

Chromosome 8q-Gain and 8p-Loss as Biomarkers of ¹⁷⁷Lu-PSMA-617 Resistance and Response in Metastatic Prostate Cancer

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Background

¹⁷⁷Lutetium-PSMA-617 (Lu-PSMA-617) improves outcomes in PSMA-avid metastatic prostate cancer. However, PSMA PET avidity only partly explains response heterogeneity. Chromosome 8 arm-level alterations are common in advanced prostate cancer and may provide complementary tissue-based biomarkers of radioligand sensitivity.

Methods

Using the Flatiron Health-Foundation Medicine Clinico-Genomic Database, we identified 201 men with metastatic prostate cancer treated with Lu-PSMA-617 monotherapy with evaluable pretreatment, tissue NGS-based, arm-level copy number calls for Chromosome 8p-loss and 8q-gain (research use only). Kaplan-Meier and multivariable Cox models were used to evaluate time to next therapy (**TTNT**) and real-world overall survival (**rwOS**). A four-group analysis was performed to assess the joint association of 8p-loss and 8q-gain with treatment outcomes. To test treatment-by-biomarker interactions, we compared Lu-PSMA-617 with taxane therapy using inverse probability of treatment weighting (IPTW). Both cohorts required prior taxane treatment for metastatic androgen pathway modulation-resistant (mAPMR) disease, yielding 152 Lu-PSMA-617-treated and 464 taxane-treated patients (636 total).

Results

Among 201 patients treated with Lu-PSMA-617, Chromosome 8q-gain (N=126; 63%) was associated with shorter TTNT (median, 6.0 v 9.5 months; HR, 1.77; P = 0.001; adjusted HR, 1.98; P < 0.001). Chromosome 8p-loss (71%) was associated with longer TTNT after adjustment but not in the unadjusted analysis (7.3 v 6.1 months; HR, 0.71; P = 0.07; adjusted HR, 0.61; P = 0.02). Patients with 8q-gain and no concurrent 8p-loss had shorter TTNT than those with 8p-loss without concurrent 8q-gain (4.5 v 9.5 months; adjusted HR, 3.30; P = 0.001). In the IPTW-weighted comparison of Lu-PSMA-617 with taxane therapy, the 8q-gain-by-treatment interaction was significant for TTNT (P < 0.001).

Chromosome 8q-gain was associated with shorter rwOS (median, 9.1 v 13.4 months; HR, 1.82; P = 0.002; adjusted HR, 2.32; P < 0.001), whereas 8p-loss was associated with longer rwOS (11.8 v 9.3

months; HR, 0.65; $P = 0.04$; adjusted HR, 0.58; $P = 0.02$). Combined 8p and 8q status stratified rwOS across four groups (overall $P = 0.001$), with intermediate survival when both alterations co-occurred. Median rwOS was 5.9 months in patients with 8q-gain and no concurrent 8p-loss versus 13.4 months in those with 8p-loss and no concurrent 8q-gain (adjusted HR, 5.97; $P < 0.001$). The 8q-gain-by-treatment interaction was also significant for rwOS ($P < 0.001$), supporting a treatment-specific association in addition to the adverse prognostic association of 8q-gain.

Conclusions

Chromosome 8 arm-level status, readily derived from pretreatment tumor genomic profiling, stratifies TTNT following Lu-PSMA-617. Chromosome 8q-gain is independently associated with shorter TTNT, while Chromosome 8p-loss is associated with longer TTNT after adjustment. The treatment interaction for 8q-gain supports its potential predictive value. These alterations are also associated with poorer and longer rwOS, respectively. If validated prospectively, Chromosome 8 status could refine patient selection for Lu-PSMA-617 beyond PSMA PET avidity.

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Conflicts of Interest Disclosure Statement

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