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Congress Report EANM 2022

A CONGRESS DIGEST ON RADIOLABELED THERANOSTICS FOR SOLID TUMORS

Report from the 35th Annual Congress of the European Association of Nuclear Medicine (EANM), October 15th – 19th, 2022, Barcelona

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Preface

Dear Colleagues,

After two years of virtual events, the nuclear medicine and oncology communities were excited to meet each other in person at the 35th Annual Congress of the European Association of Nuclear Medicine, held in Barcelona, Spain, and virtually from 15th – 19th October 2022. The event has celebrated its status as the world's leading meeting for nuclear medicine, with more than 7000 participants from 121 countries presenting and discussing groundbreaking clinical updates and scientific research advancements in several disease areas. More than 1,000 oral abstracts and 865 e-posters were presented at the event in 223 scientific sessions.

Since the radioligand therapy with ^{177}Lu-PSMA-617 (Pluvicto®) was approved by both FDA and EMA in 2022 for metastatic castration-resistant prostate cancer (mCRPC), this memo inOncology special issue provides not only an insight into the latest advancements in imaging and treatment of mCRPC but also of neuroendocrine tumors (NETs).

The prostate cancer imaging section includes results from two phase 3 trials, PYTHON and SPOTLIGHT, investigating novel radio-diagnostic tracers for PET imaging as well as biomarker analysis from the TheraP trial assessing the predictive benefit of PSMA- and FDG-PET with clinical outcomes.

Next, the latest developments in prostate cancer treatment are highlighted with emphasis on patient-reported outcomes from the VISION trial and quality of life data of ^{177}Lu-PSMA-617 in a palliative setting. Multiple clinically relevant trials are summarized using Lu-PSMA (both PSMA-617 & PSMA-I&T) prospectively and in a real-world setting. Moreover, radioligand therapy for mCRPC using alpha emitters such as ^{225}Ac-PSMA, which have gained importance in recent years as a last-resort treatment option in mCRPC patients, is also described.

Data regarding two promising fluorine-18 labeled somatostatin analogues (SSA) targeting PET/CT alternatives, as well as a retrospective analysis of 1000 NET patients with somatostatin receptor SSR-PET/CT and matching liver MRI performed within a short interval are included in the imaging section of NETs.

Finally, the promising efficacy and safety data of ^{177}Lu-DOTATATE in a first randomized trial in advanced progressive SSR-positive pancreatic NET patients as well as from a multi-center registry, are summarized in the final section. As an add-on, you can find retrospective


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data of ^{225}Ac-DOTATOC in the upfront as well as salvage treatment setting in patients with NETs.

Overall, this meeting once again highlighted that the era of theranostics offers an excellent opportunity to improve cancer care with new treatment paradigms and innovations on the horizon. Based on the intensive scientific exchange at the EANM 2022, theranostics are on the rise to becoming an imminent core of personalized cancer treatment.

We hope you enjoy reading this special issue!

Oana C. Kulterer, MD
Division of Nuclear Medicine, Department of Biomedical Imaging and Image-Guided Therapy, Medical University Vienna, Vienna, Austria

Advances in PSMA radiotracers for prostate cancer imaging

[^{18}F]DCFPyL tops [^{18}F]Flurocholine in the recurrent setting: PYTHON

Prostate-specific membrane antigen (PSMA)-targeting positron emission tomography/computed tomography (PET/CT) imaging is increasingly used to characterize prostate cancer (PCa). However, in Europe, there is still an unmet need for radiotracers to localize biochemical recurrences in PCa. The phase III PYTHON trial is designed to establish the efficacy and safety of [^{18}F]DCFPyL- compared to [^{18}F]Flurocholine-PET/CT in patients with first biochemical recurrence after initial definitive therapy (prostatectomy, external beam radiotherapy or brachytherapy) for histopathologically confirmed prostate adenocarcinoma per original diagnosis [1]. The primary objective is the per-patient detection rate (DR) of both tracers, while the secondary objective includes the assessment of the im-

pact on patient treatment management, the per-region detection rate, the sensitivity and specificity on a per-patient and per-region basis, the concordance rate between both tracers, and the safety.

A total of 205 patients were enrolled in the study, with 73.2 % undergoing radical prostatectomy as initial treatment and 38.7 % belonging to a high D'Amico risk class. DR of [^{18}F]DCFPyL-PET/CT was higher than [^{18}F]Flurocholine-PET/CT (58.2 % vs. 40.3 %; p < 0.0001, **Figure 1**) and was independent of the initial treatment or prostate-specific antigen (PSA) detection, D'Amico risk class, or International Society of Urologic Pathologists (ISUP) grade. Safety results were similar between the two tracers, with all treatment-emergent adverse events (TEAEs) reported being unrelated to the tracer injection. Moreover, [^{18}F]DCFPyL-PET/CT showed a higher impact on patient treatment management.

The positive efficacy and safety results from the PYTHON trial reinforced the diagnostic performance of [^{18}F]DCFPyL-PET/CT shown previously in its pivotal US clinical trials, OSPREY [2] and CONDOR [3], which led to its FDA approval in May 2021.

^{18}F-rhPSMA-7.3 PET informs salvage therapy decisions in recurrent prostate cancer: additional results from Phase 3 SPOTLIGHT Study

^{18}F-rhPSMA-7.3 – a radiohybrid (rh) platform – represents a new class of high-affinity PSMA-targeted theranostic PET radiopharmaceuticals with the potential for low bladder activity being investigated for diagnostic imaging in patients with prostate cancer. The phase III SPOTLIGHT trial included patients with suspected prostate cancer recurrence based on elevated PSA following prior therapy, and being eligible for salvage therapy with curative intent. Patients were imaged with 296 MBq of ^{18}F-rhPSMA-7.3, followed by PET/CT 50–70 minutes post-injection. Three blinded central readers evaluated the scans [4].

A clinically significant 57 % Standard of Truth (SoT)-verified DR was presented at ASCO GU 2022, where composite SoT consisting of either histopathology or conventional imaging was used to confirm positive findings [4].

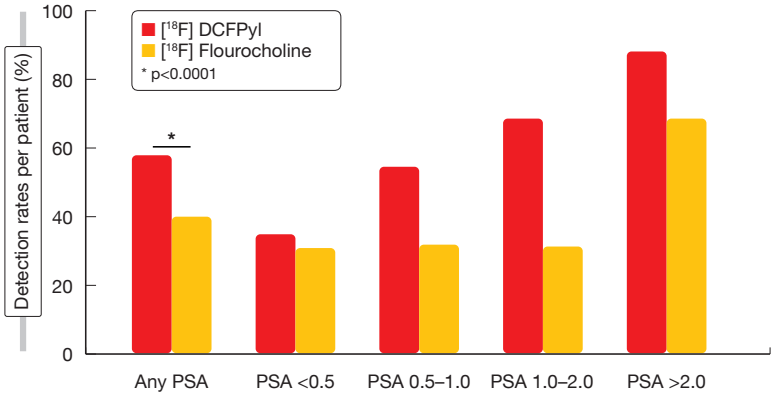

Figure 1: Detection rates for [^{18}F]DCFPyL- and [^{18}F]Flurocholine-PET/CT based on patient's PSA values

At EANM 2022, Hermsen et al. presented an exploratory analysis of the true positive (TP) ^{18}F-rhPSMA-7.3 scans in pelvic lymph nodes or extra-pelvic (metastatic) regions that led to upstaging in a subgroup of patients who had presented a negative baseline conventional imaging ≤118 days before PET [5].

Of the 366 men who were scanned and had sufficient data to determine SoT, 250 (68 %) had conventional imaging indicating negative at baseline, comprised mainly of ^{99m}Tc-bone scan (56 %) or CT (46 %). According to the 3 blinded readers, TP lesions in pelvic lymph nodes were detected in 18–21 % of patients who had undergone prostatectomy and 6.5 % of patients who had received radiotherapy. The TP rates in extra-pelvic metastatic sites leading to upstaging accounted for 21–26 % of patients who had undergone prostatectomy and 20–30 % of patients who had received radiotherapy.

These data showed that investigational ^{18}F-rhPSMA-7.3 PET/CT frequently identified TP pelvic nodal and metastatic lesions, supporting its potential clinical utility in men with recurrent prostate cancer to help define sites of disease recurrence and inform salvage therapy decisions.

Predictive benefit of PSMA- and FDG-PET in mCRPC: TheraP trial analysis

TheraP trial is the first randomized trial demonstrating that the treatment with [^{177}Lu]Lu-PSMA-617 improves the PSA response rate by more than 50 % from baseline (PSA-50RR; 66 % vs. 37 %) and delays progression-free survival (hazard ratio (HR) 0.63; 95 % CI 0.46-0.86; p = 0.0028) compared to cabazitaxel in patients with metastatic castration-resistant prostate cancer (mCRPC) [6]. Inclusion criteria were high PSMA uptake (maximum standardized uptake value (SUVmax) ≥20) on a [^{68}Ga]Ga-PSMA-11 PET (PSMA-PET) scan at a disease site and no [^{18}F]fluoro-2-deoxy-D-glucose (FDG)-positive/PSMA-negative lesions. Buteau et al. presented data from a prespecified tertiary endpoint of PSMA-PET and FDG-PET imaging parameters as well as predictive and prognostic biomarkers in the TheraP trial population [7, 8].

mCRPC patients who had prior docetaxel treatment and were eligible for cabazitaxel treatment were assigned 1:1 to either cabazitaxel (20 mg/m² IV every 3 weeks for up to 10 cycles) or [^{177}Lu]Lu-PSMA-617 (6·0–8·5 GBq IV every 6 weeks for up to six cycles). High PSMA uptake (SUVmean of ≥10 on PSMA-PET) was evaluated as a predictive biomarker for response and metabolic tumor volume (MTV) of ≥200 mL in FDG-PET as a prognostic biomarker, respectively.

Out of the 200 randomized patients, 35 % of the [^{177}Lu]Lu-PSMA-617 and 30 % of the cabazitaxel treatment arm had a high PSMA uptake (SUVmean ≥10) which in turn predicted a higher likelihood of favorable response to [^{177}Lu]Lu-PSMA-617 than cabazitaxel (Odds ratio (OR) 12.2 vs. 2.2; p = 0.03). Moreover, a PSA50-RR benefit of 91 % vs. 47 % in patients with SUVmean ≥10 and 52 % vs. 32 % in patients with SUVmean <10 was reported **(Figure 2)**.

On the other hand, high-volume disease measured by FDG-PET (MTV ≥200 mL) was noted in 30 % of patients

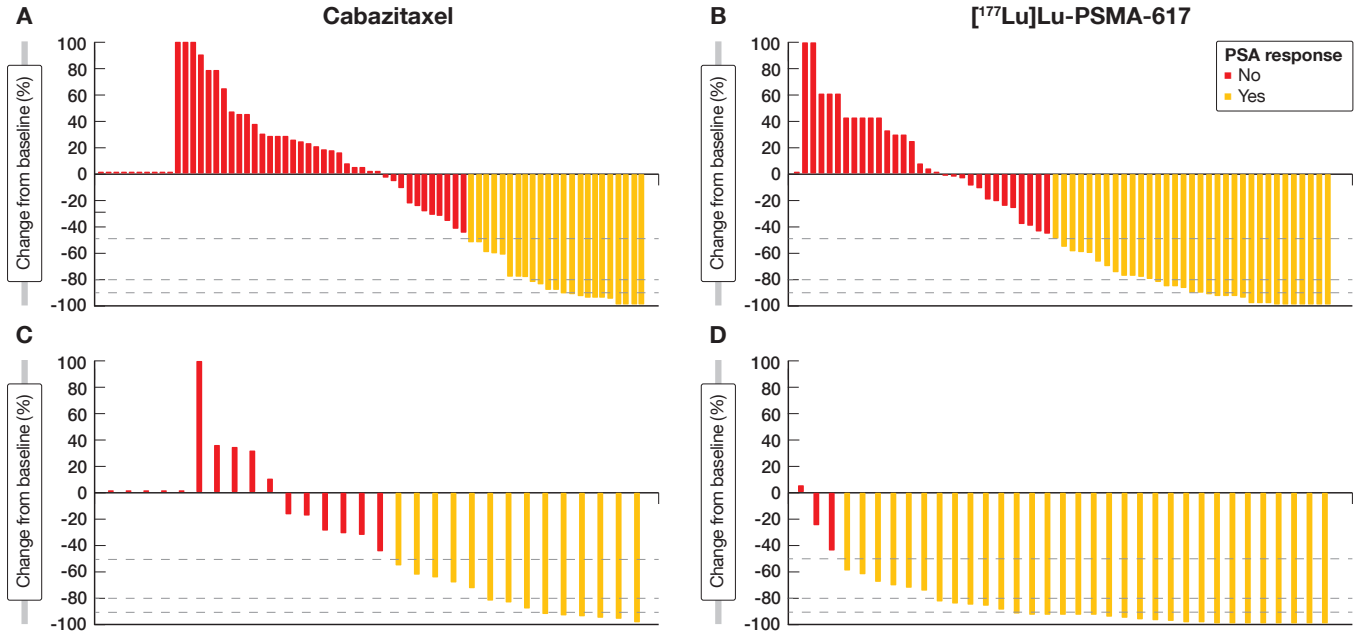

Figure 2: Waterfall plots of the best PSA decline from baseline for patients with PSMA SUVmean <10 (A, B) and PSMA SUVmean ≥10 (C, D) who were allocated cabazitaxel (A, C) vs [^{177}Lu]Lu-PSMA-617 (B, D)

in both treatment arms. The PSA50-RR for randomized groups combined for FDG MTV ≥200 mL vs. <200 mL were 23/60 (38 %) vs. 79/140 (56 %), respectively. After accounting for treatment, higher FDG volume was suggested as a prognostic marker for worse response to either [^{177}Lu]Lu-PSMA-617 or cabazitaxel (OR 0.44; p = 0.01).

The authors concluded PSMA-PET SUVmean as a potential predictive biomarker for a higher likelihood of favorable response to [^{177}Lu]Lu-PSMA-617 than cabazitaxel, providing guidance for optimal [^{177}Lu]Lu-PSMA-617 use in mCRPC patients. High FDG-PET MTV was associated with lower responses regardless of assigned treatment, warranting further investigation for treatment intensification. ■

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Latest developments in prostate cancer treatment

Favorable complementary mechanisms: $^{223}RaCl_2$ followed by ^{177}Lu-PSMA (RALU)

The positive efficacy and safety data of ^{177}Lu-PSMA-617 in the treatment of mCRPC patients from the Lu-PSMA and VISION trials led to its FDA approval and designation as a breakthrough therapy for later lines of mCRPC treatment [1,2]. ^{223}Ra-dichloride ($^{223}RaCl_2$) is a targeted α-therapy and prolongs OS in patients with bone-predominant mCRPC [3].

RALU is a retrospective study investigating the safety and clinical effectiveness of ^{177}Lu-PSMA radioligand therapy (^{177}Lu-PSMA-617 or ^{177}Lu-PSMA-I&T) in mCRPC patients who already received $^{223}RaCl_2$ in routine clinical practice [4]. Data were analyzed from 133 patients who received either ^{177}Lu-PSMA-617 (65 %) or ^{177}Lu-PSMA-I&T (35 %) after $^{223}RaCl_2$.

The median PSA and alkaline phosphatase (ALP) among enrolled patients were 285.5 ng/ml and 146.0 U/L, respectively, with 56 % receiving ≥4 therapies before starting ^{177}Lu-PSMA. All patients received prior $^{223}RaCl_2$; other prior treatments included abiraterone (71 %), enzalutamide (70 %), docetaxel (74 %), and cabazitaxel (23 %). All patients had bone metastases, and 27 % had visceral metastases at baseline. Overall, 73 % of patients received 1-4 cycles of ^{177}Lu-PSMA, and 27 % received ≥5 cycles.

Any grade and grade 3/4 TEAEs occurred in 79 % and 28 % of patients, respectively, during and after ^{177}Lu-PSMA till the end of a 30-day follow-up period. Overall, 10 % stopped, interrupted, or delayed ^{177}Lu-PSMA treatment due to TEAEs. Grade 3/4 hematologic laboratory abnormalities up to 90 days post-^{177}Lu-PSMA occurred in 30 %, 13 % and 2 % of patients for anemia, thrombocytopenia and neutropenia, respectively. The most common TEAEs of any grade, excluding lab abnormalities, were dry mouth (15 %), nausea (9 %), and fatigue (8 %). The median OS was 13.2 months (95 % CI 10.5-15.6) from the first dose of ^{177}Lu-PSMA treatment, with the median OS extending to 33.4 months (95 % CI 31.2-37.4) from the first dose of $^{223}RaCl_2$ **(Figure 1)**. ^{177}Lu-PSMA-617 and ^{177}Lu-PSMA-I&T use had similar OS outcomes and similar toxicity profiles. During ^{177}Lu-PSMA treatment, 42 % of patients had a PSA50 response, and 19 % had an ALP30 response (defined as a decrease of ≥30 % in ALP from baseline).

In a real-world setting, the earlier incorporation of $^{223}RaCl_2$ in the treatment sequence with subsequent ^{177}Lu-PSMA therapy was clinically feasible in heavily pretreated patients with mCRPC. These results are similar to those reported in previous phase III and real-world studies [5-7].

Benefit in patient-reported outcomes with ^{177}Lu-PSMA-617: Updated VISION

In the phase 3 VISION study, ^{177}Lu-PSMA-617 plus standard-of-care (SoC) showed a significant benefit in the radiographic progression-free survival (rPFS) (HR 0.40; 99.2 % CI 0.29-0.57) and OS (HR 0.62; 95 % CI 0.52-0.74) versus SoC (both p<0.001) [2]. Hermann et al. presented the VISION study's secondary endpoints: health-related quality of life (HRQoL), pain, time to first symptomatic skeletal event (SSE), and updated safety data [8].

The VISION study is a randomized phase 3 trial in adults with PSMA-positive mCRPC previously treated with at least one androgen receptor pathway inhibitor (ARPI) and one or two taxane chemotherapy regimens. Eligible participants were randomized 2:1 to SoC therapy plus six cycles of ^{177}Lu-PSMA-617 versus SoC alone.

The two patient-reported outcomes evaluated in the study were the FACT-P score and the BPI-SF pain intensity score. Time to worsening for both of these metrics favored the addition of ^{177}Lu-PSMA-617 to SOC with a delay of 7.3 months (9.7 vs. 2.4 months (HR 0.46; p<0.001)) for the FACT-P score and 11.4 months (14.3 vs. 2.9 months (HR 0.45; p<0.001)) for the BPI-SF pain intensity score **(Figure 2)**.

Moreover, the time to first SSE or death was delayed from 6.8 months to 11.5 months by ^{177}Lu-PSMA-617 addition to SoC (HR 0.50; 95 % CI 0.40-0.62; p<0.001) regardless of bone-targeted therapy being part of SoC. Spinal cord compression, the most deleterious SSE, was less frequent in the ^{177}Lu-PSMA-617 arm compared to SoC alone (1.3 % vs. 5.6 %).

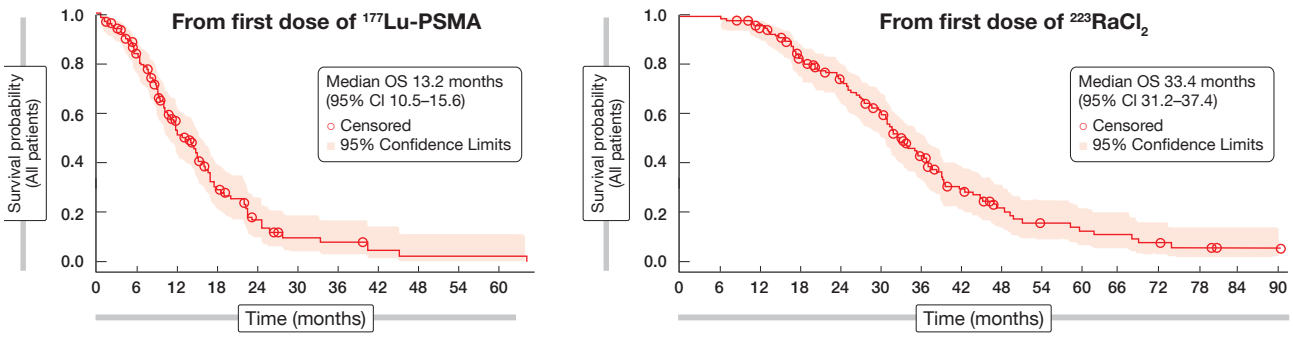

Figure 1: Overall survival with Lu-PSMA treatment since the first dose of Lu-PSMA (left) and the first dose of $^{223}RaCl_2$ (right) in the RALU study

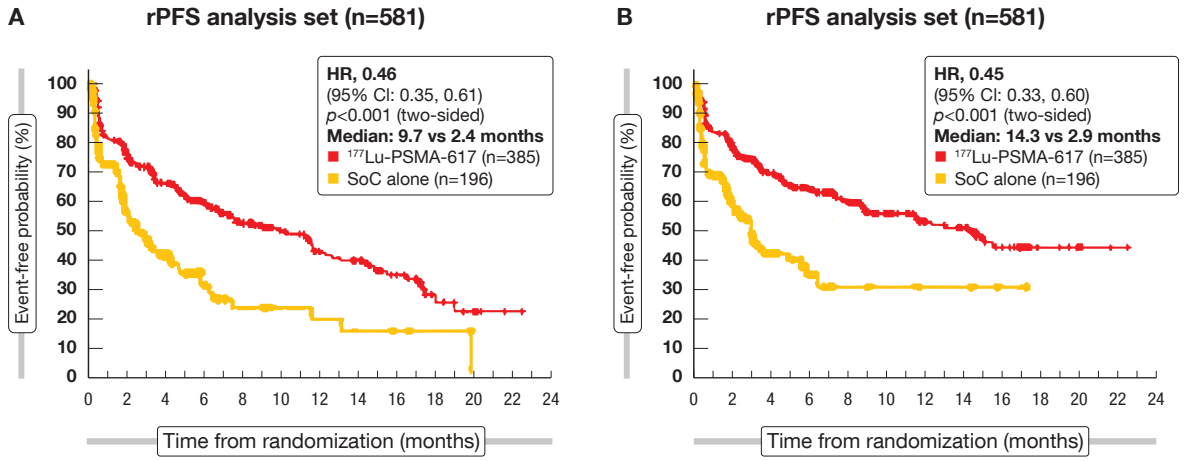

Figure 2: Kaplan-Meier estimates of time to worsening in FACT-P total score **(A)** and BPI-SF pain intensity **(B)** in the rPFS analysis set of the VISION study

An updated assessment of TEAEs confirmed that the addition of ^{177}Lu-PSMA-617 was generally well-tolerated. However, a higher incidence of grade 3-5 TEAEs occurred in patients treated with ^{177}Lu-PSMA-617 related to bone marrow suppression, dry mouth, nausea/vomiting, and renal effects. A low incidence of grade 3/4 creatinine abnormalities was observed in both arms, with creatinine levels being stable throughout the entire duration of the study.

The updated results from the secondary endpoints of the VISION study support the use of ^{177}Lu-PSMA-617 as a subsequent treatment option in mCRPC patients who have received at least one ARPI or taxane-containing regimen.

^{177}Lu-PSMA I&T efficacious with good safety profile: data from prospective Swiss-registry study

^{177}Lu-ITG-PSMA-1, also known as ^{177}Lu-PSMA I&T, is a DOTAGA-chelated urea-based PSMA inhibitor currently being tested in a prospective, randomized phase 3 trial in patients with progressive mCRPC (ECLIPSE, NCT05204927). At EANM, Nicolas and Chirindel et al. presented data regarding the safety and efficacy of ^{177}Lu-PSMA I&T implemented in daily clinical practice in Switzerland [9].

Patients with mCRPC, who were PSMA+ and unfit for chemotherapy, who progressed on androgen receptor-axis-targeted therapies (ARAT), received ^{177}Lu-PSMA I&T (6-8 GBq, 4-6 cycles every 6 weeks). The primary endpoint was safety, and key secondary endpoints included PSA response and OS.

Of the 107 registered patients, 93 were included based on sufficient follow-up data for the preliminary two-year analysis. Compared to the VISION trial, a higher proportion of patients with lymph node (78 %) or soft tissue metastases (30 %) were enrolled in the study [2]. On the other hand, the proportion of patients who received prior chemotherapy was lower in this study than in the VISION trial (64 % vs. 97 %), with patients receiving fewer Lu-PSMA treatment cycles (median 3 vs. 5).

The preliminary safety analysis showed a high incidence of grade ≥3 lymphopenia (20 %) and anemia (13 %) with ^{177}Lu-PSMA I&T treatment. No grade ≥3 xerostomia event was observed, with low incidences of grade ≥3 thrombocytopenia (3 %) reported. The preliminary efficacy results of ^{177}Lu-PSMA I&T treatment regarding biochemical response (any PSA-response: 71 %; PSA50-response: 47 %) and median OS (15 months) were similar to those reported with ^{177}Lu-PSMA-617 treatment in the VISION trial.

This preliminary analysis from a real-world setting adds to the tolerable safety profile and efficacy of Lu-PSMA radioligand therapies in the treatment of mCRPC patients.

^{177}Lu-PSMA-617 impacts QoL in mCRPC patients in a palliative setting

Improving the patient's quality of life (QoL) while providing disease control is the ultimate goal of palliative care. Scheer et al. evaluated the impact on QoL of ^{177}Lu-PSMA-617 in patients with advanced mCRPC treated in a palliative setting [10]. QoL was prospectively assessed in 44 patients (age 58-84 years) at the beginning of every treatment cycle, using the QLQ-c30 score. Before every ^{177}Lu-PSMA-617 treatment cycle, serum PSA levels were analyzed as an indicator of tumor burden, and renal and salivary gland function, as an indicator of safety. Patients were treated at an 8-to-10-week interval and divided into three groups based on the number of treatment cycles received (≥2; ≥3; ≥4).

Treatment discontinuations occurred with an increasing number of treatment cycles. In this context, deterioration of the general condition, progressive disease, and renal failure were the main reasons for discontinuations. Interestingly, symptom burden decreased from the first to the third treatment cycle but increased in the fourth. Excretion from salivary glands decreased continuously, particularly after the fourth treatment. Effect on blood serum PSA reached nadir before the third treatment cycle, with ~50 % of patients experiencing a decrease of serum PSA levels of >90 % from the first to fourth treatment cycle.

The results indicated that palliative treatment with ^{177}Lu-PSMA-617 had a positive effect on patients' QoL, especially if the patients were able to receive multiple cycles of treatment. Of note, the tumor burden of the patients increased slightly during therapy. So far, no relevant therapy-associated side effects concerning bone marrow suppression, salivary gland, and kidney function were reported in the study.

	No of deaths	Median OS (in months) (95% CI)	OS rate at 6 months (in %) (95% CI)	OS rate at 12 months (in %) (95% CI)
3.7–4.4 GBq	23	17.4 (7.4–27.4)	79.4 (61.6–89.6)	55.9 (37.8–70.6)
5.5 GBq	12	19.8 (13.8-NE)	94.6 (80.1–98.6)	83.7 (64.5–93.0)

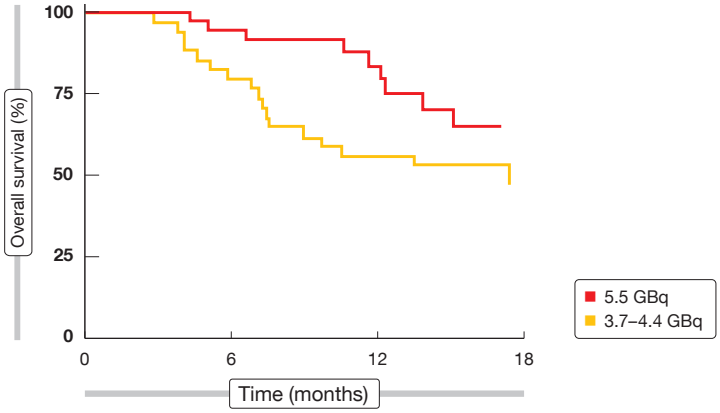

Figure 3: Overall survival curves in mCRPC patients based on the dose of ^{177}Lu-PSMA-617 received

^{225}Ac-PSMA in mCRPC patients progressing after androgenic treatment

Radioligand therapy using alpha emitters, such as ^{225}Ac-PSMA (both PSMA-617 & PSMA-I&T), have gained importance in recent years as a last-resort treatment option in mCRPC patients when all others have been exhausted [11,12]. The successful results were attributed to their short-range, high linear energy transfer causing double-strand breaks in DNA. In a retrospective study, 23 progressive mCRPC patients, who relapsed after new-generation anti-androgenic treatment and could not receive further systemic treatments, received ^{225}Ac-PSMA treatment at a single center [13]. Further inclusion criteria were having received two or more cycles of ^{177}Lu-PSMA therapy and discontinuation of treatment due to progression or unresponsiveness.

Enrolled patients received 1-4 cycles of ^{225}Ac-PSMA with a mean dose of 7.63 MBq (6.2-10 MBq) per cycle. The mean interval time between two doses of ^{225}Ac-PSMA was 116 days. One case of grade 3 hematological- and nephro-toxicity each was reported. Xerostomia grade 1-2 was observed in 40 % of patients.

Treatment response was evaluated in 16 patients whose ^{68}Ga-PSMA PET/CT images were available before and after the first course of ^{225}Ac-PSMA treatment. Partial responses and stable disease were observed in 5 patients (31 %) each, whereas 6 patients (38 %) showed disease progression, resulting in a disease control rate of 62 %. Around 32 % of patients had ≥50 % PSA decline, and 58 % had any PSA decline after the first cycle of ^{225}Ac-PSMA treatment. The mean PFS and OS were 3.1 and 7.3 months, respectively, comparatively shorter than previously reported pooled data from a meta-analysis of 9 studies [14].

In conclusion, ^{225}Ac-PSMA showed promise with its high disease control rate and favorable toxicity profile in advanced mCRPC patients for whom all treatment options were exhausted. Future randomized, controlled, and prospective trials are needed to further evaluate the therapeutic effects and survival benefits compared with existing clinical treatments.

Reduced dose of ^{177}Lu-PSMA might lead to OS benefits among elderly and heavily pretreated mCRPC patients

In the randomized TheraP trial, a high proportion of mCRPC patients had an excellent response to ^{177}Lu-PSMA-617 treatment even though they did not receive all six planned treatment cycles [15]. Thus, a prospective phase II trial was conducted to test two different therapeutic schemes of ^{177}Lu-PSMA-617 according to age and previous therapies [16].

Patients aged over 75 years or who had received docetaxel were given 3.7-4.4 GBq every 8-12 weeks for 4-6 cycles. Patients under 75 years or who had not received docetaxel were given 5.5 GBq every 8-12 weeks for 4-6 cycles. Infusion with mannitol and external cooling plus polyglutamate folate tablets were given during and after each treatment cycle to reduce kidney and salivary gland uptake. The main objective was to evaluate the PSA response rate from baseline. The secondary endpoints included acute and late toxicity, PFS, and OS.

A total of 80 patients with a median age of 71 years were evaluated. The median Gleason Score at diagnosis was 8 and the median PSA level was 50.7 ng/ml among the enrolled study population. More than one-third (36 %) had already received three lines of treatment. A high proportion of patients showed a PSA decrease of more than 30 % (53.7 %) and more than 50 % (41.3 %) from baseline. No grade 3 or 4 adverse events or toxicity on parotid glands occurred. The median PFS was approximately 7 months in both groups, but OS was better in the high-dose group, with 94.6 % vs. 79.4 % at 6 months and 83.7 vs. 55.9 % at 12 months, respectively **(Figure 3)**. Potential confounders were not corrected prior to survival analysis, such as the age difference and prior treatment between the two dose groups. The median OS for the entire patient population was 19.8 months.

Overall, a lower dose of 3.7-4.4 GBq/cycle of ^{177}Lu-PSMA-617 in selected patients was well tolerated and could thus be considered the minimum effective dosage. However, a 5.5 GBq/cycle dose for 4-6 cycles led to a higher biochemical response in advanced mCRPC patients. ■

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Neuroendocrine tumor imaging updates

Little impact of interim PET/CT staging during PRRT for NETs

Guideline recommendations for peptide receptor radionuclide therapy (PRRT) using ^{177}Lu- DOTA-0-Tyr^3-Octreotate (DOTATATE) in patients with neuroendocrine tumors (NETs) include 3-5 cycles with a dose ranging from 5.5-7.4 GBq per cycle with 6-12 weeks intervals [1]. While PET with radionuclide-labeled somatostatin analogs (SSAs) is mandatory before PRRT, interim PET imaging is not routinely recommended. Since 20-30 % of patients show early disease progression (PD), a multicentric analysis of the impact of interim PET staging with SSTR-analogs after 2 cycles of ^{177}Lu-PRRT in neuroendocrine tumor (NET) patients was conducted, and data were presented at EANM 2022 [2].

A total of 225 NET patients were included in the analysis with radiographic response in ^{68}Ga-DOTATATE / -DOTATOC PET/CT at baseline and after two cycles of ^{177}Lu-DOTATATE treatment. Interim PET revealed partial response (PR) in 27 (12 %), stable disease (SD) in 157 (70 %), and PD in 41 (18 %) patients. No significant difference was observed for primary tumors and the Ki-67 index between responders and non-responders. ^{177}Lu-DOTATATE treatment was interrupted in 57 patients (25 %), with no significant difference in interim PET results between patients with and without treatment interruption. Despite PD in interim PET, treatment was continued in 19 patients (33 %). The future retrospective evaluation of this group of patients would be of interest regarding metabolic and molecular response, ^{18}F-FDG-PET, and textural analysis.

In this large cohort study presented, interim PET/CT staging after two cycles of ^{177}Lu-DOTATATE had a minor impact and is of limited value in the current clinical management of NET patients concerning interruption of treatment. The authors concluded that the results support continued PRRT for 4 cycles in case of good clinical tolerance.

Previous SSA treatment does not impact [^{18}F]SiTATE-PET/CT imaging

NETs express somatostatin receptors (SSRs) and are frequently treated with SSAs as well as staged and monitored with radionuclide-labeled SSAs. Any previous treatment with SSAs could potentially reduce the sensitivity of the SSA radiotracer in PET/CT. A new SSR-targeting PET/CT imaging compound, [^{18}F]SiTATE, has been developed for NETs [3]. Sheikh et al. presented data from a study evaluating the impact of previous long-acting SSAs

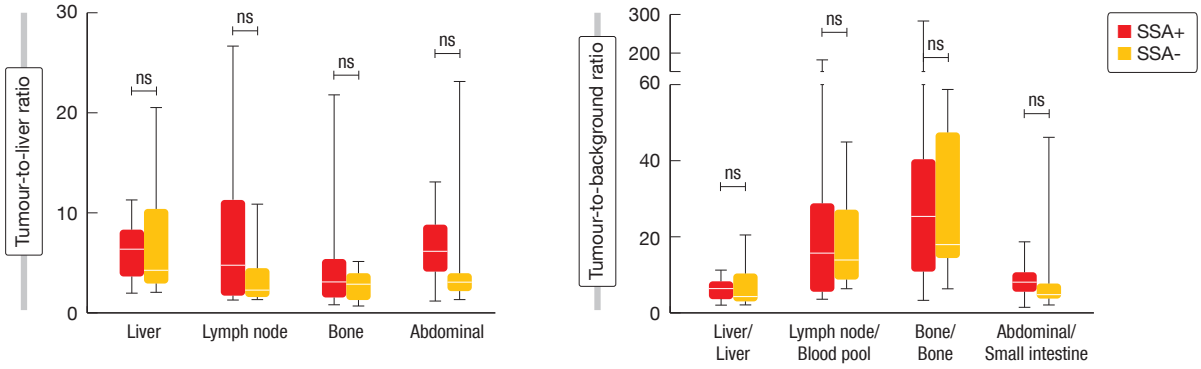

Figure 1: Box-plots representing the tumor-to-liver ratio **(A)** and tumor-to-background ratio **(B)** in GEP-NET patients based on whether they previously received SSA for treatment.

treatment, in patients with differentiated gastro-entero-pancreatic NETs (GEP-NETs), on the SSR expression as measured by [^{18}F]SiTATE-PET/CT [4]. The study aimed to evaluate the necessity of pausing SSA treatment before [^{18}F]SiTATE-PET/CT.

In total, 77 patients with well-differentiated metastatic or non-resectable GEP-NETs were included in the study. Forty had received SSAs within the last 28 days before PET/CT, whereas 37 patients received no pre-treatment with SSAs. Patients were infused with [^{18}F]SiTATE around 90 mins before PET/CT, with a scan time of 15-20 mins. Maximum and mean standardized uptake value ratios (SUVR) between primary tumors or metastases were compared to background tissue and specific organs in patients with and without SSA pre-treatment.

Significantly lower [^{18}F]SiTATE uptake was observed in the spleen and liver of patients who had received prior SSAs, whereas blood [^{18}F]SiTATE was significantly higher compared to SSA treatment-naïve patients. The tumor-to-liver and the specific tumor-to-background SUVRs were not significantly impacted, irrespective of whether the patients had previously received SSAs **(Figure 1)**.

Overall, the data do not support the need for pausing SSA treatment prior to [^{18}F]SiTATE PET/CT imaging in NET patients.

SSR-PET/CT could be used as an alternative to liver MRI in NET metastases detection

There are no established guidelines on whether to choose SSR-targeting PET/CT or liver magnetic resonance imaging (MRI) for detecting NET liver metastases [5]. Grawe et al. presented data from a retrospective analysis of medical reports of 1000 NET patients (Grade 1 or 2) with SSR-PET/CT and matching liver MRI performed within an interval of 3 months [6]. Hepatic involvement detected by liver MRI but not in SSR-PET/CT were rated false-negative, whereas those observed in SSR-PET/CT but not by MRI were rated false-positive.

Of the 2383 imaging cases included, patient-based metastatic hepatic involvement was reported in 71 % of liver MRI and 69 % of SSR-PET/CT cases **(Table 1)**. There were 2 % false-negative and 1 % false-positive cases. SSR-PET/CT demonstrated a sensitivity of 97.0 % (95 % CI 96.0 %-97.7 %) and a specificity of 97.7 % (95 % CI 96.3 %-98.7 %).

The most frequent reason for false-negative results in SSR-PET/CT was the small size of lesions (<1.2 cm) located in the subcapsular region or near big vessels. The reasons for false-positive findings in SSR-PET/CT were hemangioma, liver cysts, or vessel/bile duct associated with increased tracer uptake.

Overall, the study confirmed the high sensitivity and specificity of SSR-PET/CT in detecting hepatic involvement in NET patients compared to liver MRI imaging as a reference standard. Although SSR-PET/CT could reduce unnecessary biopsies and optimize clinical patient management, awareness of possible pitfalls is essential.

[^{18}F]AIF-NOTA-octreotide shows non-inferiority to [^{68}Ga]Ga-DOTA-SSA PET imaging in NET patients

Gallium-68-labeled SSAs, such as [^{68}Ga]Ga-DOTATATE and [^{68}Ga]Ga-DOTATOC, used in combination with PET/CT imaging, are the gold standard for staging and post-therapy follow-up of SSR-positive NETs [7]. Despite the high tumor detection rates, recent challenges have emerged with using gallium-68 tracers, such as limited availability, high cost, and relatively low throughput. Hence, novel alternatives have emerged, such as fluorine-18 labeled SSR ligands offering advantages concerning availability, production capacity, and image resolution. [^{18}F]AIF-NOTA-octreotide ([^{18}F]AIF-OC) is a promising fluorine-18-labeled SSA alternative for NETs [8]. Two studies were presented at EANM 2022 comparing [^{68}Ga]Ga-DOTATATE versus

TABLE 1 **Proportion of patients based on hepatic involvement detected by liver MRI and SSR-PET/CT**

		MRI		
		positive	negative	N_{total}
SSR-PET/CT	positive	1634	**16**	1650
	negative	**51**	682	733
	N_{total}	1685	698	2383

TABLE 2 **Tumor-to-liver ratio (TLR) and tumor-to-spleen ratio (TSR) of [^{68}Ga]Ga-DOTATATE and [^{18}F]AIF-OC at different metastasis sites**

		[^{68}Ga]Ga-DOTATATE	[^{18}F]AIF-OC	*p*-value
Liver	**SUVmax (TLR)**	4.2 ± 4.0	3.8 ± 2.3	0.40
	SUVmax (TSR)	1.6 ± 1.9	1.0 ± 0.7	0.15
Bone	**SUVmax (TLR)**	2.1 ± 0.8	3.0 ± 1.8	0.17
	SUVmax (TSR)	0.7 ± 0.5	0.7 ± 0.5	0.67
Lymph node metastases	**SUVmax (TLR)**	3.8 ± 3.9	3.3 ± 2.3	0.86
	SUVmax (TSR)	1.1 ± 1.2	0.8 ± 0.6	0.07
Other sites metastases	**SUVmax (TLR)**	3.6 ± 6.0	3.1 ± 3.7	0.96
	SUVmax (TSR)	1.0 ± 1.2	0.8 ± 1.1	0.11
Primary tumor	**SUVmax (TLR)**	4.8 ± 2.4	6.0 ± 2.9	0.14
	SUVmax (TSR)	1.1 ± 0.4	1.1 ± 0.5	0.46

[^{18}F]AIF-OC PET/CT imaging in NET patients.

Haeger et al. presented data from a prospective trial of stage IV, biopsy-proven NET patients (n=20) who underwent both imaging scans [9]. The maximum and mean SUV were assessed in NET lesions and specific organs on [^{18}F]AIF-OC and [^{68}Ga]Ga-DOTATATE PET/CT images. Tumor-to-liver (TLR) and tumor-to-spleen ratios (TSR) were calculated and compared between the two scans.

[^{68}Ga]Ga-DOTATATE PET was performed before [^{18}F]AIF-OC PET with a mean interval of 12.8 ± 7.9 days (range: 2-30 days) between the scans. The uptake of [^{68}Ga]Ga-DOTATATE was significantly higher than that of [^{18}F]AIF-OC in most organs. However, no statistical differences were observed regarding the comparative analysis of TLR and TSR between both tracers, suggesting a better target-to-background ratio of [^{18}F]AIF-OC than [^{68}Ga]Ga-DOTATATE **(Table 2)**. Few lesions were detected in only one of two scans (three only by [^{68}Ga]Ga-DOTATATE and one only by [^{18}F]AIF-OC), but the differences were not significant.

In another prospective, multicenter trial, [^{18}F]AIF-OC was tested for non-inferiority to ^{68}Ga-DOTA-SSA as a PET imaging tracer in NET patients [10]. Patients with histologically confirmed NET, having undergone [^{68}Ga]Ga-DOTA-TATE/-NOC PET within the last 3 months as routine clinical scans or scheduled for one, and with at least one known tumor lesion outside the head region, were enrolled. Study participants underwent a whole-body PET/CT scan with low-dose CT two hours after IV administration of 4 MBq/kg [^{18}F] AIF-OC. Tumor lesions were counted in consensus by two experienced readers, blinded for patient data and radiopharmaceutical, in random order. Following unblinding, the DR was determined for each scan in every patient as the reference. The differential detection ratio (DDR), the difference in DR between [^{18}F]AIF-OC and [^{68}Ga]Ga-DOTA-TATE/-NOC per patient, was the primary endpoint.

In 75 patients, a total of 4709 unique tumor lesions were counted. Patients had a median interval between the study scan and routine [^{68}Ga]Ga-DOTATATE (n=56) or [^{68}Ga]Ga-DOTANOC (n=19) PET of 7 days (range: -30 to +32 days). The mean DR with [^{18}F]AIF-OC was significantly higher than with [^{68}Ga]Ga-DOTA-TATE/-NOC (91.1 % vs. 75.3 %), with the mean DDR being 15.8 % (95 % CI 9.6 %-22.0 %). The lower margin of its 95 % CI was higher than -15 %, the prespecified boundary for the primary endpoint. The trial was thus positive, demonstrating both non-inferiority and superiority of [^{18}F]AIF-OC compared with [^{68}Ga]Ga-DOTA-TATE/-NOC.

In total, the results from these two studies demonstrated that [^{18}F]AIF-OC is a promising alternative to [^{68}Ga]Ga-DOTATATE in SSR PET imaging for NET patients. More recently published data support [^{18}F]AIF-OC as a valid option in routine clinical practice [11]. ■

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Recent progress in the treatment of neuroendocrine tumors

Positive efficacy with ^{177}Lu-octreotate in PanNET: Phase II OCLURANDOM

Five systemic therapeutic options are currently approved for advanced pancreatic neuroendocrine tumors (PanNET): Streptozotocine-based chemotherapy, everolimus, sunitinib, lanreotide, and PRRT with ^{177}Lu-DOTA-octreotate (OCLU). For PRRT, data from retrospective studies have reported partial responses in advanced PanNET patients [1]. So far, no prospective randomized trial has reported data regarding PRRT in patients with advanced PanNET. OCLURANDOM, a phase II study, is the first randomized phase II trial evaluating PRRT with OCLU in advanced, sporadic PanNET patients with an incidence of less than 1 in 100,000 (NCT02230176) [2].

Advanced PanNET patients who had progressed in the last 12 months and were positive on somatostatin receptor scintigraphy were randomized 1:1 to either 4 cycles of OCLU (7.4 GBq/cycle at 8±1 week intervals) or sunitinib (SUN). The primary endpoint was the PFS rate at 12 months; key secondary endpoints included median PFS and safety.

In 5 years, 84 patients were enrolled in the study (41 OCLU; 43 SUN) with the baseline characteristics well balanced between the study arms. Almost 90 % of patients received 4 cycles of OCLU. After a median follow-up of 40 months, the primary endpoint was met, with a 12-month-PFS rate of 80.5 % in the OCLU arm vs. 42 % in the SUN arm **(Figure 1)**.

The median PFS was 20.7 months in the OCLU arm vs. 11 months in the SUN arm. Among the total patients treated, grade 3/4 AEs were experienced in 44 % of patients in the OCLU arm vs. 63 % in the SUN arm, with the most frequent AEs being blood-related, digestive, and hypertension. The OCLU arm had one case each of thymoma, basal cell carcinoma, and myelodysplastic syndromes (MDS) compared to the SUN arm, which had one case each of gastrointestinal stromal tumor (GIST) and MDS.

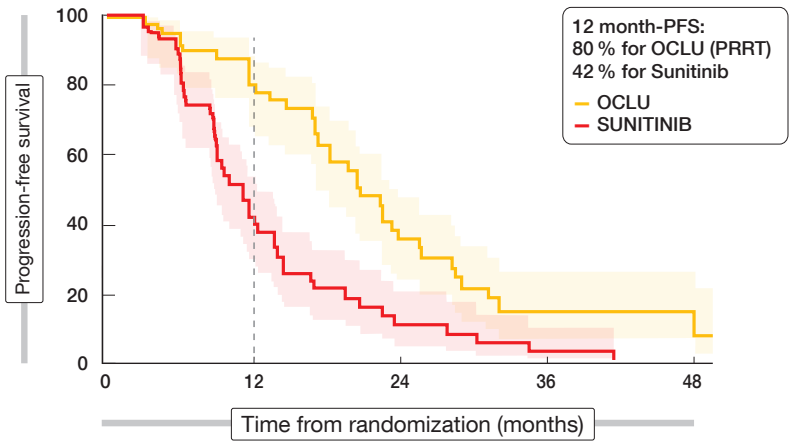

Figure 1: Progression-free survival curves of patients treated with either ^{177}Lu-DOTA-octreotate (OCLU) or sunitinib (SUN) in the OCLURANDOM trial

In conclusion, ^{177}Lu- DOTA-Octreotate showed positive promising efficacy and a tolerable safety profile compared to sunitinib in the first PRRT randomized trial in advanced progressive SSR-positive PanNET patients. These positive PRRT data can potentially change the treatment paradigm in progressive advanced SSR+ PanNET patients by starting PRRT treatment prior to sunitinib. Ongoing randomized phase 3 trials, COMPETE (NCT03049189) & COMPOSE (NCT04919226), assessing PRRT with ^{177}Lu-Edotreotide in advanced PanNETs as part of a larger GEP-NETs patient population will help confirm the efficacy and safety of ^{177}Lu-based PRRT and provide the best treatment sequencing in this patient population.

^{225}Ac-DOTATOC shows promise in upfront and salvage PanNETs treatment

Studies have demonstrated that alpha-PRRT (PRART) elicits tumor responses in patients who have become resistant or are unsuitable to beta-PRRT [3-5]. PRART using ^{225}Ac-labeled SSA has shown promising results and improved OS, even in patients refractory to prior ^{177}Lu-PRRT treatment, with transient and acceptable adverse effects [6]. Kulkarni et al. presented data from a retrospective analysis that estimated the response at 3 months and PFS after 2-4 cycles of PRART using ^{225}Ac-DOTATOC in progressive metastatic neuroendocrine neoplasms (NENs) [7].

A total of 41 patients with confirmed NENs on ^{68}Ga-DOTATOC PET/CT were treated with PRART using 2-4 cycles of ^{225}Ac-DOTATOC at 8-12-week intervals. Of these patients, 36 had progressed after previous PRRT (2-11 cycles) using beta-emitters (Lu-177 / Y-90) and received PRART as a salvage treatment. On the other hand, 5 patients with disseminated liver metastases received upfront PRART. The primary endpoint was objective response 3 months post-therapy measured by RECIST 1.1. Secondary endpoints included OS, PFS, and toxicity after upfront or salvage PRART.

All patients receiving upfront PRART and 50 % receiving salvage PRART demonstrated a PR of the disease at 3 months post-therapy. SD was seen in 38.9 %, and PD in 11.1 % after salvage PRART. All patients tolerated PRART well, with grade 1-2 anemia in 34 %, bicytopenia in 27 %, and pancytopenia in 7 % of all patients treated. Two patients experienced mild renal dysfunction

(grade 2). There was no grade 3-4 hematological or renal toxicity or worsening of hepatic function post-therapy. The median PFS after salvage PRART was 14 months (range 9-19). The median PFS after upfront PRART and the median OS in all patients had not been reached **(Figure 2)**.

In conclusion, PRRT using ^{225}Ac-labeled DOTATOC was shown to be efficacious with a relatively good safety profile in the upfront as well as salvage treatment settings in patients with NENs. However, prospective clinical studies are required to optimally select patients for the PRART upfront therapy or in the beta-emitter refractory setting.

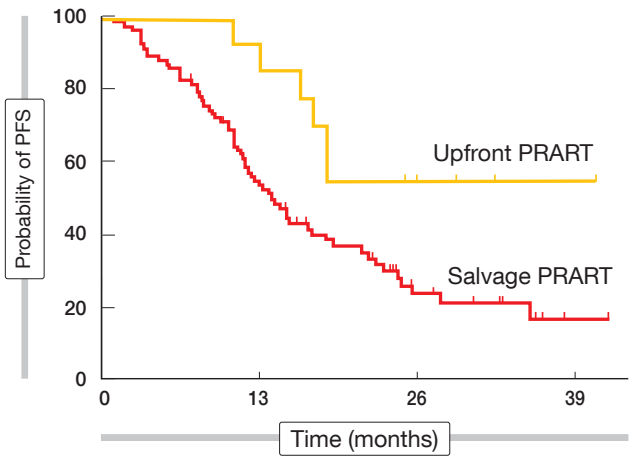

Figure 2: Progression-free survival curves of patients treated with PRART either as upfront or salvage treatment

^{177}Lu-DOTATATE shows similar results in pancreatic and midgut NETs: Results of the SEPTRALU study

The phase 3 NETTER-1 trial established the efficacy and safety of ^{177}Lu-DOTATATE therapy in patients with advanced midgut grade 1-2, SSR-positive NETs progressing to long-acting octreotide [8]. However, no phase 3 trial data exist for patients with PanNET. SEPTRALU is a national, multi-center registry of 533 patients with advanced NET (PanNET: n=187) treated with ^{177}Lu-DOTATATE in clinical practice to analyze the efficacy and safety of ^{177}Lu-DOTATATE [9]. Previous treatments, number of treatment cycles per patient, response, survival, and toxicity were analyzed.

Among the 187 PanNET patients analyzed, ^{177}Lu-DOTATATE was usually performed as the third (31 %) or later (46 %) treatment option, with the previous treatments being SSAs (92 %), surgery (48 %), everolimus (43 %) or tyrosine kinase inhibitors (36 %). The overall response rate (ORR; complete and partial response) was 36.8 %, and the disease control rate (DCR; ORR + stable disease) was 73.6 %. Progression occurred in 13.2 % of patients. Conversely, midgut NET patients had an ORR of 23.7 % and a DCR of 78.4 % **(Figure 3)**.

The median PFS was 28.9 months, and the median OS was 41 months. The median PFS results were worse for patients who underwent more lines of treatment (0-1 lines: 66.2 months; 2 lines: 17 months; >2 lines: 14.6 months). The better response for PanNET patients did not translate into a better PFS or OS compared to NETs of other locations. Grade 1-2 toxicities included nausea (36 %), hematological (31 %), and emesis (26 %); grade 3-4 toxicities were hematological (5 %), emesis (1 %), and nephrotoxicity (1 %).

In conclusion, advanced PanNET patients treated with ^{177}Lu-DOTATATE in this clinical practice series showed similar efficacy and safety data to those reported in midgut NET patients. ■

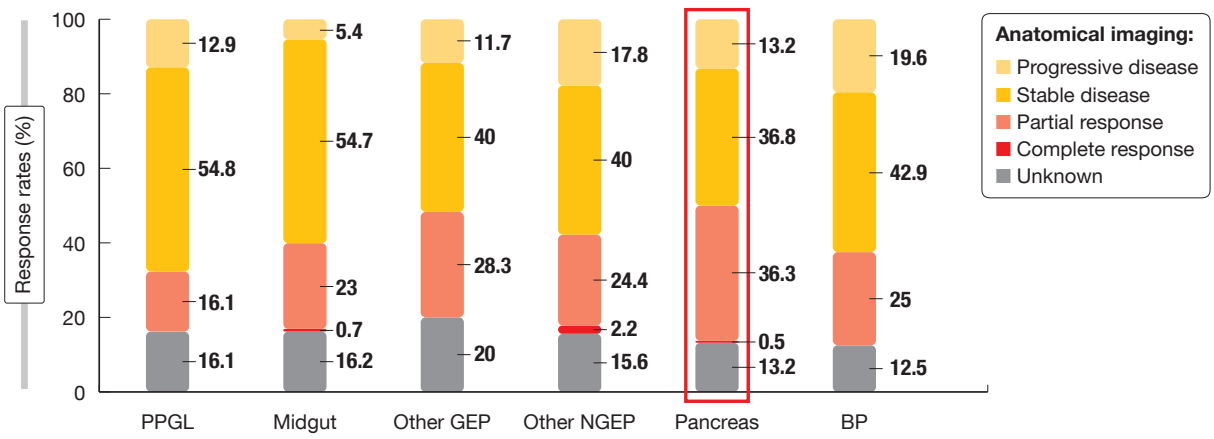

Figure 3: Response rates among NET patients after ^{177}Lu-DOTATATE treatment based on histology type (PPGL, pheochromocytomas and paragangliomas; BP, Bronchopulmonary)

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