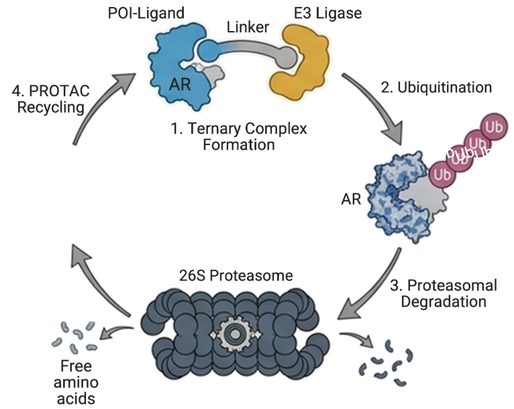
Antagonist



Must occupy the pocket continuously and out-compete ligand. Loses to amplification, to reshaped pockets, and to mutations that convert it into an agonist.

This is why LBD mutation becomes a question of **molecular coverage** rather than a verdict on the target.

Degrader



Needs only to engage the receptor long enough to tag it, then acts catalytically on the next one. Removes the protein rather than silencing it.

And it is the limit of the class too: a degrader that binds the LBD still needs an LBD. **AR-V7 has none.**

AR DEGRADERS IN CLINICAL DEVELOPMENT

Where each degrader stands

Agent	Modality	Phase · N	PSA50 mutant / WT	PSA50 in L702H	Toxicity that drives the decision
Bavdegalutamide ARV-110	PROTAC (cereblon)	1/2 · 248	**36% / —**	**8%**	AE discontinuation 10%
Luxdegalutamide ARV-766 → JSB462	PROTAC (cereblon)	1/2 · 164	**41% / —**	**50%**	No grade ≥4 AEs; discontinuation 4%
HP518 Hinova	PROTAC	1 · 22	**19% (3/16), unselected**	**not reported**	No DLT or AE discontinuation; G1–2 nausea
BMS-986365 CC-94676	Ligand-directed degrader + antagonist	1 · 95	**55% / 27%**	**not retrieved**	QTc prolongation 47% (G3 9%) Bradycardia 34%
rechARge CA071-1000	BMS-986365 vs docetaxel or 2nd ARPI	3 · 960	—	—	Readout 09-2027
AC176	Oral AR degrader	1 · 28 and 8	—	—	Both terminated
ACE-232	AR degrader	1 · 88	—	—	Recruiting · 12-2028
Masofaniten EPI-7386 + enzalutamide	AR N-terminal domain inhibitor	1/2 · 18 + 120	**88% (ph 1, ARPI-naïve)**	**not applicable**	1 G3 rash. Ph 2 PSA90 64% vs 73% enz; stopped
Pyrvinium pamoate repurposed anthelmintic	AR DBD / AR-V inhibitor	Preclinical in prostate	—	—	No prostate cancer trial

PSA50 = confirmed ≥50% decline. "Mutant" = activating mutation in the AR ligand-binding domain. Cross-row comparisons are cross-trial; populations are not equivalent.

PSA50 IN L702H TUMOURS

Degraders: a generational leap, not a new target

Bavdegalutamide · first generation

8%

11.1 months rPFS in T878A/T878S without co-occurring L702H; PSA50 54% overall

Luxdegalutamide · second generation

50%

Same target, same modality. No grade 4 events; 4% discontinuation rate

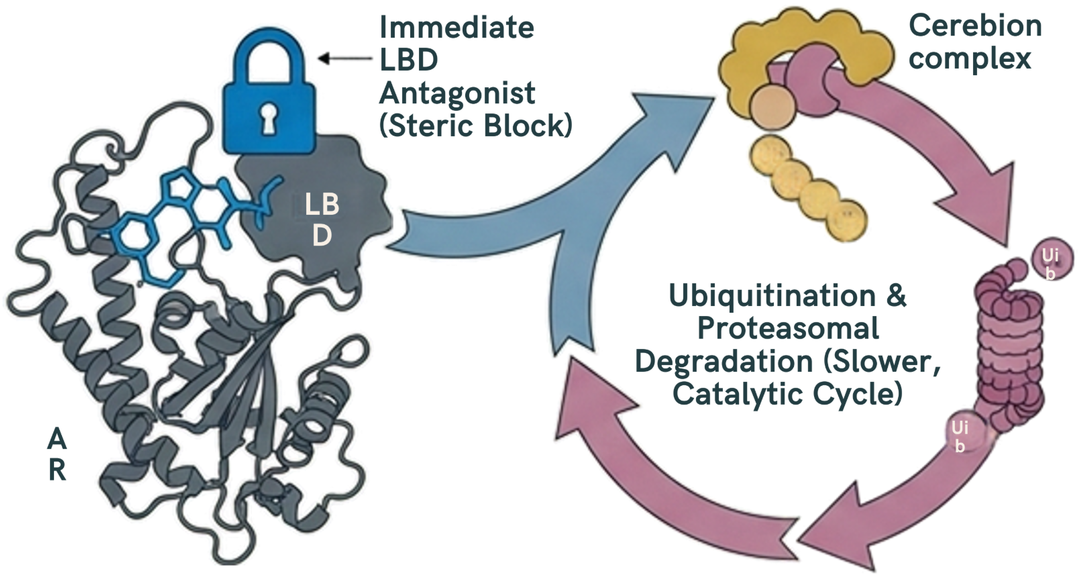
The lesson is not that degradation works. It is that **a class can fail for molecular reasons and be misread as a failed target.**

DUAL DEGRADER AND ANTAGONIST · PHASE 1 · N = 95

BMS-986365: the fullest dataset

PSA50	LBD-mutant	Wild-type
Opevesostat	53%	15%
BMS-986365	**55%**	**27%**
Luxdegalutamide	41%	not reported
ARPI switch · CONTACT-02	median PFS 4.2 months — the bar every one of these clears	

Dual ligand-directed degrader + immediate LSD antagonist.



rPFS 6.3 months overall — **16.5 months chemo-naïve versus 5.5 post-chemotherapy.**

27% in wild-type breaks the assumption that these drugs only serve the mutant tumour.

Two toxicity signatures

Degraders · BMS-986365

QTc prolongation **47%**, grade 3 in **9%**; Bradycardia **34%**. Dose-modifiable, zero attributable discontinuations.

CYP11A1 inhibition

Treatment-related adrenal insufficiency **36.2%** in phase 1, reduced to **13.3%** at the 5 mg twice-daily phase 2 dose.

Mandatory glucocorticoid and mineralocorticoid replacement, stress-dose education, a written emergency plan.

MASOFANITEN · PSA90 AT 12 WEEKS

N-terminal domain inhibition: a negative result

64%

masofaniten + enzalutamide

73%

enzalutamide alone

Population Naïve to second-generation antiandrogens, surrogate endpoint, against a comparator that already performs superbly in that setting.

The class was tested where it had least room to improve, and not where its rationale — AR-V7, ligand independence — predicts activity. **That result invalidates the design.**

CYPIDES · UPSTREAM BLOCKADE

CYP11A1: the strongest biology

53 / 15

PSA50, LBD-mutant vs wild-type (%)

68 / 29

PSA30, LBD-mutant vs wild-type (%)

19 / 5

Objective response, LBD-mutant vs wild-type (%)

Circulating testosterone fell from a median 3.0 ng/dL to undetectable **within the first week in 46 of 53 patients (87%)**, in men already progressing after at least one novel hormonal agent and one taxane. Dosing requires mandatory steroid replacement.

2026 → 2030

The three trials that will decide this

Trial	Population	Size · sites	Read-out
rechARge	BMS-986365; comparator includes docetaxel	960 · 212 sites	**September 2027**
OMAHA-004	CYP11A1 inhibition, pre-chemotherapy	1,314 · 330 sites	**May 2028**
OMAHA-003	CYP11A1 inhibition, post-chemotherapy	1,310 · 288 sites	**August 2028, possibly 2030**

Nothing is approved by EMA or FDA.

V

Two design problems

And what I would do on Monday

3,600 RANDOMIZED MEN

Stratifying is not selecting

Stratified by AR-LBD status

What rechARge, OMAHA-003 and OMAHA-004 all do. Everyone enrols; the subgroup is a planned analysis.

THIS IS THE ONLY ONE THAT EXISTS

Selected by AR-LBD status

Where all the signal is concentrated: 53 vs 15, 55 vs 27. Individually these mutations run at 7–8% in real-world ctDNA.

NOBODY IS RUNNING IT

Perhaps 15–20% of patients may supply most of the effect. **Globally positive, and we get a broad label and no idea whom to treat. Globally negative, and we bury an active class.**

THE SECOND DESIGN PROBLEM

The comparator problem

4.2

months — ARPI switch

The control arm of the CYP11A1 programme is ARPI switch — **the strategy EAU 2026 tells us to avoid.** Beating it establishes very little.

rechARge deserves credit here: it is the only one of the three whose comparator includes docetaxel.

NONE OF THESE REQUIRE A NEW DRUG

What I would do on Monday (if ...)

1 Test ctDNA at mCRPC entry

HRR and MSI change what you do today; AR status opens a trial door tomorrow. Low tumour fraction gives false negatives.

2 Change mechanism, not molecule

Docetaxel, cabazitaxel, ^{177}Lu-PSMA where avidity supports it, radium-223 with enzalutamide in bone-predominant disease.

3 Second ARPI as exception

One direction only, enzalutamide after abiraterone, with a 12-week stopping rule agreed in advance.

4 Clinical trials

The next generation is promising: degraders and N-terminal inhibitors act where the ligand-binding domain has escaped. Enrol whenever possible.