ATNM-400: A First-in-Class Actinium-225 Antibody Radioconjugate Demonstrating Durable, Mutation-Agnostic Anti-Tumor Activity in Non-Small Cell Lung Cancer Models

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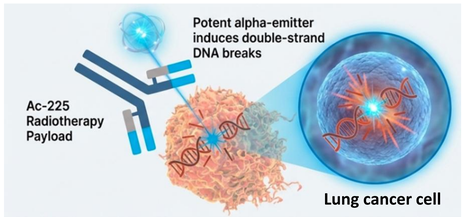
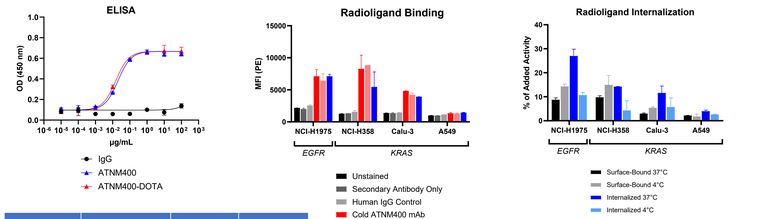
BACKGROUND

- Non-small cell lung cancer (NSCLC) accounts for ~85% of lung cancer cases with 40-50% of them harboring mutations in *EGFR* and *KRAS*. Although approved EGFR inhibitor (osimertinib) and *KRAS G12C* inhibitors (sotorasib and adagrasib) provide benefit in molecularly defined NSCLC subsets, responses are heterogeneous and resistance is inevitable, highlighting the need for mutation-agnostic therapeutic strategies.
- ATNM-400 is a novel Actinium-225 (225Ac) antibody radioconjugate targeting a broadly expressed cell-surface antigen.
- Previous immunohistochemistry studies have demonstrated membrane expression of ATNM-400 target in ~98% of NSCLC tumors, with high expression observed in ~70%, preserved across *EGFR, KRAS*, and other actionable oncogenic driver-defined subgroups. Furthermore, target expression has been shown to be increased in NSCLC that is resistant to approved inhibitors of *EGFR, KRAS* and immune checkpoint pathways.
- Here, we evaluated the anti-tumor activity of ATNM-400 across multiple NSCLC xenograft models with different oncogenic driver-defined subgroups to assess its potential as a mutation-agnostic antibody radioconjugate therapy.



- The target for ATNM-400 is implicated in lung cancer biology and treatment resistance.
- 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.

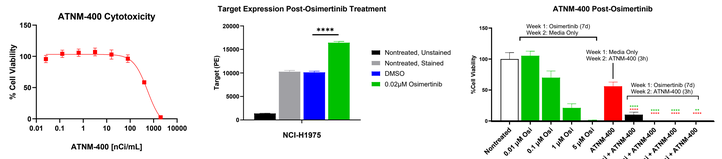
ATNM-400 Exhibits Cellular Binding and Internalization in *EGFR*-mutant and *KRAS*-mutant Lung Cancer Cell Lines Supporting Broad Therapeutic Potential



Cell Line	*EGFR* Mutation	*KRAS* Mutation	Target Expression
NCI-H1975	L858R & T790M	WT	+
NCI-H358	WT	G12C	+
Calu-3	WT	G13D	+
A549	WT	G12S	-

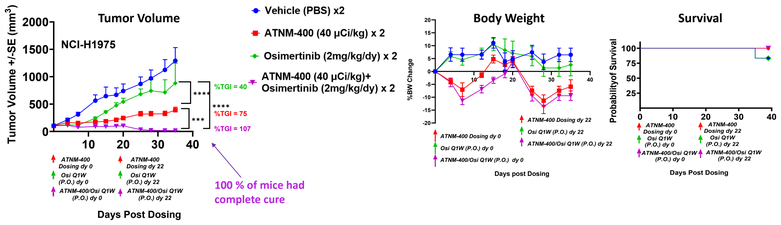
- ATNM-400 demonstrated retained target protein binding following DOTA conjugation, as assessed by ELISA, indicating preserved receptor engagement.
- ATNM-400 demonstrated target-specific binding and internalization in *EGFR*- and *KRAS*-mutant lung cancer models, validated by flow cytometry and radioactive quantification using a gamma counter.

ATNM-400 Causes Cytotoxicity in *EGFR*-mutant Lung Cancer Cells



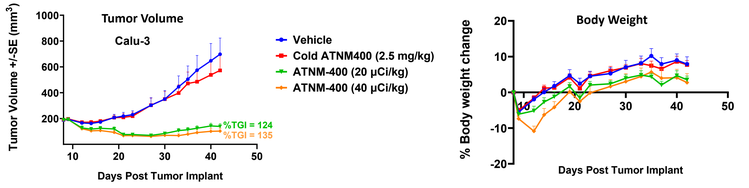
- Strong dose-dependent cytotoxicity was observed in NCI-H1975 lung cancer cells harboring *EGFR* mutation.
- *EGFR* inhibitor Osimertinib significantly increased the expression of ATNM-400 target and enhanced cell killing when it was combined with ATNM-400 in NCI-H1975 cells.

ATNM-400 Exhibits Potent Efficacy as Monotherapy and Enhanced Anti-Tumor Effect When Combined with Osimertinib in an *EGFR*-mutant NSCLC Model



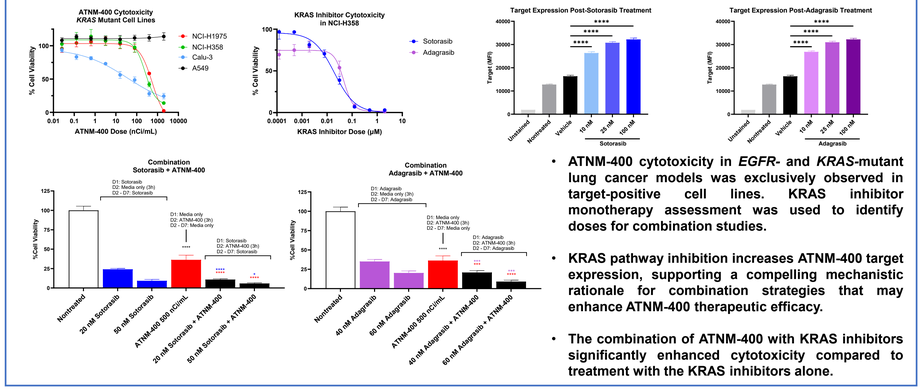
- In NCI-H1975 NSCLC xenograft tumors (*EGFR L858R/T790M* mutation), ATNM-400 monotherapy (40 µCi/kg, days 0 and 22) achieved 75% tumor growth inhibition (TGI), compared with 40% for osimertinib; the combination (ATNM-400 + osimertinib) produced 107% TGI, resulting in complete tumor regression and indicating strong synergistic activity.
- Treatments were well tolerated with no observable toxicity.

ATNM-400 Demonstrates Dose-Dependent Robust Efficacy in a *KRAS G13D*-mutant NSCLC Model



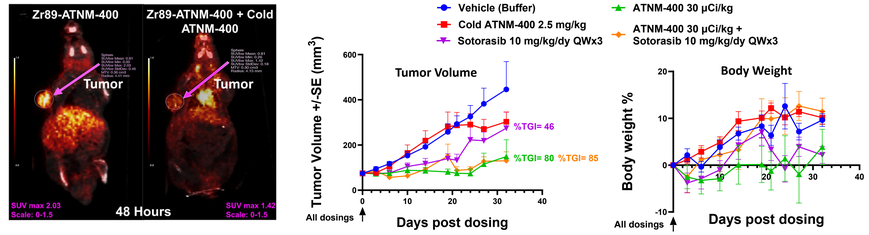
- In Calu-3 xenograft tumors (*KRAS G13D*-mutation), a single dose of ATNM-400 (20 or 40 µCi/kg, day 0) achieved 124% and 135% tumor growth inhibition (TGI), respectively, indicating marked antitumor potency.
- ATNM-400 was well tolerated, with recovery of body weight and no apparent toxicity at both doses.

ATNM-400 Induces Potent, Target-Dependent Cytotoxicity in *KRAS*-mutant NSCLC Cell Lines



- ATNM-400 cytotoxicity in *EGFR*- and *KRAS*-mutant lung cancer models was exclusively observed in target-positive cell lines. KRAS inhibitor monotherapy assessment was used to identify doses for combination studies.
- KRAS pathway inhibition increases ATNM-400 target expression, supporting a compelling mechanistic rationale for combination strategies that may enhance ATNM-400 therapeutic efficacy.
- The combination of ATNM-400 with KRAS inhibitors significantly enhanced cytotoxicity compared to treatment with the KRAS inhibitors alone.

ATNM-400 Drives Tumor-Specific Uptake and Outperforms Standard-Of-Care Sotorasib, with Combination Efficacy in a *KRAS G12C*-mutant NSCLC



- PET-CT imaging shows that Zr-89-labeled ATNM-400 selectively localizes to tumors in the NCI-H358 *G12C KRAS*-mutant NSCLC model, with markedly lower signal observed in the cold-blocked control, demonstrating strong signal for target-specific uptake.
- ATNM-400 demonstrates superior anti-tumor activity compared to the standard-of-care sotorasib and further enhances sotorasib's efficacy when used in combination in the *G12C KRAS*-mutant NCI-H358 NSCLC xenograft model.

CONCLUSIONS

- ATNM-400 demonstrates potent and durable anti-tumor activity with favorable tolerability across multiple preclinical NSCLC models independent of oncogenic driver mutation status.
- Broad target expression, including in treatment-resistant disease, together with the high-linear energy transfer of 225Ac, supports ATNM-400 as a mutation-agnostic targeted alpha therapy with potential to address key limitations of genotype-restricted systemic treatments in NSCLC.
- These findings support further translational development and clinical evaluation of ATNM-400 in patients with advanced NSCLC.

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