

# Autolus

Nasdaq: AUTL



## Next Generation Programmed T Cell Therapies

January 2020

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# Investment highlights

## Broad clinical-stage pipeline

- > 4 product candidates
- > 4 hematological indications
- > 1 solid tumor program

## Multiple upcoming milestones

- > AUTO1 long term follow up in aALL
- > POC for AUTO3 in DLBCL
- > POC for AUTO4 in PTCL

## Proprietary manufacturing process

- > Fully enclosed, semi-automated
- > Designed to be economical at commercial scale
- > Expanding to new US/UK facilities

## Modular programming approach

- > Enables rapid cycle of innovation
- > 4 next generation versions of lead programs to enter clinical development in 2020
- > Designed to address:
  - Targeting & control
  - Tumor defenses & microenvironment
  - GvHD & immune rejection (Allogeneic)
  - Manufacturing
- > Portfolio of owned and in-licensed intellectual property; 85 patent families

## Strong Fundamentals

- > \$229 million at September 30, 2019
- > Worldwide rights retained for all programs
- > Cash runway into H2 2021

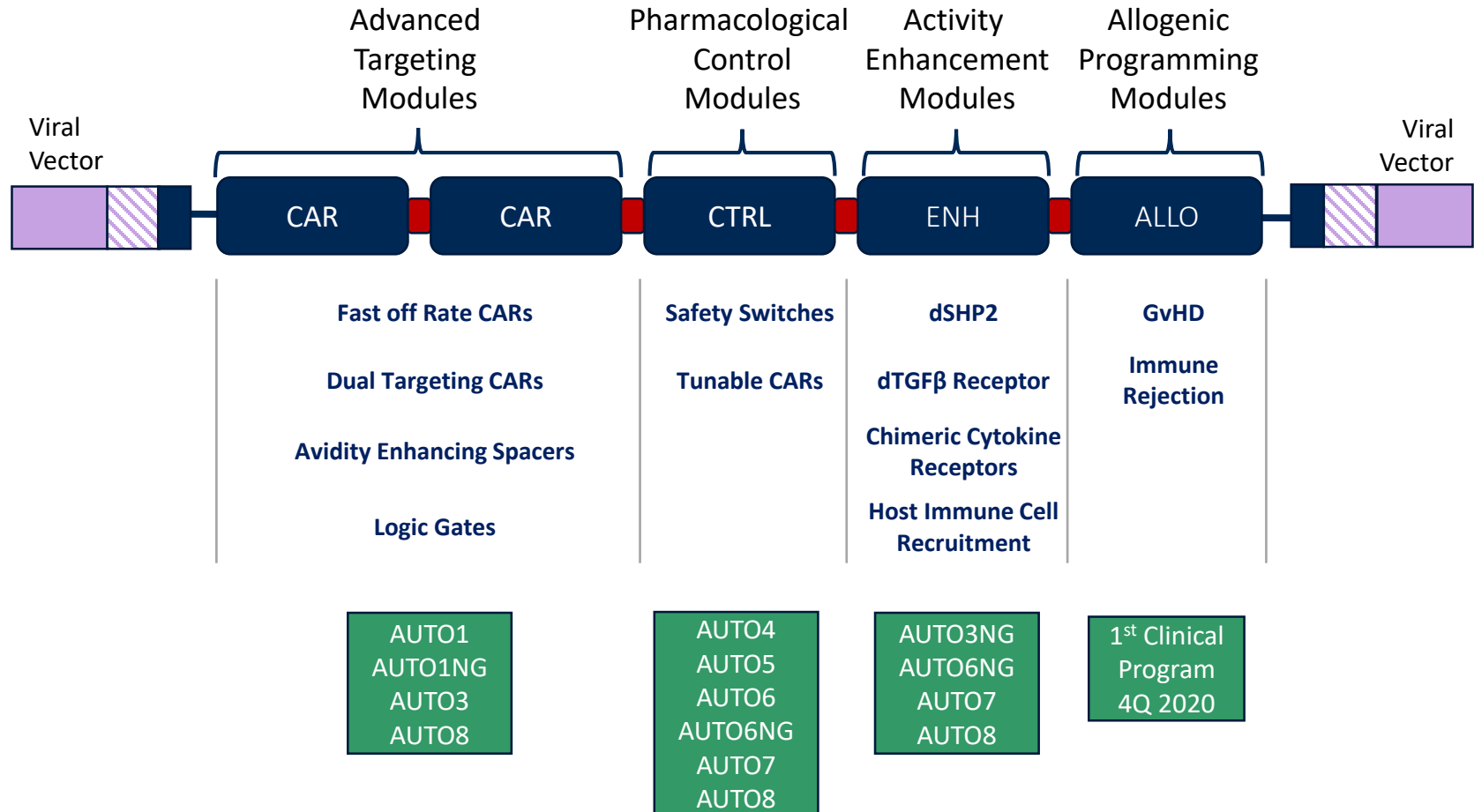
# Broad pipeline of clinical and next generation programs

## Designed to address limitations of current T cell therapies

Product	Indication	Target	Preclinical	Phase 1/2	Phase 2/3
B Cell Malignancies					
AUTO1	Adult ALL	CD19	ALLCAR19		
AUTO1	Pediatric ALL	CD19	CARPALL		
AUTO1NG	ALL	CD19 & CD22			
AUTO3	DLBCL	CD19 & CD22	ALEXANDER		
AUTO3NG	DLBCL	CD19 & CD22			
Multiple Myeloma					
AUTO8	Multiple Myeloma	BCMA & CAR X			
T Cell Lymphoma					
AUTO4	TRBC1+ Peripheral TCL (LibrA T1)	TRBC1	LibrA T1		
AUTO5	TRBC2+ Peripheral TCL	TRBC2			
GD2+ Tumors					
AUTO6	Neuroblastoma	GD2	CRUK		
AUTO6NG	Neuroblastoma; Melanoma; Osteosarcoma; SCLC	GD2			
Prostate Cancer					
AUTO7	Prostate Cancer	Undisclosed			

# Advanced T cell programming

Building on our core principles of modular innovation with protein-based cell programming



# Economical & scalable product delivery platform

Semi-automated and parallel processing

## Clinical supply & commercial launch

- > Multiple samples to be processed within the same environment
- > CGT Catapult (UK)
- > Global clinical supply since Q3 2019



## Planned US commercial supply

- > Collaboration with Alexandria Real Estate Partners (ARE)
- > Fully scaled commercial site for cell process supply
- > Planned capacity of 5,000 patients p.a.



# Adult Acute Lymphoblastic Leukemia

Adult ALL is a significant commercial opportunity

- > Potential market size in adult ALL
  - Up to 8,400 new cases of adult ALL diagnosed yearly worldwide
- > High unmet medical need
  - Combination chemotherapy enables 90% of adult ALL patients to experience CR, but only 30% to 40% will achieve long-term remission
  - Median overall survival is < 1 year in r/r ALL
- > No CAR T therapy currently approved in adult ALL
- > Only approved redirected T cell therapy approved for adults generally is blinatumomab
- > AUTO1 granted FDA orphan drug designation for ALL

Sources: Prevalence calculated using SEER and EUCAN and extrapolated using IMS; American Cancer Society

# AUTO1 is designed for long term persistence and reduced high-grade CRS

## Unmet need in adult ALL patients

- > Generally more fragile, more co-morbidities, and less likely to tolerate toxicity
- > Durable benefit in adult ALL will require long term pressure on the leukemia
- > Often higher tumor burden in the bone marrow, increasing risk of toxicities

### Current treatments

- > Conventional CD19 CAR-Ts use identical high affinity CD19 binder (FMC63)
- > A fast on-rate and a very slow off-rate may lead to over-activation and high-grade CRS

### AUTO1

- > Designed to reduce severe CRS ( $\geq$ G3) through the introduction of a proprietary optimized CD19 CAR with a lower affinity and a fast off rate
- > Engages efficiently with cancer cells, delivering a kill, but disengages rapidly like a normal T cell

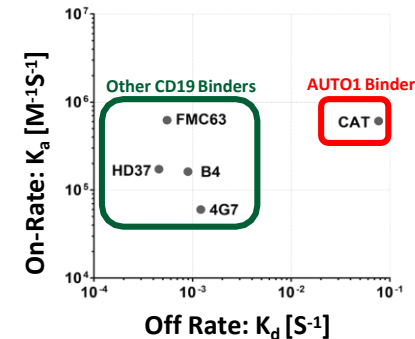


# AUTO1 shows enhanced activity vs FMC63 CARs

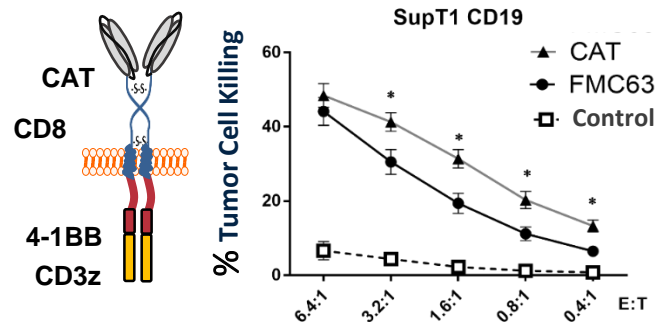
Preclinical data show higher cytotoxicity and proliferation

- > AUTO1 (CAT) binder with lower affinity for CD19
- > Half-life of target interaction very short compared to Kymriah® (FMC63) binder\*:
  - AUTO1 = 9.8 seconds
  - Kymriah® = 21 minutes

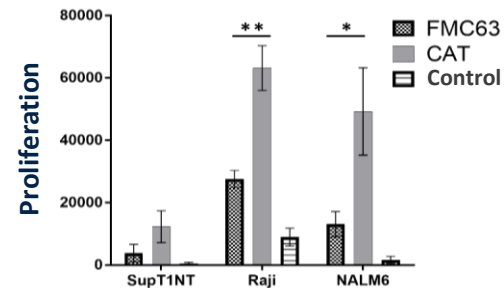
## Fast Off-Rate



## Enhanced Cytotoxicity

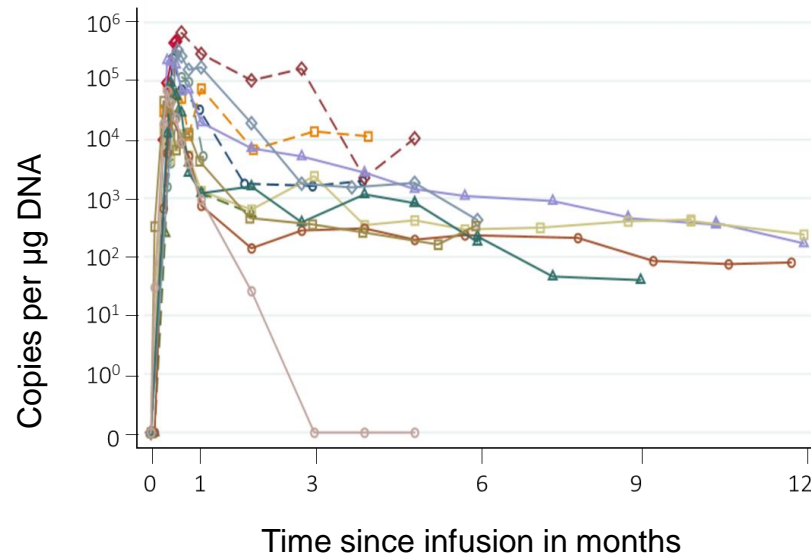


## Enhanced Proliferation



\*Similar binders are used in Yescarta® and JCAR-017  
Amrolia et al., (2019) Nature Medicine.

# Robust AUTO1 expansion and persistence in Adult ALL patients support potential for sustained responses



PK analysis		
Parameters	AUTO1 <sup>1</sup>	Kymriah <sup>2</sup>
Patient numbers	13	52
<u>AUC (0 to 28) (copies/ug DNA)</u>		
Geometric mean	634,719	342,732
<u>Half life (days)</u>		
Median	26.3	14.2
<u>Maximum CAR T Level (copies/ug DNA)</u>		
Geometric mean	111,239	47,988

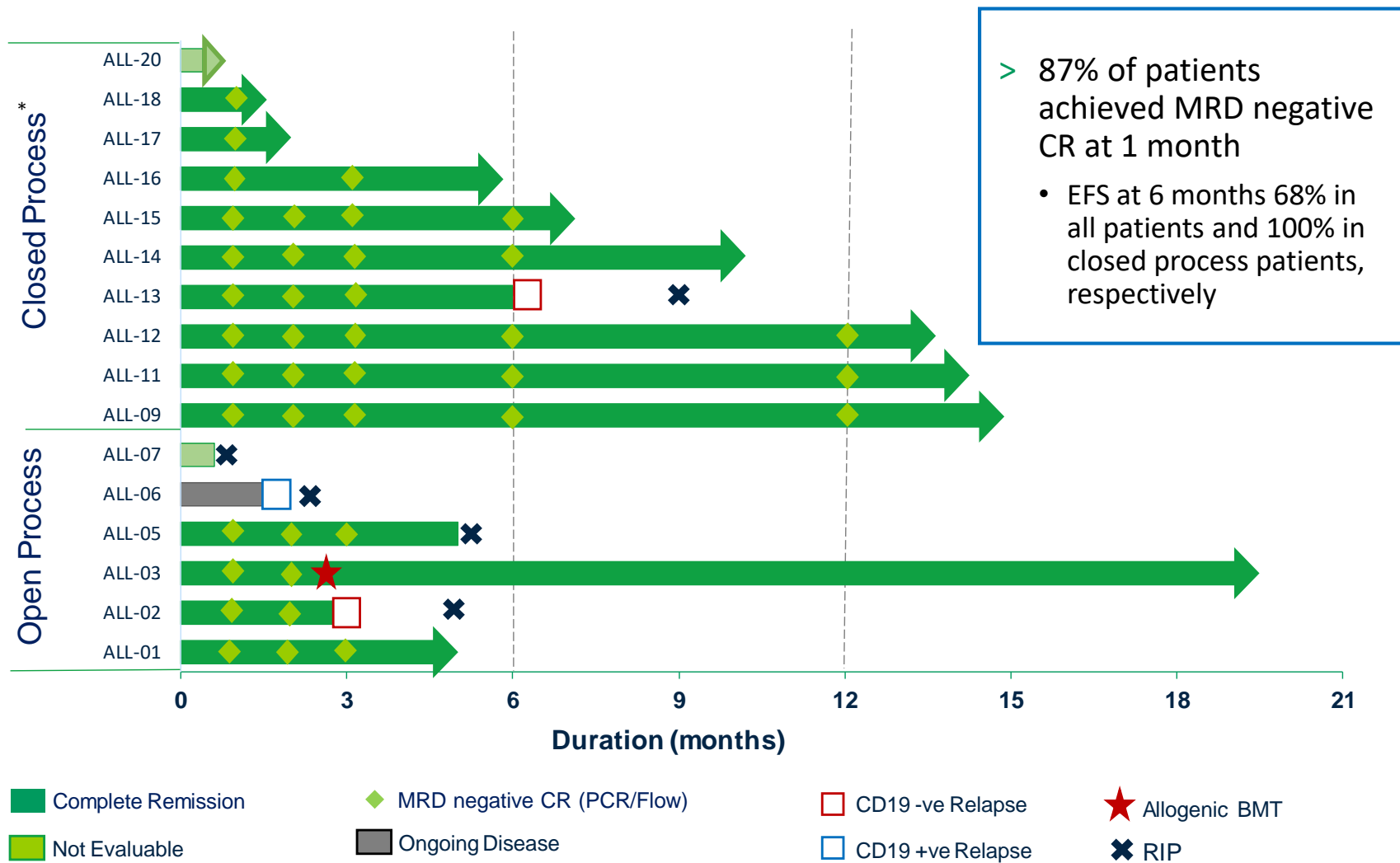
1 Roddie et al., (2019) ASH presentation

2 Mueller et al., (2017) Blood

- > Prolonged CAR T cell persistence was observed
  - 14 of 16 patients at last follow up
- > Manageable safety profile, despite high disease burden and heavily pre-treated patients

# High level of response and durability

10/15 (67%) evaluable patients remain disease-free<sup>1</sup>



Roddie et al., (2019) ASH presentation

<sup>1</sup>Median 11 months follow up (range 0.5 – 21m)

MRD < 10<sup>-4</sup> by PCR or < 5 x 10<sup>-4</sup> based on limits of detection of assay

Data cutoff 25-Nov-2019, Evaluable = All patients with at least M1 follow-up or RIP prior to Month 1.

\*Commercial manufacturing process

# Relapsed/refractory aALL clinical data

AUTO1 may be best-in-class redirected T cell therapy

	<sup>2</sup> AUTO1		
	<sup>1</sup> Blincyto	All patients	Closed Process <sup>3</sup>
Patient Numbers	271	16	9
CR Rate	42%	87%	100%
EFS 6m	31%	68%	100%
CRS ≥ Grade 3	3%	0%*	0%
Neurotox ≥ Grade 3	13%	19%†	12%‡

\* One patient had G3 CRS by UPenn Criteria, per protocol assessment

† All three patients had > 50% tumor burden

Data cutoff 25-Nov-2019

<sup>1</sup>Kantarjian et al., 2017

<sup>2</sup>Roddie et al., ASH 2019 presentation

<sup>3</sup>Commercial manufacturing process

- > AUTO1 preliminary data suggests manageable safety profile and a high level of clinical activity

# Data is consistent between pediatric and adult cohorts

	CARPALL Cohort 1	ALL CAR All Patients	ALLCAR Closed Process*
Evaluable Patients	14	15	9
CR Rate	86%	87%	100%
EFS	6m: 71% (39% to 88%)	6m: 68% (33%, 87%)	6m: 100% (-, -)
CRS ≥ Grade 3 <sup>‡</sup>	0%	0% <sup>#</sup>	0%
Neurotox ≥ Grade 3	7% <sup>##</sup>	19% (3/16)	12% (1/9)

\*Commercial manufacturing process

<sup>‡</sup> Graded as per Lee criteria

<sup>#</sup> One patient had G3 CRS by UPenn Criteria, per protocol assessment

<sup>##</sup> Deemed more consistent with fludarabine than CAR-associated neurotox

## CARPALL Highlights

- > 12/14 (86%) patients in cohort 1 achieved molecular CR; in cohort 2, 7/7 (100%) patients treated using the closed process achieved molecular CR
- > 6 /12 responding patients remain in molecular complete remission, first patients reaching 36 months
- > 12 month EFS is 54%, no relapses observed after 12 months
- > 5 of 6 relapsing patients had CD19 loss at time of relapse

# AUTO1 in aALL - Potential for best-in-class profile

First Autolus program to move to late stage development

## Potential pivotal study in adult ALL:

- > CTA filed in UK in Nov, 2019 US IND to be filed in Q1 2020
- > Single arm study
- > 100 relapsed / refractory adult ALL patients
- > Primary endpoint: overall complete response rate (CR/CRi)
- > Secondary endpoints include MRD-negative CR EFS and DoR
- > BLA filing targeted for Q4 2021

# Pediatric ALL – Focus on AUTO1/AUTO1NG

## AUTO3 data support dual antigen targeting hypothesis

- > Development in pediatric ALL will focus on AUTO1 and AUTO1NG, building on the long-term persistence observed with AUTO1 in pALL
- > Key driver for relapse with AUTO1 is CD19 antigen loss
- > Dual-targeting AUTO1NG with CD19 CAR of AUTO1 and a novel CD22 CAR planned to enter clinical testing in H1 2020

# Diffuse Large B Cell Lymphoma (DLBCL)

DLBCL is a large commercial opportunity

- > Potential market size in DLBCL
  - Approx. 24,000 patients diagnosed in the US every year\*
  
- > Aggressive and rapidly advancing cancer
  - Most common type of Non-Hodgkin Lymphoma
  - High dose chemotherapy + mAb leads to remission in about 50-60% of patients
  
- > Two approved CAR T products (Yescarta® and Kymriah®)



# AUTO3: CD19 and CD22 targeting bicistronic CAR

Approach designed to address antigen escape & PDL-1 mediated inhibition

## Rationale

- > CD19 CARs are highly active in r/r DLBCL
- > Unmet need remains with CD19 CAR T Cell Therapy
  - 29-37% durable CRR in DLBCL<sup>1,2</sup>. The potential causes for relapse include:
    - PD-L1 upregulation<sup>3</sup> which contributes to CAR T exhaustion
    - CD19 antigen loss<sup>4</sup>
  - Rate of severe (grade  $\geq 3$ ) cytokine release syndrome (CRS 13-22%) and neurotoxicity (NT 12-28%)<sup>2,4</sup>

<sup>1</sup>Locke F et al Lancet Oncol 2019

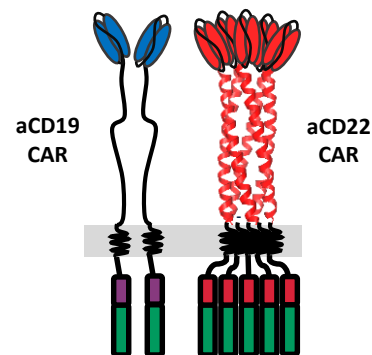
<sup>2</sup>Schuster S et al NEJM 2019

<sup>3</sup>Neelapu S et al ASCO 2018

<sup>4</sup>Neelapu S et al NEJM 2017

## Hypothesis

- > Simultaneous targeting of CD19 and CD22 reducing the probability of antigen escape mechanism
- > Prevent early PD1/PDL1 related CAR T cell exhaustion by adding pembrolizumab to the preconditioning regimen



# AUTO3: Adverse events of special interest

Manageable safety profile alone and in combination with pembrolizumab

	50 x10 <sup>6</sup> AUTO3 no pem (n=4)	50 x10 <sup>6</sup> AUTO3 D14 pem (n=3)	150 x10 <sup>6</sup> AUTO3 D14 pem (n=4)	450 x10 <sup>6</sup> AUTO3 D14 pem (n=4)	450 x10 <sup>6</sup> AUTO3 D-1 pem (n=1)	Total (n=16)
All grades CRS	1	0	2	1	1	5 (31.3%)
≥ G3 CRS	0	0 <sup>1</sup>	0	0	0	0
All grades NT	1	0	0	0	0	1 (6.3%)
≥ G3 NT	1	0	0	0	0	1 (6.3%)

<sup>1</sup> 1 patient who had no CRS with primary infusion, developed G3 CRS (severe hypoxia) with re-treatment 1 year later which happened in a setting of no CAR T expansion and significant disease burden in lung that had been treated with radiation

- > With primary infusion
  - No grade 2 or higher CRS<sup>2</sup>
  - No ICU admission for CRS management
  - Only 1 patient received tocilizumab for CRS
- > Only 1 case of grade 3 NT resolved quickly with steroids

<sup>2</sup> CRS grading as per Lee et al., *Blood* 2014

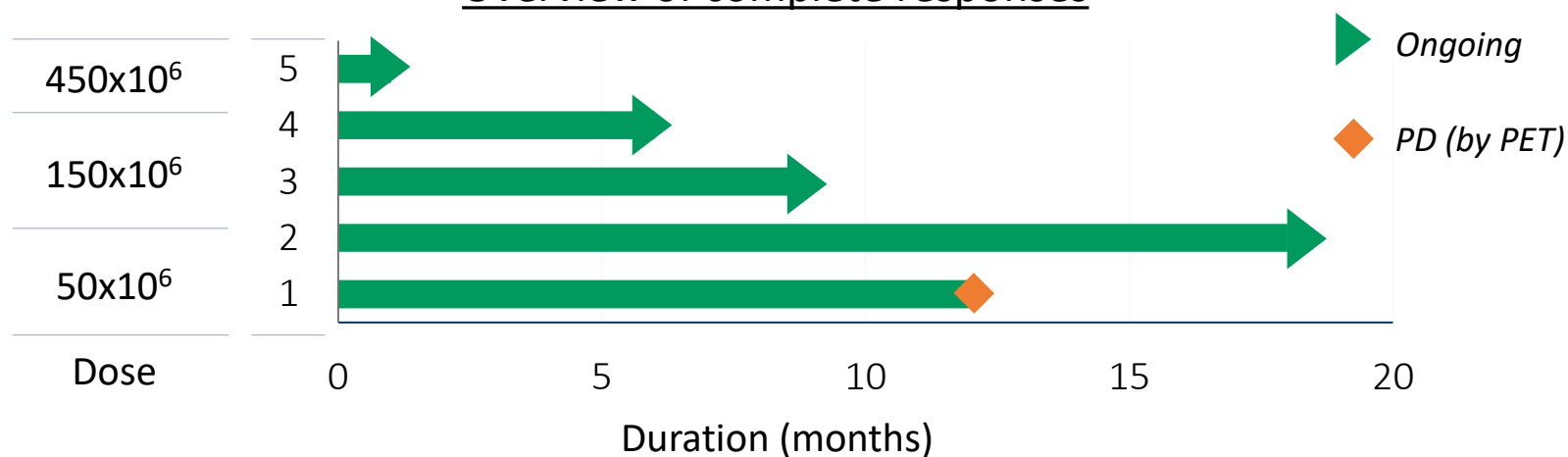
Ardeshta et al., ASH 2019

# Preliminary efficacy of AUTO3 in DLBCL

## Overview of responding patients

	50 x10 <sup>6</sup> No Pem N=4	50 x10 <sup>6</sup> D14 Pem N=3	150 x10 <sup>6</sup> D14 Pem N=4	450 x10 <sup>6</sup> D14 Pem N=4	450 x10 <sup>6</sup> D-1 Pem N=1
CR	1	1	2	1	n/a
PR	1	1	0	1	n/a
NE	0	1	0	1 (too early)	1 (too early)

## Overview of complete responses



**4 out of 5 (80%) CRs ongoing**

# CRs achieved in high risk patients without significant toxicities

## Examples of ongoing CRs

### PATIENT A

#### Pre-CAR T-cells



#### Post-CAR T-cells



**Dose:**  $50 \times 10^6$

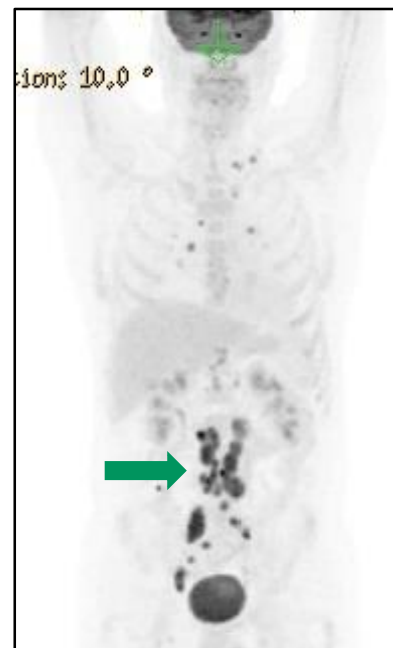
**DLBCL:** ABC, Primary refractory & refractory to RCHOP/RICE/RESHAP

**No CRS or NT**

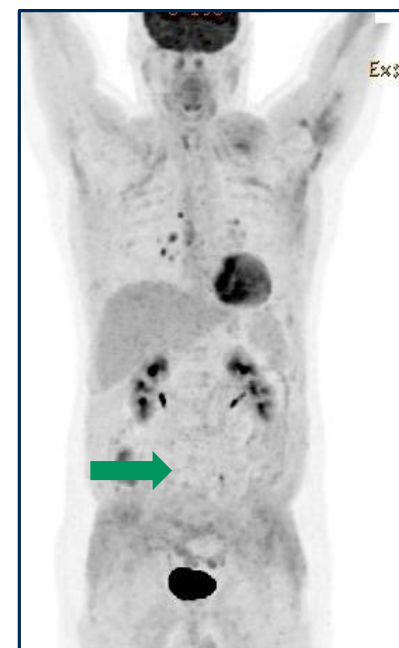
**CR duration 18 months+**

### PATIENT B

#### Pre-CAR T-cells



#### Post-CAR T-cells



**Dose:**  $150 \times 10^6$

**tDLBCL from FL:** R/R, 8 lines of prior therapy

**G1 CRS, no NT**

**CR duration 9 months +**

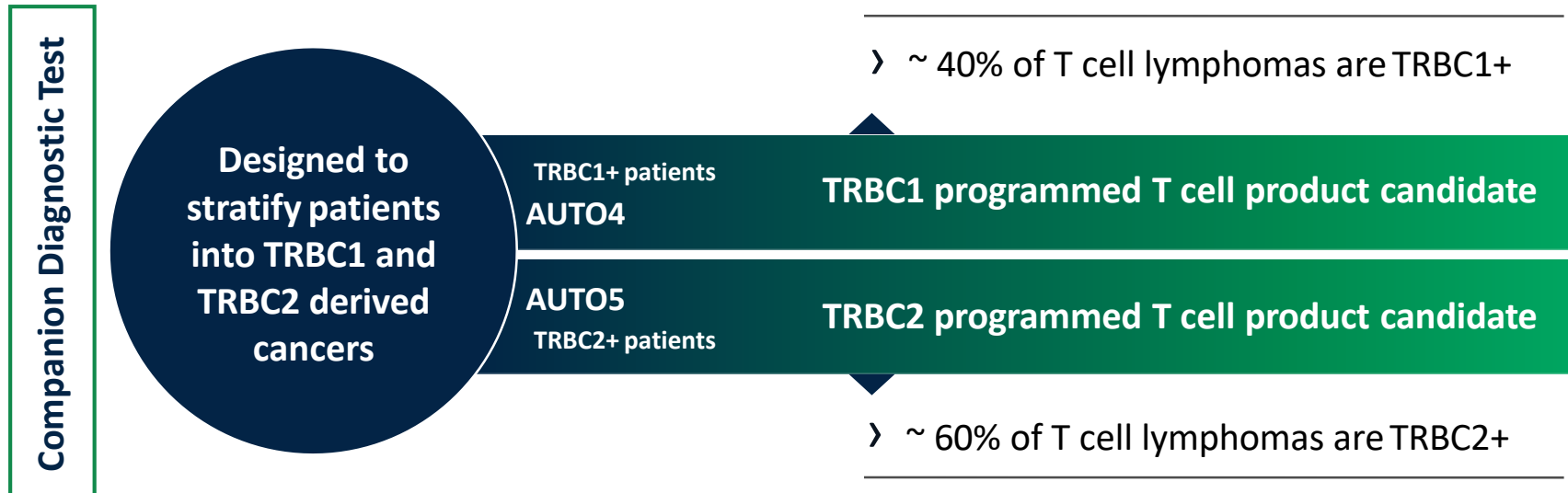
# AUTO3 in DLBCL

Early data encouraging – full read-out expected in mid-2020

- > AUTO3 product was successfully made for all patients
  - Products manufactured at Cell and Gene Therapy Catapult at Stevenage in the UK for US and EU use
- > 0% severe CRS and 1/14 (7%) severe NT with primary infusion
- > 4/5 CRs ongoing
- > Pembrolizumab on D-1 x single dose is being evaluated
- > Decision for triggering Phase 2 initiation planned for mid 2020

# Addressing T cell lymphomas

No standard of care after first relapse - patient prognosis is poor

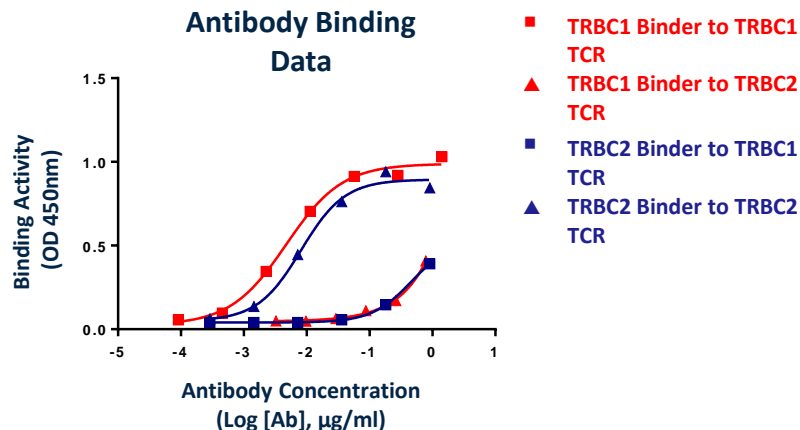
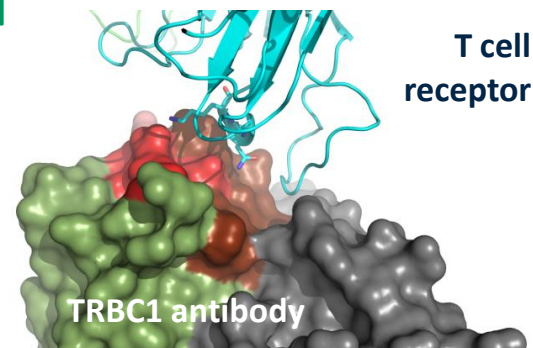


# AUTO4/5 in Peripheral T Cell Lymphoma

Unique targeting of TRBC1 and TRBC2 opens new therapeutic approach

Differences between TRBC1 and TRBC2 are small

		NK-KN 4/5	F-Y 36
TRBC1	1	EDLNKVFPPPEVAVFEPSEAEISHTQKATLVCLATGFF	PDHVELSWVNGK
TRBC2	1	EDLNKVFPPPEVAVFEPSEAEISHTQKATLVCLATGFF	PDHVELSWVNGK
TRBC1	51	EVHSGVSTDPQPLKEQPALNDSRYCLSSRLRVSATFWQNPРНHFRСQVQF	
TRBC2	51	EVHSGVSTDPQPLKEQPALNDSRYCLSSRLRVSATFWQNPРНHFRСQVQF	
TRBC1	101	YGLSENDEWTQDRAKPVTOIVSAEAWGRADCGFTS	VSYQQGVLSAT
TRBC2	101	YGLSENDEWTQDRAKPVTOIVSAEAWGRADCGFTS	VSYQQGVLSAT
		V-E 135	



- > Patient enrolment on AUTO4 Phase 1 study ongoing
- > Expect to present initial AUTO4 Phase 1 data H2 2020
- > AUTO5 Phase 1 decision based on AUTO4 data
- > Companion diagnostic development continuing in sync with overall timeline

# AUTO6: GD2-targeted programmed T cell therapy

Designed to drive anti-tumor activity without inducing neurotoxicity

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## > Programmed T cell product candidate:

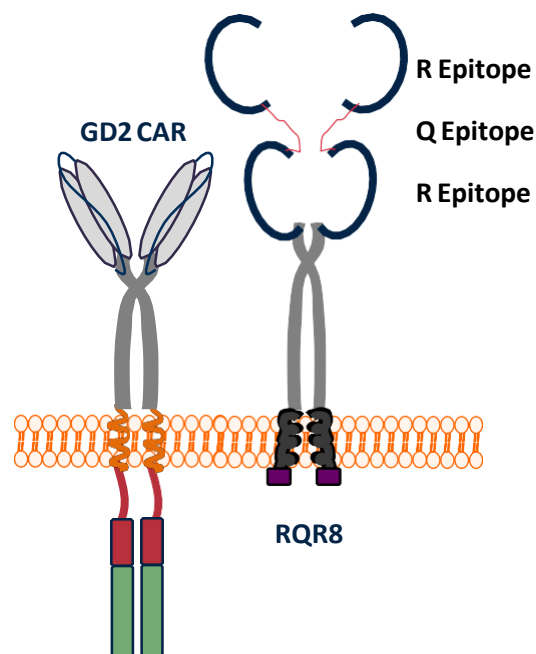
- New binder to minimize on-target, off-tumor toxicity
- Humanized binder to reduce immunogenicity
- RQR8 safety switch

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## > Phase 1 clinical trial in r/r neuroblastoma conducted by CRUK\* in collaboration with UCL

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## > Autolus has exclusive worldwide rights to clinical data and patents

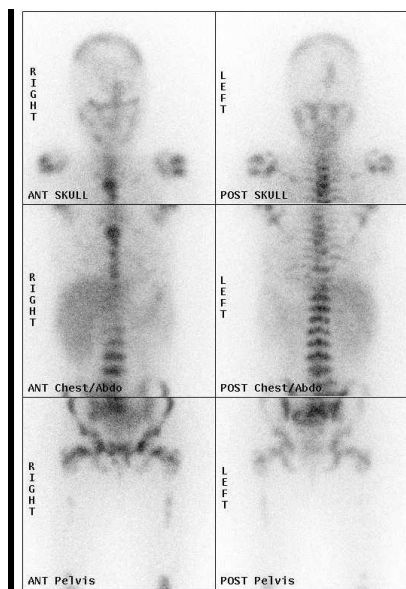




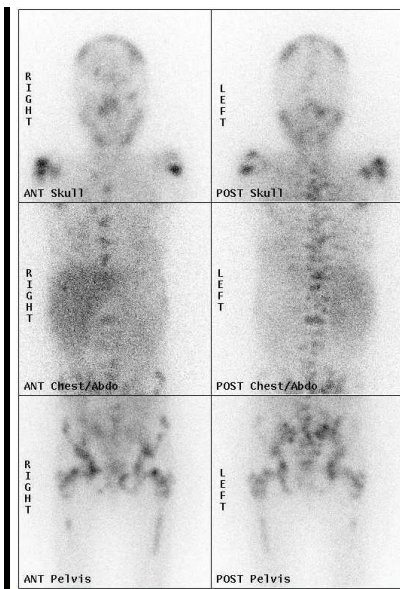
# AUTO6 proof of principle presented at AACR 2018

## Patient 10: AUTO6 anti-tumor activity without inducing neurotoxicity

Day 0



Day 28

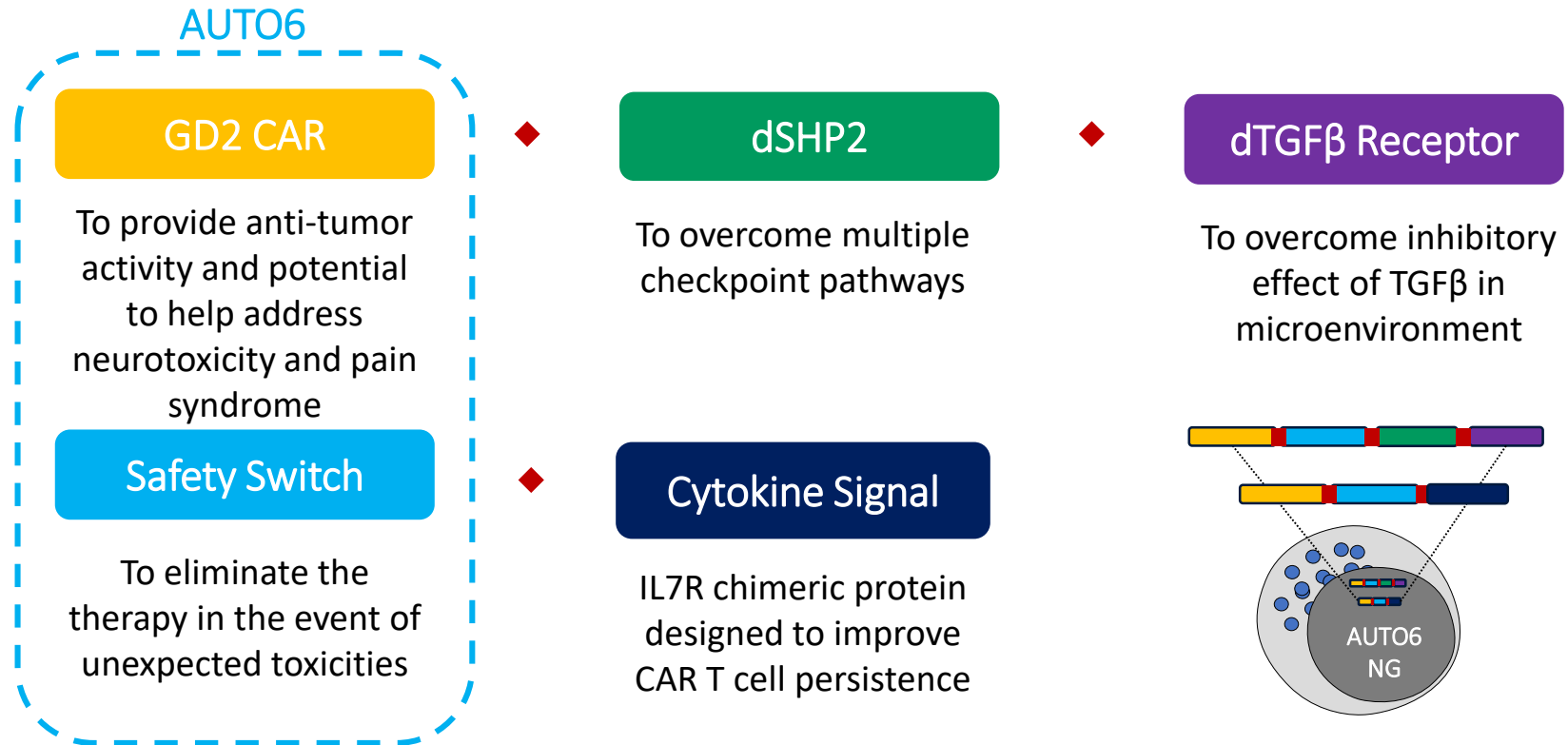


MIBG: iodine-123-meta-iodobenzylguanidine

- > Significant decrease in disease hot spots in patient 10 by MIBG scan after therapy
- > No DLTs and no neurotoxicity or pain syndrome observed
- > First GD2 CAR reported to demonstrate CRS and tumor lysis syndrome in solid tumor setting
- > AUTO6 next generation program in advanced pre-clinical development

# AUTO6NG – Building on AUTO6 therapeutic window

Modular Approach: Designed to address a hostile tumor micro-environment

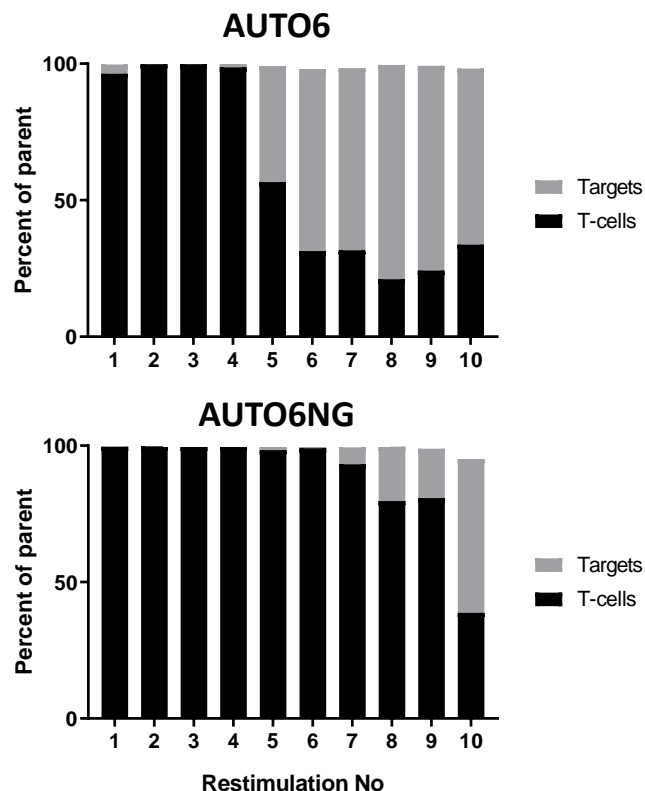


## > AUTO6NG:

- Utilizes the GD2 CAR from AUTO6
- Designed to address persistence, control and tumor defenses
- Target neuroblastoma, osteosarcoma, melanoma and small cell lung cancer amongst others

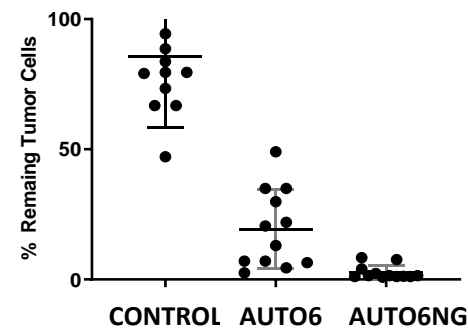
# AUTO6NG Shows Superior Activity *In Vitro*

## Enhanced Persistence



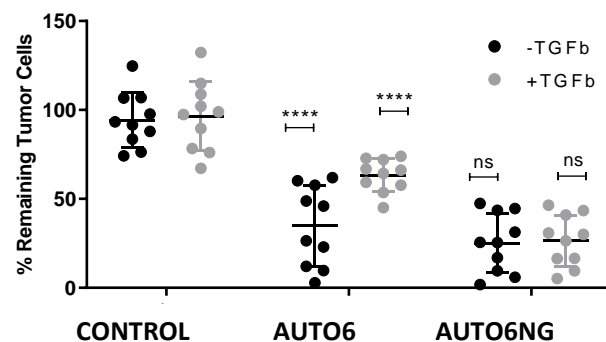
- Cytokine signal extends AUTO6NG activity through multiple rounds of restimulation

## Checkpoint Resistance



- dSHP2 enhances AUTO6NG activity against PDL1+ tumor cells.

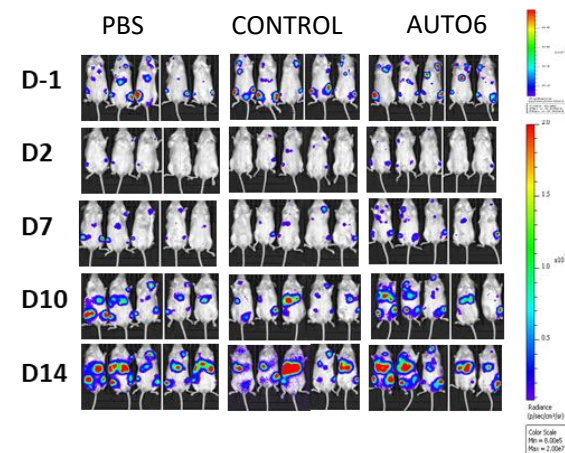
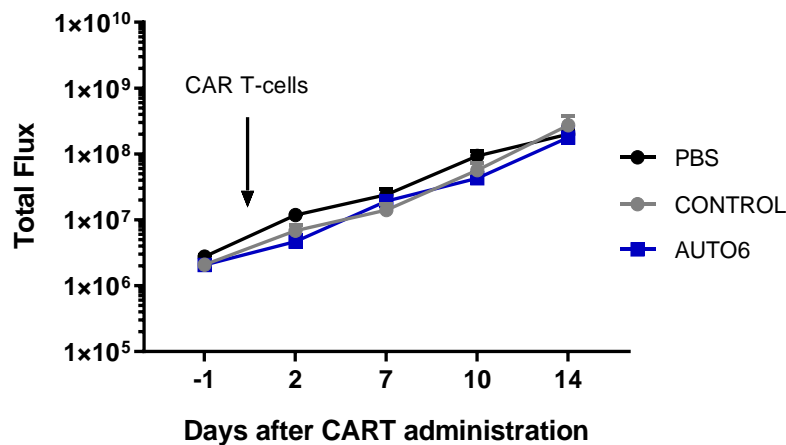
## TGFβ Resistance



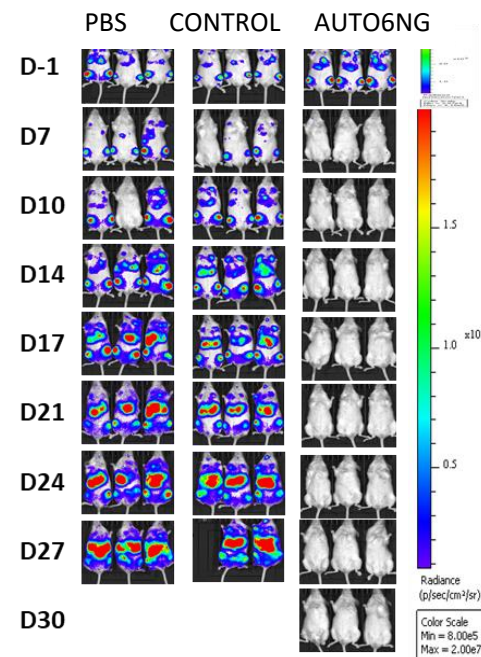
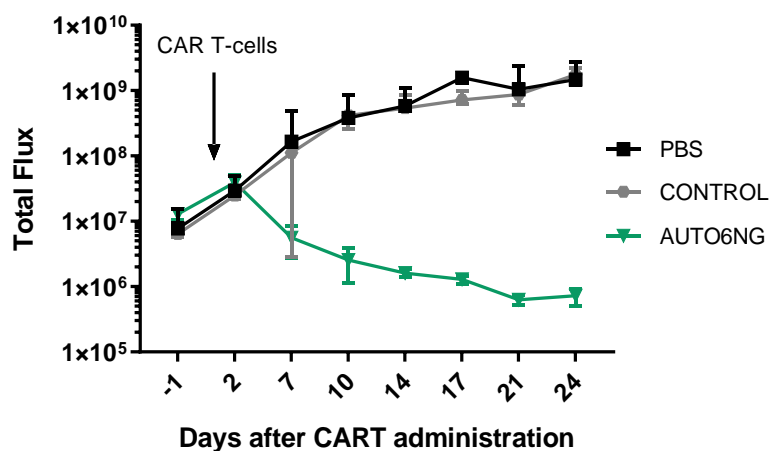
- dTGFβ Receptor enhances AUTO6NG activity in the presence of TGFβ

# AUTO6NG Exhibits Potent Anti-tumor Activity and Extends Survival in Challenging *In Vivo* Model

AUTO6



AUTO6NG



# AUTO6NG

Positioned for additional value inflection in 2020

- > Plan to commence Phase 1 H2 2020
- > Encouraging preclinical data on three T cell programming modules presented at SITC 2019
  - Constitutively signaling IL7 cytokine receptor (IL7R\_CCR module) is shown to enhance persistence
  - Dominant negative TGFbRII (dnTGFbRII module) observed to block TGFβ signaling
  - Truncated SHP2 (dSHP2 module) observed to confer resistance to inhibitory signals such as those from PD1
  - In established tumor model AUTO6NG eliminated the tumor, whereas AUTO6 did not

# Towards a Unique Approach to Allogeneic T Cell Therapies

## Modular programming without the requirement for gene editing

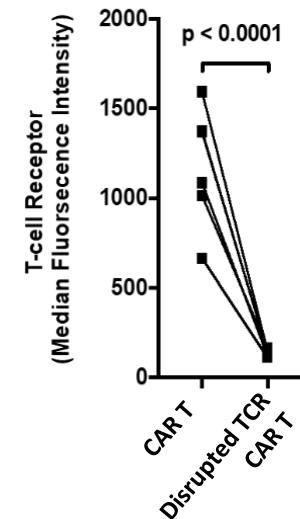
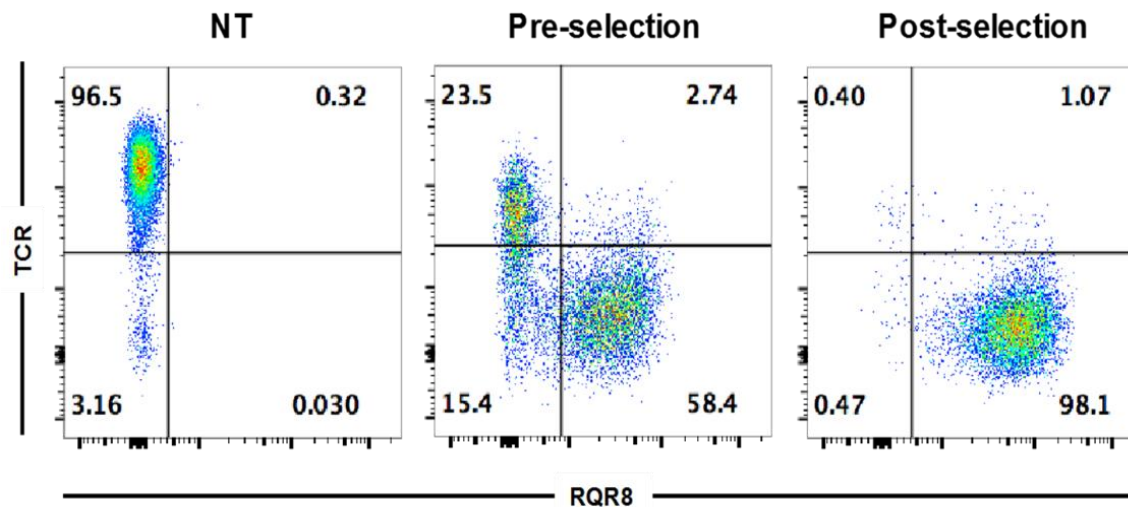
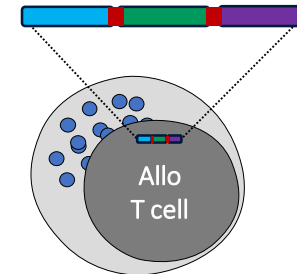
- > Key challenges
  - Graft vs Host Disease – mediated by TCR of donor cells
  - Immune rejection – recognition of MHC on donor cells by host cells
  
- > Novel approach using protein-based programming integrates with Autolus' existing T cell programming and manufacturing platform:
  - TCR expression is disrupted by intracellular retention and degradation using a single programming module
  - Programming modules are also in development to protect the donor cells from immune rejection
  - Approach can be combined with all other T cell programming modules under development at AUTL
  - Approach fits current manufacturing approach at AUTL
  
- > Avoids technical and IP complexities of gene editing

# Allogeneic CAR T

## Complete TCR down regulation in primary T cells

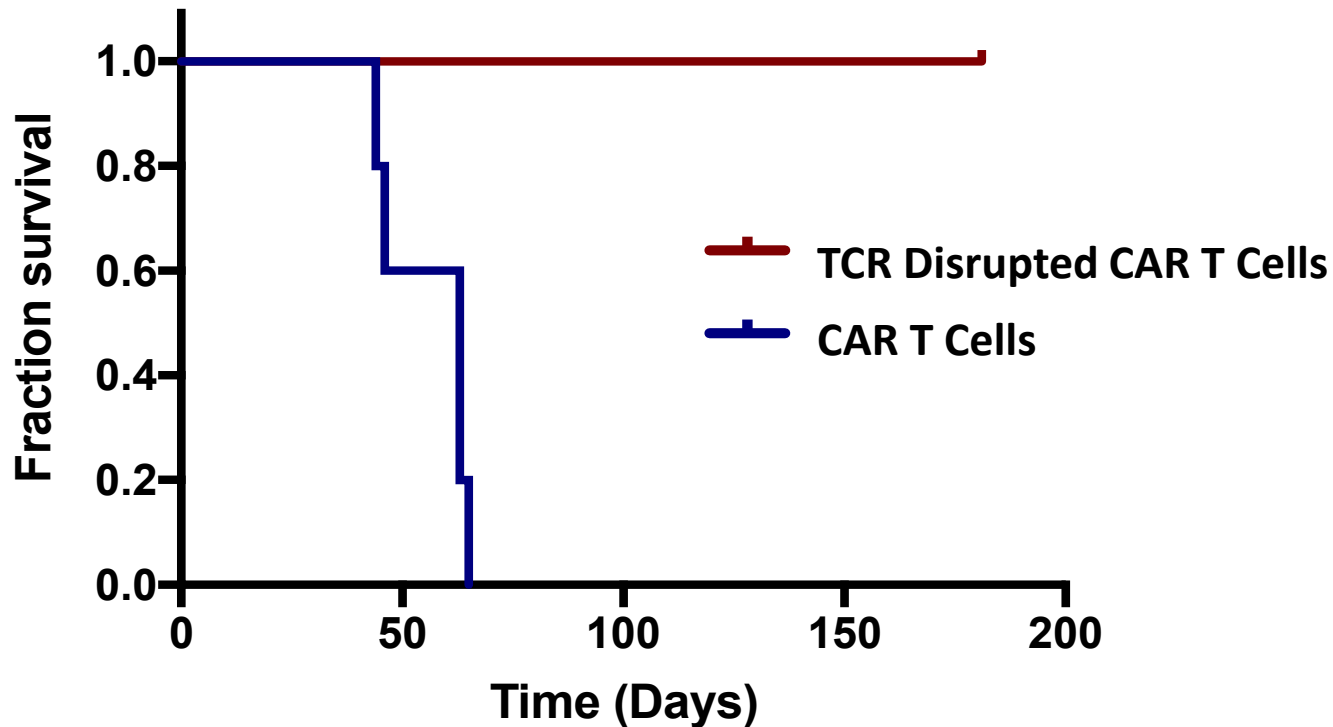


- > TCR Disruption module is co-expressed with the CAR and safety switch in the same viral vector
- > Potential for rapid and simple manufacturing using positive or negative magnetic bead selection



# Allogeneic CAR T

TCR disrupted cells prevent GvHD and prolong survival in sensitive mouse model



- > Exploratory phase 1 clinical trial incorporating the TCR Disruption Module planned to start in Q4 2020 with an academic partner

Macocia et al., 2018 (ASH)  
NSG xeno-GvHD Mouse Model  
Median survival 63 days versus not reached  
Hazard Ratio = 20.6,  $p = 0.002$   
 $n = 5$  per group



# Clinical newsflow expected through 2020

Product	Indication	Target	Event
B Cell Malignancies			
AUTO1	Adult ALL	CD19	<ul style="list-style-type: none"> <li>Ph 1 long-term follow up Q2 &amp; Q4 2020</li> <li>Start pivotal program H1 2020</li> </ul>
AUTO1NG	Pediatric ALL	CD19 & 22	<ul style="list-style-type: none"> <li>Start Ph 1 H1 2020</li> </ul>
AUTO3	DLBCL	CD19 & 22	<ul style="list-style-type: none"> <li>Ph 1 data Q2 &amp; Q4 2020</li> <li>Decision on Ph 2 transition mid 2020</li> </ul>
AUTO3NG	DLBCL	CD19 & 22	<ul style="list-style-type: none"> <li>Start Ph 1 H2 2020</li> </ul>
Multiple Myeloma			
AUTO8	Multiple Myeloma	BCMA & CAR X	<ul style="list-style-type: none"> <li>Start Ph 1 study H2 2020</li> </ul>
T Cell Lymphoma			
AUTO4	TRBC1+ Peripheral TCL	TRBC1	<ul style="list-style-type: none"> <li>Ph 1 interim data Q4 2020</li> </ul>
GD2+ Tumors			
AUTO6NG	Neuroblastoma; Melanoma; Osteosarcoma; SCLC	GD2	<ul style="list-style-type: none"> <li>Start Ph 1 H2 2020</li> </ul>
Allogeneic Approach			
NA	NA	NA	<ul style="list-style-type: none"> <li>Start Ph 1 Q4 2020</li> </ul>

# Investment highlights

## Broad clinical-stage pipeline

- > 4 product candidates
- > 4 hematological indications
- > 1 solid tumor program

## Multiple upcoming milestones

- > AUTO1 long term follow up in aALL
- > POC for AUTO3 in DLBCL
- > POC for AUTO4 in PTCL

## Proprietary manufacturing process

- > Fully enclosed, semi-automated
- > Designed to be economical at commercial scale
- > Expanding to new US/UK facilities

## Modular programming approach

- > Enables rapid cycle of innovation
- > 4 next generation versions of lead programs to enter clinical development in 2020
- > Designed to address:
  - Targeting & control
  - Tumor defenses & microenvironment
  - GvHD & immune rejection (Allogeneic)
  - Manufacturing
- > Portfolio of owned and in-licensed intellectual property; 85 patent families

## Strong Fundamentals

- > \$229 million at September 30, 2019
- > Worldwide rights retained for all programs
- > Cash runway into H2 2021



**Thank you**