

ATNM-400: A First-in-Class Actinium-225 HER3 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 approximately 85% of lung cancers and is molecularly heterogeneous, with oncogenic drivers including EGFR and KRAS mutations and ALK-rearranged (mutant), several of which define clinically actionable molecular subgroups (Figure 1A). Although molecularly targeted therapies provide substantial clinical benefit in selected patient populations, heterogeneous responses and the emergence of acquired resistance remain major therapeutic challenges, supporting the development of oncogenic driver-agnostic treatment strategies (1, 2).
- HER3 (ERBB3) is a kinase-impaired member of the HER receptor family that functions as a potent signaling scaffold. Following transphosphorylation by kinase-active partners (including EGFR, HER2, and MET), HER3 recruits PI3K and activates PI3K/AKT survival signaling; HER3-containing receptor complexes can also engage MAPK and JAK/STAT pathways (3, 4).
- HER3 is broadly expressed on NSCLC tumor cells. In an analysis of 203 advanced/metastatic NSCLC specimens, membrane HER3 expression was detected in 98.5% of tumors, 70.4% demonstrated 3+ membrane staining intensity, and the median membrane H-score was 140. HER3 expression was detected across EGFR-activating, EGFR exon 20 insertion, KRAS G12C-mutant, and ALK-rearranged (mutant) molecular subgroups (Figure 1B) (5).

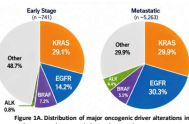
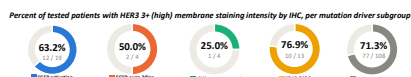


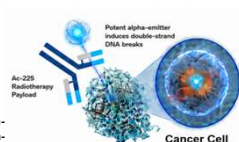
Figure 1A. Distribution of major oncogenic driver alterations in early-stage and metastatic lung adenocarcinomas. Adapted from Gosselin 7 and Hirsch 8 et al. (2).



Mutation status	Tested (n)	Samples with Positive HER3 Staining Intensity Score of 1+ to 3+ (n (%))	Samples with Intensity Score of 3+ from Positive HER3 Staining Samples (n (%))	Membrane HER3 IHC Score, median (range)
EGFR activating	66	19/66 (28.8)	12/19 (63.2)	135.0 (100-170)
EGFR exon 20 insertion	55	4/55 (7.3)	2/4 (50.0)	129.5 (120-170)
ALK rearrangement	77	3 (3.9)	1/4 (25.0)	132.5 (0-250)
KRAS G12C	36	13 (36.1)	10/13 (76.9)	180.0 (115-205)
Unknown driver	108	107/108 (99.1)	77/108 (71.3)	135.0 (115-500)

Figure 1B. HER3 membrane expression across oncogenic driver-defined lung adenocarcinoma subgroups. (Adapted from Soo NA, et al. (5))

- HER3 also functions as a bypass signaling node during targeted therapy. In EGFR-mutant NSCLC, MET amplification can restore PI3K/AKT signaling through HER3, while EGFR-TKI treatment can increase tumor-cell HER3 expression (6, 7). In ALK-rearranged (mutant) NSCLC, HER3 activation, including NRG1/HER3 signaling, has been implicated in ALK-TKI tolerance and resistance (8, 9).



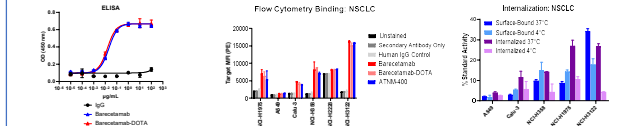
- 225Ac-barorectamab-DOTA (ATNM-400) is a HER3-targeted Actinium-225 (225Ac) antibody radioconjugate (ARC) designed to deliver high-linear-energy-transfer α -particle radiation to HER3-expressing tumor cells. Following HER3 binding and internalization, ATNM-400 induces α -particle-mediated DNA damage, including irreversible double-strand DNA breaks and γ H2AX induction, leading to tumor-cell death.

Cell Line	EGFR Mutation	KRAS Mutation	ALK rearranged (mutant)	BRAF Mutation	HER3 Expression
NCI-H1975	L858R & T790M				+
NCI-H358		G12C			+
Cellu-3		G130			+
A549		G12S			-
NCI-H3122			TMLK-ALK variant 1		+
HCC364				V600E	+

+ HER3 membrane expression detected
- HER3 membrane expression not detected

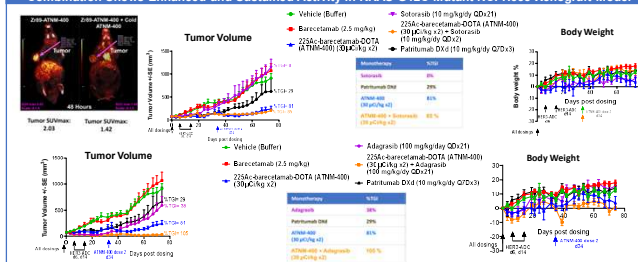
- Here, we evaluated the anti-tumor activity of ATNM-400 across multiple NSCLC xenograft models representing distinct oncogenic driver-defined subgroups to assess its potential as a mutation-agnostic ARC therapy.

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



- 225Ac-barorectamab-DOTA (ATNM-400) demonstrates retained HER3 target protein binding following DOTA conjugation, as assessed by ELISA assay, indicating preserved receptor engagement.
- ATNM-400 demonstrates target-specific binding and internalization in EGFR- and KRAS-mutant lung cancer models, validated by flow cytometry and radioactive quantification using a gamma counter.

225Ac-barorectamab-DOTA (ATNM-400) Demonstrates Greater Anti-Tumor Activity Versus SOC Sotorasib, Adagrasib and HER3 ADC; With ATNM-400 Sotorasib Combination Shows Equivalent, While Adagrasib Combination Shows Enhanced and Sustained Activity in KRAS G12C-Mutant NCI-H358 Xenograft Model



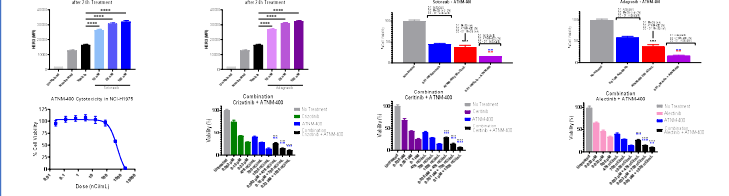
- PET-CT imaging shows that Zr-89 labeled ATNM-400 selectively localizes to tumors in NCI-H358 KRAS- G12C mutant NSCLC model, with markedly lower signal observed in the cold-blocked control at 48h post-injection, demonstrating strong signal for target-specific uptake.
- In the KRAS G12C-mutant NCI-H358 NSCLC model, 225Ac-barorectamab-DOTA (ATNM-400) demonstrated substantially greater anti-tumor activity (81% TGI) than sotorasib (~28% TGI) and Patritumab Dxd (HER3-ADC) (29% TGI). Combination of ATNM-400 with sotorasib maintained strong tumor control (85% TGI). All doses containing ATNM-400 were well tolerated.
- ATNM-400 demonstrated greater anti-tumor activity (81% TGI) than adagrasib (38% TGI) and Patritumab Dxd (29% TGI) in the KRAS G12C-mutant NCI-H358 model. Combination of ATNM-400 with adagrasib further enhanced efficacy, achieving 105% TGI, consistent with tumor regression. All doses containing ATNM-400 were well tolerated.

ATNM-400 in Combination with Chemotherapy Produced Greater Tumor Growth Inhibition than Comparator Regimens in the EGFR-Mutant NCI-H1975 Xenograft Model



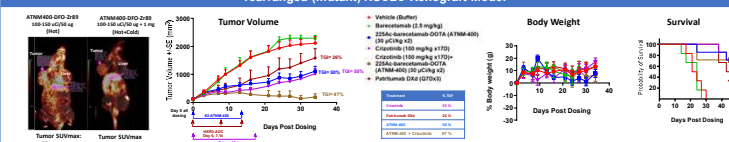
- In an EGFR-mutant NSCLC model NCI-H1975, ATNM-400 monotherapy (63% TGI) demonstrated greater tumor growth inhibition than chemotherapy (36% TGI), amivantamab (5% TGI), and lazertinib (47% TGI). When compared to approved SOC combos amivantamab + chemotherapy (52% TGI), and amivantamab + lazertinib (48% TGI), ATNM-400 + chemotherapy combo produced the greatest anti-tumor activity (86% TGI) and was associated with prolonged survival of animals during the study period.

ATNM-400 Exhibits Dose-Dependent Cytotoxicity and Enhanced Cytotoxicity in Combination with SOC Inhibitors in *in vitro* NSCLC Models



- Following 24h treatment of KRAS-G12C inhibitors (sotorasib or adagrasib), the surface HER3 expression on KRAS-mutant lung cancer cell line NCI-H358 increases in a dose-dependent manner as quantified by flow cytometry. ATNM-400 in combination with sotorasib or adagrasib exhibits enhanced cytotoxicity in NCI-H358 due to the increased expression of surface HER3 following 24h sotorasib or adagrasib treatment.
- ATNM-400 exhibit dose-dependent cytotoxicity in EGFR-mutant lung cancer cell line NCI-H1975.
- ATNM-400 in combination with ALK inhibitors (crizotinib, ceritinib, or alectinib) exhibits enhanced dose-dependent cytotoxicity compared to single agent monotherapy in ALK-rearranged (mutant) lung cancer cell line NCI-H3122.

ATNM-400 is Most Potent in Combination with SOC Crizotinib, Comparable to Crizotinib and Superior to HER3-ADC in an ALK rearranged (mutant) NSCLC Xenograft Model



- PET-CT imaging with Zr-89-labeled ATNM-400 shows selective, target-specific tumor localization in the NCI-H3122 ALK rearranged (mutant) NSCLC model, with markedly lower signal observed in the cold-blocked control at 72h post-injection.
- In the ALK-rearranged (mutant) NCI-H3122 NSCLC model, ATNM-400 monotherapy (50% TGI) showed activity comparable to crizotinib (55% TGI) and greater than Patritumab Dxd (26% TGI). ATNM-400 combined with crizotinib markedly enhanced tumor control (97% TGI) relative to either monotherapy. All doses containing ATNM-400 were well tolerated and extended overall survival compared to controls and HER3-ADC. Higher dose of ATNM-400 as monotherapy and with SOC combos are being investigated in this model and will be presented in the future.

Conclusions

- 225Ac-barorectamab-DOTA (ATNM-400) demonstrates robust and durable anti-tumor activity across molecularly diverse NSCLC models, including EGFR-mutant, KRAS G12C-mutant and ALK-rearranged (mutant) models, suggestive of a mutation-agnostic activity that is not restricted to a single oncogenic driver genotype in these models.
- HER3 is broadly expressed across NSCLC molecular subtypes and serves as a key survival and bypass-signaling node implicated in disease progression and resistance to approved targeted therapies, providing a compelling biological rationale for HER3-directed treatment across heterogeneous NSCLC.
- ATNM-400 combines broad HER3 targeting with the high-linear-energy-transfer cytotoxicity of 225Ac and resulted in tumor growth inhibition of a similar magnitude to that achieved by genotype-directed agents in these model systems, with further enhancement when combined with approved targeted agents or chemotherapy.
- Collectively, these findings support a strong preclinical rationale for ATNM-400 as a HER3-targeted α -particle radioconjugate across molecularly heterogeneous and treatment resistance NSCLC models in a mutation-agnostic manner, supporting continued advancement toward clinical evaluation.

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