ATNM-400, a first-in-class Actinium-225 antibody radioconjugate, demonstrates potent anti-tumor activity and overcomes resistance to enzalutamide and 177Lu-PSMA-617 in prostate cancer models

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Background: Prostate cancer (PCa) initially responds to androgen deprivation therapy, but most cases progress to metastatic castration-resistant prostate cancer (mCRPC), a lethal stage with limited options. Standard treatments with androgen receptor (AR) inhibitors such as enzalutamide often lead to treatment resistance. Targeted radiotherapies have emerged as promising alternatives. The PSMA-targeted radiotherapy Pluvicto® (Novartis, active agent 177Lu-PSMA-617) is approved for treatment of mCRPC, yet many patients eventually develop resistance or fail to respond. To address these unmet needs, we are developing ATNM-400, a first-in-class antibody radioconjugate armed with the alpha-emitter Actinium-225 (225Ac). ATNM-400 targets a non-PSMA protein overexpressed in PCa that drives tumor survival and resistance pathways. Target expression correlates with rapid disease progression, shorter time to castration resistance, and poor survival in mCRPC. We hypothesized that ATNM-400 would provide superior efficacy compared to current options and overcome resistance to AR inhibitors (enzalutamide) and PSMA-directed radioligands (177Lu-PSMA-617 or 225Ac-PSMA-617).

Methods: ATNM-400 was synthesized by conjugating the ATNM400 antibody with p-SCN-Bn-DOTA and radiolabeling with 225Ac. Binding affinity and internalization were assessed in target-positive PCa cell lines. Biodistribution (BioD), pharmacokinetics (PK), and in vivo efficacy were evaluated in preclinical mouse models for PCa. Activity was tested in both enzalutamide–resistant and 177Lu-PSMA-617–resistant models.

Results: ATNM-400 showed high binding specificity and rapid internalization in target-positive PCa cells, with potent, dose-dependent cytotoxicity driven by DNA damage. Consistent activity was observed in both PSMA-high and PSMA-low PCa models, regardless of PSMA-expression levels. In vivo BioD and PK studies demonstrated durable tumor accumulation up to 144 hours with rapid clearance from most normal tissues. PET imaging with 89Zr-ATNM400 confirmed selective tumor uptake with minimal healthy tissue distribution.

In efficacy studies, a single 40 µCi/kg dose of ATNM-400 produced potent tumor growth inhibition across PCa models, with responses dependent on target expression. Multi-dose treatment induced durable tumor control (>100 days) and was superior to enzalutamide monotherapy. Combination therapy with enzalutamide was synergistic, leading to complete tumor regressions in 40% of treated mice and prolonged overall survival. ATNM-400 also showed strong, durable efficacy in enzalutamide-resistant PCa models.

Importantly, ATNM-400 outperformed 177Lu-PSMA-617 and 225Ac-PSMA-617 in head-to-head studies in PCa models. Multi-dose 40 µCi/kg ATNM-400 achieved greater tumor control and survival benefit compared to 40 mCi/kg 177Lu-PSMA-617, including in 177Lu-PSMA-617–resistant models, highlighting the advantage of targeted alpha therapy.

Conclusions: ATNM-400 showed robust and durable anti-tumor efficacy and a favorable safety profile in preclinical PCa models. These findings support ATNM-400 as a next-generation Actinium-225 therapy - with potential as 1) Monotherapy in CRPC (pre-177Lu-PSMA-617), 2) Combination therapy with AR pathway inhibitors, or 3) Sequential therapy after ARPI or 177Lu-PSMA-617 failure. ATNM-400 holds promise to address critical gaps in mCRPC treatment landscape.

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