

ATNM-400, a First-in-Class Actinium-225 HER3 Radioconjugate Improves Response to Standard-Of-Care Therapeutics in Colorectal Cancer Models

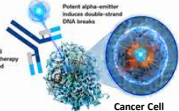
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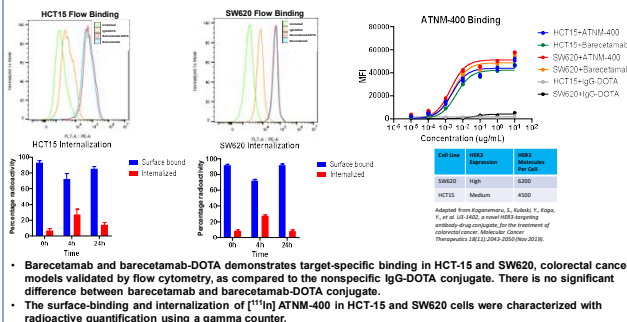


Background

- Colorectal cancer (CRC) remains a major global health burden. In the United States, an estimated 154,270 new cases and 52,900 deaths occurred in 2025, with an overall 5-year relative survival of approximately 64%. Globally, CRC accounted for approximately 1.9 million new cases and >900,000 deaths in 2022, making it the third most commonly diagnosed cancer and second leading cause of cancer death (1,2).
- CRC treatment is guided by disease stage and molecular characteristics and incorporates surgery, when feasible, together with standard-of-care (SOC) systemic therapies including fluoropyrimidine-, oxaliplatin-, and/or irinotecan-based regimens, anti-angiogenic agents such as bevacizumab, and biomarker-directed targeted and immune therapies. Despite these advances, treatment resistance and disease progression remain major challenges in advanced CRC, underscoring the need for new therapies with activity across molecular subtypes (3).
- HER3 (ERBB3) is frequently expressed in CRC, with surface expression significantly enriched in advanced/metastatic disease (Figure 1) (4). Independent clinical studies report high HER3 expression in approximately 75-82% of colorectal liver metastases, with HER3 expression frequently maintained between primary tumors and metastatic sites, supporting HER3 as a therapeutically relevant target in advanced CRC (5,6).
- Preclinical studies have reported modulation of HER3 signaling following cetuximab, EGFR pathway inhibition, including HER3 upregulation/activation and heregulin-associated HER2-HER3/AKT signaling in CRC models (7,8).
- 225Ac-barecatamab-DOTA (ATNM-400) is a novel Actinium-225 (225Ac) antibody radioconjugate (ARC) targeting HER3. Following HER3 binding and internalization, ATNM-400 delivers high-linear-energy-transfer α -particle radiation, inducing irreversible DNA double-strand breaks and γ H2AX induction, leading to tumor cell death (Figure 1B).
- Here, we evaluated the anti-tumor activity and translational potential of ATNM-400 as monotherapy and in combination with CRC SOC across molecularly distinct CRC models with differential HER3 expression.

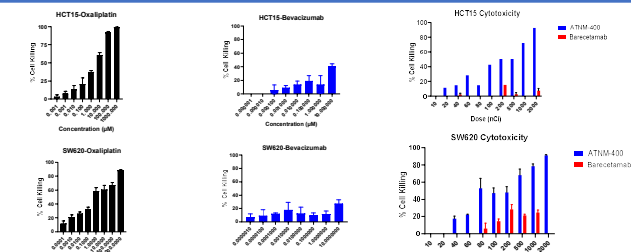


ATNM-400 Exhibits Cellular Binding and Internalization in Colorectal Cancer Cell Line Models



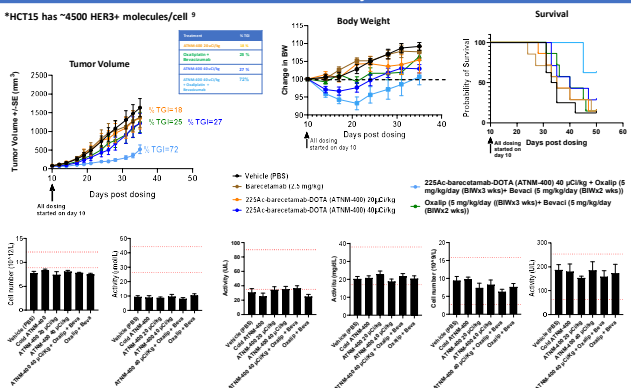
- Barecatamab and barecatamab-DOTA demonstrates target-specific binding in HCT-15 and SW620, colorectal cancer models validated by flow cytometry, as compared to the nonspecific IgG-DOTA conjugate. There is no significant difference between barecatamab and barecatamab-DOTA conjugate.
- The surface-binding and internalization of [¹²⁵I] ATNM-400 in HCT-15 and SW620 cells were characterized with radioactive quantification using a gamma counter.

ATNM-400 Exhibits Dose-Dependent Cytotoxicity in *in vitro* Colorectal Cancer Models



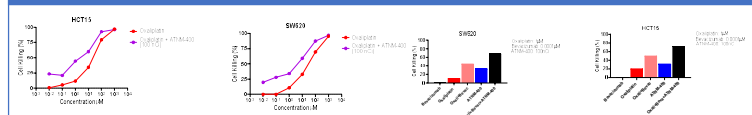
- ATNM-400 exhibits strong dose-dependent cytotoxicity in both HCT-15 and SW620 as compared to barecatamab alone. Oxaliplatin exhibits strong dose-dependent cytotoxicity in both HCT-15 and SW620 cell line models, but bevacizumab shows a lesser cytotoxicity response in both cell lines.

ATNM-400 Combined With Oxali/Beva (SOC) Showed Marked Combinatorial Anti-Tumor Activity in the HER3-medium* HCT15 CRC Mouse Xenograft Model With Extended Survival and Favorable Safety Profile



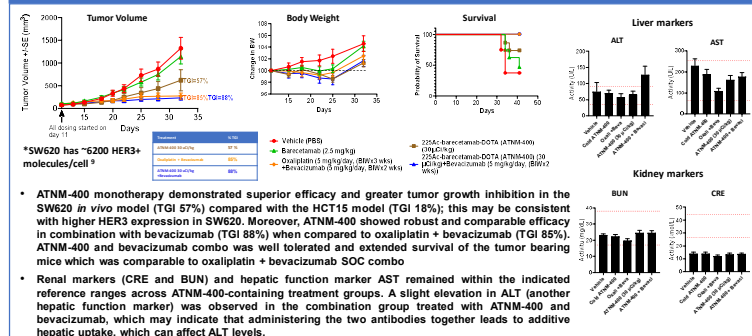
- In the HCT15, HER3 medium model, where both 225Ac-barecatamab-DOTA (ATNM-400) monotherapy (TGI 27%) and bevacizumab plus oxaliplatin (TGI 25%) showed limited efficacy, the combination of ATNM-400 with bevacizumab plus oxaliplatin marked enhanced antitumor activity, achieving a TGI of 72%. The combination of ATNM-400 with bevacizumab plus oxaliplatin was well tolerated and extended survival of the tumor bearing mice.
- Both ATNM-400 monotherapy and its combination with bevacizumab and oxaliplatin exhibited no treatment-related abnormalities in the assessed renal (CRE, BUN), hepatic (ALT, AST), or hematological (RBC, WBC) parameters.

ATNM-400 Exhibits Dose-Dependent Cytotoxicity and Enhances Cytotoxicity in Combination with Oxaliplatin and Bevacizumab in *in vitro* Colorectal Cancer Models



- ATNM-400 exhibits enhanced cytotoxicity in both HCT-15 and SW620 when cells were treated in conjunction with Oxaliplatin. Bevacizumab alone shows little to no cytotoxicity in both HCT-15 and SW620, but when used in combination with Oxaliplatin, and with ATNM-400 and Oxaliplatin cytotoxicity was enhanced and increased.

ATNM-400/Beva and Oxali/Beva (SOC) Showed Comparable, Robust Antitumor Efficacy and Extended Survival in the HER3-high* SW620 CRC Mouse Xenograft Model With Favorable Safety Profile



- ATNM-400 monotherapy demonstrated superior efficacy and greater tumor growth inhibition in the SW620 *in vivo* model (TGI 57%) compared with the HCT15 model (TGI 18%); this may be consistent with higher HER3 expression in SW620. Moreover, ATNM-400 showed robust and comparable efficacy in combination with bevacizumab (TGI 88%) when compared to oxaliplatin + bevacizumab (TGI 85%). ATNM-400 and bevacizumab combo was well tolerated and extended survival of the tumor bearing mice which was comparable to oxaliplatin + bevacizumab SOC combo
- Renal markers (CRE and BUN) and hepatic function marker AST remained within the indicated reference ranges across ATNM-400-containing treatment groups. A slight elevation in ALT (another hepatic function marker) was observed in the combination group treated with ATNM-400 and bevacizumab, which may indicate that administering the two antibodies together leads to additive hepatic uptake, which can affect ALT levels.

Conclusions

- 225Ac-barecatamab-DOTA (ATNM-400) demonstrated robust antitumor activity across CRC models spanning medium-to-high HER3 expression and differing sensitivity to standard therapies.
- HER3 is increasingly recognized as an important mediator of CRC progression and therapeutic adaptation, with expression enriched in advanced disease and metastatic lesions and signaling linked to resistance to EGFR-directed therapy.
- HER3 ARC-directed delivery of 225Ac provides a differentiated cytotoxic mechanism against a biologically relevant CRC target, enabling high-LET α -particle-mediated tumor-cell killing independent of conventional pathway inhibition.
- ATNM-400 showed strong combination potential with CRC standard-of-care (SOC): addition to oxaliplatin/bevacizumab markedly improved efficacy in poorly responsive HCT15 tumors, while ATNM-400/bevacizumab achieved efficacy and survival comparable to Oxaliplatin/Bevacizumab in SW620 tumors.
- ATNM-400-containing regimens were well tolerated in these preclinical studies, supporting continued translational development of ATNM-400 as a potential monotherapy and combination strategy for CRC.

References

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