LY4101174

NECTIN-4 ANTIBODY-DRUG CONJUGATE

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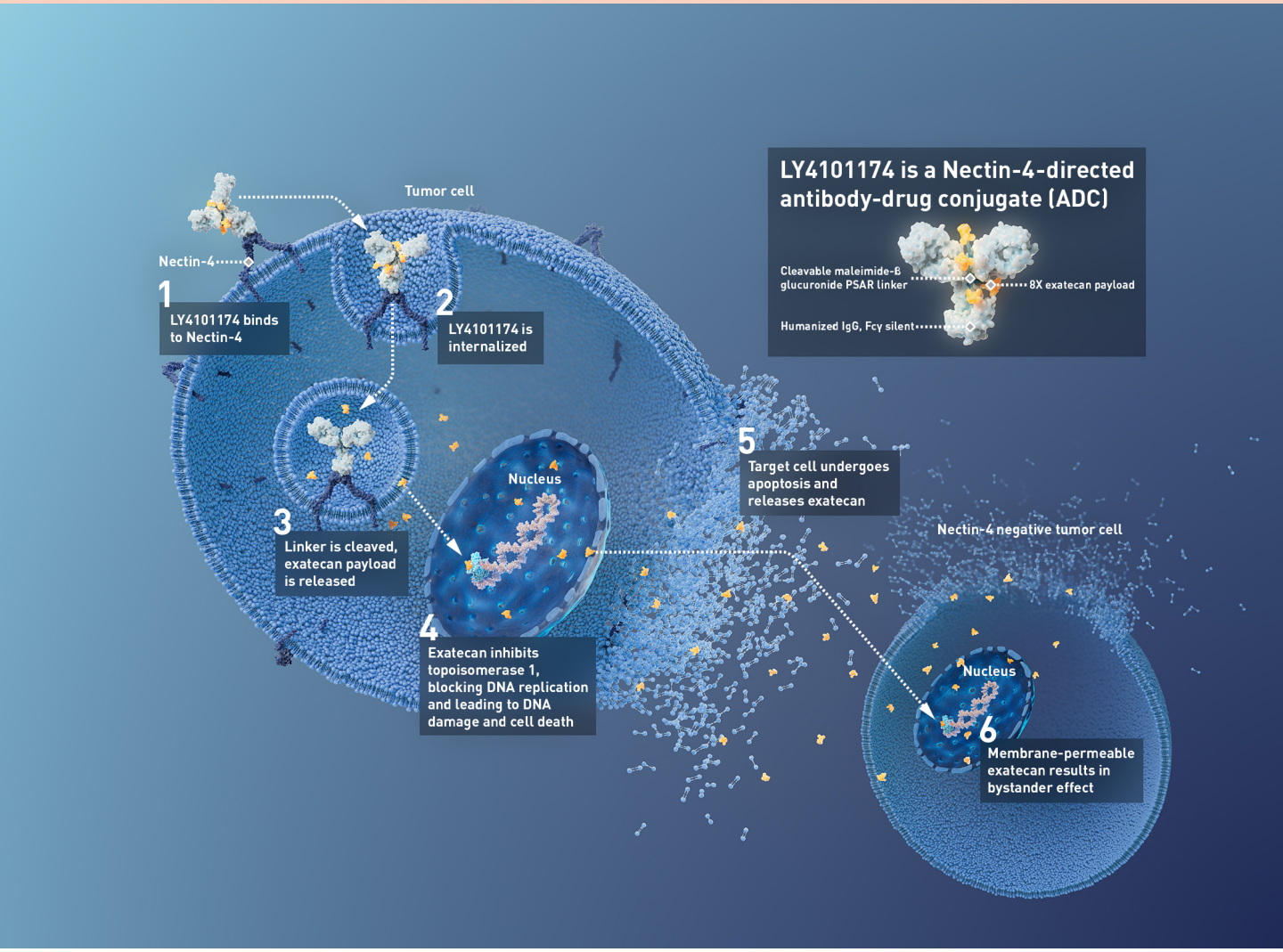
MECHANISM OF ACTION[1-4]



Dumontet C, et al[1]; Challita-Eid PM, et al[2]; Heath EI, et al[3]; Fares J, et al[4]

Abbreviation: RECIST v1.1=Response Evaluation Criteria in Solid Tumors version 1.1.

References: 1. Dumontet C, et al. *Nat Rev Drug Discov*. 2023;22(8):641-661. **2.** Challita-Eid PM, et al. *Cancer Res*. 2016;76(10):3003-3013. **3.** Heath EI, Rosenberg JE. *Nat Rev Urol*. 2021;18(2):93-103. **4.** Fares J, et al. Preclinical characterization of ETx-22 (LY4101174), a next-generation antibody drug conjugate (ADC) targeting Nectin-4. Poster presented at: AACR-NCI-EORTC Annual Meeting; October 11-15, 2023; Boston, MA.

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TARGET

Nectin-4 is a type I transmembrane polypeptide and a member of the nectin glycoprotein family.[1] Nectin-4 is primarily expressed in the placenta during fetal development and is weakly expressed in some adult human tissues, such as skin.[1,2] Overexpression of nectin-4 has been observed in several solid tumor types including urothelial, breast, cervix, lung, and ovarian cancers,[2,3] and is associated with promoting tumor proliferation and metastasis.[1] The higher expression of nectin-4 in tumor cells compared to healthy cells makes the protein a target for tumor-specific delivery of cytotoxic agents via an antibody-drug conjugate (ADC).[1]

MOLECULE

LY4101174 is a next-generation anti-nectin-4 targeting ADC. It is comprised of a humanized IgG1 Fc-silent monoclonal nectin-4 antibody linked to the topoisomerase 1 inhibitor, exatecan, via a maleimide-B-glucuronide poly-sarcosine linker with a homogeneous drug-antibody ratio (DAR) of 8. In preclinical *in vivo* models, LY4101174 has shown anti-tumor activity across a range of nectin-4 expression levels including a nectin-4 MMAE ADC resistant model.

CLINICAL DEVELOPMENT

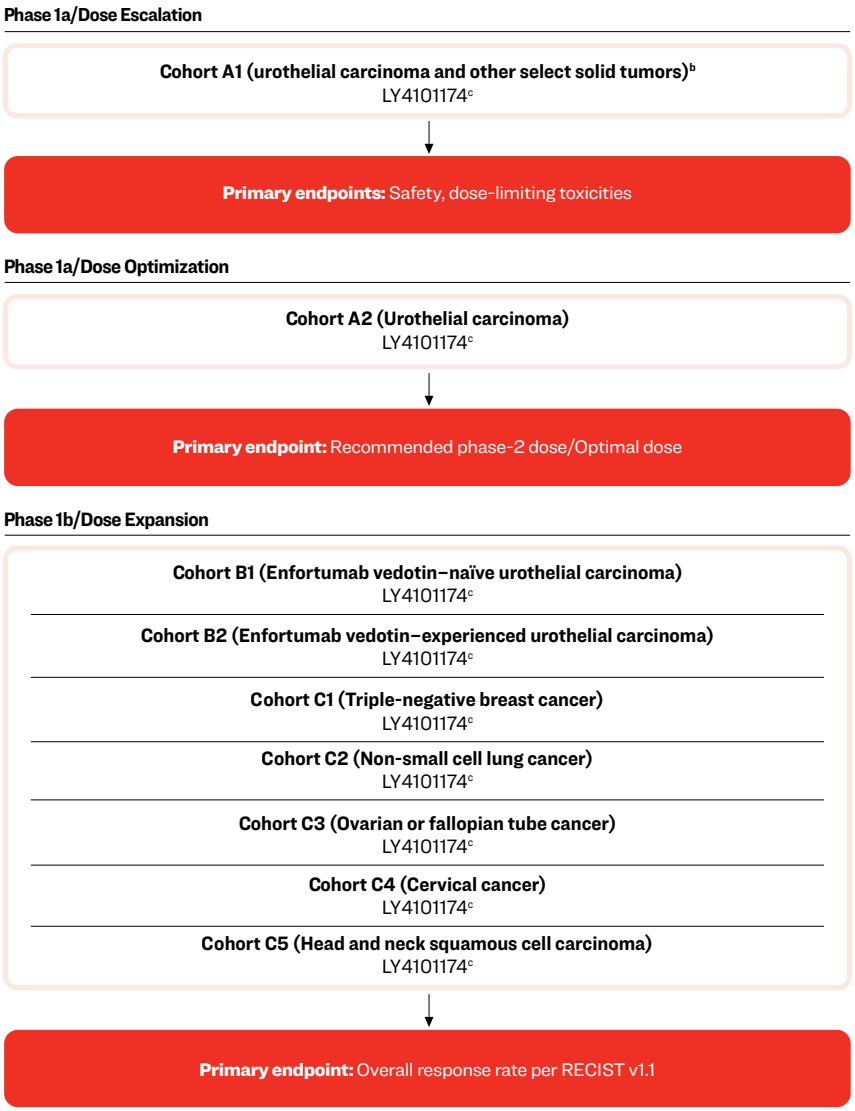
LY4101174 is being investigated in a global open-label, multicenter, phase 1a/1b study in patients with advanced or metastatic urothelial carcinoma and select solid tumors.

References: 1. Heath EI, Rosenberg JE. *Nat Rev Urol*. 2021;18(2):93-103. **2.** Fares J, et al. Preclinical characterization of ETx-22 (LY4101174), a next-generation antibody drug conjugate (ADC) targeting Nectin-4. Poster presented at: AACR-NCI-EORTC Annual Meeting; October 11-15, 2023; Boston, MA. **3.** Challita-Eid PM, et al. *Cancer Res*. 2016;76(10):3003-3013.

LY4101174 NECTIN-4 ANTIBODY-DRUG CONJUGATE

NCT06238479

A Phase 1 Trial Investigating LY4101174, an Antibody-Drug Conjugate Targeting Nectin-4, in Participants With Recurrent, Advanced, or Metastatic Solid Tumors[a]



[a]This clinical trial is being conducted globally. [b]One of the following solid tumor cancers: triple-negative breast cancer, non-small cell lung cancer, esophageal cancer, pancreatic cancer, ovarian cancer, cervical cancer (squamous cell carcinoma), head and neck squamous cell carcinoma, or prostate cancer. [c]LY4101174 is administered intravenously as monotherapy. **Abbreviation:** RECIST v1.1=Response Evaluation Criteria in Solid Tumors version 1.1.

Please visit clinicaltrials.gov for more information on this clinical trial [NCT06238479].

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NCT06238479

A Phase 1 Trial Investigating LY4101174, an Antibody-Drug Conjugate Targeting Nectin-4, in Participants With Recurrent, Advanced, or Metastatic Solid Tumors (cont.)

KEY INCLUSION CRITERIA

- Prior systemic therapy criteria:
  - Cohorts A1 and C1-5: Participant has received all standard therapies for which the participant was deemed to be an appropriate candidate by the treating investigator; OR there is no standard therapy available for the disease. There is no restriction on number of prior therapies
  - Cohorts A2, B1, and B2: Participant must have received at least one prior regimen in the advanced or metastatic setting. There is no restriction on number of prior therapies
- Prior enfortumab vedotin specific requirements:
  - Cohorts A1, A2, and C1-5: Prior treatment with enfortumab vedotin is allowed, but not required
  - Cohort B1: Participant must be enfortumab vedotin naïve in the advanced/metastatic setting
  - Cohort B2: Participant must have received enfortumab vedotin in the metastatic/advanced setting
- Measurability of disease:
  - Cohort A1: Measurable or non-measurable disease as defined by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1)
  - Cohorts A2, B1, B2, and C1-5: Measurable disease required as defined by RECIST v1.1
    - Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
    - Adequate archival tumor tissue sample available or undergo a screening biopsy if allowed per country-specific regulations

KEY EXCLUSION CRITERIA

- Uncontrolled central nervous system metastases
- Uncontrolled hypercalcemia
- Uncontrolled diabetes
- Evidence of corneal keratopathy or history of corneal transplant
- Any serious unresolved toxicities from prior therapy
- Significant cardiovascular disease
- Current or prior intestinal obstruction in the previous 3 months
- Recent thromboembolic event or bleeding disorder
- Prolongation of the QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥470 ms
- History of pneumonitis/interstitial lung disease
- History of grade ≥3 skin toxicity when receiving enfortumab vedotin
- Pregnant, breastfeeding, or plan to breastfeed during study or within 30 days of last dose of study intervention

Please visit clinicaltrials.gov for more information on this clinical trial [NCT06238479].

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Pipeline information is current through May 6, 2024.