‘Conquering the Challenging Cases in mCSPC/mCRPC’

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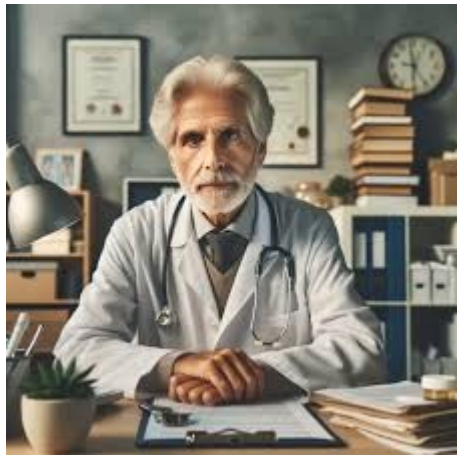
Challenging case

- 77/M, physician, admitted for severe low back pain.
- MRI-T12 pathological fracture with bone metastases.
- PSA >5000 ng/mL,
- Staging CT TAP + Bone Scintigraphy: bulky lymphadenopathy in pelvis and mets involving spine & right femur.
- U/w T11-L1 internal fixation and Pathologic review of T12 corpectomy specimen: metastatic prostate adenocarcinoma.
- NGS : microsatellite stable, low tumor mutational burden, wild-type homologous recombination repair genes, wild-type TP53, PTEN and RB1.



Ionescu F, Zhang J. How We Treat Metastatic Castration-Sensitive Prostate Cancer. Cancer Control. 2024 Jan-Dec;31:10732748241274190. doi: 10.1177/10732748241274190. PMID: 39150340; PMCID: PMC11329962.

Challenging case

- 65/M, presented with complaints of lower abdominal pain and lower urinary tract symptoms.
- DRE - Hard prostate with a nodular contour
- PSA level of 299 ng/ml
- TRUS biopsy: Acinar adenocarcinoma involving both lobes, Gleason score: 7
- 68Ga-PSMA PET/CT scan: PSMA avid multifocal prostate lesions with PSMA avid metastatic abdominopelvic and mediastinal lymphadenopathy, as well as multiple metastatic bone lesions, staging of T3bN1M1c.
- Initial Rx- ADT + Abiraterone from feb 2022 – March 2023. PSA nadir 14ng/ml in Dec 22.
- March 2023 : PSA 71 → mCRPC, PSMA PET- new PSMA avid bone mets, started on Docetaxel
- Post 3# Docetaxel – Progression in PSA and Bone mets in PSMA PET.

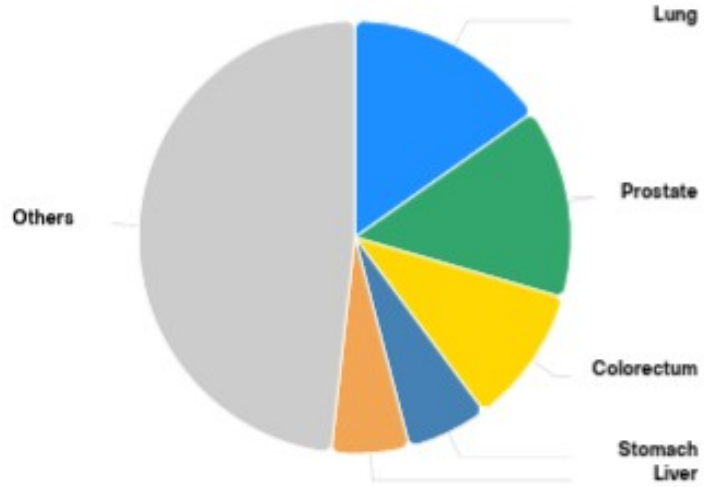
Moghrabi S, Al-Houwari R, Ruzzeh S, Al-Ibraheem A. Therapeutic Challenges in Metastatic Castration-Resistant Prostate Cancer: A Case Study and Review of Prostate-Specific Membrane Antigen-Targeted Therapy Failures in Highly Prostate-Specific Membrane Antigen-Avid Disease. Cureus. 2024 Dec 22;16(12):e76224. doi: 10.7759/cureus.76224. PMID: 39845214; PMCID: PMC11751113.

- (cont.)
- So, then referred to nuclear medicine team for prostate-specific membrane antigen radioligand therapy (PSMA PRLT)
- 1st dose – Oct 2023,
- 2° dose – Dec 2023
- PSA kept on rising, FDG / PSMA PET done – PSMA avid / FDG faint bony mets + , progressive disease
- So, planned for Actinium PRRT – but,patient's general condition got worse and ultimately planned for supportive care alone.

Top 5 most frequent cancers: Globocan 2022 & WHO 2020

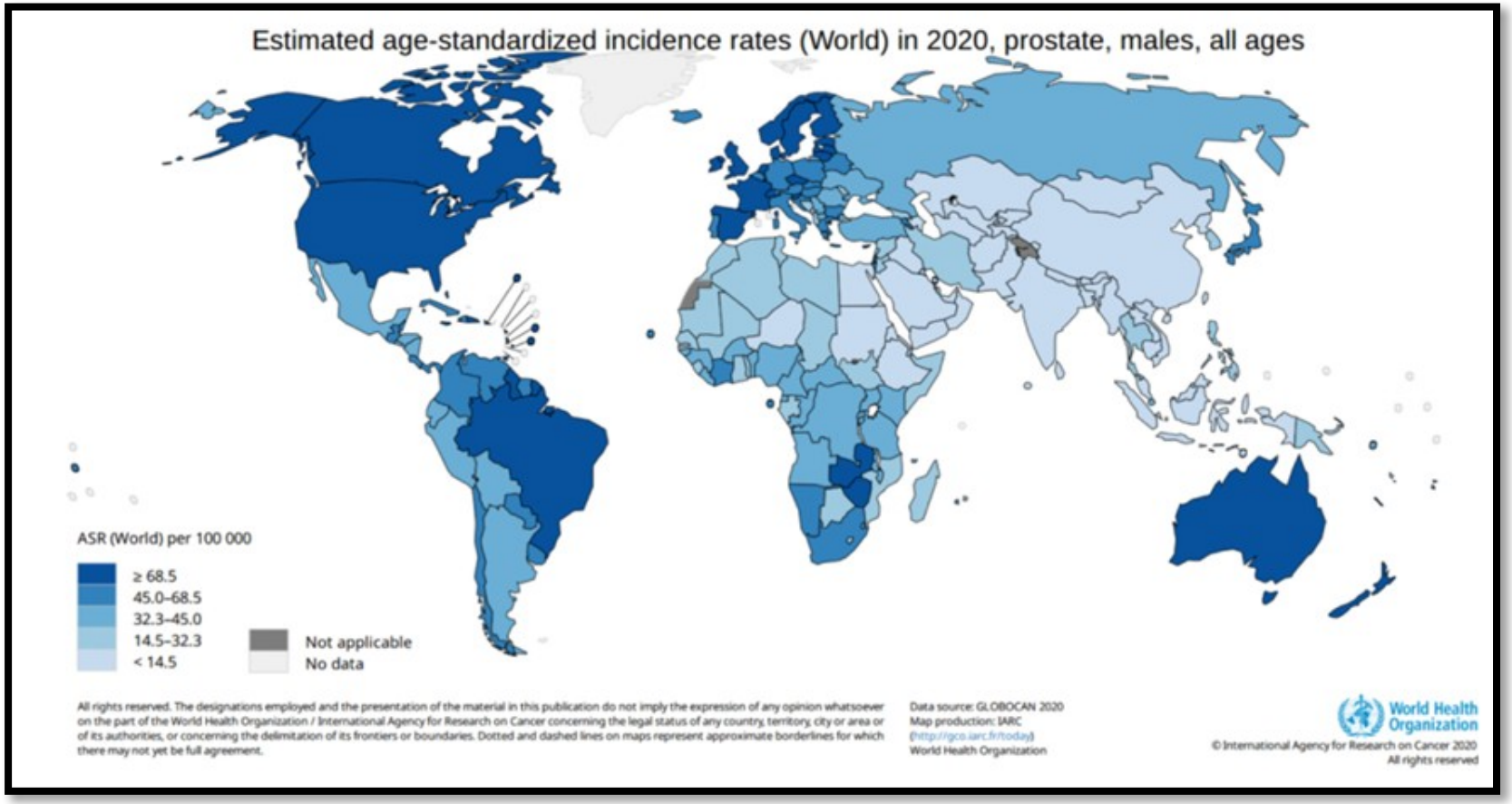
Top 5 most frequent cancers

Males



Total: 10 311 610

Rank	Cancer site	Number of cases	Percent
1st	Lung	1 572 045	15.2%
2nd	Prostate	1 467 854	14.2%
3rd	Colorectum	1 069 446	10.4%
4th	Stomach	627 458	6.1%
5th	Liver	600 676	5.8%
-	Others	4 974 131	48.2%



https://gco.iarc.who.int/media/globocan/factsheets/populations/900-world-fact-sheet.pdf

Ca Prostate: Current Trend

- Median age at diagnosis ~67 years
- More than 50% of prostate cancer risk is attributable to genetic factors
- At diagnosis, approx 75% are cancer localized to prostate, associated with 5-year survival rate of ~ 100%.
- Despite definitive therapy, 2% to 56% of men with localized disease develop distant metastases, depending on tumor risk factors.
- At presentation, approximately 14% of patients have metastases to regional lymph nodes
- An additional 10% of men have distant metastases that are associated with a 5-year survival rate of 37%

JAMA. 2025;333(16):1433-1446. doi:10.1001/jama.2025.0228

ASCO Special Articles

Systemic Therapy in Patients With Metastatic Castration-Resistant Prostate Cancer: ASCO Guideline Update

2nd May 2025 update

10 Most Common Co-Occurring Chronic Conditions Among

TABLE 3. 10 Most Common Co-Occurring Chronic Conditions Among Male Medicare Beneficiaries With Prostate Cancer (N = 1,016,617), 2011

Beneficiaries <65 Years (n = 26,243)		Beneficiaries 65 Years and Older (n = 990,374)	
Condition	No. (%)	Condition	No. (%)
Prostate cancer prevalence, %	0.9	Prostate cancer prevalence, %	8.8
Top 10 co-morbidities		Top 10 co-morbidities	
Hypertension	17,767 (67.7)	Hypertension	693,283 (70.0)
Hyperlipidemia	13,589 (51.8)	Hyperlipidemia	590,154 (59.6)
Diabetes	9,982 (38.0)	Ischemic heart disease	457,844 (46.2)
Ischemic heart disease	9,291 (35.4)	Anemia	337,957 (34.1)
Anemia	8,478 (32.3)	Diabetes	312,519 (31.6)
Arthritis	7,833 (29.9)	Arthritis	308,537 (31.2)
Chronic kidney disease	6,286 (24.0)	Chronic kidney disease	239,960 (24.2)
Depression	6,162 (23.5)	Cataract	235,241 (23.8)
COPD	4,646 (17.7)	Heart failure	203,231 (20.5)
Heart failure	4,636 (17.7)	COPD	145,818 (14.7)

https://ascopubs.org/doi/pdf/10.1200/JCO-25-00007

Disease States: Prostate Cancer

Disease state	5-year overall survival
Newly diagnosed localized	>90%
Newly diagnosed locally advanced	80-90%
BCR after local treatment	88%
Newly diagnosed M1	40%
M0 CRPC	35%
mCRPC	2-10%

Proposed Risk Stratification Criteria for mCSPC

CHAARTED High-Volume Criteria[8]	**Visceral Metastasis OR ≥4 Bone Metastases including at least 1 outside the vertebral column or pelvis**
LATITUDE criteria[9]	At least 2 of the following: 1) Visceral metastases 2) ≥ 3 bone metastases 3) Grade group ≥4

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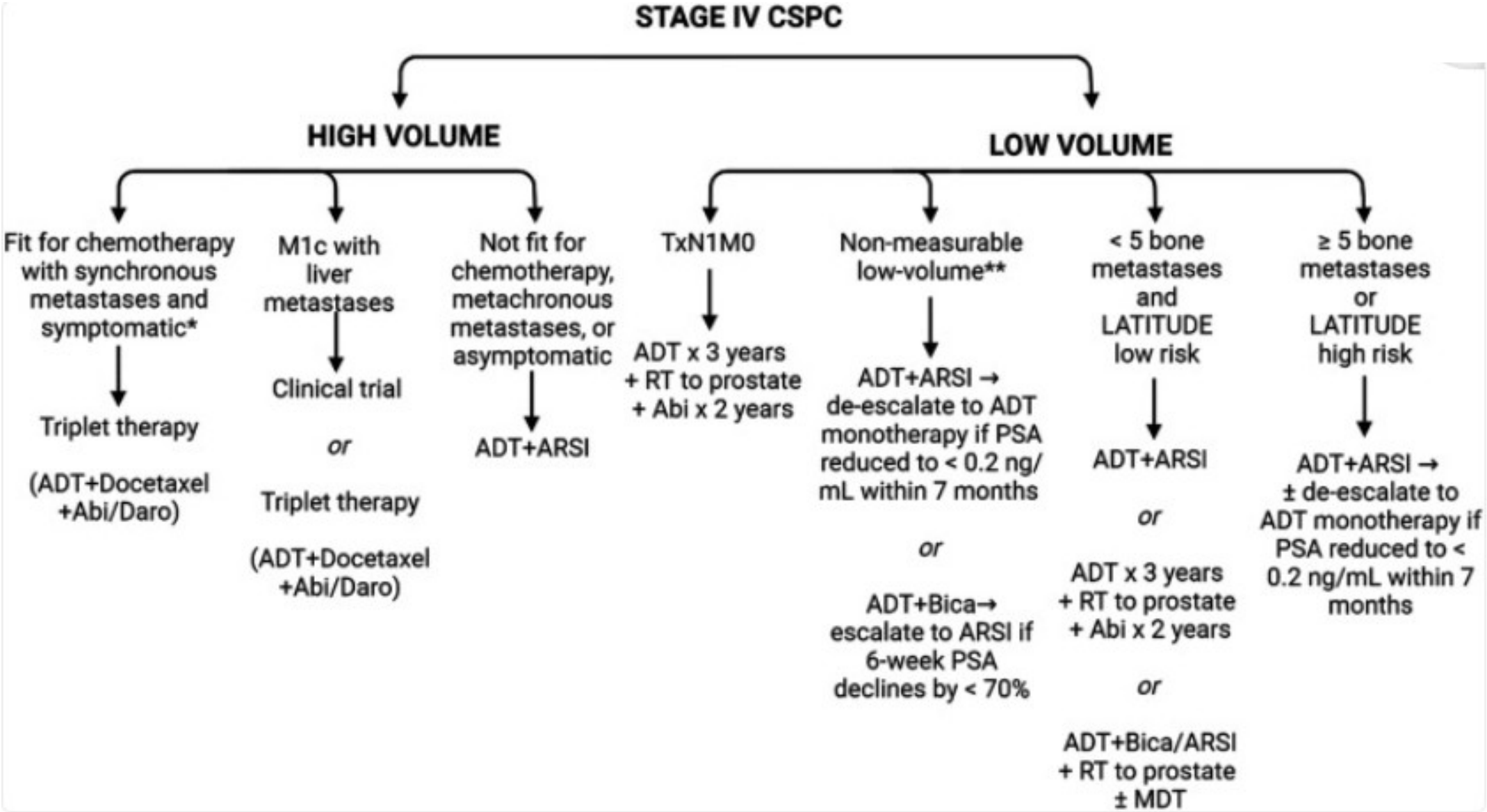
Treatment schema: mCSPC



Guidelines: First-line treatment of HSPC

Recommendations	Strength rating
First-line treatment	
Discuss all patients with hormone-sensitive metastatic disease in a multidisciplinary team.	Strong
Offer immediate systemic treatment with androgen deprivation therapy (ADT) to palliate symptoms and reduce the risk for potentially serious sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction) to M1 symptomatic patients.	Strong
Offer short-term administration of an older generation androgen receptor (AR) antagonist to M1 patients starting luteinising hormone-releasing hormone (LHRH) agonist to reduce the risk of the 'flare-up' phenomenon.	Weak
At the start of ADT offer LHRH antagonists or orchiectomy to patients with impending clinical complications such as spinal cord compression or bladder outlet obstruction.	Strong
Do not offer AR antagonist monotherapy to patients with M1 disease.	Strong
Do not offer ADT monotherapy to patients whose first presentation is M1 disease if they have no contra-indications for combination therapy and have a sufficient life expectancy to benefit from combination therapy (≥ 1 year) and are willing to accept the increased risk of side effects.	Strong
Offer ADT combined with abiraterone acetate plus prednisone or apalutamide or enzalutamide to patients with M1 disease who are fit for the regimen.	Strong

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Guidelines: First-line treatment of HSPC

Offer ADT combined with darolutamide to patients with M1 disease who are fit for the regimen.	Weak
Offer docetaxel only in combination with ADT plus abiraterone or darolutamide to patients with M1 disease who are fit for docetaxel.	Strong
Offer ADT combined with prostate radiotherapy (using doses up to the equivalent of 72 Gy in 2 Gy fractions) to patients whose first presentation is M1 disease and who have low volume of disease by CHAARTED criteria.	Strong
Do not offer ADT combined with surgery to M1 patients outside of clinical trials.	Strong
Only offer metastasis-directed therapy to M1 patients within a clinical trial setting or a well-designed prospective cohort study.	Strong
Supportive care	
Assess osteoporosis risk factors and perform a dexa scan when commencing long-term ADT, to mitigate osseous complications.	Strong
Offer bone protection to avoid fractures in patients receiving combination treatment.	Strong
Offer calcium and vitamin D supplementation when prescribing either denosumab or bisphosphonates and monitor serum calcium.	Strong
Treat painful bone metastases early on with palliative measures such as intensity-modulated radiation therapy/volumetric arc radiation therapy plus image-guided radiation therapy and adequate use of analgesics.	Strong

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Status of the different ARPIs

	High-risk localised & locally advanced**	High-risk BCR	mHSPC	nmCRPC	mCRPC
Abiraterone	X*		X		X
Enzalutamide		X	X	X	X
Apalutamide			X	X	
Darolutamide			X	X	

** Unlicenced indication*

*** STAMPEDE definition*

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Recommendations for follow-up during hormonal treatment

Recommendations	Strength rating
The follow-up strategy must be individualised based on stage of disease, prior symptoms, prognostic factors and the treatment given.	Strong
In patients on long-term androgen deprivation therapy (ADT), measure initial bone mineral density to assess fracture risk.	Strong
In patients receiving combination treatment offer bone protection to avoid fractures.	Strong
In M1 patients, schedule follow-up at least every three to six months including imaging at regular intervals.	Strong
During follow-up of patients receiving ADT, check PSA and testosterone levels and monitor patients for symptoms associated with metabolic syndrome as a side effect of ADT.	Strong
In patients on long-term ADT, as a minimum requirement, include a medical history including assessment of ADT-induced complications, haemoglobin, serum creatinine, alkaline phosphatase, lipid profiles and HbA1c level measurements.	Strong
Counsel patients (especially with M1b status) about the clinical signs suggestive of spinal cord compression.	Strong
When disease progression is suspected, restaging is needed and the subsequent follow-up adapted/individualised.	Strong
In patients with suspected progression, assess the testosterone level. By definition, castration-resistant PCa requires a testosterone level < 50 ng/dL (< 1.7 nmol/L).	Strong

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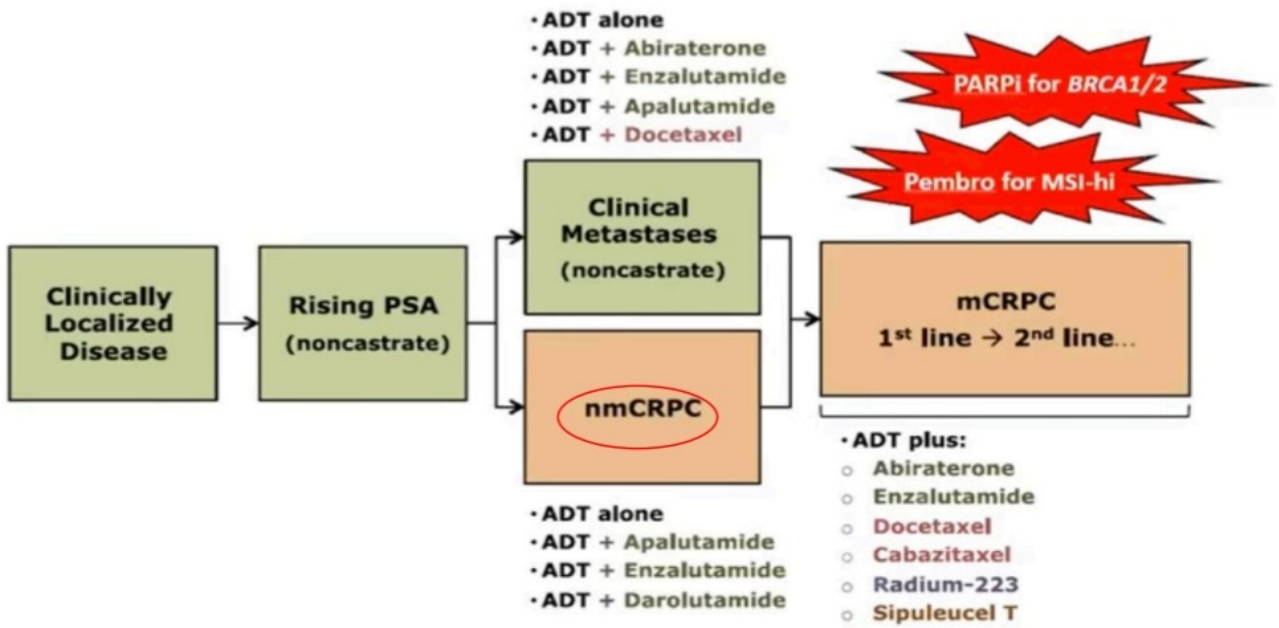
Ongoing de-escalation Trials: mCSPC

Trial name	Design	Patient profile	Study endpoint
A-DREAM trial	Phase II adaptive Stopping and starting rules based on PSA response in mCSPC treated with ADT + ARSI.	patients who achieve PSA <0.2 ng/mL after 18-24 months of ADT + ARSI undergo a treatment break with reinitiation of treatment in the event of PSA rise ≥5 ng/mL, radiographic, or clinical progression	primary end point of A-DREAM is 18-month eugonadal treatment-free survival following treatment interruption.
EORTC-2238 GUCG (De-Escalate)	Randomized pragmatic	iADT in patients achieving a PSA ≤0.2 ng/mL after 6-12 months of ADT + ARSI.	study endpoints include OS at 3 years and the proportion of patients on iADT at 1 year, as well as health-related quality of life and health economics parameters.
Phase III LIBERTAS trial	Intermediate de-escalation strategy	mCSPC having achieved a PSA nadir of ≤0.2 ng/mL within the first 7 months of combined ADT + Apa are randomized to iADT or cADT while continuing Apa monotherapy.	Co-primary endpoints are radiographic PFS and the severity of the Adjusted Hot Flash Score at 18 months (OS is a key secondary endpoint).

Treatment Landscape for nmCRPC



Phase III controlled trials – nmCRPC

Study	Intervention	Comparison	Selection criteria	Main outcomes
ARAMIS 2019, 2020 [1249, 1326]	ADT + darolutamide	ADT + placebo	nmCRPC; baseline PSA ≥ 2 ng/mL PSA-DT ≤ 10 mo	59% reduction of distant progression or death Median MFS: darolutamide 40.4 vs. placebo 18.4 mo; 31% reduction in risk of death HR = 0.69 (95% CI: 0.53–0.88) p = 0.003
PROSPER 2018, 2020 [1247, 1327]	ADT + enzalutamide	ADT + placebo	nmCRPC; baseline PSA ≥ 2 ng/mL PSA-DT ≤ 10 mo	71% reduction of distant progression or death Median MFS: enzalutamide 36.6 vs. placebo 14.7 months; 27% reduction in risk of death HR = 0.73 (95% CI: 0.61–0.89) p = 0.001
SPARTAN 2018, 2021 [1248, 1328]	ADT + apalutamide	ADT + placebo	nmCRPC; baseline PSA ≥2 ng/mL PSA-DT ≤ 10 mo	72% reduction of distant progression or death Median MFS: apalutamide 40.5 vs. placebo 16.2 months; 22% reduction in risk of death HR = 0.78 (95% CI: 0.64–0.96) p = 0.0161

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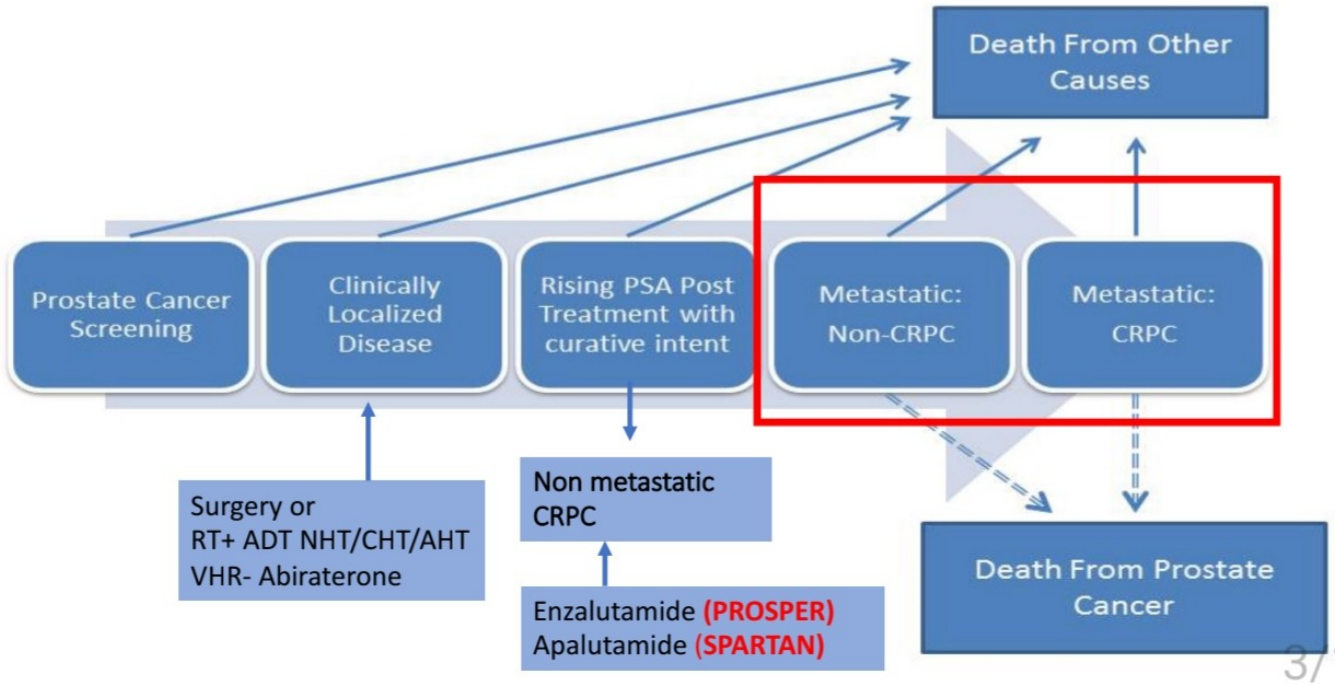
Systemic therapy in prostrate cancer



Phase II/III- second-line/third-line trials in mCRPC

Study	Intervention	Comparison	Selection criteria	Main outcomes
ABIRATERONE				
COU-AA-301 2012 [1277]	abiraterone + prednisone HR	placebo + prednisone	- Previous docetaxel - ECOG 0–2 - PSA or radiographic progression	OS: 15.8 vs. 11.2 mo. (p < 0.0001, HR: 0.74; 95% CI: 0.64–0.86; p < 0.0001). FU: 20.2 mo. rPFS: no change
COU-AA-301 2011 [1276]				OS: 14.8 vs. 10.9 mo. (p < 0.001 HR: 0.65; 95% CI: 0.54–0.77). FU: 12.8 mo. rPFS: 5.6 vs. 3.6 mo.
CABAZITAXEL				
TROPIC 2013 [1333]	cabazitaxel + prednisone	mitoxantrone + prednisone	- Previous docetaxel - ECOG 0–2	OS: 318/378 vs. 346/377 events (OR: 2.11; 95% CI: 1.33–3.33). FU: 25.5 months OS ≥ 2 yr. 27% vs. 16% PFS

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Phase II/III- second-line/third-line trials in mCRPC

CABAZITAXEL				
TROPIC 2010 [1272]				OS: 15.1 vs. 12.7 mo. (p < 0.0001, HR: 0.70; 95% CI: 0.59–0.83). FU: 12.8 mo. PFS: 2.8 vs. 1.4 mo. (p < 0.0001, HR: 0.74, 95% CI: 0.64–0.86)
CARD 2019 [1237]	cabazitaxel (25 mg/m^2 Q3W) + prednisone + G-CSF	ARPI: abiraterone + prednisone OR Enzalutamide	- Previous docetaxel - Progression ≤ 12 mo. on prior alternative ARPI (either before or after docetaxel)	Med OS 13.6 vs. 11.0 mo. (p = 0.008, HR: 0.64, 95% CI: 0.46–0.89). rPFS 8.0 vs. 3.7 mo. (p < 0.001, HR: 0.54, 95% CI: 0.40–0.73). FU: 9.2 mo.

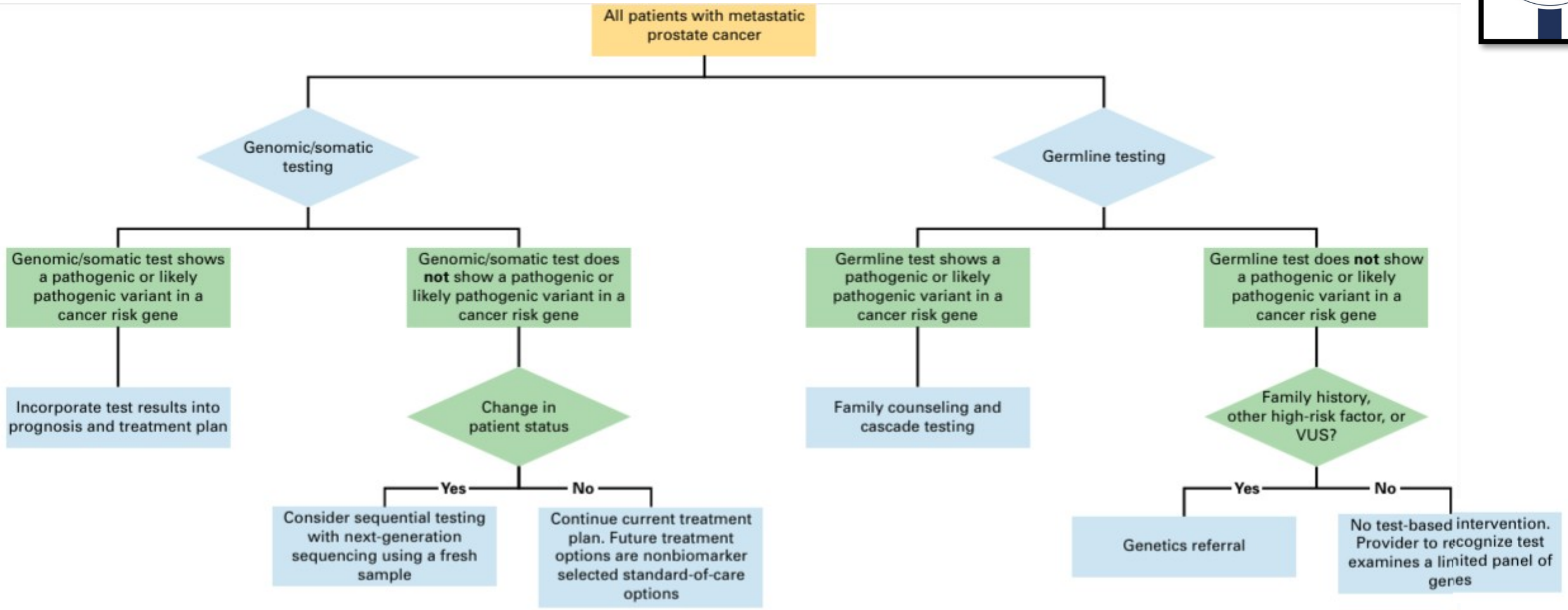
Phase II/III- second-line/third-line trials in mCRPC

ENZALUTAMIDE				
AFFIRM 2012 [1278]	enzalutamide	Placebo	- Previous docetaxel. - ECOG 0–2.	OS: 18.4 vs. 13.6 mo. (p < 0.001, HR: 0.63; 95% CI: 0.53–0.75). FU: 14.4 mo. rPFS: 8.3 vs. 2.9 mo. (HR: 0.40; 95% CI: 0.35–0.47, p < 0.0001).
PARP inhibitor				
PROfound 2020 [273, 1225, 1288]	olaparib	abiraterone + prednisolone or enzalutamide; cross-over allowed at progression	- Previous ARPI, alterations in HRR genes	rPFS: 7.39 vs. 3.55 mo. (p < 0.0001, HR: 0.34; 95% CI: 0.25–0.47), conf. ORR 33.3% vs. 2.3% (OR 20.86, 95% CI: 4.18–379.18). OS: 19.1 mo vs. 14.7 mo (in patients with BRCA1/2, ATM alterations) (p = 0.0175; HR 0.69; 95% CI: 0.5–0.97).

Germline genetic testing and next-generation sequencing of tumor tissue

- **Germline genetic testing on blood**
  - 5 to 10 percent of patients with germline mutations in DNA mismatch repair genes are eligible for PARP inhibitors
- Next-generation sequencing of prostate tumor tissue for somatic genomic alterations may reveal potentially targetable abnormalities for which approved drugs are available regardless of tumor type
  - ***A PARP inhibitor*** for those with homologous recombination repair deficiency,
  - ***Pembrolizumab*** for tumors associated with deficient mismatch repair [dMMR]/high levels of microsatellite instability [MSI-H]
  - ***Tropomyosin receptor kinase [TRK] inhibitor*** for rare neurotrophic tyrosine receptor kinase [NTRK] fusions

Germline & Somatic genomic testing for mPCa



Patients with metastatic prostate cancer should undergo both germline & somatic DNA sequencing using panel-based assays.

M.J. Karpinski, K. Rahbar, M. Bögemann et al., Updated Prostate Cancer Risk Groups by Prostate-specific Membrane Antigen Positron Emission Tomography Prostate Cancer Molecular Imaging Standardized Evaluation (PPP2): Results from an International Multicentre Registry Study, Eur Urol (2025)

Germline & Somatic genomic testing for mPCa

Gene	Location	PCa risk	Findings
BRCA2	13q12.3	RR 2.5 to 4.6 [40, 41] - PCa at 55 years or under: RR: 8–23 [42, 43]	• Up to 12 % of men with metastatic PCa harbour germline mutations in 16 genes (including *BRCA2* [5.3%]) [31] • 2% of men with early-onset PCa harbour germline mutations in the *BRCA2* gene [42] • *BRCA2* germline alteration is an independent predictor of metastases and worse PCa-specific survival [36, 44]
HOXB13	17q21.2	OR 3.4–7.9 [33, 45]	• Significantly higher PSA at diagnosis, higher Gleason score and higher incidence of positive surgical margins in the RP specimen than non-carriers [46]
CHEK2	22q12.1	OR 3.3 [40, 41]	• Up to 12% of men with metastatic PCa harbour germline mutations in 16 genes (including *CHEK2* [1.9%]) [31]
BRCA1	17q21	RR: 1.8–3.8 at 65 years or under [47, 48]	• Higher rates of lethal PCa among mutation carriers [38] • Up to 12% of men with metastatic PCa harbour germline mutations in 16 genes (including *BRCA1* [0.9%]) [31]
ATM	11q22.3	RR: 6.3 for metastatic PCa [31]	• Higher rates of lethal PCa among mutation carriers [38] • Up to 12% of men with metastatic PCa harbour germline mutations in 16 genes (including *ATM* [1.6%]) [31]
MMR genes *MLH1* *MSH2* *MSH6* *PMS2*	3p21.3 2p21 2p16 7p22.2	RR: 3.7 [49]	• Mutations in *MMR* genes are responsible for Lynch syndrome [50] • *MSH2* mutation carriers are more likely to develop PCa than other MMR gene mutation carriers [51]

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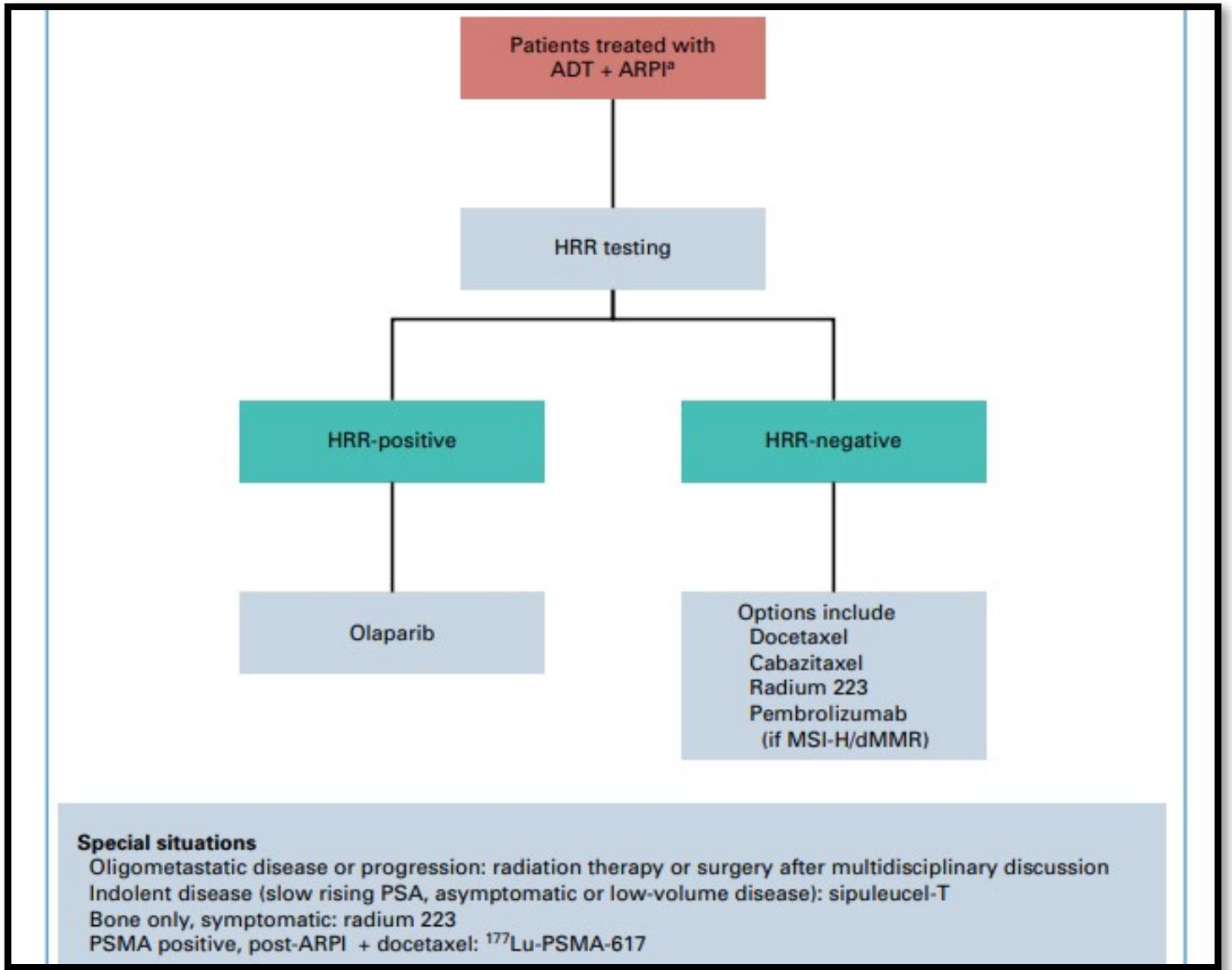
Pathogenic germline mutations in the BRCA2 and HOXB13 genes, but also in the genes CHEK2, BRCA1, ATM, NBS1, and genes involved in Lynch syndrome, have been suggested to increase the risk of PCa

Algorithm for Previously Treated With ADT & ARPI

ASCO Special Articles



https://ascopubs.org/doi/pdf/10.1200/JCO-25-00007

Personalizing Treatment for mCRPC

Key Studies for FDA-Approved Poly(ADP-ribose) Polymerase Inhibitors and Combinations in mCRPC

Approved Drug/ Combination	Key Study	Design	Primary End Point	Result	FDA Approval
Rucaparib	TRITON2[11]	Single-arm phase II post-ARPI post-taxane	ORR in *BRCA2/BRCA1* patients	ORR, 44%, 95% CI, 31% to 57%	*BRCA2, BRCA1* after an ARPI and taxane
Olaparib	PROFOUND[15]	Phase III RCT *v* physician's choice second-line ARPI	rPFS in cohort A (*BRCA2, BRCA1, ATM*)	HR, 0.34, 95% CI, 0.25 to 0.47 (cohort A only)	14 DDR genes after an ARPI
Olaparib + abiraterone acetate	PROPEL[26]	Phase III RCT in first-line mCRPC *v* abiraterone alone	rPFS in the overall population (unselected, retrospective genomic profiling)	HR, 0.24, 95% CI, 0.12 to 0.45 (*BRCA2/1*)	*BRCA2, BRCA1* in first-line mCRPC
Niraparib + abiraterone acetate	MAGNITUDE[23]	Phase III RCT in first-line mCRPC *v* abiraterone alone	rPFS in patients with DDR gene mutations	HR, 0.53, 95% CI, 0.36 to 0.79 (*BRCA2/1*)	*BRCA2, BRCA1* in first-line mCRPC
Talazoparib + enzalutamide	TALAPRO-2[24]	Phase III RCT in first-line mCRPC *v* enzalutamide alone	rPFS in the overall population, prospective genomic profiling	HR, 0.45, 95% CI, 0.33 to 0.61 (12 DDR genes)	12 DDR genes in first-line mCRPC

PARP Inhibitors: Conclusions

- Olaparib and Rucaparib are both FDA-approved for mCRPC
- Niraparib and Talazoparib are in development
- PARP inhibitors:
  - ❑ Work best for *BRCA2*
  - ❑ Some activity in *BRCA1* and *PALB2*
  - ❑ Limited activity in *ATM, CDK12, CHEK2*
  - ❑ Need more data for others (*FANCA/L, BRIP1, BARD1, NBN, RAD51/54*)
- New combinations (new "synthetic lethalities") should be studied

Two alternative sequences Cabazitaxel & 177Lu-PSMA-617: (LuCaS)

- Comparison of two alternative sequences with Cabazitaxel and 177Lu-PSMA-617 in metastatic castration-resistant prostate cancer: A retrospective multicenter study (LuCaS)
- A total of 68 patients with mCRPC who received sequential ^{177}Lu-PSMA-617 and Cabazitaxel
- (PFS-2), was similar in patients treated with ^{177}Lu-PSMA-617 first (LU-CA) and those receiving Cabazitaxel (CA-LU) first (10.8 and 11.7 months, respectively; p = 0.422).
- Median overall survival (OS) was also similar in the LU-CA and CA-LU groups (16.6 and 19.9 months, respectively; p = 0.917).
- Objective response rate (ORR) for ^{177}Lu-PSMA-617 was 23.1 % when used first and 16.1 % after Cabazitaxel. ORR for Cabazitaxel was 25.6 % and 31.3 % when used as the first agent and when used after ^{177}Lu-PSMA-617, respectively.

European Journal of Cancer
Volume 217, 25 February 2025, 115226

ASCO GU 2025: PET Imaging for Metastatic Castration Sensitive Prostate Cancer (mCSPC) for Patients with PSA Response After Systemic Therapy: A Multicentric Ambispective Analysis

60 patients

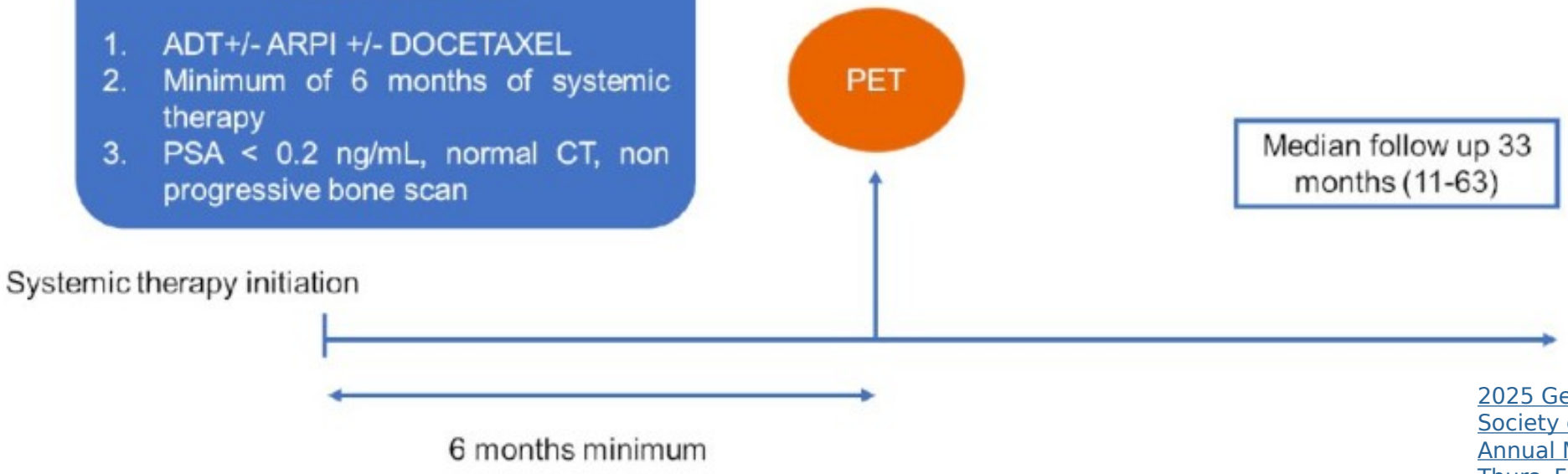
Between August 2022 and September 2024

PET choline or PSMA

4 comprehensive cancer centers

Inclusion criteria

1. ADT+/- ARPI +/- DOCETAXEL
2. Minimum of 6 months of systemic therapy
3. PSA < 0.2 ng/mL, normal CT, non progressive bone scan



2025 Genitourinary (GU) American Society of Clinical Oncology (ASCO) Annual Meeting, San Francisco, CA, Thurs, Feb 13 – Sat, Feb 15, 2025.

ASCO GU 2025: PET Imaging for Metastatic Castration Sensitive Prostate Cancer (mCSPC) for Patients with PSA Response After Systemic Therapy: A Multicentric Ambispective Analysis

- Among mCSPC patients treated with ADT +/- an ARPI +/- docetaxel and who had a serum PSA level <0.2 ng/ml, an 81% complete response is observed when PSMA PET imaging is performed.
- Although routine PSMA PET imaging is not recommended in this setting,
- This additional information could be an additional surrogate measure to identify patients who may benefit from further treatment intensification or deintensification in this setting.
- While treatment intensification in this setting is strongly recommended given documented survival benefits, this raises question as to which patients (and when) to receive subsequent treatment deintensification.

Incorporating novel biomarkers, including novel imaging modalities, is potentially key in this setting.

2025 Genitourinary (GU) American Society of Clinical Oncology (ASCO) Annual Meeting, San Francisco, CA, Thurs, Feb 13 – Sat, Feb 15, 2025.

1st line PARPi + Enza prolongs time for (GHS/QOL) definitive deterioration: TALAPRO-2

- 805 men, 49 patients were included in this subgroup analysis (TALA + ENZA n= 22, PBO + ENZA n= 27).
- A statistically significant and clinically meaningful estimated overall change from baseline favoured TALA + ENZA in physical functioning (20.5 [95% confidence interval {CI}: 8.8, 32.2]; P=0.0007), role functioning (20.4 [95% CI 4.8, 35.9]; P=0.0103), pain (32.9 [95% CI 50.3, 15.5]; P=0.0002), and constipation (12.5 [24.4, 0.6]; P=0.0399).
- Subgroup analyses of Novel Hormonal therapy pre-treated patients, significant differences in patient reported outcome favouring TALA + ENZA were observed.

https://ascopubs.org/doi/pdf/10.1200/JCO.2024.42.4_suppl.116

ICI combination therapy trials in mCRPC

NCT number	Phase	Estimated patients	Study description	Results
NCT02985957[67]	2	90	A study of nivolumab + ipilimumab, ipilimumab alone, or cabazitaxel in men with mCRPC	Higher ORR (25%) in pre-chemotherapy cohort 1 *vs.* post-chemotherapy cohort 2 (10%). Grade 3-5 AEs were present in a significant proportion of study patients, with treatment-related deaths
NCT03016312[69]	3	772	Atezolizumab + enzalutamide *vs.* placebo + enzalutamide in mCRPC	Primary endpoint of OS was not met
NCT03834493[70]	3	1,244	Pembrolizumab + enzalutamide *vs.* placebo + enzalutamide in mCRPC	Primary endpoint of OS was not met
NCT03834519[71]	3	529	Pembrolizumab + olaparib for patients with previously treated and biomarker-unselected mCRPC	Primary endpoints of rPFS and OS were not met
NCT03834506[74]	3	1,030	Pembrolizumab + docetaxel *vs.* docetaxel in mCRPC	Primary endpoints of rPFS and OS were not met
NCT04100018[76]	3	984	Nivolumab + docetaxel *vs.* placebo + docetaxel in mCRPC	Primary endpoints of rPFS and OS were not met

Khorasanchi et al. Cancer Drug Resist. 2025;8:9

Algorithm: De Novo or Treatment Emergent Small Cell Neuroendocrine PCa

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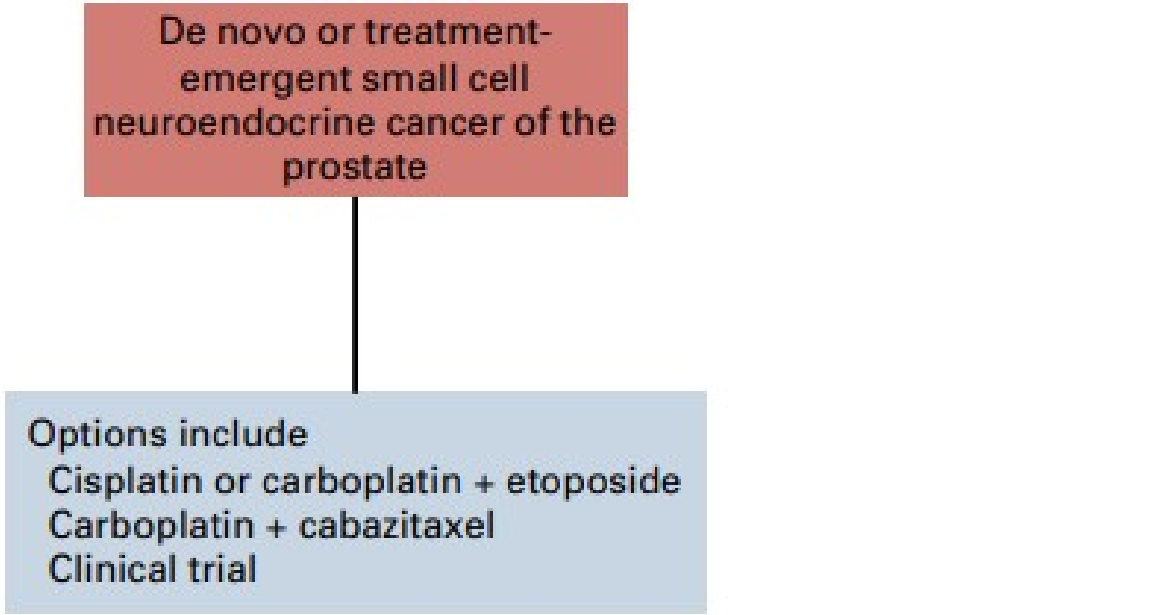

https://ascopubs.org/doi/pdf/10.1200/JCO-25-00007

Summary

- Prostate cancer (PCa) is a leading cause of cancer-related deaths globally with management complications in metastasis
- Challenging cases in mCSPC & mCRPC needs precision approach, as per cues from ongoing & established landmark trials/guidelines
- The treatment of mCSPC & mCRPC has seen remarkable breakthroughs over the last few years
- Growing adoption of PET imaging, PSA-adapted approach, combination therapy ADT +/- ARPI +/- Chemo, PARPi, ^{177}Lu-PSMA are enabling patient care