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Platinum Priority – Editorial

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Prostate-specific Membrane Antigen Across the Spectrum of Prostate Cancer: Detection, Surgery, and Theranostics

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It is already clear that prostate-specific membrane antigen (PSMA) positron emission tomography (PET) is transforming the landscape for diagnosis of prostate cancer (PC). The past 5 yr has seen a surge in the number of publications in this area [1], with impressive specificity and sensitivity reported for PC detection in both the biochemical recurrence and primary staging settings [2,3]. It has been reported that PSMA PET increases the accuracy of pelvic lymph node staging in cases of higher-risk PC [4], and technologies have now been developed to enhance the detection of these lymph nodes intraoperatively. Radioguided surgery, using an acoustic intraoperative gamma probe following intravenous injection of radiolabelled PSMA ligand, has the potential to enhance the accuracy of pelvic lymph node dissection [5]. Prospective trials are under way to compare the accuracy of PSMA PET to conventional imaging in the primary staging setting and evaluate the management impact [6]. Already, reports suggest that the added value of PSMA PET leads to a management change in approximately 50% of cases [7].

However, the scope of PSMA does not stop at detection and radioguided surgery. Another exciting extension of a PSMA-based approach is the potential to not just identify metastatic PC but also to treat PC using a theranostic approach. Most of the emerging therapeutic data used the β-emitter ^{177}Lu radiolabel attached to the small molecule PSMA-617, and initial retrospective reports demonstrated good tolerability and encouraging oncological efficacy in heavily pretreated men with advanced PC [8].

In this issue of *European Urology*, Heck et al. [9] retrospectively review their experience of using a slightly different PSMA ligand, PSMA-I&T. For 100 men with metastatic castration-resistant PC (mCRPC) who had failed multiple previous lines of therapy, ^{177}Lu-PSMA-I&T was offered on a compassionate access basis according to institutional protocols [9]. Almost all men had bone metastases, 87% had lymph node disease, and 35% had visceral metastases. A median of two cycles of therapy were administered, with very low rates of significant toxicity and no treatment-related discontinuation. Overall, 38% of men had a >50% decline in their prostate-specific antigen (PSA) levels; clinical progression-free survival was 4.1 mo, with overall survival of 12.9 mo. On multivariable analysis, predictors of poorer outcomes were the presence of visceral disease, younger age, and high lactase dehydrogenase levels. Overall, ^{177}Lu-PSMA-I&T was well tolerated and produced encouraging responses in this group of heavily pretreated men with mCRPC.

These results suggest that ^{177}Lu-PSMA-I&T has similar tolerability and performance characteristics to ^{177}Lu-PSMA-617, which has been retrospectively described in comparable populations with similar outcomes [8]. Interestingly, in our prospective phase 2 evaluation of ^{177}Lu-PSMA-617 in a similar heavily pretreated population of patients with mCRPC, we observed better PSA responses, with 57% of patients experiencing a >50% decline in PSA levels [10]. Whilst the patient characteristics in our series, most notably a lower rate of visceral metastases, may account for the differences in outcomes, we believe that the main

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contributory factor is patient selection. In our prospective study, we performed FDG PET in addition to PSMA PET as part of screening to identify patients with sites of low PSMA expression. We excluded patients with discordant disease—for example, hepatic metastases that were avid on FDG PET but negative on PSMA PET—from ^{177}Lu-PSMA therapy. We have subsequently reported very poor outcomes for this group of patients, with overall survival of only 2.4 mo [11].

Overall, this series from Heck et al suggests that Lu-PSMA therapy is well tolerated with encouraging efficacy in men with very advanced prostate cancer, whether the ^{177}Lu labelling is of PSMA-617 or PSMA-I&T. The planned acquisition of PSMA-617 by Novartis for USD$2.2bn clearly demonstrates that there is considerable optimism about the future potential for Lu-PSMA therapy. Ongoing randomised phase 2 and 3 studies will further define the role of this therapy in the future, and it will be exciting to see if it proves effective in earlier-stage disease.

Conflicts of interest: Declan G. Murphy has received reimbursement for advisory board activity/speaker duty from Astellas, Janssen, Ipsen, Ferring, Sanofi, and AstraZeneca. Arun A. Azad has received reimbursement for advisory board activity/speaker duty from Astellas, Janssen, Novartis, Amgen, Bayer, Sanofi, AstraZeneca, and Tolmar. Shahneen Sandhu has received reimbursement for advisory board activity/speaker duty/grant support from Tolmar, Pfizer, Amgen, Janssen, Merck, Merck Serono, Bristol Myer Squibb, and AstraZeneca. Michael S. Hofman has received honoraria from Endocyte for participation in an advisory board. Endocyte has contributed research funds to the Peter MacCallum Cancer Centre. John Violet has nothing to disclose.

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