CART Global Program Team,
Global Drug Development,
Novartis Pharmaceuticals Co

Chimeric Antigen Receptor (CAR)-T cells

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London, UK
November 15, 2016

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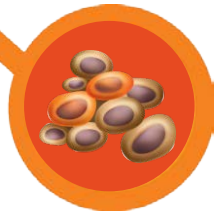
Disclaimer

- This presentation contains information about investigational compounds that have not been approved in any country or region of the world.
- Efficacy and safety have not been established.
- The information presented should not be construed as recommendations for use.

Cell & gene therapies are a new pillar of the life science industry

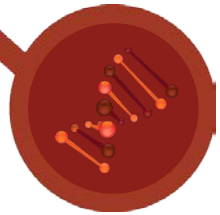
Cell & Gene Therapies



Cell & Gene Transfer

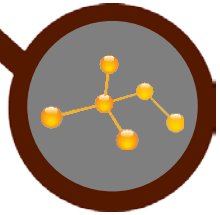
- Cell therapy: transfer cells with relevant function into patient[1]
- Gene therapy: transfer of genetic material into appropriate cells of the body[1]

Biologics



Protein engineering

Small Molecules



Chemical engineering

Reference: 1. American Society of Gene & Cell Therapy. FAQs. Retrieved March 9, 2015 from http://www.asgct.org/general-public/educational-resources/faqs#faq10.

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Collaboration with University of Pennsylvania

Penn
University of Pennsylvania

Cell therapy research collaboration[1]

Collaboration on study of chimeric antigen receptor (CAR) technology for cancer treatment;
exclusive worldwide license
to CARs developed through the collaboration

References: 1. http://www.novartis.com/newsroom/media-releases/en/2014/1877920.shtml.

CTL019

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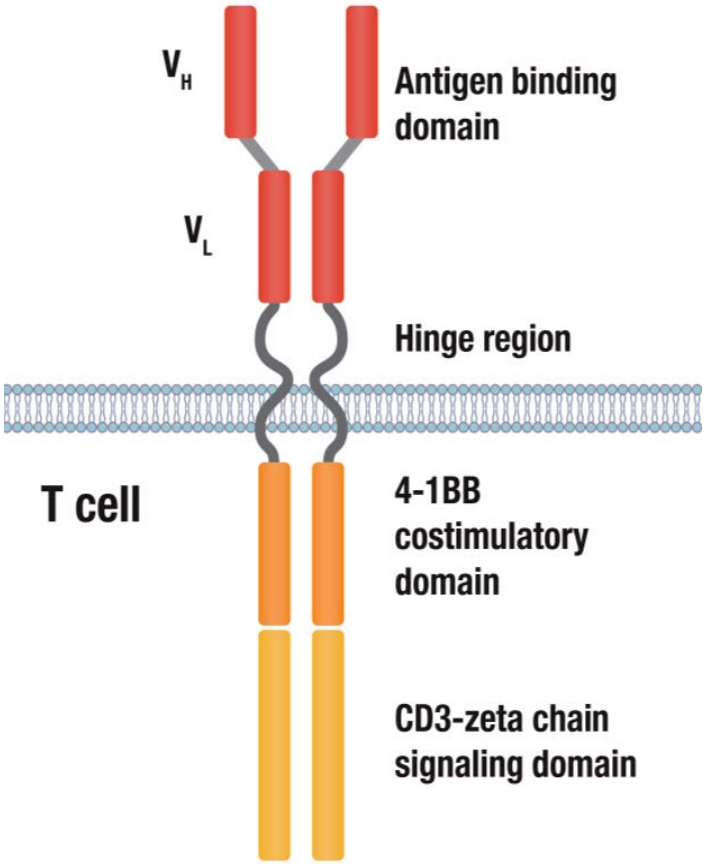
Design of CD19-targeted CTL019

- FDA granted "breakthrough therapy" designation to CTL019, the anti-CD19 CAR T-cell therapy developed at the University of Pennsylvania (July 2014)
- CTL019 CAR consists of T-cell activation domains coupled to an anti-CD19 single-chain variable fragment[1-3]

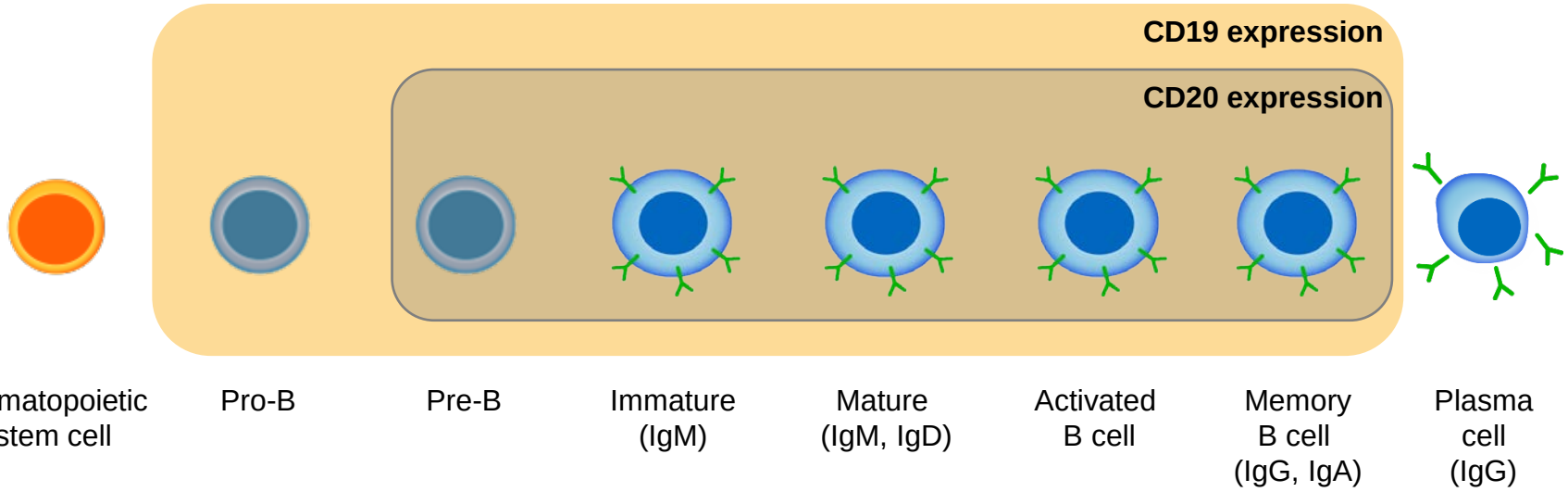


UPenn construct scFv-41BB-CD3ζ

1. Milone MC, et al. *Mol Ther.* 2009;17:1453-1464; 2. Zhang H, et al. *J Immunol.* 2007;179:4910-4918; 3. Kalos M, et al. *Sci Transl Med.* 2011;3:95ra73.

CD19: An ideal target for CAR T-cells

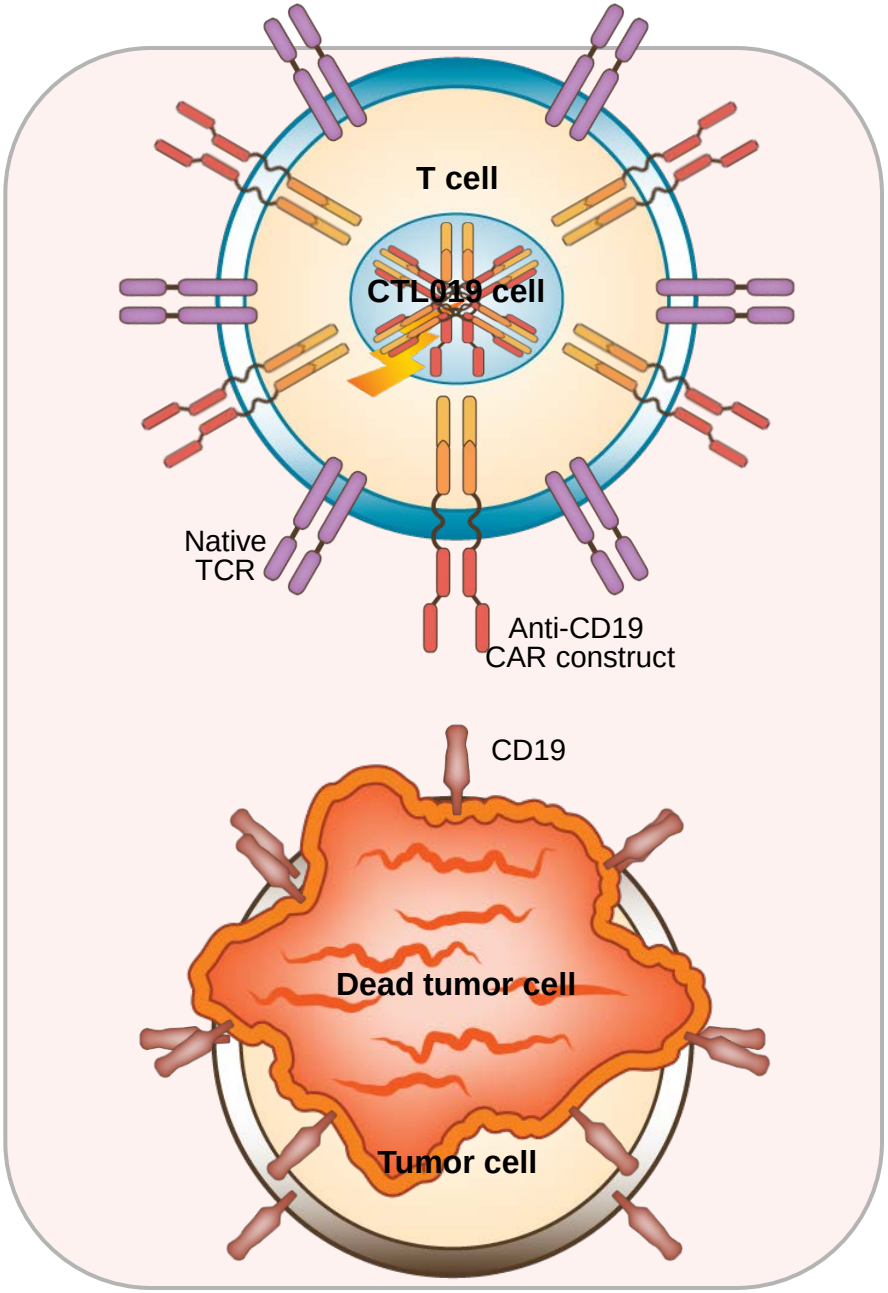
- CD19 is a cell surface protein whose expression is restricted to B cells and B cell precursors[1]
  - Importantly, CD19 is not expressed on hematopoietic stem cells[1]
- CD19 is expressed by most B-cell malignancies[1]
  - CLL, B-ALL, DLBCL, FL, MCL[1]



1. Scheuermann RH, et al. *Leuk Lymphoma*. 1995;18:385-397.
Image adapted from Scheuermann RH, et al. *Leuk Lymphoma*. 1995;18:385-397.

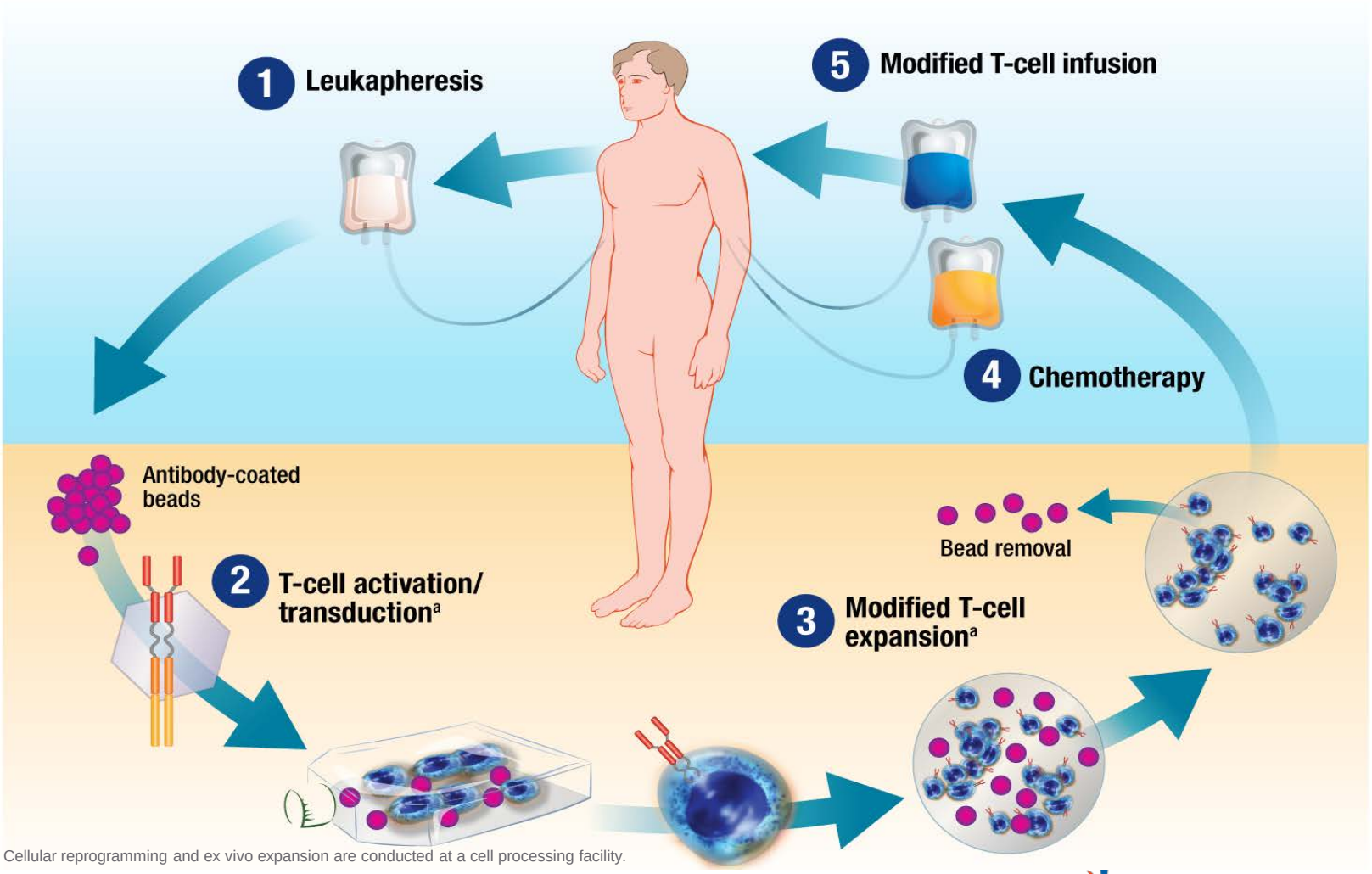
Mechanism of action of CTL019

- Gene transfer technology is used to stably express CARs on T cells, conferring novel antigen specificity[1,2]
- CTL019 therapy takes advantage of the cytotoxic potential of T cells, thereby killing tumor cells in an antigen-dependent manner[1,3]
- Persistent CTL019 cells consist of both effector (cytotoxic) and central memory T cells[3]



1. Milone MC, et al. *Mol Ther.* 2009;17:1453-1464; 2. Hollyman D, et al. *J Immunother.* 2009;32:169-180; 3. Kalos M, et al. *Sci Transl Med.* 2011;3:95ra73.

CTL019 is designed to hunt and destroy CD19-positive B-cell cancers in patients



a. Cellular reprogramming and ex vivo expansion are conducted at a cell processing facility.

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CD19-targeted CAR therapies under investigation

Academic Group	Company (Drug)	Costimulatory Domain	Vector Delivery	Indications
UPenn	Novartis (CTL019)	4-1BB	Lentiviral	ALL, CLL, DLBCL, FL
MSKCC	Juno (JCAR 015)	CD28	Retroviral	ALL, CLL, various B-cell malignancies
Fred Hutchinson	Juno (JCAR 017)	4-1BB	Lentiviral	
NCI (NIH)	Kite Pharma (KTE-C19)	CD28	Retroviral	DLBCL
Baylor	Bluebird/Celgene	CD28	Retroviral	ALL, CLL
MDACC	Ziopharm/Intrexon	CD28 → 4-1BB	Transposon/ transposase	Adjuvant, pre/post transplant
Institut Pasteur	Cellectis/Pfizer (UCART19)	4-1BB	Lentiviral	ALL, CLL, AML, MM
Baylor	Bellicum (BPX-401)	MyD88 + CD40	Retroviral	Various
Dartmouth	Cardio3	DAP-10 transmembrane	Retroviral	AML, MDS, MM

CAR T cell Therapy – Leukemia as a Model

Shannon Maude MD PhD
Center for Childhood Cancer Research
Children's Hospital of Philadelphia
University of Pennsylvania Perelman School of Medicine

ASGCT, May 7, 2016

CTL019 experience in ALL

Pediatric ALL phase 1/2a study (N = 59):

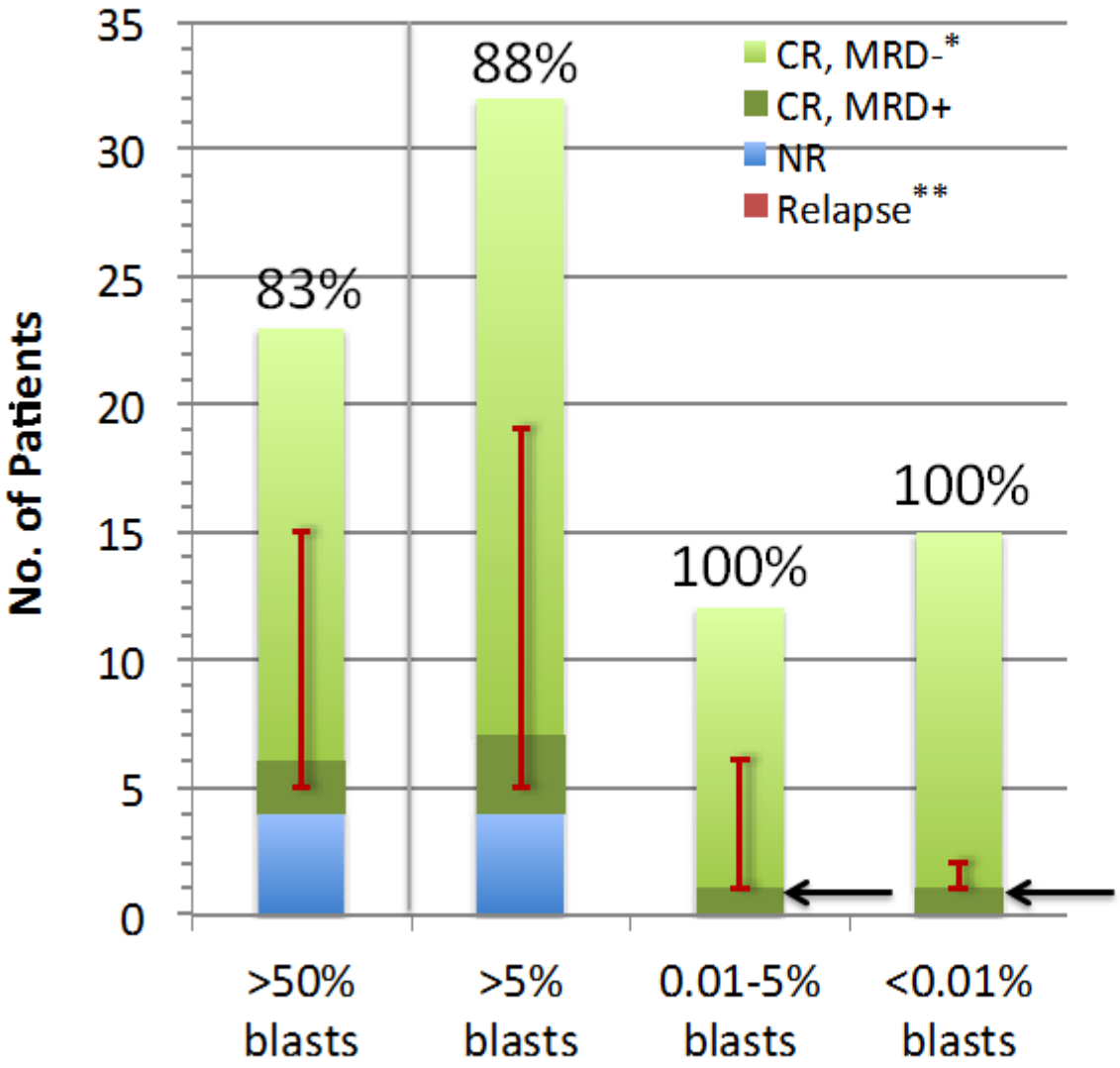
Population

- 2nd or greater relapse or refractory
- 2/3 relapsed post SCT

Outcomes

- 55/59 (93%) in complete remission at 1 month
- 18 patients in remission ≥1 year, 13 without further therapy
- Median follow-up 12 months, range 1-43 months
- 20 relapses, 7 CD19(+) and 13 CD19(-)
- 6 patients proceeded to SCT, 1 to DLI

Disease Burden and Response



Patient population

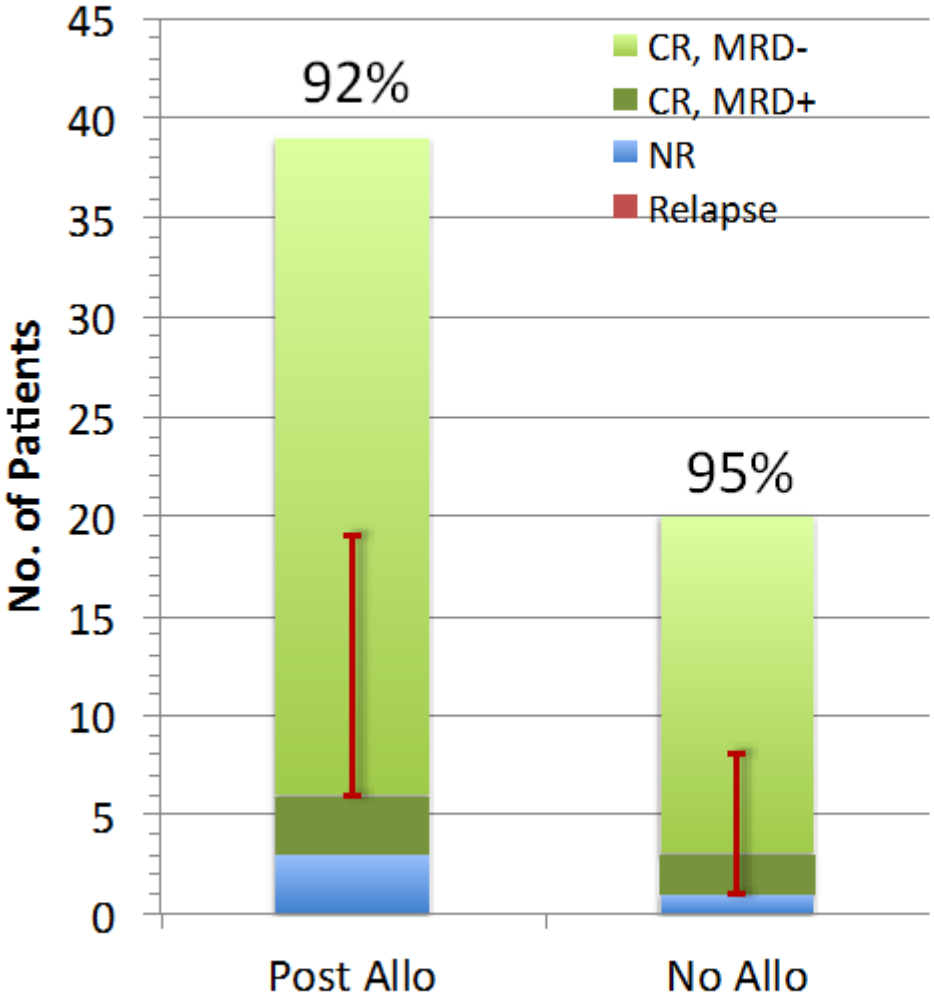
- ≥ 2nd relapse or refractory
- Majority refractory to multiple prior therapies

* <0.01% MRD by flow cytometry

** ⅓ CD19+, ⅔ CD19- MRD- by 3 months without further therapy

Abbreviations: CR, complete response, MRD, minimal residual disease; NR, no response

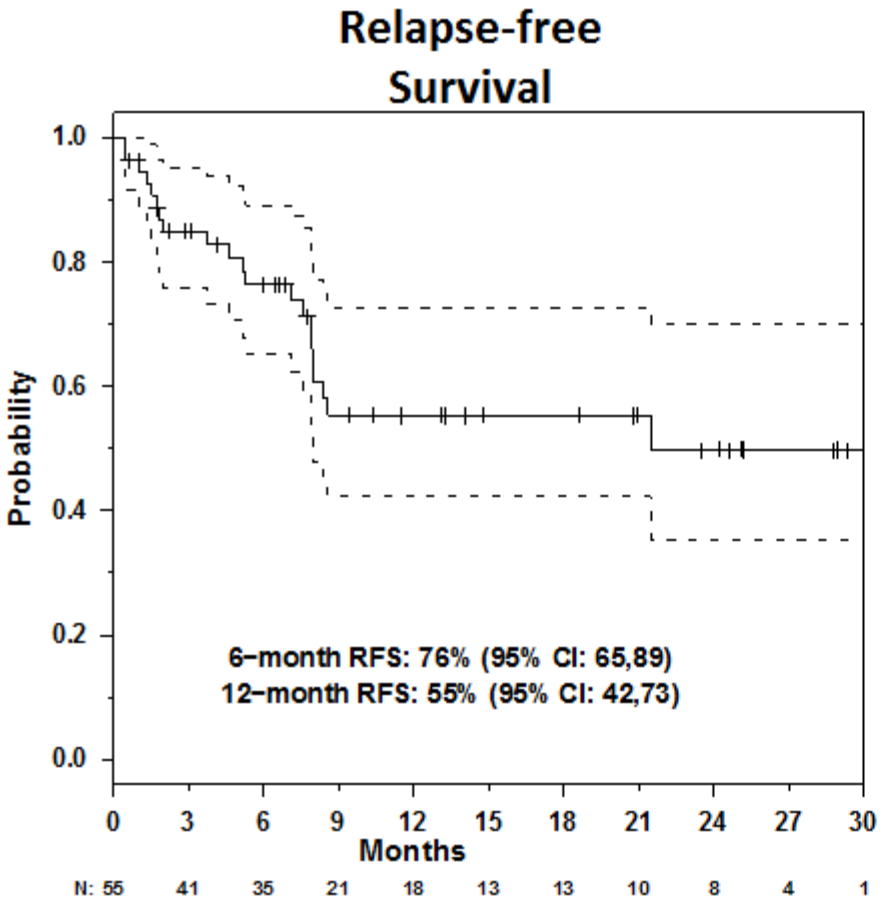
Most patients treated POST allo

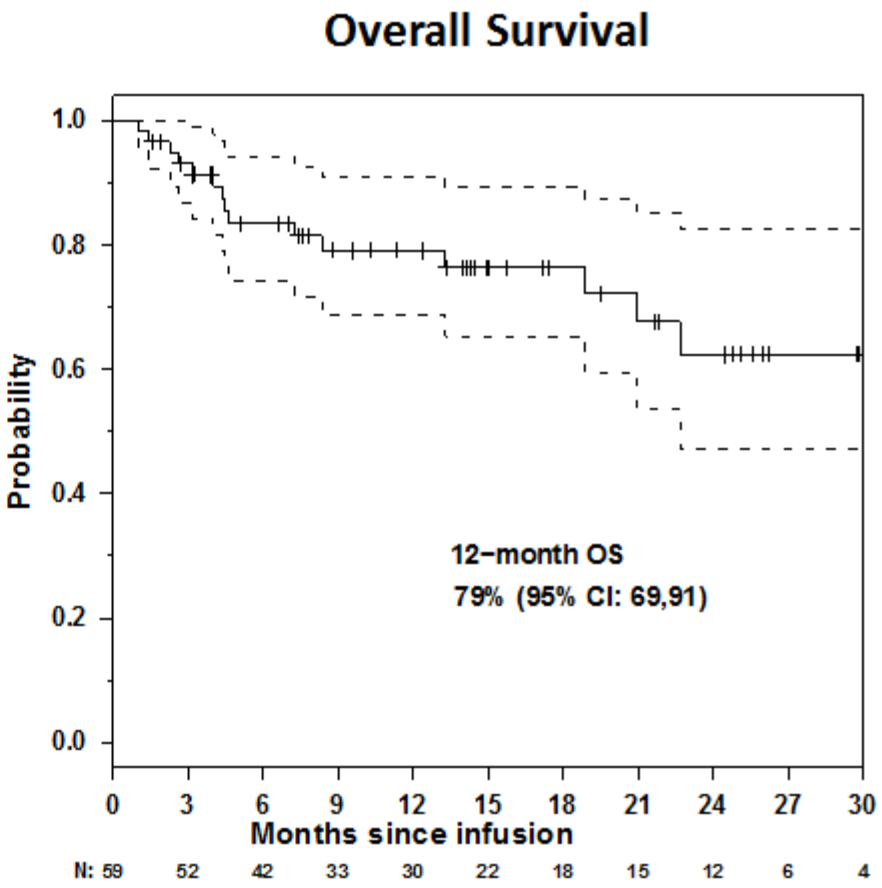


- 39 patients post-allo SCT
- T cells collected from patient
  - No evidence of GVHD
  - 6 months post-SCT
- Median donor chimerism 100%
- No GVHD to date

Abbreviations: GVHD, graft-versus-host, disease; SCT, stem cell transplant

Relapse-free and Overall Survival





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Toxicity

- Cytokine Release Syndrome (CRS)
  - Correlates with T cell proliferation and efficacy
  - Severity related to disease burden
  - Observed in 88%; 27% required hemodynamic and/or respiratory support
  - Reversed with novel approach – cytokine blockade
- Neurotoxicity
  - Seen in several CD19 immunotherapy trials: NCI, CHOP/UPenn, MSKCC, Blinatumomab
  - In our experience - generally untreated, fully resolves
- Chronic B cell aplasia requiring Ig replacement

Cytokine Release Syndrome

CRS is related to T cell expansion and is likely necessary for efficacy

- Symptoms typically occur 1-14 days after CTL019 cell infusion in ALL

Fever
Myalgias
Nausea/Vomiting

Hypotension
Respiratory insufficiency
Renal insufficiency
Coagulopathy

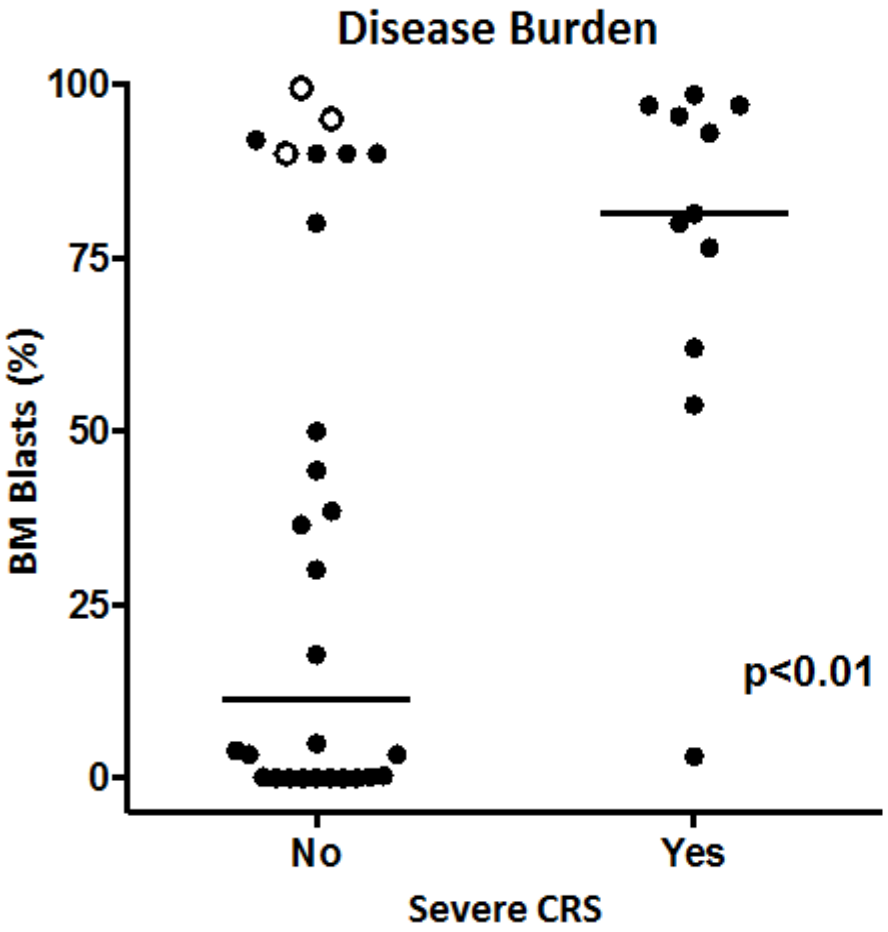
- Severity scales with disease burden

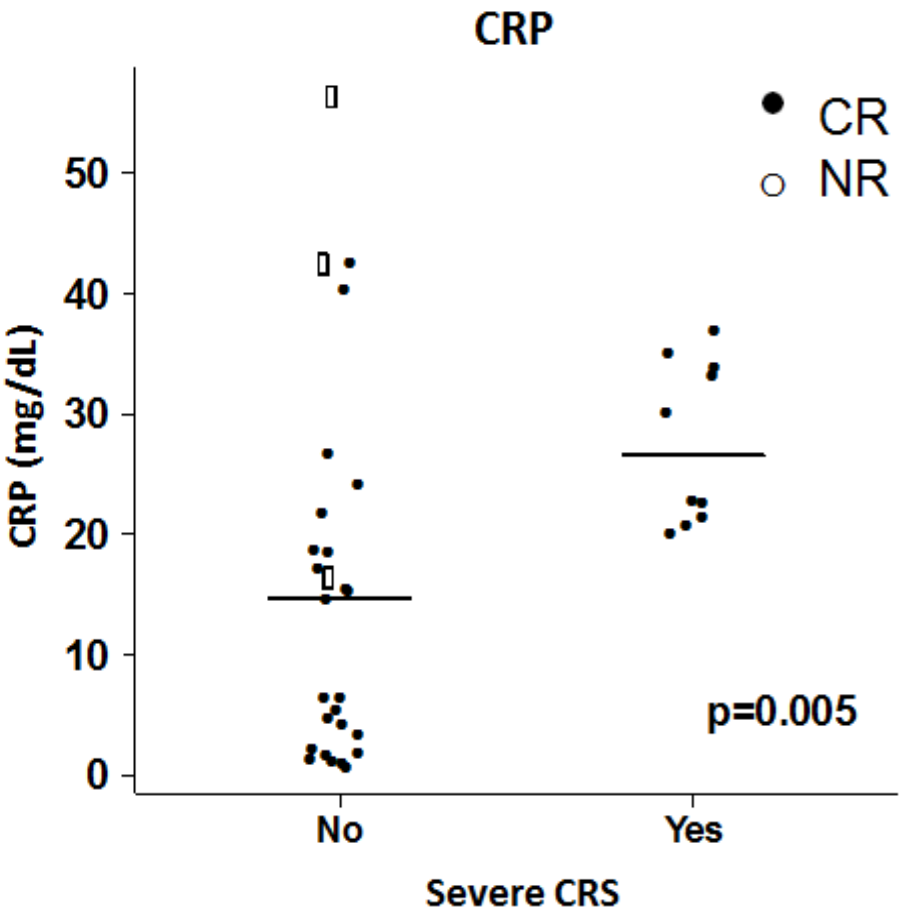
Severe CRS management

- Supportive Care
  - Vasopressors
  - O2, CPAP, ventilation
  - Blood products (FFP, cryo)
- Lympholytics
  - Steroids tried with some effect but potential to reduce efficacy
- Cytokine-directed therapy
  - IL-6 noted to be very elevated
  - Anti-IL-6 therapy highly effective with no apparent effect on efficacy

Grupp et al. NEJM 2013

Disease Burden Correlates with CRS Severity





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The Leukemia & Lymphoma Society®

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Novel approaches in patients with aggressive lymphomas: Chimeric antigen receptor modified T cell and other CD19-directed T cell therapies

Stephen J. Schuster, M.D.

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Robert and Margarita Louis-Dreyfus Associate Professor of CLL & Lymphoma
Perelman School of Medicine, University of Pennsylvania

EBMT 2016

Study Design: CTL019 T Cells in NHL

Enrollment started Feb 2014

Key eligibility criteria

- Adult histologically proven CD19+ relapsed or refractory DLBCL, FL or MCL
- Measurable disease
- ECOG PS 0 or 1

Single IV dose of CTL019 cells, 1 - 4 days after lymphodepletion chemotherapy

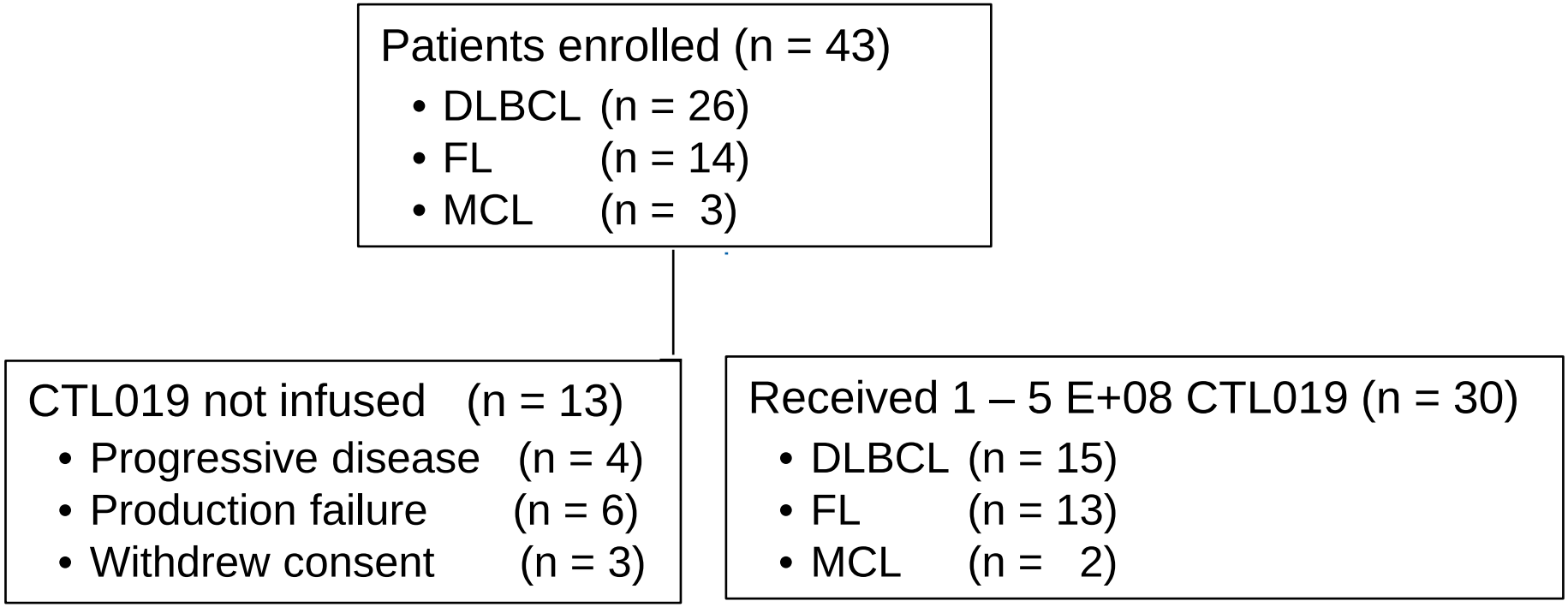
→

Initial tumor response assessed 3 months after infusion using IWG response criteria

Primary Objectives: ORR at 3 months; determine response rate by lymphoma histology

Secondary endpoints: Determine CTL019 cell manufacturing feasibility; safety; best response; PFS; in vivo expansion of CTL019 cells

Patient allocation



Results: Diffuse Large B Cell Lymphoma

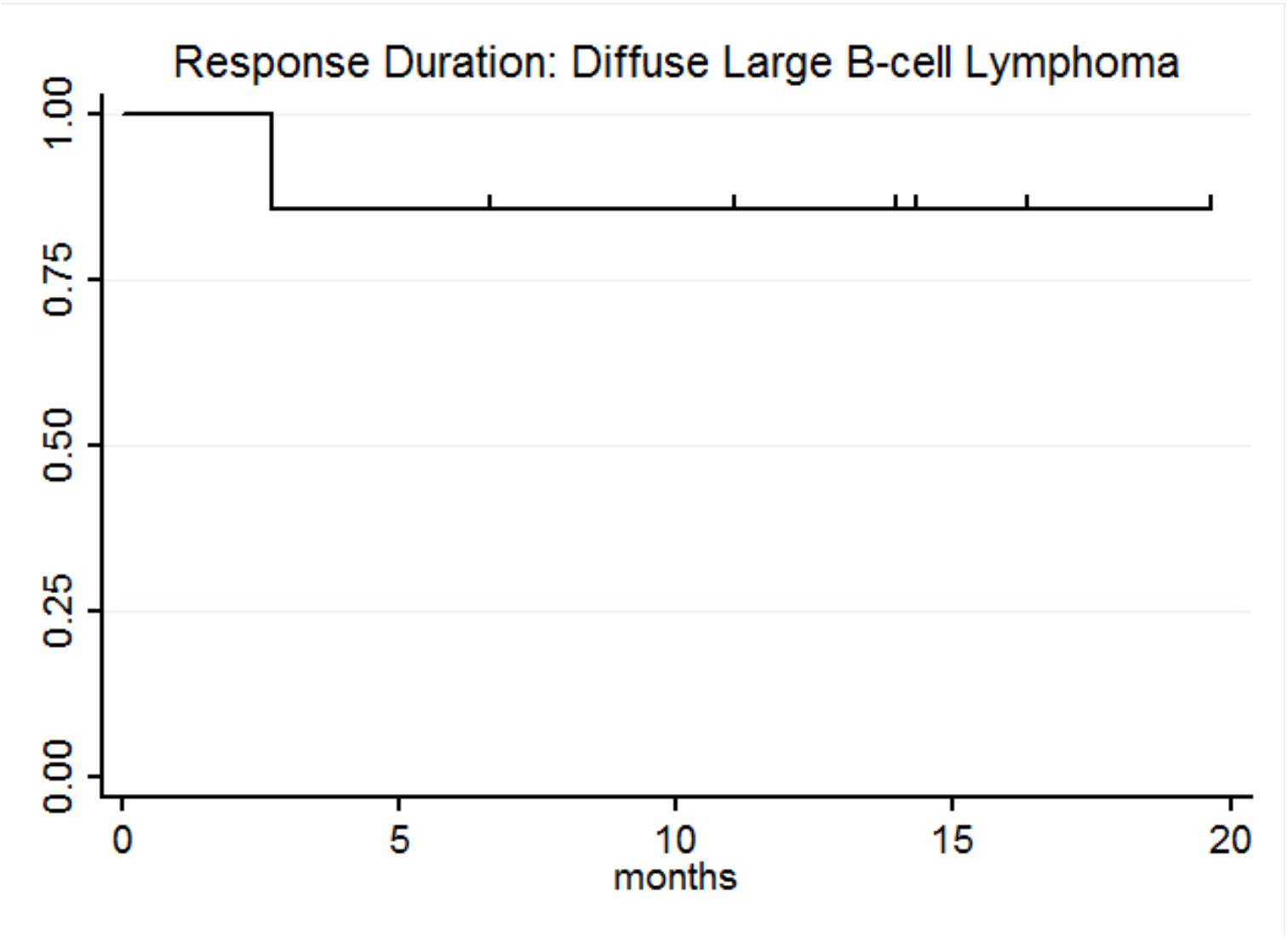
DLBCL: Patient Characteristics (n = 26 enrolled)	
Median age	54.5 years (range 25 - 77)
Sex	18 (69%) men
Median prior therapies	3 (range 1 - 8)
Prior stem cell transplant	9 (35%)
Stage III – IV (enrollment)	19 (73%)
Increased LDH (enrollment)	20 (77%)
> 1 extranodal site (enrollment)	11 (42%)
Median ECOG PS (enrollment)	1 (range 0 - 1)
Lymphodepleting therapy (n = 15)	2 EPOCH (w/o vincristine); 7 hyperfractionated cyclophosphamide (1.8 gm/m^2); 2 bendamustine (180 mg/m^2); 2 cyclophosphamide (1 gm/m^2); 1 XRT (4000 cGy) + cyclophosphamide (750 mg/m^2); 1 infusional etoposide + bolus cyclophosphamide ("EPOCH" dosing)

Response: Diffuse Large B Cell Lymphoma

DLBCL: ORR at 3 months 47% (N = 15)	DLBCL: Best Response Rate 47% (N = 15)
- CR: 3 - PR: 4 - PD: 8	- CR: 6 - PR: 1 - PD: 8

- 3 patients with PRs by CT criteria at 3 months converted to CRs by 6 months
- 1 patient with PR at 3 months had PD at 6 months

Duration of Response: DLBCL



EBMT 2016

Adverse Events at least possibly related: ≥ Grade 3 (N=30)

AE	G3	G4	G5	Total ≥ G3	AE	G3	G4	G5	Total ≥ G3
Acute kidney injury	2			2	Headache	1			1
Alk. phos. increased	1			1	Hypoxia	1			1
Atrial fibrillation	1			1	Hypertension	1			1
Agitation	1				Hypotension	1	1		2
Delirium	2			2	Hypocalcemia	1			1
Encephalitis			1	1	Hyponatremia	1			1
CRS	2	2		4	Hypophosphatemia	3	1		4
Chest pain	1			1	Insomnia	2			2
Dyspnea	1			1	Laryngeal edema	1			1
Edema	1			1	Anemia	5			5
Fatigue	1			1	Lymphopenia	10	8		18
Fever	1			1	Neutropenia	7	7		14
Febrile neutropenia	2			2	Thrombocytopenia	4	2		6
Pneumonia	1			1	Weight loss	1			1

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Novartis

Our patients and their families

Adverse Events and Management

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CRS across different B-Cell malignancies

- CRS is observed in NHL and ALL patients treated with CTL019[1-3]
- CRS for a patient with ALL and NHL typically occurs 1-14 days after CAR T-cell therapy infusion[1,4,5,6]
- Severe CRS manifests earlier at approximately 1-3 days after infusion, compared with >3 days for non-severe cases in patients with ALL[4]
- Severity and incidence CRS varies with disease setting
  - Pediatric ALL : 35-45% Grade 3/4 CRS (no Grade 5 CRS)
  - Adult NHL : 16% Grade 3/4 CRS (no Grade 5 CRS)
  - Adult ALL : 85% Grade 3,4 or 5 CRS (3 cases with Grade 5 CRS)
    - Dose and schedule in r/r adult ALL is under investigation

1. Porter DL, et al. *N Engl J Med*. 2011;365:725-733; 2. Grupp SA, et al. *N Engl J Med.* 2013;368:1509-1518; 3. Kalos M, et al. *Sci Tranl Med.* 2011;3:95ra73; 4. Maude SL, et al. *N Engl J Med.* 2014;371(16):1507-1517; 5. Maude SL, et al. *Cancer* J. 2014;20(2):119-122; 6. Frey NV, et al. *Blood*. 2014;124 [abstract 2296].

Summary of Novartis sponsored trials with CTL019

- In 2015, Novartis initiated phase 2 studies in both pediatric ALL and adult diffuse large B-cell lymphoma patients
  - Novartis CTL019 paediatric ALL program granted Breakthrough Therapy Designation by US FDA (April 2016) & designated as a Priority Medicine (PRIME) by EMA (June 2016)

Study No.	Sponsor	Patient Population	Phase	Status
NCT02435849 (ELIANA)	Novartis	Pediatric patients with relapsed and refractory B-cell ALL	2	Enrolled
NCT02445248 (JULIET)	Novartis	Adult patients with diffuse large B-cell lymphoma	2	Enrolled

We are pursuing personalized cellular immunotherapy with a portfolio of CARTs

CART therapy pipeline

- **Exploratory CTL019 in clinical trials for adult ALL and CLL**
- **Exploratory CART trials in multiple myeloma (BCMA target)**
- **Multiple CART programs are in discovery and pre-clinical research, and exploratory clinical trials, for both heme and solid tumors**

CTL019 is an investigational therapy. Efficacy and safety have not been established. There is no guarantee CTL019 will become commercially available.

Lessons learned along the way (1/3)

Need for harmonization across the globe

- Our goal is to conduct global development programs to address serious conditions with unmet medical need
  - Endorse efforts for regulatory convergence where ultimately a single MAA dossier will meet registration requirements across regions
  - Great need for uniform manufacturing & quality standards
  - Need for exceptional release process in clinical setting

Lessons learned along the way (2/3)

Need for harmonization across EU

- Clinical Trial Application review and approval process under existing Directive 2001/20/EC can be complex & time consuming for gene therapy products
  - Due to need for individual MS review & approval
  - Difficult to enable efficient start to multi-center, multi-national clinical trials
- Welcome the implementation of the Clinical Trials Regulation (EU No 536/2014) provided
  - Adequate resources and qualified ATMP reviewers onboard to assure timely & efficient review without unwarranted administrative clock stops due to resource limitations

Lessons learned along the way (3/3)

Need for harmonization across EU

- Similar need for harmonized centralized Environmental Risk Assessment for ATMPs that are considered GMOs
  - National requirements differ across MS again making efficient initiation of clinical trials difficult
- Manufacturing licenses for product manipulations also have different requirements across MS

Looking toward the future

- Manufacturing changes will be frequent and mechanisms should be in place to permit rapid review, approval and implementation of such changes that enhance consistent product yield and quality
- Current health economic systems are
  - Not set up to deliver such complex therapies
  - Apt to undervalue ATMPs, reducing incentives to develop them
  - Not set up to properly fund ATMPs, thus limiting access
- Encourage continued support for parallel Scientific Advice to assure HTA input at early stages of clinical development program to help de-risk these uncertainties

CTL019 and CAR T-Cell therapy outlook

- Clinical data to date shows that CAR T-cell therapy leads to a high rate of complete and durable remission in patients with r/r B-cell ALL and DLBCL
- CRS is a class effect observed with all CD19-directed CAR-T therapies, and can generally be managed with supportive care with or without anti-cytokine therapy (including tocilizumab)
- Pivotal studies of CTL019 in pediatric ALL and lymphomas are ongoing
  - First BLA submission in 1Q2017

CTL019 is an investigational therapy. Efficacy and safety have not been established. There is no guarantee CTL019 will become commercially available.

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Questions

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