ATNM-400: A First-in-Class Non-PSMA Actinium-225 Antibody Radioconjugate Demonstrates Superior Efficacy to PSMA-617 Radioligands and ARPIs With Favorable Safety Profile in Prostate Cancer Models

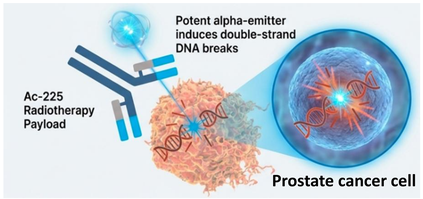
Sumit Mukherjee, Karina Peregrina, Debbie Lewis, Jason Li, Victor Sanz Chavez, Lily Lumkong, Monideepa Roy, Shiva Kazerounian, Adeela Kamal

Actinium Pharmaceuticals, Inc. New York, NY, USA

INTRODUCTION

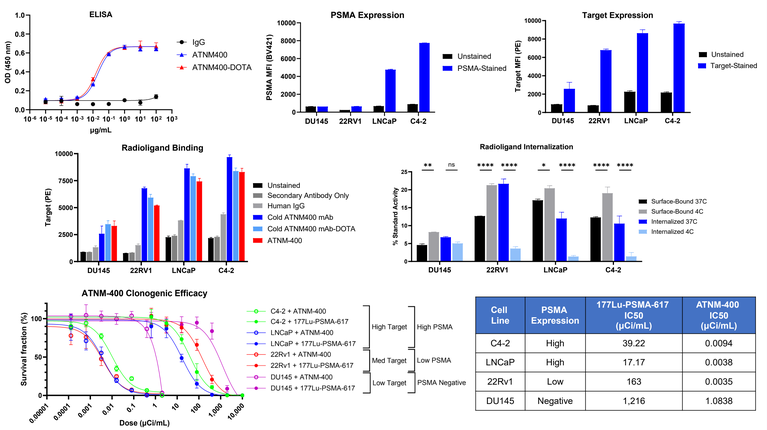
- Standard-of-care therapies in advanced prostate cancer (PCa), including androgen receptor pathway inhibitors (ARPIs) and PSMA-targeted radioligand therapy, are limited by intrinsic/acquired resistance, heterogeneous target expression, and eventual disease progression in many patients.
- ATNM-400 is a first-in-class Actinium (^{225}Ac) antibody radioconjugate (ARC) targeting a non-PSMA antigen broadly overexpressed across PCa, including PSMA-variable and metastatic castration resistant PCa (mCRPC) disease; the target is also linked to aggressive PCa disease biology.
- ATNM-400 exhibits durable efficacy and a favorable safety profile across dosing regimens with translational superiority across PCa models, including comparable or superior activity to PSMA-targeted radioligand therapies.
- ATNM-400 demonstrates potent, PSMA-independent antitumor activity with superior efficacy versus ARPIs (enzalutamide, apalutamide, darolutamide) in resistant mCRPC models, including 22Rv1.
- ATNM-400 overcomes ARPI resistance and shows enhanced tumor control in combination with ARPIs, supporting a synergistic strategy in refractory PCa.

ATNM-400 Mechanism Of Action



- ATNM-400 target receptor is implicated in disease biology and treatment resistance in PCa.
- ATNM-400 binds to the target receptor, internalizes and causes potent alpha particle-mediated double-stranded DNA (dsDNA) breaks which increase phospho-H2AX (p-H2AX) leading to apoptosis of target-positive tumor cells.

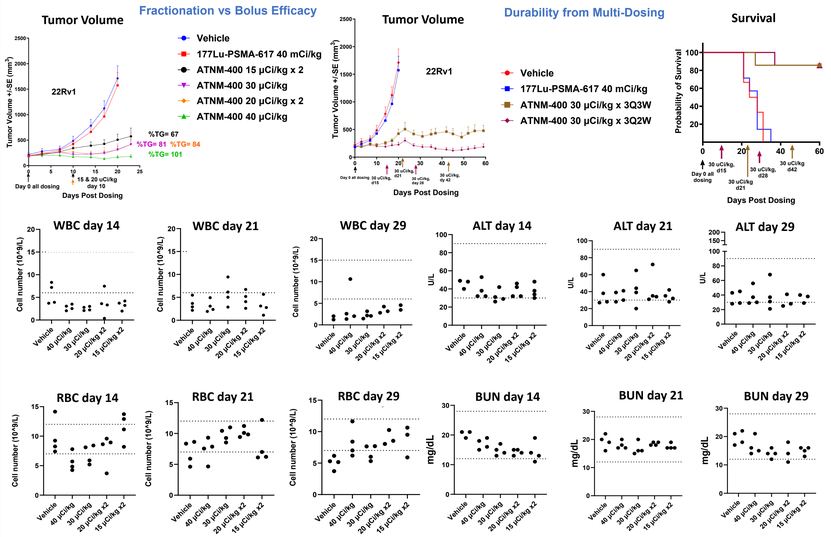
ATNM-400 Exhibits Potent Cytotoxicity Independent of PSMA Expression in Both Low- and High-ATNM-400 Target Expressing PCa Cells



Cell Line	PSMA Expression	177Lu-PSMA-617 IC50 (µCi/mL)	ATNM-400 IC50 (µCi/mL)
C4-2	High	39.22	0.0094
LNCaP	High	17.17	0.0038
22Rv1	Low	163	0.0035
DU145	Negative	1,216	1.0838

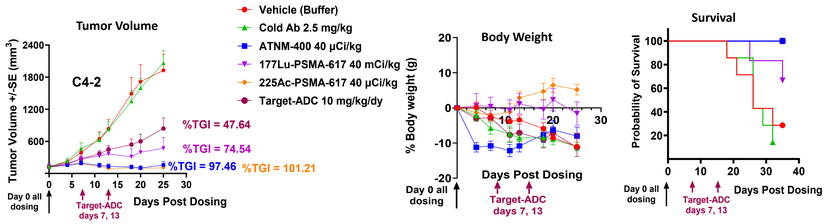
- PSMA-high cells (LNCaP & C4-2) were more responsive to 177Lu-PSMA-617 than PSMA-low cells (22Rv1 & CWR-R1) and PSMA-negative (DU145), which was anticipated.
- ATNM-400 demonstrated robust, PSMA-independent antitumor activity across PCa models, including PSMA-low, PSMA-negative, and PSMA-targeted therapy-resistant disease.

In a Low-PSMA, Moderate-Target–Expressing PCa Tumor Model, ATNM-400 Bolus And Repeat-Dose Regimens Demonstrated Superior Tumor Control and Durable Survival Versus Fractionated Dosing, With Consistent Safety And Minimal Off-Target Toxicity Across Regimens.



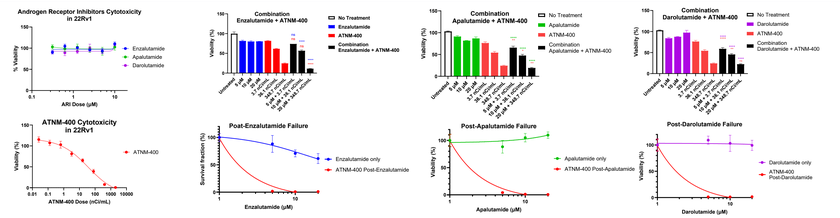
- A single bolus dose of ATNM-400 at either 40 µCi/kg or 30 µCi/kg was more effective than administering two fractionated doses (20+20 µCi/kg or 15+15 µCi/kg) given 10 days apart.
- A multi-dose regimen of 30 µCi/kg administered every two weeks for three doses (middle panel) was as effective as a single higher dose of 40 µCi/kg (left panel).
- Administration of 30 µCi/kg three times at either two- or three-week intervals resulted in dose-dependent, robust tumor control and sustained survival through day 60.
- All tested doses of ATNM-400 were superior to 177Lu-PSMA-617 (40 mCi/kg).
- ATNM-400, administered either as a single bolus dose (40 or 30 µCi/kg) or as two fractionated doses (20+20 or 15+15 µCi/kg) given 10 days apart, demonstrated minimal deviation from vehicle control reference ranges in hematologic, hepatic, and renal toxicity markers across all assessed timepoints (days 14, 21, and 29).

ATNM-400 Demonstrated Superior Efficacy to 177Lu-PSMA-617 and Comparable Activity to 225Ac-PSMA-617 in a High-PSMA, High-Target Expressing PCa Xenograft Model



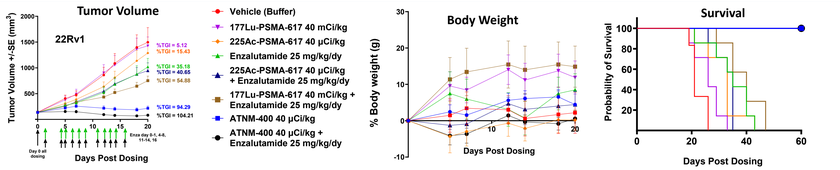
- ATNM-400 (40 µCi/kg) demonstrated superior efficacy compared with 177Lu-PSMA-617 (40 mCi/kg) and Target-ADC in C4-2 (high PSMA and high target expressing) in vivo PCa model.
- ATNM-400 showed comparable efficacy to 225Ac-PSMA-617 (40 µCi/kg), a PSMA-targeted radioligand, delivered durable survival benefit relative to other treatment groups and maintained favorable tolerability.

ATNM-400 is Cytotoxic in PCa cells that are Resistant to ARPI's - Enzalutamide, Apalutamide, or Darolutamide



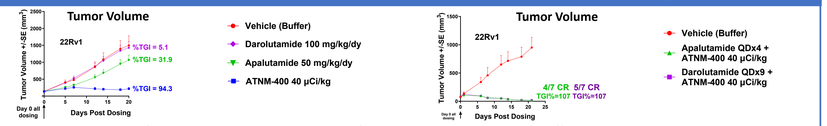
- 22Rv1 cells are resistant to ARPI's enzalutamide, apalutamide and darolutamide but ATNM-400 treatment caused potent dose-dependent cytotoxicity.
- Combining ATNM-400 with ARPIs enzalutamide, apalutamide and darolutamide, increased efficacy in resistant 22Rv1
- ATNM-400 is highly efficacious after ARPI failure in an ARPI resistant prostate cancer model.

ATNM-400 Monotherapy and in Combination with Enzalutamide Demonstrated Superior Efficacy and Survival Versus Other PSMA-Targeted Therapies in a in Low-PSMA, Moderate-Target Expressing PCa Preclinical Model



- ATNM-400 (40 µCi/kg) in combination with enzalutamide demonstrated superior efficacy, achieving superior tumor control and improved survival compared with 225Ac-PSMA-617 (40 µCi/kg) and 177Lu-PSMA-617 (40 mCi/kg) combination regimens with enzalutamide in the 22Rv1 PCa in vivo model.
- ATNM-400 monotherapy provided stronger tumor growth control in direct comparison with other monotherapy arms as well as enzalutamide-containing combination regimens.
- Both ATNM-400 monotherapy and its combination with enzalutamide were well tolerated, showing no observable adverse effects and exhibited durable survival through day 60.

ATNM-400 Outperformed ARPIs Apalutamide and Darolutamide as Monotherapy and Delivered Durable Tumor Control in Combination With Both ARPIs in an ARPI-resistant PCa Xenograft Model



- In 22Rv1 ARPI-resistant PCa in vivo model, ATNM-400 (40 µCi/kg) demonstrated superior efficacy second-generation ARPIs (apalutamide and darolutamide), while combination treatment with either apalutamide or darolutamide produced sustained, durable tumor control, with at least 57% of tumor-bearing mice achieving complete response (CR) in both combination arms.

CONCLUSIONS

- ATNM-400 demonstrates superior and durable anti-tumor activity across PCa models resistant to approved ARPIs (enzalutamide, apalutamide and darolutamide) and PSMA-targeted radiotherapies (177Lu-PSMA-617 and 225Ac-PSMA-617).
- By targeting a disease-driving, tumor-associated protein linked to progression and therapy resistance, ATNM-400 provides a mechanism-based strategy distinct from PSMA-directed and tumor microenvironment-targeted approaches.
- ATNM-400 consistently overcomes ARPI resistance and enhances efficacy when combined with ARPIs, supporting both monotherapy and rational combination strategies in mCRPC.
- These findings support clinical translation of ATNM-400 as a next-generation 225Ac antibody radioconjugate to address key gaps in current prostate cancer treatment paradigms.

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SNMMI Annual Meeting, Los Angeles, California, May 30 - June 2, 2026