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Point of Focus Debate: Con

Prostate-specific Membrane Antigen Theranostics for Prostate Cancer Care: A Need to Prove Clinical Utility

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Despite major advances in prostate cancer (PC) care, improved imaging and treatment of aggressive PCs remains an urgent unmet medical need [1]. The transmembrane protein prostate-specific membrane antigen (PSMA) has been the subject of intense investigation for 25 yr, with recent citations increasing exponentially owing to the rapid increase in theranostic studies. While PSMA is highly expressed in many prostatic cancers, with expression increasing further still in metastatic castration-resistant PC (mCRPC), PSMA is also expressed in other benign and neoplastic tissues [2]. Despite burgeoning theranostic data, there remains arguably insufficient knowledge regarding why, how, and when this protein is expressed, with its precise roles in PC remaining debatable. It does, however, appear that as PC cells transform into a more "basal/neuroendocrine" type and truly AR-independent CRPC, they lose PSMA expression [3,4]. Interestingly, PSMA is a largely extracellular protein with short intramembranous and intracellular domains, and possesses glutamate carboxypeptidase/folate hydrolase enzyme activity, suggesting it may be involved in folate and glutamate metabolism and AKT signalling [5–7]. These characteristics may, in part, help to explain why PSMA appears most highly expressed in DNA repair–defective PCs [3], with DNA repair defects known to sensitise to DNA-damaging treatments including radiation.

Multiple PSMA-targeting agents, including radionuclides (antibodies or small molecules), PSMA-targeting immunotherapies, and antibody-drug conjugates, are currently in clinical development [8,9] and have encouraging antitumour activity. Of these, the ^{177}Lu radioimmunoconjugate ^{177}Lu-PSMA-617 is the most studied. In one multicentre study involving 145 mCRPC patients, ^{177}Lu-PSMA-617 reduced prostate-specific antigen (PSA) levels in 60%, with PSA declines $\geq$50% in 45% [10]. In a phase 2 study of ^{177}Lu-PSMA-617, the median PSA progression-free survival was 7.6 mo and overall survival 13.5 mo [11]. Notably, however, in these studies patients underwent ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) and were excluded if sites of FDG-positive disease without high PSMA expression were identified. Therefore, evidence to date supports the use of PSMA-targeting therapies only in biomarker-positive patients in whom the majority of lesions are PSMA-PET–avid, which we estimate comprises less than half of all advanced disease. Results from ongoing phase 3 clinical trials validating these initial studies and using such patient selection are eagerly awaited (NCT03511664). However, until such results are known and appropriate approvals granted, ^{177}Lu-PSMA-617 remains an investigational medicinal product (IMP), making its off-trial administration (at high fiscal cost) in multiple EU countries to mCRPC patients concerning since insufficient data are available at this juncture to confirm its clinical benefit. Better regulation of unapproved, off-trial use of radionuclide IMPs is urgently needed.

PSMA-targeted tracer availability for PET imaging has also led to a surge in PSMA-PET use for detecting PC [12–14], largely because of the limitations of conventional imaging; prospective, randomised studies confirm lower sensitivity (38%, 95% confidence interval [CI] 24–52% vs 85%, 95% CI 74–96%) and specificity (91%, 95% CI 85–97% vs 98%, 95% CI 95–100%) for detection of pelvic nodes and distant metastases in high-risk PC with CT and bone scans when compared to PSMA PET-CT [15]. However, while such studies have demonstrated that PSMA-PET is more accurate than

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conventional imaging modalities, contributing to a change in management for a significant proportion of patients with high-risk PC, none of these studies have to date included clinical endpoints relating to progression-free or overall survival [15,16]. Consequently, whether such changes in management translate into better outcomes for patients remains uncertain. Despite this, PSMA-PET is being broadly utilised, thereby increasing the possibility of patients being subjected to unjustified treatment intensification that may cause morbidity without improving outcome, or, more concerningly, being denied potentially beneficial treatment and worsening outcomes [17]. While such studies have similarly not previously been conducted for conventional imaging modalities, these have been incorporated into numerous phase 3 trials of treatments shown to improve patient survival, which in turn have informed clinicians as to their appropriate interpretation, limitations, and role in the management of PC. Ultimately, while the need for more accurate imaging in PC is incontrovertible and is likely to improve treatment and outcomes, this must first be proven through prospective randomised trials before we change the standard of care.

A major challenge for PSMA-based theranostics, as with other personalised therapies, is increasing evidence of intrapatient and interpatient heterogeneity in PSMA expression [3,18]. PSMA targeting and detection via imaging depends on PSMA expression by PC cells; however, not all PC cells express PSMA to the same degree, with some PC cells not expressing PSMA at all [3,4]. Hence, phase 2/3 trials have applied careful patient selection, using PSMA PET and other imaging modalities that detect both PSMA-negative and PSMA-positive disease, and excluding patients with a significant PSMA-negative disease burden. Hence, the consequences of PSMA-negative prostate cells and of PSMA-positive nonmalignant cells on PSMA-PET imaging is a concern that is currently not properly assessed in clinical trials. This is critical, since the future successful utilisation of PSMA-based theranostics will largely depend on how clinicians use and interpret this imaging modality and therapeutic strategy. Careful analyses of emerging phase 3 trial data and suitable design of future studies will be of critical importance to ensure delivery of maximal benefit and minimal harm to the patients we serve. A better understanding of the factors regulating PSMA overexpression in PC may also help to improve this delivery [3] and enable the development of rational drug combinations to improve the efficacy of PSMA-directed therapies by upregulating PSMA expression in PC cells before PSMA targeting.

In conclusion, PSMA theranostics are becoming important tools for managing PC; however, prospective evidence from randomised clinical trials validating their clinical benefit are urgently needed to prove efficacy. Until such prospective data demonstrating improved survival outcomes are obtained, prospective trials generating level 1 evidence should remain our primary priority. Until then, off-trial use of such agents must be better regulated to minimise the risk of causing harm, including overtreatment and undertreatment. Finally, radionuclides should be regulated like other IMPs and made available to cancer patients for free on prospective clinical trials that are key to rapidly transforming cancer care until regulatory approval.

Conflicts of interest: Johann S. de Bono has served as a principal investigator for the VISION trial of Lutetium PSMA (AAA/Novartis) and the Thorium PSMA radioimmunoconjugate (Bayer), and has served as advisory board member for AAA, Bayer, AstraZeneca, Daiichi Sankyo, Eisai, Genentech/Roche, Astellas, Pfizer, Sanofi-Aventis, Merck Serono, and MSD. Bertrand Tombal has served as an advisory board member for AAA, Bayer, Astellas, Pfizer, and Sanofi-Aventis. Alec Paschalis has nothing to disclose.

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