Patients may benefit from re-challenge therapy with the novel radiohybrid PSMA-ligand [177Lu]Lu-rhPSMA-10.1 after progression with [177Lu]Lu-PSMA-I&T [Abstract]

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Abstract

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Introduction: Radioligand therapy (RLT) is becoming increasingly important in the treatment of metastatic, castration resistant prostate cancer (mCRPC). Radiohybrid ligands targeting the prostate-specific membrane antigen (PSMA) are a novel group of theranostic agents, for which higher tumor absorbed radiation doses have been demonstrated compared to established PSMA ligands. Here, we report data from 9 patients who were treated within a compassionate use program with the radiohybrid PSMA-ligand [^{177}Lu]Lu-rhPSMA-10.1 (rh10) after experiencing disease progression under treatment with [^{177}Lu]Lu-PSMA-I&T (I&T) and who had no remaining therapeutic options.

Methods: Nine patients with advanced CRPC were switched to treatment with rh10 after progression on treatment with I&T (2-6 cycles, cumulative dose of 14.1 to 44.4 GBq). The interval between the last I&T cycle and the first rh10 cycle ranged from 7 to 12 weeks. Patients were included in the compassionate use program following recommendation by the local multidisciplinary tumor team. All patients provided informed consent. The patients received 1-3 cycles of rh10 (~7.4 GBq per cycle) with an interval of 6 weeks between cycles. Adverse events were categorized using CTCAE 5.0 criteria. Prostate-specific antigen (PSA) values were monitored at a minimum of every 6 weeks. After the 2nd cycle of rh10, a PSMA-PET/CT was performed for radiographic response assessment according to RECIP criteria.

Results: After one cycle of re-challenge treatment with rh10, 4 of 9 patients (44%) showed serological partial remission (PR). Of the 4 patients with serological partial remission, a radiographical PR was observed in 2 Patients (2/9 or 22%), with an overall survival of 9 months and 5 months after commencing re-challenge. Remarkably, in both cases death was neither caused by tumor progression nor our therapy. Of the 4 patients responding to rh10 re-challenge, 3 had initially responded to I&T but had progressed during further treatment. Intriguingly, one patient who had showed a continuous PSA-progression under I&T (890 ng/mL to 1700 ng/mL) responded to rh10, with a PSA decrease after the first cycle to 1300 ng/mL. Re-challenge treatment with rh10 was generally well tolerated, only 1 of 9 patients showed grade 3 leucopenia and grade 4 thrombopenia, 2 of 9 patients showed grade 3 anemia (Table), however both patients had progression of intensive bone marrow metastases No serious adverse events were observed.

Conclusions: Patients showing tumor progression while receiving treatment with I&T may still benefit from a change to the novel radiohybrid PSMA-ligand, rh10. Higher tumor absorbed radiation doses with rh10 may overcome intrinsic and acquired radiation resistance. Our preliminary data suggest that particularly patients who initially responded to RLT with I&T might benefit from rh10 re-challenge.

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