

Managing Advanced Prostate Cancer: Biomarker directed therapies in hormone sensitive disease

Dr. Patrick Pilié, MD
Associate Professor
GU Medical Oncology
Co-Director, BRCA & Genome Integrity Center

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Disclosures

Advisory Board- Astrazeneca, Johnson & Johnson
Patent- Replication stress response gene signature

Key Takeaways

- Early Escalation: data continues the trend of increasing systemic therapy earlier in the disease course
 - Perioperative apalutamide (PROTEUS) in high risk localized and tala + enza (TALAPRO-3) in metastatic hormone sensitive
 - PSMAaddition improves rPFS but not OS: is rPFS a good surrogate?
- One size no longer fits all: genomic and AI-path classifiers help identify patient who need and those who can avoid treatment intensification
 - Early biomarker testing (molecular and AI) can guide treatment sequencing across the continuum
- New targets & mechanisms in APMR: RIPTAC & TCEs promising clinical developments

Terminology: APMN/APMS/APMR = AR pathway modulator–naïve/–sensitive/–resistant (replaces hormone-sensitive / castration-resistant terms).

Prostate Cancer Treatment Landscape

High-risk localized through metastatic disease — updated to NCCN Guidelines for Prostate Cancer, v3–5.2026

High-Risk / Very-High-Risk Localized

Metastatic Disease

Hormone-Sensitive/APMS

Hormone-Resistance/APMR

HGNE/SCC

High-/Very-High-Risk Localized

- RP + pelvic lymph node dissection +/- apa/ADT
- EBRT + long-term ADT ± brachy boost
- + Abiraterone ×2y (N1 / very-high-risk)
- + Docetaxel (very-high-risk)

~2–3 years

median time to ARPI (APMR) resistance in mHSPC
OS after APMR has not meaningfully improved despite multiple new agents approved in mCRPC

APMR develops

245 potential treatment sequences with NCCN guidelines alone

mHSPC

ADT plus:

- ARPI doublet: abiraterone, enzalutamide, apalutamide, or darolutamide
- Triplet (high-vol., preferred): + docetaxel + abiraterone (PEACE-1) or darolutamide (ARASENS)
- BRCA2m: + abiraterone + niraparib (AMPLITUDE)

¹⁷⁷Lu-PSMA-617

PSMA+, post-ARPI; taxane-naïve or post-taxane
Docetaxel
Radium-223 (bone only)

PARPi +/- ARPI (HRR-altered)
Pembrolizumab (MSI-H, TMB-H)

¹⁷⁷Lu-PSMA-617

PSMA+, post-ARPI; taxane-naïve or post-taxane
Docetaxel/Cabazitaxel +/- Carboplatin
Radium-223 (bone only)
ARPI switch

PARPi +/- ARPI (HRR-altered)
Pembrolizumab (MSI-H, TMB-H)

¹⁷⁷Lu-PSMA-617

PSMA+, post-ARPI; taxane-naïve or post-taxane
Docetaxel
Radium-223 (bone only)
ARPI switch

PARPi +/- ARPI (HRR-altered)
Pembrolizumab (MSI-H, TMB-H)

Largely biomarker-agnostic treatment selection & sequencing

Once resistance to ADT + an ARPI develops, few validated biomarkers guide the choice or order of therapy. Exceptions: HRR alterations (PARP inhibitors), MSI-H/dMMR/TMB-H (pembrolizumab). Otherwise, sequencing among taxanes, radium-223, lutetium-PSAMA and ARPI switches remains largely empiric.

Abiraterone or Enzalutamide
ARPI-naïve mCRPC · or Docetaxel

t-SCNC

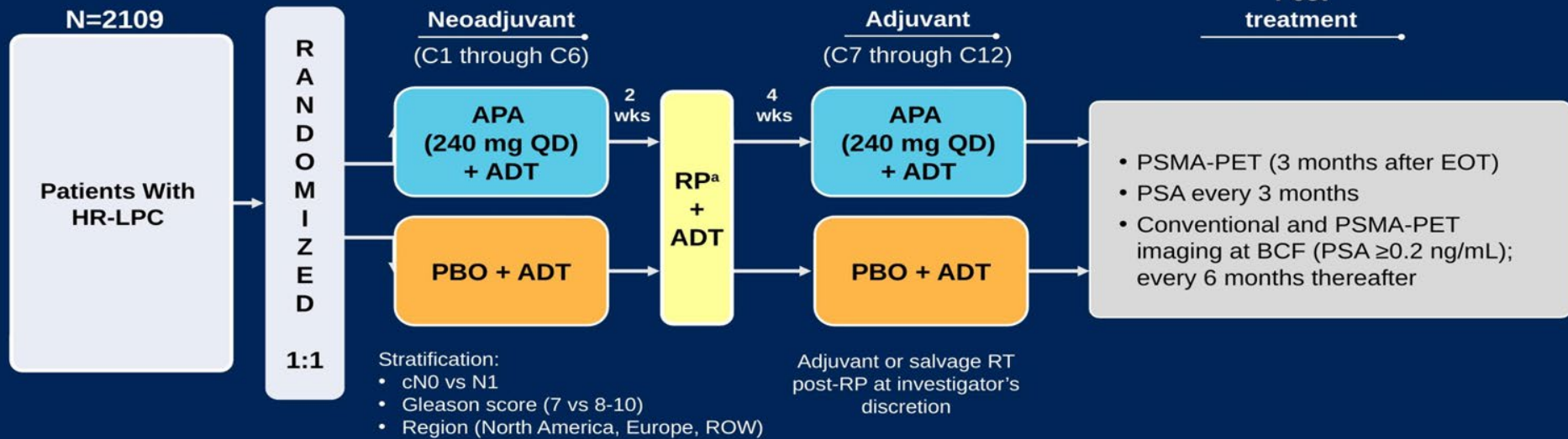
Platinum-based chemotherapy +/- atezo

The Clinical Conundrum

- 1) **Patient outcomes in advanced prostate cancer (high risk localized and metastatic) are highly heterogeneous, with baseline *predictive* biomarkers lacking**
- 2) **The depth and duration of response from anti-androgen therapy remain strong prognostic indicators**
- 3) **Pathways for cancer progression to APMR are multifactorial, and data are lacking on the right treatment selection and sequence for the right patient at the right time**

High-Risk Localized Prostate Cancer

PROTEUS: Perioperative Apalutamide + ADT



Context: The Unmet
Need in High-Risk
Localized Disease

- **Long-term (2 year) ADT + ARPi already SOC with XRT for very high risk localized disease**
- **More than half of high-risk patients relapse after radical prostatectomy alone**
- **PROTEUS asks: does adding 1 year perioperative apa + ADT improve pCR and long term outcomes vs ADT alone**

PROTEUS: Perioperative Apalutamide in High-Risk Localized Disease

Phase 3 RCT (ASCO 2026, Abstract LBA1) | Taplin ME, et al. | N=2,109 high-risk localized/locally advanced prostate cancer

8.9% vs 1.0%

Pathologic CR/MRD

Apalutamide+ADT vs placebo+ADT (OR 10.17)

HR 0.80

Metastasis-free survival

95% CI 0.67–0.96; p=0.02

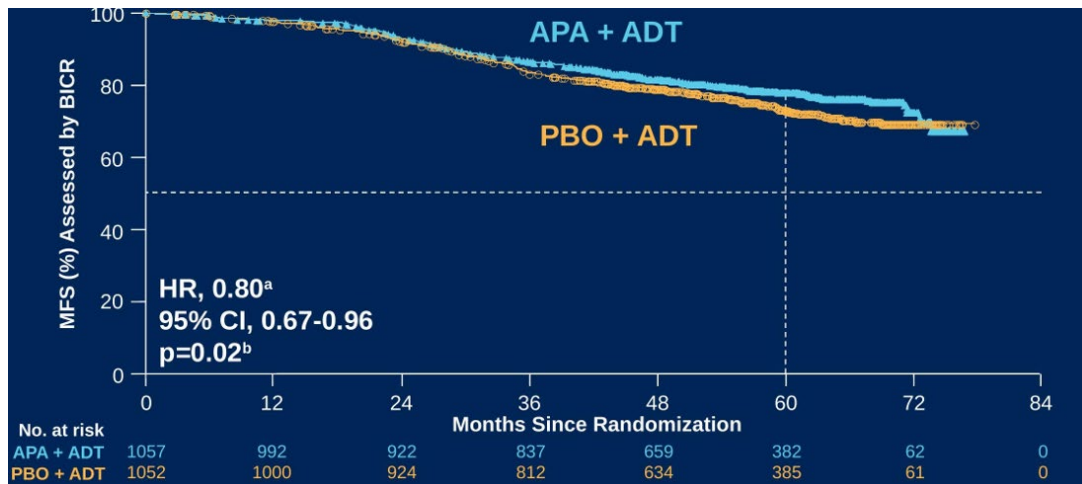
HR 0.71

Event-free survival

29% risk reduction (57.1 vs 38.4 mo)

- N=2,109 randomized 1:1 to apalutamide 240 mg/day + ADT vs placebo + ADT — 6 months neoadjuvant, radical prostatectomy, then 6 months adjuvant
- **Primary endpoint met: pathologic CR/MRD improved 9-fold with apalutamide (8.9% vs 1.0%); ypT0 rate 5.1% vs 0.4%**
- Time to first subsequent therapy: HR 0.65 — nearly 3 years added (74.2 vs 41.5 months)
- **Clinical implication:** Consider perioperative apalutamide + ADT for Gleason 8–10, ≥T3, or node-positive disease before radical prostatectomy
- **Safety:** Grade ≥3 treatment-related AEs 27.5% vs 18.9%; skin rash most common AE of special interest (33.0% vs 15.3%) — consistent with known apalutamide profile

PROTEUS: Perioperative Apalutamide in High-Risk Localized Disease



- **20% reduction in risk of metastasis or death from apa + ADT**
- Testosterone recovery to ≥ 200 ng/dL was slightly delayed (median 8.1 vs 6.6 months) but occurred in $>80\%$ of patients in both arms
- Discuss neoadjuvant/adjuvant ARPI intensification for patients with Gleason 8–10, $\geq T3$, or node-positive disease before surgery
- Early molecular and imaging staging (PSMA-PET) may help better select and monitor candidates
- Unclear if pathCR/MRD is a true surrogate; OS data not available; standard of care remains prostatectomy without ADT at all & many patients choose surgery currently as it does not require chemical castration

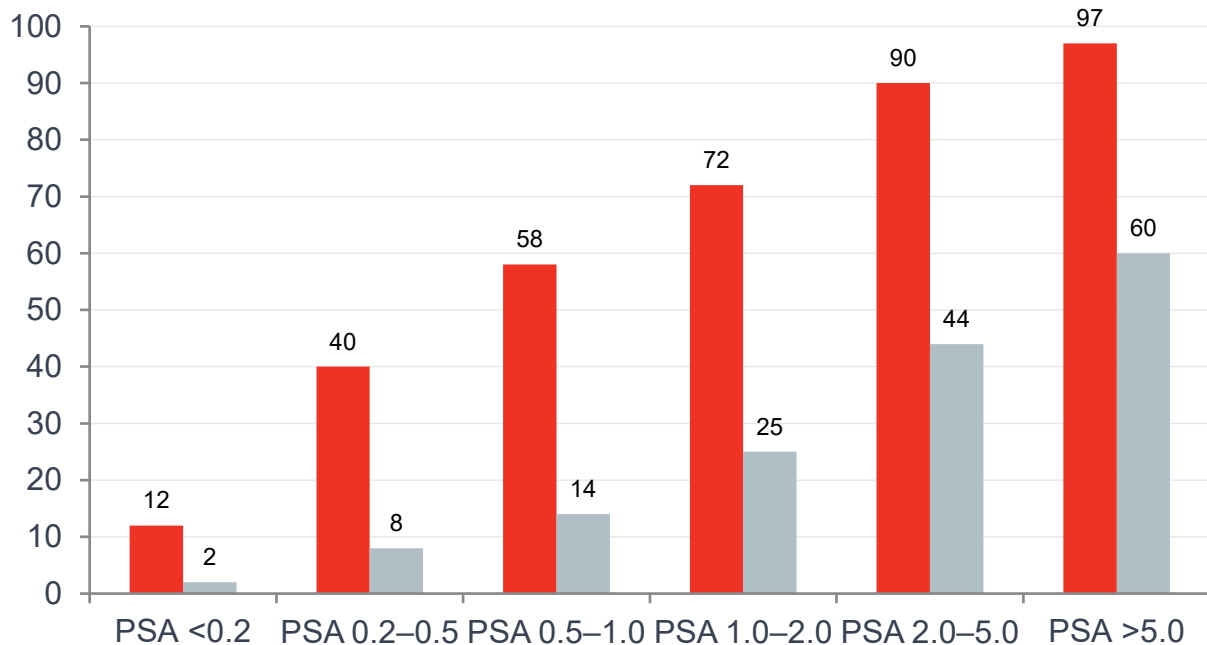
SECTION 2

Biochemical Recurrence & Oligometastatic Disease

PSMA PET — POSEIDON — EXTEND — EMBARK

PSMA PET Detection Rates by PSA Level: Redefining "Non-Metastatic" BCR

Detection Rate (%) by PSA Level (ng/mL)



Impact on BCR Classification

Most patients with BCR (PSA >0.5) previously thought to have "no detectable disease" by conventional imaging are now found to have localizable disease on PSMA PET — often oligometastatic.

Practical Thresholds (2025)

PSA <0.2: Very low yield; watch and wait

PSA 0.2–0.5: ~40% yield; image if planning targeted MDT

PSA >0.5: High yield; image routinely to guide therapy

Major guideline principle (EAU 2024): A negative PSMA PET should NOT delay salvage radiotherapy if clinically indicated.

POSEIDON: Hormone Therapy with Salvage RT

Kishan AU, et al. Lancet 2026;407:1059–1071 (MARCAP IPD meta-analysis, ASCO GU 2026 Plenary) — 6,057 patients, 6 phase 3 RCTs, median follow-up 9.0 years, pre-PSMA PET era

HR 0.79

10-yr MFS: 77.9% vs 74.1%
HT+PORT vs PORT alone (sig.)

HR 0.87

10-yr OS: 84.3% vs 83.6%
(not significant, $p=0.06$)

PSA 0.5

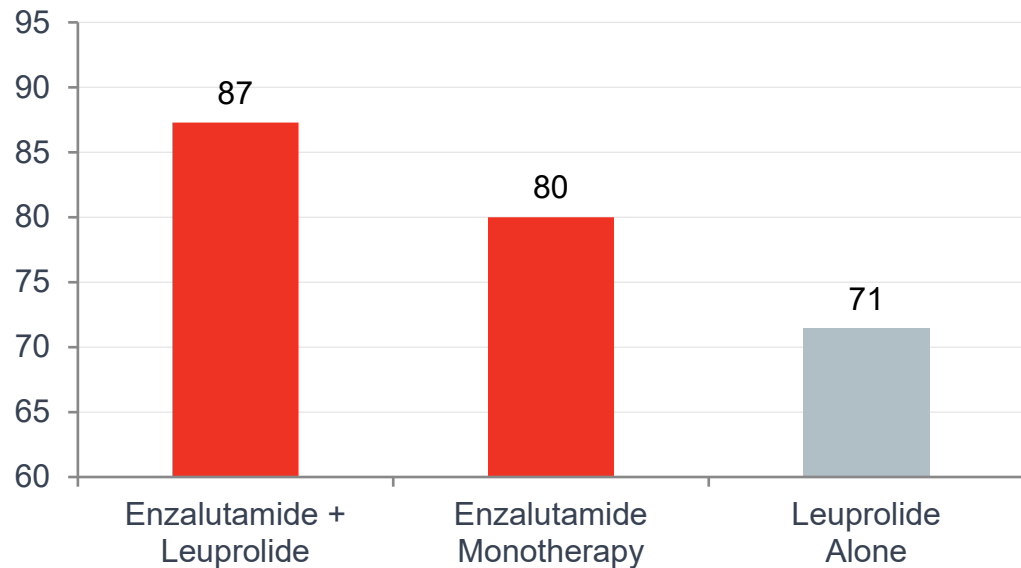
ng/mL threshold aligns with
PSMA PET positivity

- $PSA \leq 0.5$ ng/mL: no OS/MFS benefit from hormone therapy — RT alone is sufficient (~85–90% of patients in modern practice)
- $PSA > 0.5$ ng/mL: significant OS + MFS benefit — short-term HT (4–6 months) is sufficient for most; consider 24-month HT only for PSA 1.6–2.4 ng/mL
- No significant interaction by HT duration ($p=0.25$) — extending short to long HT does not further improve OS
- **Limitations:** Trial timespan 1998–2015, pre-PSMA PET era; bicalutamide monotherapy in 70% of long-term HT (RTOG 9601); Decipher unavailable — biomarker trials ongoing (BALANCE, PSMA-SRT)

HT = hormone therapy; PORT = post-prostatectomy (post-op) radiotherapy.

EMBARK: Metastasis-Free Survival — Putting the Numbers in Context

5-Year Metastasis-Free Survival (EMBARK, n=1068)



5-yr MFS 87.3% (Enza+ADT) vs 71.4% (ADT alone) — 15.9 percentage point absolute improvement

Who Is EMBARK For?

- BCR after RP or primary RT
- PSADT (PSA doubling time) ≤ 9 months (high-risk feature)
- PSA ≥ 1 (post-RP) or ≥ 2 above nadir (post-RT)
- No metastases on conventional imaging
- Testosterone ≥ 150 ng/dL

Practical Considerations

- Treatment suspended at wk 37 if PSA < 0.2 ng/mL → restarted when PSA rises
- Enzalutamide well-tolerated; no new safety signals
- QoL maintained vs leuprolide alone
- Benefit consistent across age groups (EJCA 2025 post-hoc)

Bottom Line: Enzalutamide + ADT is now a standard of care option for high-risk BCR, with confirmed OS benefit (NEJM 2025); ENZA mono did not reach OS significance in longer term follow up

"Is More Always Better?" — A Clinical Decision Framework

Tailoring Anti-Androgen + Radiation Therapy by Disease State

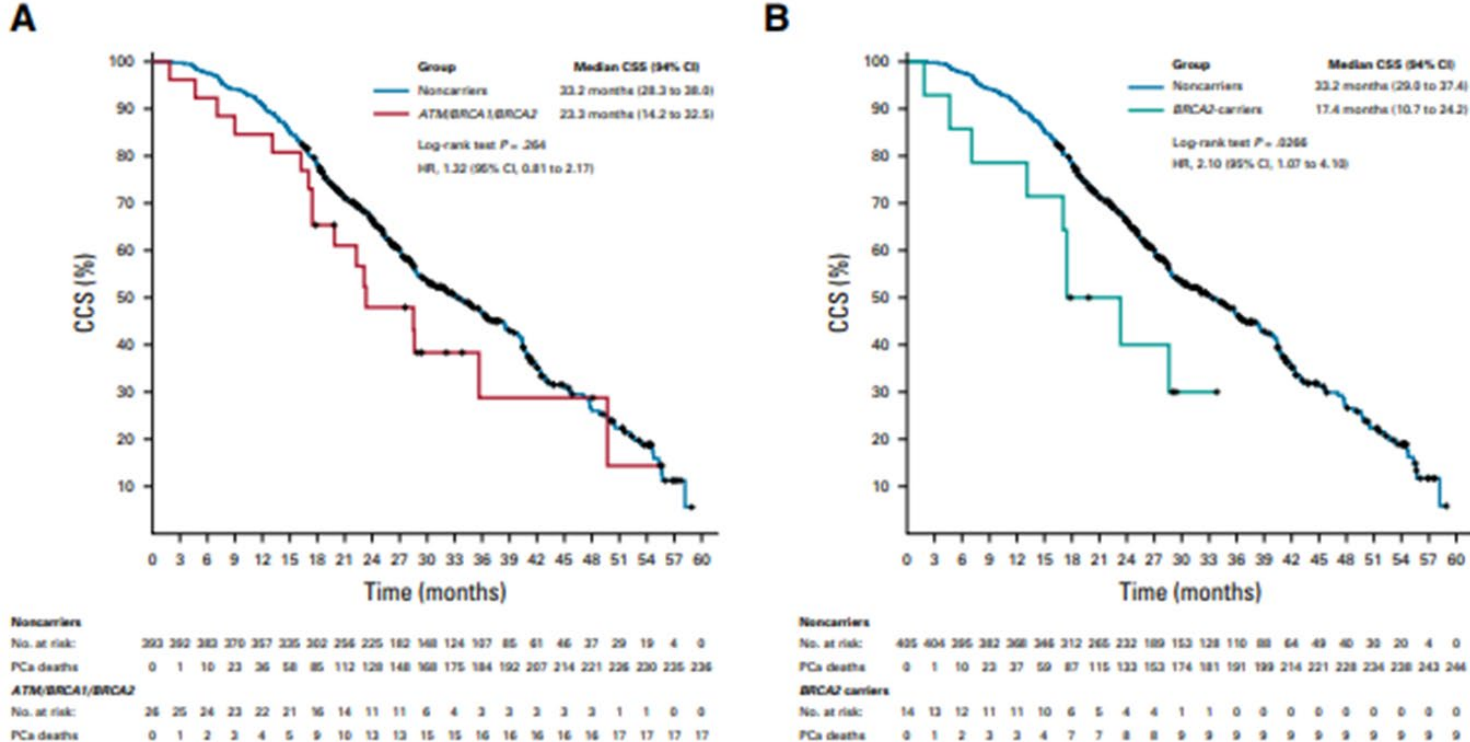
Disease State	Recommended Approach	Key Evidence	Is "More" Better?
High-Risk Localized/ Locally Advanced (NOMO)	RT + Long-term ADT (3 yr) + Abiraterone (2 yr)	STAMPEDE (Attard, Lancet 2023)	✓ Yes — Abiraterone + ADT + RT improves MFS and OS
Low-Burden Metastatic (de novo, <4 bone mets)	ADT + Abiraterone + RT to Prostate	STAMPEDE Parker Lancet 2018	✓ Yes — RT to prostate improves OS
BCR Post-RP (Higher risk: PSA ≥0.7, GG 4–5, PSADT ≤6 mo)	Salvage RT + ADT 6–24 months (duration per risk)	RTOG 9601, GETUG-AFU 16, SPPORT; AUA/ASTRO/SUO 2025	✓ Yes — ADT adds benefit
BCR Post-RP (Lower risk: PSA <0.7, favorable features)	Salvage RT alone (no ADT) or short-course ADT	RTOG 9601 subgroup; AUA/ASTRO/SUO 2025	? Uncertain — ADT may not add benefit/may harm
High-Risk BCR (Post-RP or Post-RT; PSADT ≤9 mo, no mets)	Enzalutamide + Leuprolide (EMBARK regimen)	EMBARK NEJM 2023 & 2025	✓ Yes — significant MFS & OS improvement
Oligometastatic BCR (≤5 lesions)	Systemic ARSI/ADT + MDT (SBRT to all lesions)	EXTEND PMID 40750497; ORIOLE (PSMA directed), STOMP	✓ Yes — combining RT to mets improves PFS

Metastatic Hormone-Sensitive Prostate Cancer

Biomarker-Driven Prognosis & Therapy Escalation

mCSPC = metastatic castration/hormone-sensitive prostate cancer; HRR = homologous recombination repair (e.g. BRCA1/2, ATM, CDK12).

BRCA2 and Risk of Death from Prostate Ca



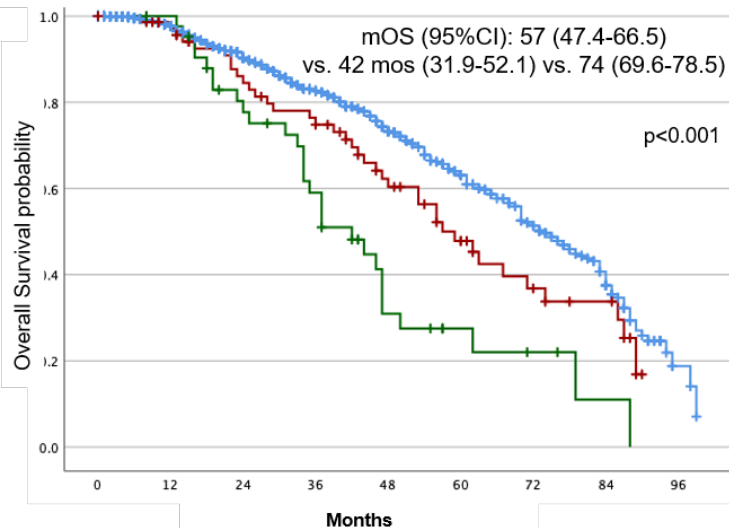
Castro et al, *JCO* 2019

- Cause-specific survival is halved in gBRCA2 carriers

Prognostic implications of BRCA alterations in mCSPC

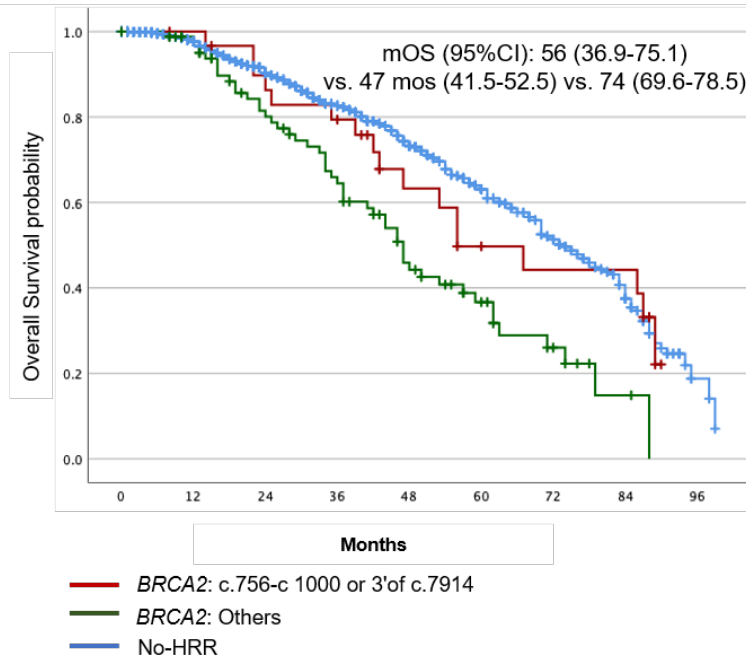
BRCA2 Functional Domains:

RAD51-BD and DBD vs. Others vs. no-HRR



BRCA2 PCCR:

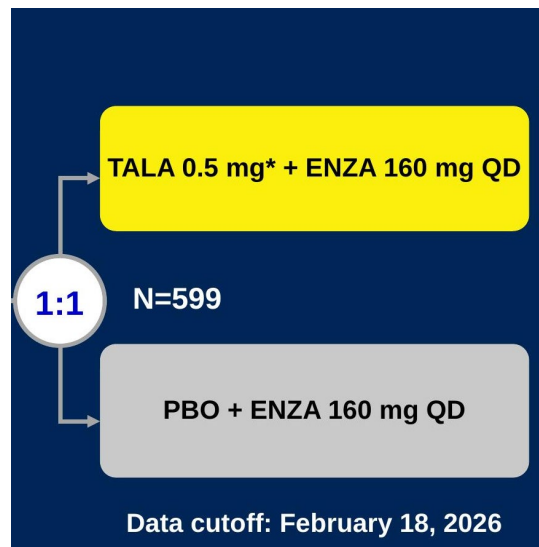
c.756-c.1000 and 3' of c.7914 vs. Others vs. no-HRR



Incorvia et al, ASCO 2026



TALAPRO-3: Talazoparib + Enzalutamide in HRR-Altered mCSPC



76.6%
TALA + ENZA, 24-mo rPFS (n=300)

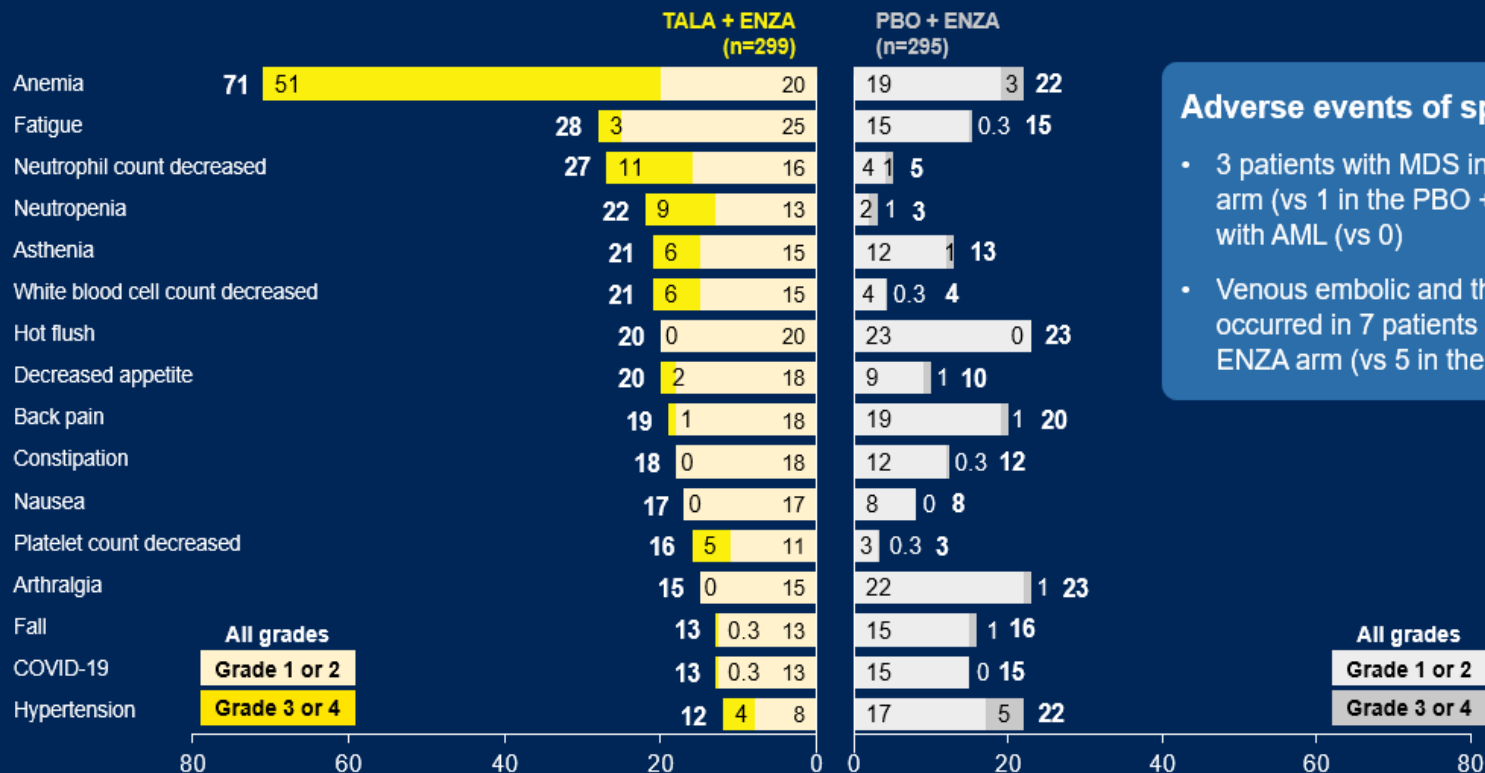
56.2%
PBO + ENZA, 24-mo rPFS (n=299)

52% reduction in risk of progression or death with TALA + ENZA -BRCA1/2-altered HR 0.37 (63% risk reduction)

HR 0.481 | 95% CI 0.357–0.647 | p<0.0001

- **Design:** Randomized 1:1 to talazoparib 0.5 mg + enzalutamide 160 mg vs. placebo + enzalutamide, both with ongoing ADT
 - **Stratification:** Stratified by de novo vs. relapsed disease, high- vs. low-volume disease, and BRCA vs. non-BRCA alteration status
 - **HRR genes tested:** ATM, ATR, BRCA1, BRCA2, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, RAD51C
 - **Endpoints:** Primary: investigator-assessed radiographic PFS met. Key secondary: Overall survival (interim): HR 0.767 (95% CI 0.564–1.044; p=0.09) — immature but favorable trend at this follow-up
 - **Safety:** Anemia and decreased neutrophil count most common; frequent dose reductions and pauses in tala
- Phase 3 RCT (LBA5007, ASCO 2026) | Agarwal N, et al. N Engl J Med 2026 May 30 (NEJMoa2604126) | N=599 HRR gene-altered mCSPC*

Most Common ($\geq 15\%$) All-Cause TEAEs



Adverse events of special interest

- 3 patients with MDS in the TALA + ENZA arm (vs 1 in the PBO + ENZA arm) and 2 with AML (vs 0)
- Venous embolic and thrombotic events occurred in 7 patients in the TALA + ENZA arm (vs 5 in the PBO + ENZA arm)

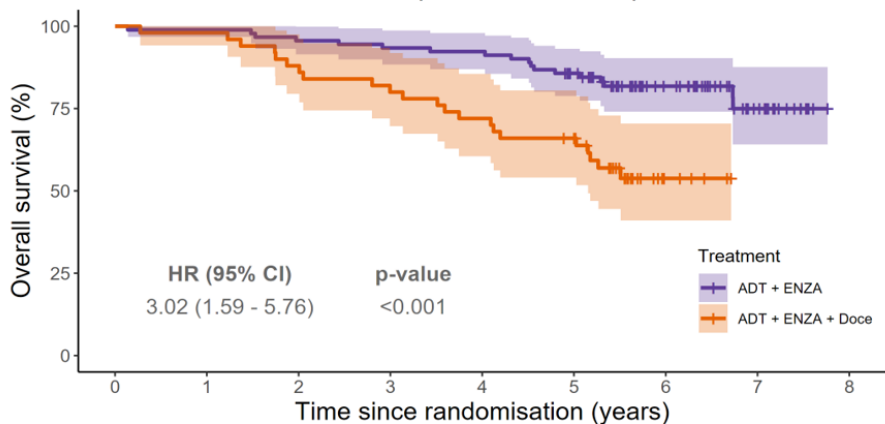
Data cutoff: February 18, 2026 (Safety population). Includes AEs occurring from the time of the first dose of study treatment through 28 days after the last dose of study treatment or before initiation of new systemic antineoplastic therapy, excluding ADT, whichever occurs first. TEAEs were graded according to NCI CTCAE v4.03.

AESI=AE of special interest; AML=acute myeloid leukemia; MDS=myelodysplastic syndrome; NCI CTCAE v4.03=National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

Decipher Genomic Classifier Predicts Docetaxel Benefit

Level 1B evidence: Decipher score >0.85 identifies who benefits from adding docetaxel

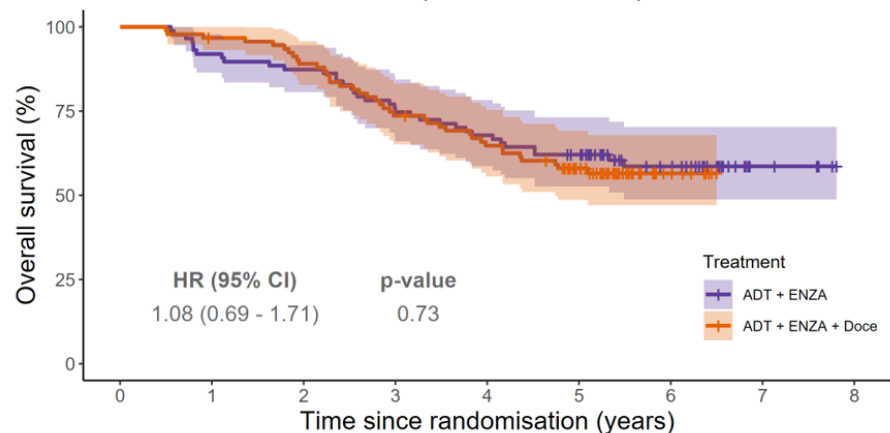
Overall survival in patients with Decipher ≤ 0.85



50	49 (98%)	44 (88%)	40 (80%)	36 (72%)	32 (66%)	5 (54%)	
91	90 (99%)	87 (96%)	85 (93%)	84 (92%)	73 (86%)	42 (82%)	17 (75%)

Number at risk (% surviving)

Overall survival in patients with Decipher > 0.85

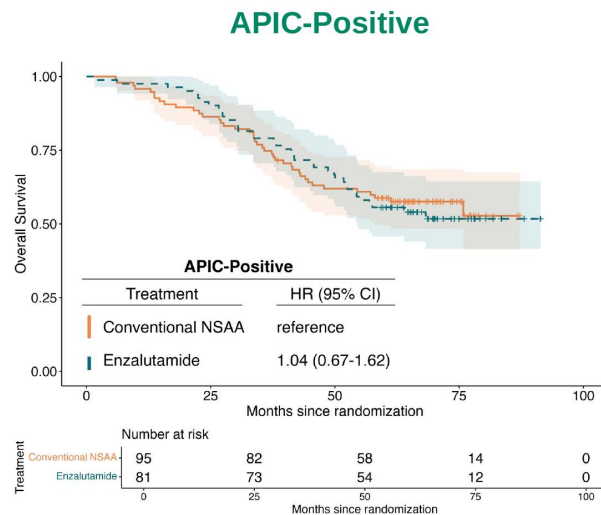
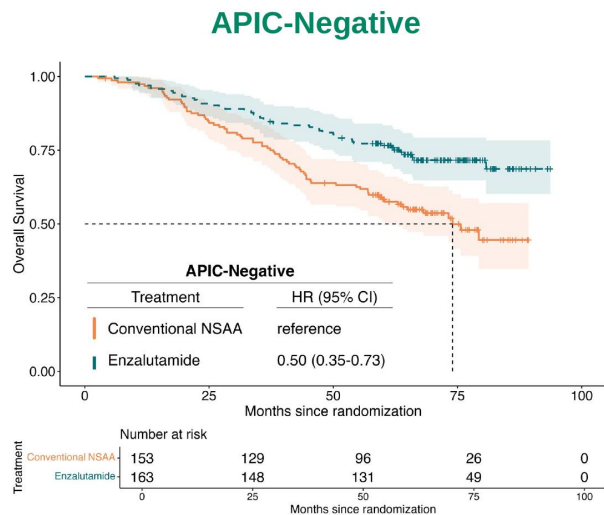


92	88 (97%)	81 (89%)	67 (74%)	58 (65%)	42 (58%)	8 (57%)	
87	80 (92%)	76 (87%)	65 (75%)	59 (68%)	50 (62%)	30 (59%)	5 (59%)

Number at risk (% surviving)

AI Pathology Classifier (APIC) Predicts Enzalutamide Benefit (ENZAmet)

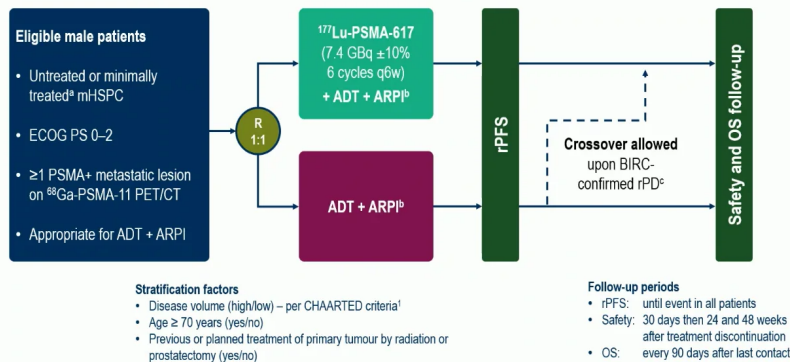
A biomarker computable from routine H&E — no additional testing required



- 1) APIC-Negative is associated with OS benefit from adding enzalutamide to ADT in mHSPC
- 2) APIC-Positive is associated with worse prognosis and may benefit from escalation with non-AR agents

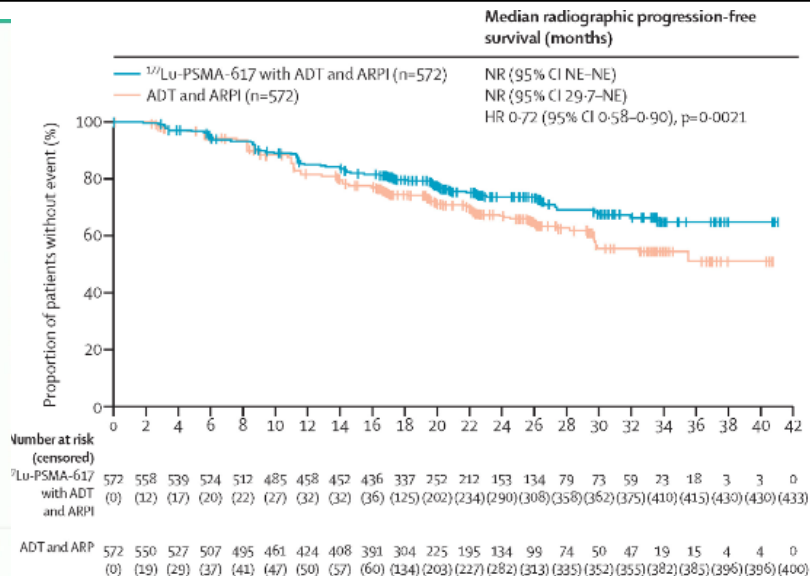
PSMAaddition: Does early escalation of PSMA radionucleotide improve PFS?

PSMAaddition: randomized phase 3 trial of ^{177}Lu -PSMA-617 in mHSPC



^a ADT in the neo-/adjuvant setting and/or up to 45 days of ADT/ARPI for metastatic disease was allowed before study entry | ^b Any ARPI with one switch allowed | ^c ADT/ARPI not mandatory after crossover
ADT, androgen deprivation therapy; BIRC, blinded independent review committee; ECOG PS, Eastern Cooperative Oncology Group performance status; OS, overall survival; PET/CT, positron-emission tomography/computed tomography; q6w, every 6 weeks; rPD, radiographic disease progression; rPFS, radiographic progression-free survival
1. Sweeney CJ et al. *N Engl J Med* 2015;373:737–46

ESMO congress



- 1144 were randomly assigned ; arms evenly balanced; 28% reduction in the relative risk of radiographic progression or death
- Grade 3 or worse adverse events occurred in 286 (51%) of 564 patients in the ^{177}Lu -PSMA-617 arm and 243 (43%) of 565 patients in the control arm
- There was no significant difference in overall survival between the ^{177}Lu -PSMA-617 arm and the control arm in the present prespecified interim intention-to-treat analysis, with a HR of 0.84 (95% CI 0.63–1.13; p=0.13); 60% of patients that had progression in control arm did crossover

Tagawa et al, *Lancet*, August 2026

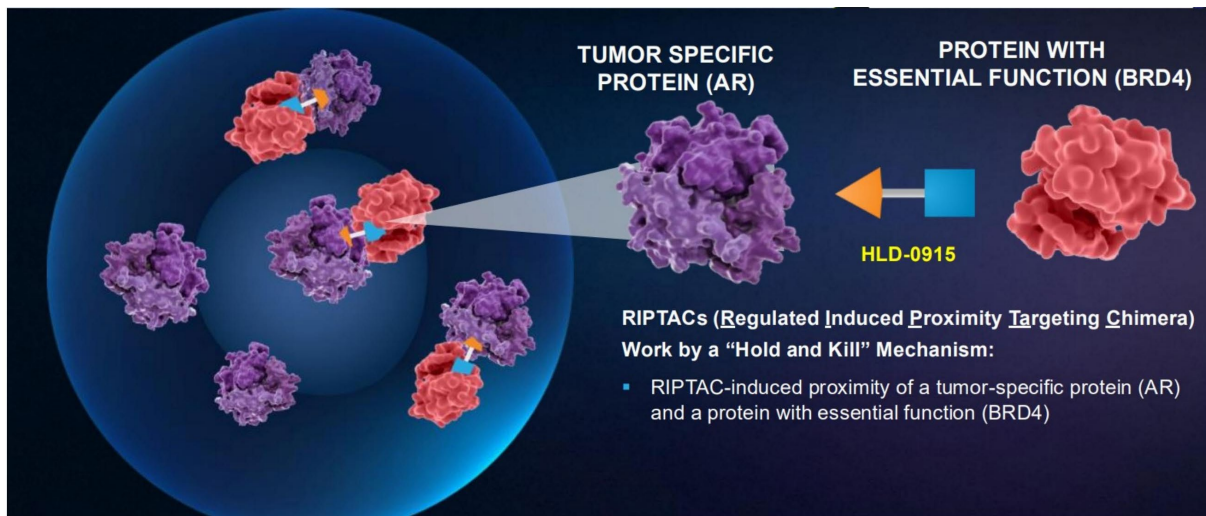
Trials and Mechanisms in HRLPC and mCRPC

HLD-0915 RIPTAC — KLK2 T-Cell Engager Pasritamig- Biomarker Development

RIPTAC: a small-molecule "hold and kill" degrader that pairs a tumor-specific protein with a cell-killing effector.

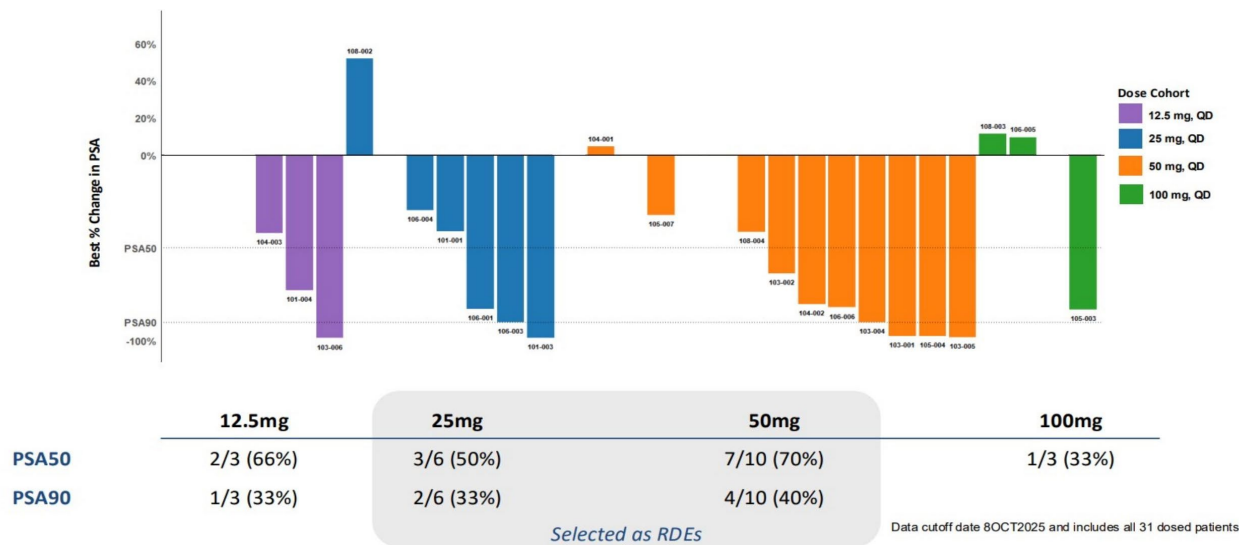
T-cell engager (TCE): a bispecific antibody that binds a tumor antigen and CD3 to redirect T cells against the tumor.

HLD-0915: A First-in-Class AR–BRD4 RIPTAC



- RIPTAC (Regulated Induced Proximity Targeting Chimera): a “hold and kill” bifunctional small molecule that pairs AR (tumor-specific) with BRD4 (essential effector) — selective in AR-expressing tumor cells only
- Active in enzalutamide-resistant preclinical models (LNCaP95, AR-V7+) — mechanism distinct from AR pathway inhibition
- **Trial design:** Phase 1/2 first-in-human trial (NCT06800313), oral once-daily, 21-day cycles
- **Eligibility:** Progressive mCRPC, ≥ 1 prior ARPI; up to 2 prior taxanes and 1 prior radioligand therapy permitted; ECOG 0–1
- **Enrollment:** 31 patients dosed across 12.5, 25, 50, and 100 mg cohorts (data cutoff 8OCT2025); FDA Fast Track (Aug 2025)

HLD-0915: Early Efficacy Across Dose Cohorts



- **Depth & durability:** Confirmed partial responses observed even after prior ARPI, taxane, and ¹⁷⁷Lu-PSMA-617 (e.g., -82.9%, -97.4% PSA reductions with ongoing response)
- **Dose selection:** 25 mg and 50 mg selected as recommended doses for expansion (RDEs); Phase 2 expansion opened late 2025 and ongoing

Pasritamig: First-in-Class KLK2 T-Cell Engager

Bispecific CD3×KLK2 T-cell engager (JNJ-78278343) | Phase 1 (NCT04898634), JCO 2026, PMID 40450573 | KLK2: androgen-regulated, near-ubiquitous in localized & mCRPC, minimal off-tumor expression. CRS = cytokine release syndrome.

7.85 mo

Median rPFS
RP2D efficacy cohort (n=33)

42.4%

PSA50 response
14/33 at RP2D

Gr.1 CRS

8.9% (4/45) — all Grade 1
outpatient-administrable

- **Phase 1 design:** 174 patients treated, median 4 prior lines; RP2D: 3.5 mg (D1) → 18 mg (D8) → 300 mg (D15), then 300 mg IV q6weeks
- **Safety:** TRAEs in 82.8% overall, Grade ≥3 in only 9.8% — infusion reactions (24.4%) and fatigue (15.6%) most common at RP2D; only ~2 hrs post-infusion observation needed
- **Activity pattern:** Response rates higher in bone/nodal disease vs. visceral metastases
- **Phase 3 underway:** KLK2-comPAS (Phase 3): 663 patients with mCRPC post-life-prolonging therapy, 2:1 randomized to pasritamig vs. placebo + supportive care; primary endpoint OS
- Second Phase 3 testing pasritamig + docetaxel vs. docetaxel alone (TPS5139, ASCO 2026)

MDACC Metastatic Prostate Cancer T Cell Engager Trials

September 13, 2026

Protocol / NCT	Trial and target	Prior treatment / cohort	Disease and key restrictions
2024-0326 NCT06826768	Hypervigilance [1] Nezastomig + cemiplimab PSMA×CD28 + PD-1	Refractory to standard care, or refusing/intolerant No required ARPI/taxane count Prior approved immunotherapy allowed	Visceral metastases allowed
2022-0448 NCT03972657	Nezastomig [2] PSMA×CD28	≥2 systemic lines beyond ADT, including an ARPI ≥2 Lu-PSMA doses or documented refusal Taxane not required	Visceral metastases allowed No prior non-RLT PSMA therapy
2022-0442 NCT05125016	REGN4336 + nezastomig [3] PSMA×CD3 + PSMA×CD28	Progressed/intolerant to ≥2 lines beyond ADT, including an ARPI. ≤2 mCRPC chemotherapy lines	No liver metastases Prior Lu-PSMA allowed
2026-0359 NCT07493512	Xaluritamig (AMG 509) STEAP1×CD3	ARPI progression + exactly 1 taxane in mCRPC Additional docetaxel in mHSPC allowed	Visceral metastases allowed No prior CD3/STEAP1 therapy
2025-0985 NCT07164443	KLK2-compAS, phase 3 [4] Pasritamig (KLK2×CD3) vs placebo, both + BSC	Progressed on ≥1 ARPI + ≥2 taxanes* + Lu-PSMA* PARPi if BRCA-mutated and available	Bone/LN only (no visceral) ECOG 0–2 No prior CD3/KLK2 therapy
2025-1407 NCT07594106	REGN15505 (PSMA×4-1BB) Alone or + cemiplimab or + REGN4336	≥2 systemic lines beyond ADT, including an ARPI Taxane not required. Prior Lu-PSMA allowed	Liver metastases only if treated and stable ≥3 months
2025-1971 NCT06095089	COSTIM Pasritamig + JNJ-87189401 KLK2×CD3 + PSMA×CD28	2C (± apalutamide): recurrent oligometastatic mHSPC No ADT/ARPI for ≥6 months	Bone/LN only. ≤5 PSMA-PET / ≤3 conventional lesions. T >150
		3 (+ Lu-PSMA): exactly 1 ARPI in mCRPC No prior cytotoxic chemotherapy† or PSMA RLT	PSMA-PET positive Visceral metastases allowed
		4 (+ RIPTAC): ≥1 ARPI No specific taxane/RLT cap	Visceral allowed (PSA ≥10) PSA ≥2 otherwise

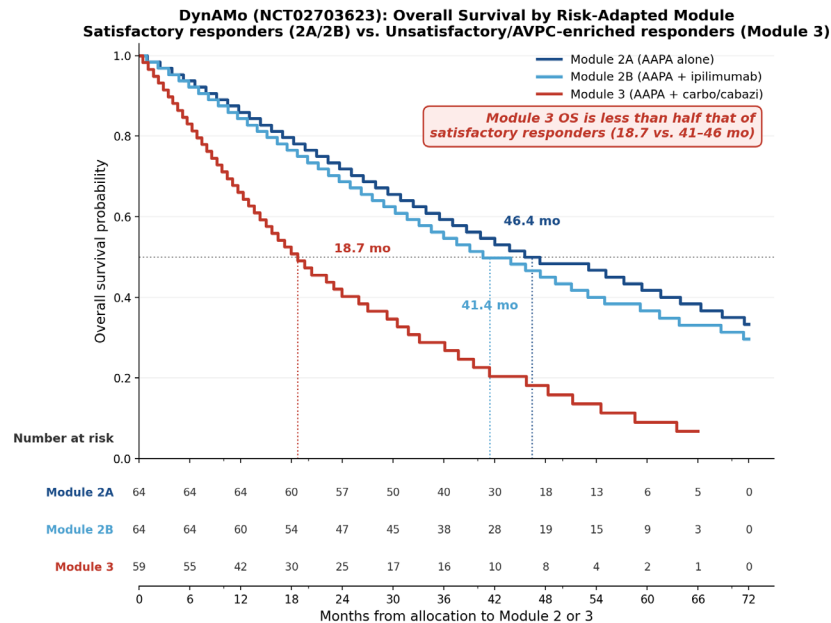
*One taxane if cabazitaxel unavailable or second taxane unsuitable. Lu-PSMA exception if unavailable, inaccessible, not indicated or unsuitable.

†Part 3 permits adjuvant/neoadjuvant taxane completed ≥12 months earlier. BSC = best supportive care. RLT = radioligand therapy.

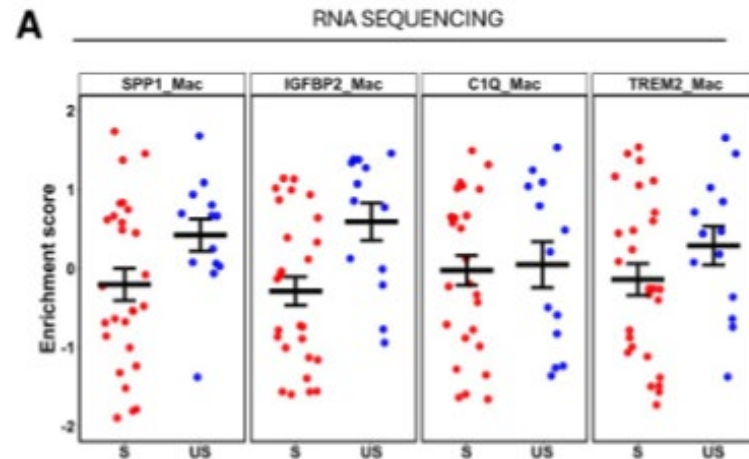
[\[1\] Siddiqui et al, ASCO GU 2026, TPS295 \(TiP\)](#) [\[2\] Siddiqui et al, AACR 2025, CT064 \(poster\)](#)

[\[3\] Kelly et al, ASCO GU 2025, TPS295 \(TiP\)](#) [\[4\] Chi et al, ASCO 2026, TPS5136 \(TiP\)](#)

DYNAMO: A Risk-Adapted Trial Reveals the Aggressive-Variant Molecular Signature



Curves: illustrative reconstruction from published summary statistics (median OS, 95% CI, n per arm).
Number-at-risk table: transcribed directly from published Figure 2B/2C.
Aparicio et al., Clin Cancer Res 2024;30:2751-63, PMID: 38683200.



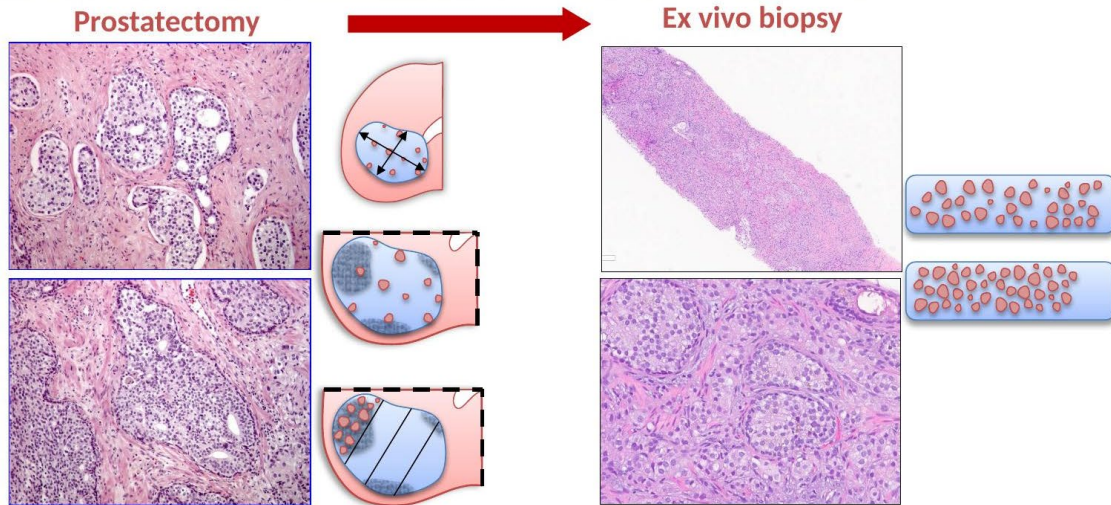
- 1) OS was roughly halved in the Unsatisfactory group despite adding carboplatin + cabazitaxel (~42 mos v. 18.7 mos)
- 2) Tumor suppressor gene loss (AVPCm) — combined defects in ≥ 2 of TP53, RB1, and PTEN — was significantly associated with Unsatisfactory/androgen-indifferent status (OR 4.3, $P=0.03$), the first prospective validation of this link
- 3) SPP1+ and IGFBP2+ macrophages emerged as candidate biomarkers/targets enriched in the androgen-indifferent tumor microenvironment

Aparicio et al. Clin Cancer Res 2024, PMID: 38683200 · Aparicio et al. Clin Cancer Res 2016, PMID: 26546618

High residual tumor density after androgen ablation predicts outcomes

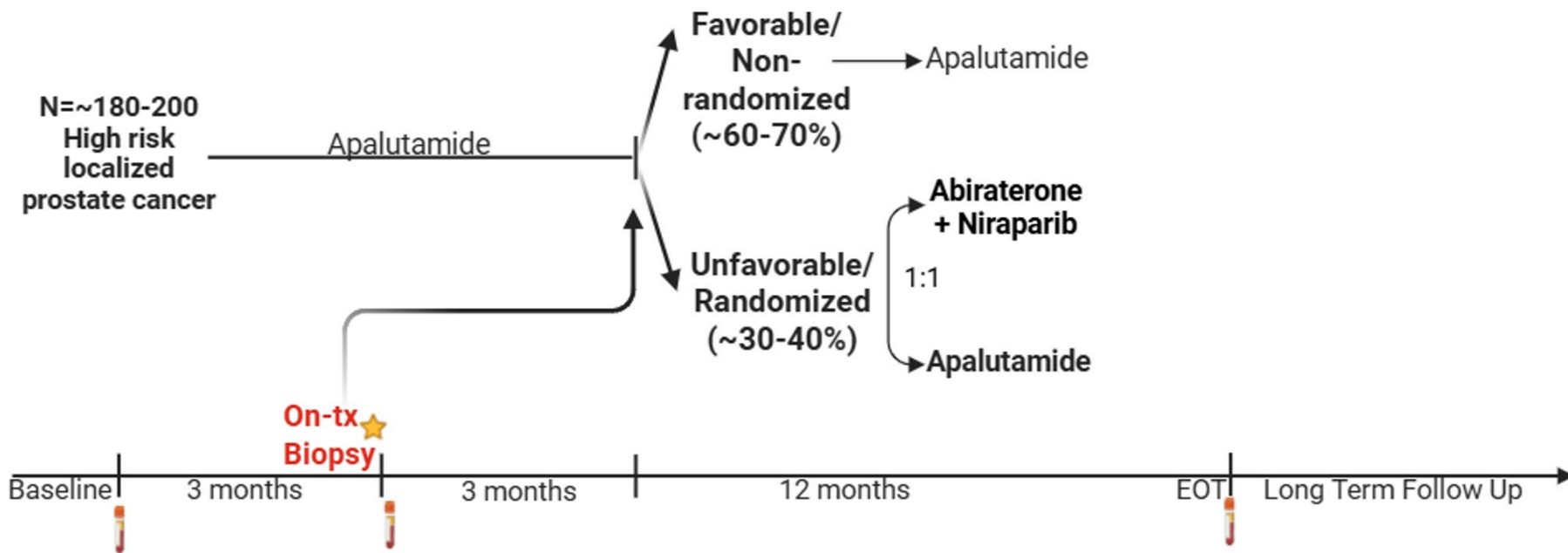
Post-ARPi Prostatectomy

	Tumour epithelial volume ($p = 0.001$)	
	≤ 0.3 cc	>0.3 cc
3-yr RFS (%)	89	61
Recurrence	8	21
No recurrence	20	11
Loss to follow-up	1	2
Death from other primary reason	0	2



Retained tumor cell density and morphology from on-treatment prostate biopsies faithfully reflect prostatectomy findings

Biopsy-rich adaptive trial of ARPi + PARPi in high risk localized prostate cancer (NCT0497275)



“Baseline” indicators do not predict outcomes

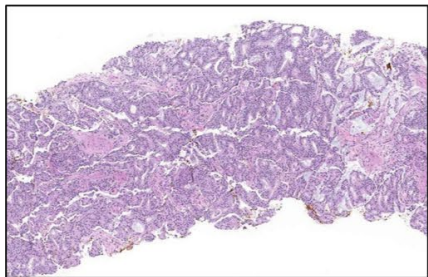
	Favorable (N=59)	Unfavorable (N=40)	Total (N=99)	P-value
T3+ Stage	24	28	52	0.11
PSA at dx	11.2 (3.4,146)	11.4 (2,221)	11.3 (2,221)	0.86
Grade Group	5 (2,5)	5 (3,5)	5 (2,5)	0.99

In addition to baseline factors, PSA response prior to initiation of radiation did not correlate with morphologic response to anti-androgens

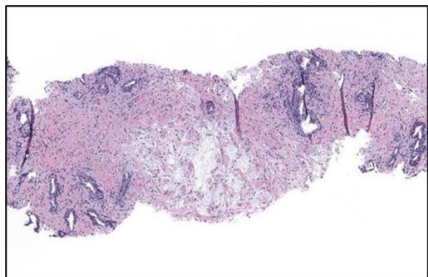
Deconvoluting Heterogeneity in Localized Prostate Cancer with Post-ARPi tissue

Patient 1-Favorable (apa+ADT)

Prostate
Pre-Tx Bx



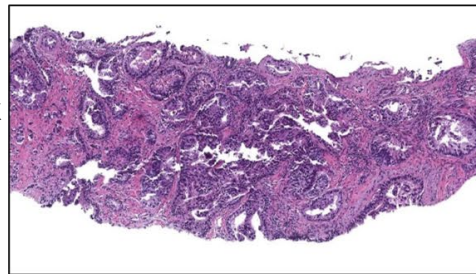
Prostate
On-Tx Bx



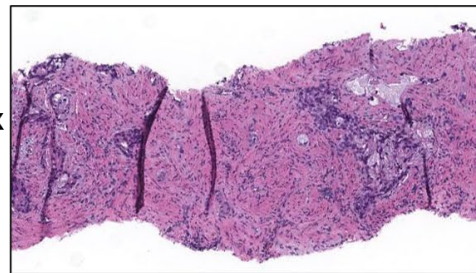
NED, PSA<0.1, TSTR wnl

Patient 2-Unfavorable (apa+ADT)

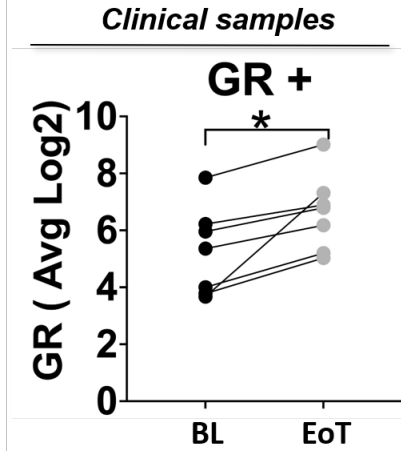
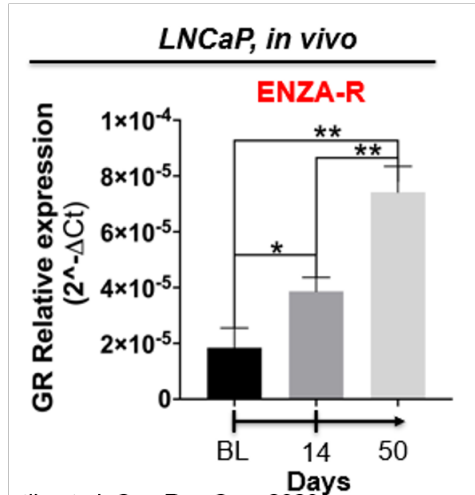
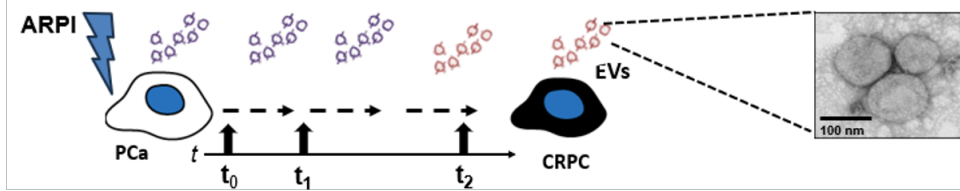
Prostate
Pre-Tx Bx



Prostate
On-Tx Bx



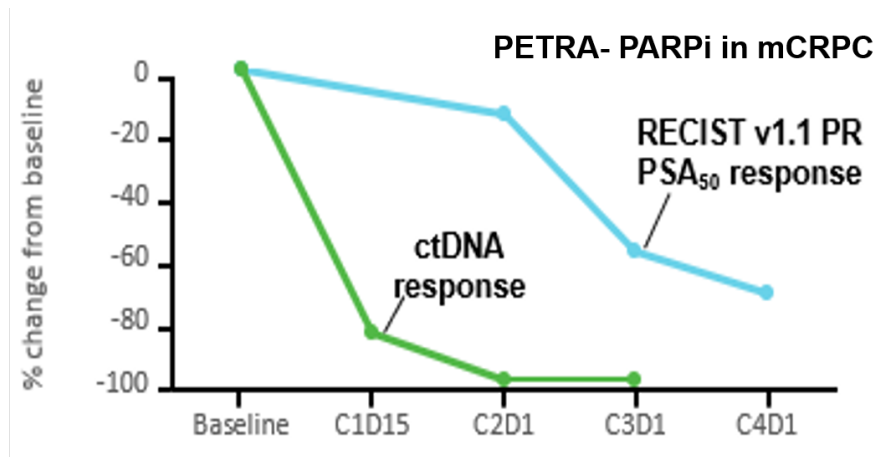
Metastatic relapse (HGNE), PSA<0.1 at progression



Applications of Extracellular Vesicles in Localized Dz

- 1) Present in earlier disease settings
- 2) Allow for evaluation of cell-cell interactions and gene expression changes driving downstream progression

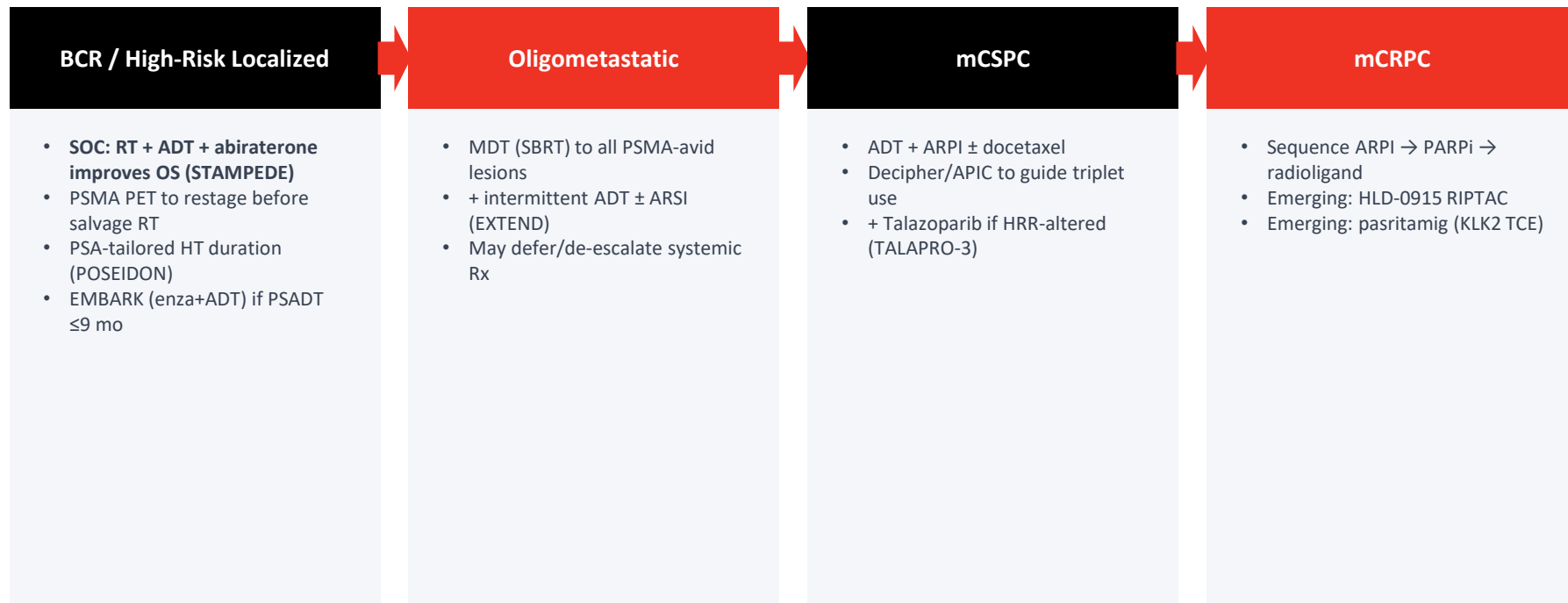
- Moving to non-invasive monitoring of biology and treatment response



Yap et al, AACR 2022

ctDNA will be assessed for early detection of relapse in current trial where PSA may fail, and identify molecular changes leading to therapy resistance

Putting It Together: An Algorithm Across the Continuum



PSMA PET and molecular biomarkers (HRR/BRCA2, Decipher, APIC) now cut across every stage — imaging and genomics, not just disease volume, increasingly drive the intensity of therapy

Key Takeaways

01 PSMA PET has redefined “non-metastatic” BCR

Most BCR with PSA >0.5 ng/mL now shows localizable, often oligometastatic disease — but a negative scan should not delay indicated salvage RT.

02 Intensification is evidence-based, not universal

POSEIDON: PSA ≤0.5 needs no added HT. EMBARK: enza+ADT is now standard for high-risk BCR. EXTEND: MDT + intermittent ADT improves PFS in oligomets.

03 HRR testing and biomarkers now gate mCSPC intensification

TALAPRO-3 brings PARP inhibition into HRR-altered mCSPC; Decipher and APIC increasingly identify who does — and doesn't — need docetaxel.

04 Two novel mCRPC mechanisms are entering the clinic

HLD-0915 (AR–BRD4 RIPTAC) and pasritamig (KLK2 T-cell engager) show early, durable activity after ARPI/taxane/radioligand failure — both now J&J assets.

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Genitourinary Medical Oncology

Christopher Logothetis
Paul Corn
Ana Aparicio
Timothy Thompson
Chuandong Geng
Gani Manyam
Theocharis Panaretakis
Estafania Labanca
Sumit Subudhi
Bilal Siddiqui
Pathology
Patricia Troncoso
Miao Zhang
Keyi Zhu
Radiation Oncology
Seungtaek Choi
Lauren Mayo
Ryan Park
Chad Tang
Phuoc Tran

Urology

Justin Gregg
John Ward
Lisly Chery
John Papadopoulos
Christine Kang

Harris Health/LBJ

Hilary Ma

Statistics

Rebecca Slack-Tidwell
Zhongya Wang
Christine Peterson

Collaborators

Jonathan Chou
Navonil DeSarkar
Timothy Yap
Timothy Heffernan

Patients & Families



MD Anderson SPORE CDA



CANCER PREVENTION & RESEARCH
INSTITUTE OF TEXAS

Johnson & Johnson



Questions:
pgpilie@mdanderson.org

