Anti-Tumor Activity of ATNM-400, a First-in-class Actinium-225 Antibody Radioconjugate, in Hormone-Positive, Triple-Negative, Tamoxifen-Resistant and Trastuzumab-Resistant Breast Cancer Models

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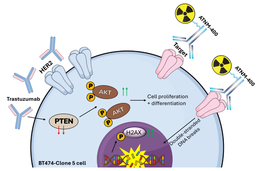
Background

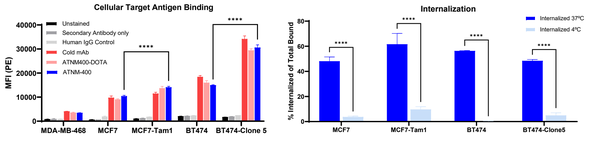
- Hormone receptor positive (HR+) breast cancer (BC) represents >70% of diagnosis, yet ~20–30% of patients relapse despite endocrine therapy such as tamoxifen.
- Similarly, relapse was also observed in HER2+ breast cancer despite HER-2 antibody trastuzumab and antibody–drug conjugates (e.g., trastuzumab deruxtecan), which can also be associated with interstitial lung disease, thereby limiting their use.
- Actinium-225 (225Ac) radioconjugates may offer potent, localized tumor killing with reduced off-target lung toxicity due to the short path length of alpha particles. We developed ATNM-400, a novel Actinium-225–based antibody radioconjugate targeting an antigen overexpressed in breast cancer, including tumors resistant to endocrine and HER2-directed therapies.
- Here, we demonstrate significant anti-tumor efficacy of ATNM-400 across preclinical HR+ and triple-negative breast cancer (TNBC) in vivo models, in addition to trastuzumab- and tamoxifen-resistant breast cancer models, supporting its potential to overcome current therapeutic limitations.

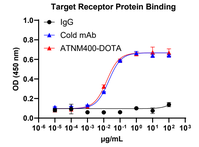
Mechanisms of Action of ATNM-400 in Breast Cancer



- In trastuzumab-resistant BT474-Clone5 cell line, phospho-AKT levels are increased compared to the parental breast cancer cell line BT474
- Increased pAKT leads to cell proliferation and differentiation. ATNM-400 binds to Target receptors and causes double-stranded DNA breaks which increase phosho-H2A.X

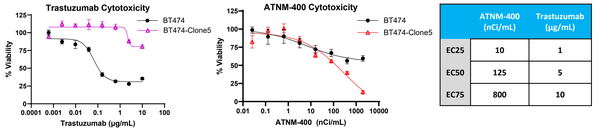
ATNM-400 Binds and Internalizes in Human Breast Cancer Cells



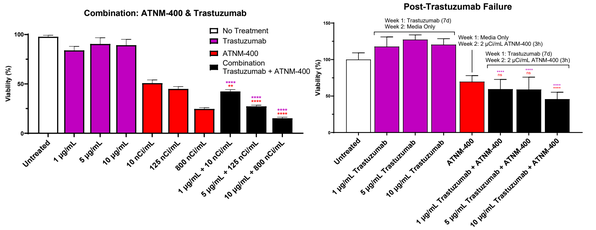


- Target expression was increased in BC cells resistant to endocrine therapy tamoxifen (MCF7-Tam1) or HER2 mAb trastuzumab (BT474-Clone5)
- ATNM-400 binds to the recombinant human target protein by ELISA and to target-positive BC by flow cytometry
- ATNM-400 internalized in the BC cell lines

Trastuzumab Resistance-Driven Target Overexpression Confers Increased Susceptibility to ATNM-400 in Breast Cancer Cells

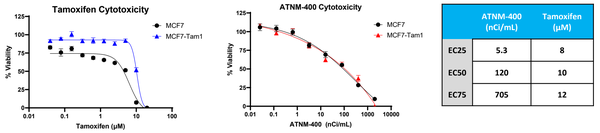


	ATNM-400 (nCi/mL)	Trastuzumab (µg/mL)
EC25	10	1
EC50	125	5
EC75	800	10

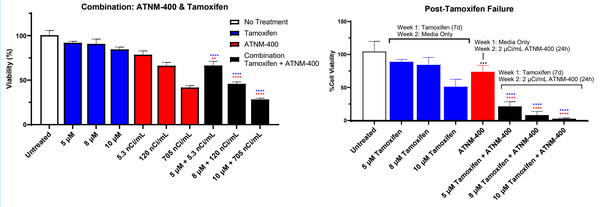


- ATNM-400 caused cytotoxicity in trastuzumab-resistant BC cell line BT474-Clone5
- Combination of ATNM-400 with trastuzumab in BT474-Clone5 had increased cytotoxicity versus monotherapy; ATNM-400 was cytotoxic in BC cells that failed trastuzumab

Potent ATNM-400 Cytotoxicity in Tamoxifen-Resistant Cells as Monotherapy, in Combination and Post-Tamoxifen Failure

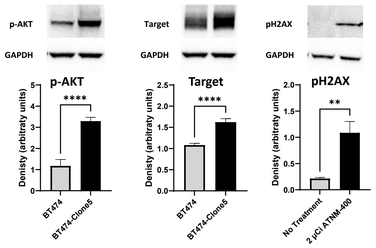


	ATNM-400 (nCi/mL)	Tamoxifen (µM)
EC25	5.3	8
EC50	120	10
EC75	705	12



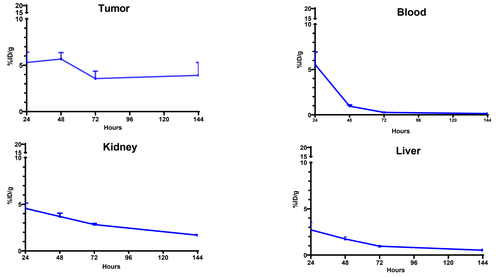
- ATNM-400 caused cytotoxicity in tamoxifen-resistant BC cell line MCF7-Tam1
- Combination of ATNM-400 with tamoxifen in MCF7-Tam1 had increased cytotoxicity versus monotherapy; ATNM-400 was cytotoxic in BC cells that had failed tamoxifen

ATNM-400 Induces Irreversible DNA Damage in Breast Cancer Cells



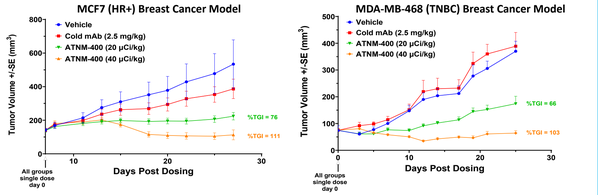
- Trastuzumab resistance activated phosphorylation of AKT (pAKT), as well as induced a significant increase in total target protein level
- ATNM-400 treatment of trastuzumab resistant BT474-Clone5 cells caused significant increase in pH2AX, indicative of double-strand DNA damage

Sustained Tumor Uptake and Rapid Clearance from Normal Organs in Breast Cancer Model



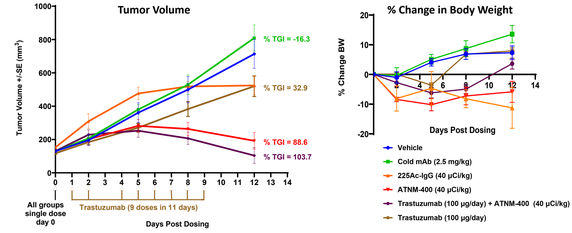
- ATNM-400 showed sustained tumor uptake up to 144 hours with rapid clearance from normal organs suggesting a favorable safety profile in BT474 WT BC model in biodistribution in vivo studies

ATNM-400 Has Robust Efficacy in HR+ Breast Cancer and TNBC In Vivo Mouse Models



- ATNM-400 caused dose-dependent tumor growth inhibition (TGI) in MCF7 hormone positive (HR+) BC model and MDA-MB-468 triple-negative breast cancer (TNBC) model. All treatments were well-tolerated with no significant change in body weight

ATNM-400 has Robust Efficacy in Trastuzumab-Resistant BT474-Clone5 Breast Cancer Model



- ATNM-400 showed robust efficacy in trastuzumab-resistant breast cancer BT474-Clone5 model with 88.6% tumor growth inhibition (TGI)
- ATNM-400 in combination with trastuzumab caused tumor regression in trastuzumab-resistant breast cancer model
- ATNM-400 was well-tolerated with no significant change in body weight (BW)

Conclusions

- ATNM-400 shows strong anti-tumor efficacy and favorable tolerability across multiple breast cancer subtypes: HR+ and TNBC, including models resistant to endocrine therapy tamoxifen and HER-2 antibody trastuzumab
- Resistance to SOC had increased target expression, resulting in potent cytotoxicity and efficacy by ATNM-400 as monotherapy and in combination with SOC
- These findings support further development of ATNM-400 as a novel therapeutic approach for patients with limited options following endocrine or HER2-targeted therapy failure - both as monotherapy and rational combination regimens
- Based on our previous publications of ATNM-400 efficacy in prostate and lung cancer, these data suggest that ATNM-400 also is efficacious in breast cancer and has pan-tumor potential

San Antonio Breast Cancer Symposium (SABCS), San Antonio, TX, December 9-12, 2025