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Reviewer #1

The authors have presented an excellent overview of PSMA RLT. The manuscript is well-written, comprehensive and concise. Addressing the following points would further strengthen the manuscript:

Protocol section (p.3)

Comment 1: Strictly speaking, the TheraP trial protocol excluded patients with discordant FDG and PSMA PET scans – please refer to the protocol and correct

- In order to further highlight the exclusion of patients with discordant FDG and PSMA PET scans section 1 was restructured based on the original protocol outline as found on clinical trials.gov for the TheraP trial.

1. *Confirmed, sufficient PSMA expression of detected metastases proven by PSMA-directed positron-emission tomography/computed tomography (PET/CT). Some institutions also perform a FDG-PET/CT at baseline to exclude patients with FDG-positive, but PSMA-negative PC metastases (15). Based on the study by Hofman et al the minimum SUVmax of metastases ought to be at least 1.5 times the SUVmean of the liver to ensure sufficient PSMA expression in potential Lu177-PSMA RLT patients (13). The EANM guidelines recommend at baseline an additional FDG-PET/CT to exclude patients with FDG-positive, but PSMA-negative PC metastases (15,17).*

Comment 2: I do not believe it is standard for all centres to admit patients to hospital for 3 days

- We agree with the reviewer's statement. Our initial statement was based on the standards as observed in many centres in Germany for radiation safety concerns. The section was formulated more cautiously.
2. *RLT using Lu177-PSMA is offered at nuclear medicine centers. Following slow intravenous application of the radionuclide (slow injection over 10-15*

min) a post-therapeutic scintigraphy is performed on day 1 or 2 after treatment to evaluate in-vivo distribution of the radionuclide. Patients are usually admitted to the hospital for 3-2-4 days under radiation-controlled conditions. The target radiation activity for Lu177-PSMA is 4-8 giga-becquerel and is determined on individual basis.

Comment 3: Likewise, I do not believe it is standard for all centres to perform re-staging after every 2nd cycle of treatment.

- The review is based on the recommendations proposed by the EANM guidelines. However, we added a more cautious formulation to underline that other centers may follow a different schedule. Another citation was added to underline the recommendation of re-staging following every two cycles as outlined both in the TheraP protocol and the EANM guidelines.
4. Restaging is most frequently performed after every second cycle of treatment as proposed by the EANM guidelines (15). While some institutions perform restaging using conventional imaging with CT and bone scan, others use molecular imaging with PSMA/CT. It has to be noted that tumor progression on imaging using PSMA-PET/CT may be detected earlier than with conventional imaging leading to shorter treatment with PSMA-RLT.

Actinium (p. 7 onwards)

Comment 4: The manuscript devotes considerable space to this alpha-emitter, which is promising but as of yet has not been subjected to randomised studies like Lu-PSMA. I feel the authors need to better acknowledge the absence of randomised trials data with Actinium

- To highlight the lack of prospective, randomized trials on Ac255 PSMA RLT we added another paragraph to the closing summary on AcPSMA.

However, to date, contrary to Lu177-PSMA, the results of a prospective, randomized trial on Ac255-PSMA are still pending and are eagerly expected is not available.

Available Reported retrospective data indicates that treatment with Actinium-255

PSMA-617 offers promising rates of tumor control. However, alpha emitter based RLT using Ac255-PSMA is associated with ~~however at the cost of~~ increased rates of xerostomia which may lead to discontinuation of treatment.

Ongoing trials

Comment 5: I feel this section was too short and could be expanded on. Certainly in terms of current trials, the authors should have mentioned UpFrontPSMA (NC-T04343885), LuTectomy (NCT04430192) and Enza-P (NCT04419402).

- We agree with the reviewer's suggestion and included the recommended trials to ensure a more comprehensive overview of ongoing and recently initiated trials.

Outlook section:

Currently recruiting studies compare the safety, tolerability and efficacy of the combination of PSMA lutetium with the immune-checkpoint inhibitor pembrolizumab (e.g. phase-1: NCT03658447, NCT03805594) or olaparib (e.g. phase-1, NCT03874884) or as stand-alone treatment (e.g. phase-2, NCT03454750, NCT04188587). The UpFrontPSMA phase-2 trial (NCT04343885) compares the safety and benefit of two inductive cycles of Lu-177-PSMA followed by six cycles of docetaxel versus six cycles of docetaxel alone patients with newly diagnosed high volume metastatic castration-sensitive PC. A non-randomized phase-1/2 trial (LuTectomy) investigates the dosimetry, efficacy and toxicity of two neoadjuvant cycles of Lu-177-PSMA in men with high-risk localized or locoregional advanced prostate cancer followed by radical prostatectomy (NCT04430192). The recently initiated open label, randomized, stratified, two-arm, multicenter phase-2 (ENZA-p) trial compares activity and safety of Lu-177-PSMA in combination with enzalutamide to enzalutamide alone in chemotherapy naïve mCRPC patients (NCT04419402). One prospective phase-3 trial (VISION study) is currently recruiting (NCT03511664).

Comment 6: In addition, the authors have missed an opportunity in my opinion to

discuss potential future trials in combination with other drugs in mCRPC and also across the spectrum of metastatic hormone-sensitive disease and even high-risk localised/locally advanced disease. A paragraph on potential future trials should be included.

- We thank the reviewer for this suggestion and added an additional closing paragraph to highlight the potential scope of future trials not only in mCRPC, but also earlier stages of the disease.

The results of these, but also further prospective trials will help identify to role of Lu177-PSMA in comparison with approved treatment regimens and its application at an earlier time point in the treatment sequence of mCRPC. Moreover, additional trials are awaited to investigate the role of Lu-177-PSMA in combination with other drugs and its application in castration-sensitive PC, e.g. combination with standard of care for metastatic hormone-sensitive disease in the UpFrontPSMA trial and application in high-risk localized/locally advanced PC in the LuTectomy trial.

Reviewer #2

The review summarizes current key evidence for PSMA radioligandtherapy. Relevant studies have been included. Interpretation of evidence is sound and statements are balanced. Summary and presentation of findings deliver a concise and informative overview of the current literature. Several aspects should be considered:

Comment 1: Page 3, Protocol for Lu177-PSMA RLT: EANM guideline should be cited (Eur J Nucl Med Mol Imaging. 2019 Nov;46(12):2536-2544. doi: 10.1007/s00259-019-04485-3.) and more closely followed for the indication/inclusion criteria. Earlier German guideline should also be cited (Nuklearmedizin. 2016 Jun 28;55(3):123-8.)

- We thank the reviewer for the recommendation. The mentioned guidelines were included and the protocol information is updated in the review.

To date, Lu177-PSMA RLT is offered to mCRPC patients within a compassionate use program as a salvage therapy after having exhausted conventional therapies or within clinical trials owing to the fact that this treatment regimen has not been approved, yet (13–16). The following course of treatment is currently used in daily routine:

Comment 2: Page 6, Anti tumor effect: There is now more ASCO/interim prospective evidence that should be included here. Among these are the following that come with important implications for radiographic response, activity escalation, and combination therapy, respectively. These aspects should be mentioned.

- We thank the reviewer for the selection of abstracts. All proposed abstracts were included at respective sections of the manuscript. This section and the respective discussion should emphasize that there are now multiple randomized and non-randomized studies, which underline RLT activity and justify the use of LuPSMA even pre VISION.

In 2018, the first [...] November 2019, Violet et al published the long-term outcomes of this same cohort including a 20-patient extension. The authors reported a median OS of 13.3 months with a statistically significant longer OS of 18.4 months in patients who had a PSA decline $\geq 50\%$ (21). Novel data presented at the ASCO 2020 of a post-hoc analysis including 43 patients with progressive mCRPC in the RESIST phase 2 trial confirmed a significantly improved longer PFS (13.4 months vs 3.3

months) and OS (20.1 months vs 11.6 months) in patients who had a PSA decline $\geq 50\%$ (29).

At ASCO 2020 the Hofman group presented preliminary results of a first randomized Phase-2-trial (TheraP), which evaluates Lu177-PSMA vs. cabazitaxel in 200 men with mCRPC upon progression to docetaxel [.....]

One explanation might be the patient selection. In addition to a PSMA-PET/CT confirming PSMA-expression in PC metastases, an FDG-PET/CT was performed at baseline ~~in order~~ to exclude FDG-positive/PSMA-negative PC metastases. With this additional imaging procedure 28% of mCRPC patients were excluded from the trial due to PSMA-negative PC metastases.

An ongoing focus of current research is focusing on improving response rates. Preliminary, promising results of a prospective phase -1/2 dose escalation trial were presented at the ASCO 2020. The data showed that fractionated dosing up to 22.2 GBq in a population unselected for PSMA expression in a single cycle was safe in this cohort of 44 mCRPC patients with a $>50\%$ PSA decline observed in 66.7% of patients and a median OS of 16 months (30). Also, the use of radiosensitizers to increase response rates is currently being investigated. Emmett et al presented updated interim data of the LuPIN trial to investigate the safety and efficacy of a combination of Lu177-PSMA with idronoxil (NOX66) at ASCO 2020. The PSA responses $> 50\%$ in 62% of 32 mCRPC patients and a median survival of 17.1 months are encouraging and warrant further trials to investigate the role of both fractionated dosing and the use of radiosensitizers to increase treatment responses (31).

Comment 3: Page 9, Outlook on PSMA RLT: Innovative trials on adjuvant/neoadjuvant LuPSMA in the setting of prostatectomy should be listed (LuTextomy from Australia and at least one trial from Israel).

- We agree with the reviewer's remark and hope to have sufficiently addressed this missing part of the outlook section. We added the LuTectomy trial as well as other innovative trials for hormone-sensitive metastasized prostate cancer to the manuscript.

Outlook on PSMA RLT

Currently recruiting studies compare the safety, tolerability and efficacy of the combination of PSMA lutetium with the immune-checkpoint inhibitor pembrolizumab (e.g. phase-1: NCT03658447, NCT03805594) or olaparib (e.g. phase-1, NCT03874884) or as stand-alone treatment (e.g. phase-2, NCT03454750, NCT04188587). The UpFrontPSMA phase-2 trial (NCT04343885) compares the safety and benefit of two inductive cycles of Lu-177-PSMA followed by six cycles of docetaxel versus six cycles of docetaxel alone patients with newly diagnosed high volume metastatic castration-sensitive PC. A non-randomized phase-1/2 trial (LuTectomy) investigates the dosimetry, efficacy and toxicity of two neoadjuvant cycles of Lu-177-PSMA in men with high-risk localized or locoregional advanced prostate cancer followed by radical prostatectomy (NCT04430192). The recently initiated open label, randomized, stratified, two-arm, multicenter phase-2 (ENZA-p) trial compares activity and safety of Lu-177-PSMA in combination with enzalutamide to enzalutamide alone in chemotherapy naïve mCRPC patients (NCT04419402). One prospective phase-3 trial (VISION study) is currently recruiting (NCT03511664).

Preliminary data of the randomized phase-2 (TheraP) trial presented at the ASCO2020 showed an improved biochemical response rate of Lu177-PSMA as compared to cabazitaxel in patients progressing upon docetaxel. The results of the prospective phase-3 VISION study investigating the efficacy of Lu177-PSMA in combination with standard of care versus best standard of care alone are eagerly anticipated.

The results of these, but also further prospective trials will help identify to role of Lu177-PSMA in comparison with approved treatment regimens and its application at an earlier time point in the treatment sequence of mCRPC. Moreover, additional trials are awaited to investigate the role of Lu-177-PSMA in combination with other drugs and its application in castration-sensitive PC, e.g. combination with standard of care for metastatic hormone-sensitive disease in the UpFrontPSMA trial and application in high-risk localized/locally advanced PC in the LuTectomy trial.