[^{225}Ac]Ac-AKY-1189, a Nectin-4-Targeted Radiopharmaceutical, in Patients With Previously Treated Locally Advanced or Metastatic Solid Tumors: Phase 1b NECTINIUM-2 Study

Timothy A. Yap[1], Omar Alhalabi[1], Yang Lu[1], Brandon R. Mancini[2], Harshad R. Kulkarni[2], Kristin Plichta[3], Serguei A. Castaneda[4], Frankis Almaguel[4], Randy Yeh[5], Ryan Reddy[6], David Benjamin[6], Abhishek Tripathi[7], Phillip Kuo[8], Ying-Hui Huang[9], Janet K. Horton[9], Matthew Galsky[5]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]BAMF Health, Grand Rapids, MI, USA; [3]University of Iowa, Iowa City, IA, USA; [4]Biogenix Molecular, Miami, FL, USA; [5]Icahn School of Medicine at Mount Sinai, New York, NY, USA; [6]Hoag Memorial Hospital Presbyterian, Newport Beach, CA, USA; [7]City of Hope Medical Center, Duarte, CA, USA; [8]Kuo Radiology LLC, Tucson, AZ, USA; [9]Aktis Oncology, Boston, MA, USA

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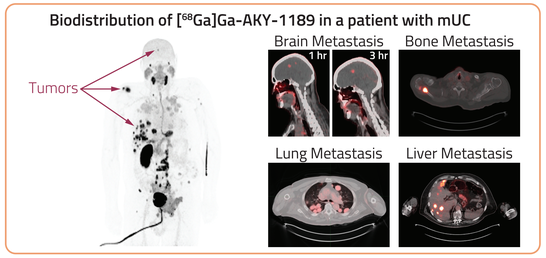
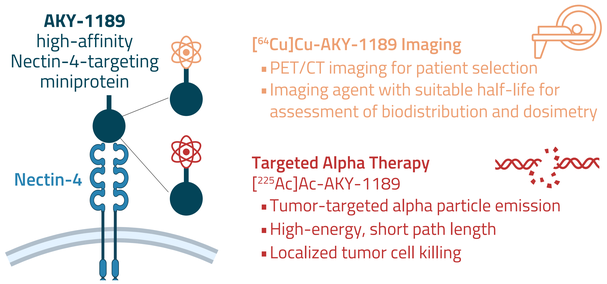
BACKGROUND

- **Nectin-4 is a clinically validated target in metastatic urothelial carcinoma (mUC) and is overexpressed across multiple additional solid tumor types, supporting broad therapeutic potential.**[1-9]
- AKY-1189 is a high-affinity, selective Nectin-4-targeted miniprotein radioconjugate that demonstrates rapid plasma clearance with favorable normal tissue biodistribution and dosimetry in humans when radiolabeled with ^{68}Ga or ^{177}Lu.[10]



- In preclinical urothelial carcinoma models, a single administration of [^{225}Ac]Ac-AKY-1189 induced tumor regression or stasis, with target-dependent antitumor activity observed at well-tolerated dose levels.
- These data supported clinical investigation of [^{225}Ac]Ac-AKY-1189.



STUDY DESIGN

NECTINIUM-2 (NCT07020117) is a first-in-human, Phase 1b, multicenter, open-label study evaluating [^{225}Ac]Ac-AKY-1189.

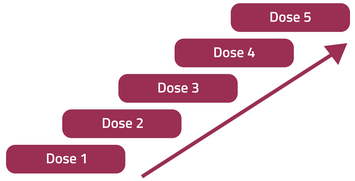
Patient Screening & Imaging Selection

- Target engagement
- Biodistribution and dosimetry assessment

- Advanced or metastatic solid tumors
- Nectin-4 uptake assessed by [^{64}Cu]Cu-AKY-1189 PET/CT
  - Tumor uptake confirms eligibility

Part 1: Dose Escalation

- Determine MTD/MAD
- Establish RP2D



- Up to 30 patients with locally advanced or metastatic solid tumors (mUC, TNBC, HR$^+$BC, cervical, CRC, H&N, NSCLC)
- Ascending dose levels of [^{225}Ac]Ac-AKY-1189
- Up to 6 treatment cycles
- Dose escalation guided by safety and tolerability

Backfill

Dose Level Before MTD/MAD
Nectin-4-positive solid tumors (n=30)

MTD/MAD Dose Level
Nectin-4-positive solid tumors (n=30)

Part 2: Dose Expansion

- Enrollment at RP2D
- 3 cohorts of Nectin-4-positive solid tumors by [^{64}Cu]Cu-AKY-1189 PET/CT
- Evaluation of clinical activity and safety

mUC = metastatic urothelial carcinoma; TNBC = triple-negative breast cancer; HR$^+$BC = hormone receptor-positive breast cancer; CRC = colorectal cancer; H&N = head and neck cancer; MAD = multiple ascending dose; MTD = maximum tolerated dose; NSCLC = non-small cell lung cancer; RP2D = recommended Phase 2 dose

OBJECTIVES

Primary Objectives

- Part 1: Evaluate the safety and tolerability of [^{225}Ac]Ac-AKY-1189
- Part 2: Determine the objective response rate by tumor type to [^{225}Ac]Ac-AKY-1189, utilizing RECIST v1.1

Secondary Objectives

- Evaluate safety and tolerability
- Characterize pharmacokinetics and dosimetry
- Determine preliminary antitumor activity

PATIENT POPULATION

Inclusion Criteria	Exclusion Criteria
• Age ≥18 years	• Prior radiopharmaceutical therapy
• Histologically or cytologically confirmed locally advanced or metastatic solid tumors	• Investigational therapy within 4 weeks
• ≥1 measurable lesion per RECIST v1.1	• Anticancer therapy or external beam radiotherapy within 3 weeks
• ECOG performance status 0-1	• Prior Nectin-4-targeted therapy except enfortumab vedotin
• Adequate end-organ function	
• Documented progression on prior systemic therapies in the metastatic setting	
• Tumor uptake confirmed by [^{64}Cu]Cu-AKY-1189 PET/CT	

CURRENT STATUS

- NECTINIUM-2 is actively enrolling in the United States.
- Dose escalation is ongoing.

CONCLUSIONS

- **NECTINIUM-2 is a first-in-human study evaluating [^{225}Ac]Ac-AKY-1189, a Nectin-4-targeted alpha-emitting radiopharmaceutical, in patients with previously treated locally advanced or metastatic solid tumors.**
- **This trial aims to define a safe and biologically active dose and to characterize early clinical activity in Nectin-4-expressing tumors.**

References: 1) Challita-Eid PM, et al. *Cancer Res.* 2016;76(10):3003-13. **2)** Powles T, et al. *N Engl J Med.* 2024;390(10):875-88. **3)** M-Rabet M, et al. *Ann Oncol.* 2017;28:769-76. **4)** Fabre-Lafay S, et al. *BMC Cancer.* 2007;7:73. **5)** Mabwell Press Release. 2024. **6)** Zhang J, et al. *Oncol Lett.* 2019;18(2):1163-70. **7)** Kobecki J, et al. *Int J Mol Sci.* 2023;24(21):15900. **8)** Sanders C, et al. *Oncotarget* 2022;13:1166-73. **9)** Takano A, et al. *Cancer Res.* 2009;69(16):6694-703. **10)** Sathekge M, et al. *Eur J Cancer.* 2024;211(suppl 1):114539.

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For more information, contact Janet Horton, MD: AKY-1189-01Inquiries@aktisoncology.com