Preclinical Development of ATNM-400, a First-in-Class Actinium-225 Radioconjugate with Pan-Tumor Efficacy in Solid Tumors

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BACKGROUND

- Therapeutic resistance limits durable responses to standard of care (SOC) therapies in prostate, lung, and breast cancers.

- ATNM-400, a first-in-class Actinium-225 (225Ac) antibody radioconjugate, targets a novel non-PSMA membrane antigen often overexpressed in advanced and therapy-refractory solid tumors across these indications, offering a strategy to overcome resistance.

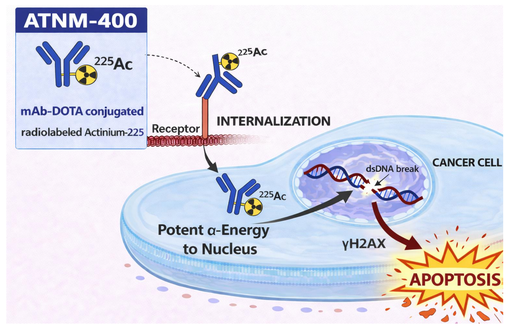
Prostate Cancer (PCa):
- PSMA-targeted 177Lu-PSMA-617 is approved for metastatic castration resistant PCa (mCRPC), but resistance develops in many patients, correlating with rapid progression and poor survival.
- The ATNM-400 target is a non-PSMA antigen overexpressed in prostate tumors; its expression correlates with rapid disease progression, earlier onset of castration resistance, and poor overall survival in mCRPC. The target also drives tumor survival and castration resistance in advanced PCa models (e.g., 22Rv1, C4-2), providing a rationale for targeted alpha radiotherapy.
- Therapeutic targeting with ATNM-400 leads to preclinical efficacy surpassing PSMA targeted agents in PCa models with varying target and PSMA expression levels.

Lung Cancer (LC):
- In EGFR-mutant (EGFR-m) LC, EGFR TKIs such as Osimertinib (Osi), as well as agents like Dato-DXd (TROP2-ADC) and Amivantamab (EGFR–cMET bispecific), have transformed care but are limited by acquired resistance and disease progression. The target for ATNM-400 is linked to Osimertinib resistance and poor prognosis.
- We therefore evaluated ATNM-400 as a targeted alpha radiotherapy in EGFR-m NSCLC preclinical models, benchmarking superior antitumor activity against approved therapies Osi (1L), Amivantamab (2L), and Dato-DXd (3L) to address current therapeutic limitations.
- ATNM-400, as monotherapy or combined with Osi delivers robust tumor control that exceeds established EGFR- and HER3/EGFR-targeted regimens (including Osimertinib + chemotherapy and Izalontamab-based ADCs), supporting its potential as a best-in-class targeted radiotherapy backbone in EGFR-m NSCLC models.

Breast Cancer (BC):
- The target of ATNM-400 is overexpressed in breast cancer subtypes, including HER2-therapy (example: trastuzumab) resistant disease.
- ATNM-400 demonstrates robust anti-tumor activity in vivo across hormone receptor+ (HR+), triple-negative (TNBC), and trastuzumab-resistant breast cancer models.

- Collectively, these data support ATNM-400 as a pan-tumor, tumor agnostic, resistance-focused targeted alpha radiotherapy with translational potential to overcome limitations of current SOCs in advanced PCa, LC and BC.

ATNM-400: MECHANISM OF ACTION



- ATNM-400 binds to the target receptor, internalizes and causes potent alpha particle-mediated double-stranded DNA (dsDNA) breaks which increase phosho-H2AX (p-H2AX) leading to apoptosis of target-positive tumor cells.

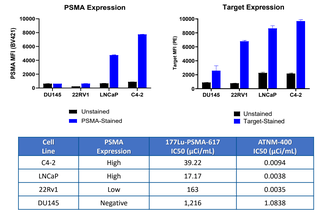
- PCa: In models with varying levels of PSMA and target expression, ATNM-400 binds to the target receptor based on target expression, internalizes and delivers potent alpha particle–mediated dsDNA breaks leading to apoptosis.

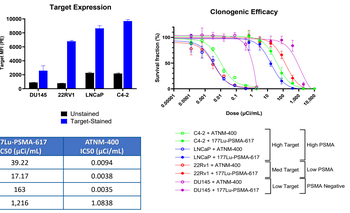
- LC: In Osi-resistant EGFR-m models, acquired resistance to Osimertinib increases expression of target antigen, enabling enhanced binding and internalization of ATNM-400 and leading to dsDNA breaks and tumor cell killing.

- BC: In trastuzumab-resistant models, expression of target antigen increases as does phospho-AKT, thus enhancing ATNM-400 binding and internalization, resulting in potent dsDNA breaks and tumor cell killing.

RESULTS

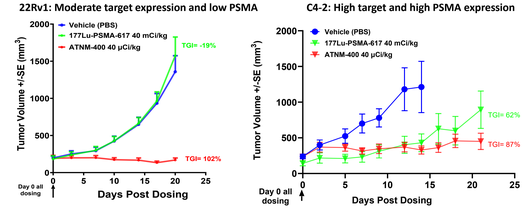
ATNM-400 has Robust Efficacy in Prostate Cancer Models with Varying Target Levels

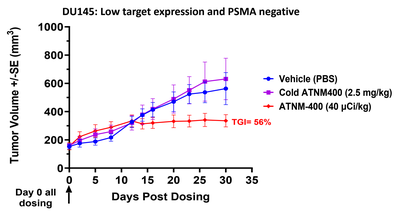




Cell Line	PSMA Expression	177Lu-PSMA-617 IC50 (µCi/mL)	ATNM-400 IC50 (µCi/mL)
C4-2	High	39.22	0.0094
LNCaP	High	17.17	0.0038
22Rv1	Low	163	0.0035
DU145	Negative	1,216	1.0838

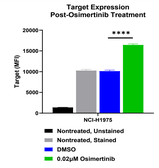
- High PSMA cells (LNCaP & C4-2) were more responsive to 177Lu-PSMA-617 than low PSMA cells (22Rv1) and PSMA negative (DU145), as expected.
- ATNM-400 is cytotoxic in both low and high PSMA PCa cells, and which have low, medium and high levels of the ATNM-400 target.

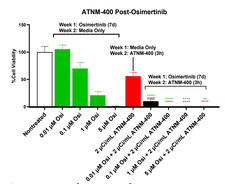




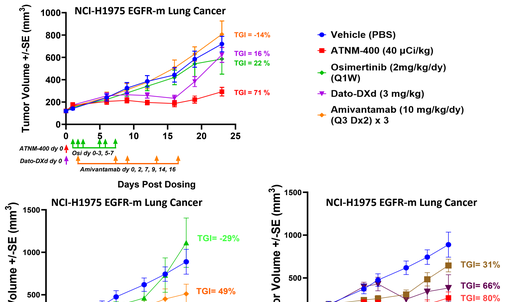
- ATNM-400 demonstrates superior anti-tumor efficacy compared to Vehicle control, unconjugated (“cold”) antibody, and 177Lu–PSMA-617 in preclinical PCa models with high (C4-2) or low (22Rv1) PSMA expression.
- ATNM-400 demonstrates efficacy in DU145 PCa model that is PSMA negative and has low levels of ATNM-400 target.

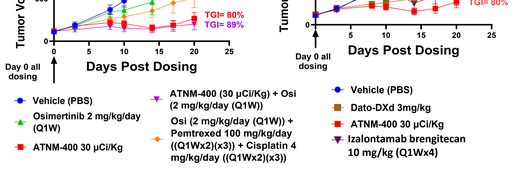
ATNM-400 has Robust Efficacy in EGFR-mutant Lung Cancer Models and is Superior to Approved Agents





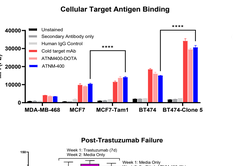
- Osimertinib treatment elevates target expression and causes synergistic combination activity in EGFR-mutant LC NCI-H1975 cells.

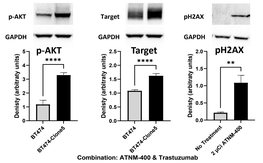


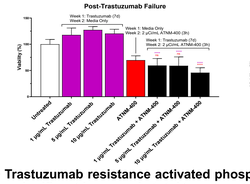


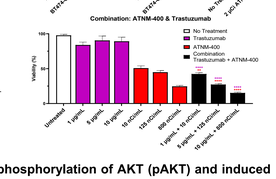
- ATNM-400 exhibits superior efficacy as monotherapy versus approved drugs Osimertinib (1L), Amivantamab (2L), and Dato-DXd (3L) in EGFR-m LC model.
- ATNM-400 (monotherapy or combination with Osimertinib) surpasses Osi + chemotherapy combination.
- ATNM-400 monotherapy surpasses Dato-DXd (TROP-2 ADC) and Izalontamab brengitecan (HER3-EGFR bispecific ADC) in efficacy.
- These results indicate that ATNM-400, as monotherapy or combined with 1L SOC agent, achieves anti-tumor efficacy that surpasses benchmark targeted agents, administered either as single agents or in combination, in EGFR-m LC.

ATNM-400 has Efficacy in HR+, TNBC and Trastuzumab-Resistant Breast Cancer Models

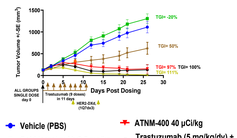


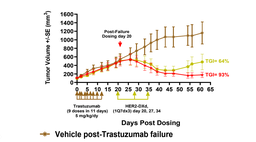


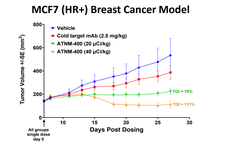


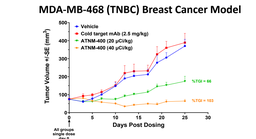


- Trastuzumab resistance activated phosphorylation of AKT (pAKT) and induced a significant increase in total target protein level.
- Trastuzumab resistance-driven target overexpression confers increased susceptibility to ATNM-400 in BC cells.









- ATNM-400 monotherapy and combination with trastuzumab (SOC) showed robust antitumor effect in trastuzumab resistant BT474 Clone-5 BC model. ATNM-400 efficacy versus HER2-ADC (DXd) was comparable.
- ATNM-400 potently inhibits tumor growth post-trastuzumab failure in trastuzumab-resistant model compared to control and HER2-ADC (DXd).
- ATNM-400 caused dose-dependent tumor inhibition in MCF7 HR+ BC model and MDA-MB-468 TNBC model.

CONCLUSIONS

- ATNM-400 delivers robust pan-tumor activity across PCa, LC, and BC models, with consistent efficacy in settings of mCRPC, EGFR-m LC, and HER2-targeted BC therapy resistance.

- In PCa, ATNM-400 shows potent activity across PSMA-high/PSMA-low mCRPC, and in PSMA-negative models, with superior tumor growth inhibition versus vehicle, cold antibody, and 177Lu–PSMA-617, supporting its potential to treat both PSMA-high and PSMA-low mCRPC. ATNM-400 doses in all three PCa models were well-tolerated.

- In EGFR-m LC, ATNM-400 monotherapy outperforms Osi (1L), Amivantamab (2L), and Dato-DXd (3L), while ATNM-400 combination with Osi exceeds the efficacy of current benchmark regimens (Osi + chemotherapy and Izalontamab (HER3-EGFR bispecific ADC) when given monotherapy or in combination. Osi-induced upregulation of ATNM-400’s target antigen and the observed synergistic activity of ATNM-400 + Osi combination highlight a rational strategy to exploit adaptive resistance mechanisms for enhanced EGFR-m LC control. ATNM-400 doses in all LC studies were well tolerated.

- In BC, ATNM-400 target upregulation in trastuzumab-resistant cells increases susceptibility to ATNM-400, which demonstrates strong antitumor activity as monotherapy and in combination with trastuzumab, with efficacy comparable to HER2-ADC. ATNM-400 also had superior efficacy post-Trastuzumab failure in this model compared to control and HER2-ADC. ATNM-400 also drives dose-dependent tumor inhibition in HR+ (MCF7) and TNBC (MDA-MB-468) models, indicating tumor agnostic broad activity across molecular subtypes and supporting its potential utility beyond HER2-positive disease. ATNM-400 doses in three BC models were well-tolerated.

- Overall, these data position ATNM-400 as a next-generation 225Ac targeted alpha radiotherapeutic backbone with broad translational potential to overcome resistance and improve outcomes across multiple refractory solid tumor indications.

Actinium Pharmaceuticals posters are available at the following QR code:

American Association for Cancer Research (AACR). San Diego, CA April 17-22, 2026