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First communication on the efficacy of combined ^{177}Lutetium-PSMA with immunotherapy outside prostate cancer

Antonia Digklia ,[1,2,3] Sarah Boughdad,[4] Krisztian Homicsko,[1,3,5] Clarisse Dromain,[3,6] Mounir Trimech,[3,7] Ana Dolcan,[1,2] Solange Peters,[1,3] John Prior ,[3,8] Niklaus Schaefer[2,3,8]

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[1]Oncology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland
[2]Sarcoma Center, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland
[3]University of Lausanne, Lausanne, Switzerland
[4]Nuclear Medicine and Molecular Imaging, University of Lausanne, Lausanne, Switzerland
[5]Precision Oncology Center, Lausanne University Hospital, Lausanne, Switzerland
[6]Radiology and Interventional Radiology, Lausanne University Hospital, Lausanne, Switzerland
[7]Pathology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland
[8]Nuclear Medicine and Molecular Imaging, Lausanne University Hospital, Lausanne, Switzerland

Correspondence to
Dr Antonia Digklia;
antonia.digklia@chuv.ch

ABSTRACT

Prostate-specific membrane antigen (PSMA)-targeted radioligand therapy is a validated treatment option for patients with advanced prostate cancer. Although PSMA expression is not limited to prostate tissue, little is known about its relevance to other types of cancer. Here, we present a case report of a patient with uterine leiomyosarcoma that is progressing while on immunotherapy and treated with ^{177}Lu-PSMA radionuclide therapy. We report for the first time that ^{177}Lu-PSMA radionuclide therapy combined with immunotherapy outside of prostate cancer. We did observe post-treatment reduction of tumor growth rate, although we did not notice disease response based on RECIST criteria. We suggest that ^{177}Lu-PSMA treatment especially combined with immunotherapy may be an option for patients with cancer without other therapeutic options. Insights: ^{177}Lu-PSMA radionuclide therapy should be considered for any tumor stained positive for PSMA.

BACKGROUND

In recent years, prostate-specific membrane antigen (PSMA)-targeted radioligand therapy has revolutionized the way we treat metastatic castration-resistant prostate cancer.

Although its name reflects a prostatic origin, PSMA is expressed in several tissues, including benign non-prostatic epithelial cells and malignant tissues such as lymphoma, melanoma, lung cancer, renal cancer and soft-tissue sarcoma (STS).[1] PSMA plays furthermore a role in enhancing metabolism in activated tumor endothelium or during endothelial cell invasion.[2 3]

STS is a heterogeneous group of rare cancers that can develop in connective and skeletal tissues. These rare cancers account for <1% of all adult malignancies. Leiomyosarcoma (LMS) is one of the most common subtypes in adults, accounting for 26% of all STS. LMS frequently occurs in the extremities, the retroperitoneum and most commonly in the uterus. Uterine LMS (ULMS) accounts for 1% of all uterine malignancies and 40% of all uterine sarcomas. It is a highly aggressive disease, with greater metastatic potential than other LMS. There are a few Food and Drug Administration-approved chemotherapeutic drugs for treating advanced LMS, including anthracyclines, ifosfamide, eribulin, trabectedin, gemcitabine alone or in combination with taxanes, but toxicity and low response rates remain significant limitations. Immune checkpoint inhibitors (ICIs) alone or in combination failed to show meaningful benefit in an unselective sarcoma patient population.

Here, we report the first case of ^{177}Lu-PSMA radionuclide treatment combined with ICI in a patient suffering from ULMS progressing on immunomonotherapy.

CASE REPORT

In October 2018, patient in her mid-50s, with a uterine mass identified as ULMS, was referred by her attending physician to our hospital which serves as national sarcoma center. Contrast-enhanced CT-scan, MRI, and FDG-PET/CT revealed a large uterine mass and peritoneal tumor implants.

The patient had been treated by palliative chemotherapy including adriamycin, ifosfamid gemcitabine/dacarbazine, trabectedin and palliative radiotherapy for pain control. In February 2021, the patient who had Eastern Cooperative Oncology Group (ECOG) perfomence status status 0, presented with tumor progression under trabectedin at a tumor growth rate (TGR (%/month)) of 23.81%/m.

Next-generation sequencing of 400 cancer-related genes revealed a tumor mutation burden of 4.05 mutations/Mb. The tumor was negative for PDL1 and TRK-staining, as well as hormone-expression (ER 0%, PR

0%) but there was a mild presence of tumor-infiltrating lymphocytes/high-powered field (3TILS/HPF).

Due to the TILS infiltration and the lack of standard treatment options, we initiated an off-label intravenous treatment with nivolumab (240 mg every 2 weeks) on February 2021. Restaging CT examinations performed 2 and 3 months after treatment initiation showed disease progression based on Response Evaluation Criteria in Solid Tumor (RECIST) Version .1.1 and immunoRECIST criteria of the previously described lung and peritoneal lesions with TGR at 36.46%/m and according to the increased rate of the TGR (dTGR >50%), experienced hyperprogressive disease (HPD). Due to the absence of standard treatment and any available clinical trial, we proposed to test the feasibility of theranostic targeting the PSMA receptor using ^{68}Ga-PSMA-11 positron emission tomography-computed tomography scan (PET/CT) followed by possible ^{177}Lu-PSMA-1 I&T (^{177}Lu-PSMA). The patient underwent ^{68}Ga-PSMA-11 imaging that detected PSMA-positive lesions in the lungs, the adrenals and the peritoneum. The patient benefited from two cycles of peptide receptor radionuclide therapy (PRRT) at 2 months interval combined with 240 mg nivolumab (every 2 weeks) given 1 week after each PRRT.

Post-treatment single-photon emission computerized tomography-scan (SPECT/CT) showed marked uptake in several lung metastases after ^{177}Lu-PSMA. The patient continued receiving Nivolumab (q2w) until 4 months after the second cycle of ^{177}Lu-PSMA. The patient supported the combination well and no treatment associated side effect occurred. At 6 months post-treatment there was a reduction of TGR from 36.46%/m to 11.25%/m (figure 1). The lung nodule (left lower lobe) with the highest PSMA uptake in pretreatment ^{68}Ga-PSMA-11 PET/CT (SUVmax 8.9) responded 6 months later with a considerable size reduction (20.1×21 mm vs 16.9×16.5 mm), whereas a neighboring node with low PSMA uptake (SUVmax 2.2) progressed from 8.6×9.7 mm to 14.3×16.3 mm (figure 2). Due to the patient's overall progressive disease, a new treatment by Pazopanib was started, but stopped early due to treatment related persistent fatigue despite the dose adaptation after 3 weeks. We decided to rechallenge chemotherapy with dacarbazine, which was well tolerated.

DISCUSSION

The theranostic ^{68}Ga-PSMA/^{177}Lu-SMA paradigm has become a standard in patients with prostate cancer.[1] Preclinical data indicate that PSMA plays a role as activator of angiogenesis. Conway *et al* demonstrated that PSMA is essential for endothelial cell invasion in vitro and PSMA-inhibition leads to endothelial cell invasion decrease.[2] Further preclinical data showed that chimeric antigen receptor-T (CAR-T) cells against

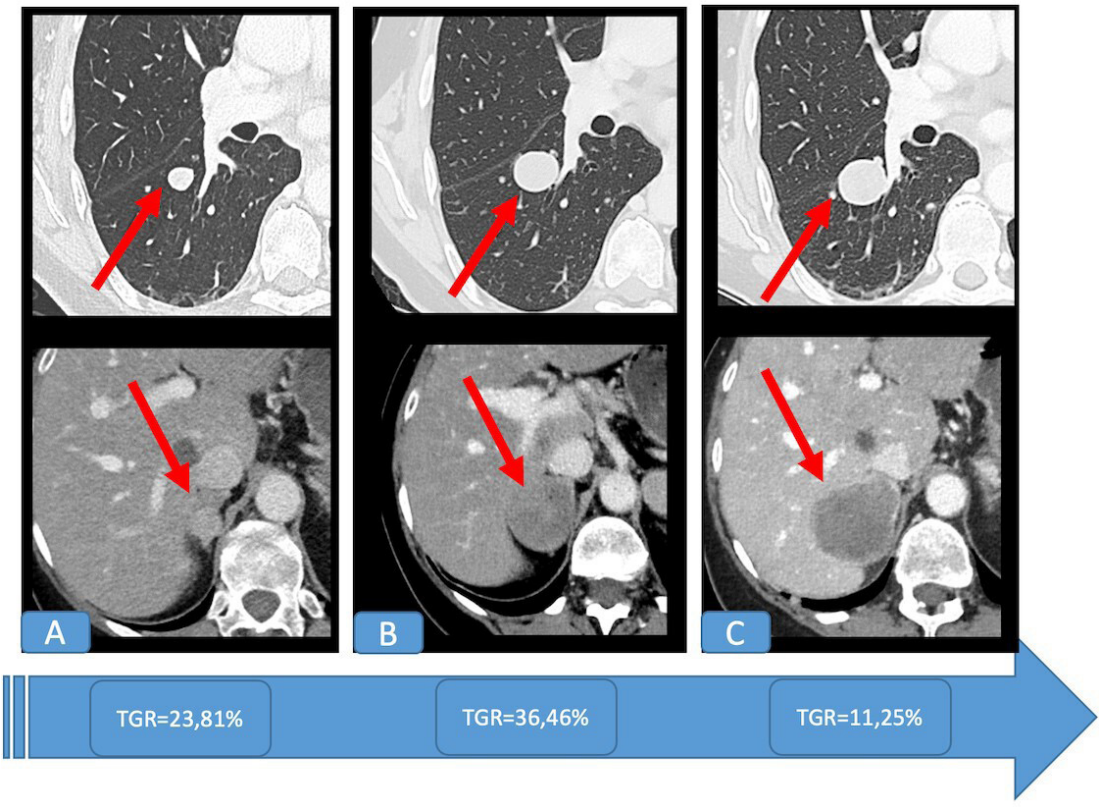

Figure 1 Tumor growth rate before and after treatment with ^{177}Lu-PSMA. Gallium CT-images of the lung (top) and liver (bottom) prior to nivolumab treatment (A), 4 months after nivolumab treatment (B), and 4 months after the second cycle of ^{117}Lu-PSMA-I&T administration (C). Arrows point to the lesions under investigation. TG;, tumor growth rate, PSMA; prostate specific membrane antigen.

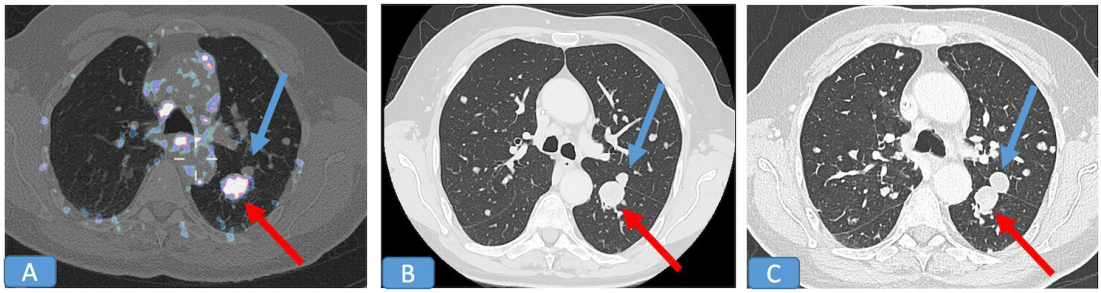

Figure 2 Effect of ^{117}Lu-PSMA treatment on PSMA-positive tumors. (A) Pretherapeutic PSMA 11 PET/CT image of the lung. Red arrow points to a PSMA-positive lesion (SUVmax 8.9) and blue arrow points to a PSMA-negative lesion (SUVmax 2.2). (B) Pretherapeutic gallium image of the lung. red arrow points to the PSMA-positive lesion (21.0×20.1 mm), blue arrow points to the PSMA-negative lesion (8.6×9.7 mm). (C) Post-therapeutic CT image 6 months after the second cycle of ^{117}Lu-PSMA-I&T. Red arrow points to the PSMA-positive lesion (16.5×16.9 mm), blue arrow points to the PSMA-negative lesion (14.3×16.3 mm). PSMA; prostate specific membrane antigen, PET; Positron Emission Tomograph.

PSMA mediate vascular disruption and lead to tumor shrinkage in gynecological cancers. In brief, activated tumor endothelium suppresses local immune responses by various processes as the endothelial expression of PD-L1 or TIM-3 or the secretion of soluble factors as TGFβ or IL-10 and can be suppressed by anti-PSMA CAR-T.[4] In our case, by combining Immunotherapy and anti-PSMA PRRT, we aimed to synergize the effect of local endoradiotherapy, to disrupt the tumor endothelium and the immune-stimulatory effect of low-dose irradiation, employing both effects to enhance immunogenicity of sarcoma tumors.

Standard-of-care treatment of chemotherapy in refractory STS does not exist, given its heterogeneity and new treatment approaches are needed. Currently, the role of immunotherapy in STS is still under investigation outside STS patients with microsatellite instability or high mutation burden. Indeed, several trials have shown that only some rare subtypes, including undifferentiated pleomorphic sarcoma and alveolar soft part sarcomas and clear cell sarcoma, may benefit from ICI as monotherapy.

To date, there are no clearly defined biomarkers that predict clinical response of specific histological subtypes to ICIs. Recently, retrospective analysis by Petitprez *et al* suggested that intratumoral tertiary lymphoid structures are associated with improved outcome in STS patients treated with ICI.[5] Furthermore, in several tumors TILs infiltration influences the efficacy of ICIs. On the other hand, PIK3CA and MAPK activation have been identified as resistance mechanisms to anti-PD1 therapy in metastatic LMS.[6] Although our patient lacked these resistance mechanisms and had modest TILs infiltration, she didn't benefit from ICI monotherapy endorsing the need of increasing LMS antigenicity by other strategies such as radiotherapy or local ablation. The above-described synergism in combining anti-PSMA PRRT and immunotherapy combined the effect of disruption of the anti-immune tumor endothelium and low-dose radiotherapy. This may explain, the decrease of TGR in our case after treatment with ^{177}Lu-PSMA, leading to clinical benefit for the patient.

The idea to disrupt tumor neoangiogenesis combined with immunotherapy is not new. Combination of pembrolizumab with a vascular endothelial growth factor inhibitor has demonstrated promising activity in alveolar soft part sarcomas.[7] In contrast to a pure antiangiogenic approach, we combined low dose irradiation with vascular disruption trying to synergize to immune-stimulatory effects to finally overcome immune desert TME. Although we did not see a radiologic response, we observed decrease of TGR, in this patient experiencing HPD under ICIs, leading to clinical benefit. On the other hand, given the fact that data about incidence and mechanisms of HPD in sarcomas treated with ICIs is limited, the interpretation of this pattern of response is difficult since it can also reflect the natural history in some sarcoma patients.[8] However, according to the TGR our patient was prior Lu-PMSA in hyperprogression under ICI monotherapy. Platelets-to-lymphocytes ratio (PLR), neutrophil-to-lymphocyte ratio (NLR) and lymphocyte-to-monocyte ratio (LMR) reflect systematic inflammation considered to contribute to tumorigenesis and immune abnormalities and in several series have been shown to be prognostic for solid tumor patients receiving CPI.[9 10] Before the start of CPI, the patient had PLR >200, NLR <5, and LMR <2 which all are associated with low survival rates. Interestingly, the levels of some ratios at d1 of the second cycle of PPRT (6 weeks after the first) were reversed with PLR <100, NLR >10. Unfortunately, this effect did not last long and 6 weeks later, PLR was at 182 and NLR at 2.2 reflecting the lack of robust immunomodulation and durability of response.

CONCLUSION

Little is known about the role of ^{177}Lu-PSMA therapy outside prostate cancer especially in combination with immunotherapy. We describe the first evidence of a vascular disruption approach combined with low-dose

radiotherapy by endoradiotherapy in a patient resistant to immunotherapy. Currently, most patients with STS do not benefit from ICI treatment with durable responses and only in limited histological subtypes. In this context, we consider our combination strategy to increase immunogenicity as potentially important.

We are currently opening a prospective clinical pilot trial exploring the feasibility of theranostic targeting the PSMA receptor by Ga-68-PSMA-11 PET/CT, followed by two cycles of ^{177}Lu-PSMA in STS patients without other therapeutic options, as well as its immunomodulation impact on tumor microenvironment.

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Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s)

Ethics approval This is a case report of a patient treated with a approved treatment but in another indication. This was approved by the patient and an Institutional Board(s) (validated in our multidisclipinary-specific tumor board). Participants gave informed consent to participate in the study before taking part.

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ORCID iDs
Antonia Digklia http://orcid.org/0000-0001-7189-3035
John Prior http://orcid.org/0000-0003-1429-1374

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