Chimeric Antigen Receptor (CAR) Modified T Cell Therapy: *Meeting the Unmet Need in Follicular Lymphoma*

Stephen J. Schuster, M.D.

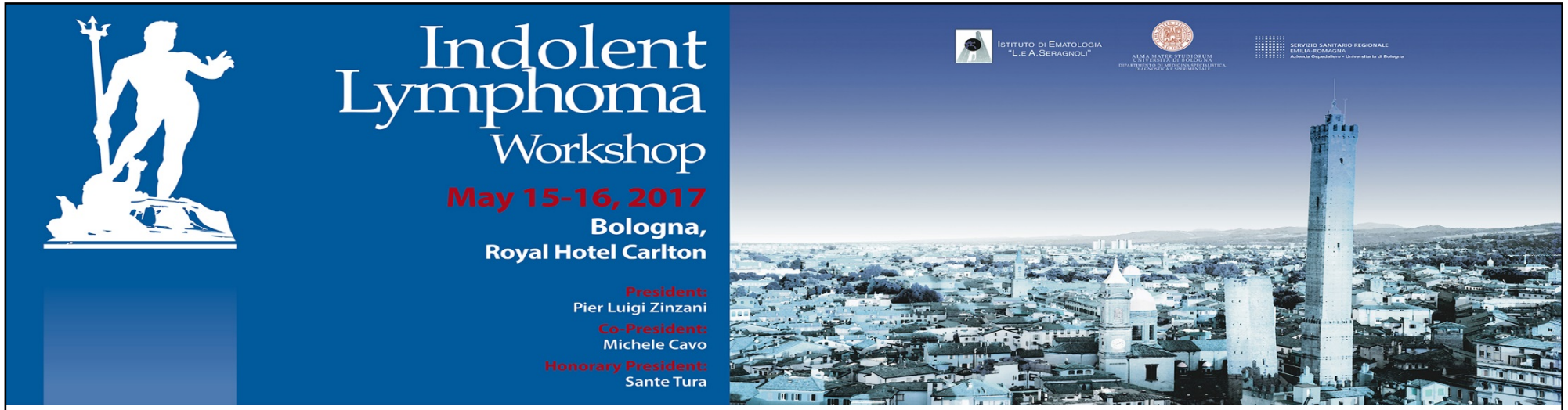
Director, Lymphoma Program & Lymphoma Translational Research,
Abramson Cancer Center

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

UNIVERSITY OF PENNSYLVANIA
Abramson Cancer Center

INDOLENT LYMPHOMA WORKSHOP

Bologna, Royal Hotel Carlton
May 15-16, 2017

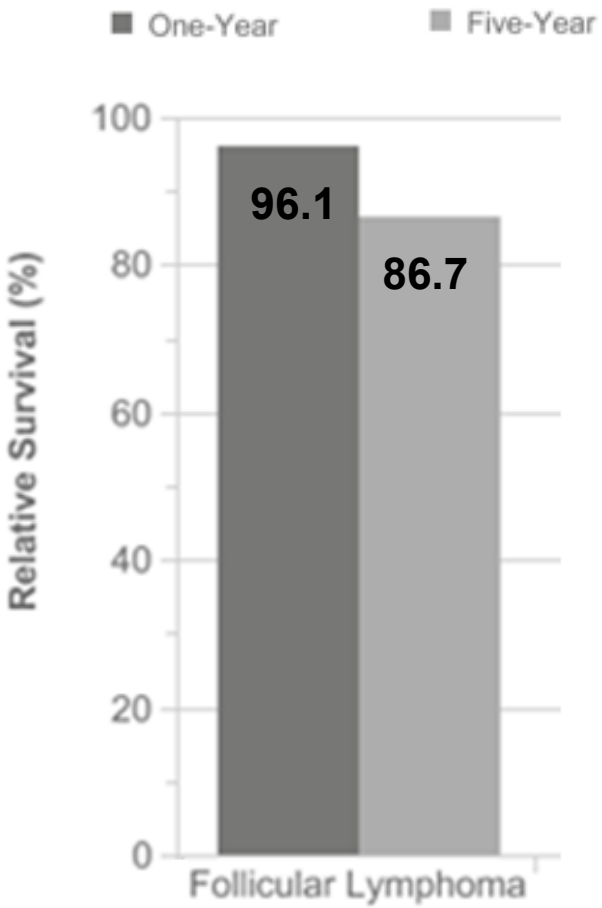


Disclosures of Stephen J. Schuster, MD

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Celgene	X		X			X	Steering Committee
Merck	X		X			X	
Pharmacyclics	X		X			X	Steering Committee
Novartis	X		X			X	
Genentech	X		X			X	
Seattle Genetics	X		X			X	
Nortic Nanovector			X			X	Scientific Advisory Board
Adaptive	X						
Janssen	X		X			X	
Bristol Meyers Squibb	X						
Kite Pharma	X						

Non Hodgkin Lymphomas in the Real World

One- and Five-Year Relative Survival (%), All Ages, 2004-2011



Haematological Malignancy Research Network (HMRN)

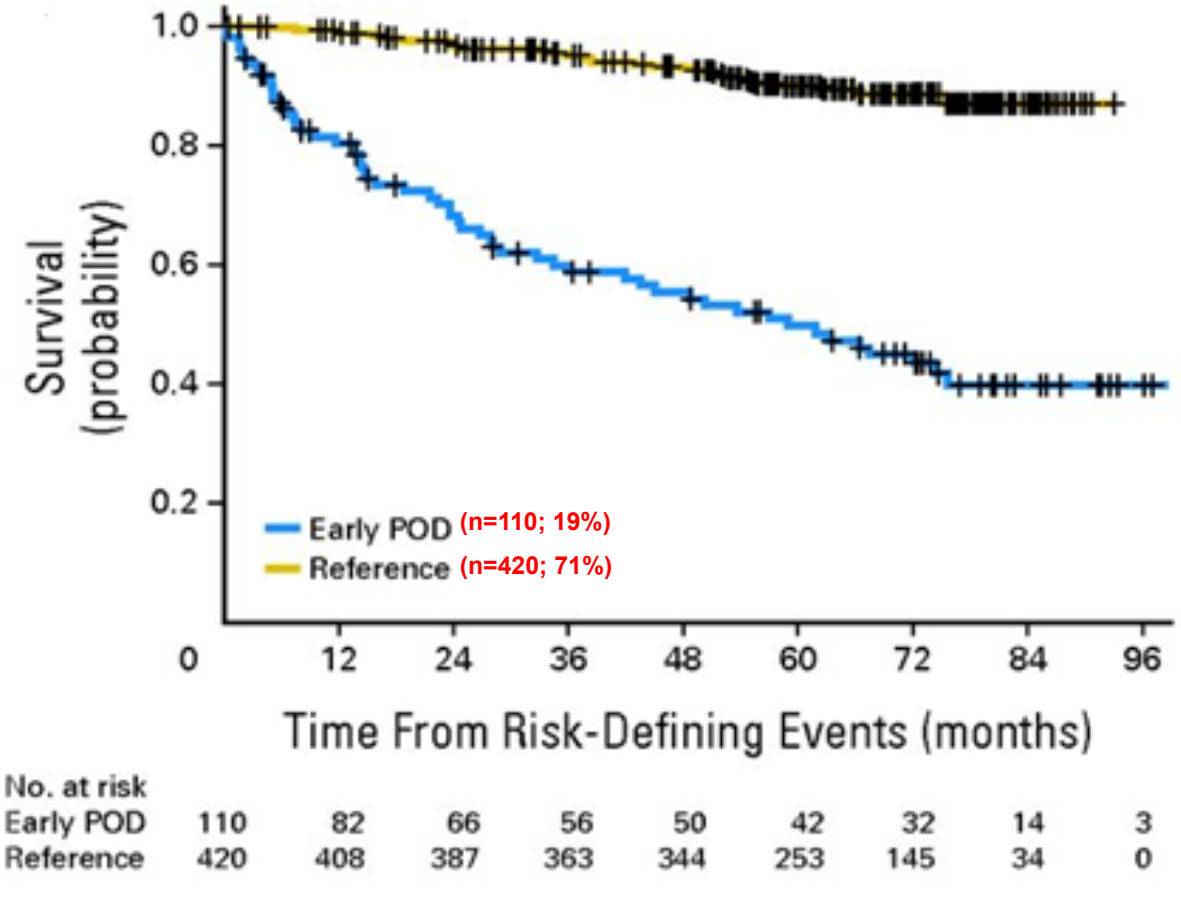
CANCER RESEARCH UK

http://info.cancerresearchuk.org/cancerstats/faqs/#How

30 Nov 2015

Follicular Lymphoma: Unmet Need

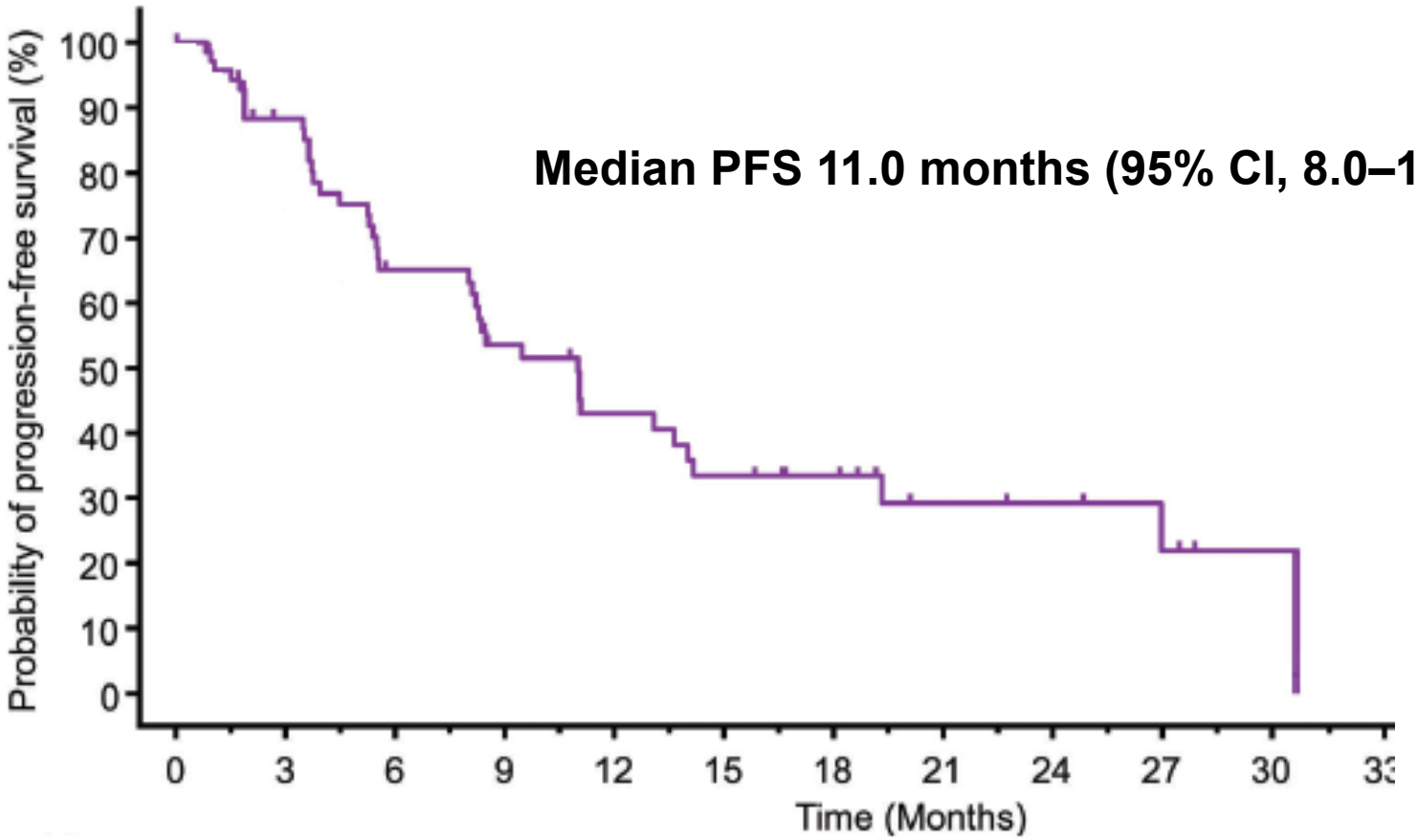
5 year survival lower in the *early-POD group* than reference group: 50% *vs* 90%



Casulo et al. JCO doi:10.1200/JCO.2014.59.7534

30 Nov 2015

Idelalisib in relapsed, rituximab- and alkylating agent-refractory follicular lymphoma: PFS

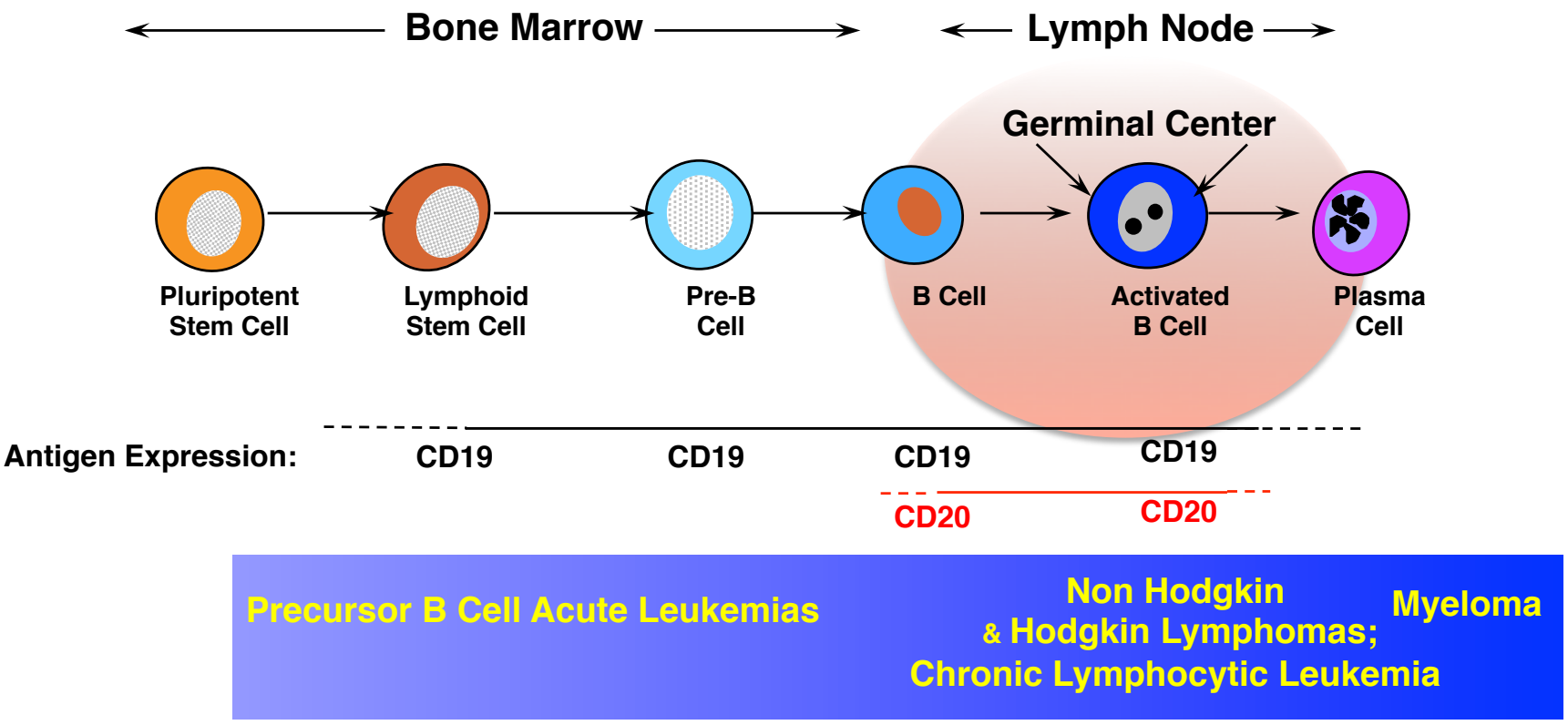


Median PFS 11.0 months (95% CI, 8.0–14.0)

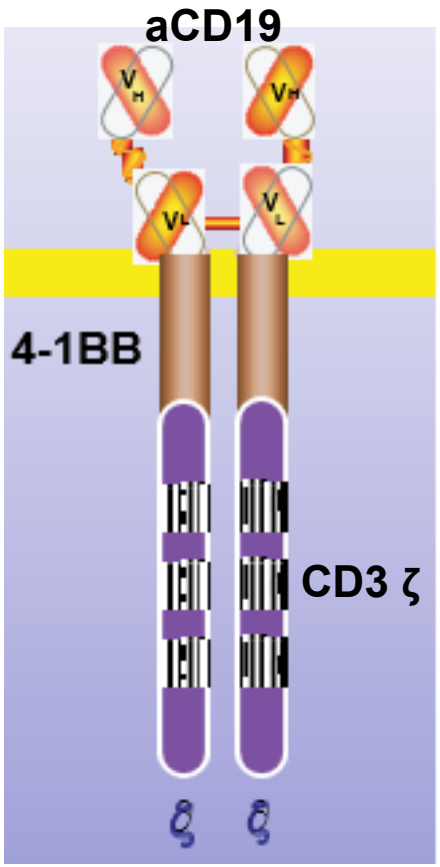
Salles G, et al Haematologica 2017;102(4).

CD19: An Ideal Target for B Cell Malignancy

Normal B Cell Life Cycle and Related B Cell Malignancy



Chimeric Antigen Receptor for CD19 (CTL019)

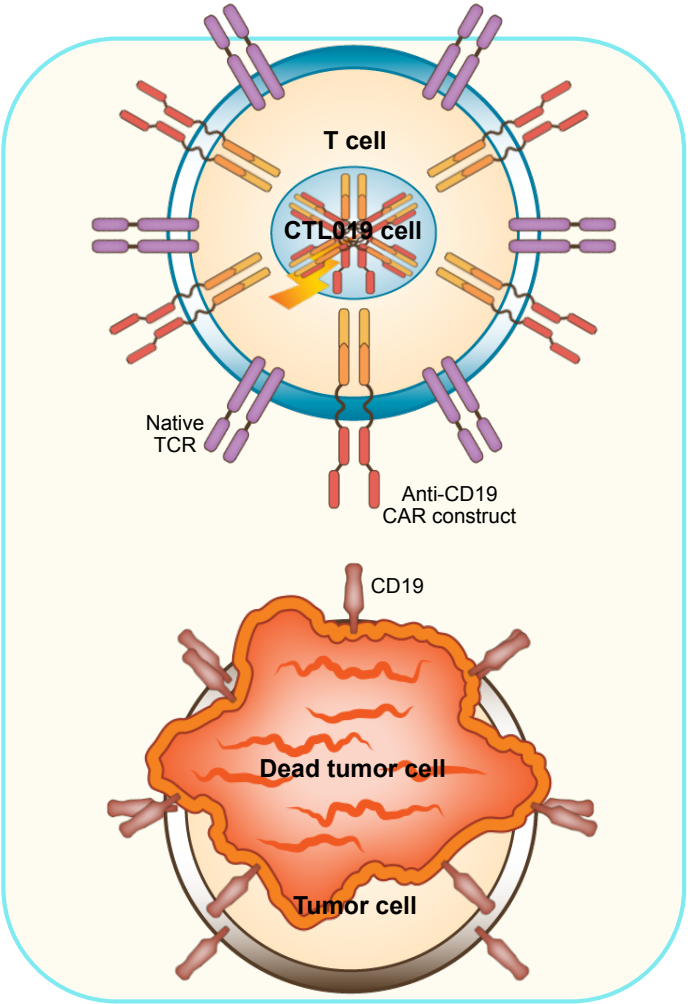


Extracellular domain
- FMC63 **mouse** hybridoma derivative

Intracellular domain
- Fusion protein

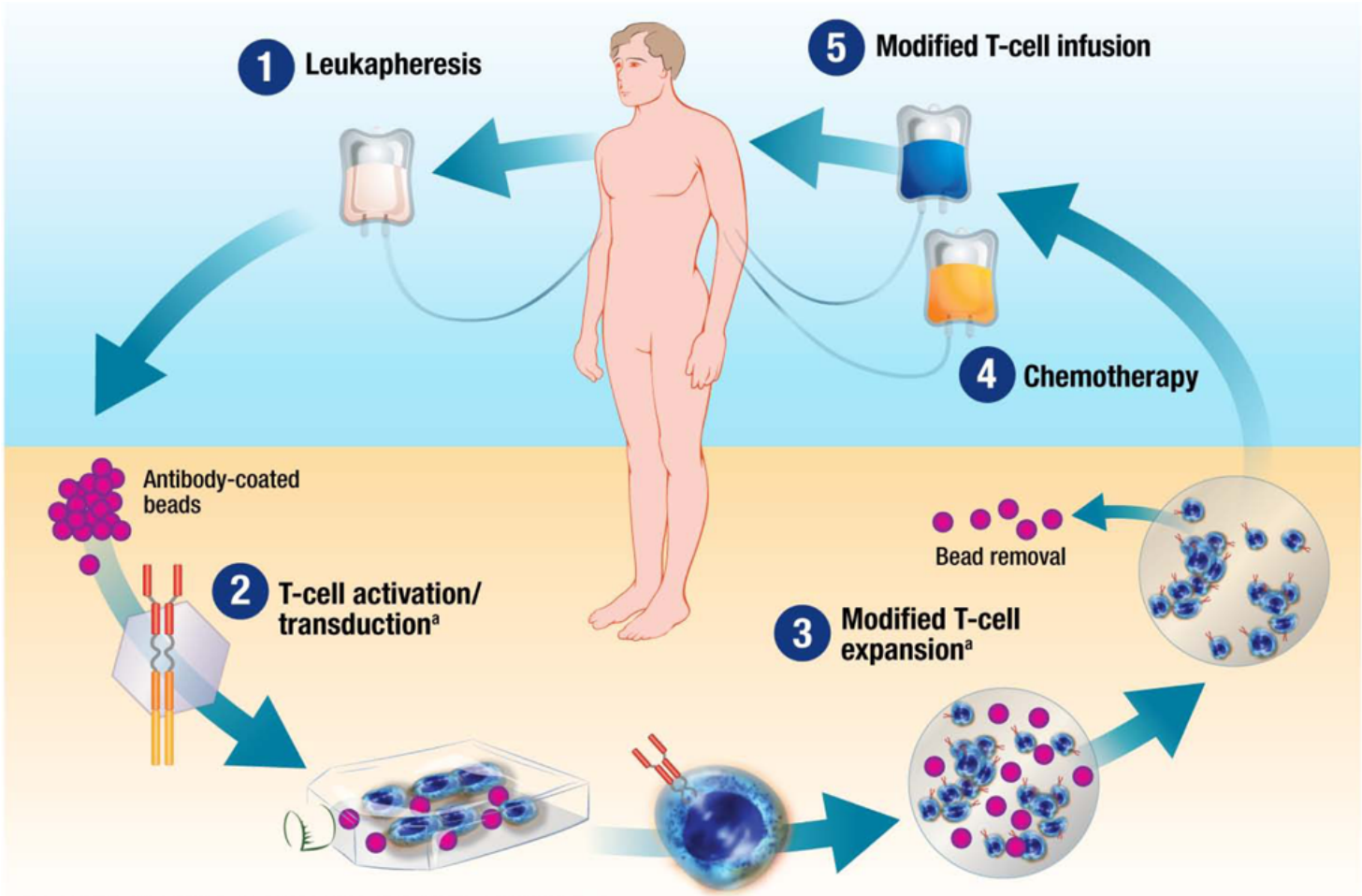
Redirecting the Specificity of T cells

- Gene transfer technology stably expresses CARs on T cells[1,2]
- CAR T cell therapy takes advantage of the cytotoxic potential of T cells, killing tumor cells in an *antigen-dependent* manner[1,3]
- Persistent CAR T cells consist of both effector (cytotoxic) and central memory T cells[3]
- **T cells are *non-cross resistant* to chemotherapy**



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.

Overview of CTL019 Therapy



T cells transduced ex vivo with a lentivirus encoding anti-CD19 scFv linked to 4-1BB and CD3-ζ signaling domains

CTL019 in Relapsed or Refractory CD19+ NHL Study Design: Hypothesis and Objectives

Hypothesis:

- CAR modified T cells directed against CD19 (CTL019) will result in antitumor responses in patients with advanced CD19+ B-cell non-Hodgkin lymphomas

Primary Objectives:

- Determine overall response rate (ORR) at 3 months
- Determine response rate by lymphoma histology

Secondary Objectives:

- Determine CTL019 cell manufacturing feasibility
- Determine safety of CTL019 cells in NHL subjects
- Evaluate best response and progression-free survival
- Determine *in vivo* expansion of CTL019 cells

NCT02030834

CTL019 T Cells in Relapsed or Refractory CD19+ NHL: Study Design

Enrollment started Feb 2014

Key eligibility criteria: FL

- Adult histologically proven CD19+ relapsed or refractory FL
- FL with ≥2 prior CIT regimens and PD <2 years after prior therapy
- Measurable disease
- ECOG PS 0 or 1

Single IV dose of CTL019 cells, 1 - 4 days after lymphodepletion chemotherapy → Immunophenotypic, cytokine and molecular studies performed at pre-specified times after T cell infusion → Initial tumor response assessed 3 months after infusion using IWG response criteria

Collection of PB and BM samples

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; effects on B cells and CD19 expression in vivo

Schuster et al. ASH 2015. Abstract 183.
- NCT02030834

Protocol Schema

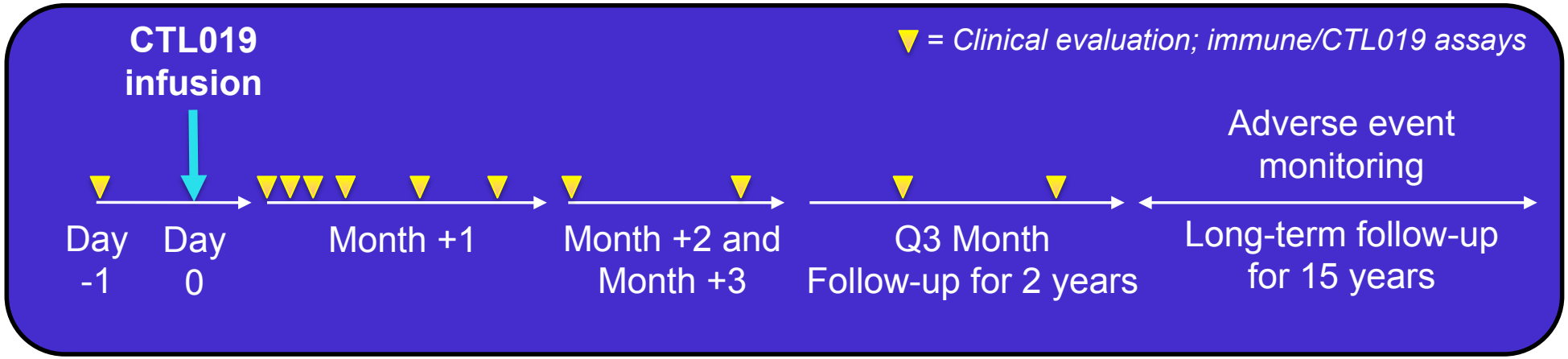
Apheresis
- Baseline immune assays

Bridging therapy
- Maintain stable disease while CTL019 was manufactured

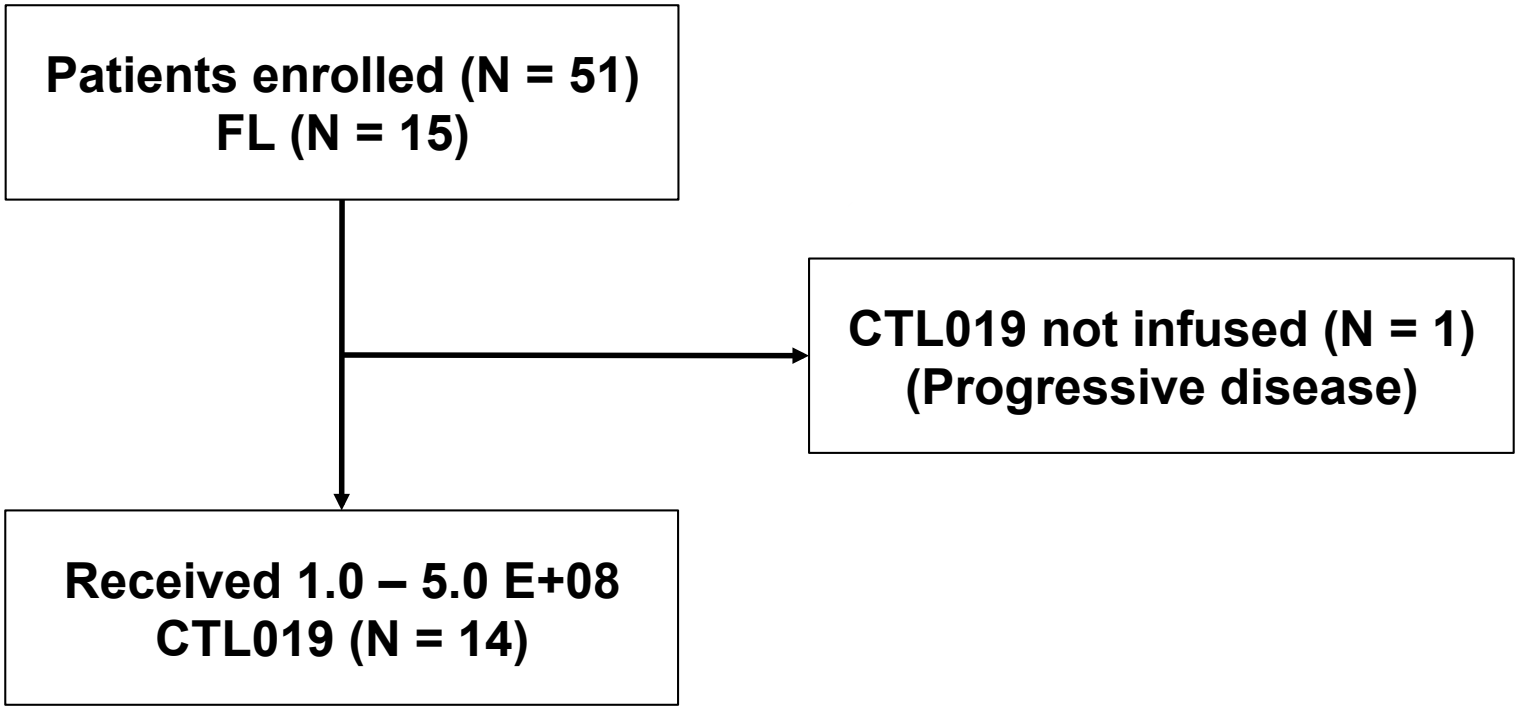
Restaging
- CT scans
- Bone marrow

Lymphodepleting therapy
- Physician's choice
- Decrease ALC
- End 1-4 days prior to CTL019

CTL019 Infusion, Monitoring and Response Assessments



Patient allocation



Results: High Risk Follicular Lymphoma

FL: Patient Characteristics (n = 15 enrolled; n = 14 infused)	
Median age	62 years (range 43 - 72)
Sex	7 (47%) men
Median prior therapies	5 (range 2 - 10)
• Prior R-CHOP/R-EPOCH	13 (87%)
• Prior R/O-bendamustine	11 (73%)
• Prior idelalisib	4 (27%)
• Prior transplant %	4 (27%)
Stage III – IV (enrollment)	13 (87%)
Increased LDH (enrollment)	10 (67%)
> 1 extranodal site (enrollment)	4 (27%)
Median ECOG PS (enrollment)	0 (range 0 – 1)

Chong, et al. ASH 2016. Abstract 1100.

Results: High Risk Follicular Lymphoma

FL: Lymphodepleting therapy (n = 14)

(n)	Regimen
6	bendamustine (90 mg/m^2) daily x 2
1	cyclophosphamide (200 mg/m^2) + fludarabine (20 mg/m^2) daily x 3
3	XRT (400 cGy) + cyclophosphamide (1 g/m^2)
1	cyclophosphamide (1 g/m^2)
1	cyclophosphamide (1.2 g/m^2) over 4 days
1	carboplatin + gemcitabine
1	modified EPOCH

Chong, et al. ASH 2016. Abstract 1100.

Response Rates: Follicular Lymphoma

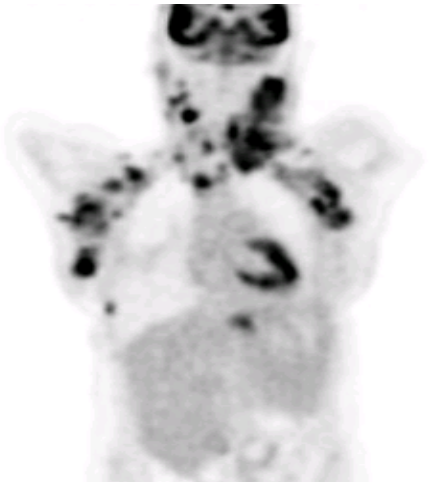
FL: ORR at 3 Months 79% (N = 14)	FL: Best Response Rate 79% (N = 14)
- CR: 7 - PR: 4 - PD: 3	- CR: 10 - PR: 1 - PD: 3

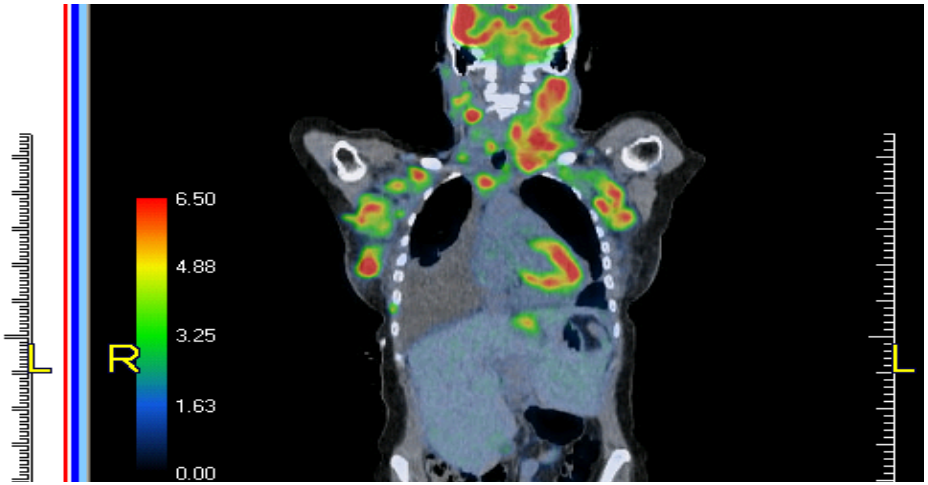
- 3 patients with PRs by anatomic criteria at 3 months converted to CRs by 6 months
- 1 patient with PR at 3 months who remained in PR at 6 and 9 months had PD at 12 months

Chong, et al. ASH 2016. Abstract 1100.

Follicular Lymphoma: 13413-19

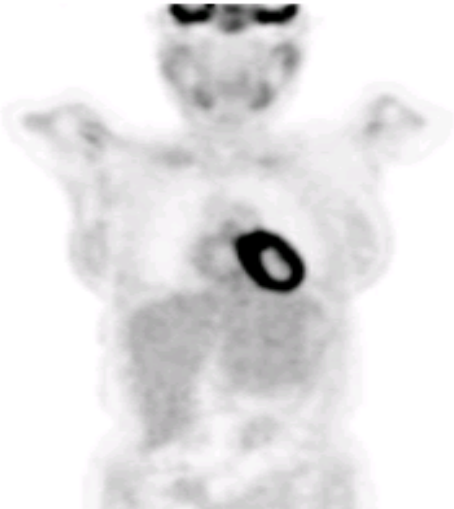
15 Oct 2014

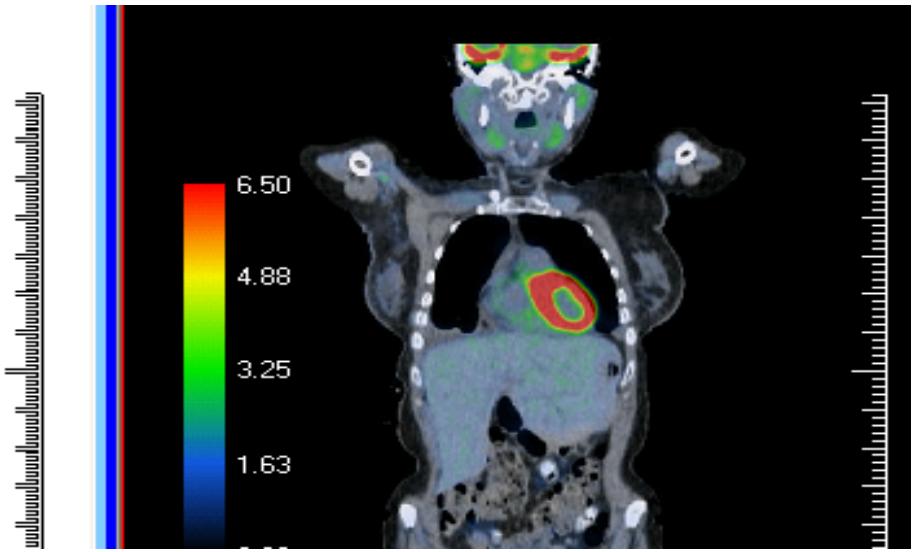




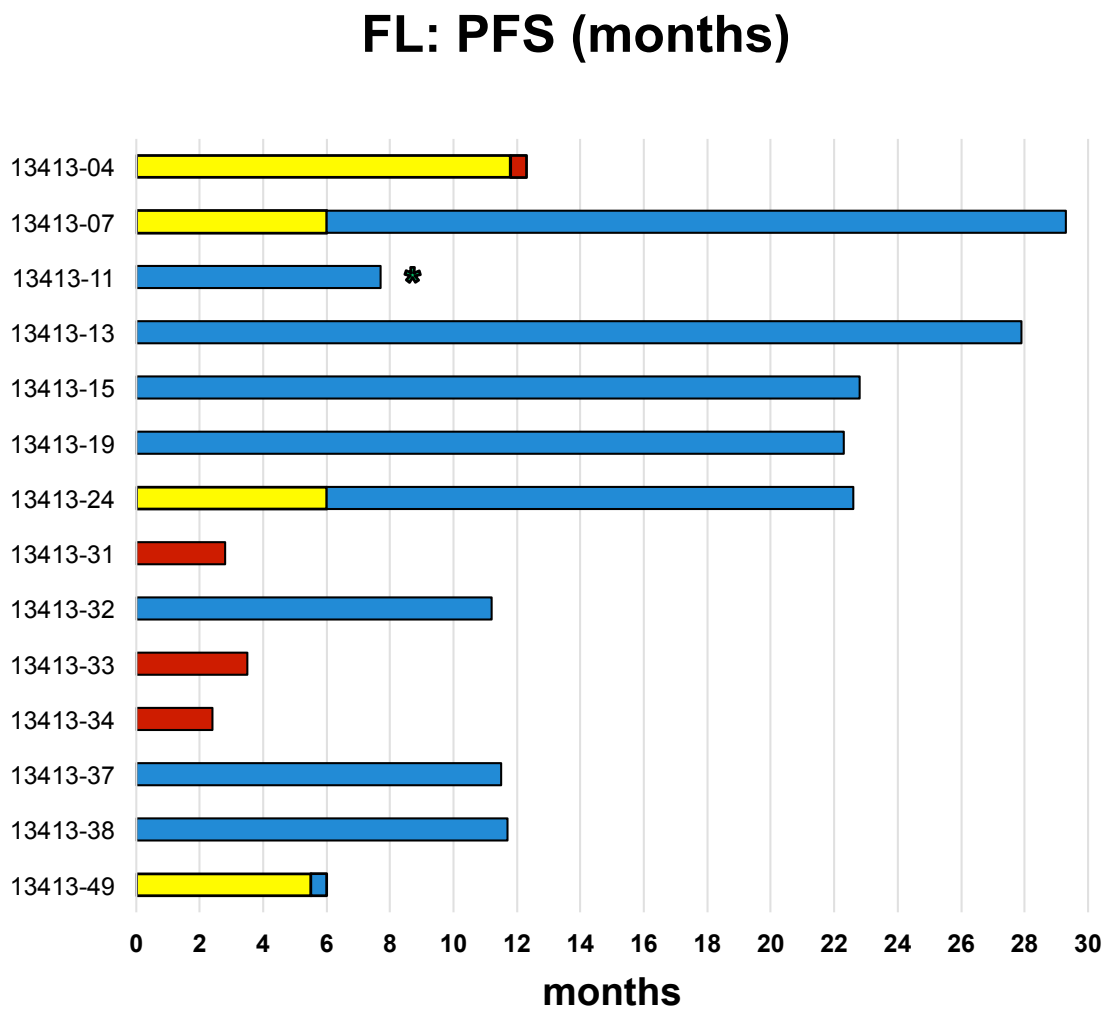
CTL019: 4 Nov 2014

3 Dec 2014





Results: Follicular Lymphoma

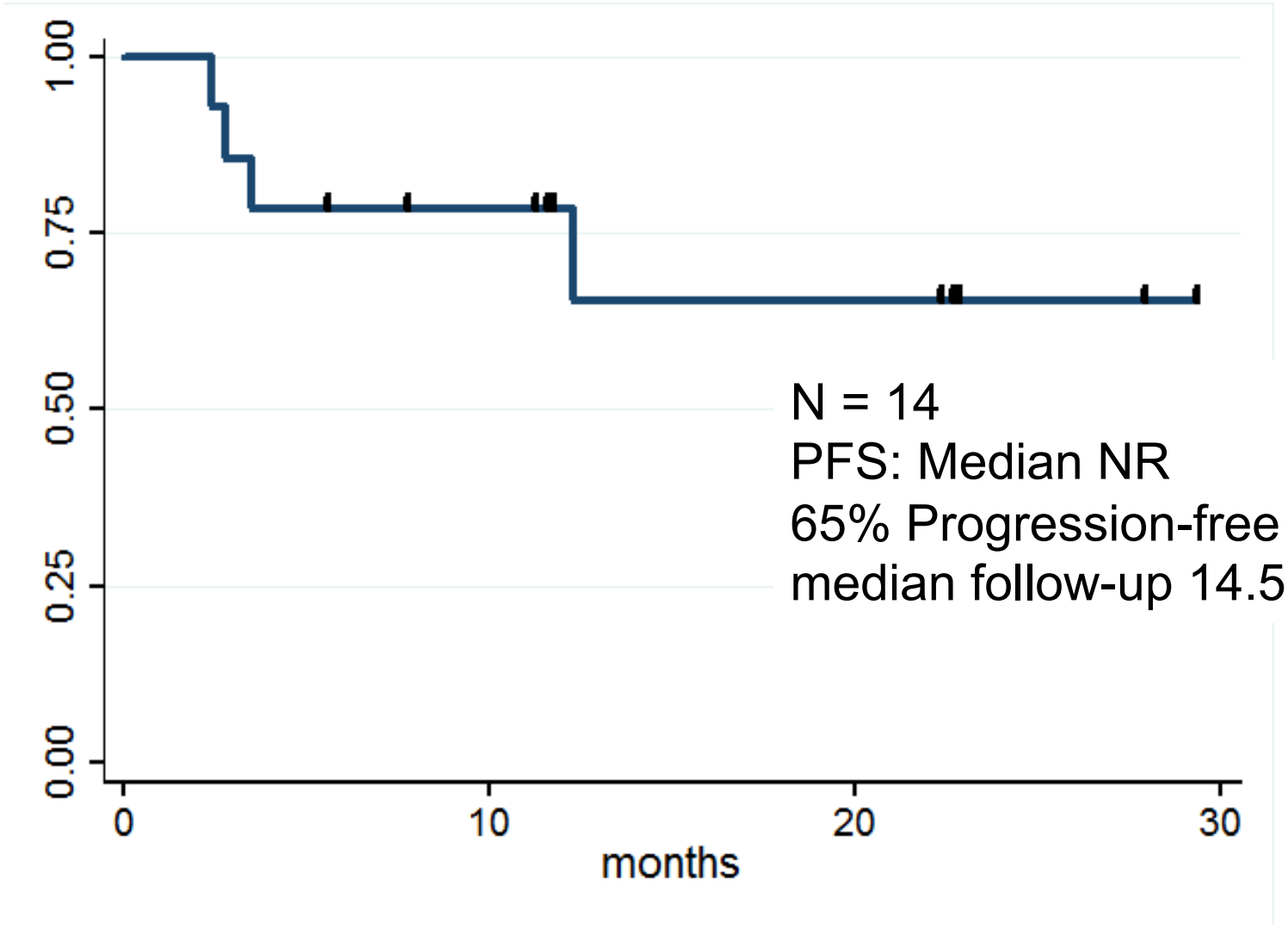


ID	Total CTL019 Dose	Peak %CD3+CAR19 +	Peak Day
13413-04	3.76E+08	0.70%	+7
13413-07	5.00E+08	3.00%	+10
13413-11	5.00E+08	38.20%	+7
13413-13	5.00E+08	3.20%	+7
13413-15	5.00E+08	40.50%	+7
13413-19	1.79E+08	1.00%	+7
13413-24	5.00E+08	8.40%	+10
13413-31	2.84E+08	3.50%	+10
13413-32	1.95E+08	5.10%	+10
13413-33	5.00E+08	23.60%	+10
13413-34	3.62E+08	40.00%	+14
13413-37	5.00E+08	41.90%	+7
13413-38	5.00E+08	26.20%	+7
13413-49	5.00E+08	12.90%	+10

Ongoing PR
Ongoing CR
Days to progressive disease
Deceased

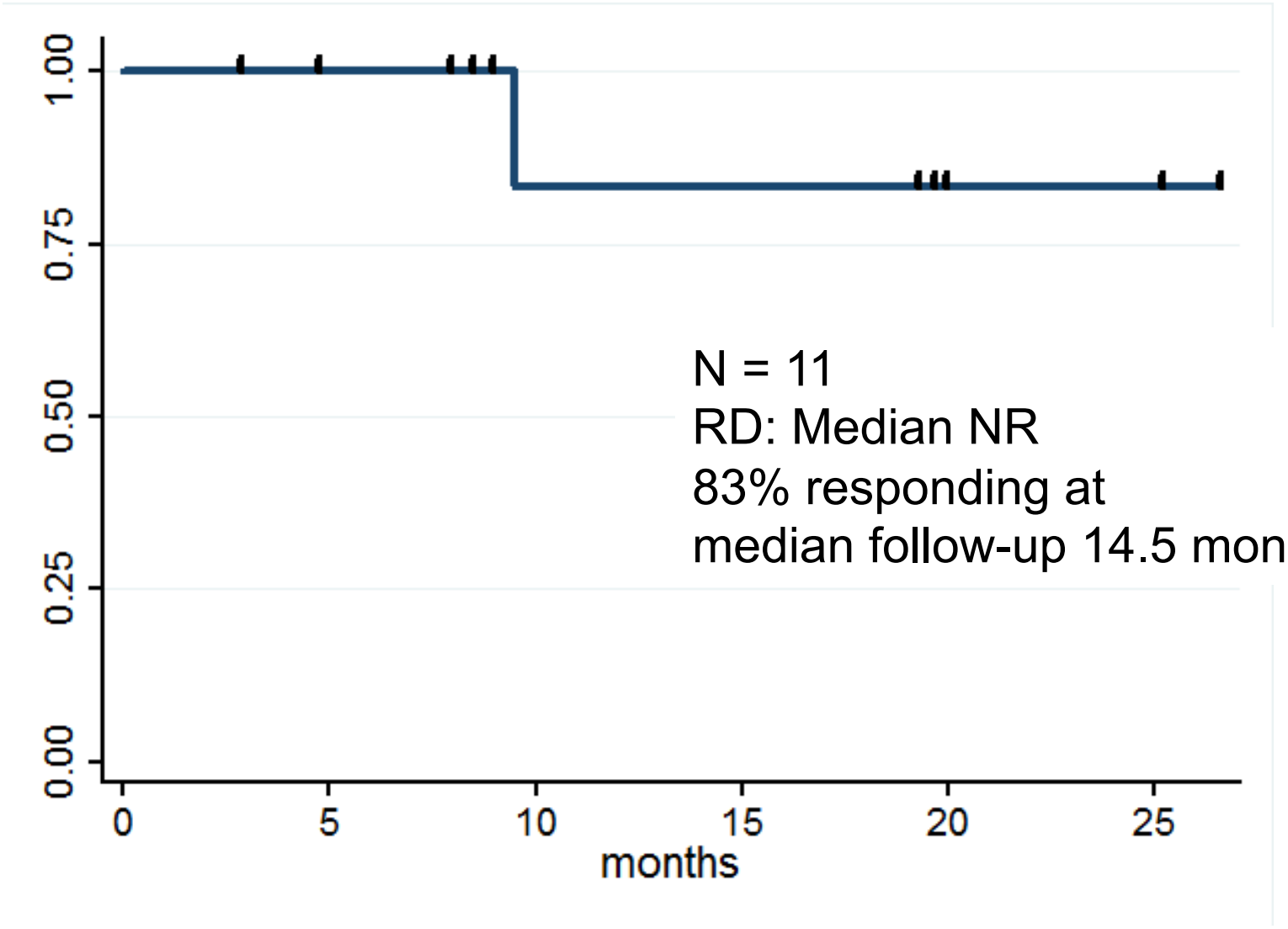
Chong, et al. ASH 2016. Abstract 1100.

FL Results: Progression-Free Survival



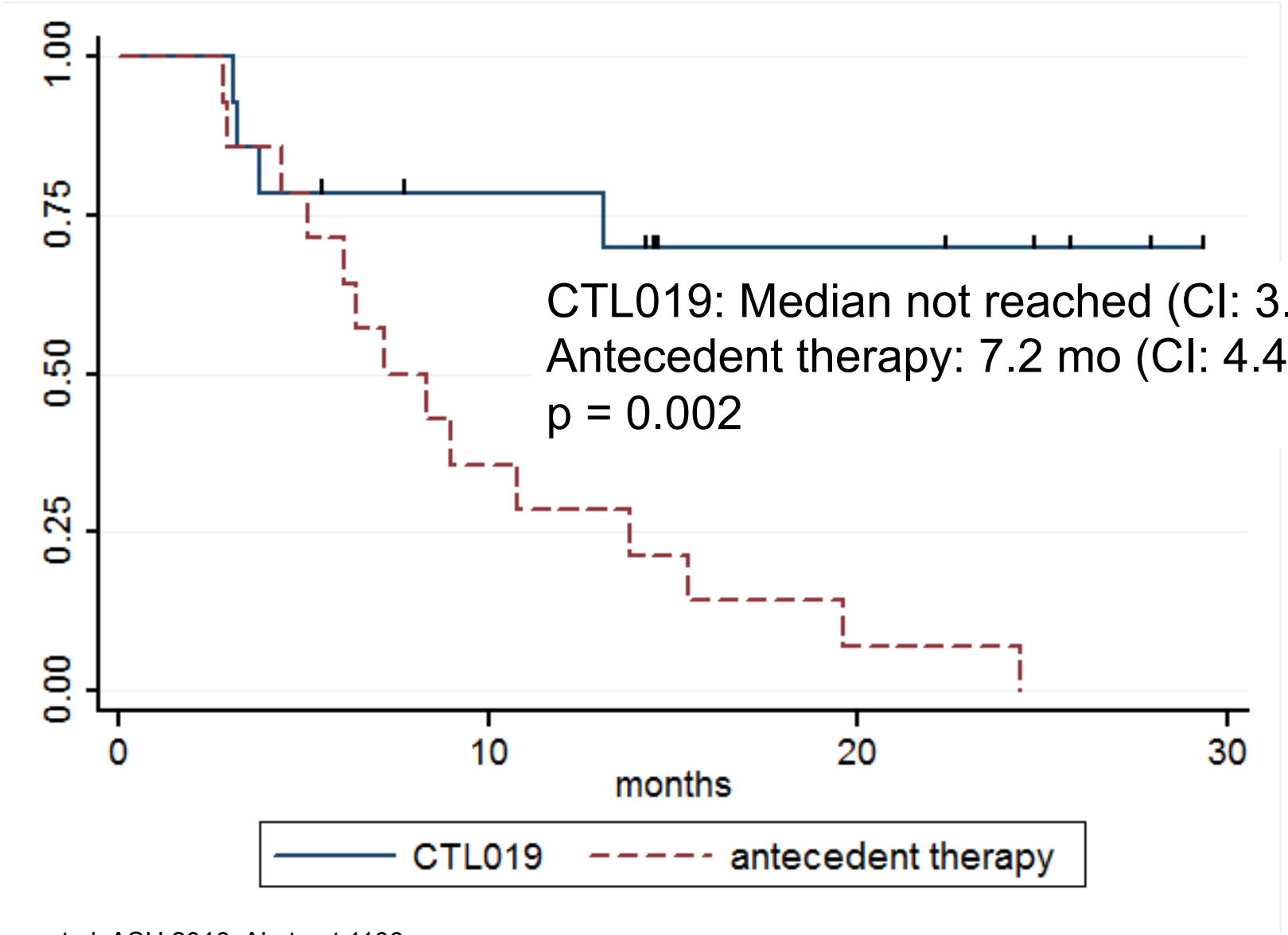
Chong, et al. ASH 2016. Abstract 1100.

FL Results: Response Duration



Chong, et al. ASH 2016. Abstract 1100.

FL Results: Time to Next Therapy



CTL019: Median not reached (CI: 3.8 - NR)
Antecedent therapy: 7.2 mo (CI: 4.4-13.8)
p = 0.002

Chong, et al. ASH 2016. Abstract 1100.

FL Adverse Events of Interest at Least Possibly Related

AE	G1	G2	G3	G4	G5	Total
Cytokine release syndrome		4	1	1		6
Hypotension		1	1	1		3
Pulmonary edema			1	1		2
Transaminitis		1				1
Hyper-bilirubinemia		1				1
Fever (non-CRS)	3					3
Headache	3					3
Confusion		2				2
Encephalitis					1	1
Tremor	1					1

AE	G1	G2	G3	G4	G5	Total
Allergic reaction		1				1
Nausea	4	2				6
Vomiting	1					1
Fatigue	2	1				3
Arthralgias	2	1				3
Anemia		1				1
Neutropenia			1			1
Rash		1				1
Pneumonia			1			1
Chest pain	1					1

Chong, et al. ASH 2016. Abstract 1100.

Conclusions: CTL019 in Follicular Lymphoma

- CTL019 can achieve durable responses in patients with relapsed or refractory CD19+ follicular lymphomas
  - All patients who achieved CR remain in CR
  - CTL019 is superior to physician's choice antecedent therapy
- Chimeric antigen receptor modified T cells directed against CD19 (CTL019) were successfully manufactured for all patients with follicular lymphoma
- The toxicity of this therapeutic approach appears acceptable
  - There were no deaths from cytokine release syndrome
- Further studies of CTL019 for treatment of follicular lymphoma are warranted

Chong, et al. ASH 2016. Abstract 1100.

Study of Efficacy and Safety of CTL019 in Adult DLBCL Patients (JULIET)

ClinicalTrials.gov Identifier: NCT02445248

Acknowledgements

Lymphoma & CLL Programs

- Stephen J. Schuster (PI)
- David L. Porter, Jakub Svoboda, Sunita Dwivedy Nasta, Anthony R. Mato, Daniel J. Landsburg

Translational Research Program

- Carl H. June, Bruce L. Levine, Saar Gill, Simon F. Lacey, Jan J. Melenhorst, Anne Chew, Katherine T. Marcucci

Novartis

Our patients and their families

UNIVERSITY OF PENNSYLVANIA
Abramson Cancer Center