AACR 2024 Abstract
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Evaluation of a synergistic drug combination with ^{177}Lu-rhPSMA-10.1 for prostate cancer: Results of an *in vitro* screen and *in vivo* proof of concept study

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Purpose:

Prostate-specific membrane antigen (PSMA)-targeted radioligand therapy (RLT) has been shown to extend survival in men with advanced prostate cancer (PCa). Novel radiohybrid (rh) PSMA-targeted ^{177}Lu-rhPSMA-10.1 has shown promising preclinical efficacy and advantageous radiation dosimetry in humans. We conducted an *in vitro* screen to identify known anticancer drugs with potential for synergistic interaction with ^{177}Lu-rhPSMA-10.1. Here we present key screening data and a subsequent *in vivo* efficacy analysis of the lead novel drug combination in PSMA-expressing 22Rv1 PCa xenografts.

Methods:

Over 150 FDA-approved anticancer drugs were screened in a clonogenic survival assay of 22Rv1 cells using the test drug alone, at a range of concentrations <20 µM to determine the IC_{50}, and results compared to incubations of the drug + 15 MBq/mL ^{177}Lu-rhPSMA-10.1 after 10 d. A focused screen of 5 lead candidates was then conducted to determine the impact of ^{177}Lu-rhPSMA-10.1 (0–25 MBq/mL) on the drug IC_{50}. A synergy score was determined using the zero interaction potency (ZIP) reference model and the multi-dimensional synergy of combinations (MuSyc) platform.

Subsequently, to evaluate the efficacy of the lead combination, ^{177}Lu-rhPSMA-10.1 (single 30 MBq iv dose) and Cobimetinib (0.25 mg orally per day for 21 d) alone and in combination were administered to 22Rv1 tumor-bearing NMRI nude mice (n = 8 per group plus untreated controls). Tumor volume was measured 2x week for 69 d. Two-way ANOVA and Tukey's multiple comparisons test (data analyzed until n = 3 remained per group) and Kaplan-Meier Log-rank survival analyses were performed.

Results:

The *in vitro* screen identified MEK inhibitor Cobimetinib as a lead candidate for synergistic combination with ^{177}Lu-rhPSMA-10.1 across a wide concentration range, with a ZIP synergy score of 13.25% (95% CI ± 2.17) and promising results on MuSyc analysis.

The ^{177}Lu-rhPSMA-10.1 + Cobimetinib combination significantly suppressed tumor growth *in vivo* vs untreated controls (from day 13–30; $p<0.01$) and ^{177}Lu-rhPSMA-10.1 alone (from day 17–30; $p<0.001$). The median survival in the combination group (49 d) was significantly longer vs the untreated group (23 d; $p=0.001$) and the group treated with ^{177}Lu-rhPSMA-10.1 alone (36 d; $p=0.002$).

Conclusions:

Through an extensive *in vitro* screen, we identified Cobimetinib to have potential for a synergistic anti-tumor effect in combination with ^{177}Lu-rhPSMA-10.1. This may be due to inhibition of the MEK-MAPK pathway by Cobimetinib during DNA damage response, resulting in radiosensitization of cancer cells to ^{177}Lu-labeled RLT agents such as ^{177}Lu-rhPSMA-10.1.

This novel combination showed an enhanced therapeutic efficacy vs the single agents in 22Rv1 xenografts and the lack of overlapping monotherapy toxicity reported in the clinic supports clinical investigation in men with PCa.