Lilly A MEDICINE COMPANY

LY4052031

NECTIN-4 ANTIBODY-DRUG CONJUGATE

The safety and efficacy of the agents for uses under investigation have not been established. Pipeline molecules may not receive regulatory approval and become commercially available for the uses being investigated. The information provided about new molecules being studied is for scientific information exchange purposes only with no commercial intent. For more information on our pipeline, please visit lillyloxooncologypipeline.com.

This document was commissioned by Lilly Medical and is intended to be used by HCPs for medical, scientific, and educational purposes.

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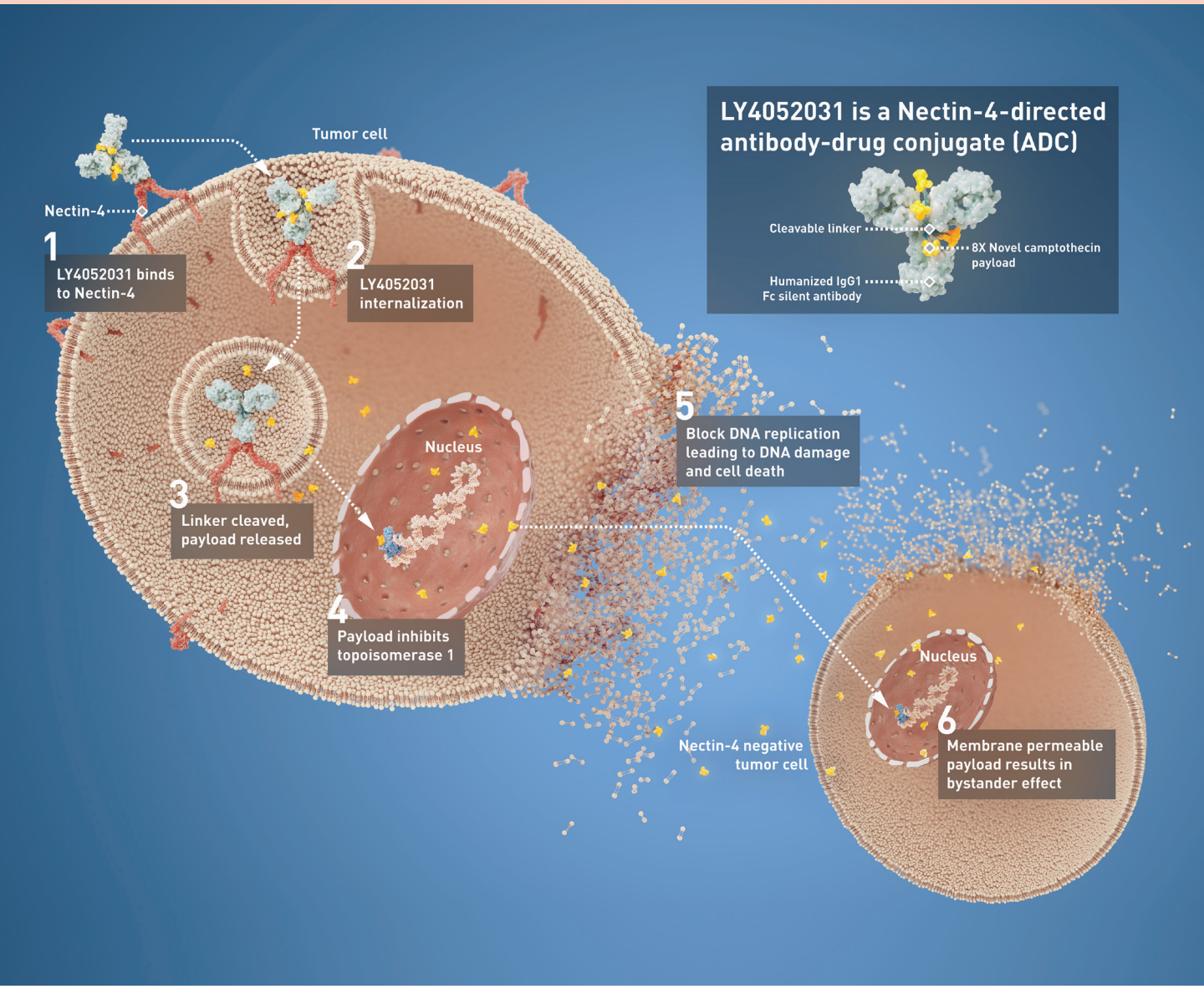

References: 1. Dumontet C, et al. *Nat Rev Drug Discov.* 2023;22(8):641–661. **2.** Challita-Eid PM, et al. *Cancer Res.* 2016;76(10):3003-3013. **3.** Heath EI, Rosenberg JE. *Nat Rev Urol.* 2021;18(2):93-103. **4.** Sagar D, et al. A next generation treatment for Nectin-4 positive cancers: preclinical characterization of LY4052031, an anti-Nectin-4 antibody, conjugated to a novel camptothecin payload. Presented at: AACR Annual Meeting; April 8, 2024; San Diego, CA.

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TARGET

Nectin-4 is a type I transmembrane protein 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 normal cells makes the protein an ideal target for tumor specific delivery of cytotoxic agents via an antibody-drug conjugate (ADC).[1]

MOLECULE

LY4052031 is a next-generation anti-Nectin-4 targeting ADC. It is comprised of a human IgG1 Fc-silent monoclonal Nectin-4 antibody linked to a novel camptothecin (topoisomerase I inhibitor) payload, via a cleavable linker with a homogeneous drug-antibody ratio (DAR) of 8:1. In preclinical in vivo models, LY4052031 has shown antitumor activity across a range of Nectin-4 expression levels, including a Nectin-4 MMAE ADC-resistant model.[4]

CLINICAL DEVELOPMENT

LY4052031 is being investigated in a global open-label, multicenter, phase 1a/1b study in patients with advanced or metastatic urothelial carcinoma and other 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 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. **4.** Sagar D, et al. A next generation treatment for Nectin-4 positive cancers: preclinical characterization of LY4052031, an anti-Nectin-4 antibody, conjugated to a novel camptothecin payload. Presented at: AACR Annual Meeting; April 8, 2024; San Diego, CA.

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NEXUS-01

A Phase 1a/1b Study of LY4052031,* an Antibody-Drug Conjugate Targeting Nectin-4, in Participants With Advanced or Metastatic Urothelial Carcinoma or Other Solid Tumors†

Phase 1a

Dose escalation:
Cohort A1 (urothelial carcinoma and other select solid tumors‡)

↓

Primary endpoint: Dose-limiting toxicities

Dose optimization:
Cohort A2 (urothelial carcinoma)

↓

Primary endpoint: Recommended phase 2 dose/Optimal dose

Phase 1b

Dose expansion:
Cohort B1 (enfortumab vedotin–naïve urothelial carcinoma)

Cohort B2 (enfortumab vedotin–experienced urothelial carcinoma)

Cohort C (non-urothelial carcinoma‡)

↓

Primary endpoint: Overall response rate per RECIST v1.1

* LY4052031 is administered intravenously as monotherapy.
† This clinical trial is being conducted globally.
‡ 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.

Please visit clinicaltrials.gov for more information on this clinical trial [NCT06465069].

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KEY INCLUSION CRITERIA

- Prior systemic therapy criteria:
  - Cohorts A1 and C1: 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: 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 nonmeasurable disease as defined by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1)
  - Cohorts A2, B1, B2, and C1: 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 deemed safe and allowed per country-specific regulations

KEY EXCLUSION CRITERIA

- Known or suspected uncontrolled central nervous system metastases
- Uncontrolled hypercalcemia
- Uncontrolled diabetes
- Evidence of corneal keratopathy or keratitis, and 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 [NCT06465069].

Pipeline information is current through July 2024.