Radiothérapie Interne Vectorisée par Lu-PSMA

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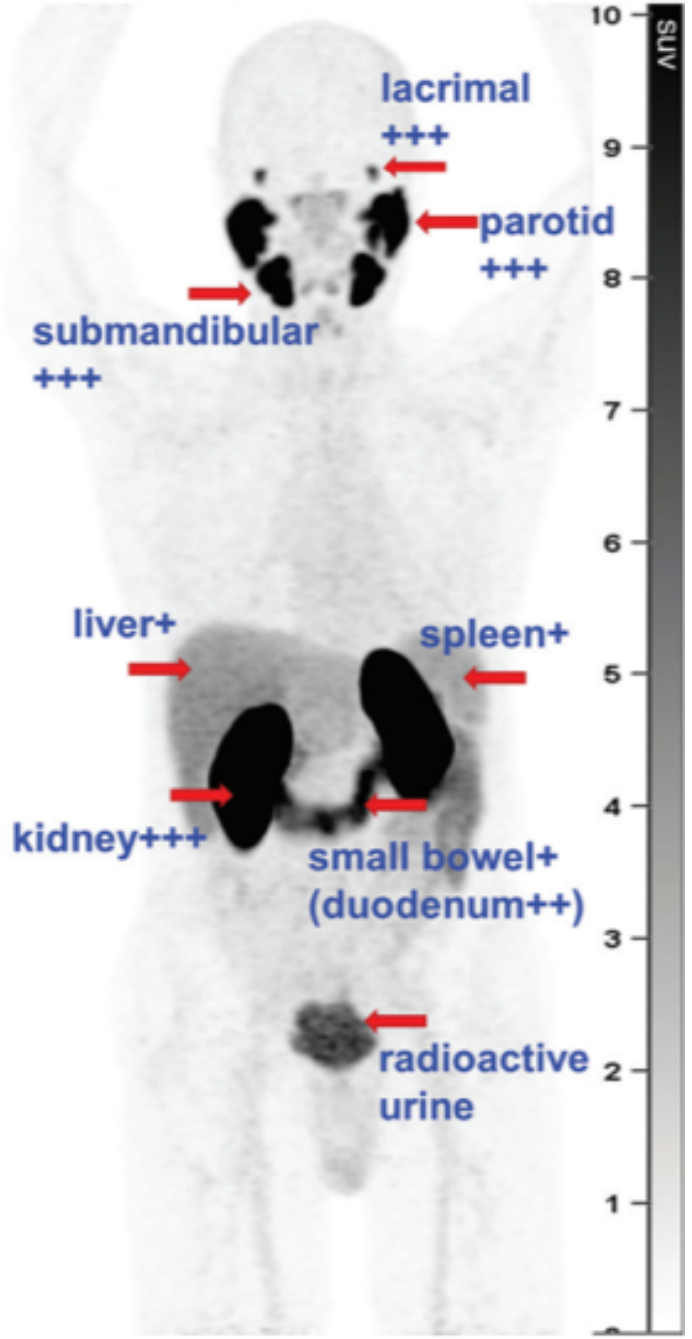
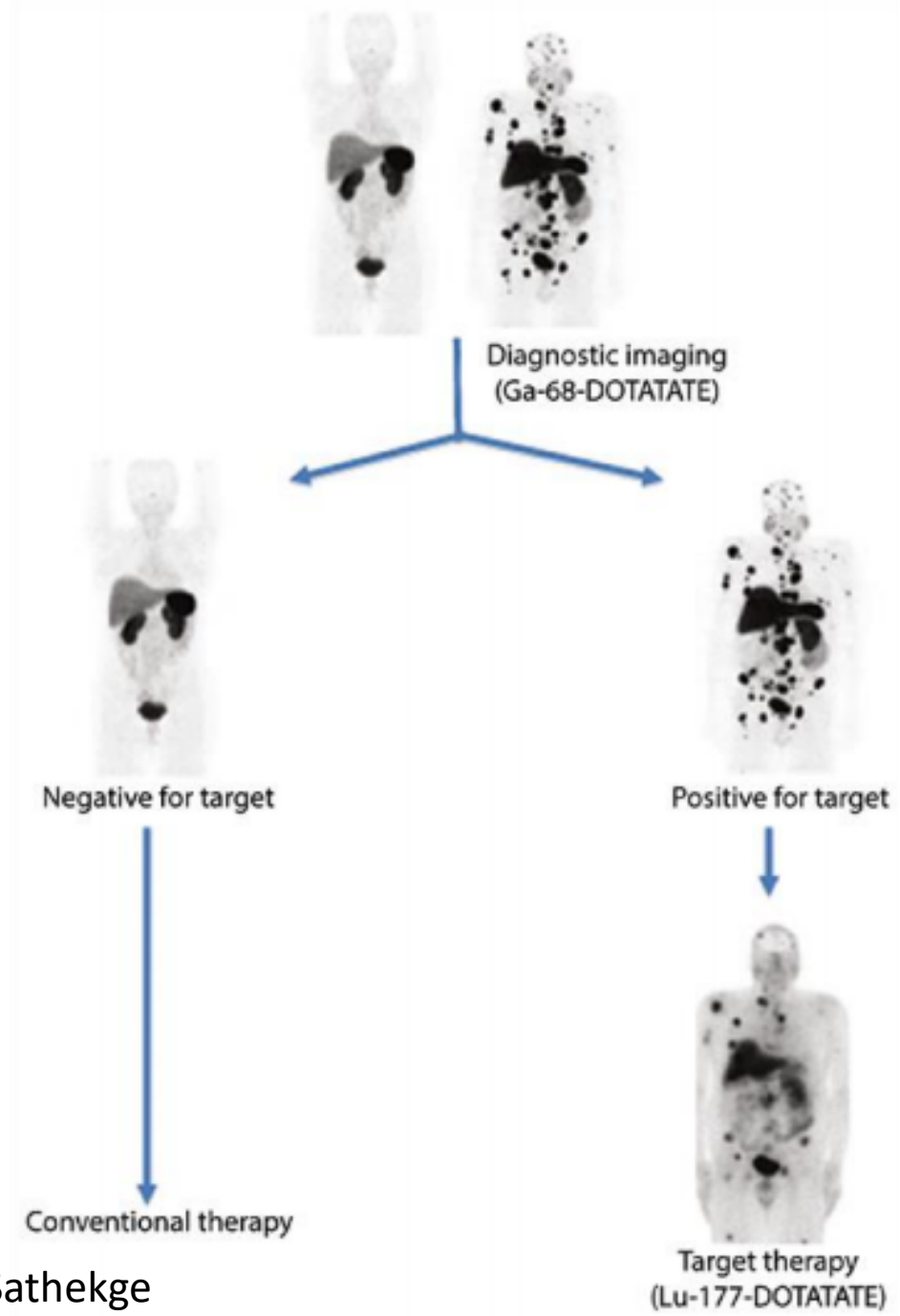
PSMA

- ✓Protéine transmembranaire avec internalisation du radiopharmaceutique
- ✓Biodistribution notamment salivaire et rénale
- ✓Expression forte en cas de tumeur de haut grade, métastatique, hormono-résistante
- ✓Expression faible dans les tissus normaux



SNMMI 2019, Phillip Kuo



M Sathekge

Approche théranostique

de l'imagerie fonctionnelle à la radiothérapie interne vectorisée

Sélection des patients exprimant le PSMA

Recherche de lésions TEP FDG + / TEP PSMA -

Sélection du patient répondeur

Personnalisation des doses

RIV dans le cancer de prostate

✓Cancer le plus fréquent chez l'homme avec apparition de métastases dans 20% des cas.

- → Cancer de prostate métastatique résistant à la castration

✓Options thérapeutiques : Abiratérone, taxanes, immunothérapie

AJR FOCUS ON:

Radioligand Therapy With ^{177}Lu-PSMA for Metastatic Castration-Resistant Prostate Cancer: A Systematic Review and Meta-Analysis

TABLE 1: Summary of Study Characteristics

Study	Agent	No. of Patients	Study Type	Age (y)	Extent of Metastasis (%)	Gleason Score[a]	Baseline PSA Level (ng/mL)	Primary Outcome	Secondary Outcome
Ahmadzadehfar et al. 2015 [12]	PSMA-617	10	Retrospective	Median, 73.5 (range, 62–81)	Local recurrence, 30; lymph node, 90; liver, 10; bone, 80	NR	298.5	Early side effects of ^{177}Lu-PSMA-617 therapy	Early response to ^{177}Lu-PSMA-617 therapy
Ahmadzadehfar et al. 2016 [13]	PSMA-617	24	Prospective	Mean, 75.2 (64–82)	Local, 45.8; lymph node, 83.8; liver, 12.5; bone, 100	NR	522	Toxicity	Biochemical, objective response
Baum et al. 2016 [14]	PSMA-I&T	56	Prospective	Median, 72 (range, 52–88)	Lymph node, 78.5; liver, 9; lung, 12.5; bone, 77; other, 5.3; brain, 1.7	8 (median)	42.3	Dosimetry	Safety, biochemical, objective, survival (progression free and overall)
Heck et al. 2016 [15]	PSMA-I&T	22	Prospective	Median, 71 (range, 46–77)	Lymph node, 82; liver, 18; lung, 14; bone, 95	NR	349	Safety	Antitumor activity of ^{177}Lu-PSMA-I&T
Kratochwil et al. 2016 [16]	PSMA-617	30	Prospective	Range, 61–85	Lung, 13.3; liver, 26.6; adrenal, 6.6; rectum, 3.3	7–9	NR	Efficacy of ^{177}Lu-PSMA-617 therapy	Dosimetry, biochemical response, toxicity
Kulkarni et al. 2016 [17]	PSMA-617, PSMA-I&T	119	Retrospective	Median, 71 (SD, 7)	Lymph node, 71; visceral, 26; bone, 81	9	NR	Efficacy of ^{177}Lu-PSMA-617	Toxicity
Rahbar et al. 2016 [18]	PSMA-617	74	Prospective	Median, 73 (range, 43–87)	Lymph node, 79; liver, 21; lung, 11; brain, 1; bone, 99	NR	342	Assess response to ^{177}Lu-PSMA-617 therapy (biochemical response)	Toxicity
Rahbar et al. 2016 [19]	PSMA-617	28	Prospective	Median, 73.4 (range, 45–87)	Lymph node, 40; lung, 25; liver, 40; bone, 100	7–10	290.5	Adverse effect	Early biochemical response
Ahmadzadehfar et al. 2017 [20]	PSMA-617	52	Prospective	Mean, 70.9 (range, 49–87)	Local, 42.3; lymph node, 75; lung, 11.5; liver, 13.5; brain, 3.8; bone, 100	7–10	194	Comparison of overall survival between responders and nonresponders	Biochemical response
Bräuer et al. 2017 [21]	PSMA-617	59	Prospective	Median, 72 (IQR, 66–76)	Lymph node, 80; liver, 34; lung, 15; bone, 93; other, 7	8 (7–9)	346	Overall survival	Prognostic parameters predicting outcome of ^{177}Lu-PSMA-617 therapy
Fendler et al. 2017 [22]	PSMA-617	15	Prospective	Median, 73 (range, 54–81)	Lymph node, 80; liver, 20; lung, 7; bone, 93; other, 13	7–10	388	Dosimetry	Safety and efficacy
Ferdinandus et al. 2017 [23]	PSMA-617	40	Prospective	Mean 71.4 (range, 43–87)	Local recurrence, 42.5; lymph node, 82.5; liver, 20; lung, 7.5; bone, 100	9 (6–10)	325.5	Effect of various pretherapeutic parameters and prior therapies on response	None
Rahbar et al. 2018 [24]	PSMA-617	104	Retrospective	Median, 70 (IQR, 64–76)	Lymph node, 77; liver, 18; lung, 16; bone, 97; other, 8	> 8	361	Overall survival	Prognostic parameters influencing survival
Scarpa et al. 2017 [25]	PSMA-617	10	Prospective	Range, 56–82	NR	> 8	129.5	Dosimetry	Biochemical, objective, and molecular response
Yadav et al. 2017 [26]	PSMA-617	31	Prospective	Median, 65.9 (range, 38–81)	Skeletal metastases, 42; skeletal and lymph node, 55; skeletal, lymph node, and liver, 3	6–10	275 (mean)	Biochemical, molecular, and clinical response	Survival
Hofman et al. 2018 [31]	PSMA-617	30	Phase 2 clinical trial	Median, 71 (range, 67–75)	Skeletal metastases > 20 (93%), < 20 (7%)	8 (7–9)	189.89	Biochemical response PCWG criteria	Radiologic response according to RECIST
Rathke et al. 2018 [27]	PSMA-617	40	Prospective	Range, 57–85	Local, 5; lymph nodes, 67.5; liver, 7.5; lung, 20; brain, 2.5; bone, 85; other, 20	NR	NR	Dose escalation study	Biochemical response

Note—PSMA = prostate-specific membrane antigen, NR = not reported, PSA = prostate-specific antigen, I&T = imaging and therapy, IQR = interquartile range, PCWG = Prostate Cancer Working Group, RECIST = Response Evaluation Criteria in Solid Tumors.

[a]Mean or mean with range in parentheses unless otherwise indicated.

Efficacité

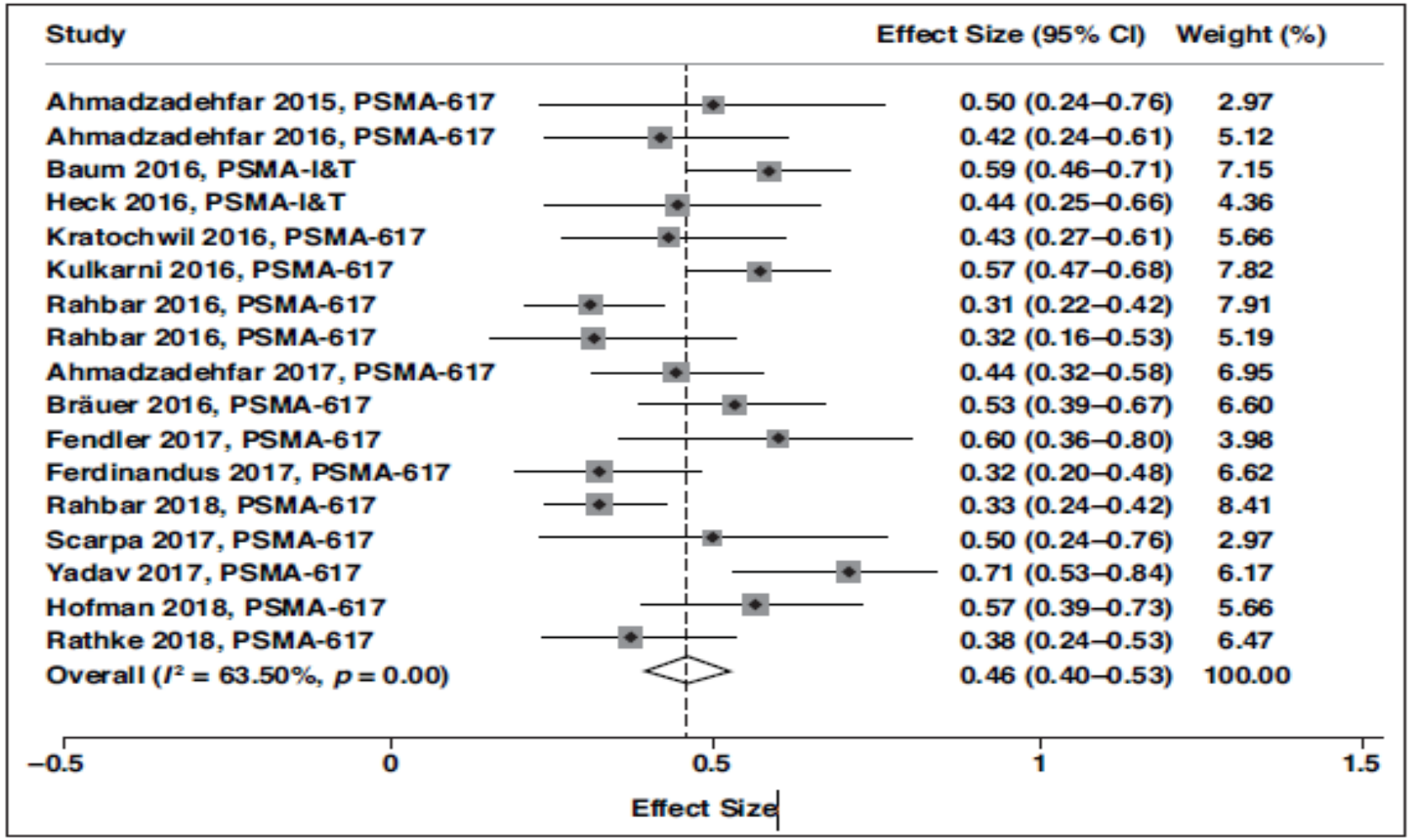


Fig. 6—Forest plot shows greater than 50% decline in prostate-specific antigen level after ^{177}Lu-labeled prostate-specific membrane antigen (PSMA) radioligand therapy. I&T = imaging and therapy.

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Baisse de PSA>50% chez 45% des patients

Survie Globale et Survie Sans Progression

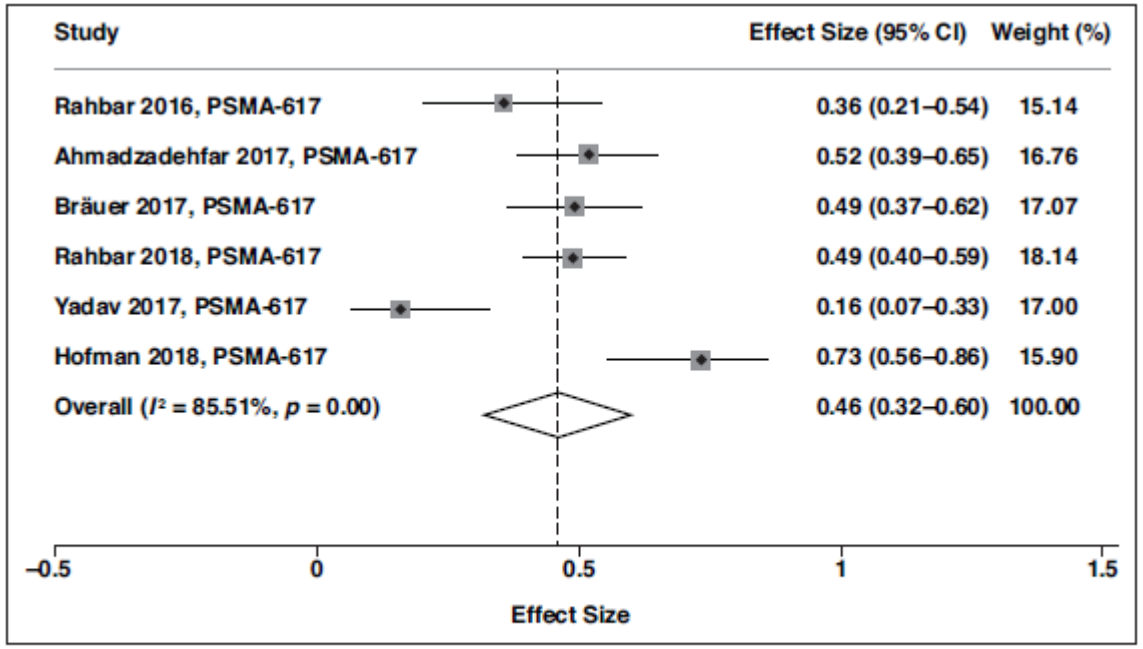

Fig. 8—Forest plot shows pooled proportion of overall survival in six articles on ^{177}Lu-labeled prostate-specific membrane antigen (PSMA) radioligand therapy.

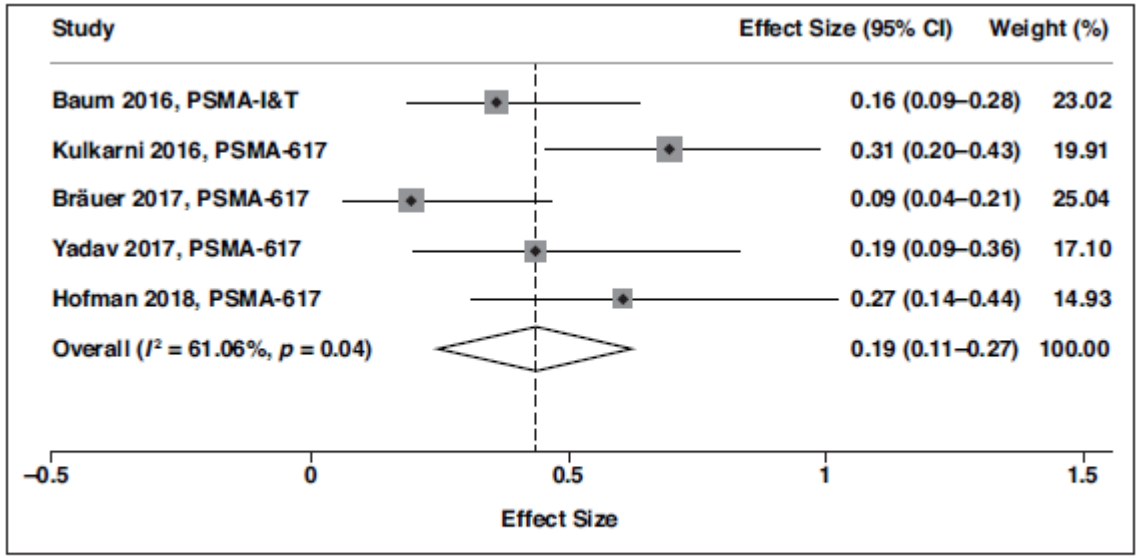

Fig. 9—Forest plot shows progression-free survival in five articles on ^{177}Lu-labeled prostate-specific membrane antigen (PSMA) radioligand therapy. I&T = imaging and therapy.

La survie globale médiane est estimée à 13.7mois

SSP médiane à 11mois

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Tolérance

TABLE 5: Overview of Toxicity Profile Across Studies

Study	Agent	Total No. of Patients	Hematologic Toxicity			Nephrotoxicity	Salivary Gland Toxicity	Other Manifestations (%)
			Hemoglobin	WBC Count	Platelets			
Ahmadzadehfar et al. 2015 [12]	PSMA-617	10	1 (10)	1 (10)	1 (10)	2 (20)	2 (20)	Fatigue, 20; nausea 20
Ahmadzadehfar et al. 2016 [13]	PSMA-617	24	9 (38)	5 (21)	4 (17)	3 (12.5)	2 (9)	Nausea and vomiting, 12.5; dry lips or mouth, 4.2; light headache, 2.2; bone pain, 4.2 (immediate side effects)
Baum et al. 2016 [14]	PSMA-I&T	56	3 (5)	9 (16)	0	0	2 (4)	None
Heck et al. 2016 [15]	PSMA-I&T	22	7 (32)	1 (5)	6 (25)	NR	8 (37)	Fatigue, 25; anorexia, 25
Kratochwil et al. 2016 [16]	PSMA-617	30	3 (10)	2 (7)	2 (7)	0	2 (7)	Fatigue grade 1, nausea grade 1
Kulkarni et al. 2016 [17]	PSMA-617 & PSMA-I&T	119	5 (4)	NR	NR	NR	NR	Mild fatigue, dryness of mouth, 4.2
Rahbar et al. 2016 [18]	PSMA-617	74	27 (36)	12 (16)	17(23)	4 (5.4)	7 (9)	Nausea grade 1, 1.4
Rahbar et al. 2016 [19]	PSMA-617	28	6 (20)	3 (11)	5 (23)	1 (4.5)	0	Nausea, 4.5
Ahmadzadehfar et al. 2017 [20]	PSMA-617	52	NR	NR	NR	NR	NR	NR
Bräuer et al. 2017 [21]	PSMA-617	59	51 (85)	23 (38)	28 (47)	51 (85)	15 (25)	Nausea, 15; diarrhea, 3; fatigue, 20; dry eye, 2
Fendler et al. 2017 [22]	PSMA-617	15	10 (67)	8 (53)	2 (13)	14 (93)	7 (46.6)	Fatigue, 33; dry mouth, 47; nausea, 33; dysgeusia, 20
Ferdinandus et al. 2017 [23]	PSMA-617	40	NR	NR	NR	NR	NR	NR
Rahbar et al. 2018 [24]	PSMA-617	104	NR	NR	NR	NR	NR	NR
Scarpa et al. 2017 [25]	PSMA-617	10	5 (50)	NR	NR	2 (20)	3 (30)	Pain, 60; fatigue, 20; nausea or loss of appetite, 10; constipation, 10
Yadav et al. 2017 [26]	PSMA-617	31	2 (7)	1 (3)	0	0	0	NR
Hofman et al. 2018 [31]	PSMA-617	30	8 (26)	32 (30)	9(30)	NR	26 (87)	Nausea, 50; fatigue, 50; fracture, 6
Rathke et al. 2018 [27]	PSMA-617	40	0	5 (12.5)	2 (5)	NR	NR	NR

Note—Unless otherwise indicated, values are number of patients with percentage in parentheses. NR = not reported. I&T = imaging and therapy.

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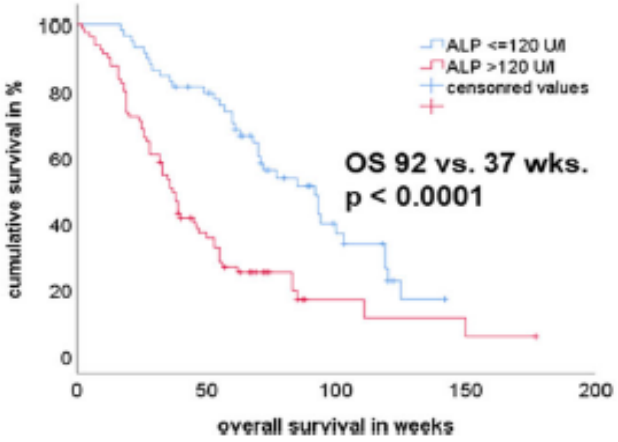
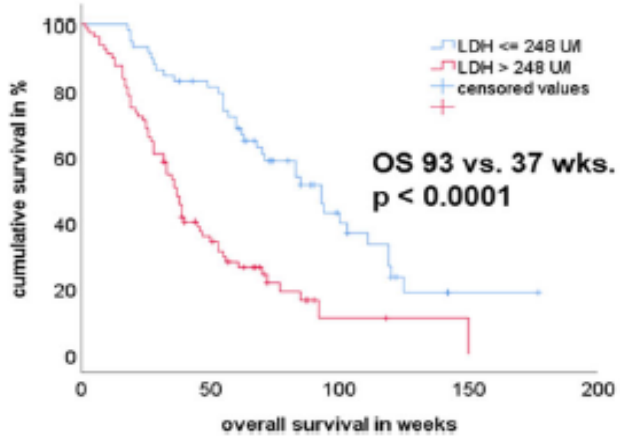
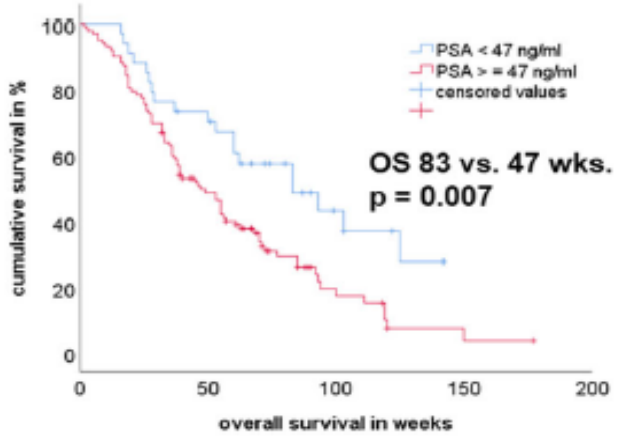
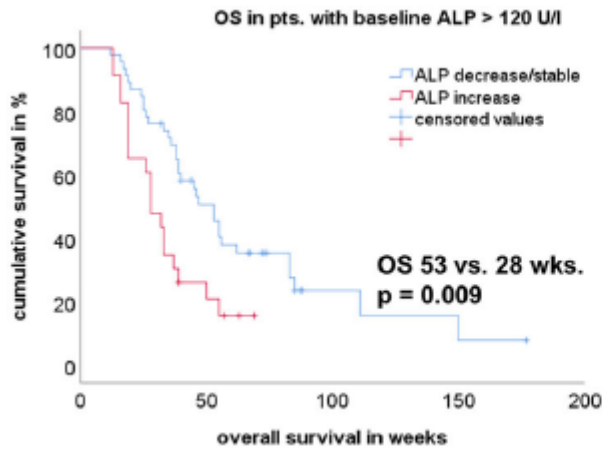
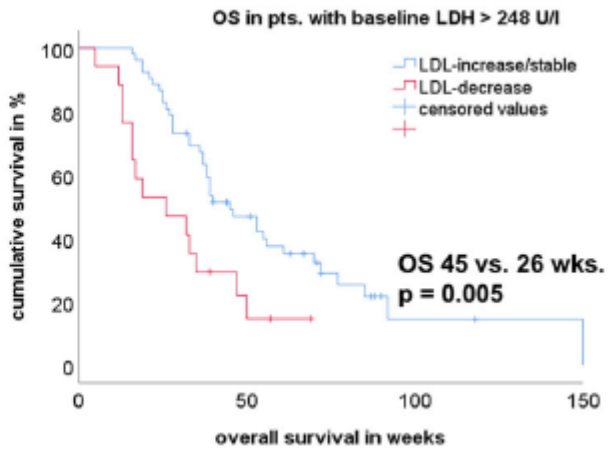
Réponse biologique

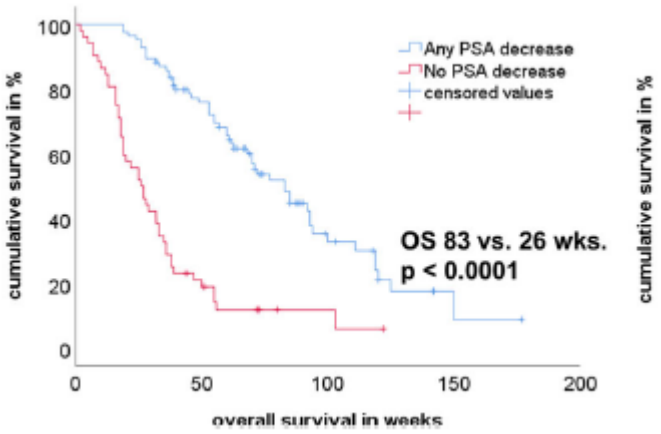












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Réponse en imagerie

Evaluation 3 mois après le dernier cycle :

Table 2: Imaging response at 3 months after the last cycle of induction LuPSMA

	Bone scintigraphy	Soft-tissue lesions on CT (nodal and &/or visceral)[1] (n=27)	PSMA PET	FDG PET
CR	16 (32%)	5 (19%)	6 (12%)	7 (14%)
PR		10 (37%)	15 (30%)	8 (16%)
SD		0	0	3 (6%)
PD	12 (24%)	9 (33%)	14 (28%)	15 (30%)
Not performed	22 (44%)	3 (11%)	15 (30%)	17 (34%)

CR: complete response. PR: partial response. SD: stable disease. PD: progressive disease. PET responses were assessed visually using Hicks criteria(*33*). RECIST 1.1 with PCWG2 caveats; CT component of post-therapy SPECT/CT was also utilized for soft tissue measurements. **Not performed: due to clinical progression or death.**

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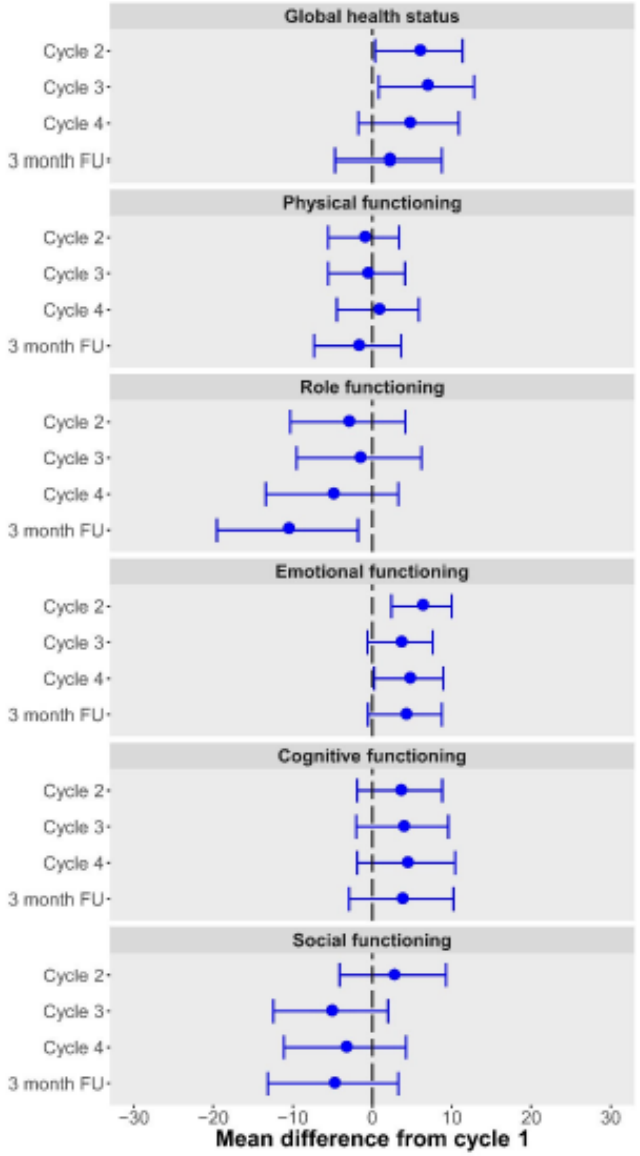
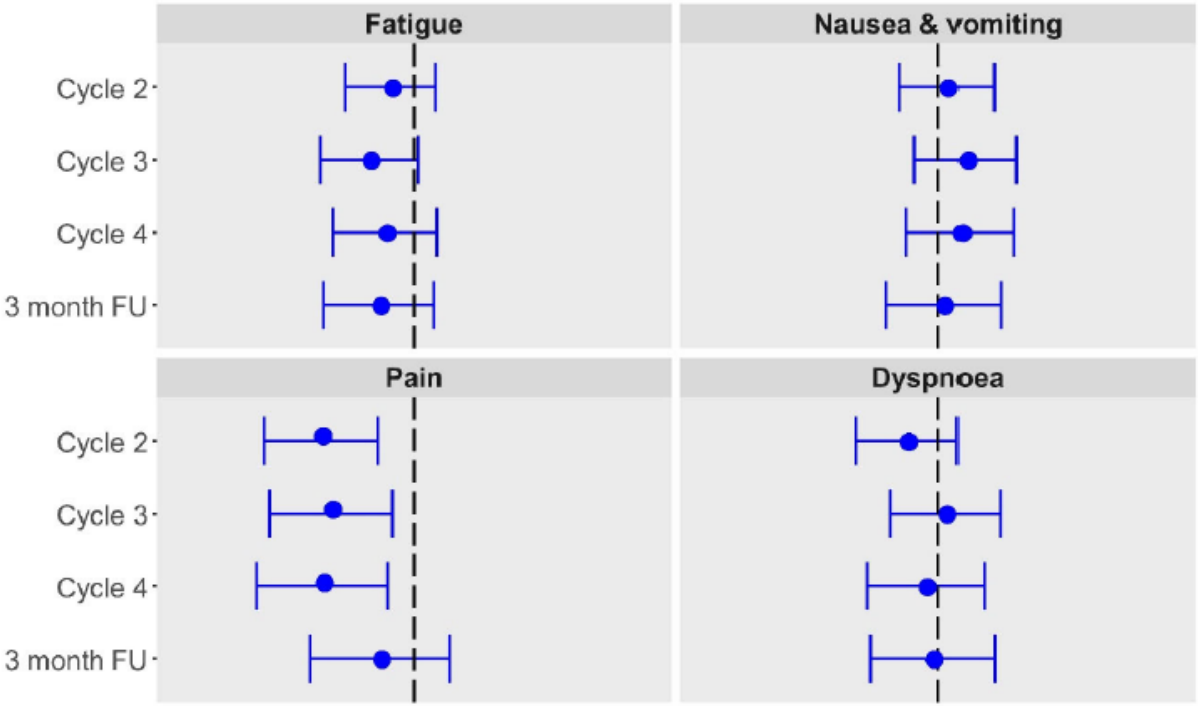
Réponse clinique





Amélioration de la qualité de vie et effets antalgiques

Violet J, et al.

EANM Guidelines

Indication : cancer de prostate métastatique résistant à la castration, en échec thérapeutique, PSMA +, pas de lésion hépatique FDG+/PSMA-

Contre indication : Espérance de vie < 6 mois, obstruction urinaire, détérioration rapide de la fct hépatique/rénale, GB<2,5G/l, pl<75

Dosimétrie : déterminer une dose individuelle dans la mesure du possible, moelle 2Gy, rein 28-40Gy, GS 35Gy. Dose rénale pouvant dépasser les 40Gy si espérance de vie < 1an

Radioprotection : dépend des exigences locales, en pratique dose mesurée à 23 +/- 6 µs/h à 6h et 7 +/- 2 µs/h à 24h post injection de 7,4GBq

Dose : de 6 à 8,5GBq, généralement 7,4GBq toutes les 6-8 semaines, 2 à 6 cycles en fct de la réponse/pronostique/risque rénal

Administration : Hydratation +/- diurétique, laxatif. Glace, ondansetron, corticoïde si atteinte cérébrale/spinale

Suivi : PSA – NF – enzyme hépatique – fonction rénale – scintigraphie intra-thérapeutique

Evaluation : PSA à chaque cycle, TEP PSMA tous les 2 cycles + autre modalité (TDM, TEP FDG)

Les études comparatives

- ✓Essai ANZUP TheraP
- ✓Essai Endocyte VISION

Etude TheraP

Date d'achèvement : Janvier 2021

Objectif

Déterminer l'activité et l'innocuité du traitement du LuPSMA par rapport au cabazitaxel chez les hommes atteints d'un cancer de la prostate progressive, métastatique et résistant à la castration

Design

Phase II, interventionnelle, multicentrique, randomisée, ouverte, à 2 bras

Traitement et Critères d'Evaluation

Taux de réponse de l'antigène spécifique de la prostate (PSA RR)

Baseline & Randomisation

n = 100 → 6 à 8,5 GBq de 177Lu-PSMA617 toutes les 6 semaines

n = 100 → 20 mg / m2 de Cabazitaxel toutes les 3 semaines + 10 mg de prednisolone

Arrêt

- maladie évolutive
- une toxicité prohibitive
- 6 cycles

- maladie évolutive
- toxicité prohibitive
- 10 cycles

Etude VISION

Date d'achèvement : Mai 2021

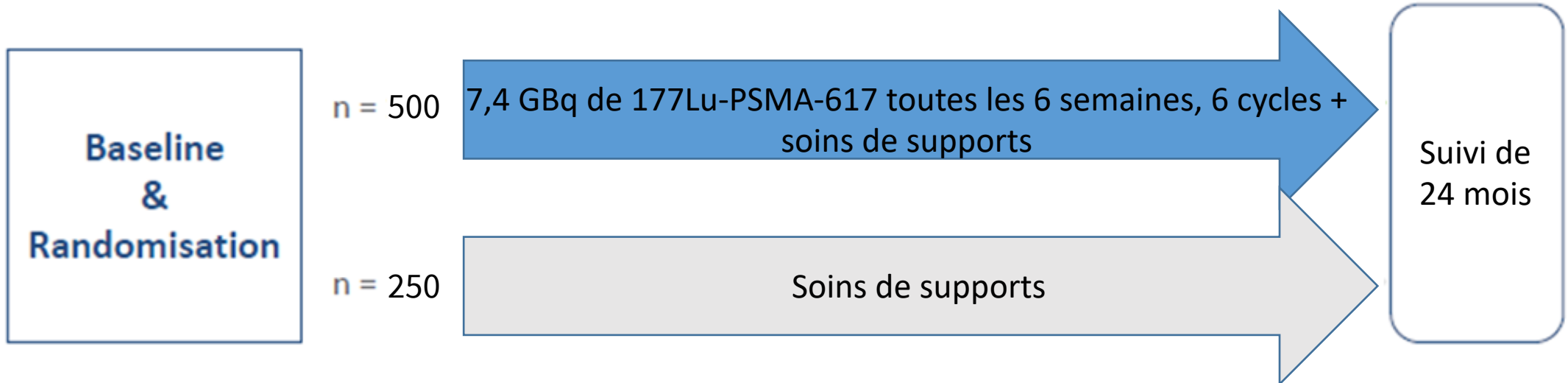
Objectif

Comparer la survie globale chez les patients atteints de mCRPC progressif avec PSMA positif qui reçoivent 177Lu-PSMA-617 et soins de supports
Vs
Patients avec soins de supports uniquement

Design

Étude de phase 3 internationale, prospective, ouverte, multicentrique, randomisée

Traitement et Critères d'Evaluation
Survie globale



Bibliographie

1. Kratochwil C, Fendler WP, Eiber M, Baum R, Bozkurt MF, Czernin J, et al. EANM procedure guidelines for radionuclide therapy with 177Lu-labelled PSMA-ligands (177Lu-PSMA-RLT). Eur J Nucl Med Mol Imaging. nov 2019;46(12):2536-44.
2. Violet J, Sandhu S, Iravani A, Ferdinandus J, Thang SP, Kong G, et al. Long term follow-up and outcomes of re-treatment in an expanded 50 patient single-center phase II prospective trial of Lutetium-177 (^{177} Lu) PSMA-617 theranostics in metastatic castrate-resistant prostate cancer. J Nucl Med. 15 nov 2019;jnumed.119.236414.
3. Yadav MP, Ballal S, Sahoo RK, Dwivedi SN, Bal C. Radioligand Therapy With ^{177} Lu-PSMA for Metastatic Castration-Resistant Prostate Cancer: A Systematic Review and Meta-Analysis. American Journal of Roentgenology. août 2019;213(2):275-85.
4. Giraudet AL. Radionuclide therapy targeting PSMA for the treatment of metastatic prostate cancer: Current point of view and ways of improvement. Médecine Nucléaire. mai 2019;43(3):275-9.
5. Turpin L, Calzada MC, Zhang Yin J, Rusu T, Dumont Bruzek A, Aveline C, et al. Radiothérapie interne vectorisée par 177Lu-PSMA-617 de l'adénocarcinome prostatique métastatique résistant à la castration : à propos d'un cas et revue de la littérature. Médecine Nucléaire. mai 2019;43(3):298-303.
6. Yordanova A, Linden P, Hauser S, Feldmann G, Brossart P, Fimmers R, et al. The value of tumor markers in men with metastatic prostate cancer undergoing [^{177} Lu]Lu-PSMA therapy. The Prostate. 3 oct 2019;pros.23912.

Merci de votre attention