



Q4-FY 2020 Investor Update Call

Immune Responses, On CueTM

Nasdaq: CUE | March 16, 2021

Forward-Looking Statements Disclaimer

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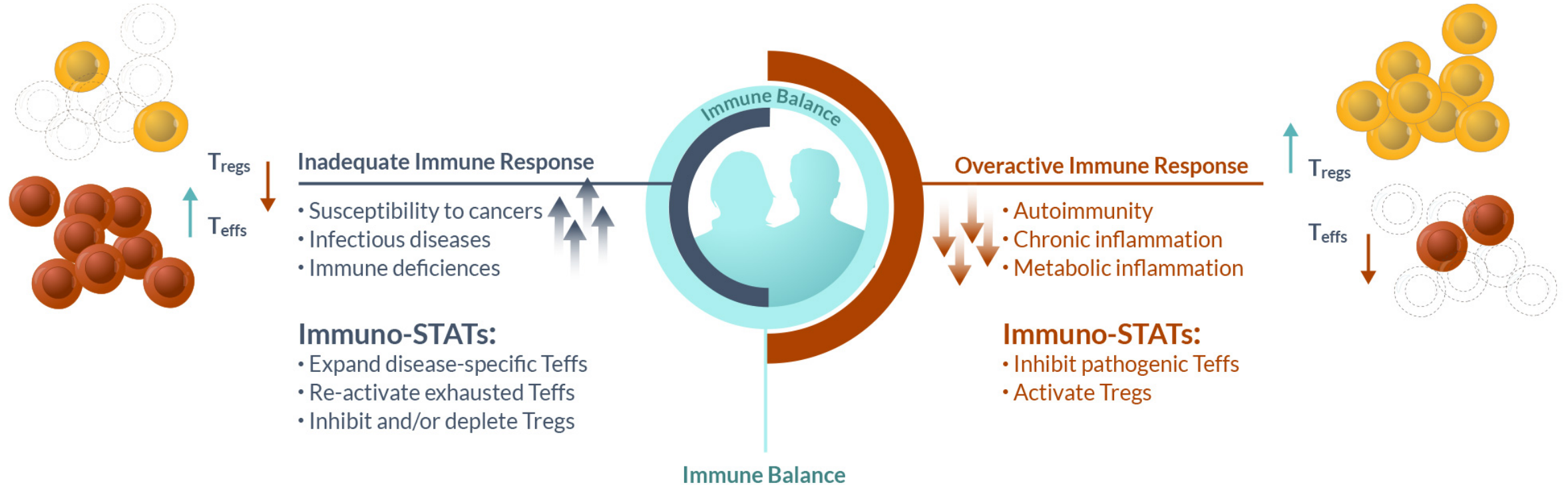
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Agenda

- **Introduction and 4Q-FY 20 Highlights** Dan Passeri, CEO
- **CUE-101 Clinical Update** Dr. Ken Pienta, Acting CMO
Dr. Matteo Levisetti,
Senior VP, Clinical Development
- **Pipeline and Platform Progress** Dr. Anish Suri, President and CSO
- **4Q-FY 20 Financial Results & Guidance** Kerri-Ann Millar, CFO
- **Concluding Remarks** Dan Passeri, CEO
- **Q&A** All

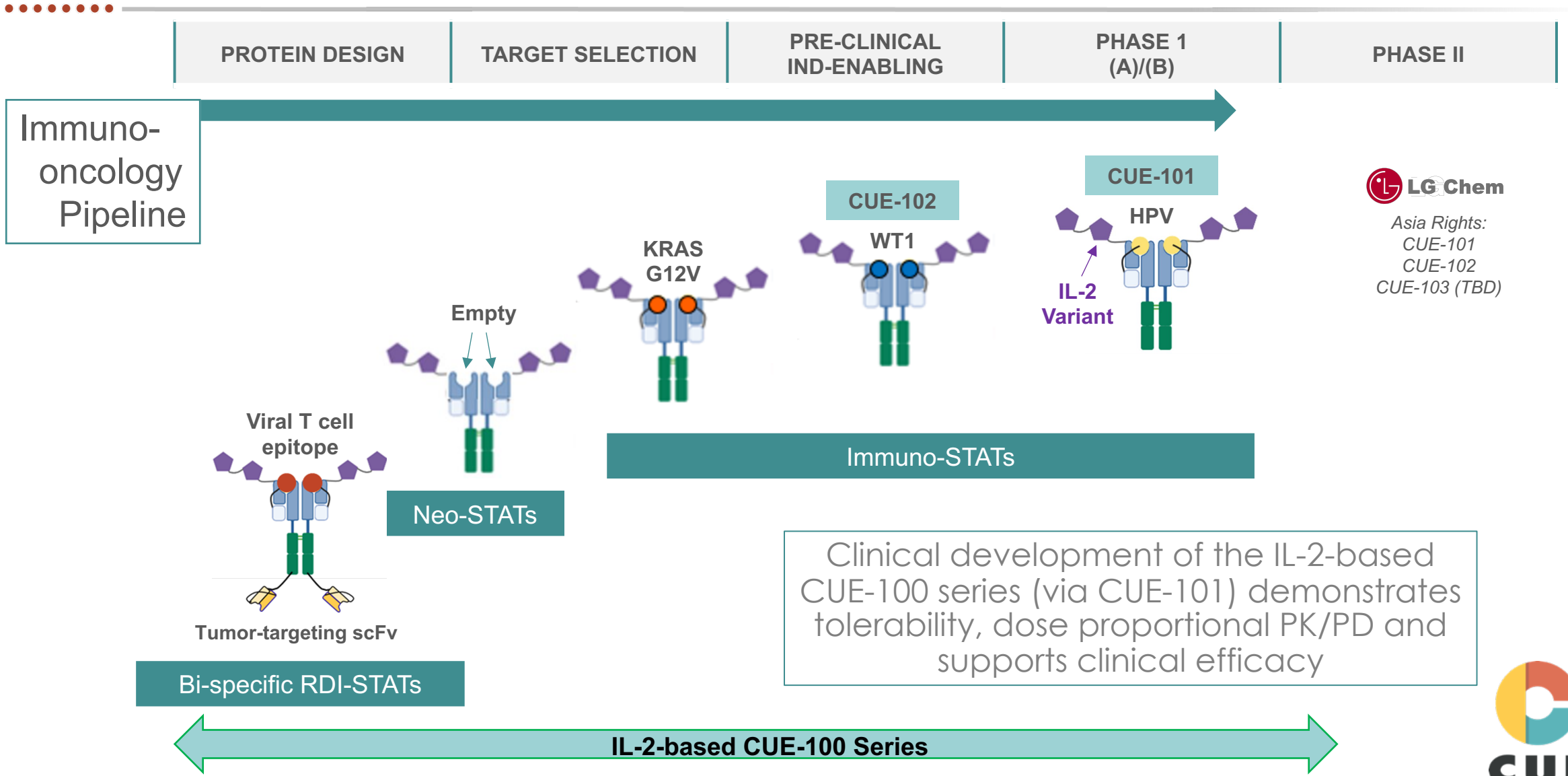
Restoring Immune Balance



Restoration of immune balance is a key pillar of human health

KEY: T_{effs}, effector T cells; T_{regs}, regulatory T cells

CUE-101, CUE-100 Series and Derivatives



CUE-101: Phase 1 Clinical Development Network

Cue Biopharma has engaged a network of nationally recognized clinical investigators and 14 Phase 1 sites are now open

- **Emory Winship Cancer Institute** | Nabil Saba
- **Karmanos Cancer Institute** | Elizabeth Heath and Ammar Sukari
- **MD Anderson Cancer Center** | Bonnie Glisson
- **Memorial Sloan Kettering Cancer Center** | Lara Dunn
- **MGH/Harvard and Dana Farber Cancer Institute** | Sara Pai and Lori Wirth
- **Moffitt Cancer Center** | Christine Chung
- **Sidney Kimmel Comprehensive Cancer Center-Johns Hopkins** | Tanguy Seiwert
- **Stanford Cancer Center** | A. Dimitrios Colevas
- **University of Arizona Center** | Julie Bauman
- **University of Michigan Rogel Cancer Center** | Frank Worden
- **University of Washington Fred Hutch Cancer Center** | Cristina Rodriguez
- **Vanderbilt-Ingram Cancer Center** | Jill Gilbert and Mike Gibson
- **Washington University Siteman Cancer Center** | Doug Adkins
- **Yale Cancer Center** | Barbara Burtness



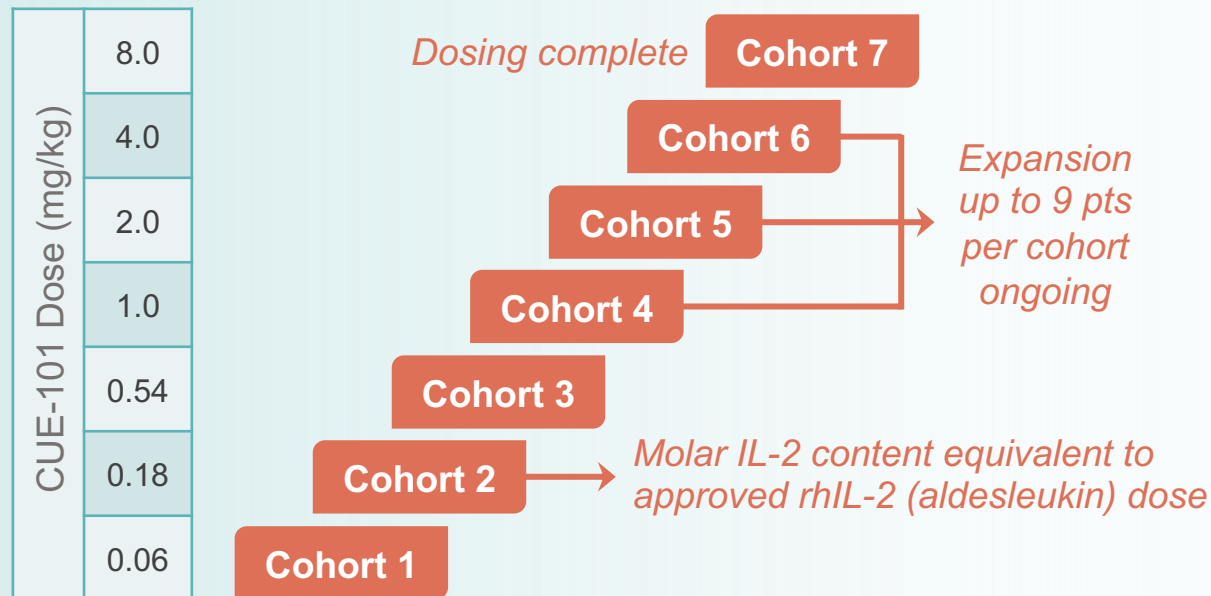
CUE-101: Ongoing Monotherapy First-In-Human Phase 1 Trial

Indication: HPV+ Recurrent or metastatic head and neck cancer with confirmed progressive disease

Heavily pretreated: Refractory or resistant to 1st line platinum-based chemotherapy and/or CPIs

Part A: Monotherapy Dose Escalation
(Q3W, 3 + 3 design, with expansion up to 9 patients per cohort)

Part B: Monotherapy Expansion
(up to 20 total patients)



Parts A & B:

Primary endpoints:

- Safety and tolerability

Secondary endpoints:

- PK/PD
- Anti-tumor activity per RECIST 1.1

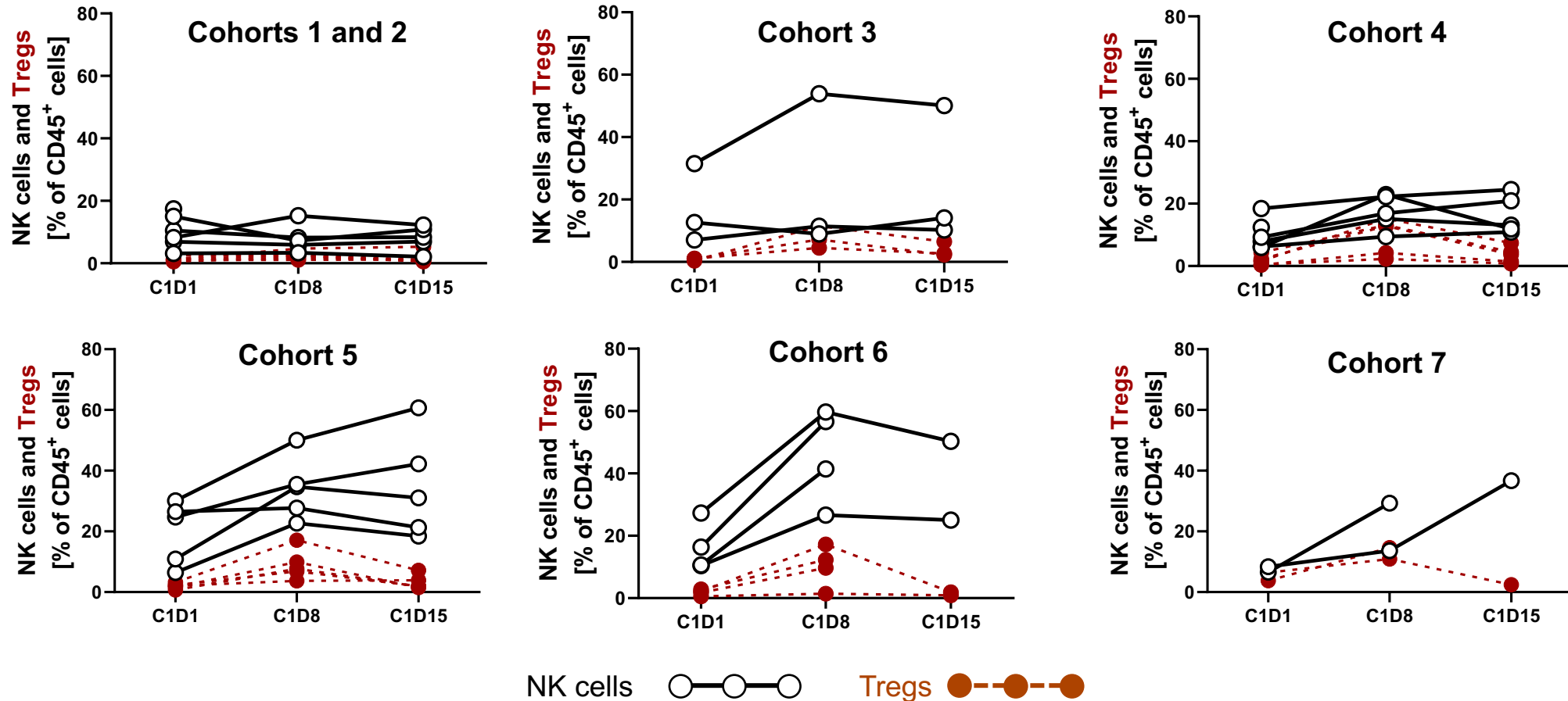
ClinicalTrials.gov: NCT03978689

CUE-101 has been well tolerated through 7 cohorts with evidence of clinical activity
Currently expanding Cohort 4, 5, and 6

Abbreviations: CPI, checkpoint inhibitors; HPV, human papilloma virus; PK/PD, pharmacokinetics/pharmacodynamics; Q3W, once every 3 weeks; rhIL-2, recombinant human interleukin-2; RECIST, Response Evaluation Criteria for Solid Tumors; RP2D, Recommended Phase 2 Dose



CUE-101: Induced Changes in NK Cells and Tregs in Cohorts 1 - 7



Dose-dependent, sustained increase in NKs with transient increase in Tregs, consistent with IL-2 pharmacology observed in the clinic

CUE-101: Cohort 4 Case Study – 3rd line Systemic Treatment

Tolerability

ECOG Status: 0 at screening; Unchanged while on CUE-101 therapy

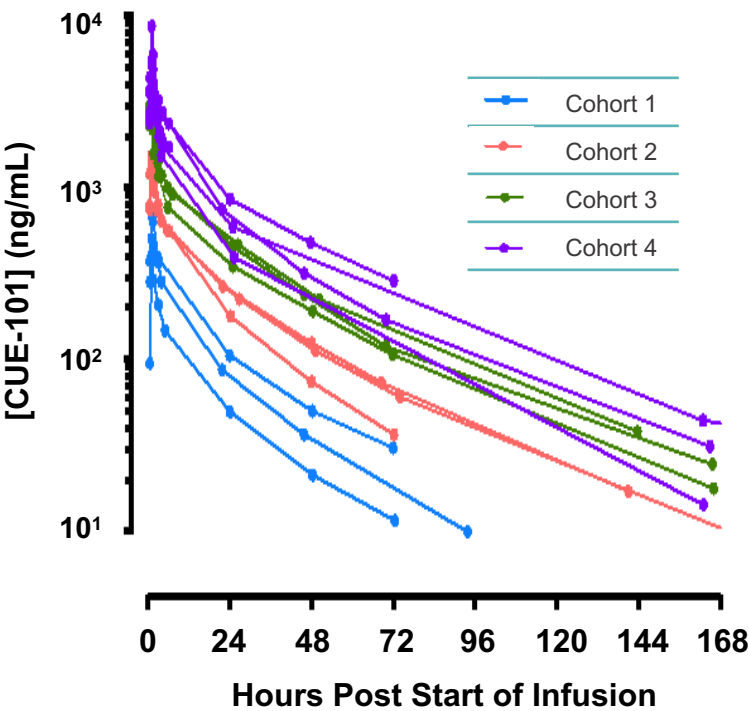
All TRAEs Grade ≤2

	Treatment	Timeline	Outcome
1	Robotic transoral resection tongue base	First intervention	Curative intent
2	Adjuvant RT	1 mo	Curative intent
3	Carboplatin + fluorouracil + cetuximab for advanced, metastatic disease	1 yr, 1 mo	Duration: 6.0 weeks Best Response = SD
4	RT to metastatic mass	1 yr, 4 mos	Palliation
5	Pembrolizumab for advanced, metastatic disease	2 yrs	Duration: 9.4 weeks Best Response = PD
6	CUE-101 (1 mg/kg, Q3W)	2 yrs, 5 mos	Duration: 18.1 weeks

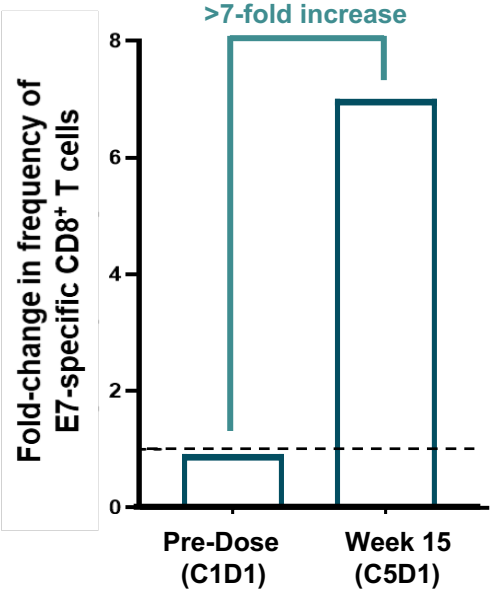
CUE-101 Best Response: Confirmed SD by RECIST 1.1 for 18 weeks

CUE-101: Cohort 4 Case Study – PK, PD, Response

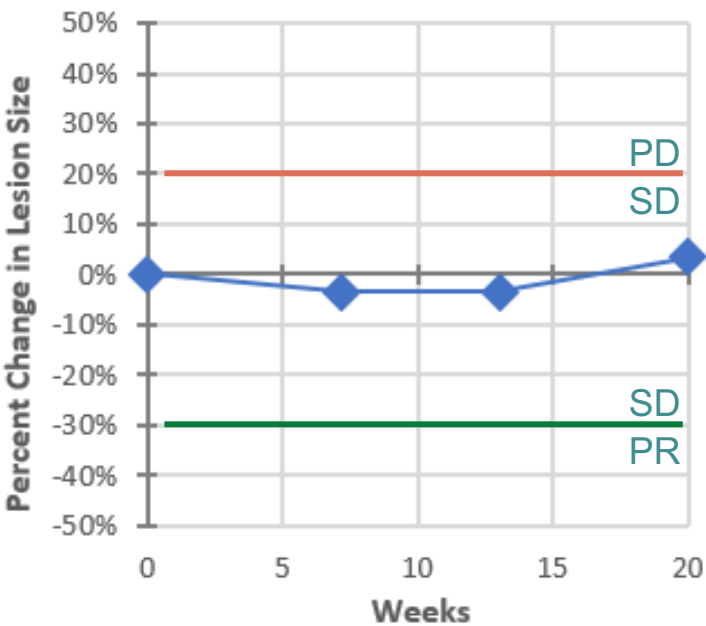
Pharmacokinetics:
Dose proportional



Pharmacodynamics:
Increase in peripheral blood E7-specific T cells



One target lesion at baseline:
Diameter: 58 mm
No change for 20 wks

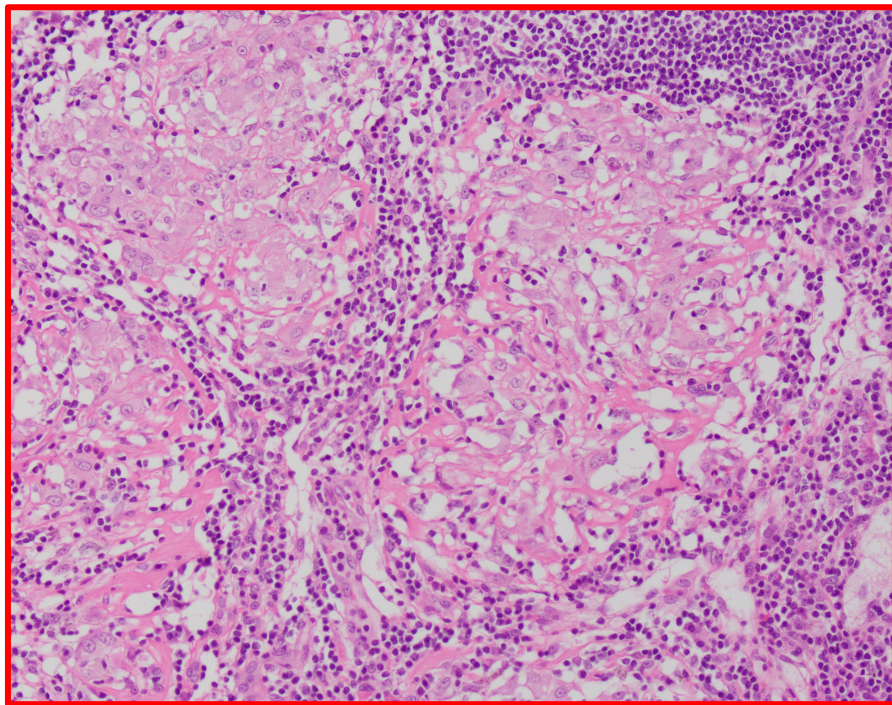


CUE-101 Best Response: Confirmed SD by RECIST 1.1 for 18 weeks

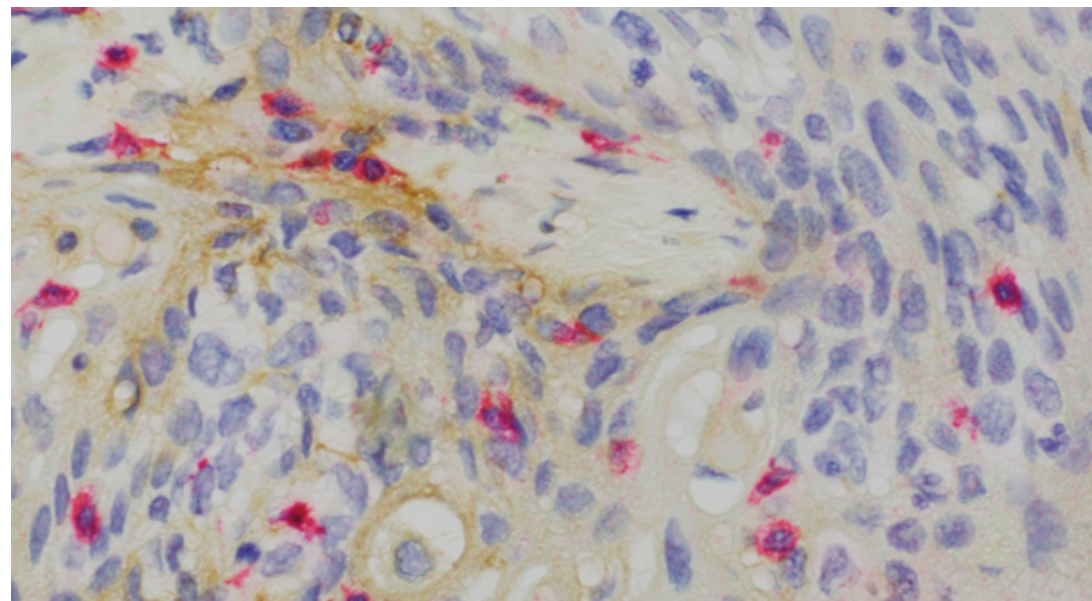


CUE-101: Cohort 4 Case Study – Necrosis and a T Cell Infiltrate

Cohort 4 (1 mg/kg) patient was on therapy for over 18 weeks



Hematoxylin and eosin stain
(cell nuclei = blue; extracellular matrix and cytoplasm = pink)



Immunostaining
(cell nuclei = blue; CD8+ T cells = rose;
PD-L1 = brown)

CUE-101: Cohort 5 Case Study – 3rd Line Systemic Treatment



Tolerability

ECOG status: 1 at screening; Unchanged while on CUE-101 therapy

TRAEs Grade ≤2:

Lightheadedness,
Chills, Joint Stiffness,
Headache, Fatigue,
Rigors, Myalgias,
Seborrheic Keratosis,
Skin Lesion, Nausea

TRAEs Grade 3:

Lymphocyte Count
Decreased, Syncope

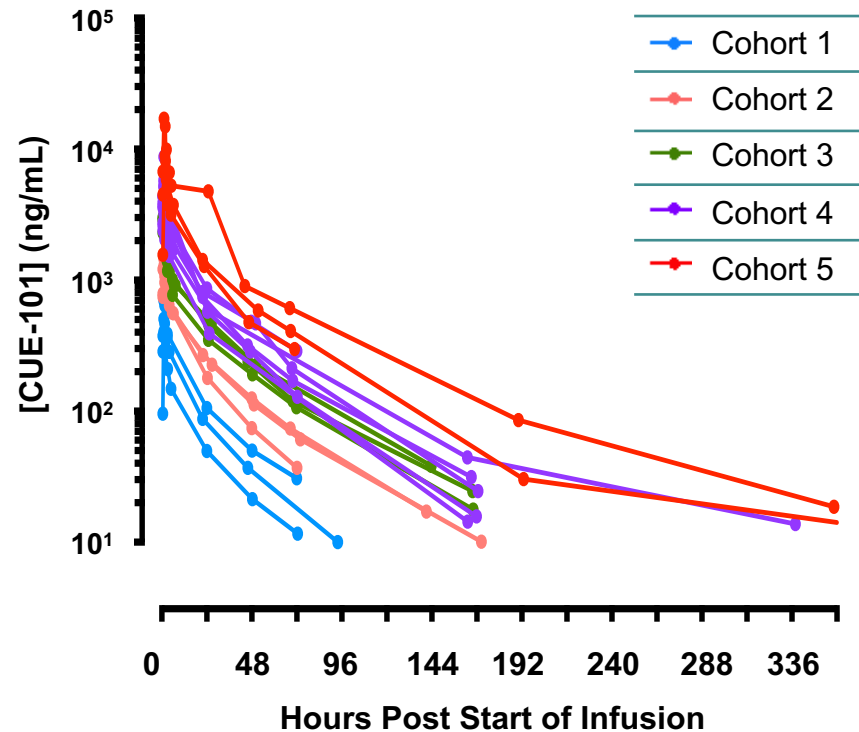
	Treatment	Timeline	Notes
1	RT tongue and neck	0	Curative intent
2	Cisplatin for maintenance	0	Duration: 6.0 weeks Best Response = CR
3	Carboplatin + fluorouracil + cetuximab for advanced, metastatic disease	1 yr, 6 mos	Duration: 6.0 weeks Best Response = PD
4	Nivolumab	1 yr, 9 mos	Duration: 28.0 weeks Best Response = SD
5	CUE-101 (2 mg/kg, Q3W)	2 yrs, 4 mos	Duration: 28.0 weeks

**CUE-101 Best Response: Confirmed SD by RECIST 1.1 for 28 weeks;
acquired COVID-19 and came off study**

CUE-101: Cohort 5 Case Study – PK, Response

Pharmacokinetics:

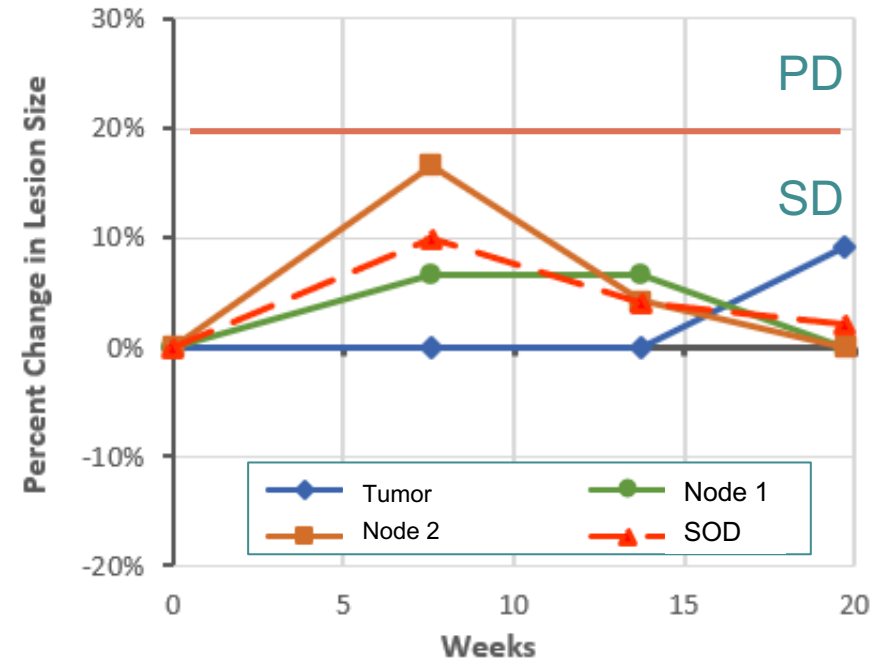
Dose proportional



Three target lesions at baseline:

- 1) Tumor mass: 11 mm
- 2) Lymph node No.1: 15 mm
- 3) Lymph node No. 2: 24 mm

Sum of Diameters (SOD) = 50 mm



**CUE-101 Best Response: Confirmed SD by RECIST 1.1 for 28 weeks;
acquired COVID-19 and came off study**

CUE-101: Ongoing Pembrolizumab Combination Study

ClinicalTrials.gov:

NCT03978689

Eligibility:

- HPV+ Head and neck cancer
- Recurrent or metastatic (R/M)
- 1st Line
- HLA-A*0201 genotype
- Life expectancy ≥ 12 weeks
- Eligible for pembrolizumab in the first-line setting

Design:

- Dosing Q3W
- Part C: 3 + 3 Dose escalation with 1-week safety follow up of 1st patient required at each dose prior to dosing patients 2 and 3
- Part C: PD and activity expansion up to 9 patients
- Part D: Expansion to total of 10-20 patients at RP2D

Part C: Pembrolizumab Combination Dose Escalation

Initiated February 2021

Pembrolizumab 200 mg, Q3W	CUE-101 Dose (mg/kg)	4.0
		2.0
		1.0

Cohort 1

Cohort 2

Cohort 3

*Same dose of CUE-101
as in Cohort 4 in the
monotherapy trial*

Part D: Combination Expansion at RP2D Dose

Objectives:

- *Primary:* Safety and tolerability
- *Secondary:* PK/PD, Anti-tumor activity

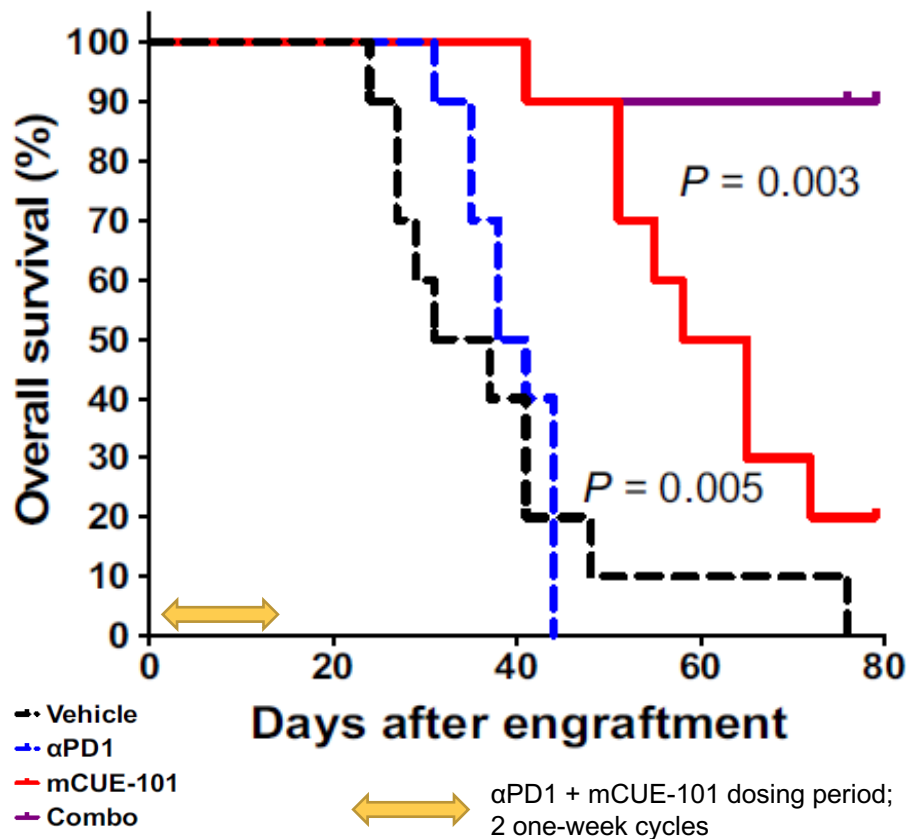
Biomarkers: (Pre/Post CUE-101 dose)

- HPV E7-specific CD8+ T cell counts and functionality
- Immunophenotyping, cytokine release, and TCR sequencing

Abbreviations: PD, pharmacodynamics; PK, pharmacokinetics; RP2D, Recommended Phase 2 Dose

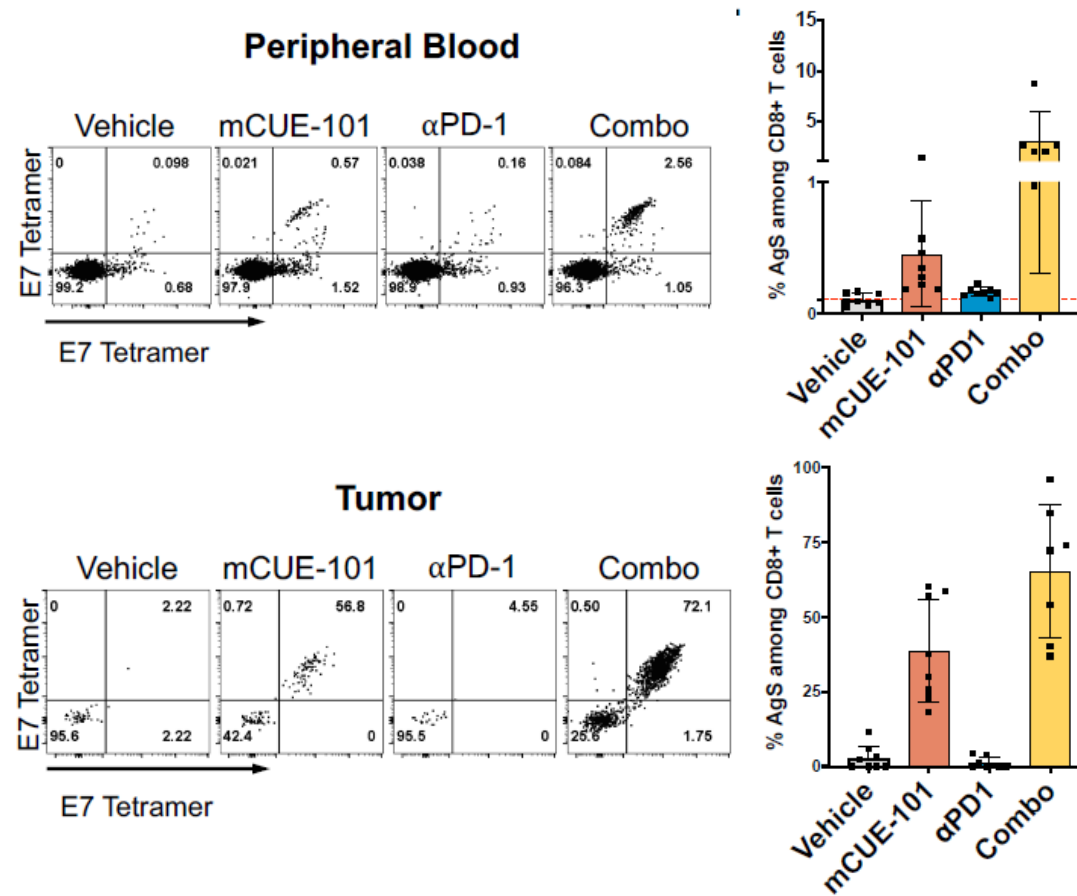
CUE-101: Preclinical Studies Support Pembrolizumab Combination

Tumor growth inhibition by mCUE-101 is greatly enhanced in combination with α PD1 blockade



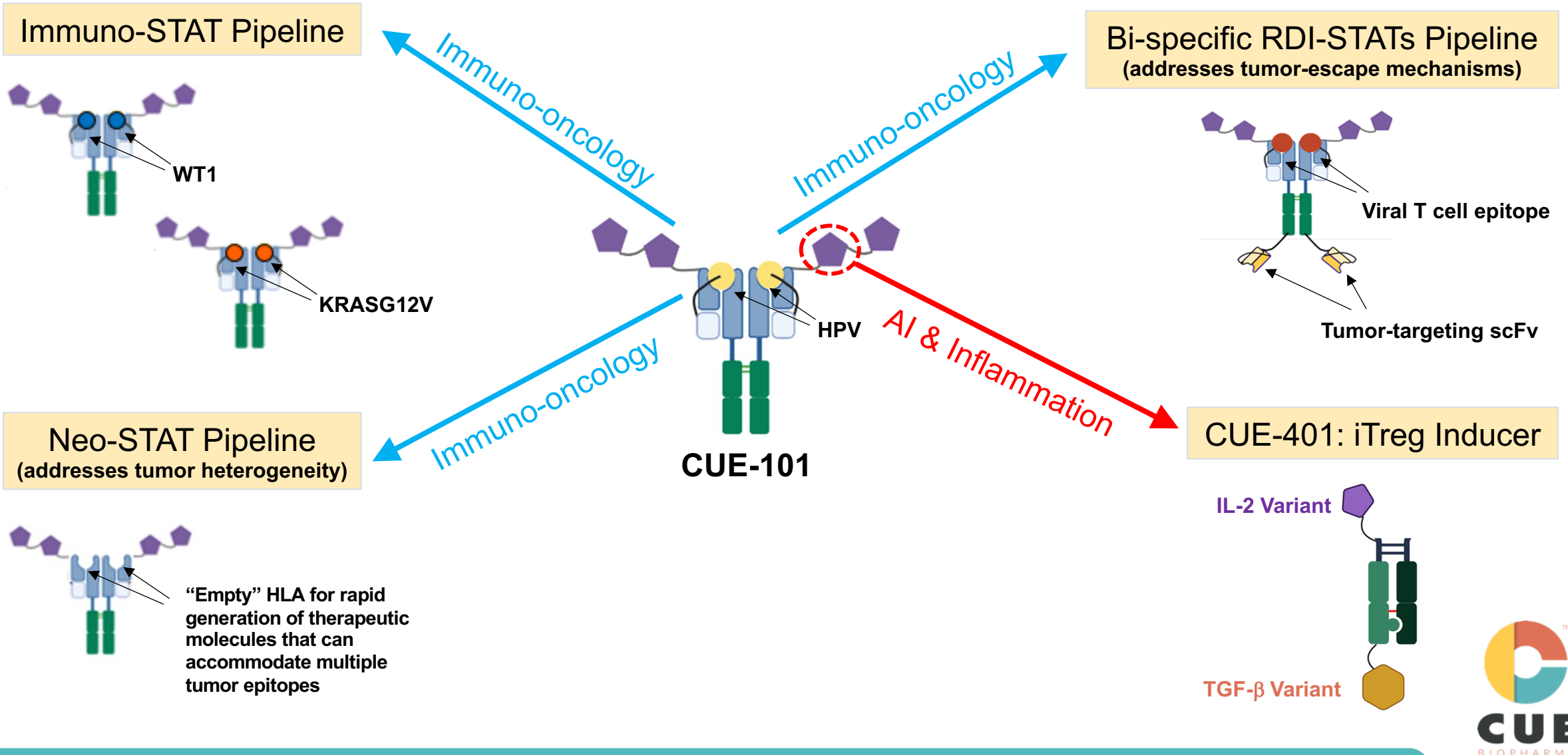
Source: Quayle SN, Girgis N, et al. Clin Canc Res 26:1953-64, 2020.

Expansion of functional HPV E7 antigen-specific CD8+ T cells in the tumor and periphery by mCUE-101 is greatly enhanced in combination with α PD1 blockade



Abbreviations: AgS, antigen-specific; mCUE-101, mouse surrogate of human CUE-101; α PD1, anti-PD1 surrogate

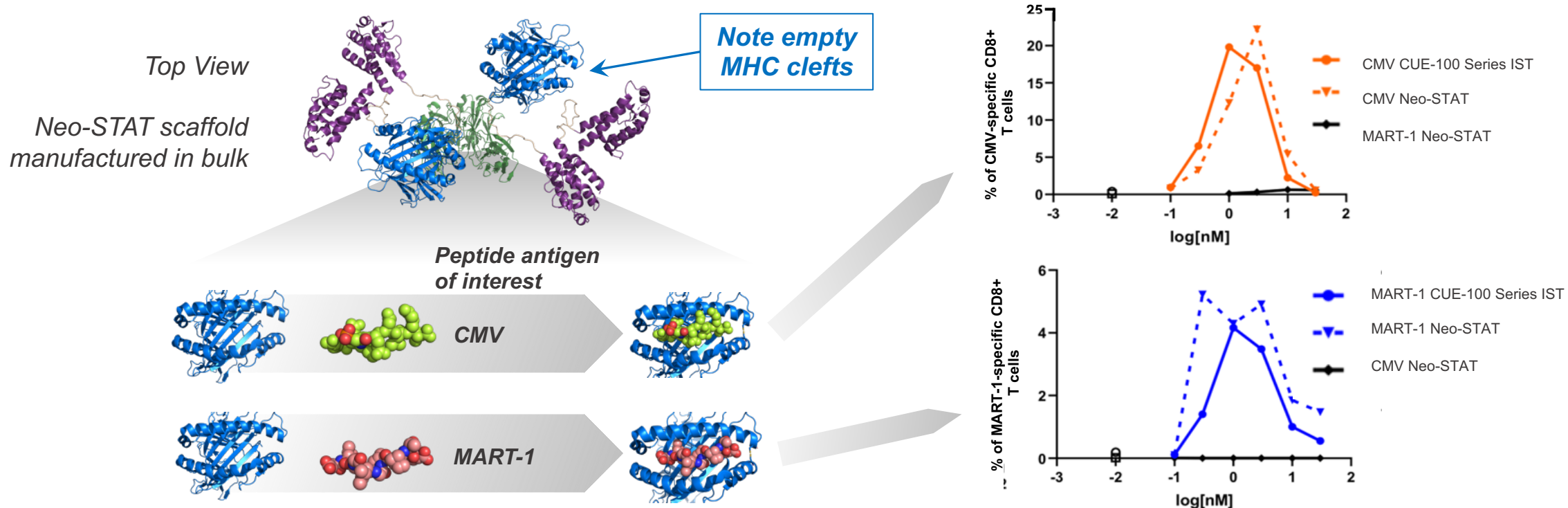
CUE-101 Experience: Potential for Broad Opportunities in IO and AI



CUE-100 Neo-STAT: Rationale and Vision

Goal:

To generate a universal immuno-STAT (IST) scaffold via a singular CMC cell line creation (e.g., MCB) enabling more competitive development metrics (time and cost savings).



Therapeutic Applications to include:

- Peptide mixes / Multi-antigen based cocktail therapy
- Integration of post-translationally modified peptides
- Difficult to manufacture peptides / Altered peptide ligands
- Extension to cancer neoantigens → Personalized medicine

RDI-STATs: Novel Bi-specifics Re-directing Viral-Specific T Cells to Tumor Cells

ARTICLE

<https://doi.org/10.1038/s41467-019-09534-1>

OPEN

Virus-specific memory T cells populate tumors and can be repurposed for tumor immunotherapy

Pamela C. Rosato¹, Sathi Wijeyesinghe¹, J. Michael Stolley¹, Christine E. Nelson¹, Rachel L. Davis¹, Luke S. Manlove¹, Christopher A. Pennell², Bruce R. Blazar³, Clark C. Chen⁴, Melissa A. Geller⁵, Valva Vezys¹ & David Masopust¹

LETTER

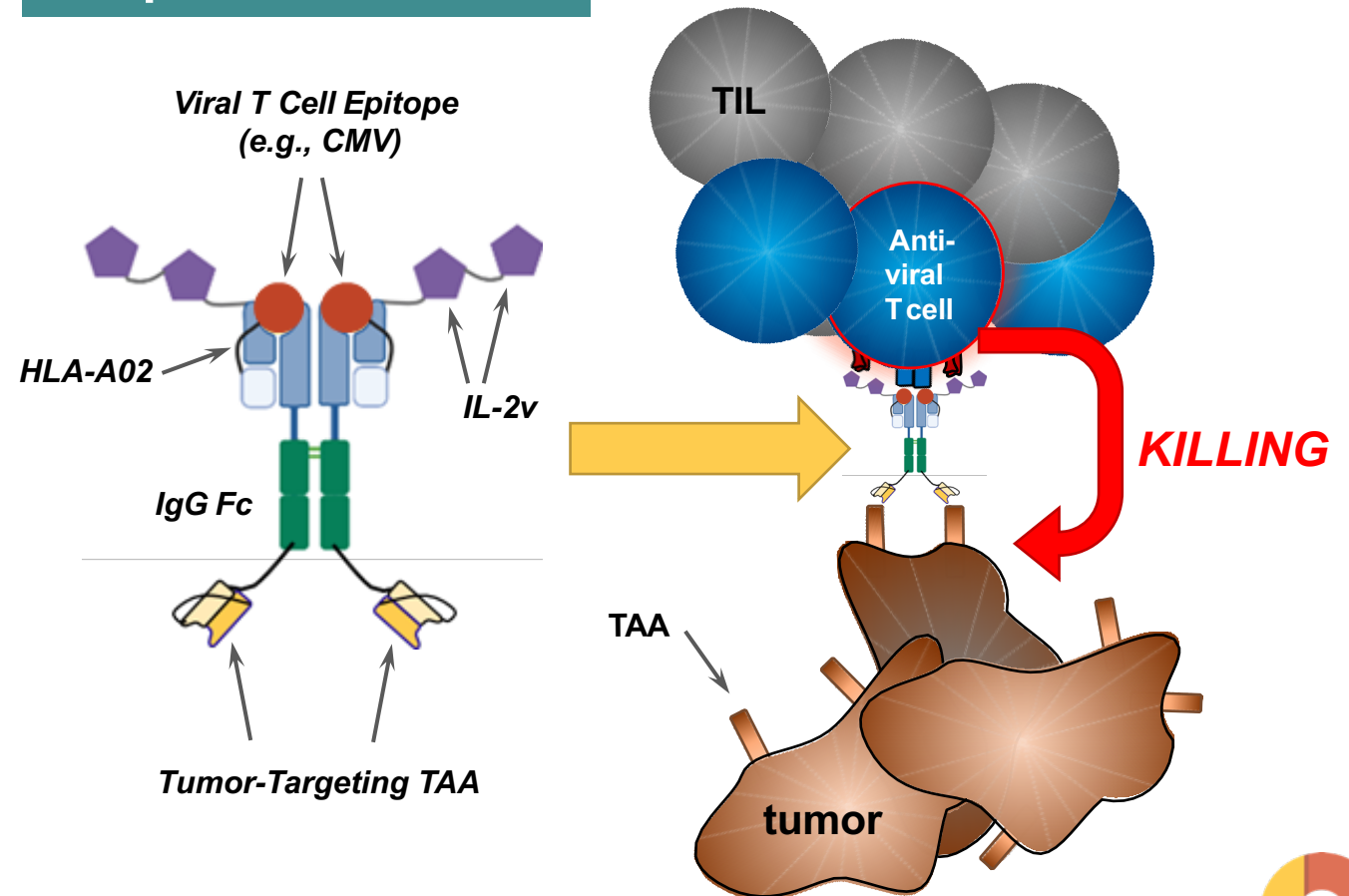
<https://doi.org/10.1038/s41586-018-0130-2>

Bystander CD8⁺ T cells are abundant and phenotypically distinct in human tumour infiltrates

Nannick Simon^{1*}, Etienne Becht², Michael Fehlings^{3,4}, Chiew Vee Loh⁵, Si-Lin Koo⁶, Karen Wei Wong Teng¹, Joe Peh Sheng Yeong^{1,4}, Rahul Natar⁷, Tong Zhang⁸, Haosen Kared⁹, Kaibo Duan⁹, Nicholas Ang¹, Michael Poldinger¹, Yin Yeng Lee¹, Anis Larbi¹, Alexis J. Khng¹, Emile Tan⁹, Cherylin Pe⁹, Rommie Mathew⁹, Melissa Teo², Wan Yock Lim¹, Chee Keong Toh¹, Boon-Hoon Ong¹, Tina Koh¹, Axel M. Hillmer⁵, Angela Takano⁴, Tony Kiat Hon Lim^{4,5,9}, Eng Huat Tan¹, Weiwei Zhao¹, Daniel S. W. Tan^{1,5}, Iain Buchan^{1,5,9} & Evan W. Newell^{1*}

- **Harnesses** a pre-existing and robust viral T cell repertoire present in high frequency
- **Superior specificity:** avoids systemic activation of ALL T cells
- **Superior safety:** minimizes cytokine release
- **De-risked** by CUE-101 clinical experience

Bi-specific RDI-STAT



CMV, cytomegalovirus; TAA, tumor-associated antigen

Approaches to Modulate Autoreactive T Cell Responses



T Cell Mediated Autoimmune Diseases

Antigen-Specific Approach

AIM: Deploy class I/II Immuno-STATs to modulate autoreactive T cells and/or generate antigen-specific inhibitory Tregs

- Focus on diseases with restricted autoreactive antigens
- Focus on earlier stages of breakdown of tolerance prior to antigen/epitope spreading

Pathway-Specific Approach

AIM: Engineered key signals to restore immune balance through generation of polyclonal induced Tregs (iTregs)

- Focus on IL-2 and TGF- β for iTreg induction and expansion
- Focus on indications and chronic disease stages with diverse self-antigens

Cue Biopharma is applying **protein engineering** and **mechanistic biology** to develop drug candidates applicable to both approaches

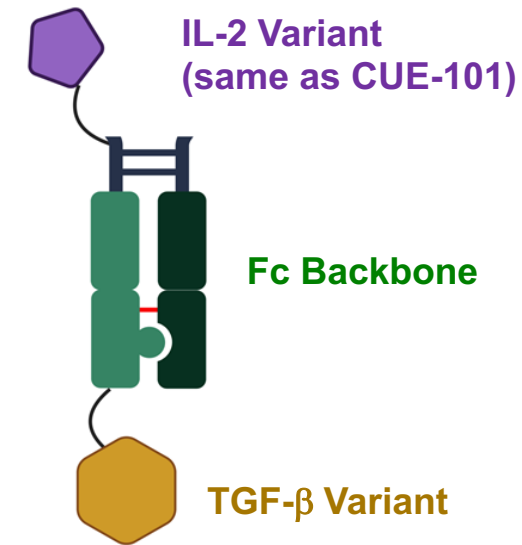


Immune Balance: Restoration via Induced Tregs (iTregs)

Advantages for iTregs vs. nTregs

- **Numbers:** nTregs are limited in numbers vs iTregs, which can be generated from the broader CD4⁺ T cell repertoire
- **Diversity:** TCR specificity of nTregs is pre-determined and fixed, while iTregs can be generated from vastly diverse polyclonal CD4⁺ T cells
- **Phenotype:** regulatory phenotype of iTregs can be achieved and sustained via IL-2 and TGF-beta signals
- **Disease impact:** Conversion of pathogenic T cells into regulatory phenotype is an attractive therapeutic strategy for immune re-set
- **Application:** Broad applications for iTregs in numerous autoimmune diseases, GVHD and transplantation

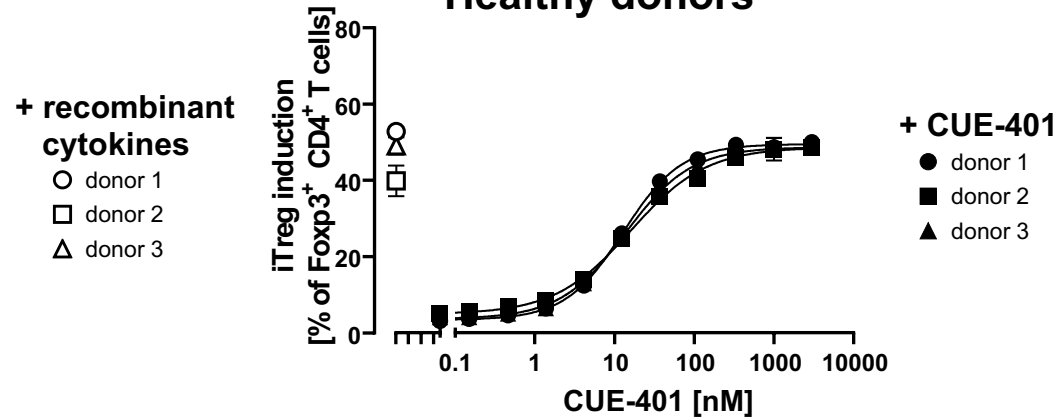
CUE-401



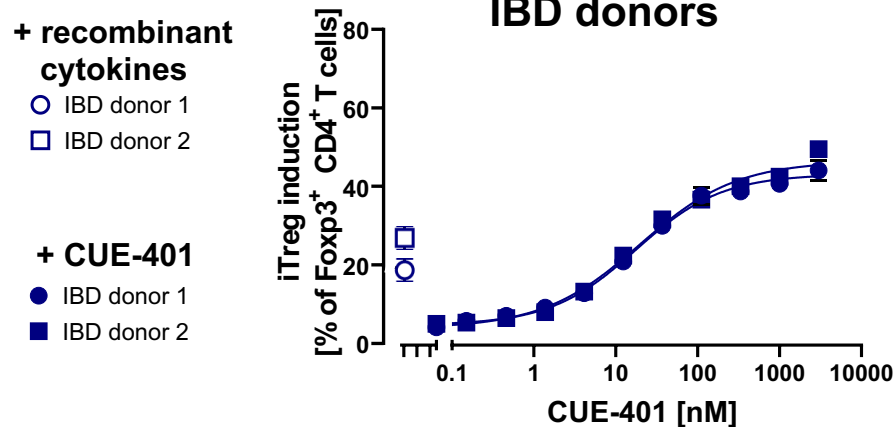
CUE-401: Induction of FoxP3+ iTregs

All assays performed in presence of TCR activation via CD3/CD28 stimulation

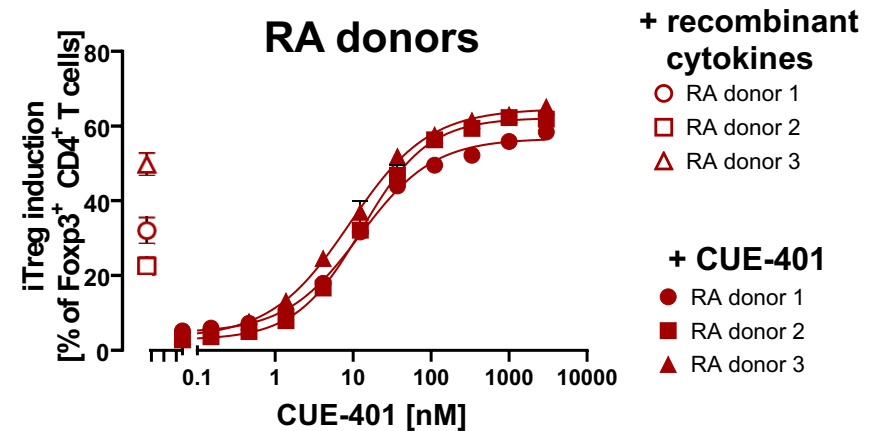
Healthy donors



IBD donors



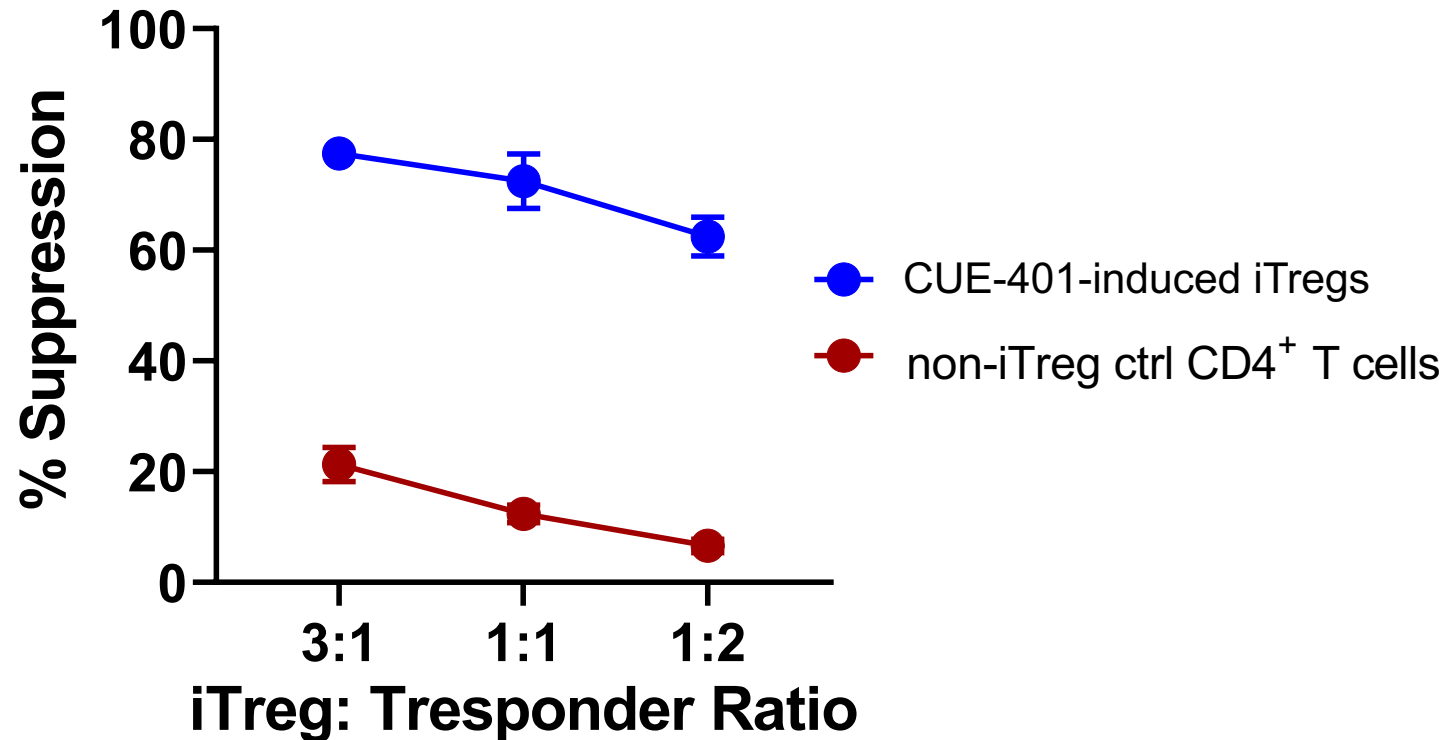
RA donors



CUE-401 enhances iTregs as measured by induction of expression of the master Treg transcription factor FoxP3

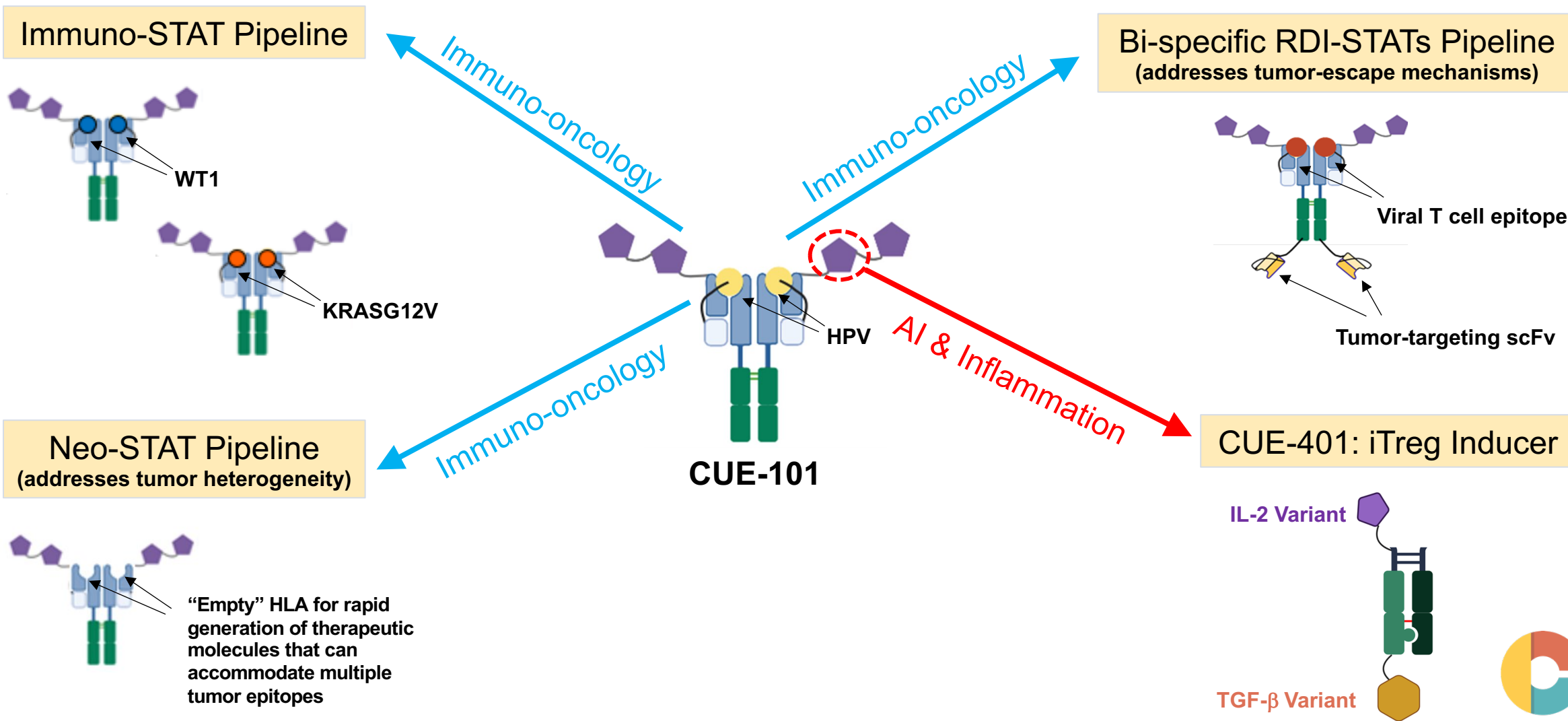
CUE-401: Suppression of T Cell Responses by iTregs Induced by CUE-401

iTreg suppression of polyclonal T cell proliferation



*Average of 3 donors
% suppression compared to T responder alone*

CUE-101 Experience: Potential for Broad Opportunities in IO and AI



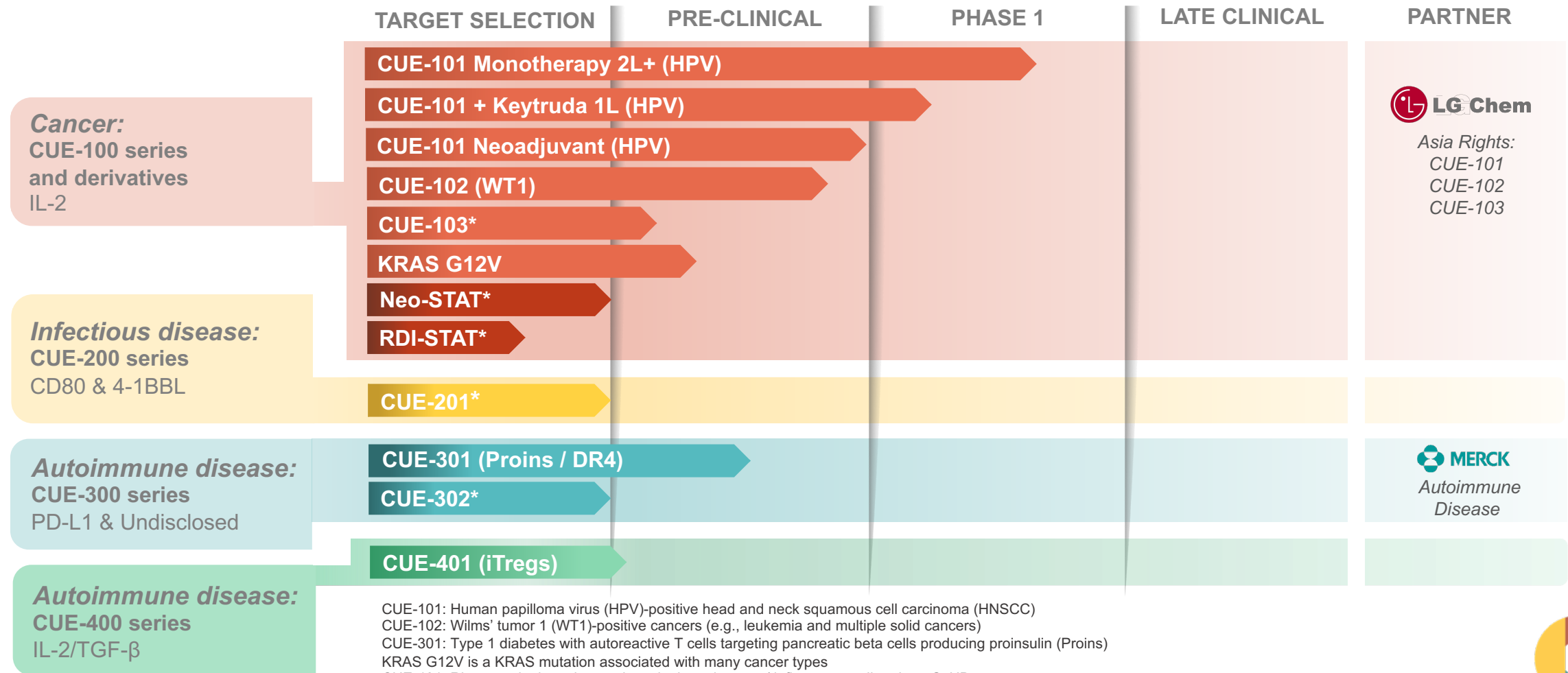
Cue Biopharma, Inc: 2020 Financial Highlights

Cue Biopharma, Inc. Condensed Consolidated Statement of Operations (in thousands, except per share information)				
	Three Months Ended December 31,		Year Ended December 31,	
	2020	2019	2020	2019
Collaboration revenue	\$ 475	\$ 1,049	\$ 3,154	\$ 3,458
Operating expenses:				
General and administrative	3,446	3,100	14,651	12,740
Research and development	8,003	6,965	33,546	27,488
Total operating expenses	11,449	10,065	48,197	40,228
Loss from operations	\$ (10,974)	\$ (9,016)	\$ (45,043)	\$ (36,769)
Other income:				
Interest income	84	110	544	419.00
Other income / (expense) net	(6)	(12)	(80)	64.00
Loss before income taxes	\$ (10,896)	\$ (8,918)	\$ (44,579)	\$ (36,286.00)
Provision for income taxes	(206)	-	(206)	(412.00)
Net loss	\$ (11,102)	\$ (8,918)	\$ (44,785)	\$ (36,699.00)
Net loss per common share – basic and diluted	\$ (0.37)	\$ (0.37)	\$ (1.56)	\$ (1.66)
Weighted average common shares outstanding – basic and diluted	30,283,249	24,146,606	28,688,625	\$22,041,792

Cue Biopharma, Inc. Selected Consolidated Balance Sheet Data (in thousands)		
	December 31, 2020	December 31, 2019
Cash and cash equivalents & marketable securities	\$ 84,869	\$ 59,410
Total assets	99,534	71,605
Total liabilities	20,622	17,021
Total stockholders' equity	78,911	54,584
Working capital	71,211	49,370



Cue Biopharma Drug Product Candidate Pipeline



CUE-101: Human papilloma virus (HPV)-positive head and neck squamous cell carcinoma (HNSCC)
 CUE-102: Wilms' tumor 1 (WT1)-positive cancers (e.g., leukemia and multiple solid cancers)
 CUE-301: Type 1 diabetes with autoreactive T cells targeting pancreatic beta cells producing proinsulin (Proins)
 KRAS G12V is a KRAS mutation associated with many cancer types
 CUE-401: Rheumatologic and gastrointestinal autoimmune/ inflammatory disorders, GvHD
 * Undisclosed

Key 2021 Anticipated Milestones: Risk Reduction and Value Creation

1

Select CUE-101 monotherapy recommended Phase 2 dose in **mid-2021**

2

Report initial results of CUE-101 + pembrolizumab Phase 1 combination trial in **2H21**

3

Initiate CUE-101 neoadjuvant study to enable intratumor PD in **2H21**

4

Continue CUE-102 IND-enabling studies with IND filing in **1H22**

5

Initiate & expand KRAS G12V, & Neo-STAT CMC activities in **2H21**

6

Achieve optimization of lead candidate for CUE-301 in **2H21**

7

CUE-401 Preclinical validation of iTreg function in **2H21**

We believe our cash, cash equivalents and marketable securities at December 31, 2020 are sufficient to support CUE-101 clinical proof of concept and pipeline advancement into the third quarter of 2022





Thank you

Immune Responses, On Cue™

Nasdaq: CUE | March 16, 2021