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PSMA-targeted radiopharmaceutical therapy in patients with metastatic castration-resistant prostate cancer

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The treatment of patients with metastatic castration-resistant prostate cancer has mostly involved androgen receptor-targeted therapies (ARTTs) and cytotoxic chemotherapy for over a decade. Prostate-specific membrane antigen (PSMA)-targeted radiopharmaceutical therapy with lutetium-177 [^{177}Lu]Lu-PSMA-617 delivers β radiation to cells expressing PSMA. The retrospective data from Germany investigating PSMA-targeted radiopharmaceutical therapy in men with metastatic castration-resistant prostate cancer were promising,[1] but the first prospective results from Australia, the LuPSMA study,[2] provided credible safety and efficacy data. In *The* Lancet, Michael Hofman and colleagues report data from the TheraP trial,[3] a prospective randomised trial comparing PSMA-targeted radiopharmaceutical therapy with chemotherapy in men with metastatic castration-resistant prostate cancer. The completion of this study is a considerable accomplishment, given the absence of a pharmaceutical industry sponsor. It is rare for a trial to be done in which the synthesis of the drug is done by the participating academic institutions.

In the TheraP trial, men with metastatic castration-resistant prostate cancer were randomly assigned to [^{177}Lu]Lu-PSMA-617 (6·**0**–8·5 GBq every 6 weeks for up to six cycles) or cabazitaxel. Overall, a higher proportion of patients in the [^{177}Lu]Lu-PSMA-617 group showed a reduction in prostate-specific antigen (PSA) of 50% or more from baseline than in the cabazitaxel group (65 [66%; 95% CI 56–75] of 99 men *vs* 37 [37%; 27–46] of 101 by intention to treat; p<0·0001) and a longer progression-free survival (hazard ratio 0·63 [95% CI 0·46–0·86]; p=0·0028). In terms of toxicity, PSMA-targeted radiopharmaceutical therapy had a lower rate of grade 3–4 events compared with chemotherapy (32 [33%] with [^{177}Lu]Lu-PSMA-617 *vs* 45 [53%] with cabazitaxel). Finally, pain improvement occurred in 60% of men in the [^{177}Lu]Lu-PSMA-617 group versus 43% in the cabazitaxel group (relative risk 1·4 [95% CI 0·9–2·2]; p=0·10), and patient-reported outcomes showed clinically meaningful improvements in quality of life and symptoms with [^{177}Lu]Lu-PSMA-617 compared with cabazitaxel.

The most important strength of the TheraP trial is the use of cabazitaxel in a control group. As shown in the TROPIC study,[4] cabazitaxel is an effective therapy for patients who have already received docetaxel. This efficacy is recapitulated in the TheraP study, as shown by the radiographic progression-free survival curves that remain matched for 6 months, at which time PSMA-targeted radiopharmaceutical therapy overtook cabazitaxel. This finding might be the most interesting aspect of this study and highlights two points. First, PSMA-targeted radiopharmaceutical therapy treatment is cumulative, unlike chemotherapy. Tumour cells receive doses of radioactivity every 6 weeks, and therefore the treatment effect might not be shown immediately. Second, a subpopulation of patients exist who have a prolonged benefit from PSMA-targeted radiopharmaceutical therapy, pushing out the tail of the PSMA-targeted radiopharmaceutical therapy progression-free survival curves.

Similar to the LuPSMA study, TheraP required both PSMA and 2-fluorine-18 [^{18}F]fluoro-2-deoxy-D-glucose (FDG) PET as part of the inclusion criteria. Both studies are unlikely to be used widely for patient selection once PSMA-targeted radiopharmaceutical therapy becomes clinically approved because of insurance coverage reasons, particularly in the USA, and so the results of this study are likely to be more positive than one would expect from treatment of all PSMA-positive patients. Over a quarter of patients (n=91 [31%]) were deemed ineligible on the basis of the combination of both PET studies, but 51 (18%) required both imaging studies to show discordant 2-[^{18}F]-FDG-avid disease.

The main limitation of this study might be the choice of the primary endpoint with a surrogate marker of response (decrease in PSA) in place of survival outcomes. Additionally, more patients withdrew after randomisation in the control group (15 dropped out in the control group *vs* none in the treatment group). Some patients might have wanted to be treated with PSMA-targeted radiopharmaceutical therapy and might have been able to find treatment elsewhere.

This trial must be placed in the context of the other PSMA-targeted radiopharmaceutical therapy trials that

are in progress. One is the VISION study (NCT03511664), which is a phase 3 randomised registration trial in patients for whom ARTT and first-line chemotherapy were unsuccessful. VISION is a larger study, but in terms of clinical relevance is substantially limited by the exclusion of the use of cabazitaxel in the control group, which many would consider a standard therapy in this patient population, especially given the results of the CARD study.[5] Next are pre-chemotherapy studies in patients with metastatic castration-resistant prostate cancer (NCT04689828 and NCT04647526), which exclude chemotherapy (both docetaxel and cabazitaxel) in the control group. Given the limited efficacy of second line ARTTs, this control group again will not tell us the relative value of PSMA-targeted radiopharmaceutical therapy compared with that of an active therapy. Although the risk of using cabazitaxel as a control is probably something only an academic venture can afford, we encourage company sponsored trials to learn from the TheraP study and consider using a more active comparator.

Overall, although TheraP is a smaller study than the studies in progress, it will be the only study to compare the efficacy of PSMA-targeted radiopharmaceutical therapy with a real competitor for a while. As we await the planned overall survival analysis from TheraP, researchers in nuclear medicine are hoping that PSMA-targeted radiopharmaceutical therapy will bring the promise that was not achieved with radium-223 for patients with metastatic castration-resistant prostate cancer, and instead replicate the benefit of somatostatin receptor-targeted radiopharmaceutical therapy for patients with neuroendocrine tumours.[6] We are in the infancy of radiopharmaceutical therapy, and over the coming years we will begin to optimise patient selection and an individualised approach using dosimetry, and leverage other radionuclides with higher energy deposition, such as α particles to maximise the benefit of PSMA-targeted radiopharmaceutical therapy.[7,8]

TAH reports consulting and advisory board fees from Curium related to PSMA-targeted imaging and therapies; grants from Advanced Accelerator Applications and advisory board fees from Blue Earth Diagnostics, both for PSMA PET imaging agents and unrelated to the topic of this Comment. JCs reports previous consulting activities related to PSMA-targeted radionuclide therapy agents for Curium Pharma, Janssen Pharmaceuticals, and POINT biopharma; previous consulting activities related to PSMA-targeted imaging agents for Advanced Accelerator Applications, Blue Earth Diagnostics, Curium Pharma, GE Healthcare, and Progenics, unrelated to the topic of this Comment; and previous speaker's fees related to PSMA-targeted imaging agents for IBA RadioPharma and Telix Pharmaceuticals, unrelated to the topic of this Comment.

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