CTL019 (tisagenlecleucel)

In pediatric and young adult patients with relapsed/refractory B-cell acute lymphoblastic leukemia

U.S. Food & Drug Administration
Oncologic Drugs Advisory Committee

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CTL019 (tisagenlecleucel)

Introduction

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Relapsed/refractory B-cell ALL in pediatric and young adult patients

- B-cell acute lymphoblastic leukemia (ALL) is the most common malignancy diagnosed in children
- Despite current treatment options, ~15% pediatric and young adult patients with ALL experience relapsed/refractory (r/r) disease[1]
- Unmet medical need for novel treatment options for pediatric and young adult patients with r/r ALL to provide
  - Deep and durable remission
  - Curative treatment opportunities
  - Improved quality of life

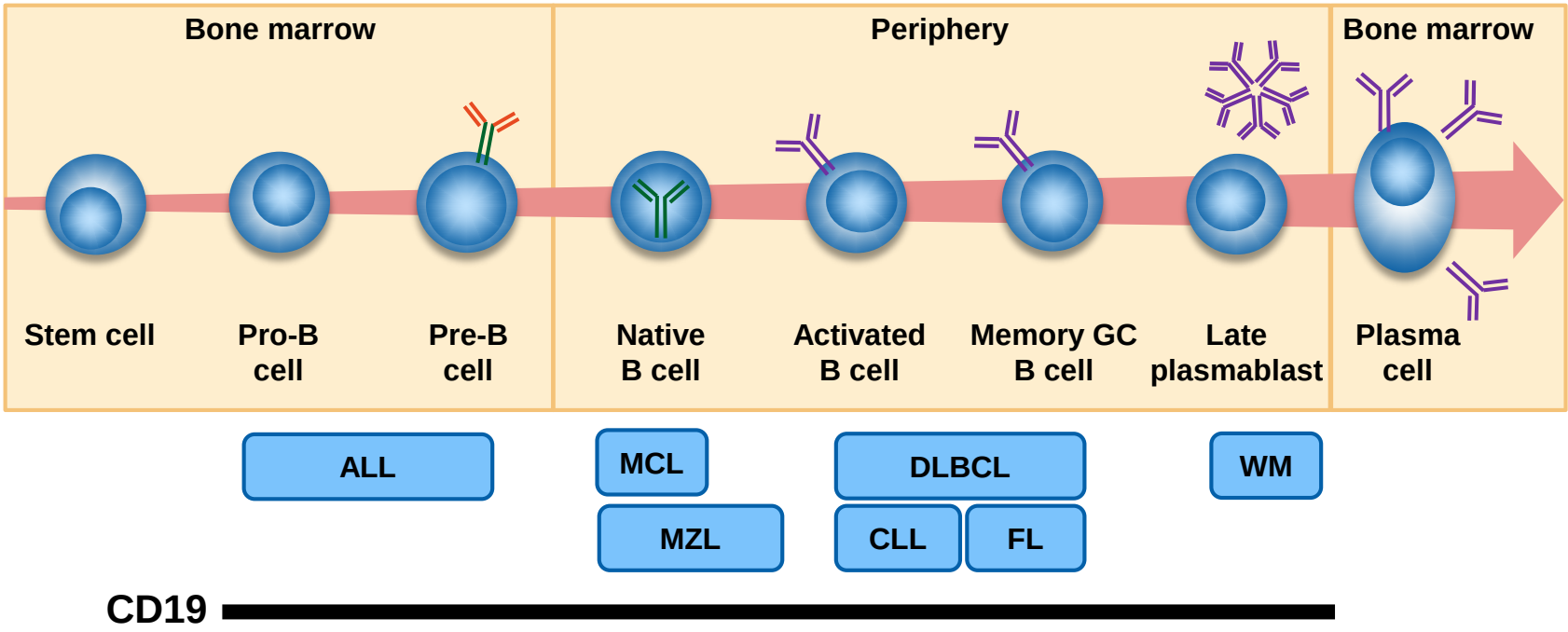
1. Pui CH, et al. *J Clin Oncol*. 2011;29(5):551-565.

CAR T-cell development and collaboration with Penn

- In 2012, Novartis and University of Pennsylvania (Penn) formed a collaboration to study chimeric antigen receptor T-cell (CAR T) therapies
- New treatment paradigm in oncology
- Designed to harness the power of a patient's own immune system to eliminate cancer cells
- Novartis early development plan included B-cell ALL
- Novartis acquired and set up a manufacturing site specific for cellular therapies in Morris Plains, NJ, USA

CD19: attractive target for CAR T-cell therapy in treating B-cell malignancies

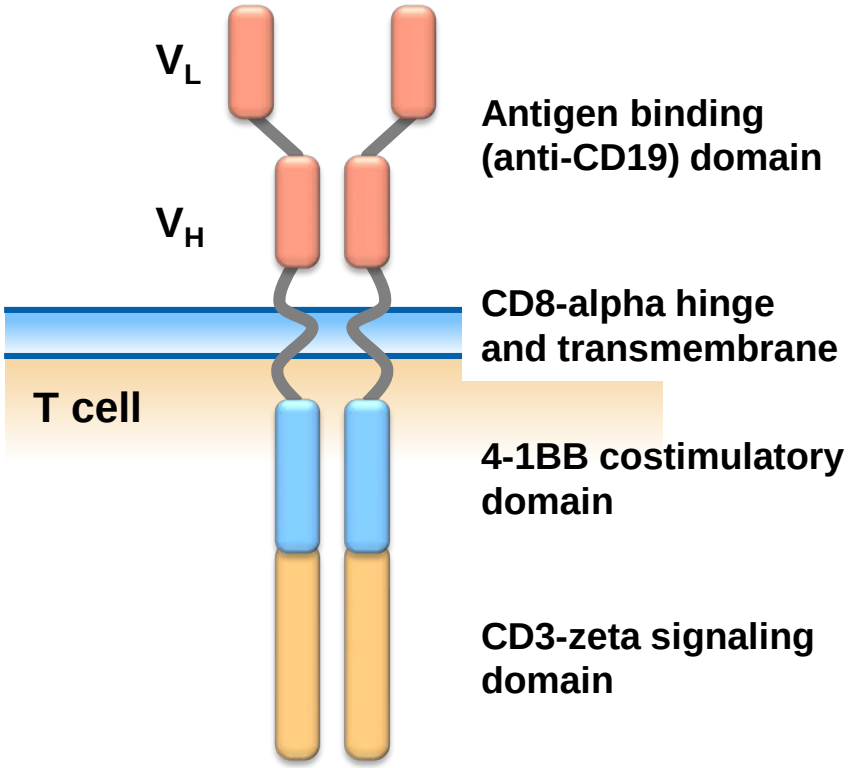
- CD19 is expressed on B cells and B-cell precursors and is not expressed on bone marrow stem cells or other tissues



Adapted from Blanc V, et al. *Clin Cancer Res*. 2011;17(20); 6448-6458.

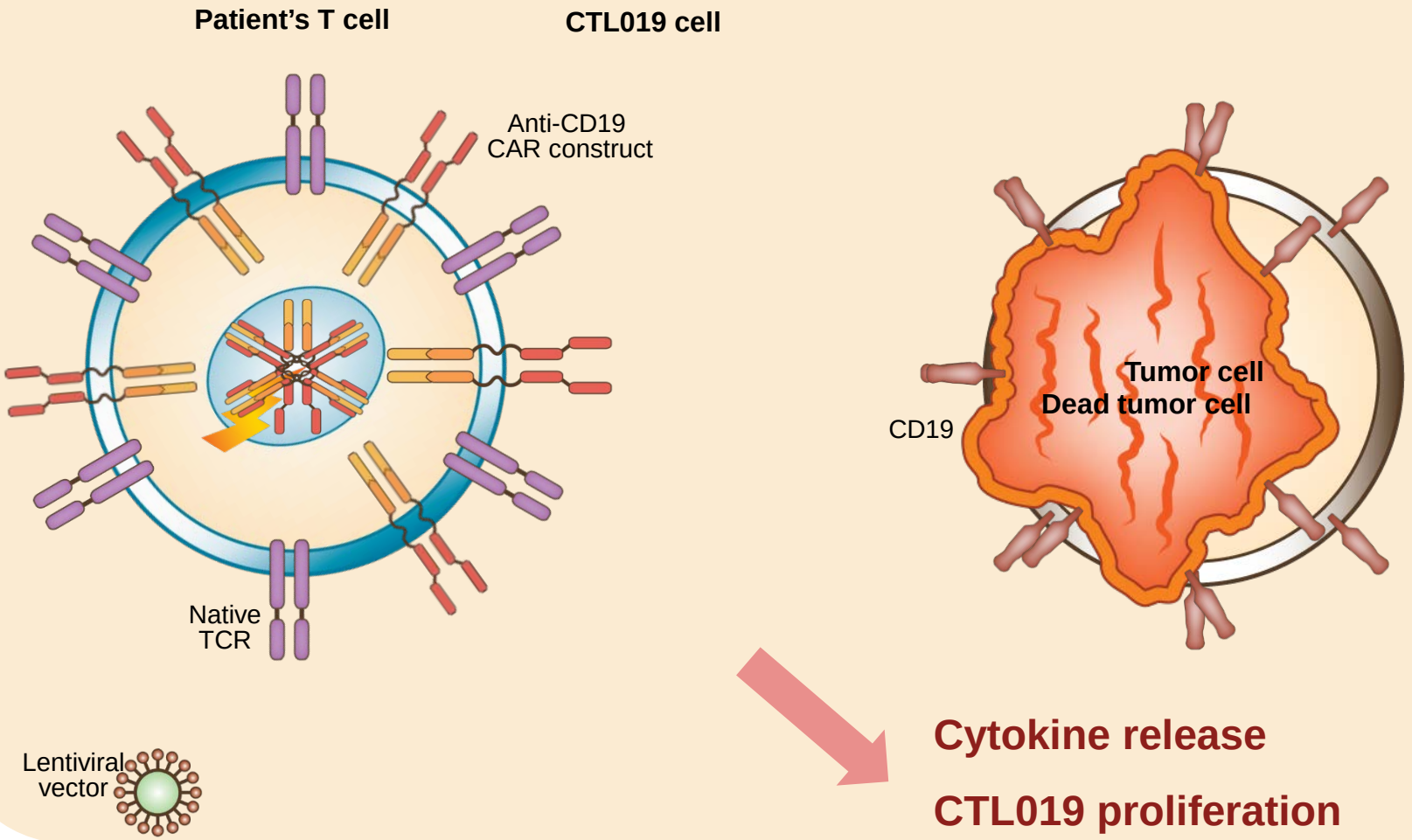
CTL019 expresses chimeric antigen receptors

- Antigen binding domain
  - Recognizes CD19 on B cells
- CD3-zeta signaling domain
  - Initiates T-cell activation
  - Mediates antitumor activity
- 4-1BB costimulatory domain
  - Augments antitumor activity
  - Enhances proliferation and persistence of CAR T cells



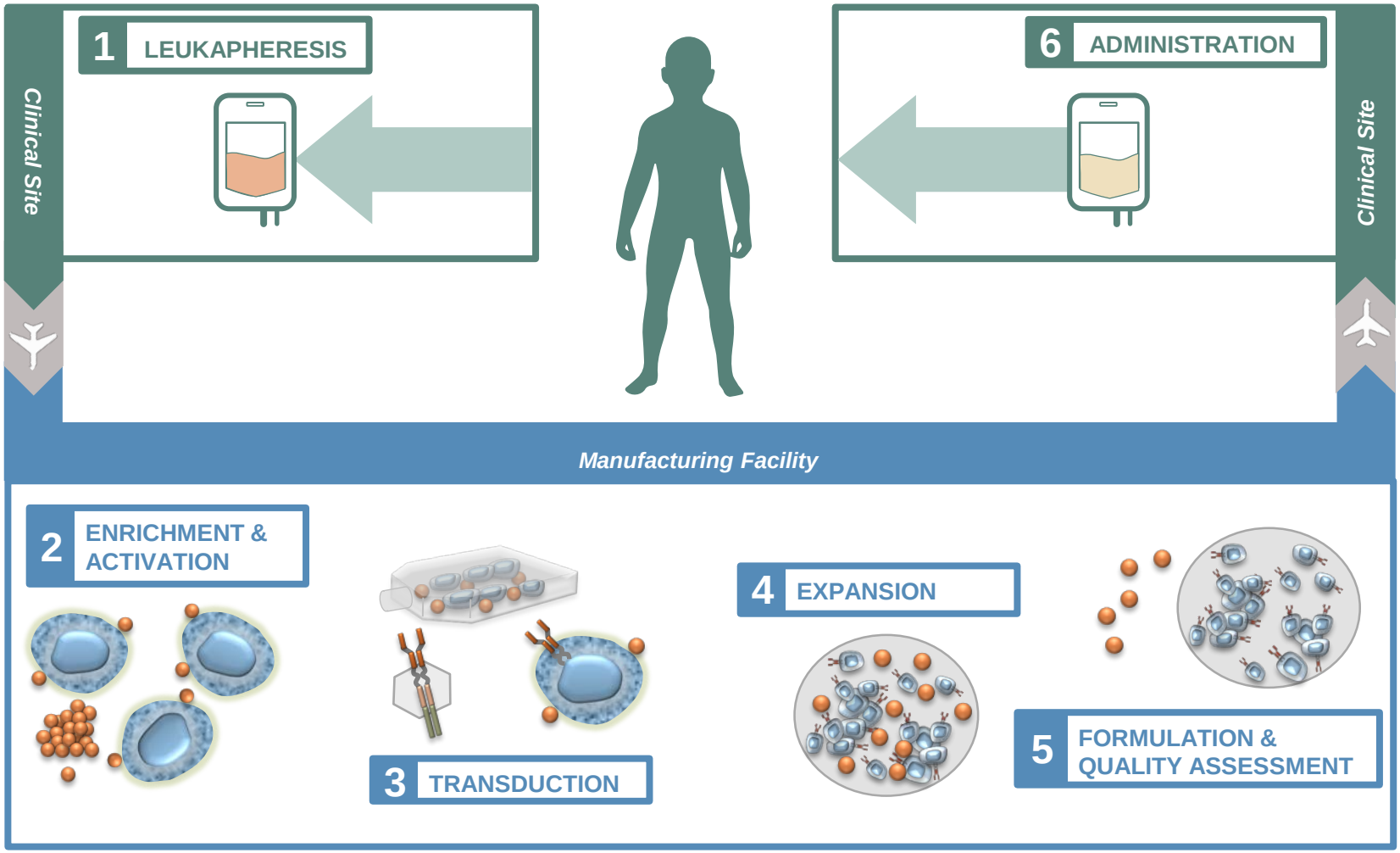
V_L: Light Chain Variable Domain
V_H: Heavy Chain Variable Domain

CTL019 is a living drug designed to target CD19+ B cells



Mechanism of action data is based on in vitro/in vivo data

CTL019 is an autologous immunocellular therapy

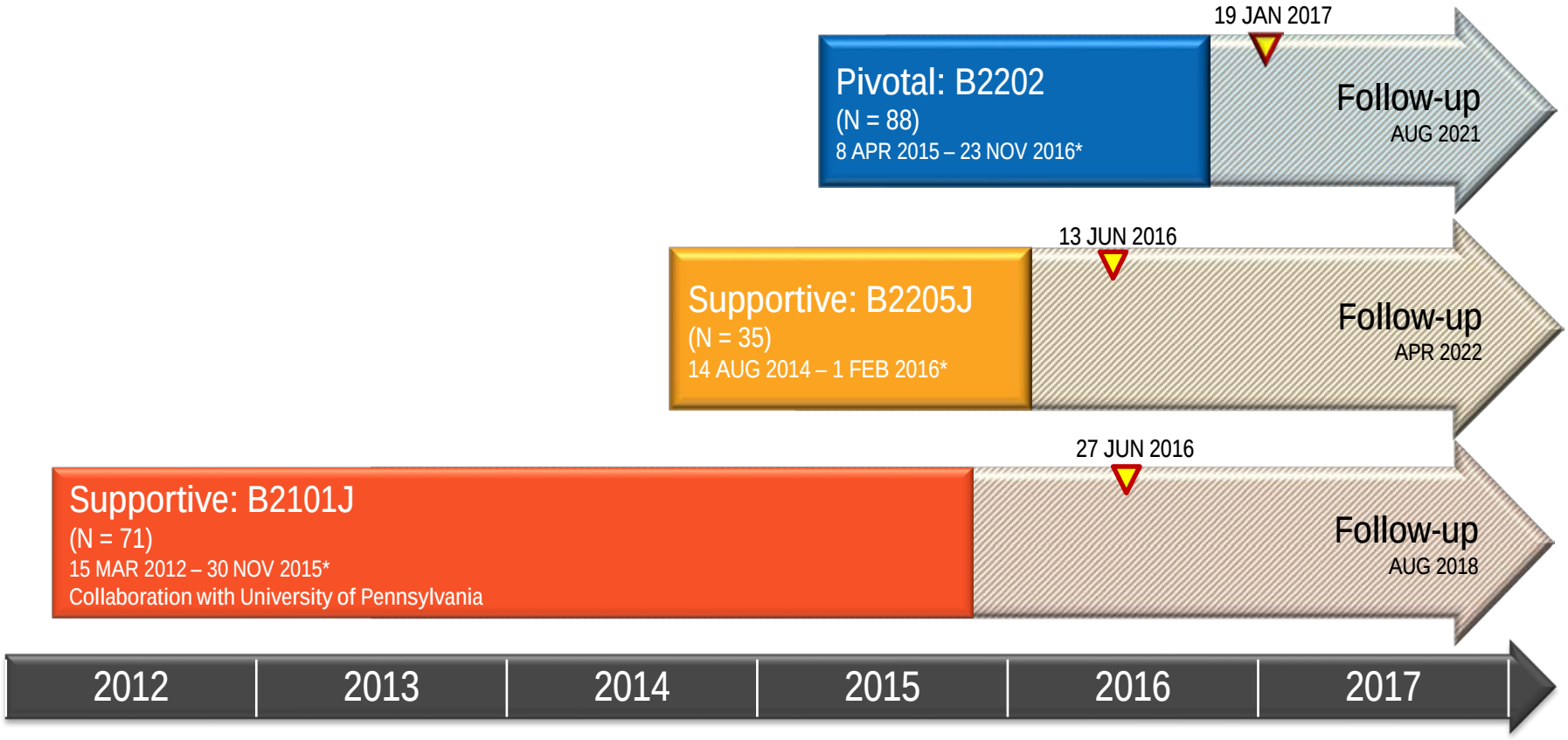


CTL019 program milestones

FDA key milestones	Date
Orphan designation granted for ALL	Jan 2014
Breakthrough designation granted (Penn IND)	Jul 2014
Breakthrough designation granted (Novartis IND)	Apr 2016
BLA submission	Feb 2017

EMA key milestones	Date
CHMP Scientific Advice for pediatric and adult r/r ALL	Apr 2014
Orphan designation granted for B-cell lymphoblastic leukemia/lymphoma	Apr 2014
Access to PRIME scheme (priority medicine) granted	Jun 2016

Overview of CTL019 BLA in pediatric and young adult patients with relapsed/ refractory B-cell ALL



* FPFV to data cut-off for interim analysis (Final analysis for study B2202 (US manufacturing)).

▽ Database lock for interim data analysis (Final analysis for study B2202 (US manufacturing)).

Proposed indication

- CTL019 (tisagenlecleucel) is a genetically modified autologous immunocellular therapy indicated for the treatment of pediatric and young adult patients 3 to 25 years of age with relapsed/refractory B-cell acute lymphoblastic leukemia

Presentation overview—AM

Presentation	Presenter
Unmet need	**Stephen P. Hunger, MD** Children's Hospital of Philadelphia
Manufacturing	**Spencer Fisk, BSc** Head, Cell & Gene Technical Development & Manufacturing Novartis Pharmaceuticals Corp.
Lentiviral vector	**James Miskin, PhD** Chief Technical Officer Oxford Biomedica (UK) Ltd.
Correlations between product attributes and clinical outcomes	**David Lebwohl, MD** CAR T Franchise Global Program Head Novartis Pharmaceuticals Corp.

Presentation overview—PM

Presentation	Presenter
Efficacy	**Samit Hirawat, MD** Head, Oncology Global Development Unit Novartis Pharmaceuticals Corp.
Safety	**David Lebwohl, MD** CAR T Franchise Global Program Head Novartis Pharmaceuticals Corp.
Clinical perspective	**Stephan Grupp, MD, PhD** Children's Hospital of Philadelphia
Conclusion	**David Lebwohl, MD**

CTL019 has positive benefit/risk profile in pediatric and young adult patients with relapsed/refractory B-cell ALL

- Significant unmet need to improve outcomes in pediatric and young adult patients with r/r B-cell ALL
- Novartis has developed a highly reproducible and safe manufacturing process
- Efficacy demonstrated in 3 clinical trials in more than 150 pediatric and young adult patients with r/r B-cell ALL
- High rate of durable remissions observed in the 3 trials
- Well characterized and manageable safety profile with appropriate site training
- Commitment to a pharmacovigilance plan including long-term safety follow-up

Unmet need in pediatric and young adult patients with relapsed/refractory ALL

Stephen P. Hunger, MD

Children's Hospital of Philadelphia

Children's Hospital of Philadelphia

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Disclosure statement

- I have received compensation for my participation in today's proceedings but have no personal financial interest in the outcome of this meeting

Epidemiology and outcome

- ALL is the most common malignancy of childhood
  - ~5000 cases of ALL diagnosed annually in US[1]
  - ~60% of ALL cases are diagnosed in patients <20 years old[1-3] (median age at diagnosis, 15 years)
  - 85% of childhood ALL cases are B lineage ALL (B-ALL)
- Current multi-agent treatment regimens achieve a cure rate of >85%[2]
- Primary refractory ALL (induction failure), although rare (2% to 3% of patients), remains a therapeutic challenge
- Approximately 15% of children and young adults with ALL will relapse[4]
  - Relapsed ALL: a leading cause of cancer death in children[5-7]

1. The Leukemia & Lymphoma Society 2016; 2. SEER Cancer Stat Facts: Acute Lymphocytic Leukemia. National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/statfacts/html/alyl.html; 3. Hunger SP, Mullighan CG. *N Engl J Med*. 2015;373:1541-1552; 4. Pui CH, et al. *J Clin Oncol*. 2011;29(5):551-565; 5. Ko RH, et al. *J Clin Oncol*. 2010;28(4):648-654; 6. Raetz EA, et al. *J Clin Oncol*. 2008;26(24):3971-3978; 7. Parker C, et al. *Lancet*. 2010;376(9757):2009-2017.

Clinically relevant endpoints in pediatric ALL trials demonstrating clinical benefit[1,2]

- Response endpoints
  - Overall remission rate (ORR)
    - Typically used in relapsed and refractory (r/r) ALL
  - Minimal residual disease (MRD)[2,3]
    - Important in newly diagnosed and relapsed ALL
- Time-to-event endpoints
  - Duration of response (DOR)
  - Overall survival (OS)

1. Devidas M, et al. *Clin Investig (Lond)*. 2013;3(9).
2. Appelbaum FR, et al. *Blood*. 2007;109:1810-1816.
3. Hunger SP, Mullighan CG. *N Engl J Med*. 2015;373:1541-1552.

Clinically relevant endpoints in pediatric ALL trials: Overall remission rate[1,2]

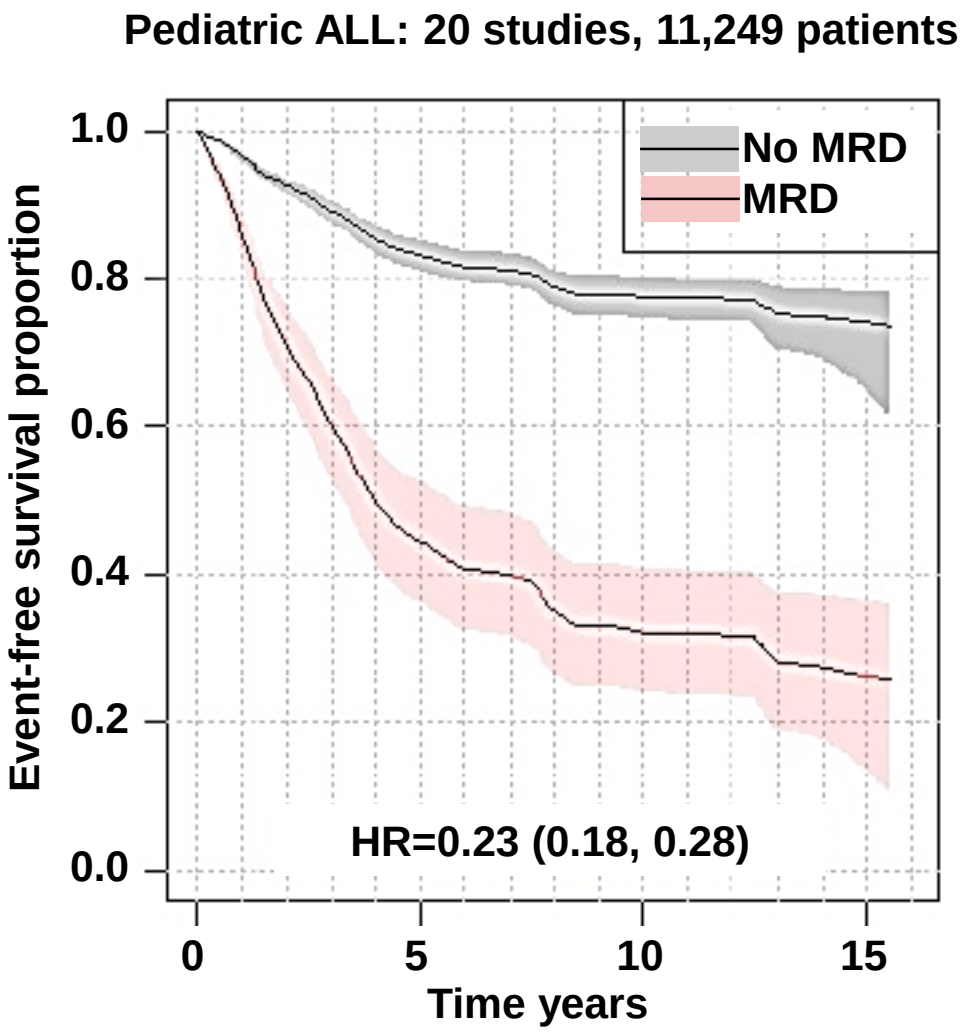
- Overall remission rate (ORR): sum of the rates of complete remission[3] (CR) and complete remission with incomplete blood count recovery (CRi)[4]
  - Recognized surrogate marker for OS
  - Used by the FDA as an endpoint for accelerated approval of new agents in r/r pediatric ALL
    - Relevant examples include clofarabine and blinatumomab

1. Devidas M, et al. *Clin Investig* (Lond). 2013;3(9).
2. Appelbaum FR, et al. *Blood*. 2007;109:1810-1816.
3. Complete Remission (CR) <5% blasts in bone marrow, <1% circulating blasts in peripheral blood, no evidence of extramedullary disease.
4. CR with incomplete blood count recovery (CRi) - all criteria for CR met, except that the following exist: neutrophils ≤1.0×10^9/L, and/or platelets ≤100×10^9/L, and/or requiring platelet and/or neutrophil transfusions

Clinically relevant endpoints in ALL trials: Minimal residual disease (MRD)

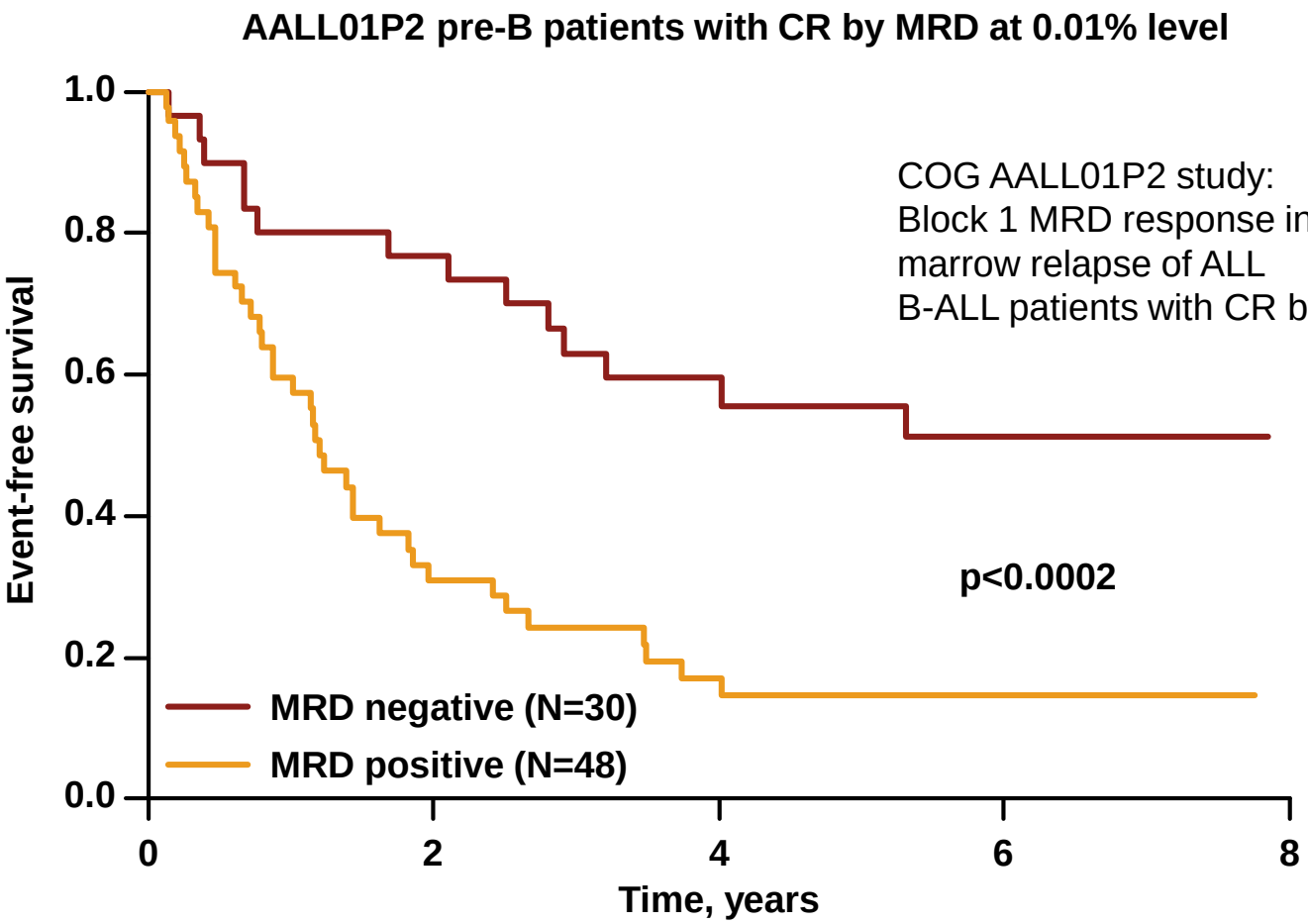
- Submicroscopic levels of leukemia cells detected by several methodologies, including flow cytometry
  - Can identify 1 ALL cell per 10^4-10^5 normal cells
- Strongest prognostic factor identifying good and poor responders and correlating with outcome
- Predicts the risk of relapse and OS when measured during and after induction therapy in both newly diagnosed and relapsed ALL

MRD is a robust indicator of relapse risk in pediatric ALL: EFS after induction (meta-analysis)[1]



1. Adapted from Berry DA, et al. *JAMA Oncol*. 2017;3(7):e170580.

MRD is a robust indicator of relapse risk in pediatric ALL: EFS after relapse (COG)



COG AALL01P2 study:
Block 1 MRD response in children with first marrow relapse of ALL
B-ALL patients with CR by MRD (0.01%)

COG=Children's Oncology Group.
Adapted from Raetz, et al. *J Clin Oncol*. 2008;26(24):3971-3978 (updated 2012).

Current treatment options: Relapsed ALL

- Re-induction chemotherapy to obtain remission
- Definitive post-induction therapy
  - Patients with off-therapy relapse and good MRD response to induction: chemotherapy alone
  - Patients with early relapse, late relapse and MRD positive post-induction, or 2nd+ relapse: chemotherapy to obtain MRD-negative status and HSCT
    - Patients MRD positive at time of HSCT rarely survive
- Intensive therapy associated with significant toxicity, treatment-related mortality, and a poor quality of life
- Patients with a second relapse have even fewer effective options

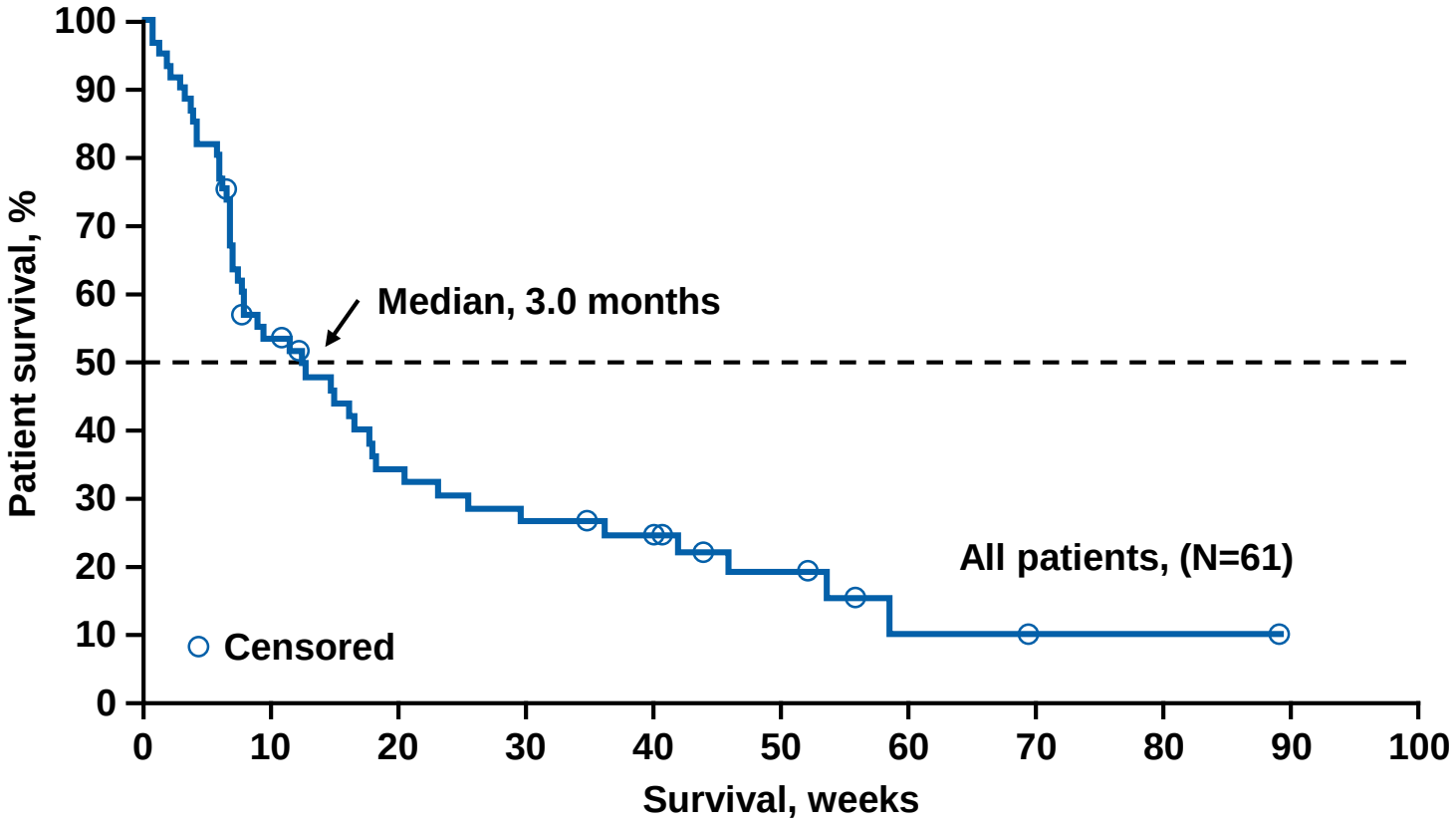
2-year survival rate of 15% after relapse following the first transplant – Baywa at al. *Bone Marrow Transpl*. 2013;48:661-665;
A second allogeneic transplant recurring after first transplant may be a reasonable treatment option in selected patients; age, disease status and conditioning regimen, duration of remission after first transplantation important in determining outcomes after second transplant. - Eapen M, et al. *Bone Marrow Transpl*. 2004;34:721-727.

Patients with r/r ALL have limited treatment options

- Standard chemotherapy and HSCT have limited efficacy
  - Patients with ALL who relapse post HSCT have a 2-year overall survival rate of 15%[1]
- New agents have limited response rates and even those patients who respond require transplant for cure: overall survival has not changed
  - Clofarabine as a single agent or in combination
  - Blinatumomab
  - Patients with r/r ALL typically have prolonged hospital stays and have an appreciable risk of treatment-related mortality

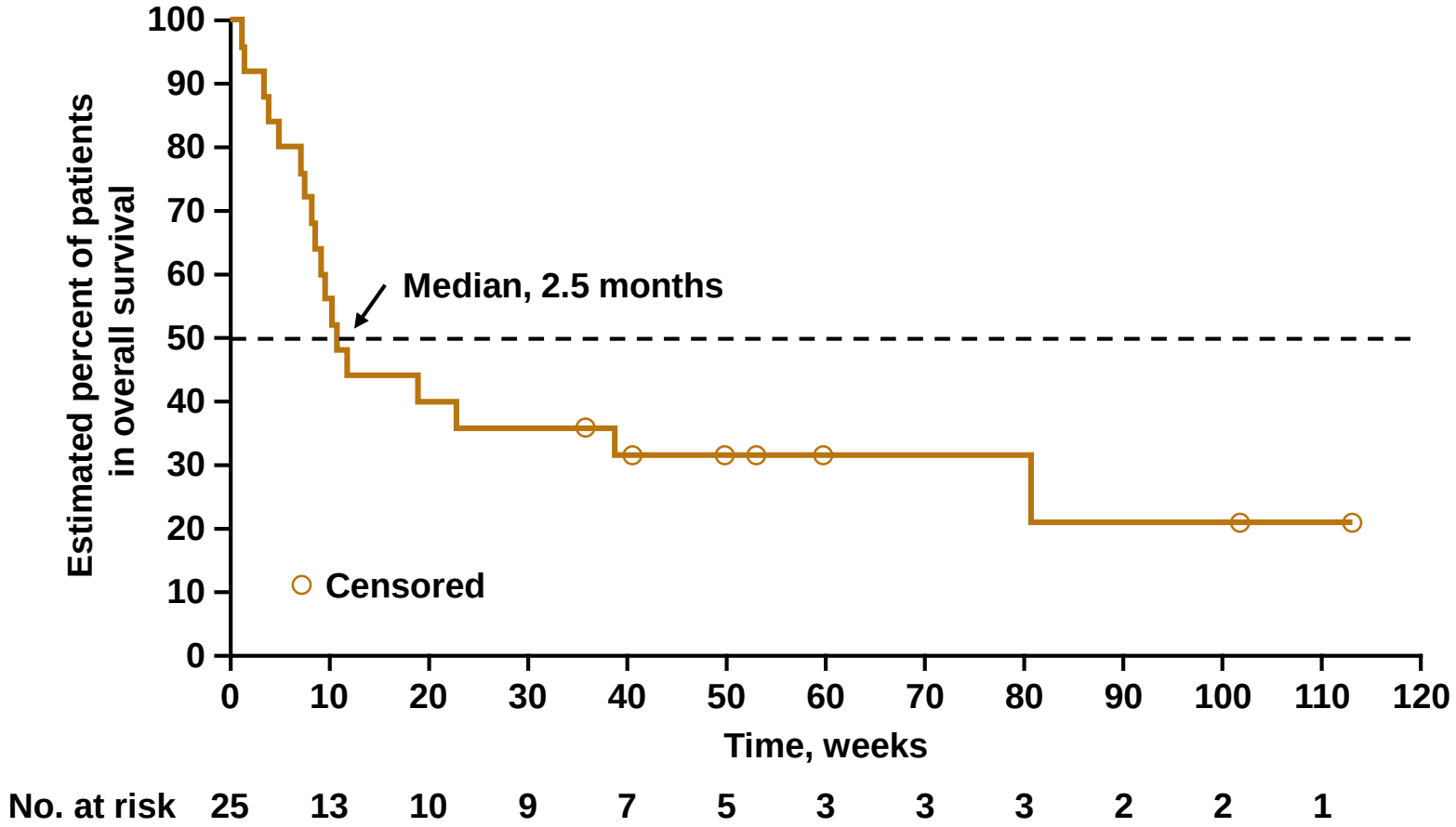
1. .Bajwa R, Bone Marrow Transplantation. 2013;48:661-665.

Clofarabine monotherapy phase 2 trial in pediatric r/r ALL (N=61)



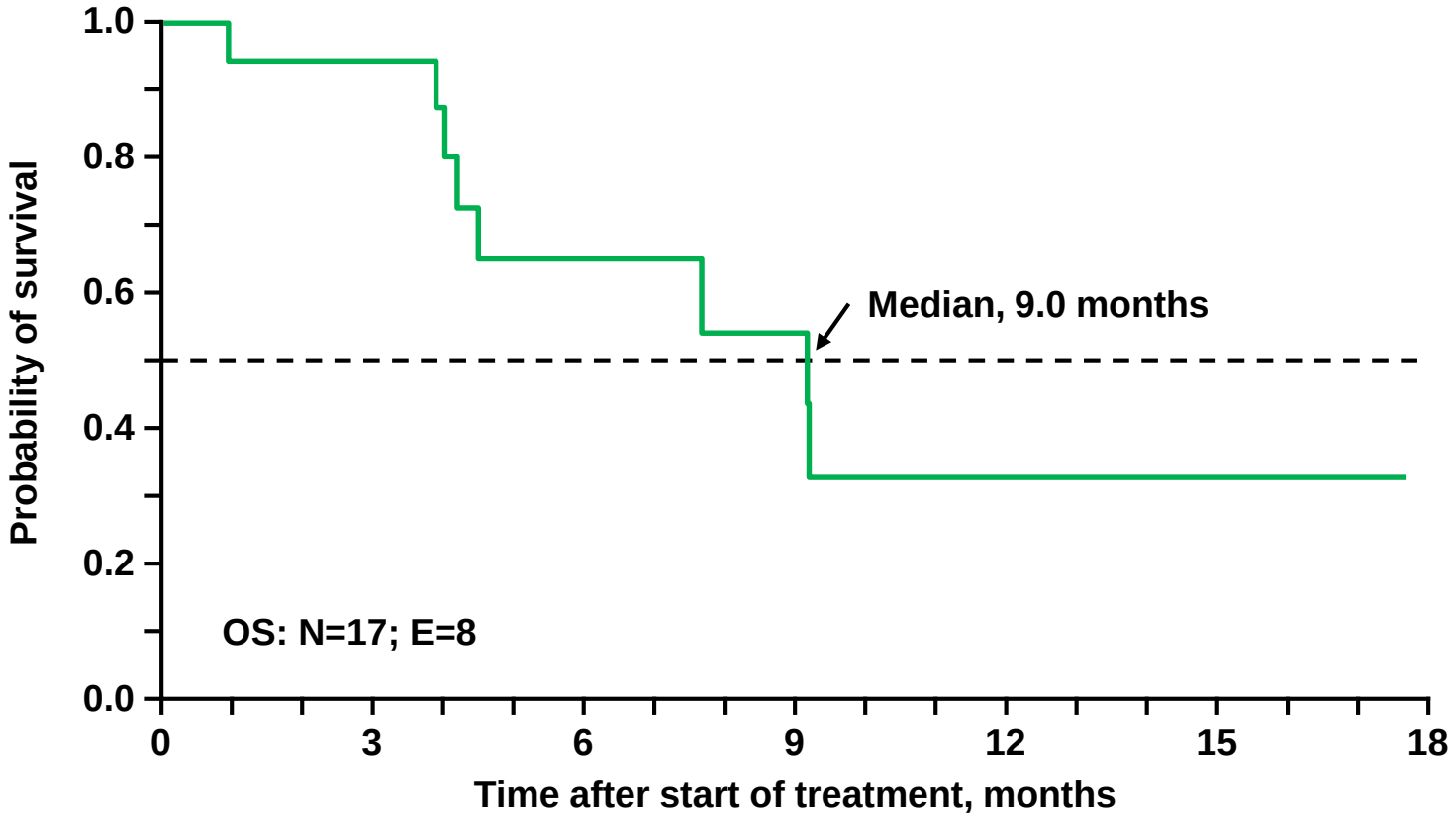
Reprinted from Jeha S, et al. *J Clin Oncol*. 2006;24(12):1917-1923.

Clofarabine+etoposide and cyclophosphamide phase 2 trial in pediatric r/r ALL (N=25)



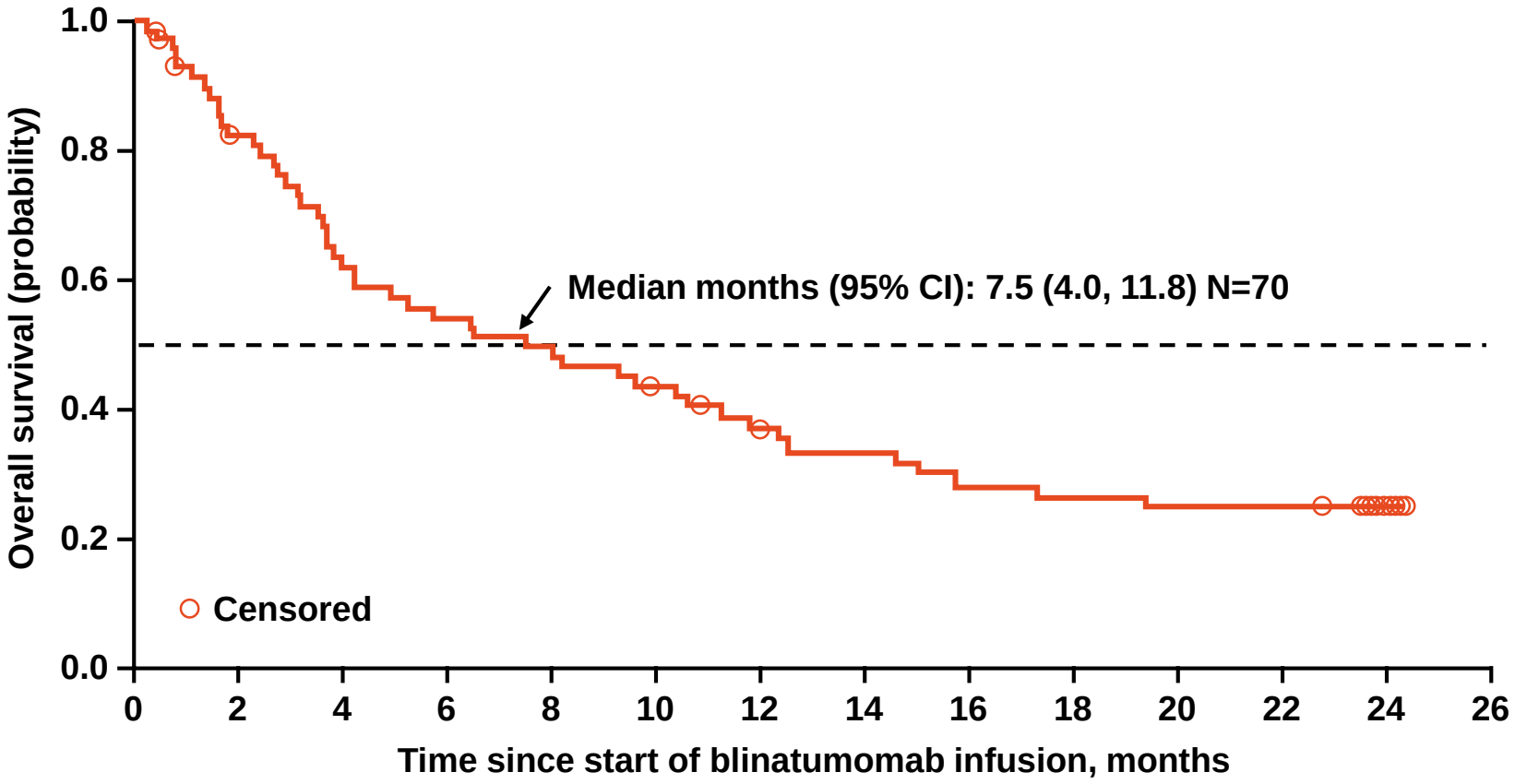
Reprinted from Hijiya N, et al. *Blood*. 2011;118(23):6043-6049.

Clofarabine+etoposide and cyclophosphamide in pediatric r/r ALL (N=17)



Adapted from Locatelli F, et al. *Brit J Haematol.* 2009;147:371-378.

Blinatumomab phase 1/2 trial in pediatric r/r ALL (N=70)



Reprinted from von Stackelberg A, et al. *J Clin Oncol*. 2016;34(36):4381-4389.

Efficacy of available treatments for pediatric and young adult r/r ALL patients: Summary

	Clofarabine mono[1]	Clofarabine + etoposide + cyclo[2]	Clofarabine + etoposide + cyclo[3]	Blinatumomab[4]
Patients, N	61	25	17	70
≥3 prior regimens	62%	28%	NA	7%
ORR (CR+CRi)	20%	44%	76%	39%
Median OS	**3.0 months**	**2.5 months**	**9.0 months**	**7.5 months**
12 months OS	20%	30%	33%	40%
Early mortality (within 30 days)	25%	20%	NA	7%

Disclaimer: Cross-trial comparisons cannot be made based upon differences in study designs, patient populations, and other factors

1. Jeha S, et al. *J Clin Oncol*. 2006;24:1917-1923.
2. Hijiya N, et al. *Blood*. 2011;118:6043-6049.
3. Locatelli F, et al. *Br J Haematol*. 2009;147(3):371-378.
4. von Stackelberg J, et al. *J Clin Oncol*. 2016;34:4381-4389.

Relapsed/refractory ALL: Significant unmet medical need

- Despite current treatment options, >600 pediatric and young adult patients with ALL experience relapse each year in US[1]
- Treatment options for patients with r/r ALL are limited and are associated with poor outcomes and high toxicity
  - Most patients with r/r ALL remain incurable
- Unmet medical need for novel treatment options for pediatric and young adult patients with r/r ALL to provide
  - Deep (MRD-negative) and durable remission
  - Curative treatment opportunities
  - Improved quality of life

1. Maude SL, et al. *Blood*. 2015;125:4017-4023.

CTL019 (tisagenlecleucel)

Manufacturing

Spencer Fisk, BSc

Head, Cell & Gene Technical Development & Manufacturing
Novartis Pharmaceuticals Corp.

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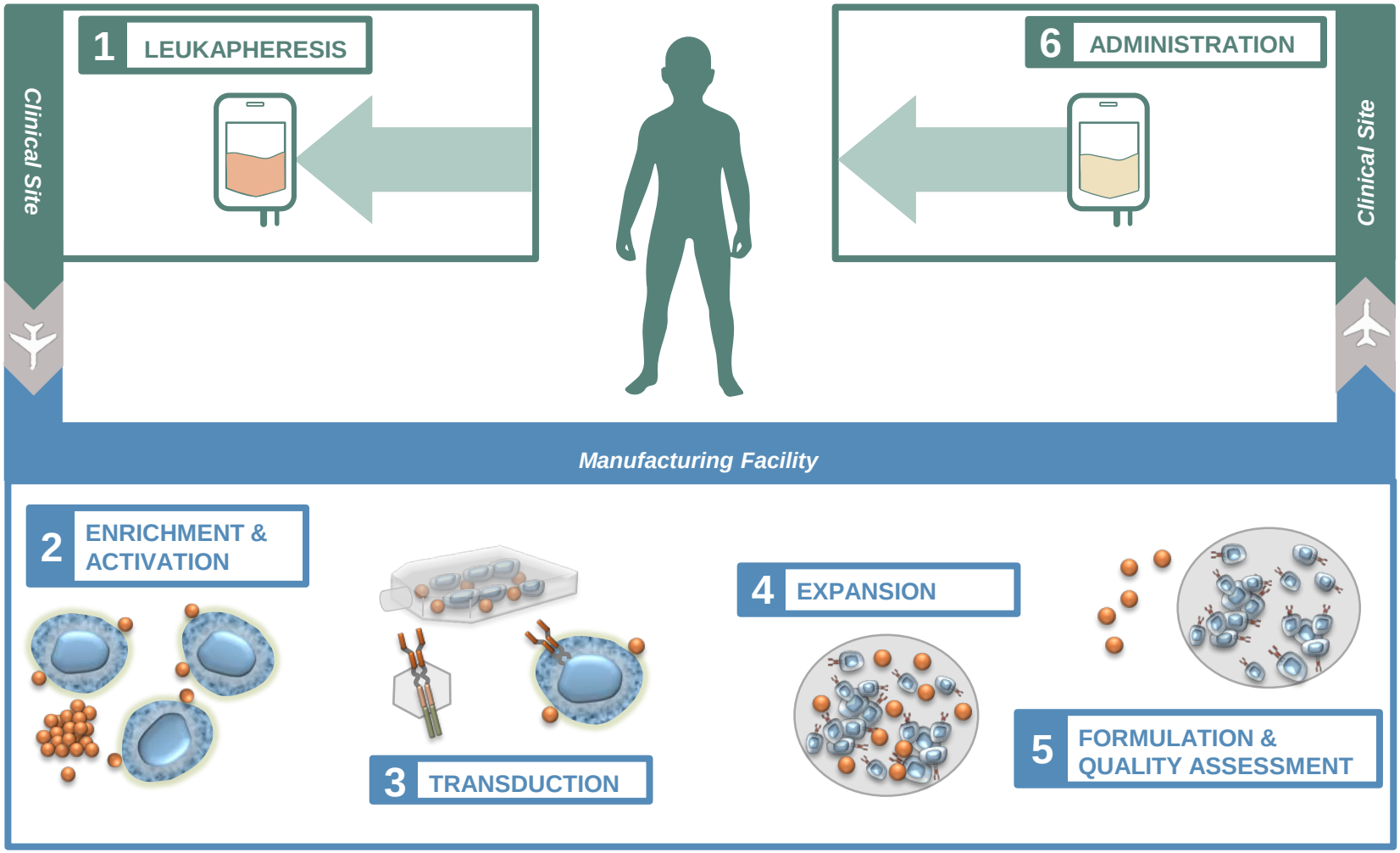
Disclaimer

Novartis is committed to an open, transparent, and public Advisory Committee process, but there are circumstances where we may not be able to discuss certain technical manufacturing data that are proprietary in nature.

CTL019 is an autologous immunocellular therapy



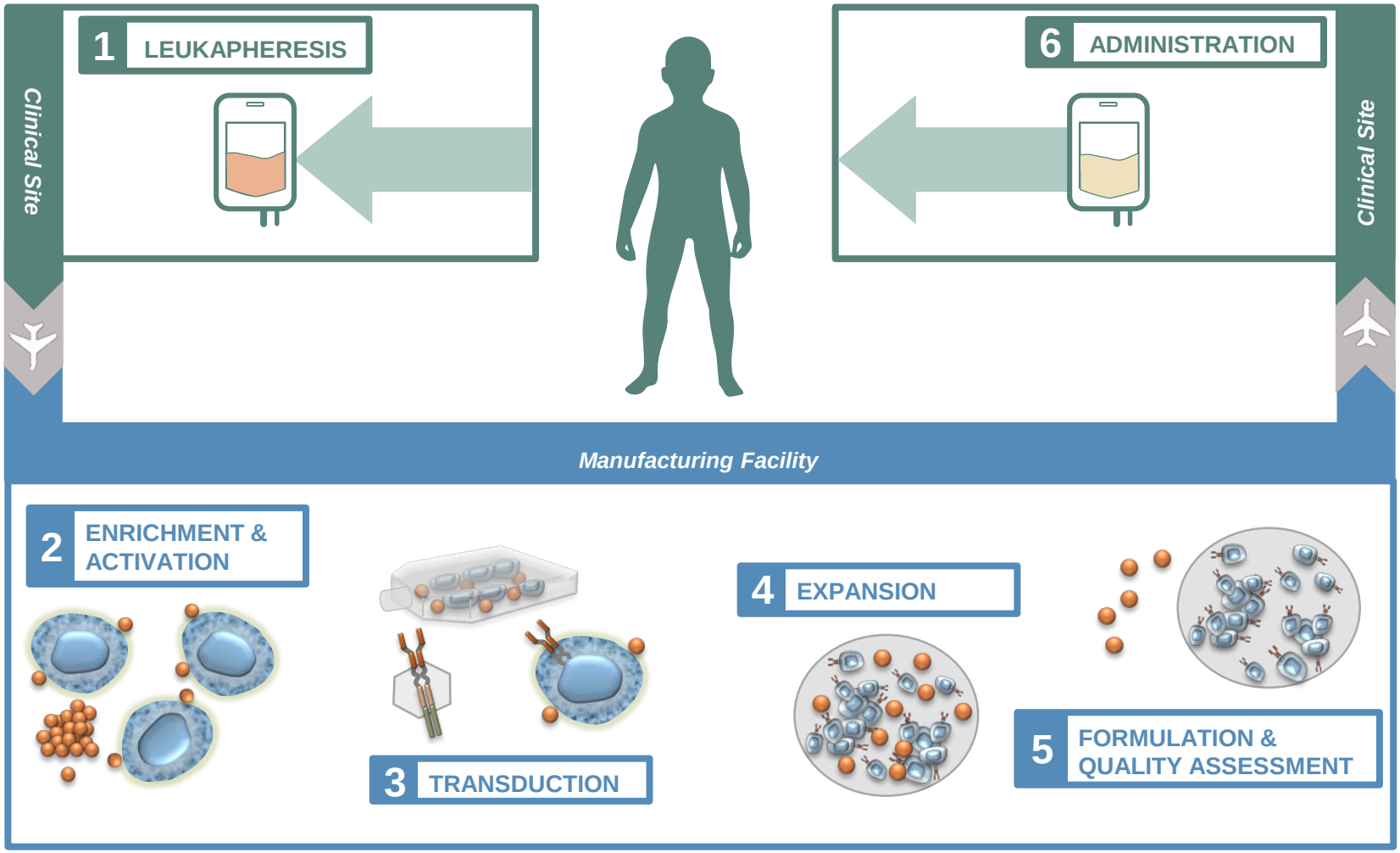
Novartis ensures a rigorous chain of identity

- Novartis uses well-established standards to maintain a rigorous chain of identity from leukapheresis, through manufacturing, to patient infusion
- Novartis leverages existing clinical standards to integrate with a Novartis quality system dedicated to managing chain of identity of patient material and final product
  - FACT (Foundation for the Accreditation of Cellular Therapy)
  - ISBT-128 (International Society of Blood Transfusion)
- Novartis utilizes product segregation controls, including dedicated personnel and equipment

Dedicated CTL019 manufacturing facility

- Novartis acquired a 170,000-sq. ft. cell-manufacturing facility in 2012
- Used to manufacture more than 250 CTL019 batches to date for Novartis clinical studies
- Designed to support anticipated commercial demand and capable of increasing production in the future

CTL019 is an autologous immunocellular therapy

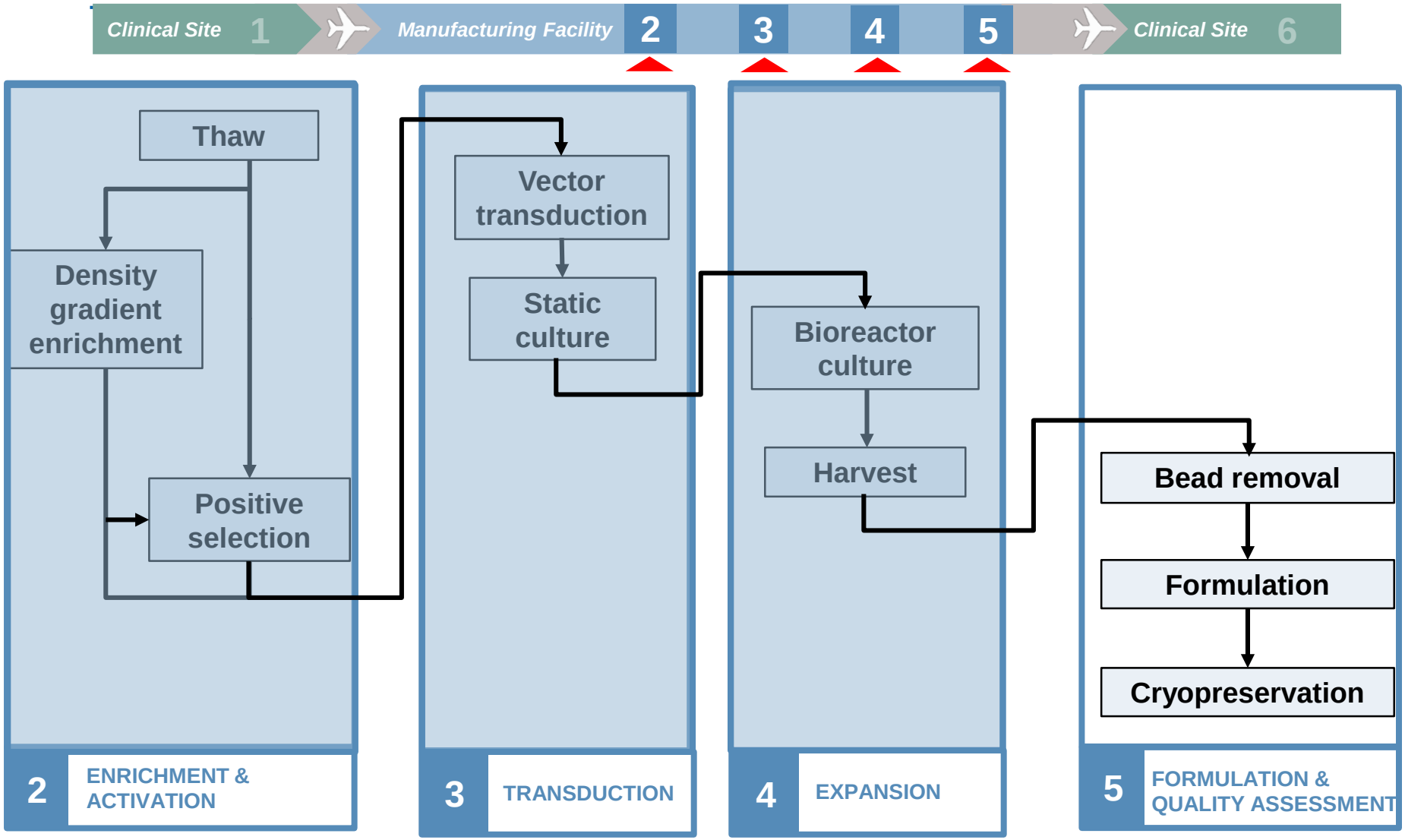


Leukapheresis site qualification and collection

- Leukapheresis is the collection of a patient's white blood cells through the use of apheresis equipment approved by FDA
- Leukapheresis sites are FACT accredited and using or implementing the ISBT-128 labelling standards
- Novartis
  - Performs on-site quality assessments
  - Maintains contracts and quality agreements with each site
  - Defines collection and processing requirements and trains the sites to those requirements
- The leukapheresis material is cryopreserved and tested

FACT=Foundation for the Accreditation of Cellular Therapy;
ISBT=International Society of Blood Transfusion.

Manufacturing process flow



Quality assurance of CTL019 cell product

Appearance and description

- Color

Safety

- Bacterial endotoxins
- Sterility
- Mycoplasma
- Determination of VSV-G DNA by quantitative PCR (surrogate for RCL)

Purity

- Percentage of viable T cells
- Determination of transduction efficiency by CAR quantitative PCR
- Cell viability

Impurities

- Determination of residual beads by microscopy
- Percentage of viable $CD19^+$ B cells

Identity

- Identity by CAR quantitative PCR (qPCR)

Quantity

- Total cell count
- Number of viable cells (calculated)
- Dose (calculated)

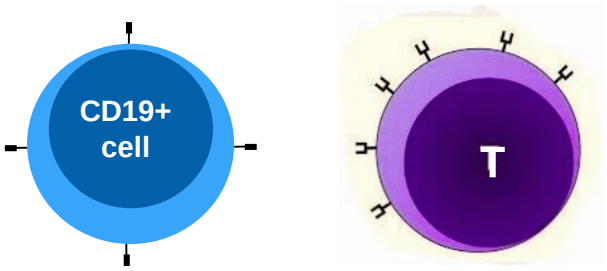
Potency

- Determination of CAR expression by flow cytometry
- Release of IFNγ in response to CD19-expressing target cells

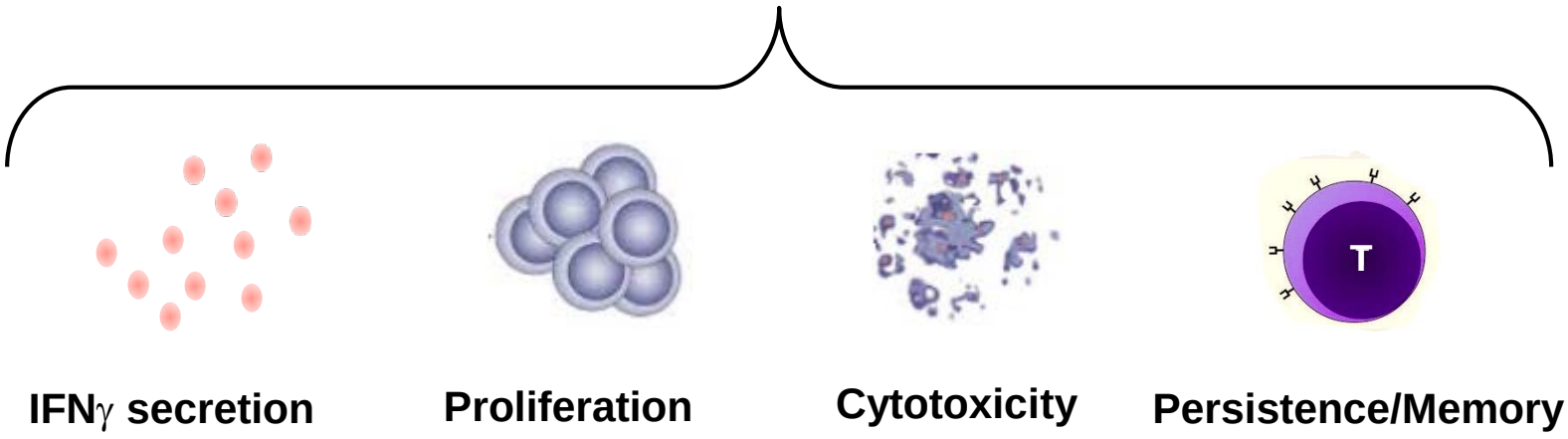
RCL=replication-competent lentivirus.

CTL019 potency assay aligns with proposed mechanism of action

- IFNγ secretion (potency) is an early response in T-cell activation

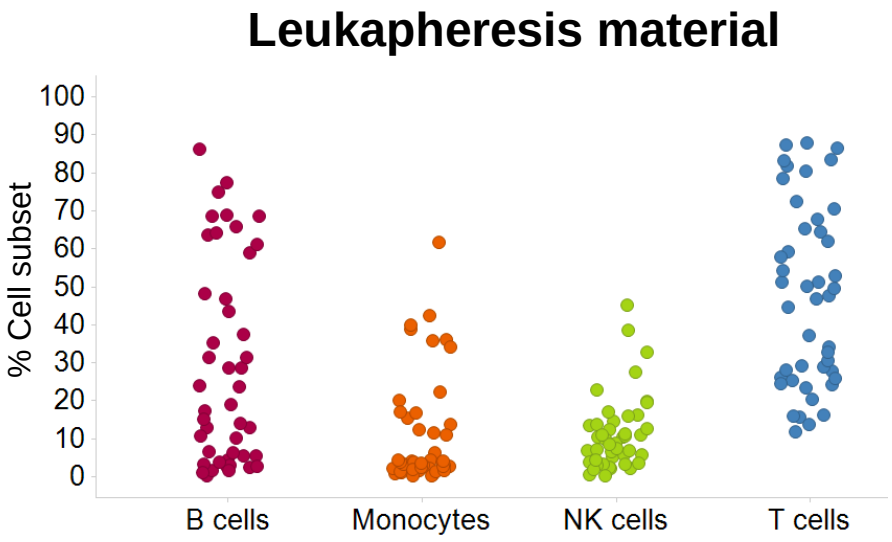


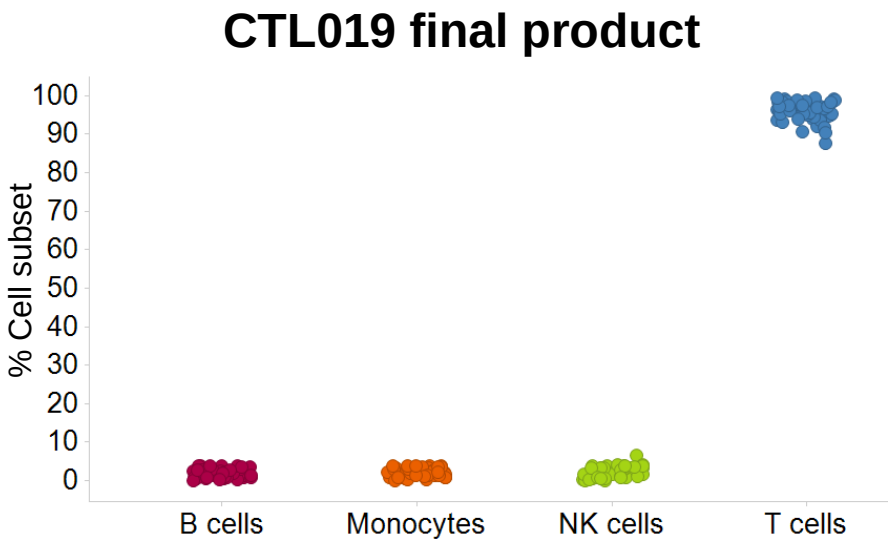
CD19⁺ cell recognition/antigen stimulation



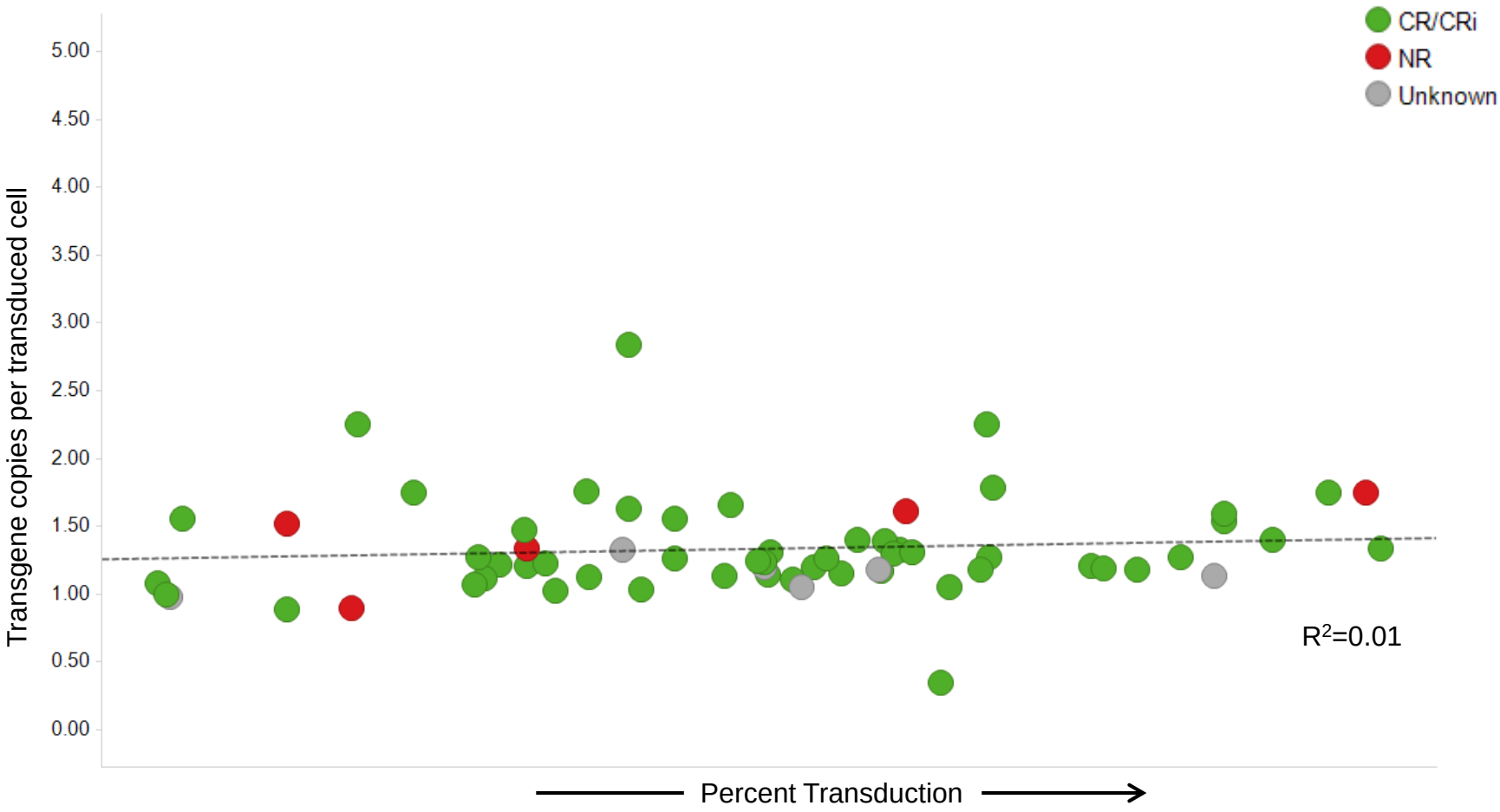
IFNγ secretion | **Proliferation** | **Cytotoxicity** | **Persistence/Memory**

Manufacturing experience: Consistent T-cell product from variable patient material Study B2202





Stable vector integration



Pediatric ALL/B2202 – 63 patients [52-CR/CRi, 5-NR, 6-Unknown]
Best Overall Response within 3 months:
CR=complete remission; CRi=complete remission with incomplete blood count recovery; NR=nonresponder; Unknown [response].

Broad application of analytical methods to ensure thorough characterization of CTL019

Routine characterization	Additional characterization
Flow cytometry	Secretome analysis (SomaScan)
Cytotoxicity	Mass cytometry (CyTOF)
Intracellular cytokine staining	TCR deep sequencing
Luminex/ELISA	RNAseq
Functional proliferation assay	Single cell RNAseq
	Multiplex gene expression analysis (Nano-string)

Administration at qualified sites

- Cryopreserved product delivered to treatment facility
- Confirmation of patient identity
- Administration of CTL019 in accordance with prescribing information

Summary

- Novartis has accrued significant experience in manufacturing patient-specific CAR T cells in global, multicenter trials
- Novartis has developed a highly reproducible manufacturing process for CTL019
- Consistent product quality has been demonstrated by extensive product testing, including assessment of product T cells, vector copies per cell, CAR functionality, and RCL


WALL of HOPE

CTL019 (tisagenlecleucel)

Lentiviral vector

James Miskin, PhD

Chief Technical Officer
Oxford BioMedica (UK) Ltd

OxfordBioMedica NOVARTIS

Advantages of the CTL019 lentiviral vector

Selection	Lentiviral vector chosen for long-term transgene expression and safety
Design	Minimize the risk of recombination events (to prevent RCL)
Manufacture	Manufactured with single-use components, chemically defined formulation and sterile filtered
Testing	Assures high-quality vector for efficient T-cell transduction No replication-competent lentivirus (RCL) Low-risk integration profile
Patient experience	No insertional oncogenesis seen to date – CTL019 and other studies Long-term follow-up in patients supports safety

CTL019 vector: Lentiviral vector selection

Feature	Benefit
Vector integration profile	Integration allows permanent genetic modification of target cells Integration profile – minimal risk of insertional mutagenesis
Transgene expression	Durable expression after infusion[1] Evidence out to 780 days postinfusion[2]
Low vector copy number (VCN)	Stable, long-term CAR expression from clinical data[1]

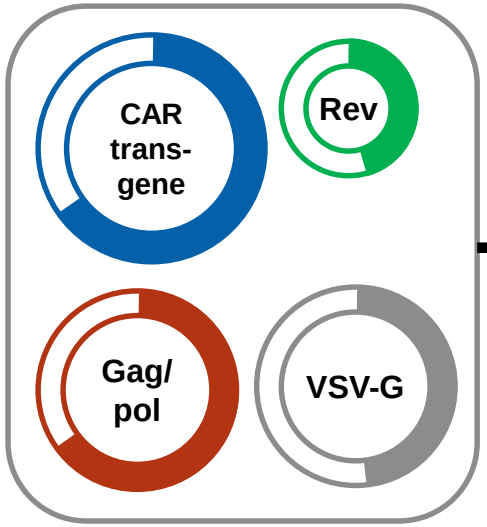
1. Porter DL, et al. *Sci Transl Med*. 2015;7(303):ra139.
2. Thudium K, et al. ASH 2016. Abstract 220.

CTL019 vector system: Design

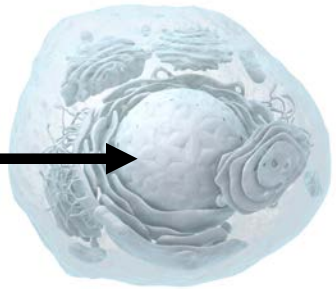
Benefit(s)	Feature
Safety—absence of replication-competent lentivirus (RCL) Yield—efficient vector production	Vector components segregated on 4 separate plasmids
	Open Reading Frames (ORFs) of nonessential accessory genes and Tat removed
	Codon-optimized Gag/Pol
	Self-inactivating long terminal repeat sequence (SIN LTR)
	Heterologous envelope (VSV-G)
High expression in target cells	Regulatory sequence for enhanced expression

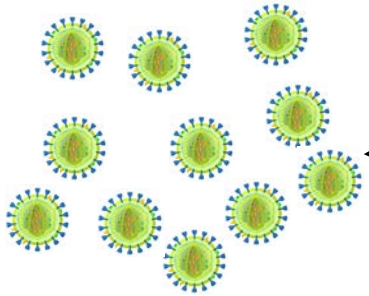
CTL019 vector: Manufacture

Cell factory containing HEK293T cells



Plasmid co-transfection





Vector harvest (filter-clarified)

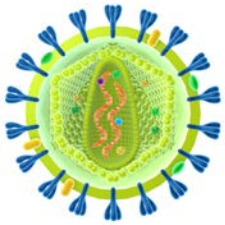
Vector substance

- Purification
- Formulation
- Volumetric concentration

Vector product

- Sterilization
- Concentration
- Vial

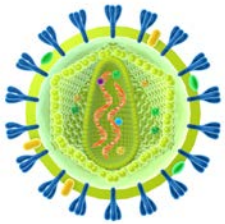
CTL019 vector: Testing



- Broad testing panel to ensure vector quality, safety, and consistent manufacture
- Testing methods guided by process/vector structure and design

Testing	Comment
Appearance and description	Appearance consistent with vector suspension
Identity	qRT-PCR to CAR-specific sequence
Safety	Assures absence of microbial contamination and RCL
Purity	Measures both vector and impurities
Quantity	p24 protein and vector RNA measured
Biological activity	Measurement of transduction of target cells

CTL019 vector: RCL Risk Management



- Adoption of state-of-the art minimal lentiviral vector – safe by design
- Patient safety ensured by thorough testing of vector and CAR T cells
- No evidence for RCL – all trials

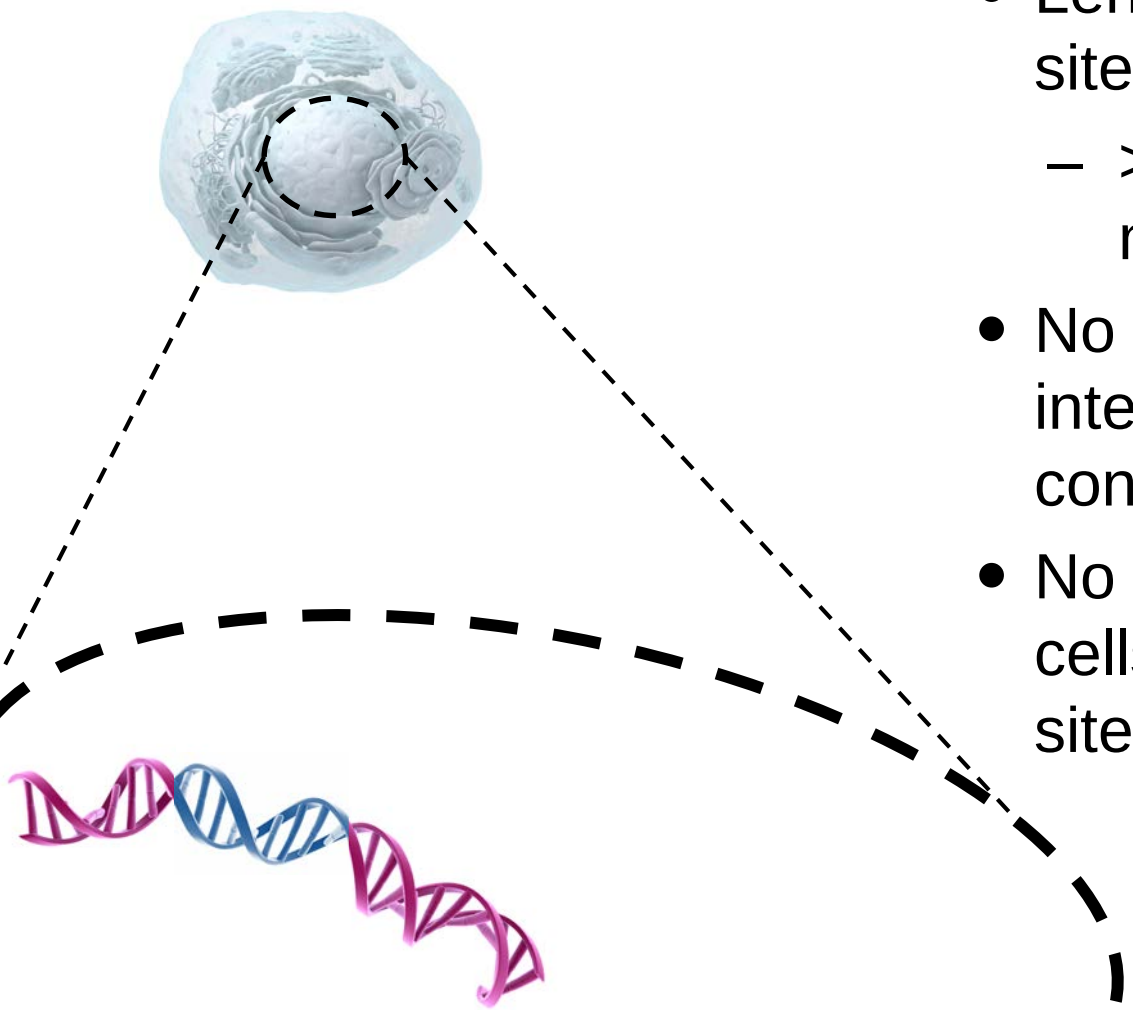
RCL risk management	Comment
Vector system	Replication-defective vector with minimal risk of RCL
RCL detection method (vector)	Highly sensitive, validated method for amplification and detection (based on RT) – end of production cells and vector
CTL019 product	Highly sensitive PCR-based testing for RCL
Available data	Extensive body of data showing absence of RCL
Residual DNA	Low levels of residual DNA, highly degraded

No evidence of RCL in clinical trials

- US academic lentiviral T-cell trial experience[1,2]
  - Hundreds of patients across decades of experience
  - No evidence of RCL in any trial
- CTL019 CART cell experience
  - >250 Novartis manufactured CTL019 cell product – all RCL negative
  - >150 infused pediatric ALL patients in B2202, B2205J, B2101J – all RCL negative
  - >80 infused DLBCL patients – all RCL negative
- Conclusion
  - Product testing ensures patient safety

1. Cameron J. Turtle, Fred Hutchinson Cancer Research Center; Michael Jensen, University of Washington; Stephen Forman, City of Hope National Medical Center; Gwendolyn Binder-Scholl, Adaptimmune LLC; Terry Fry, National Cancer Center; Carl H. June, University of Pennsylvania.
2. Cornetta K et al* “Absence of Replication Competent Lentivirus in the Clinic: Analysis of Infused T Cell Products”, submitted 2016.

CTL019 vector: Integration sites



- Lentiviral vector integration site analysis (LISA)
  - >90,000 unique sites in multiple samples
- No evidence for preferential integration near genes of concern
- No preferential outgrowth of cells harboring integration sites of concern

Summary

- CTL019 vector designed to be safe and to prevent RCL
- No evidence for insertional mutagenesis using third-generation lentiviral vectors in T-cell engineering therapies
- Oxford BioMedica has considerable experience making CTL019 vector
- Highly reproducible manufacturing process
- Comprehensive testing further assures quality and safety of the vector

CTL019 (tisagenlecleucel)

Correlations between product attributes and clinical outcomes

David Lebwohl, MD

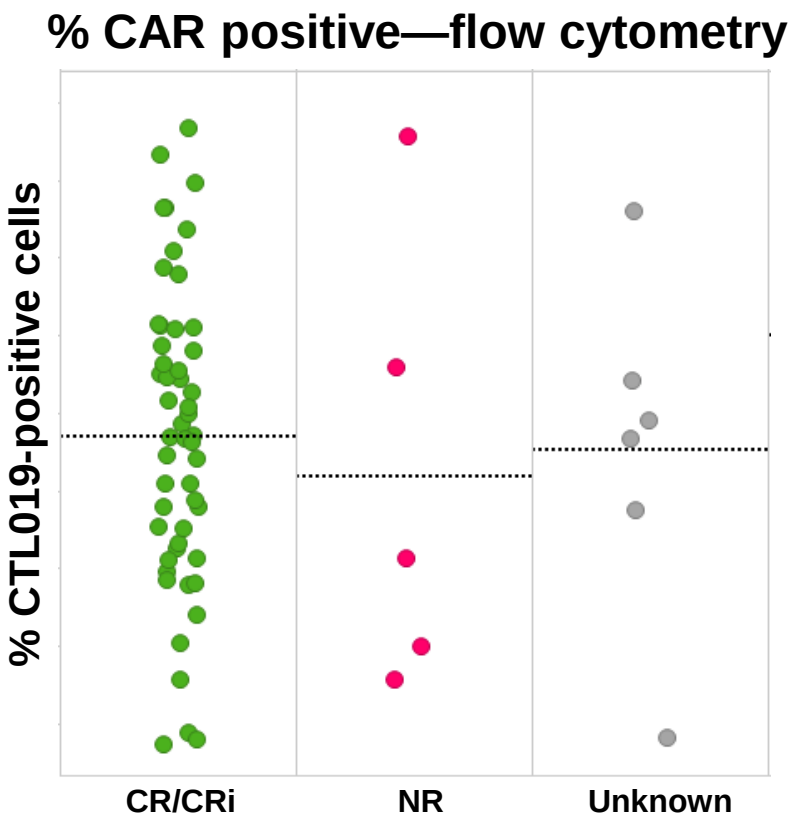
CAR T Franchise Global Program Head
Novartis Pharmaceuticals Corp.

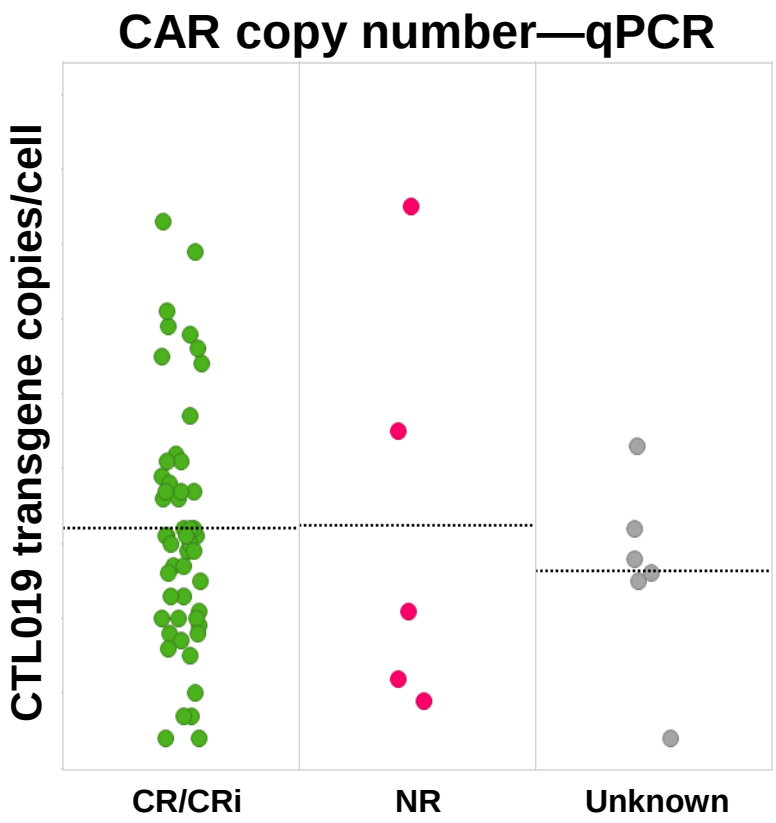
NOVARTIS

Clinical outcomes vs product attributes

- Critical product attributes
  - CAR transduction
  - Product in vitro potency
- Clinical outcomes
  - Best overall response
  - Cytokine release syndrome (CRS)

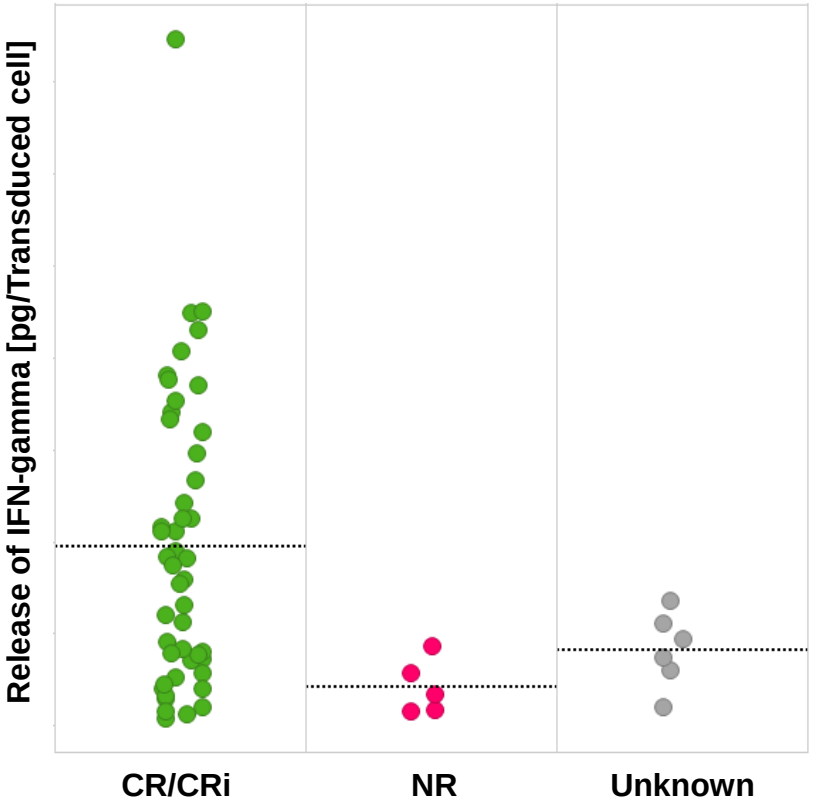
Response vs CAR transduction Study B2202





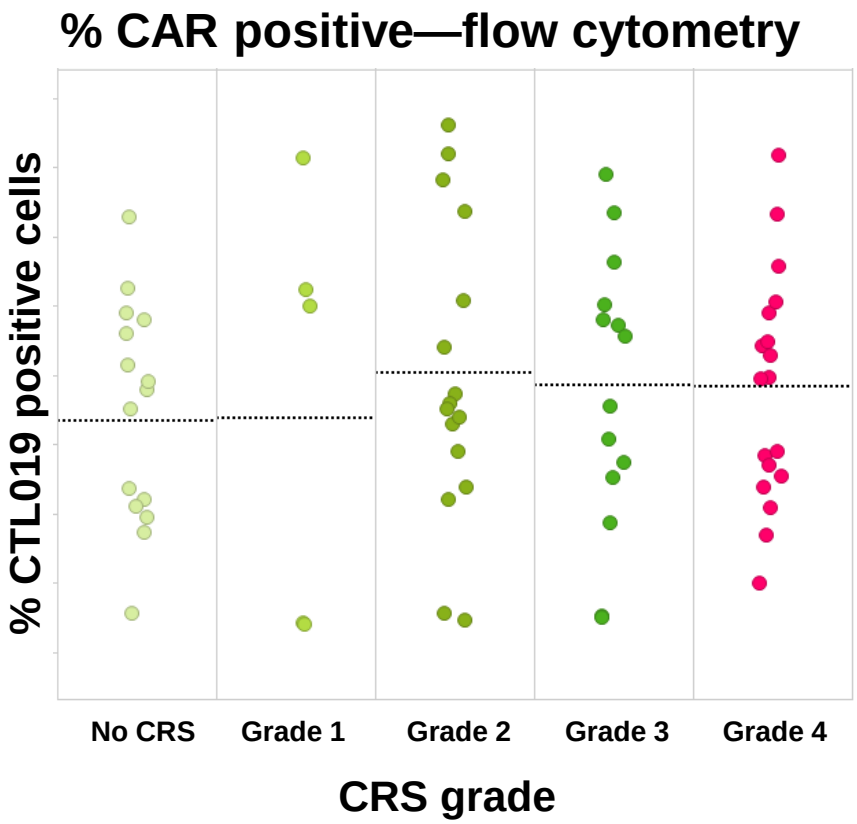
Pediatric ALL/B2202—63 patients [52-CR/CRi, 5-NR, 6-Unknown].
Best Overall Response within 3 months:
CR=complete remission; CRi=complete remission with incomplete blood count recovery; NR=nonresponder; Unknown [response].

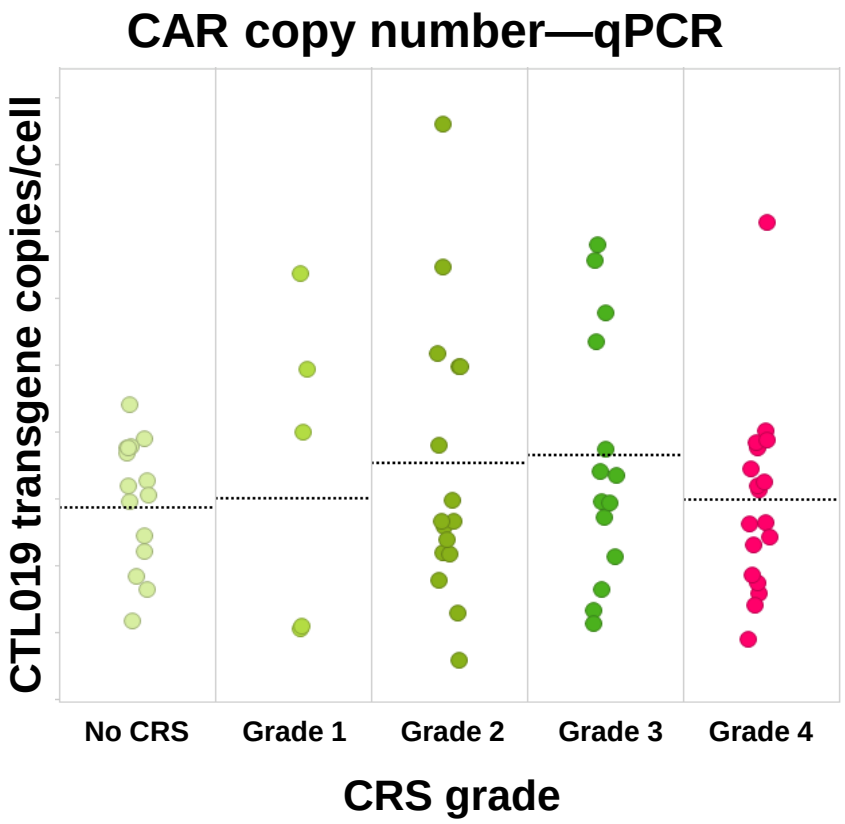
Response vs product in vitro potency Study B2202



Pediatric ALL/B2202—63 patients [52-CR/CRi, 5-NR, 6-Unknown]
Best Overall Response within 3 months:
CR=complete remission; CRi=complete remission with incomplete blood count recovery; NR=nonresponder; Unknown [response].

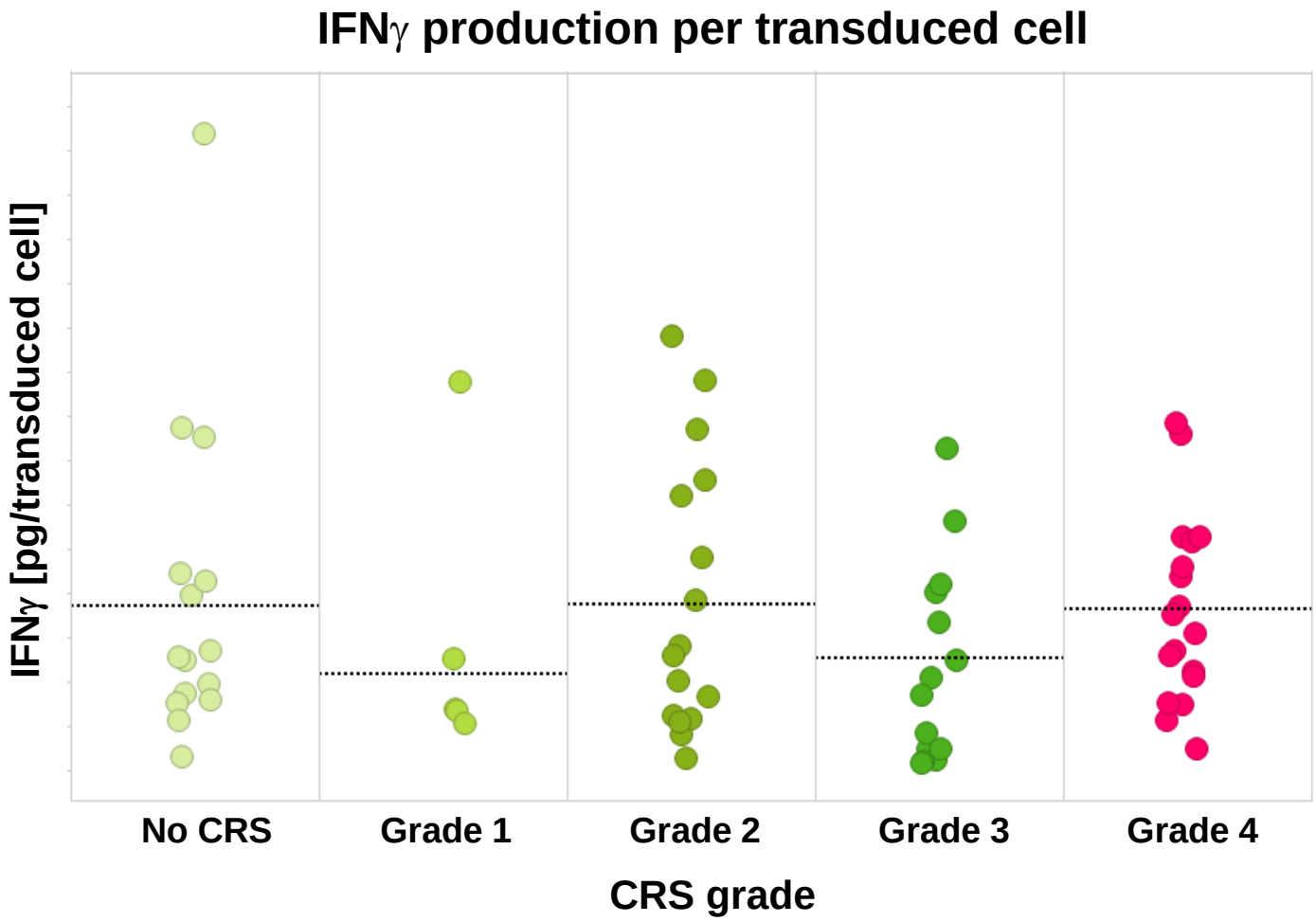
CRS vs CAR transduction Study B2202





Pediatric ALL/B2202—68 patients [15-No CRS, 5-Gr1, 16-Gr2, 14-Gr3, 18-Gr4].

CRS vs product in vitro IFNγ secretion Study B2202



Pediatric ALL/B2202—68 patients [15-No CRS, 5-Gr1, 16-Gr2, 14-Gr3, 18-Gr4].

Overall summary of Novartis presentations

- Novartis has accrued significant experience manufacturing patient-specific CAR T cells
- Novartis has developed a highly reproducible manufacturing process
  - Comprehensive testing further assures quality and safety of the vector and cell product
- CTL019 vector is designed to prevent replication and recombination
  - Patient RCL testing is not warranted for third-generation vectors for gene modified T-cell therapy
- Positive clinical outcomes observed across the allowable range of product quality attributes

CTL019 (tisagenlecleucel)

In pediatric and young adult patients with relapsed/refractory B-cell acute lymphoblastic leukemia

U.S. Food & Drug Administration
Oncologic Drugs Advisory Committee

July 12, 2017

NOVARTIS

Presentation overview—PM

Presentation	Presenter
Efficacy	**Samit Hirawat, MD** Head, Oncology Global Development Unit Novartis Pharmaceuticals Corp.
Safety	**David Lebwohl, MD** CAR T Franchise Global Program Head Novartis Pharmaceuticals Corp.
Clinical perspective	**Stephan Grupp, MD, PhD** Children's Hospital of Philadelphia
Conclusion	**David Lebwohl, MD**

Opportunity to address an important medical need

- Despite current treatment options, >600 pediatric and young adult patients with ALL experience relapse each year in the US[1]
- Treatment options are limited
  - Associated with poor outcomes, high toxicity
  - Median overall survival is 3 to 9 months[2-5]
- CTL019 offers new hope
  - Highly reproducible manufacturing process
  - Quality criteria correlate with positive patient outcomes
  - Chain of identity is rigorously maintained

1. Maude SL, et al. Blood. 2015;125:4017-4023
2. Jeha S, et al. *J Clin Oncol*. 2006;24:1917-1923.
3. Hijiya N, et al. *Blood*. 2011;118:6043-6049
4. Locatelli F, et al. *Br J Haematol*. 2009;147(3):371-378.
5. von Stackelberg J, et al. *J Clin Oncol*. 2016;34:4381-4389.

CTL019 (tisagenlecleucel) Clinical efficacy

Samit Hirawat, MD

Head, Oncology Global Development Unit
Novartis Pharmaceuticals Corp.

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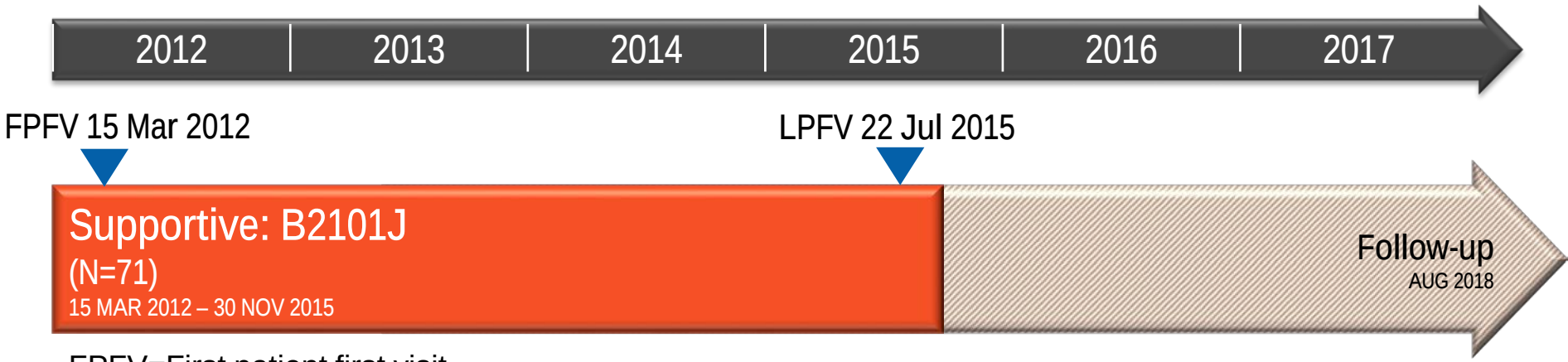
CTL019 clinical studies in pediatric and young adult patients with r/r B-cell ALL

Study	Phase	N[1]	Design	Endpoints
B2202 (pivotal)	2	68	Single arm Global Multicenter	• Primary: ORR • Secondary: MRD, DOR, OS, safety, PRO
B2205J (supportive)	2	29	Single arm US Multicenter	• Primary: ORR • Secondary: MRD, DOR, OS, safety
B2101J (supportive)	1/2a	55	Single arm US Single center	• Primary: safety and feasibility • Secondary: antitumor response

1. Treated patients.

Efficacy, long-term safety, and persistence demonstrated in Study B2101J



FPFV=First patient first visit
LPFV=Last patient first visit

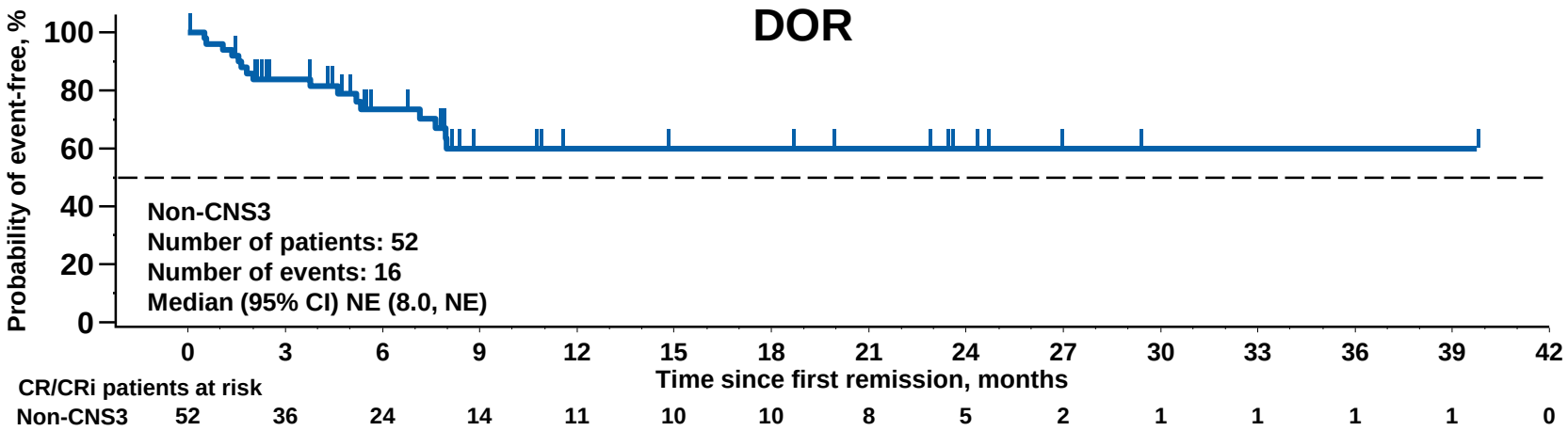
- First academic trial establishing feasibility of CTL019 manufacturing
- Demonstrated high rate of durable complete remissions
- Provided long-term safety in pediatric ALL patients
  - First use of tocilizumab to successfully reverse severe CRS
- Demonstrated long-term persistence of CTL019 cells
  - First pediatric patient treated has been in remission for 5 years

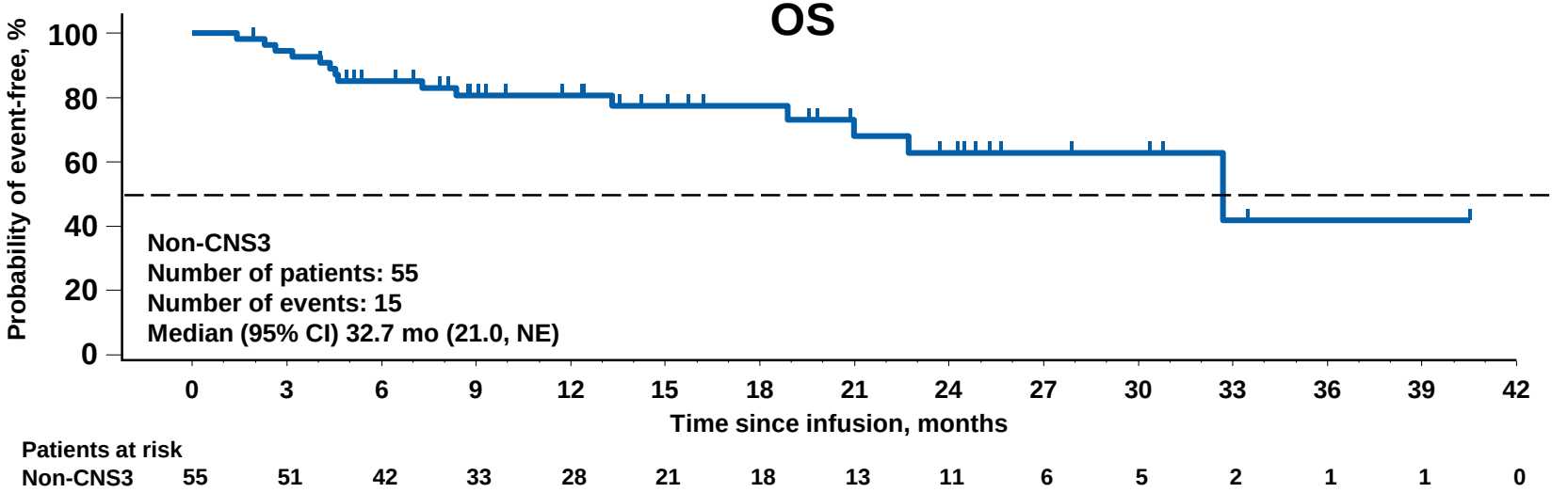
95% ORR at interim analysis Study B2101J

	Non-CNS3 ALL, n (%) N=55
Overall remission rate[1] (CR+CRi)[2]	52 (**95**)
CR or CRi with MRD-negative bone marrow	49 (**89**)

1. Based on investigator's assessment.
2. CR=complete remission; CRi=complete remission with incomplete blood count recovery.

Long DOR and OS
Study B2101J





Pivotal Study B2202

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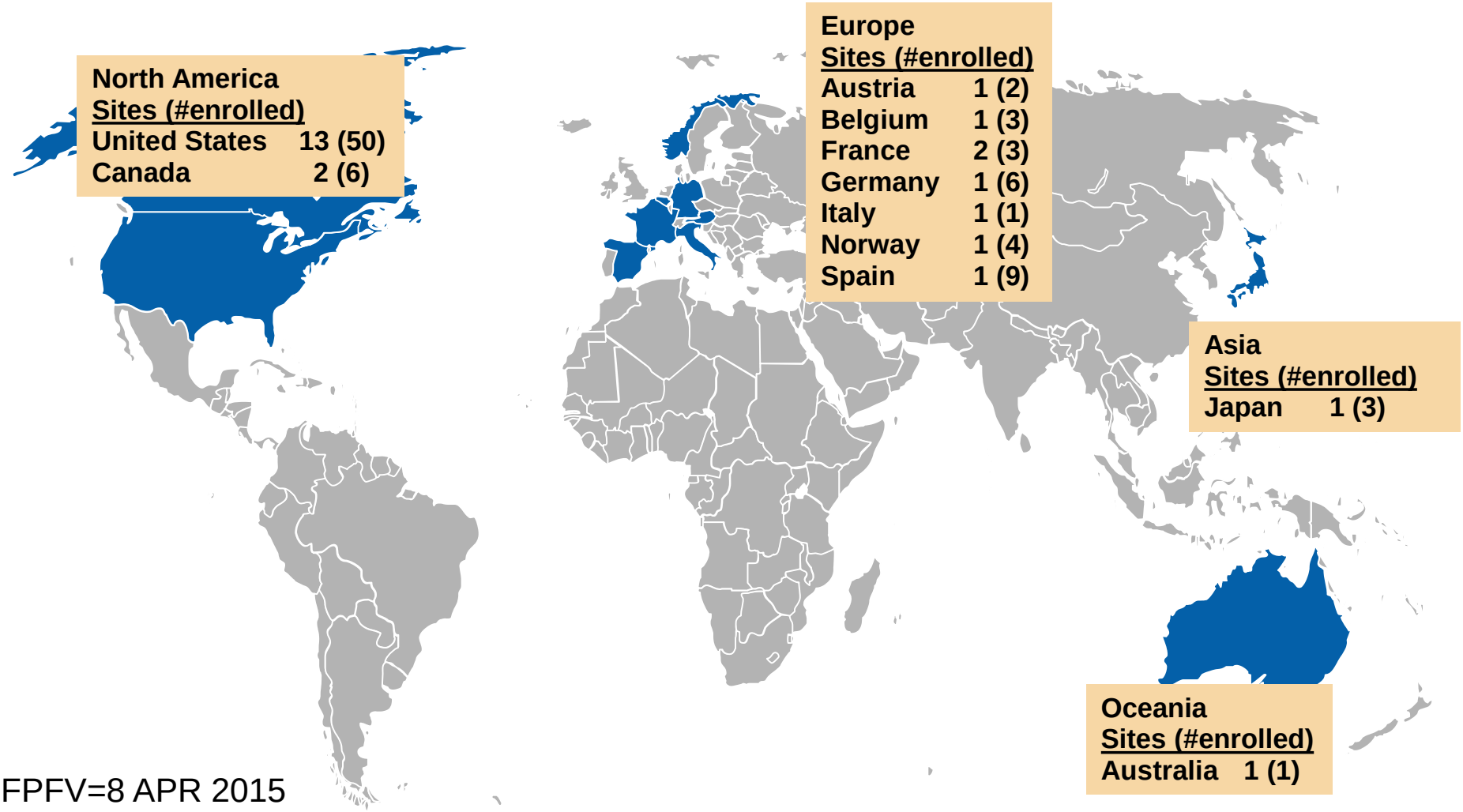
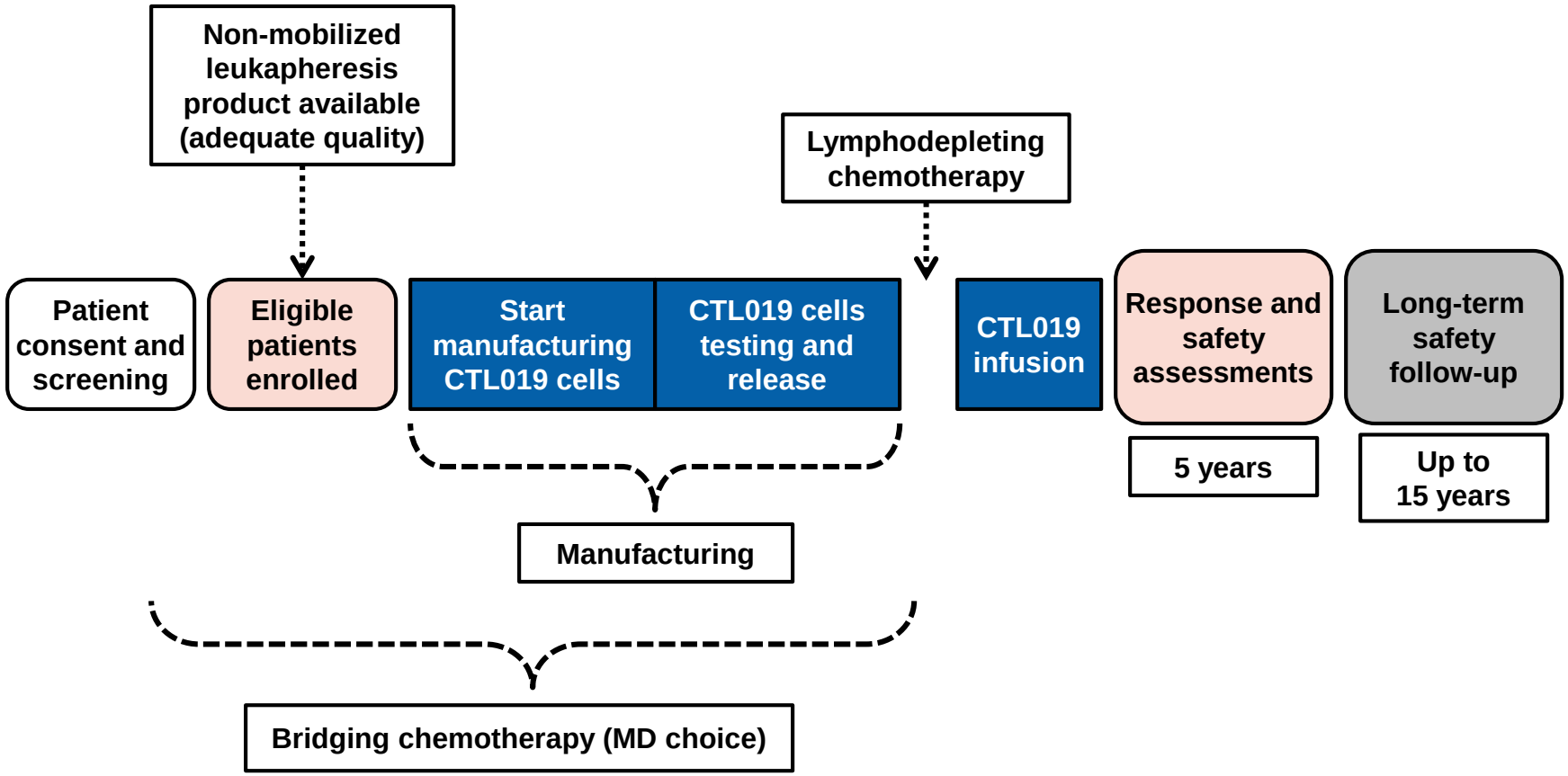
Global, multicenter trial
Study B2202



FPFV=8 APR 2015
Data cutoff: 23 NOV 2016

Trial design
Study B2202



- Lymphodepleting chemotherapy: fludarabine (30 mg/m^2 IV daily for 4 doses) plus cyclophosphamide (500 mg/m^2 IV daily for 2 doses)

Dose used in clinical trials Study B2202

- Single IV infusion
- Based on the experience from phase 1 pediatric ALL (B2101J) and adult CLL studies (B2102J and A2201)
  - Remissions seen across all doses
  - Safety established in pediatric and young adult ALL and CLL patients
- Protocol-specified dose range
  - 0.2 to 5.0×10^6 transduced viable T cells/kg (for pts ≤50 kg, weight adjusted)
  - 0.1 to 2.5×10^8 transduced viable T cells (for pts >50 kg)
- Wide dose range considered acceptable because there is no relationship between expansion in vivo and dose

Key eligibility criteria Study B2202

Inclusion

- 2nd or greater bone marrow relapse or primary refractory B-cell ALL
- ≥5% bone marrow lymphoblasts
- Age 3 years at the time of screening to age 21 years at the time of initial diagnosis
- Adequate organ function

Exclusion

- Prior gene therapy
- Prior anti-CD19 therapy
- Active CNS involvement

Efficacy endpoints
Study B2202

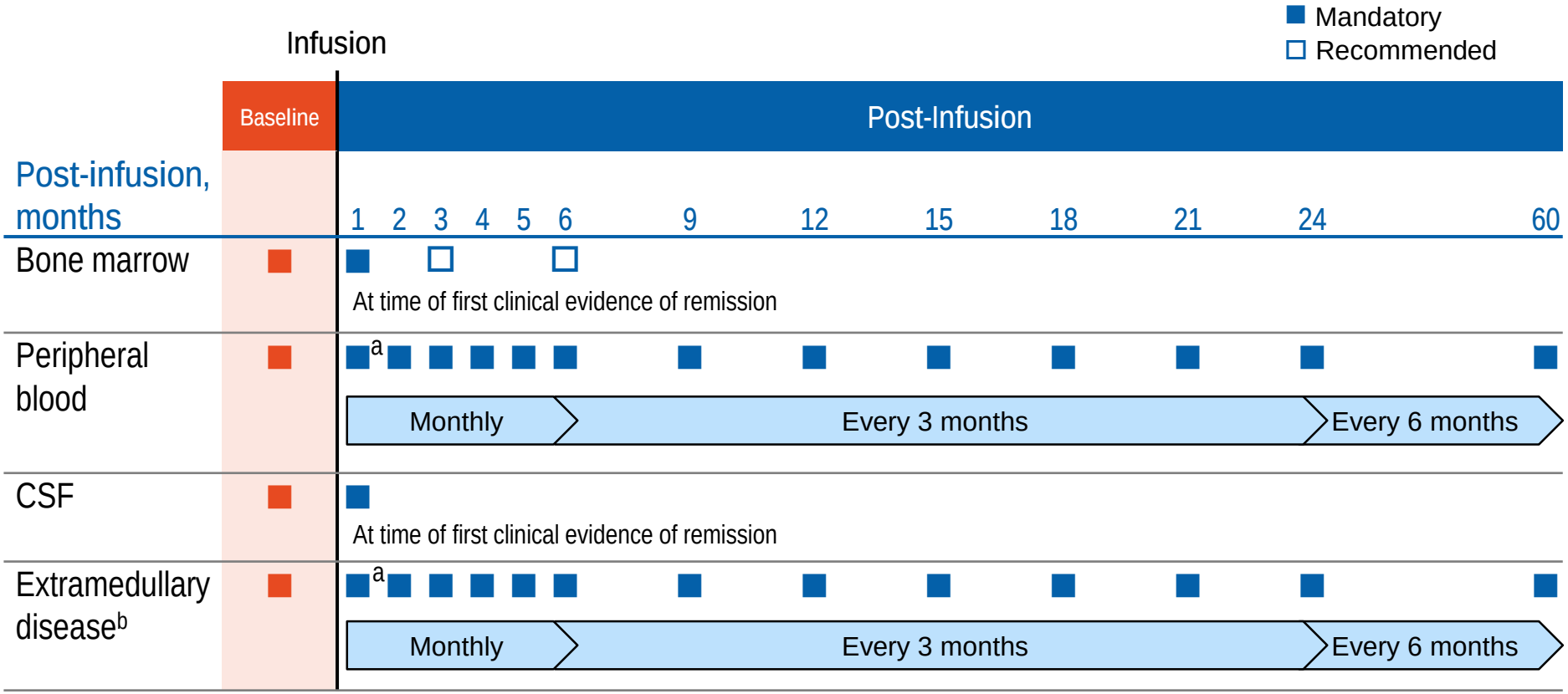
Primary endpoint
- Overall remission rate (ORR=CR+CRi) within 3 months after CTL019 administration (by IRC)

Key secondary endpoints[1]
- Remission rate (CR/CRi) with MRD-negative bone marrow within 3 months

Other efficacy endpoints include
- Duration of remission (DOR)
- Overall survival (OS)

1. Key secondary endpoints also include ORR and MRD in patients receiving CTL019 manufactured in the US.

Efficacy assessment schedule Study B2202



[a] Confirmed 4 weeks after initial assessment.

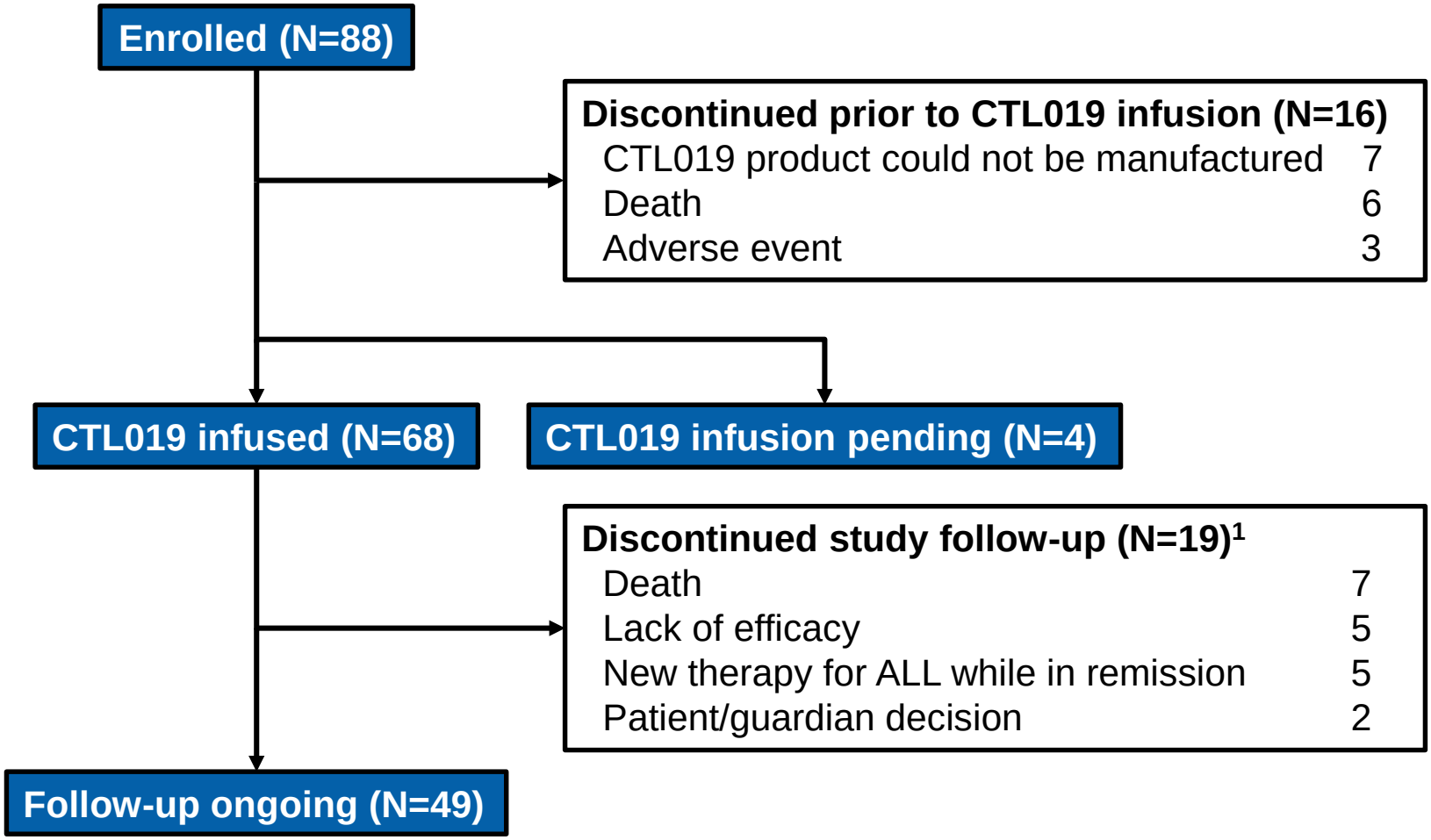
[b] Via physical exam, including assessment of CNS symptoms. CNS imaging (CT/MRI) conducted as clinically indicated.

Statistical considerations for efficacy endpoints Study B2202

- Sample size
  - 76 infused patients provide >95% power to reject null hypothesis of 20%[1] under alternative hypothesis of ≥45%; 1-sided alpha 0.025
  - 1 interim analysis (IA) after first 50 infused patients completed 3 months of follow-up or discontinued
- Primary endpoint considered met at IA if 1-sided p value <0.0057[2]
- Key secondary endpoints were tested sequentially (after primary endpoint was significant) to control overall alpha

1. Jeha S, et al. *J Clin Oncol*. 2006;24:1917-1923.
2. O'Brien-Fleming boundary.

Patient disposition Study B2202



- Median time from infusion to data cut-off (range) 8.8 mo (0.3-18.5)

[1] Patients alive are still followed for survival status.

Baseline characteristics Study B2202

Select baseline characteristics	Full analysis set N=68
Median age, years (range)	12 (3-23)
Sex, %	
Female	44
Male	56
Race, %	
White	75
Asian	9
Black	1
Other	15
Previous lines of therapy, median (range)	3 (1-8)
Prior HSCT, %	59
Primary refractory, %	9
Morphologic blast count in bone marrow, %, median (range)	73 (5-99)

Analysis sets
Study B2202

Analysis set	All patients (N=107) n (%)
Screened set	107 (100)
Enrolled set	88 (82)
Full analysis set (FAS)/Safety set[1]	68 (64)
Efficacy analysis set (EAS)[2]	63 (59)
Interim efficacy analysis set (IEAS)[3]	50 (47)

1. FAS/Safety Analysis set comprises all patients infused with CTL019.
2. EAS comprises all patients infused with CTL019 at least 3 months prior to data cutoff of 23 NOV 2016.
3. IEAS comprises first 50 patients infused with CTL019.

Performed analyses Study B2202

- Interim analysis (data cut-off for IA: 17 Aug 2016)
  - 50 patients infused (US manufacturing only) with CTL019 with 3 months of follow-up or discontinued earlier
  - Primary and all key secondary endpoints were met
- **Final analysis with US manufacturing (data cut-off: 23 Nov 2016)**
  - 63 patients infused with 3 months of follow-up or discontinued earlier
  - 50 infused patients with 6 months or discontinued earlier
- Study is ongoing to evaluate additional patients infused with CTL019 manufactured by EU facility
  - 5 patients infused (EU manufacturing) included in the safety analysis

83% ORR (US manufacturing analysis) Study B2202

	Final analysis of ORR[1] N=63		
	n (%)	**95% CI**	**p value**
Primary endpoint			
Overall remission rate (CR+CRi) within 3 months	52 (**83%**)	(71%, 91%)	<0.0001[2]

CR=complete remission; CRi=complete remission with incomplete blood count recovery.

1. Final analysis with US manufacturing.
2. No formal significance testing was conducted as the endpoint was met at the interim analysis. Nominal p value is presented.

Primary and key secondary endpoints met Study B2202

Efficacy variables	Interim analysis N=50 n (%)	95% CI	p value	Final analysis[1] N=63 n (%)	95% CI	p value
Primary endpoint						
Overall remission rate (CR+CRi) within 3 mo	41 (82%)	(69%, 91%)	<0.0001[2]	52 (83%)	(71%, 91%)	<0.0001[4]
CR	34 (68%)			40 (63%)		
CRi	7 (14%)			12 (19%)		
Key secondary endpoint						
CR or CRi within 3 mo and MRD-negative bone marrow	41 (82%)	(69%, 91%)	<0.0001[3]	52 (83%)	(71%, 91%)	<0.0001[4]

CR=complete remission; CRi=complete remission with incomplete blood count recovery; ORR=overall remission rate.
Interim efficacy analysis set=the first 50 patients who received CTL019 infusion.

1. Final analysis with US manufacturing.
2. Indicates statistical significance (1-sided) at the 0.0057 level so that the null hypothesis that ORR ≤ 20% was rejected.
3. Indicates statistical significance (1-sided) at the 0.0057 level so that the null hypothesis that MRD ≤ 15% was rejected.
4. No formal significance testing was conducted as the endpoint was met at the interim analysis. Nominal p value is presented.

ORR sensitivity analysis shows consistent benefit Study B2202

	n/N (%)	95% CI
ORR (CR+CRi)		
EAS (primary analysis)	52/63 (83%)	(71%, 91%)
EAS plus enrolled patients who discontinued prior to CTL019 infusion	52/79 (66%)	(54%, 76%)

- 100% concordance between IRC and investigator review

EAS=Efficacy analysis set

ORR within 3 months by median time from enrollment to CTL019 infusion Study B2202

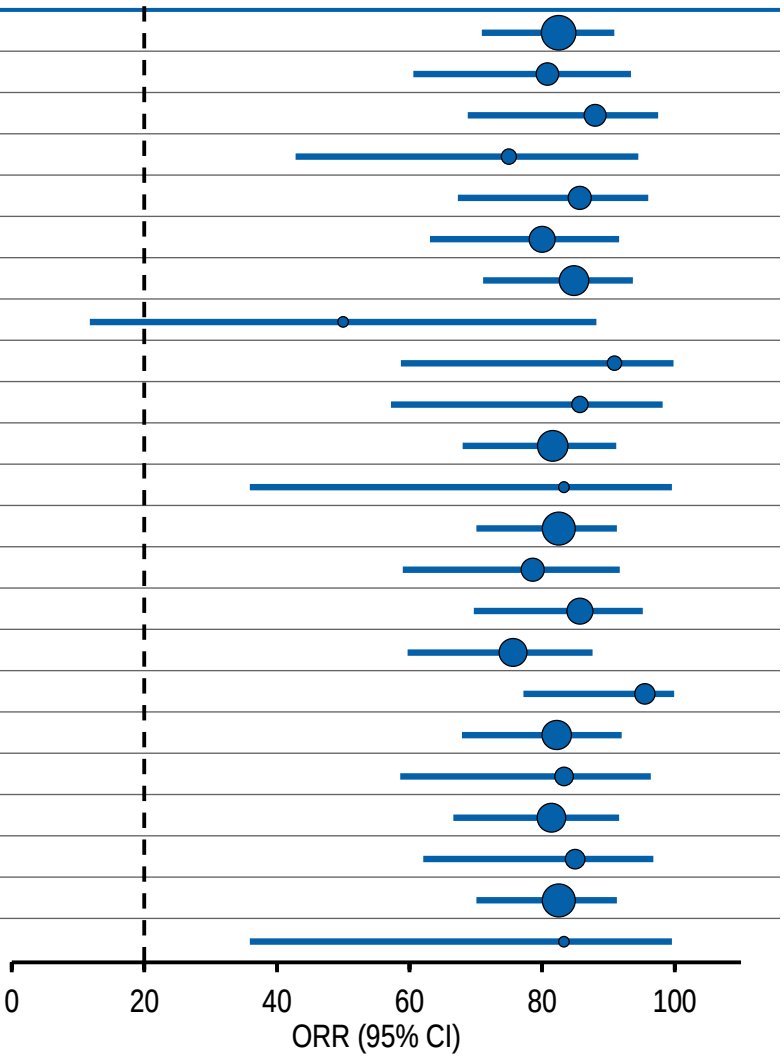
ORR (CR+CRi)	% (n/N)	95% CI
≤ Median	**82** (27/33)	(65, 93)
> Median	**83** (25/30)	(65, 94)

- The median time from enrollment to CTL019 infusion was 42 days

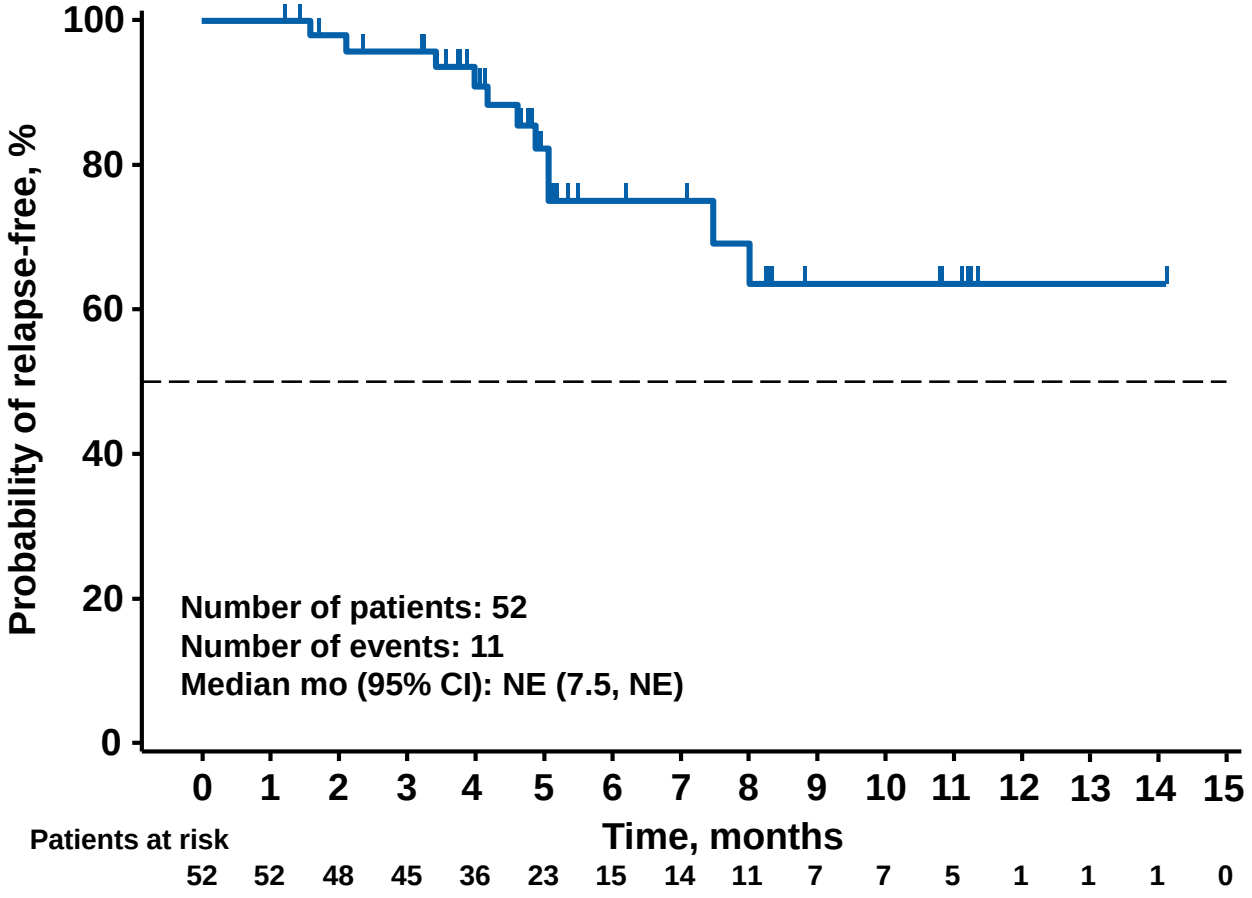
The 95% CIs are exact Clopper-Pearson CIs.

ORR consistent across subgroups Study B2202

		n
Overall		63
Age	<10	26
	≥10- <18	25
	≥18	12
Sex	Female	28
	Male	35
Race	White	46
	Asian	6
	Other	11
Ethnicity	Hispanic or Latino	14
	Other	49
Response status at study entry	Primary refractory	6
	Relapsed disease	57
Prior SCT therapy	No	28
	Yes	35
Enrollment bone marrow tumor burden	High	41
	Low	22
Complex karyotypes (≥5 unrelated abnormalities)	No	45
	Yes	18
Any high-risk mutations	No	43
	Yes	20
Down syndrome	No	57
	Yes	6

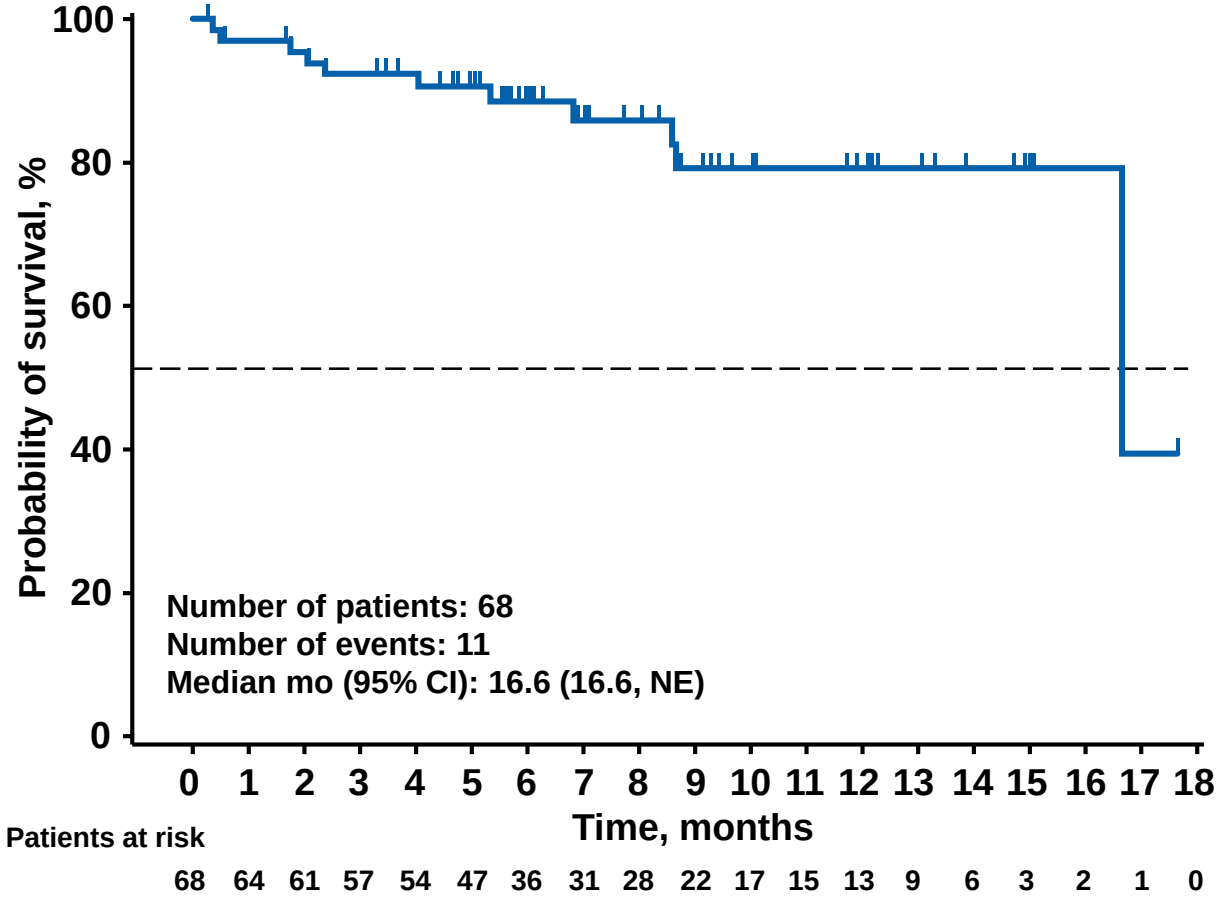


DOR: 75% relapse-free 6 months after onset of remission Study B2202



- DOR by IRC assessment with 6 patients censored at time of SCT

OS: 89% at 6 months, 79% at 12 months Study B2202



- Overall survival (full analysis set)

Clinical pharmacology

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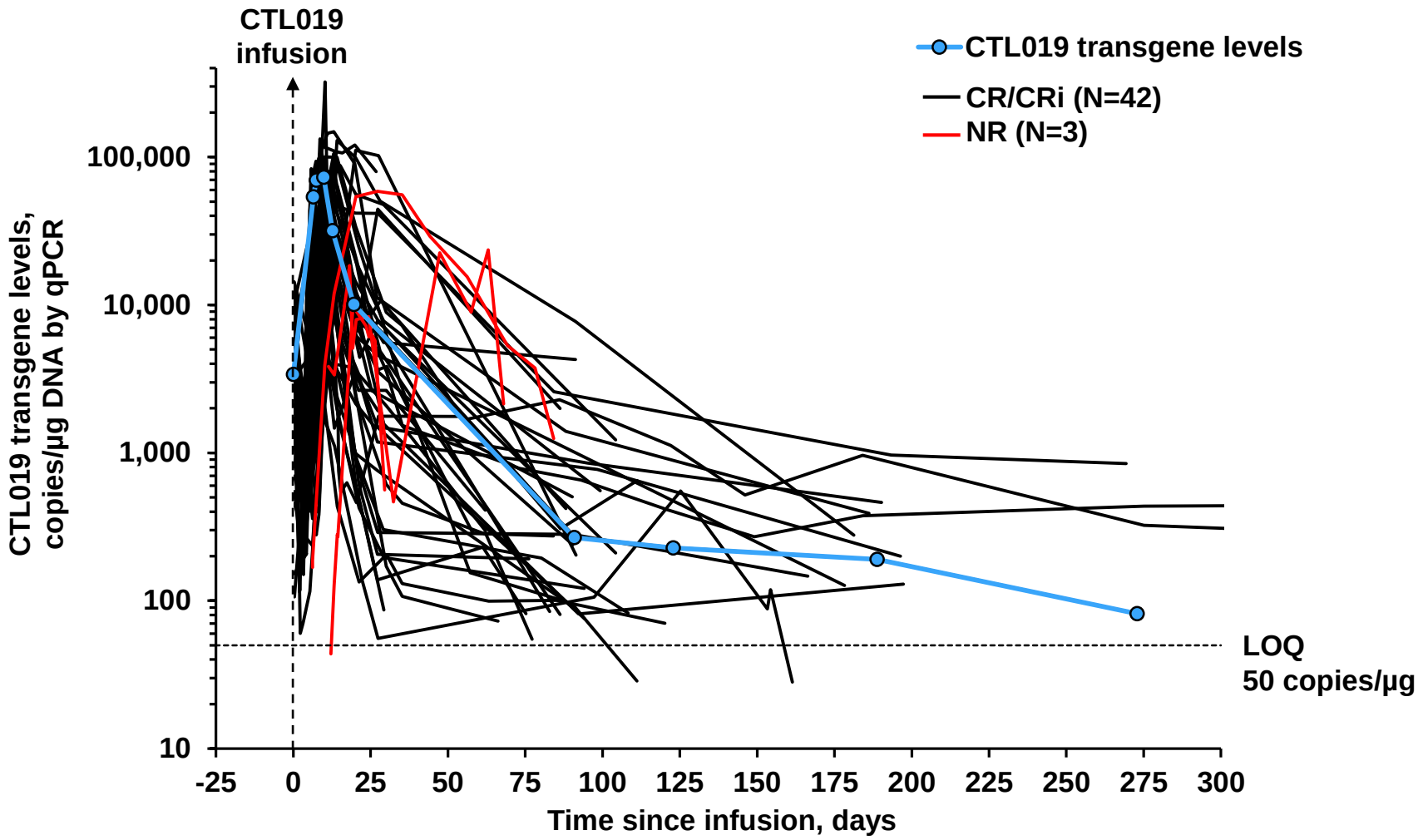
Cellular kinetics: long-term persistence of CTL019 transgene Study B2202



LOQ = Lower limit of quantitation.

Cellular kinetics 2-fold higher expansion in responders vs nonresponders and delayed T_{max} in nonresponders (Study B2202)

	Responder N=42	Nonresponder N=3
Geometric mean (CV%)		
$AUC_{0\text{-}28d}$, copies/µg·day	349,000 (159)	210,000 (152)
C_{max}, copies/µg	41,000 (136)	23,500 (110)
Median (range)		
T_{max}, days	10 (0-27)	27 (19-63)
T_{last}, days	93 (27-366)	68 (29-84)

Key dose-related findings with CTL019 from clinical trials

Based on dose range used in clinical trials

Efficacy

- Responses observed across entire dose range studied
- Response rates were similar across all dose quartiles
- Probability of response at lowest doses tested carries a favorable benefit-risk

Safety

- No impact of dose on CRS (all grades, Grade 3-4)
- No impact of dose on neurotoxicity or cytopenias

Efficacy summary

- Study B2202
  - Primary endpoint was met
    - 83% ORR
    - Consistent IRC and local investigator assessment
    - Subgroup analyses consistent with primary analysis
  - All patients in CR/CRi had MRD-negative bone marrow (83%)
  - Responses are durable; median DOR has not been reached
    - 75% relapse-free rate at 6 months after onset of remission
  - Survival probability 89% at 6 months and 79% at 12 months
- Consistent results for key endpoints across trials

Safety and Risk Management

David Lebwohl, MD

CAR T Franchise Global Program Head
Novartis Pharmaceuticals Corp.

NOVARTIS

Safety populations
Pediatric/young adult patients with relapsed/refractory B-cell ALL

Study	Phase	Enrolled	Infused	Design	Transduced viable T-cell dose
Multicenter studies					
B2202	2	88	68	Single arm Global	Single infusion 0.2 to 5.0×10^6/kg (for pts ≤50 kg) 0.1 to 2.5×10^8 (for pts >50 kg)
B2205J	2	35	29	Single arm US	
Pooled		123	97		
Single-center study					**Total T-cell dose**
B2101J	1/2a	65	55	Single arm US	Split dosing Up to a total dose of 1.5×10^7 to 5×10^9 (0.3×10^6 to 1.0×10^8/kg) total T cells

Similarity of Studies B2202 and B2205J justifies data pooling

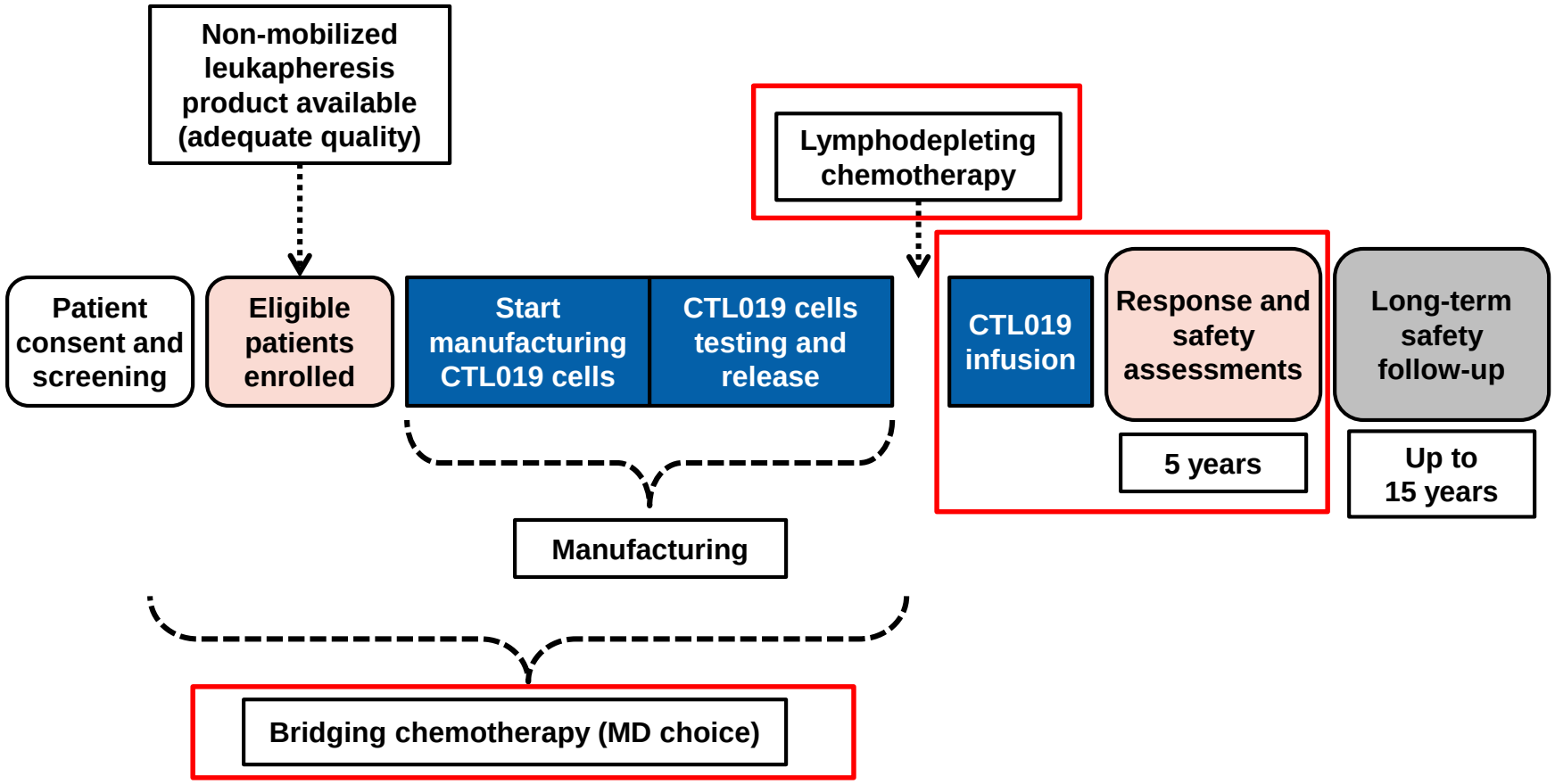
	Studies B2202 and B2205J	Study B2101J
Number of sites	Multicenter	Single center
Dosing	Single infusion	Split dosing
Population	≥5% blasts at enrollment No prior anti-CD19 therapy	Any % blasts, including CR Prior anti-CD19 therapy allowed
Lymphodepleting chemotherapy	Fludarabine and cyclophosphamide (preferred), or cytarabine and etoposide	Multiple choices depending on the patient's underlying disease and prior therapies
Safety reporting	Safety reporting was consistent	Reporting followed different safety reporting conventions

CR=complete remission.

Managing patient safety during the trials

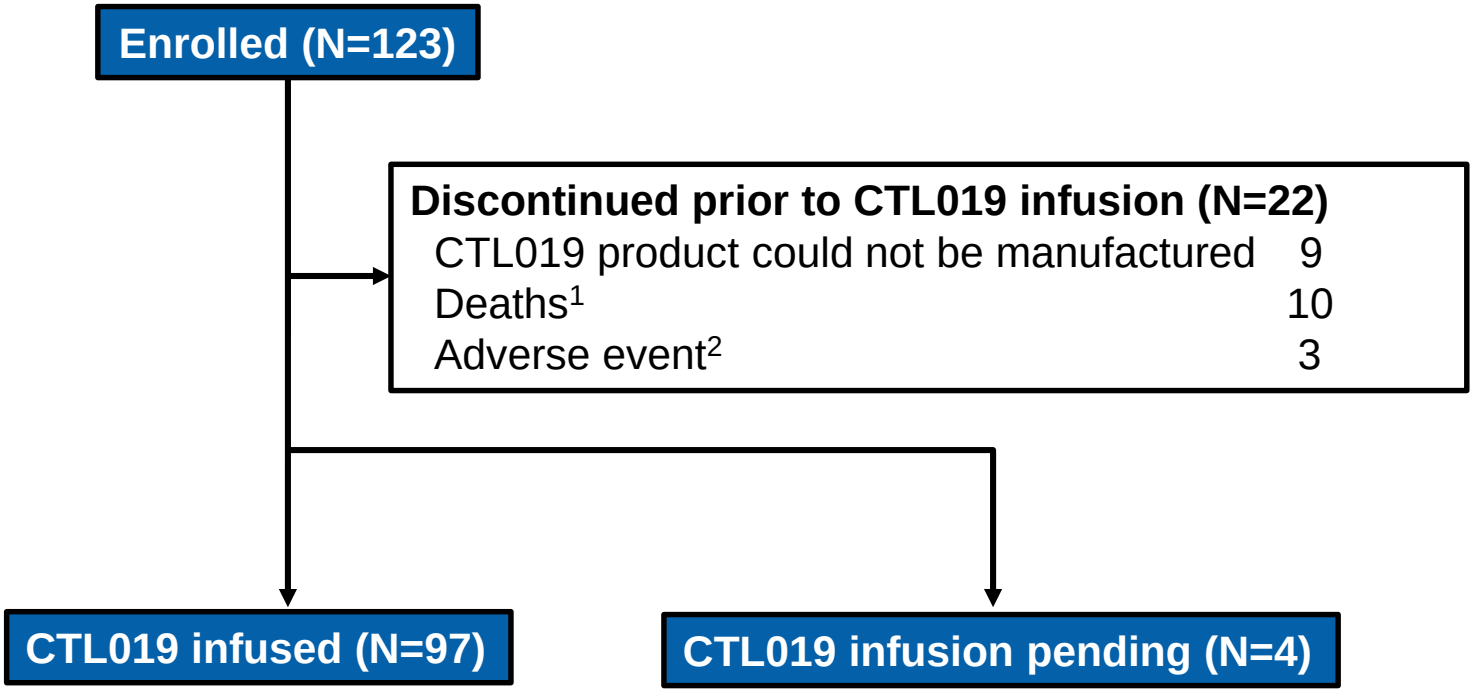
- Comprehensive site training program (leukapheresis, stem-cell laboratory, clinical centers)
- Educate patient and family
- Maintain chain of identity for patient material
- Prior to CTL019 infusion
  - Influenza testing
  - Assess performance status, disease status, and laboratory abnormalities
  - Chemotherapy nonhematologic toxicities must be resolved
  - No active infections or accelerating leukemia
  - Assess risk and provide prophylaxis for tumor lysis syndrome (TLS)
- Following CTL019 infusion
  - Monitor and manage adverse events (AEs) such as CRS and neurologic events

Safety reporting periods Studies B2202 and B2205J



- Lymphodepleting chemotherapy: fludarabine (30 mg/m^2 IV daily for 4 doses) plus cyclophosphamide (500 mg/m^2 IV daily for 2 doses)

Patient disposition
Studies B2202 and B2205J (enrolled set)



1. Deaths: 5 ALL; 3 infection; 2 organ failure.
2. Reasons for AE: 2 infections; 1 GVHD.

Grade 3/4 AEs after enrollment and prior to lymphodepleting (LD) chemotherapy

	All enrolled patients N=123	
Preferred term	Grade 3 %	Grade 4 %
≥1 AE*	**33**	**42**
Febrile neutropenia	20	1
Anemia	18	1
Thrombocytopenia	3	7
Neutropenia	1	8
Neutrophil count decreased	2	7
Platelet count decreased	0	8
Stomatitis	7	1
Hypotension	5	2

- Expected AEs for multiagent chemotherapy and r/r ALL
- 3 non-ALL deaths: 1 sepsis, 1 fungemia, and 1 pneumonia
- 5 deaths due to ALL

*Limited AE were collected prior to LD chemo.
Cut-off: Grade 3/4 AEs occurring in ≥7% of patients.

Grade 3/4 AEs after LD chemotherapy and before infusion

Preferred term	All patients who received LD chemo N=94 Grade 3 %	Grade 4 %
≥1 AE	**12**	**28**
White blood cell count decreased	3	10
Neutrophil count decreased	1	6
Febrile neutropenia	7	0
Hypokalemia	3	3
Anemia	6	0
Platelet count decreased	1	4
Lymphocyte count decreased	0	4
Neutropenia	1	3

- Expected AEs for multiagent chemotherapy and r/r ALL
- 2 deaths: 1 respiratory failure, 1 multiple organ dysfunction

Cut-off: Grade 3/4 AEs occurring in ≥4% of patients.

AEs occurring ≤8 weeks vs >8 weeks to 1 year post-infusion

	≤8 weeks N=97 %	>8 weeks to 1 year N=80 %
Any SAE	72	24
Suspected to be CTL019 related	69	4
Grade 3/4 AE	82	41
Suspected to be CTL019 related	72	19

AEs of special interest[1]

	All patients N=97		
	All grades %	Grade 3 %	Grade 4 %
Cytokine release syndrome[2]	81	20	25
Infections	44	19	3
Neurologic events[3]	40	11	0
Febrile neutropenia	36	34	2
Cytopenias not resolved by day 28	35	13	16
Tumor lysis syndrome	3	3	0

1. Adverse events occurring within 8 weeks of CTL019 infusion.
2. Penn CRS grading scale.
3. MedDRA SMQ: non-infectious encephalopathy/delirium.

CTL019 safety profile: Cytokine release syndrome (CRS)

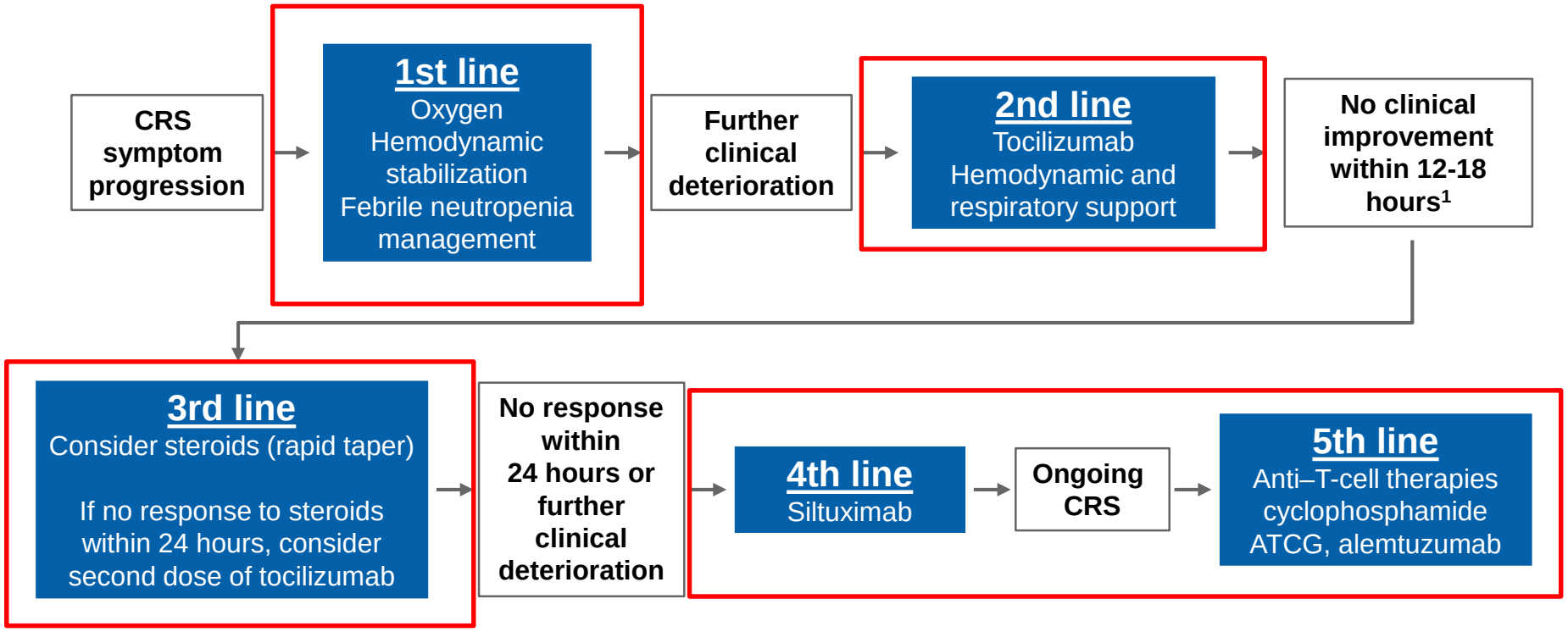
- CRS was the most frequent on-target SAE associated with CTL019 therapy
  - Consequence of CTL019 cell activation and expansion
  - High tumor burden and early fever onset associated with severe CRS
  - Symptoms may include high fever, rigor, myalgia, arthralgia, nausea, vomiting, anorexia, fatigue, headache, hypotension, encephalopathy, dyspnea, tachypnea, and hypoxia
- CRS management in clinical trials is based on CRS management algorithm developed by Novartis and University of Pennsylvania
  - Supportive measures and anti-cytokine therapy resulted in CRS improvement or resolution
  - No fatalities due to refractory CRS

Cytokine release syndrome (CRS)

	All infused patients N=97
Total patients with CRS	81%
Median time to onset of CRS, days (range)[1]	3 (1-22)
Median duration of CRS, days (range)[1]	8 (1-36)
Admitted to ICU	44%
Median duration of ICU stay, days (range)[2]	8 (1-34)
Systemic anti-cytokine therapy	34%
High-dose vasopressors	27%
Intubation	16%
Dialysis	11%

1. Statistics are based on patient with CRS.
2. Among patients admitted to ICU.

CRS management algorithm



1. At all times, provide hemodynamic and respiratory support, and consider other diagnoses that might cause clinical deterioration (eg, TLS, sepsis, adrenal insufficiency).

Resolution of Grade 3/4 cytopenias beyond Day 28 post-CTL019

Grade 3/4 thrombocytopenia

- 47/97 (48%) patients had Grade 3/4 thrombocytopenia not resolved by Day 28
  - 30/47 (64%) resolved: 22 (47%) by Month 2, and 30 (64%) by Month 4
  - 17/47 (36%) were ongoing or had discontinued

Grade 3/4 neutropenia

- 59/97 (61%) patients had Grade 3/4 neutropenia not resolved by Day 28
  - 42/59 (71%) resolved: 22 (37%) by Month 2, and 36 (61%) by Month 4
  - 17/59 (29%) were ongoing or had discontinued

Neurologic events ≥3% within 8 weeks

	All patients N=97		
	All grades %	Grade 3 %	Grade 4 %
Any neurologic event	**40**	**11**	**0**
Confusional state	12	0	0
Encephalopathy	9	4	0
Delirium	8	3	0
Agitation	6	0	0
Tremor	6	0	0
Irritability	5	0	0
Hallucination	4	0	0
Somnolence	4	1	0
Cognitive disorder	3	1	0
Lethargy	3	0	0
Seizure	3	1	0

- No cases of cerebral edema reported
- Neurologic events are usually associated with CRS
- Neurologic events managed by optimal best supportive care

B-cell aplasia

- Prolonged B-cell aplasia is an expected on-target effect of CTL019 therapy
- All patients who achieved CR/CRi developed B-cell aplasia
  - Long-term data from early patients suggest that B-cell aplasia may persist for >3 years
- B-cell aplasia is managed with immunoglobulin replacement and other standard measures

Serious AEs post-infusion

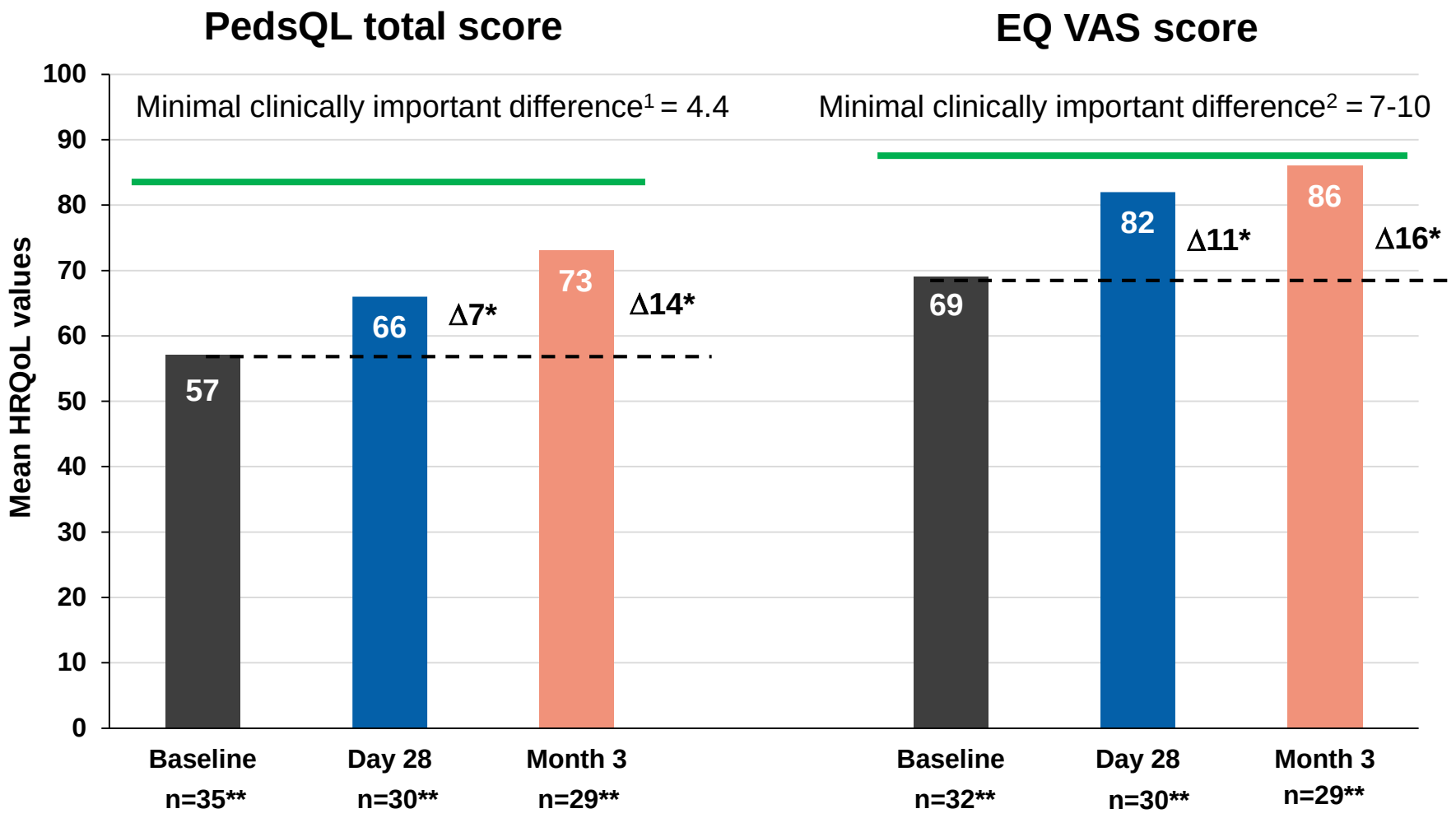
	All patients N=97		
Preferred term	All grades[1] %	Grade 3 %	Grade 4 %
≥1 SAE	**76**	**29**	**41**
Cytokine release syndrome	65	19	25
Febrile neutropenia	25	24	1
Hypotension	12	2	10
Pyrexia	7	1	0
Acute kidney injury	6	2	4
Hypoxia	6	3	3
Respiratory failure	4	0	4
Upper respiratory tract infection	4	4	0

1. Serious adverse events reported in ≥4% of patients at any time following CTL019 infusion.

Deaths post-infusion

Timeframe Principal cause of death	All patients N=97 n (%)
≤30 days of CTL019 infusion	**4 (4)**
Acute lymphoblastic leukemia	2 (2)
Cerebral hemorrhage	1 (1)
Embolic stroke (infectious)	1 (1)
>30 days after CTL019 infusion	**17 (18)**
Acute lymphoblastic leukemia	14 (14)
Encephalitis	1 (1)
Lower respiratory tract infection bacterial	1 (1)
Systemic mycosis	1 (1)

Patient-reported QoL post-CTL019 infusion improves vs baseline in responders Study B2202



*Mean change from baseline in patients who had both baseline and post-baseline score.
**Only patients 8 years or older were required to complete the assessments.

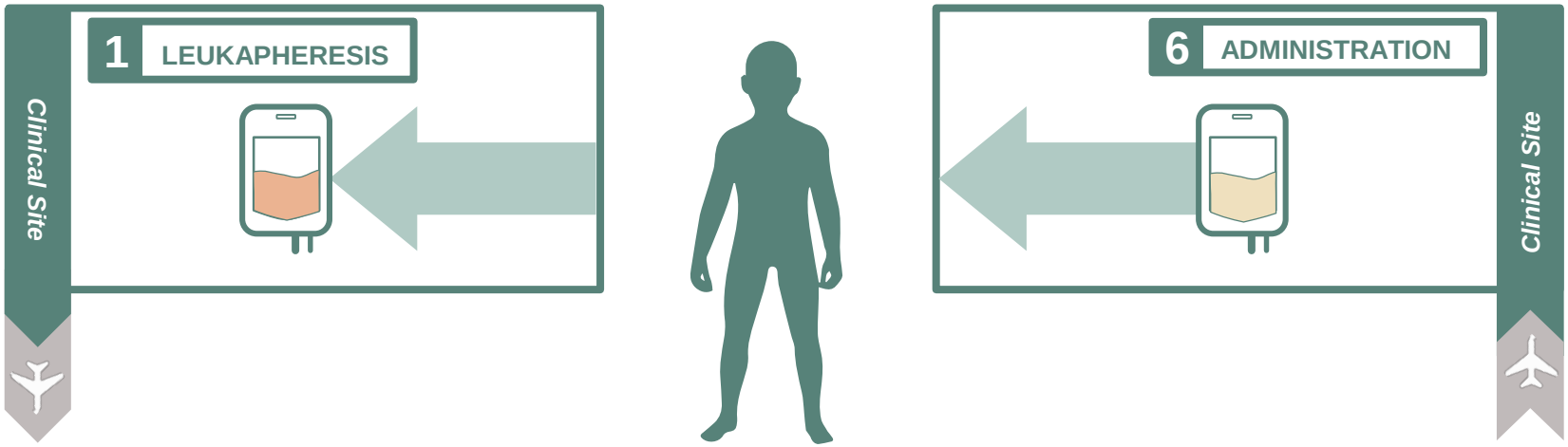
1. Varni et al. *Ambul Pediatr.* 2003;3(6):329-31; 2. Pickard et al. *Health Qual Life Outcomes*. 2007;5:70.

Pharmacovigilance and long-term safety follow-up

	Study A2205B All clinical trials	Study B2401 Registry (commercial) CIBMTR/EBMT
Type of study	**Interventional (15 years per FDA guidance)**	**Observational**
AEs tisagenlecleucel related	✓	✓
Efficacy	✓	✓
Immunogenicity	✓	–
CD19 CAR transgene persistence	✓	**Monitor surrogate: B-cell levels**
RCL by VSV-g q-PCR	✓	**Event-driven investigation**
Second malignancies (insertional mutagenesis)*	✓	✓

CIBMTR – Center for International Blood and Marrow Transplant Research
EBMT – European Society for Blood and Marrow Transplantation
* Frequency is at 3, 6, 9, 12, and at every 6 months thereafter

Center Selection and Qualification

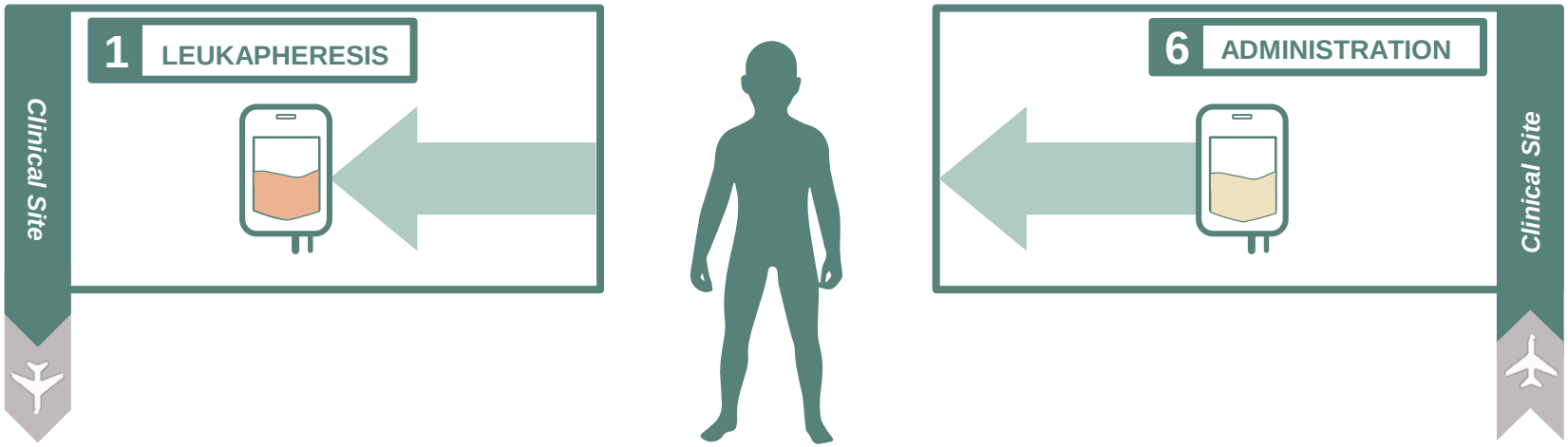


Treatment center selection

- 30-35 initial centers (13 involved in clinical trials)
- Geographic coverage
- FACT certification
- Experience with T-cell therapies and leukemia

FACT=Foundation for the Accreditation of Cellular Therapy.

Training and Education



- Novartis will train centers on processes for cell collection, cryopreservation, transport, chain of identity, safety management, and logistics for CTL019
- Novartis will provide educational resources for patients and caregivers

Proposed REMS to mitigate risks of CRS and neurological events

Novartis actions

- Ensure authorized representative at site
- Provide training on CRS and neurotoxicity risk and management
- Ensure only certified prescribers can order CTL019 via validated IT system
- Monitor compliance and performance

Site actions

- Designate authorized representative
- Complete staff training and assessment on CRS and neurologic events
- Verify availability of anti-cytokine medications
- Ensure patients/caregivers stay within 2 hours of site for 3-4 weeks post-infusion
- Provide wallet card reminders to patients/caregivers for signs and symptoms of AEs

REMS=Risk Evaluation and Mitigation Strategy.

Safety summary

CTL019 safety profile is well characterized and generally manageable with application of specific management guidelines and executed at sites with appropriate site training

- CRS was the most common severe adverse event
  - CRS was limited to the first 4 to 6 weeks post-CTL019 infusion
  - No fatal cases due to refractory CRS were observed
- Neurologic events started within 30 days after CTL019 infusion and were transient
- B-cell aplasia in responding patients was managed with immunoglobulin replacement therapy
- Infections were common and managed by routine standard of care
- Improved QoL vs baseline among responders
- No replication-competent lentivirus or insertional oncogenesis observed

Clinical Perspective

Stephan Grupp, MD, PhD

Children's Hospital of Philadelphia

Children's Hospital of Philadelphia

NOVARTIS

Disclosure statement

- Research support and consultancy from Novartis
- I have no personal financial interest in the outcome of this meeting

Medical need for durable therapies for pediatric and young adult patients with relapsed/refractory ALL

- Modern therapy serves many patients very well, but those who are left behind by modern therapy have very few treatment options
- Getting patients back into remission is increasingly difficult as patients suffer subsequent relapses
- Getting patients into a transplantable remission requires extremely high-dose chemotherapy with a high morbidity, high infection risk, and many weeks in the hospital
  - Current treatment options do not meet the needs of these patients

Efficacy of available treatments for pediatric and young adult r/r B-cell ALL patients: Summary

	Clofarabine mono[1]	Blinatumomab[2]	CTL019 (B2202)
Patients (N)	61	70	68
≥3 prior regimens	62%	7%	60%
ORR (CR+CRi)	20%	39%	83%[3]
MRD negative	NA	20%	83%[3]
Median OS	**3 months**	**7.5 months**	**16.6 months**
12 months OS	20%	40%	79%
Early mortality (within 30 days)	25%	7%	3%

Disclaimer: Cross-trial comparisons cannot be made based upon differences in study designs, patient populations, and other factors.

1. Jeha S, et al. *J Clin Oncol*. 2006;24:1917-1923.
2. von Stackelberg A, et al. *J Clin Oncol*. 2016;34:4381-4389.
3. ORR based on 63 patients in Efficacy Analysis Set (EAS).

Efficacy, long-term safety, and persistence
Study B2101J

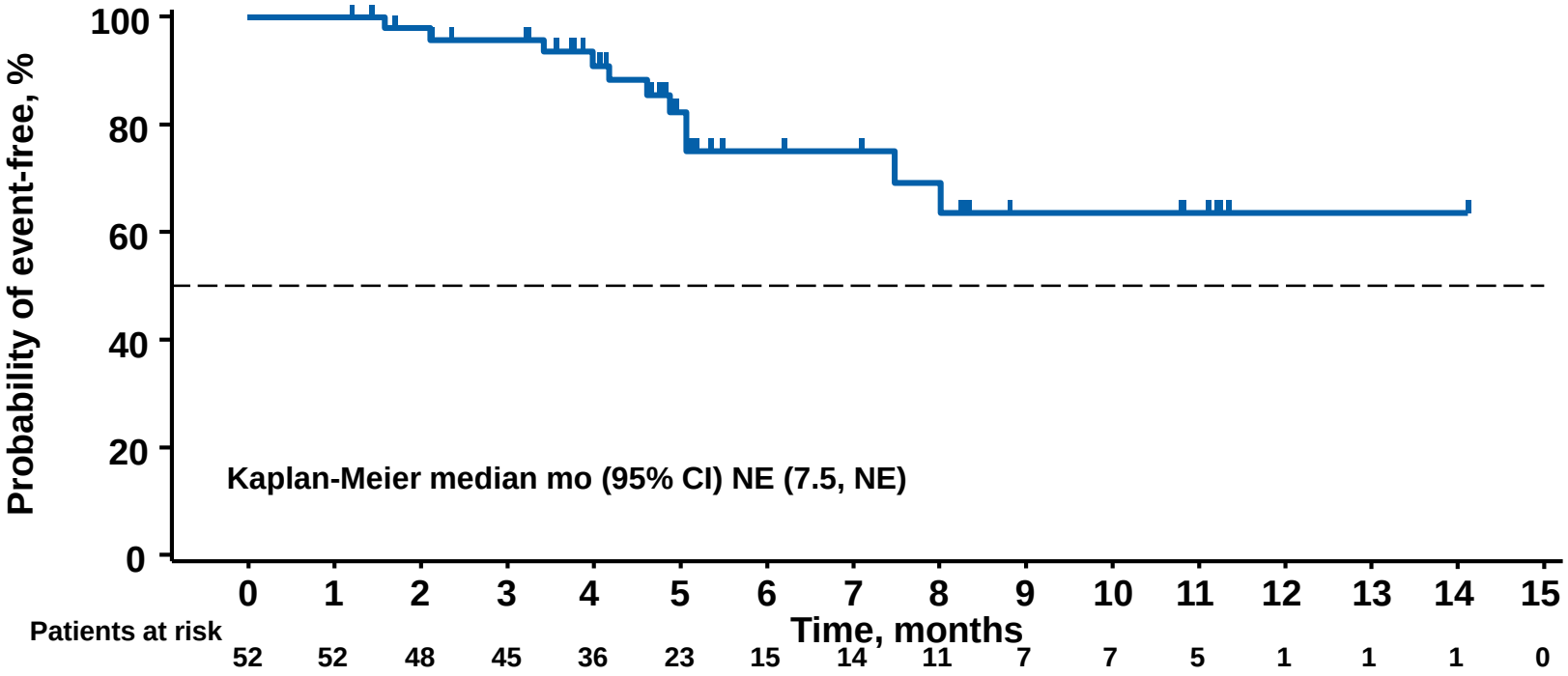
- First academic trial establishing feasibility of CTL019 manufacturing
  - First patient first visit March 15, 2012
- High rate of durable complete remissions and long-term safety in pediatric ALL patients
  - 95% CR/CRi, 89% MRD negative
  - Median DOR not met; median OS, 32.7 months
  - First use of tocilizumab to successfully reverse severe CRS
  - CRS grading and CRS management guidelines established
- Long-term persistence of CTL019 cells
  - First pediatric patient treated has been in remission for 5 years

CTL019: Successful execution of a global cell therapy trial

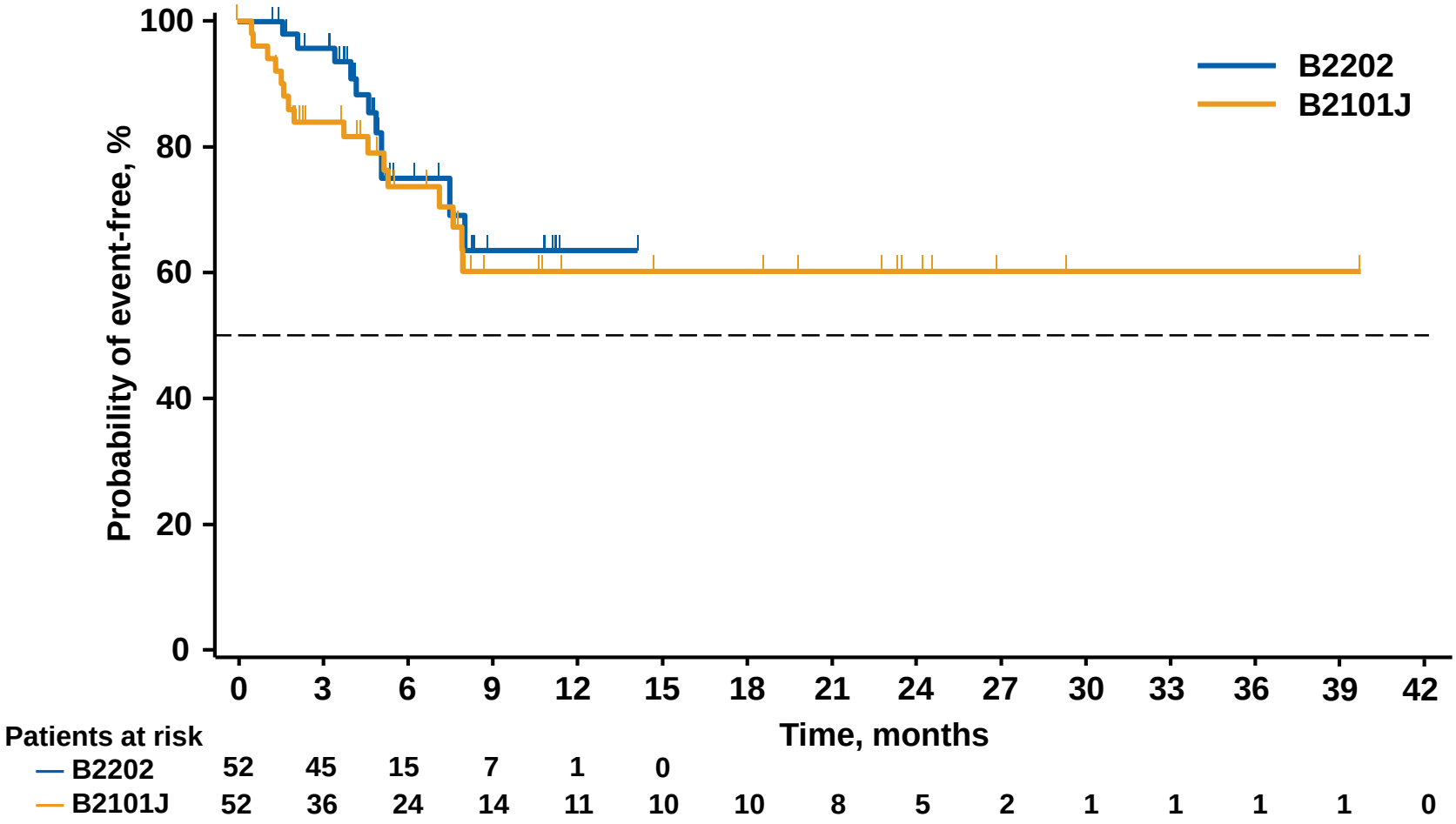
- Study B2202
  - First global, multicenter trial
  - First with a global supply chain
- ORR: 83% CR/CRi
  - Efficacy was similar compared with the single-institution trial
  - Safety was consistent with the single-institution trial
    - Clear toxicity management program
    - Comprehensive site training

CTL019 is associated with durable remission in Study B2202

- All patients who achieved BOR as CR or CRi (83%) also achieved bone marrow MRD-negative remission
- Median DOR has not been reached, with estimated 6-month DOR of 75% as assessed by IRC



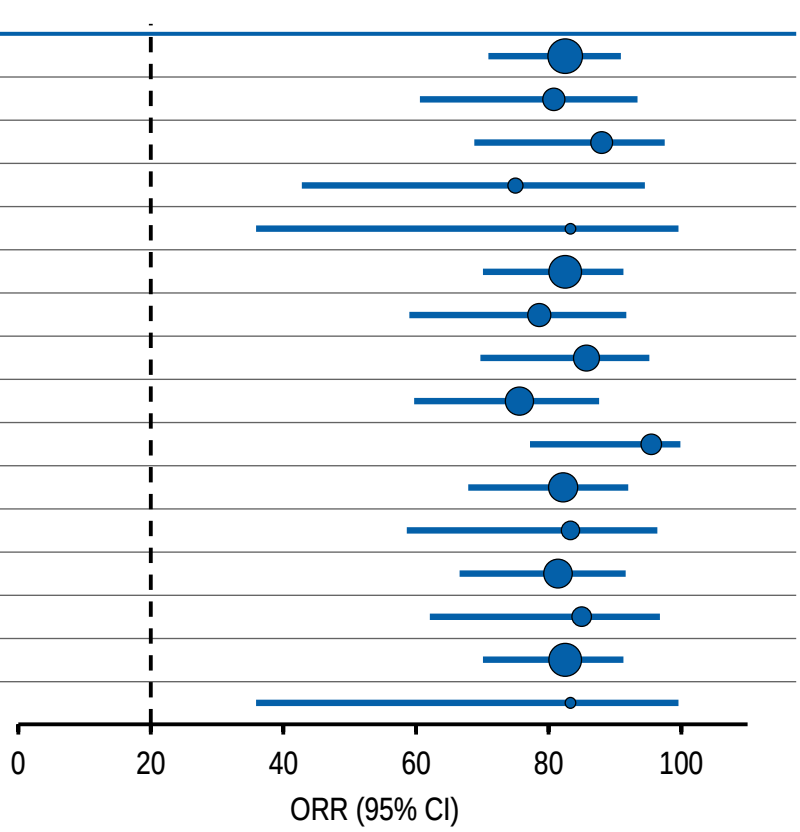
DOR in B2202 and B2101J



Children's Hospital of Philadelphia

CTL019 benefit regardless of patient characteristics Study B2202

		n
Overall		63
Age	<10	26
	≥10- <18	25
	≥18	12
Response status at study entry	Primary refractory	6
	Relapsed disease	57
Prior SCT therapy	No	28
	Yes	35
Enrollment bone marrow tumor burden	High	41
	Low	22
Complex karyotypes (≥5 unrelated abnormalities)	No	45
	Yes	18
Any high-risk mutations	No	43
	Yes	20
Down syndrome	No	57
	Yes	6



CTL019 adverse events: Cytokine release syndrome (CRS)

- CRS is common and expected with CTL019 adoptive T-cell therapy
  - Spectrum of symptoms from fever and myalgias to significant clinical instability
- Prognostic factors for severe CRS
  - High pre-infusion tumor burden
  - Early onset of fever or CRS
- CRS grading scale and CRS management algorithm are available and have been successfully employed across multiple trial sites and countries
  - IL-6 blockade is the centerpiece of CRS management

CTL019 adverse events: Neurologic

Neurologic events are reported with CTL019 adoptive T-cell therapy

- Can be concurrent with high fever (during CRS) or delayed (after CRS has resolved); the incidence increases with severe CRS
- Symptoms: headaches, confusion, irritability, seizures, and encephalopathy
- Managed with supportive care
  - Workup to rule out other causes such as bleeding, infection, and CNS leukemia should be considered
- Majority of events are self-limited and resolve without intervention

CTL019 adverse events: Neutropenia and infections

- Febrile neutropenia is common in these patients
  - Usually occurs concurrent with CRS
  - Evaluate for infection and manage with broad-spectrum antibiotics
- Prolonged neutropenia (ongoing >28 days after CTL019 infusion)
  - Pre-existing severe neutropenia can predispose to prolonged cytopenias after CTL019
  - Severe infections are observed in 20% to 30% of these patients
- Infections are observed before and after CTL019 infusion
  - Patients with B-cell aplasia leading to low immunoglobulin levels may experience an increased risk of infections
    - Immunoglobulin replacement indicated

Patient example

- 12-year-old female, diagnosed at age 7 with high-risk ALL, WBC 68K, CNS negative
- Relapsed 3 months off ALL therapy →
  - Second remission, unrelated donor (URD) BMT, mild GVHD
- 2-year post-BMT experienced second relapse
  - No response to re-induction with 3 regimens
- Enrolled with active disease and infused with CTL019 (20% ALL on enrollment marrow)
  - MRD-negative CR on D28 with excellent CTL019 proliferation
  - Remains in remission with functional persistence (B-cell aplasia, 0% CD19) >1 year

Clinical perspective

- Urgent need for higher rates of durable remissions
  - Refractory disease, multiple therapies, comorbidities, no other treatment options
- CTL019 results in
  - High remission rate
  - Deep remission: all responding patients are MRD negative
  - Transplant can become an option for these patients
    - Risks associated with transplant are significant
  - However, durable clinical responses suggest patients may not need transplant to consolidate their remission
  - Predictable adverse events
  - Return to near-normal quality of life in responding patients
- CTL019 offers an important treatment option for pediatric and young adult patients with r/r B-cell ALL

Conclusion

David Lebwohl, MD

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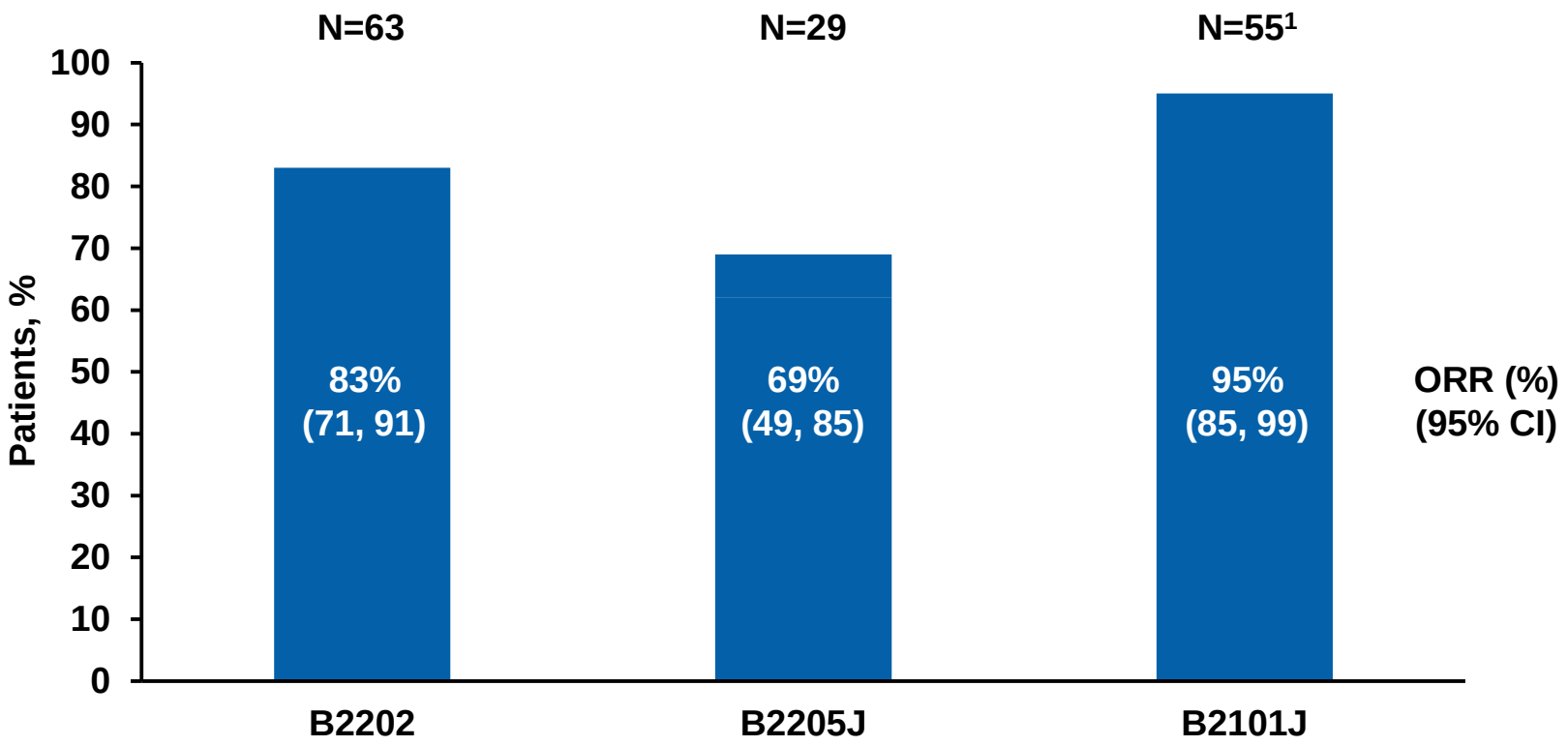
Novartis Pharmaceuticals Corp.

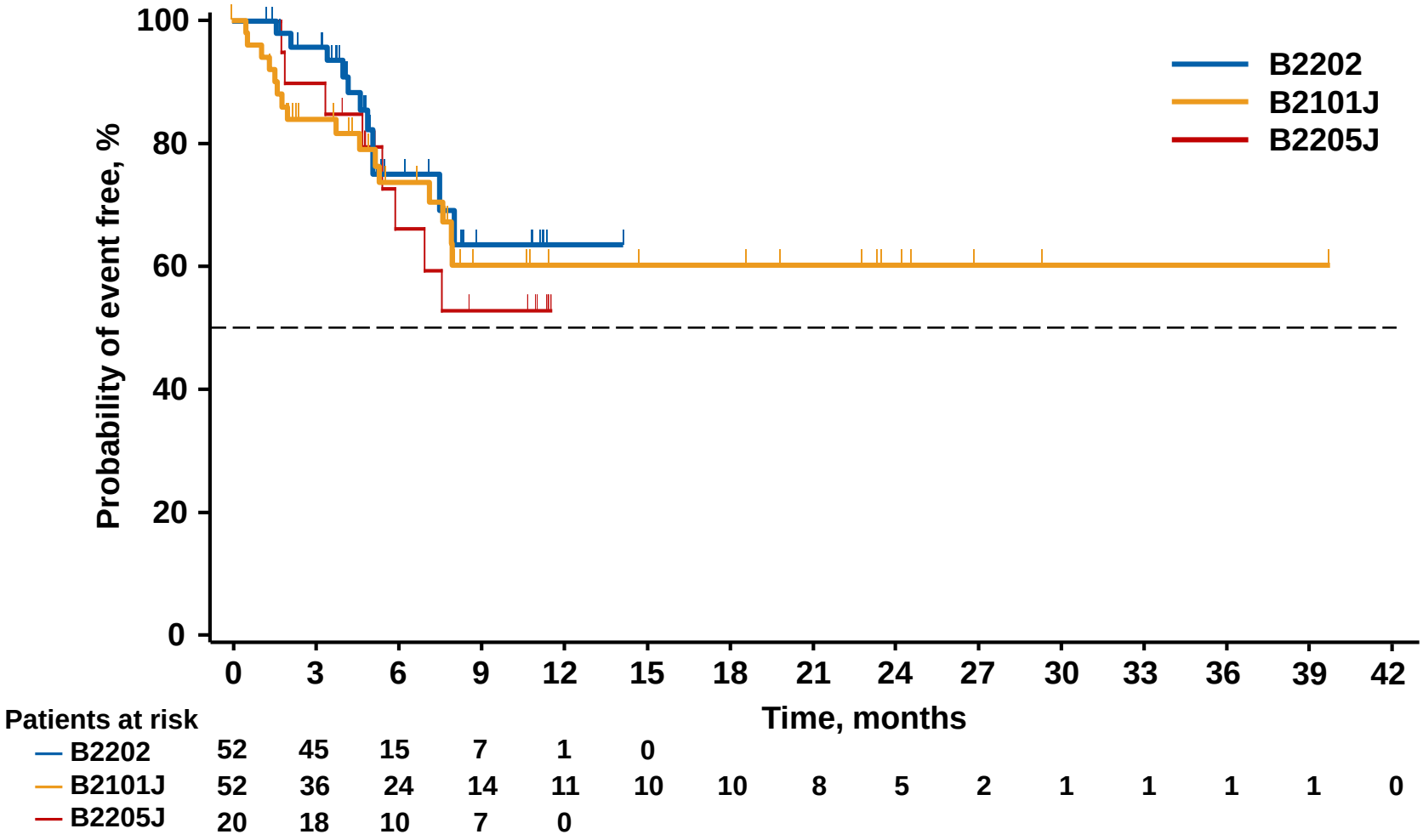
NOVARTIS

High overall remission rates across 3 trials



1. Overall remission rates at Day 28 in non-CNS3 ALL patients.

Durable remissions across 3 trials

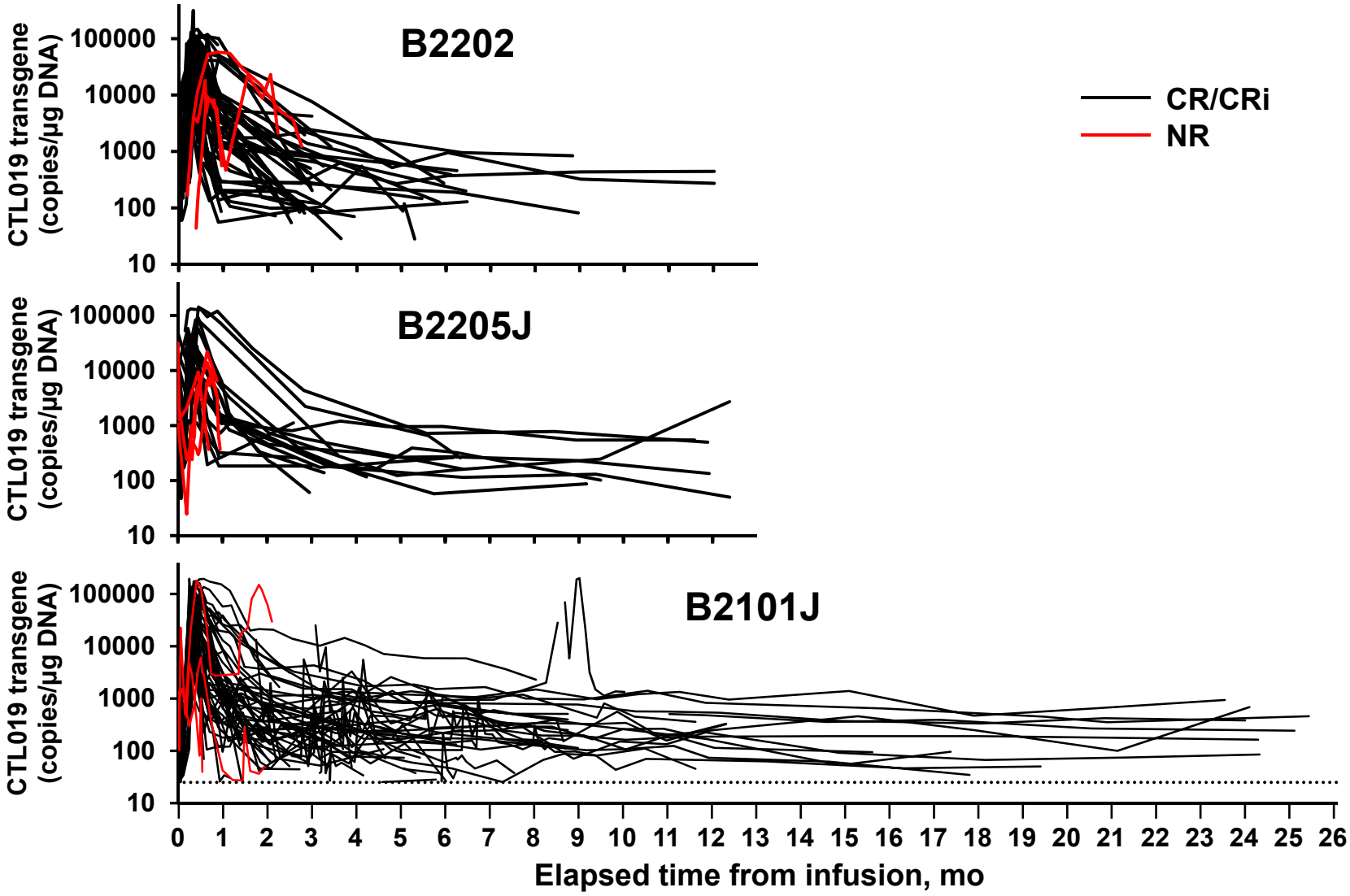


CTL019 has a positive benefit/risk profile in pediatric and young adult patients with relapsed/refractory B-cell ALL

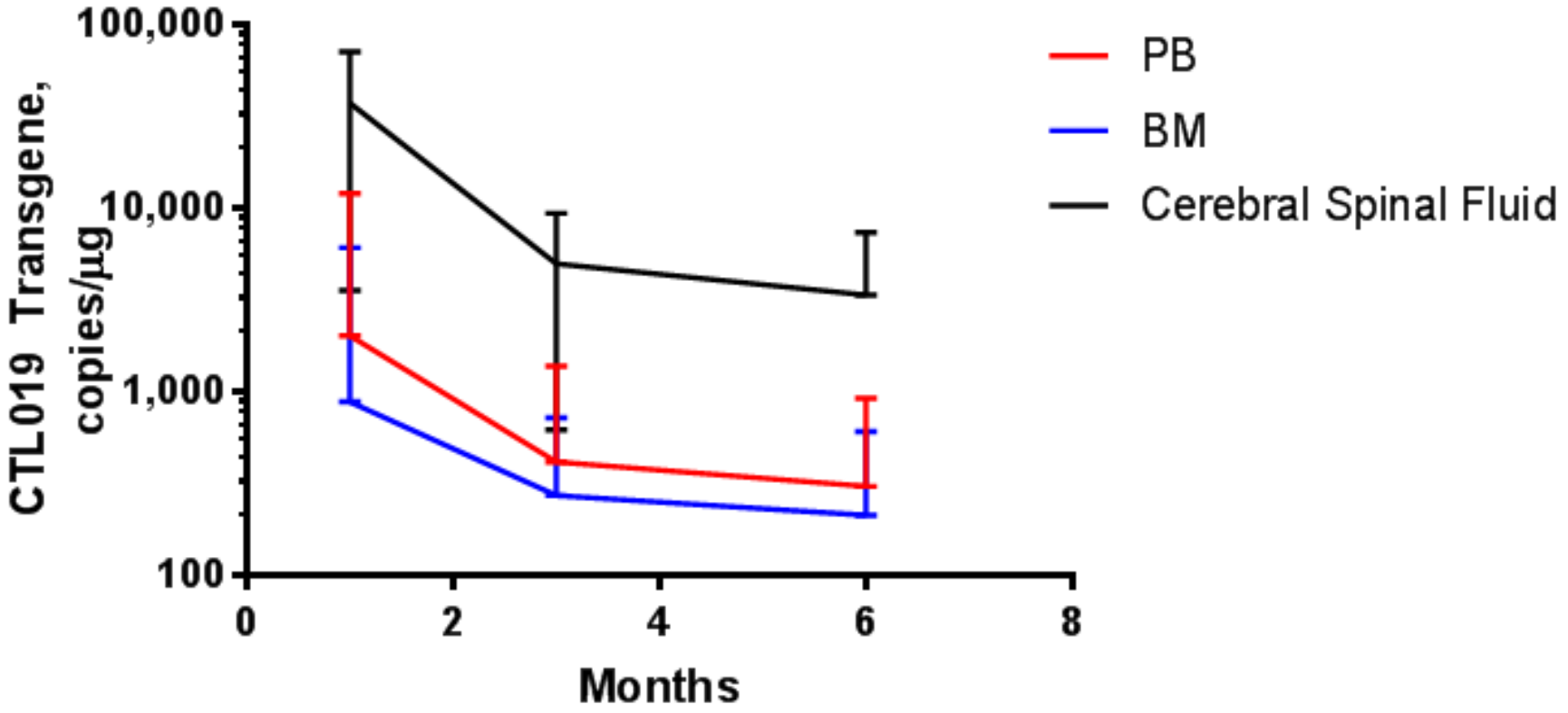
- Significant unmet need to improve outcomes in pediatric and young adult patients with r/r B-cell ALL
- Efficacy demonstrated in 3 clinical trials in more than 150 pediatric and young adult patients with r/r B-cell ALL
- High rate of durable complete remissions observed in the 3 trials without additional therapy in the majority of patients
  - Pivotal study B2202 demonstrated an 83% ORR
- Prolonged overall survival relative to currently available therapies
- Well-characterized and generally manageable safety profile with appropriate site training and some patients requiring ICU care
- Potentially definitive therapy with prolonged remissions and improved quality of life; many patients do not require further therapy

BACK UP SLIDES

CTL019 concentration in peripheral blood over time (B2202, B2205, B2101J)



CTL019 detectable in multiple matrices at high levels (B2101J)



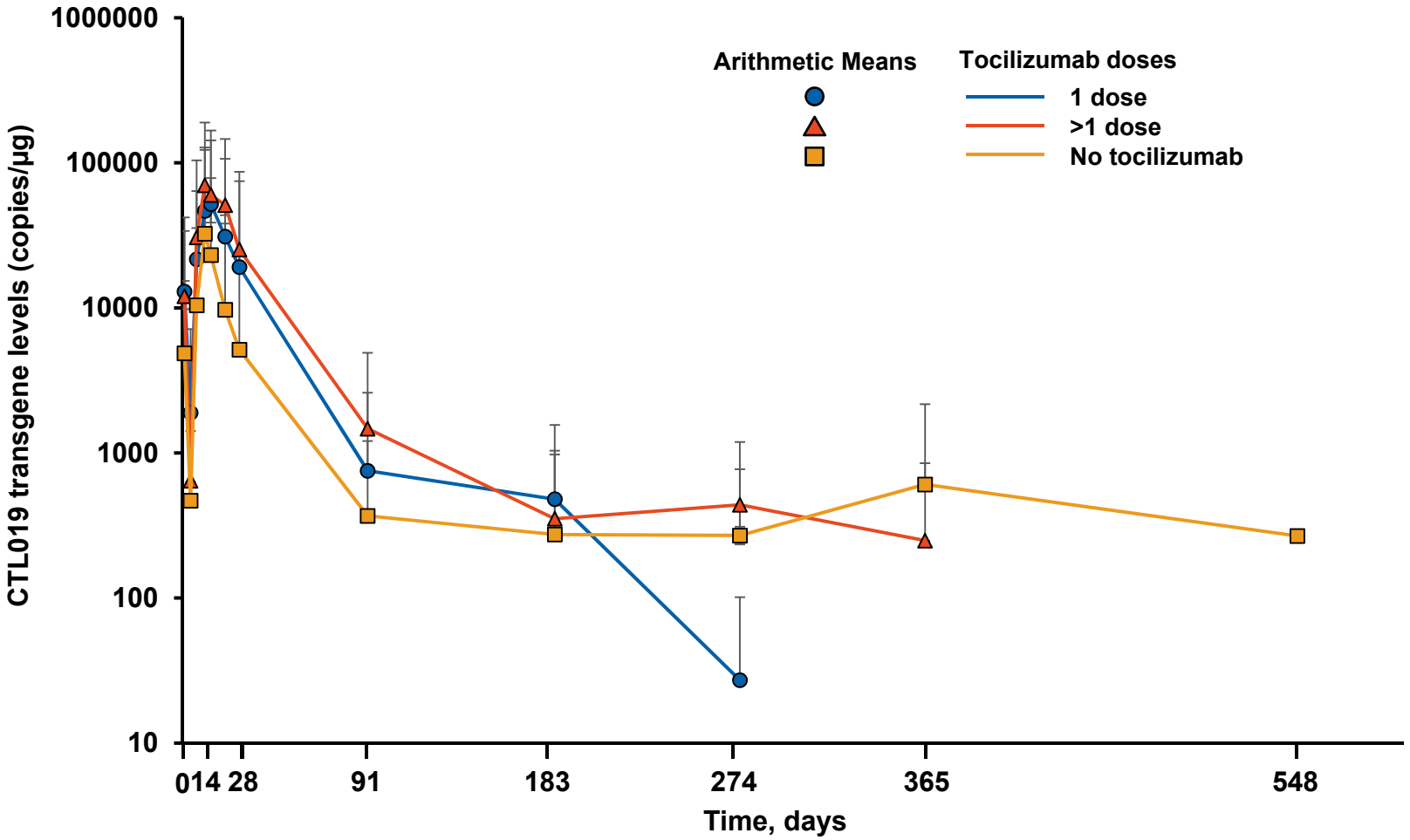
PB=peripheral blood; BM=bone marrow.

B2202 CTL019 dose infused

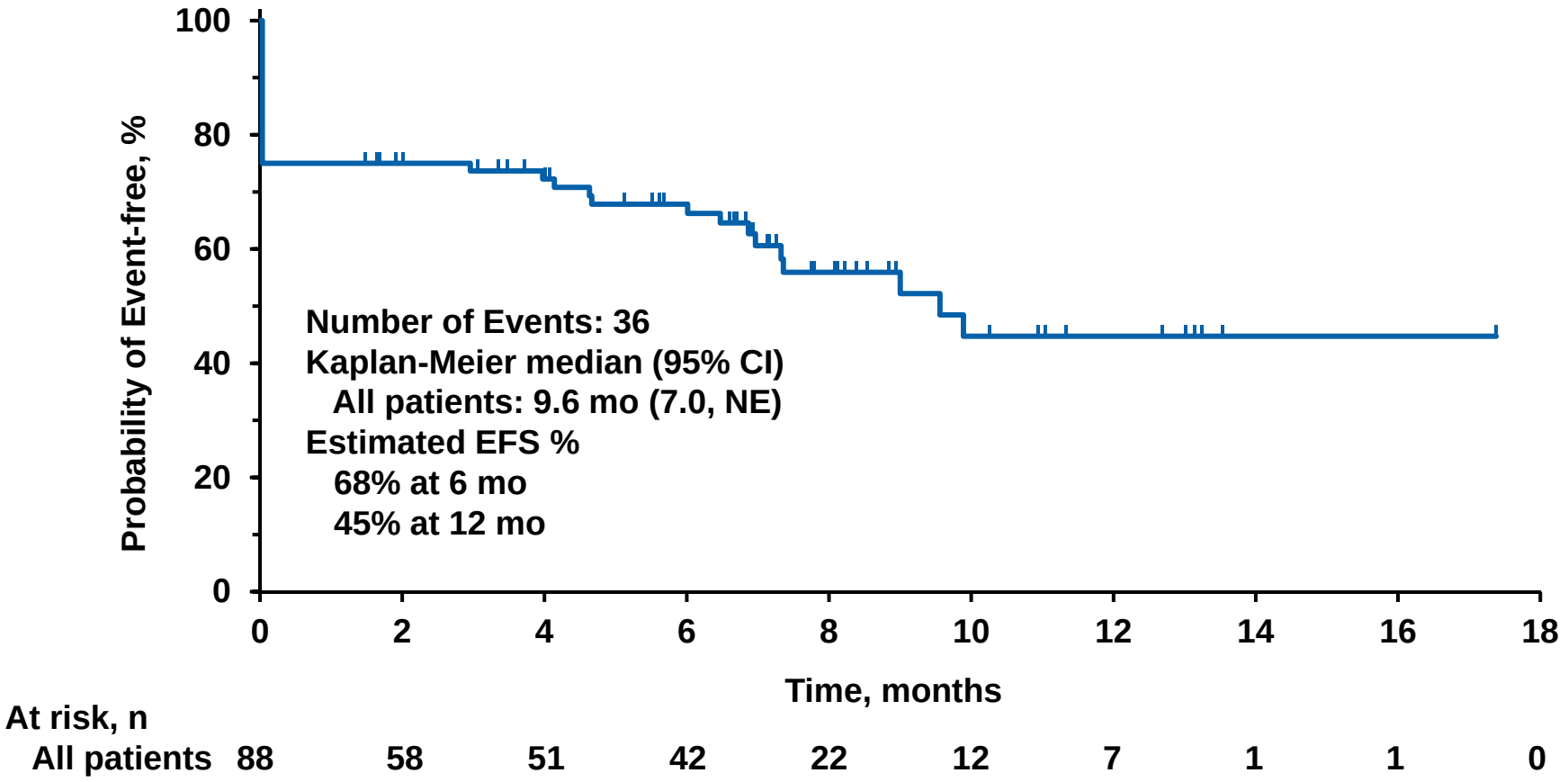
Description	All patients N=68
CTL019 transduced cell dose infused (10^8 cells)	
Mean (SD)	1.15 (0.622)
Median	1.00
Min-Max	0.03-2.60
Weight adjusted CTL019 transduced cell dose infused (10^6 cells/kg)	
Mean (SD)	2.88 (1.121)
Median	3.00
Min-Max	0.2-5.4
Patients >50 kg CTL019 transduced cell dose infused (10^8 cells) (n=22)	
Mean (SD)	1.58 (0.61)
Median	1.85
Min-Max	0.2-2.39
Patients ≤50 kg CTL019 transduced cell dose infused weight (10^6 cells/kg) (n=46)	
Mean (SD)	3.08 (1.18)
Median	3.07
Min-Max	0.192-5.42

1. The target dose range is 2 to 5x10^6 CTL019 transduced cells/kg for patients ≤50 kg, and 1 to 2.5x10^8 CTL019 transduced cells for patients >50 kg.

CTL019 transgene concentration time profile by number of doses of tocilizumab (B2202 and B2205J)



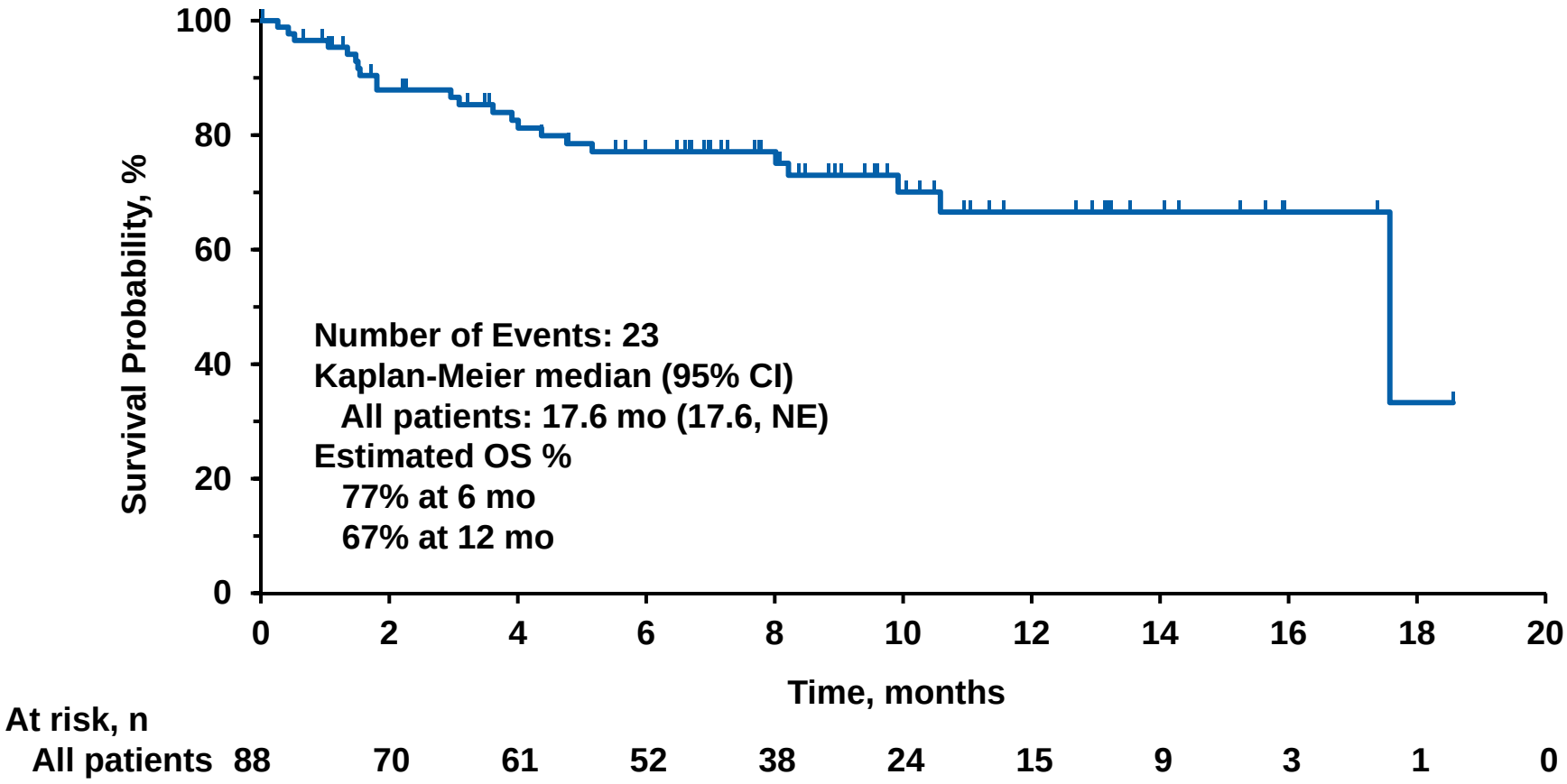
Event-free survival—enrolled Set Study B2202



EFS defined as time from enrollment to the earliest of treatment failure, relapse or death.

- 68 patients infused with CTL019
- 4 patients were pending CTL019 infusion (censor at Day 1)
- 16 patients were enrolled but discontinued without CTL019 infusion (event at Day 1)
  - Manufacturing failure (n=7), death (n=6), AE (n=3)

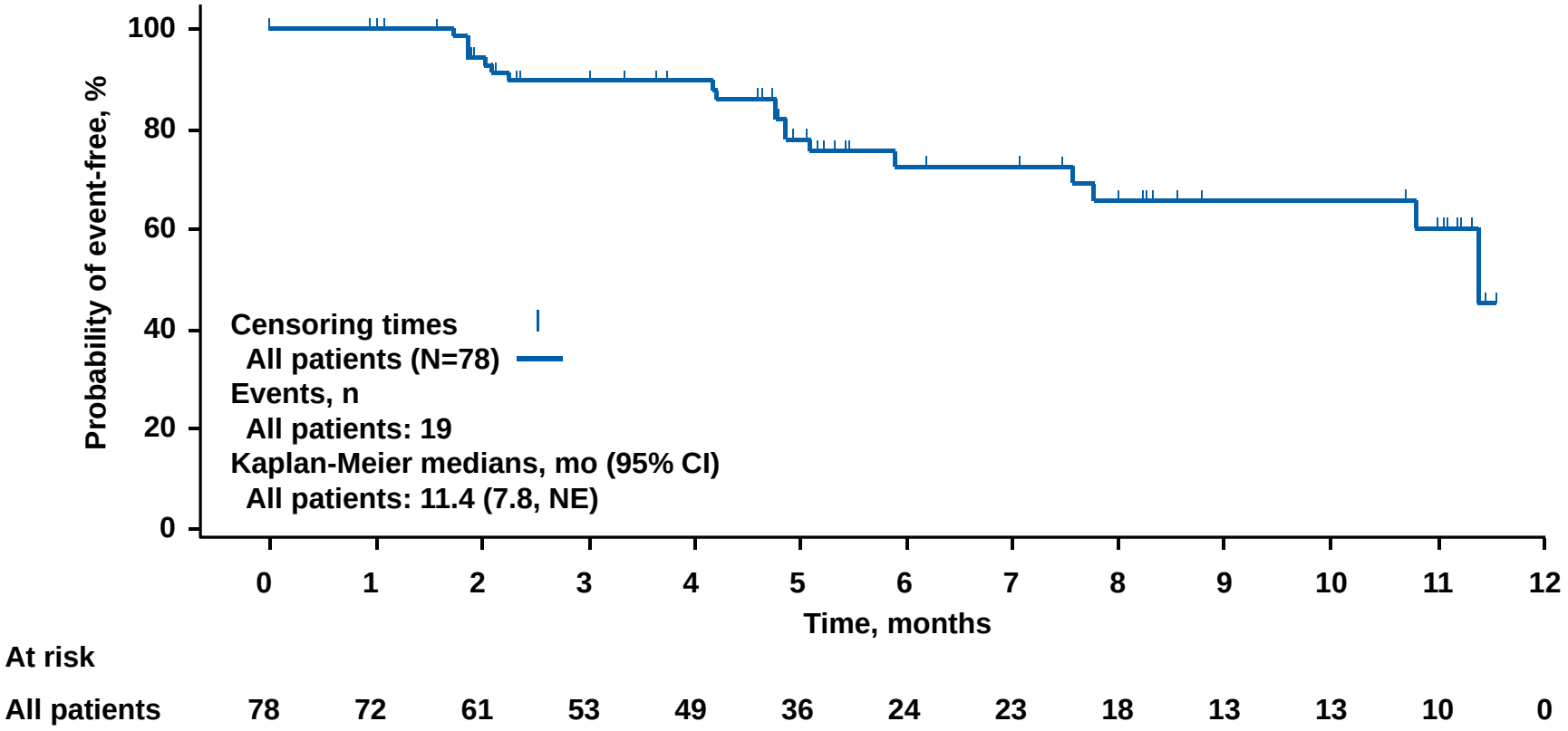
Overall survival—enrolled Set Study B2202



OS defined as time from enrollment to death, or censored at last known alive.

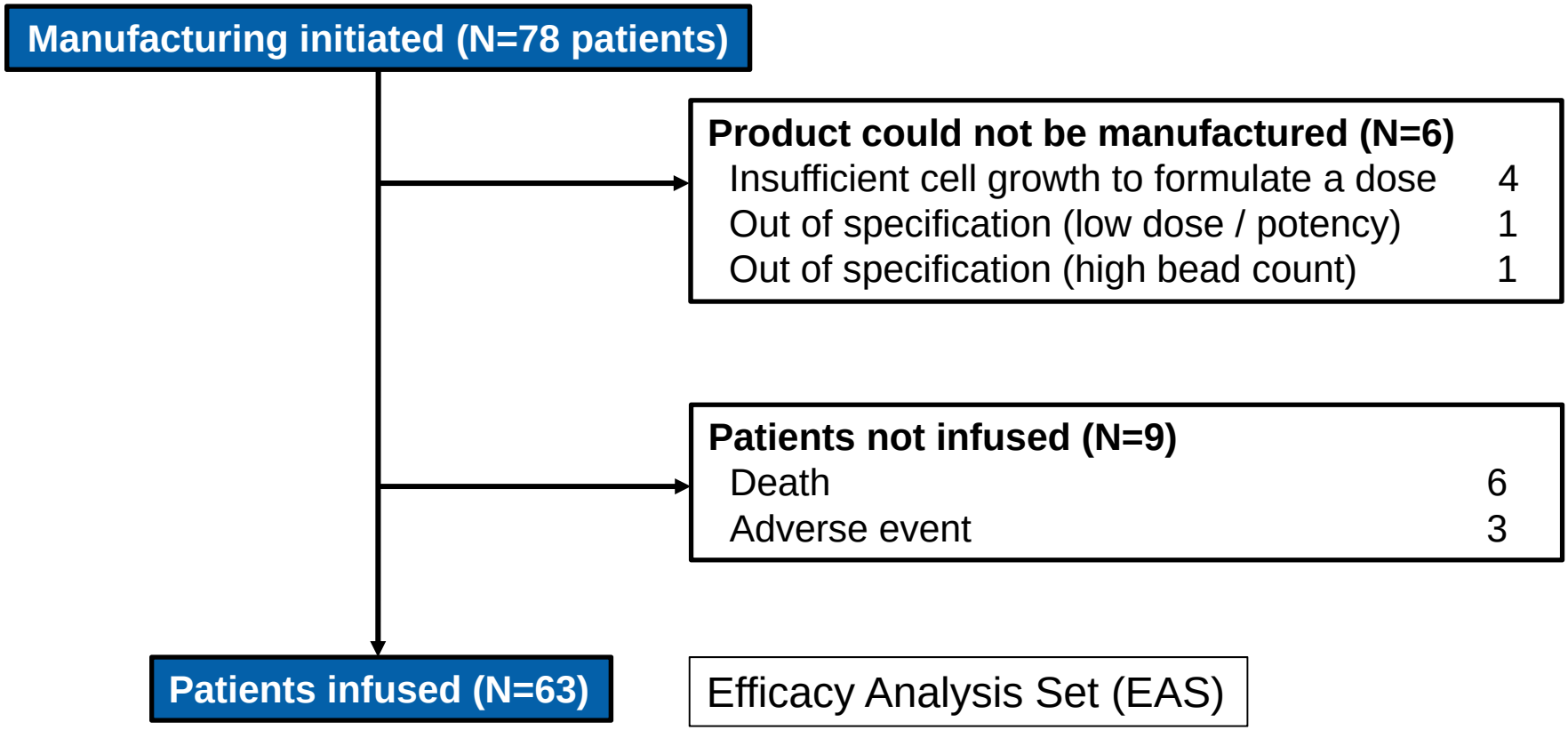
- 12 patients died prior to CTL019 infusion
- 11 patients died post CTL019 infusion

Time to B-cell recovery among patients who achieved response at any time Studies B2202 and B2205J



- B cell recovery time = time from onset of remission to percentage of CD19+ total B cell among viable WBC in blood is ≥1%

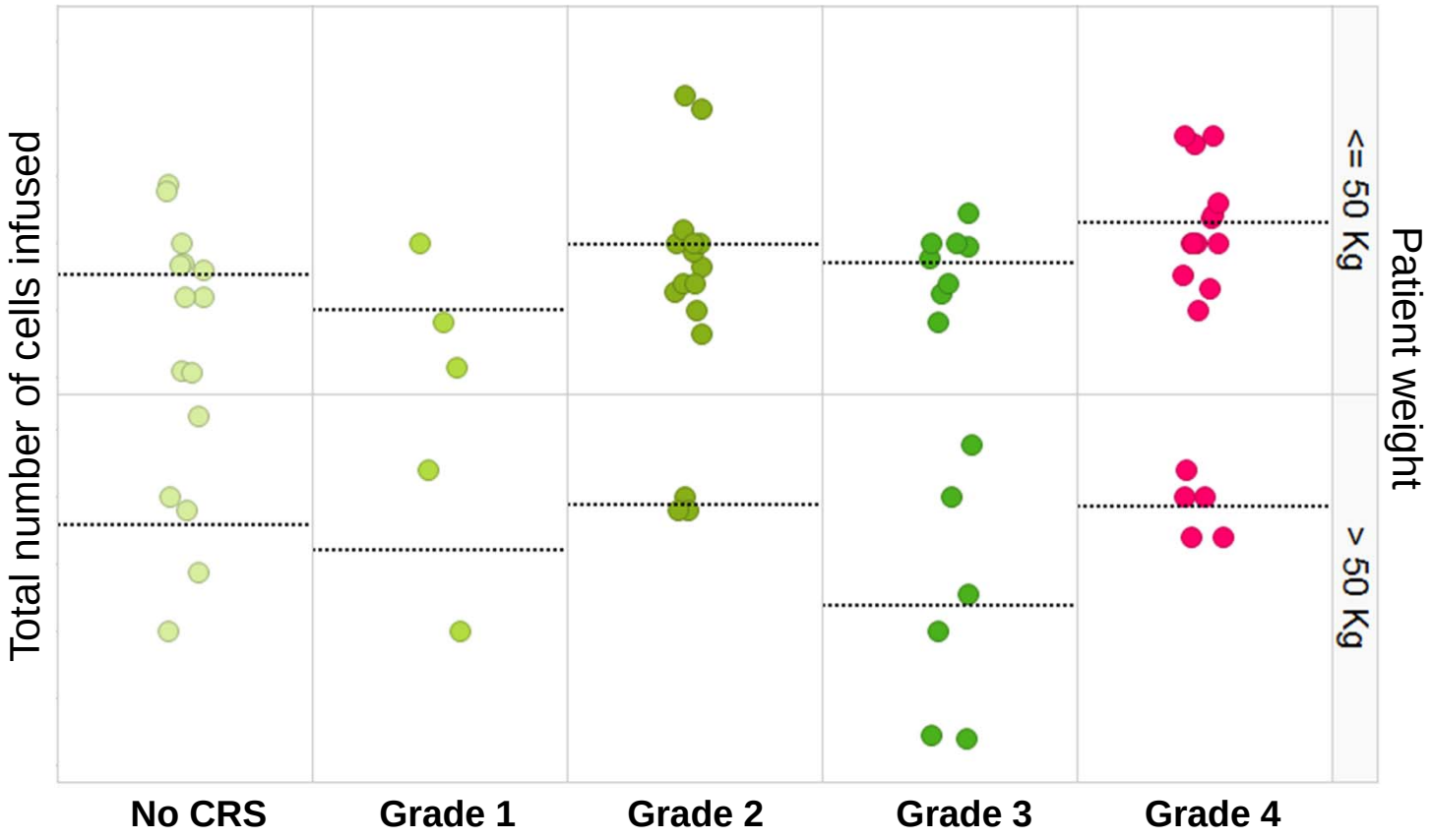
MP manufacturing Study B2202



Optimized end-to-end throughput time at launch is 22 days

Actions	Duration
1. Receive leukapheresis material (Day 0)	1 day
2. Core manufacturing	10-11 days
3. Testing and disposition	9 days
4. Pack and ship	1 day
Total throughput time	22 days

No correlation between CRS and total number of cells infused



Pediatric ALL/B2202 – 68 patients [15-No CRS, 5-Gr1, 16-Gr2, 14-Gr3, 18-Gr4].