journées scientifiques de l'association algérienne de médecine nucléaire libérale, à Oran 4 juin 2022

PSMA diagnotique et thérapeutique

Le théranostic avec du PSMA !

Pr F COURBON

Biophysique & Médecine Nucléaire : UFR MédecineToulouse Rangueil
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Liens d’intérêt:

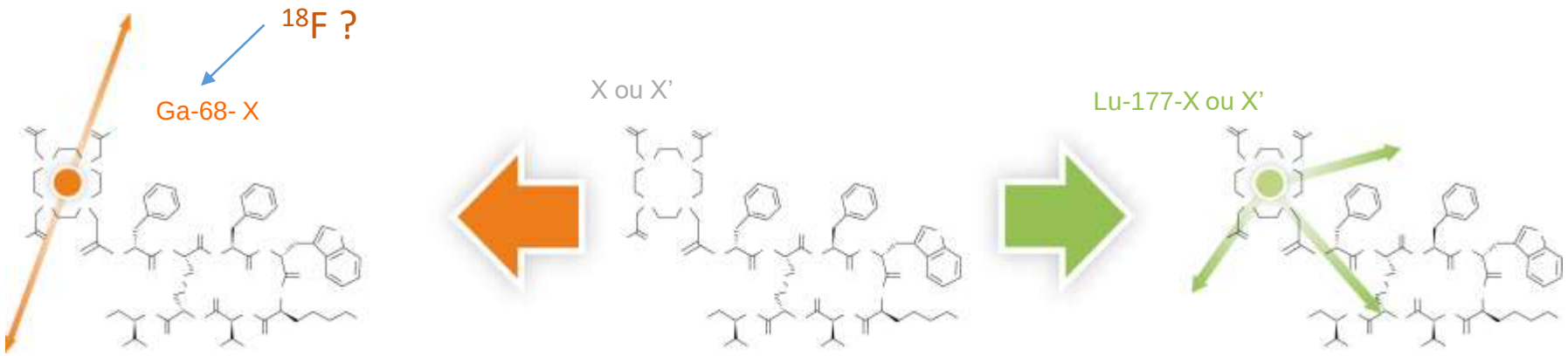
Financements recherche

Curium , IBA, Roche, GEHC

Expertise

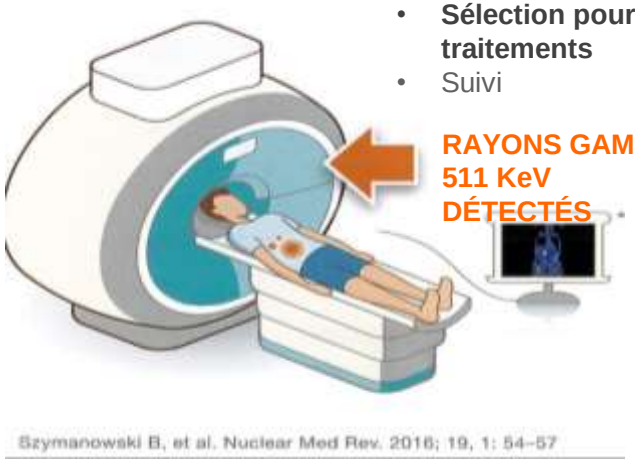
Covidien/Mallinkrodt, Ipsen, Novartis, Norgine, Bayer, GEHC, Cyclopharma, AAA

THERANOSTIC



Ga-68 PET

- Diagnostic
- **Sélection pour RIV ou autres traitements**
- Suivi



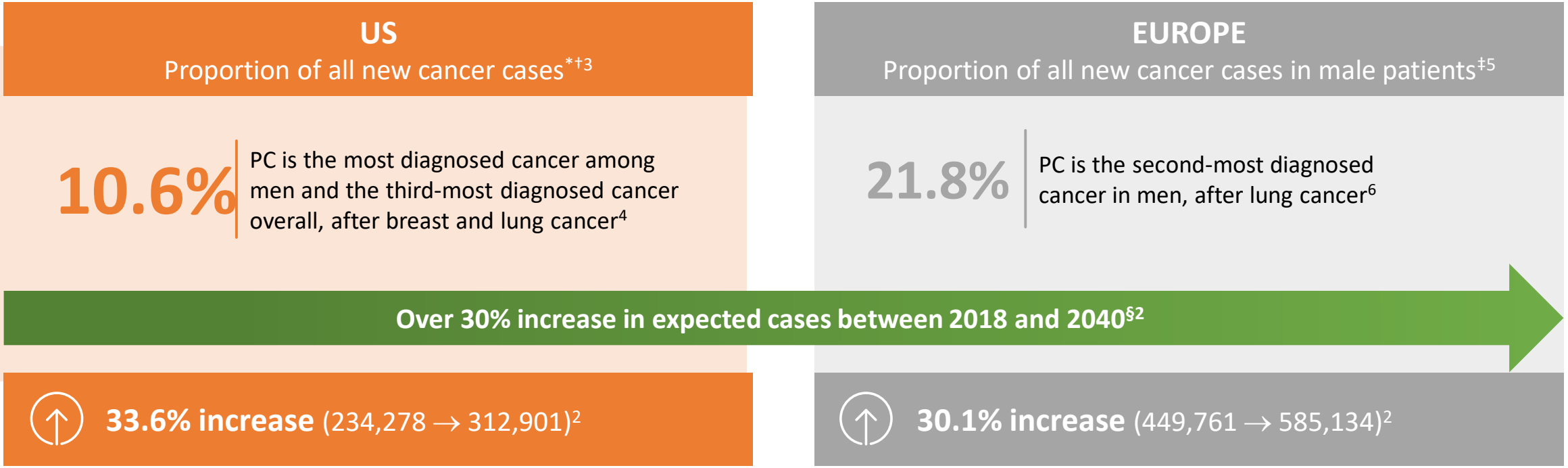
RAYONS GAMMA
511 KeV
DÉTECTÉS

Szymanowski B, et al. Nuclear Med Rev. 2016; 19, 1: 54–57

Lu-177 RIV

TRAITEMENT PAR RADIOTHERAPIE INTERNE VECTORISEE
IMAGERIE POST- DOSE
DOSIMETRIE

Cancer de la prostate



Epidémiologie

En France, cancer le plus fréquent chez l'homme > 50 ans (50 000 nouveaux cas par an)[1]
2ème cancer (9 000 décès par an)[1] [1.] AFU Association Française d'Urologie http://www.urofrance.org/congres-et-formations/formation-initiale/referentiel-du-college/tumeurs-de-la-prostate.html

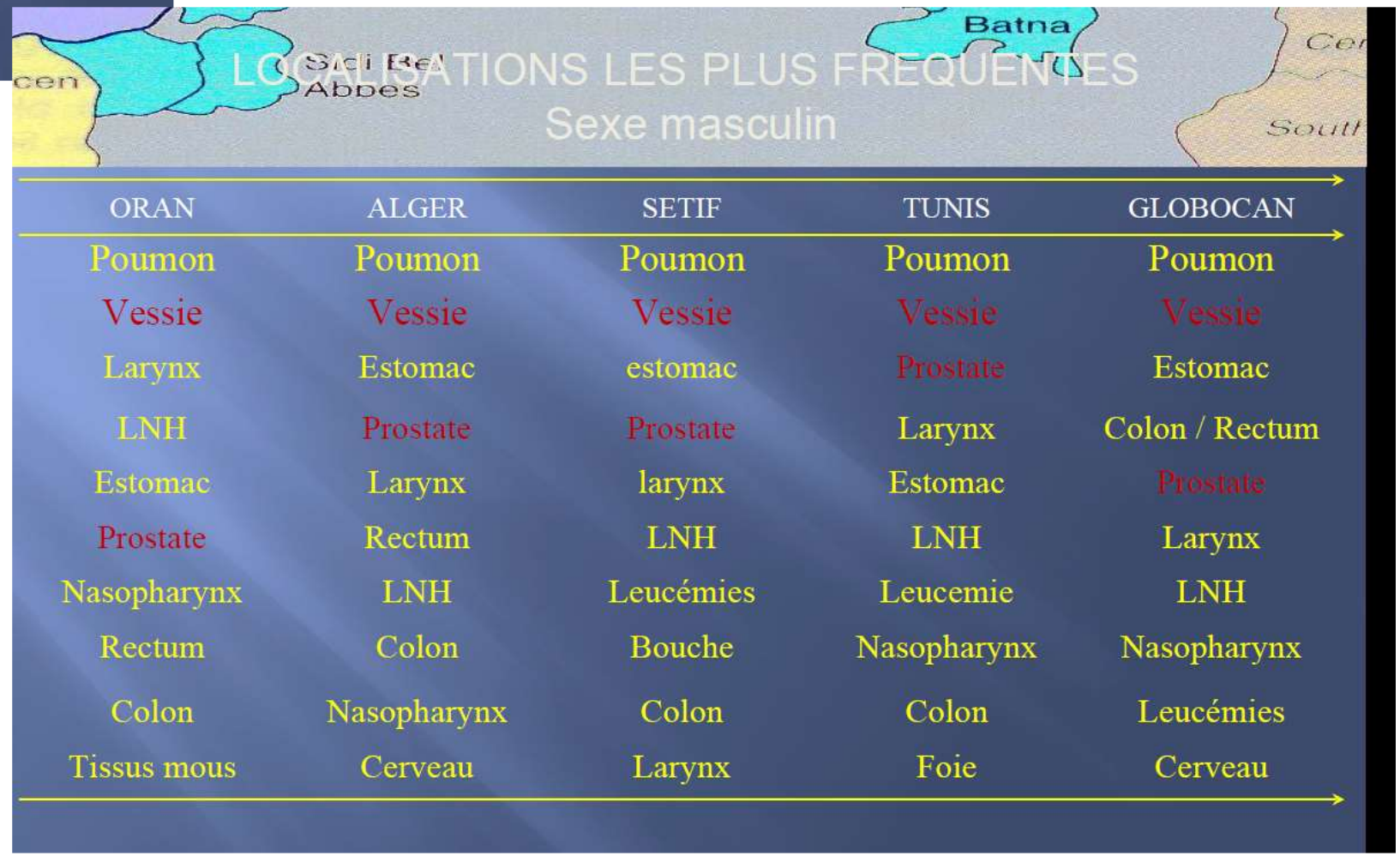
1. AFU Association Française d'Urologie http://www.urofrance.org/congres-et-formations/formation-initiale/referentiel-du-college/tumurs-de-la-prostate.html

Male and female patients; †US proportion estimated for 2020; ‡Europe proportion in 2018; §Expected increase from 2018 to 2040 in the US and Europe.

1. American Cancer Society. Global Cancer Facts & Figures 4th Edition. https://www.cancer.org/research/cancer-facts-statistics/global.html (accessed November 2020);
2. 2. World Health Organization. International Agency for Research on Cancer. Cancer Tomorrow. https://gco.iarc.fr/tomorrow/home (accessed November 2020);
3. National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) Program. Cancer stat facts: prostate cancer. https://seer.cancer.gov/statfacts/html/prost.html (accessed November 2020);
4. 4. National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) Program. Cancer stat facts: common cancer sites. https://seer.cancer.gov/statfacts/html/common.html (accessed November 2020);
5. 5. Ferlay J, et al. Eur J Cancer. 2018;103:356–387; 6. American Cancer Society, in partnership with WHO IARC. The cancer atlas: Europe. https://canceratlas.cancer.org/the-burden/europe/ (accessed November 2020).

http://www.santetropicale.com/santemag/algerie/comptes_rendus/jicc2010/13.pdf

PLACE DES CANCERS UROLOGIQUES DANS LE REGISTRE DU CANCER DE SETIF



ORAN	ALGER	SETIF	TUNIS	GLOBOCAN
Poumon	Poumon	Poumon	Poumon	Poumon
Vessie	Vessie	Vessie	Vessie	Vessie
Larynx	Estomac	estomac	Prostate	Estomac
LNH	Prostate	Prostate	Larynx	Colon / Rectum
Estomac	Larynx	larynx	Estomac	Prostate
Prostate	Rectum	LNH	LNH	Larynx
Nasopharynx	LNH	Leucémies	Leucemie	LNH
Rectum	Colon	Bouche	Nasopharynx	Nasopharynx
Colon	Nasopharynx	Colon	Colon	Leucémies
Tissus mous	Cerveau	Larynx	Foie	Cerveau

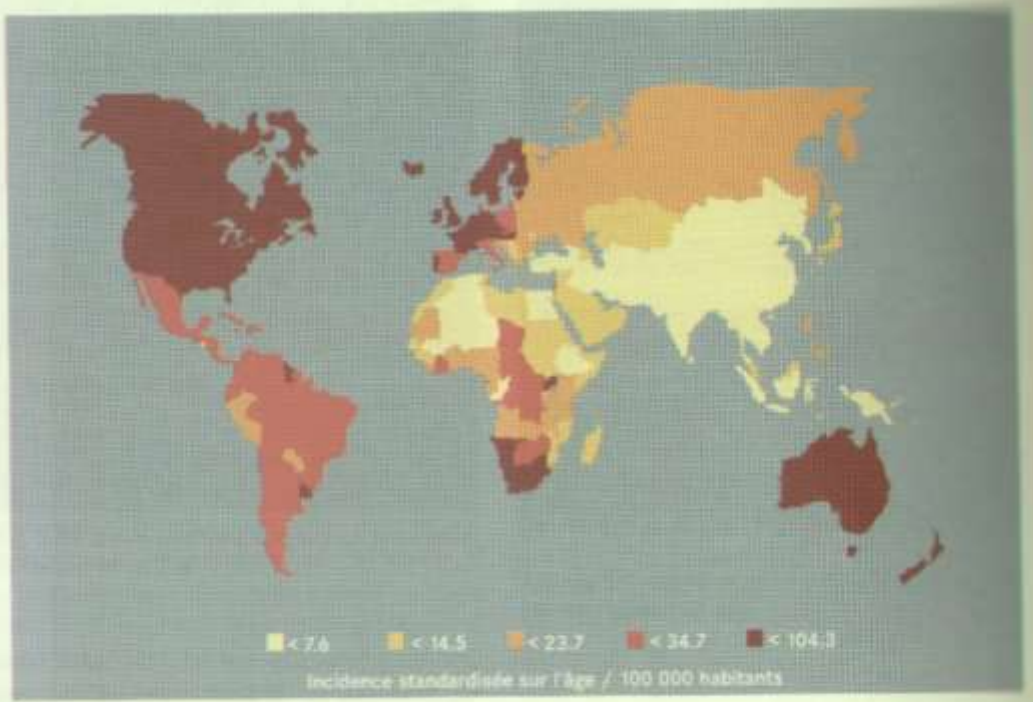
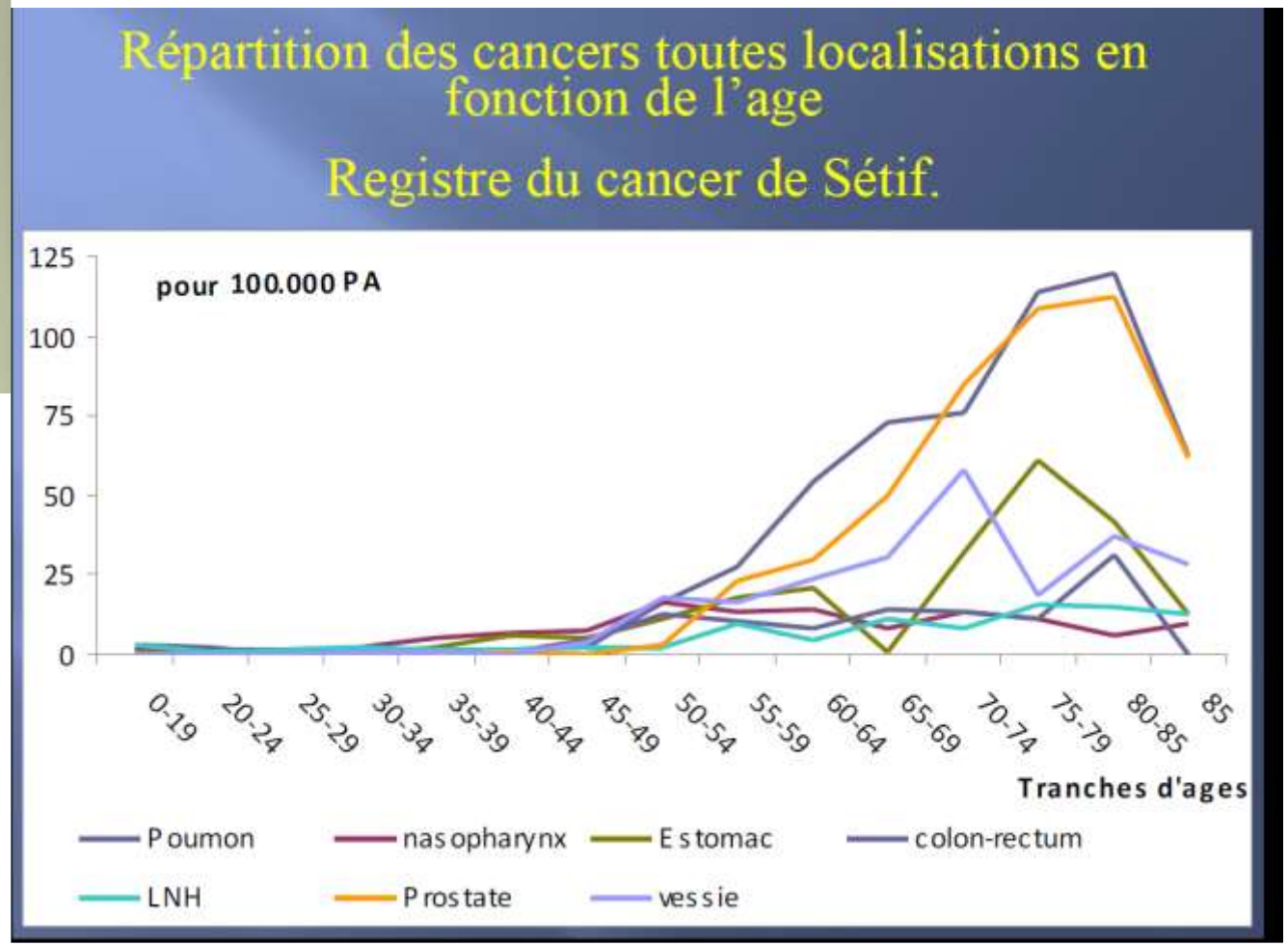
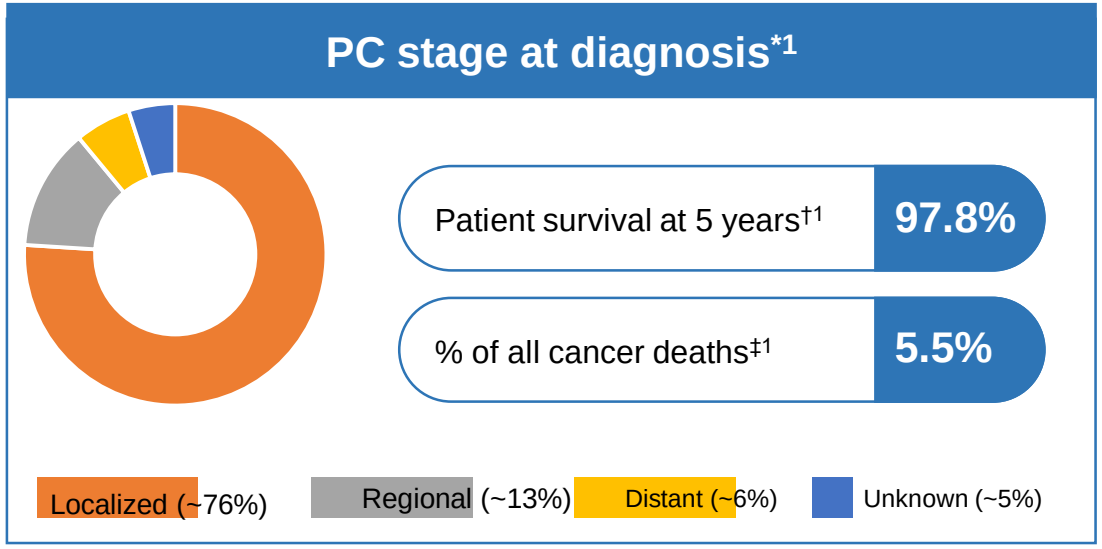
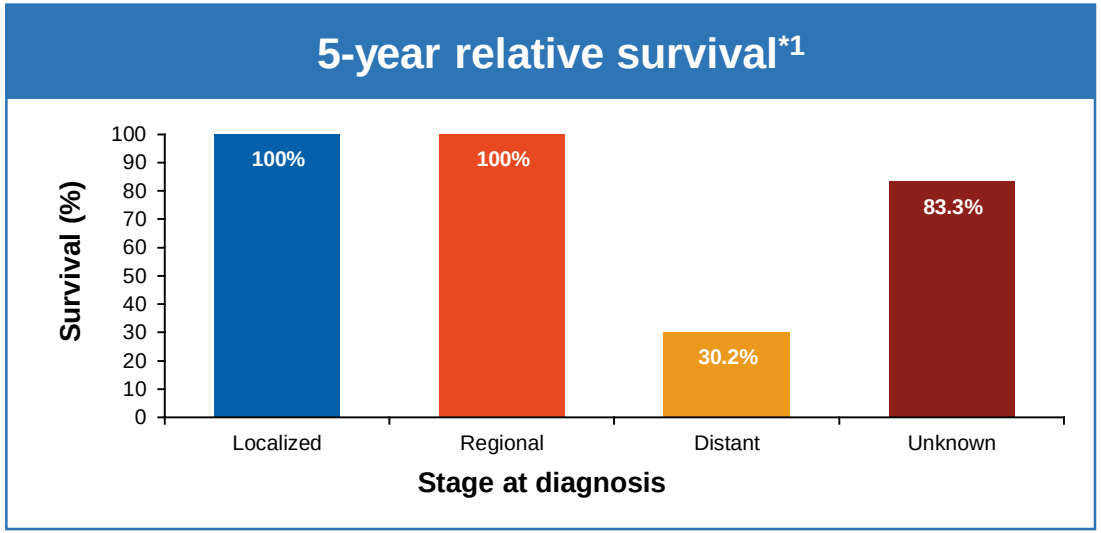


Fig. 5.45 Incidence mondiale du cancer de la prostate. Les taux les plus élevés s'observent dans les pays développés et dans certaines régions d'Afrique.



Le (s) cancer(s) de la prostate
Dans la majorité des cas : localisés et curables





L'extension fait le pronostic

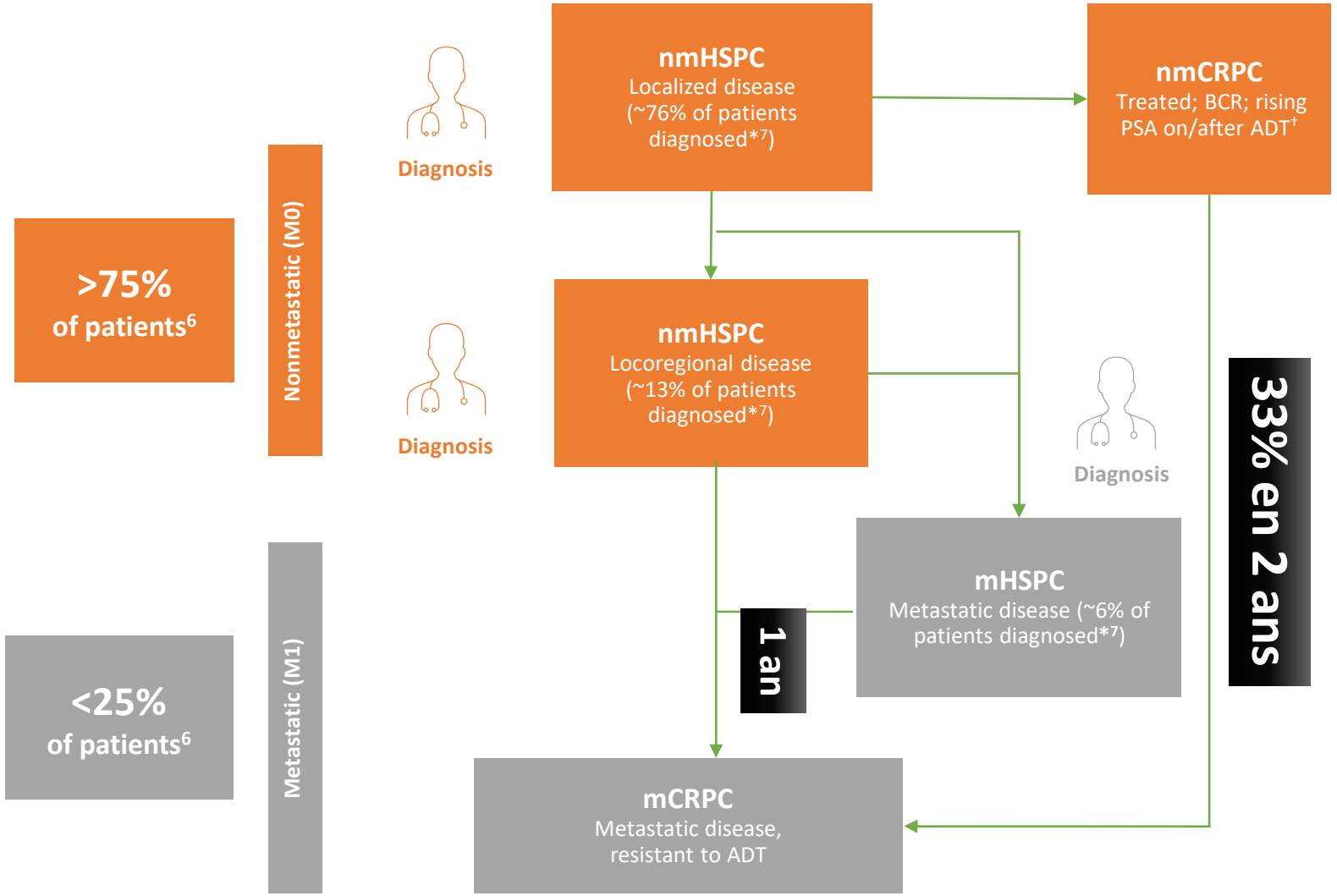
*Male patients of all races in the US (2010–2016); †Of all patients diagnosed with PC in the US (2010–2016); ‡Estimated deaths in 2020 in the US

1. National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) Program. Cancer stat facts: prostate cancer. https://seer.cancer.gov/statfacts/html/prost.html (accessed November 2020); 2. McPhail S, et al. Br J Cancer. 2015;112(suppl 1):S108–S115; 3. Pettersson A, et al. Ann Oncol. 2018;29(2):377–385 PC, prostate cancer.

Mais des patients vont développer une résistance à la castration CRPC

- 10 à 20 % dans les 5 ans nmHSPC -> nmCRPC ou mHSPC ou mCRPC
- 100% dans les formes métastatique d'emblée

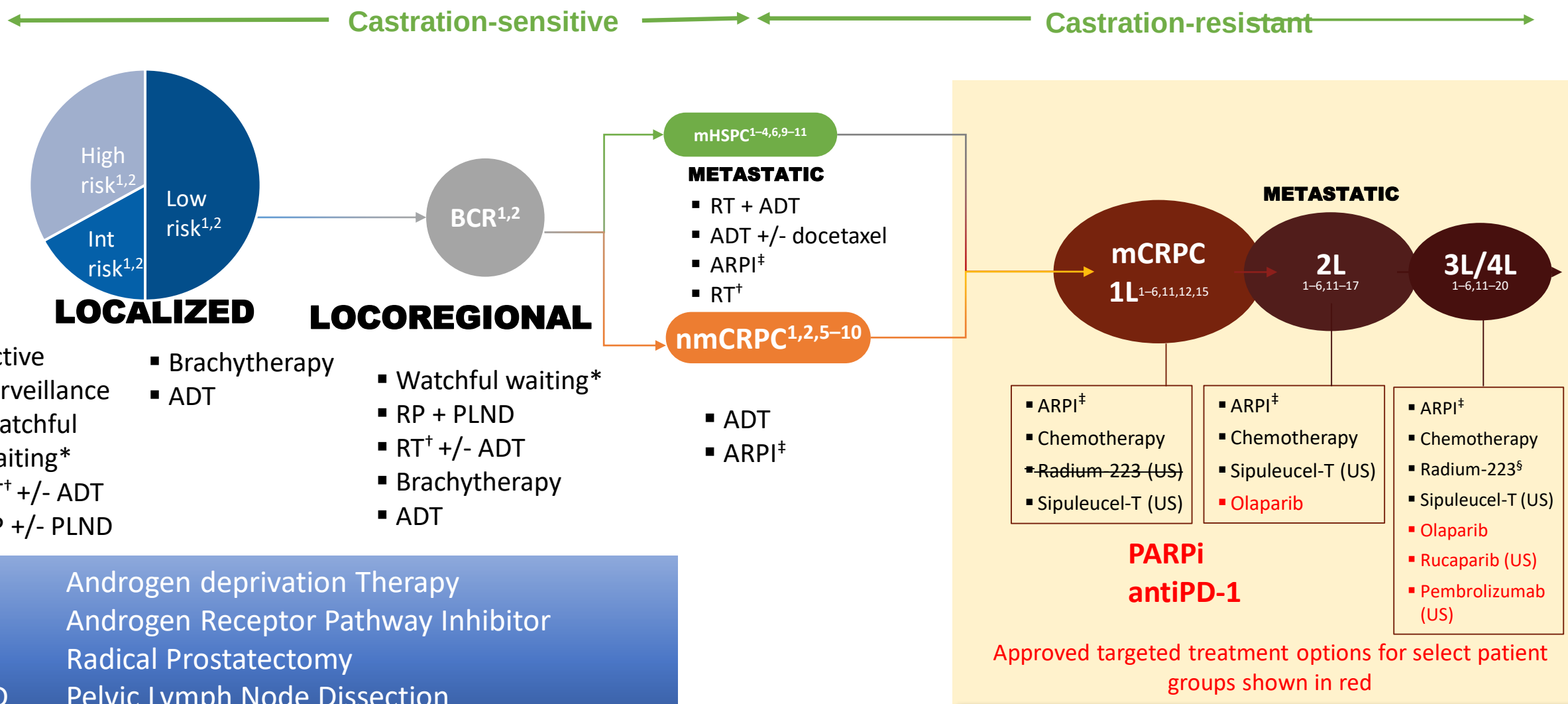
Quels sont les patient à risque ?



*Male patients of all races in the US (2010–2016); diagnosis rates in other countries may vary. †During early stages of PSA recurrence, PC patients are usually hormone-sensitive (HSPC) and spared by ADT; hormone therapy is usually administrated in later stages of recurrence (i.e., in association with SRT and/or in case of PSA failure after salvage treatments).[8]

1. Kirby M, et al. Int J Clin Pract. 2011;65(11):1180–1192;
2. Anttinen M, et al. Eur Urol Oncol. 2020 Jul 13. doi: 10.1016/j.euo.2020.06.012 [Epub];
3. Gravis G, et al. Lancet Oncol. 2013;14(2):149–158;
4. James ND, et al. Eur Urol. 2015;67(6):1028–1038;
5. Sweeney CJ, et al. N Engl J Med. 2015;373:737–746;
6. Liede A, et al. ESMO Open. 2016;1(2):e000040;
7. National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) Program. Cancer stat facts: prostate cancer. https://seer.cancer.gov/statfacts/html/prost.html (accessed November 2020);
8. Deandreis D, et al. Eur J Nucl Med Mol Imaging. 2020;47:2804–2815.

Panorama thérapeutique



ADT	Androgen deprivation Therapy
ARPI	Androgen Receptor Pathway Inhibitor
RP	Radical Prostatectomy
PLND	Pelvic Lymph Node Dissection
RT	Radiotherapy

➢ AMM 223Ra mRCPC **Douloureux** en échec de toutes les lignes

*1. Mottet N, et al. EAU guidelines: prostate cancer. https://uroweb.org/guideline/prostate-cancer/#6 (accessed April 2021);
2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Prostate cancer, v2.2020. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf (accessed April 2021);
3. Zytiga 250 mg tablets (abiraterone acetate). SmPC. Janssen-Cilag International NV; May 2016;
4. Zytiga® (abiraterone acetate) tablets. Prescribing information. Janssen Biotech, Inc; June 2019;
5. Xtandi 40 mg soft capsules (enzalutamide). SmPC. Astellas Pharma Europe BV; February 2018;
6. Xtandi® (enzalutamide) capsules/tablets. Prescribing information. Astellas Pharma US, Inc; August 2020;
7. Nubeqa 300 mg film-coated tablets (darolutamide). SmPC. Bayer AG; March 2020;
8. Nubeqa (darolutamide) tablets. Prescribing information. Bayer HealthCare Pharmaceuticals Inc; July 2019;
9. Erleada 60 mg film-coated tablets (apalutamide). SmPC. Janssen-Cilag International NV; January 2019;
10. Erleada® (apalutamide) tablets. Prescribing information. Janssen Pharmaceutical Companies; July 2020;
11. Taxotere 20 mg/0.5 mL concentrate and solvent for solution for infusion (docetaxel). SmPC. Sanofi Mature IP; November 2005;
12. Taxotere (docetaxel) injection. Prescribing information. Sanofi-Aventis US LLC; May 2020;
13. Jevtana 60 mg concentrate and solvent for solution for infusion (cabazitaxel). SmPC. Sanofi-Aventis Deutschland GmbH; November 2015;
14. Jevtana® (cabazitaxel) injection. Prescribing information. Sanofi-Aventis US LLC; March 2020;
15. Provenge® (sipuleucel-T) suspension for intravenous infusion. Prescribing information. Dendreon Pharmaceuticals LLC; July 2017;
16. Lynparza® (olaparib) tablets. Prescribing information. AstraZeneca Pharmaceuticals LP; May 2020;
17. Lynparza capsules (olaparib). SmPC. AstraZeneca AB; November 2020;
18. European Society for Medical Oncology. EMA restricts use of prostate cancer medicine Radium-223 dichloride. https://www.esmo.org/Oncology-News/EMA-Restrict Prostate-Cancer-Medicine-Radium-223-Dichloride (accessed November 2020);
19. Rubraca® (rucaparib) tablets. Prescribing information. Clovis Oncology Inc; May 2020;
20. Keytruda® (pembrolizumab) injection. Prescribing information. Merck Sharp & Dohme Corp; June 2020;
21. Shore N, et al. Urology. 2017;109:6–18; 22. He L, et al. Medicine (Baltimore). 2020;99(15):e19760;
23. Zheng H, et al. Biomed Res Int. 2017;2017:3941217.

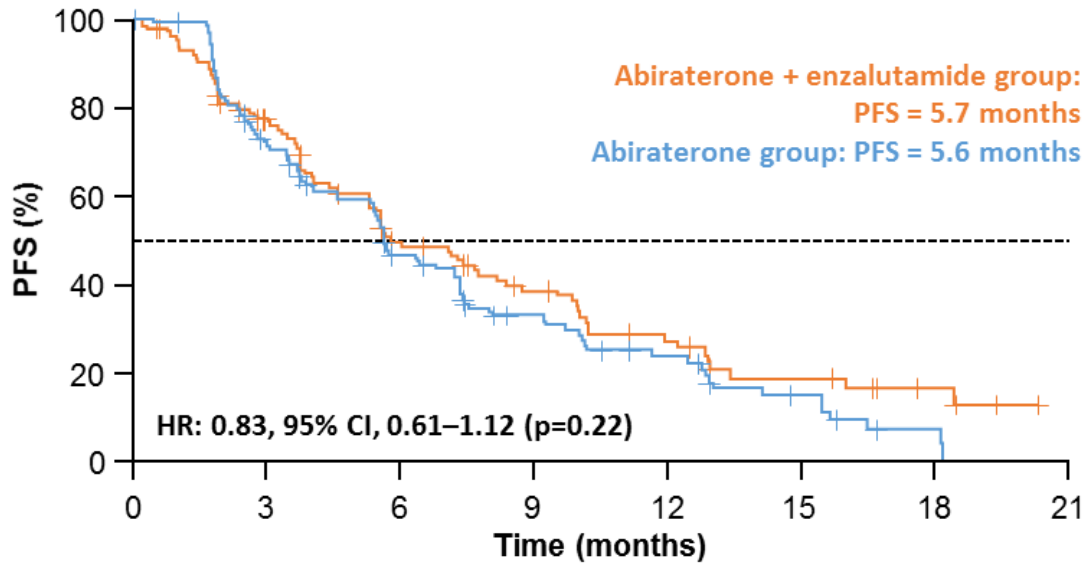
Quelle sequence ?

> Résistance croisée

> Gérer le temps

Abi puis Enza ?

Pre-treatment with enzalutamide resulted in limited response to both abiraterone and combination ARPI

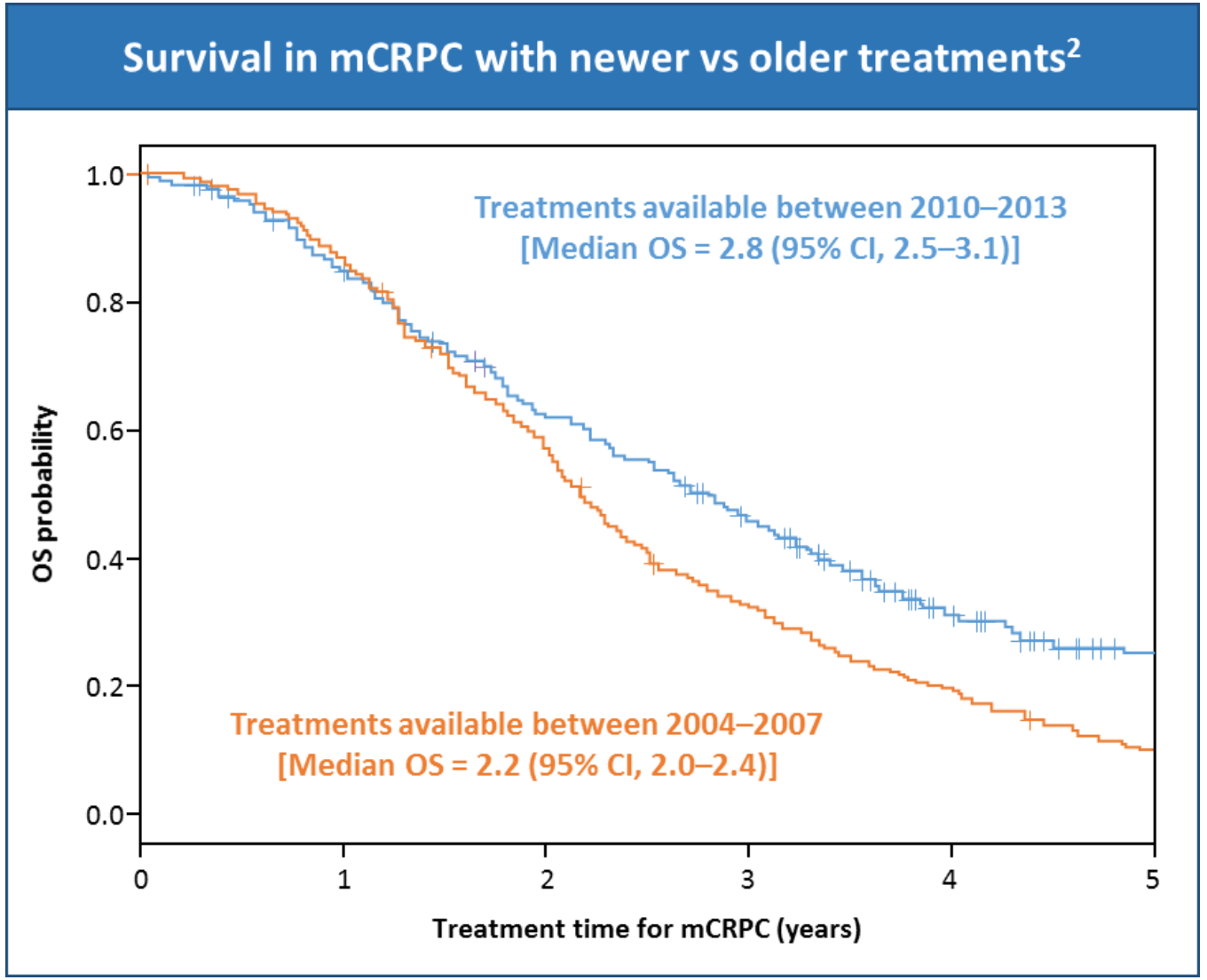


Study	Prior treatment(s)	Treatment received	Main outcomes
Attard et al.[5] (n=125)	Enzalutamide	Abiraterone	**Only 2% of patients had PSA ≥50%**
Noonan et al.[2] (n=30)	Docetaxel and enzalutamide	Abiraterone and prednisone	**Only 11% of patients had PSA ≥30%**

mCRPC = garde un mauvais prognostic

- Men with mCRPC have poor outcomes[1]
  - **83% de mortalié à** 41 mois
  - **SG :** 13–34 mois[1,2]
  - **S à 5 ans** 15%[1]
- Survival outcomes have modestly improved with the changing treatment landscape, but remain poor[2–6]

- <u>Des progress encore lents 2010–2013 vs 2004–2007</u>
  - **Médiane de survie :** 2.8 vs 2.2 years
  - **3-year OS rate:** 46% vs 33%
  - **41% decreased risk of death** (p <0.0001)



Séquence

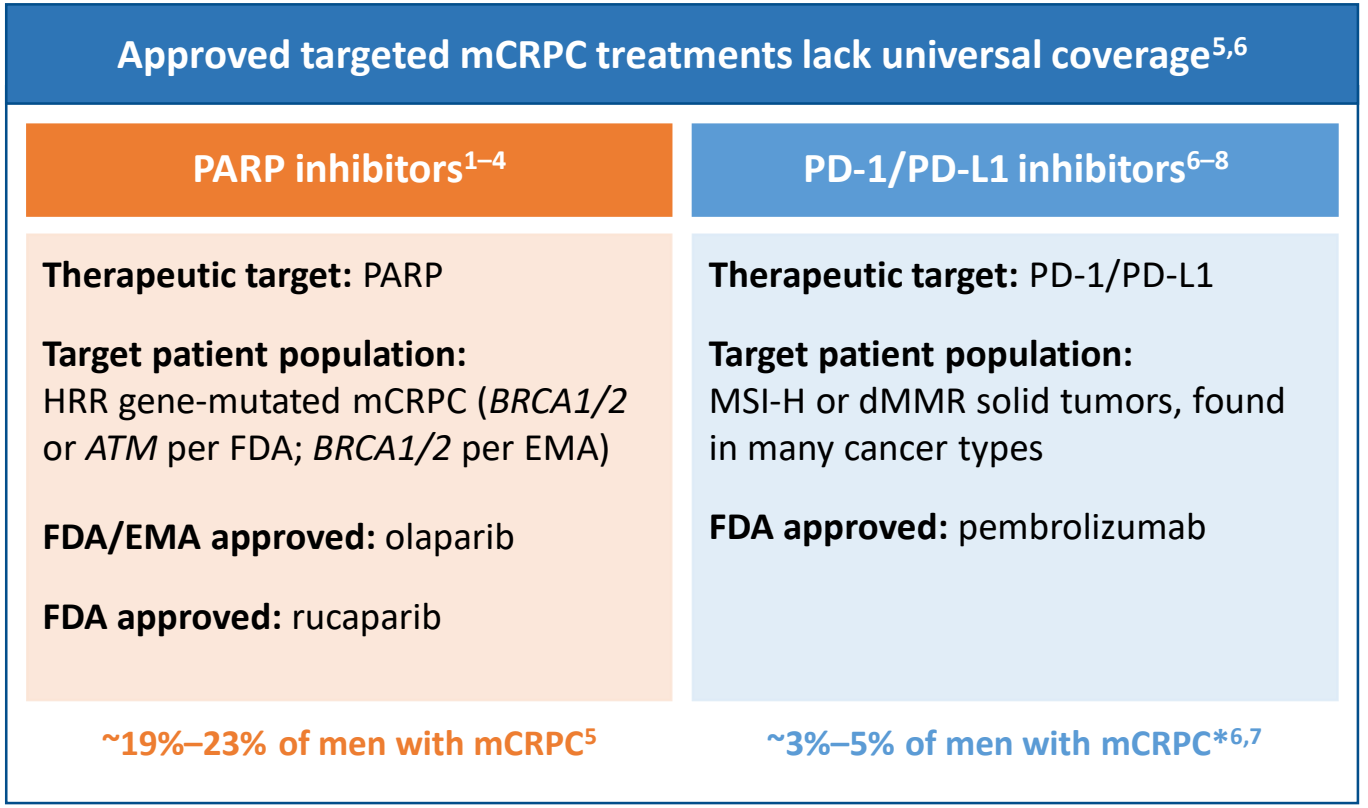
1. Loriot Y, et al. Ann Oncol. 2013;24(7):1807–1812;
2. 2. Noonan KL, et al. Ann Oncol. 2013;24(7):1802–1807;
3. 3. Badrising S, et al. Cancer. 2014;120(7):968–975;
4. 4. Bianchini D, et al. Eur J Cancer. 2014;50(1):78–84;
5. 5. Attard G, et al. J Clin Oncol. 2018;36(25):2639–2646;
6. 6. Khalaf DJ, Lancet Oncol. 2019;20(12):1730–1739;
7. . Zhao J, et al. Molec Can Ther. 2020 May 19. doi: 10.1158/1535-7163.MCT-20-0015 [Epub].

mCRPC

1. Moreira DM, et al. Clin Genitourin Cancer 2017;15:60–66.e2;
2. Francini E, et al. Prostate Cancer Prostatic Dis. 2019;22(3):420–427;
3. Summers N, et al. Curr Med Res Opin. 2017;33:1995–2008;
4. Ryan CJ, et al. Lancet Oncol. 2015;16(2):152–160;
5. Beer TM, et al. Eur Urol. 2017;71(2):151–154;
6. Smith M, et al. Lancet Oncol. 2019;20(3):408–419.

mCRPC et Thérapies ciblées (non hormonales ou radioactives)

- PARP inhibitors,
  - ~19%–23% des mCRPC ont une alteration des reparations des liaisons double brins de l'AND
- Use of PD-1/PD-L1
  - ~3%–5% MSI-H/dMMR (InsatbilitéµSat et Mis Match Repair



PSMA “la meilleure” des cibles

Molecular alteration	Frequency of expression in advanced PC*
High levels of PSMA expression ☺	 **(>80%)[1–5]**
AR pathway mutations/alterations	 (63%–71%)[6]
PTEN-PI3K-AKT pathway alterations	 (49%)[6]
Cell cycle (CDK) pathway alterations	 (21%)[6]
DNA repair pathway alterations	 (19%–23%)[6]
WNT pathway alterations	 (18%)[6]
MSI-H, dMMR	(~3–5%)[7,8]

- PSMA appears to be the most broadly applicable potential biomarker and actionable target in advanced PC[1–6]

Cibles

.

1. Hope TA, et al. J Nucl Med. 2017;58(12):1956–1961;
2. Hupe MC, et al. Front Oncol. 2018;8:623;
3. Pomykala KL, et al. J Nucl Med. 2020;61(3):405–411;
4. Minner S, et al. Prostate. 2011;71(3):281–288;
5. Bostwick DG, et al. Cancer. 1998;82(11):2256–2261;
6. Robinson D, et al. Cell. 2015;161(5):1215–1228;
7. Abida W, et al. JAMA Oncol. 2019; 5(4):471-478;
8. Lindh C, et al. APMIS. 2019; 127(8):554-560.

***Based on targeted sequencing analysis of a case series of 1551 tumors from 1346 patients with PC.**

1. Lynparza (olaparib) tablets. Prescribing information. AstraZeneca Pharmaceuticals LP; May 2020;
2. Lynparza capsules (olaparib). SmPC. AstraZeneca AB; November 2020;
3. 3. Rubraca (rucaparib) tablets. Prescribing information. Clovis Oncology Inc; May 2020;
4. 4. Rubraca tablets (rucaparib). SmPC. Clovis Oncology Ireland Ltd; March 2019;
5. 5. Robinson D, et al. Cell. 2015;161(5):1215–1228;
6. 6. Ku S, et al. Nat Rev Urol. 2019;16(11):645–654;
7. 7. Abida W, et al. JAMA Oncol. 2019;5(4):471–478;
8. 8. Keytruda (pembrolizumab) injection. Prescribing information. Merck Sharp & Dohme Corp; June 2020.

IMAGERIE

The Utility of Molecular Imaging in Prostate Cancer

Sooriakumaran et al Curr Urol Rep 2016

Diagnostic initial

Récidive Précoce

Bilan d'extension initial ou secondaire (M)

Nouvelles indications

- Ciblage radiologique
- Ciblage en RTE

➢ Evaluation thérapeutique des stades avancés

➢ Théranostique (de l'imagerie à la radiothérapie "moléculaire")

Vers un changement de paradigme ?

How else can we approach prostate cancer biomarker discovery?

Richard R. Drake, Peggi M. Angel, Jennifer Wu, Russell K. Pachynski & Joseph E. Ippolito

To cite this article: Richard R. Drake, Peggi M. Angel, Joseph E. Ippolito (2019): How else can we approach Review of Molecular Diagnostics, DOI: 10.1080/1473

To link to this article: https://doi.org/10.1080/147

Emerging Molecular Biomarkers in Advanced Prostate Cancer: Translation to the Clinic

Himisha Beltran, MD, Emmanuel S. Antonarakis, Gerhardt Attard, MD, PhD

Nat Rev Urol. 2018 February ; 15(2): 81–82. doi:10.1038/nrurol.2017.210.

Advances in imaging

Andreas G. Wibmer, Hebert Alberto Vargas, Hedvig Hricak

JAMA Oncology | Review

Imaging Locally Advanced, Recurrent, and Metastatic Prostate Cancer
A Review

Maria L. Lindenberg, MD; Baris Turkbey, MD; Esther Mena, MD; Peter L. Choyke, MD

Quelle sera la place de l'imagerie ?

- score pronostique
- caractérisation de l'hétérogénéité tumorale
- monitoring thérapeutique personnalisé

→ Raisonnement Bayésien

↓

Maîtriser la complexité et la masse des données

IMAGERIE DANS l'HISTOIRE NATURELLE DES CANCERS DE LA PROSTATE

IRM

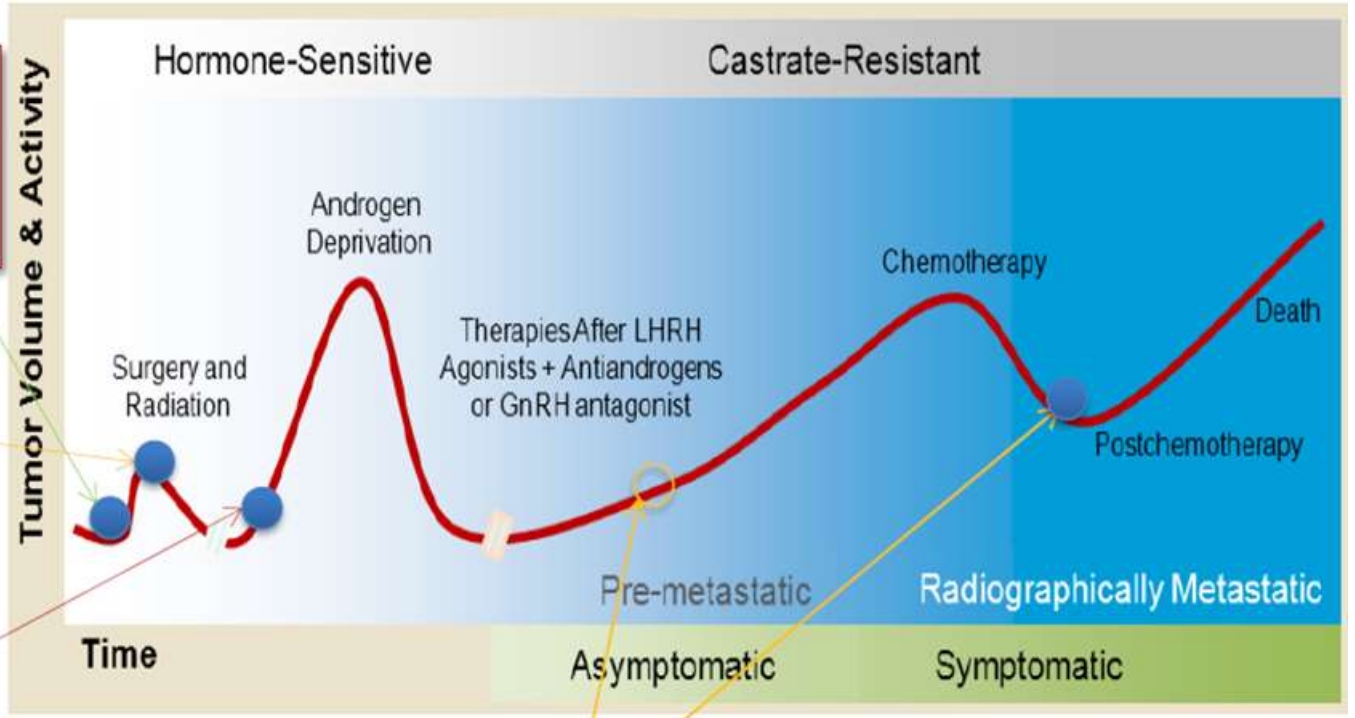
Diagnosis

- *biopsy target*
- *active sureveillance*

IRM
TEP

Staging

***N-M** in High Risk or Very High Risk*



IRM
TEP

Restaging

*early **BCR** in patients elegible for Salvage treatments*

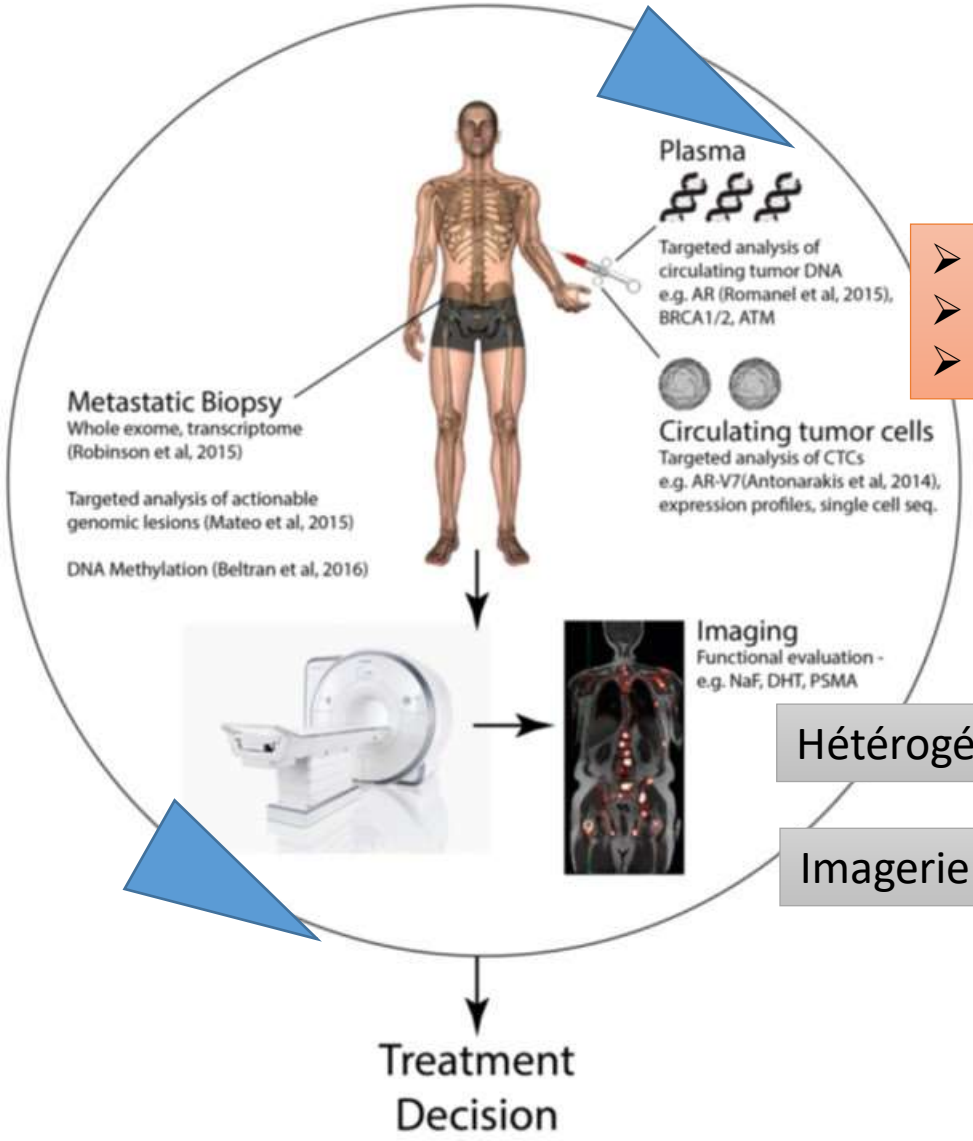
Advanced disease

- *assess early response & therapy monitoring in **mCRPC ?***
- *select patients for ^{223}**Ra** or PSMA **RLT** & assess response*

Dr. Paolo Castellucci, ACOMEN meeting - 2017

1. AFU Association Française d'Urologie http://www.urofrance.org/congres-et-formations/formation-initiale/referentiel-du-college/tumeurs-de-la-prostate.html

FIGURE 1. Schematic of Various Types of Molecular Biomarkers



SYSTEMIQUE

- précision analytique ?
- Disponibilité et reproductibilité?
- impact ?

LOCAL

Hétérogénéité tumorale

Imagerie phénotypique

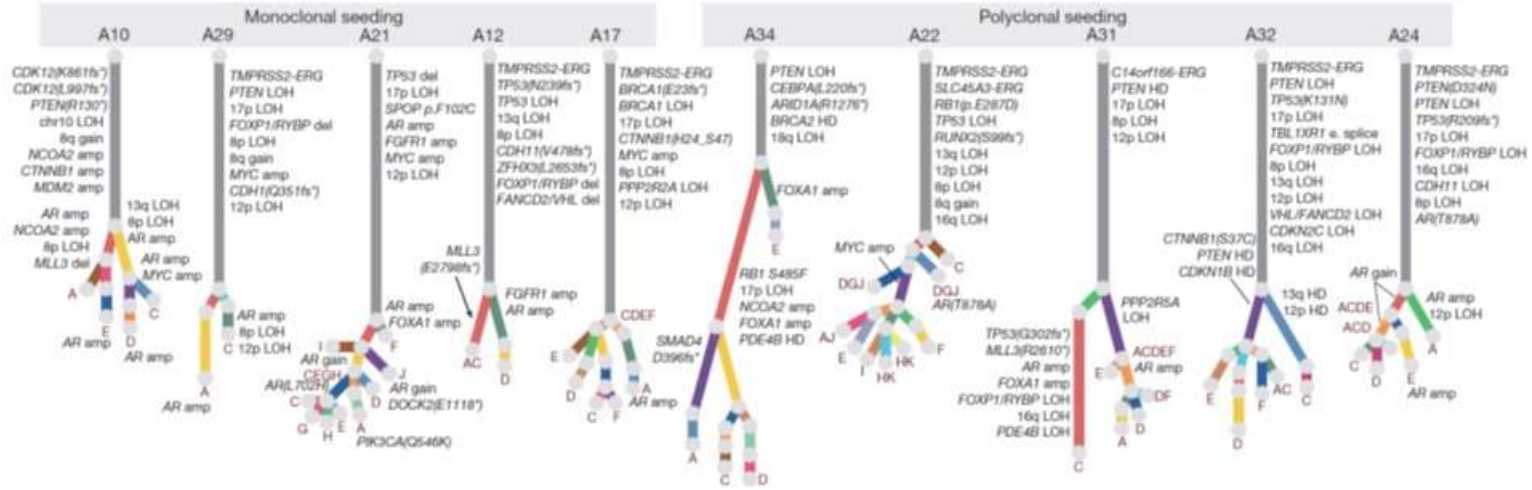
LETTER

doi:10.1038/nature14

La guerre des clones en imagerie

The evolutionary history of lethal metastatic prostate cancer

Gunes Gundem[1], Peter Van Loo[1,2,3], Barbara Kremeyer[1]



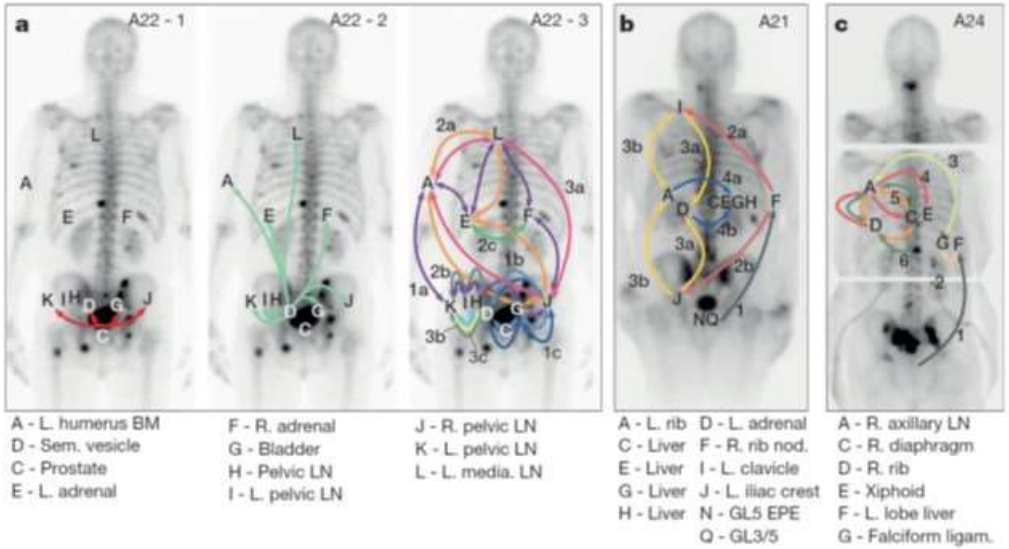
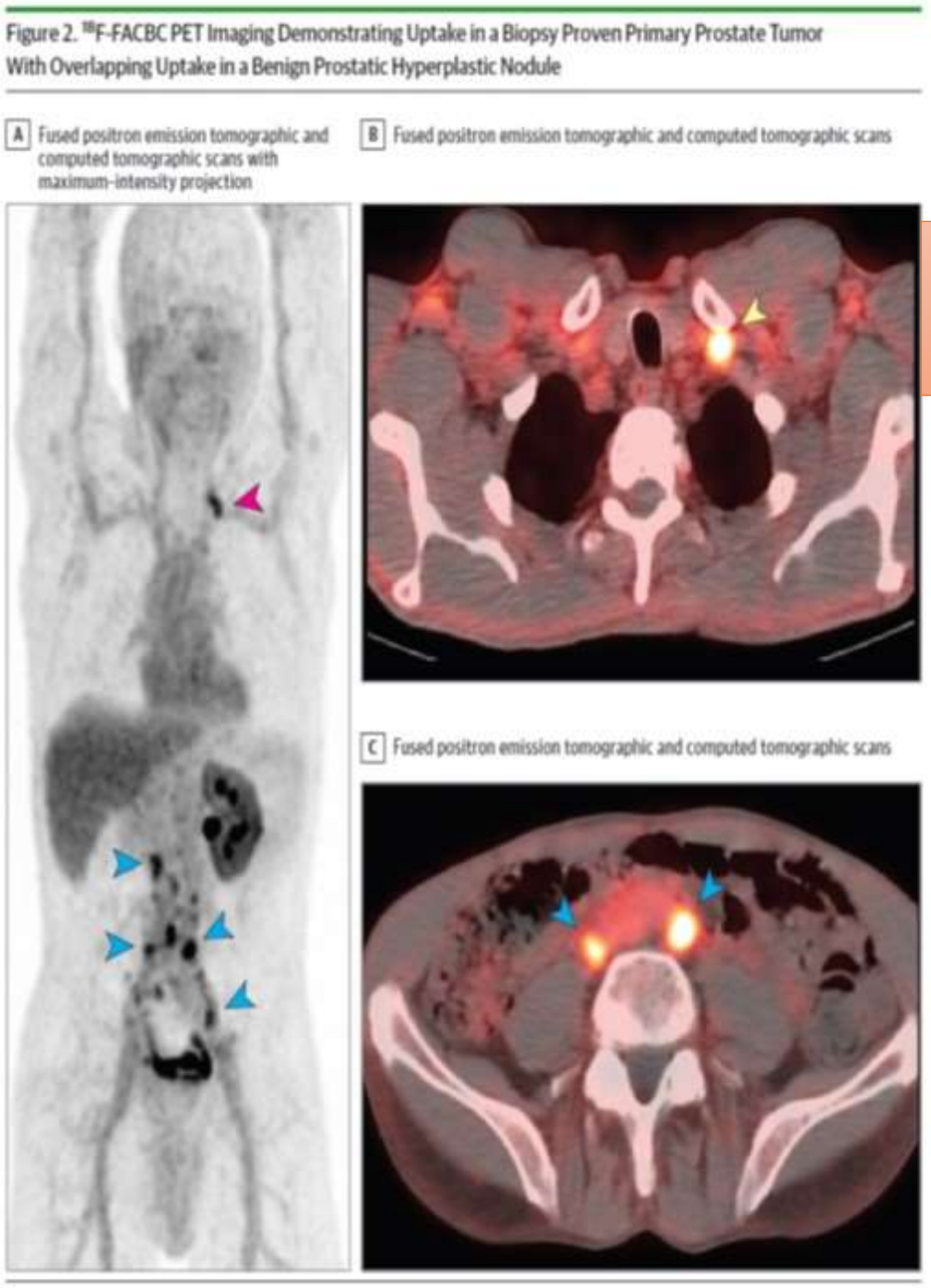


Figure 3 | Metastasis-to-metastasis seeding occurs either by a linear or by a branching pattern of spread. **a**–**c**, Body maps show the seeding of all tumour sites from A22 (**a**), A21 (**b**) and A24 (**c**). Sites shown include samples subject to targeted sequencing (A22-L, A24-F, A24-G) in addition to WGS samples. Seeding events are represented with arrows colour-coded according to Supplementary Table 3 and with double-heads when seeding could be in either direction. When the sequence of events may be ordered from the acquisition of mutations, arrows are numbered chronologically. Subclones on branching clonal lineages are labelled with the same number but with different letters, for example, 4a & 4b. See Supplementary Information section 4e for a detailed discussion of the body map in these cases. ligam., ligament. GL, Gleason grade; EPE, extrapostatic extension.

Figure 2. ^{18}F-FACBC PET Imaging Demonstrating Uptake in a Biopsy Proven Primary Prostate Tumor With Overlapping Uptake in a Benign Prostatic Hyperplastic Nodule

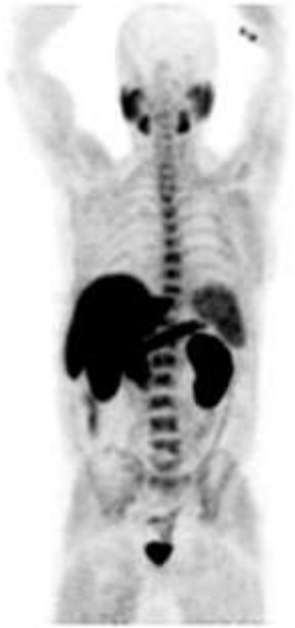


A, T2-weighted magnetic resonance imaging (MRI) scan shows a low-signal-intensity focus in the left mid peripheral zone (blue arrowheads); B, which demonstrates ^{18}F FACBC uptake on the positron emission tomographic (PET) scan. C, Combined PET/MR images; this was confirmed by histopathology as a Gleason 3 + 4 tumor. ^{18}F-FACBC uptake also demonstrates a focus of uptake in the right anterior prostate lobe, fusing to a BPH nodule (pink arrowhead).

La TEP a « découvert » de « nouveaux » sanctuaires de la maladie Métastatique

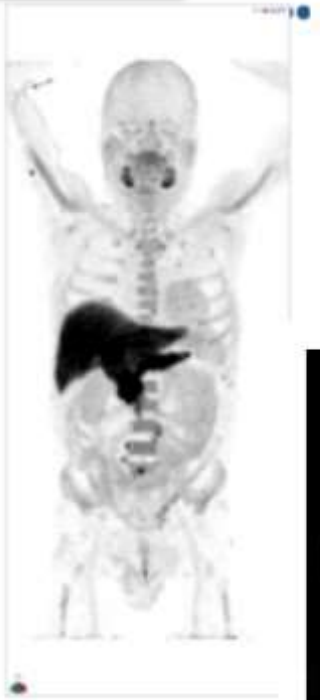
Indian J Nucl Med. 2017 Jan-Mar; 32(1): 13–15.
Rare Sites of Metastases in Prostate Cancer Detected on Ga-68 PSMA PET/CT Scan—A Case Series
Sugandha Dureja, et al

TEPs et TEPs !



F Choline

PSMA



FACBC

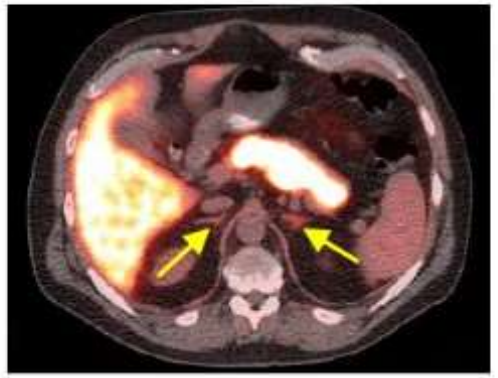
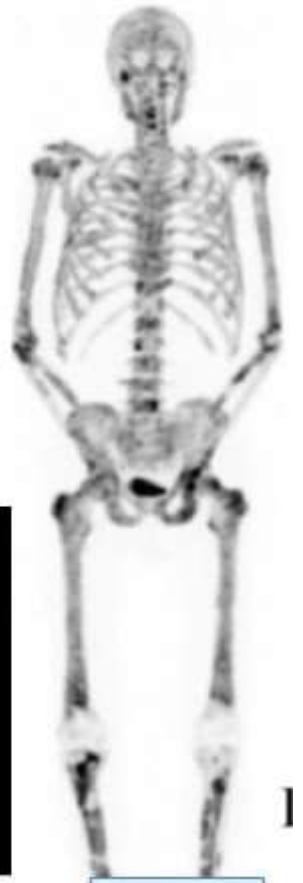


Figure 3: **Adrenal activity - normal variant**

(PET/CT transaxial)



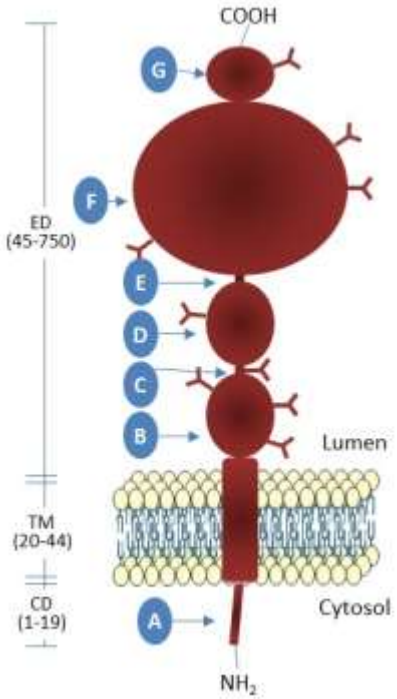
F Na

NB
Fx Neg
Méta hépatique
Effet halo
Fx Pos
Paget, ganglion inflammatoire

NB
Fx Neg
Méta lytique
Fx Pos
Non Spécifique

PSMA :

Un standard de pratique .. Sauf en France … ATU nominative
Si et seulement Si F Choline **négative**
Pb : c'est pas les mêmes indications



Eur J Nucl Med Mol Imaging
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GUIDELINES

^{68}Ga-PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0

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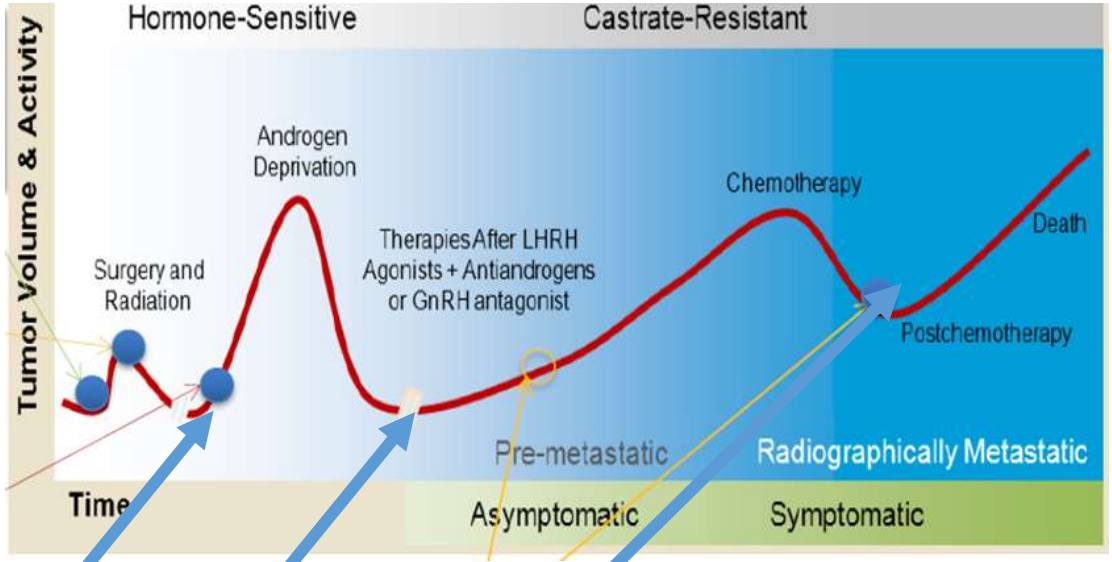


Schülke et al., PNAS 2005

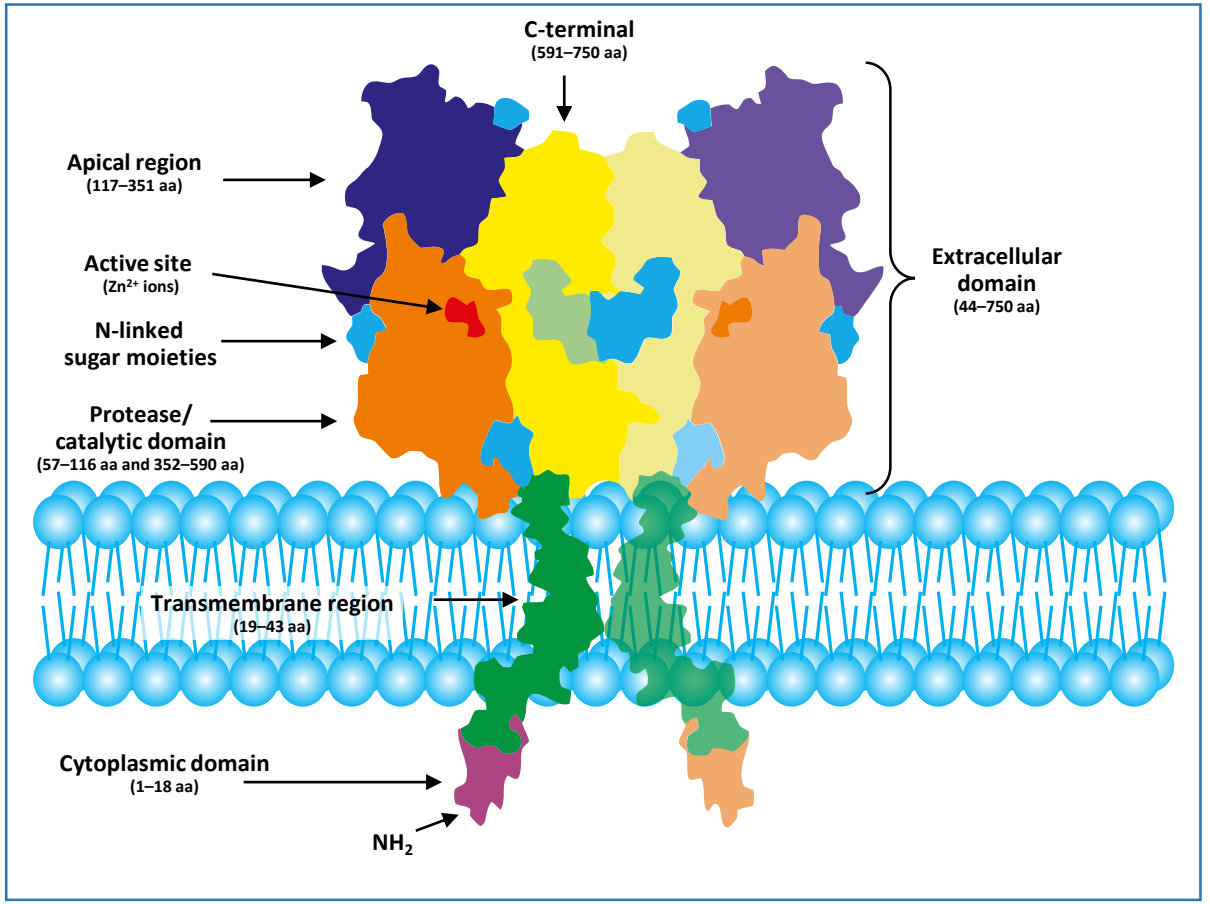
Pas les mêmes enjeux
Pas la même maladie

D'après la communication de S. Perner, PSMA Expression in Prostate Cancer, EANM 2015

PSMA protéine trans membranaire

- PSMA Tissus de la prostate
- Mais aussi diiférentes tumeurs

Regions of PSMA expression	
Healthy non-prostate tissues	**Tumor-associated neovasculature**
Small intestine[7,8]	Renal carcinoma[7–9]
Proximal renal tubules[7–9]	Colon carcinoma[7,8,12]
Salivary glands[10]	Gastric carcinoma[8,12]
Some neuroendocrine cells[11]	Thyroid carcinoma[13]



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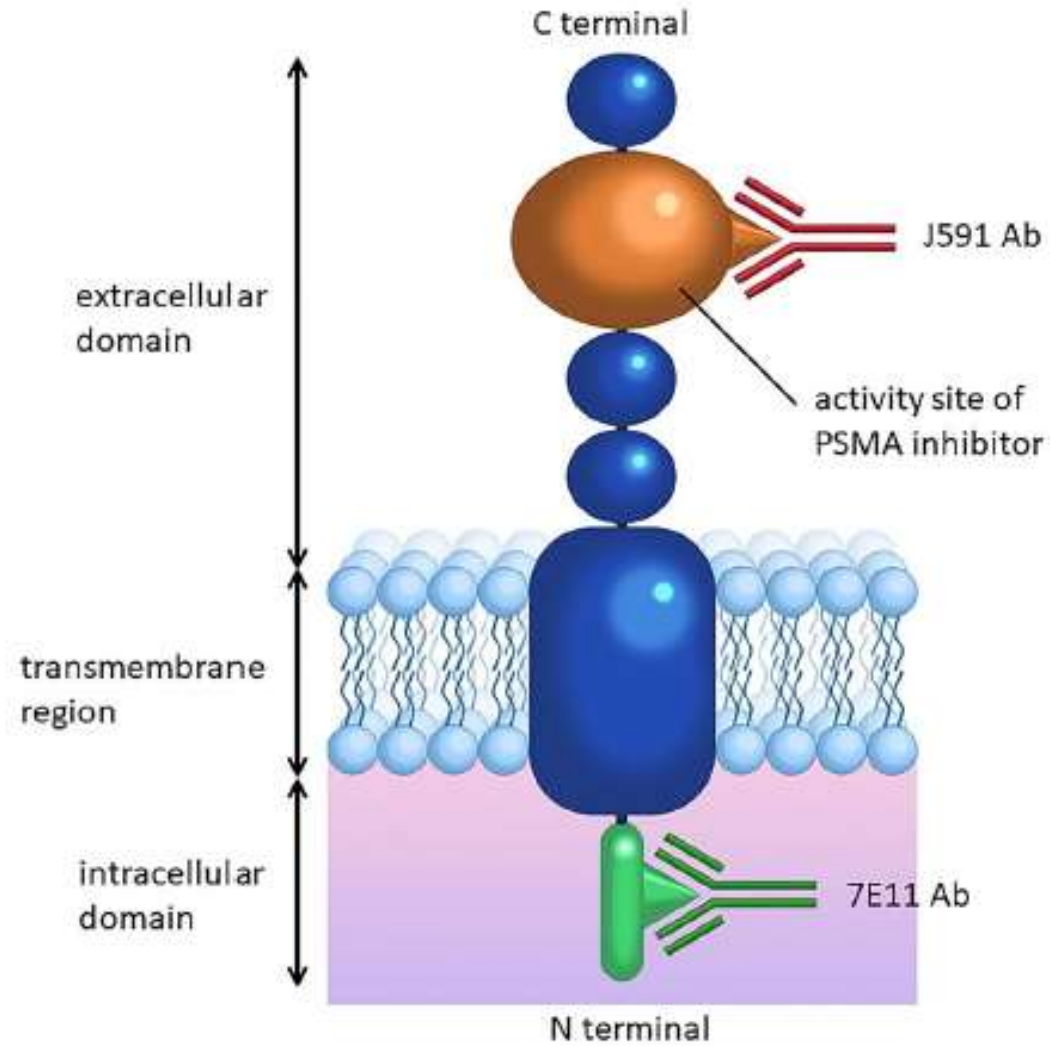
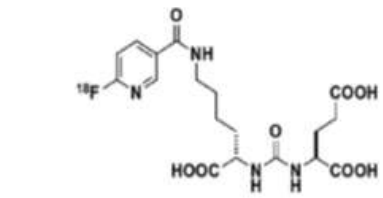


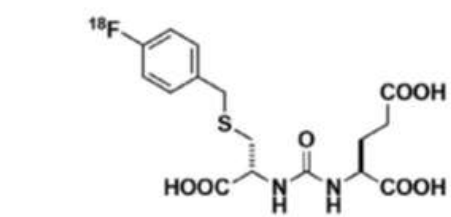
Figure 1. Molecular structure of prostate-specific membrane antigen (PSMA). Prostate-specific membrane antigen (PSMA) monomer has three domains. J591 antibody binds to activity site of extracellular domain which has 707 amino acids. 7E11 antibody binds to intracellular domain which has 19 amino acids. The homodimeric form of PSMA has enzymatic activity as glutamate carboxypeptidase II or folate hydrolase.

PSMAs et PSMAs



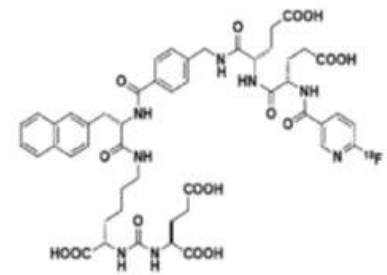
^{18}F-DCFPyL

Figure 3. Chemical structure of ^{18}F-DCFPyL.



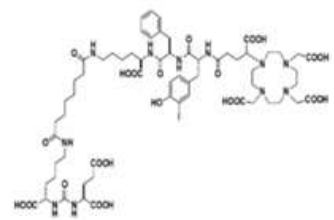
^{18}F-DCFBC

Figure 2. Chemical structure of ^{18}F-DCFBC.



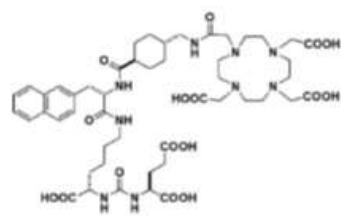
^{18}F-PSMA-1007

Figure 4. Chemical structure of ^{18}F-PSMA-1007.



PSMA-I&T

Figure 6. Chemical structure of PSMA-I&T ^{68}Ga and ^{177}Lu can bind to PSMA-I&T.



PSMA-617

Figure 5. Chemical structure of PSMA-617 ^{68}Ga and ^{177}Lu can bind to PSMA-617.

Table 3. Clinical use of PSMA ligands (Oct 2019)

18F-PSMA ligands		Organization or company	Clinical phase
1	^{18}F-DCFPyL	Progenics Pharmaceuticals	Phase 3
2	^{18}F-PSMA-1007	ABX	Clinical study
3	^{18}F-CTT1057	Novartis (AAA)	Phase 1
4	^{18}F-rhPSMA-7.3	Blue Earth Diagnostics	Phase 1
5	^{18}F-FSU-880	Kyoto University	Phase 2
^{68} Ga-PSMA ligands		Organization or company	Clinical phase
1	^{68}Ga-PSMA-11	Telix Pharmaceuticals	Phase 3
2	^{68}Ga-PSMA-617	Novartis (Endocyte)	Clinical study
3	^{68}Ga-PSMA-I&T	Technical University of Munich	Clinical study
PSMA ligands for RLT		Organization or company	Clinical phase
1	^{177}Lu-PSMA-617	Novartis (Endocyte)	Phase 3
2	^{225}Ac-PSMA-617	Novartis (Endocyte)	Phase 1
3	^{177}Lu-TX591	Telix Pharmaceuticals	Phase 2
4	^{177}Lu-PSMA-R2	Novartis (AAA)	Phase 1/2
5	^{227}Th-PSMA-TTC	Bayer	Phase 1

Abbreviation: RLT, radioligand therapy.

ATU

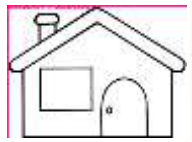
ATU

Le 11
Le 617
Le 1057
Le …

JAMA Oncology | Review

Imaging Locally Advanced, Recurrent, and Metastatic Prostate Cancer
A Review

2017



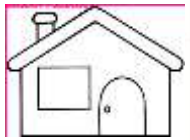


Table. Mechanism and Diagnostic Efficacy of Positron Emission Tomographic (PET) Radioligands for Prostate Cancer Imaging

Radiotracer	Mechanism of Action	% Sensitivity	% Specificity	Advantages	Disadvantages
[^{11}C]choline	Cell membrane synthesis	38-98	50-100	Minimal bladder excretion; available in the United States	Variable sensitivity and specificity for BCR, especially at lower PSA levels; requires on-site cyclotron (short half-life)
^{18}F-choline	Cell membrane synthesis	47-92	33-99	Longer half-life than [^{11}C]; can be produced off-site	Variable sensitivity and specificity for BCR, especially at lower PSA levels; limited availability in the United States
[^{11}C]acetate	Lipid synthesis	42-90	64-96	Minimal bladder excretion	Short half-life requiring an on-site cyclotron; only few centers in the United States are producing it
^{18}F-FACBC	Amino acid transport	89-100	67	More sensitive at lower PSA levels than choline and acetate; slow urinary excretion improving signal	Moderate specificity; only moderate performance at lower PSA levels; larger study validation needed
^{18}F-FDHT	Androgen receptor	63	NA	Uses AR, which plays an important role in prostate growth	Used mainly in specific drug development; needs validation in BRC and metastatic prostate cancer
^{18}F-NaF	Chemisorption in bone matrix	87-89	80-91	Well-validated. Better sensitivity compared with conventional ^{99m}Tc-bone scan. Rapid bone specific uptake; lack of blood pool; good axial skeleton visualization. More rapid acquisition than conventional bone scan	Lower specificity with a high false-positive rate detection; approved but not yet reimbursed
^{68}Ga-PSMA	PSMA analog	63-86	95-100	High sensitivity and specificity even at low PSA levels	Relatively newer radiotracer, still under investigation; requires considerable up-front expenditure and a radiopharmacy
^{18}F-DCFBC	PSMA inhibitor and/or antibodies	92	88	F 18 is a superior positron emitter compared with ^{68}Ga with longer half-life	Significant blood pool activity; still under investigation with need for further validation in larger studies
^{18}F-DCFPyL	PSMA inhibitor and/or antibodies	NA	NA	Higher tumor to background ratios owing to high affinity; may be more sensitive than ^{68}Ga in detecting BCR	Newer radiotracer that needs further validation in larger studies

ATU

Abbreviations: AR, androgen receptor; PET, positron emission tomography; PSMA, prostate specific membrane antigen.

PET PSMA > F CHOLINE

- Haberkorn et al Eur J Nucl Mol Imaging 2013; 40 : 819-823
- F choline manque de de sensibilité Ploussar et al. – J UROL 2015
- Intérêt du 68Ga PSMA dans les stades précoces Afhar-Oromich et al. Eur J Nucl Med 2014 ; 41 : 11-20
- PSMA > Fcholine surtout pour PSA <2 ng/mL Morigi et al. Co EANM 2015 et J.N.M. 2015 ; 56 : 1185-1190

Table 4. Large-scale clinical studies of PSMA–PET/CT

References	Year	Study design	Type of patients evaluated	Tracer	Study objectives	Study results
Treglia et al. (16)	2019	Meta-analysis of 6 studies	BRPCa (n = 645)	^{18}F-PSMA	Perform a meta-analysis about the DR of ^{18}F-PSMA–PET/CT in BRPCa patients	DR 81% (per patient analysis) 86% for PSA ≥ 0.5 ng/ml 49% for PSA < 0.5 ng/ml
Perera et al. (23)	2019	Systematic review of 37 studies	Advanced prostate cancer (n = 4790)	^{68}Ga-PSMA	Provide updated data on the predictors of a positive ^{68}Ga-PSMA–PET with sensitivity and specificity and additionally to identify locational patterns of PSMA-avid lesions in the setting of prostate cancer staging in both primary and biochemical recurrence situations	Positive ^{68}Ga-PSMA–PET in BRPCa patients 33% for PSA 0.0–0.19 ng/ml 45% for PSA 0.2–0.49 ng/ml 59% for PSA 0.5–0.99 ng/ml 75% for PSA 1.0–1.99 ng/ml 95% for PSA ≥2 ng/ml NSD: Gleason sums ≤7 and ≥ 8 Primary staging (per node analysis): sensitivity 75% and specificity 99%

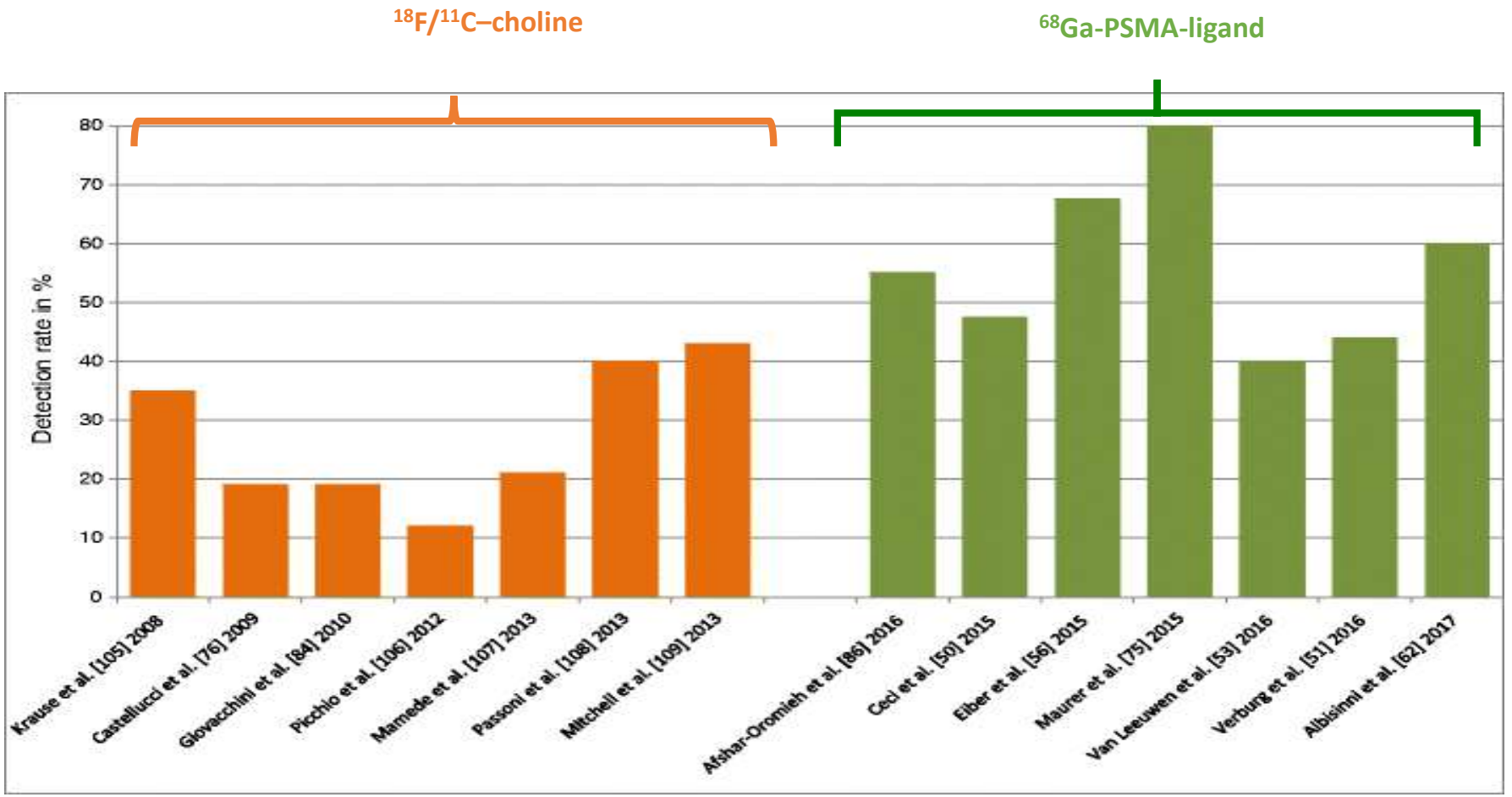
Abbreviations: BRPCa, biochemical recurrent prostate cancer; DR, detection rate; NSD, no significant difference.

Cut off PSA 0,5

Cut off PSA 0,2; 0,5; 1; 2

Gleason

Si PSA < 1,0 ng/ml imagerie au Ga-PSMA > Choline



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oligometastatic disease might benefit from targeted therapies Gillessen et al 2017

7 Gillessen S et al. Management of patients with advanced prostate cancer: the report of the advanced prostate cancer consensus conference APCCC 2017. Eur. Urol 10.1016/j.eururo.2017.06.002 (2017).

^{68}Ga-PSMA-11. Afshar-Oromieh A et al. Diagnostic performance of 68Ga-PSMA-11 (HBED-CC) PET/CT in patients with recurrent prostate cancer: evaluation in 1007 patients. Eur. J. Nucl. Med. Mol. Imaging 44, 1258–1268 (2017). [

Taux de positivité 801 pts sur 1007 (**80%),**

Probabilité de positivité = PSA

Tx de + :

46% PSA ≤0.2 ng/ml

57% PSA ≤1 ng/ml,

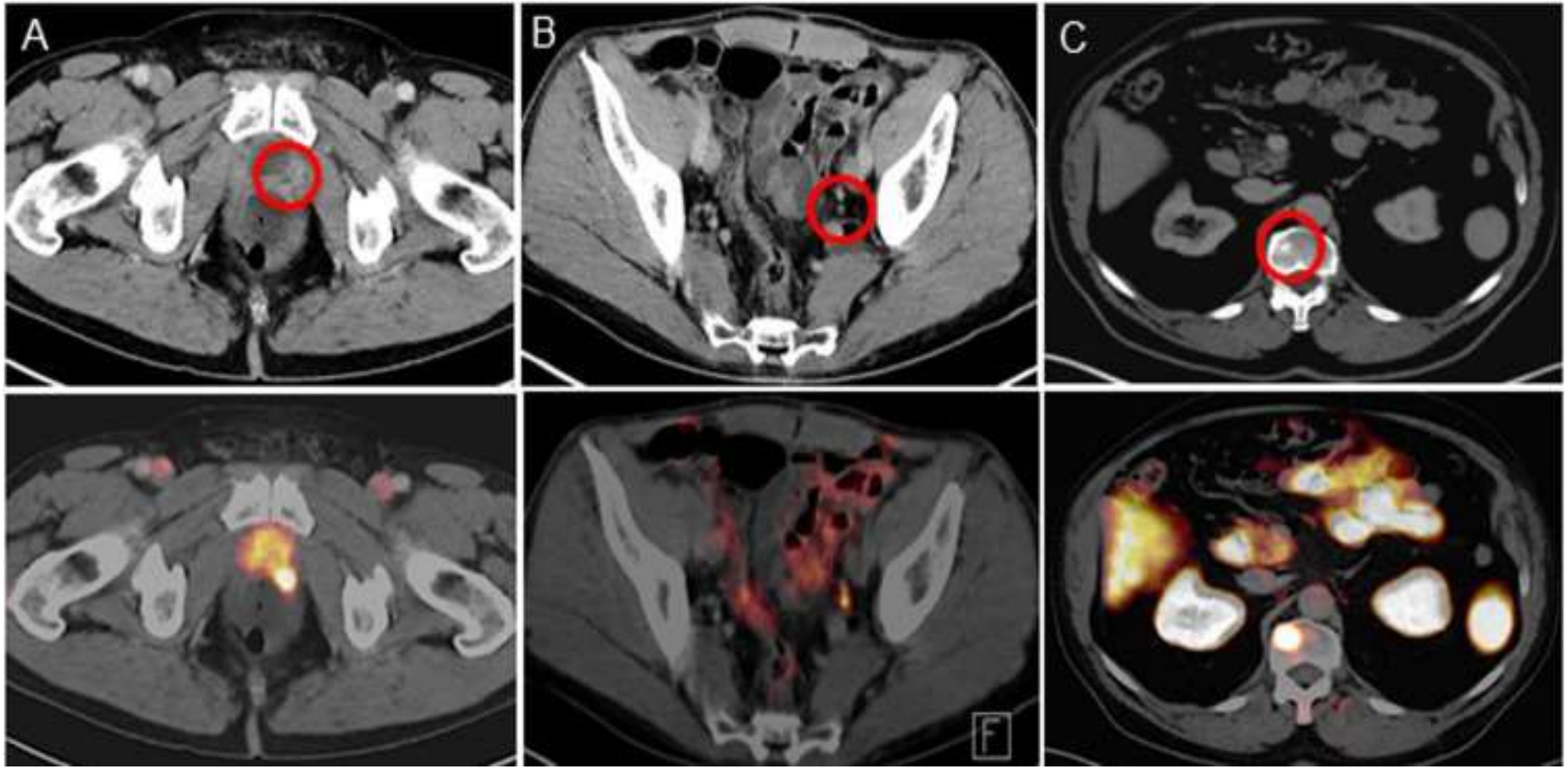
>90% PSA >3 ng/ml.

Identification d'une cible 1/2

Quelle conséquence sur OS et PFS ?

68Ga-PSMA récidive biologique

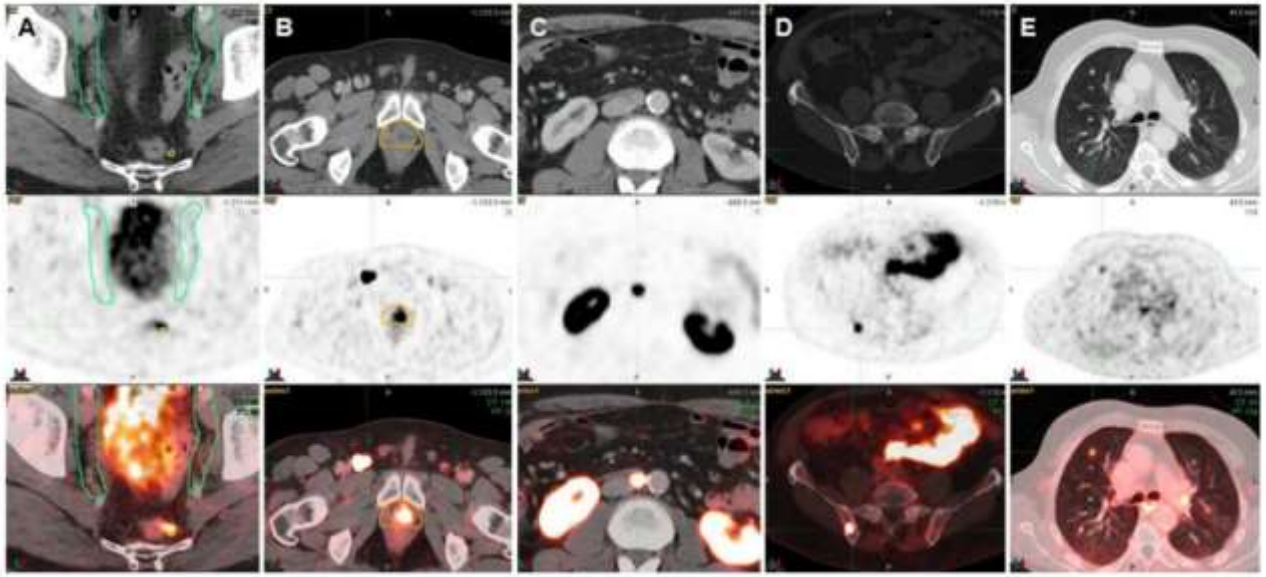
Rechute locale PSA 0,39ng/mL **Rechute ganglionnaire PSA 0,63ng/mL** **Rechute Méta Os PSA 0,33ng/mL**



Eur Urol. 2018 May;73(5):656-661. doi: 10.1016/j.eururo.2018.01.006. Epub 2018 Jan 19.
Efficacy, Predictive Factors, and Prediction Nomograms for 68Ga-labeled Prostate-specific Membrane Antigen-ligand Positron-emission Tomography/Computed Tomography in Early Biochemical Recurrent Prostate Cancer After Radical Prostatectomy.
Rauscher I1, Düwel C2, Haller B3, Rischpler C1, Heck MM2, Gschwend JE2, Schwaiger M1, Maurer T2, Eiber M4.

68Ga-PSMA PET/CT mapping of prostate cancer biochemical recurrence following **radical prostatectomy in** 270 patients with PSA < 1.0ng/mL: Impact on Salvage Radiotherapy Planning[1]

	n = 270
Major impact on SRT planning - *Outside of RTOG CTV recurrence*	**52 (19%)**
Extension of the pelvic consensus CTV	19 (7%)
Superior extension to cover para-aortic LNs	5 (2%)
Oligometastasis-directed SBRT (≤5 M1a or M1b)	22 (9.5%)
RT futile due to polymetastatic or visceral disease (>5 M1a,M1b or M1c)	6 (2.5%)
Minor impact on SRT planning – *Covered by planning based on consensus CTV*	**80 (29.5%)**
Dose-escalation to gross disease (*^{68}Ga-PSMA-11 PET-positive disease)*	
No impact on SRT planning - *Negative ^{68}Ga-PSMA-11 PET/CT*	**138 (51%)**



Examples of PSMA-positive lesions which are localized outside of consensus CTV : perirectal LN (A), inguinal LN (B), lumbo-aortic LN (C), bone (D), lung (E)

1. 68Ga-PSMA PET/CT mapping of prostate cancer biochemical recurrence following radical prostatectomy in 270 patients with PSA < 1.0ng/mL: Impact on Salvage Radiotherapy Planning Calais J, et al. J Nucl Med. 2018

^{68}Ga-PSMA-11 PET-CT > ^{18}F-fluciclovine PET-CT

Lancet Oncol. 2019 Sep;20(9):1286-1294. 30.

^{18}F-fluciclovine PET-CT and ^{68}Ga-PSMA-11 PET-CT in patients with early biochemical recurrence after prostatectomy: a prospective, single-centre, single-arm, comparative imaging trial.

Unicentrique
Test de supériorité de 20% : PSMA > Fluciclovine = 50 pts
PSA de 0,2 to 2,0 ng/m

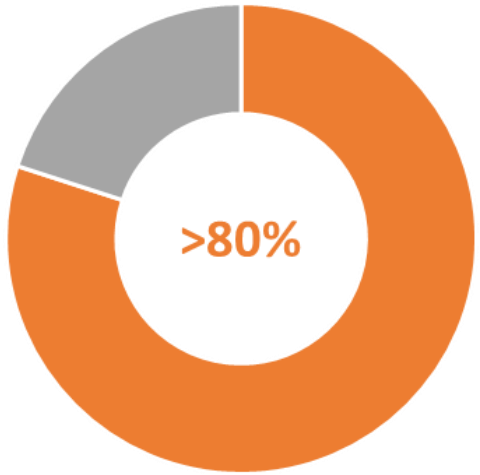
Avantage PSMA !
Détection 28 pts vs 13 ; pelvis et méta à distance

Expression tumorale du PSMA

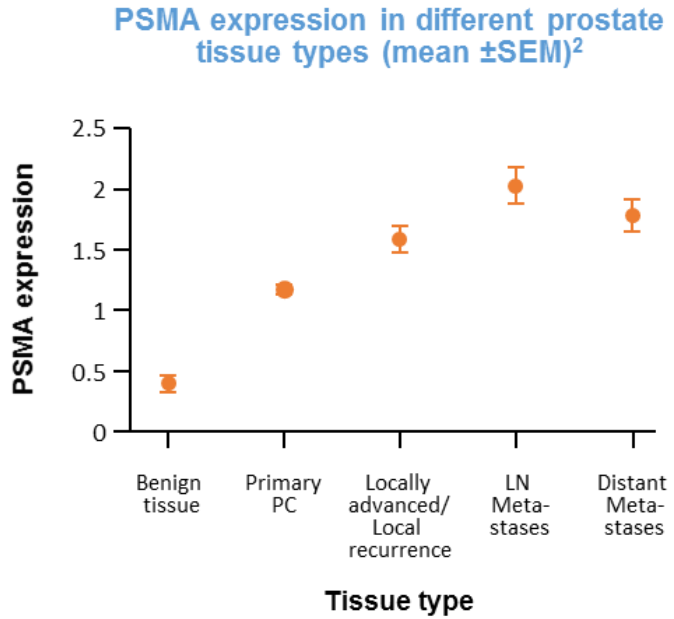
	Faible	Modéré	Fort	Total positif
Cancer de la Prostate (n = 141) • Hormono-résistant (n = 44) • Hormono-sensible (n = 97)	10,6 % 13,6 % 9,3 %	15,6 % 15,9 % 15,5 %	39,7 % 40,1 % 39,2 %	65,9 % 70,5 % 63,9 %
Cancer urothélial de la vessie(n = 346)	11 %	4,6 %	1,4 %	17 %
carcinome spinocellulaire (n = 297) (tête et cou, peau, pénis, vessie, œsophage)	8,4 %	0,3 %	0 %	8,7 %
Adénocarcinomes (n = 278) (œsophage, estomac, intestins, colon, pancréas, poumon, vessie, glandes salivaires)	12,2 %	1 %	2,1 %	15,3 %
Glioblastome multiforme (n = 52) (uniquement les tumeurs du cerveau positives)	3,8 %	1,9 %	0 %	5,7 %

Mhawech-Fauceglia P et al., Histopathology 2007

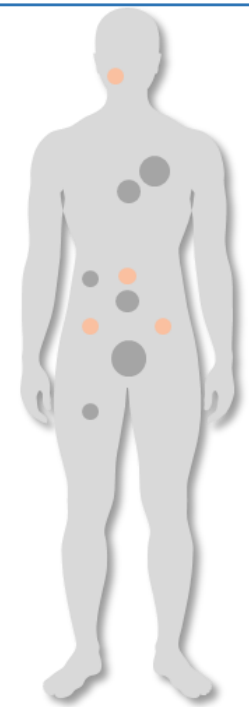
D'après la communication de S. Perner, PSMA Expression in Prostate Cancer, EANM 2015



PSMA is highly expressed in prostate carcinoma cells within the tumor tissue of >80% of men with PC[1–5]



The proportion of PSMA-positive cells* is significantly higher in PC tissue than in benign prostate tissue[5]



PSMA can be highly expressed in both primary prostate carcinoma cells and metastatic tumor cells †[6,7]

PSA et PSMA

PSMA

Characteristics

- Not entirely prostate-specific[1]
- Cell-surface membrane protein, not secreted[2]

Expression levels

- Highly expressed on most PC cells[2,3]
- **Expression upregulated with clinical progression[4–6]**
- **Expression increased following short-term ADT[7,8]**
- Elevated levels can fall in response to treatment[9]
- Long-term ADT decreased expression[10–12]

Practical applications

- Radiolabeled PSMA ligands have been developed for imaging:[3,13]
  - Prognostic value[9,14]
  - Locating recurrence – where there is rising PSA[13]
  - Detecting metastases[15]
- In the future, PSMA-targeted imaging may identify patients likely to respond to PSMA-targeted therapy (currently in development)[16,17]

PSA

Characteristics

- Prostate-specific[18]
- Secreted into the blood[2,18]

Expression levels

- Serum levels are increased in PC[18]
- Increasing PSA after local treatment can indicate disease relapse[13]
- Serum levels decrease following ADT[9]
- A considerable fraction of cancers present with low PSA akin to levels found in men without PC[18]

Practical applications

PSA test: the most commonly used serum marker for PC:[9,14,18]

- Screening
- Risk stratification and staging value
- Post-treatment monitoring

- Useful for risk stratification, treatment selection, and disease monitoring in early/localized PC[19]
- In metastatic disease, PSA decline can be used to evaluate treatment response, but stable PSA is not enough to determine non-progression[19]

PSMA expression et extension du cancer de la prostate

*Based on immunoreactivity for PSMA in 184 radical prostatectomy specimens.

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2. Hupe MC, et al. Front Oncol. 2018;8:623;
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5. Bostwick DG, et al. Cancer. 1998;82(11):2256–2261;
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PSA vs PSMA

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5. 5. Minner S, et al. Prostate. 2011;71(3):281–288;
6. 6. Bostwick DG, et al. Cancer. 1998;82(11):2256–2261;
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PSMA fait son entrée dans les EAU guidlelines
MAIS n'est pas disponible en France (hors ATU)

https://uroweb.org/individual-guidelines/oncology-guidelines/

6.2.6.6 Recommendations for the management of persistent PSA after radical prostatectomy

Recommendations	Strength rating
Offer a prostate-specific membrane antigen positron emission tomography (PSMA PET) scan to men with a persistent PSA > 0.2 ng/mL to exclude metastatic disease.	Weak
Treat men with no evidence of metastatic disease with salvage radiotherapy and additional hormonal therapy.	Weak

6.3.4.4 Guidelines for imaging in patients with biochemical recurrence

Prostate-specific antigen (PSA) recurrence after radical prostatectomy	LE	Strength rating
Perform PSMA PET/CT if the PSA level is > 0.2 ng/mL and if the results will influence subsequent treatment decisions.	2b	Weak
In case PSMA PET/CT is not available, and the PSA level is ≥ 1 ng/mL, perform Fluciclovine PET/CT or Choline PET/CT imaging if the results will influence subsequent treatment decisions.		Weak
PSA recurrence after radiotherapy		
Perform prostate multiparametric magnetic resonance imaging to localise abnormal areas and guide biopsies in patients fit for local salvage therapy.	3	Strong
Perform PSMA PET/CT (if available) or fluciclovine PET/CT or choline PET/CT in patients fit for curative salvage treatment.	2b	Strong

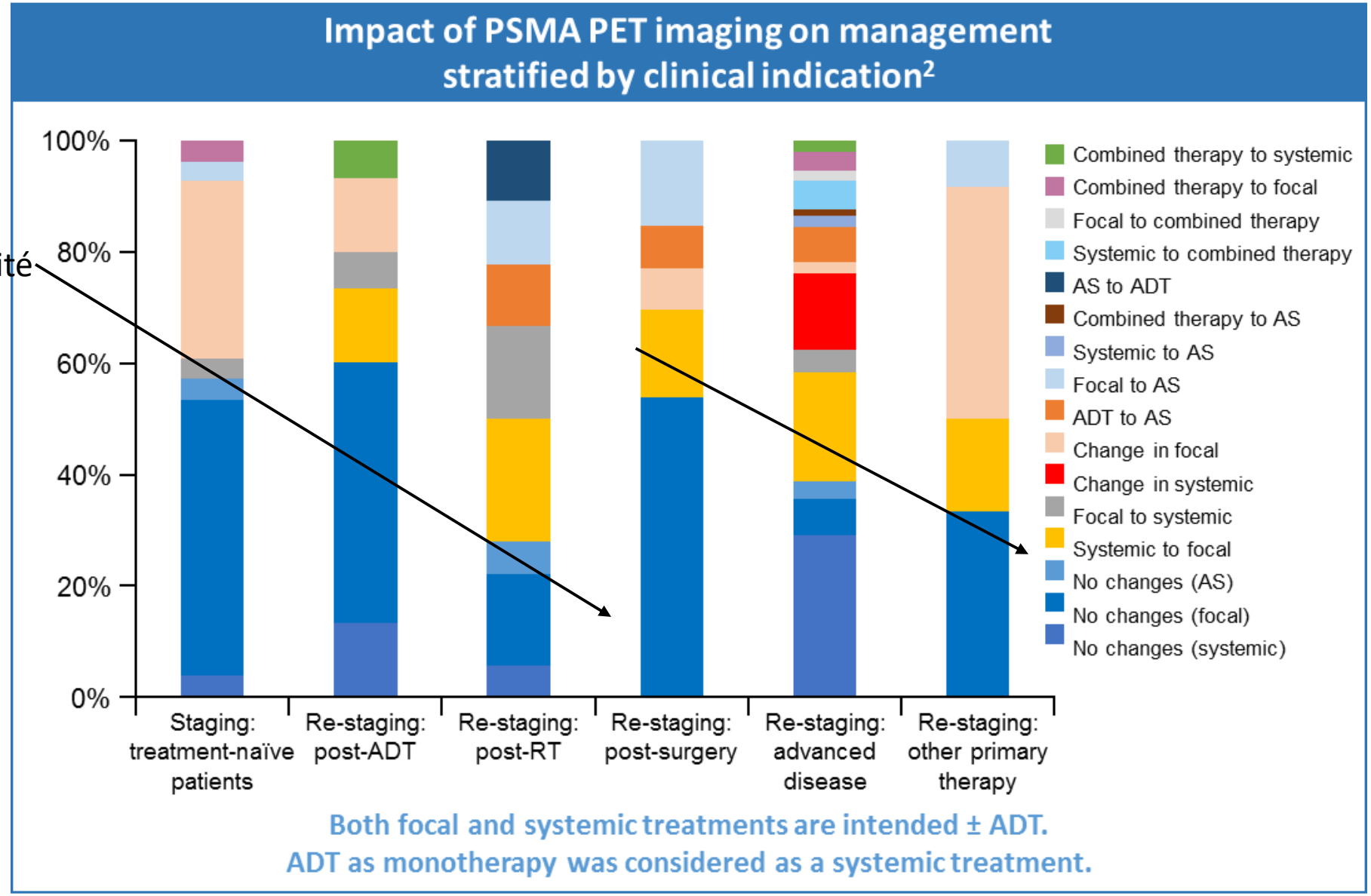
MAJ 2022
https://uroweb.org/guidelines/prostate-cancer/summary-of-changes

5.3.5 Summary of evidence and guidelines for staging of prostate cancer

Summary of evidence	LE
PSMA PET/CT is more accurate for staging than CT and bone scan for high-risk disease but to date no outcome data exist to inform subsequent management.	1b

Recommendation	Strength rating
High-risk localised disease/locally advanced disease	
When using PSMA PET or whole body MRI to increase sensitivity, be aware of the lack of outcome data of subsequent treatment changes.	Strong

PSMA PET



1. Perera M, et al. Eur Urol. 2020;77(4):403–417;
2. 2. Sonni I, et al. J Nucl Med. 2020;61(8):1153–1160;
3. 3. Fendler WP, et al. Eur J Nucl Med Mol Imaging. 2017;44:1014–1024.

PSMA TEP ; A game changer !

EAU–ESTRO–ESUR–SIOG[9]

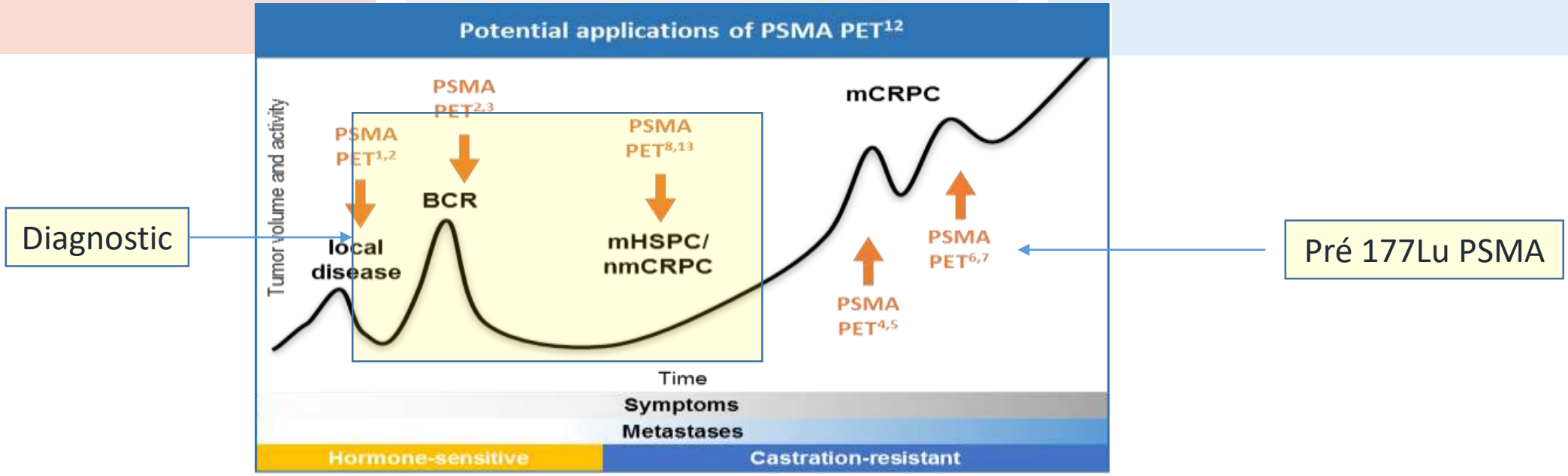
- Perform in men with persistent PSA >0.2 ng/mL after RP or with BCR after RP if PSA >0.2 ng/mL
- Perform in men with BCR after RT if fit for curative salvage treatment

EANM–SNMMI[10]

- Perform to identify site of recurrence and guide salvage treatment
- Perform in primary staging of high-risk patients before surgery/EBRT

ESMO[11]

- May be used in staging of intermediate or high-risk localized disease



9. Mottet N, et al. EAU Guidelines: Prostate Cancer. https://uroweb.org/guideline/prostate-cancer/#6 (accessed November 2020);
10. Fendler WP, et al. Eur J Nucl Med Mol Imaging. 2017;44(6):1014–1024;
11. Parker C, et al. Ann Oncol. 2020;31(9):1119–1134.

En synthèse : PSMA TEP et Cancer de la prostate

Bilan d'extension initial : Pas un standard MAIS pourrait remplacer TDM et Sc Os pour les formes agressive

Gandaglia G, Ploussard G, Valerio M, et al. A novel nomogram to identify candidates for extended pelvic lymph node dissection among patients with clinically localized prostate cancer diagnosed with magnetic resonance imaging-targeted and systematic biopsies. Eur Urol. 2019;75(3):506–14.

Récidive biochimique (en intention de traitement de rattrapage) = standard de pratique

Cf Guillon et al JFMN 2002 Évaluation de l'impact en vie réelle de l'autorisation temporaire d'utilisation nominative du 68Ga-PSMA-11 **: 39%**

Pas encore pour l'évaluation de la réponse

From molecular imaging to molecular radiotherapy

^{68}Ga PSMA PET/CT
Avant 1ère PRLT

1ère PRLT
3,6 GBq
^{177}Lu PSMA

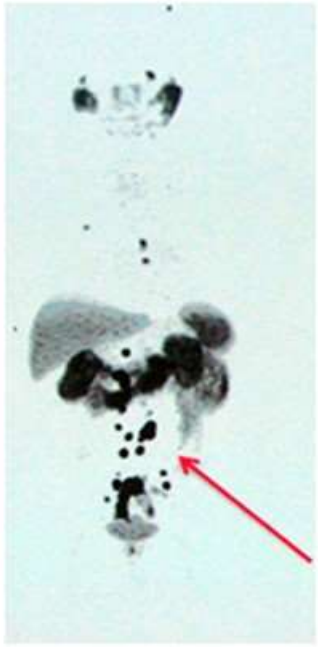
Dosimétrie

Glandes parotides
15 Gy
4,2 mgGy/MBq

Reins
3,7 Gy
1mGy/MBq

Lésions ganglionnaires
114-280 Gy
32-78 mGy/MBq

^{68}Ga PSMA PET/CT
Après 1ère PRLT



2ème PRLT
4 GBq
^{177}Lu PSMA

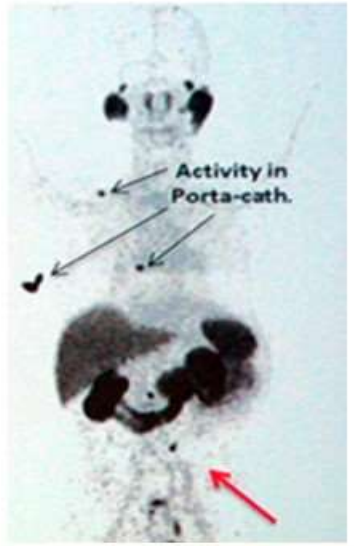
Dosimétrie

Glandes parotides
10 Gy
2,6 mgGy/MBq

Reins
4,8 Gy
1,2 mGy/MBq

Lésions ganglionnaires
33-61 Gy
8-15 mGy/MBq

^{68}Ga PSMA PET/CT
Après 2ème PRLT



Résolution presque totale
des lésions ganglionnaires

D'après la communication de C. Schuchardt, Therapy of Metastasized Prostate Cancer Using a Lu-177 Labeled PSMA Inhibitor (I&T): Frist Dosimetric Results in Patients, abstract OP239, EANM 2015

PSMA-targeted RLT 177Lu
les avantages de l131l sans les inconvénients

Characteristics of common investigational radionuclides

	^{131}I	^{177}Lu	^{225}Ac
Particles	β and γ (high energy)[1]	β (medium energy) and γ (low energy)[3]	α (high energy)[7]
Maximum/mean energy	0.806 / – MeV[1]	0.5 / 0.13 MeV[3]	5.83 / – MeV[8]
Mean particle range	–	0.7 mm[4]	–
Maximum particle range	2.4 mm in soft tissue[2]	2 mm in soft tissue[3,5]	50–80 µm (few cell diameters)[7]
Half-life	8.04 days[1]	~6.7 days[3–6]	10 days[7,8]

1. Stanford University. I-131 Radionuclide safety data sheet. https://ehs.stanford.edu/wp-content/uploads/I-131_Inorganic.pdf (accessed November 2020); 2. Rahbar K, et al. Mol Imaging. 2018;17:1536012118776068; 3. EMA. EMA/CHMP/404078/2016: llutetium chloride. https://www.ema.europa.eu/en/documents/assessment-report/endolucinbeta-epar-public-assessment-report_en.pdf (accessed November 2020); 4. Dash A, et al. Nucl Med Mol Imaging 2015;49(2):85–107; 5. Kassis AI, et al. Semin Nucl Med 2008;38(5):358–66; 6. Grupen C, 2010. Introduction to Radiation Protection. Springer-Verlag Berlin Heidelberg. DOI: 10.1007/978-3-642-02586-0; 7. Scheinberg DA, et al. Curr Radiopharm. 2011;4(4):306–320; 8. Kozempel J, et al. Molecules. 2018;23(3):581.
Ac, actinium; I, iodine; Lu, lutetium; PSMA, prostate-specific membrane antigen; RLT, radioligand therapy.

^{177}Lu-PSMA-617 ou I&T

- Etudes monocentriques
- Etudes rétrospectives
- Méta-analyse....MAIS

JNM | NUCLEAR MEDICINE

German Multicenter Study Investigating 177Lu-PSMA-617 Radioligand Therapy in Advanced Prostate Cancer Patients. Rahbar K et al, 2017

THE LANCET Oncology

[^{177}Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study Michael S Hofman et al, 2018

CLINICAL AND TRANSLATIONAL IMAGING

Finn Edler von Eyben et al, 2018

PSMA diagnostics and treatments of prostate cancer become mature

Third-line treatment and ^{177}Lu-PSMA radioligand therapy of metastatic castration-resistant prostate cancer: a systematic review

Finn Edler von Eyben et al, 2018

EUROPEAN JOURNAL OF NUCLEAR MEDICINE AND MOLECULAR IMAGING

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

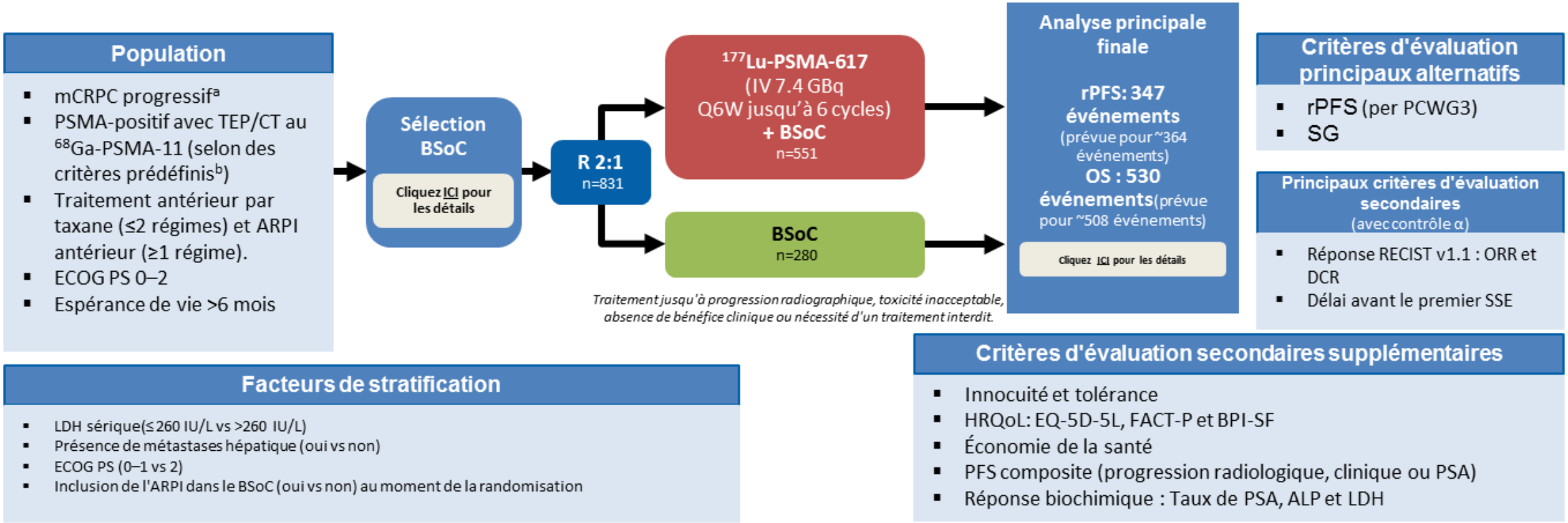
Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Cancer

O. Sartor, J. de Bono, K.N. Chi, K. Fizazi, K. Herrmann, K. Rahbar, S.T. Tagawa, L.T. Nordquist, N. Vaishampayan, G. El-Haddad, C.H. Park, T.M. Beer, A. Armour, W.J. Pérez-Contreras, M. DeSilvio, E. Kpamegan, G. Gericke, R.A. Messmann, M.J. Morris, and B.J. Krause, for the VISION Investigators*

1. https://clinicaltrials.gov/ct2/results?cond=&term=177Lu-PSMA&cntry=&state=&city=&dist=

VISION :

Une étude internationale, prospective, ouverte, multicentrique et randomisée, de phase 3 (NCT03511664) du 177Lu-PSMA-617 dans le traitement des patients atteints d'un cancer de la prostate métastatique résistant à la castration (mCRPC) progressif PSMA-positif



Endocyte. Protocol no. PSMA-617-01, v4.0; 2. ClinicalTrials.gov. NCT03511664. https://clinicaltrials.gov/ct2/show/NCT03511664 (dernier accès en avril 2021); 3. Morris M, et al. Présentation orale lors de la réunion annuelle de l'ASCO 2021 ; 6 juin 2021 ; Résumé LBA4

Les patients atteints de mCRPC progressif et PSMA-positif ont été sélectionnés à l'aide de TEP/CT scans au ^{68}Ga-PSMA-11[1-3].

Critères principaux d'inclusion

- **TEP/CT au ^{68}Ga-PSMA-11 confirmant l'éligibilité à l'aide de critères prédéfinis et de lecteurs centraux.**
- **Traitement antérieur par ≥1, mais pas >2, régimes de taxane.**
- Taux de castration de la testostérone sérique <50 ng/dL ou <1,7 nmol/L
- mCRPC[a] progressif documenté
- ECOG PS 0–2
- Fonctionnement adéquat de la moelle osseuse, du foie et des reins.
- Le partenaire et/ou le patient doivent utiliser une méthode de contraception avec une protection barrière adéquate jugée acceptable par l'invetigateur principal pendant l'étude et pendant 6 mois après la dernière administration du médicament à l'étude.

En Sc Os 2+2

Critères principaux d'exclusion

- Traitement antérieur dans les 6 mois précédant la randomisation : Sr-89, Sm-153, Re-186, Re-188, Ra-223, ou irradiation hémicorporelle
- Précédente RLT ciblant le PSMA
- Toute thérapie anticancéreuse systémique dans les 28 jours précédant la randomisation.
- Tout agent expérimental dans les 28 jours précédant la randomisation.
- Chimiothérapie, immunothérapie, RLT ou thérapie expérimentale concomitante.
- Transfusion dans le seul but de rendre un sujet éligible à l'étude.
- Un superscan à la scintigraphie osseuse de base.

Les patients éligibles présentaient ≥1 lésion métastatique PSMA-positive [1-3].

- Admissibilité déterminée par l'imagerie TEP/CT de base au ^{68}Ga-PSMA-11 **lue de manière centralisée**.
- La TEP/TDM au ^{18}F-FDG n'a pas été réalisée.
- Sont Exclut tous les patients présentant des lésions négatives (selon les critères à droite) à la TEP/TDM au ^{68}Ga-PSMA-11.

Sites de maladies positives au PSMA

- ≥1 lésions PSMA-positives n'importe où dans le corps (captation du ligand PSMA en imagerie TEP ≥ foie)
- Aucun critère de taille n'a été appliqué sur les lésions PSMA-positives.

Exclusion pour RLT

- Capture du ligand PSMA PET ≤ foie
- Grand(s) ganglion(s) lymphatique(s) PSMA-PET négatif(s), de taille ≥2,5 cm (axe court)
- Métastase osseuse négative avec composante des tissus mous, de taille ≥1,0 cm (axe court).
- Métastase viscéral PSMA-négatif, avec une taille ≥1,0 cm (axe court).

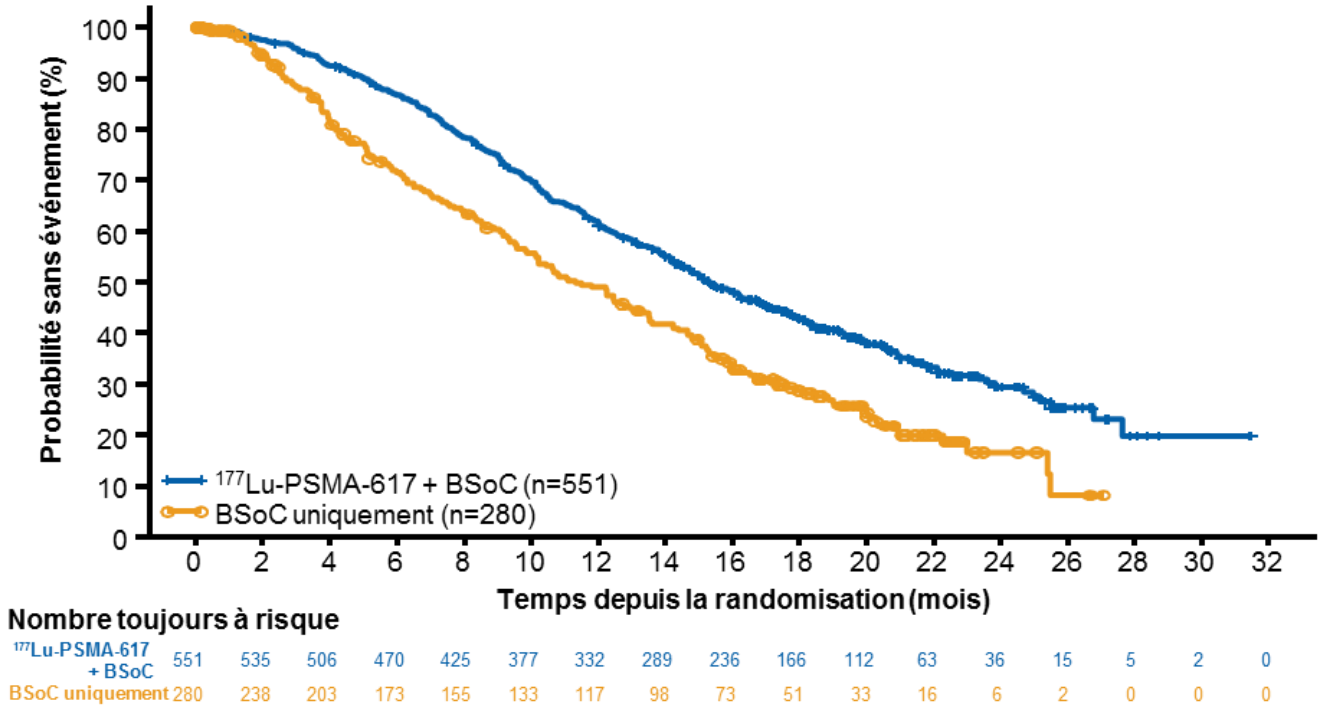
Bien vérifier l'absence d'infiltration du mur post

87 % des patients scannés répondaient aux critères pré-spécifiés pour le mCRPC PSMA-positif.

Les caractéristiques de base étaient bien équilibrées entre les bras d'étude et les sous-population (1/3)

Disposition	Full OS population (n=831)		rPFS population (n=581)	
	^{177}Lu-PSMA-617 + BSoC (n=551) – n (%)	BSoC uniquement (n=280) – n (%)	^{177}Lu-PSMA-617 + BSoC (n=385) – n (%)	BSoC uniquement (n=196) – n (%)
Âge (en années)				
Médiane (fourchette)	70,0 (48 ; 94)	71,5 (40 ; 89)	71,0 (52 ; 94)	72,0 (51 ; 89)
Ethnie[a] – n (%)				
Blanc	486 (88,2)	235 (83,9)	336 (87,3)	166 (84,7)
Noir ou Afro-Américain	34 (6,2)	21 (7,5)	29 (7,5)	14 (7,1)
Asiatique	9 (1,6)	11 (3,9)	6 (1,6)	9 (4,6)
Statut ECOG[b] – n (%)				
0 – 1	510 (92,6)	258 (92,1)	352 (91,4)	179 (91,3)
2	41 (7,4)	22 (7,9)	33 (8,6)	17 (8,7)
Site de la maladie métastatique – n (%)				
Poumon	49 (8,9)	28 (10,0)	35 (9,1)	20 (10,2)
Foie	63 (11,4)	38 (13,6)	47 (12,2)	26 (13,3)
Ganglion lymphatique	274 (49,7)	141 (50,4)	193 (50,1)	99 (50,5)
Os	504 (91,5)	256 (91,4)	351 (91,2)	179 (91,3)

Survie globale

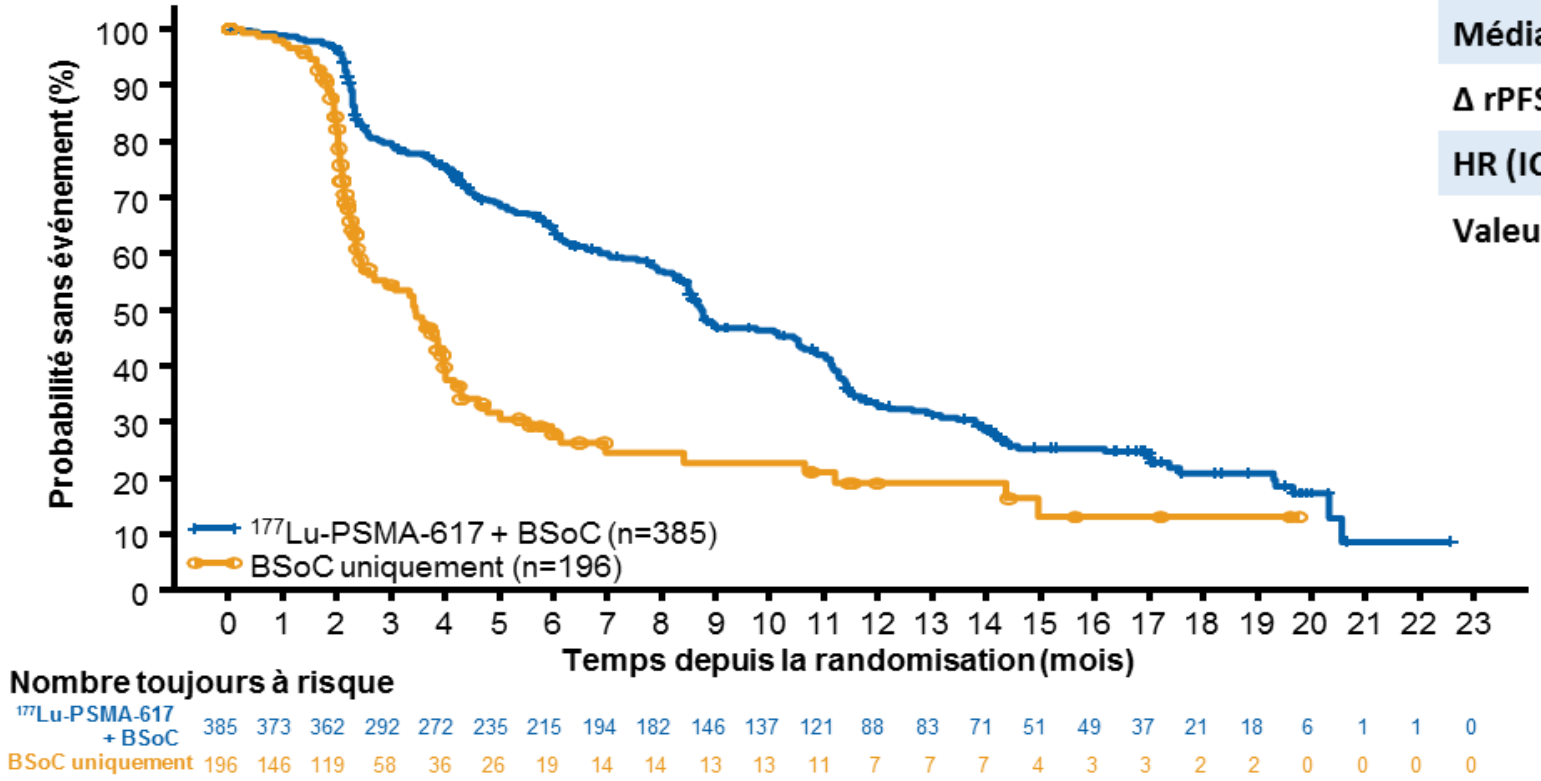


	^{177}Lu-PSMA-617 + BSoC (n=551)	BSoC uniquement (n=280)
Médiane OS - mois	15,3	11,3
Δ OS - mois	4,0	
HR (IC de 95 %)	0,62 (0,52–0,74)	
Valeur *p*, unilatérale	<0,001	

NB OS + 4 mois : Ne perdons pas des mois à faire le bilan pré thérapeutique

La durée de vie était significativement plus longue dans le groupe ^{177}Lu-PSMA-617 + BSoC que dans le groupe BSoC seul (HR 0,62 ; IC 95 % 0,52-0,74 ; *P*<0,001)

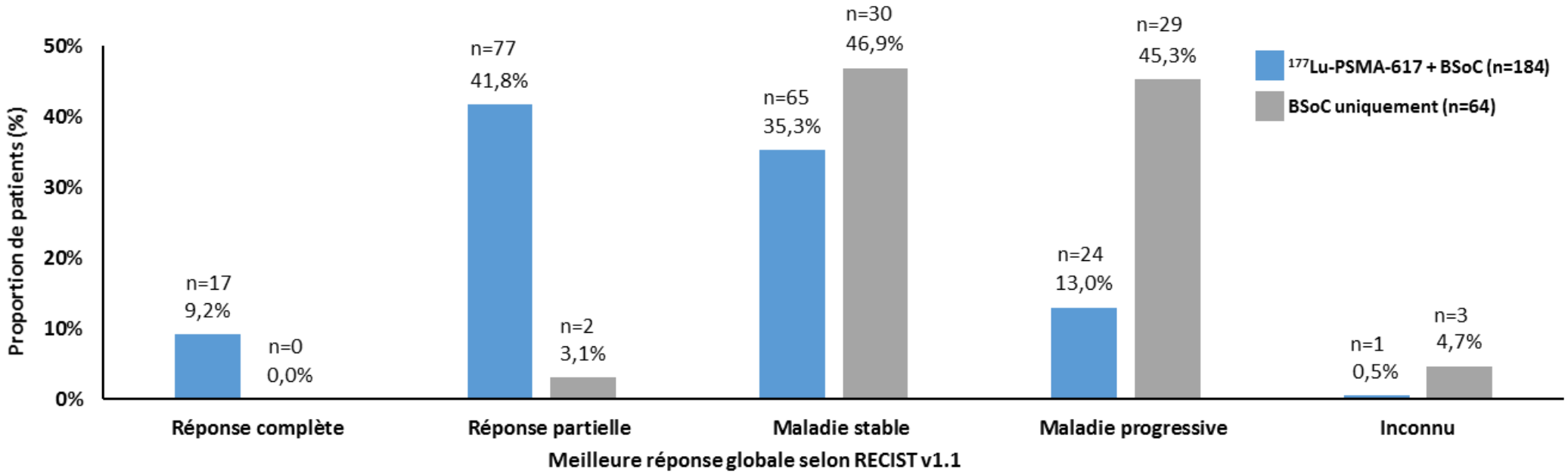
survie sans progression radiologique



	^{177}Lu-PSMA-617 + BSoC (n=385)	BSoC uniquement (n=196)
Médiane rPFS – mois	8,7	3,4
Δ rPFS – mois	5,3	
HR (IC 99,2 %I)	0,40 (0,29 - 0,57)	
Valeur *p*, unilatérale	<0,001	

L'ajout de ^{177}Lu-PSMA-617 à la BSoC a prolongé de manière significative la rPFS par rapport à la BSoC seule (HR 0,40 ; 99,2% CI 0,29-0,57 ; *P*<0,001)

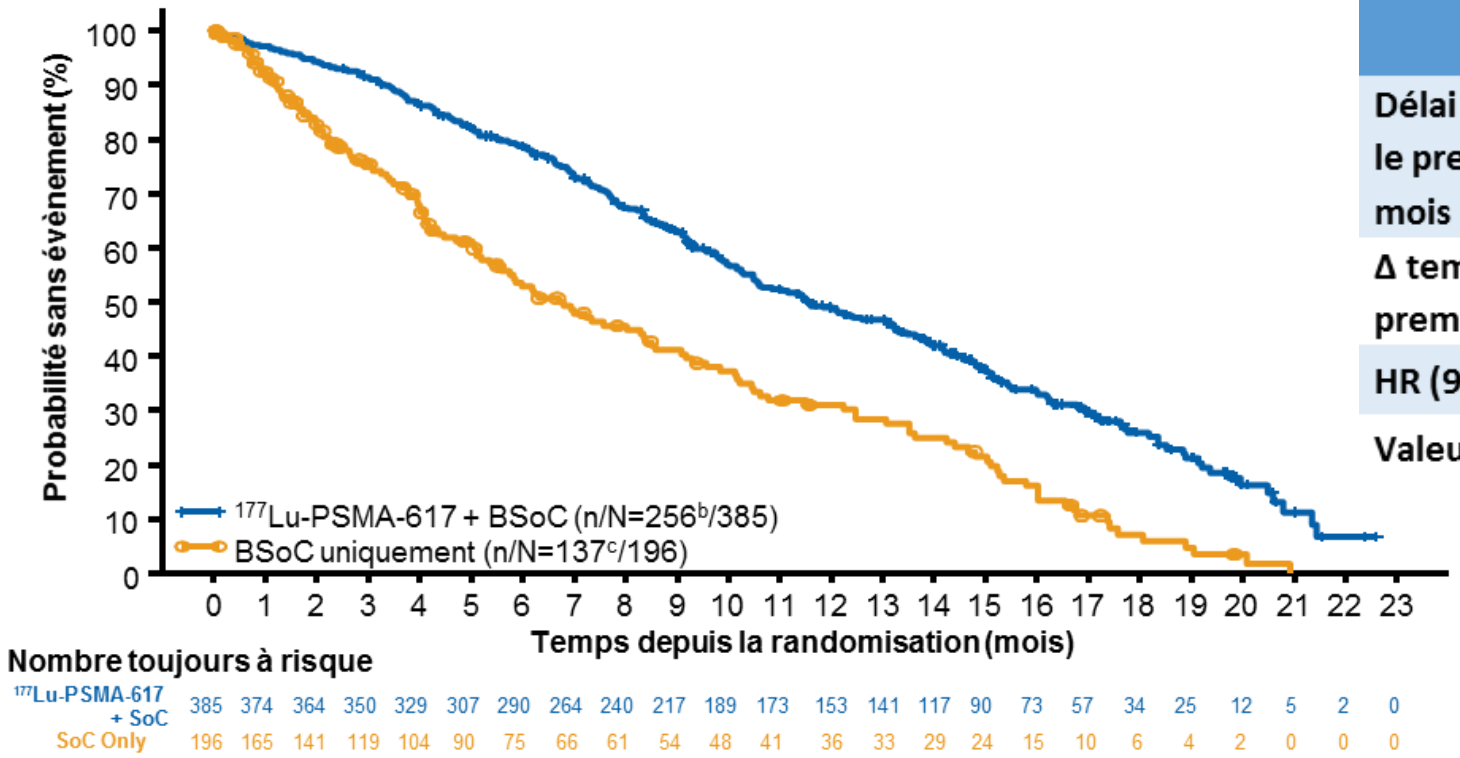
^{177}Lu-PSMA-617 ajouté au BSoC a amélioré les réponses selon RECIST v1.1[a] chez les patients dont la maladie est mesurable



ORR : 51,1 % des patients ont présenté une RC ou une RP dans le groupe 177Lu-PSMA-617 + BSoC, contre 3,1 % dans le groupe BSoC uniquement (*P*<0,001 bilatéral) ;
Le taux de contrôle de la maladie était de 86,4 % contre 50,0 % (*P*<0,001 bilatéral)

[a] ^{177}Lu-PSMA-617 est un agent expérimental et n'est pas approuvé pour quelque usage que ce soit.
Figure présentée avec la permission de M. Morris.

Survie sans évènement



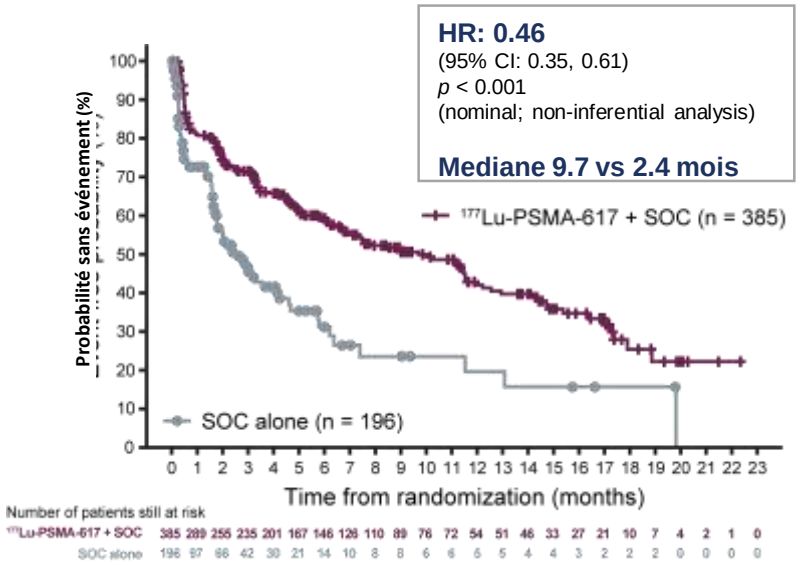
	177Lu-PSMA-617 + BSoC (n=385)	BSoC uniquement (n=196)
Délai médian avant le premier SSE - mois (IC 95 %)	11.5	6.8
Δ temporel avant le premier SSE - mois	4.7	
HR (95% CI)	0.50 (0.40–0.62)	
Valeur *P*, bilatérale	<0.001	

Le délai avant le premier SSE était significativement plus long dans le groupe ^{177}Lu-PSMA-617 + BSoC que dans le groupe BSoC uniquement (HR 0,50 ; 95% CI 0,40–0,62) ; *P*<0,001)

HRQoL et résultats relatifs à la douleur en faveur du bras 177Lu-PSMA-617 + BSoC

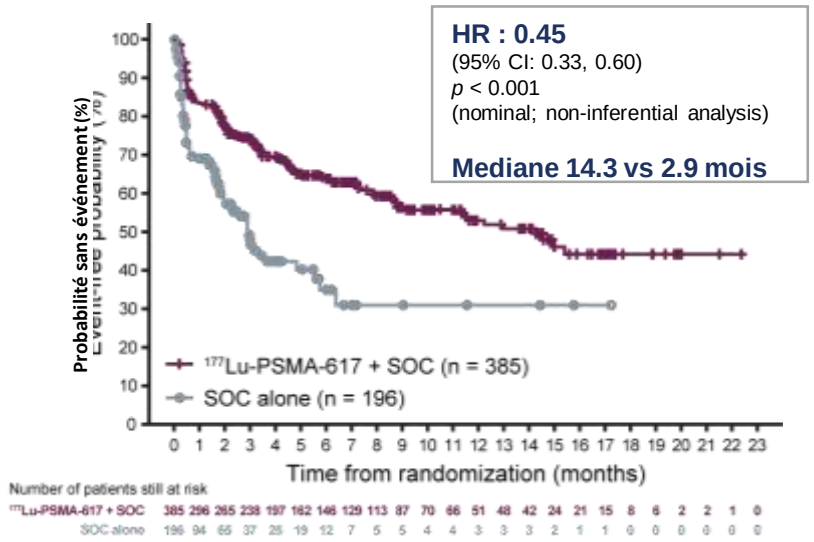
***Ad hoc* analyses**

Score FACT-P total (n=581)



Time to the first occurrence of ≥ 10-point decrease in FACT-P total from baseline

BPI-SF (intensité de la douleur)

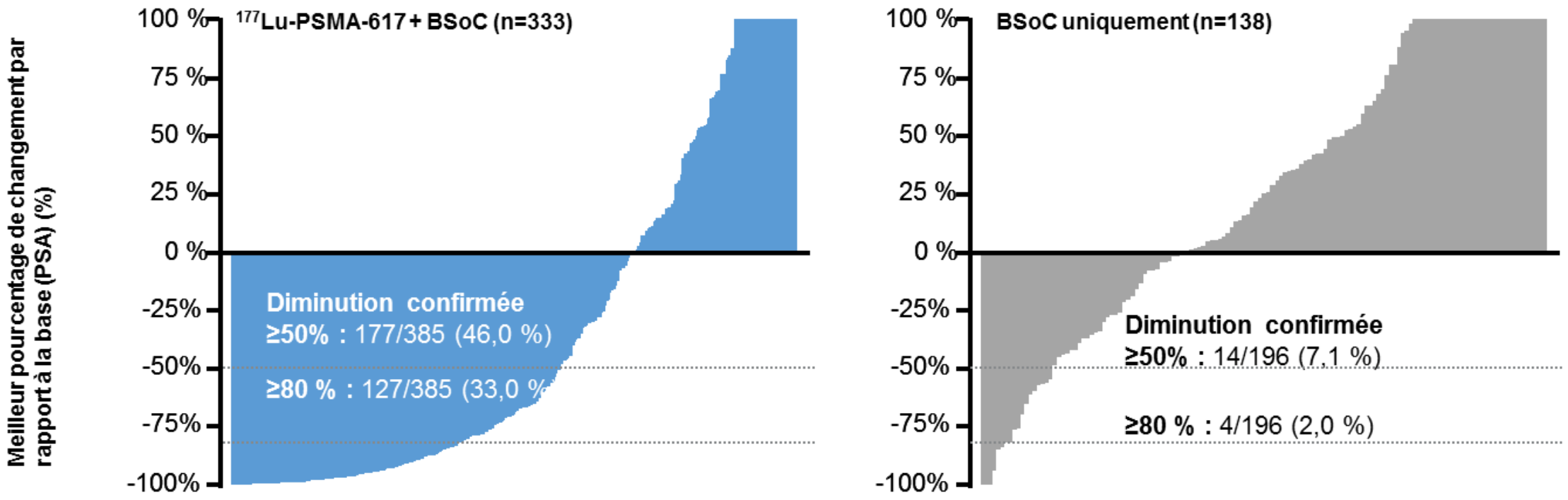


Time to the first occurrence of ≥ 30% or ≥ 2-point increase in BPI-SF pain intensity from baseline

Présenté par Karim Fizazi, 576MO – Mini oral. Sep 19, 2021

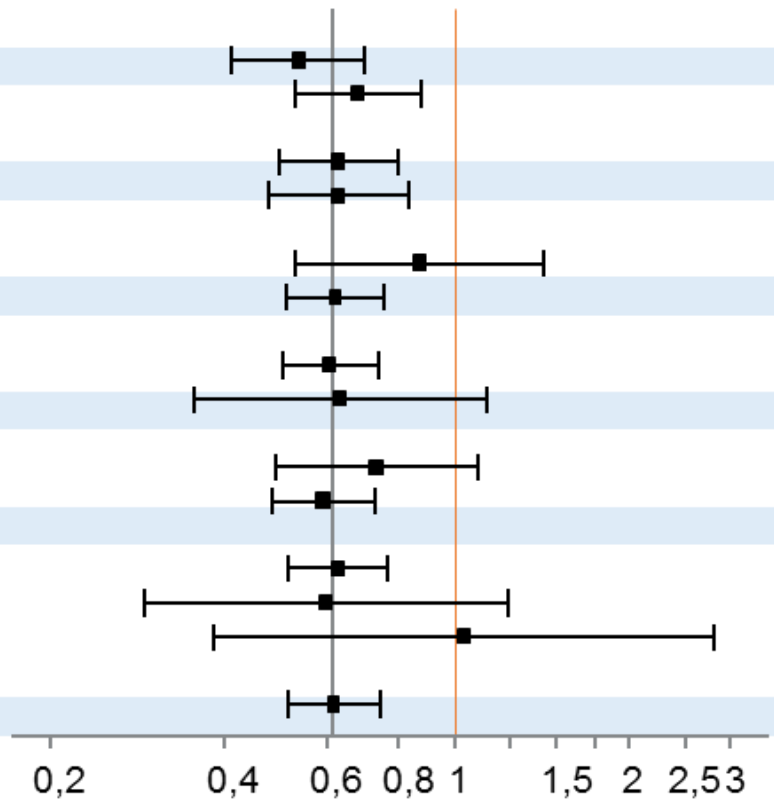
BPI-SF, Brief Pain Inventory – Short Form; CI, confidence interval; FACT-P, Functional Assessment of Cancer Therapy – Prostate; PSMA, prostate-specific membrane antigen; SOC, protocol-permitted standard of care

PSA



46,0 % vs 7,1 % des patients ont connu une baisse du PSA de ≥50 % dans le bras 177Lu-PSMA-617 + BSoC vs bras BSoC seul, respectivement

Sous-groupe	Ensemble d'analyse OS (n=831) ^{177}Lu-PSMA-617 + BSoC (n=551) – n/N (%)	BSoC uniquement (n=280) – n/N (%)	Rapport de risques (IC de 95 %)
ARPI dans le cadre de la BSoC attribuée			
Oui	135/243 (55,6)	96/146 (65,8)	0,54 (0,41 - 0,70)
Non	208/308 (67,5)	91/134 (67,9)	0,68 (0,53–0,87)
LDH			
≤260 IU/L	202/368 (54,9)	107/182 (58,8)	0,63 (0,50–0,80)
>260 IU/L	140/182 (76,9)	80/97 (82,5)	0,63 (0,48–0,84)
Présence de métastases au foie			
Oui	40/48 (83,3)	28/34 (82,4)	0,87 (0,53–1,43)
Non	303/503 (60,2)	159/246 (64,6)	0,62 (0,51–0,76)
ECOG PS			
0 – 1	305/510 (59,8)	170/258 (65,9)	0,61 (0,50 - 0,74)
2	38/41 (92,7)	17/22 (77,3)	0,63 (0,35 - 1,13)
Âge			
<65 ans	82/145 (56,6)	38/60 (63,3)	0,73 (0,49 - 1,10)
≥65 ans	261/406 (64,3)	149/220 (67,7)	0,59 (0,48 - 0,73)
Ethnie			
Blanc	300/486 (61,7)	159/235 (67,7)	0,63 (0,52 - 0,77)
Noir ou Afro-Américain	20/34 (58,8)	12/21 (57,1)	0,60 (0,29 - 1,24)
Asiatique	9/9 (100)	7/11 (63,6)	1,04 (0,38 - 2,81)
Tous les patients	**343/ 551 (62,3)**	**187/ 280 (66,8)**	**0,62 (0,52 - 0,74)**



Toxicité

Patients présentant des événements TEAE dans un domaine de sécurité présentant un intérêt particulier[b]	Ensemble d'analyse de sécurité (N=734)[a]			
	Tous les Grades		Grade 3–5[c]	
	^{177}Lu-PSMA-617 + BSoC (n=529)	BSoC uniquement (n=205)	^{177}Lu-PSMA-617 + BSoC (n=529)	BSoC uniquement (n=205)
Fatigue	260 (49.1)	60 (29.3)	37 (7.0)	5 (2.4)
Myélosuppression	251 (47.4)	36 (17.6)	124 (23.4)	14 (6.8)
Leucopénie	66 (12.5)	4 (2.0)	13 (2.5)	1 (0.5)
Lymphopénie	75 (14.2)	8 (3.9)	41 (7.8)	1 (0.5)
Anémie	168 (31.8)	27 (13.2)	68 (12.9)	10 (4.9)
Thrombocytopénie	91 (17.2)	9 (4.4)	42 (7.9)	2 (1.0)
Sécheresse buccale	208 (39.3)	2 (1.0)	0 (0.0)	0 (0.0)
Nausée et vomissements	208 (39.3)	35 (17.1)	8 (1.5)	1 (0.5)
Hypersensibilité	55 (10.4)	7 (3.4)	5 (0.9)	0
Hépatotoxicité	54 (10.2)	16 (7.8)	15 (2.8)	5 (2.4)
Effets rénaux	46 (8.7)	12 (5.9)	18 (3.4)	6 (2.9)
Tumeurs secondaires	11 (2.1)	2 (1.0)	4 (0.8)	1 (0.5)
Prolongation du QT	9 (1.7)	1 (0.5)	7 (1.3)	1 (0.5)
Hémorragie intracrânienne	7 (1.3)	3 (1.5)	5(0.9)	2 (1.0)

L'incidence de la fatigue, de la myélosuppression, de la sécheresse buccale et des nausées/vomissements était plus élevée dans le bras ^{177}Lu-PSMA-617 + BSoC, et pour la plupart transitoire, sans effet inattendu.

https://doi.org/10.1007/s00259-021-05245-y

GUIDELINES

E-PSMA: the EANM standardized reporting guidelines v1.0 for PSMA-PET

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3 niveaux de référence
1. Le sang
2. Le foie
3. Les glandes salivaires

Table 2 Qualitative evaluation of PSMA expression through a 4-point scale

PSMA expression V (visual score)	Grade of PSMA expression
Score=0	Below blood pool
Score=1	Equal to or above blood pool and lower than liver
Score=2	Equal to or above liver and lower than parotid gland
Score=3	Equal to or above parotid gland

Table 3 Regional classification of PSMA-PET findings

Class	Description
Local tumor (T)	
miT0	No local tumor
miT2	Organ-confined tumor
miT3a	Non-organ-confined tumor (extracapsular extension)
miT3b	Non-organ-confined tumor (seminal vesicles invasion)
miT4	Tumor invading adjacent structures (other than seminal vesicles)
miTr	Presence of local recurrence after radical prostatectomy
Regional nodes (N)	
miN0	No positive regional lymph nodes
miN1	Positive regional lymph nodes
Distant metastases (M)	
miM0	No distant metastases
miM1a	Extra-pelvic lymph nodes
miM1b	Bone metastasis
miM1c	Non-nodal visceral metastasis: report involved organ(s)

Mr D 52 ans 108 Kg 180 cm Cancer de la prostate résistant à la castration

OMS 1- 2 Douleur de la hanche gauche

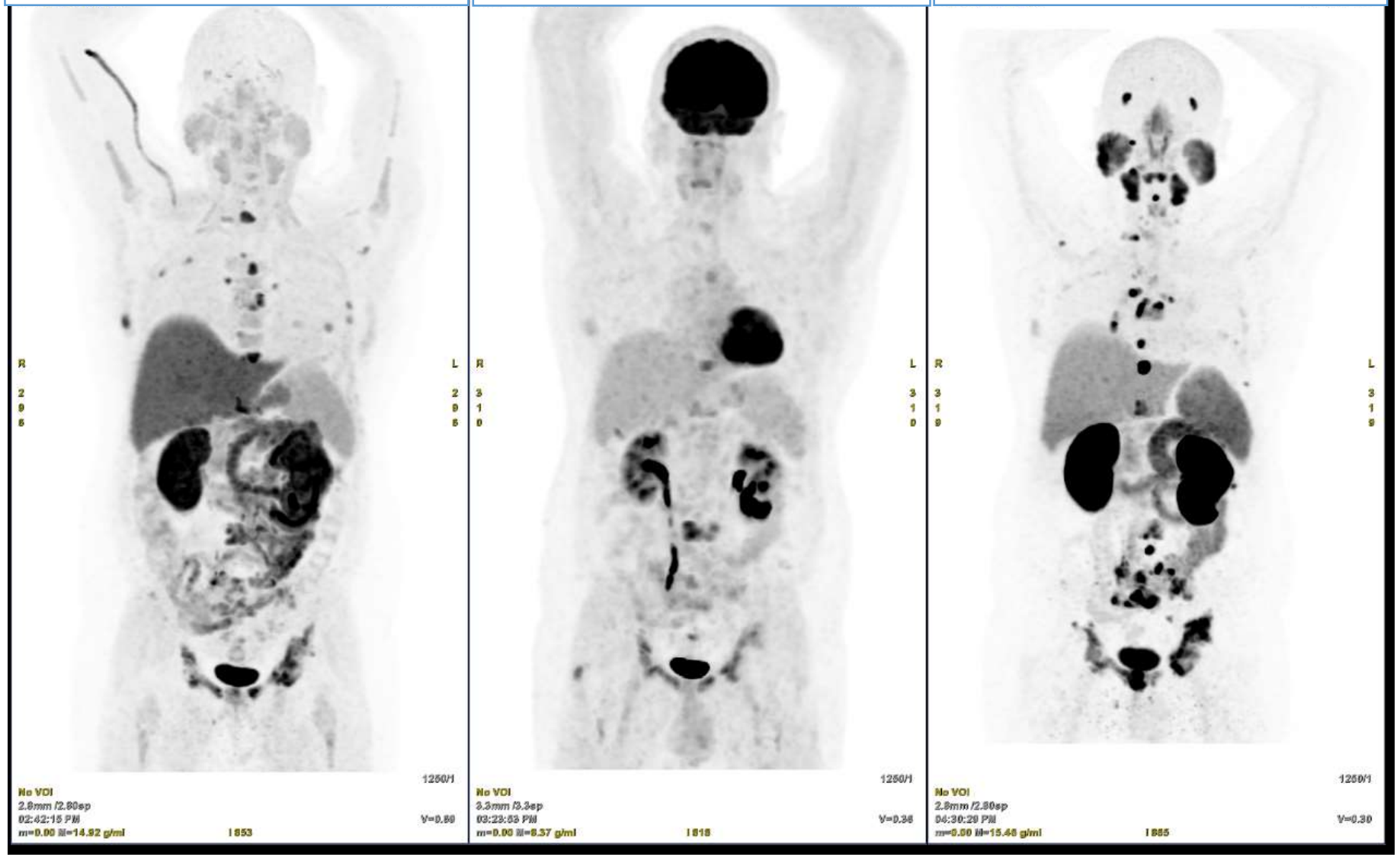
Pathologie métastatique d'emblée diagnostiquée en 2017 considérée résistante à la castration depuis, traitée ensuite par **acétate d'abiratérone puis CABAZITAXEL.**

☺ **N'a jamais été transfusé.**
☹A été irradié à de multiples reprises (**30-40% du squelette)**

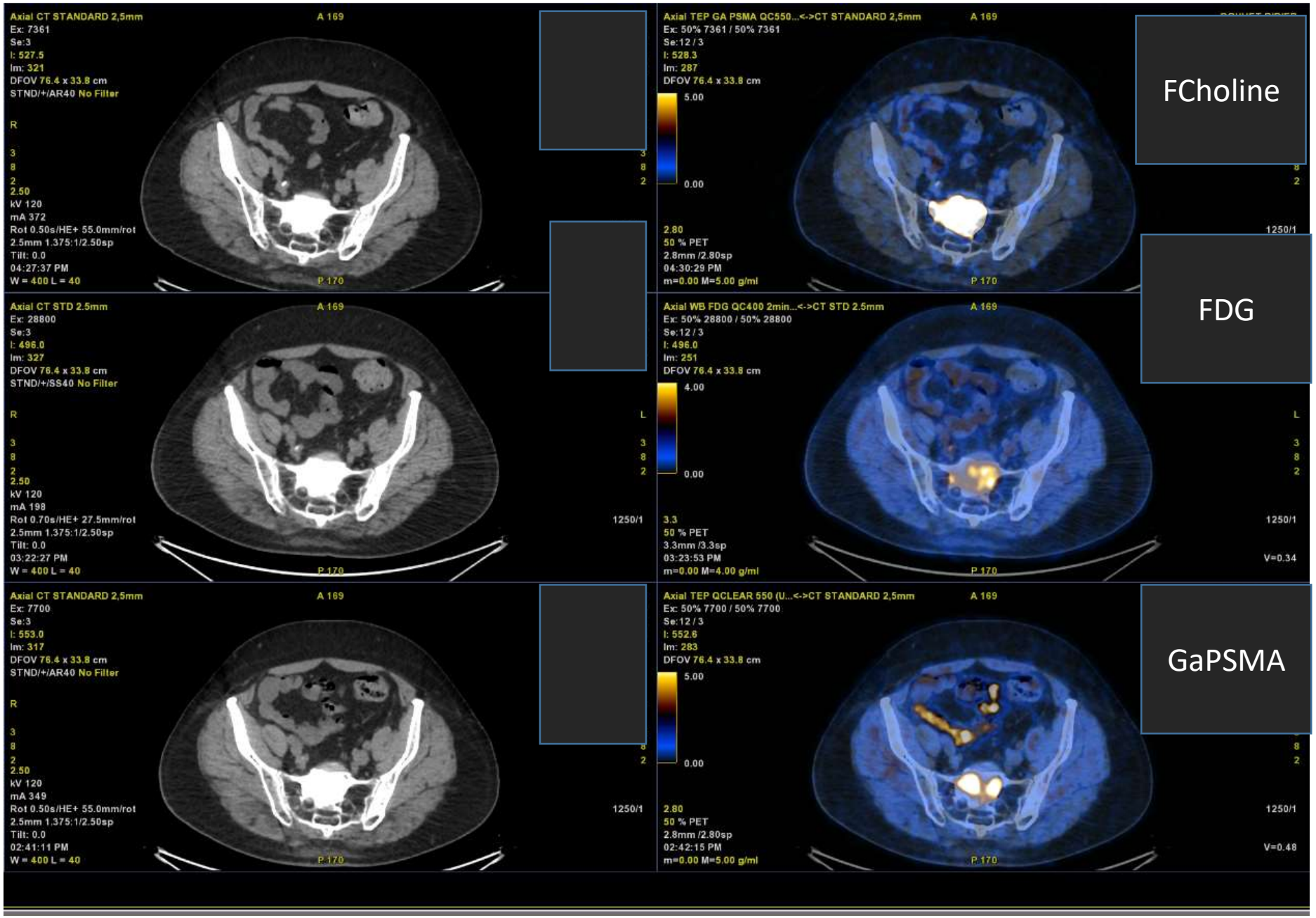
Progression des PSA 104ng/mL le 17 sept, à 181 le 19 janvier.
Sur le plan biologique**, pas de contre-indication** au traitement.
Anémie G1 (11.7g/dL)

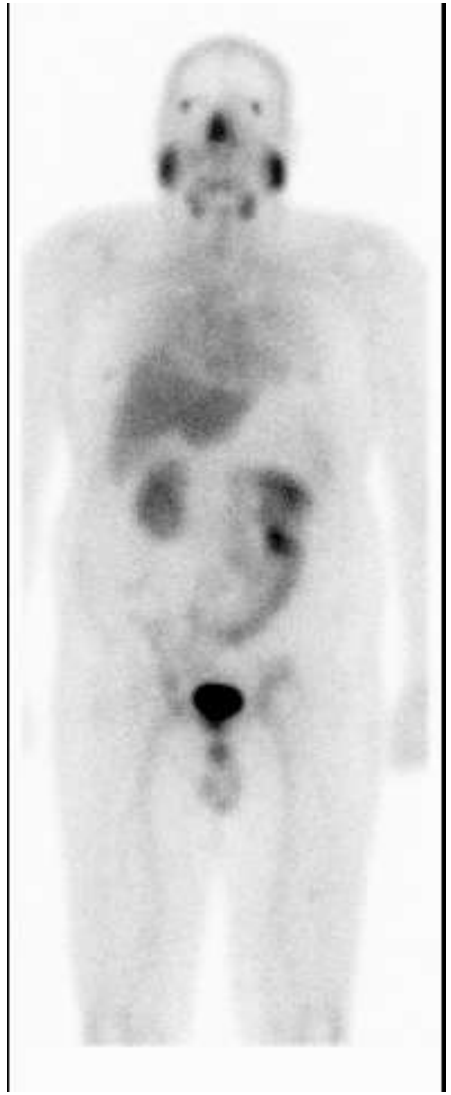
TRAITEMENT ACTUEL
- méthadone 100 mg matin et soir
- méthadone 20 mg à la demande
- paracétamol 3 g/jour
- pantoprazole 40
- **solupred 20 mg le matin**
- bisoprolol
- 5/hydrochlorothiazide 6,25
- primperan à la demande
- **cacit d3**
- **denosumab mensuel**
- **decapeptyl lp 11,25**

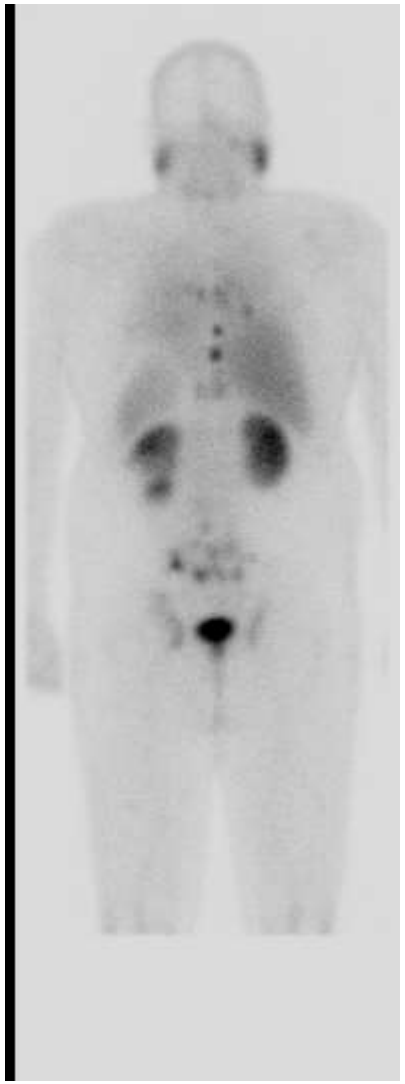
18F Choline 216 MBq @ 45 min DMI GEHC 5 pas de 2min	18FDG 216 MBq @ 60 min DMI GEHC 5 pas de 2min	68GaPSMA 228MBq @ 60 min DMI GEHC 5 pas de 2min



La fixation du PSMA au niveau des cibles osseuses et ganglionnaires est significativement supérieure au bruit de fond hépatique (>1.5SUVmoy)


Axial CT STANDARD 2,5mm
A 169
Ex: 7361
Se:3
I: 527.5
Im: 321
DFOV 76.4 x 33.8 cm
STND/+/AR40 No Filter
R
3
8
2
2.50
kV 120
mA 372
Rot 0.50s/HE+ 55.0mm/rot
2.5mm 1.375:1/2.50sp
Tilt: 0.0
04:27:37 PM
W = 400 L = 40
P 170
Axial TEP GA PSMA QC550...<->CT STANDARD 2,5mm
A 169
Ex: 50% 7361 / 50% 7361
Se:12 / 3
I: 528.3
Im: 287
DFOV 76.4 x 33.8 cm
5.00
0.00
2.80
50 % PET
2.8mm /2.80sp
04:30:28 PM
m=0.00 M=5.00 g/ml
P 170
1250/1
FCholine
Axial CT STD 2.5mm
A 169
Ex: 28800
Se:3
I: 496.0
Im: 327
DFOV 76.4 x 33.8 cm
STND/+/SS40 No Filter
R
L
2.50
kV 120
mA 198
Rot 0.70s/HE+ 27.5mm/rot
2.5mm 1.375:1/2.50sp
Tilt: 0.0
03:22:27 PM
W = 400 L = 40
P 170
1250/1
Axial WB FDG QC400 2min...<->CT STD 2.5mm
A 169
Ex: 50% 28800 / 50% 28800
Se:12 / 3
I: 496.0
Im: 251
DFOV 76.4 x 33.8 cm
4.00
0.00
3.3
50 % PET
3.3mm /3.3sp
03:23:53 PM
m=0.00 M=4.00 g/ml
P 170
1250/1
V=0.34
FDG
Axial CT STANDARD 2,5mm
A 169
Ex: 7700
Se:3
I: 553.0
Im: 317
DFOV 76.4 x 33.8 cm
STND/+/AR40 No Filter
R
2.50
kV 120
mA 349
Rot 0.50s/HE+ 55.0mm/rot
2.5mm 1.375:1/2.50sp
Tilt: 0.0
02:41:11 PM
W = 400 L = 40
P 170
1250/1
Axial TEP QCLEAR 550 (U...<->CT STANDARD 2,5mm
A 169
Ex: 50% 7700 / 50% 7700
Se:12 / 3
I: 552.6
Im: 283
DFOV 76.4 x 33.8 cm
5.00
0.00
2.80
50 % PET
2.8mm /2.80sp
02:42:15 PM
m=0.00 M=5.00 g/ml
P 170
1250/1
V=0.48
GaPSMA

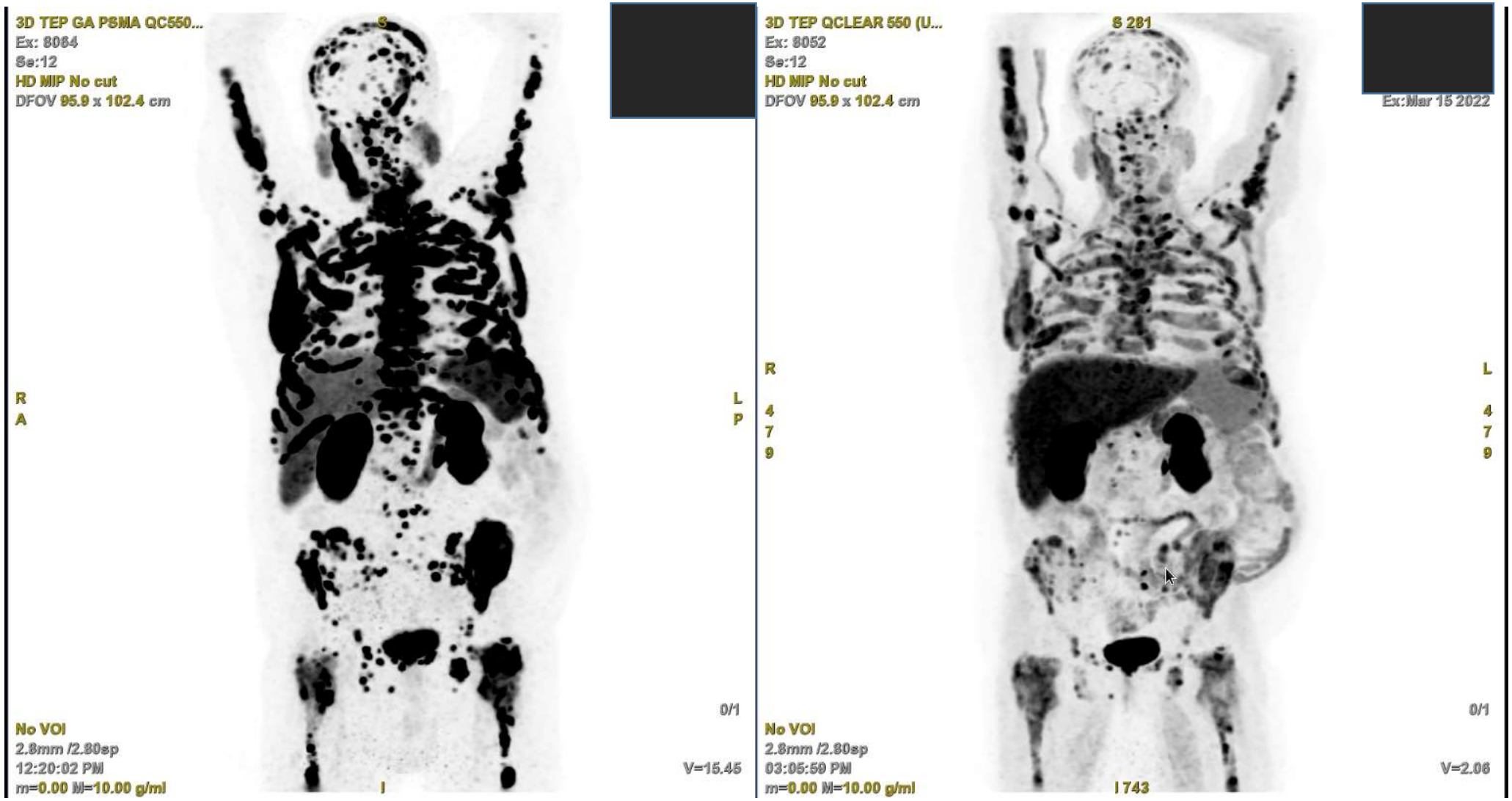




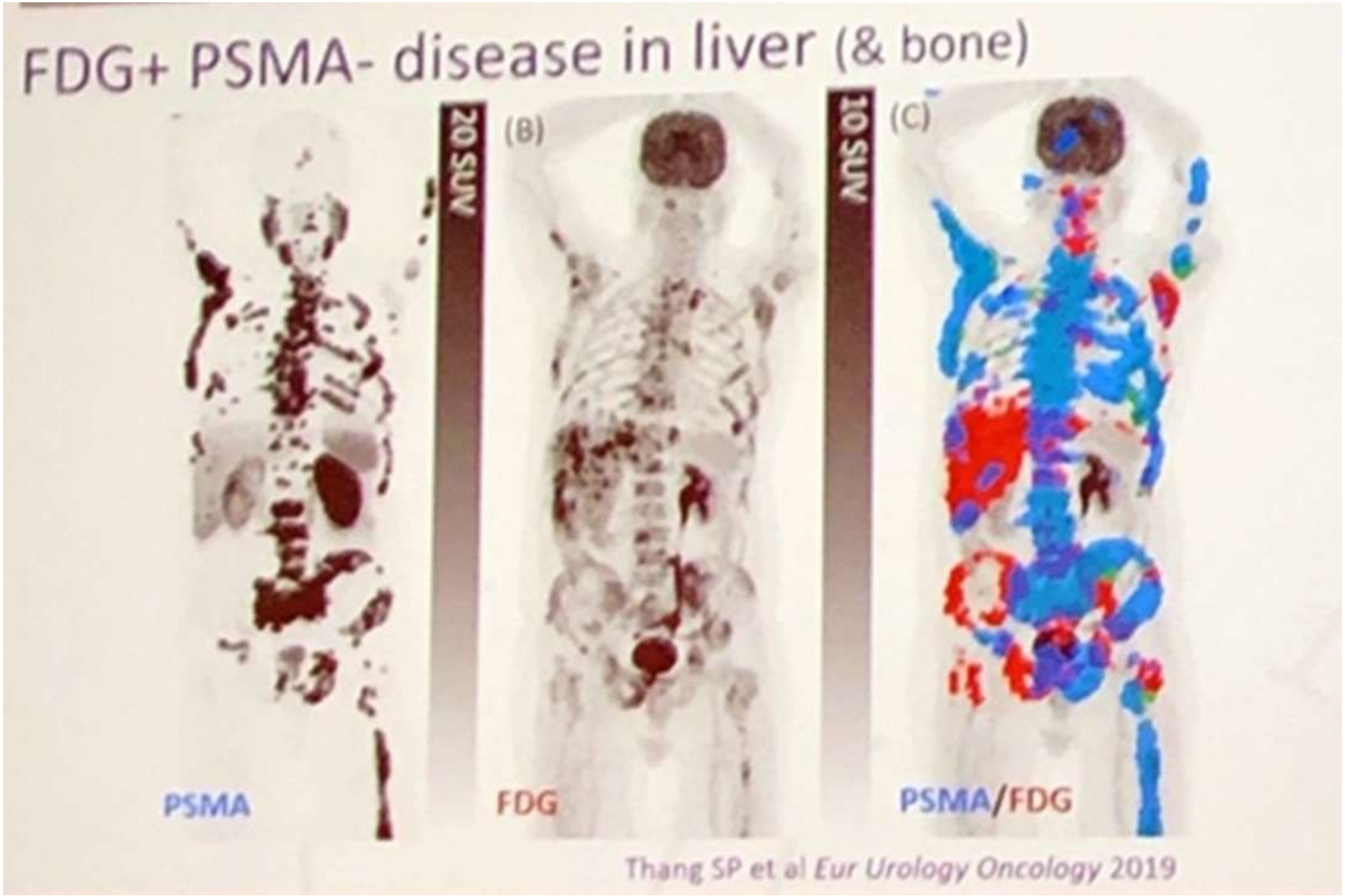
4h post 7,4GBq 177LuPSMA iv périph (pompe péristaltique + hydrat) en ambulatoire 2 Mars
☹ pas de captation médiastinale…

PSA janv 181, fev 261 mars 222 ng/ml (après PRRT)
Réduction de la douleur de hanche

Mauvaise indication



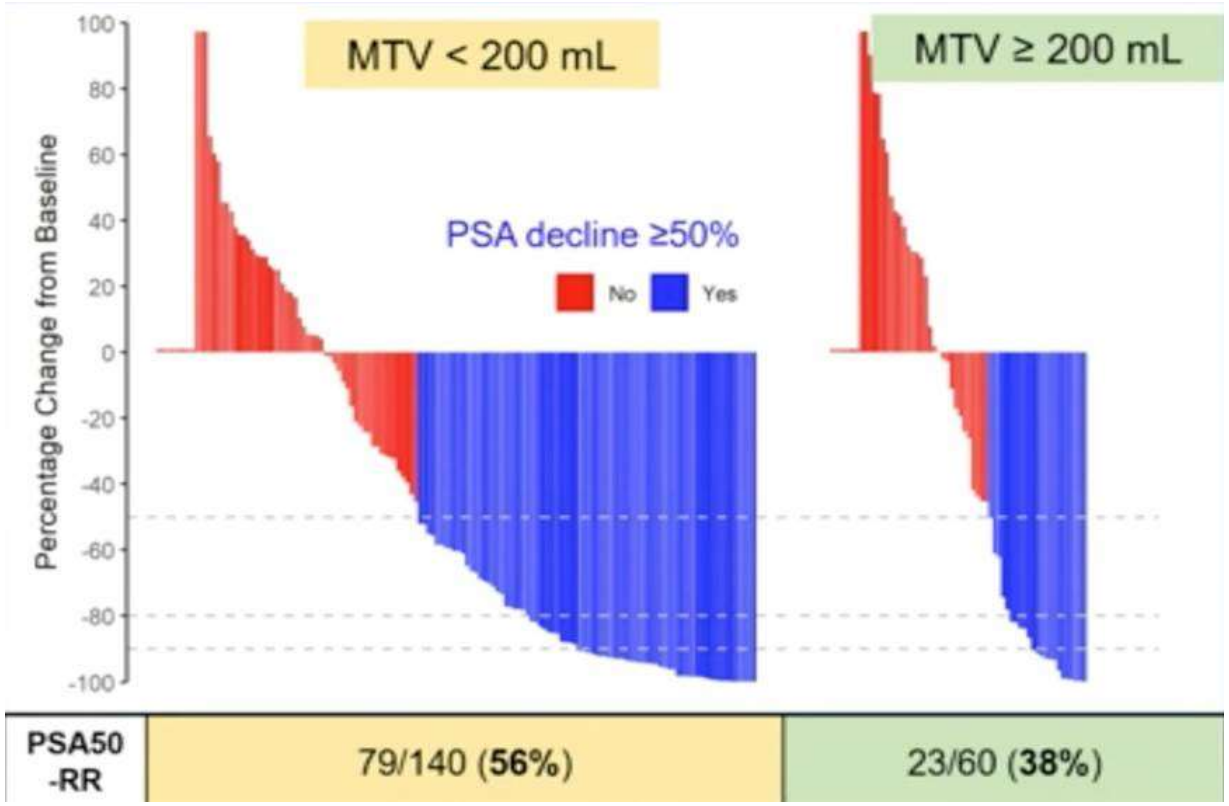
L’hétérogénéité tumorale en imagerie

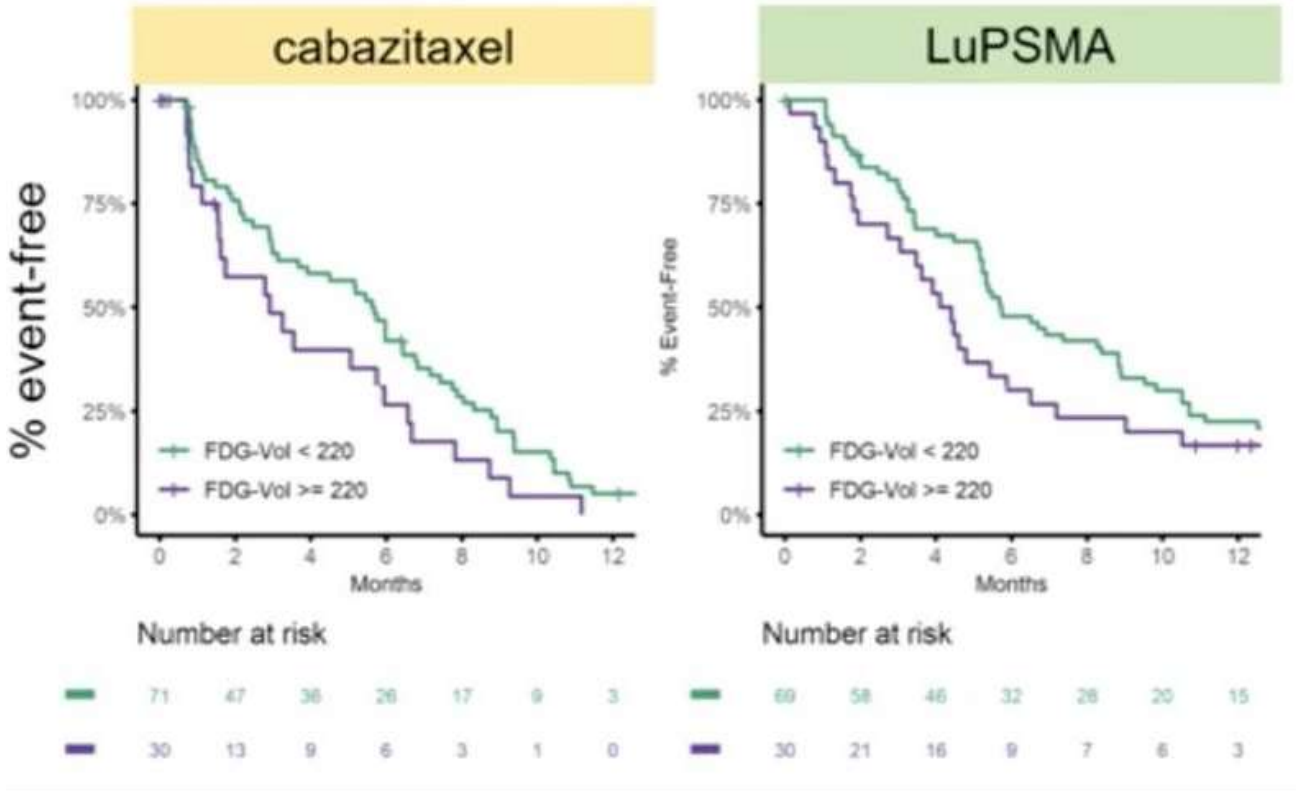


Randomized Phase 2 Trial of 177Lu-PSMA-617 Versus Cabazitaxel in mCRPC Progressing after Docetaxel: TheraP ANZUP 1603

Clinical trial information: NCT03392428. Presented by: Michael S. Hofman, 2022 American Society of Clinical Oncology Genitourinary (ASCO GU) Cancers Symposium, Thursday Feb 17 – Saturday Feb 19, 2022

18FDG

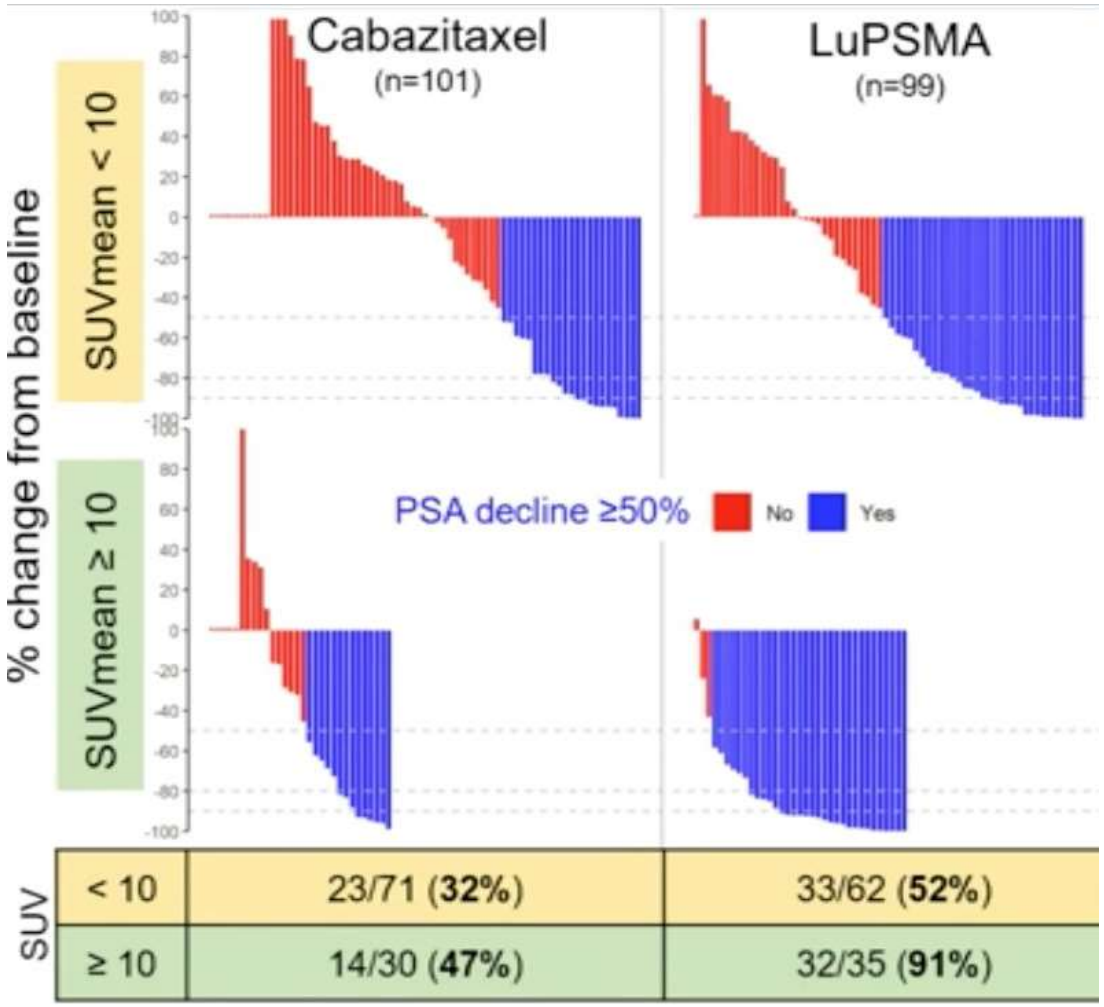




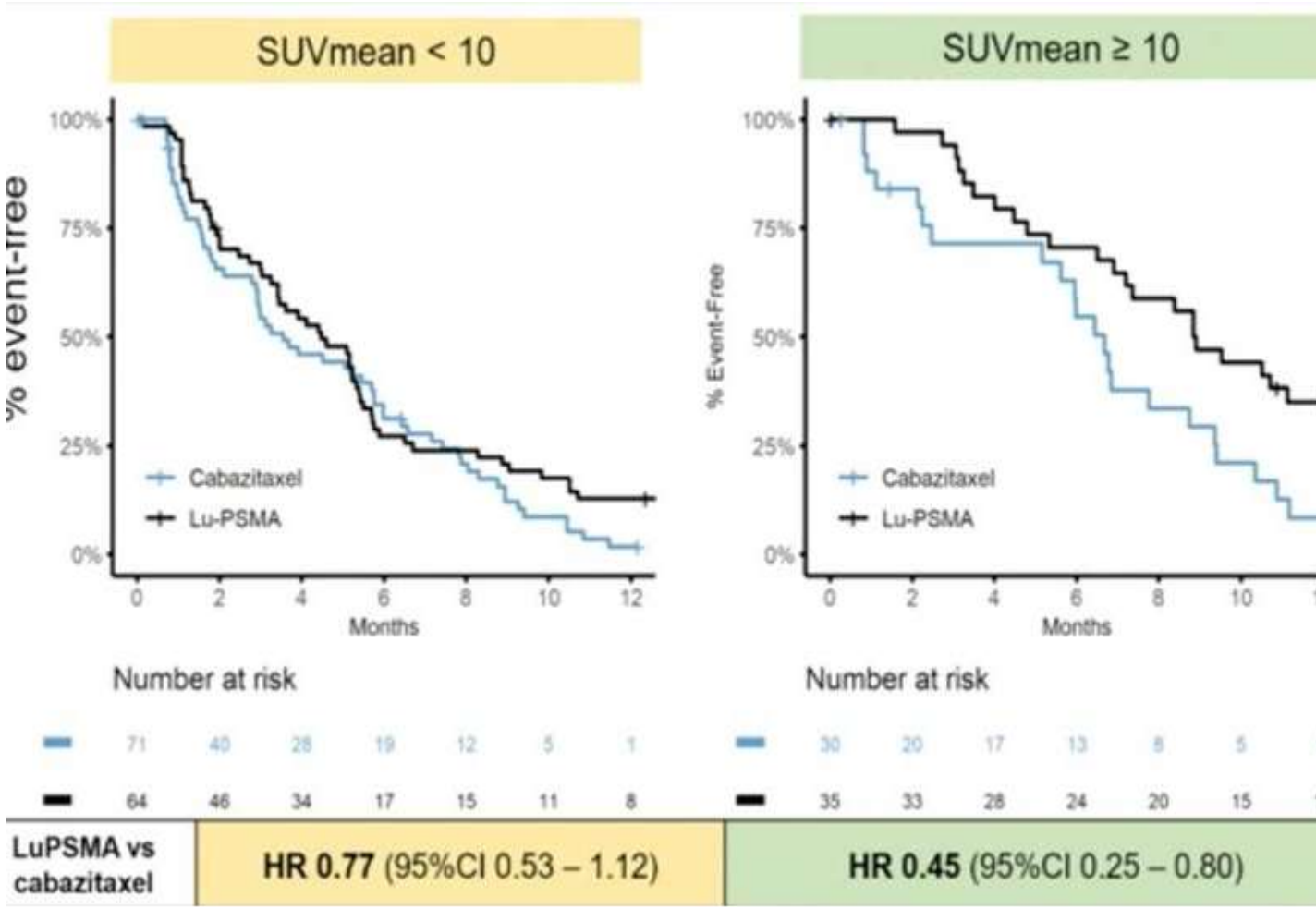
<200 mL = ☺

>200mL = ☹

68Ga PSMA



SUV			
	< 10	23/71 (**32%**)	33/62 (**52%**)
	≥ 10	14/30 (**47%**)	32/35 (**91%**)

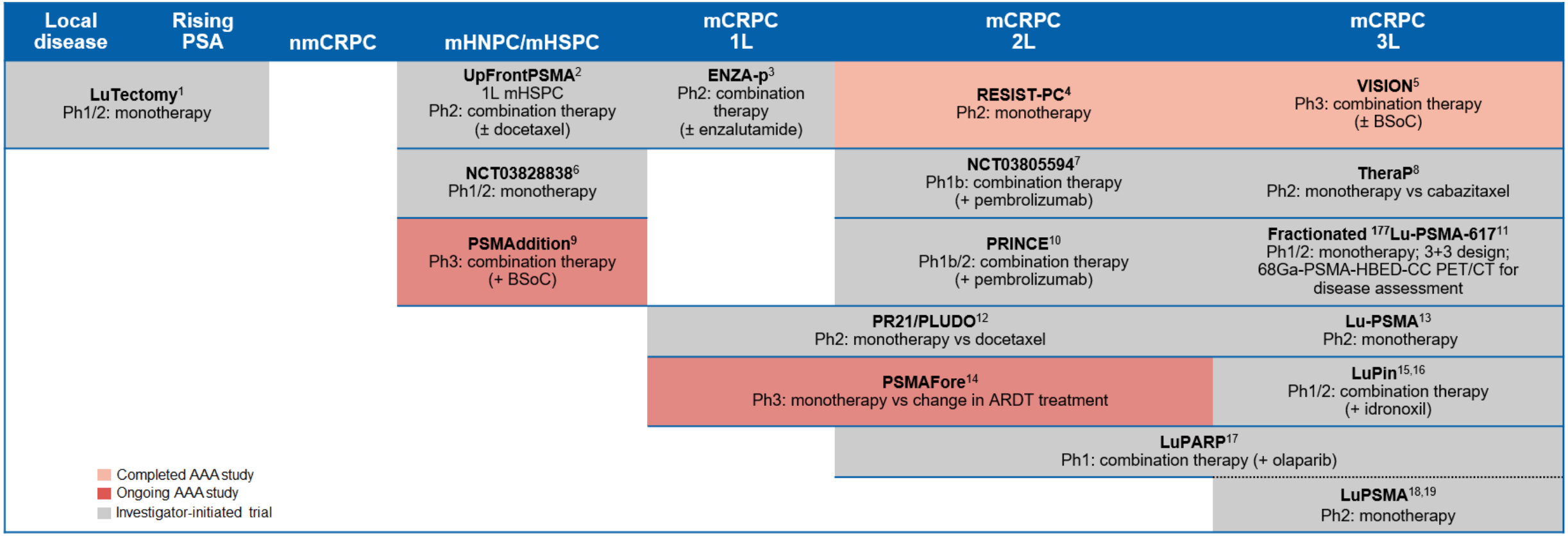


LuPSMA vs cabazitaxel		
	HR 0.77 (95%CI 0.53 – 1.12)	**HR 0.45** (95%CI 0.25 – 0.80)

> 10 = ☺

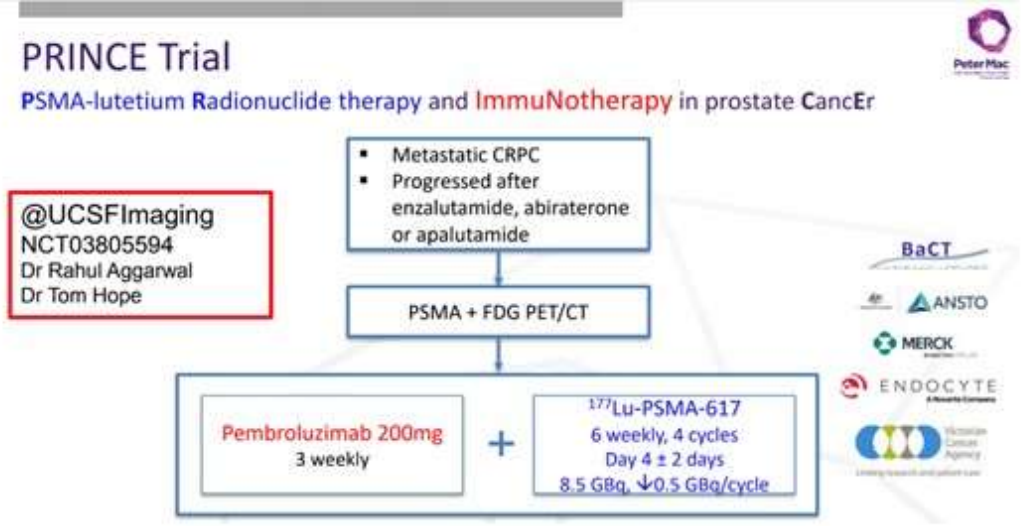
< 10 = ☹

Développement du ^{177}Lu-PSMA-617 (données AAA)

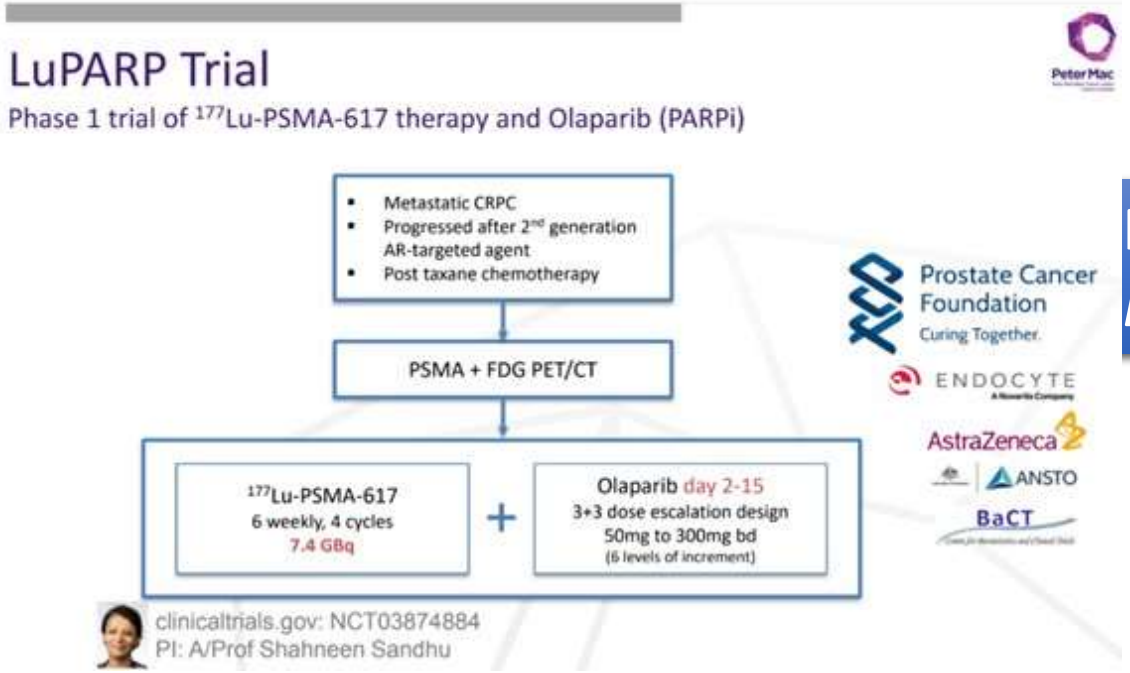


^{177}Lu-PSMA-617 is an investigational agent and is not approved for any use.

1. ClinicalTrials.gov. NCT04430192. https://clinicaltrials.gov/ct2/show/NCT04430192 (accessed March 2021); 2. ClinicalTrials.gov. NCT04343885. https://www.clinicaltrials.gov/ct2/show/NCT04343885 (accessed March 2021); 3. ClinicalTrials.gov. NCT04419402. https://clinicaltrials.gov/ct2/show/NCT04419402 (accessed March 2021); 4. ClinicalTrials.gov. NCT03042312. https://clinicaltrials.gov/ct2/show/NCT03042312 (accessed March 2021); 5. ClinicalTrials.gov. NCT03511664. https://clinicaltrials.gov/ct2/show/NCT03511664 (accessed March 2021); 6. ClinicalTrials.gov. NCT03828838. https://clinicaltrials.gov/ct2/show/NCT03828838 (accessed March 2021); 7. ClinicalTrials.gov. NCT03805594. https://clinicaltrials.gov/ct2/show/NCT03805594 (accessed March 2021); 8. ClinicalTrials.gov. NCT03392428. https://clinicaltrials.gov/ct2/show/NCT03392428 (accessed March 2021); 9. ClinicalTrials.gov NCT04720157. https://clinicaltrials.gov/ct2/show/NCT04720157 (accessed March 2021); 10. ClinicalTrials.gov. NCT03658447. https://clinicaltrials.gov/ct2/show/NCT03658447 (accessed July 2020); 11. ClinicalTrials.gov. NCT03042468. https://clinicaltrials.gov/ct2/show/NCT03042468 (accessed March 2021); 12. ClinicalTrials.gov. NCT04663997. https://clinicaltrials.gov/ct2/show/NCT04663997 (accessed March 2021); 13. Paganelli G, et al. Eur J Nucl Med. 2020;47:3008–3017; 14. ClinicalTrials.gov. NCT04689828. https://clinicaltrials.gov/ct2/show/NCT04689828 (accessed March 2021); 15. ANZCTR. ACTRN12618001073291. https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=374100 (accessed March 2021); 16. Emmett L, et al. J Clin Oncol. 2020;38(suppl 15):5557; 17. ClinicalTrials.gov. NCT03874884. https://clinicaltrials.gov/ct2/show/NCT03874884 (accessed March 2021); 18. Hofman M, et al. Lancet Oncol. 2018;19(6):825–833; 19. Violet J, et al. J Nucl Med. 2020;61(6):857–865. 1L, first line; 2L, second line; 3L, third line; ARDT, androgen receptor-directed therapy; BSoC, best standard of care; CT, computed tomography; ^{68}Ga, gallium-68; HSPC, hormone-sensitive prostate cancer; IIT, investigator-initiated trial; Lu, lutetium; mCRPC, metastatic castrate-resistant prostate cancer; mHNPC, metastatic hormone-naive prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; nmCRPC, non-metastatic castrate-resistant prostate cancer; PC, prostate cancer; PET, positron emission tomography; Ph, phase; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen.



Rationnel issu de la RTE Bystander effect
la PRRT est elle aussi « Pro inflammatoire »?



Rationnel : lésions doubles brins radio-induites
Est-ce le mécanisme lésionnel principal de la PRRT ?

Imagerie et biomarqueurs compagnons

Measurement of Circulating Cell-Free DNA in Relation to 18F-Fluorocholine PET/CT Imaging in Chemotherapy-Treated Advanced Prostate Cancer

Sandi Kwee, M.D., M.Sc.[1,2], Min-Ae Song, M.Sc.[1,3], Iona Cheng, Ph.D.[1], Lenora Loo, Ph.D.[1], and Maarit Tiirikainen, Ph.D.[1]

Clin Trans Sci 2012; Volume 5: 65–70

Conclusions: Chemotherapy is associated with significant changes in plasma cfDNA content and FCH PET/CT-detected tumor activity.
These interrelated measures are potential candidate markers of therapeutic response in HRPC.

TAKE HOME MESSAGES

^{18}F CHOLINE récidives PSA > 1

^{68}Ga PSMA plus performant pour PSA <1 et ADP

disponibilité réduite (générateur) ATUc après F choline

approche théranostique 177LuPSMA ATUc après F choline

ATTENTION AUX FX +

Adénomégalie inflammatoire

Paget

réactions dysimmunitaires (Thyroïdes, poumons, etc)

De nouveaux sanctuaires de la maladie Métastatique

La PSMA thérapie arrive ….. Il faut s'organiser !!

En cas de remboursement 22154 cycles/ an en France (8x 177LuDOTATATE ;TNE)

FORMATION DES MED NUCL
RESEAU DE SOIN
MULTIDISCIPLINARITE
RCP

Merci