Re: [177Lu]Lu-PSMA-617 Versus Cabazitaxel in Patients with Metastatic Castration-resistant Prostate Cancer (TheraP): A Randomised, Open-label, Phase 2 Trial

Re: Hofman MS, Emmett L, Sandhu SK, et al
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Experts' summary:

TheraP, a randomised, open-label, phase 2 trial, compared the prostate-specific membrane antigen (PSMA) radioligand [177L]Lu-PSMA-617 (Lu-PSMA) with cabazitaxel in metastatic castrate-resistant prostate cancer (mCRPC). A total of 200 men were randomised to either Lu-PSMA 6.0–8.5 GBq every 6 wk for up to six cycles, or cabazitaxel 20 mg/m2 every 3 wk for up to ten cycles. The primary endpoint was a ≥50% reduction in prostate-specific antigen (PSA) from baseline. Other outcomes included the safety profile for Lu-PSMA. The study found a PSA response of 66% for Lu-PSMA versus 37% for cabazitaxel ($p = 0.0001$) in the intention-to-treat analysis. Grade 3–4 adverse effects were experienced by 33% of the Lu-PSMA versus 53% of the cabazitaxel group.
Experts' comments:

The authors should be congratulated for this potentially game-changing study. Since the results of the CARD trial [1] and subsequent US Food and Drug Administration approval of cabazitaxel in June 2010, there have been no new alternatives for the majority of patients with mCRPC. Agents such as radium-223 can be offered to patients with predominantly symptomatic bone metastases who have received prior docetaxel [2]. It has been demonstrated that pembrolizumab alone or in combination with either enzalutamide or olaparib had favourable antitumour activity in the KEYNOTE-199 [3] and KEYNOTE-365 [4] studies. These results are yet to change clinical practice for a broader population.

TheraP shows for the first time in a prospective, randomised, multicentre study the antitumour activity of Lu-PSMA in men with mCRPC and provides a safe and effective new line of therapy for those who have progressed on docetaxel or androgen receptor targeted agents (ARTA) [5]. Beyond the evidence of a PSA response, data on overall survival will be needed. There are plans to continue follow-up in TheraP and the VISION trial (NCT03511664) [6], a study comparing Lu-PSMA plus standard/best supportive care (BSC) versus standard/BSC alone.

While TheraP recruited patients with mCRPC, it focused on patients with positive findings on 68Ga-PSMA positron emission tomography (PET), using a cutoff for maximum standardised uptake value (SUVmax) of >20 at a single site and >10 at other sites. This might limit the potential clinical generalisability of the data. In addition, the study excluded 28% of patients with discordant 18F-fluorodeoxyglucose PET/computed tomography and Lu-PSMA. This means that patients with highly aggressive but non–PSMA-expressing cancers may not benefit from this treatment strategy. This subcohort of patients has poor prognosis [7]. Furthermore, TheraP recruited patients with previous androgen receptor targeted agents (ARTA). Literature data suggest that prolonged exposure to androgen deprivation therapy has an impact on PSMA ligand uptake, which could reduce visibility and average tracer uptake by up to 71% [8]. Conversely, shorter exposure may increase PSMA expression [8]. It

would be interesting to know the number of patients on androgen therapy (and its duration) who were assessed for eligibility but excluded because of low PSMA tracer uptake.

It was noted in the TheraP study that 64/98 patients in the Lu-PSMA arm discontinued their treatment early, with 43% of these cases discontinuing because of radiological or PSA progression. It will be worth characterising the genomic characteristics, quantitative PET SUVmax/mean activity, and radiation dosimetry across disease sites to further understand disease heterogeneity.

While this study is a potential game-changer, the major limitation for adoption will be the cost and availability of the radiotracer and dedicated nuclear medicine facilities. We hope that these health care system barriers can be overcome in future so that the promise of radiopharmaceutical therapies can be harnessed for patient benefit, as they may mark a new era for the treatment of mCRPC.

Conflicts of interest: The authors have nothing to disclose.

CRediT authorship contribution statement
Sola Adeleke: Conceptualization, Data curation, Investigation, Writing - original draft, Writing - review & editing. Athar Haroon: Data curation, Investigation, Writing - review & editing. Veeru Kasivisvanathan: Conceptualization, Data curation, Investigation, Supervision, Writing - review & editing.

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