IL TEAM INTERDISCIPLINARE NEL CARCINOMA DELLA PROSTATA

NEGRAR DI VALPOLICELLA 6-7 DICEMBRE 2019

Sala Perez - IRCCS Ospedale Sacro Cuore Don Calabria

IRCCS Sacro Cuore Don Calabria
Cancer Care Center
Negrar di Valpolicella (Vr)

Terapia Radiometabolica nel carcinoma prostatico. Cosa ci riserva il futuro?

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mCRPC Metastatic Castration Resistent Prostate Cancer

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PHASE III mCRPC

Study	Agents	*n*	Indication	HR (95% CI)	OS
Tax-327 [6]	Docetaxel + P vs Mitoxantrone + P	1006	mCRPC	0.76 (0.62–0.94)	18.9 *vs.* 16.5
D9901 and D9902 [27,28]	Sipuleucel T *vs.* Po	225	mCRPC pre docetaxel	1.5 (1.10–2.05)	32.2 *vs.* 18.9
IMPACT [29]	Sipuleucel T *vs.* Po	512	mCRPC pre docetaxel	0.78 (0.61–0.98)	25.8 *vs.* 21.7
COU-AA-301 [17]	Abiraterone + P *vs.* P	1195	mCRPC post docetaxel	0.65 (0.54–0.77)	14.8 *vs.* 10.9
COU-AA-302 [18,19]	Abiraterone + P *vs.* p	1088	mCRPC pre docetaxel	0.75 (0.61–0.93)	NR *vs.* 27.2
AFFIRM [22]	Enzalutamide *vs.* Po	1199	mCRPC post docetaxel	0.63 (0.53–0.75)	18.4 *vs.* 13.6
PREVAIL [23]	Enzalutamide *vs.* Po	1717	mCRPC pre docetaxel	0.71 (0.60–0.84)	32.4 *vs.* 30.2
TROPIC [24]	Cabazitaxel + P *vs.* Mitoxantrone + P	755	mCRPC post docetaxel	0.70 (0.59–0.83)	15.1 *vs.* 12.7
ALSYMPCA [30]	Radium-223 *vs.* Po	Po921	mCRPC pre docetaxel	0.7 (0.55–0.88)	14 *vs.* 11.2
FIRSTANA [25]	Cabazitaxel 25 mg/m^2 (C25) *vs.* 20 mg/m^2 (C20) *vs.* docetaxel 75 mg/m^2 (D75)	1168	mCRPC pre docetaxel	C20 *vs.* D75 1.01 (0.85–1.20) C25 *vs.* D75 0.97 (0.82–1.16)	24.5 C20 25.2 C25 24.3 D75
PROSELICA [26]	Cabazitaxel 25 mg/m^2 (C25) *vs.* 20 mg/m^2 (C20)	1200	mCRPC post docetaxel	1.024	13.4 *vs.* 14.5

HR: hazard ratio; mCRPC, metastatic castrate-resistant prostate cancer; NR, not reached; OS, overall survival; P, prednisone; Po, placebo; CI, confidence interval.

Currently SIX therapies are approved for **CRCP** based on capacity to **improve OS i**n randomized control trials

Pagliuca, Drugs. 2019 Mar;79(4):381-400.

mCRPC Metastatic Castration Resistent Prostate Cancer

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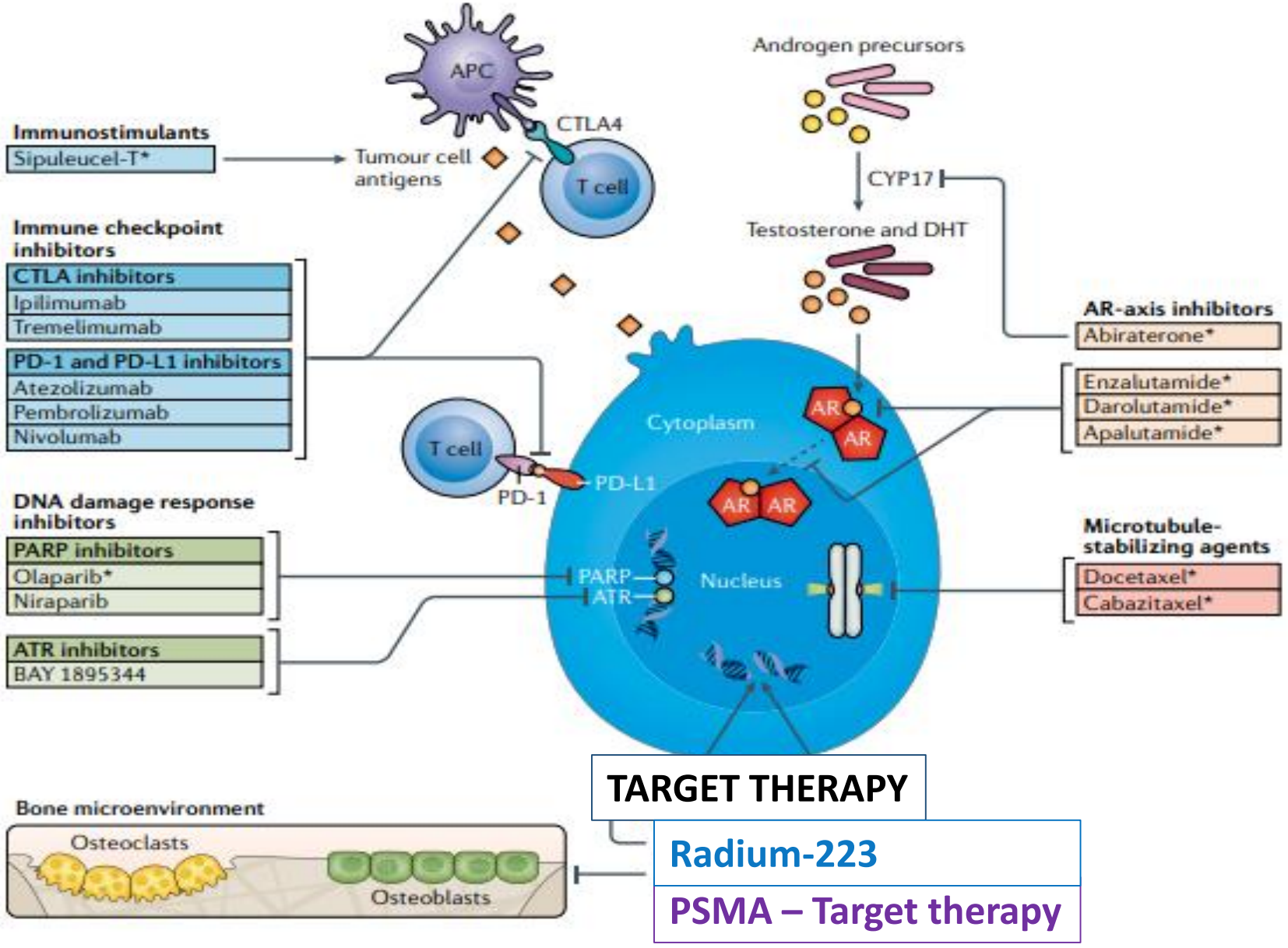


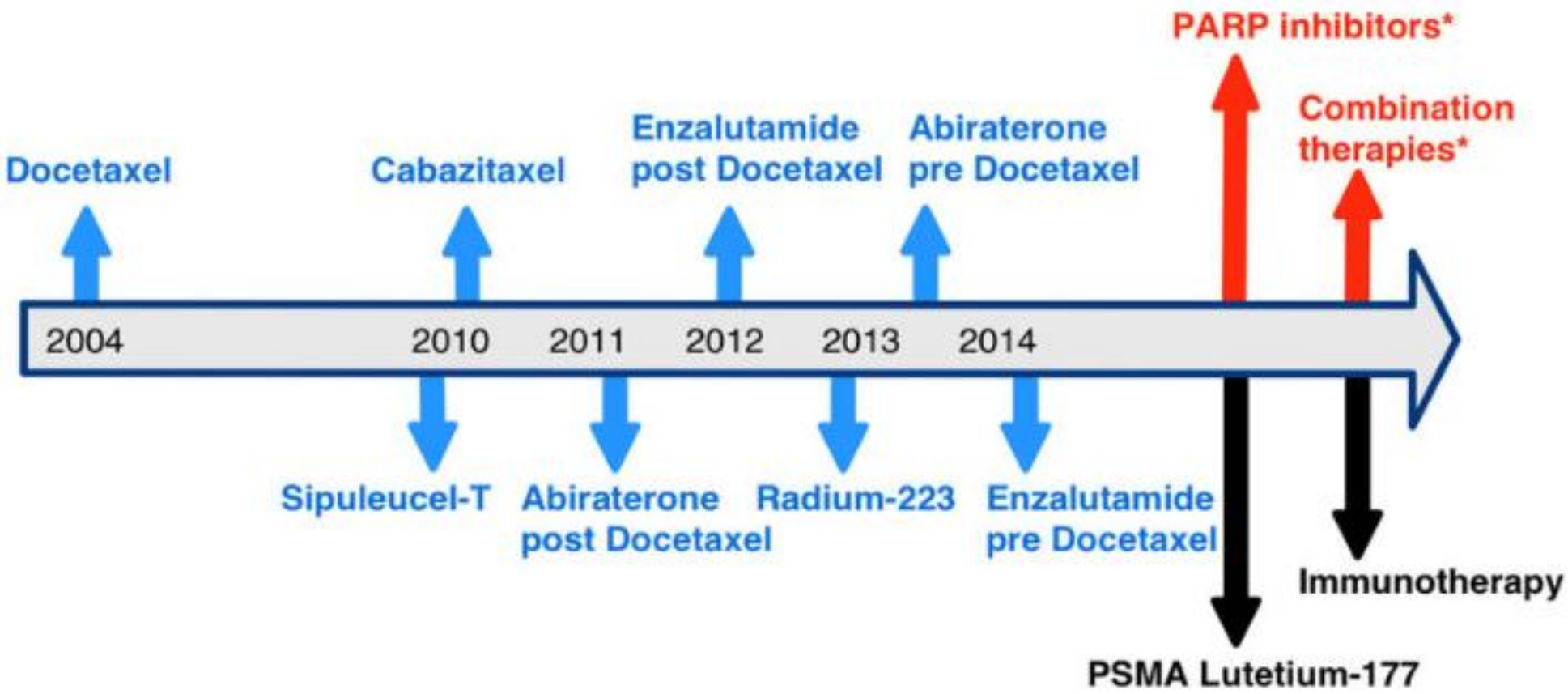
TARGET THERAPY

Radium-223

PSMA – Target therapy

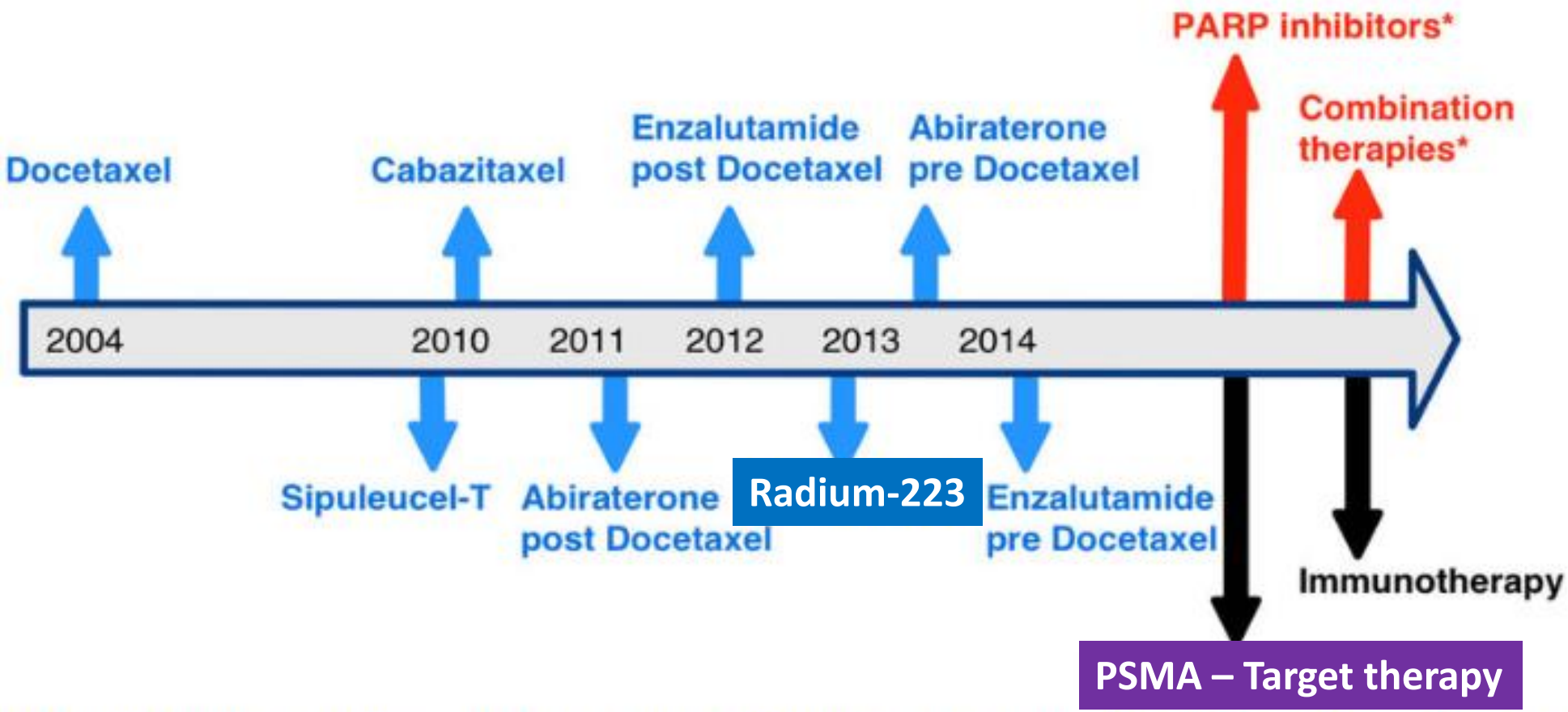
Morris; et al Nature 2019

mCRPC Metastatic Castration Resistent Prostate Cancer



Overview of approved agents in metastatic castration resistant prostate cancer (blue arrows) including their year of approval. Future new treatment options are highlighted in black, treatment options discussed in this manuscript are marked in red with *. PARP poly ADP ribose polymerase, PSMA prostate-specific membrane antigen

mCRPC Metastatic Castration Resistent Prostate Cancer



Overview of approved agents in metastatic castration resistant prostate cancer (blue arrows) including their year of approval. Future new treatment options are highlighted in black, treatment options discussed in this manuscript are marked in red with *. PARP poly ADP ribose polymerase, PSMA prostate-specific membrane antigen

Radium-223

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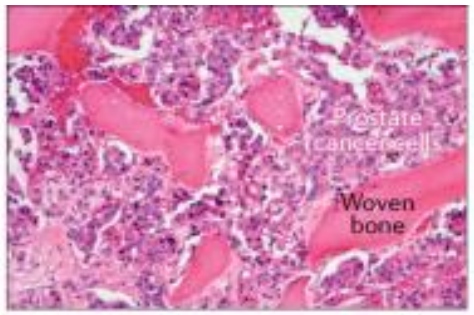
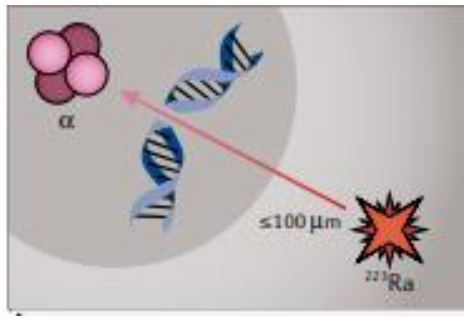
Ra223 (alpha emitter)

- ✓ mCRPC
- ✓ No visceral disease
- ✓ **Symptomatic bone lesion**
- ✓ No bowel disease





6 treatments e.v. every 4 weeks

- **AL**pharadin**SYM**ptomatic**P**rostate**CA**ncer → **223Ra** vs. BoC

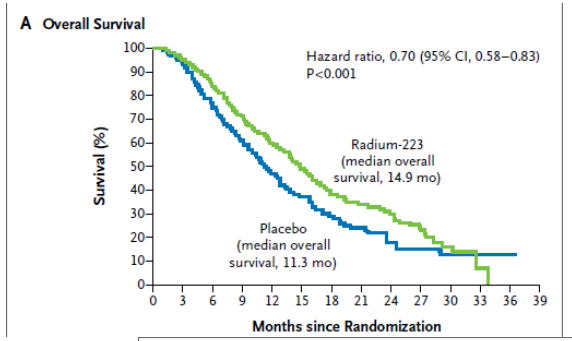
  Regardless prior DOCETAXEL use:

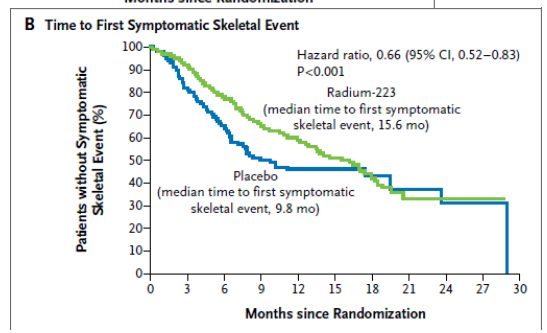
  low incidence of hematological toxicity (<10%, higher in ChT) [a]

  223Ra: improvement in OS, SSE free survival (..) [b]

  BoC (best of care): defined as routine care of each 136 center:
  local RBRT, glucocorticoids, antiandrogens,
  ketoconazole and estrogens

  Long-term safety is confirmed at 3 years follow-up analysis [c]





a) Sartor et al; ALSYMPCA trial Lancet Oncol. **2014** Jun;15(7):738-46
b) Parker et al ASYMPCA 2013 NEJM 2013; 369: 213-223
c) Parker et al; Eur Urol Eur Urol. 2017 Jul 10 doi: 10.1016/j.eururo.2017.06.021..

Radium-223

- **REASSURE trial:**
  - Prospective single-arm, non-interventional study
  - mCRPC treated with Ra-223 in routine clinical practice
  - Primary end point: long-term safety (including the incidence of second primary malignancies) over a 7-year period
  - Exclusion criteria: previous treated with Ra223 currently participating in any clinical trial, or systemic treatment with other radiopharmaceuticals
  - On-going

  - Interim results: planned after enrolment of the first 600 patients.
    - Haematological TEAEs occurred more frequently in the prior ChT group (decreased bone marrow function as a consequence of more advanced disease and prior exposure to cytotoxic therapy)
    - Patients who had NO previous ChT: lower burden of disease at baseline, lower rate of discontinued radium-223 treatment.

Eur J Nucl Med Mol Imaging. 2019; 46(5): 1102–1110.

Radium-223

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- **CHEMOTHERAPY +/- 223Ra: NOT YET** been established (On-going Trials)

Combination treatment with ^{223}Ra	Mechanism of action	Trial phase and design	Primary outcomes	Patient characteristics (estimated enrolment)	Estimated completion date (primary)	Trial ID
Hormone therapies						
Abiraterone[140]	CYP17 inhibitor	Phase III (vs abiraterone only)	Symptomatic skeletal event-free survival	CRPC with asymptomatic or mildly symptomatic BM (n = 806)	December 2019 (February 2018)	NCT02043678[a]
Enzalutamide[93]	AR inhibitor	Phase III (vs enzalutamide only)	Radiological progression-free survival	CRPC with asymptomatic or mildly symptomatic BM (n = 560)	April 2021 (November 2019)	NCT02194842
Enzalutamide[150]	AR inhibitor	Phase II	Safety (grade ≥3 AEs, by NCI CTCAE version 4)	Progressing mCRPC; BM and VD allowed (n = 44)	April 2021 (July 2017)	NCT02225704
Chemotherapy						
Docetaxel[109]	Microtubule inhibitor	Randomized phase III (vs docetaxel only)	Overall survival	mCRPC (n = 738)	June 2023 (June 2022)	NCT03574571
Immunotherapy						
Atezolizumab[151]	PD-L1 inhibitor	Phase I	DLT; adverse events; objective response (RECIST v1.1)	Progressing mCRPC; BM and VD allowed (n = 44)	March 2020	NCT02814669
Pembrolizumab[121]	PD-1 inhibitor	Randomized phase II (vs ^{223}Ra only)	Extent of immune cell infiltration	mCRPC with BM (n = 45)	June 2024 (June 2020)	NCT03093428
Sipuleucel-T[112]	ACT using PA2024-pretreated cells to stimulate tumour-specific immune responses	Randomized phase II (vs sipuleucel-T only)	Immune responses measured by peripheral PA2024 T cell proliferation	CRPC with asymptomatic or minimally symptomatic BM (n = 34)	December 2020 (December 2018)	NCT02463799
DNA damage response						
Niraparib[131]	PARP inhibitor	Phase Ib	Maximum tolerated dose of niraparib to combine with standard dose of ^{223}Ra	mCRPC; BM and VD allowed (n = 27)	November 2020 (November 2021)	NCT03076203
Olaparib[132]	PARP inhibitor	Randomized phase I/II (vs ^{223}Ra only)	Maximum tolerated dose of olaparib and ^{223}Ra; radiographic progression-free survival	CRPC with BM (n = 138)	April 2020	NCT03317392

Radium-223

- **ERA-223 study: Abiraterone (AA) plus Prednisone/Prednisolone +/- 223Ra**
  - 806 asymptomatic or mildly symptomatic mCRPC patients
  - randomised, double-blind, placebo-controlled
  - The arm with **223Ra** + AA + P **vs.** Placebo + AA + P arm

  have increased incidence of **fractures** **(28.6%** vs 11.4%) **and deaths** **(38.5%** vs 35.5%)

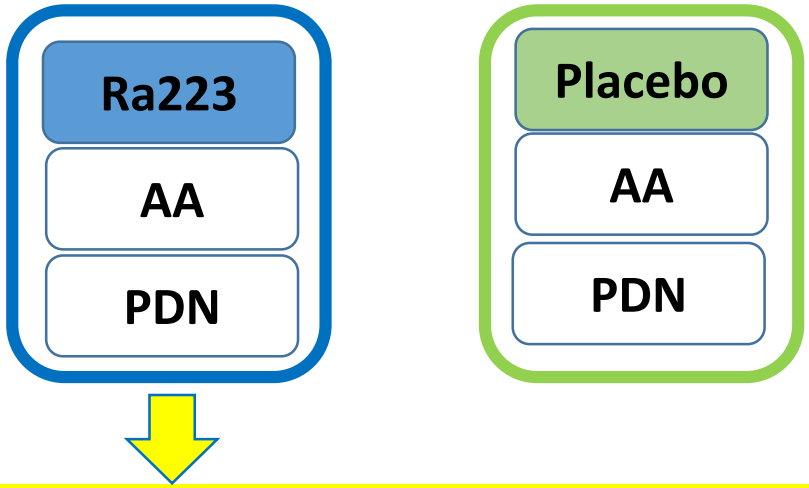
  - ‘’ALSYMPCA had a greater disease burden, disease-related symptoms, and higher alkaline phosphatase, lactate dehydrogenase, and prostate-specific antigen concentrations than ERA-223’’

  Safety and efficacy with the combination of Xofigo and agents other than gonadotropin-releasing hormone analogues have not been established

Smith et all; ERA-223 study **Lancet Oncol**. 2019 Mar;20(3):408-419.

Radium-223

- **ERA-223 study:** showed an increased number of **BONE FRACTURES** in **Ra223** treated patients, The majority in non-metastatic bone sites
- Bone Fracture Risk: **18%** vs **9%.**



METHODOLOGICAL PROBLEM???

- **NO Bone assessment**
- **NO Difosfonate Therapy**

''The finding that use of bone health agents was associated with decreased fracture frequency in both groups in our study shows the importance of the use of these drugs to prevent skeletal morbidity in patients with metastatic castration-resistant prostate cancer''

Possible explanations

- ✓ Glucocorticoid induced inhibition of bone formation (PDN eccess)
- ✓ Inhibition of osteoblast maturation and function (PDN eccess
- ✓ Maybe AA increase accumulation on healthy bone of Ra223 (bone remodeling areas with high osteoblastic activity)

Lancet Oncol. 2019

After ERA223 study

Radium-223

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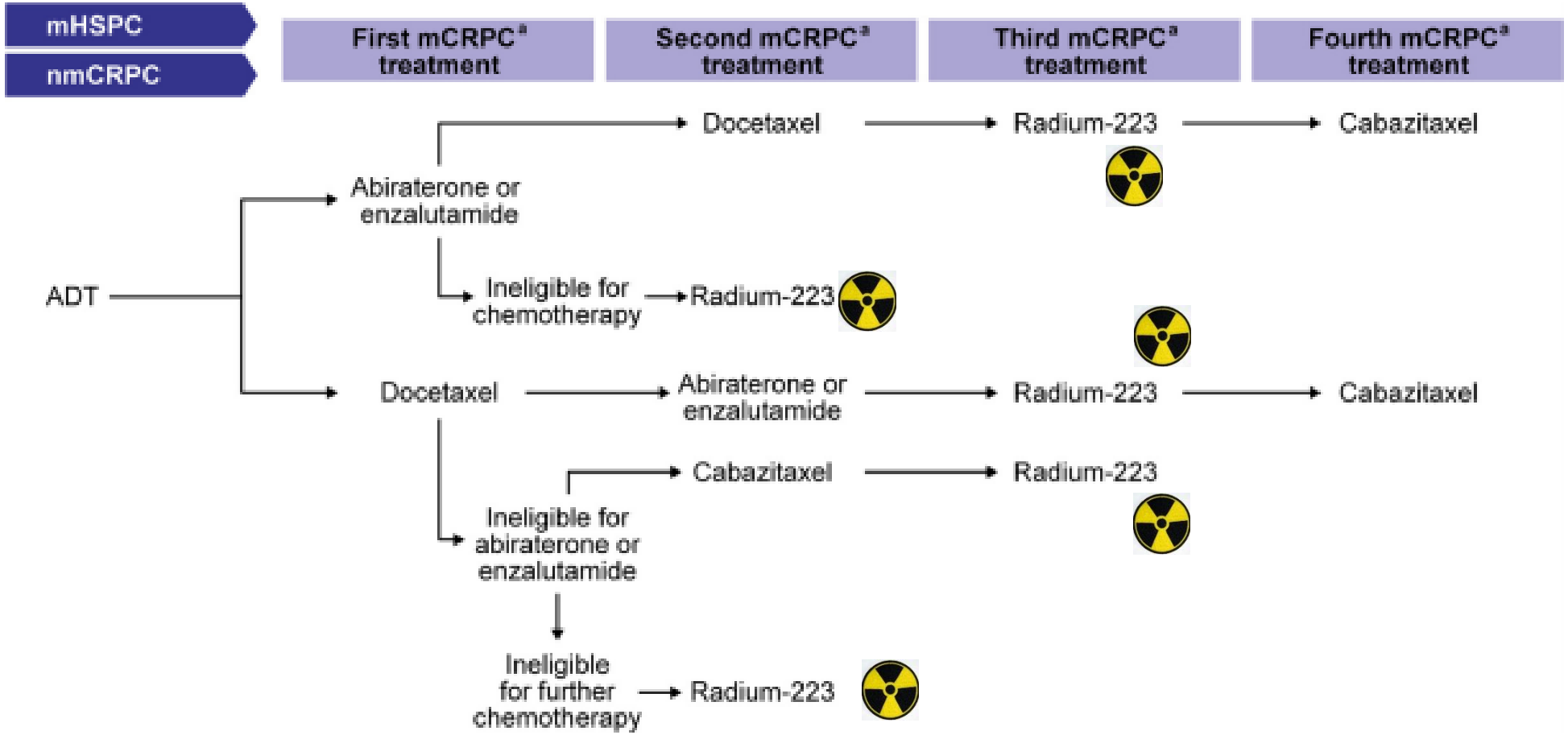

Fig. 2 – Sequencing of systemic therapies for mCRPC. Potential sequencing options for approved life-prolonging agents following progression on ADT. These are illustrative algorithms based on the revised EU indication for radium-223. Not all potential treatment options are shown. Concurrent use of bone health agents to treat osteoporosis or for patients with bone metastases is recommended. Sequential use of abiraterone and enzalutamide (or vice versa) is not considered as an option due to likely futility of treatment. Consider clinical trials or best supportive care after all available systemic therapies have been administered. ADT = androgen deprivation therapy; EU = European Union; mCRPC = metastatic castration-resistant prostate cancer; mHSPC = metastatic hormone-sensitive prostate cancer; nmCRPC = nonmetastatic castration-resistant prostate cancer. [a] mCRPC with bone metastases and no visceral metastases.

O'Sullivan et al, EUO 2019, 190:9

After ERA223 study

Agenzia Italiana del Farmaco

Home > Informazione e comunicazione > Pillole dal Mondo > Attivazione Registro XOFIGO

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Attivazione Registro XOFIGO

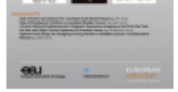
Pillole dal Mondo n. 1743 - L'Agenzia Italiana del Farmaco informa gli utenti dei Registri di Monitoraggio che, a partire dal 22/11/2019, è presente sulla piattaforma web il Registro del medicinale XOFIGO per la seguente indicazione terapeutica:

- in monoterapia o in associazione con un analogo dell'ormone di rilascio dell'ormone luteinizzante (Luteinising Hormone-Releasing Hormone, LHRH) è indicato per il trattamento di pazienti adulti affetti da carcinoma prostatico metastatico resistente alla castrazione (metastatic Castration-Resistant Prostate Cancer,mCRPC), con metastasi ossee sintomatiche e senza metastasi viscerali note, in progressione dopo almeno due precedenti linee di terapia sistemica per il mCRPC (diverse dagli analoghi del LHRH) o non eleggibili ai trattamenti sistemici disponibili per il mCRPC.

Inoltre, si informano gli utenti che in funzione di quanto previsto dalla Determina pubblicata in G.U., i dati relativi al periodo che va dal 11/06/2015 al 22/11/2019 dovranno essere trasferiti nella piattaforma web con la data effettiva di inizio trattamento compilando le singole prescrizioni e dispensazioni finora somministrate.

Pubblicato il: 29 novembre 2019

European Association of Urology



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Real-world Outcomes of Sequential Androgen-receptor Targeting Therapies with or Without Interposed Life-prolonging Drugs in Metastatic Castration-resistant Prostate Cancer: Results from the Dutch Castration-resistant Prostate Cancer Registry

Background: Cross resistance between androgen-receptor targeting therapies (ARTs) (abiraterone acetate plus prednisone [ABI + P] or enzalutamide [ENZ]) for treatment of metastatic castration-resistant prostate cancer (mCRPC) may affect responses to second ART (ART2).

Objective: To establish treatment duration and prostate-specific antigen (PSA) response of ART2 in real-world mCRPC patients treated with or without other life-prolonging drugs (LPDs; ie, docetaxel, cabazitaxel, or radium-223) between ART1 and ART2.

Design, setting, and participants: Castration-resistant prostate cancer patients, diagnosed between 2010 and 2016 were retrospectively registered in Castration-resistant Prostate Cancer Registry (CAPRI). Patients treated with both ARTs were clustered into two subgroups: ART1 > ART2 or ART1 > LPD > ART2.

Outcome measurements and statistical analysis: Outcomes were ≥50% PSA response and treatment duration of ART2. Descriptive statistics and binary logistic regression after multiple imputations were performed.

Results and limitations: A total of 273 patients were included with a median follow-up of 8.4 mo from ART2. Patients with ART1 > ART2 were older and had favourable prognostic characteristics at ART2 baseline compared with patients with ART1 > LPD > ART2. No differences between ART1 > ART2 and ART1 > LPD > ART2 were found in PSA response and treatment duration. Multivariate analysis suggested that PSA response of ART2 was less likely in patients with visceral metastases (odds ratio [OR] 0.143, $p = 0.04$) and more likely in patients with a relatively longer duration of androgen-deprivation treatment (OR 1.028, $p = 0.01$) and with ABI + P before ENZ (OR 3.192, $p = 0.02$). A major limitation of this study was missing data, a common problem in retrospective observational research.

Conclusions: The effect of ART2 seems to be low, with a low PSA response rate and a short treatment duration irrespective of interposed chemotherapy or radium-223, especially in patients with short time on castration, visceral disease, and ENZ before ABI + P.

Patient summary: We observed no differences in outcomes of patients treated with sequential abiraterone acetate plus prednisone (ABI + P) and enzalutamide (ENZ) with or without interposed chemotherapy or radium-223. In general, outcomes were lower than those in randomised trials, questioning the additional effect of second treatment with ABI + P or ENZ in daily practice.

doi.org/10.1016/j.euo.2019.09.005 2588-9311/© 2019 European Association of Urology.

Research beyond 223Ra

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	Radium-223	177Lu- PSMA
Emits	α-particles	β-particles; γ-rays
Half-life	11.4 days	6.7 days
Attaches to	Tissues that uptake calcium	Prostate cancer cells expressing the prostate-specific membrane antigen (PSMA)
Destroys metastases in	Bone only (areas of active calcium uptake)	Bone, lymph nodes, viscera, systemic micrometastases
Destructive range	Shorter range: < 0.1 mm or about 8 cells	Longer range: ~ 0.25 mm or about 125 cells
Cancer cell killing power	Higher	Lower
Imaging	Not detectable	Gamma camera (scintigraphy) or SPECT
Toxicity	Gastrointestinal, edema, myelosuppression	Myelosuppression (of platelets, neutrophils, and leukocytes)

Lu177-PSMA

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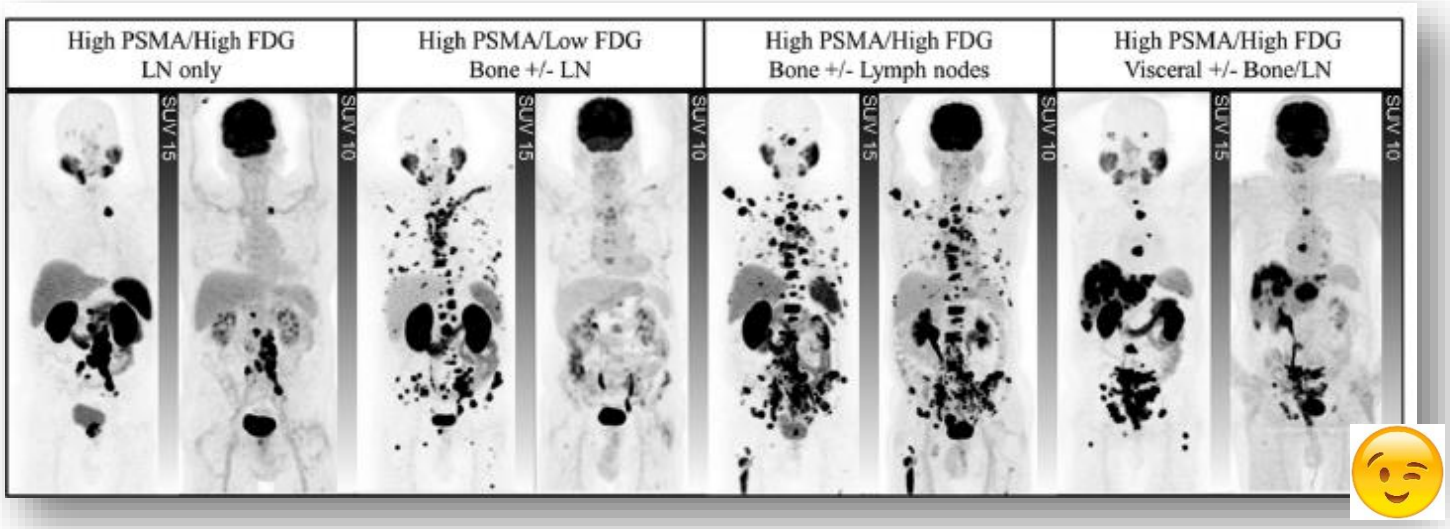
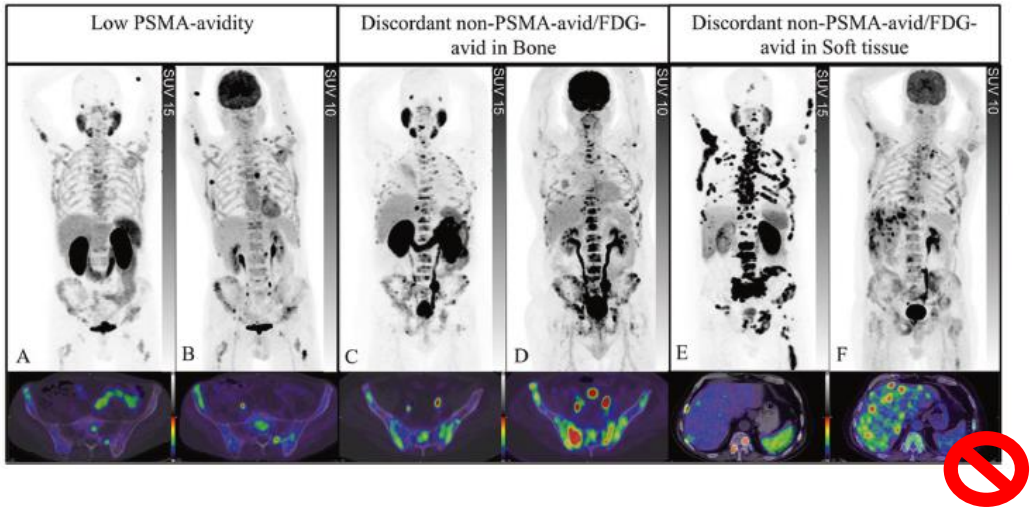
- **Theragnostic:** imaging and therapy with similar radiopharmaceutical

Diagnostic → **Target – Therapy**

- **PET-PSMA**: SUVmax at dominant sites of tumour involvement > 1.5 times the SUVmean of liver
- **PET- FDG:** to exclude patients with active disease sites lacking PSMA expression





Lu177-PSMA

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- **Theragnostic:** imaging and therapy with similar radiopharmaceutical

Diagnostic → **Target – Therapy**

- **PET-PSMA**: SUVmax at dominant sites of tumour involvement > 1.5 times the SUVmean of liver
- **PET- FDG:** to exclude patients with active disease sites lacking PSMA expression

Administered activity per treatment:
- Observational data range from 100–250 mCi
- An ongoing phase III study (VISION TRIAL NCT03511664)

implemented a standard activity of 200mCi at 6-week intervals for a total of four to six cycles.

Time interval between cycles: 6–8 weeks

Number of cycles: two to six (depending on response, prognosis and renal risk factors)

European Journal of Nuclear Medicine and Molecular Imaging
https://doi.org/10.1007/s00259-019-04485-3

GUIDELINES

Check for updates

EANM procedure guidelines for radionuclide therapy with ^{177}Lu-labelled PSMA-ligands (^{177}Lu-PSMA-RLT)

Clemens Kratochwil[1] · Wolfgang Peter Fendler[2] · Matthias Eiber[3] · Richard Baum[4] · Murat Fani Bozkurt[5] · Johannes Czernin[6] · Roberto C. Delgado Bolton[7] · Samer Ezziddin[8] · Flavio Forrer[9] · Rodney J. Hicks[10] · Thomas A. Hope[11] · Levant Kabasakal[12] · Mark Konijnenberg[13] · Klaus Kopka[1] · Michael Lassmann[14] · Felix M. Mottaghy[15] · Wim Oyen[16,17,18] · Kambiz Rahbar[19] · Heiko Schöder[20] · Irene Virgolini[21] · Hans-Jürgen Wester[22] · Lisa Bodei[20] · Stefano Fanti[23] · Uwe Haberkorn[1] · Ken Herrmann[2]

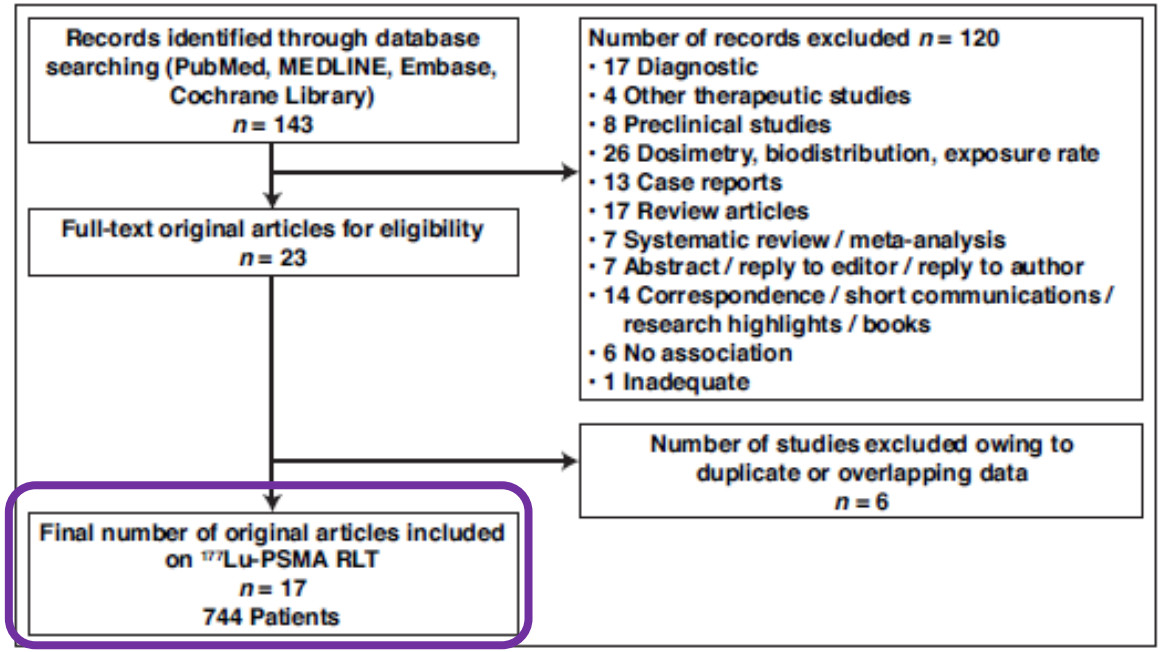
Established tolerance limits for
- red marrow are 2 Gy (single exposure)
- kidneys are 28–40 Gy (depending on risk factors; data for 177Lu-PRRT considered more appropriate than literature data for external beam radiotherapy)
- salivary glands are 35 Gy

Lu177-PSMA

- **Since 2013** an increasing number of clinical publication promising efficacy of PSMA theranostic
- **Meta-analysis and reviews**

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

Yadav MP[1], Ballal S[1], Sahoo RK[2], Dwivedi SN[3], Bal C[1].



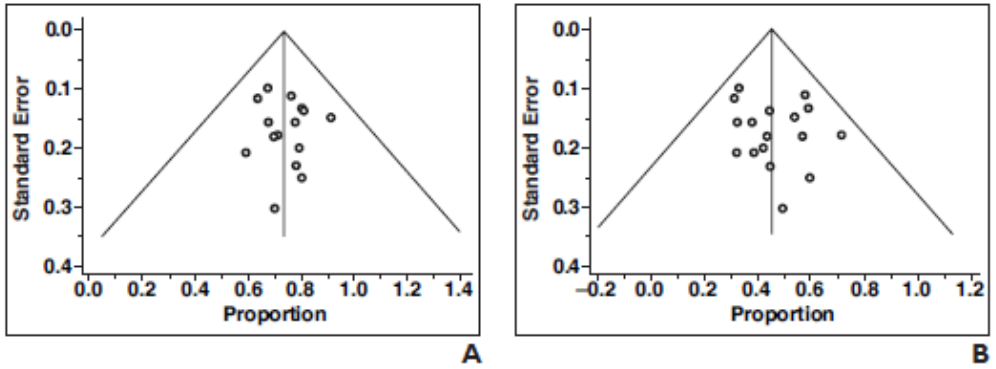


Fig. 2—Bias across studies.
A, Funnel plot shows frequency of any prostate-specific antigen (PSA) decline after ^{177}Lu-labeled prostate-specific membrane antigen (PSMA) radioligand therapy (RLT).
B, Funnel plot shows frequency of greater than 50% PSA decline after ^{177}Lu-PSMA RLT.

AJR 2019 Aug; 213 (2) 275-285

Meta-analysis

Lu177-PSMA

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Any PSA decline

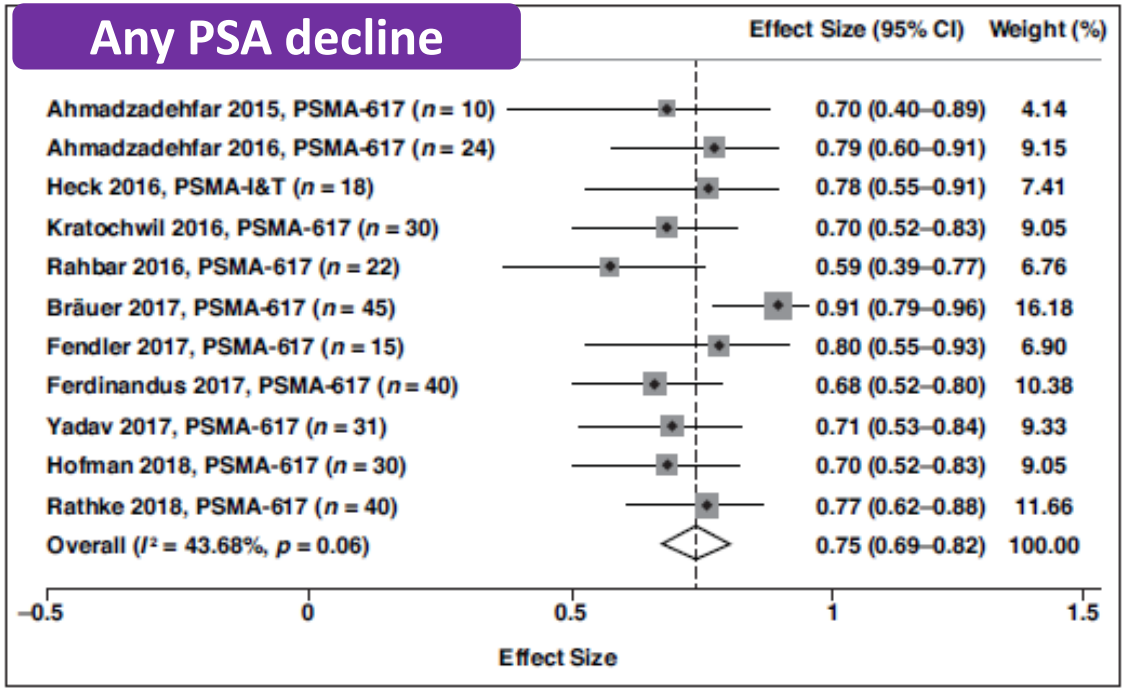

Fig. 4—Forest plot shows results of subgroup analysis for any prostate-specific antigen decline in 11 articles with patient population less than 50. PSMA = prostate-specific membrane antigen, I&T = imaging and therapy.

PSA decline >50%

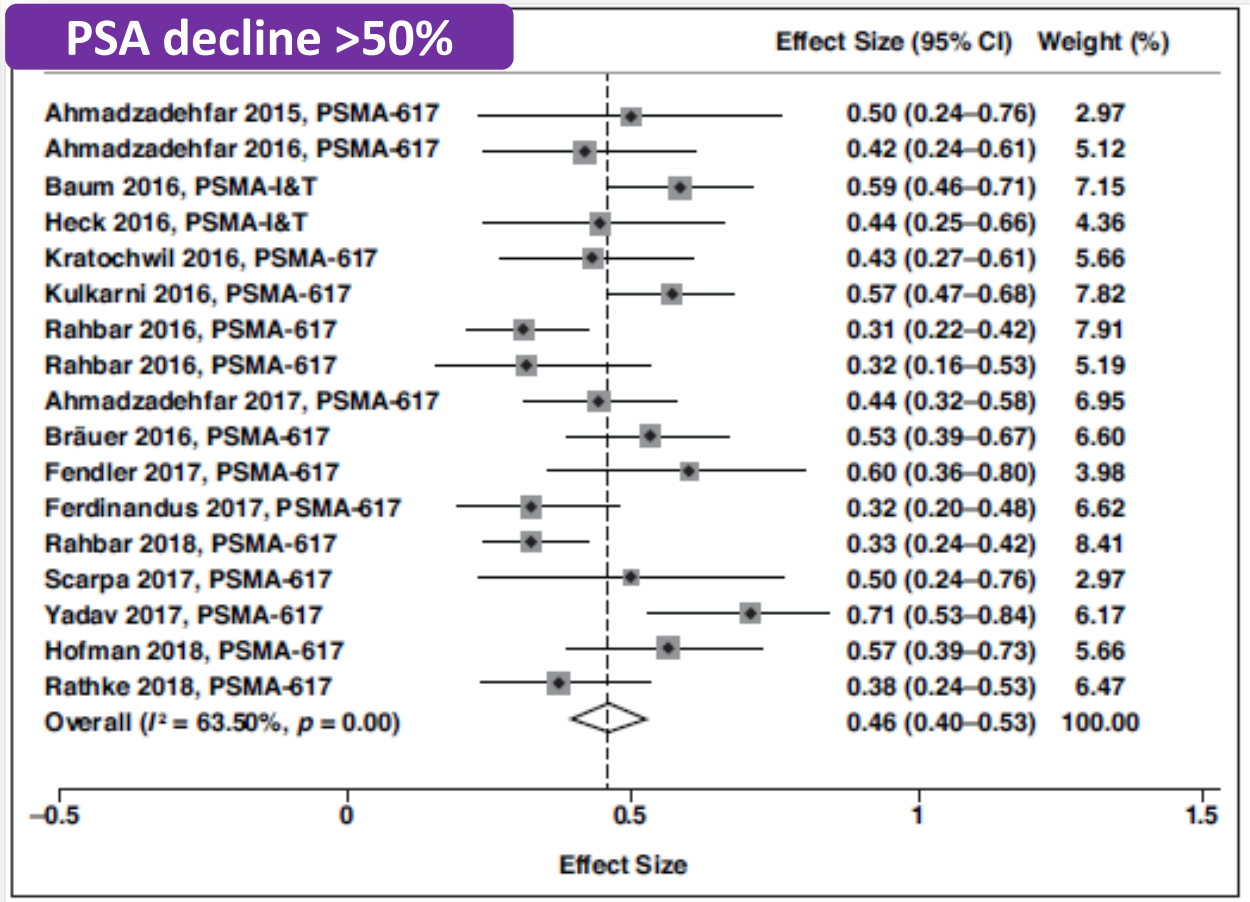

Fig. 6—Forest plot shows greater than 50% decline in prostate-specific antigen level after ^{177}Lu-labeled prostate-specific membrane antigen (PSMA) radioligand therapy. I&T = imaging and therapy.

AJR 2019 Aug; 213 (2) 275-285

Meta-analysis

Lu177-PSMA

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OS

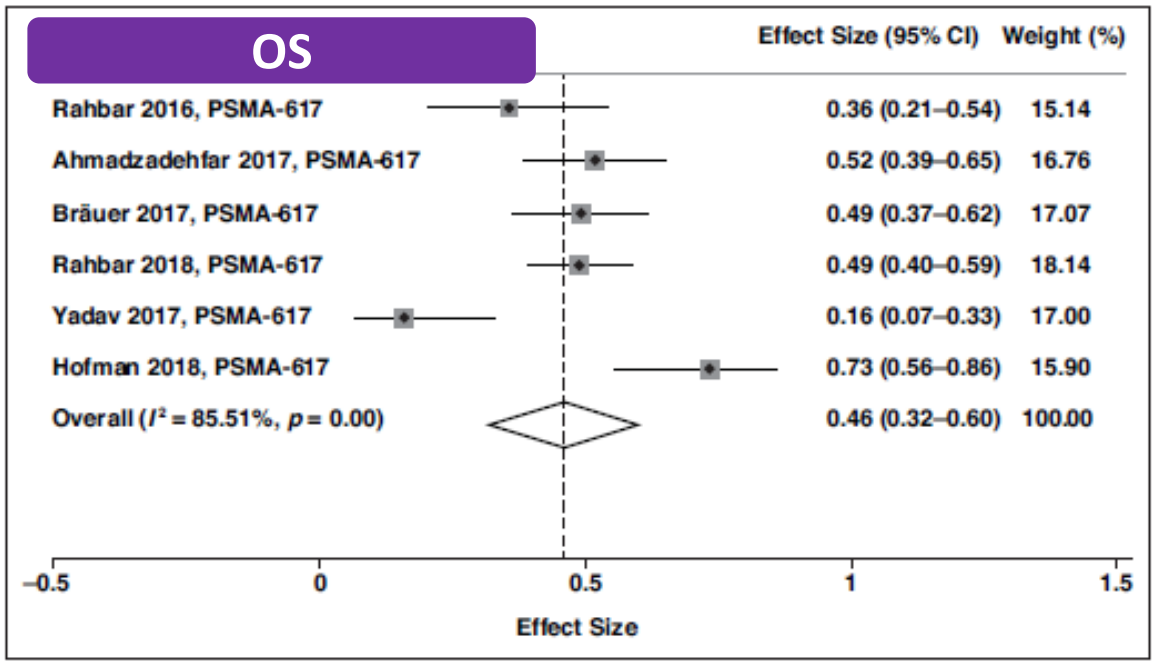

Fig. 8—Forest plot shows pooled proportion of overall survival in six articles on ^{177}Lu-labeled prostate-specific membrane antigen (PSMA) radioligand therapy.

PFS

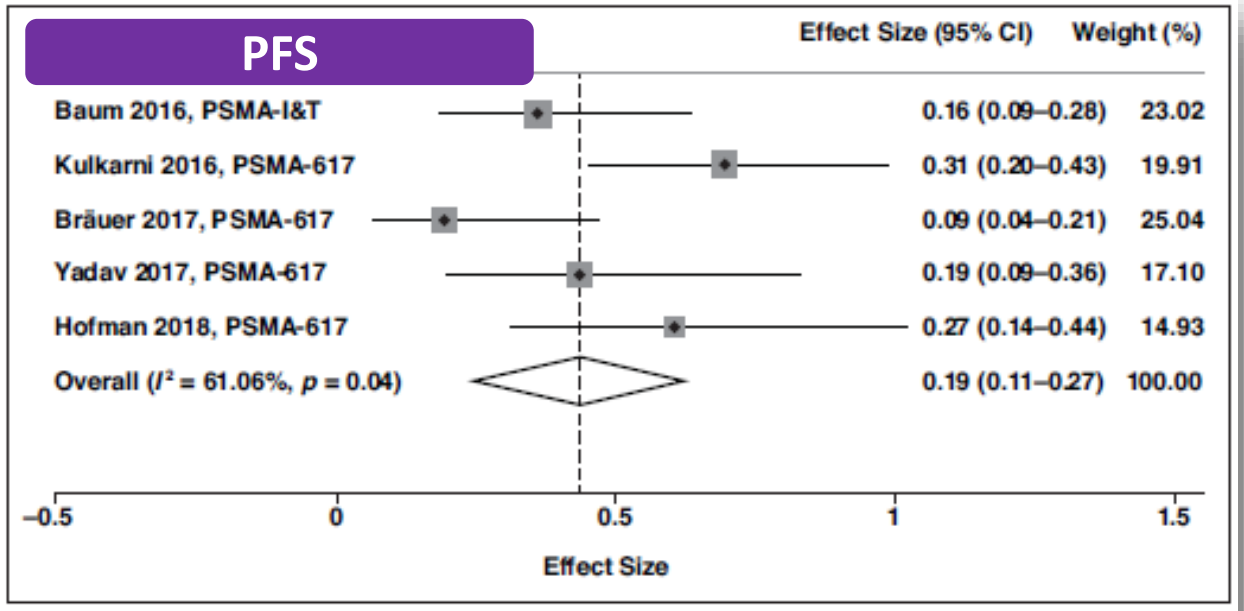

Fig. 9—Forest plot shows progression-free survival in five articles on ^{177}Lu-labeled prostate-specific membrane antigen (PSMA) radioligand therapy. I&T = imaging and therapy.

AJR 2019 Aug; 213 (2) 275-285

Meta-analysis

Lu177-PSMA

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Toxicities

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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On-going studies

Lu177-PSMA

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- **VISION Trial: 177Lu-PSMA-617 vs standard of care**
  - Phase III trial (2 : 1)
  - Randomized **750 patients** with mCRPC → at least one regime of ChT and secondary hormonal manipulation
  - Primary end point: OS and PFS
  - Enrollment end in 2019

If VISION succeeds, it establishes a new line of therapy for prostate cancer that becomes the developmental paradigm for theranostics; the ability to use ^{68}Ga-PSMA-617-based imaging to identify patients for treatment with ^{177}Lu-PSMA-617. If successful, it may become impossible to conduct any subsequent study testing whether the VISION target population benefits from ^{177}Lu-PSMA-617 in terms of overall survival. Alternatively, if VISION fails, meaning that the largest well-designed and executed study of a theranostic pair has failed, this would be a draw back for the entire field of theranostics. Independent of the activity of the drug, success or failure is in the hands of the clinical investigators and their ability to maintain the integrity of the VISION study as it is designed.

Journal of Nuclear Medicine August 28, 2019

On-going studies

Lu177-PSMA

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- **TheraP: 177Lu-PSMA-617 (up to 6 cycles) vs Cabazitaxel (II°line ChT, up to 10 cycles)**
  - Phase II trial
  - 200 patients with mCRPC → progression despite hormonal therapy and first line ChT
  - Primary end point: PSA response rate
  - Secondary end point: pain response, PFS, QoL and averse events

- **LuPARP: 177Lu-PSMA-617 +/- Olaparib**
  - Phase I trial, open-label, multicenter
  - mCRPC progressed with androgen receptor target therapy (abiraterone or enxalutamide or apalutamide) and No prior exposure to platinum agents
  - Primary end point: safety and tolerability
  - Secondary end point: pain response, PFS, QoL and averse events
  - Enrollment ended

- **PRINCE trial: 177Lu-PSMA-617 +/- Pembrolizumab**
  - Phase I/II trial
  - mCRPC
  - Primary end point: PSA response rate and adverse events.

Lu177-PSMA

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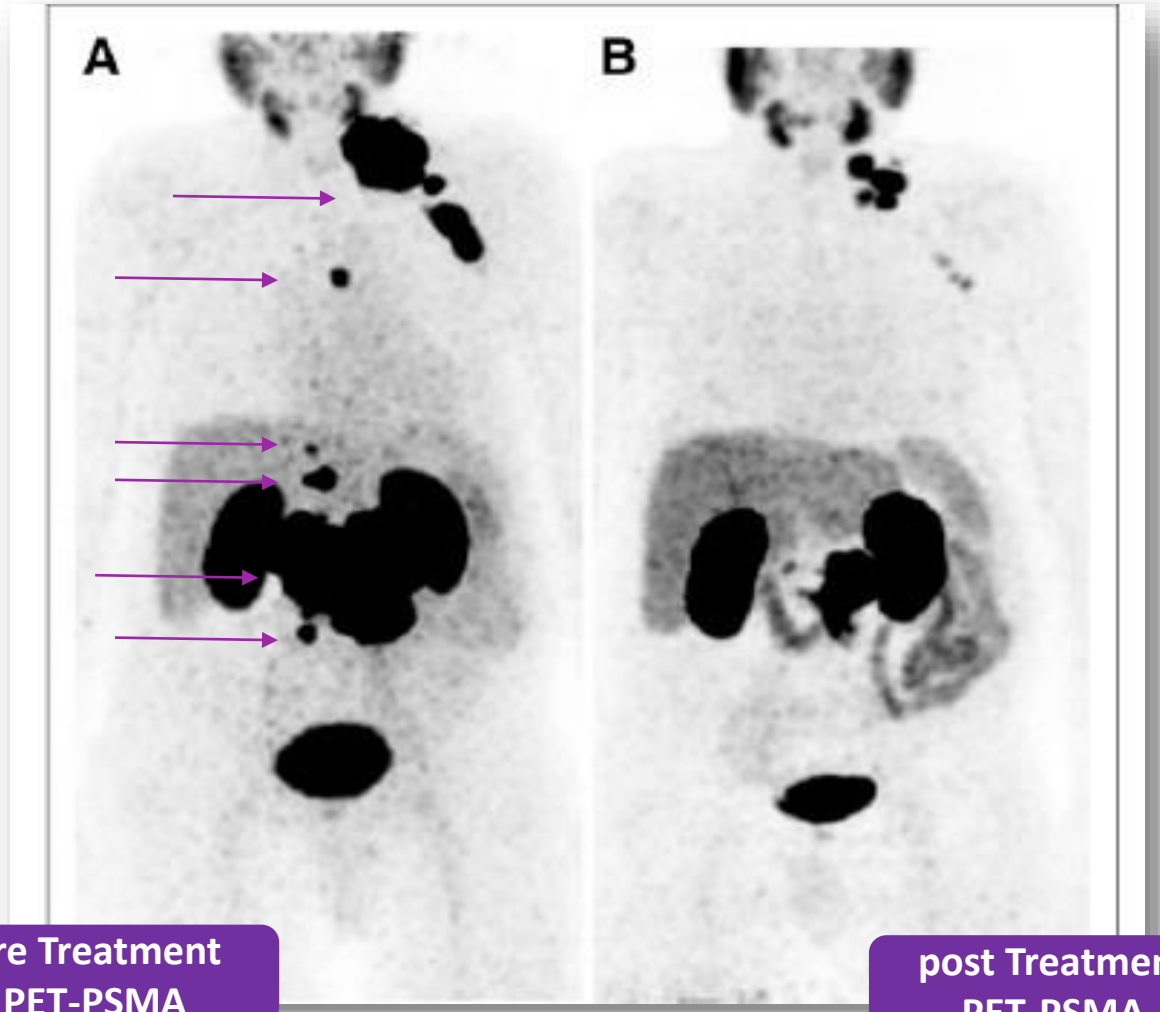
Initial stage: cT3acN1cM0 GS4+3
Hormone ablation therapy +EBRT
mCRPC → several systemic therapies (Abiraterone acetate, Docetaxel and Enzalutamide) → PD (lymphnodes)

3 Cycles of 177Lu-PSMA



pre Treatment PET-PSMA

post Treatment PET-PSMA

J Nucl Med 2019; 60:13S–19S

Lu177-PSMA

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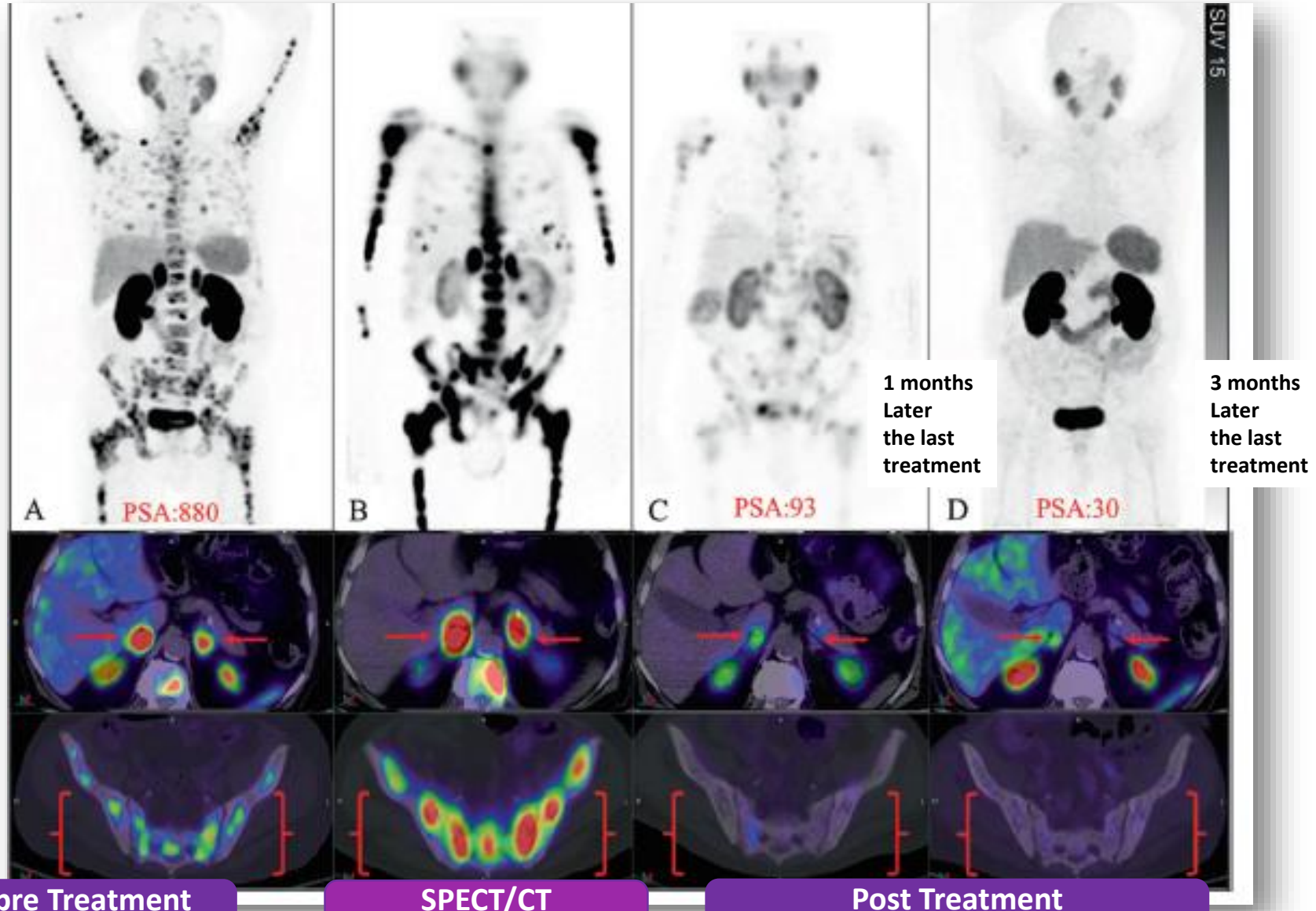

pre Treatment PET-PSMA

SPECT/CT Lu177 PSMA I°cycle

Post Treatment PET-PSMA (total III°cycles)

Nadir after 17Lu-PSMA:
PSA 7,3 ng/ml

Phase II prospective trial
Hofman et al JCO 2019; 37: 228

Lu177-PSMA

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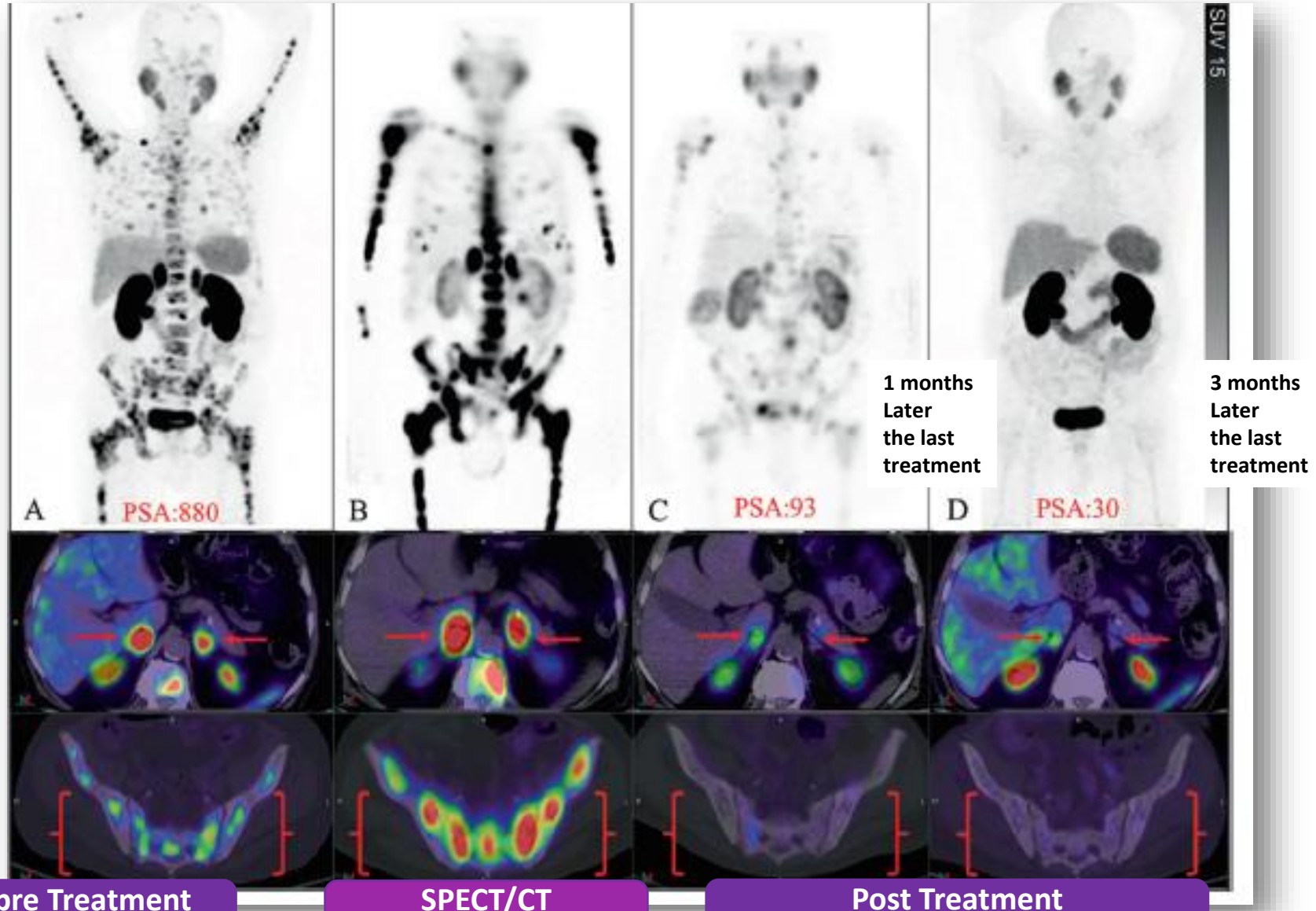
Exceptional responders 16% (8/50)

NOT completed the schedule IV°cycles due to lack of residual disease

This exceptional response should be studied maybe with DNA sequencing for germline or somatic mutations in DNA repair pathways



Nadir after 17Lu-PSMA: PSA 7,3 ng/ml

Phase II prospective trial
Hofman et al JCO 2019; 37: 228

Lu177-PSMA

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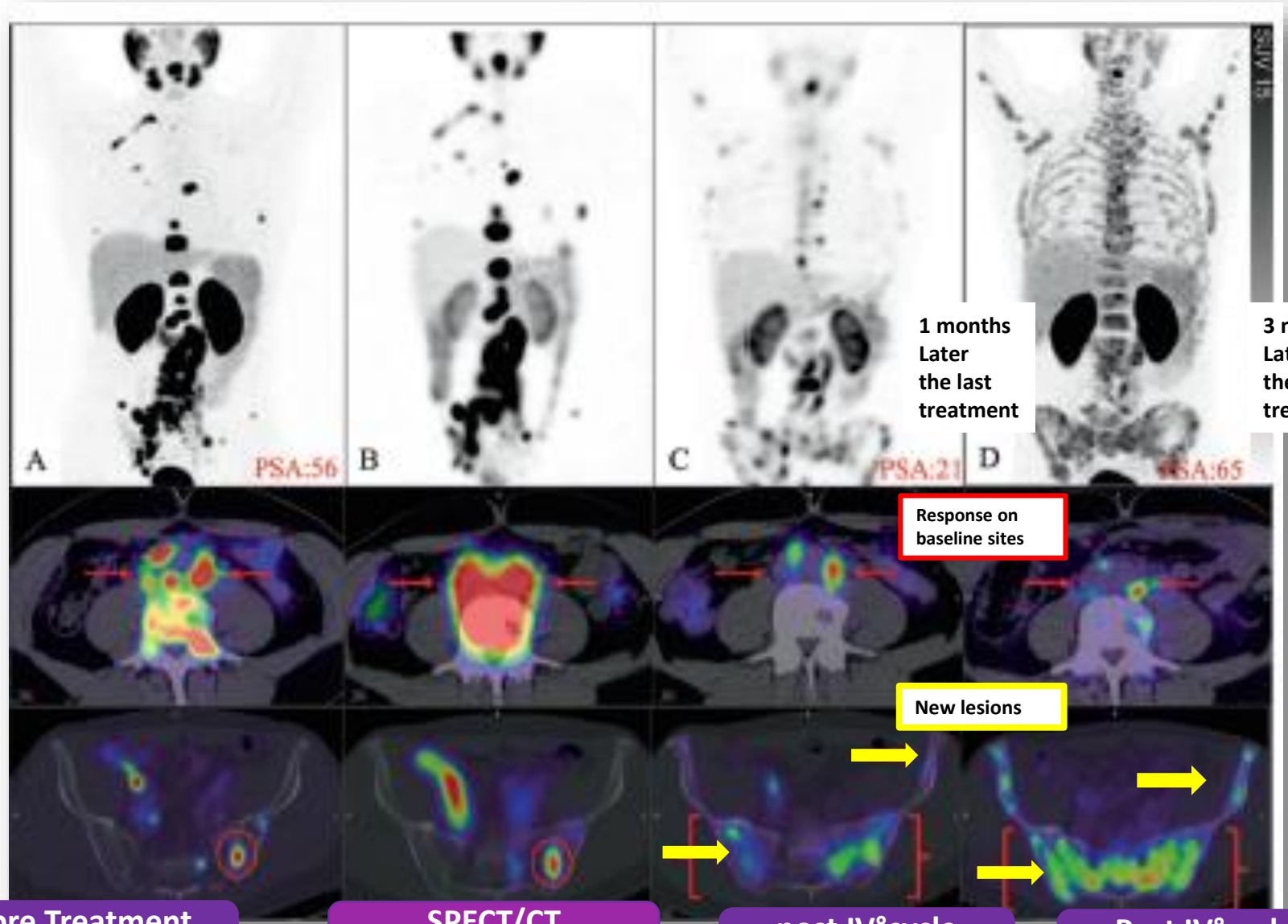

Iravani, Springer Nature 2019

Lu177-PSMA

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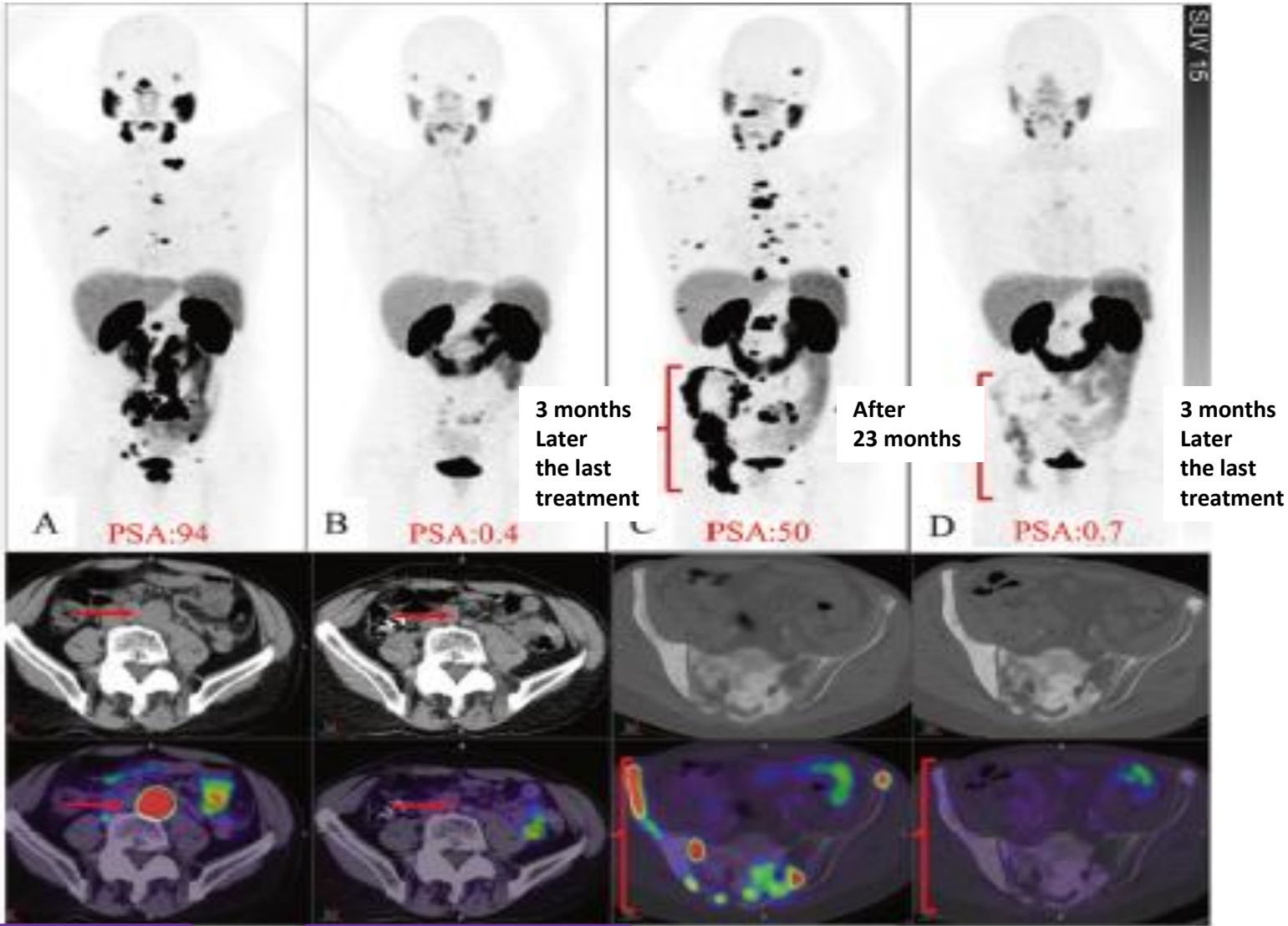
Cancer Care Center
Negrar di Valpolicella (Vr)

Retreatment
First treatment: III Cycles

After 23 months:
II more cycles.



pre Treatment PET-PSMA

SPECT/CT Lu177 PSMA I°cycle

post IV°cycle IV PET-PSMA

Post IV°cycle PET-PSMA

Iravani, Springer Nature 2019

225Ac-PSMA

- **Alpha therapy** with radiolabeled PSMA inhibitors

- Some issues:
  - Side effect
    - Xerostomia (nonspecific binding to normal tissues such as salivary gland and kidneys) and in a study 10% discontinued therapy due to this side effect. → Several groups are trying different techniques of blocking the salivary glands.
    - Hematologic toxicity in the form of anemia was seen in 37% (but mild: mainly G1-2)
  - Limited availability of 225Ac but new techniques have been investigated such as 225Ac production with low energy proton accelerators.

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