Développement et place du ^{177}Lu PSMA dans le cancer de prostate avancé

10 février 2022

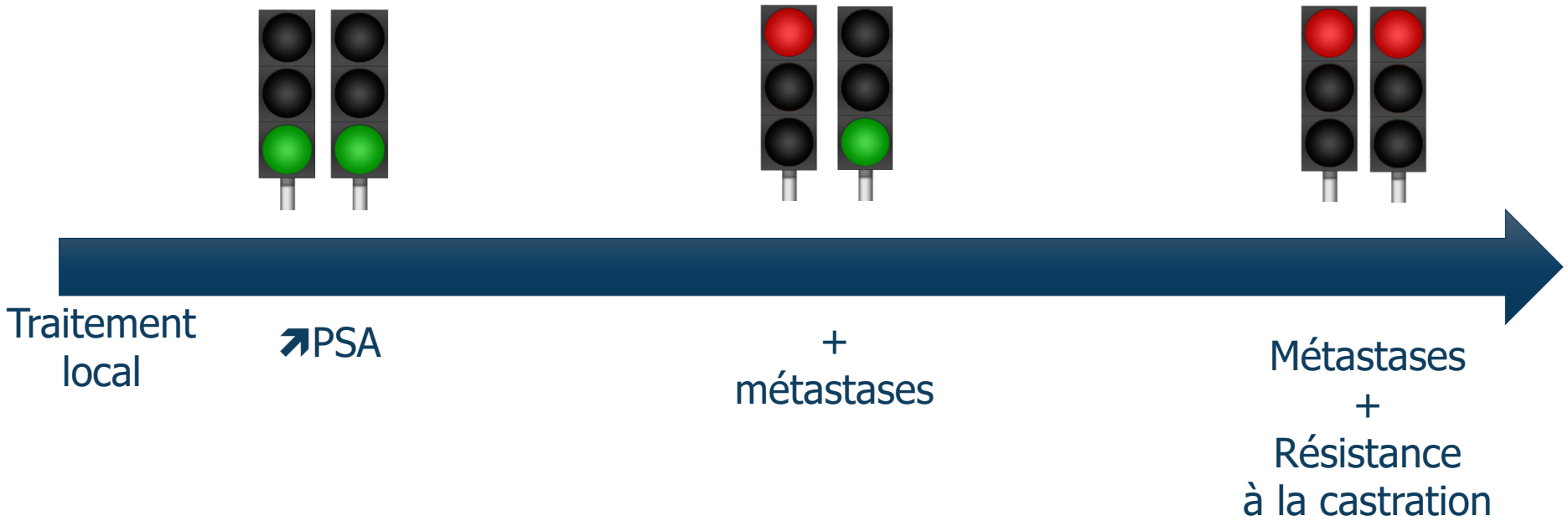
Bordeaux

Guilhem ROUBAUD

UPDATE EN MÉDECINE NUCLÉAIRE

RADIOTHÉRAPIE INTERNE VECTORISÉE ET THÉRANOSTIQUE

Evolution la plus classique



Avant 2004

CP hormono résistant

Il n’y avait que l’hormonothérapie par castration chimique ou chirurgicale

2004 -> le docétaxel

2004
docétaxel[13,14]
↑survie globale!

13- Tannock NEJM 2004; 14- Petrylak NEJM 2004

2010 – 2012 -> l'optimisation POST docétaxel

2004
docétaxel[13,14]
↑SG

2010 – 2012
cabazitaxel[15]
abiratérone[16]
enzalutamide[17]
↑SG

13- Tannock NEJM 2004; 14- Petrylak NEJM 2004; 15- de Bono Lancet 2010; 16- de Bono NEJM 2011; 17- Scher HI NEJM 2012

2013-2014 -> l'optimisation PRE docétaxel

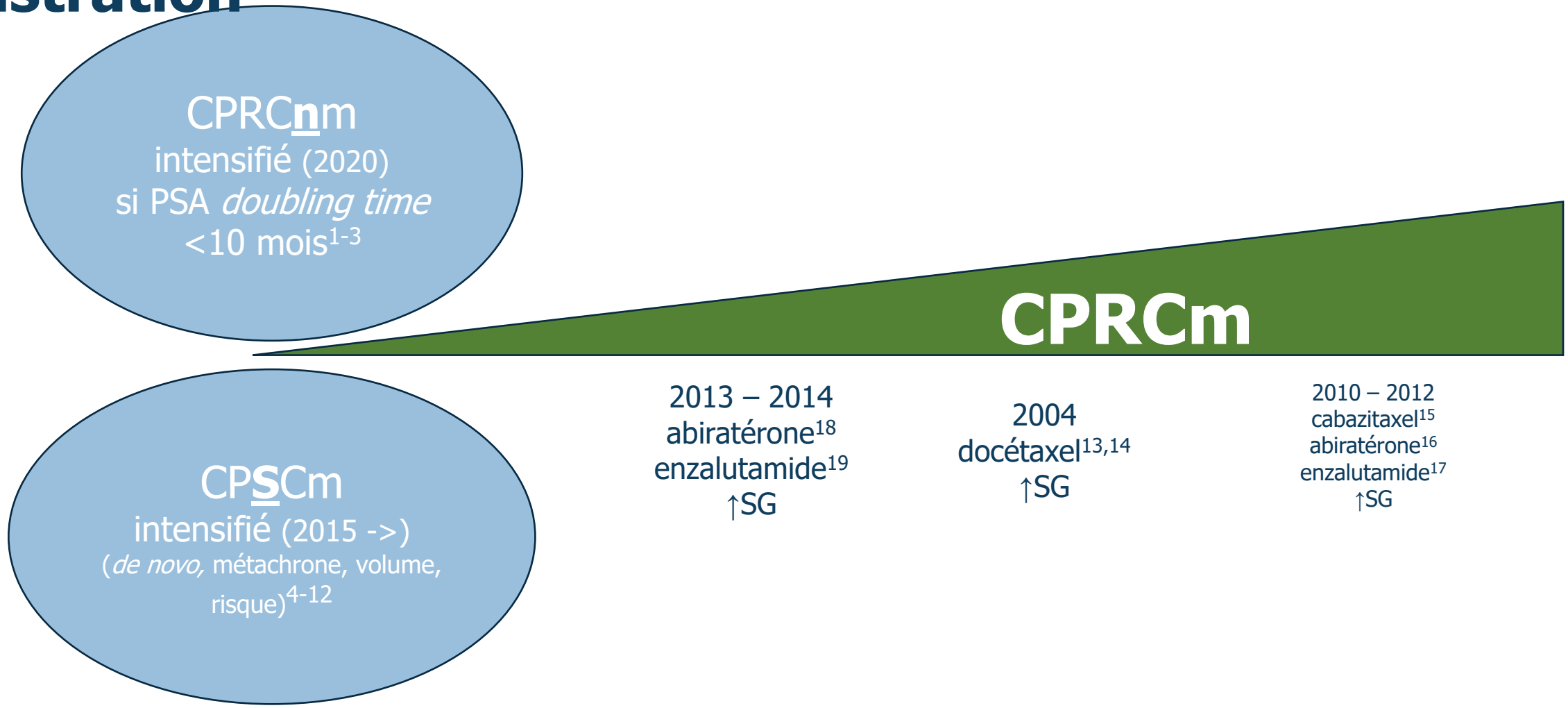
2010 – 2012
cabazitaxel[15]
abiratérone[16]
enzalutamide[17]
↑SG

2004
docétaxel[13,14]
↑SG

2013 – 2014
abiratérone[18]
enzalutamide[19]
↑SG

13- Tannock NEJM 2004; 14- Petrylak NEJM 2004; 15- de Bono Lancet 2010; 16- de Bono NEJM 2011; 17- Scher HI NEJM 2012; 18- Ryan CJ NEJM 2013; 19- Beer TM NEJM 2014

2015 – 2021 : optimisation avant résistance à la castration



1- Sternberg NEJM 2020; 2- Smith MR Eur Urol 2021; 3- Fizazi NEJM 2020; 4- Sweeney NEJM 2015; 5- Kyriakopoulos J Clin Oncol 2018; 6- James ND Lancet 2016; 7- Clarke NW Ann Oncol 2019; 8- Fizazi Lancet 2019; 9- James ND abs 6110 ESMO 2020; 10- Davis NEJM 2019; 11- Chi KN NEJM 2019; 12- Aggarwal N J Clin Oncol 2021; 13- Tannock NEJM 2004; 14- Petrylak NEJM 2004; 15- de Bono Lancet 2010; 16- de Bono NEJM 2011; 17- Scher HI NEJM 2012; 18- Ryan CJ NEJM 2013; 19- Beer TM NEJM 2014

2019 – 2021 -> optimisation séquence ; arrivée médecine de précision

CPRC**n**m
intensifié (2020)
si PSA *doubling time*
<10 mois[1-3]

CP**S**Cm
intensifié (2015 ->)
(*de novo,* métachrone, volume, risque)[4-12]

CPRCm

2013 – 2014
abiratérone[18]
enzalutamide[19]
↑SG

2004
docétaxel[13,14]
↑SG

2010 – 2012
cabazitaxel[15]
abiratérone[16]
enzalutamide[17]
↑SG

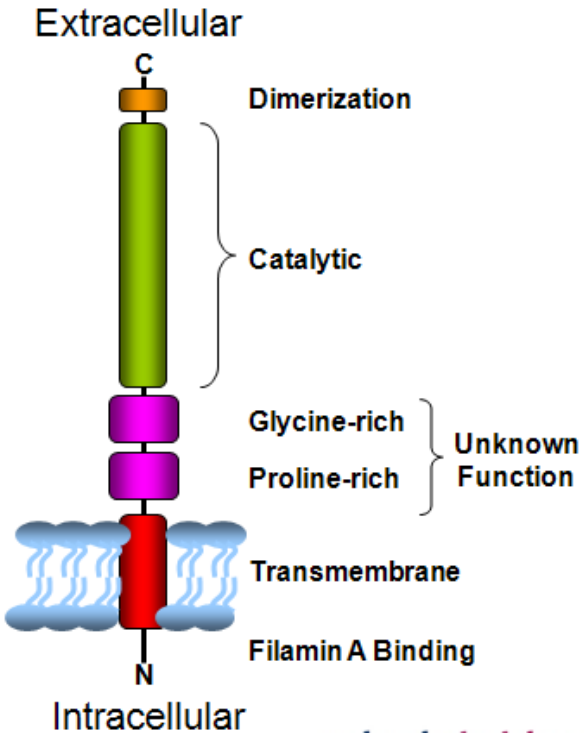
2019
cabazitaxel 3ème ligne (Se NHT<12 mois)[20]

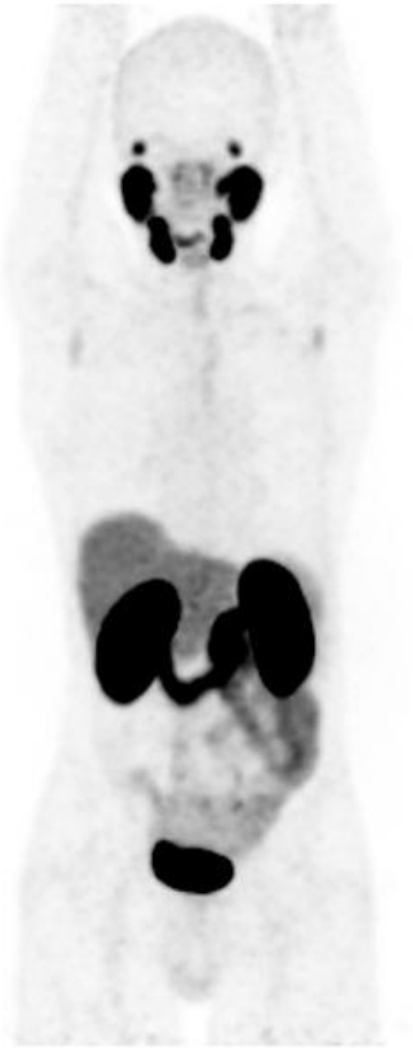
2020
olaparib (Δ *BRCA1,2)*[21]

2021
Lu-PSMA (+/-NHT)[22]

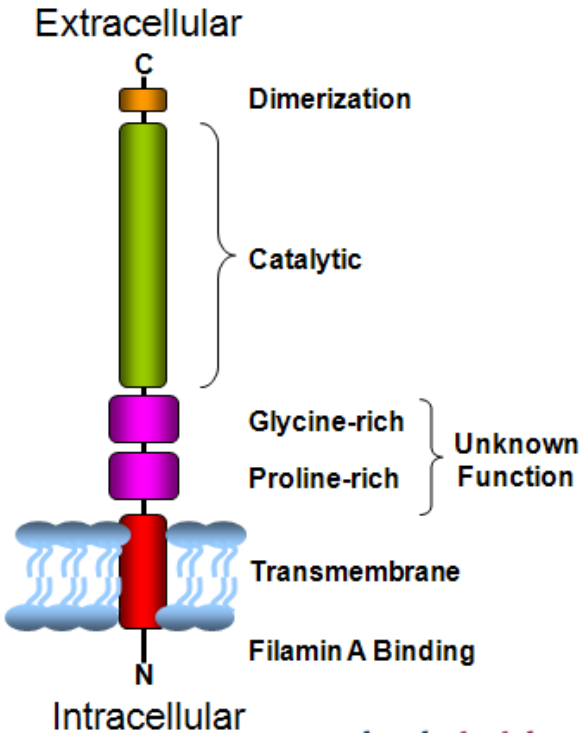
1- Sternberg NEJM 2020; 2- Smith MR Eur Urol 2021; 3- Fizazi NEJM 2020; 4- Sweeney NEJM 2015; 5- Kyriakopoulos J Clin Oncol 2018; 6- James ND Lancet 2016; 7- Clarke NW Ann Oncol 2019; 8- Fizazi Lancet 2019; 9- James ND abs 6110 ESMO 2020; 10- Davis NEJM 2019; 11- Chi KN NEJM 2019; 12- Aggarwal N J Clin Oncol 2021; 13- Tannock NEJM 2004; 14- Petrylak NEJM 2004; 15- de Bono Lancet 2010; 16- de Bono NEJM 2011; 17- Scher HI NEJM 2012; 18- Ryan CJ NEJM 2013; 19- Beer TM NEJM 2014; 20- de Wit NEJM 2019; 21- de Bono JS NEJM 2020; 22- Sartor O NEJM 2021

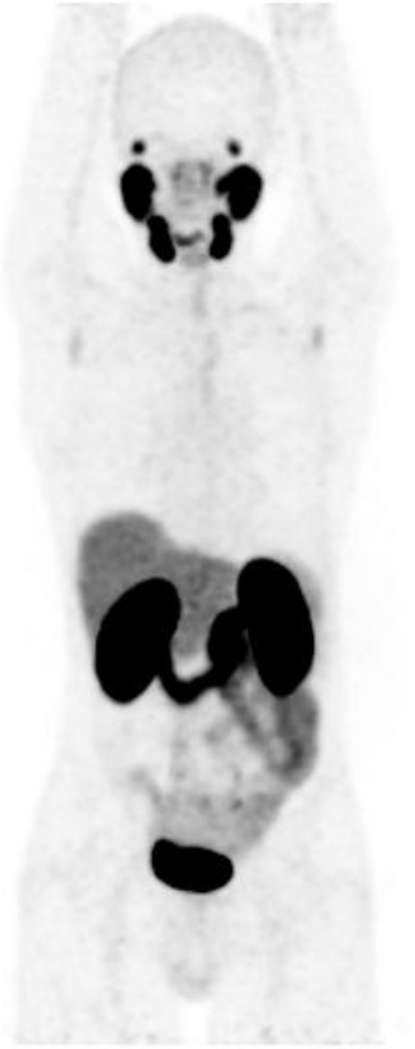
PSMA = Ag de membrane

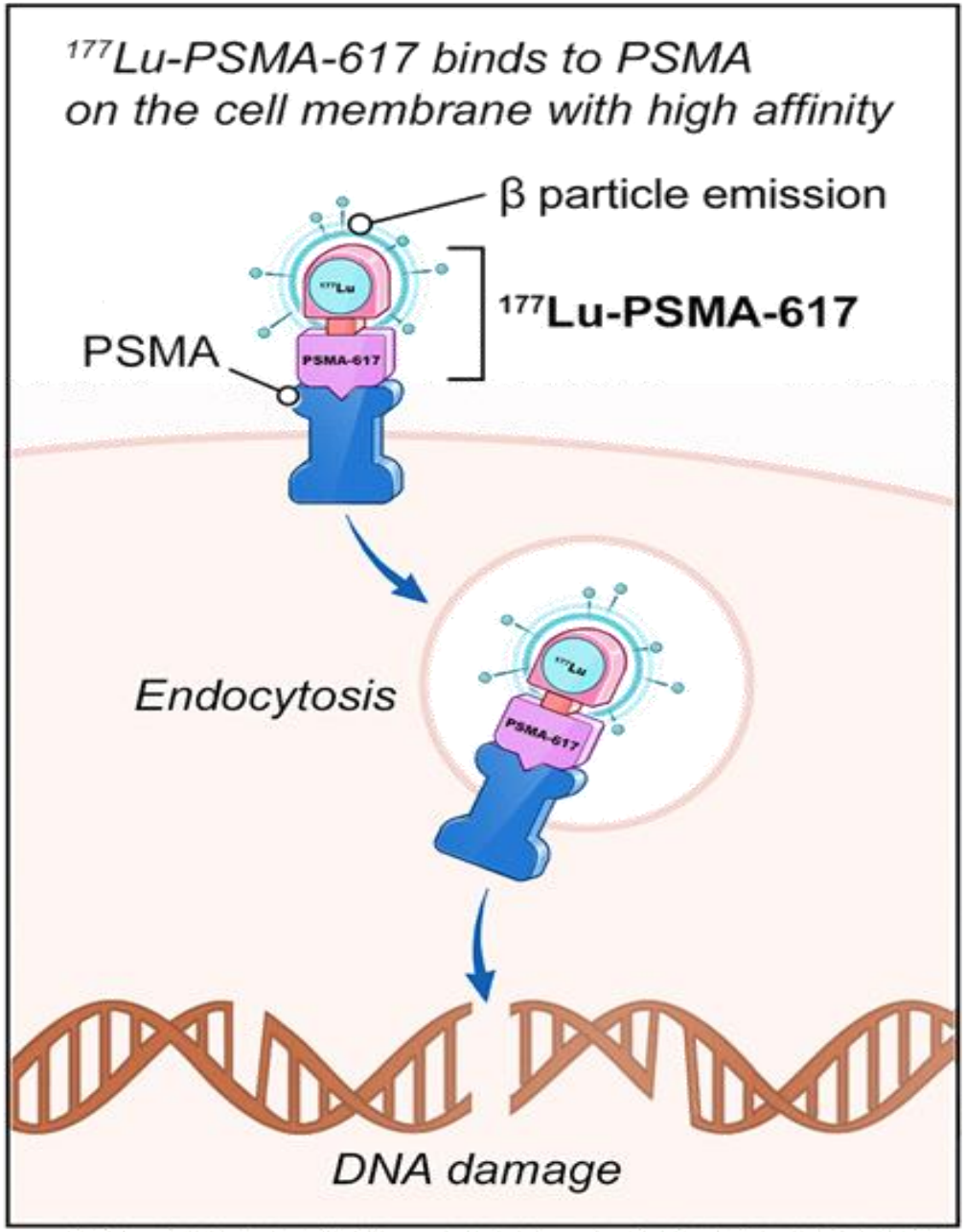




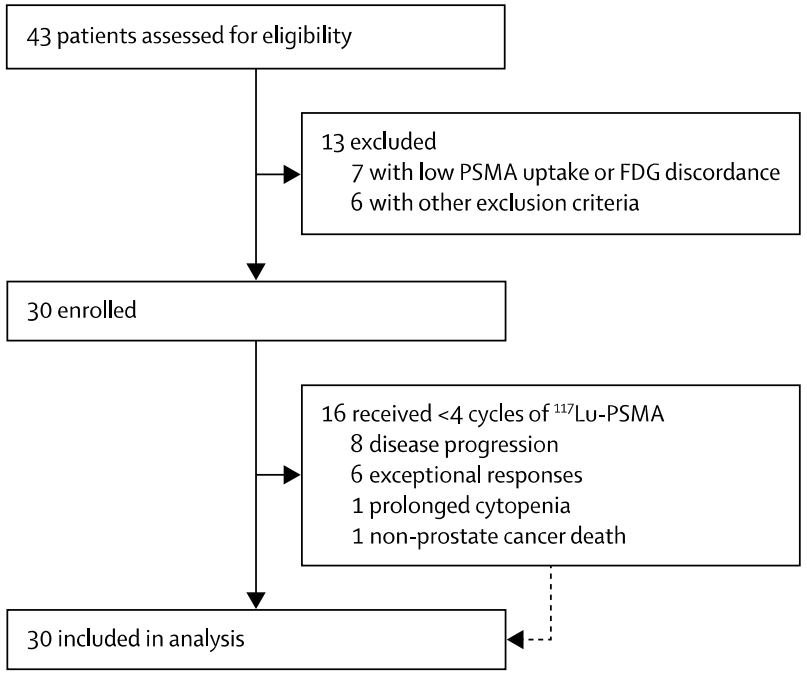
Radiothérapie interne vectorisée (RIV)

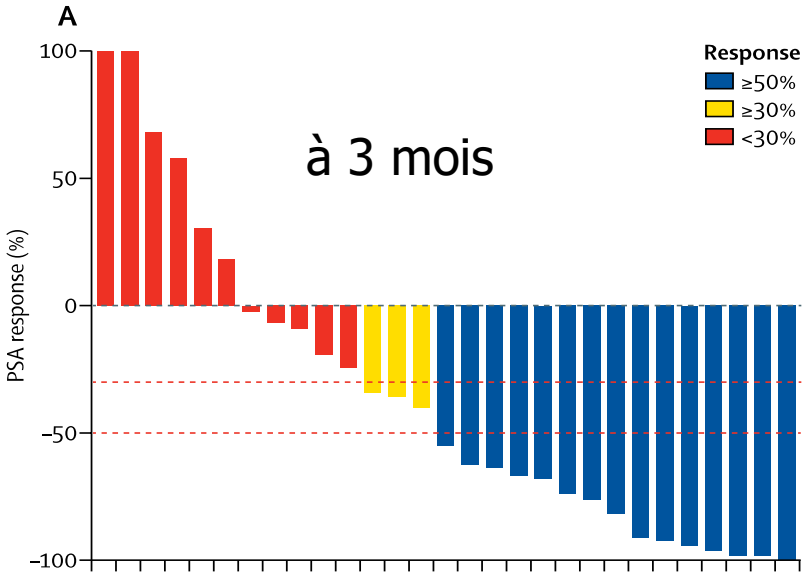


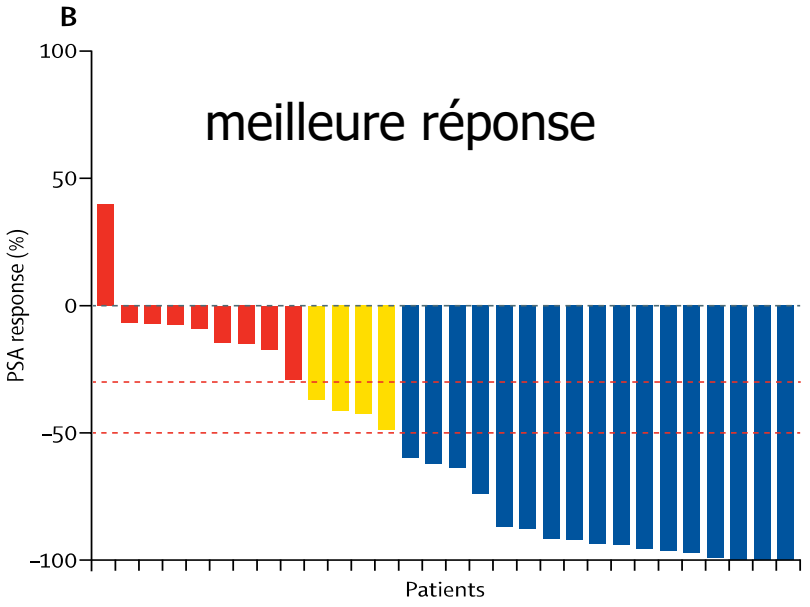




^{177}Lu PSMA-617 phase II





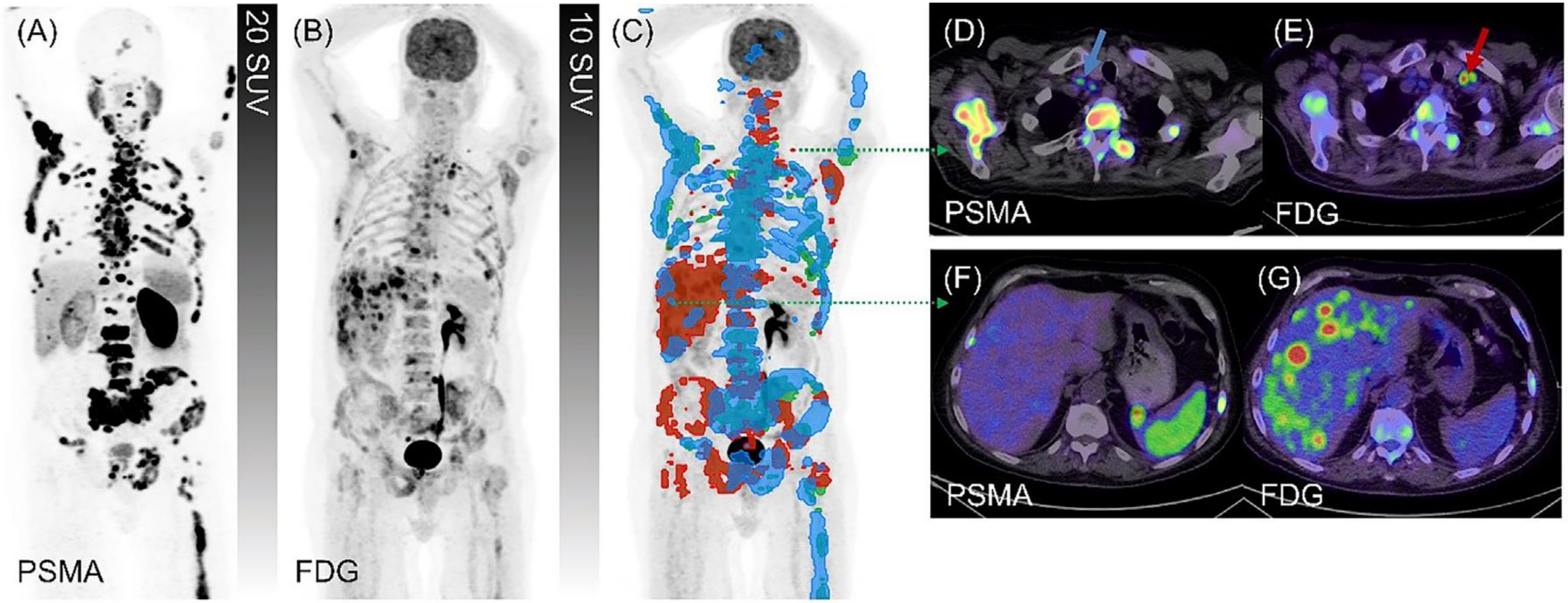


Toxicité

Cytopénie
Nausée
Asthénie
Xerostomie
Néphropathie

Hofman Lancet Oncol 2018; Violet J J Nuc Med 2019

TEP FDG et ^{68}Ga TEP PSMA



Thang Eur Urol Oncol 2019

TheraP LuPSMA vs caba phase II

KEY ELIGIBILITY

- mCRPC post docetaxel suitable for cabazitaxel
- Progressive disease with rising PSA and PSA ≥ 20 ng/mL

^{68}Ga-PSMA + ^{18}F-FDG PET/CT

- PSMA SUVmax > 20 at any site
- Measurable sites SUVmax > 10
- **No FDG positive/PSMA negative sites of disease**
- Centrally reviewed

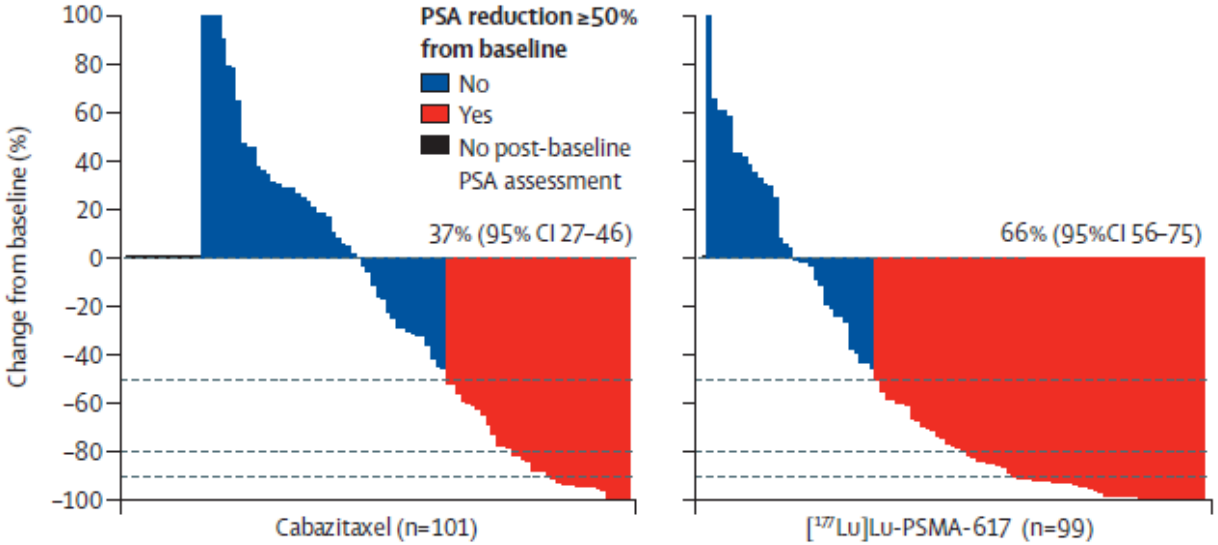
R

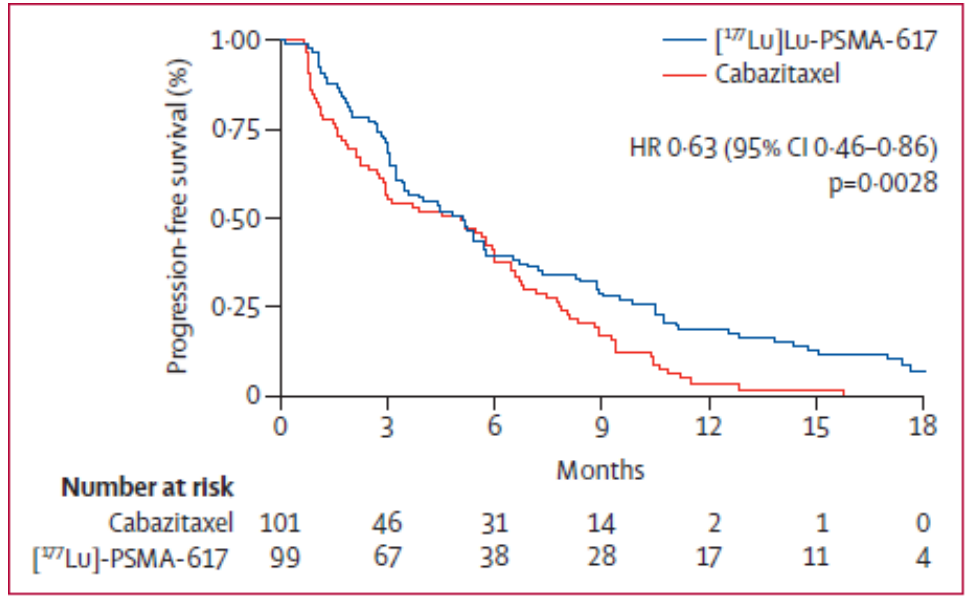
^{177}Lu-PSMA-617
8.5 GBq IV q6 weekly
↓ 0.5GBq each cycle
Up to 6 cycles

200 men 1:1 randomisation
11 sites in Australia
Stratified by:

- Disease burden (>20 sites vs ≤ 20 sites)
- Prior enzalutamide or abiraterone
- Study site

CABAZITAXEL
20mg/m^2 IV q3 weekly,
Up to 10 cycles





rPFS (0·64 [0·46–0·88]; p=0·0070)

Toxicité Gr 3-4 : caba 56% vs 36%

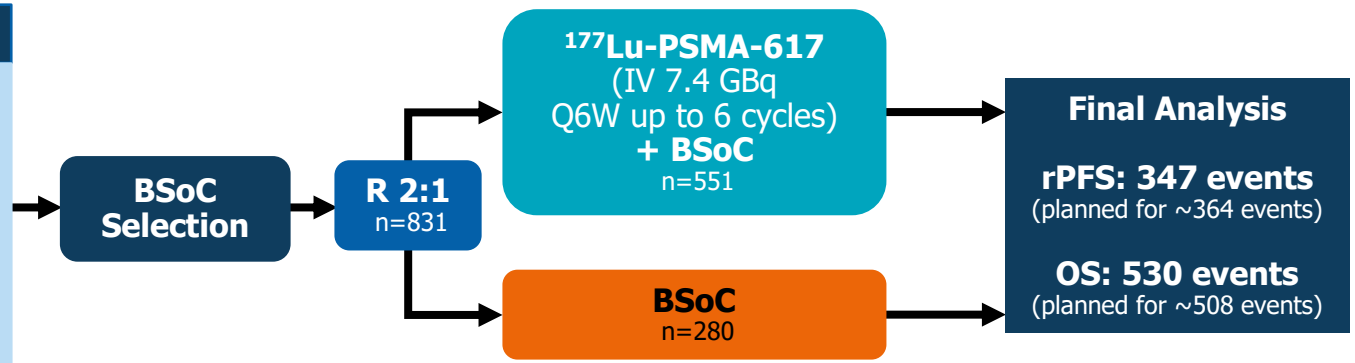
Hofman Lancet Oncol 2021

VISION

Schéma d'étude

Population

- Progressive[a] mCRPC
- PSMA-positive with ^{68}Ga-PSMA-11 PET/CT scan Previous taxane (≤2 regimens) therapy and previous ARPI (≥1 regimen)
- ECOG PS 0–2
- Life expectancy >6 months



Treated until radiographic progression, unacceptable toxicity, lack of clinical benefit, or requirement for a prohibited treatment

Alternate Primary Endpoints

- **rPFS (per PCWG3)**
- **OS**

Key Secondary Endpoints (with α control)

- RECIST v1.1 response: ORR and DCR
- Time to first SSE

Stratification Factors

- Serum LDH (≤ 260 IU/L vs >260 IU/L)
- Presence of liver metastases (yes vs no)
- ECOG PS (0–1 vs 2)
- Inclusion of ARPI in BSoC (yes vs no) at time of randomization

Additional Secondary Endpoints

- Safety and tolerability
- HRQoL: EQ-5D-5L, FACT-P and BPI-SF
- Health economics
- Composite PFS (radiological, clinical or PSA progression)
- Biochemical response: PSA, ALP and LDH levels

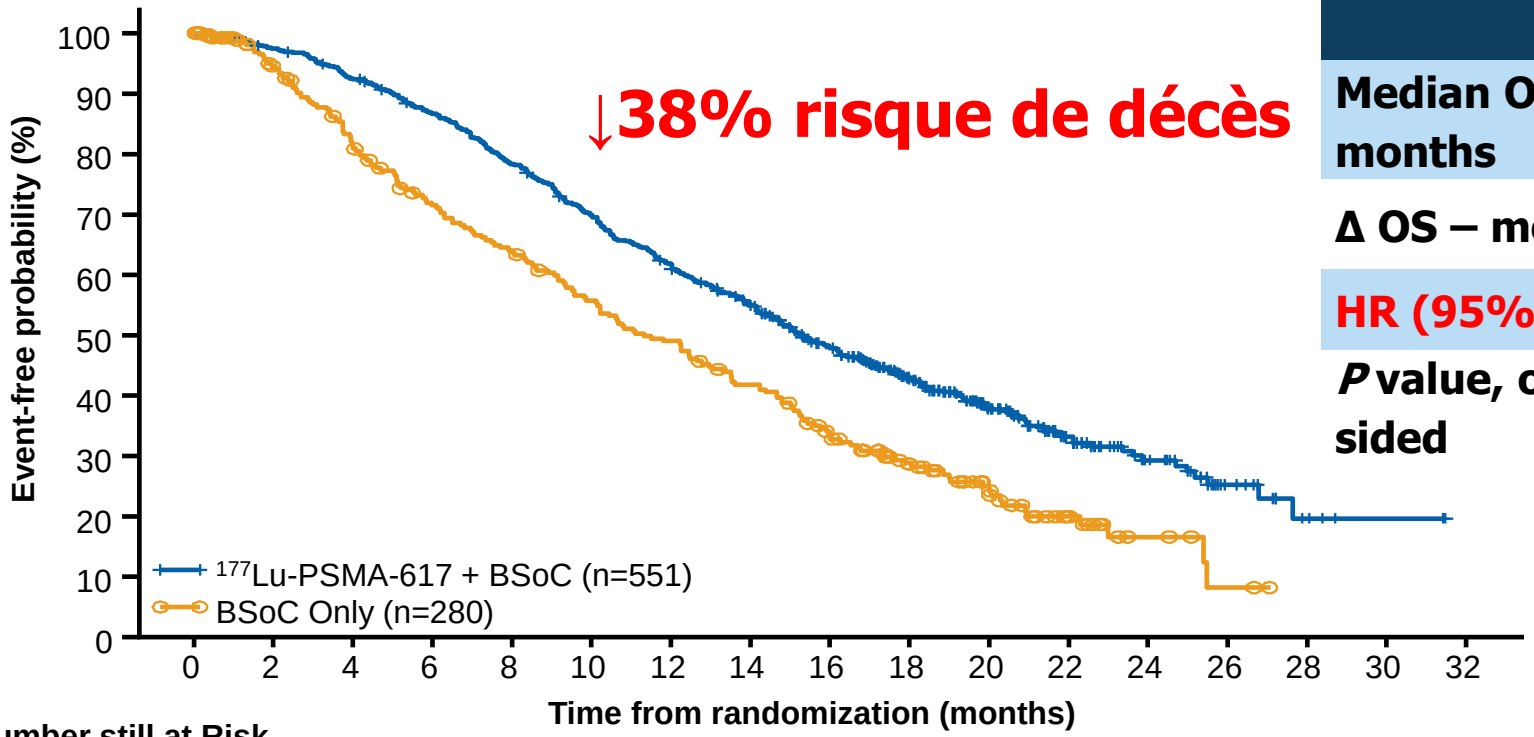
Sartor O *et al.* N Engl J Med 2021

Caractéristiques population

Disposition	OS Analysis Set (n=831)		rPFS Analysis Set (n=581)	
	^{177}Lu-PSMA-617 + BSoC (n=551) – n (%)	BSoC only (n=280) – n (%)	^{177}Lu-PSMA-617 + BSoC (n=385) – n (%)	BSoC only (n=196) – n (%)
Age (years)				
Median (range)	70.0 (48–94)	71.5 (40–89)	71.0 (52–94)	72.0 (51–89)
Race[a] – n (%)				
White	486 (88.2)	235 (83.9)	336 (87.3)	166 (84.7)
Black or African American	34 (6.2)	21 (7.5)	29 (7.5)	14 (7.1)
Asian	9 (1.6)	11 (3.9)	6 (1.6)	9 (4.6)
ECOG Performance Status[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 of disease – n (%)				
Lung	49 (8.9)	28 (10.0)	35 (9.1)	20 (10.2)
Liver	63 (11.4)	38 (13.6)	47 (12.2)	26 (13.3)
Lymph node	274 (49.7)	141 (50.4)	193 (50.1)	99 (50.5)
Bone	504 (91.5)	256 (91.4)	351 (91.2)	179 (91.3)

Sartor O N Engl J Med 2021

Résultat -> survie globale



Number still at Risk

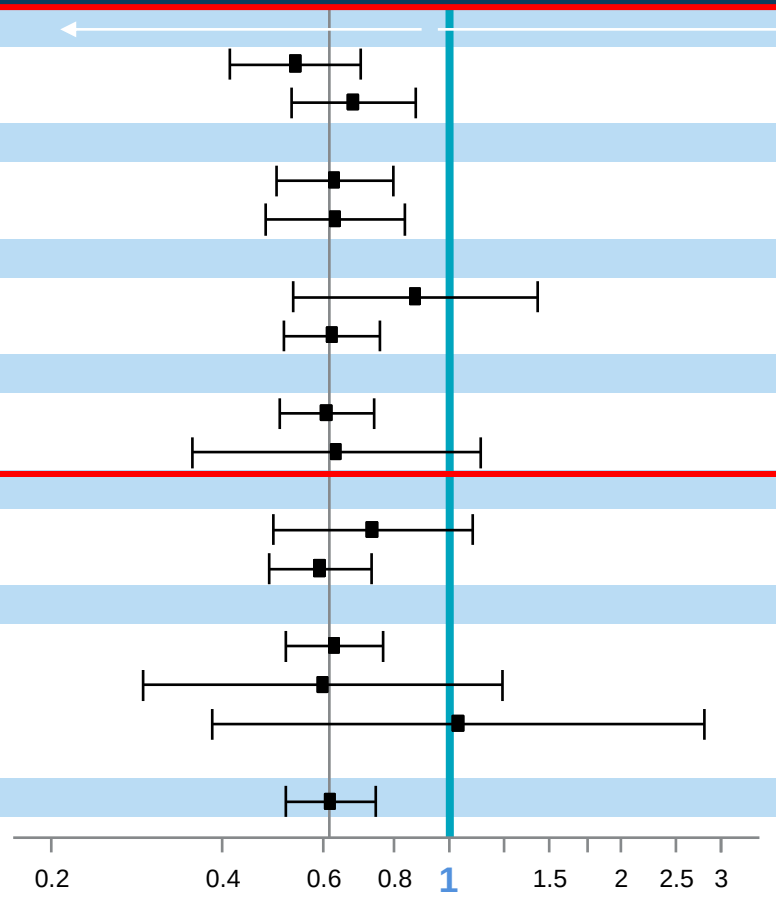
^{177}Lu-PSMA-617 + BSoC	551	535	506	470	425	377	332	289	236	166	112	63	36	15	5	2	0
BSoC Only	280	238	203	173	155	133	117	98	73	51	33	16	6	2	0	0	0

	^{177}Lu-PSMA-617 + BSoC (n=551)	BSoC only (n=280)
Median OS – months	15.3	11.3
Δ OS – months	4.0	
HR (95% CI)	0.62 (0.52–0.74)	
P value, one-sided	<0.001	

SG significativement prolongée dans le bras ^{177}Lu-PSMA-617 + meilleur traitement standard *versus* meilleur traitement standard seul

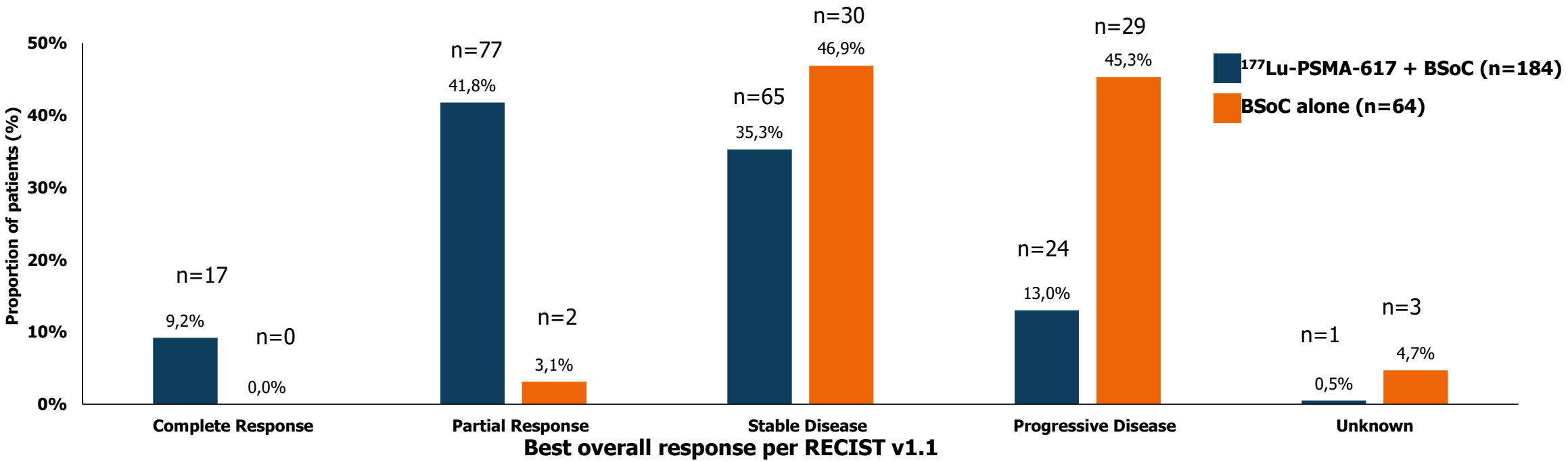
Analyse sous-groupes (facteurs de stratification) sur survie globale

Subgroup	OS Analysis Set (n=831)		Hazard Ratio (95% CI)
	^{177}Lu-PSMA-617 + BSoC (n=551) – n/N (%)	BSoC only (n=280) – n/N (%)	
ARPI as part of assigned BSoC			
Yes	135/243 (55.6)	96/146 (65.8)	0.54 (0.41–0.70)
No	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)
Presence of Liver Metastases			
Yes	40/48 (83.3)	28/34 (82.4)	0.87 (0.53–1.43)
No	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)
Age			
<65 years	82/145 (56.6)	38/60 (63.3)	0.73 (0.49–1.10)
≥65 years	261/406 (64.3)	149/220 (67.7)	0.59 (0.48–0.73)
Race			
White	300/486 (61.7)	159/235 (67.7)	0.63 (0.52–0.77)
African American or Black	20/34 (58.8)	12/21 (57.1)	0.60 (0.29–1.24)
Asian	9/9 (100)	7/11 (63.6)	1.04 (0.38–2.81)
All Patients	**343/ 551 (62.3)**	**187/ 280 (66.8)**	**0.62 (0.52–0.74)**



^{177}Lu-PSMA-617 is an investigational agent and is not approved for any use.
Figure presented with permission from M. Morris.
Data displayed as the number of events (n) / the number of patients in treatment arm (N). Red line shows no effect point, and (new) bold line shows overall treatment effect point. Subgroup classes with at least 10 patients are presented.
ARPI, androgen receptor pathway inhibitor; BSoC, best standard of care; ECOG PS, Eastern Cooperative Oncology Group Performance Score; LDH, Lactate dehydrogenase
Morris M, et al. Oral presentation at the 2021 ASCO Annual Meeting; June 6, 2021; Abstract LBA4

Résultats -> taux de réponse objective (RO) selon RECIST v1.1
(patients avec maladie mesurable)



Taux de RO : 51,1% bras expérimental *versus* 3,1% bras standard (two-sided *P*<0.001)
Taux de contrôle de la maladie : 86,4% *versus* 50,0% (two-sided *P*<0.001)

Temps jusqu'à 1er événement osseux symptomatique

	^{177}Lu-PSMA-617 + BSoC (n=385)	BSoC only (n=196)
Median time to first SSE – months (95% CI)	11.5 (10.3–13.2)	6.8 (5.2–8.5)
Δ time to first SSE – months	4.7	
HR (95% CI)	0.50 (0.40–0.62)	
***P* value, two-sided**	<0.001	

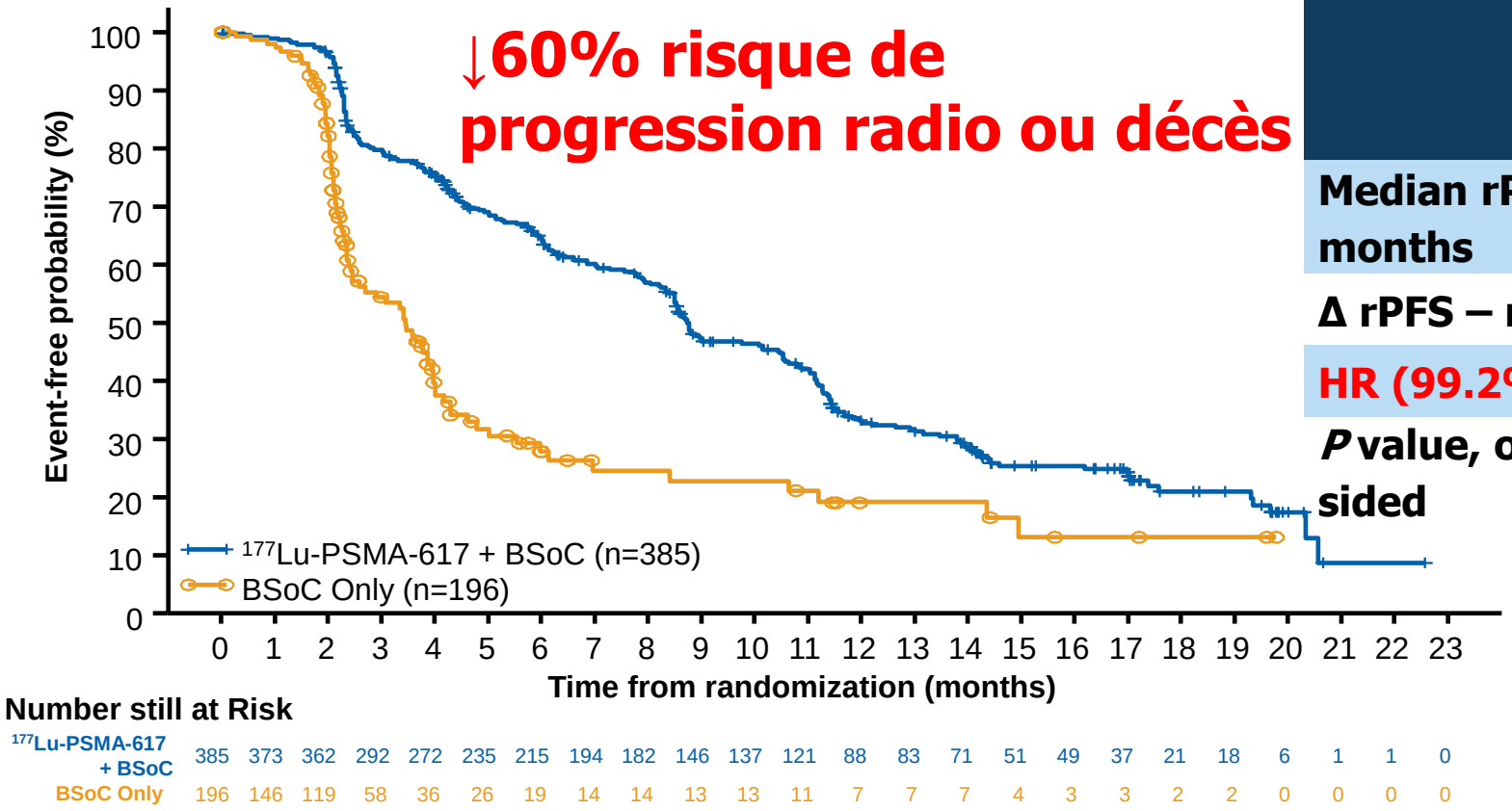
Le délai de survenue du premier événement osseux symptomatique était significativement plus long dans le bras ^{177}Lu-PSMA-617 + meilleur traitement standard vs le bras meilleur traitement standard seul (HR 0.50; 95% CI 0.40–0.62); *P*<0.001)

Toxicité

Patients with TEAE events in safety topic of special interest[a]	All Grades		Grade 3–5[b]	
	^{177}Lu-PSMA-617 + BSoC (n=529)	BSoC only (n=205)	^{177}Lu-PSMA-617 + BSoC (n=529)	BSoC only (n=205)
Fatigue – n (%)	260 (49.1)	60 (29.3)	37 (7.0)	5 (2.4)
Bone marrow suppression – n (%)	251 (47.4)	36 (17.6)	124 (23.4)	14 (6.8)
Leukopenia	66 (12.5)	4 (2.0)	13 (2.5)	1 (0.5)
Lymphopenia	75 (14.2)	8 (3.9)	41 (7.8)	1 (0.5)
Anemia	168 (31.8)	27 (13.2)	68 (12.9)	10 (4.9)
Thrombocytopenia	91 (17.2)	9 (4.4)	42 (7.9)	2 (1.0)
Dry mouth – n (%)	208 (39.3)	2 (1.0)	0 (0.0)	0 (0.0)
Nausea and vomiting – n (%)	208 (39.3)	35 (17.1)	8 (1.5)	1 (0.5)
Renal effects – n (%)	46 (8.7)	12 (5.9)	18 (3.4)	6 (2.9)
Second primary malignancies – n (%)	11 (2.1)	2 (1.0)	4 (0.8)	1 (0.5)
Intracranial hemorrhage – n (%)	7 (1.3)	3 (1.5)	5 (0.9)	2 (1.0)

Fatigue, myélosuppression, sécheresse buccale, nausées/vomissements bras expérimental > bras standard
EIs grade 3-5 faibles dans les deux bras
Pas d'événement indésirable inattendu

Résultats -> survie sans progression radiologique



Number still at Risk

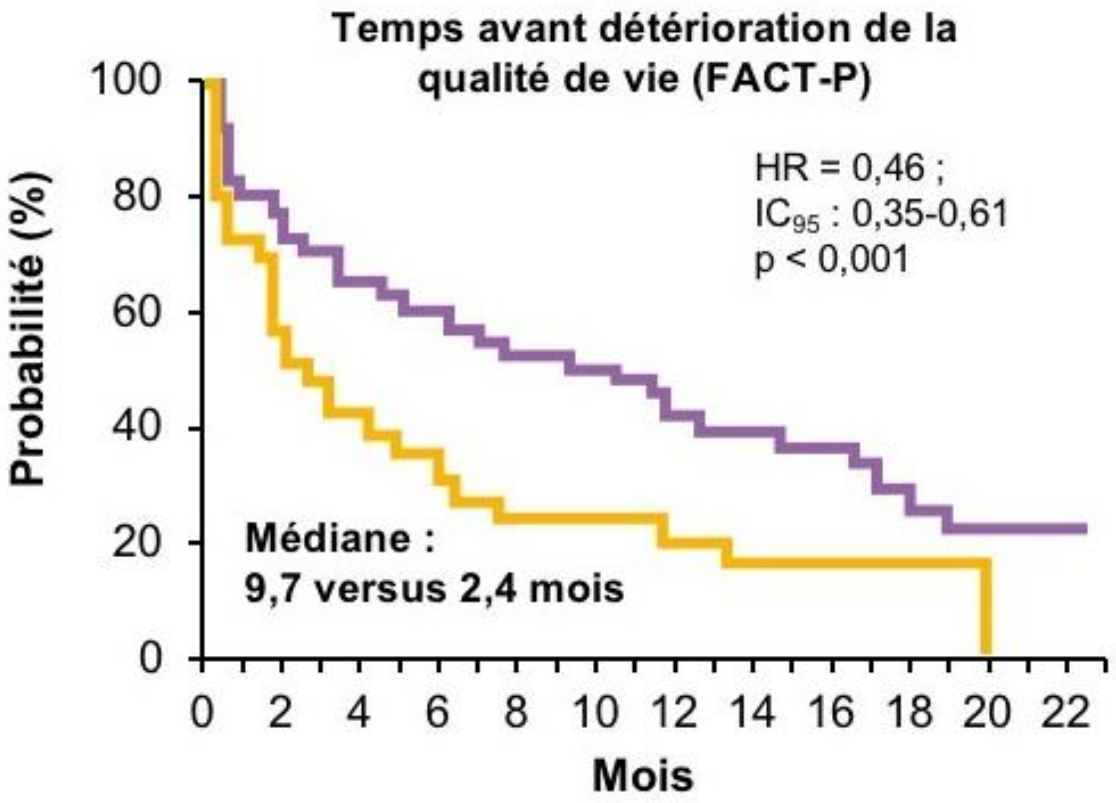
^{177}Lu-PSMA-617 + BSoC	385	373	362	292	272	235	215	194	182	146	137	121	88	83	71	51	49	37	21	18	6	1	1	0
BSoC Only	196	146	119	58	36	26	19	14	14	13	13	11	7	7	7	4	3	3	2	2	0	0	0	0

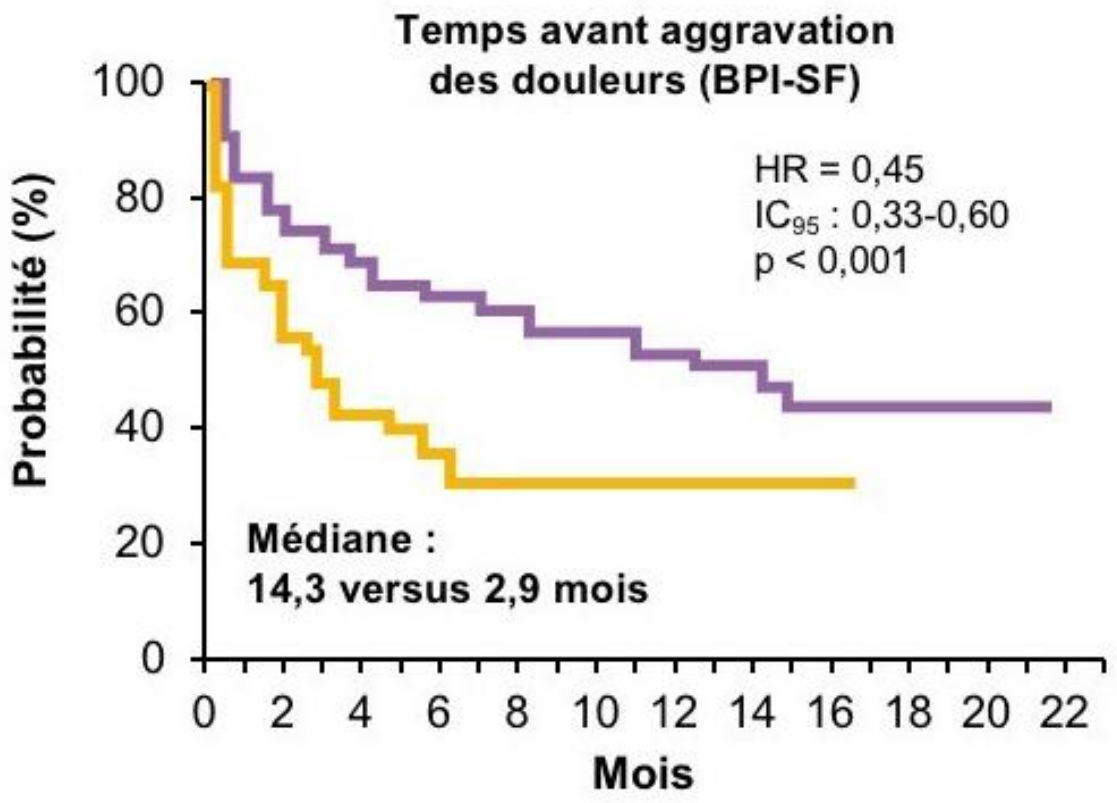
	^{177}Lu-PSMA-617 + BSoC (n=385)	BSoC only (n=196)
Median rPFS – months	8.7	3.4
Δ rPFS – months	5.3	
HR (99.2% CI)	**0.40 (0.29–0.57)**	
***P* value, one-sided**	<0.001	

SSPr significativement prolongée dans le bras ^{177}Lu-PSMA-617 + meilleur traitement standard *versus* meilleur traitement standard seul

VISION

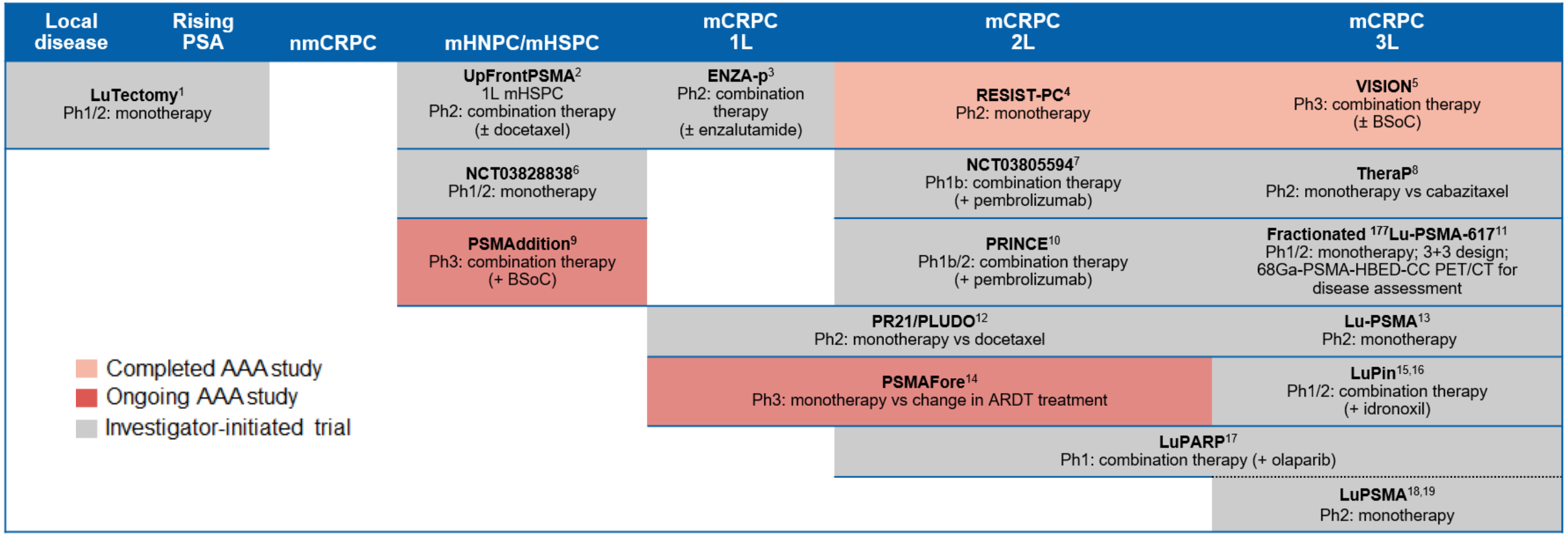
Données rapportées par les patients (n=581) ; objectifs secondaires





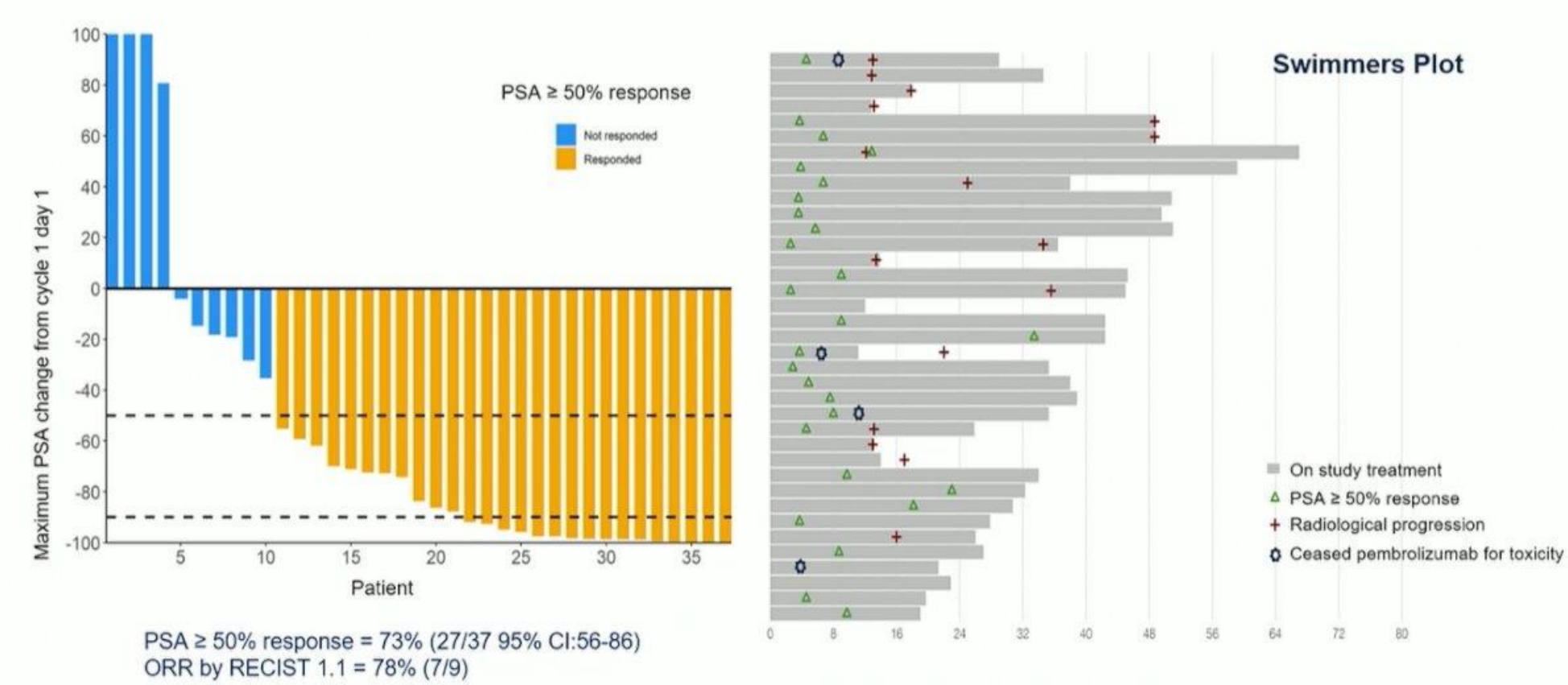
Fizazi K *et al.* Abs 576 M0 ESMO 2021

Développement du [^{177}Lu]Lu-PSMA-617



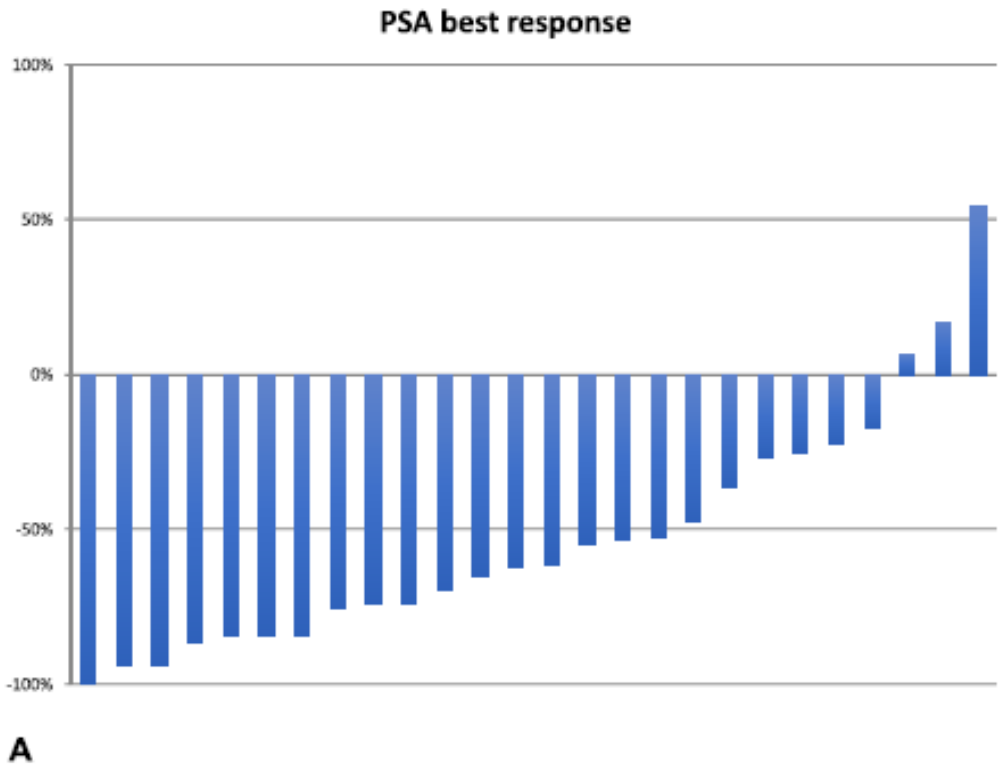
1. NCT04430192; 2. NCT04343885; 3. NCT04419402; 4. NCT03042312; 5. NCT03511664; 6. NCT03828838; 7. NCT03805594; 8. NCT03392428; 9. NCT04720157; 10. NCT03658447; Sandu S ESMO 2021; 11. NCT03042468; 12. NCT04663997; 13. Paganelli G, et al. Eur J Nucl Med. 2020;47:3008–3017; 14. NCT04689828; 15. ANZCTR. ACTRN12618001073291; 16. Emmett L, et al. J Clin Oncol. 2020;38(suppl 15):5557; 17. NCT03874884; 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.

Analyse intermédiaire PRINCE



Sandu S ESMO 2021

Ac-225 PSMA (actinium = émetteur α)



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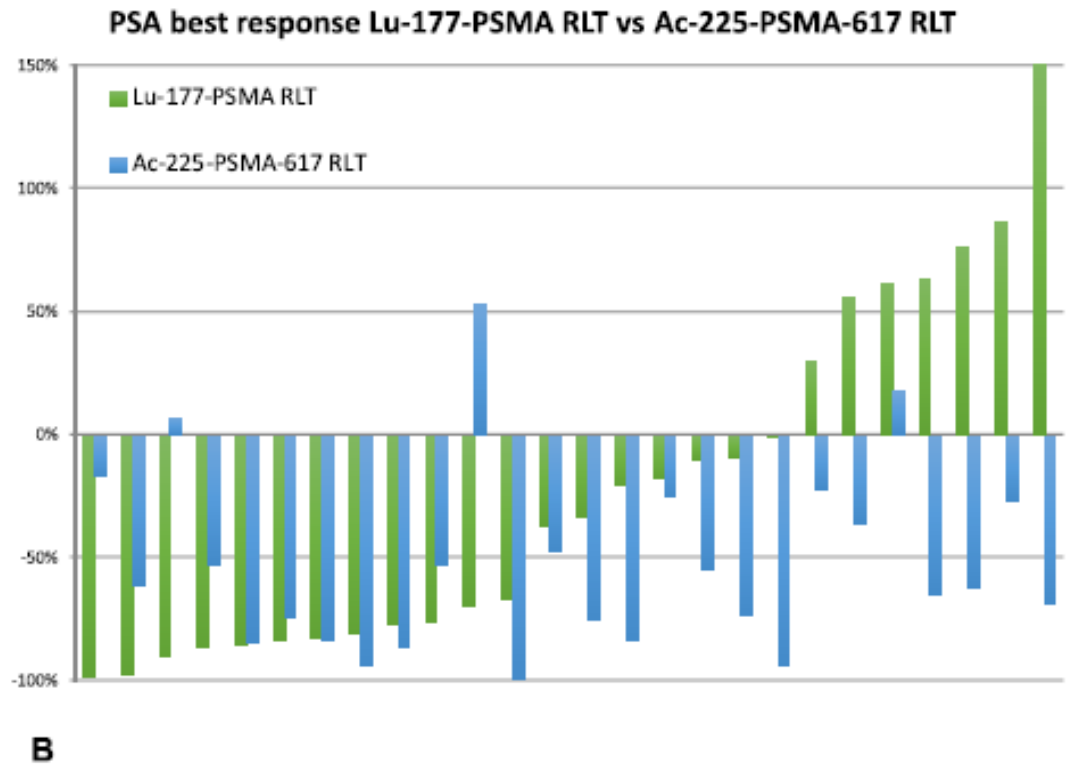

B

Feuerecker Eur Urol 2020

Conclusion

- ^{177}LuPSMA chez patients avec CPRCm
  - Améliore la survie globale et sans progression radiologique
  - Maintien la QdV et allonge le temps jusqu'à 1er événement osseux symptomatique
  - Améliore le taux de RO
  - Bien toléré (nausée, xerostomie, toxicité hématologique)

- Perspectives
  - Utilisation plus précoce
  - En association
  - Actinium


MERCI
www.onco-nouvelle-aquitaine.fr