Abstract LBA4: Phase 3 study of lutetium-177-PSMA-617 in patients with metastatic castration-resistant prostate cancer (VISION)

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Background: Despite recent therapeutic advances, metastatic castration-resistant prostate cancer (mCRPC) remains invariably fatal. Prostate-specific membrane antigen (PSMA) is highly expressed in mCRPC lesions. $^{177}$Lu-PSMA-617 is a targeted radioligand therapy that delivers β-particle radiation to PSMA-expressing cells and surrounding microenvironment.

Method: VISION was an international, randomized, open-label phase 3 study evaluating $^{177}$Lu-PSMA-617 in men with PSMA-positive mCRPC previously treated with next-generation androgen receptor signaling inhibition and 1–2 taxane regimens. PSMA positivity (threshold greater than liver) was determined by central review of $^{68}$Ga-PSMA-11 scans. Patients were randomized 2:1 to $^{177}$Lu-PSMA-617 (7.4 GBq every 6 weeks x 6 cycles) plus standard of care (SOC) versus SOC alone. SOC was investigator determined but excluded cytotoxic chemotherapy and radium-223. The alternate primary endpoints were radiographic progression-free survival (rPFS) using PCWG3 criteria by independent central review (ICR) and overall survival (OS). Under the null hypothesis, median rPFS was assumed to be 4 months and OS 10 months for $^{177}$Lu-PSMA-617 + SOC for a hazard ratio (HR) of 1.00. Under the alternative hypothesis, median rPFS was assumed to be 6 months for a HR of 0.67 and median OS was assumed to be 13.7 months for a HR of 0.7306. Key secondary endpoints were objective response rate (ORR; RECIST v1.1), disease control rate (DCR), and time to first symptomatic skeletal event (SSE).

Results: Between 4 June 2018 and 23 October 2019, 831 of 1179 screened patients were randomized 2:1 to receive $^{177}$Lu-PSMA-617 + SOC (n = 551) or SOC only (n = 280). Median study follow-up was 20.9 months at the data cut-off (27 January 2021). Treatment groups were balanced in terms of demographics and baseline characteristics. $^{177}$Lu-PSMA-617 + SOC significantly improved rPFS versus SOC alone (median rPFS, 8.7 vs 3.4 months; HR, 0.40 [99.2% CI: 0.29, 0.57]; p < 0.001, one-sided). The alternate primary endpoint of OS was also significantly improved versus SOC alone (median OS, 15.3 vs 11.3 months; HR, 0.62 [95% CI: 0.52, 0.74]; p < 0.001, one-sided). All key secondary endpoints were statistically significant between the treatment arms in favor of $^{177}$Lu-PSMA-617 + SOC, including ICR-determined ORR.
(29.8% vs 1.7%), ICR-determined DCR (89.0% vs 66.7%) and time to first SSE (median time, 11.5 vs 6.8 months; HR, 0.50). While a higher rate of high-grade treatment-emergent adverse events was observed with $^{177}$Lu-PSMA-617 (52.7% vs 38.0%), therapy was well tolerated.

**Conclusion:** $^{177}$Lu-PSMA-617 plus SOC treatment is a well-tolerated regimen that improves rPFS and prolongs OS compared with SOC alone in men with advanced-stage PSMA-positive mCRPC, supporting its adoption as a standard of care.

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*View the author disclosures*