metastatic PCa to ADT with or without prostate radiotherapy between 2004 and 2014. The majority of patients (67%) had more than five bone metastases, and the median prostate-specific antigen level was 142 ng/ml. After a median follow-up of 47 mo, no significant difference was found in OS.

The present study by the STAMPEDE investigators represents the first randomised trial showing a benefit of radiotherapy to the prostate in metastatic PCa patients with a low metastatic burden [1]. The optimal definition of a low metastatic burden is still unclear and needs to be refined further, especially given the evolving landscape of more sensitive imaging tools such as prostate specific membrane antigen positron emission tomography. The current definition of a metastatic burden is based on conventional imaging.

As acknowledged by the authors, several other questions remain unanswered, which include the optimum radiotherapy dose schedule, the role of additional metastasis-directed therapy in this setting, and the value of abiraterone in men receiving radiotherapy. Furthermore, it is unknown whether the results of this trial can be extrapolated to radical prostatectomy in metastatic PCa. While it seems plausible given the hypothesis that an intact primary tumour may continue to shed metastasis, there may be radiation-specific mechanisms such as immunomodulation or an interplay between radiation and androgen deprivation, which contribute to the observed survival benefit by radiotherapy. Results from randomised studies currently underway are needed to answer this question.

Conflicts of interest: The authors have nothing to disclose.

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Re: [^{177}Lu]-PSMA-617 Radionuclide Treatment in Patients with Metastatic Castration-resistant Prostate Cancer (LuPSMA Trial): A Single-centre, Single-arm, Phase 2 Study

Hofman MS, Violet J, Hicks RJ, et al

Lancet Oncol 2018;19:825–33

Experts' summary:

The authors report on the first prospective, single-arm, phase 2 trial exploring the role of [^{177}Lu]-prostate-specific membrane antigen (PSMA)-617 in heavily pretreated patients with metastatic castration-resistant prostate cancer (CRPC) [1]. This is a highly personalized approach using PSMA positron emission tomography (PET)/computed tomography (CT) for noninvasive imaging and quantitation of PSMA expression to select patients most likely to benefit from treatment. This trial provides proof of concept that [^{177}Lu]-PSMA-617 has promising antitumour activity, low toxicity, and improves quality of life in CRPC patients.

Experts' comments:

PSMA is a transmembrane protein expressed in aggressive variants of localized PC and is further upregulated in metastatic and CRPC [2]. Several PSMA PET/CT radiotracers have been developed and are rapidly replacing conventional imaging in settings such as biochemically recurrent PC [3]. In addition to its potential as a diagnostic tool, PSMA is also suitable as a theranostic agent for attachment to radioactive molecules for targeted delivery of radiation to PSMA-positive tumor sites. In the current study, such a targeted approach was applied by selecting [^{68}Ga]-PSMA positive patients and excluding patients with [^{18}F]-fluorodeoxyglucose-positive PSMA-negative lesions [1].

The results presented by Hoffman and colleagues are promising, with 57% of the patients experiencing a prostate-specific antigen decline of >50% (primary outcome), especially when taking into account that >80% patients had received previous chemotherapy and/or second-line novel anti-androgens [1]. In 14 out of 17 patients with eligible lesions according to RECIST criteria, an objective

response was observed, with 29% of patients experiencing a complete response. In addition, all patients experiencing pain (90% of the study population) experienced an improvement in their pain and in 37% of patients a global health score improvement of at least 10 points was observed. The treatment seemed to be well tolerated: the majority of patients experienced only grade 1–2 toxicity, with dry mouth reported most frequently (87%). Grade $\geq$3 hematological toxicity attributed to Lu-PSMA might be a concern, as it was observed in up to 33% of patients, with one patient experiencing grade 4 thrombocytopenia.

Several aspects deserve additional attention in future studies. It is unknown how many cycles of [^{177}Lu]-PSMA-617 are required to achieve an optimal response. Moreover, approximately one in three patients are only short-term responders and further cycles of PSMA treatment are often hampered by hematological toxicity. The results of the phase 3 VISION trial (NCT03511664) will shed more light on the role of Lu-PSMA in metastatic CRPC.

Conflicts of interest: The authors have nothing to disclose.

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