Celyad Oncology

Research and Development Day Virtual Webinar

July 20, 2021

Forward Looking Statements

This presentation may contain forward-looking statements, within the meaning of applicable securities laws, including the Private Securities Litigation Reform Act of 1995. Forward-looking statements include statements about our expectations and next steps for our armored CAR T franchise and our plans to build next generation allogenic candidates**;** statements regarding the clinical activity and safety and tolerability of CYAD-211, CYAD-203, and CYAD-101; expectations regarding enrollment and the announcement of additional clinical data; outcomes and timelines of the IMMUNICY-1 clinical trial and KEYNOTE-B79 Phase 1b trial; and the timeline of submission of IND application for CYAD-203. Forward-looking statements may involve known and unknown risks and uncertainties which might cause actual results, financial condition, performance or achievements of Celyad Oncology to differ materially from those expressed or implied by such forward-looking statements. Such risk and uncertainty include the duration and severity of the COVID-19 pandemic and government measures implemented in response thereto. A further list and description of these risks, uncertainties and other risks can be found in Celyad Oncology's U.S. Securities and Exchange Commission (SEC) filings and reports, including in its Annual Report on Form 20-F filed with the SEC on March 24, 2021 and subsequent filings and reports by Celyad Oncology. These forward-looking statements speak only as of the date of publication of this document and Celyad Oncology's actual results may differ materially from those expressed or implied by these forward-looking statements. Celyad Oncology expressly disclaims any obligation to update any such forward-looking statements in this document to reflect any change in its expectations with regard thereto or any change in events, conditions or circumstances on which any such statement is based, unless required by law or regulation.

Today's Agenda

Topic	Speaker
Welcome & Introductions	Filippo Petti
Redefining Allogeneic CAR T	Filippo Petti
Update on CYAD-211 for r/r MM	Charlie Morris, M.D.

shRNA Platform
• Armored CAR T Franchise
  • Introduction to CYAD-203
• Optimized for Multiplexed CAR Ts
  • Future programs
	David Gilham, Ph.D.

Update on CYAD-101 for mCRC	Charlie Morris, M.D.
Final Remarks and Q&A	All

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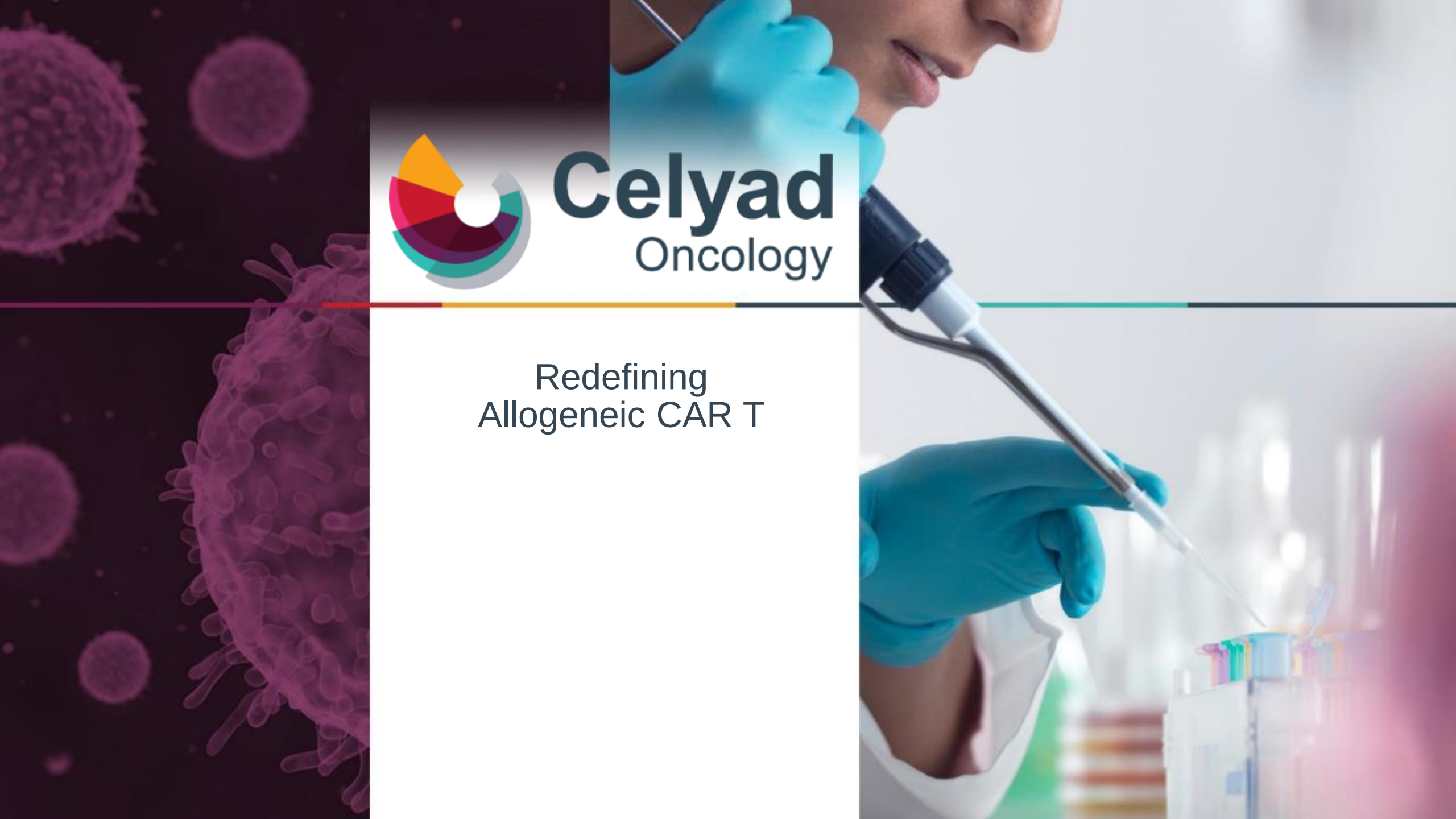
Redefining Allogeneic CAR T



Evolution of CAR T Landscape Towards Off-the-Shelf Approaches

Allogeneic CAR Ts offer several benefits compared to autologous CAR Ts

Quality of Therapy

- Derived from healthy donor T cells
- Opportunity to optimize manufacturing process to decrease variability between therapies

Speed / Access

- Faster turnaround time from cancer treatment decision to infusion – days vs. months
- Improved intent-to-treat metrics given therapy is “on demand”
- Potential to address larger patient populations with less logistical hurdles

Cost Effective

- Scalability of manufacturing to generate dozens of treatments vs. single patient treatment
- Potential to improve pharmacoeconomic benefits

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Expected Real-World Benefits of Our Approach to Allogeneic CAR T

Differentiation Factor	Key Characteristics	Expected Real-World Benefit(s)
• All-in-One Vector	• Single vector for all elements of the CAR T therapy	• Lower cost of goods sold (COGS) – vector costs are a major contributor to COGS. Using a single vector avoids the costs associated with multi-vector technologies
	• Single transduction / expansion enables shorter manufacturing times	• T cells age with longer culture times. Short culture times maintain an optimal 'fit' T cell phenotype associated with therapeutic potential
• Multiplex Gene Engineering (Next-Generation Candidates)	• Ability to potentially knockdown simultaneously multiple gene targets of interest	• shRNA can target genes that are not suitable for gene editing • Opportunity to optimize therapy based on indication / disease of interest

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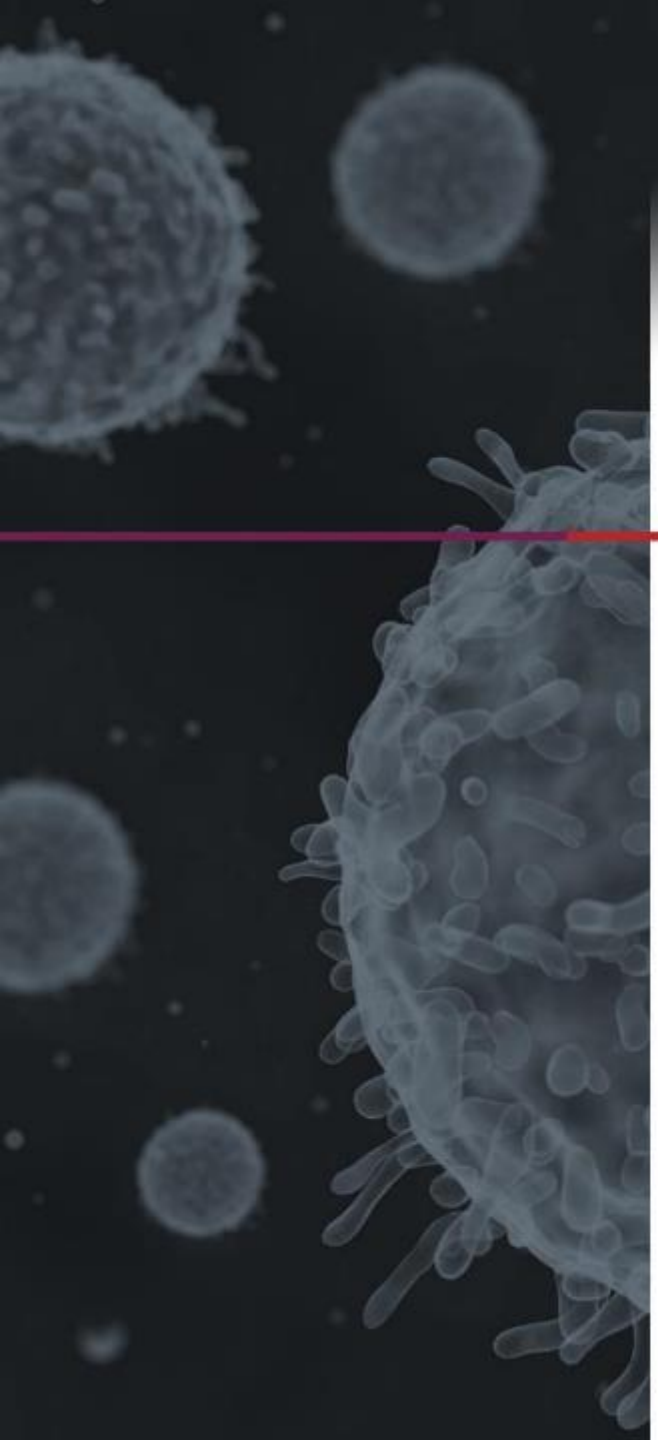
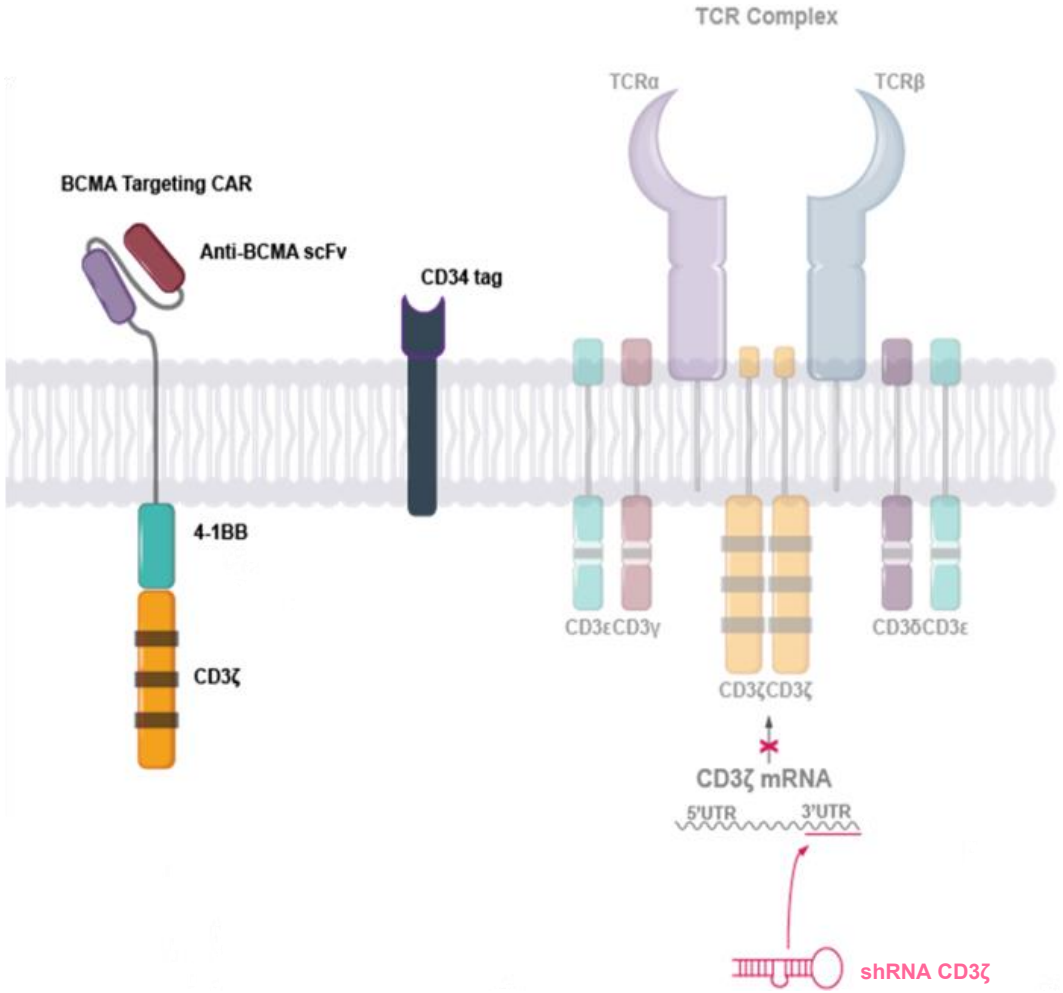
Update on CYAD-211 for r/r MM



CYAD-211 – shRNA-based Allogeneic CAR T Candidate for r/r MM

Background on CYAD-211

- CYAD-211 is our first allogeneic CAR T candidate utilizing our All-in-One vector approach based on the shRNA technology
- CYAD-211 co-expresses:
  - CAR with a BCMA-specific engager
  - Allogeneic technology – single shRNA targeting CD3ζ component of TCR complex
  - Selection marker – truncated cell surface CD34 tag allows for positive cell enrichment during manufacturing



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BCMA: B-cell maturation antigen; r/r MM: relapsed/refractory multiple myeloma.

shRNA as a Novel Allogeneic Technology for CAR T

Keys to establishing technology proof-of-concept

- No evidence of GvHD
- Cell kinetics
- Initial clinical activity

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CYAD-211 – IMMUNICY-1 Phase 1 Trial

Open-label, Phase 1 dose-escalation trial in relapsed or refractory multiple myeloma patients

Study Design (1)

- Primary objective: safety and recommended dose of CYAD-211
- Dose escalation:
  - $30x10^6$, $100x10^6$ and $300x10^6$ cells per infusion
- Standard preconditioning: Cyclophosphamide 300 mg/m² / Fludarabine 30 mg/m² (3 days)

Patient Background

- Eight patients enrolled across three dose levels
- Median prior lines of therapy: four
- Six of eight (75%) patients exposed to all three major MM drug classes (proteasome inhibitors, immunomodulatory drugs, and CD38 specific therapy)

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1. NCT04613557 Safety, Activity and Cell Kinetics of CYAD-211 in Patients With Relapsed or Refractory Multiple Myeloma (IMMUNICY-1).

CYAD-211 – Summary of Initial Clinical Data – EHA June 2021

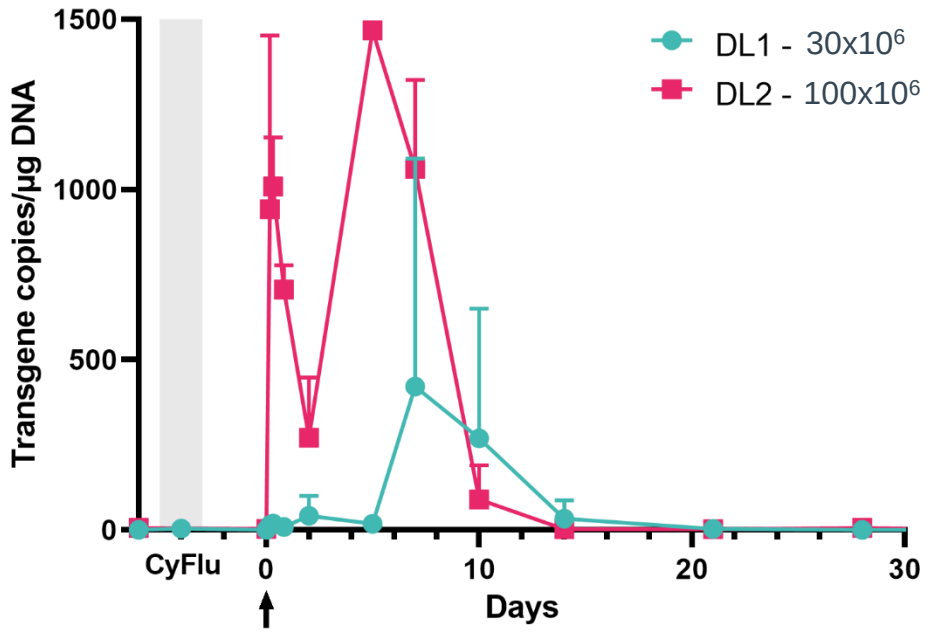
Favorable Tolerability Profile

- Of the six patients dosed at the first two dose levels ($30x10^6$ and $100x10^6$ cells per infusion):
  - No DLTs, no GvHD and no CAR T cell-related encephalopathy syndrome (CRES)
  - One cytokine release syndrome (CRS) Grade 1 (fever) reported at dose level 1

Signs of Clinical Activity

- Five evaluable patients:
  - Two patients achieved partial response (PR)
  - Three additional patients presented with stable disease (SD)

Positive Systemic Cell Engraftment



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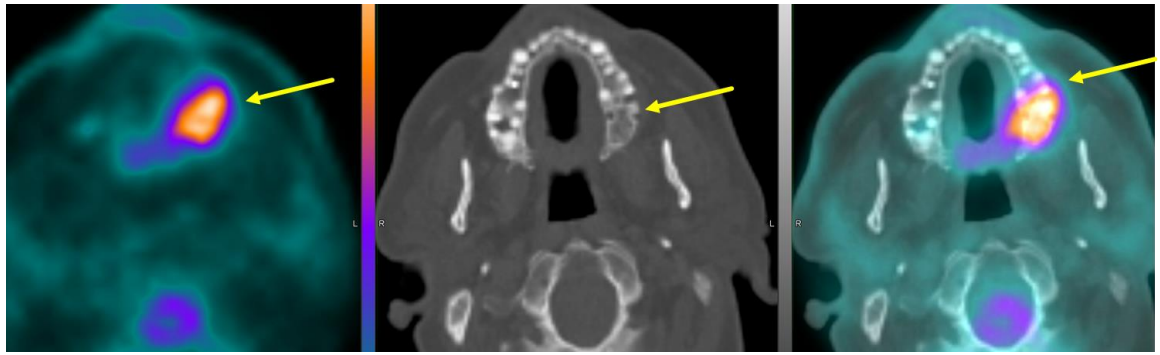
EHA: European Hematology Association; DLT: Dose-limiting toxicity; GvHD: Graft versus Host Disease. | Data from uncleaned database (May 24, 2021).

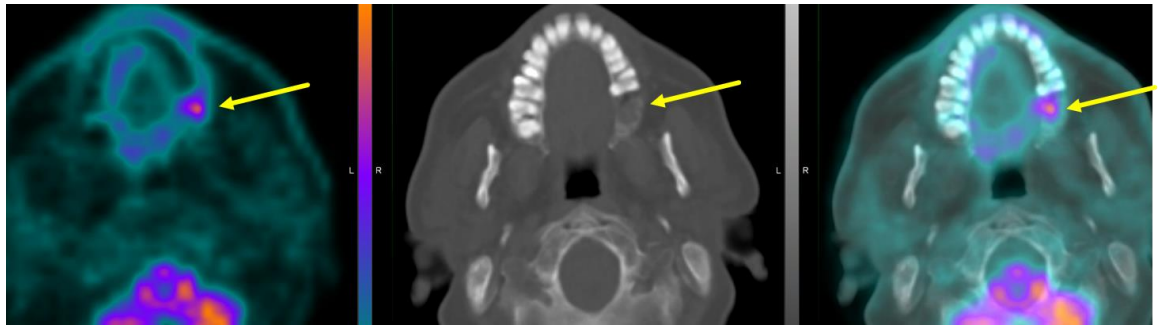
CYAD-211 Case Study – Response in Individual Lesions in Patient 5

Left Maxillary Bone

1 month prior to infusion (SUV 6.2)

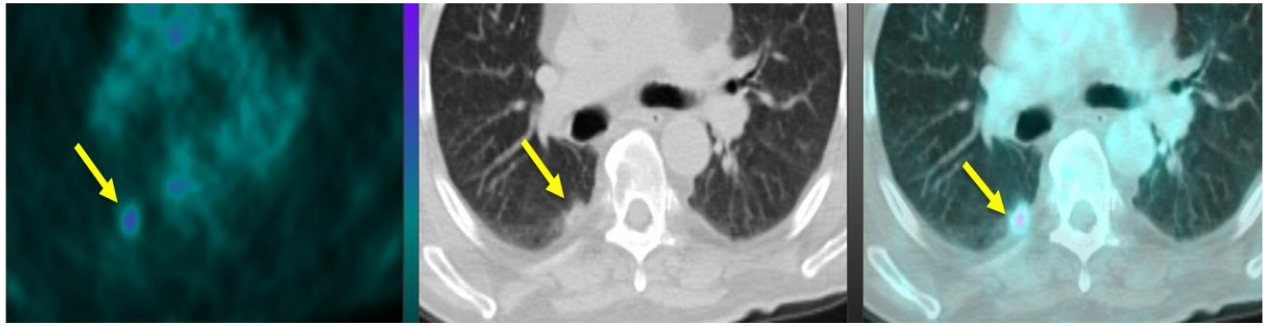


D57 post infusion (SUV 5)

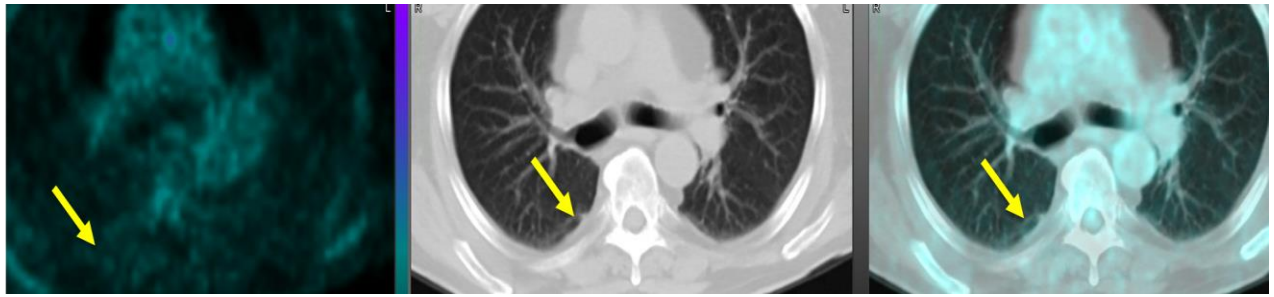


Right Lower Lobe (Superior segment)

1 month prior to infusion (SUV 2.5 – 1.6 x 0.8 cm)



D57 post infusion Resolved



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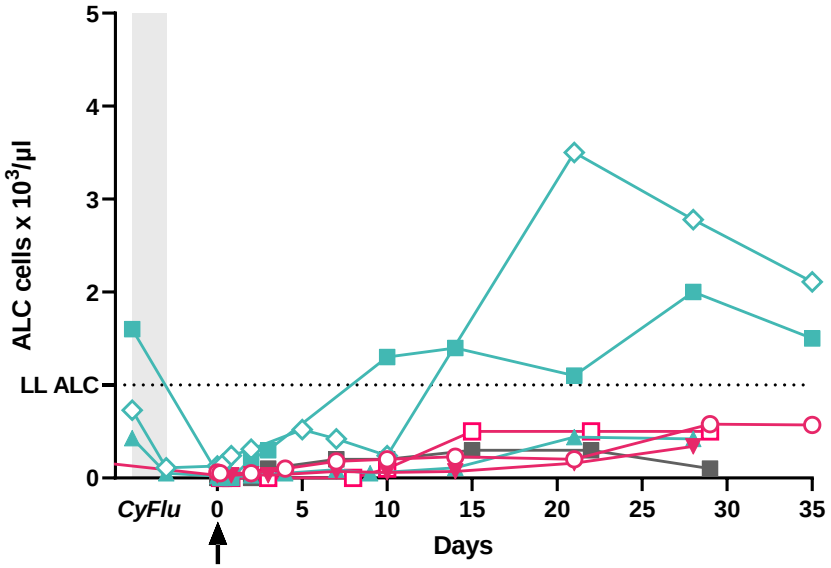
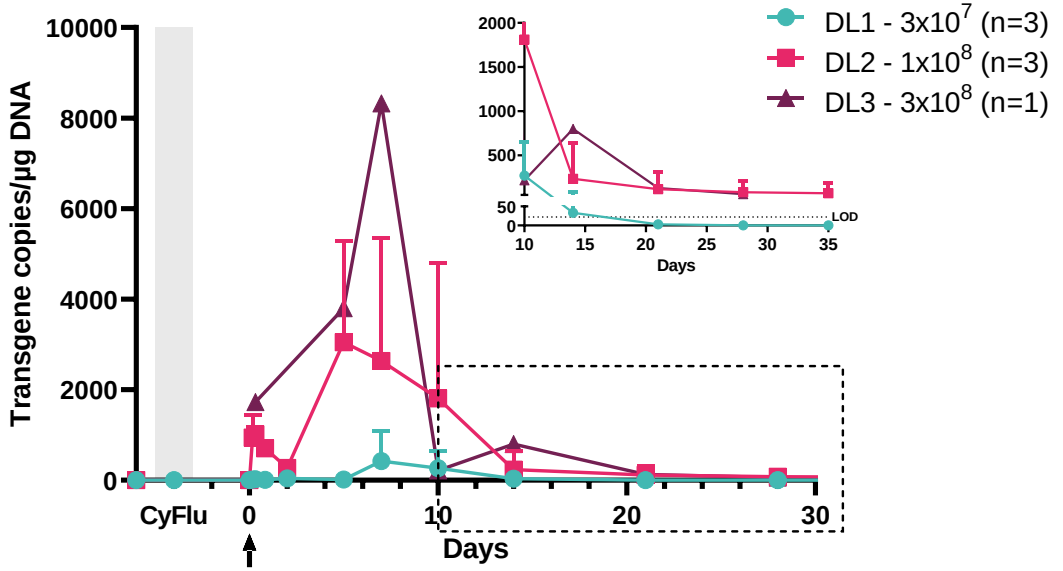
Cell Kinetics Updated with First Patient at Dose Level 3

CYAD-211 cell levels detected by PCR-based methods in all patients

Peripheral Blood Lymphocyte Count



CYAD-211 Cell Engraftment



- Duration and depth of lymphodepletion was variable in dose level 1 patients while patients in dose levels 2 and 3 showed similar lymphodepletion
- CYAD-211 cell levels detected by PCR-based methods in all patients
- Consistent with a dose dependent increase in cell engraftment
- No GVHD reported to date

DL: Dose level.

shRNA as a Novel Allogeneic Technology for CAR T

Keys to establishing technology proof-of-concept

- ☑ No evidence of GvHD
- ☑ Cell kinetics
- ☑ Initial clinical activity

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Next Steps for CYAD-211 IMMUNICY-1 Trial

- Enrollment ongoing in dose level 3 ($300x10^6$ cells per infusion)
- Plan to explore higher dose preconditioning regimens after dose level 3
- Additional data from the dose escalation trial expected during second half 2021

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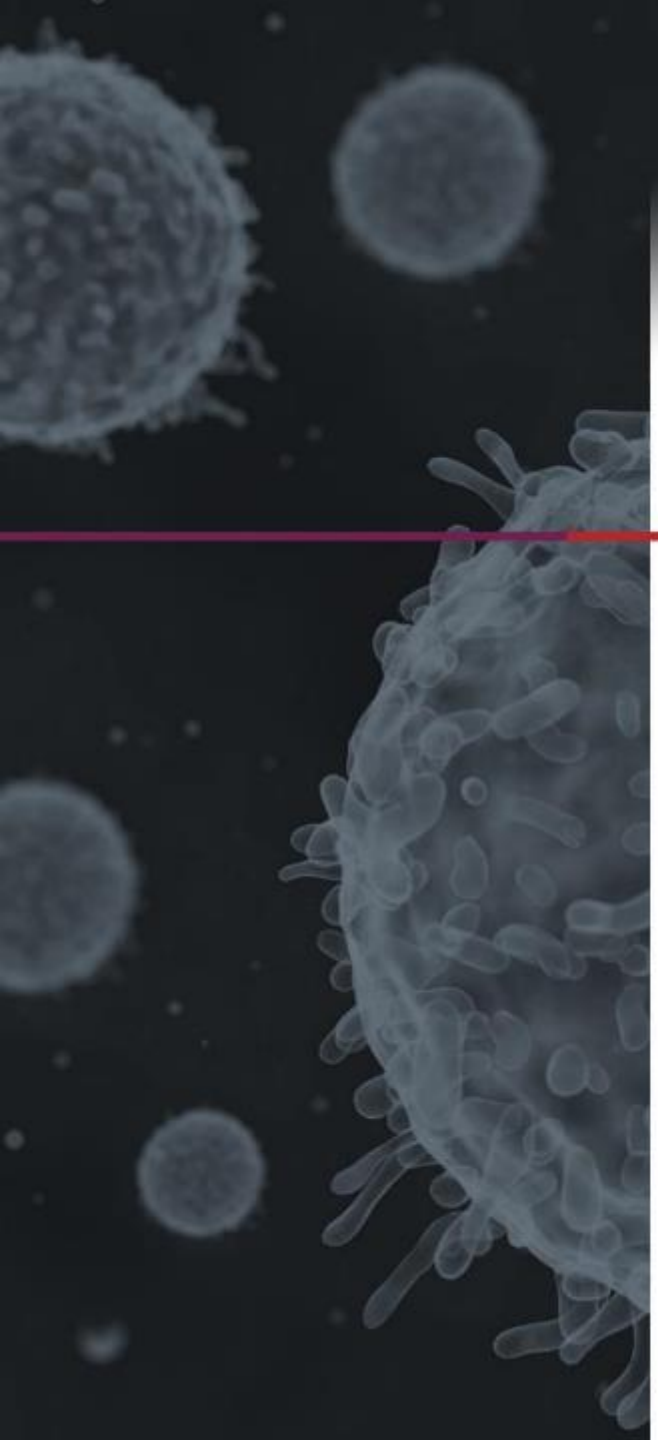
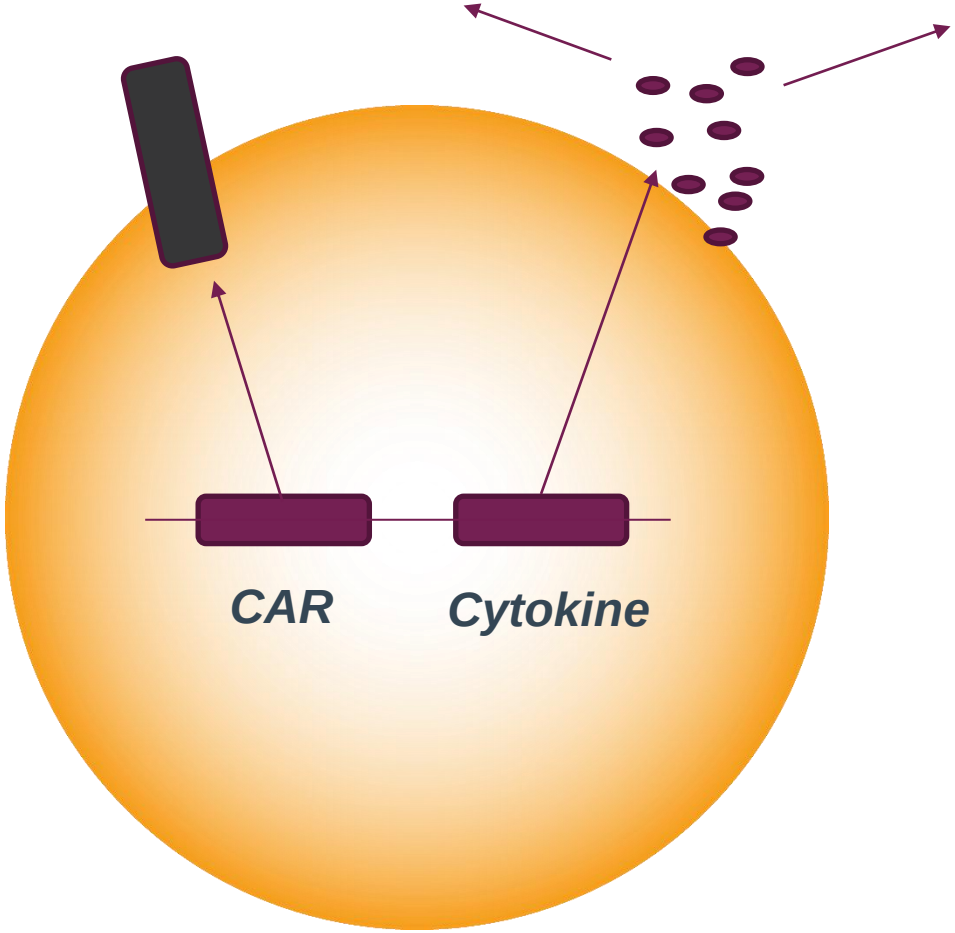
shRNA Platform – Armored CAR T Franchise



Armored CAR Ts to Target the Tumor Microenvironment

Autocrine effect –
CAR T function



Paracrine effect –
Impact the tumor microenvironment

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Armored CARs Using Interleuken-18 (IL-18)

Cell Reports. 2017 Dec 12;21(11):3205-3219. doi: 10.1016/j.celrep.2017.11.063.
PMID: 29241547.

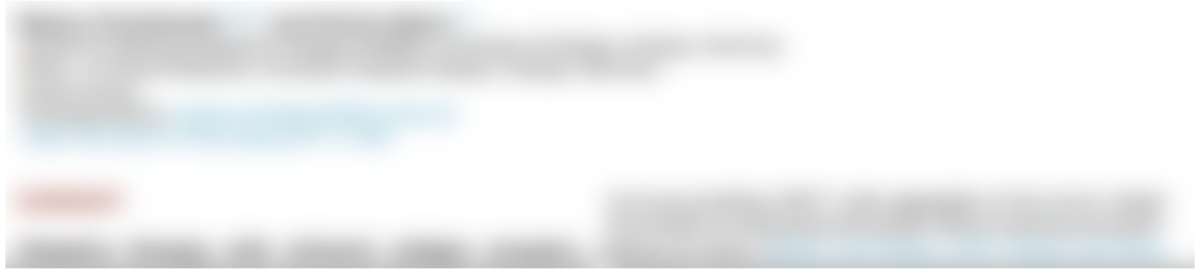
CAR T Cells Releasing IL-18 Convert to T-Bet^{high} FoxO1^{low} Effectors that Exhibit Augmented Activity against Advanced Solid Tumors

Markus Chmielewski and Hinrich Abken

Cell Reports. 2017 Sep 26;20(13):3025-3033. doi: 10.1016/j.celrep.2017.09.002.
PMID: 28954221; PMCID: PMC6002762.

Augmentation of Antitumor Immunity by Human and Mouse CAR T Cells Secreting IL-18

Biliang Hu, Jiangtao Ren, Yanping Luo, Brian Keith, Regina M. Young, John Scholler, Yanging Zhao and Carl H. June



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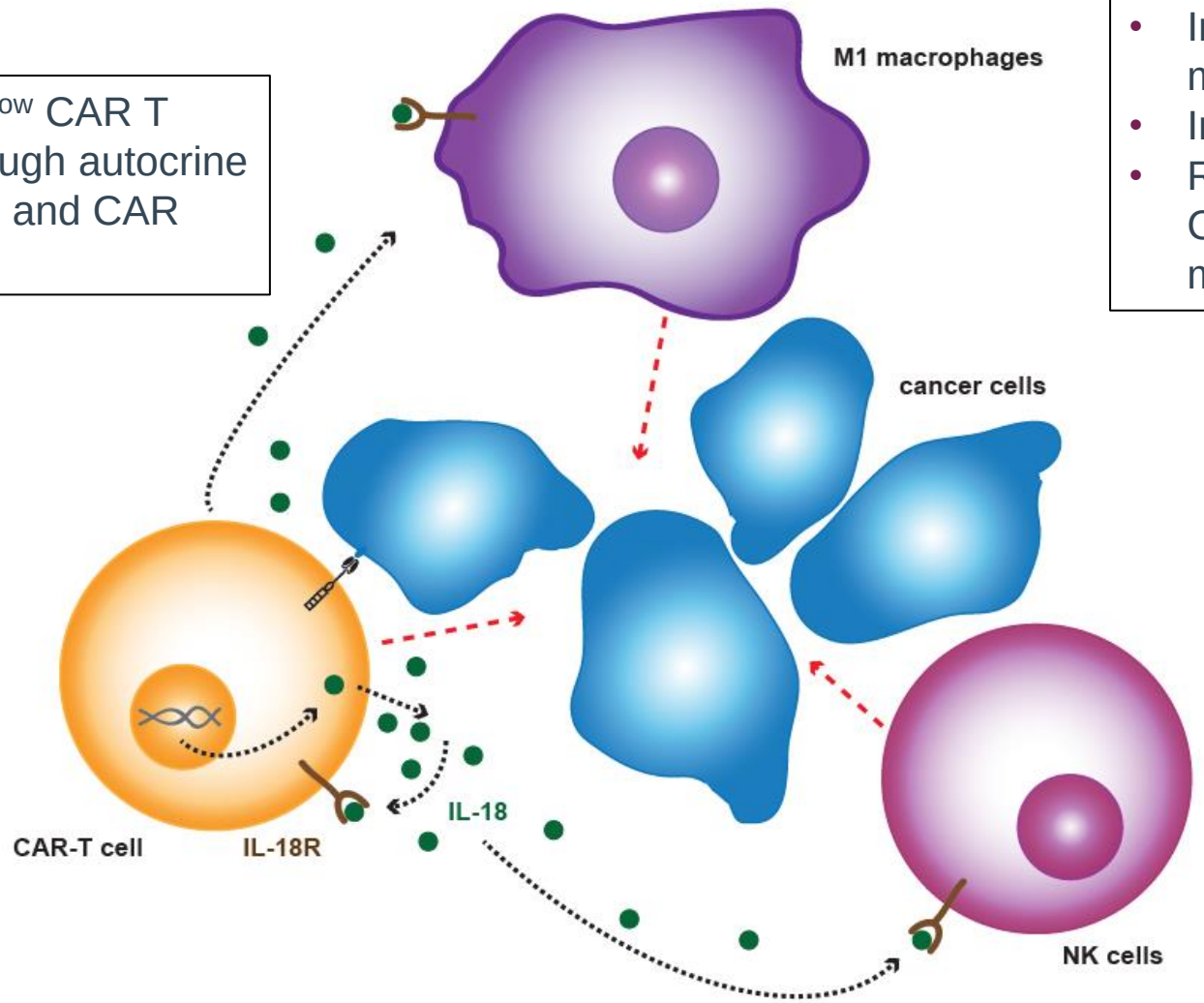
Expected Mechanism of Action – IL-18 Influence on CAR T Cells Local Environment

Strong proliferation and anti-tumor activity in vivo

Tbet^{high} FoxO1^{low} CAR T phenotype through autocrine activity of IL-18 and CAR stimulation



Mouse models: IL-18

- Increased CD206^{-} M1 macrophages
- Increased NKG2D^{+} NK cells
- Reduced Treg, suppressive CD103^{+} dendritic cells and M2 macrophages

- IL-18 binding protein is present in serum (2-3,000 pg/mL) at levels far in excess of IL-18 (80-120 pg/mL)
- High affinity of IL-18BP for IL-18 (400 pM)
- Role of IL-18BP is thought to be in controlling excessive pro-inflammatory responses

Dinarello et al. (2013) Frontiers in Immunology 4(article 289) 1-10

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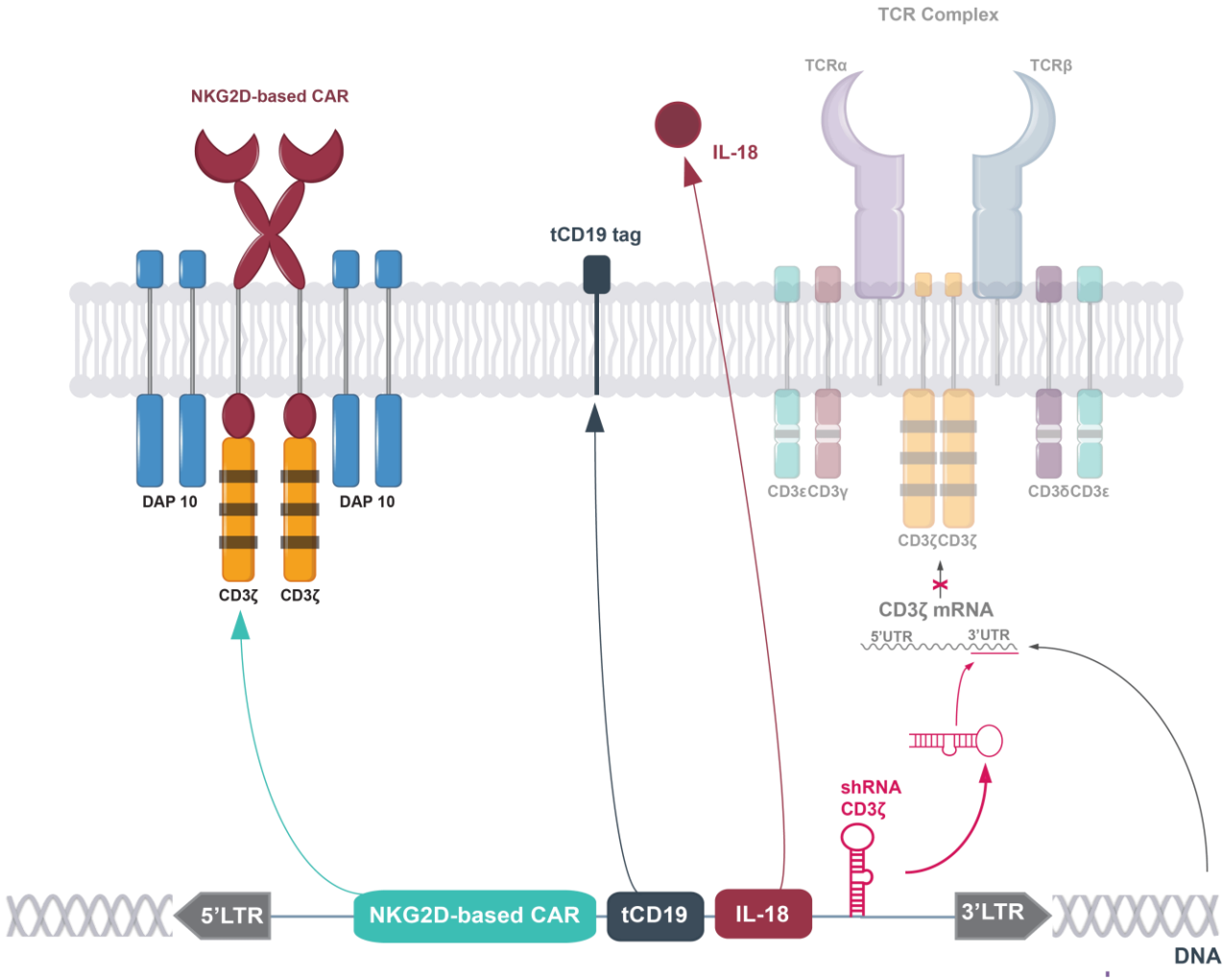
CYAD-203 – Armored NKG2D Receptor Allogeneic CAR T for Solid Tumors

Background on CYAD-203

- CYAD-203 is a novel allogeneic, armored CAR T candidate using shRNA technology within our All-in-One vector approach.
- CYAD-203 co-expresses:
  - NKG2D-based CAR
  - Allogeneic technology – single shRNA targeting CD3ζ component of TCR complex
  - Active form of IL-18
  - Selection marker – truncated cell surface CD19 tag allows for cell purification during manufacturing



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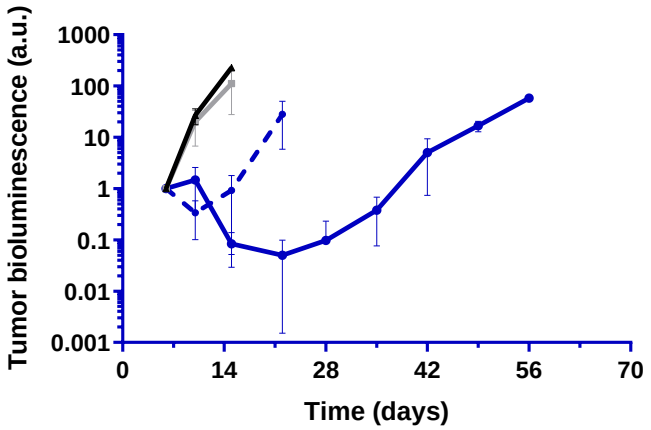
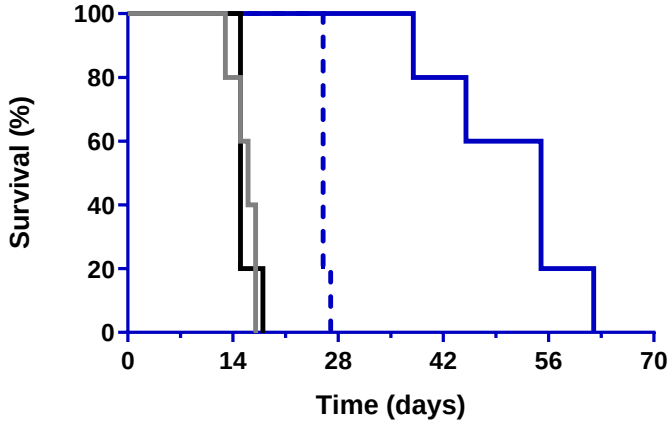
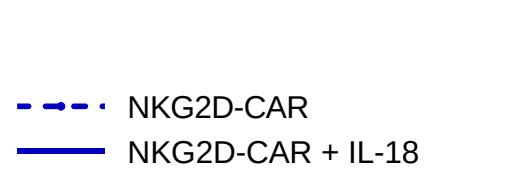
IL-18 Secretion Enhances Activity of NKG2D Receptor CAR T Cells

Proof-of-principle of IL-18 established in preclinical models

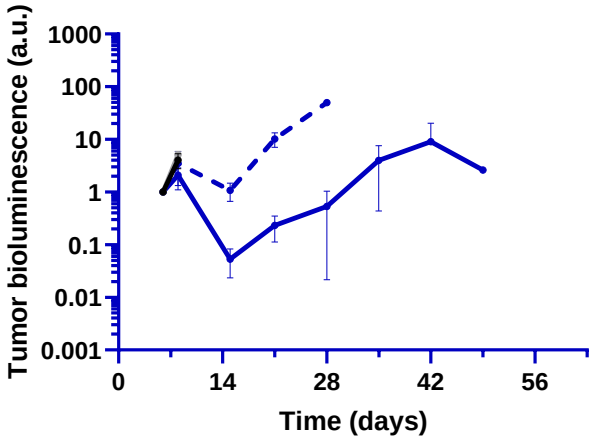
NKG2D CAR + IL-18

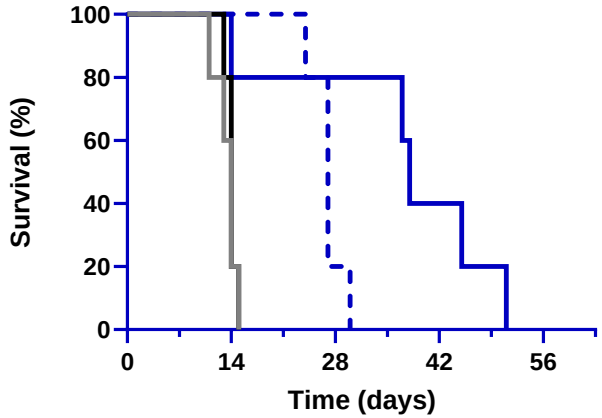


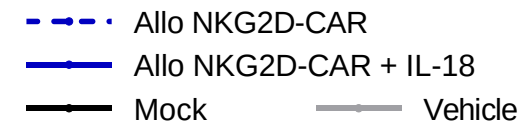




NKG2D CAR + IL-18 + shRNA CD3ζ







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Next Steps for Armored CAR T Franchise

CYAD-203 Program

- Investigational New Drug (IND) enabling studies ongoing
- Anticipate submission of IND application in mid-2022
- To our knowledge, CYAD-203 on track to be first IL-18 secreting *allogeneic* CAR T candidate

Additional Armored CAR Ts

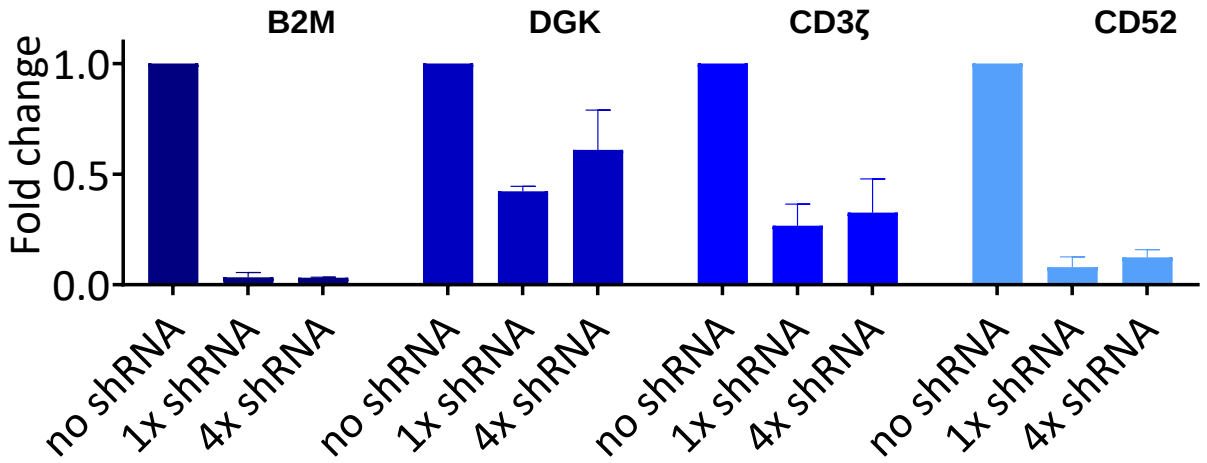
- Currently evaluating the co-expression of IL-18 in multiple discovery stage next-generation, shRNA-based allogeneic CAR T candidates
- Opportunity to drive series of differentiated candidates for both solid tumors and hematological malignancies

shRNA Platform – Optimized for Multiplexed CAR Ts

Evolution of shRNA Technology for Next-Generation Allogeneic CAR T

Transition from Single shRNA to Multiplexing

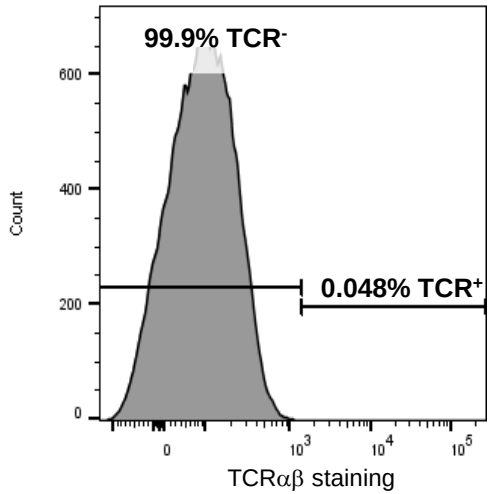
- CYAD-211 and CYAD-203 employ a single shRNA targeting CD3ζ (CD247)
- Targeting multiple genes with shRNA to optimize functionality is an obvious next step given the breadth of the technology
  - At ASCO 2020, demonstrated concurrent knockdown of up to four different gene products (multiplexing) in T lymphocyte cell line with our first-generation shRNA scaffold



Ongoing shRNA Multiplex Research Focused on Key Targets

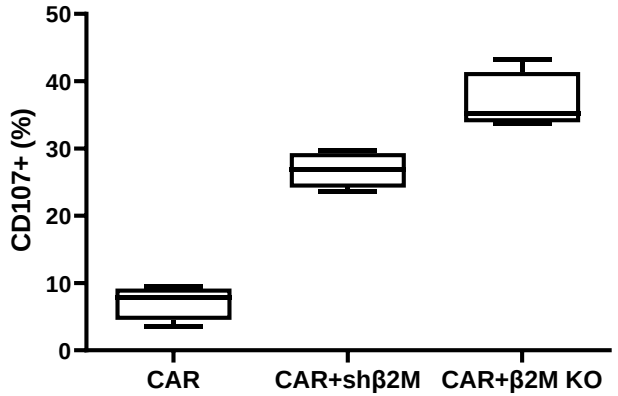
CD3ζ (CD247)

- Component of the TCR complex
  - Knockdown of TCR designed to prevent Graft versus Host Disease (GvHD)
- shRNA targeting approach validated through CYAD-211 program



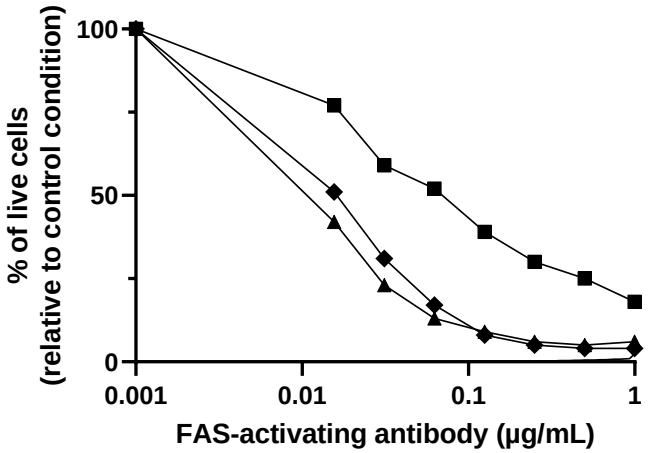
Beta-2-microglobulin (β2M)

- Component of the MHC Class I molecules
  - Knockdown of β2M designed to prevent Host versus Graft disease (HvG) allowing for greater cell persistence



FAS (CD95)

- Cell surface death receptor whose activation leads to apoptosis
  - Knockdown of FAS designed to prevent apoptosis and improve persistence



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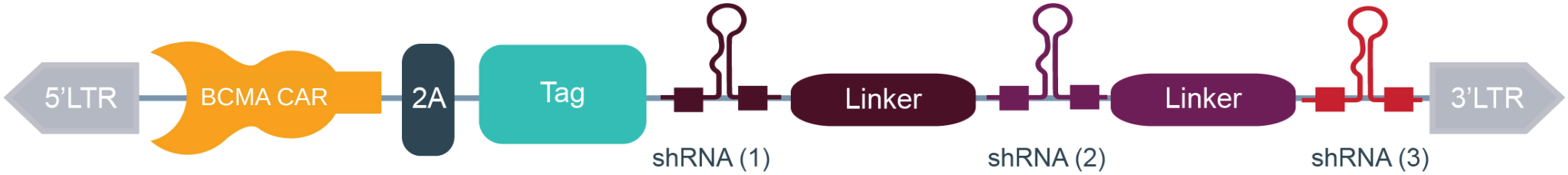
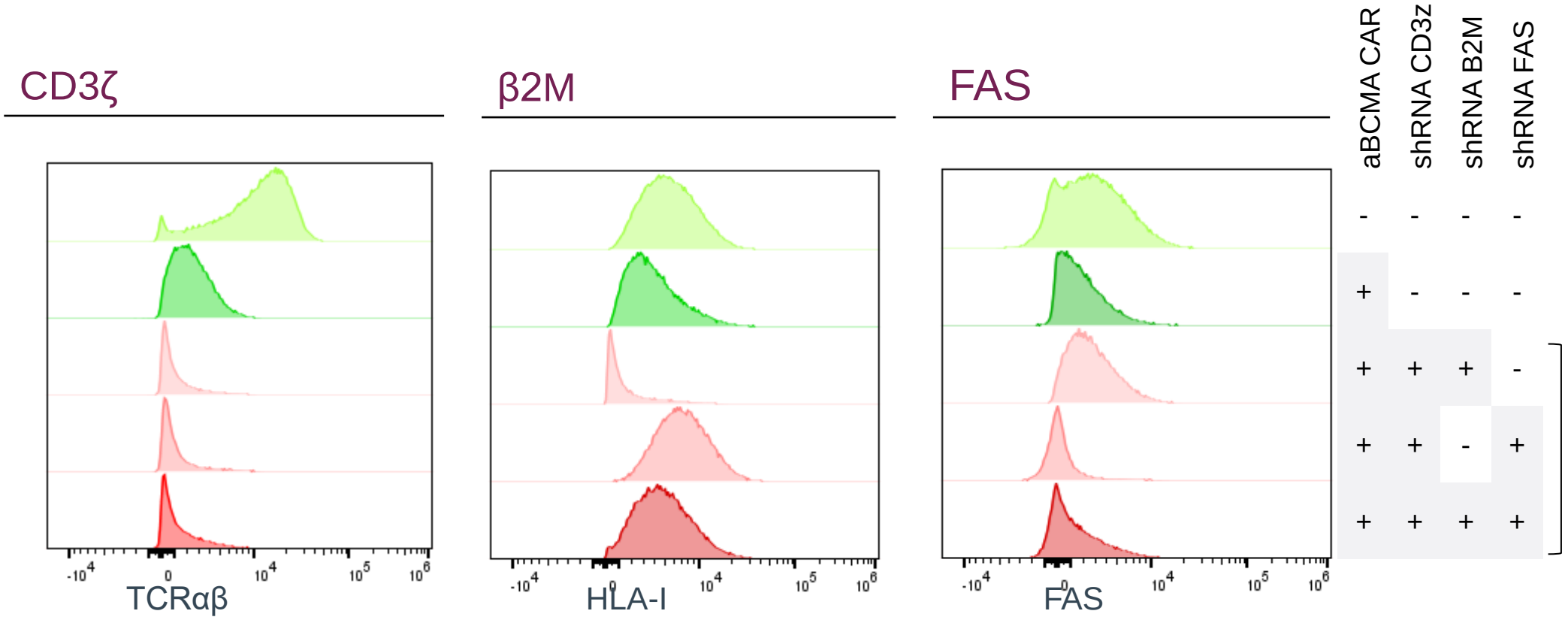
Multiplexing with First Generation shRNA Scaffold

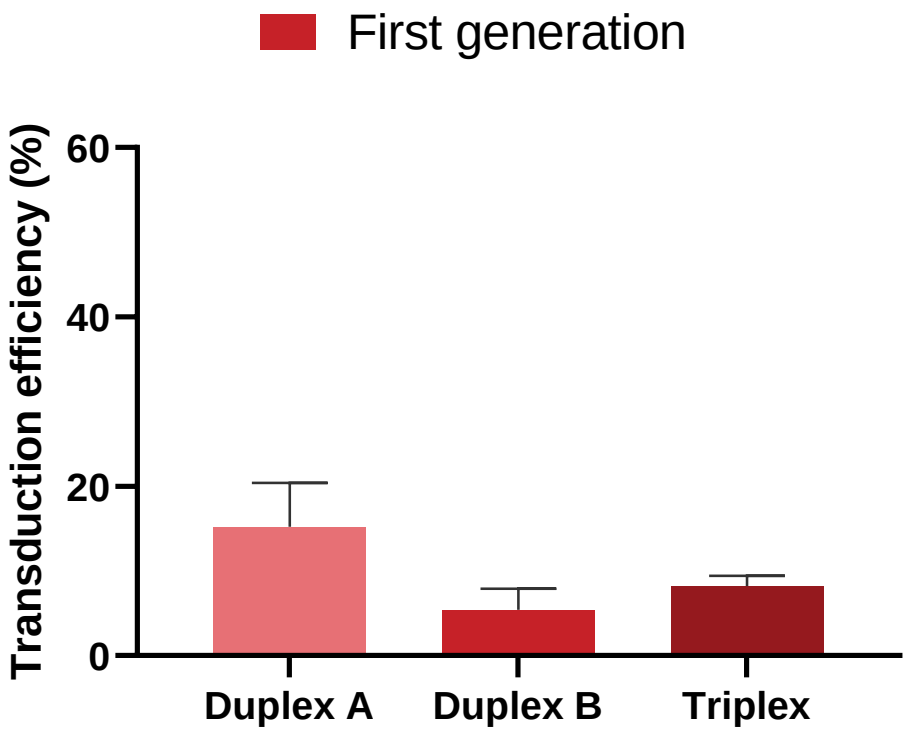




BCMA: B-cell maturation antigen

First Generation shRNA Scaffold – Transduction Efficiency

Targeting multiple genes using first generation shRNA scaffold impacts transduction efficiencies



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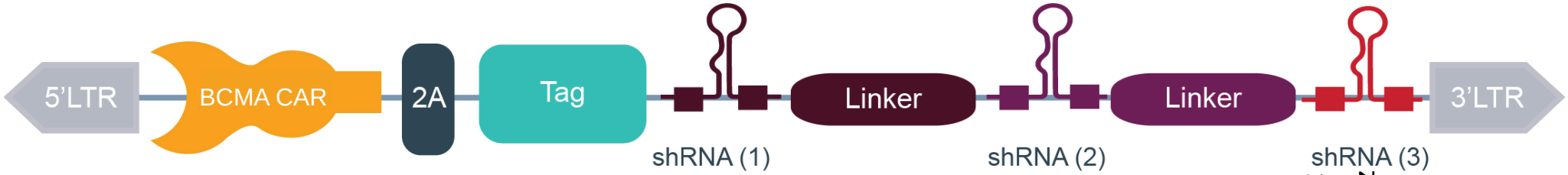
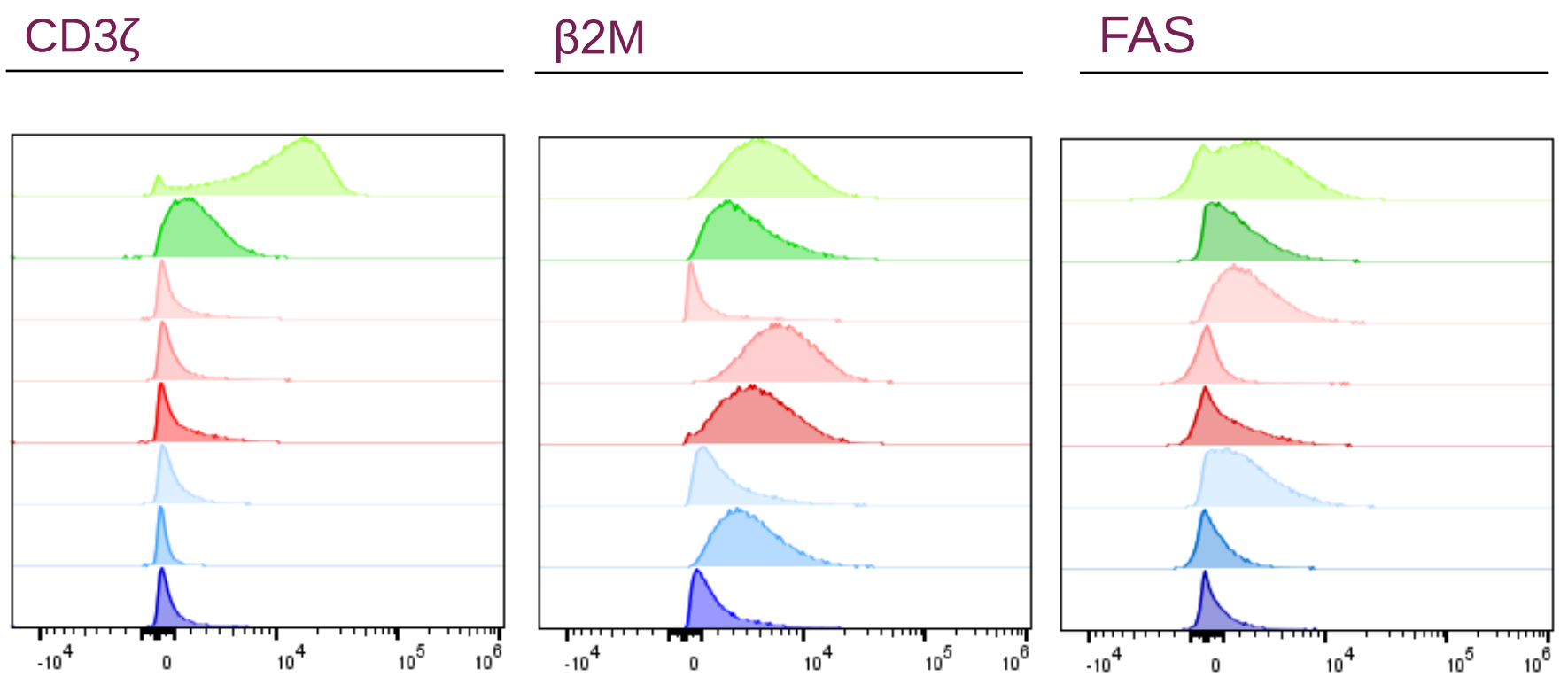
Multiplexing with Novel Second Generation shRNA Scaffold





aBCMA CAR	shRNA CD3z	shRNA B2M	shRNA FAS	
-	-	-	-	
+	-	-	-	
+	+	+	-	First Generation
+	+	-	+	First Generation
+	+	+	+	First Generation
+	+	+	-	Second Generation
+	+	-	+	Second Generation
+	+	+	+	Second Generation

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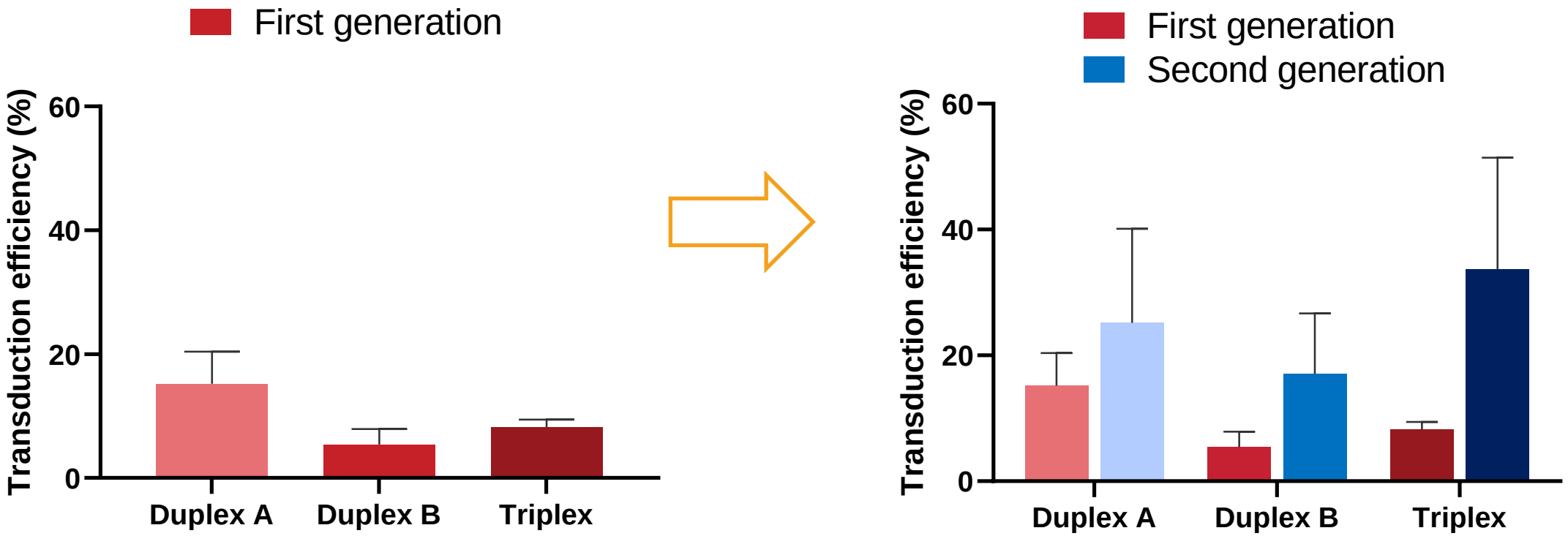
Second Generation shRNA Scaffold – Transduction Efficiency

Broad increase in transduction efficiencies with second generation shRNA scaffold



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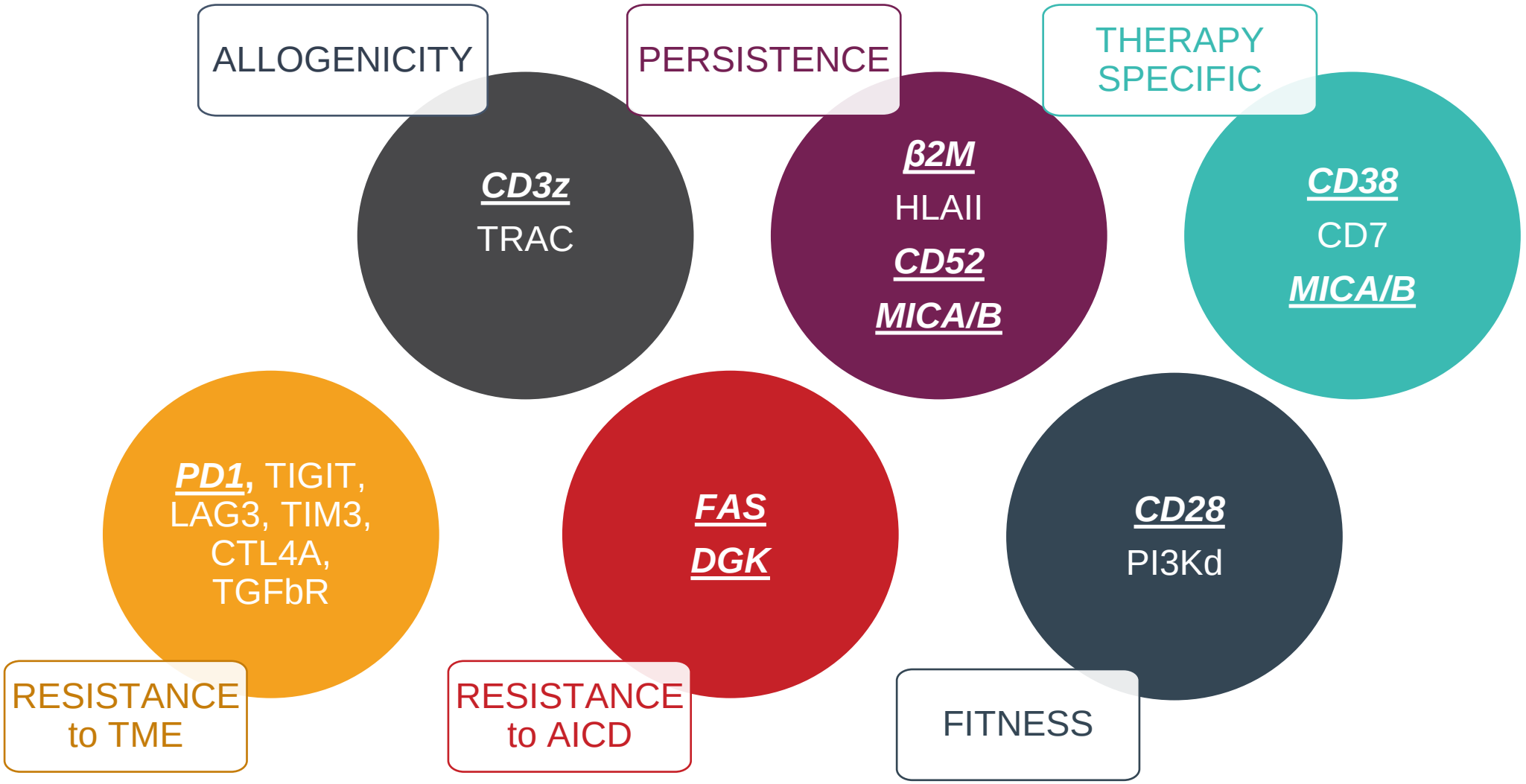
Next Steps for Multiplexing Research – Illustrative shRNA Targets



Bold/italicized/underlined targets currently evaluated in-house

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TME: Tumor microenvironment; AICD: Activation induced cell death

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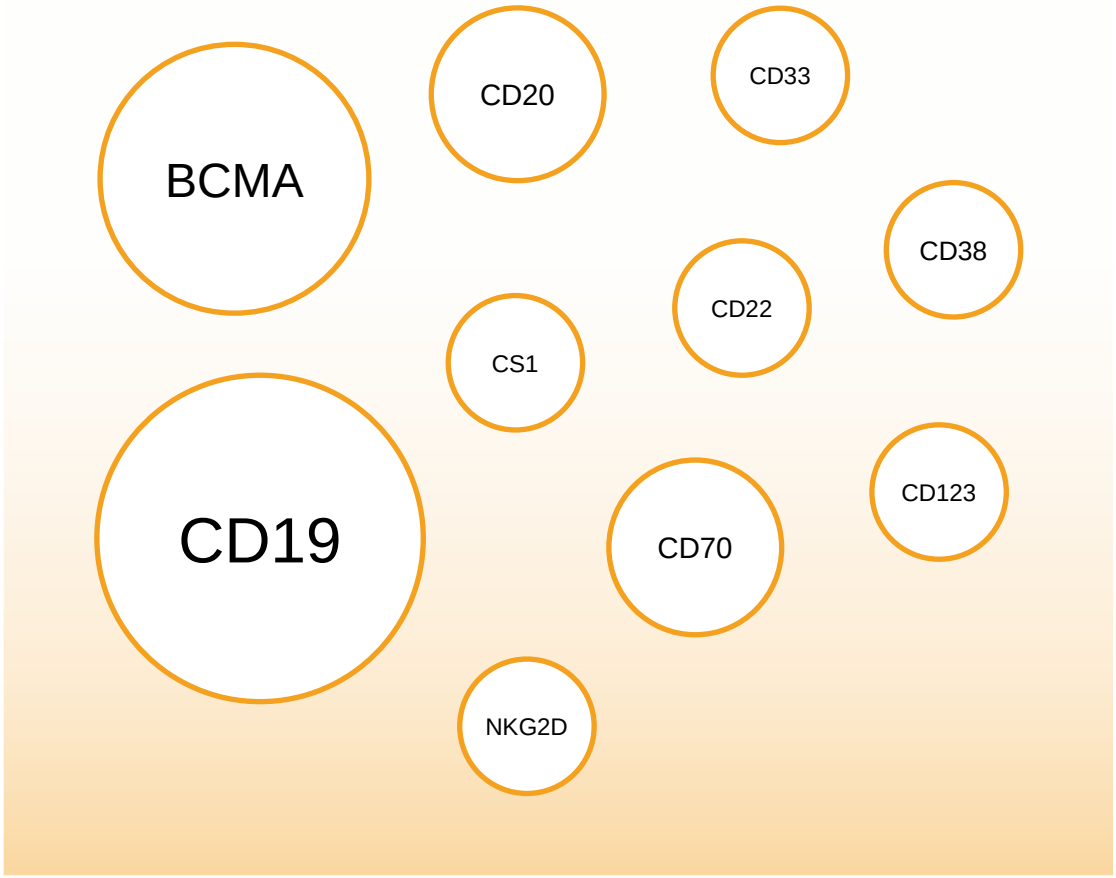
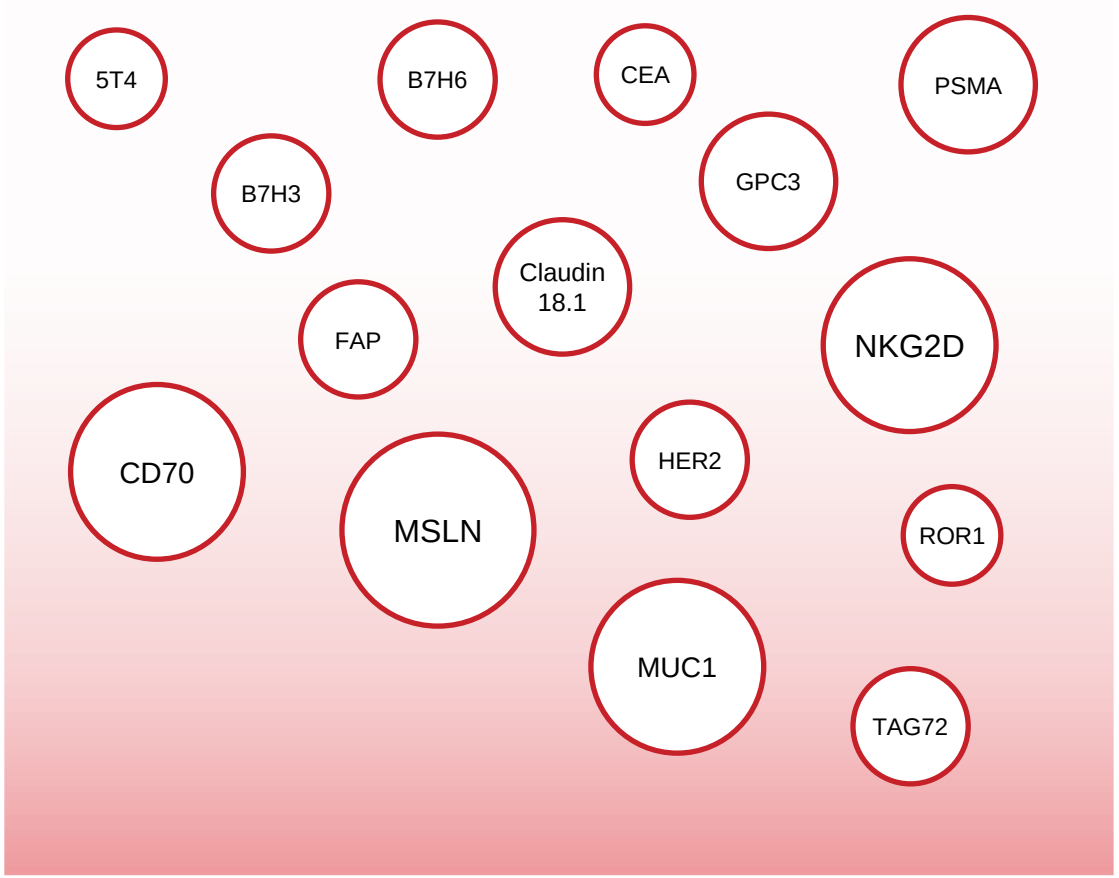
shRNA Platform – Future Programs

Allogeneic CAR T Competitive Landscape – Key Targets of Interest

Hematological



Solid Tumors



Target represented by number of clinical/preclinical candidates in development

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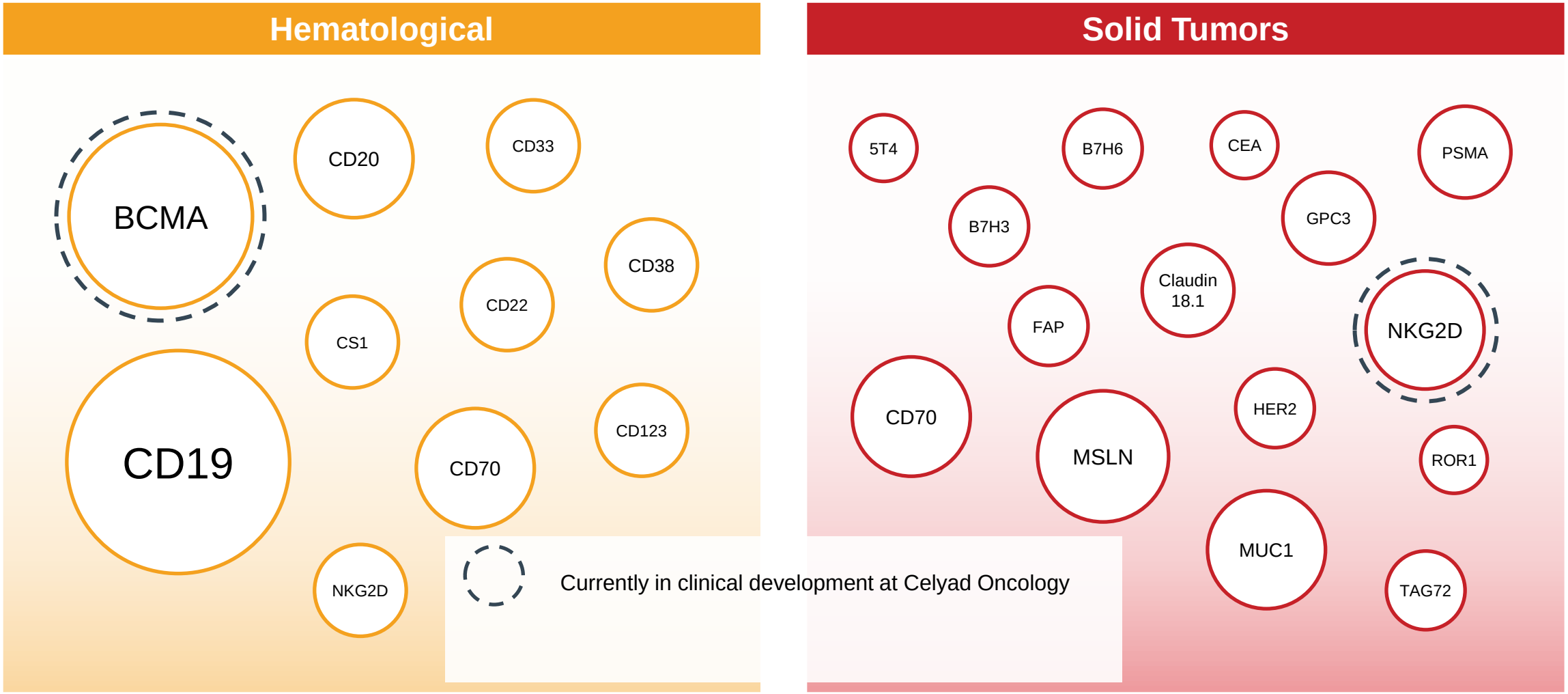
Source: Company disclosures. Includes αβ T cell, γδ T cell and IPSC-derived T cells.

Allogeneic CAR T Competitive Landscape – Key Targets of Interest



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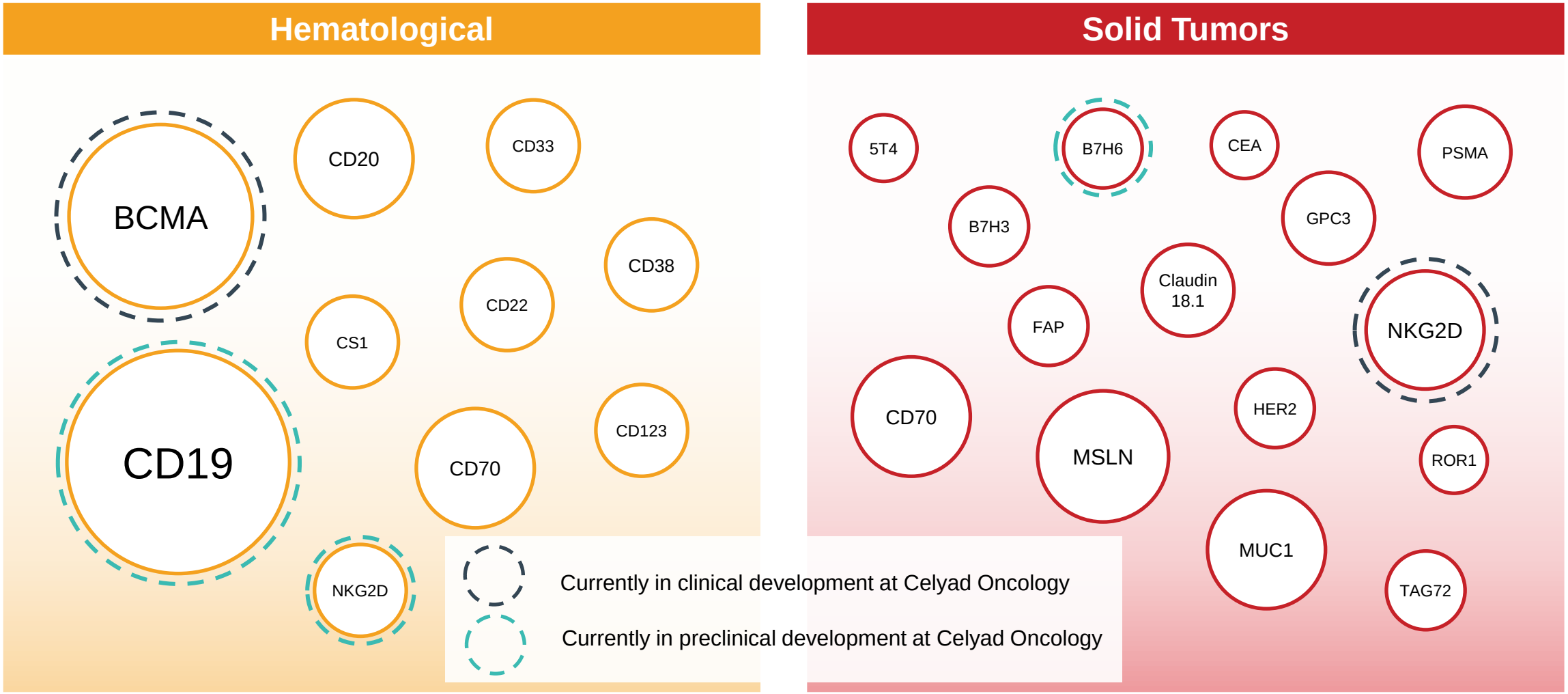
Allogeneic CAR T Competitive Landscape – Key Targets of Interest



Target represented by number of clinical/preclinical candidates in development

Source: Company disclosures. Includes αβ T cell, γδ T cell and IPSC-derived T cells.

Allogeneic CAR T Competitive Landscape – Key Targets of Interest

Hematological

BCMA

CD20

CD33

CD19

CD70

NKG2D

Solid Tumors

5T4

B7H6

CEA

PSMA

B7H3

GPC3

Claudin 18.2

FAP

NKG2D

HER2

CD70

MSLN

ROR1

MUC1

TAG72

- We recently acquired an exclusive license from the Moffitt Cancer Center for an antibody directed to Tumor-associated Glycoprotein (TAG-72)
- TAG-72 has been shown to be expressed in a wide variety of epithelial malignant tissues including breast, colon and pancreatic cells and will expand the Company's program portfolio in solid tumor targets (1)

Currently in clinical development at Celyad Oncology

Currently in preclinical development at Celyad Oncology

Target represented by number of clinical/preclinical candidates in development

Source: Company disclosures. Includes αβ T cell, γδ T cell and IPSC-derived T cells

1: Shu R, Evtimov VJ, Hammett MV, Nguyen NN, Zhuang J, Hudson PJ, Howard MC, Pupovac A, Trounson AO, Boyd RL. Engineered CAR-T cells targeting TAG-72 and CD47 in ovarian cancer. Mol Ther Oncolytics. 2021 Jan 16;20:325-341. doi: 10.1016/j.omto.2021.01.002. PMID: 33614914; PMCID: PMC7868933.

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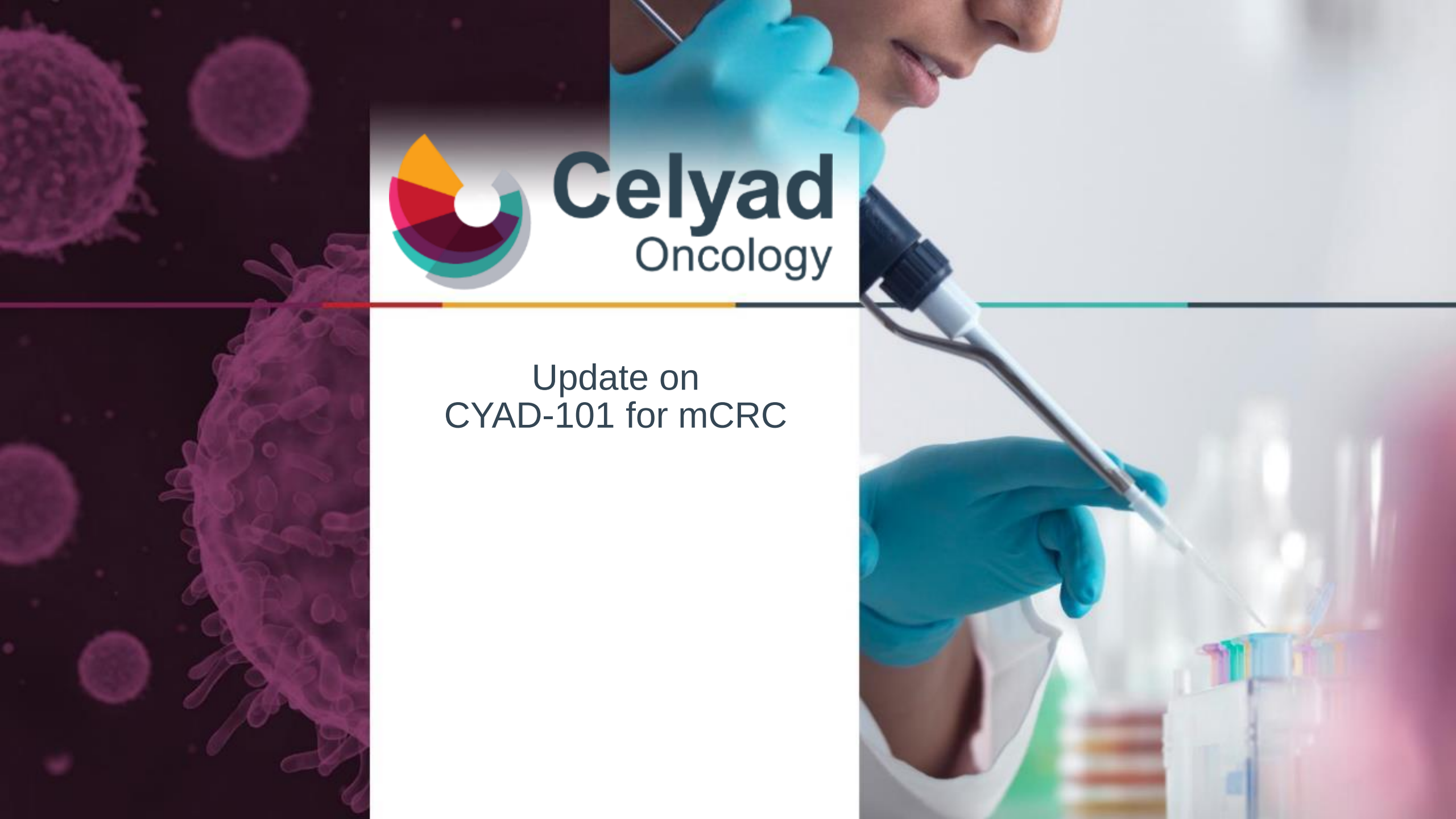
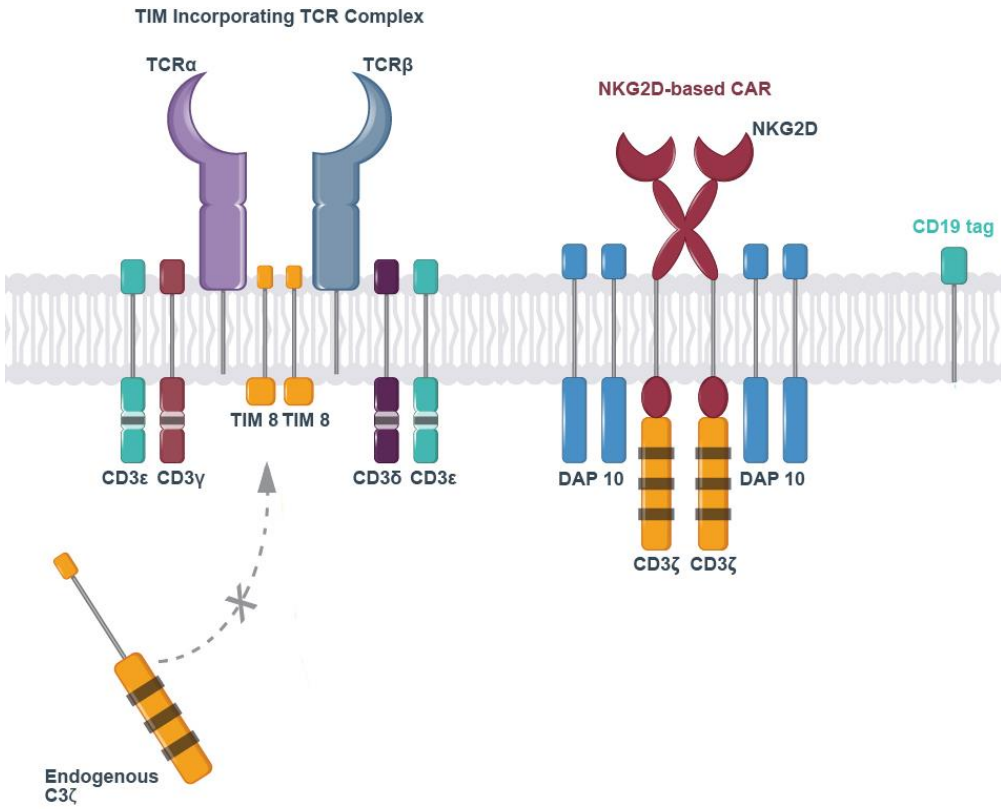
Update on CYAD-101 for mCRC



CYAD-101 – Leading Allogeneic CAR T Candidate for mCRC

Background on CYAD-101

- NKG2D receptor-based CAR, TCR Inhibitory Molecule (TIM) and selection marker
  - All-in-One vector approach based on TIM technology
  - Single transduction
  - Avoids multiple genetic modifications and cost associated with additional GMP grade materials
- TIM inhibits CD3ζ and reduces signaling of TCR complex
  - Believed to reduce potential for Graft versus Host Disease (GvHD)
- alloSHRINK Phase 1 trial is evaluating CYAD-101 with preconditioning chemotherapy for the treatment of recurrent/progressing mCRC



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CYAD-101 – alloSHRINK Phase 1 Trial

Study Overview (1)

- Patient population
  - mCRC after at least one metastatic treatment line
  - FOLFIRI segment: PD under FOLFIRI
- Treatment schedule
  - Three CYAD-101 infusions administered Q2W 48 hrs post preconditioning chemotherapy
- Primary objective: Safety (GvHD, CRS, CRES)
- Secondary objective: Clinical activity
- Exploratory evaluation: CYAD-101 engraftment

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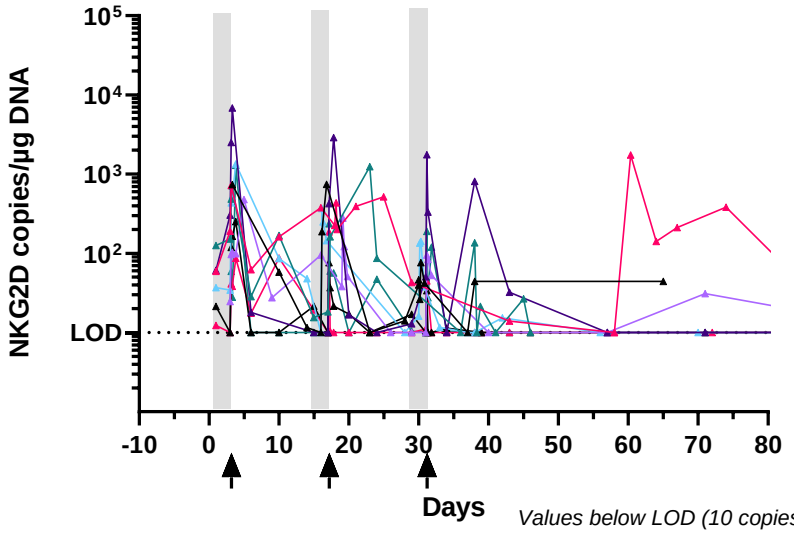
1. NCT03692429: Standard Chemotherapy Regimen and Immunotherapy With Allogeneic NKG2D-based CYAD-101 Chimeric Antigen Receptor T-cells (alloSHRINK).

alloSHRINK – CYAD-101 Following FOLFOX Showed Encouraging ORR

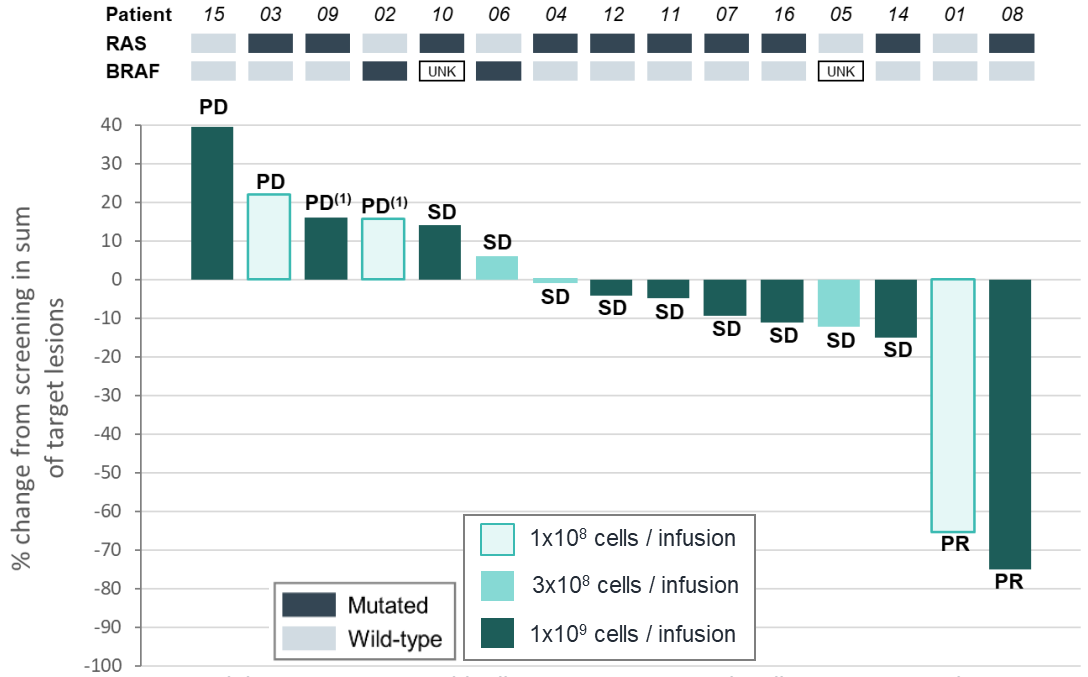
FOLFOX Preconditioning Cohorts



Values below LOD (10 copies/µg DNA) set at LOD
Arrows indicate CYAD-101 infusions

- 15 patients were treated at 3 dose-levels
  - Absence of GvHD
  - No treatment-related adverse events ≥ Grade 3
  - 1x10^9 CYAD-101 cells/infusion defined as the recommended dose

Best Tumor Burden Response



PR: Partial response; SD: Stable disease; PD: Progressive disease; UNK: Unknown.
(1) Progression of non-target lesions.

- Two partial responses (PRs)
- mPFS: 3.9 months (range: 1.2-8.1 months)
- mOS: 10.6 months (range: 1.9-18.7 months)

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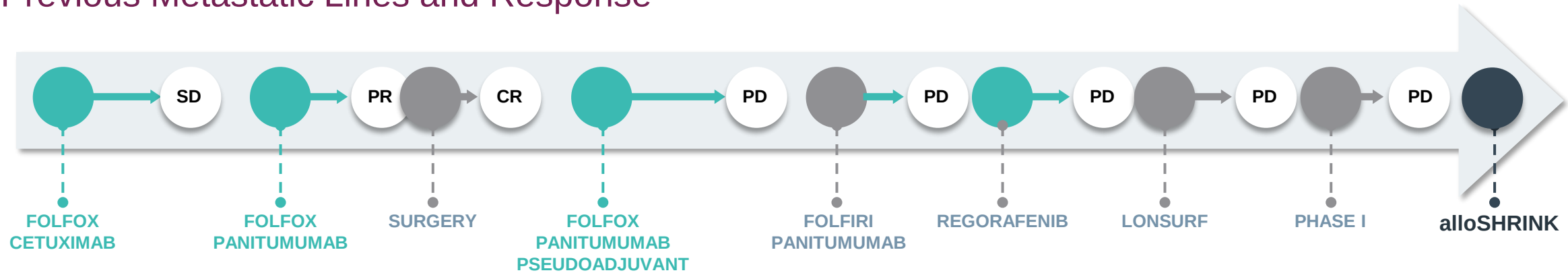
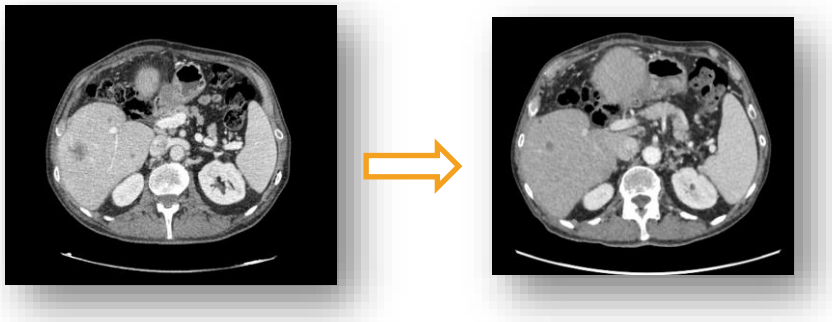
mPFS: Median progression free survival; mOS: Median overall survival; PD: Progressive disease; SD: Stable disease; ORR: Overall response rate.

Case Study – alloSHRINK Patient 01 (Partial Response, Dose Level 1)

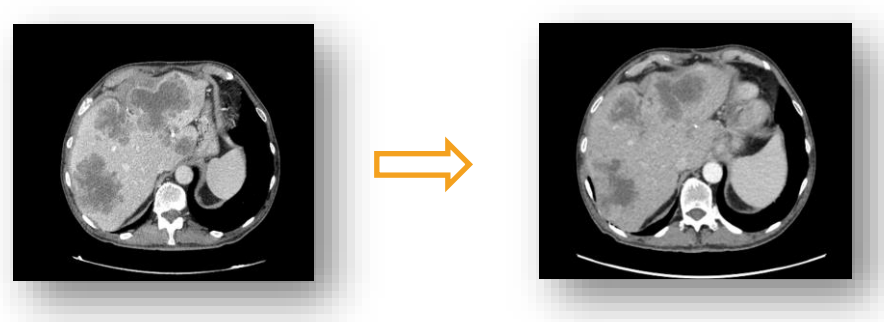
Previous Metastatic Lines and Response



Responses on CYAD-101 + FOLFOX preconditioning



CONFIRMED PARTIAL RESPONSE



CONFIRMED PARTIAL RESPONSE

Male, 74 years old; ECOG 1 | Left colon | RAS wild type; BRAF wild type; MSS

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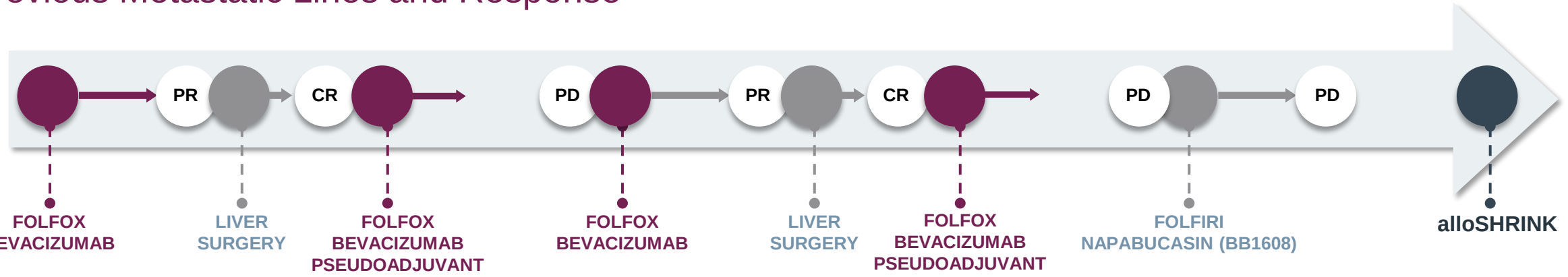
CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease.

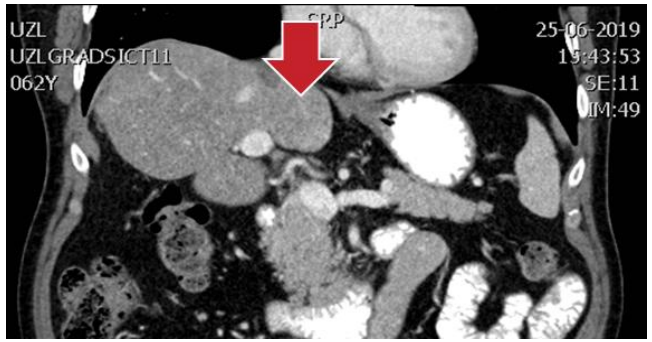
Case Study – alloSHRINK Patient 08 (Partial Response, Dose Level 3)

Previous Metastatic Lines and Response



Responses on CYAD-101 + FOLFOX preconditioning

CEA = 10.9 µg/L



CONFIRMED PARTIAL RESPONSE
No better clinical response under FOLFOX alone

CEA = 6.3 µg/L

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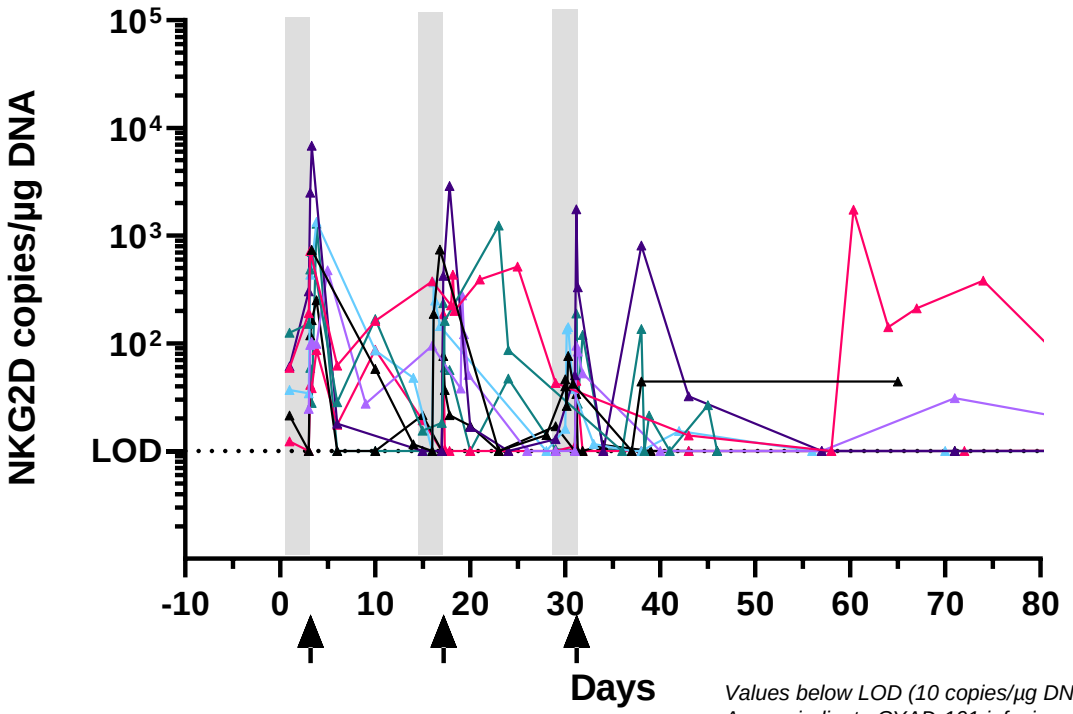
CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease.

Male, 62 years old; ECOG 0 | Rectum cancer | RAS mutated; BRAF wildtype; MSS

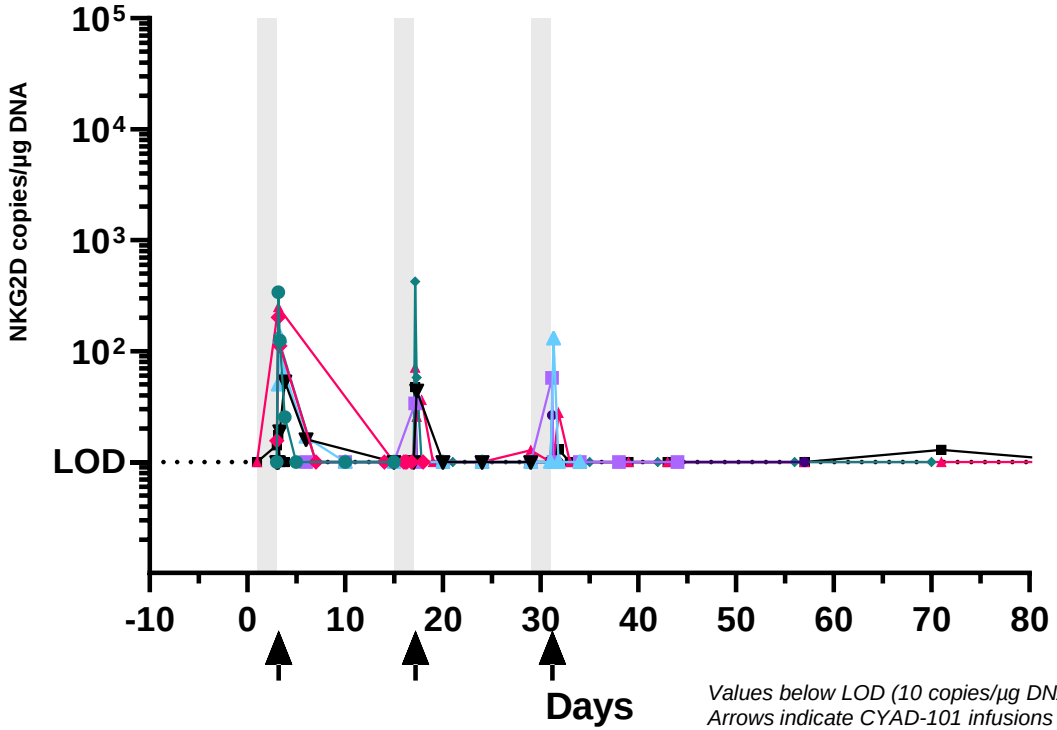
Shorter Persistence of CYAD-101 Cells Observed After FOLFIRI vs. FOLFOX

Cell Engraftment following FOLFOX



Values below LOD (10 copies/µg DNA) set at LOD
Arrows indicate CYAD-101 infusions

Cell Engraftment following FOLFIRI



Values below LOD (10 copies/µg DNA) set at LOD
Arrows indicate CYAD-101 infusions

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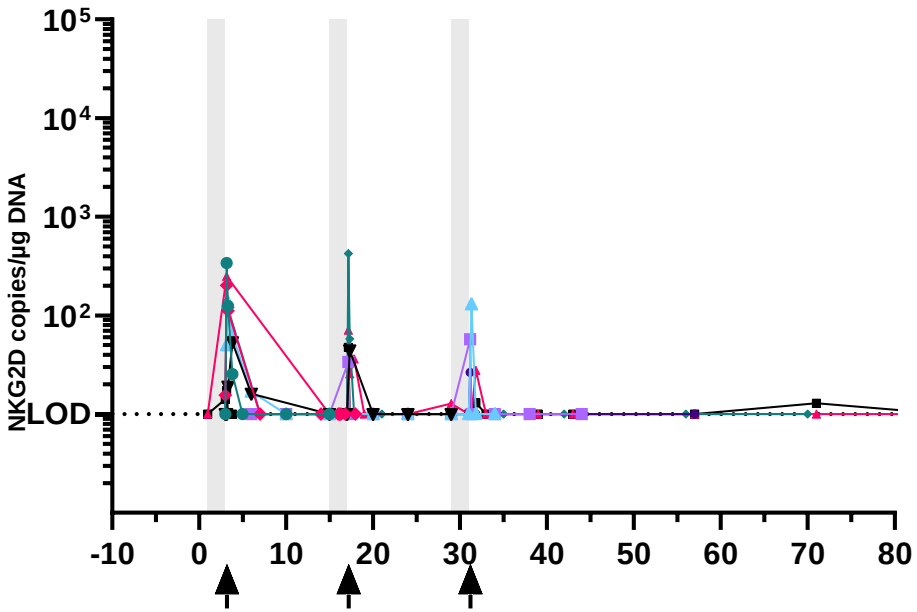
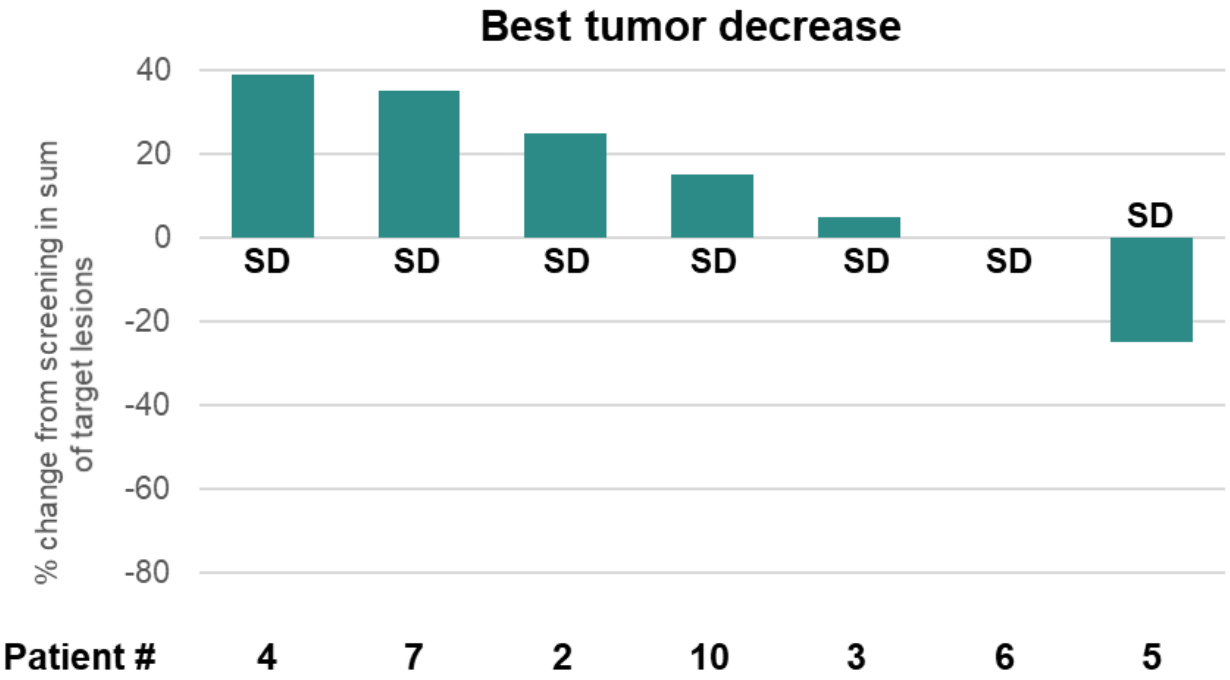
alloSHRINK Expansion Cohort Update

Cell Engraftment following FOLFIRI



Values below LOD (10 copies/µg DNA) set at LOD
Arrows indicate CYAD-101 infusions

Best Tumor Burden Response



- CYAD-101 following FOLFIRI generally well-tolerated
- No objective response observed with nine of ten patients achieving stable disease (SD) at first tumor assessment

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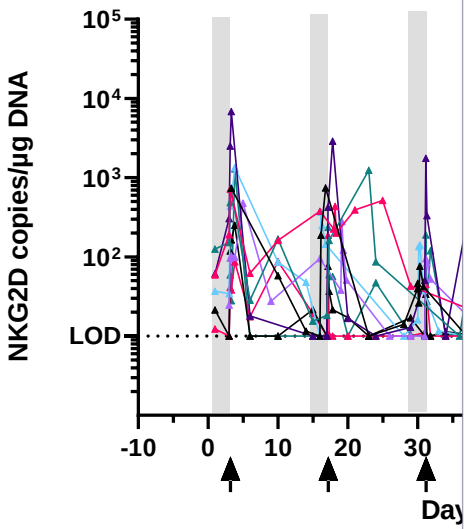
Shorter Persistence of CYAD-101 Cells Observed After FOLFIRI vs. FOLFOX

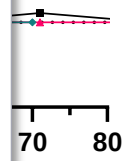
Cell Engraftment fol … FOLFIRI



British Journal of Cancer (2002) 87, 144-150
Cancer Research UK. All rights reserved 007-920/02
www.bjcancer.com

Irinotecan pharmacokinetics-pharmacodynamics: the clinical relevance of prolonged exposure to SN-38

RHJ Mathijssen, J Verweij, WJ Loos, P de Bruijn, K Nooster and A parreboom
- British Journal of Cancer (2002) 87, 144-150 - ©2002 Cancer Research UK



Days

Values below LOD (10 copies/µg DNA) set at LOD
Arrows indicate CYAD-101 infusions
LOD at LC

- No relevant differences between CYAD-101 batches used
- CYAD-101 cells may be impacted (lysis) by irinotecan metabolite
- *In vitro* testing is ongoing to investigate lead hypothesis

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KEYNOTE-B79 Trial – CYAD-101 with KEYTRUDA® in Refractory mCRC

alloSHRINK Highlights

- Encouraging clinical activity observed in incurable mCRC patients
- Therapy well tolerated. No evidence of GvHD
- Evidence of new T-cell clones entering the hyper-expanded TCR repertoire post-treatment with CYAD-101
- Modulation of the endogenous immune response

Expected Complementary MoAs

- NKG2D CAR T cells may convert the TME from immunosuppressive to immunostimulatory
- Anti-PD1 blocks the co-inhibitory interaction of cancer cells with immune cells and restores the immune response
- The anti-PD1 therapy, KEYTRUDA® (pembrolizumab), could enhance the CYAD-101-sculpted TME, thereby driving a more durable anti-tumor response

KEYNOTE-B79 Trial

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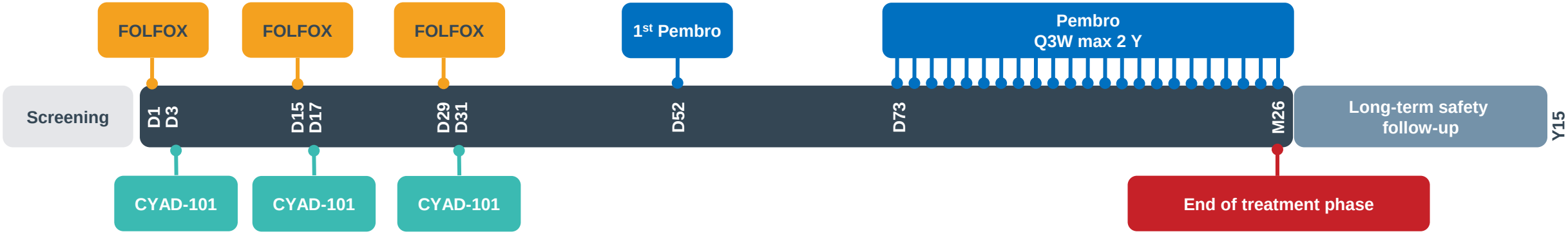
mCRC: Metastatic colorectal cancer; MoA: Mechanism of action; TME: Tumor microenvironment

KEYNOTE-B79 Phase 1b Trial Design

- Patient population:
  - mCRC with recurrent/progressing disease after at least one line of systemic therapy for metastatic disease which must include FOLFOX chemotherapy
  - Microsatellite stable (MSS) / mismatch-repair proficient (pMMR) tumor status
- Treatment schedule:
  - Three CYAD-101 infusions administered Q2W 48 hrs post FOLFOX preconditioning chemotherapy
  - Pembrolizumab (200 mg Q3W) initiated three weeks post third (and last) CYAD-101



- Primary objective: Safety (GvHD, CRS, CRES)
- Secondary objective: Clinical activity
- Exploratory evaluation: CYAD-101 engraftment

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Next Steps for CYAD-101 Program

alloSHRINK

Phase 1

- Continue to monitor patients
- Analyze SN-38 serum levels in study patients
- Evaluate sensitivity of CYAD-101 cells to SN-38 *in vitro*

KEYNOTE-B79

Phase 1b

- Regulatory process for review of protocol complete in U.S. and Belgium
- Study initiation by early fourth quarter 2021

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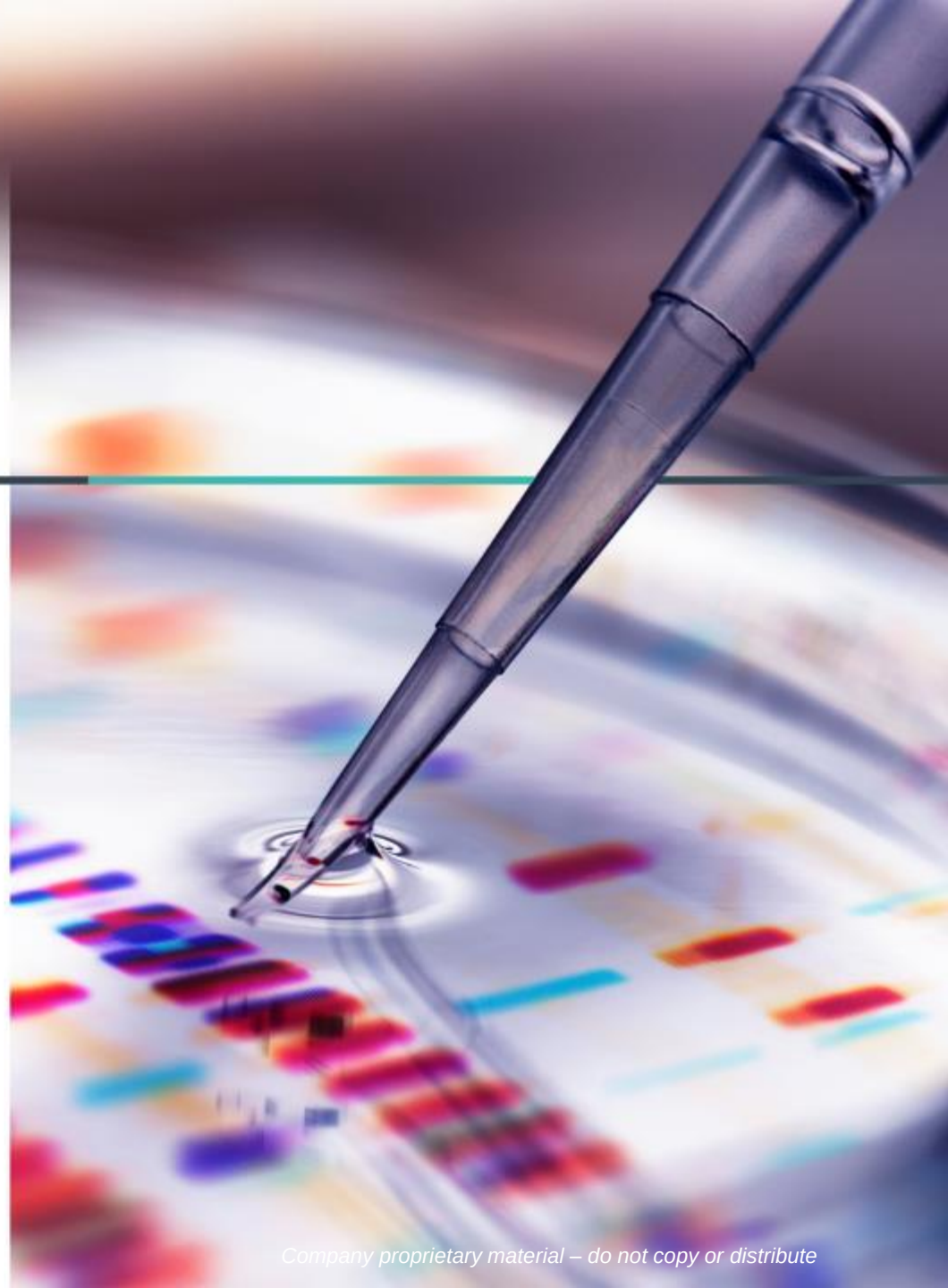
Final Remarks and Q&A



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Building Next Generation Allogeneic Candidates

CYAD-101 for mCRC

- Initiate Phase 1b KEYNOTE-B79 trial with KEYTRUDA® in patients with MSS / pMMR disease

CYAD-211 for r/r MM

- Report additional clinical activity data from dose-escalation IMMUNICY-1 trial

CYAD-203 for Solid Tumors

- Submit IND application

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MM: Multiple myeloma; mCRC: Metastatic colorectal cancer; MDS: Myelodysplastic syndrome; MSS: Microsatellite stable; pMMR: Proficient mismatch repair; r/r: relapse/refractory.

Differentiated Pipeline of Allogeneic CAR T Candidates

	TARGET	*INDICATION*	*IND ENABLING*	*PHASE 1*	*PHASE 2*	*PHASE 3*
CYAD-101	NKG2DL	mCRC				
CYAD-203	NKG2DL + IL-18	Solid tumors				
CYAD-211	BCMA	r/r MM				

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MM: Multiple myeloma; BCMA: B-cell maturation antigen; IL-18: Interleuken-18; mCRC: Metastatic colorectal cancer; NKG2DL: Natural killer group 2D ligands; r/r: relapse/refractory.

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Research and Development Day Virtual Webinar

July 20, 2021