

ADC Therapeutics Pipeline and Expanded Platforms



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ADCT-402

Exatecan
Platform

PSMA-ADC



Table of Contents

Topic	Slide
Introduction to ADC Therapeutics	4
Advancing Next-Generation PBD-Based ADCs in Hematologic Cancers and Solid Tumors	
Loncastuximab Tesirine (ADCT-402) ●	11
PSMA-ADC ●	21



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





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

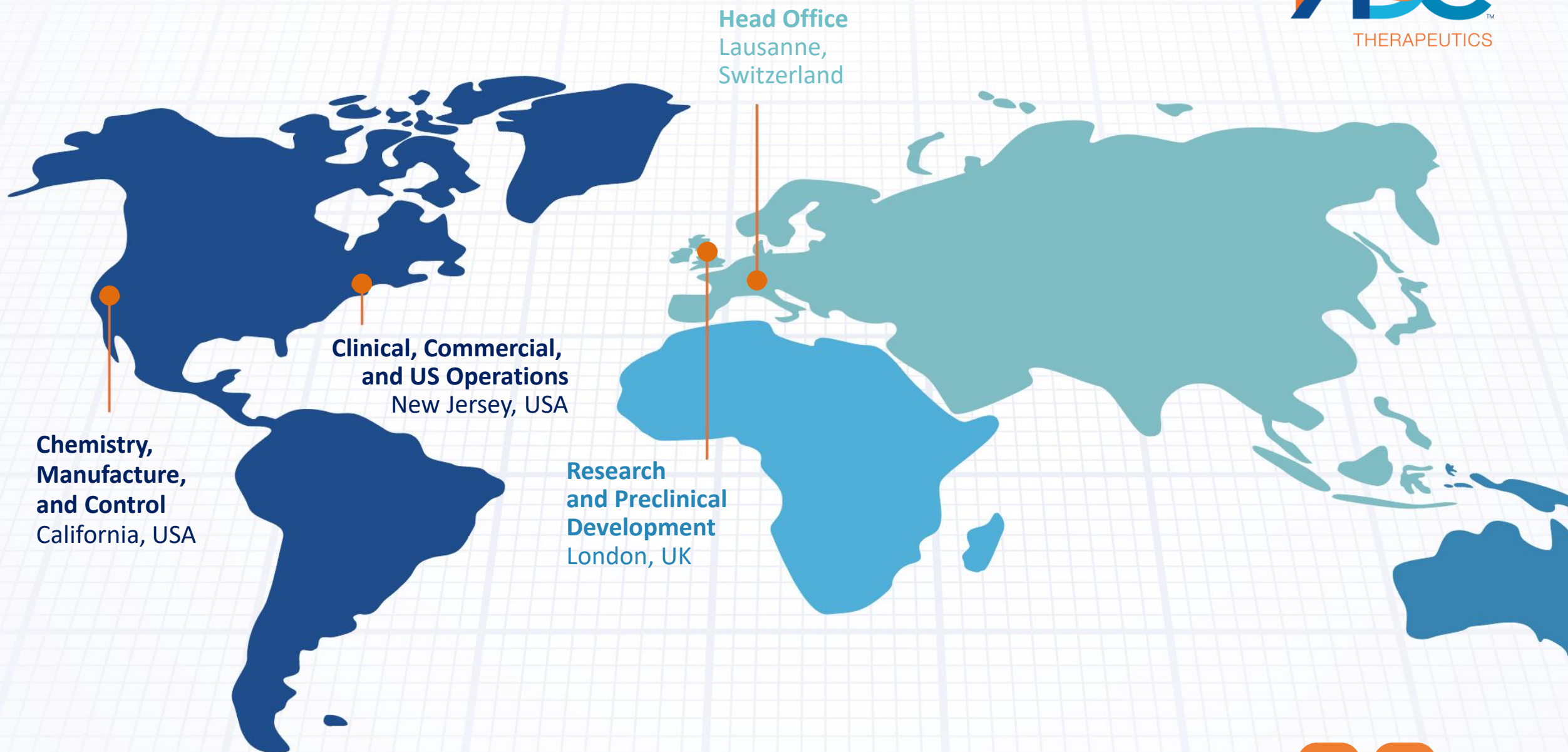
ADCT encourages individuals to continually learn and grow so that everyone can work at their full potential.



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Head Office
Lausanne,
Switzerland

**Clinical, Commercial,
and US Operations**
New Jersey, USA

**Research
and Preclinical
Development**
London, UK

**Chemistry,
Manufacture,
and Control**
California, USA



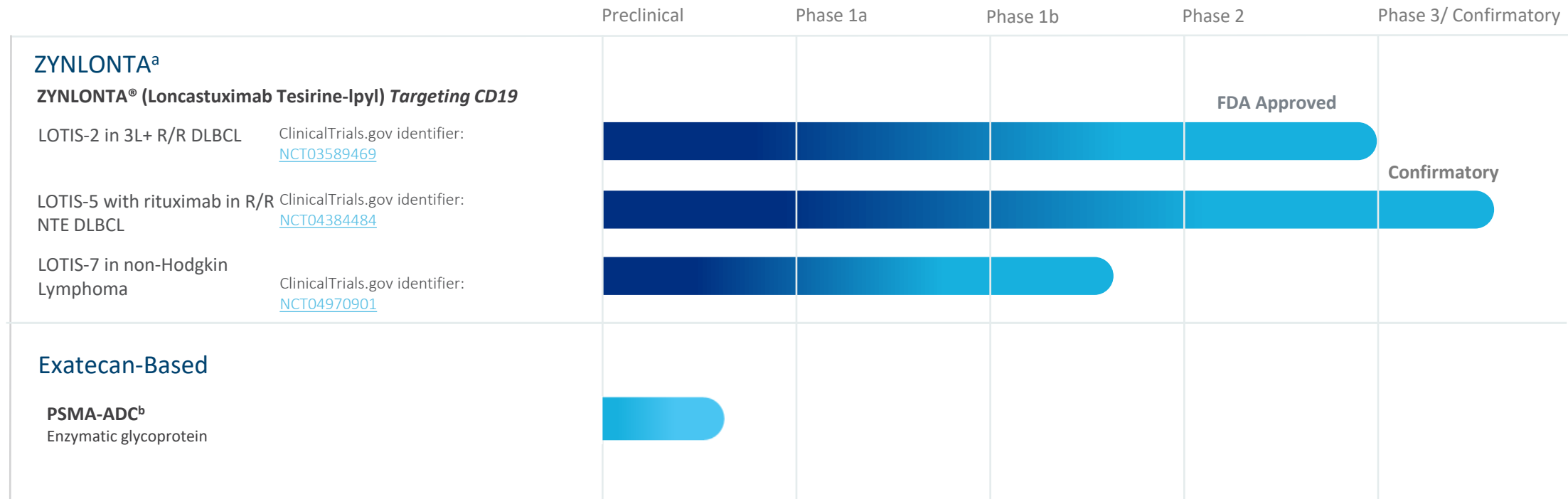
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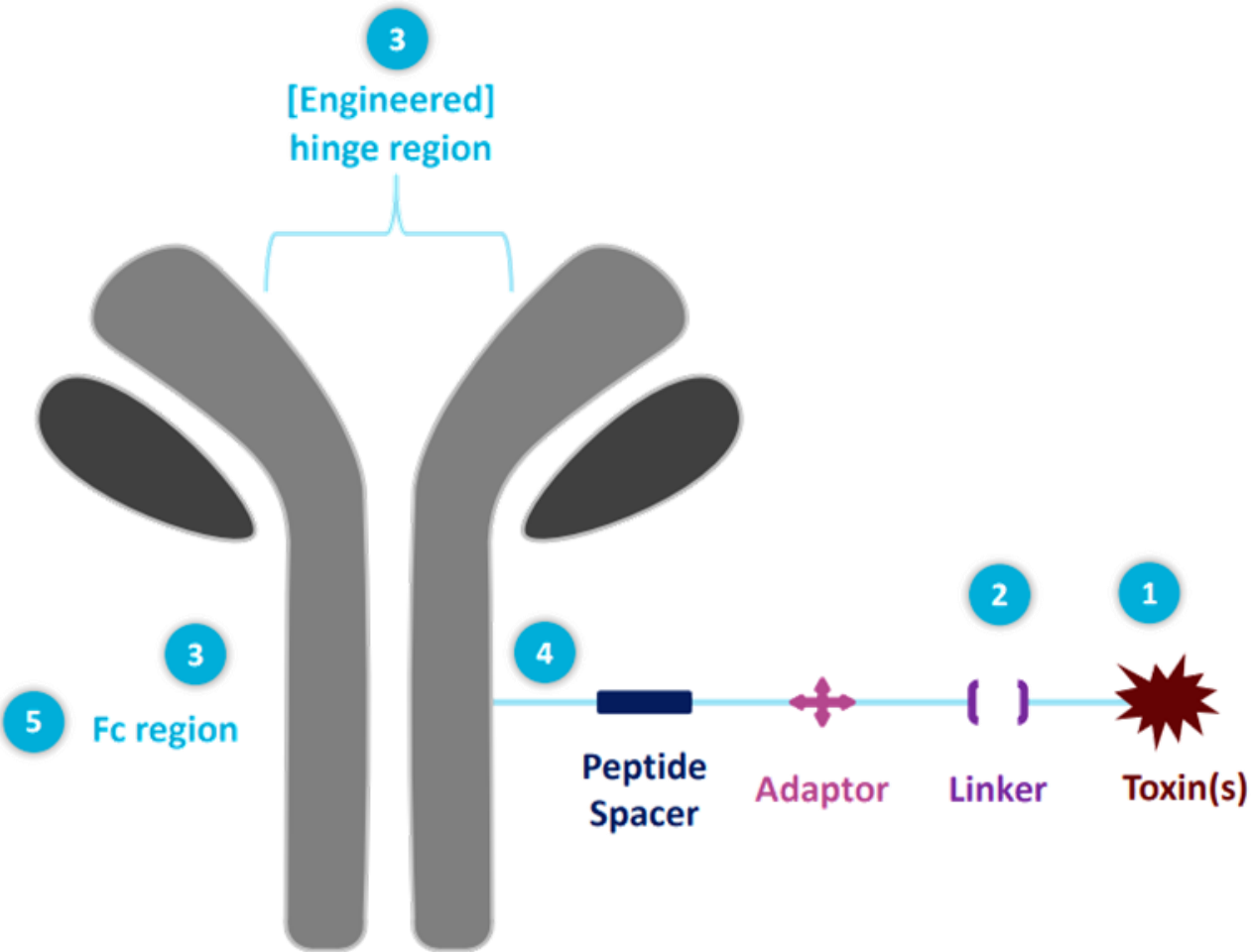
ADCT Pipeline



^aIn 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. ^bIND-enabling



Developing New ADC Platforms



ADC Platform Optionality

1 Toxin

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

2 Linker

- ☐ Cleavable
- ☐ Reducible
- ☐ Non-cleavable

3 Drug to Antibody Ratio

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

4 Conjugation chemistry

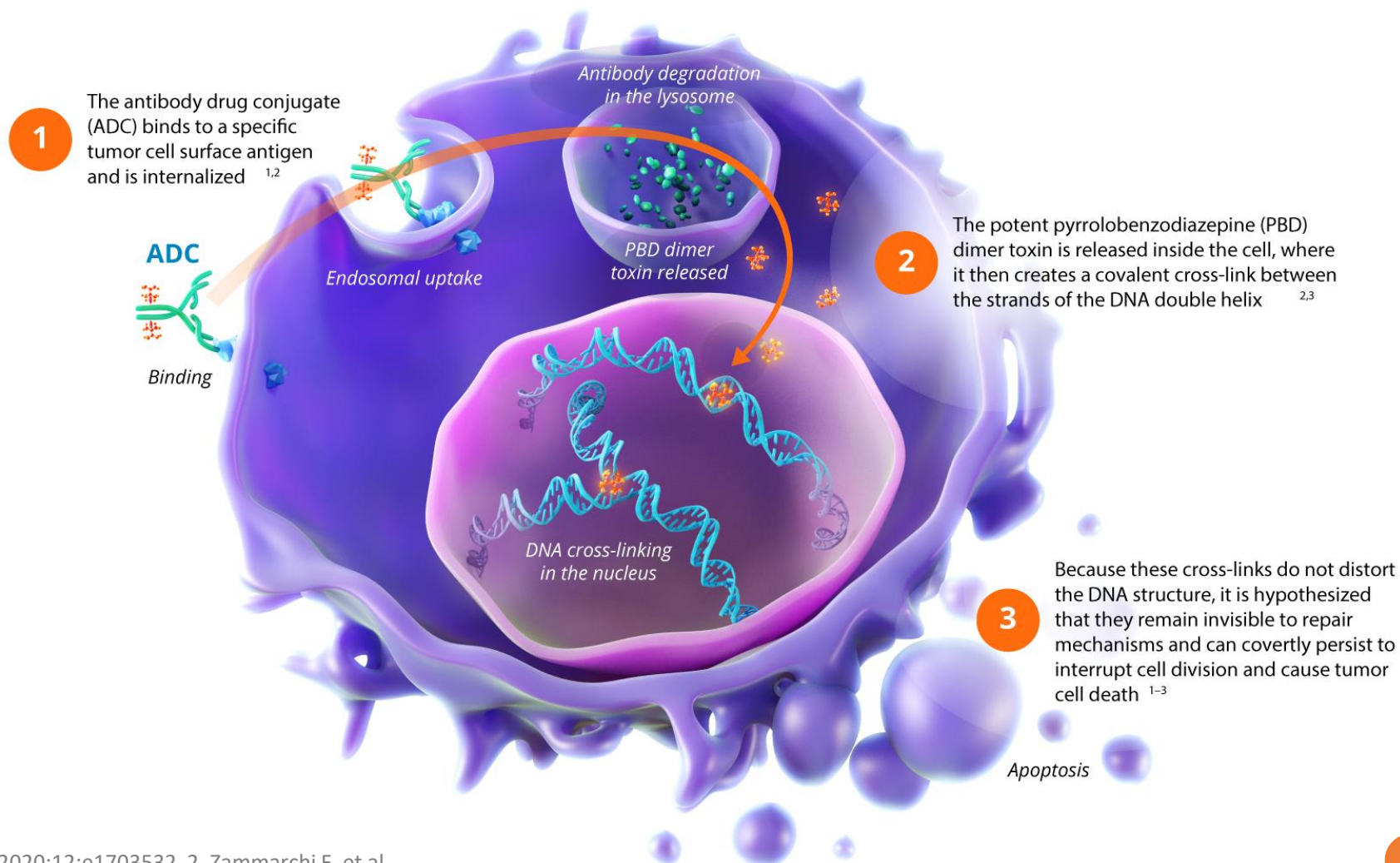
- ☐ Amino acid modification
- ☐ Thiomab
- ☐ Glycan-remodeling
- ☐ Hinge cysteine-conjugation

5 Fc receptor silencing

- ☐ Yes
- ☐ No



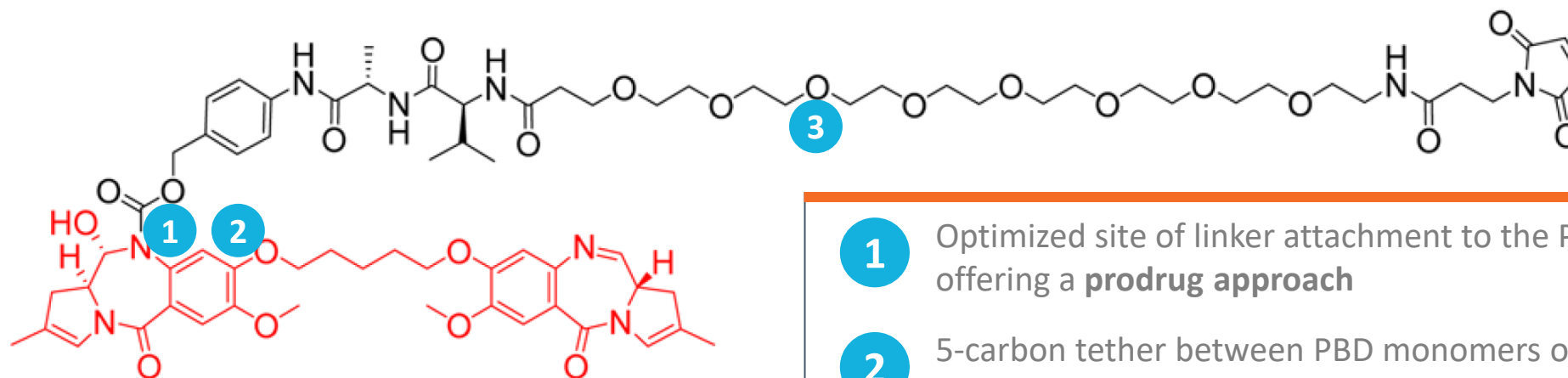
Mechanism of Action and Properties of PBD-based ADCs





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



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Loncastuximab Tesirine (ADCT-402)

Hematology Franchise





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).



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 therapy¹

Lonca combined with rituximab

- Preclinical data have demonstrated durable synergistic activity between Lonca and rituximab-induced cytotoxicity²
- Rituximab, an anti-CD20 monoclonal antibody, is part of standard frontline and subsequent DLBCL immunotherapy³

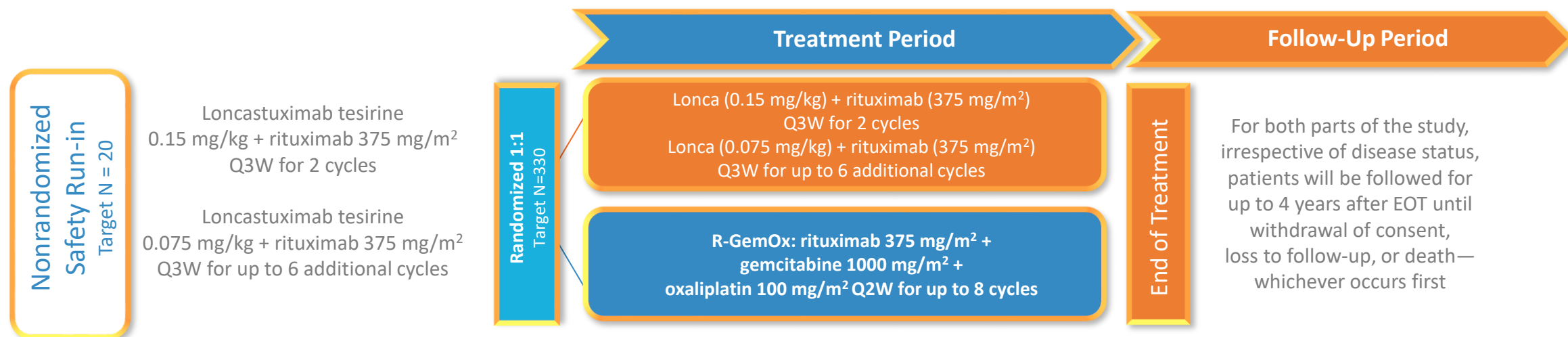
1. Zynlonta (loncastuximab tesirine-lpyl) prescribing information. Murray Hill, NJ; ADC Therapeutics; October 2022.

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

^aDefined 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 therapy¹

Lonca combined with glofitamab or mosunetuzumab

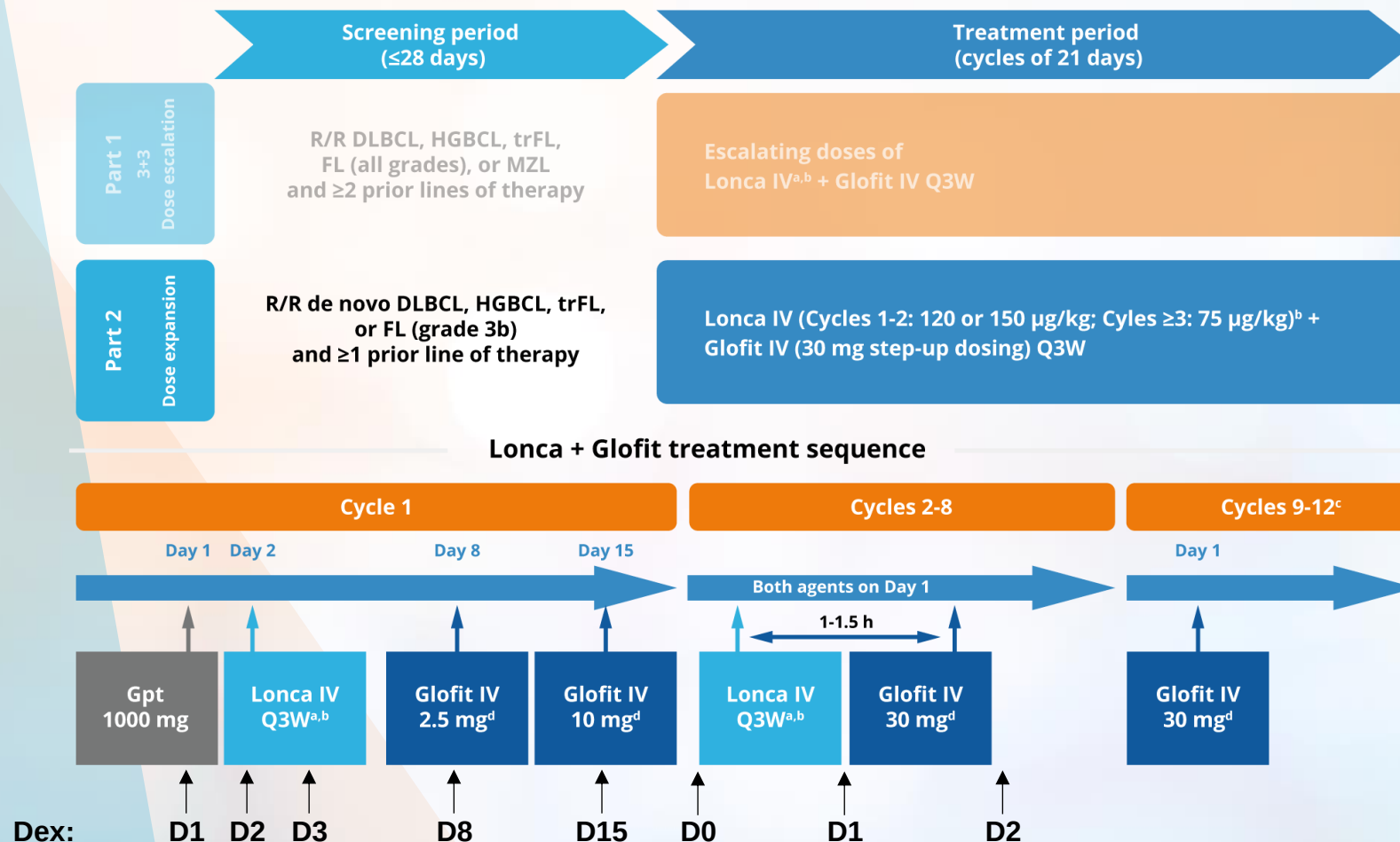
- Glofitamab and mosunetuzumab target different B-cell surface antigens (CD20) from Lonca (CD19) and leverage different mechanisms of action, with different safety profiles
- Combining agents with these complimentary mechanisms of action is hypothesized to have additive or possibly synergistic efficacy along with maintaining a manageable safety profile^{2,3}

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. 3. <https://ir.adctherapeutics.com/press-releases/press-release-details/2024/ADC-Therapeutics-Announces-Updates-on-LOTIS-7-Clinical-Trial-Evaluating-ZYNLONTA-in-Combination-with-Glofitamab-or-Mosunetuzumab-in-Patients-with-RelapsedRefractory-B-cell-Non-Hodgkin-Lymphoma/default.aspx>. Accessed May 9, 2024.



LOTIS-7 STUDY DESIGN & PATIENT POPULATION



Study population

- Patients with 3L+ R/R B-NHL (part 1) and 2L+ R/R LBCL (part 2)
- ECOG PS score of 0-2
- Prior autologous SCT (>100 days) or CAR-T therapy (>100 days) is allowed
- Measurable disease (per 2014 Lugano Classification)
- Excludes patients with clinically significant third-space fluid accumulation

Endpoints

- **Primary:** safety and tolerability; MTD and/or RDE
- **Secondary:** ORR, DOR, CR rate, PFS, RFS, and OS; PK and immunogenicity
- **Exploratory:** Glofit concentration in circulation; biomarker and PK correlations with clinical outcomes

2L+, second line or later; 3L+, third line or later; B-NHL, B-cell non-Hodgkin lymphoma; CAR-T, chimeric antigen receptor T cell; CR, complete response; CRS, cytokine release syndrome; D, day; Dex, dexamethasone; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FL, follicular lymphoma; Glofit, glofitamab; Gpt, obinutuzumab; HGBCL, high-grade B-cell lymphoma; IV, intravenous; Lonca, loncastuximab tesirine; MTD, maximum tolerated dose; MZL, marginal zone lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetic; Q3W, every 3 weeks; RDE, recommended dose for expansion; RFS, relapse-free survival; R/R, relapsed or refractory; SCT, stem cell transplant; trFL, transformed follicular lymphoma.

^aDose level 1, 90 µg/kg; dose level 2, 120 µg/kg; and dose level 3, 150 µg/kg. ^bIf the starting dose of Lonca is 120 µg/kg or 150 µg/kg, the dose will be reduced to 75 µg/kg for Cycles ≥3 per label. ^cParticipants may continue Glofit up to 12 cycles and may continue lonca up to 8 cycles (or until disease progression, unacceptable toxicity, or other discontinuation criteria, whichever occurs first). The follow-up period is for ≤2 years from the end of treatment. ^dThe first dose of Glofit on Cycle 1, Day 8 has a 24-hour mandatory hospitalization; subsequent doses require hospitalization if grade ≥2 CRS occurs.



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 therapy¹

Lonca in patients with hepatic impairment

- Lonca has not been studied in patients with moderate or severe hepatic impairment¹
- Optimal dose adjustment of Lonca for patients with baseline moderate-to-severe hepatic impairment is not clear²

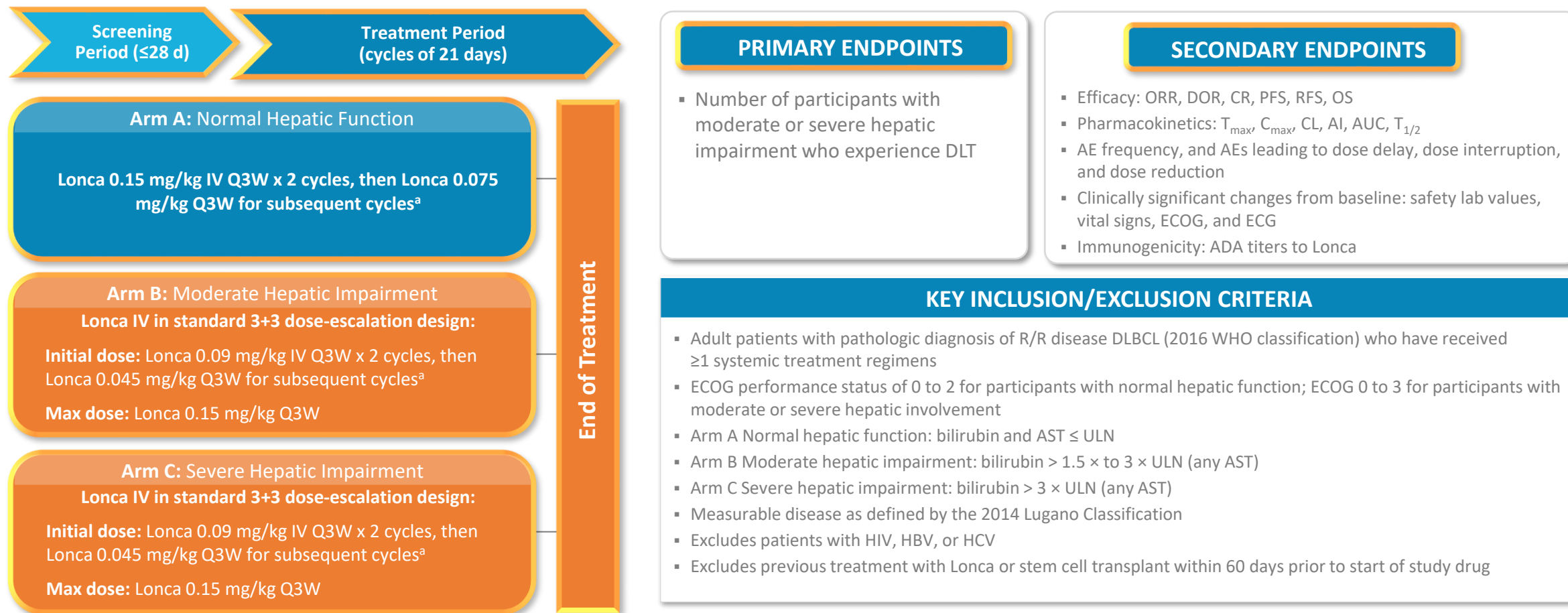
1. Zynlonta (loncastuximab tesirine-lpyl) prescribing information. Murray Hill, NJ; ADC Therapeutics; October 2022.

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 impairment¹

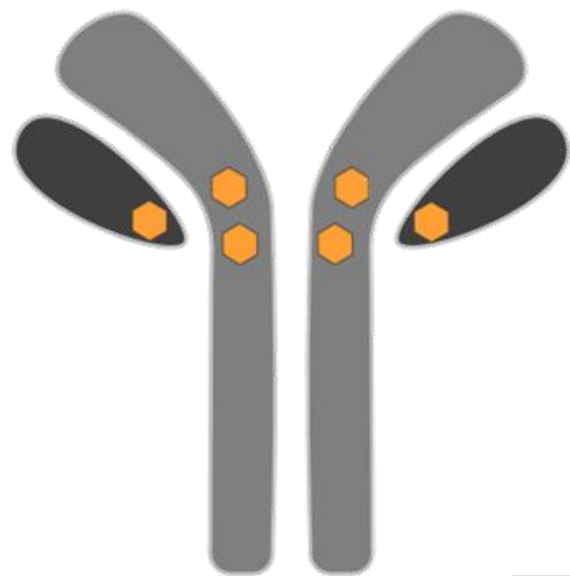


^aParticipants who have a toxicity meeting the criteria for dose reduction will have subsequent doses reduced by 50%. If the toxicity recurs, subsequent doses must be reduced by an additional 50%. A maximum of 2 dose reductions are allowed. Participants who have a toxicity meeting the criteria for dose 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.

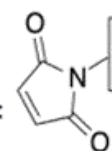
<https://clinicaltrials.gov/ct2/show/NCT05660395>. Accessed May 6, 2024.



A Novel Exatecan-based ADC Platform¹

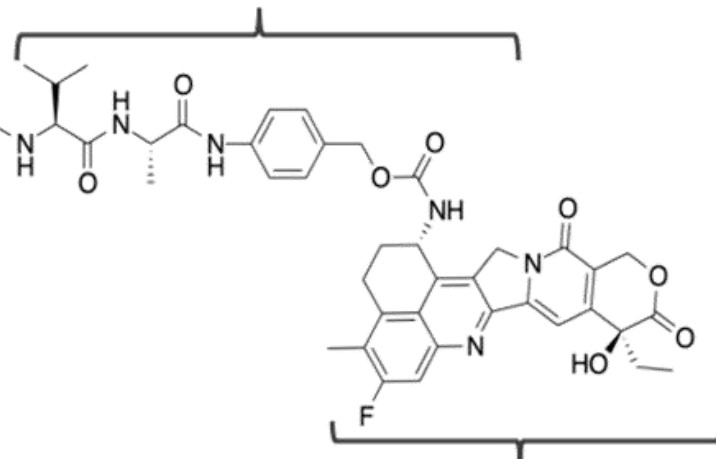


PL2202



Hydrophilic linker

Val-Ala-PABC



Exatecan

Key Advantages of the Exatecan Platform

- **Superior therapeutic index** vs Dxd and other approved Topo1 inhibitors²
 - 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 Dxd²
- **Increased bystander effect and potency** vs Dxd²
- Not a PgP substrate; **enhanced intracellular presence**
- **Novel hydrophilic, highly stable, protease cleavable linker**
 - Enables traceless release of exatecan
 - Offsets the hydrophobicity of exatecan



ADCT-402

Exatecan
Platform

PSMA-ADC

PSMA-ADC (PSMA-PL2202)

Solid Tumors Franchise





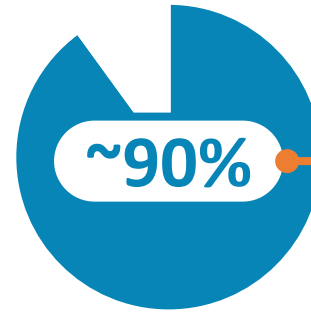
ADCT-241 Targeting PSMA

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 intestine¹
- Has a poorly defined physiological role in prostate cells¹
- May promote cancer progression by redirecting cell survival signaling to the pro-survival pathway mediated by PI3K-AKT signaling¹

Tumor Expression



Expression of PSMA in mCRPC²

Key Takeaways

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

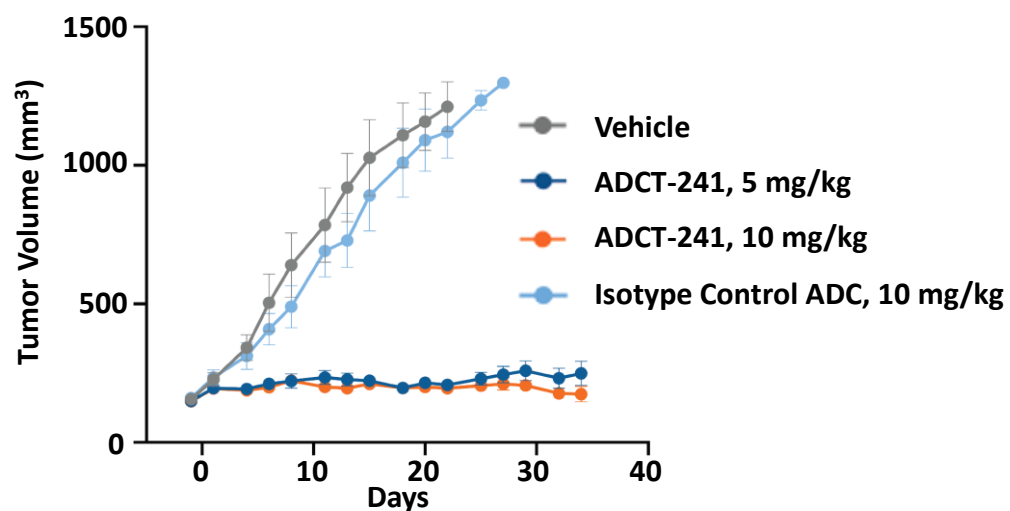
PSMA-ADC is an investigational agent, and its safety and efficacy have not yet been established.



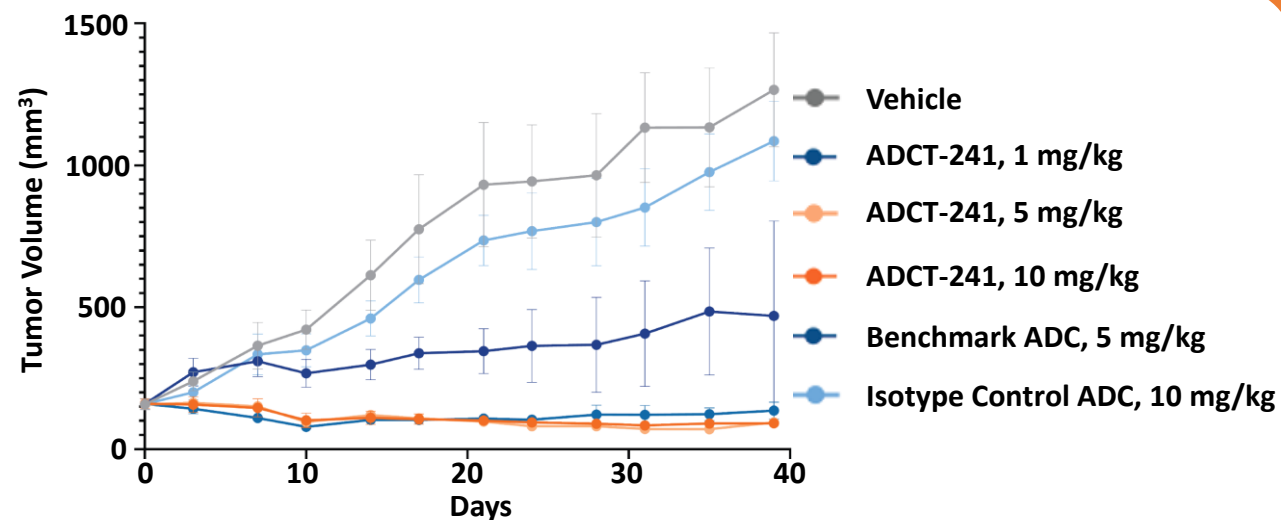
ADCT-241 Preclinical Studies

<i>In vitro</i> cytotoxicity	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*

^aModel of prostate cancer. ^bADCT-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.