Cidara Drug-Fc-Conjugates (DFCs): A New Approach To Treatment Of Cancer

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DISCLOSURES

Employee and shareholder of Cidara Therapeutics

REZAFUNGIN AND CLOUDBREAK PROGRAMS

REZAFUNGIN

- Echinocandin antifungal treatment & prevention
- Positive Phase 3 data
- NDA submitted, July 2022
- Approved by FDA in March 2023

Program	Indications	IND-Enab.	Phase 1	Phase 2	Phase 3	Approved	Collaborations
REZAFUNGIN	Treatment of Candidemia and Invasive Candidiasis						melinta therapeutics (U.S) / mundipharma (Ex-US/Ex-Japan)
REZAFUNGIN	Prevention of Invasive Fungal Disease in Blood & Marrow Transplant Patients						melinta therapeutics (U.S) / mundipharma (Ex-US/Ex-Japan)

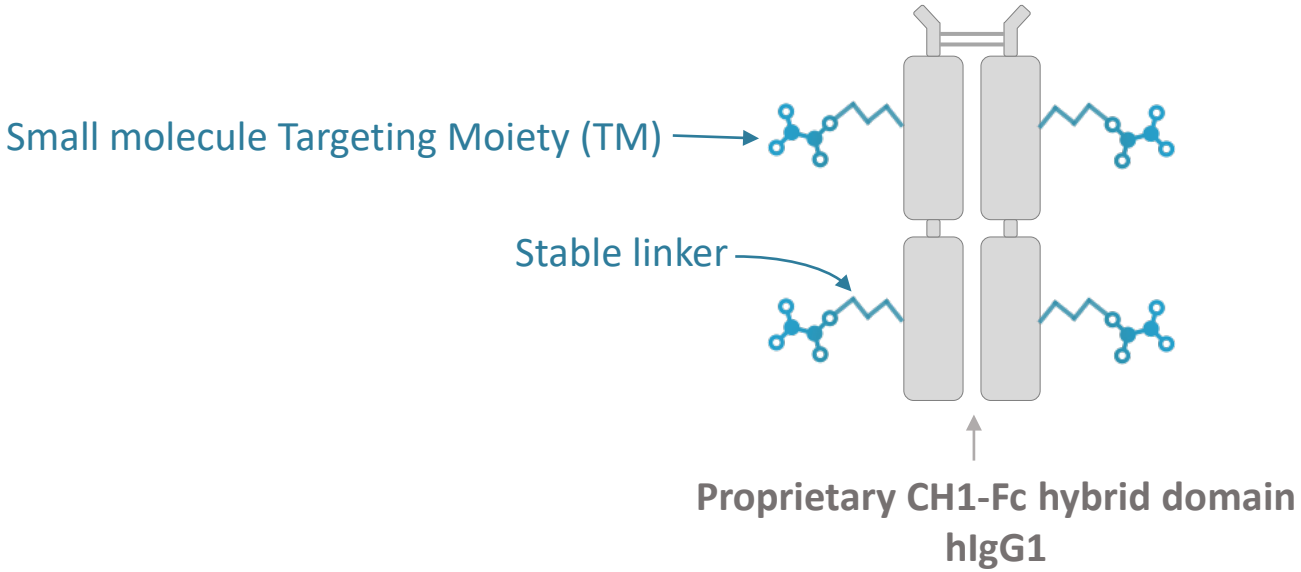
CLOUDBREAK

- Novel immunotherapy platform: antiviral & oncology
- Clinical stage (influenza) – CD388; Phase 2a interim data released March 1, 2023
- Preclinical (oncology) – CD73; preclinical data presented at ESMO-TAT; IND-enabling studies underway
- Opportunity to drive future value

Program	Indications	Discovery	Preclinical	IND-Enab.	Phase 1	Phase 2	Collaborations
CD388	Prevention of Seasonal Influenza						Janssen (Worldwide License)
CD73	Solid Tumors						
Target 2* (Undisclosed)	Solid Tumors						
Combination DFC 1**	Solid Tumors						
Combination DFC 2**	Solid Tumors						

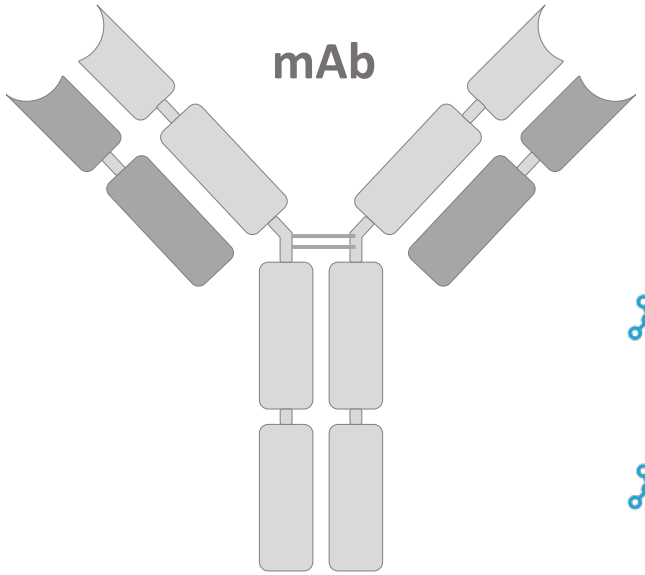
*Targets a unique cancer pathway **Targeting multiple cancer pathways using a single DFC

Drug Fc Conjugate

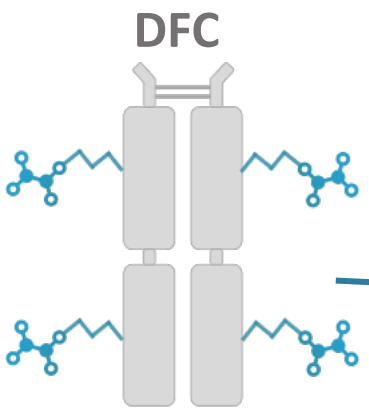


DFCs are designed to engage extracellular targets

DFCs ARE SMALLER THAN mAbs, AND ALLOW FOR PRECISION TARGETING



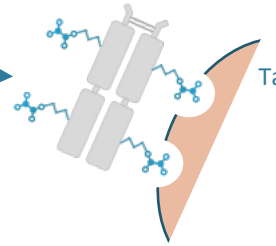
150 kDa



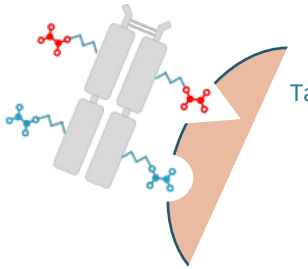
65-70 kDa

The smaller size of DFCs allows for faster and more robust distribution to tissues

Small molecule TMs can selectively target enzyme active sites/receptors

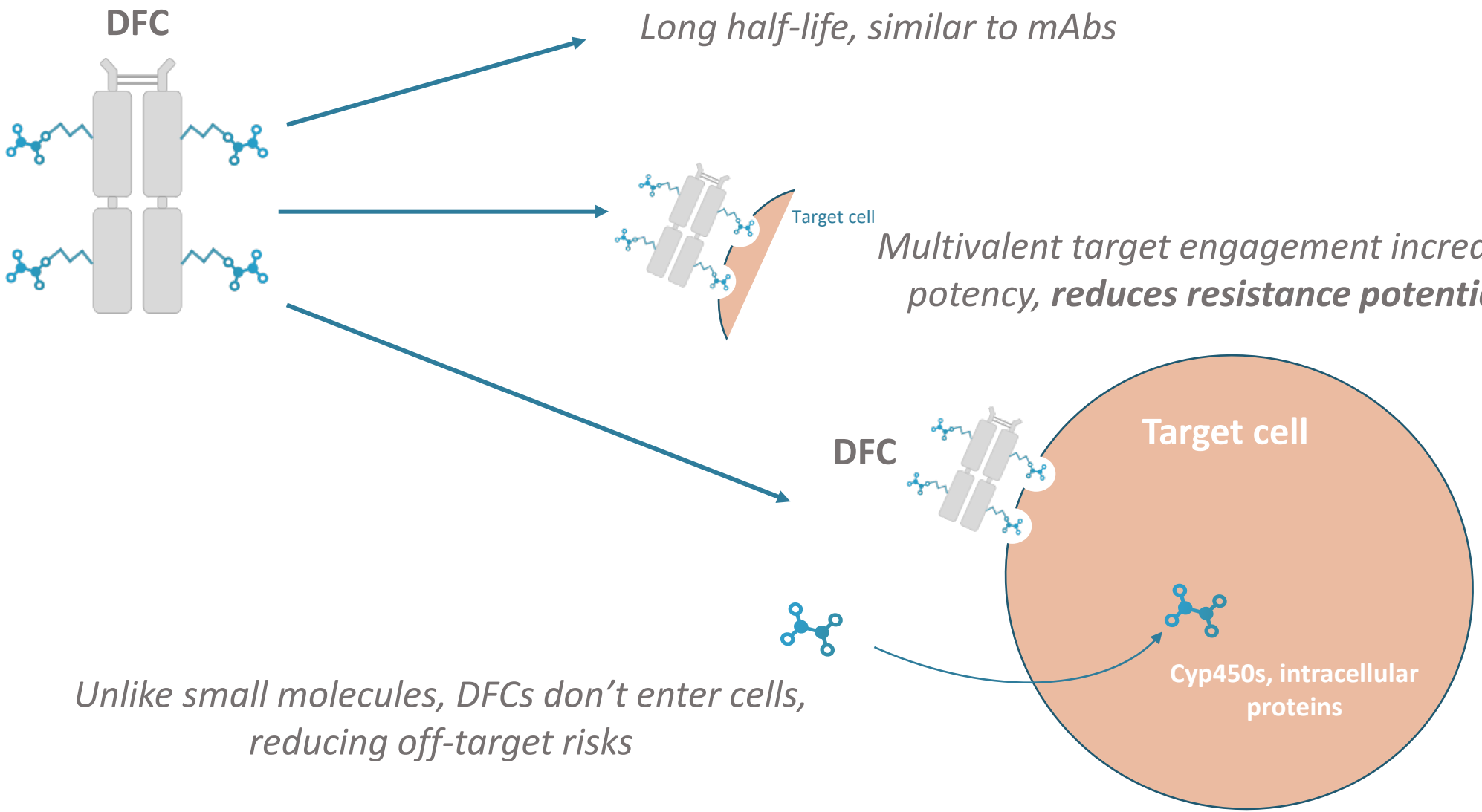


Drug-Fc-ratio and linkers can be tuned to maximize avidity

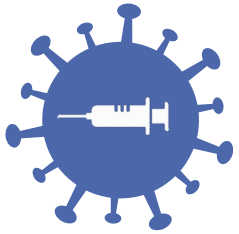


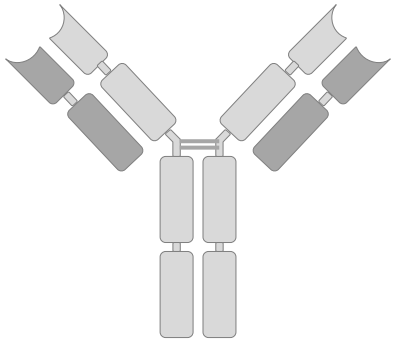
Multi-targeting agents in a small package

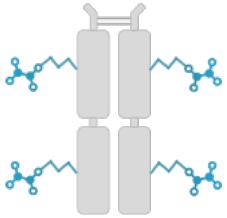
DFCs CAN IMPROVE SMALL MOLECULE DRUG PERFORMANCE AND SAFETY



CD388 DFC ADDRESSES THE SHORTCOMINGS OF THE FLU VACCINE AND ANTIBODIES







	Vaccines	Monoclonal Antibodies	CD388 DFC
Universal protection: multiple viruses	No	No	Yes
Potential to protect all high risk groups	Low	High	High
Potential for prevention and treatment	No	Limited	Yes
Scale and cost	Attractive	Expensive	Attractive

CD388 PHASE 2A DATA CONFIRM THE TPP

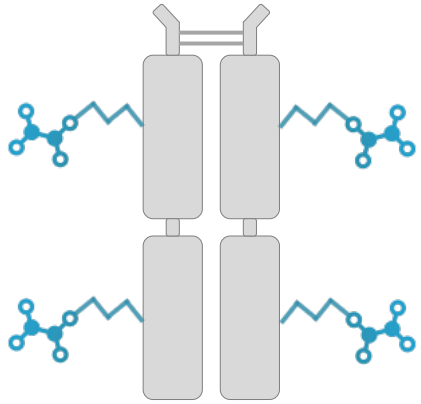
INFLUENZA

	DFCs
Universal protection: all strains	Yes
Potential to protect all high risk groups	High
Potential for prevention and treatment	Yes
Scale and cost	Attractive

CIDARA THERAPEUTICS / janssen

CD388 is being developed for universal, season-long flu protection in all patient populations.

Neuraminidase inhibitor

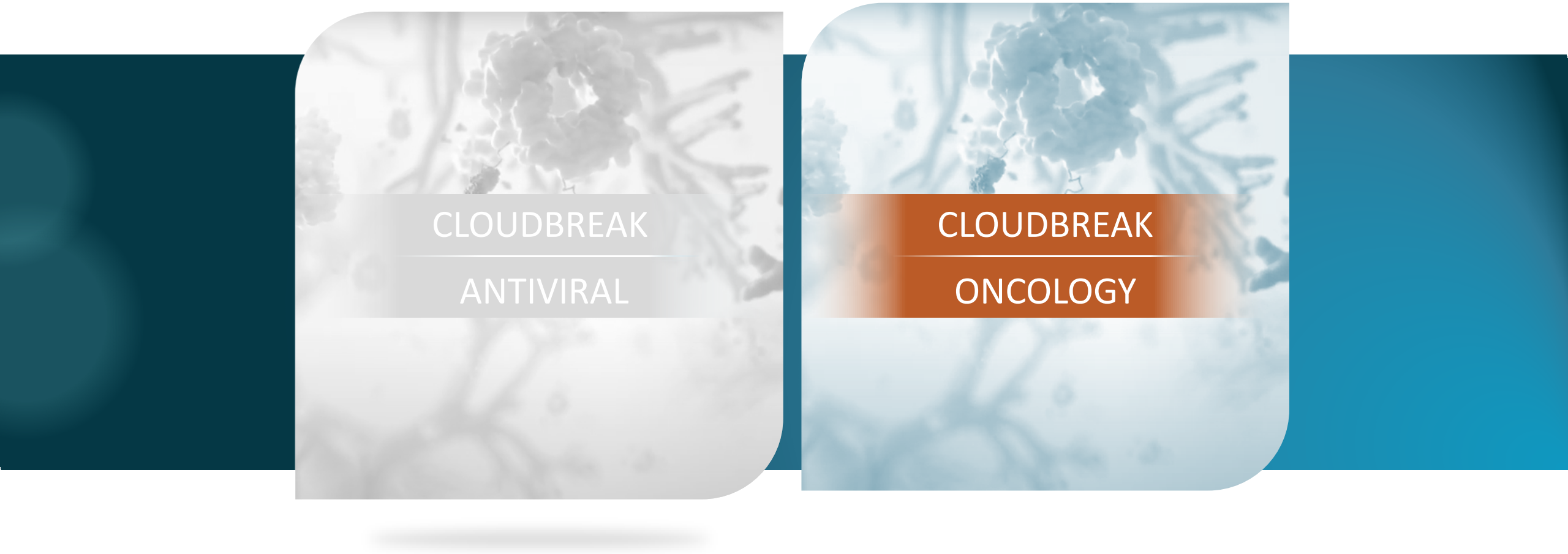


- Single dose /~4-6 months
- Successful Phase 2a interim data*

Data available at https://www.cidara.com/cloudbreak/influenza/ and at https://clinicaltrials.gov/ct2/show/NCT05285137

* https://www.cidara.com/news/cidara-therapeutics-announces-promising-interim-phase-2a-data-assessing-the-safety-and-efficacy-of-a-single-dose-of-cd388-in-an-influenza-challenge-model/

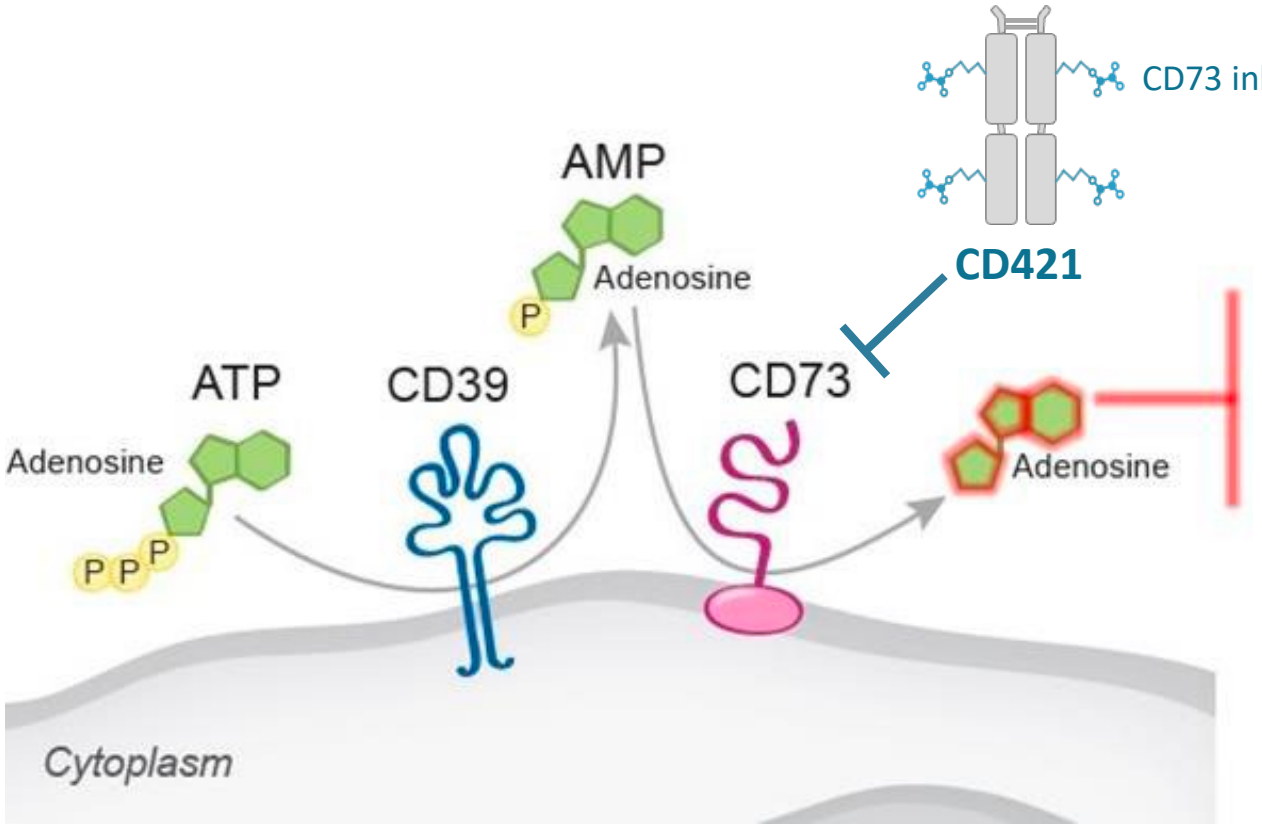
CIDARA'S PIPELINE TARGETS MULTIPLE UNMET MEDICAL NEEDS



CIDARA THERAPEUTICS

ADENOSINE MEDIATES IMMUNOSUPPRESSION AND THERAPEUTIC RESISTANCE VIA ADENOSINE PRODUCTION

CD73 is expressed on endothelial cells, stromal cells, some tumors, subsets of T cells (CD4 10%, CD8 50%) and B-cells (70%)



T cell priming
T cell expansion
T cell activation/cytolytic activity NK degranulation
Macrophage M1 polarization, DC maturation/activation

CD421 is Cidara's development candidate

CD421 COMBINES ATTRIBUTES OF mAb AND SMALL MOLECULE INHIBITORS

- CD421 attributes (potency, efficacy, PK, safety) compared with most advanced CD73 small molecule and mAb clinical candidates targeting CD73

Activity	Small molecule	mAb	DFC
Soluble CD73 inhibition	+++	–/+	**+++**
Cell-anchored CD73 inhibition	+++	–/++	**+++**
Receptor internalization	–	–/+++	**+++**
Half-Life	+	+++	**+++**
Tissue/tumor penetration	+++	+	**++**
Potential safety profile*	++	+++	**+++**
Ability to combine MOAs	–	+	**+++**

*mAbs and DFCs do not enter the intracellular space, reducing potential for off-target toxicities

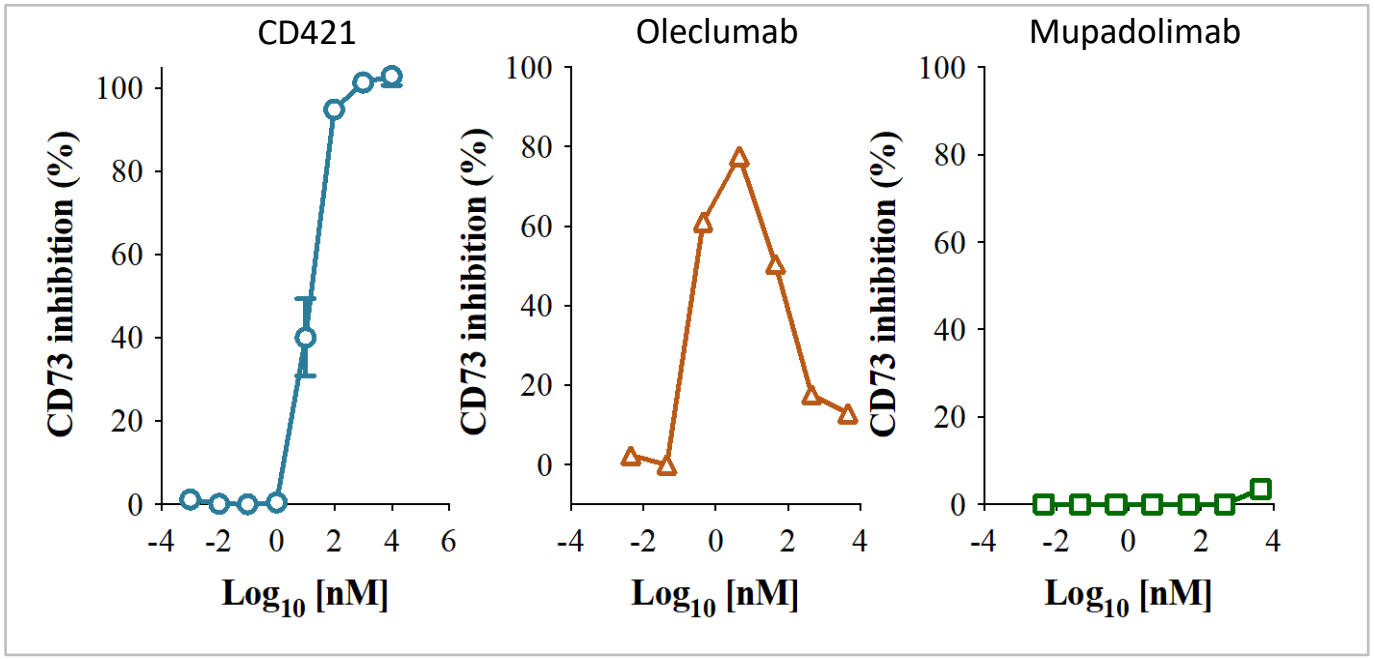
CD73 SHED BY TUMORS IS A PROGNOSTIC FACTOR IN SEVERAL CANCERS

- *E.g.* metastatic melanoma – **CD421 inhibits soluble CD73, mAb inhibitors do not**

Activity	Small molecule	mAb	DFC
Soluble CD73 inhibition	+++	–/+	+++

Soluble CD73 inhibition assay (IC_{50} in nM)

	Test article	IC_{50}
	CD421	*13.81*
Small molecules	AB680	4.01
Small molecules	OP-5244	3.79
mAbs	Oleclumab*	n.c.
mAbs	Mupadolimab#	>100



*Oleclumab biosimilar is a partial catalytic inhibitor of CD73
#Mupadolimab biosimilar

CD421 ALSO POTENTLY INHIBITS CELL ANCHORED CD73

- **CD421 is a potent inhibitor of cell anchored CD73 on tumor cells and immune cells**

Activity	Small molecule	mAb	DFC
Cell-anchored CD73 inhibition	+++	–/++	+++

Cell-based CD73 inhibition assay (IC_{50} in nM)

	Test article	Human MDA-MB-231	Human PBMCs median (range, n=3)
	CD421	*3.09*	*0.61 (0.59 – 0.62)*
Small molecules	AB680	0.38	0.022 (0.015 – 0.028)
Small molecules	OP-5244	0.87	0.011 (0.006 – 0.028)
mAbs	Oleclumab*	0.67	0.56 (0.48 – 4.15)
mAbs	Mupadolimab#	3.82	2.85 (1.68 – 3.71)

*Oleclumab biosimilar is a partial catalytic inhibitor of CD73
#Mupadolimab biosimilar

CD421 ALSO POTENTLY INHIBITS CELL ANCHORED CD73

- **CD421 activity in functional assays rivals best-in-class small molecules in clinical testing**

Activity	Small molecule	mAb	DFC
Cell-anchored CD73 inhibition	+++	–/++	+++

PBMC rescue assay of AMP suppressed cells (median EC_{50} in nM, n = 3)

	Test article	$CD8^+ CD25^+$	Granzyme B^+
	CD421	*15*	*34*
Small molecules	AB680	10	47
Small molecules	OP-5244	7	8
mAbs	Oleclumab*	>1,000	>1,000
mAbs	Mupadolimab#	84	83

*Oleclumab biosimilar
#Mupadolimab biosimilar

CD421 EXHIBITS ADDITIONAL CD73 INHIBITION MECHANISMS

- **CD421 mediates receptor downregulation via CD73 internalization**

Activity	Small molecule	mAb	DFC
Receptor internalization	–	–/+++	+++

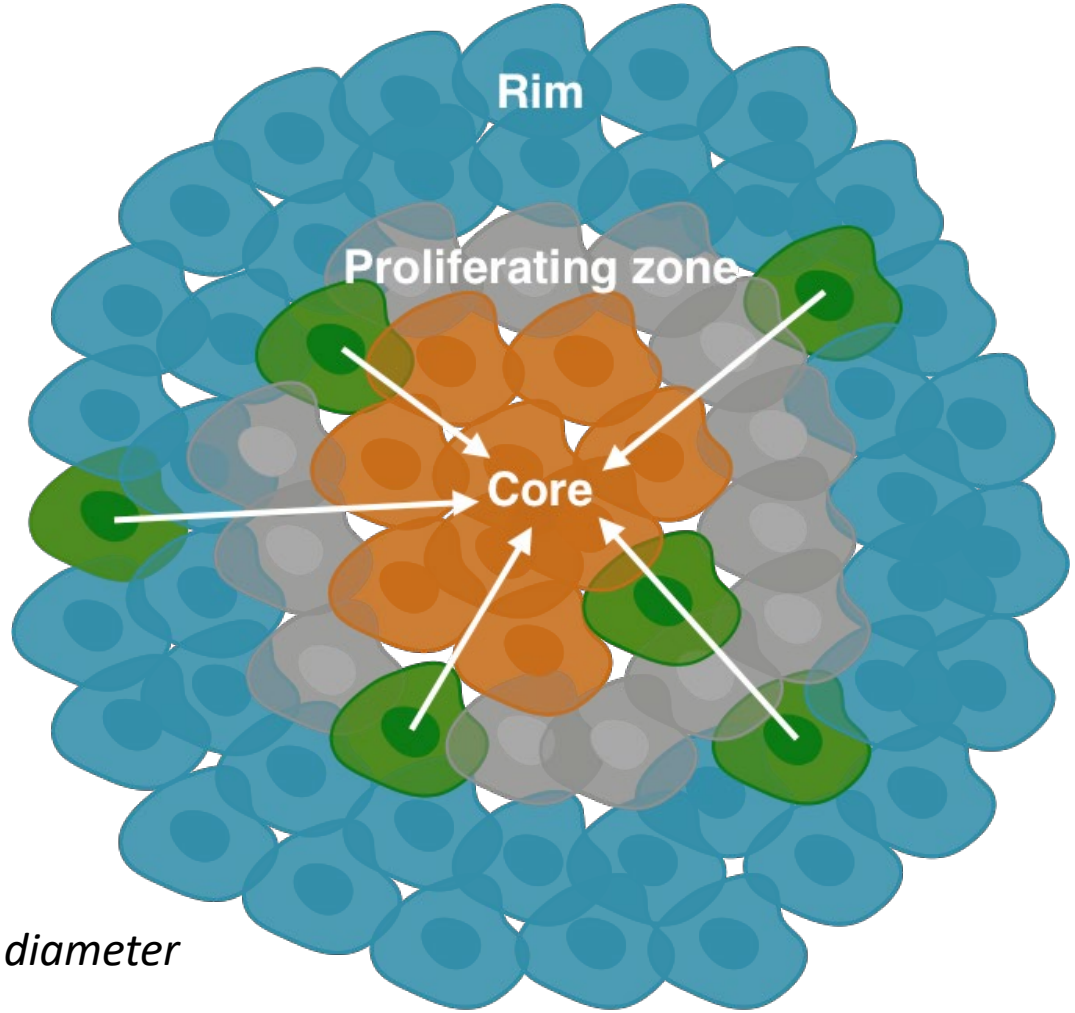
Receptor internalization (MDA-MB-231, EC_{50} in nM)

	Test article	EC_{50}
	CD421	*0.14*
Small molecules	AB680	No Activity
Small molecules	OP-5244	No Activity
mAbs	Oleclumab*	<0.03
mAbs	Mupadolimab#	0.055

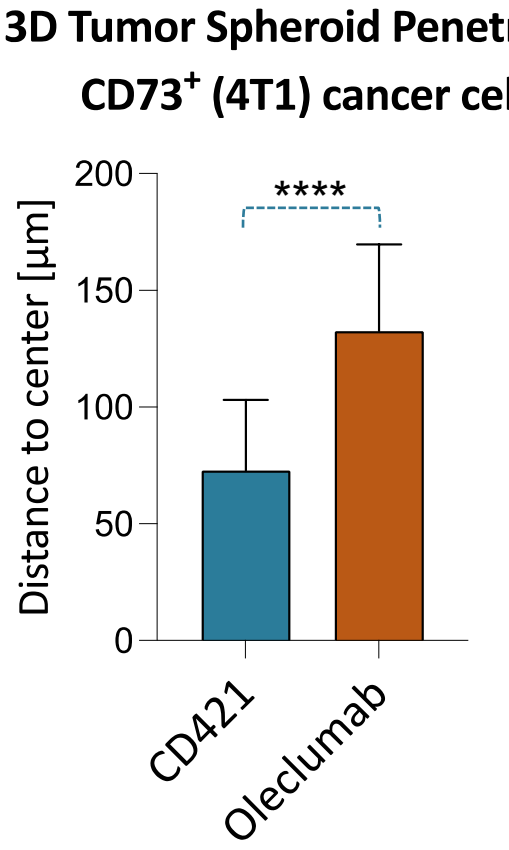
*Oleclumab biosimilar
#Mupadolimab biosimilar

CD73 DFCs DEMONSTRATE SUPERIOR TUMOR PENETRATION VS mAbs

- **CD421 penetrates deeper into 3D tumor spheroids (4T1)**



400 µm diameter

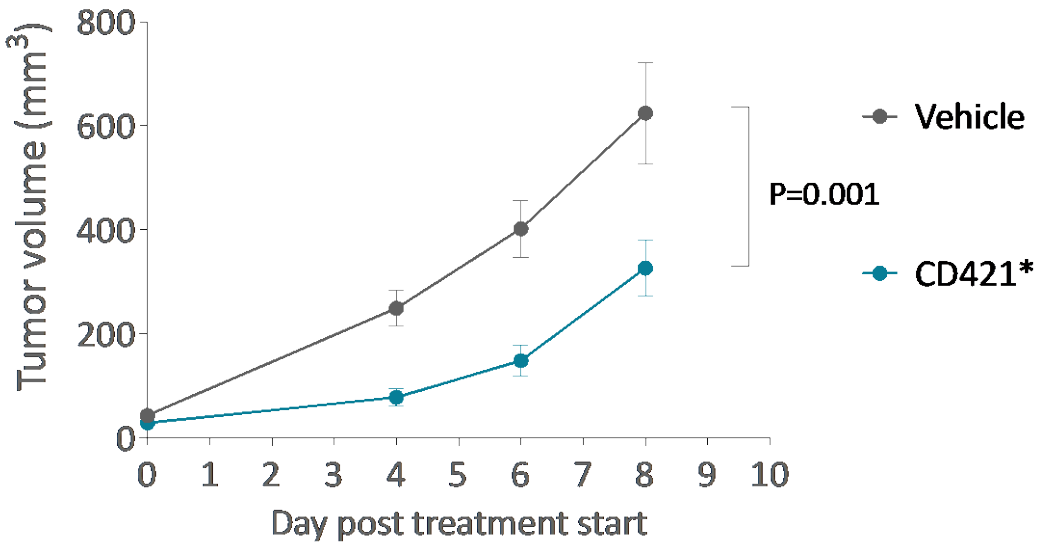


CD421 DEMONSTRATES ROBUST ACTIVITY *IN VIVO* AGAINST MULTIPLE MURINE CANCER CELL LINES

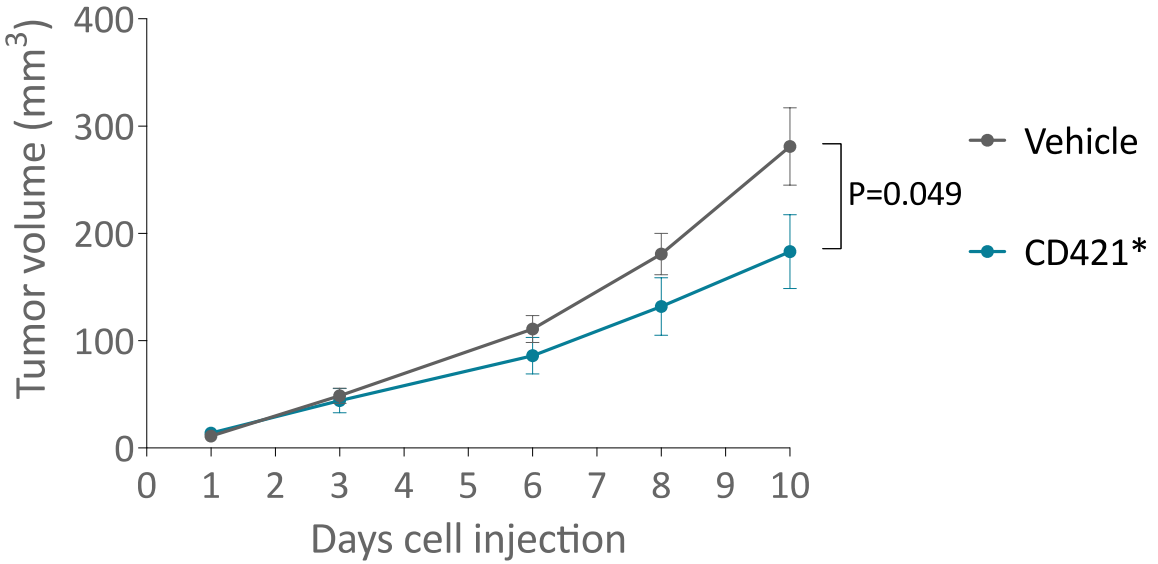
CD421 in vitro potency translates to activity in murine efficacy models

CT26 = CD73-
EMT6 = CD73+

Tumor Volume (CT26)
(Single 20 mg/kg dose)

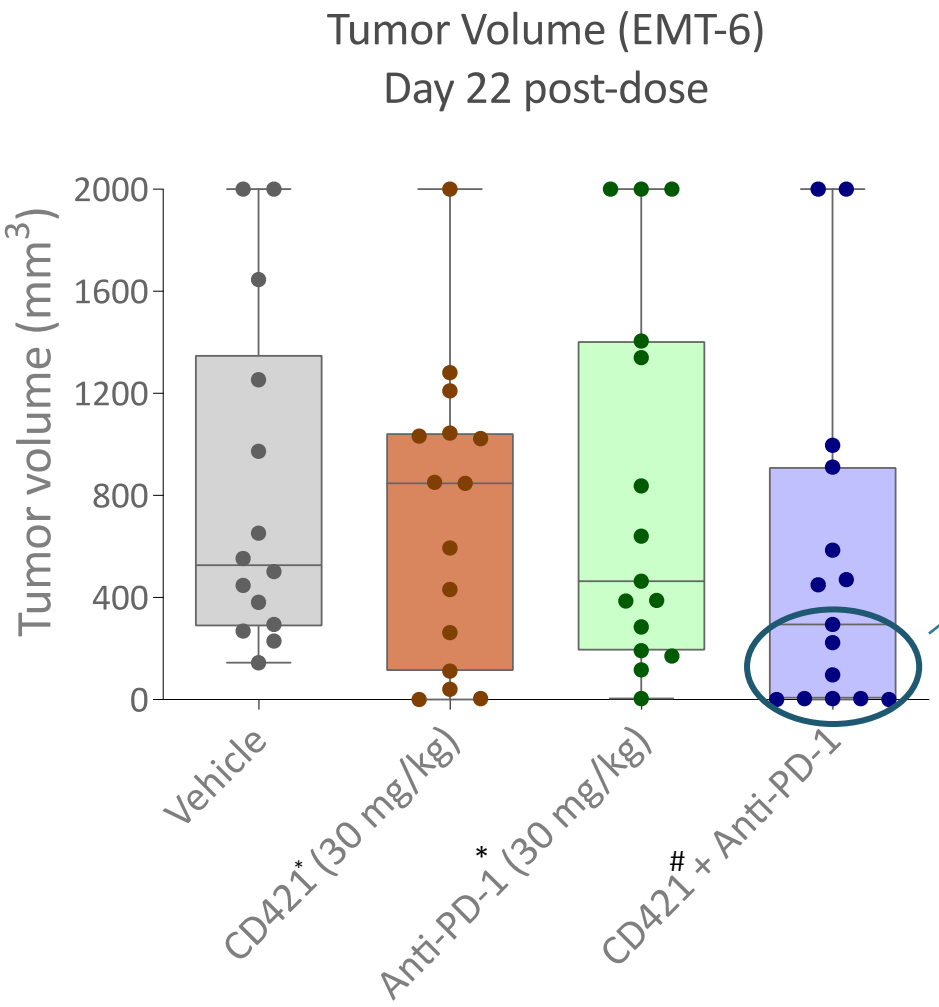


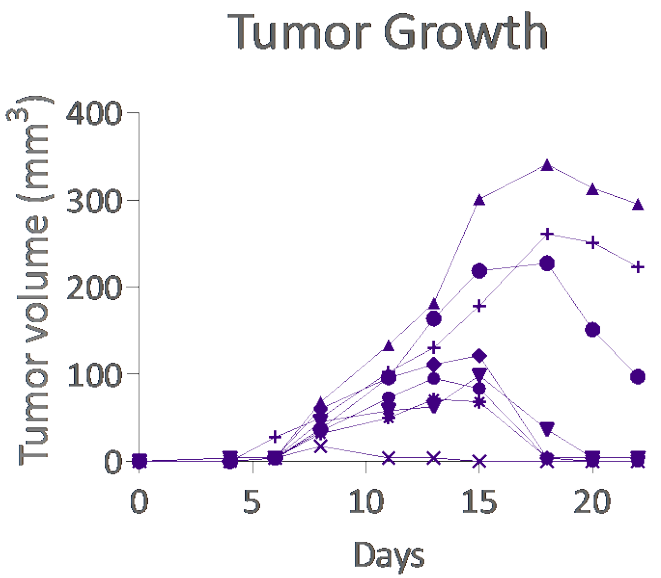
Tumor Volume (EMT-6)
(30 mg/kg dose, 2x/wk)



* Earlier version of CD421 with a different immune silencing amino acid substitution

CD73 - PD-1 INHIBITOR COMBINATIONS REVERSED TUMOR GROWTH IN >50% OF MICE

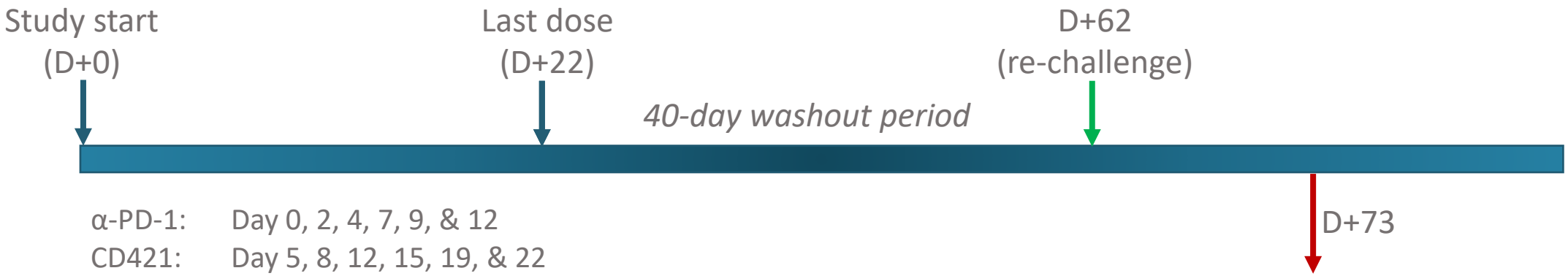




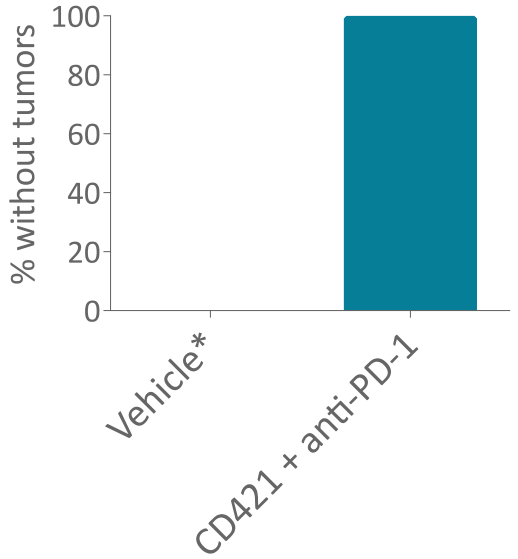
Study Arm	% Tumor regression	% Complete response (Day 36)
Vehicle	0	0
CD421	27 (4/15)	13 (2/15)
Anti-PD-1	13 (2/15)	7 (1/15)
CD421 + Anti-PD-1	**53 (8/15)**	**40 (6/15)**

*RMP1-14
#Earlier version of CD421 with a different immune silencing amino acid substitution

MICE WITH FULL TUMOR REGRESSION DEMONSTRATE IMMUNITY



% of Regressed Mice with Full Tumor Immunity



CD421 HAS SIGNIFICANT POTENTIAL FOR DIFFERENTIATION

- **Data suggests that CD421 could demonstrate best-in-class activity:**
  - CD421 fully inhibits cell-anchored and soluble forms of CD73
  - CD421 induces receptor internalization and downregulation of CD73 receptors expressed on a human breast cancer cell line
  - CD421 demonstrates superior activity to biologic CD73 inhibitors in restoring activation of human peripheral blood mononuclear cells (PBMCs) in the presence of AMP
  - Combined attributes of CD421 translate to activity in murine solid tumor models, particularly in combination with a PD-1 inhibitor
  - Preclinical evidence that CD421 penetrates tumors more deeply than CD73 targeting mAbs
  - Promising non-GLP safety data in rat and monkey

CIDARA THERAPEUTICS

Acknowledgements – *Preclinical development of CD421*

Cidara Therapeutics:

Les Tari (CSO) and the rest of the management team
Department of Chemistry
Department of Protein Chemistry
Department of Microbiology
Department of Immunology
Department of Preclinical Development

All questions and comments welcome

CIDARA THERAPEUTICS