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Targeted radioactive therapy for prostate cancer

Progressive metastatic castration-resistant prostate cancer is a highly lethal disorder. In the randomised trial reported by Michael Hofman and colleagues,[1] lutetium-177 [^{177}Lu]Lu-PSMA-617, a small molecule delivering targeted radiation by binding to prostate-specific membrane antigen (PSMA), led to a higher proportion of patients having a 50% or more decrease in prostate-specific antigen (PSA) compared with cabazitaxel (66% *vs* 37% by intention to treat; p<0·0001) and fewer grade 3 or 4 adverse events.[1] Remarkably, some patients did not receive all six planned [^{177}Lu]Lu-PSMA-617 courses due to excellent response.[1] Also, in a previous trial, a 96% or more decrease in PSA, with minor or no residual foci on PSMA imaging, led to a decision to suspend treatment in 20% of patients.[2] In both trials, however, disease ultimately progressed. Some patients responded to additional [^{177}Lu]Lu-PSMA-617 cycles offered at progression.[1,2] To explain disease resurgence after "exceptional response", the authors postulate that ^{177}Lu is less effective in targeting microscopic deposits.[2] Radiation-absorbed doses to small metastases can be boosted using radionuclides emitting alpha particles or low energy Auger electrons.[3] Terbium-161 (^{161}Tb) is of particular interest as it has similar chemical properties and decay characteristics as ^{177}Lu, except for additional emissions of Auger electrons.[3–5] Monte Carlo simulations showed a 2-fold to 4-fold higher radiation dose deposit with ^{161}Tb over ^{177}Lu in micrometastases and single tumour cells.[3] In-vivo studies in mice bearing tumour xenografts documented superior efficacy of ^{161}Tb-PSMA-617 compared with [^{177}Lu]Lu-PSMA-617 with similar, excellent, tolerance.[4] The opinion of Hofman and colleagues, on whether novel radionuclides could be used to deepen response, would be appreciated.

We declare no competing interests.

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Michael Hofman and colleagues[1] report more frequent prostate-specific antigen response and prolonged progression-free survival with lutetium-177 [^{177}Lu]Lu-PSMA-617, compared with cabazitaxel, in patients with metastatic castration-resistant prostate cancer with high prostate-specific membrane antigen (PSMA) expression. Nevertheless, the median progression-free survival was 5·1 months in both arms, but a subpopulation of 19% of patients had a 1-year progression-free survival with [^{177}Lu]Lu-PSMA-617 versus 3% with cabazitaxel. The authors deliberately excluded 30% of patients who were unlikely to benefit from [^{177}Lu]Lu-PSMA-617 therapy according to baseline imaging, recognising a direct cause-and-effect mechanism of visualising target expression in the theranostic framework. However, it would be interesting to verify if patients with 1-year progression-free survival benefit were associated with higher uptake on pretherapeutic imaging.

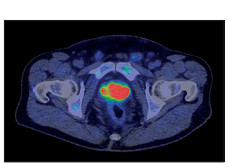
In a phase 2 study on [^{177}Lu]Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer, we showed better progression-free and overall survival in 25 patients with normal circulating *AR* versus 15 patients with *AR* gene amplification.[2] Interestingly, circulating *AR* status seems to be associated with before treatment PSMA uptake.

In a retrospective analysis, whole-exome sequencing data on 25 patients with metastatic castration-resistant prostate cancer treated with [^{177}Lu]Lu-PSMA-617 showed that *BRCA2* mutations can predict favourable progression-free and overall survival.[3] *BRCA2* and DNA damage repair aberrations present in 15–20% of metastatic castration-resistant prostate cancers are associated with higher PSMA expression.[4]

Testing for *BRCA2* is currently recommended in all patients with metastatic castration-resistant prostate cancer in international guidelines.[5]

In this scenario, is it conceivable to select patients for [^{177}Lu]Lu-PSMA-617 according to gallium-68-PSMA-11 and fluorine-18-fluorodeoxyglucose PET-CT or evaluate the molecular stratification to personalise the approach to these patients?

We declare no competing interests.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Authors' reply

Elif Hindié and colleagues ask about optimal radionuclides for use with prostate-specific membrane antigen (PSMA)-targeted approaches in the treatment of prostate cancer, and whether radionuclides other than lutetium-177 (^{177}Lu) might deepen and extend the duration of responses. The TheraP trial[1] used [^{177}Lu]Lu-PSMA-617, a radiolabelled small molecule that binds to PSMA to deliver beta particles resulting in double stranded DNA damage and subsequent cell death. Therapies using beta emissions require a relatively high number of particles to enter a cell to be effective. Other radionuclide therapies including alpha particles[2] or auger electrons need fewer particles for cell death and have a shorter path length. Whether these characteristics improve therapeutic responses is unknown. An advantage and disadvantage of ^{177}Lu is its relatively long path length of around 1 mm. This enables a so-called cluster bomb effect that kills adjacent cells, including those with low PSMA-expression.[3] This effect could overcome intralesional tumour heterogeneity—a fundamental limitation of many therapies in oncology. Conversely, for microscopic residual disease, a 1 mm path length might not result in effective targeting of the smallest deposits. Radionuclides with shorter path lengths could be more effective in targeting microscopic disease at the cost of inferior targeting of adjacent low PSMA-expressing cells. This limitation might be overcome by using tandem radionuclides—ie, radionuclides that have multiple emissions,[4] or novel combinations with other effective systemic agents.

Ugo De Giorgi and colleagues ask whether PET imaging or genomic features of the tumour could enable better selection of men for [^{177}Lu]Lu-PSMA-617 therapy. Although not reported in this initial publication of TheraP, all gallium-68-PSMA-11 and fluorine-18-fluorodeoxyglucose (^{18}F-FDG) PET-CT imaging data and germline and multi-timepoint plasma samples were centrally collected. Analysis of these samples will enable us to define predictive and prognostic biomarkers. TheraP was one of the first studies that used quantitative PET parameters for patient selection. We hypothesise that PSMA intensity is predictive of response to [^{177}Lu]Lu-PSMA-617, whereas tumour metabolic volume on ^{18}F-FDG PET-CT has prognostic value.[5] Depending on the outcomes, it might be possible to select patients most likely to benefit on the basis of molecular imaging and genomic alterations. In particular, identifying the subset of men least likely to have clinically meaningful responses to [^{177}Lu]Lu-PSMA-617 would be of great clinical value. More broadly, given the expanding number of treatments for men with advanced prostate cancer, this might enable better personalised medicine, optimising sequencing of [^{177}Lu]Lu-PSMA-617 relative to or in combination with other therapies.

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Lung health in LMICs: tackling challenges ahead

We welcome Jamilah Meghji and colleagues' Review[1] about improving lung health in low-income and middle-income countries (LMICs), and we are particularly encouraged by the focus on the frequently neglected field of