Lutetium for metastatic castrate resistant prostate cancer (VISION Trial)

By Kalli Spencer

Despite recent research advances, metastatic castration-resistant prostate cancer continues to be fatal. Prostate-specific membrane antigen (PSMA) is highly expressed in metastatic castration-resistant prostate cancer. Lutetium-177 (177Lu)–PSMA-617 is a radioligand therapy that distributes beta-particle radiation to PSMA-expressing cells and the adjacent microenvironment. It is capable of targeting prostate cancer cells whilst leaving most normal tissues intact in patients who have been chosen with the aid of imaging to confirm radionuclide binding. Research has previously shown that it has been linked to encouraging biochemical and radiographic response rates, reduced toxicity levels and less pain.

An international, open-label, phase 3 trial was undertaken by the VISION Trial Team, evaluating 177Lu-PSMA-617 in patients who had metastatic castration-resistant prostate cancer (with at least one metastatic lesion on baseline MRI, bone scan or CT) previously treated with at least one androgen-receptor–pathway inhibitor and one or two taxane chemotherapy regimens and who had PSMA-positive gallium-68 (68Ga)–labelled PSMA-11 positron emission tomographic–computed tomographic scans (PET-CT Scan)[1]. A positive PSMA PET scan was defined as at least one PSMA-positive metastatic lesion and no PSMA-negative lesions. In the protocol, the existence of PSMA-positive lesions was defined as 68Ga-PSMA-11 uptake greater than that of liver parenchyma in one or more metastatic lesions of any size in any organ system. The presence of PSMA-negative lesions was defined in the protocol as PSMA uptake equal to or lower than that of liver parenchyma in any lymph node with a short axis of at least 2.5 cm, in any metastatic solid-organ lesions with a short axis of at least 1.0 cm, or in any metastatic bone lesion with a soft-tissue component of at least 1.0 cm in the short axis. Patients had to attain an Eastern Cooperative Oncology Group (ECOG) performance-status score of <3, life expectancy >6 months and satisfactory organ and bone marrow function.

Patients were randomly assigned in a 2:1 ratio to receive either 177Lu-PSMA-617 (7.4 GBq every 6 weeks for 4-6 cycles) plus protocol-permitted standard care or standard care only. Protocol-permitted standard care excluded immunotherapy, chemotherapy, radium-223 (223Ra), and investigational drugs. Follow-up MRI or CT and technetium-99m (99mTc)–labelled methylene diphosphonate bone scans were scheduled to take place every 8 weeks for 24 weeks and then every 12 weeks after that. Patients received sustained standard care, with or without 177Lu-PSMA-617, until an impermissible level of toxic effects occurred, imaging documented disease progression was noted, a determined lack of clinical benefit was identified, or a proscribed treatment was considered critical. Patients whose condition was deemed to be suitable for additional chemotherapy could terminate the trial treatment and receive chemotherapy at their physician's discretion. The alternate primary end points were imaging-based progression-free survival and overall survival. Key secondary end points were disease control, objective response, and time to symptomatic skeletal events. Adverse events during treatment were those presenting less than 30 days after the final dose and prior to subsequent anticancer therapy. Health-related quality of life was determined with the aid of the Functional Assessment of Cancer Therapy– Prostate questionnaire and pain evaluated with the use of the Brief Pain Inventory–Short Form.

Between June 2018 and mid-October 2019, a total of 831 of 1179 screened patients underwent randomization. The baseline characteristics of the patients were balanced between the groups. The median follow-up was 20.9 months. 177Lu-PSMA-617 plus standard care significantly prolonged survival, as compared with standard care, both imaging-based progression-free survival (median, 8.7 vs. 3.4 months) and overall survival (median, 15.3 vs. 11.3 months). The prevalence of adverse events of grade 3 or above was greater with 177Lu-PSMA-617 than without (52.7% vs. 38.0%), but quality of life was not negatively affected.

The lack of a placebo control and of a double-blind design is a self-reported study limitation. This is owing to the limitations of clinical trials of radiopharmaceuticals in general, due to the challenges related to radiation protection regulations and the ease of detecting radioactivity in the smartphone era.

Radioligand therapy with 177Lu-PSMA-617 is therefore capable of prolonging imaging-based progression-free survival and survival overall when combined with standard care in patients with advanced PSMA-positive metastatic castration-resistant prostate cancer. Future studies could determine whether Lutetium can provide therapeutic assistance earlier in the treatment sequence than used in this trial, as compared with alternative treatments.

Reference

Sartor O et al. Lutetium-177–PSMA-617 for metastatic castration-resistant prostate cancer. N Engl J Med 2021; 385(12): 1091-1103.

About the Author

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Kalli is an internationally renowned Urological Surgeon, specialising in oncology and robotic surgery. He trained and worked in South Africa, before relocating to Australia where he has worked at Macquarie University Hospital and Westmead Hospital. His passion for what he does extends beyond the operating room, through publichealth advocacy, education and community awareness of men's health, cancer and sexuality.

Kalli has been involved with the Prostate Cancer Foundation of Australia for many years, advocating for improved cancer care and facilitating community prostate cancer support groups.