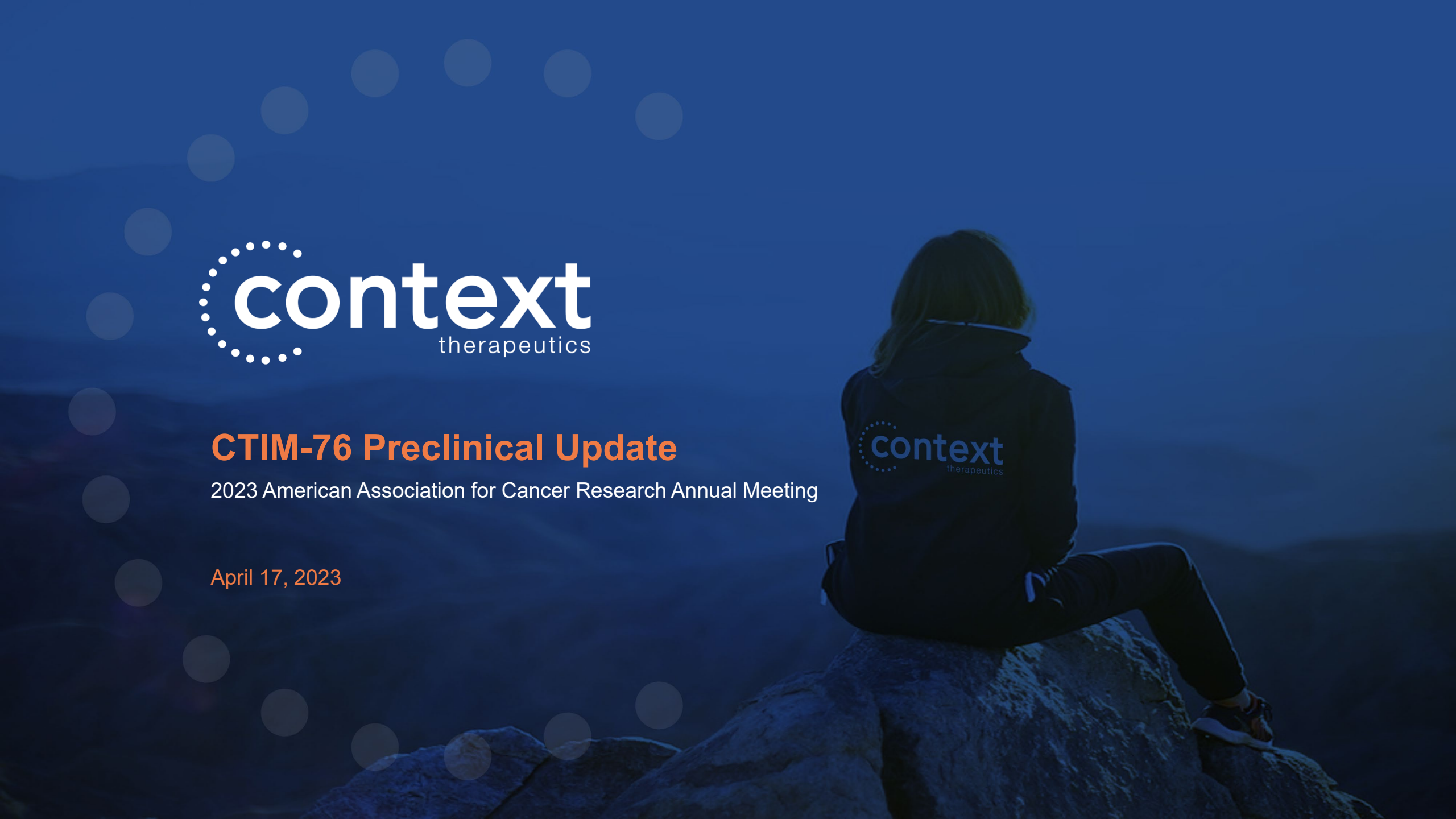
CTIM-76 Preclinical Update

2023 American Association for Cancer Research Annual Meeting

April 17, 2023



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Overview

Martin Lehr – Chief Executive Officer

Claudin 6 Target Biology

Eric Butz, PhD – Scientific Lead

Discovery of CTIM-76

Joseph Rucker, PhD – Research Lead

Concluding Remarks

Martin Lehr – Chief Executive Officer

Q&A Session

Overview

Martin Lehr – Chief Executive Officer

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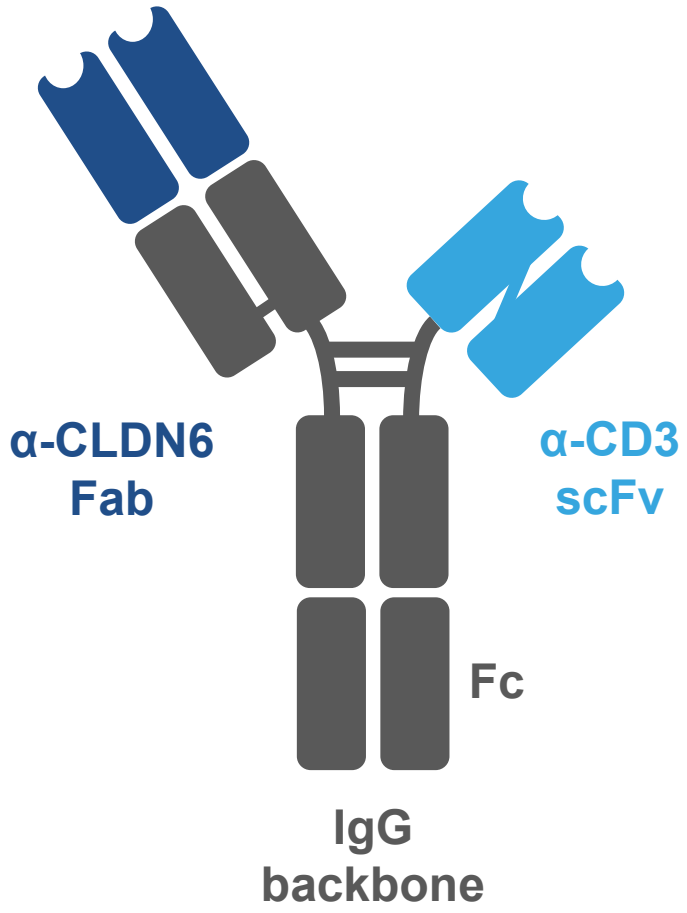
CTIM-76: Claudin 6 x CD3 Bispecific Antibody



Wide therapeutic window

- Highly selective CLDN6 binding fragment antibody-binding (Fab) arm
- Immunostimulatory CD3 binding single-chain fragment variable (scFv) domain is designed to be functionally monovalent to avoid aberrant T-cell activation, potentially enhancing safety profile
- The fragment crystallizable region (Fc region) is the tail region of an antibody that interacts with cell surface receptors called Fc receptors. A mutation has been inserted into the Fc domain to silence the Fc domain function and avoid T-cell activation by Fc-gamma receptor positive cells

Convenient dosing with low immunogenicity risk

- T-cell dependent cellular cytotoxicity with no or minimal activation of circulating cytokines
- Humanized CLDN6 and CD3 binding domains

Ease of manufacturing

- IgG backbone is highly stable and enables high yield

Claudin 6 Target Biology

Eric Butz, PhD – Scientific Lead

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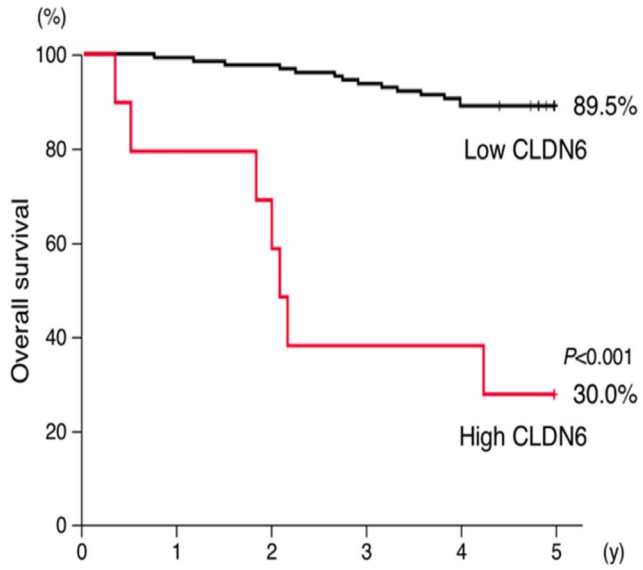
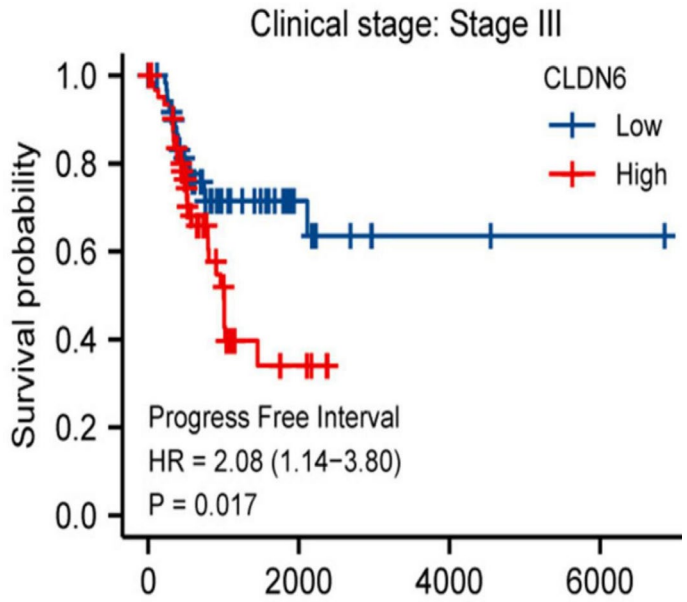
High CLDN6 Associated with a Worsened Prognosis in Cancer Patients

Endometrial Cancer[1]



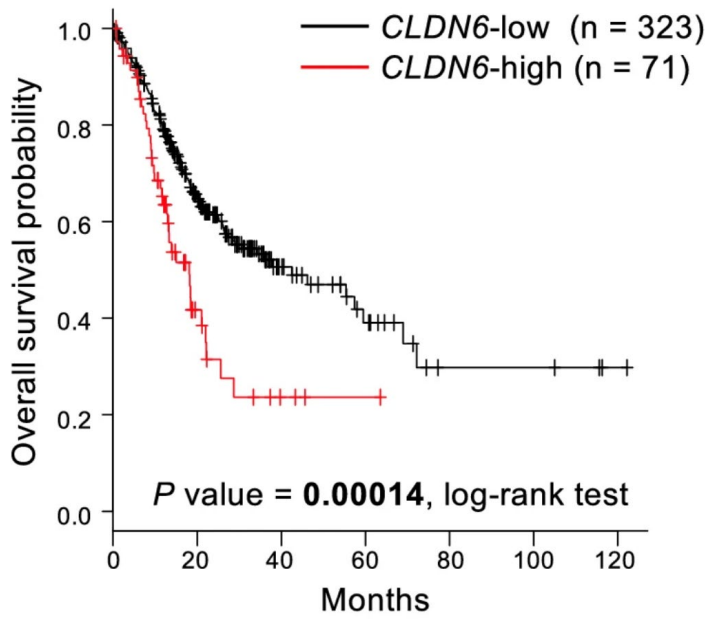
Overexpression of CLDN6 is associated with worse overall survival in endometrial cancer patients

Bladder Cancer[2]



Overexpression of CLDN6 is associated with worse overall survival and higher disease stage (more aggressive) in bladder cancer patients

Stomach Cancer[3]



Overexpression of CLDN6 is associated with worse overall survival in stomach cancer patients

1 Kojima, Cancers, 2020
2 Zhang, Front. Cell Dev. Biol., 2021
3 Kohmoto, Gastric Cancer, 2020

Claudin 6 (CLDN6) is an Ideal Target for Bispecific Antibodies

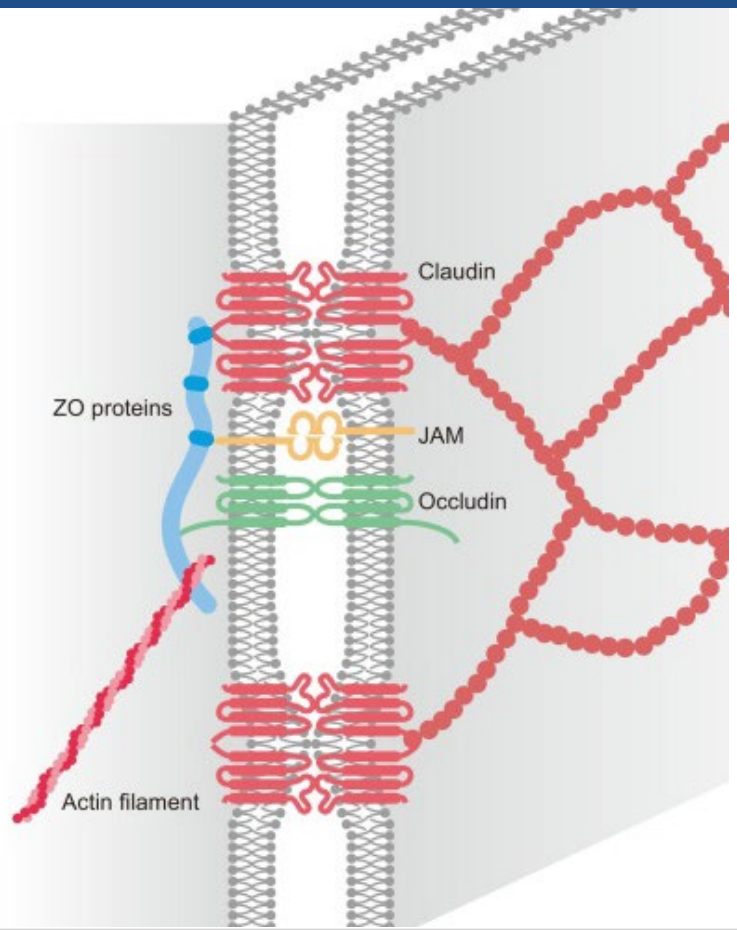
Opportunity	• CLDN6 is a **tumor-specific protein** that is present at high surface density across many adult and pediatric cancers[1] • CLDN6 is expressed at **very low levels or absent** in normal adult tissue
Challenge	• CLDN6 antigen is **conformationally dependent,** which limits access to antibody-antigen binding and antibody development • The CLDN6 antigen binding region is **highly conserved** with CLDN3, CLDN4, and CLDN9, which increases the risk of off-target binding and potential side effects associated with CLDN3 (pancreas), CLDN4 (kidney, pancreas), and CLDN9 (ear, gut)
Target Validation	• BioNTech's BNT211 CAR-T cell therapy establishes **Proof of Concept**[2]: – BNT211 cell therapy evaluated in Phase 1 dose-escalation study in CLDN6-positive solid tumors – **50% response rate** (ORR) in second dosing cohort
CTIM-76	• **Selective for CLDN6:** limited off-target effects • **Potent:** effective CLDN6-positive tumor killing at low doses • **Wide therapeutic window:** decreased risk of dangerous immune response • **Manufacturability:** ability to treat many patients

1 Faber MS, et al. Bispecific claudin-6 x CD3 antibodies AACR Annual Meeting; 2021; Virtual. Abstract 1860
2 Haanen JB, et al. BNT211: A Phase I trial. ESMO Annual Meeting; 2022; Paris, France. LBA38

Claudin (CLDN) Protein Family

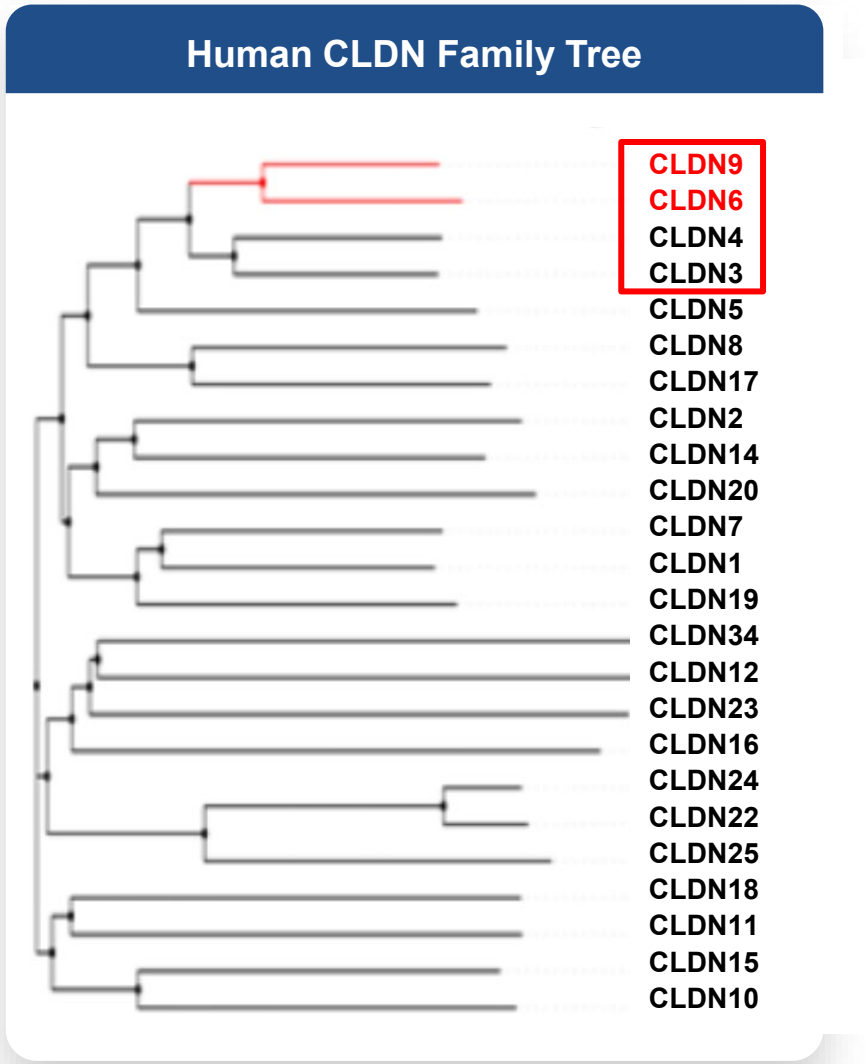
- Tight junctions (TJ) regulate cell barrier and permeability
- CLDN proteins constitute a structural core of TJ, along with junction adhesion molecule (JAM) and occludin
- 27 CLDN proteins have been characterized to date
- Dysregulation of CLDN protein expression and function occurs in multiple diseases, including cancer

Tight Junction Structure



Otani, Trends in Cell Biology, 2020

The Challenge: developing a highly selective CLDN6 antibody



- CLDN6 antigen is **conformationally-dependent**, which limits access to antibody-antigen binding
- Antigen binding region is **highly conserved** with CLDN3, CLDN4, and CLDN9, making target selectivity a challenge[1]
- CLDN6 **selectivity is required** to avoid off-target liabilities identified in murine knockout studies with CLDN3 (pancreas)[2], CLDN4 (kidney, pancreas)[3], and CLDN9 (ear)[4]

1 Screnci, Cancer Res, 2022
2 Tanaka, J Hepatol, 2018
3 Cordat, Physiology, 2019; Li, FEBS Open Bio, 2020
4 Nakano, PLoS Genet, 2009;

CLDN6 Has the Potential to Reach a Large Patient Population

~62,500 patients per year in the US only in Relapse/Refractory Setting

Initial indications of interest based on:

- CLDN6 prevalence
- Patient population size
- Observed clinical responses
- Eligibility for Orphan Designation

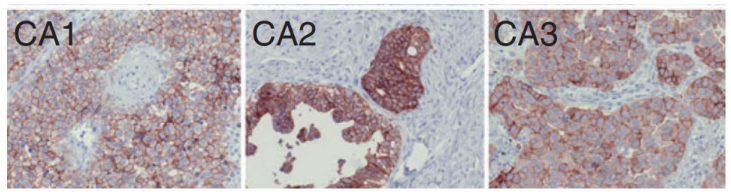
Selected Cancer indications	Incidence	R/R Incidence	CLDN6 Positive	Patient Population Based on R/R Incidence
Testicular	9,910	400	95%[1]	**380**
Ovarian	19,900	12,800	54-55%[1,2]	**6,982**
Non-Small Cell Lung	201,229	110,653	6-50%[3,4,5]	**35,221**
Gastric	26,380	11,090	13-55%[8,9]	3,771
Malignant Rhabdoid	50	500	29-44%[1,2,6,7]	183
Breast	290,600	43,800	2-41%[1,10,11]	9,417
Endometrial	65,900	12,500	20-31%[1,12,13]	3,188
Glioma	19,000	10,000	21%[8]	2,100
Bladder	81,180	17,100	2-8%[1,13]	855
Small Cell Lung	35,511	19,527	2%[1]	391

1 Reinhard, Science, 2020; 2 Wang, Diagn Pathol., 2013; 3 Gao, Oncol Lett., 2013; 4 Kohmoto, Gastric Cancer, 2020; 5 Lin, Diagn Pathol., 2013; 6 Micke, Intl J Cancer, 2014; 7 Soini, Pol J Path, 2022; 8 Antonelli, Brain Pathol., 2011; 9 Sullivan, Am J Surg Pathol., 2012; 10 Jia, Intl J Clin Exp Pathol., 2019; 11 Yafang, J Breast Cancer, 2011; 12 Kojima, Cancers, 2020; 13 Ushiku, Histopath., 2012

Incidences based on public estimates; Relapsed/refractory (R/R) or last-line patient population approximated by annual mortality; CLDN6 target prevalence is based on IHC or RNAseq from published reports. Patient population derived from midpoint of CLDN6 positive population multiplied by R/R incident population.

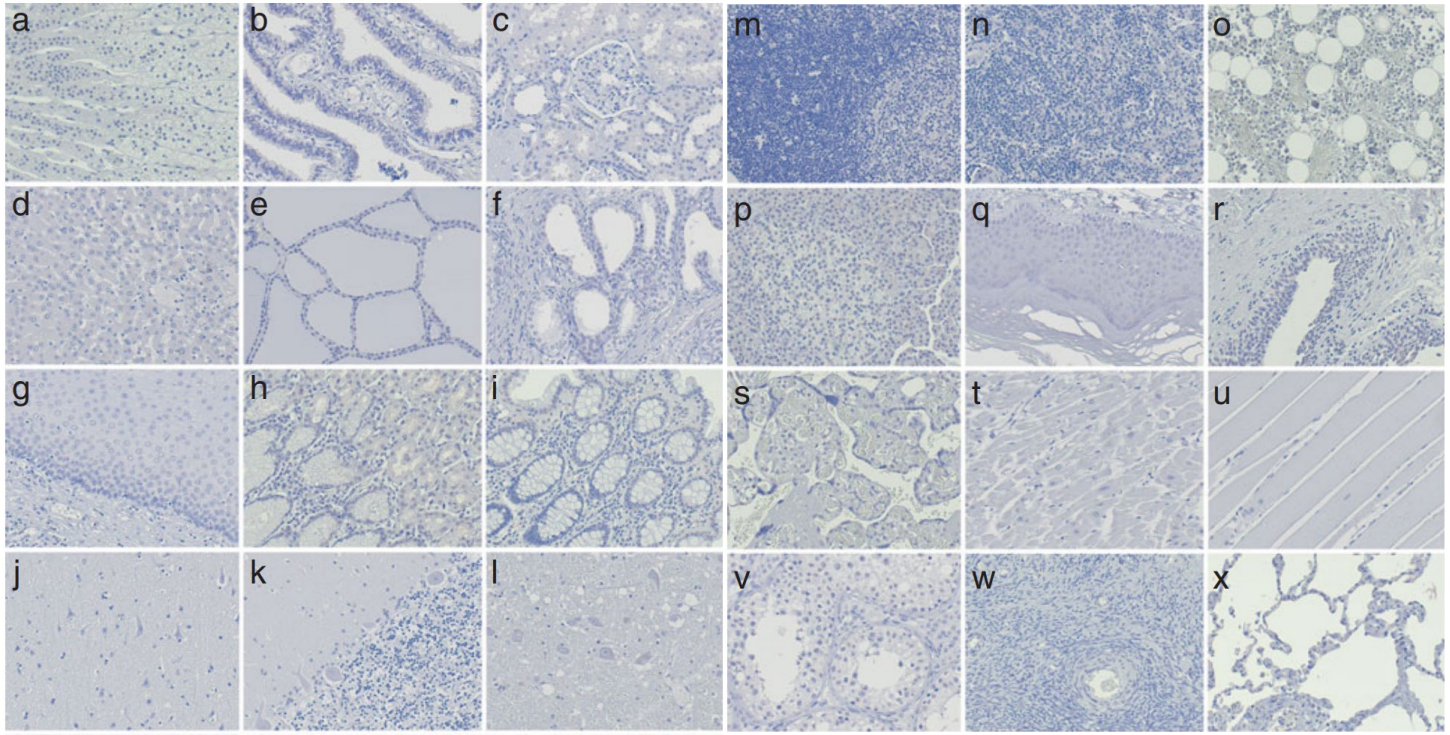
CLDN6 is Selectively Expressed on Cancer Cells

Cancer Tissue



(CA1) testicular cancer, (CA2) ovarian cancer, and (CA3) lung cancer

Normal Tissue



(a) adrenal gland, (b) fallopian tube, (c) kidney, (d) liver, (e) thyroid, (f) prostate, (g) esophagus, (h) stomach, (i) colon, (j) cerebrum, (k) cerebellum, (l) spinal cord. (m) thymus, (n) spleen, (o) bone marrow, (p) pancreas, (q) skin, (r) bladder, (s) placenta, (t) heart muscle, (u) striated muscle, (v) testis, (w) ovary, (x) lung

Reinhard, Science, 2020

Discovery of CTIM-76

Joseph Rucker, PhD – Research Lead

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Bispecific Antibody Considerations

Bispecific scaffold and CLDN6/CD3 arms evaluated to optimize selectivity, potency, and manufacturability

CLDN6 Targeting Arm

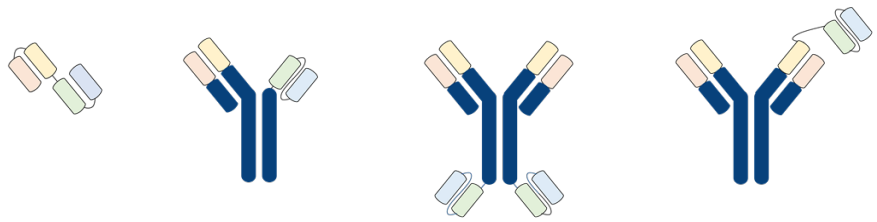
- High affinity anti-CLDN6 binding
- High specificity for CLDN6 vs other CLDN
  - Especially CLDN3, CLDN4, CLDN9

CD3 T-cell Engaging Arm

- Clinically validated
- Freedom to operate
- Explore a range of potencies

Bispecific Scaffolds

- Multiple formats evaluated



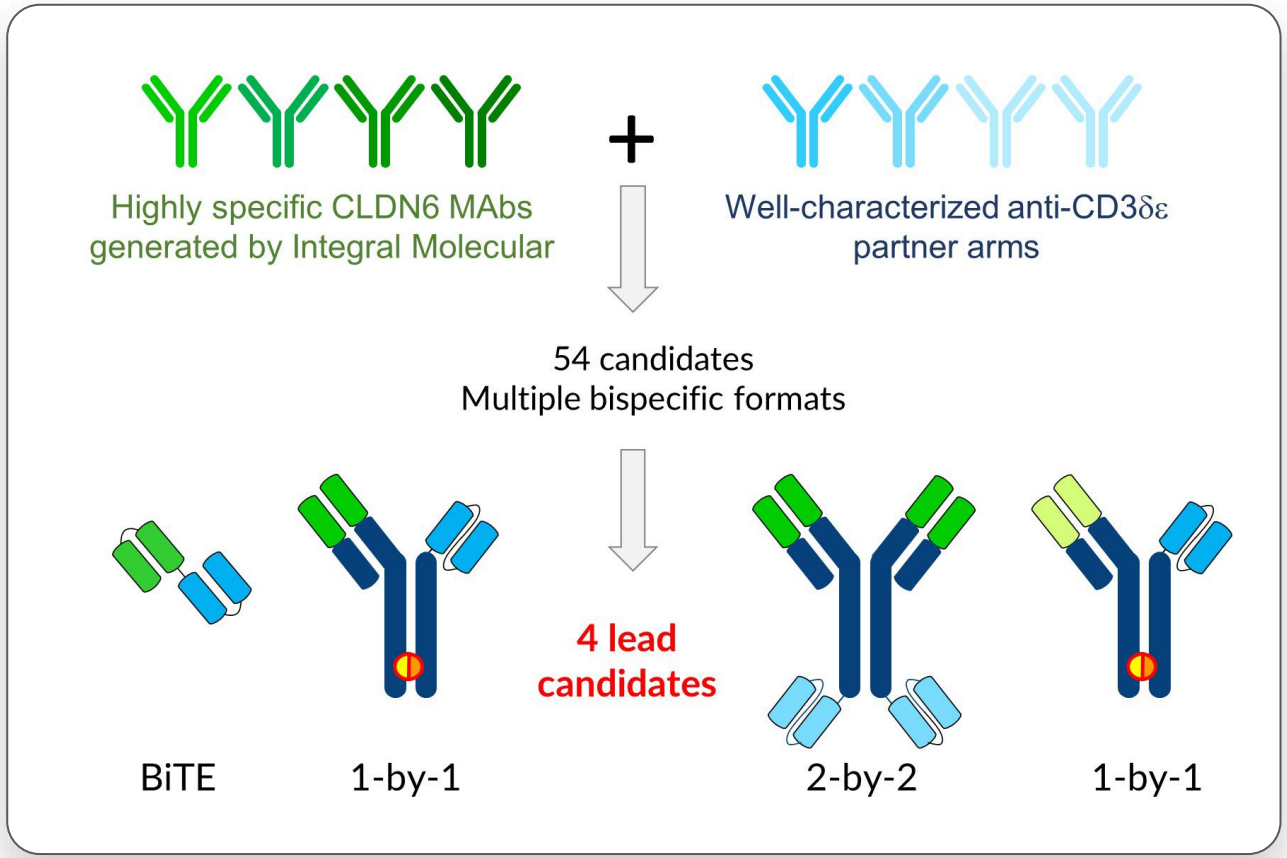
Other Factors

- Cross reactivity to NHP desirable for both arms
- Silencing variants to eliminate FcR binding
- FcRn binding for half-life extension

NHP = non-human primate
FcR = fragment crystallizable region (Fc region) is the tail region of an antibody that interacts with cell surface receptors called Fc receptors (FcRn) and some proteins of the complement system

Initial Panel Generation

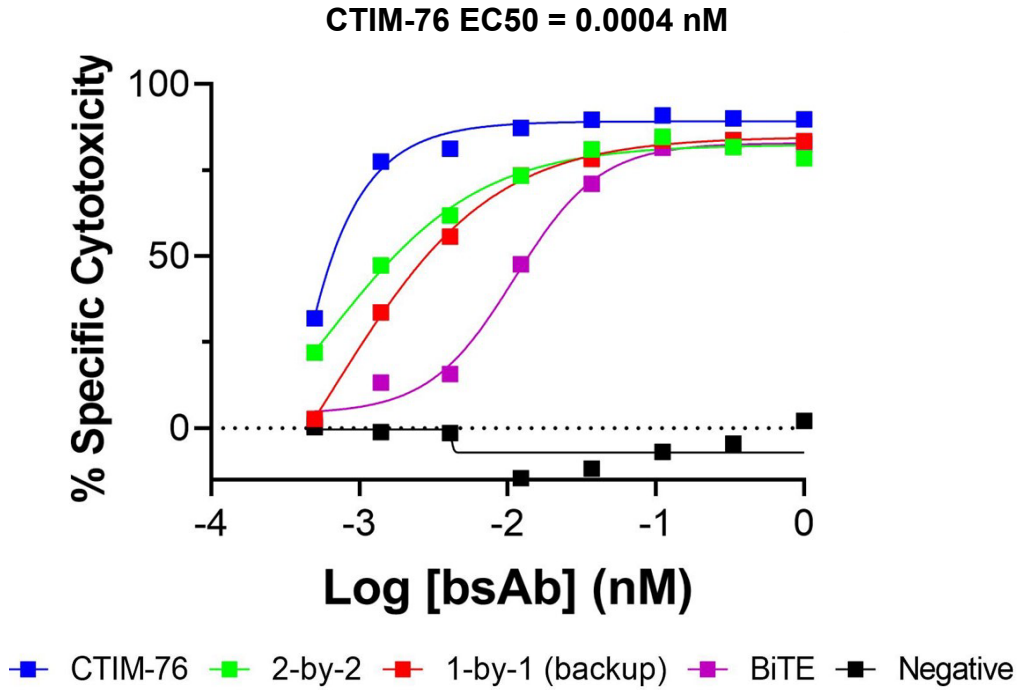
- Lead candidate MAbs that show best-in-class specificity for CLDN6 were isolated and humanized
- 54 candidate molecules were selected for functional characterization and safety profiling, these represented multiple bispecific formats, including a 2-by-1 format which was subsequently eliminated due to poor developability
- Four candidates were chosen for further characterization leading to the nomination of CTIM-76 as the development candidate



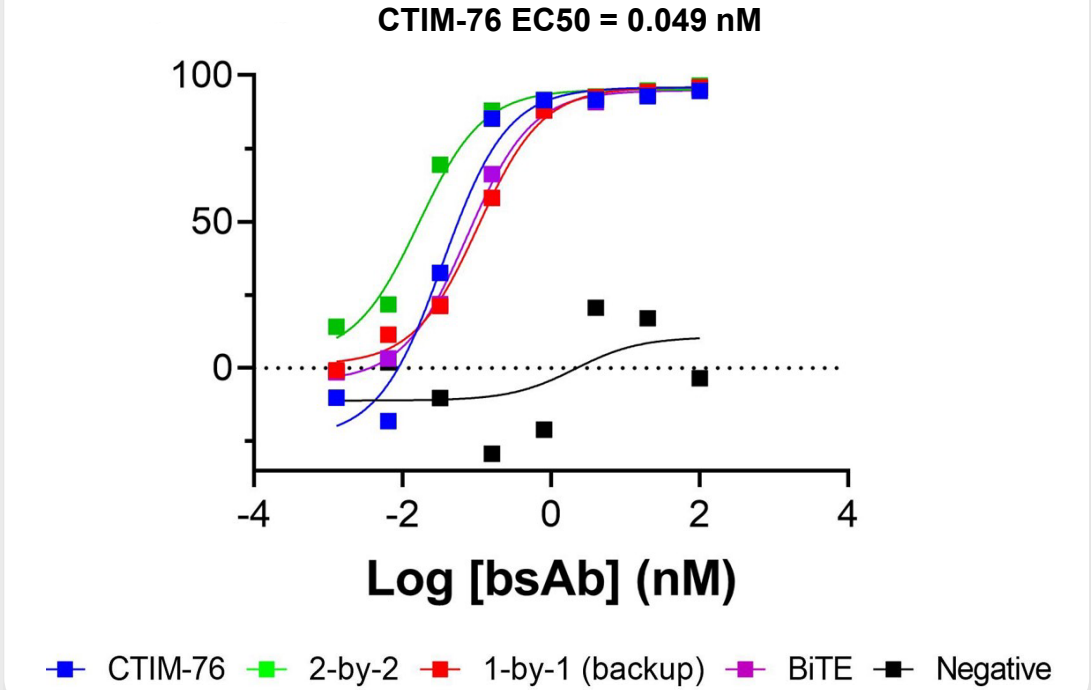
CTIM-76 Potency in Cell Death Assay

- Data evaluated multiple bispecific constructs utilizing identical (or similar) CLDN6 and CD3 sequences in CLDN6 high expression (K562-CLDN6) and medium expression (OV90) cell lines
- CTIM-76 shows improved activity over formats with identical (or similar) CLDN6 and CD3 binder arms

K562-CLDN6 Cell Line



OV90 Cell Line

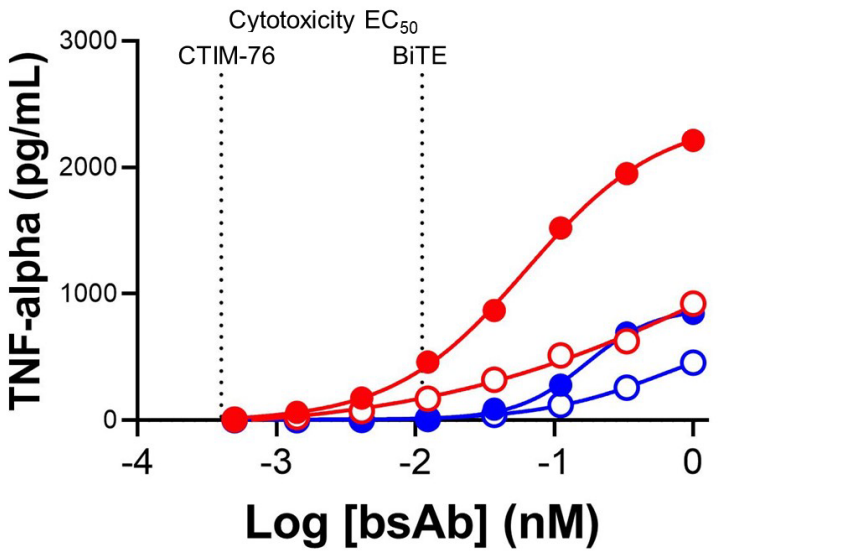


Experimental Design: K562 cells stably expressing CLDN6 or OV90 cells endogenously expressing CLDN6 were co-cultured with human T cells at an E:T ratio of 10:1 for 48 hours. Cytotoxicity was determined by luminescence imaging.

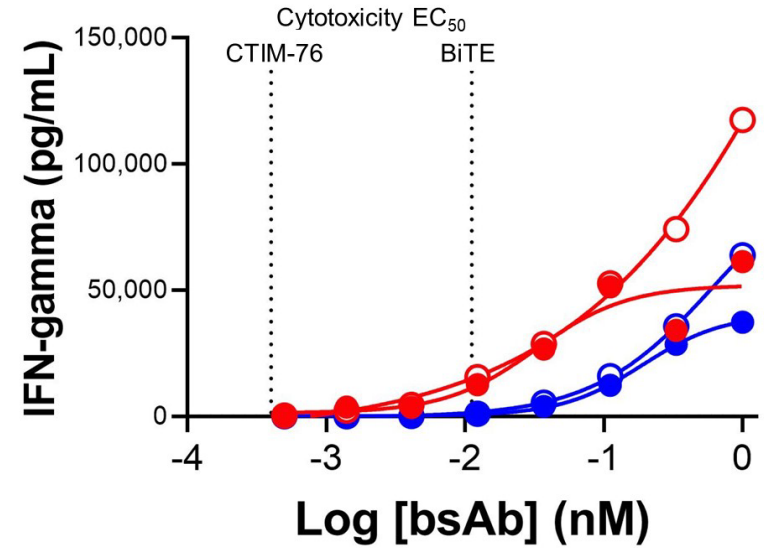
CTIM-76 Potency in Cytokine Release Assay

- Low cytokine release at CTIM-76 concentrations within 2 log of cytotoxicity EC50 indicating a better therapeutic window compared to a BiTE molecule with identical binder arms

TNFα



IFNγ

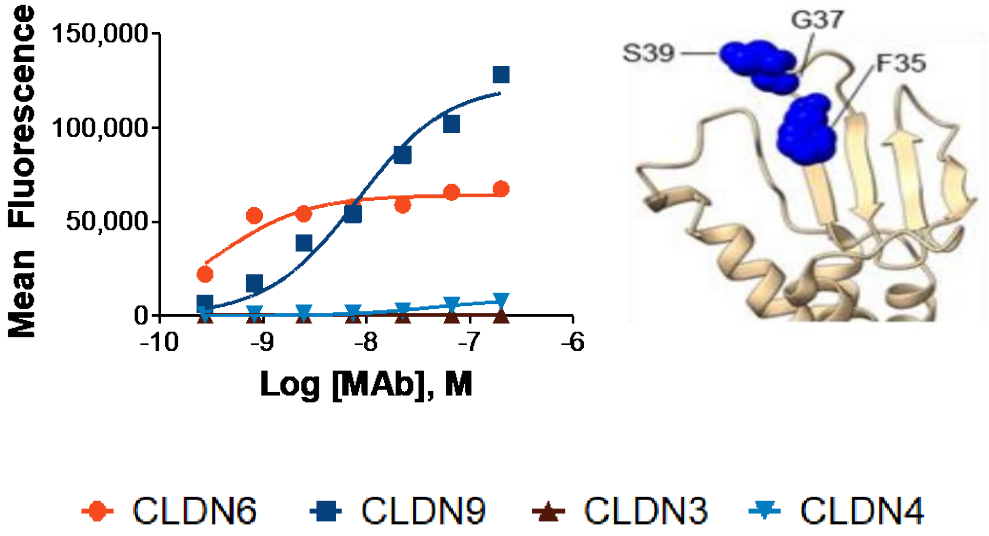


Experimental Design: K562 cells stably over-expressing CLDN6 and luciferase were co-cultured with human T cells at an E:T ratio of 10:1 for 48 hours. Cytotoxicity was determined by luminescence imaging. Cytokine levels were assayed at 24 and 48 hours.

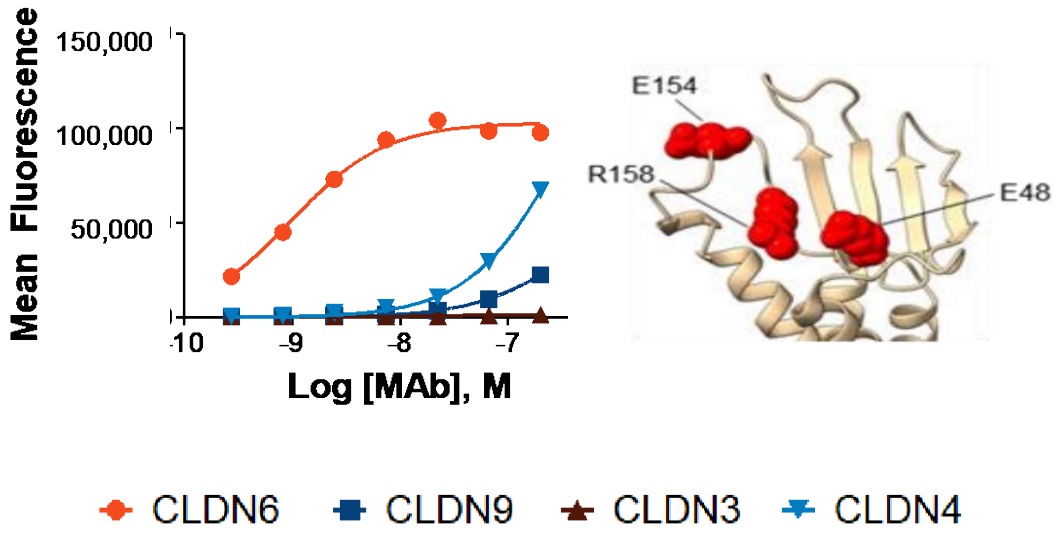
CTIM-76 Specificity

- CLDN6 specificity determined by recognition of Q156 γ carbon. In CLDN9, the native L156 leads to steric inhibition of MAb binding
- IM301 (CLDN6 arm of CTIM-76) exhibits high CLDN6 selectivity[1]
- Epitope mapping of IM301 identifies unique binding location relative to benchmark IMAB027/ASP150 (Ganymed/Astellas)

IMAB027/ASP1650



IM301 (CTIM-76)

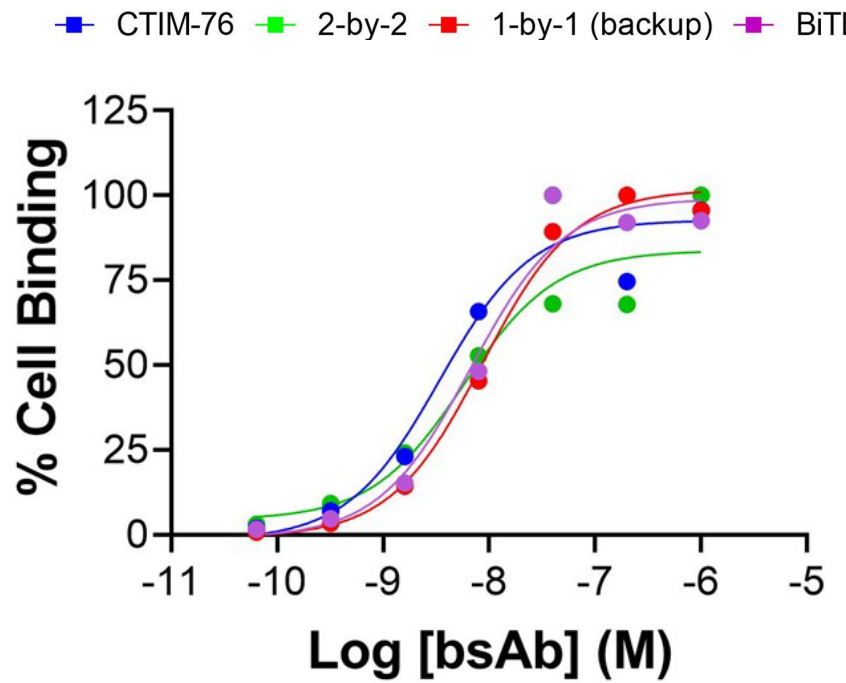


Experimental Design: Critical residues for MAb binding were identified using a CLDN6 alanine-scanning library expressed in HEK-293T cells. 1 Screnci, iScience, 2022

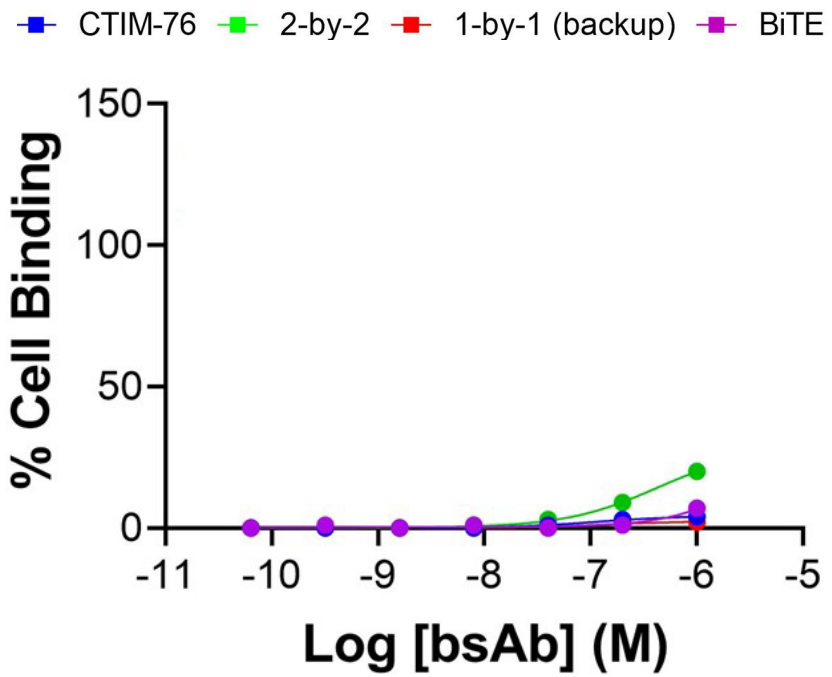
CTIM-76 Binding is Highly Specific for CLDN6

- All constructs bound to CLDN6 expressing cells, minimal binding was detected in cells expressing CLDN9

Bispecific Binding to CLDN6



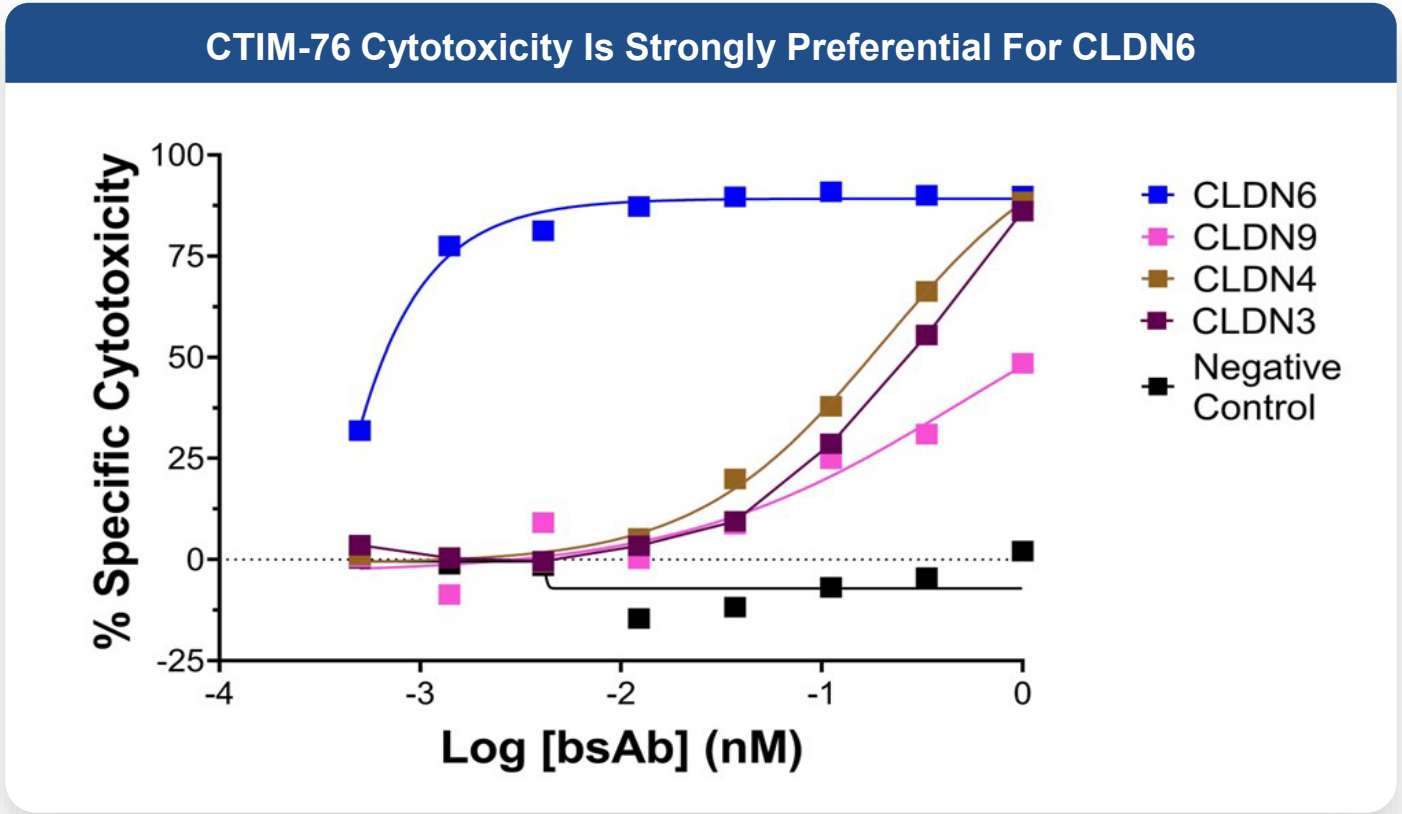
Bispecific Binding to CLDN9



Experimental design: Binding of bispecific constructs of various formats to K562 cells stably over-expressing CLDN6 or CLDN9 as measured by flow cytometry.

CTIM-76 Cytotoxicity is Strongly Preferential for CLDN6

- CTIM-76 preferentially targets CLDN6, with minimal binding and cytotoxicity against CLDN9-expressing cells
- No binding and minimal cytotoxicity are observed to other closely related CLDN family protein



Next Steps and Summary

Encouraging Efficacy Signals

- Dose responsive activity in xenograft studies
- CLDN6-selective activity across binding and cytotoxicity

Encouraging Tolerability

- No significant safety findings to date
- Preferential cytotoxicity over activation of free circulating cytokines
- PK consistent with IgG backbone

Progress Toward the Clinic

- IND-enabling studies ongoing
- IND submission expected in Q1 2024

Concluding Remarks

Martin Lehr – Chief Executive Officer

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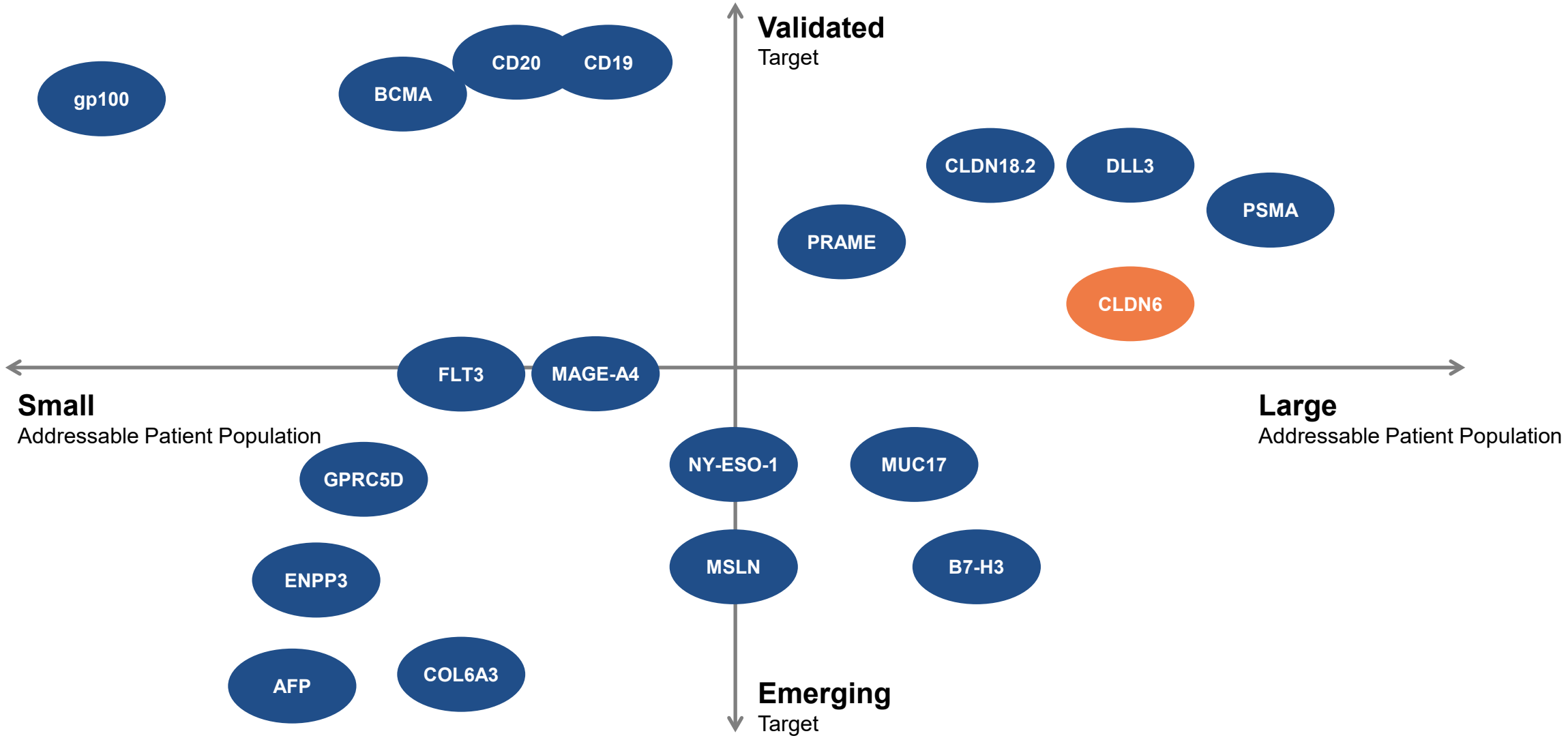
Mapping the T-cell Directed Therapy Landscape[1]



1 Analysis based upon publicly available information and represents a non-head-to-head summary comparison

CLDN6 – Drug Development Strategy Comparison

CLDN6 is a tumor-associated antigen (TAA) for tumor-targeting therapeutics such as CAR-T and T cell engaging bispecific antibodies

Drug Development Strategy	CLDN6 Dependence / Rationale	Supporting Evidence
Monoclonal Antibody (mAb)	Receptor-mediated signaling	**Poor** Weak signaling dependence[1]
Bispecific Antibody (bsAb)	Cell surface antigen for T-cell targeting	**High** *In vivo* PoC + BNT211 clinical PoC[2,3]
Antibody-Drug Conjugate (ADC)	Receptor internalization	**Poor** Weak internalization[4]
CAR-T	Cell surface antigen for T-cell targeting	**High** BNT211 clinical PoC[3]

1 https://www.clinicaltrialsregister.eu/ctr-search/trial/2013-002755-15/results .
2 Context internal
3 Haanen J, et al. AACR Annual Meeting 2022; Oral presentation CT002.
4 Data courtesy of Integral Molecular and Dr. Andrew Tsourkas (UPenn)

CLDN6 Competitive Landscape[1]

Programs differentiated based upon treatment modality and selectivity for CLDN6 over CLDN9

	Preclinical	Phase 1
Antibody Drug Conjugate (ADC)	**GB-7008-01** CLDN6/CLDN9 + MMAE *(~1x, non-selective)*	**UCLA-23-ADC** CLDN6 + MMAE *(~27x)* **DS-9606a** CLDN6/CLDN9 + DXd *(~1x, non-selective)*
Bispecific Antibody	**XmAb541** 2+1 bsAb CLDN6xCD3 *(~10x)* **TJ-C64B** 2+2 bsAb CLDN6x4IBB *(not disclosed)* **CTIM-76** bsAb CLDN6xCD3 *(>1,000x)*	**SAIL66** bsAb CLDN6xCD3 *(~10x)* **BNT142** mRNA encoded BsAb CLDN6xCD3 *(~7x)* **AMG794** BiTE CLDN6xCD3 *(~630x)*
Cell Therapy		**BNT211** CAR-T + CARVac *(~7x)* **CLDN6-CAR-NK** CAR-NK + IL7 *(not disclosed)*

1 Analysis based on publicly available information compiled as of February 21, 2023

Potential for CTIM-76 to Separate From the Competition

	Company	Program (Development Stage)	Description / Details[3]
Active Programs	**BioNTech**	**BNT211:** CLDN6CAR-T + CARVac (Phase 1)	Initial data for BNT211 were presented April 2022 (AACR), with an update in Sept 2022 (ESMO). Received PRIME Designation for testicular cancer June 2022
		BNT142: CLDN6 mRNA encoded bsAb (Phase 1)	Initiated Phase 1 development for BNT142 in mid-2022
	Amgen	**AMG794:** CLDN6 BiTE (Phase 1)	AMG794 candidate were presented April 2022 (AACR). Initiated Phase 1 development for AMG794 in Q1 2023.
	Guangzhou Medical University	**CLDN6-CAR-NK:** CAR-NK + multiple gene edits (Phase 1)	Engineered to express IL7/CCL19 and/or SCFVs against PD1/CTLA4/Lag3, initiated Phase 1 development in mid-2022
	Daiichi	**DS-9606a:** CLDN6/CLDN9 ADC (Phase 1)	Initiated Phase 1 development for DS-9606a in mid-2022
	Chugai	**SAIL66:** CLDN6 bsAb CLDN6xCD3 (Phase 1)	Initiated Phase 1 development for SAIL66 in Feb 2023
	I-Mab	**TJ-C64B:** CLDN6 bsAb CLDN6x4IBB (Preclinical)	Initial data presented April 2021 (AACR), IND filing is expected in 2H 2023
	Xencor	**XmAb541:** CLDN6 bsAb CLDN6xCD3 (Preclinical)	Initial data presented April 2021 (AACR), IND filing is expected in 2023
Notable Deprioritized Programs	**Astellas/Ganymed**	**IMAB027/ASP1650:** CLDN6 mAb (Phase 2)	Lack of single agent activity in Phase 2 trial relapse/refractory testicular germ cell tumors[1]
	Abbvie/Stemcentryx	**SC004:** CLDN6/CLDN9 ADC (Phase 1)	Dose-limiting toxicity (loss of hearing, diarrhea) attributed to CLDN9 binding observed in Phase 1 in patients with ovarian cancer[2]

1 Adra, Invest New Drugs, 2022
2 Hamilton, Cancer Res, 2020

3 Analysis based on publicly available information compiled as of February 21, 2023

Q&A Session

MARTIN LEHR
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ERIC BUTZ, PhD
Scientific Lead

JOSEPH RUCKER, PhD
Research Lead

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Advancing Medicines for Solid Tumors