Reply to Letter to the Editor on 'Phase I/II trials of ^{186}Re-HEDP in metastatic castration-resistant prostate cancer: post-hoc analysis of the impact of administered activity and dosimetry on survival'

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We would like to thank Liepe [1] for his interest in our recent article and giving us the opportunity to further expand upon some additional aspects of the study [2].

The data used for the present study [2] belong to two National Institute of Health (NIH) funded activity escalation phase I [3] and fixed administered activity phase II [4] clinical trials. A total of 57 patients were recruited between 1996 and 2003, before availability of ^{223}Ra-dichloride or chemotherapy agents such as docetaxel and/or abiraterone. The aims of these trials were to investigate the feasibility and toxicity profile of high administered activities of ^{186}Re-HEDP and autologous peripheral blood stem cell transplantation (PBSCT) in patients with castration-resistant prostate cancer metastatic to bone (mCRPC). The results of these studies were previously published [3, 4]. A maximum tolerated activity of 5 GBq of ^{186}Re-HEDP was determined in the phase I trial, with a statistically significant prostate-specific antigen (PSA) improved response in patients receiving activities above 3.5 GBq. The phase II study demonstrated the safe delivery of a fixed 5 GBq of ^{186}Re-HEDP and PBSCT in a group of 38 patients with mCRPC. The aim of our recent publication was to use the long-term survival and imaging data available to study the potential of imaging and dosimetry to predict response and outcome. Our study did not intend to discuss whether high administered activities and PBSCT are the best treatment strategy for patients with mCRPC [2].

Liepe raises concerns about the lack of a sample size calculation for the overall survival (OS) analysis according to administered activity levels, the capture of patient follow-up and the inclusion of patients treated with ^{223}Ra-dichloride or docetaxel. Our post-hoc analysis showed a statistically significant difference in survival between the low and high activity groups and a sample size calculation was not included as this is was not an end-point to the original trials and it is not needed for this type of analysis. As stated in our publication [2], follow-up time was used for OS analysis as the time interval between administration of ^{186}Re-HEDP and death, which was documented for 50 of the 57 patients. Seven patients were censored at the last point of contact, or at the time they received a treatment prolonging survival. Our results showed a statistically significant difference in overall survival for both groups, with a median OS advantage of 13 months, which could not be explained by differences in baseline prognostic factors. Unfortunately, imaging was not available for all patients, so it was not possible to determine whether patients treated with > 3.5 GBq received higher absorbed doses that could have affected survival. Nonetheless, this result was considered of potential interest for future studies. Particularly, in light of newly emerging radiopharmaceuticals also showing a prolonged survival for higher administered activities [5].

A concern regarding the ‘severe’ grade III thrombocytopenia in 21% of patients treated with 5 GBq of ^{186}Re-HEDP along with the lack of bone marrow dosimetry was also raised. Assessment of toxicity levels and the use of PBSCT were described in detail in the original publications [3, 4]. Thrombocytopenia was limited to grade III and reported as not severe but transient, recovering within 9 days of nadir levels. The incidence rate of toxicity was higher than that observed with ^{223}Ra-

dichloride, but well tolerated and comparable to other treatments using beta-emitting radiopharmaceuticals in mCRPC. Grade IV thrombocytopenia was observed in 45% of patients treated with ^{177}Lu-PSMA-J591 [5]; and combination of docetaxel and ^{153}Sm-EDTMP resulted in 28% of patients experiencing grade III haematological toxicity [6] and a 43% occurrence of grade IV neutropenia [7]. Data were not available to calculate bone marrow absorbed doses and therefore correlations with toxicity levels were outside of the scope of our study [2]. One of our previous publications from the same data, reported correlations of whole-body absorbed doses and haematological toxicity and showed that these can be used as a surrogate for bone marrow dosimetry [8]. A kinetic model was presented to predict the whole-body absorbed doses from patient-specific baseline biochemical and physiological measurements, with an average difference between predicted and measured values of 15%. This model showed the potential for personalised treatment planning.

In agreement with Liepe's comment, the use of repeated radiopharmaceutical administrations and/or combination with chemotherapy have been successful in the management of mCRPC. However a number of issues need further consideration. Six cycles of ^{223}Ra-dichloride at 4-week intervals have shown a survival advantage of 3.6 months as compared to placebo [9]. Evidence that this benefit is due to the repeated administrations is not presently available as all patients follow the same treatment protocol. The study by Biersack et al [10] found a survival advantage in patients treated with three or more administrations of ^{188}Re-HEDP as compared to a single treatment (4.5 vs 17.7 months). Administrations were based on a fixed activity of 3.0 – 3.3 GBq and therefore patients receiving a higher number of treatments would have received higher activities, with a potential impact on survival. Furthermore, direct comparison of repeated administrations of radiopharmaceuticals with brachytherapy or fractionated radiotherapy is not possible given the differences in dose delivery methods and absorbed dose rates. A systematic review of randomised clinical trials in bone pain palliation has shown comparable pain relief rates for single and multiple fractions of radiotherapy [11]. Single high absorbed dose treatments can exploit the apparent low α/β ratio of prostate cancer, and hypo-fractionation approaches are being explored in both, localised and oligometastatic disease [12, 13]. In molecular radiotherapy, high activities could potentially prolong survival by reducing the amount of metastatic disease volume, which is a known prognostic biomarker of survival in patients with mCRPC; whilst repeated treatments could also offer longer durations of pain relief. The former approach can be of particular relevance for alpha-emitting radiopharmaceuticals, given the low toxicity levels observed [9]. However, all these treatment strategies need to be balanced against cost-effectiveness, practicality and availability of resources.

Our study provided an indication of the need of patient-specific imaging and dosimetry to improve the use of molecular radiotherapy in mCRPC and the potential to predict treatment response and patient outcome. It is our belief that patients should be treated according to the absorbed doses delivered as routinely performed in external beam radiotherapy, and not with fixed or weight-based levels of

administered activities. Nonetheless, further clinical trials are required to determine the optimum level of activity, number and frequency of administrations and to optimise combination therapies in the management of patients with mCRPC.

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