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04/23

memo – inOncology SPECIAL ISSUE

Congress Report EANM 2023

A CONGRESS DIGEST ON RADIOLABELED THERANOSTICS FOR SOLID TUMORS

Report from the 36th Annual Congress of the European Association of Nuclear Medicine (EANM), September 9th – 13th, 2023, Vienna

IMPRESSUM/PUBLISHER

Media owner and publisher: Springer-Verlag GmbH, Professional Media, Prinz-Eugen-Straße 8–10, 1040 Vienna, Austria, **Tel.:** +43(0)1/330 24 15-0, **Fax:** +43(0)1/330 24 26, **Internet:** www.springernature.com, www.SpringerMedizin.at. **Copyright:** © 2023 Springer-Verlag GmbH Austria. Springer Medizin is a Part of Springer Nature. **Managing Directors:** Joachim Krieger, Juliane Ritt, Dr. Alois Sillaber. **Medical Writer:** Florence Boulmé, PhD; Christine Rous, PhD. **Publishing Editor:** Anna Fenzl, PhD. **Layout:** Alexander Svec. **Published in:** Vienna. **Produced in:** Fulda. **Printer:** FRIEDRICH Druck & Medien GmbH, 4020 Linz;
The editors of "memo, magazine of european medical oncology" assume no responsibility for this supplement.

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Preface

Dear Colleagues,

The 36th annual congress of the European Association of Nuclear Medicine (EANM) was held in Vienna, Austria, and virtually from 9th to 13th September. As always, the very much-anticipated event brought more than 7,600 leading experts from across the globe together to learn and discuss the groundbreaking updates and scientific advancements in nuclear medicine, which were covered in nearly 2,000 oral presentations and e-posters in 156 sessions.

The first chapter of this memo inOncology report sets the stage for groundbreaking new developments in the diagnosis of neuroendocrine tumors (NETs) and spotlights innovative approaches utilizing SSTR-antagonists such as ^{68}Ga-DATA^{5m}-LMA, [^{18}F]-AlF-NOTA-LM3, [^{68}Ga]Ga-DATA^{5m}-LM4 or [^{99m}Tc]Tc-TECANT 1 radiotracers.

Subsequently, the latest advancements in NETs are highlighted with emphasis on combining radioligand therapy with standard treatments in patients with progressive advanced non-resectable gastroenteropancreatic NETs. Moreover, the utility of ^{177}Lu-DOTATATE following peptide receptor radionuclide therapy (PRRT) in patients with bronchopulmonary neuroendocrine neoplasms and a personalized PRRT-regime using tailored ^{177}Lu-DOTATATE activity in patients with overexpressing SSTR NETs are outlined.

The section on NET theranostics overviews the interim data of the first-in-class alpha-emitting radiopharmaceutical ^{225}Ac-DOTATATE, data gleaned from a human pilot study with ^{212}Pb-VMT-α-NET, as well as the promising prospects of personalized dosimetry-based PRRT, combining mixed doses of [^{177}Lu]Lu- and [^{90}Y]Y-DOTATATE. It further delves deeper into assessing the predictive potential of full-body longitudinal somatostatin receptor imaging features for predicting clinical outcomes in metastatic NET patients receiving PRRT.

Within the realm of prostate cancer, we witness the transformative potential of non-invasive nuclear medicine techniques, offering both diagnostic and targeted therapeutic solutions. Thus, this report accentuates the early prediction of response to ^{177}Lu-PSMA therapy with ^{68}Ga-PSMA or the new class of ^{18}F-rhPSMA-7.3 PET/CT. Additionally, interim data on the utility of ^{18}F-PSMA-1007 as a surrogate marker for ^{177}Lu-PSMA imaging and treatment effectiveness are summarized.

Furthermore, this special issue encompasses the encouraging advances in PSMA-based therapy in metastatic castration resistant prostate cancer, including insights from the phase III ProstACT GLOBAL study, findings from the phase II IRST-185.03, an overview of the prospective national Swiss registry assessing ^{177}Lu-PSMA for imaging and therapy, as well as a compilation of results from different combinations of ^{225}Ac-TAT/^{177}Lu-PSMA-I&T.


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Finally, the section regarding further benefits of PET imaging in prostate cancer covers results from the VISION and the LuTectomy trial, while further discussing the implementation of PSMA-PET imaging after prostate cancer salvage radiotherapy in recurrent or persistent prostate cancer patients after surgery.

Once again, the EANM congress was not only a platform for exchanging groundbreaking scientific insights but also continued to bolster our growth as a specialist community. With the data presented, it is needless to say that the present of nuclear medicine is bright, and that the future holds even greater promise.

I hope you enjoy reading this special issue!

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New developments in the diagnosis of neuroendocrine tumors

Neuroendocrine neoplasms (NENs) comprise a rare group of heterogenous neoplasms that originate from cells with a neuroendocrine phenotype and can arise in almost every organ or region of the body [1]. They display a variable biological behavior; in fact, in some patients the disease may be stable for years, whereas in others, it might be very aggressive [2]. NENs are often divided into two subgroups in terms of cell morphology, genetics, and prognosis. Well-differentiated, low-proliferating neuroendocrine tumors (NETs) (low to intermediate grade indolent tumors) and poorly differentiated, highly proliferating neuroendocrine carcinoma (NECs) (high grade aggressive carcinomas) [3]. The gastrointestinal tract (70 %) and the lung (20 %) are the most frequent primary affected sites [4]. Overall, 90 % of NENs express

somatostatin receptors (SSTRs) on their cell surface [2].

^{68}Ga-DATA^{5m}-LM4: first-in-human study

As first SSTR agonist, ^{68}Ga-DOTATATE was already granted approval in several European countries and by the FDA in 2016 as a novel diagnostic imaging agent for the detection of rare NETs. Furthermore, in 2018 ^{177}Lu-DOTATATE was approved for the treatment of gastroenteropancreatic neuroendocrine tumors (GEP-NETs) [5]. Notably, SSTR-antagonists demonstrated to target a greater number of binding sites on tumor cells than SSTR-agonists, due to their ability to bind to SSTR independently of receptor activation [6, 7]. Especially, in patients with low or no SSTR agonist binding, ^{177}Lu-DOTA-LM3 has proven its effectiveness and safety in the treatment of metastatic NENs. This is achieved by offering a favorable biodistribution and delivering higher tumor radiation doses than SSTR agonists [8]. A first-in-human study presented at EANM 2023 aimed at evaluating the feasibility of the innovative kit-type SSTR antagonist ^{68}Ga-DATA^{5m}-LMA for PET imaging in metastatic NETs [9].

The objectives of this trial were to assess the safety, biodistribution and diagnostic efficacy of ^{68}Ga-DATA^{5m}-LMA. In total, 27 patients (70 % male; mean age, 61 years) showing histopathologically confirmed well-differentiated NETs underwent ^{68}Ga-DATA^{5m}-LMA PET/CT imaging for staging and restaging or patient selection for PRRT. The mean intravenous injection activity was 151 ± 54 MBq and the average uptake time 76 min (range, 50-128). The normal organ uptake of ^{68}Ga-DATA^{5m}-LMA was significantly lower, particularly in the liver as compared to ^{68}Ga-DOTATATE (3.90 ± 0.88 *vs.* 9.12 ± 3.64; p < 0.000001). Compared to ^{68}Ga-DOTATOC, there was a significantly lower uptake of ^{68}Ga-DATA^{5m}-LMA reported in the liver and spleen, too.

Regarding NET patients, there was a very high uptake reported in the tumor lesions (standardized uptake value, SUV_{max}, 44.5 ± 36.2; range, 12.3-167.9). The calculated tumor-to-background ratios (TBRs) reached 20.32 ± 19.97 in healthy liver parenchyma, 4.30 ± 3.03 in the kidneys and 38.63 ± 35.97 in the blood. The authors reported that with ^{68}Ga-DOTA^{5m}-TOC PET/CT, further small CT and/or MRI "invisible" lesions were identified in different organs of NET patients. The advantageous imaging characteristics of the novel SSTR antagonist ^{68}Ga-DATA^{5m}-LMA, which include higher tumor contrast and lower uptake in normal tissues compared to SSTR agonists, along with its kit-type production features, establish ^{68}Ga-DATA^{5m}-LMA as a potential new powerful radiopharmaceutical for diagnosing NETs and detecting very small metastases.

Head-to head comparison between [^{18}F]-AlF-NOTA-LM3 and ^{68}Ga-DOTATATE

SSTRs on the cell membrane of NETs are promising candidates both as diagnostic tools (γ or β-emissions) or for therapeutic purposes (β-emissions) [10]. Due to their high specificity and sensitivity, ^{68}Ga-labelled SSTR agonist agents are widely used for imaging of NETs. However, SSTR antagonists have already shown their superiority over SSTR agonists in terms of lower physiological uptake and higher detection rates [9]. Specifically, ^{18}F-labelled tracers have a longer half-life and a lower positron energy, which, in turn, enables better image quality [11]. At this year's EANM, Meixi Liu presented a study aiming at prospectively assessing the safety and biodistribution of [^{18}F]-AlF-NOTA-LM3 and to compare its diagnostics efficacy with the gold-standard ^{68}Ga-DOTATATE [12].

The patients included in the study had histologically confirmed, well-differentiated NETs (grade 1 or grade 2), with no long-acting somatostatin analog treatment within the past four weeks and no PRRT therapy within the last eight weeks. Patients underwent two whole-body PET/CT scans: one 60 to 90 minutes after the intravenous infusion of [^{18}F]-AlF-NOTA-LM3 (3.7-5.55 MBq/kg) and the other conducted 60 minutes after the intravenous infusion of ^{68}Ga-DOTATATE (111-185 MBq). Both scans were conducted within a week, with a minimum of 24 hours between the two scans. Of note, the first eight patients receiving [^{18}F]-AlF-NOTA-LM3 underwent dynamic PET scans.

Out of 17 patients screened, 15 were enrolled in this trial. The median age was 52 years and 60 % were males. The primary sites of malignant lesions were as follows: the pancreas (46.7 %), the duodenum (20.0 %), the lungs and the rectum (6.7 % each). Most patients (60 %) had grade 2 NET tumors. In terms of safety outcomes, a significant decrease in heart rate was observed two hours after injection (p = 0.006), with no other significant alterations in vital signs reported.

A high physiological uptake of [^{18}F]-AlF-NOTA-LM3 was observed in pituitary and adrenal glands, as well as in the spleen. Compared to ^{68}Ga-DOTATATE, [^{18}F]AlF-NOTA-LM3 showed a significant lower physiological uptake in the liver (2.9 *vs.* 6.2), the spleen (6.9 *vs.* 20.2),

TABLE 1 **Comparison between [^{18}F]AlF-NOTA-LM3 and ^{68}Ga-DOTATATE in terms of number of metastases, SUV_{max} and TBR.**

		Al^{18}F-NOTA-LM3	^{68}Ga-DOTATATE	P value
Pancreatic lesions	Number	21	20	0.317
	SUV_{max}	16.3 (7.5–24.4)	16.1 (10.7–27.8)	0.117
	TBR	9.3 (4.7–15.9)	4.2 (2.1–6.8)	**<0.001**
Duodenal lesions	Number	5	5	1.000
	SUV_{max}	23.3 (12.0–70.6)	31.6 (12.9–57.4)	1.000
	TBR	10.0 (6.1–12.3)	10.2 (5.5–19.6)	0.465
Liver metastases	Number	275	219	**0.028**
	SUV_{max}	32.1 (13.0–49.6)	32.0 (16.7–47.8)	0.634
	TBR	13.4 (5.9–22.5)	5.6 (1.7–6.6)	**<0.001**
Lymph node metastases	Number	21	14	**0.020**
	SUV_{max}	56.6 (14.1–84.2)	53.9 (12.9–85.0)	0.826
	TBR	36.4 (13.8–60.4)	14.4 (6.1–31.8)	0.084
Bone metastases	Number	5	6	0.317
	SUV_{max}	12.0 (2.7–97.7)	6.9 (4.3–64.2)	0.225
	TBR	13.3 (2.4–108.6)	4.9 (1.6–45.9)	**0.043**

the pancreas (1.8 *vs.* 2.8), the stomach (2.7 *vs.* 6.2), the small intestine (2.6 *vs.* 5.8), the renal cortex (10.3 *vs.* 12.2) but a significant higher uptake in the blood (1.6 *vs.* 0.5) and the lung (0.6 *vs.* 0.3). In 78% of patients with liver metastases, [^{18}F]AlF-NOTA-LM3 detected more lesions (275 *vs.* 219; p = 0.028) in comparison to ^{68}Ga-DOTATATE. Similarly, in 76% of patients with lymph node metastases, [^{18}F]AlF-NOTA-LM3 revealed more lesions (21 *vs.* 14; p = 0.020). Otherwise, both tracers were comparable regarding primary tumor and bone lesion detection, as well as tumor specific uptake parameters (SUV_{max}). Moreover, a higher TBR of liver, pancreatic and bone metastases was observed with [^{18}F]AlF-NOTA-LM3 **(Table 1)**.

The authors concluded that [^{18}F]AlF-NOTA-LM3 is a promising SSTR antagonist, exhibiting a superior detection rate and a better performance in detecting liver and lymph node lesions compared to the standard ^{68}Ga-DOTATATE. Furthermore, [^{18}F]AlF-NOTA-LM3 demonstrated good safety, with no AEs related to the radiopharmaceutical reported. Consequently, in the authors' opinion, it represents a valuable new option for imaging NETs.

[^{68}Ga]Ga-DATA^{5m}-LM4 *versus* [^{68}Ga]Ga-DOTANOC PET/CT

An interim analysis of a retrospective study comparing the diagnostic efficacy of the SSRT ligand antagonist [^{68}Ga]Ga-DATA^{5m}-LM4 with [^{68}Ga]Ga-DOTANOC in terms of detection of primary tumors and metastases in histologically proven GEP-NET patients was presented by Rahul Viswanathan at this year's EANM [13].

Overall, 29 patients (52% men) with a mean age of 49 years (range, 25-67) were enrolled in this study. Thirteen patients had low-grade (G1) NETs, seven patients had intermediate grade (G2) NETs, and nine patients had high grade (G3) NETs. In total, 51.7% of patients had distant metastases and 48.2% a locally advanced disease. Cross-sectional diagnostic CT confirmed 390 lesions (25 primary tumors, 261 liver metastases, 69 lymph node metastases, 28 bone metastases and 7 lung metastases). Patients received a mean injection dose of 99.9 MBq/kg of [^{68}Ga]Ga-DOTANOC or 159.1 MBq/kg of [^{68}Ga]Ga-DATA^{5m}-LM4. The lesion-based sensitivity reached 84.0% for [^{68}Ga]Ga-DATA^{5m}-LM4 PET and 66.6% for [^{68}Ga]Ga-DOTANOC PET (p < 0.0001). A higher number of metastases were detected with [^{68}Ga]Ga-DATA^{5m}-LM4 compared to [^{68}Ga]Ga-DOTANOC in all primary tumors and lesions analyzed, especially in liver (87% *vs.* 67%; p < 0.0001) and bone metastases (100% *vs.* 32%; p < 0.0001). Similarly, the qualitative and quantitative (SUV corrected for lean body mass, SUL_{max}/SUL_{avg}) analyses revealed a significant higher uptake (SUL_{max} and SUL_{avg}) of [^{68}Ga]Ga-DATA^{5m}-LM4 compared to [^{68}Ga]Ga-DOTANOC (p < 0.05) in liver and bone metastases.

In conclusion, the [^{68}Ga]Ga-DATA^{5m}-LM4 radiotracer has demonstrated encouraging interim results in patients with GEP-NETs. Nevertheless, further analysis in clinical trials with larger sample sizes are warranted.

TECANT: phase 1 study with ^{99m}Tc-labelled SSTR antagonist

NENs, which have been traditionally considered as rare diseases, are often diagnosed at a late stage due to the absence of specific symptoms [1]. Hence, early detection plays a crucial role in the management of NEN patients, influencing therapy selection and disease monitoring. At EANM 2023, Marta Opalińska presented the first results of the multicenter phase 1 TECANT trial (NCT05871320) which aims to initiate a clinical feasibility study with a novel ^{99m}Tc-labelled SSTR2-antagonist as a sensitive probe to assess the SSTR status in NEN patients, and to develop a robust, reproducible quantitative imaging method [14]. After conducting comprehensive preclinical in vitro and in vivo studies, [^{99m}Tc]Tc-TECANT1 was selected among two potential candidates due to its longer tumor residence time, as well as lower kidney and liver uptake. In total, ten patients with advanced SSTR-positive NENs underwent single photon emission computed tomography (SPECT) scan combined to CT scans. The administration of [^{99m}Tc]Tc-TECANT1 resulted in a rapid distribution with predominant renal excretion. No related adverse events were observed. [^{99m}Tc]Tc-TECANT1 tumor uptake was visible as early as five minutes following administration and retained 24 hours post-injection. The highest TBRs was detected four hours post-injection. Moreover, the contrast in the images was superior to those obtained with a ^{68}Ga-SSTR agonist for most of the analyzed lesions.

As [^{99m}Tc]Tc-TECANT1 - a SSTR antagonist - has demonstrated high-quality imaging results along with a favorable toxicological and pharmacological profile, this novel radionuclide holds the potential to become an innovative tool in the diagnostic and therapeutic pathways for patients with NENs. ■

REFERENCES

1 Oronsky B et al. Nothing but NET: a review of neuroendocrine tumors and carcinomas. Neoplasia 2017; 19(12): 991-1002
2 Merola E et al. Peptide receptor radionuclide therapy (PRRT): innovations and improvements. Cancers (Basel) 2023; 15(11)
3 Bosman FT et al. World Health Organization (WHO) Classification of tumours of the digestive system. 4th ed. Geneva, Switzerland: WHO Press. 2010
4 Dasari A et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. JAMA Oncol 2017; 3(10): 1335-1342
5 Hennrich U et al. [(68)Ga]Ga-DOTA-TOC: the first FDA-approved (68)Ga-radiopharmaceutical for PET imaging. Pharmaceuticals (Basel) 2020; 13(3)
6 de Herder WW et al. Somatostatin receptors in gastroentero-pancreatic neuroendocrine tumours. Endocr Relat Cancer 2003; 10(4): 451-458
7 Nicolas GP et al. Sensitivity comparison of (68)Ga-OPS202 and (68)Ga-DOTATOC PET/CT in patients with gastroenteropancreatic neuroendocrine tumors: a prospective phase II imaging Study. J Nucl Med 2018; 59(6): 915-921
8 Baum RP et al. First-in-humans study of the SSTR antagonist (177)Lu-DOTA-LM3 for peptide receptor radionuclide therapy in patients with metastatic neuroendocrine neoplasms: dosimetry, safety, and efficacy. J Nucl Med 2021; 62(11): 1571-1581
9 Zhang J et al. First-in-human study of an optimized, potential kit-type, SSTR antagonist ^{68}Ga-DATA^{5m}-LM4 in neuroendocrine tumors. EANM 2023 (Oral abstract OP-302)
10 Zhu W et al. Head-to-head comparison of (68)Ga-DOTA-JR11 and (68)Ga-DOTATATE PET/CT in patients with metastatic, well-differentiated neuroendocrine tumors: a prospective study. J Nucl Med 2020; 61(6): 897-903
11 Leupe H et al. (18)F-labeled somatostatin analogs as PET tracers for the somatostatin receptor: ready for clinical use. J Nucl Med 2023; 64(6): 835-841
12 Liu M et al. A prospective evaluation of [^{18}F]AlF-NOTA-LM3 in patients with well-differentiated neuroendocrine tumors: head-to-head comparison with ^{68}Ga-DOTATATE. EANM 2023 (Oral abstract OP-303)
13 Viswanathan R et al. Comparison of [^{68}Ga]Ga-DOTANOC and [^{68}Ga]Ga DATA^{5m}-LM4 PET/CT in the same patient group with neuroendocrine tumors. EANM 2023 (Oral abstract OP-307)
14 Opalinska M et al. Novel ^{99m}Tc-labelled somatostatin antagonists in the diagnostic algorithm of neuroendocrine neoplasms" - results of a multicenter phase I clinical trial - TECANT. EANM 2023 (Oral abstract OP-306)

Recent progress in the treatment of neuroendocrine tumors

Combined radioligand and CAPTEM therapy in patients with advanced, non-resectable, progressive GEP-NET

Capecitabine plus temozolomide (CAPTEM) is widely used for the treatment of advanced, unresectable, and progressive neuroendocrine tumors (NETs). However, data are limited regarding its association with radioligand therapy (RLT)/peptide receptor radionuclide therapy (PRRT) [1-3]. PRRT is a radionuclide-targeted therapy that is based on the intravenous administration of radiolabeled somatostatin analogs that selectively target SSTR expressing cells [4]. At EANM 2023, Jarosław B. Ćwikła presented results of a prospective, single-arm, open-label, case series study (NCT04194125) that assessed the efficacy and safety of RLT and CAPTEM in patients with progressive advanced non-resectable gastroenteropancreatic neuroendocrine tumors (GEP-NETs), so called pancreatic (panNET) and midgut NETs [5]. The primary endpoint was the locally assessed progression free survival (PFS) according to RECIST v1.1. Secondary endpoints included the overall survival (OS), the objective response rate (ORR), the best objective response rate (BORR), the disease control rate (DCR), the clinical response based on a potential improvement of the performance status (PS – ECOG), and safety.

Out of 23 screened patients 21 were enrolled in the study (14 PanNET, 7 Midgut). All patients received RLT/PRRT (3 to 4 cycles of [^{177}Lu]^{177}LuDOTA-TOC of 5.55 - 7.4 GBq at each treatment session) at 8 to 12 weekly intervals, and concomitant CAPTEM. One patient received two treatment sessions, only. At baseline, the mean age was 58.6 years and 62 % of patients were women. Overall, seven patients presented with a NET grade 1, ten with a NET grade 2 and three with a NET grade 3 tumor. Eighty-six percent of tumors were classified as clinical stage IV, the rest was clinical stage III.

After a follow-up of at least 48 months, the median PFS was 31.5 months (IQR, 16.0-not reported [nr]) for the overall population (n=21). In the PanNET group, the mPFS was 28.0 months (IQR, 14.0-nr) and in the Midgut group 32.0 months (IQR, 24.5-nr), respectively. The median OS had not been reached yet. In terms of the ORR a partial response (PR) was reported in nine patients (42 %), while eleven patients (52 %) exhibited stable disease (SD) after six weeks of follow-up. At Month 12, one patient had a complete response (CR), ten had a PR (56 %), five a SD (26 %) and two a disease progression (DP) (11 %) **(Figure 1)**. The DCR was 90 % at Week 6 and still 73 % after two years of follow-up. Moreover, the ECOG score of most patients improved.

The most frequently occurring adverse event (AE) related to the treatment was a transient hematological suppression. During the follow-up period, the most common AE was temporary lymphopenia, with 44 % classified as grade 2, 8 % as grade 3, and 2 % as grade 4. In total, 7 % of patients experienced thrombopenia. Other grade ≥3 AEs, such as increased gamma-glutamyl transferase [GGT], thrombocytopenia and anemia were observed sporadically. Notably, there were no other grade 4 AE reported either during or after the therapy.

Overall, the combined therapy based on RLT/PRRT and CAPTEM was efficient and well tolerated in most cases in patients with gastroenteropancreatic neuroendocrine (GEP-NETs) tumors (PanNET and Midgut), whereas a significant benefit in terms of ORR was reported in panNET patients only.

^{177}Lu-DOTATATE in BP-NENs: results of SEPTRALU registry

The efficacy and safety of ^{177}LU-DOTATATE therapy (PRRT) in patients with advanced midgut grade 1/2 SSTR-positive NENs progressing to long-acting octreotide has already been shown in the phase 3 NETTER-1 trial [6]. Based on these data, it was assumed that PRRT could be effective in other tumors expressing SSTR, such as bronchopulmonary-NENs (BP-NENs). At this year's EANM, Mercedes Mitjavila Casanovas presented an analysis conducted on patients from the Spanish multicenter (23 centers) SEPTRALU registry. Patients included in this analysis had advanced, non-resectable BP-NENs and had undergone treatment with PRRT between 2014 and 2022 (NCT04949282) [7, 8]. The dataset included treatments prior to PRRT, number of PRRT-cycles per patient, response to treatment, and disease progression. The response rate was assessed according to RECIST v1.1 criteria and the safety was evaluated with the Common Terminology Criteria for Adverse Events (CTCAE) v3.0.

Of the 706 NEN-patients included in this registry 9.35 % (n=66) had BP-NENs, with a median age of 62 years and 78 % of them were women. At the time of diagnosis, 84 % of patients had a performance status (PS - ECOG) of 0 or 1. Atypical carcinoid was the most common histological subtype found in 53 % of patients,

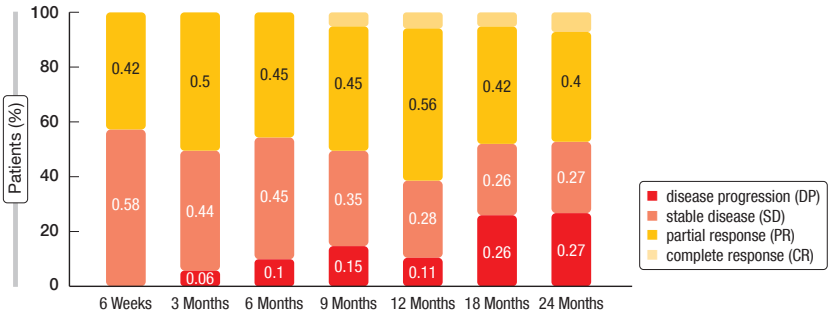

Figure 1: Objective response rate of the overall population (n=21) from 6 weeks to 24 months according to RECIST v1.1 criteria.

followed by typical carcinoid (31%) and NE carcinomas (16%). Metastases were mainly located in the liver (80%), lymph nodes (53%) and bones (48%). Most patients had received prior treatments before undergoing PRRT: 54% underwent surgery, somatostatin analogs were administered to 92%, and 43% received everolimus. Overall, PRRT served as the second-line treatment for 31% of patients, the third-line treatment for 58% and was given after the third line in 12% of cases, respectively. On average, the median duration from diagnosis to the initiation of PRRT was 35 months (95% CI, 3-52).

The DCR in this study was 86%, with 34% of patients having a response (ORR=CR + PR, n=22) and 52% a SD (n=34). In contrast, other studies reported a median ORR of 30% (15-80%) and a median DCR of 68% (61-100%) [9]. These differences in results might be attributed to the heterogeneity of the studied population, the relatively small sample size and variations in the criteria used for response analysis [8]. After a median follow-up of 31 months, the median PFS reached 18.4 months (95% CI: 15.8-33.4) and the median OS was 47.9 months (95% CI: 20-not applicable [NA]). This result is in line with previously published data (mPFS, 18.5 months; mOS, 48.6 months) in patients with typical/atypical lung carcinoids [9], but the group presented also includes patients with NE carcinoma. Of note, mPFS and mOS were shorter in PRRT-treated patients with BP-NETs compared to other NEN-sites [7, 9].

Grade 1-2 toxicities included neutropenia (44%), nausea (40%), and emesis (25%). Seven patients (10%) experienced grade 3 or 4 AEs, mostly hematological AEs (5.8% of patients, no specific treatment was required) and nausea (1.5%).

Overall, ^{177}Lu-DOTATATE was shown to be an efficient and well tolerated therapeutic option in patients with advanced BP-NENs further supporting phase 3 studies.

Personalized ^{177}Lu-DOTATATE PRRT of NETs

PRRT is widely administered with a fixed injected activity per cycle, leading to a high interpatient variability in healthy tissue dosimetry and a risk of under-treatment [10]. In this context, the updated efficacy and safety results of a prospective, open-label, single-center, phase 2 study (NCT02754297) were presented by Marc-André Morin at EANM 2023. In this trial a personalized PRRT-regime with a tailored ^{177}Lu-DOTATATE activity was used to deliver a prescribed renal absorbed dose in PRRT-naïve patients with inoperable progressive and/or symptomatic NETs overexpressing SSTRs [10, 11].

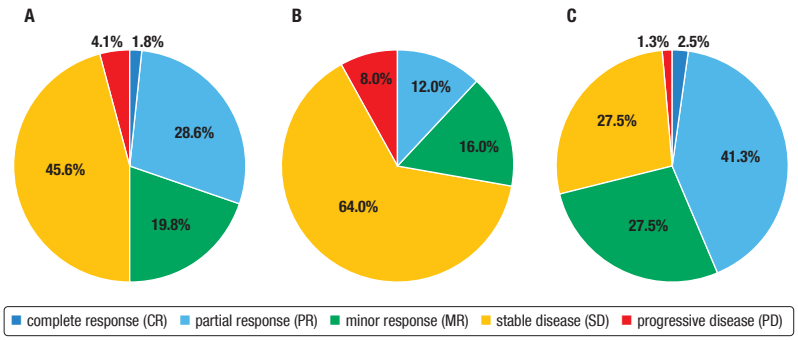

Figure 2: Best radiological response (BRR) of the overall population **(A)**, the NETTER-1 **(B)** and the pNET subgroup **(C)**.

Eligible patients received up to four induction cycles of ^{177}Lu-DOTATATE every eight weeks with activity tailored to achieve a cumulative renal absorbed dose of 26.5 Gy (assessed by quantitative SPECT/CT-based dosimetry). As clinical endpoints, the best radiological response (BRR), the PFS according to RECIST v1.1 criteria, the OS, and the safety were assessed. Subgroup analyses were conducted in Midgut NET patients meeting NETTER-1 eligibility criteria and in pNET patients [6].

A total of 226 patients were enrolled with the majority being males (58%, n=130). Overall, 21% of patients (n=48) had a NET Grad 1, 47% (n=105) a NET Grad 2 and 8% (n=17) a NET Grad 3 tumor. The median age was 63 years. The primary tumors of the patients were predominantly located in the midgut (40%) and pancreas (37%). The primary metastasis sites were the liver (88%), lymph nodes (72%) and bones (46%). Prior systemic treatments included somatostatin analogues (88%), everolimus (30%), sunitinib (6%), CAPTEM (6%) or other chemotherapy regimens (15%).

Overall, patients received 813 induction cycles containing an average of 9.54 GBq of ^{177}Lu-DOTATATE per cycle. The cumulative renal dosimetry accounted for 22.91 Gy (2.08-35.66 Gy). The 4th induction cycle was completed by 74% of patients with a cumulative renal dosimetry of 25.56 Gy.

In the overall population (n=217), the ORR was 39.4% with a DCR of 95.9%. In the NETTER-1 subgroup (n=50), the ORR was 12.0% with a DCR of 92.0%, while in the pNET subgroup (n=80), the ORR was 43.8%, with a DCR of 98.8%, respectively **(Figure 2)**. Median PFS reached 26.0 months in the overall population, 36.0 months in the NETTER-1 subgroup and 24.4 months in the pNET subgroup. The median OS was 44.0 months in the overall population, 42.3 months in the NETTER-1 subgroup and 44.0 months in the pNET subgroup.

The main subacute toxicities (<12 months) experienced by the patients were thrombocytopenia (14.6%), leucopenia (11.5%), anemia (11.1%), and neutropenia (8.8%). The most frequent chronic toxicities (>12 months) were thrombocytopenia (2.4%), leucopoenia (3.2%), anemia (3.2%), and neutropenia (1.6%) as well as renal impairment (2.4%). Overall, 44% of these AEs occurred after the fourth induction cycle, while in 9%, the induction cycle was interrupted because of AEs. Of note, three patients (1.3%) developed a myelodysplastic syndrome and one patient (0.4%) an acute myeloid leukemia.

Based on these findings, the authors concluded that personalized ^{177}Lu-DOTATATE PRRT, guided by renal dosimetry, demonstrated promising efficacy and a tolerable safety profile. These encouraging results may pave the way for higher injected activity in patients presenting with overexpressing SSTR NETs.

Outcome prediction in GEP-NETs treated with ^{177}Lu-DOTATATE PRRT

Although PRRT has shown efficacy in managing patients with advanced NETs

that express SSTRs, there is a need for a strong imaging biomarker to predict PRRT efficacy [12, 13]. Magdalena Mileva presented the results from the LuMEn study (^{177}Lu-octreotate treatment prediction using multimodality imaging in refractory NETs), a prospective, monocentric phase II clinical-imaging study in metastatic or locally advanced, non-resectable histologically proven GEP-NET patients (NCT01842165) [12]. The study aimed to determine if multimodality imaging parameters and the tumor absorbed dose are reliable early predictors for the outcome of patients with GEP-NETs during treatment with ^{177}Lu-DOTATATE PRRT. Lesion-based time to progression (TTP) serves as primary endpoint, while PFS and best morphological response (according to RECIST v1.1) were secondarily analyzed.

Enrolled patients were treated with four cycles of 7.4 GBq of ^{177}Lu-DOTATATE, given 11 to 13 weeks apart and injected intravenously with simultaneous infusion of an amino acid solution. At baseline and 10-12 weeks after the first injection, ^{68}Ga-DOTATATE-PET/CT and FDG-PET/CT were performed. A maximum of five target lesions per patients were used to measure the specific uptake parameters ($SUV_{max/mean}$, tumor-to-blood, tumor-to-spleen ratio) and volumetric parameters (SSTR-tumor volume [TV], total-lesion SSTR expression).

The 37 patients included in the study had a mean age of 66 years and 51 % were men. The primary tumors were mainly located in the small-intestine (62 %), the pancreas (27 %) and the colon/rectum (11 %). Most of the tumors were classified as grade 1 (32 %) or grade 2 (59 %) and less frequently as grade 3 (8 %). The metastases were predominantly found in the liver (86 %), lymph nodes (84 %), bones (59 %) and peritoneum (32 %). In total, 75 % of patients received four PRRT-cycles.

Regarding the overall population, the median PFS was 28 months, and 30 % of patients achieved a PR. The median lesion TTP was not reached yet. After a median follow-up of 57 months, 14 % of target lesions have progressed. A patient-based analysis combining imaging parameters revealed that a decrease of SSTR-TV of ≥ 10 % after C1 from baseline was associated with a longer PFS of 51.3 months compared to 22.8 months for patients with < 10 % decrease (p = 0.003; HR: 0.35; 95 % CI: 0.16-0.75). Similarly, an absorbed dose of ≥ 35 Gy received by all target lesions in C1 was associated with a longer PFS compared to an absorbed dose of < 35 Gy (48.1 *vs* 26.2 months; p = 0.02; HR: 0.37; 95 % CI: 0.17-0.82). Of note, neither the uptake parameters on ^{68}Ga-DOTATATE PET/CT (baseline and changes after C1), nor the average and maximal tumor absorbed dose were associated with the PFS.

To conclude, in patients with GEP-NETs, changes in the volumetric parameter on ^{68}Ga-DOTATATE-PET/CT after the first cycle of ^{177}Lu-DOTATATE treatment might be useful for early response assessment. However, further studies are warranted. ■

REFERENCES

1 Claringbold PG et al. Phase I-II study of radiopeptide ^{177}Lu-octreotate in combination with capecitabine and temozolomide in advanced low-grade neuroendocrine tumors. Cancer Biother Radiopharm 2012; 27(9): 561-569
2 Kunz PL et al. Randomized study of temozolomide or temozolomide and capecitabine in patients with advanced pancreatic neuroendocrine tumors (ECOG-ACRIN E2211). J Clin Oncol 2023; 41(7): 1359-1369
3 Claringbold PG et al. Pancreatic neuroendocrine tumor control: durable objective response to combination ^{177}Lu-octreotate-capecitabine-temozolomide radiopeptide chemotherapy. Neuroendocrinology 2016; 103(5): 432-439
4 Merola E et al. Peptide receptor radionuclide therapy (PRRT): innovations and improvements. Cancers (Basel) 2023; 15(11): 2975
5 Cwikla JB et al. Evaluation of progression-free survival (PFS) in patients with advanced, non-resectable, progressive GEP-NET treated using combine radioligand and CAPTEM therapy. EANM 2023 (Oral abstract OP-231)
6 Strosberg J et al. Phase 3 Trial of (177)Lu-DOTATATE for midgut neuroendocrine tumors. N Engl J Med 2017; 376(2): 125-135
7 Mitjavila M et al. Efficacy of [(177)Lu]Lu-DOTATATE in metastatic neuroendocrine neoplasms of different locations: data from the SEPTRALU study. Eur J Nucl Med Mol Imaging 2023; 50(8): 2486-2500
8 Mitjavila M et al. Efficacy and safety of ^{177}Lu-DOTATATE in lung neuroendocrine tumors: a multicenter study. EANM 2023 (Oral abstract OP-233)
9 Naraev BG et al. Peptide receptor radionuclide therapy for patients with advanced lung carcinoids. Clin Lung Cancer 2019; 20(3): e376-e392
10 Del Prete M et al. Personalized (177)Lu-octreotate peptide receptor radionuclide therapy of neuroendocrine tumours: initial results from the P-PRRT trial. Eur J Nucl Med Mol Imaging 2019; 46(3): 728-742
11 Morin MA et al. Efficacy and safety of dosimetry-based, personalized ^{177}Lu-DOTATATE PRRT of neuroendocrine tumours: an update from the P-PRRT trial. EANM 2023 (Oral abstract OP-236)
12 Mileva M et al. Outcome prediction in patients with gastroenteropancreatic neuroendocrine tumours (GEPNETs) treated with ^{177}Lu-DOTATATE peptide receptor radionuclide therapy (PRRT): results from a prospective phase II clinical trial. EANM 2023 (Oral abstract OP-238)
13 Liberini V et al. The challenge of evaluating response to peptide receptor radionuclide therapy in gastroenteropancreatic neuroendocrine tumors: The present and the future. Diagnostics (Basel) 2020; 10(12):1083

Theranostics: recent developments in neuroendocrine tumors

^{225}Ac-DOTATATE daughter nucleotide emissions

RYZ101 (^{225}Ac-DOTATATE) is a first-in-class alpha-emitting radiopharmaceutical being developed for somatostatin receptor-2-expressing (SSTR2+) solid tumors [1]. The ongoing phase 1b/3 ACTION-1 trial (NCT05477576) is currently comparing RYZ101 with standard therapy in patients with well-differentiated gastroenteropancreatic neuroendocrine tumors (GEP-NETs) who have progressed after ^{177}Lu-labelled somatostatin analogue (SSA) therapy. At EANM 2023, results from a dosimetry phase 1b sub-study in nine patients were presented [2].

The alpha decay series of ^{225}AC-DOTATATE includes a total of four α-particle emissions (^{221}Fr, ^{217}At, ^{213}Bi and ^{213}Po) [3]. Thus, a key question of this study was whether the emissions of the ^{225}Ac-DOTATATE daughter products are only found in the tumor lesions, or also affect other organs, causing off-target effects.

So far, 26 patients were enrolled in the phase 1b of the ACTION-1 trial. Seventeen patients were treated with ^{225}Ac-DOTATATE at a dose of 120 kBq/kg (32 µCi/kg) administered intravenously for up to four cycles and observed for dose-limiting toxicities during Cycle 1 (8 weeks), whereas nine patients were enrolled in the dosimetry study. Dosimeter calculations were performed using SPECT/CT images acquired for Cycle 1 and Cycle 4 at 4 ± 1h, 24 ± 2h and 168 ± 24 h post-infusion. Two different energy windows were acquired to localize ^{221}Fr and ^{213}BI (218.2 keV ± 20 % and 440 keV ± 20 %). The activity was quantified in liver, kidneys, spleen, red bone marrow and tumors.

The results of the SPECT images of Cycle 1 showed that ^{221}Fr and ^{213}Bi mainly remained in the tumor, with only a small amount of free ^{213}Bi reaching the kidneys. These results were confirmed by calculating the mean time-integrated activity coefficient (TIAC) (MBq-h/MBq) – see **Table 1**.

TABLE 1 **Cycle 1 time-integrated activity (TIAC) coefficient.**

	Mean (SD) TIAC, MBq-h/MBq (hours)	
Organs/lesions	**^{221}Fr**	**^{213}Bi**
Kidneys	2.10 (1.05)	3.76 (1.00)
Liver	11.70 (6.65)	13.50 (5.82)
Red bone marrow	0.67 (0.55)	1.11 (0.59)
Spleen	2.55 (1.33)	2.14 (1.12)
Lesions 1-5	2.64 (3.98)	2.02 (3.47)

Assuming a similar dose distribution for each cycle, the mean estimated total absorbed dose of RYZ101 for the entire treatment period of four cycles (40.8 MBq [1,100 µCi]) is 11.7 Gy for tumors, 22.3 Gy for kidneys, 17.7 Gy for liver, 1.1 Gy for red bone marrow and 35.6 Gy for spleen, respectively.

These data implicate that imaging and obtaining quantitative information for dosimetry of ^{225}Ac is feasible when ^{221}Fr and ^{213}Bi are directly and simultaneously imaged by SPECT/CT. For the first time, it has now been shown that the daughter products of ^{225}Ac mostly stay with the delivery agent (DOTATATE) and only a minor fraction reaches the kidneys. Overall, these initial data suggest a favorable tumor-background profile for RYZ101 in SSTR+ GEP-NETs.

^{212}Pb-VMT-α-NET: interim results from first in human pilot study

Alpha particles (such as ^{225}Ac/^{212}Pb) possess nearly 500 times the particle energy of beta particles (such as ^{177}Lu). The high linear energy transfer radiation from alpha particles targets DNA inside the cell nuclei causing difficult to repair double-strand DNA breaks. [4, 5]

^{212}Pb-VMT-α-NET is a modified peptide targeting the somatostatin receptor with improved pharmacokinetic properties used to treat SSTR2+ NETs. The VMT chelator efficiently binds both ^{212}Pb and its daughter isotope ^{212}Bi. Due to the short half-lives of the ^{212}Bi daughter isotopes ^{208}Tl (3 min) and ^{212}Po (0.3 µs) and the strong chelating abilities of VMT-α-NET, the alpha particles of the decay series are mainly emitted in the targeted tissue. In tumor bearing mice, ^{212}Pb-VMT-α-NET therapy was shown to be effective and well tolerated with a complete response rate of 100 % [6].

At EANM 2023, Dharmender Malik presented interim results from an open-label first in human pilot study evaluating the safety and efficacy of ^{212}Pb-VMT-α-NET in patients with SSTR+ metastatic NETs who have failed at least one prior line of treatment [7]. Ten patients received ^{212}Pb-VMT-α-NET therapy at a dose of 2.5 MBq/kg body weight 8-weekly for up to four cycles (with amino-acid co-infusion for renal protection). Of the included patients, three had gastrointestinal NETs, five pancreatic NETs and two a medullary thyroid carcinoma. Four patients had previously been treated with ^{117}Lu-DOTATATE-peptide receptor radionuclide therapy (PRRT), and one person had also received ^{225}Ac-DOTATATE-PRRT.

Patients who received one to four doses of ^{212}Pb-VMT-α-NET showed a partial response already after the first administration; this effect increased with further doses of ^{212}Pb-VMT-α-NET **(Figure 1)**. A decrease in tumor size was observed in both the primary tumor and metastases. Moreover, quality of life benefits, as measured by the EORTC QLQ-GLNET21 score, showed an improvement in patients' symptoms and quality of life after treatment with ^{212}Pb-VMT-α-NET.

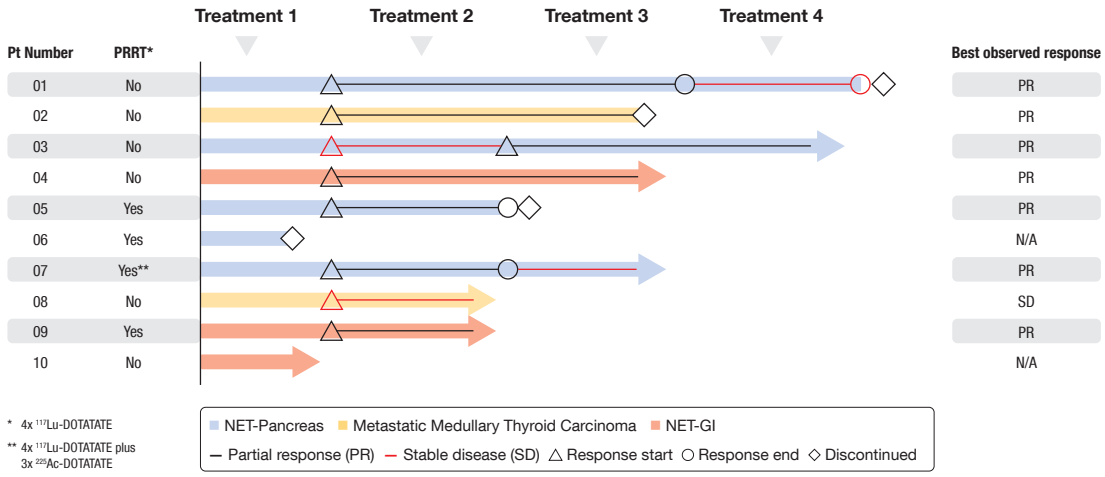

Figure 1: Interim results of patients with SSTR+ late-stage NETs treated with ^{212}Pb-VMT-α-NET.

Treatment-related adverse events (TRAEs) were assessed 2-weekly and after four months of ^{212}Pb-VMT-α-NET, therapy patients had stable values for hemoglobin level, total leucocyte count, platelet count and serum creatinine level. Most AEs were mild; they included grade I anemia, alopecia, or fatigue, which usually resolved within a week. No significant adverse effects on renal or hepatic function were reported. Currently, seven patients are still being treated with ^{212}Pb-VMT-α-NET.

Overall, ^{212}Pb-VMT-α-NET exhibited a favorable toxicity profile in NET patients, with high response rates at an initial dose. Upcoming survival data will provide further insights after a longer follow-up period.

Personalized, dosimetry-based PRRT

PRRT is an effective treatment for patients with advanced SSTR expressing NETs [8]. However, there is still no consensus regarding the optimal PRRT treatment algorithm [9].

Thus, the multicenter, randomized phase III DUONEN trial (EUDRACT No: 2020-006068-99) aims to develop a dosimetry-based, personalized algorithm for tandem PRRT (mixed doses of [^{177}Lu]Lu- and [^{90}Y]Y-DOTATATE), and to evaluate the efficacy of personalized therapy with mixed doses of [^{177}Lu]Lu- and [^{90}Y]Y-DOTATATE compared to the treatment with [^{177}Lu]Lu-DOTATATE in standard doses (7,400 MBq) [10].

In this study, adult patients with advanced, unresectable, well-differentiated (G1 and G2) NETs progressing on long-acting somatostatin analogues, are randomized into four groups: (A) 7,400 MBq [^{177}Lu]Lu-DOTATATE per cycle; (B) [^{177}Lu]Lu-DOTATATE plus [^{90}Y]Y-DOTATATE starting at 3,700:1,850 MBq/MBq with [^{90}Y]Y-DOTATATE activity being adjusted in Cycle 2 to Cycle 4 based on bone marrow and kidney dosimetry to achieve the highest radiation dose in tumor tissue; (C) [^{177}Lu]Lu-DOTATATE plus 1,850 MBq [^{90}Y]Y-DOTATATE with [^{177}Lu]Lu-DOTATATE depending on dosimeter results; and (D) analogous to Arm A, followed by individualized dose adjustment based on dosimeter results. Moreover, PRRT dose in subsequent cycles will depend on individualized dosimetry results for critical organs (bone marrow, kidneys), with a kidney dose limit of 23 Gy and a bone marrow dose limit of 2 Gy (maximum of 0.5 Gy per cycle) for all PRRTs.

Treatment efficacy is assessed using morphological imaging (TK or MR) according to RECIST v1.1. The safety of PRRT is assessed by measuring the biochemical function of the kidneys and bone marrow.

At EANM 2023, Marta Opalińska presented data obtained from 21 patients (Arm A, n=5; Arm B, n= 6; Arm C, n= 4; Arm D, n=5; one patient awaiting randomization). A total of 39 PRRT cycles were administered, including 23 fixed doses (first doses or Arm A). In the 16 cycles scheduled for adjustment, the dose of radiopharmaceutical was increased in eleven patients, while being decreased in five. Four patients dropped-out due to disease progression or AEs. So far, both patients who underwent the first post-PRRT assessment according to RECIST v1.1 criteria achieved a partial response (Arm A) and a complete response (Arm B), respectively.

The preliminary results showed significant interindividual and intraindividual differences in absorbed radiation doses by critical organs, such as kidney and bone marrow, compared to the tumor tissue. This emphasizes the importance of personalized dosimetry allowing for PRRT dose adjustment (frequent increases) in subsequent treatment cycles, while maintaining the safety of the therapy.

Full-body longitudinal analysis of individual lesions in NET patients receiving PRRT

Baseline somatostatin receptor image features (SRIFs) correlate with peptide receptor radionuclide therapy (PRRT) outcomes in patients with metastatic neuroendocrine tumors (mNETs). Study data demonstrated that a reduced ^{68}Ga-DOTATATE uptake in tumors following the first cycle of PRRT not only served as a predictor for the time to disease progression but was also linked to improved clinical symptoms among patients with well-differentiated NETs [11]. Nevertheless, the potential predictive value of longitudinal SRIFs obtained from each specific lesion has yet to be investigated. A recent study, presented by Victor Santoro-Fernandes at EANM 2023, addressed this question by examining the extent to which the longitudinal assessment of SRIFs enhances the prediction of progres-

sion-free survival (PFS) of mNET patients receiving PRRT [12].

Data from ^{68}Ga-DOTATATE PET/CT scans of mNET patients - taken before (baseline) and after ^{177}Lu-DOTATATE PRRT - were retrospectively analyzed. PFS was determined from medical records (median follow-up of 54 months) and used to stratify patients into poor and good responders. All lesions were contoured (lesion contouring), lesions were matched between imaging time points, and feature variation was calculated. Subsequently, lesion-level features were aggregated into patient-level features, which were further categorized into baseline and longitudinal sets.

In total, longitudinal images of 34 mNET patients were analyzed (mPFS, 20 months; min = 4, max = 54), with 18 patients classified as poor responders (PFS <31 months). Overall, a total of 2,521 lesions were identified (median: 38.5 per patient; min=5, max=381). The multivariate linear regression (MLR) model using longitudinal SRIFs resulted in more accurate PFS prediction **(Figure 2)** compared with single time-point baseline SRIFs reported by Haug AR et al. in 2010 [11] (RMSE, 13.5 *vs.* 14.1), and classification accuracy was also higher (AUROC, 0.81 *vs.* 0.74). Patient stratification was significant for longitudinal SRIFs but not for baseline SRIFs (log-rank test, p=0.003 *vs.* 0.06); this finding was further supported by the hazard ratios of 0.92 (95% CI, 0.88-0.96; p<0.001) *versus* 0.96 (95% CI, 0.92-1.00; p=0.04), respectively. While the MLR model outperformed all other machine learning models in predicting PFS, this may be attributed to the limited number of available training samples.

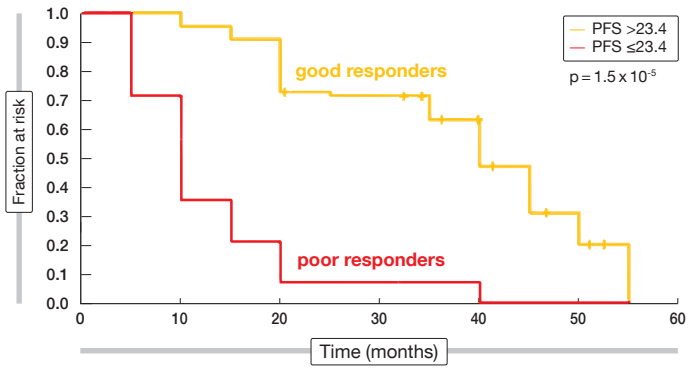

Figure 2: Multivariate linear regression using longitudinal SRIFs.

This work represents the first study to highlight the utility of full-body longitudinal SRIFs for predicting clinical outcomes. In mNET patients receiving PRRT, these results suggested that longitudinal SRIFs bring an additional benefit to PFS prediction compared to baseline SRIFs. ■

REFERENCES

1 Rubira L et al. (225)Ac-labeled somatostatin analogs in the management of neuroendocrine tumors: from radiochemistry to clinic. Pharmaceutics 2023; 15(4): 1051

2 Ulaner G et al. ^{225}Ac-DOTATATE dosimetry results from part 1 of the ACTION-1 trial. EANM 2023 (Oral abstract OP-672)

3 Shi M et al. Alpha-peptide receptor radionuclide therapy using actinium-225 labeled somatostatin receptor agonists and antagonists. Front Med (Lausanne) 2022; 9: 1034315

4 Harris PE et al. The evolution of PRRT for the treatment of neuroendocrine tumors; what comes next? Front Endocrinol (Lausanne) 2022; 13: 941832

5 Kunikowska J et al. Targeted alpha-emitter therapy of neuroendocrine tumors. Semin Nucl Med 2020; 50(2): 171-176

6 Liu D. [203/212Pb]VMT-α-NET theranostic pair achieved complete response in SSTR2+ preclinical tumor model. https://www.isotopes.gov/sites/default/files/2022-10/203-212Pb%20Group%20panel%20meeting%20DOE_10042022%20%20-%20%20Read-Only.pdf. Letzter Zugang Oktober 2023

7 Malik D et al. Early results of ^{212}Pb-VMT-alpha-NET targeted therapy in metastatic gastro-entero-pancreatic neuroendocrine tumors: first in human clinical experience on safety and efficacy. EANM 2023 (Oral abstract OP-673)

8 Hope TA et al. Neuroendocrine tumors and peptide receptor radionuclide therapy: when is the right time? J Clin Oncol 2022; 40(24): 2818-2829

9 Adant S et al. Combination treatments to enhance peptide receptor radionuclide therapy of neuroendocrine tumours. Eur J Nucl Med Mol Imaging 2020; 47(4): 907-921

10 Opalinska M et al. Personalized, dosimetry-based PRRT therapy in patients with neuroendocrine tumors using [^{177}Lu]Lu-DOTATATE or [^{177}Lu]Lu/[^{90}Y]Y-DOTATATE mixture - the initial results of DUONEN multicenter study. EANM 2023 (Oral abstract OP-675)

11 Haug AR et al. ^{68}Ga-DOTATATE PET/CT for the early prediction of response to somatostatin receptor-mediated radionuclide therapy in patients with well-differentiated neuroendocrine tumors. J Nucl Med 2010; 51(9): 1349-1356

12 Santoro-Fernandes V et al. Quantitative somatostatin receptor image assessment for survival prediction: a full-body, longitudinal, individual lesion analysis of neuroendocrine tumors in patients treated with peptide receptor radiation therapy. EANM 2023 (Oral abstract OP-676)

Early prediction of the response to ^{177}Lu-PSMA therapy in metastatic prostate cancer

PSMA (prostate-specific membrane antigen) is a glycoprotein highly expressed on the surface of malignant prostate tumor cells. Thus, it represents a suitable target for both imaging and therapy of prostate cancer (PCa). In fact, PSMA ligands are widely used either as tracers for positron emission tomography/computed tomography (PET/CT) imaging or as therapeutic agents comprising PSMA-directed radionuclide therapy and immunotherapy [1]. Notably, ^{177}Lu-PSMA-617 (vipivotide tetraxetan) received approval by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in March 2022 and December 2022, respectively. It is authorized for treating PSMA-positive metastatic castration-resistant prostate cancer (mCRPC) patients, who constitute approximately 30 % of PCa-patients, and have previously been treated with androgen receptor pathway inhibitors and taxanes [2].

PSA levels and the probability of detecting metastases at primary PCa staging

While PSMA is a valid target for both imaging and therapy in PCa, with radiolabeled ligands commonly used in PET/CT scans, the measurement of prostate-specific antigen (PSA) levels in the bloodstream serves as a standard method to assess disease progression [3]. The objective of a retrospective study presented at EANM 2023 by Luining Wietske was to evaluate whether PSA levels correlate with findings on PSMA PET/CT for primary staging, regarding the proportion and site of prostate cancer metastases [4].

Patients newly diagnosed for PCa between January 2017 and April 2022, presenting with evaluable PSMA-PET/CT results for primary staging and PSA values, were retrospectively analyzed. Data were stratified based on PSA levels, and the primary objective was to evaluate the risk of metastatic disease on PSMA PET/CT. Additionally, the proportion of PSMA-positive lesions in different anatomical locations was investigated. Correlations between PSMA PET/CT and PSA levels were analyzed by logistic regression.

A total of 1,306 patients with a median PSA of 16.5 ng/mL (IQR, 8.4-40.4) were included. PSMA PET/CT scans revealed metastases in 548 patients (42 %): 15 % had metastases in regional lymph nodes (miN1), 16 % in extra-pelvic lymph nodes (miM1a), 22 % in bones (miM1b) and 2.5 % in soft tissues (miM1c, according to EANM standardized reporting guidelines v1.0 [5]). The percentage of patients with metastases correlated positively with PSA levels **(Table 1)**. Overall, the initial PSA level was a significant predictor for detecting metastases in PSMA PET/CT scans that were found in 42 % of patients at primary staging.

The authors concluded that these results support the use of PSMA PET/CT scans in the initial staging of PCa.

^{68}Ga-PSMA PET/CT parameters used as diagnostic tool

The efficacy of ^{177}Lu-PSMA radioligand therapy (^{177}Lu-PSMA-RLT) is highly variable and early prediction of its outcome, especially in terms of survival, still needs to be established. However, the utility of ^{68}Ga-PSMA PET/CT to assess the local and metastatic burden of advanced PCa, typically in biochemically recurrent or advanced disease, has already been extensively utilized [6]. A retrospective study presented by Burak Demir at this year's EANM aimed at determining useful parameters, derived from ^{68}Ga-PSMA PET/CT, in predicting the efficacy of ^{177}Lu-PSMA-RLT in mCRPC patients [7].

A total of 55 patients with mCRPC who received two to six cycles of ^{177}Lu-PSMA-RLT and had evaluable pre-treatment ^{68}Ga-PSMA PET/CT results were retrospectively analyzed. They were separated into responders and non-responders based on PSA response, defined as a reduction of at least 50 % of the baseline value according to PCWG3 criteria (Prostate Cancer Clinical Trials Working Group 3) [8]. The standard uptake volume (SUV) $_{max}$, SUV_{mean}, SUV_{peak}, total tumor metabolic volume (TT-MV) and total tumor PSMA uptake (TT-PSMA) – as well as overall survival (OS) were determined.

Patients in the responder group had significantly higher SUV values and TT-PSMA than in the non-responder group (47.78 *vs* 26.80 for SUV_{max}, $p = 0.002$; 13.62 *vs* 8.47 for SUV_{mean}, $p = 0.038$; 32.25 *vs* 16.96 for SUV_{peak}, $p = 0.007$; 839.68 *vs* 1627.00 for TT-PSMA). While the median TT-MV was slightly lower in the responder group compared to the non-responder group (162.12 *vs* 168.61 cm^3), the median OS was significantly longer (17.1 *vs* 10.2 months; $p = 0.003$). Similarly, patients with a TT-MV lower than 162.12 cm^3 before treatment showed a significant longer median OS than those with a TT-MV of at least 162.12 cm^3 (18.9 *vs* 9.3 months; $p < 0.001$) **(Figure 1)**.

The receiver operating characteristic (ROC) curve analysis was used on ^{68}Ga-PSMA PET/CT parameters in predicting the PSA response to ^{177}Lu-PSMA-RLT treatment. AUC values for SUV_{max}, SUV_{mean} and SUV_{peak} at baseline were 0.772, 0.681 and 0.736, respectively, and the most specific cut-off to predict a positive PSA response was determined to be a SUV_{max} value of 50.70, with a sensitivity of 47.1 % and a specificity of 87.9 %, respectively.

TABLE 1 **PSA levels at primary prostate cancer staging and the associated proportions of patients with metastases.**

PSA levels (ng/mL)	<10	10-15	15-20	20-35	35-50	50-100	>100
Patients with metastases (%)	19	30	39	41	60	73	89

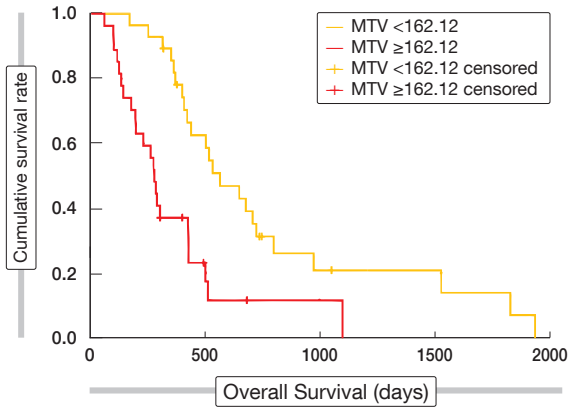

Figure 1: Kaplan-Meier curve of the overall survival of mCRPC patients treated by ^{177}Lu-PSMA-RLT with high versus low total metabolic tumor volume (MTV, cut-off 162.12 cm^3) at baseline determined by ^{68}Ga-PSMA PET/CT.

Considering these results, the authors concluded that this approach might help to select mCRPC patients benefitting from a ^{177}Lu-PSMA-RLT therapy.

^{18}F-rhPSMA-7.3 PET/CT parameters following ^{177}Lu-PSMA RLT

PET/CT imaging of primary PCa and mCRPC is based on PSMA radiolabeled ligands such as the first PET imaging agent – gozetotide (^{68}Ga-PSMA-11) – approved at the end of 2020. However, a new class of ^{18}F-labeled-PSMA-ligands attracts growing attention with the recent approval of piflufolastat (^{18}F DCFPyL) by the FDA in May 2021 and the EMA in July 2023 [9]. The ^{18}F-radiohybrid prostate-specific membrane antigen-7.3 (^{18}F-rhPSMA-7.3) belongs to these innovative PET imaging compounds and is currently under investigation in two multicenter phase 3 trials. At EANM 2023, Kimberley Hansen described how baseline ^{18}F-rhPSMA-7.3 parameters could be predictive of the clinical response to ^{177}Lu-PSMA-RLT in mCRPC patients [10].

A retrospective analysis was performed on 188 mCRPC patients having received ^{177}Lu-PSMA-RLT and showing reliable pre-treatment data (routine clinical and laboratory parameters as well as ^{18}F-rhPSMA-7.3 PET/CT imaging). Tumoral lesions were analyzed using a PROMISE® software and a series of quantitative parameters were calculated, such as SUV_{max}, SUV_{mean}, SUV_{peak}, total lesion number and total tumor volume (TTV).

The median OS was 11.8 months (95 % CI, 10.0-13.0). Negative prognostic factors for OS revealed by univariable COX regression included the total lesion number, the TTV, increasing levels of alkaline phosphatase, lactate dehydrogenase (LDH) and PSA, a decreasing level of hemoglobin, as well as prior chemotherapy and visceral metastases at baseline. The further multivariate analysis identified the total lesion number, increasing levels of LDH and prior visceral metastases as significant negative prognostic factors. A cut-off was established using the median TTV value of 394 ml, revealing that patients with a lower TTV experienced a significantly longer OS (15.9 *vs* 10.1 months; $p < 0.001$). The median number of prior-to-treatment metastases demonstrated similarly that patients with less than 127 lesions on ^{18}F-rhPSMA-7.3 PET had a significantly increased OS (16.3 *vs* 9.7 months; $p < 0.001$).

This retrospective study in mCRPC patients indicates that ^{18}F-rhPSMA-7.3 PET/CT increasingly replacing ^{68}Ga-PSMA-11 has prognostic value for the ^{177}Lu-PSMA-RLT outcome. Moreover, TTV prior ^{177}Lu-PSMA-RLT seems to be an independent prognostic factor of survival.

Early prediction of ^{177}Lu-PSMA-I&T response with interim ^{18}F-PSMA-1007-PET/CT

The efficacy of ^{177}Lu-PSMA for imaging and therapy (^{177}Lu-PSMA-I&T) is usually evaluated after four cycles of therapy based on serum PSA and PSMA-PET/CT imaging. However, there are several confounding factors affecting PSA. Thus, the objective of a study presented by Shing-Kee William-Cheung at EANM 2023 was to evaluate if ^{18}F-PSMA-1007 would be a good surrogate biomarker of ^{177}Lu-PSMA-I&T treatment effectiveness in mCRPC patients [11].

Patients with mCRPC recruited between August 2020 and December 2022 were subjected to four ^{177}Lu-PSMA-I&T cycles of approximately 7.4 GBq each at six-week intervals. Additionally, patients underwent PSA measurement and ^{18}F-PSMA-1007 PET/CT at baseline (bPET), after two cycles of therapy (iPET, interim PET) and a final evaluation (fPET) three months after the last treatment cycle. A positive PSA response was defined as a reduction by ≥ 50 % of the baseline value as per PCWG3 criteria [8]; an imaging response was evaluated based on tumor volume as per RECIP 1.0 [12] and classified as complete (CR, all lesions normalized), partial (PR, reduction of ≥ 30 % of tumor volume and no new lesion) or non-response (NR).

A total of 24 patients, with a mean age of 73.5 years, were enrolled in the study. After the second cycle of ^{177}Lu-PSMA, a positive PSA response was observed in 79 % of patients while a positive imaging response was detected in 46 % of the

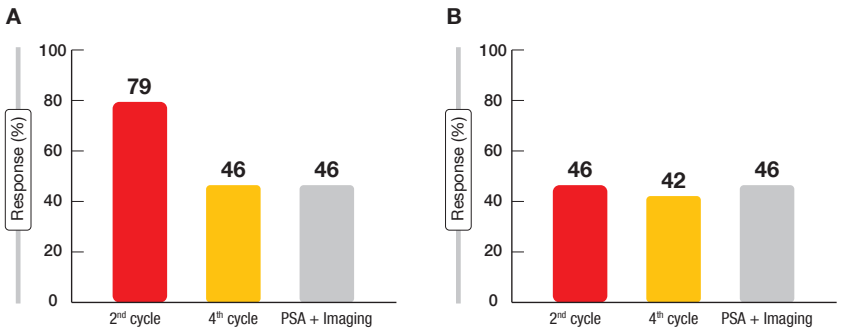

Figure 2: PSA response (A) and imaging response (B) compared to post-treatment outcome

patients with one patient showing a CR and ten patients a PR. At the final evaluation, a positive PSA response was reported in 46 % of the patients and a positive imaging response in 42 % (all PR), respectively. Overall, 46 % of the patients were considered as responders based on the combined "PSA + imaging responses" **(Figure 2)**.

While the interim imaging response was consistent with the classification of patients in responders or non-responders, the interim PSA response incorrectly classified 8/19 patients (42 %) as positive responders, despite the discovery of new lesions on iPET/fPET.

This study showed that after the 2nd cycle of ^{177}Lu-PSMA-I&T treatment in mCRPC patients, interim ^{18}F-PSMA-1007 PET/CT serves as a valuable surrogate biomarker for monitoring treatment progress and predicting the ultimate therapeutic outcome. ■

REFERENCES

1 Luining W et al. Targeting PSMA revolutionizes the role of nuclear medicine in diagnosis and treatment of prostate cancer. Cancers (Basel). 2022; 14(5): 1169
2 Parent E et al. ^{177}Lu-PSMA Therapy. J Nucl Med Technol. 2022; 50(3): 205-212
3 Zavridou M et al. Development and Analytical Validation of a 6-Plex Reverse Transcription Droplet Digital PCR Assay for the Absolute Quantification of Prostate Cancer Biomarkers in Circulating Tumor Cells of Patients with Metastatic Castration-Resistant Prostate Cancer. Clin Chem. 2022; 68(10): 1323-1335
4 Luining W et al. The probability of prostate cancer metastases within different prostate-specific antigen ranges using primary staging prostate-specific membrane antigen PET/CT in patients with newly diagnosed prostate cancer. EANM 2023 (e-poster abstract EPS-105)
5 Ceci F et al. E-PSMA: the EANM standardized reporting guidelines v1.0 for PSMA-PET. Eur J Nucl Med Mol Imaging. 2021; 48(5): 1626-1638
6 Perera M et al. Gallium-68 Prostate-specific Membrane Antigen Positron Emission Tomography in Advanced Prostate Cancer-Updated Diagnostic Utility, Sensitivity, Specificity, and Distribution of Prostate-specific Membrane Antigen-avid Lesions: A Systematic Review and Meta-analysis. Eur Urol. 2020; 77(4): 403-417
7 Demir B et al. Pre-treatment ^{68}Ga-PSMA PET/CT parameters could predict response to ^{177}Lu-PSMA treatment and overall survival in metastatic castration resistant prostate carcinoma patients treated with ^{177}Lu-PSMA. EANM 2023 (e-poster abstract EPS-116)
8 Scher H et al. Prostate Cancer Clinical Trials Working Group 3. Trial design and objectives for castration-resistant prostate cancer: updated recommendations from the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol. 2016; 34(12): 1402-1418
9 Voter A et al. Piflufolastat F-18 (^{18}F-DCFPyL) for PSMA PET imaging in prostate cancer. Expert Rev Anticancer Ther. 2022; 22(7): 681-694
10 Hansen K et al. Predictive ^{18}F-rhPSMA-7.3 PET parameters for outcome assessment of ^{177}Lu-PSMA-RLT. EANM 2023 (e-poster abstract EPS-124)
11 Cheung S et al. Significance of interim ^{18}F-PSMA-1007 PET/CT for early prediction of ^{177}Lu-PSMA-I&T treatment effect in metastatic castration-resistant prostate cancer patients. EANM 2023 (e-poster abstract EPS-114)
12 Gafita A et al. Novel framework for treatment response evaluation using PSMA PET/CT in patients with metastatic castration-resistant prostate cancer (RECIP 1.0): an international multicenter study. J Nucl Med. 2022; 63(11): 1651-1658

Advances in PSMA-based immunotherapy in metastatic castration-resistant prostate cancer

Metastatic castration-resistant prostate cancer (mCRPC) has a very bad prognosis with most patients dying within two years of diagnosis [1]. Available therapies for mCRPC are often associated with poor tissue selectivity, and side effects including high systemic toxicity and drug resistance. Great progress has been made with the help of PSMA (prostate-specific membrane antigen), a glycoprotein highly expressed on the cell membrane of malignant prostate tumor cells, which constitutes an attractive therapeutic candidate for both diagnosis and treatment of mCRPC [2]. Briefly, PSMA-based immunotherapy specifically targets tissues expressing the protein, either the primary tumor or metastases. However, PSMA is expressed in normal tissues such as salivary glands, kidney, ovary, breast, the neo-vasculature of non-prostatic tumors and intestine, too, and high uptakes of radiopharmaceuticals might lead to dose-limiting toxicities [2-4].

ProstACT GLOBAL: a phase 3 study with ^{177}Lu-DOTA-rosopatamab

TLX591 consists of the humanized monoclonal antibody rosopatamab (HuJ591), targeting an epitope of the extracellular domain of PSMA, conjugated to DOTA, a chelating agent (DOTA-HuJ591). This chelator conjugated antibody can be linked to different radioisotopes for diagnostic (^{89}Zirconium) or therapeutic purposes (^{177}Lutetium, ^{111}Indium or ^{90}Yttrium) [5, 6]. Rosopatamab has a high affinity for PSMA, its target epitope, and does not bind to complement [6]. So far, ^{177}Lu-HuJ591 has been tested in more than 100 patients in four phase 1 and 2 studies with single as well as repeated and fractionated doses [5]. Rosapatamab has further been evaluated in combination with standard-of-care docetaxel in a phase 1 study including 15 patients with progressive mCRPC and showed preliminary encouraging efficacy [7]. During EANM 2023, Neel Patel presented the design of the ongoing ProstACT GLOBAL multinational, multicenter, randomized, controlled, open-label phase 3 study (NCT04876651) [8]. The efficacy and safety of ^{177}Lu-DOTA-rosopatamab plus best standard of care

(SoC), as compared to best SoC alone, is investigated in patients with progressive mCRPC despite previous treatment with a novel androgen-axis drug (NAAD). Patients considered eligible must present with a PSMA-positive disease and at least one metastatic site, as assessed by ^{68}Gallium-PSMA-11 positron emission tomography/computerized tomography (^{68}Ga-PSMA-11 PET/CT) scan, have received prior therapy with either enzalutamide or abiraterone plus prednisone, as well as prior taxane therapy unless they have refused it or are ineligible; patients must also present adequate hematological function as demonstrated by normal platelet count (≥ 150 x 10^9/L) and normal hemoglobin (≥ 10 g/dL).

The planned 387 patients will be randomized 2:1 to either two 14-days-apart single intravenous injections of 76 millicuries (mCi) each of ^{177}Lu-DOTA-rosopatamab (equivalent to a 45 mCi/m^2 dose in a standard 1.7 m^2 individual) on top of best SoC, or best SoC alone. Stratification factors will be based on prior taxane therapy, prior NAAD setting (non-metastatic versus castration-sensitive), disease burden as defined by bone metastases number with a cut-off at 10, and visceral disease (or not).

The primary objective of ProstACT GLOBAL is the radiographic progression-free survival (rPFS); secondary endpoints further evaluate the 5-year overall survival (OS), the tumor objective response rate (ORR) and the time to symptomatic skeletal event (TTSSE), as well as the assessment of treatment-related adverse events (TRAEs).

The study is currently ongoing and will provide new insights into the benefits of combined radiotherapy and immunotherapy, in addition to efficient ^{68}Ga-PSMA-11 PET/CT-base selection of patients with mCRPC.

Good tolerance to low dose ^{177}Lu-PSMA-617 therapy

At this year's EANM, Irene Marini presented preliminary results of IRST-185.03, an open-label, single-center, phase 2, prospective study (NCT03454750) evaluating the efficacy and toxicity of low-dose radiometabolic therapy with ^{177}Lu-PSMA-617 in advanced mCRPC. The study enrollment started in April 2017 and closed in October 2022 [9]. The primary objective of the study was efficacy, as assessed by best biochemical response (BR) defined as a PSA reduction of at least 50 % versus baseline value. Secondary objectives encompassed safety, PFS and OS. Inclusion criteria comprised histologically confirmed progressive prostate cancer with metastases documented by ^{68}Gallium-PSMA-11 PET/CT scan, adequate hematological organ function and ECOG score ≤ 2.

In total, 43 patients were included in the low-dosage (LD) group (3.7-4.4 GBq per cycle) and 99 patients in the high-dosage (HD) group (5.5 GBq per cycle) based on age (cut-off at 75 years), prior treatment with docetaxel and risk factors for toxicity. The median age was 70.2 years and median PSA value was 45.7 ng/mL at baseline. Overall, 90.1 % of patients had received prior treatment with abiraterone/enzalutamide and 62.7 % with docetaxel, while 29.6 % had been rechallenged with cabazitaxel or docetaxel. To note, 37.2 % of patients presented more than 20 bone metastatic lesions and 17.6 % had visceral metastases. Both groups received a median of four cycles (up to six) of ^{177}Lu-PSMA-617, eight to twelve weeks apart, with concomitant mannitol intra-venous infusion for kidney protection and polyglutamate folate tablets orally for salivary glands protection [10].

After a median follow-up of 28.8 months, the PSA ≥50 % was achieved in 40.1 % of all patients; in more detail, a PSA reduction of ≥50 % was observed in 42.4 % patients in the HD group and in 34.9 % of patients in the LD group **(Figure 1)**. Moreover, 51.4 % of the overall patient population showed a PSA reduction < 30 % or a PSA increase. The overall median PFS was 7.0 months (95 % CI: 5.5-7.6) and the 12-month PFS rate was 18.9 % (95 % CI: 12.2-26.6). The overall median OS was 16.8 months (95 % CI: 12.1-20.4) – 13.5 months (95 % CI: 8.4-19.2) in the LD group and 16.4 months (95 % CI: 12.1-25.3) in the HD group. The overall 12-month OS rate was 60.4 % (95 % CI: 50.5-68.6) - 51.1 % (95 % CI: 35.5-64.8) in the LD group and 64.9 % (95 % CI: 51.9-75.1) in the HD group.

The most common side effect was grade 1 anemia reported in 19 patients. Grade 3 toxicity was observed in seven patients, with five experiencing anemia and two experiencing renal toxicity. No grade 4 toxicity was reported.

These preliminary results show that ^{177}Lu-PSMA-617, even at low doses, is efficient and well tolerated in selected, heavily pretreated mCRPC patients and justify further investigation of the minimum effective and non-toxic dosage of this radiometabolic therapy.

Swiss registry of mCRPC patients treated with ^{177}Lu-PSMA-I&T

The objective of this prospective national registry is to assess the efficacy and the safety of ^{177}Lu-PSMA-I&T (for imaging and therapy) therapying mCRPC implemented in daily clinical practice in Switzerland. Between February 2021 and

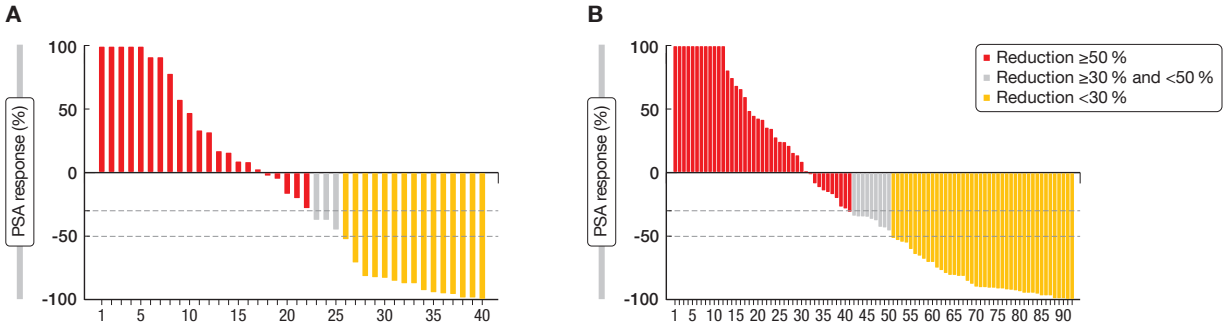

Figure 1: PSA response after **(A)** low-dose (3.7-4.4 GBq) and **(B)** high-dose (5.5 GBq) ^{177}Lu-PSMA-617 treatment in mCRPC.

May 2023, eight sites enrolled 246 patients with mCRPC, defined by PSMA-positivity, who failed or were unfit for chemotherapy, and had a progressive disease despite androgen-signaling inhibition therapy. During last year's EANM, Nicolas Guillaume already presented preliminary safety (primary endpoint) and efficacy (key secondary endpoint) data from 107 patients receiving 7 GBq of ^{177}Lu-PSMA-I&T every six weeks [11]. This year, Alin Chirindel presented an update on 147 evaluable patients [12]; a follow-up is planned until May 2024.

The enrolled patients had a median age of 75 years, a median baseline PSA of 72 ng/ml and metastases mostly in bones (95 % of patients) and/or lymph nodes (77 %). In the prior phase 3 VISION trial (NCT03511664), 50 % of patients had lymph node metastases and 21 % had metastases in soft tissues, compared to 30 % in the Swiss registry [13]. In total, 70 % of patients had a Gleason score between eight and ten, 71 % had received previous chemotherapy (97 % in VISION) and 99 % had underwent androgen-signaling inhibition therapy or orchidectomy (100 % in VISION). Patients received a median of three treatment cycles (IQR: 2-5) with a median of 7.1 GBq ^{177}Lu-PSMA (IQR: 6.5-7.5), while VISION patients received a median of five cycles (IQR: 1-6).

A biochemical response was observed in 58.1 % of patients, with PSA levels ≤80 % in 18.2 % and ≤50 % in 39.9 % of patients. An objective imaging response - as evaluated by the tumor total volume [14] - was observed in 78 % of patients. The median PSA response and the median OS (15.2 months) are in line with the efficacy parameters observed with ^{177}Lu-PSMA-617 in the VISION trial (**Table 1** and [13]).

Treatment related grade ≥3 adverse events (AEs), shown in **Table 1**, include lymphopenia (27.8 %), anemia (13.6 %), leukopenia (3.4 %), kidney dysfunction (1.4 %) and thrombocytopenia (1.4 %).

The preliminary Swiss registry radioligand therapy data show that ^{177}Lu-PSMA-I&T has a good safety profile and is efficient in mCRPC patients in a real-life setting.

Combined therapy with ^{225}Ac-PSMA-617 and ^{177}Lu-PSMA

Treatment options in patients with mCRPC after failure of guideline-conform or ^{177}Lu-PSMA-radioligand therapies are very limited [15]. While ^{225}Ac-PSMA-617-targeted alpha therapy (TAT) has demonstrated promising results in these patients, its associated adverse effects could substantially affect the quality of life of these patients [16]. A combination treatment regimen with ^{177}Lu-PSMA and reduced ^{225}Ac-TAT may improve tolerability, while maintaining an acceptable antitumor activity. At EANM 2023, Gabriel T. Sheikh presented the study outcomes in terms of response and adverse events in patients receiving different combinations of ^{225}Ac-TAT/^{177}Lu-PSMA-I&T (ALCT) [17].

A total of 22 mCRPC patients who failed previous guideline-based and/or ^{177}Lu-PSMA-radioligand therapy were treated with ALCT: ten patients (Group 1) received 4 MBq ^{225}Ac and 4000 MBq ^{177}Lu, three patients (Group 2) received 6 MBq ^{225}Ac and 1000 or 2000 MBq ^{177}Lu, and nine patients (Group 3) received 8 MBq ^{225}Ac and 1000 MBq ^{177}Lu per therapy cycle. Clinical parameters (PSA, alkaline phosphatase, lactate dehydrogenase, hemoglobin, leukocyte count, thrombocyte count, creatinine) and imaging parameters from ^{18}F-PSMA-PET/CT (Tumor Total Volume, SUV_{max}, SUV_{mean}) were collected at baseline and after two cycles of therapy. AEs were evaluated according to CTCAE v5.0 and ^{18}F-PSMA-PET/CT according to RECIP 1.0 (response evaluation criteria in PSMA PET/CT, [18]).

Regarding the efficacy of the three ALCT combinations, as evaluated by either clinical or imaging parameters, there was no statistically significant difference between the groups. AEs in Group 1, 2 and 3 after two cycles of ALCT included anemia in 20 %, 0 % and 33 %; thrombocytopenia in 10 %, 0 % and 0 %; leukopenia in 40 %, 33 % and 22 %; weight loss in 10 %, 0 % and 22 %, as well as xerostomia in 30 %, 33 % and 56 %, respectively. Overall, a higher ^{177}Lu-activity was associated with bone marrow toxicity, while higher ^{225}Ac-activity was more frequently associated xerostomia.

The three tested combinations of ^{225}Ac-TAT/^{177}Lu-PSMA-I&T showed an overall similar efficacy but different tolerability. Therefore, ALCT with low ^{225}Ac-activity could be a favorable choice to minimize adverse effects on salivary glands. Nevertheless, it is imperative to closely monitor these patients for any changes in hematology parameters. ■

TABLE 1 **Preliminary safety and efficacy results from the Swiss registry and the VISION phase 3 trial.**

Preliminary safety results	Swiss Registry (^{177}Lu-PSMA-I&T)	VISION trial (^{177}Lu-PSMA-617)
Grade ≥3 anemia	13.6 % (20/147)	12.9 % (68/529)
Grade ≥3 thrombocytopenia	1.4 % (2/147)	7.9 % (42/529)
Grade ≥3 lymphopenia	27.8 % (40/144)	7.8 % (41/529)
Grade ≥3 leukopenia	3.4 % (5/147)	2.5 % (13/529)
Grade ≥3 xerostomia	0 % (0/150)	0 % (0/529)
Grade ≥3 kidney dysfunction	1.4 % (2/141)	0 % (0/529)
Preliminary efficacy results		
Biochemical response (PSA_{50})	39.9 % (57/143)	46.0 % (177/385)
Biochemical response (PSA_{80})	18.2 % (26/143)	33.0 % (127/385)
Any PSA decrease	66.4 % (95/143)	71.4 % (275/385)
Objective imaging response	78 % (92/118) TTV	51.1 % (94/148) RECIST 1.1
Median OS (months)	15.2	15.3

Data are given as percentage and number. TTV = total tumor volume.

REFERENCES

1 Lowrance WT et al. Castration-Resistant Prostate Cancer: AUA Guideline Amendment 2018. J Urol. 2018; 200(6): 1264-1272
2 Sekhoacha M et al. Prostate cancer review: genetics, diagnosis, treatment options, and alternative approaches. Molecules. 2022; 27(17): 5730
3 Wang F et al. Advances in PSMA-targeted therapy for prostate cancer. Prostate Cancer Prostatic Dis. 2022; 25(1): 11-26
4 Langbein T et al. Salivary Gland Toxicity of PSMA-Targeted Radioligand Therapy with ^{177}Lu-PSMA and Combined ^{225}Ac- and ^{177}Lu-Labeled PSMA Ligands (TANDEM-PRLT) in Advanced Prostate Cancer: A Single-Center Systematic Investigation. Diagnostics (Basel). 2022; 12(8): 1926
5 Niaz MO et al. Review of lutetium-177-labeled anti-prostate-specific membrane antigen monoclonal antibody J591 for the treatment of metastatic castration-resistant prostate cancer. Cureus. 2020; 12(2): e7107
6 Sartor O et Baghian A. Prostate specific membrane antigen binding radiopharmaceuticals: Current data and new concepts. Front Med (Lausanne). 2022; 9:1060922
7 Batra JS et al. Phase I trial of docetaxel plus lutetium-177-labeled anti-prostate-specific membrane antigen monoclonal antibody J591 (^{177}Lu-J591) for metastatic castration-resistant prostate cancer. Urol Oncol. 2020; 38(11): 848.e9-848.e16
8 Patel N et al. ProstACT GLOBAL: a phase 3 study of ^{177}Lu-DOTA-rosopatamab (TLX591) with and without the best standard of care for patients with PSMA expressing metastatic castration-resistant prostate cancer progressing despite prior treatment with a novel androgen axis drug. EANM 2023 (Oral abstract OP-718)
9 Marini I et al. ^{177}Lu-PSMA-617 therapy in advanced mCRPC patients: preliminary results of the phase 2 prospective trial IRST-185.03. EANM 2023 (Oral abstract OP-723)
10 Paganelli G et al. Dosimetry and safety of ^{177}Lu PSMA-617 along with polyglutamate parotid gland protector: preliminary results in metastatic castration-resistant prostate cancer patients. Eur J Nucl Med Mol Imaging. 2020; 47(13): 3008-3017
11 Nicolas G et al. Safety and efficacy of PSMA targeted radionuclide therapy with ^{177}Lu-ITG-PSMA-1 in metastatic castration resistant prostate cancer patients: preliminary results of a Swiss wide prospective multicentre registry study. EANM 2022 (Oral abstract OP-381)
12 Chirindel A et al. Safety and efficacy of PSMA-targeted radionuclide therapy with ^{177}Lu-ITG-PSMA-1 in metastatic castration resistant prostate cancer patients: Update on the prospective, multicenter, Swiss registry study. EANM 2023 (Oral abstract OP-716)
13 Sartor O et al. VISION investigators. Lutetium-177-PSMA-617 for metastatic castration-resistant prostate cancer. N Engl J Med. 2021; 385(12): 1091-1103
14 John N et al. ^{177}Lu-PSMA SPECT Quantitation at 6 weeks (dose 2) predicts short progression-free survival for patients undergoing ^{177}Lu-PSMA-I&T therapy. J Nucl Med. 2023; 64(3): 410-415
15 Unterrainer LM et al. Total Tumor Volume on ^{18}F-PSMA-1007 PET as Additional Imaging Biomarker in mCRPC Patients Undergoing PSMA-Targeted Alpha Therapy with ^{225}Ac-PSMA-I&T. Biomedicines. 2022; 10(5): 946
16 Ma J et al. Efficacy and safety of ^{225}Ac-PSMA-617-targeted alpha therapy in metastatic castration-resistant prostate cancer: a systematic review and meta-analysis. Front Oncol. 2022; 12: 796657
17 Sheikh G et al. Systematic evaluation of response and adverse events in mCRPC patients treated with different combinations of ^{225}Ac/^{177}Lu-PSMA-therapy. EANM 2023 (Oral abstract OP-717)
18 Gafita A et al. Novel framework for treatment response evaluation using PSMA PET/CT in patients with metastatic castration-resistant prostate cancer (RECIP 1.0): an international multicenter study. J Nucl Med. 2022; 63(11): 1651-1658

Further benefits of PET imaging in prostate cancer

Prostate cancer was the most frequently diagnosed cancer in men in 112 countries around the world in 2020, with 1.4 million newly diagnosed cases leading to more than 375,000 deaths [1].

VISION: association between baseline PSMA-PET scans and clinical outcomes in patients with mCRPC

The open-label, multi-center, randomized phase 3 VISION study (NCT03511664) demonstrated the efficacy and safety of ^{177}Lu-PSMA-617 targeted radioligand therapy in patients with progressive prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) [2]. These positive results led to FDA approval and breakthrough therapy designation for ^{177}Lu-PSMA-617 in later lines of mCRPC treatment [3,4]. Additionally, at last year's EANM, Herrmann K. et al. presented data from the VISION study on health-related quality of life, pain, and safety [5]. All patients in VISION had to have PSMA-positive mCRPC, based on visual assessment of baseline gallium-68-radiolabelled prostate-specific membrane antigen 11 (^{68}Ga-PSMA-11) PET/CT scans.

At the EANM 2023 congress, Phillip H. Kuo presented an exploratory post hoc analysis that examined the association between quantitative parameters from baseline ^{68}Ga-PSMA-11 PET scans and the response to ^{177}Lu-PSMA-617 in VISION [6]. The endpoints analyzed

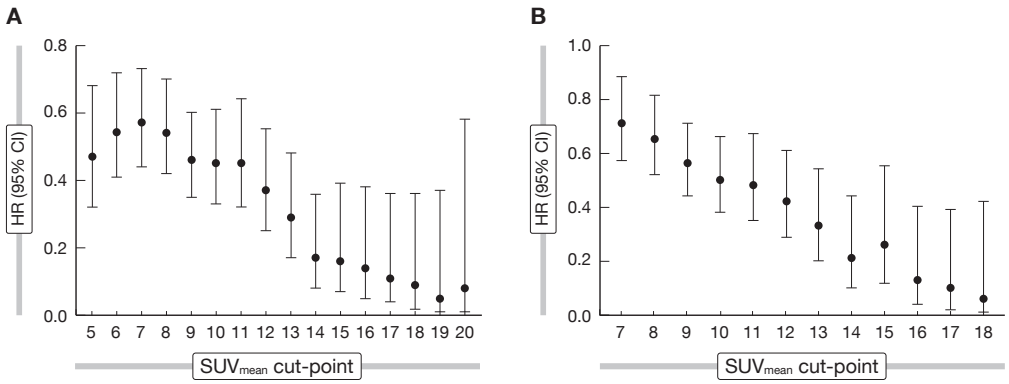

Figure 1: ^{68}Ga-PSMA-11 whole-body tumor SUV_{mean} cut-point analysis within the ^{177}Lu-PSMA-617 arm of VISION for **(A)** rPFS and **(B)** OS.

were radiographic progression-free survival (rPFS), overall survival (OS), objective response rate (ORR) and prostate specific antigen (PSA) response. The 831 patients were randomized 1:1 to ^{177}Lu-PSMA-617 plus standard of care (SoC) or SoC only. Four quantitative ^{68}Ga-PSMA-11 PET parameters from 826 patients were extracted: mean and maximum standardized uptake value (SUV_{mean} and SUV_{max}) and tumor volume and load in bone, lymph node, liver, soft tissue, and the whole body. Higher SUV indicates higher PSMA expression, which may increase ^{177}Lu-PSMA-617 tumor dose uptake, enhance anti-tumor activity, and lead to improved outcomes.

Baseline ^{68}Ga-PSMA-11 whole-body SUV_{mean} was the best predictor of outcomes in treatment-adjusted multivariate modeling. A 1-unit increase in whole-body tumor SUV_{mean} was associated with a 12 % decrease in the risk of an rPFS event and a 10 % decrease in the risk of death. Compared with SoC alone, ^{177}Lu-PSMA-617 improved outcomes across all whole-body SUV_{mean} quartiles, but with greater benefits in patients with higher uptake values. In the highest whole-body SUV_{mean} quartile (rPFS, ≥ 10.2; OS, ≥ 9.9) median rPFS was 14.1 months *versus* 3.9 months (HR, 0.34; 95 % CI: 0.20-0.56) and median OS was 21.4 months *vs* 15.0 months (HR, 0.47; 95 % CI: 0.32-0.68). In the lowest quartile (rPFS, < 6.0; OS, < 5.7), median rPFS was 5.8 months *versus* 3.9 months (HR, 0.75; 95% CI: 0.45-1.26) and median OS was 14.5 months *versus* 11.3 months (HR, 0.87; 95 % CI: 0.60-1.27). However, no SUV_{mean} cut-point was better than any other for dividing patients receiving ^{177}Lu-PSMA-617 into subgroups with longer or shorter rPFS and OS. Outcomes improved continuously with each unit increase in whole-body tumor SUV_{mean} **(Figure 1)**. Additionally, in both study groups, shorter rPFS and OS were associated with higher whole-body tumor load and the presence of lesions in bone or liver on ^{68}Ga-PSMA-11 PET.

The VISION study was not powered for PET subgroup analysis and PET scanners as well as parameters differed among sites. Despite these limitations, high whole-body tumor ^{68}Ga-PSMA-11 uptake at baseline emerged as the strongest predictor of ^{177}Lu-PSMA-617 efficacy in patients with PSMA-positive mCRPC, although efficacy was evident at all uptake levels in VISION. These results show that study eligibility criterion based visual assessment of ^{68}Ga-PSMA-11 PET/CT scans allows selection of patients with a range of whole-body tumor radiotracer uptake levels, but who are suitable candidates for ^{177}Lu-PSMA-617 targeted radioligand therapy.

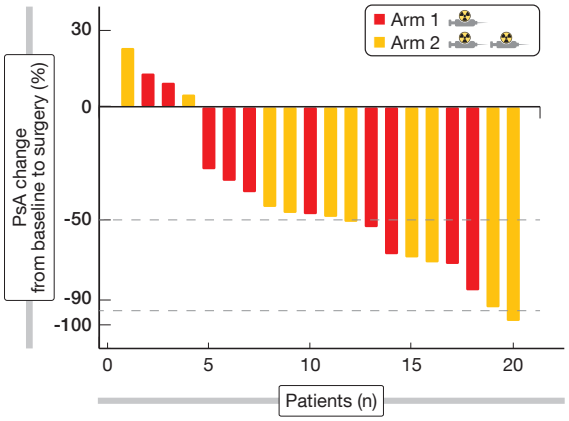

Figure 2: PSA change from baseline to surgery in patients having received one (red bars) or two (yellow bars) cycles of LuPSMA.

LuTectomy: ^{177}Lu-PSMA-617 prior to radical prostatectomy in men with high-risk localized prostate cancer

High-risk localized prostate cancer (HRCaP) is associated with a high probability of local and systemic recurrence [7]. LuTectomy is a phase 1/2 study (NCT04430192) in patients with HRCaP who are eligible for radical prostatectomy (RP). It evaluates the dosimetry, efficacy, and toxicity of lutetium (^{177}Lu) vipivotide tetraxetan – so called ^{177}Lu-PSMA-617 or LuPSMA –, whose beneficial effect have already been demonstrated in patients with metastatic castration-resistant prostate cancer [8]. The primary objective of this study is to determine the radiation dose absorbed by the tumor and involved lymph nodes. First results were presented by Michael S. Hofman at EANM 2023 [9].

Patients with HRCaP (prostate specific antigen, PSA > 20 ng/mL, ISUP grade group 3-5, status ≥ cT2c or N1), high tumor uptake (SUV_{max} ≥ 20) on ^{68}Ga-PSMA-11 PET/CT and scheduled for RP were included in this study. Cohort A (n = 10) received one cycle of 5 GBq LuPSMA and Cohort B (n = 10) received two cycles of 5 GBq LuPSMA (6 weeks apart). The radiation dose was estimated by SPECT/CT at 4-, 24- and 96-hours post-therapy. Safety assessments and RP surgery were scheduled six weeks after LuPSMA treatment.

Twenty patients with a median age of 66 years were enrolled; 30 % of patients (6/20) had N1 disease. The median PSA level was 18 ng/mL (IQR, 11-35) and the median PSMA-PET SUV_{max} was 31 (IQR, 26-36) at baseline. The highest tumor absorbed dose after Cycle 1 was in median 35.5 Gy (IQR, 19.5-50.1) for all lesions, 19.6 Gy (IQR, 11.3-48.4) for the prostate and 37.9 Gy (IQR, 33.1-50.1) for lymph nodes.

All patients underwent robotic RP, with surgical difficulty levels as expected in most patients (15/20) and slightly higher in five of them. After histopathologic analyses, 80 % of patients (16/20) patients showed a partial response and one patient had minimal residual disease, while no complete responses were obtained. The imaging response showed a stable SUV_{max} in 40 % of patients (8/20) and ≥ 30 % decrease in 55 % patients (11/20), while the rest presented with an SUV_{max} increase of more than 30 %. PSA was significantly reduced by 49 % (median, IQR, 32-67), with a reduction rate of at least 50 % in 45 % of patients (9/20) **(Figure 2)**. After a median follow-up of 13.8 months, the biochemical recurrence-free survival reached 80 %.

Patients reported the following grade 1 adverse events (AEs), fatigue (40 %), nausea (35 %), dry mouth (30 %), thrombocytopenia (20 %) and lymphopenia (20 %); renal impairment of grade 2 was reported in one patient, while no grade 3/4 serious AEs (SAEs) occurred.

Overall, the authors concluded that ^{177}Lu-PSMA-617 plus radical prostatec-

tomy is safe in men with HRCaP with encouraging responses. Thus, further research is justified.

PSMA-PET/CT after salvage radiotherapy for recurrent or persistent prostate cancer after surgery

PSMA-PET is increasingly used to guide salvage radiotherapy (sRT) following radical prostatectomy in patients with recurrent or persistent prostate cancer [10]. In prostate cancer patients with biochemical recurrence after radical prostatectomy, PSMA-PET should be the tracer of choice when PET-CT imaging is considered for subsequent treatment management decisions [11]. In this context, sites of recurrence were clarified by PSMA-PET and disease localization translated into modified treatment in 68 % of patients with biochemical recurrence of prostate cancer [12]. Constantinos Zamboglou and colleagues investigated whether the implementation of PSMA-PET imaging improved the outcome after prostate cancer sRT in recurrent or persistent prostate cancer patients after surgery; these data were presented at EANM 2023 [13].

Patients having underwent sRT were selected from two databases: i) 344 patients from the multicenter phase III SAKK 09/10 trial (28 centers, 3 countries, non-PSMA-guided sRT for cMO); and ii) 1,548 patients from a retrospective multicenter cohort (11 hospitals, 5 countries, PSMA-guided sRT for cMO). Patients with positive lymph nodes in primary surgery, cM1 status (initial or visible in PET imaging), PSA > 0.5 ng/mL before sRT or missing stratification variables were excluded. Moreover, the cohorts were balanced based on age, ISUP score, PSA before sRT, T-stage and PSA recurrence versus persistence. The biochemical recurrence-free survival (BRFS) and recurrence patterns were compared, with biochemical recurrence defined as PSA nadir after sRT +0.2 ng/mL.

A total of 717 patients were included in two well-balanced cohorts: Cohort 1 consisted in 255 patients (median follow-up of 75 months) and Cohort 2 in 462 patients (median follow-up of 36 months). In Cohort 2, local recurrence occurred in 33.8 % of patients and nodal recurrence in 22.3 %, associated to irradiation of lymph nodes in 22.3 % of patients.

The 3-year BRFS rates were 70 % (95 % CI: 64-77) and 78 % (95 % CI: 73-83) for Cohort 1 and Cohort 2 (p = 0.012, weighted log-rank test). This significant improvement in BRFS when PSMA-PET was used for sRT guidance can be explained by individualized sRT field based on PET. Thus, a consortium for further validation based on prospective data has been created: Co-IMPACT (Consortium for Implementation of PSMA-PET in Prostate Cancer Radiotherapy Trials) currently including approx. 7,000 patients from 13 countries in 38 centers dispatched in four cohorts. Co-IMPACT 1 will consist of 2,000 patients with primary prostate cancer, Co-IMPACT 2 will include 3,500 patients with recurrent prostate cancer after surgery and Co-IMPACT 4 will include 1,500 patients with recurrent prostate cancer after radiotherapy. CO-IMPACT 4 will assess the outcomes after PSMA-PET based radiotherapy in the castration-resistant setting. ■

REFERENCES

1 Sung H et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021; 71(3): 209-249
2 Kuo PH et al. Why we did what we did: PSMA PET/CT selection criteria for the VISION trial. J Nucl Med. 2022; 63(6): 816-818
3 Hofman MS et al. [^{177}Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study. Lancet Oncol. 2018; 19(6):825-8 33
4 Sartor O et al. Lutetium-177-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer. N Engl J Med. 2021; 385(12): 1091-1103
5 Hermann K et al. Health-related quality of life (HRQoL), pain and safety outcomes in the phase 3 VISION study of ^{177}Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer. EANM 2022 (Oral abstract OP-161)
6 Kuo PH et al. Association of baseline quantitative [^{68}Ga]Ga-PSMA-11 PET imaging parameters with clinical outcomes in patients with mCRPC receiving [^{177}Lu]Lu-PSMA-617: a VISION sub-study. EANM 2023 (Oral abstract OP-340).
7 Reina Y et al. Advances in high-risk localized prostate cancer: Staging and management. Curr Probl Cancer. 2023; 47(4): 100993
8 Dhiantravan N et al. Clinical trial protocol for LuTectomy: a single-arm study of the dosimetry, safety, and potential benefit of ^{177}Lu-PSMA-617 prior to prostatectomy. Eur Urol Focus. 2021; 7(2): 234-237
9 Hofman M et al. LuTectomy: phase 1/2 study evaluating dosimetry, safety and potential benefit of pre-surgery [^{177}Lu]Lu-PSMA-617 radioligand therapy in patients with high-risk localized prostate cancer. EANM 2023 (Oral abstract OP-338).
10 Zamboglou C et al. Development and Validation of a Multi-institutional Nomogram of Outcomes for PSMA-PET-Based Salvage Radiotherapy for Recurrent Prostate Cancer. JAMA Netw Open. 2023; 6(5): e2314748
11 Calais J et al. 18F-fluciclovine PET-CT and ^{68}Ga-PSMA-11 PET-CT in patients with early biochemical recurrence after prostatectomy: a prospective, single-centre, single-arm, comparative imaging trial. Lancet Oncol. 2019; 20(9): 1286-1294
12 Fendler WP et al. Impact of ^{68}Ga-PSMA-11 PET on the Management of Recurrent Prostate Cancer in a Prospective Single-Arm Clinical Trial. J Nucl Med. 2020; 61(12): 1793-1799
13 Zamboglou C et al. Implementation of PSMA-PET/CT improves treatment outcomes after salvage radiotherapy for recurrent or persistent prostate cancer after surgery. EANM 2023 (Oral abstract OP-337).

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