ADC Therapeutics
Pipeline and Expanded Platforms

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● Hematology franchise ● Solid tumor franchise

Introduction to ADC Therapeutics and Advancing Next-Generation ADCs in Hematologic Cancers and Solid Tumors

ADC™ THERAPEUTICS
Innovating Science. Inspiring Hope.

OUR COMPANY

ADC Therapeutics is a clinical-stage oncology biotechnology company leading the development and commercialization of next-generation antibody-drug conjugates (ADCs) with highly potent and targeted pyrrolobenzodiazepine (PBD) dimer technology.

OUR MISSION

To confront cancer with the full potential of our science to bring unique, targeted therapies and hope to patients and their families.

OUR VISION

To transform what patients and their families can expect from cancer therapy.

OUR VALUES

Patients

Patients and their families are at the core of everything we do; they inspire our scientific creativity and innovation.

Character

We are open, honest, trustworthy, and respectful in our words and actions.

Urgency

We operate with a sense of urgency in all that we do.

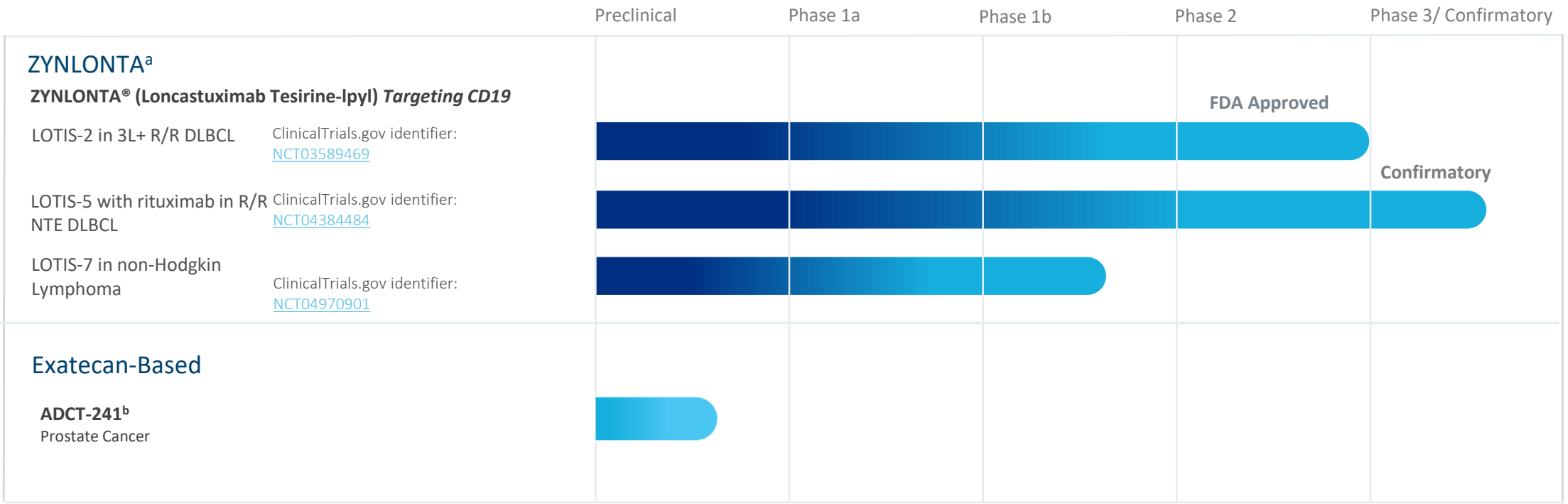
People

ADCT encourages individuals to continually learn and grow so that everyone can work at their full potential.

Head Office
Lausanne,
Switzerland

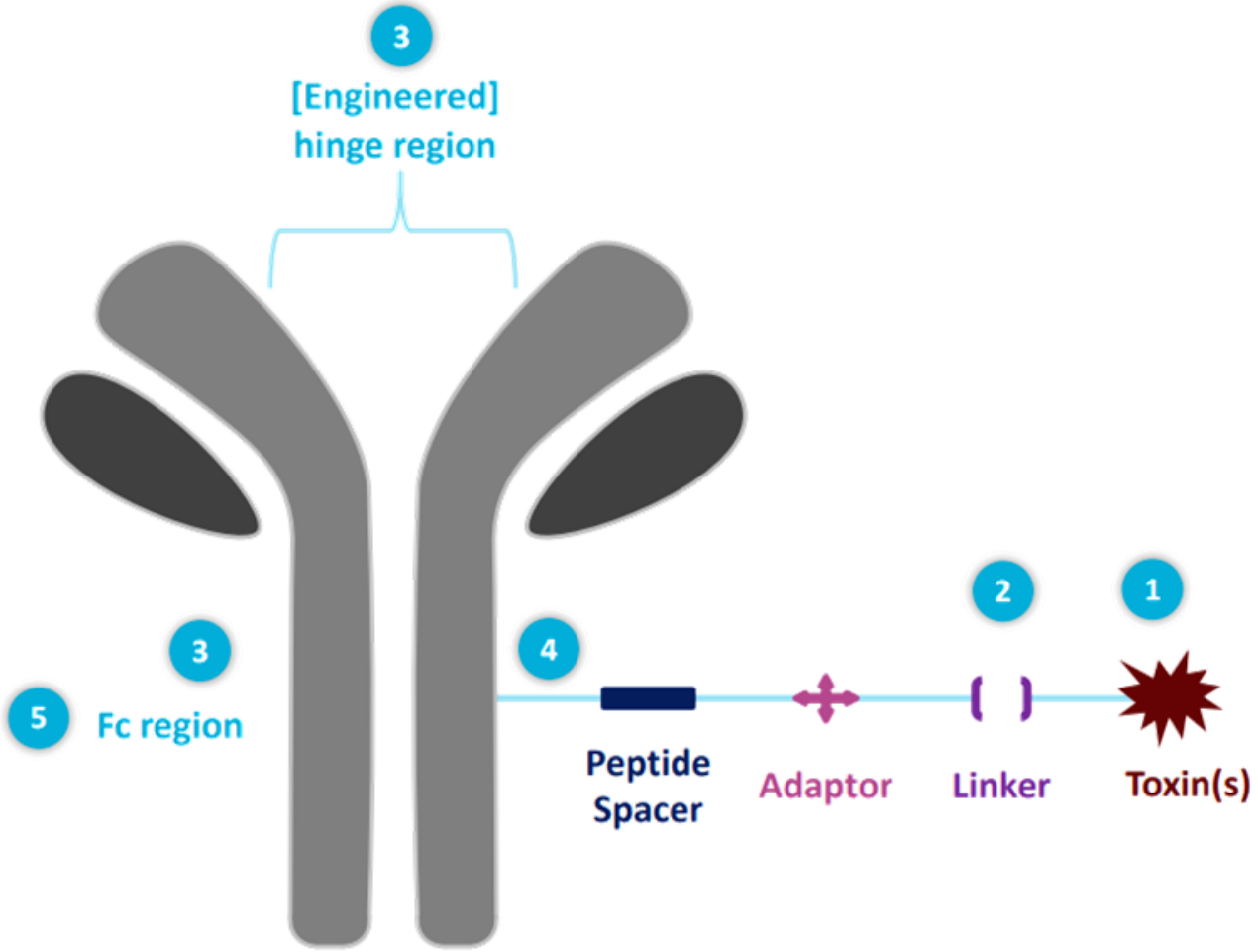
Clinical, Commercial, and US Operations
New Jersey, USA

ADCT Pipeline



[a]In addition to the clinical trials listed here, the LOTIS-10 clinical trial will investigate Lonca in adult patients with R/R DLBCL or HGBCL and moderate and severe hepatic impairment; this trial is a regulatory requirement from the FDA. LOTIS-10 is currently enrolling patients. [b]IND-enabling

Developing New ADC Platforms



ADC Platform Optionality

1 Toxin

- ◯ Exatecan
- ◯ DNA damaging agents
- ◯ Immunomodulators
- ◯ PBD
- ◯ Dual Payloads

2 Linker

- ◯ Cleavable
- ◯ Non-cleavable
- ◯ Reducible

3 Drug to Antibody Ratio

- ◯ DAR 2 / 4 / 6 / 8: [engineered] hinge region
- ◯ DAR 2 / 4: Fc region

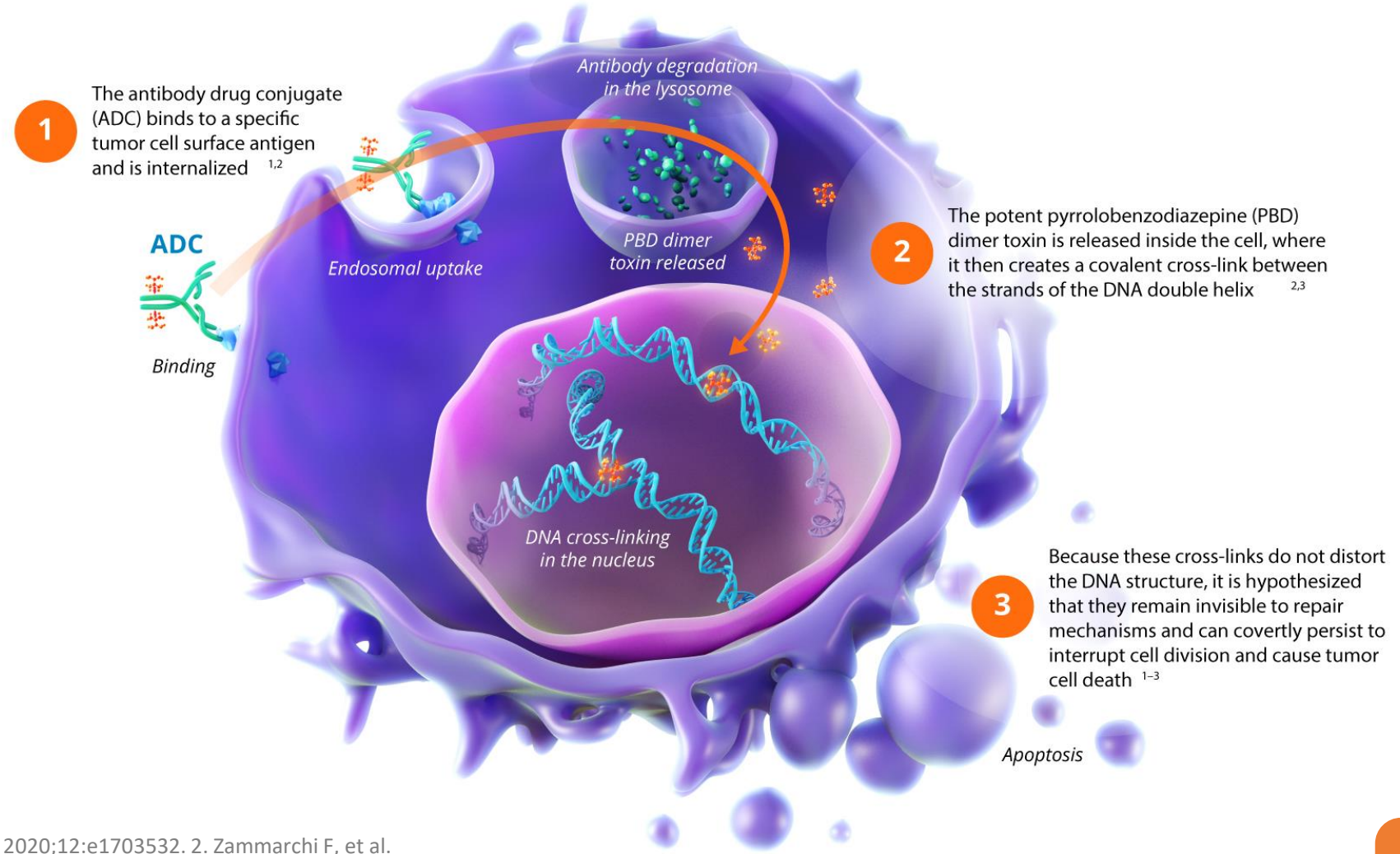
4 Conjugation chemistry

- ◯ Amino acid modification
- ◯ Glycan-remodeling
- ◯ Thiomab
- ◯ Hinge cysteine-conjugation

5 Fc receptor silencing

- ◯ Yes
- ◯ No

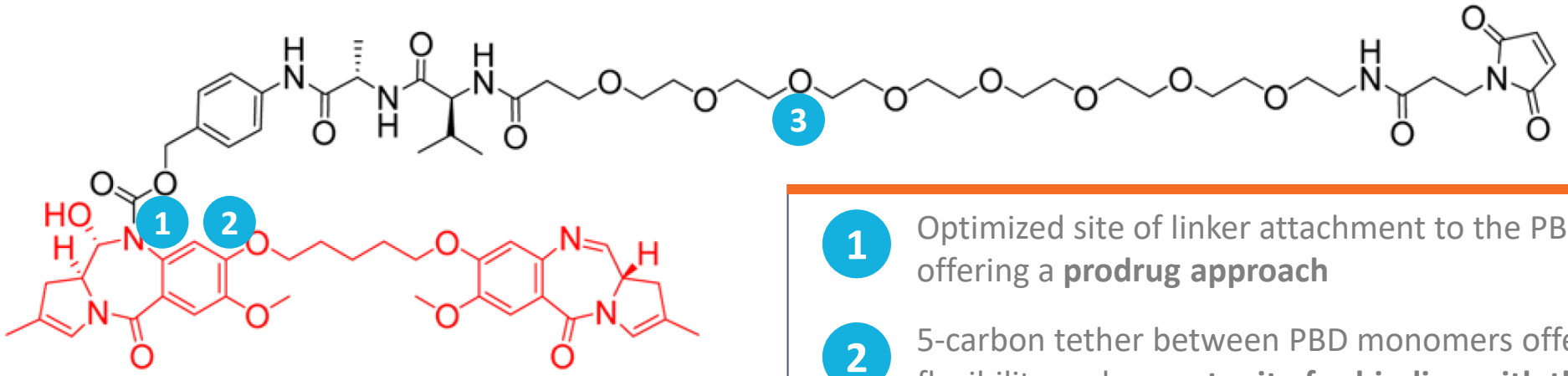
Mechanism of Action and Properties of PBD-based ADCs



1. Kaplon H, et al. *mAbs*. 2020;12:e1703532. 2. Zammarchi F, et al. *Blood*. 2018;131:1094–1105. 3. Hartley JA, et al. *Sci Rep*. 2018;8:10479.

Next-Generation Technology Optimizes Linker and Payload Characteristics

- **Tesirine**, which comprises the **PBD dimer SG3199** plus all linker components, was designed to combine potent, antitumor activity with enhanced physicochemical properties



SG3249, Tesirine, Payload (drug-linker)
clogD = 2.11

1. Optimized site of linker attachment to the PBD dimer, offering a **prodrug approach**
2. 5-carbon tether between PBD monomers offers flexibility and **opportunity for binding with the minor groove** within the DNA helix
3. Long PEG spacer has **lower hydrophobicity**, contributing to low aggregation

Tiberghien AC *et al*. *ACS Med Chem Lett.* 2016;7(11):983–987.

Loncastuximab Tesirine (ADCT-402)

Hematology Franchise

ADC™ THERAPEUTICS
Innovating Science. Inspiring Hope.

Indication and Usage

Loncastuximab tesirine (Lonca) is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low-grade lymphoma, and high-grade B-cell lymphoma.

This indication is approved under accelerated approval based on the overall response rate. Continued approval for this indication may be contingent upon the verification and description of the clinical benefit in a confirmatory trial(s).

Zynlonta (loncastuximab tesirine-lpyl) prescribing information. Murray Hill, NJ; ADC Therapeutics; October 2022.

Loncastuximab Tesirine (ADCT-402) Clinical Development

LOTIS-7 — B-NHL

- Phase 1b trial of Lonca and Glofitamab in 2L+ DLBCL
- Trial is currently enrolling

LOTIS-5 — 2L DLBCL ASCT ineligible

- Phase 3 confirmatory trial in combination with rituximab
- Completed enrolment
- Intended to support a supplemental BLA in 2L R/R DLBCL patients who are not eligible for ASCT

LOTIS-2 — 3L+ DLBCL

- Pivotal Phase 2 monotherapy trial in 3L+ DLBCL, basis of FDA accelerated approval
- Supports broad use in the 3L+ DLBCL patient population

1. Zynlonta (loncastuximab tesirine-lpyl) prescribing information. Murray Hill, NJ; ADC Therapeutics; October 2022.
2. Caimi P, et al. *Lancet Oncol.* 2021;22(6):790-800. 3. https://www.adctherapeutics.com/our-pipeline/. Accessed May 6, 2024.
4. https://clinicaltrials.gov/ct2/show/NCT04970901. Accessed May 9, 2024.
5. https://clinicaltrials.gov/ct2/show/NCT04384484. Accessed May 9, 2024.
6. https://clinicaltrials.gov/ct2/show/NCT05660395. Accessed May 9, 2024.

LOTIS-5 Trial Rationale

Lonca in R/R DLBCL

- Lonca is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma, including DLBCL, after ≥2 lines of systemic therapy[1]

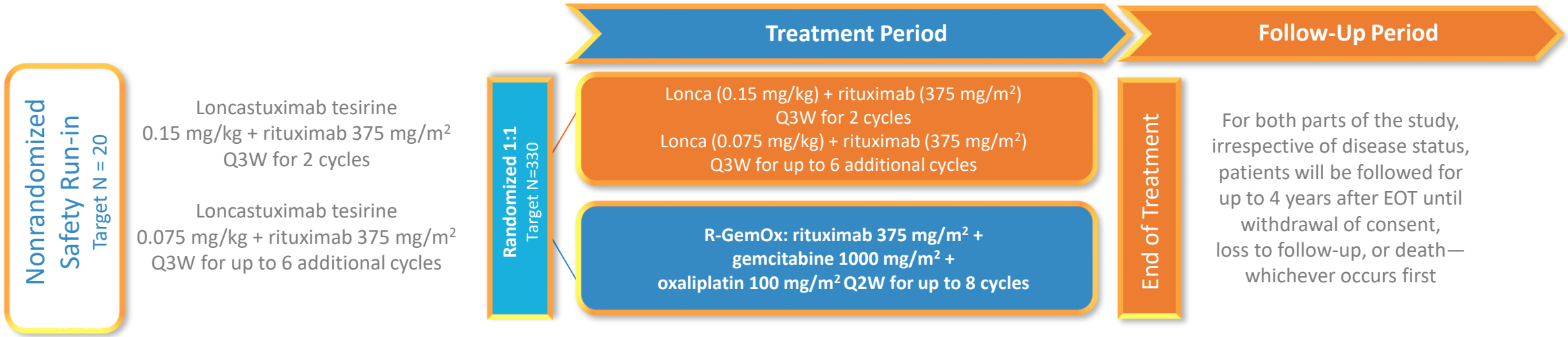
Lonca combined with rituximab

- Preclinical data have demonstrated durable synergistic activity between Lonca and rituximab-induced cytotoxicity[2]
- Rituximab, an anti-CD20 monoclonal antibody, is part of standard frontline and subsequent DLBCL immunotherapy[3]

1. Zynlonta (loncastuximab tesirine-lpyl) prescribing information. Murray Hill, NJ; ADC Therapeutics; October 2022.
2. Ryan MC, et al. *Blood*. 2017; 130(18):2018-2026. 3. Sehn LH and Salles G. *N Engl J Med*. 2021;38:842-858.

LOTIS-5 Trial Design

Phase 3 trial of Lonca in combination with rituximab[1,2]



PRIMARY ENDPOINTS

- PFS[a] by independent central review

SECONDARY ENDPOINTS

- OS, ORR, CRR, DOR
- Frequency and severity of AEs and laboratory parameters
- PK parameters, for Lonca total Ab, PBD-conjugated Ab, and free SG3199
- ADA titers to Lonca
- Changes in PROs from baseline

KEY INCLUSION/EXCLUSION CRITERIA

- Adults with a pathologic diagnosis of R/R DLBCL (including DLBCL transformed from indolent lymphoma) or HGBCL, with *MYC* and *BCL2* and/or *BCL6* rearrangements
- R/R disease following ≥1 multi-agent systemic treatment regimen
- Measurable disease (2014 Lugano classification)
- Not a candidate for SCT based on performance status, advanced age, and/or significant medical comorbidities (as considered by the investigator)
- If patient had received previous CD19 directed therapy, biopsy proven CD19 expression required
- ECOG performance status of 0-2
- Excludes previous treatment with Lonca or R-GemOx

[a]Defined as time between randomization and the first documentation of recurrence or progression, or death from any cause.

1. Kwiatek M, et al. Poster presented at: SOHO 2023. September 6-9, 2023. Houston, TX, USA.
2. https://clinicaltrials.gov/ct2/show/NCT04384484. Accessed May 6, 2024.

LOTIS-7 Trial Rationale

Lonca in R/R B-NHL

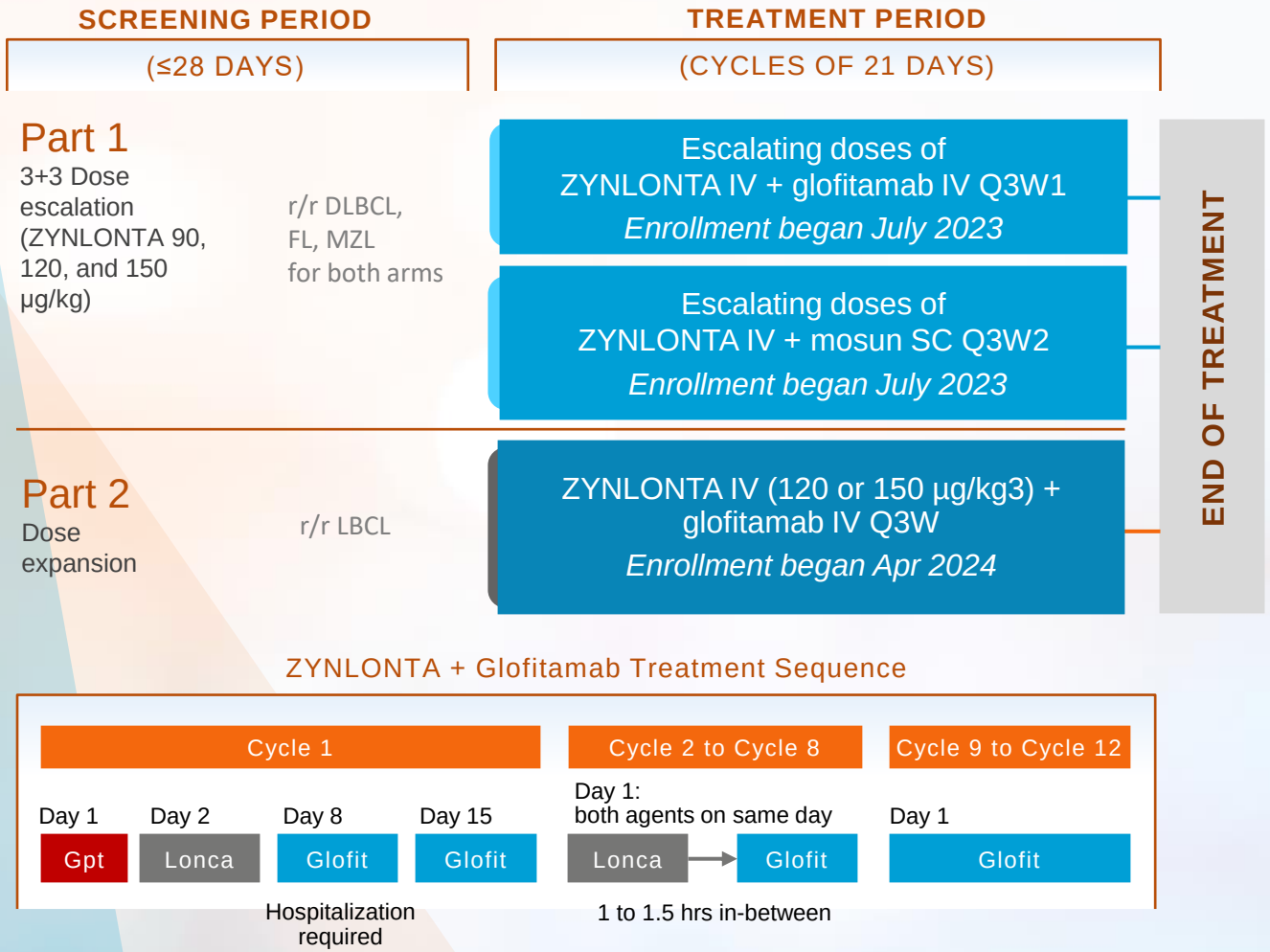
- Lonca is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma, including DLBCL, after ≥2 lines of systemic therapy[1]

Lonca combined with glofitamab or mosunetuzumab

- Glofitamab targets different B-cell surface antigens (CD20) from Lonca (CD19) and leverage different mechanisms of action, with different safety profiles
- Combining agents with these complimentary mechanisms of action is hypothesized to have additive or possibly synergistic efficacy along with maintaining a manageable safety profile[2]

1. Zynlonta (loncastuximab tesirine-lpyl) prescribing information. Murray Hill, NJ; ADC Therapeutics; October 2022.
2. Li Y, et al. Poster presented at: AACR 2024. April 5-10, 2024; San Diego, CA USA.

LOTIS-7: PHASE 1B TRIAL OF ZYNLONTA IN COMBINATION WITH GLOFITAMAB



Study Population

- Relapsed or Refractory B-NHL patients, ECOG PS 0 – 2, and have received:
  - Part 1: ≥2 systemic treatment regimens
  - Part 2: ≥1 systemic treatment regimens
- Prior autologous SCT or CAR-T (>100 days) is allowed
- Measurable disease per 2014 Lugano Classification and based on investigator assessment
- Excludes patients with clinically significant 3rd space fluid accumulation

Endpoints

- Primary: Safety and tolerability; MTD and/or RD
- Secondary:
  - Efficacy: ORR, DOR, CRR, PFS, RFS, OS
  - Pharmacokinetics and Immunogenicity

Trial Status

- Dose escalation complete with no DLTs
- Dose expansion ongoing in ZYNLONTA (150 µg/kg) + glofitamab with target of ~100 patients to be enrolled in 1H2026

Obinutuzumab pretreatment 1000mg on C1D1; ZYNLONTA administered on C1D2; administration of 1st and 2nd step-up dose(s) of IV glofitamab (2.5mg on C1D8 & 10mg on C1D15); ZYNLONTA plus glofitamab 30mg on C2D1 and beyond (reduce ZYNLONTA to 75 ug/kg at C3 if starting dose is 120 ug/kg or higher)

ZYNLONTA plus subcutaneous mosunetuzumab 1st step-up dose of 5 mg on C1D1, followed by mosunetuzumab 2nd step-up & target dose of 45 mg for C1D8 & C1D15; ZYNLONTA plus 45mg of subcutaneous mosunetuzumab on C2D1 and beyond (reduce ZYNLONTA to 75 µg/kg at C3 if starting dose is 120 ug/kg or higher)

ZYNLONTA dose reduced to 75 µg/kg at C3

LOTIS-10 Trial Rationale

Lonca in R/R DLBCL

- Lonca is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma, including DLBCL, after ≥2 lines of systemic therapy[1]

Lonca in patients with hepatic impairment

- Lonca has not been studied in patients with moderate or severe hepatic impairment[1]
- Optimal dose adjustment of Lonca for patients with baseline moderate-to-severe hepatic impairment is not clear[2]

1. Zynlonta (loncastuximab tesirine-lpyl) prescribing information. Murray Hill, NJ; ADC Therapeutics; October 2022.
2. Baek GT, et al. *Cancer*. 2023; 129(15):2279-2283.

LOTIS-10 Trial Design

Phase 1b trial of Lonca in R/R DLBCL or HGBCL with moderate and severe hepatic impairment[1]

Screening Period (≤28 d) → Treatment Period (cycles of 21 days)

Arm A: Normal Hepatic Function

Lonca 0.15 mg/kg IV Q3W x 2 cycles, then Lonca 0.075 mg/kg Q3W for subsequent cycles[a]

Arm B: Moderate Hepatic Impairment

Lonca IV in standard 3+3 dose-escalation design:

Initial dose: Lonca 0.09 mg/kg IV Q3W x 2 cycles, then Lonca 0.045 mg/kg Q3W for subsequent cycles[a]

Max dose: Lonca 0.15 mg/kg Q3W

Arm C: Severe Hepatic Impairment

Lonca IV in standard 3+3 dose-escalation design:

Initial dose: Lonca 0.09 mg/kg IV Q3W x 2 cycles, then Lonca 0.045 mg/kg Q3W for subsequent cycles[a]

Max dose: Lonca 0.15 mg/kg Q3W

→ End of Treatment

PRIMARY ENDPOINTS

- Number of participants with moderate or severe hepatic impairment who experience DLT

SECONDARY ENDPOINTS

- Efficacy: ORR, DOR, CR, PFS, RFS, OS
- Pharmacokinetics: T_{max}, C_{max}, CL, AI, AUC, $T_{1/2}$
- AE frequency, and AEs leading to dose delay, dose interruption, and dose reduction
- Clinically significant changes from baseline: safety lab values, vital signs, ECOG, and ECG
- Immunogenicity: ADA titers to Lonca

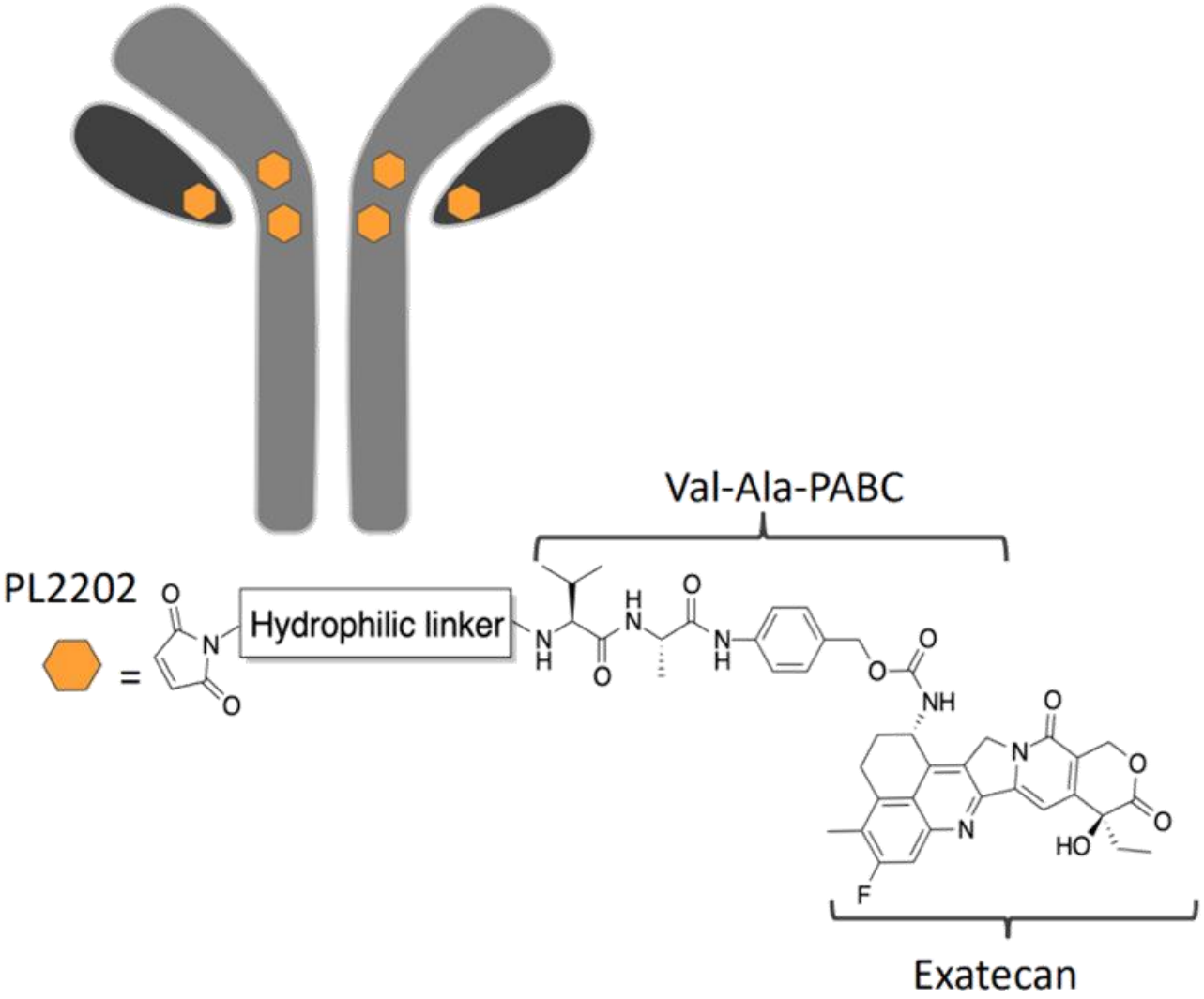
KEY INCLUSION/EXCLUSION CRITERIA

- Adult patients with pathologic diagnosis of R/R disease DLBCL (2016 WHO classification) who have received ≥1 systemic treatment regimens
- ECOG performance status of 0 to 2 for participants with normal hepatic function; ECOG 0 to 3 for participants with moderate or severe hepatic involvement
- Arm A Normal hepatic function: bilirubin and AST ≤ ULN
- Arm B Moderate hepatic impairment: bilirubin > 1.5 × to 3 × ULN (any AST)
- Arm C Severe hepatic impairment: bilirubin > 3 × ULN (any AST)
- Measurable disease as defined by the 2014 Lugano Classification
- Excludes patients with HIV, HBV, or HCV
- Excludes previous treatment with Lonca or stem cell transplant within 60 days prior to start of study drug

[a]Participants who have a toxicity meeting the criteria for dose reduction will have subsequent doses reduced by 50%. If the toxicity recurs, subsequent doses must be reduced by an additional 50%. A maximum of 2 dose reductions are allowed. Participants who have a toxicity meeting the criteria for dose reduction following Cycle 2 will receive the protocol-specified dose of 50% of initiate dose for Cycle 3, i.e., they will not have an additional dose reduction for Cycle 3.

https://clinicaltrials.gov/ct2/show/NCT05660395. Accessed May 6, 2024.

A Novel Exatecan-based ADC Platform[1]



Key Advantages of the Exatecan Platform

- **Superior therapeutic index** vs Dxd and other approved Topo1 inhibitors[2]
  - Preclinical data in cynomolgus monkey supports **strategy to dose ADC > 5 mg/kg in patients**
  - Enables **combinability** with standard of care
- **No signs of interstitial lung disease (ILD)**, a severe adverse event associated with Dxd[2]
- **Increased bystander effect and potency** vs Dxd[2]
- Not a PgP substrate; **enhanced intracellular presence**
- **Novel hydrophilic, highly stable, protease cleavable linker**
  - Enables traceless release of exatecan
  - Offsets the hydrophobicity of exatecan

1. ADC Therapeutics. 2024 Research Investor Event. Presented April 9, 2024. 2. Data on file. ADC Therapeutics SA.

ADCT-241 (PSMA-PL2202)

Solid Tumors Franchise

THERAPEUTICS
Innovating Science. Inspiring Hope.

ADCT-241 Targeting PSMA

PSMA Target

PSMA:

- Is a type II membrane glycoprotein with enzymatic activity that facilitates neuronal glutamate synthesis in the brain and mediates folate absorption in the intestine[1]
- Has a poorly defined physiological role in prostate cells[1]
- May promote cancer progression by redirecting cell survival signaling to the pro-survival pathway mediated by PI3K-AKT signaling[1]

Tumor Expression

Expression of PSMA in mCRPC[2]

Key Takeaways

- PSMA shows limited expression on normal prostate tissue and healthy tissue in general
- PSMA is a clinically validated target

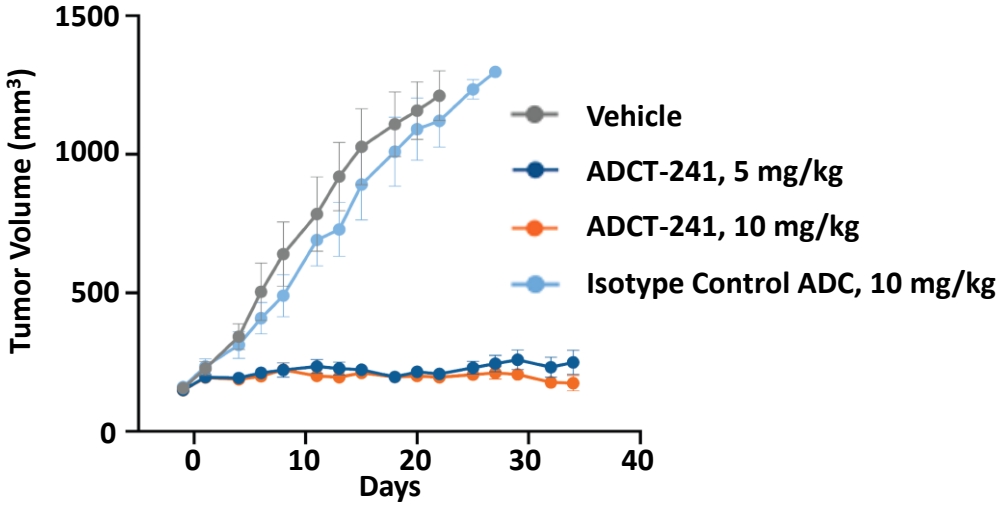
PSMA-ADC is an investigational agent, and its safety and efficacy have not yet been established.

1. Niaz MO, et al. *Cureus*. 2020;12(2):e7147. 2. Calais J and Czernin J. *J Nucl Med.* 2021;62(11)1489-1491.

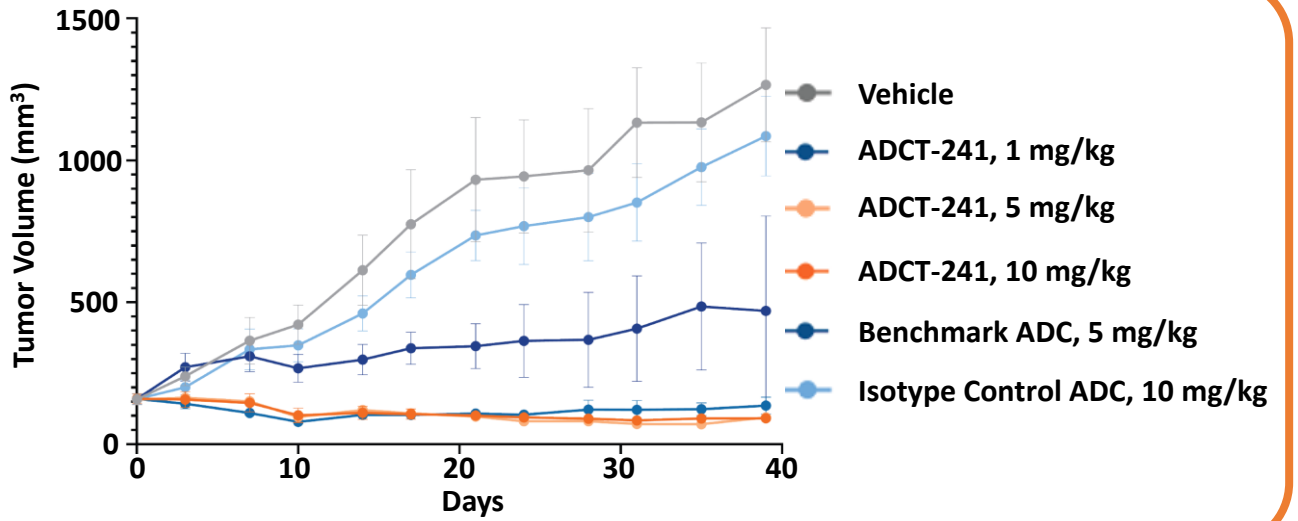
ADCT-241 Preclinical Studies

In vitro cytoxicity	LNCaP[a]	C4-2[a]	CWRRv1[a]	PC3[a]
PSMA status	****	***	*	-
ADCT-241 EC_{50} (nM)	0.495	1.03	37.0	186
Isotype Control ADC EC_{50} (nM)	54.3	27.3	113.0	N/A

In Vivo Antitumor Activity



LNCaP xenograft model[b]



C4-2 xenograft model[b]

ADCT-241 was well tolerated in rats and cynomolgus monkeys and demonstrated potent and specific antitumor activity both *in vitro* and *in vivo*

[a]Model of prostate cancer. [b]ADCT-241 and isotype control ADC were administered as single IV dose (day 0) in treatment groups of 10 mice. Vehicle control group was also included.
Leatherdale B, et al. Poster presented at: AACR 2025. April 25-30, 2024. Chicago, IL, USA.