

Clinical management of metastatic castration-resistant prostate cancer

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**13th Belgian Multidisciplinary
Meeting on Urological Cancers**

Conflicts of interest

- I have no potential conflict of interest to report



Agenda

- Scenarios from mHSPC treatment choices
 - The (rarer and rarer) ARPI-naïve mCRPC patients
 - Patients progressing on ADT+ARPI
 - Patients progressing after triplet therapy
- Support therapies
- Transformation to NEPC



ARPI-naïve mCRPC patients

Patients who have received... (in mHSPC)

- ADT monotherapy
- ADT + Docetaxel

ARPI is gold standard

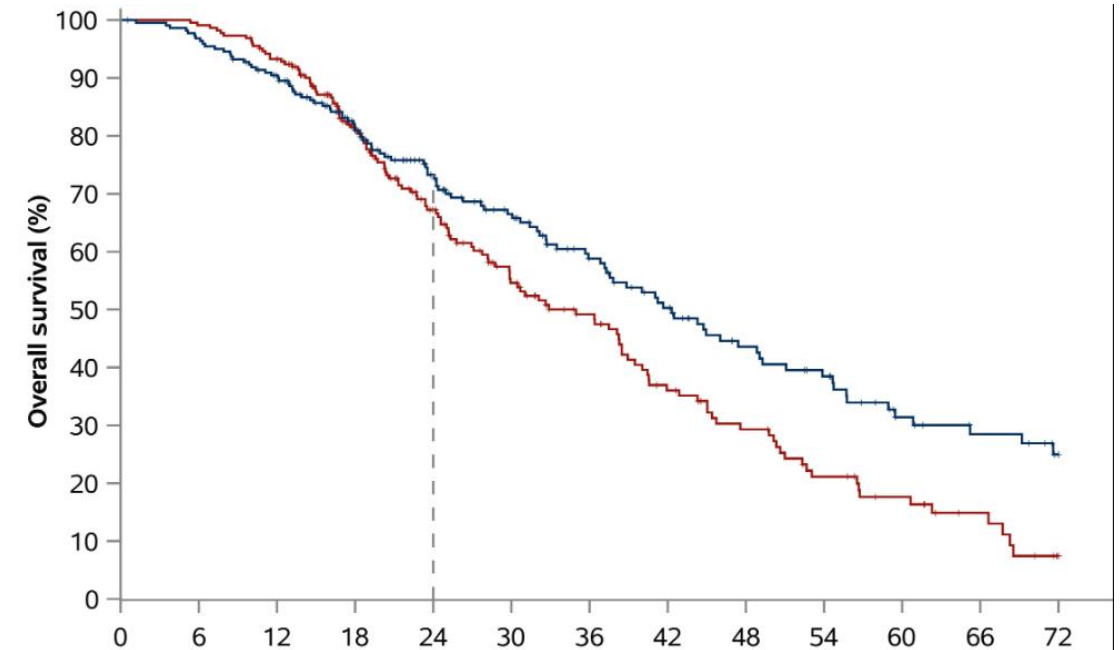
- Enzalutamide
 - Abiraterone acetate + prednisolone
 - ✗ Darolutamide
 - ✗ Apalutamide
-  No Phase III trials in this setting



Enzalutamide plus Radium223

- Bone mets +/- lymph nodes, but no visceral mets
- Prior abiraterone was allowed, but only 11 patients received it in the study
- 29.8% received priori docetaxel
- Mandatory denosumab/zoledronic acid

PEACE-3

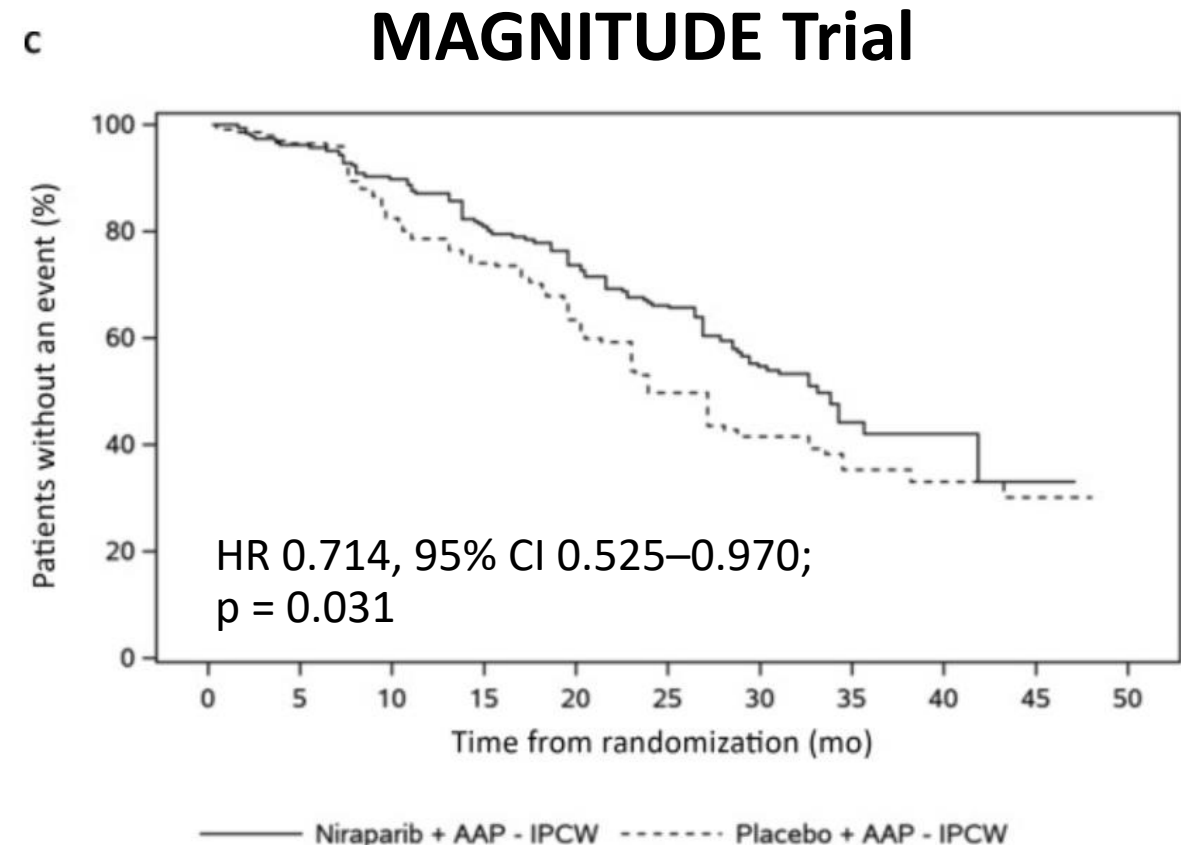


	Time in months												
	Patients at risk												
Enza-	224	222	206	152	107	77	58	40	30	20	14	8	1
Enza + Ra223-	222	214	194	149	114	92	71	57	43	36	23	18	12
	No. cumulative events												
Enza-	0	2	15	40	64	83	90	105	112	120	123	125	129
Enza + Ra223-	0	7	21	39	53	63	73	83	90	95	101	103	105

Somatic genomic testing

If not already obtained, perform NGS on archival or new tissue samples to investigate **HRR** and MSI status.

- Combination significantly improved PFS or TSP
- No formal advantage in OS, but most patients in placebo arm received PARPi afterwards
- Advantage in OS when this was taken into account

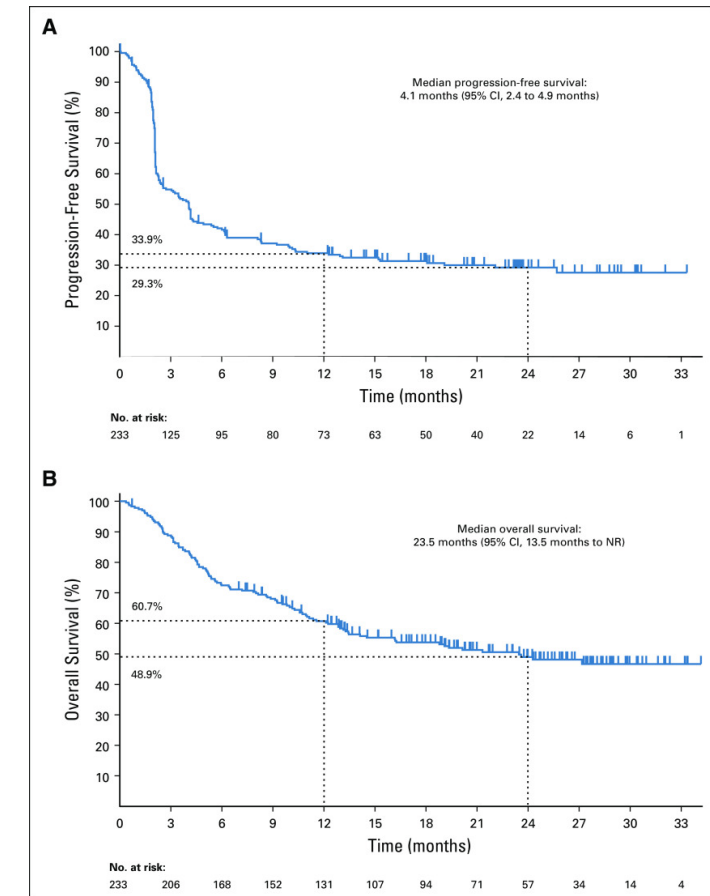


Somatic genomic testing

If not already obtained, perform NGS on archival or new tissue samples to investigate HRR and **MSI status**.

Keynote – 158, NEPTUNES, INSPIRE trials

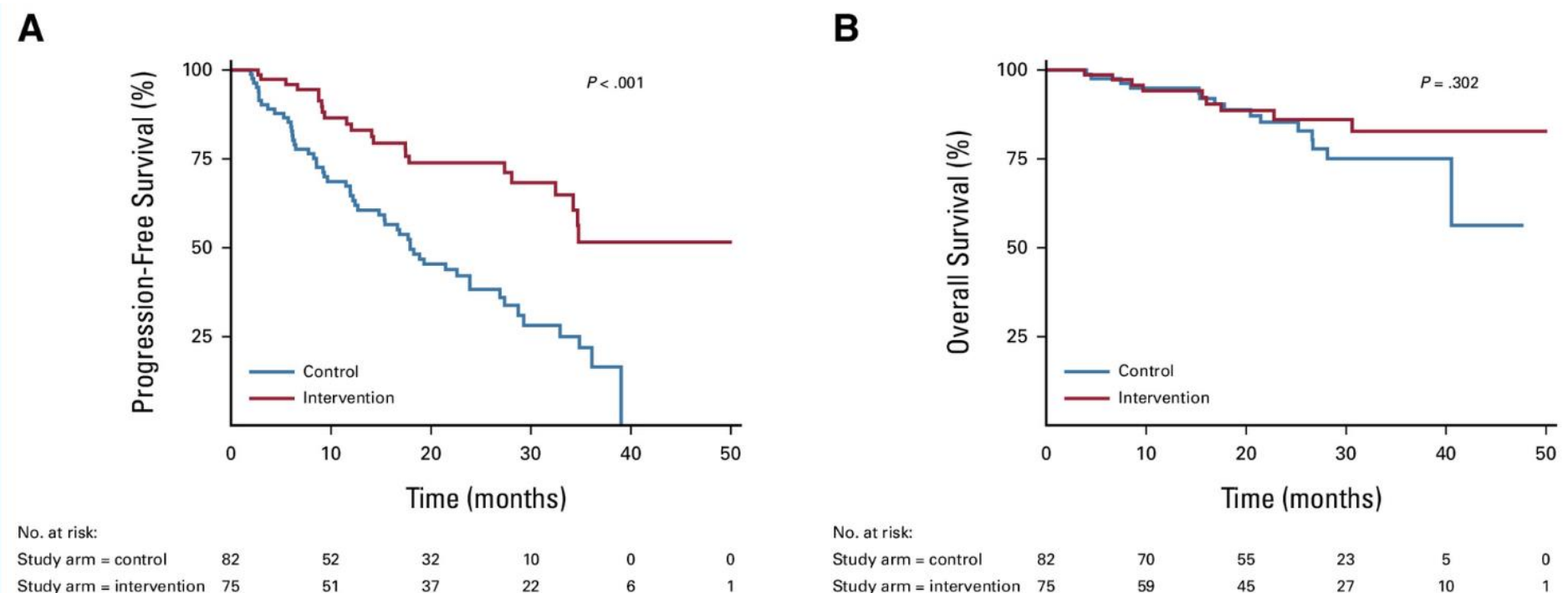
- Pembrolizumab is an effective treatment for MSI-H mCRPC
- Combinations of Nivolumab and Ipilimumab followed by nivolumab maintenance may achieve deeper and longer responses at the price of increased toxicity
- For mCRPC in patients already exposed to ARPI and Docetaxel (or unfit/refusing docetaxel)



Metastases-directed therapy

For patients with oligorecurrent, oligometastatic disease, consider SBRT to all lesions.

ARTO Trial → Abiraterone + SBRT vs Abiraterone alone



Patients who received ADT monotherapy for mHSPC

1. Is it really mCRPC?

- Check testosterone (T<50 ng/dL, <1.7 nmol/L)

2. Why ADT monotherapy?

- Previous toxicity which led to early ARPI interruption → **Try different ARPI**
- Patients with low burden metachronous disease, who decided to avoid extra toxicity from ARPI → **Metastases-directed therapy**
- **Frail/older patient**



Frail/Older patients

- Darolutamide has very low blood–brain barrier penetration, which seems to be associated with less CNS symptoms compared to enzalutamide/apalutamide (no direct comparisons)
- Consider best-supportive care, especially for patients asymptomatic with low burden of disease and with significant comorbidities (competitive risk)
- Geriatric evaluation
- Delay treatment until symptomatic disease



Patients progressing on ADT+ARPI

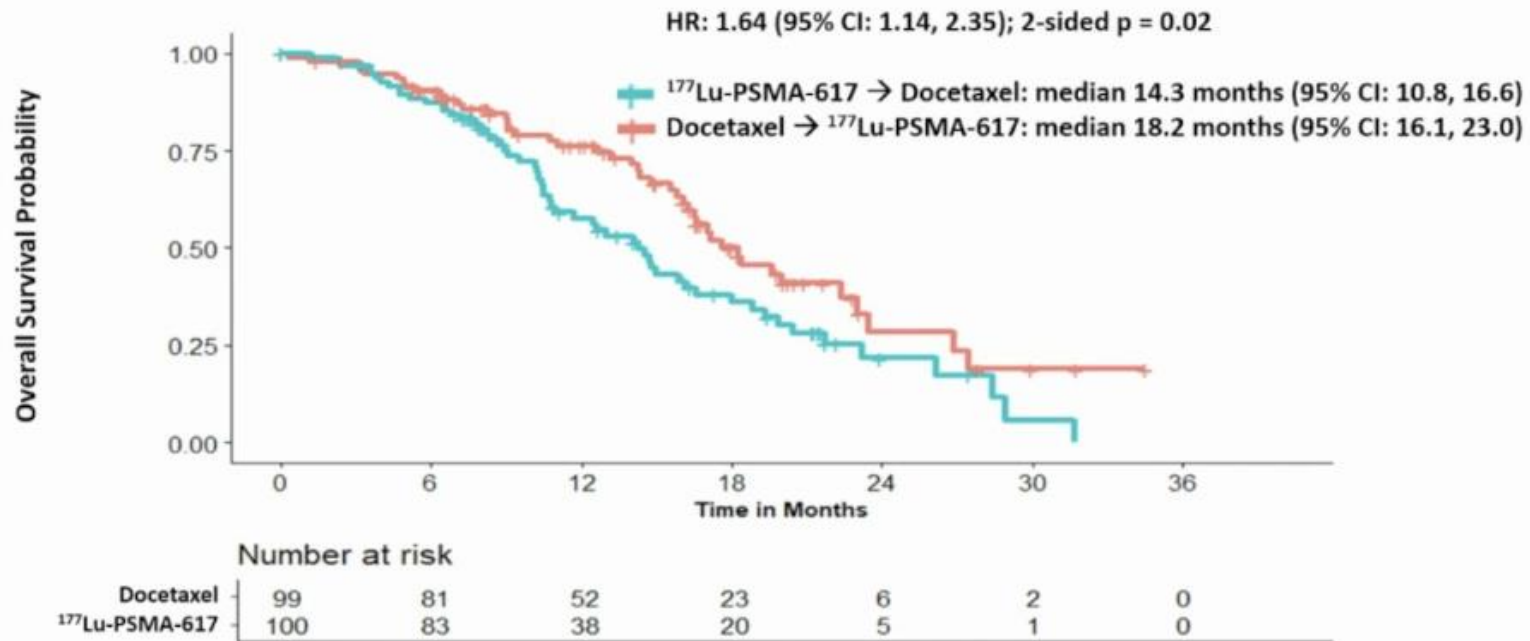
Docetaxel and (177 Lu)–PSMA-617 (assuming PSMA+ disease at PET scan)

Best sequence?

PR.21 Trial

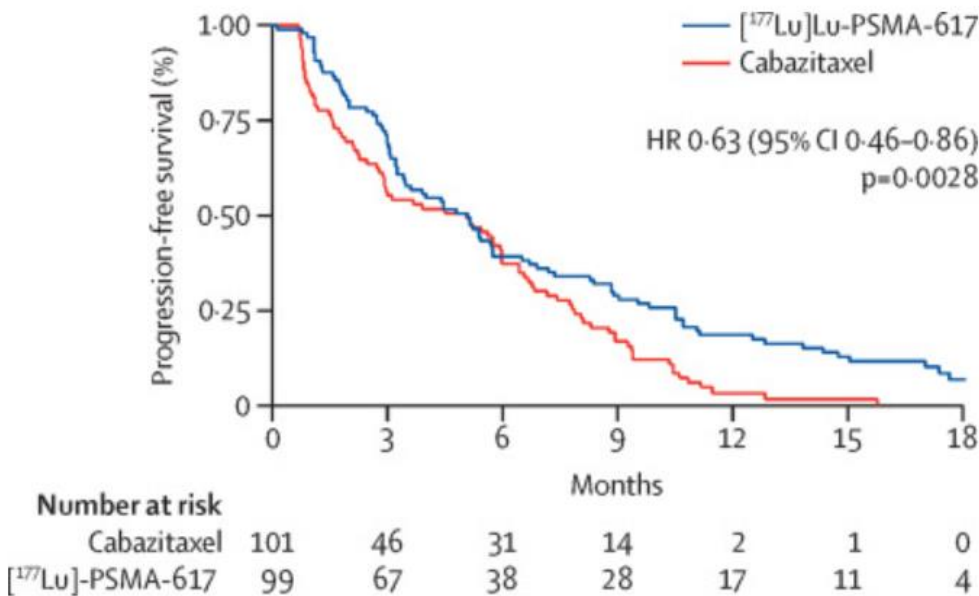
Overall Survival

- No differences in rPFS 1-2 between Lu-PSMA→Doce versus Doce→Lu-PSMA
- Doce→Lu-PSMA led to better OS, very likely due to attrition rate



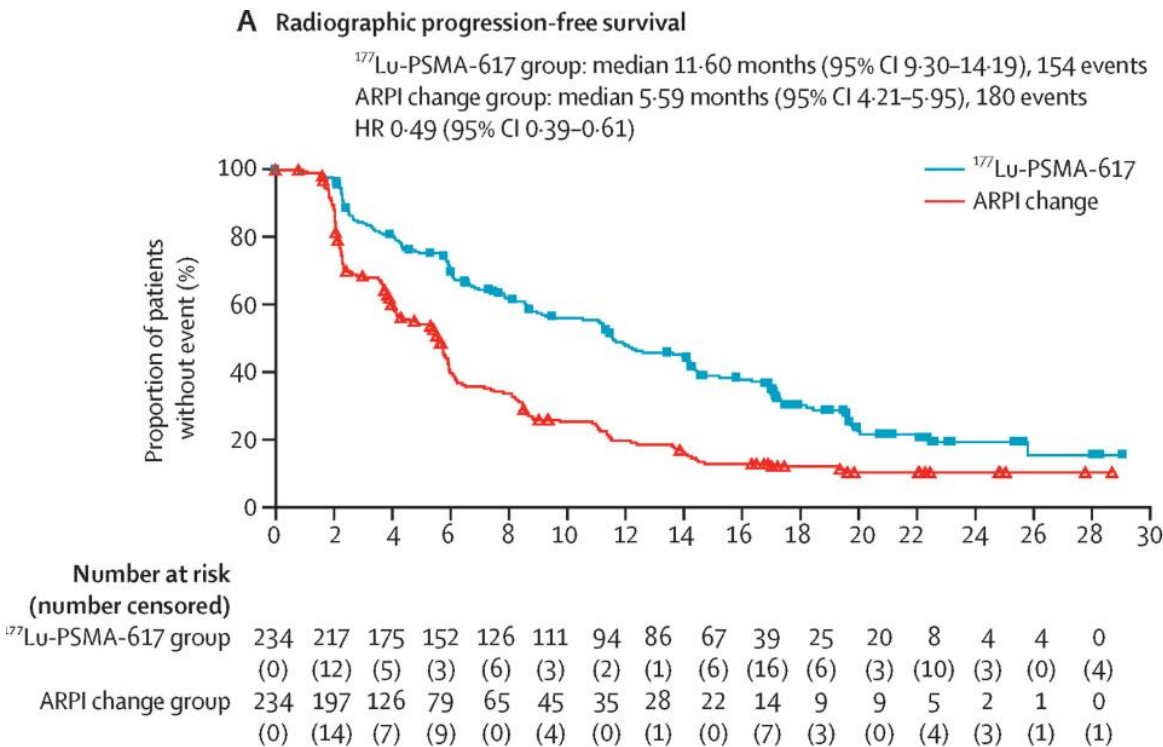
Patients progressing after triplet therapy

TheraP trial



Hofman M, et al. [¹⁷⁷Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial. The Lancet, 2021; 397, 797-804

PSMAfore trial



Morris M, et al. ¹⁷⁷Lu-PSMA-617 versus a change of androgen receptor pathway inhibitor therapy for taxane-naïve patients with progressive metastatic castration-resistant prostate cancer (PSMAfore): a phase 3, randomised, controlled trial. The Lancet, 2024; 404, 1227-1239

Patients progressing after triplet therapy

Docetaxel rechallenge?

> [Urol Oncol](#). 2022 Dec;40(12):539.e17-539.e22. doi: 10.1016/j.urolonc.2022.09.010.
Epub 2022 Oct 20.

UnCHAARTED territory: The role of docetaxel rechallenge following chemohormonal therapy for metastatic castration-sensitive prostate cancer

Mary Mahle
Christina Ca

► [Cureus](#). 2025 Aug 27;17(8):e91143. doi: [10.7759/cureus.91143](#) 

Docetaxel Rechallenge After Chemohormonal Therapy in High-Volume Metastatic Castration-Sensitive Prostate Cancer

[Kenichi Hata](#)^{1,✉}, [Yuki Takiguchi](#)², [Yuya Iwamoto](#)², [Taisuke Yamazaki](#)², [Takahiro Kimura](#)³

Clinical Trial > [Eur Urol](#). 2018 May;73(5):696-703. doi: 10.1016/j.eururo.2017.09.022.

Epub 2017 Oct 23.

Anticancer Activity and Tolerance of Treatments Received Beyond Progression in Men Treated Upfront with Androgen Deprivation Therapy With or Without Docetaxel for Metastatic Castration-naïve Prostate Cancer in the GETUG-AFU 15 Phase 3 Trial

[Pernelle Lavaud](#)¹, [Gwenaëlle Gravis](#)², [Stéphanie Foulon](#)³, [Florence Joly](#)⁴, [Stéphane Oudard](#)⁵, [Frank Priou](#)⁶, [Igor Latorzeff](#)⁷, [Loïc Mourey](#)⁸, [Michel Soulié](#)⁹, [Remy Delva](#)¹⁰, [Ivan Krakowski](#)¹¹, [Christine Théodore](#)¹³, [Jean Marc Ferrero](#)¹⁴, [Philippe Beuzeboc](#)¹⁵, [Frédéric Rolland](#)¹⁷, [Gael Deplanque](#)¹⁸, [Damien Pouessel](#)¹⁹, [Sylvie Zanetta](#)²⁰, [Jerome Dauba](#)²¹, [Marjorie Baciuchka](#)²³, [Christian Platini](#)²⁴, [Nicole Tubiana-Mathieu](#)²⁶, [Jean Pascal Machiels](#)²⁷, [Claude El Kouri](#)²⁸, [Anne Suc](#)³⁰, [Jean Christophe Eymard](#)³¹, [Ali Hasbini](#)³², [Guilhem Bousquet](#)³³, [Jean-Marie Boher](#)³⁵, [Gabrielle Tergemina-Clain](#)³, [Clémence Legoupil](#)³,

We need more real-world data and predictive factors

- Gleason score ≥ 8 (?)
- Docetaxel free interval 36 months (APCCC 2023)

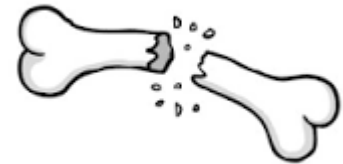
Later lines options

- Cabazitaxel 20 mg/mq (post-docetaxel and Lu-PSMA)
- Radium 223 (bone only disease or bone + small lymph nodes)
- Dexamethasone 0.5 mg for symptomatic control
- Clinical trials



Bone protection

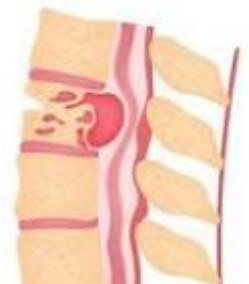
All patients with mCRPC and bone metastases should receive a bone-protective agent to prevent skeletal-related events (fractures, MSCC)



Denosumab > Zoledronic Acid

- Monthly dosing, could be de-escalated to 3-monthly doses after initial period, continue indefinitely.
- Calcium + vitamin D mandatory
- Dental assessment required before starting, avoid dental procedures during treatment
- Even patients without bone metastases should at least receive a lower dose of bone protective agent (such as denosumab 60 mg/6months), same as mHSPC

Metastatic Spinal
Cord Compression (MSCC)



Neuroendocrine Prostate Cancer (PCa)

General information

- 10-20% transformation rate
- When to suspect neuroendocrine transformation?
 - Radiological progression with low/not rising PSA despite high burden of disease
 - Uncommon metastatic pattern (liver, bulky abdominal lesions, lithic bone lesions)
 - High uptake of FDG on PET scan (mixed PSMA uptake)
 - RB1+PTEN+TP53 mutations (2/3 mutations)
- Markers: chromogranin A, NSE



Neuroendocrine Prostate Cancer (PCa)

Treatment

- Platinum-Based chemotherapy
 - Cisplatin/Carboplatin + Etoposide (+ Atezolizumab) for pure small cell aggressive variants
 - Carboplatin + Docetaxel for mixed phenotype
- Maintain ADT(+ARPI) to keep hormone-dependent clones under control
- Emerging therapies: DLL3 targeted therapies
- Clinical trials



Summary

HSPC Treatment	mCRPC sequence
ADT monotherapy	Abi or Enza (+Radium223) → Docetaxel → Lu-PSMA* → Cabazitaxel
ADT monotherapy (Frail patients)	Darolutamide (if possible) → Lu-PSMA* ...(Radium223)
ADT+Docetaxel	Abi or Enza (+Radium223) → (<i>Docetaxel rechallenge</i>) → Lu-PSMA* → Cabazitaxel
ADT+ARPI	Docetaxel → Lu-PSMA* → Cabazitaxel ... (Radium223)
ADT+ARPI+Docetaxel	Lu-PSMA* → (<i>Docetaxel rechallenge</i>) → Cabazitaxel ... (Radium223)

Actionable mutations	mCRPC sequence
HRR gene mutations	Niraparib + Abi or single agent PARPi → consider plat-based chemo → <i>then as above</i>
MSI-H	Immune checkpoint inhibitor(s) (Pembro or Nivo+Ipi) after ARPI and docetaxel

*Only for PSMA positive disease on PSMA-PET scan

For all patients

- Offer bone protective agents
- Consider metastases-directed therapy for oligometastatic/oligoprogressive patients
- Offer participation in clinical trials
- Watch out for NEPC



Thank you for your attention

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