CAR-T cell therapy pros and cons

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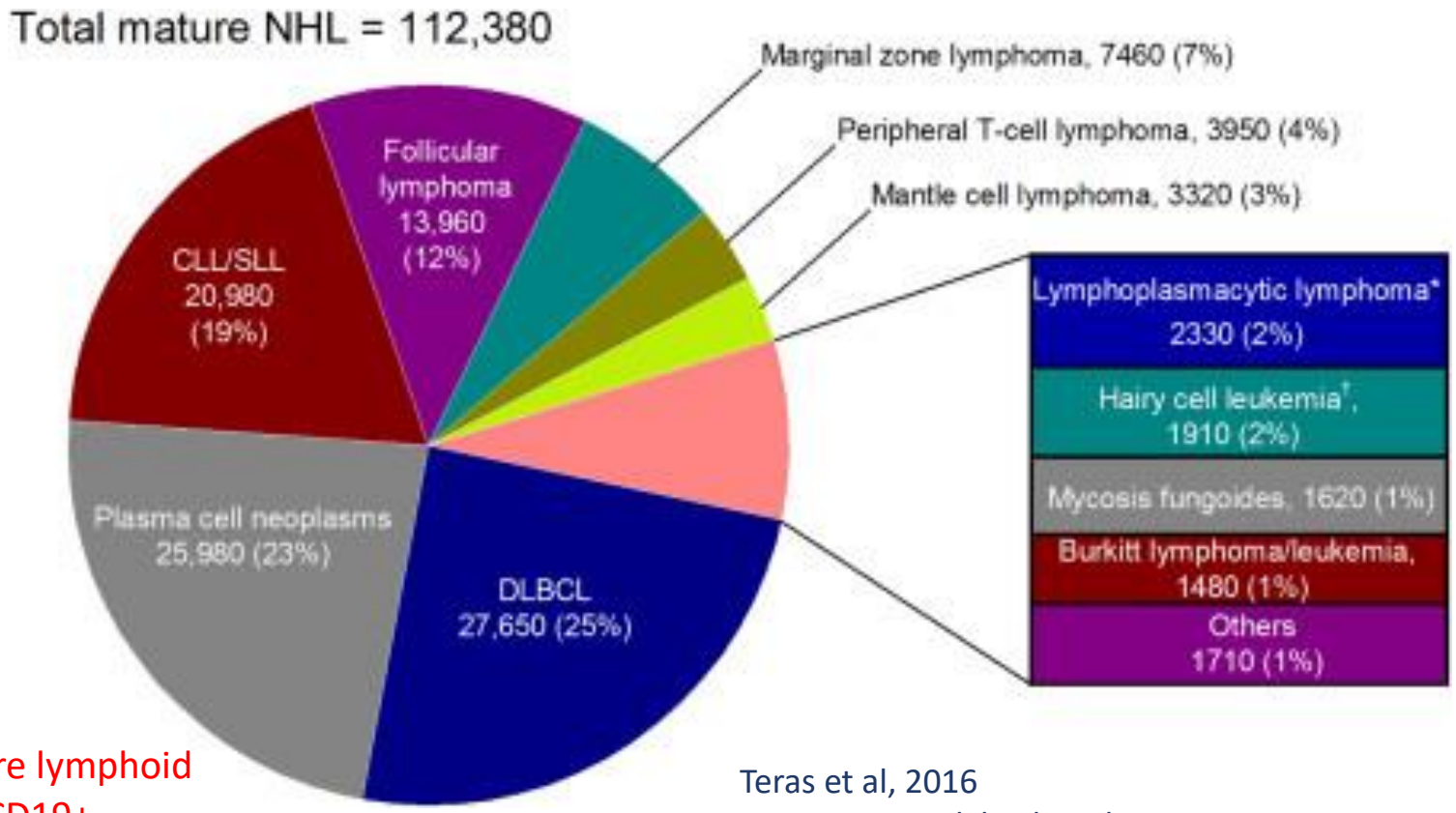
Unmet challenges in high risk hematological malignancies: from benchside to clinical practice

Turin, September 13-14, 2018
Torino Incontra Centro Congressi

Estimated Cases and Distribution of Mature Lymphoid Neoplasm Subtypes

United States, 2016



≈ 70% of all mature lymphoid neoplasms are CD19+

≈ 45% are CD19+ neoplasms other than DLBCL

Teras et al, 2016

NHL = non-Hodgkin lymphoma;

CLL/SLL = chronic lymphocytic leukemia/small lymphocytic lymphoma.

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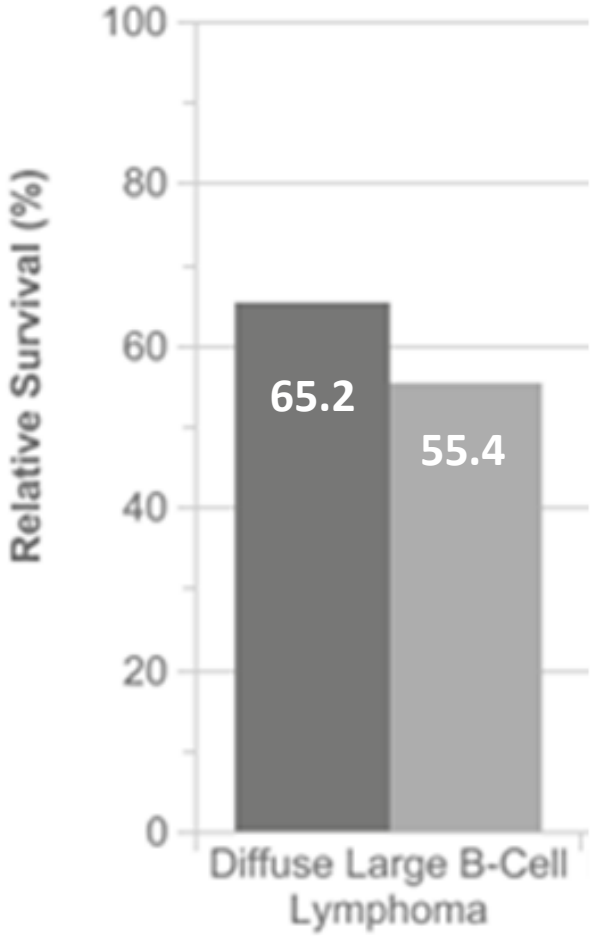
DLBCL: Real World Prognosis

- 1- and 5-Year Survival (%), All Ages, 2004-2011



Prepared by Cancer Research UK, 2014
Haematological Malignancy Research Network

Ideal World Outcomes*

Treatment outcomes for advanced DLBCL	
R-CHOP[1]:	66% 5 year DFS
	34% relapse / fail therapy
HD chemo + ASCT[2]:	31% salvaged* (3 year EFS)
	76% long term remissions
unmet need	**≈ 24% of patients with DLBCL**

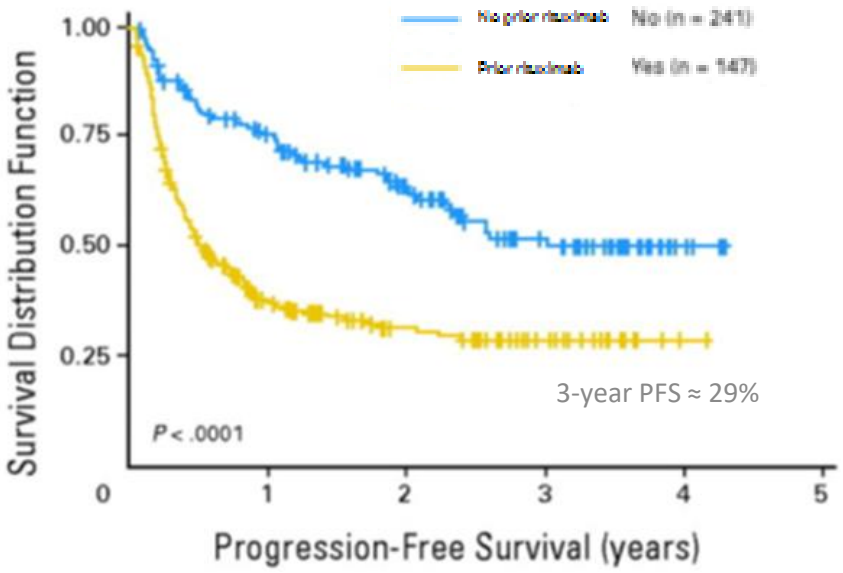
*assumes all relapsed or refractory patients are eligible for high dose chemotherapy and ASCT

[1]J Clin Oncol 2005; 23:4117-4126.
[2]J Clin Oncol 2010; 28:4184-4190.

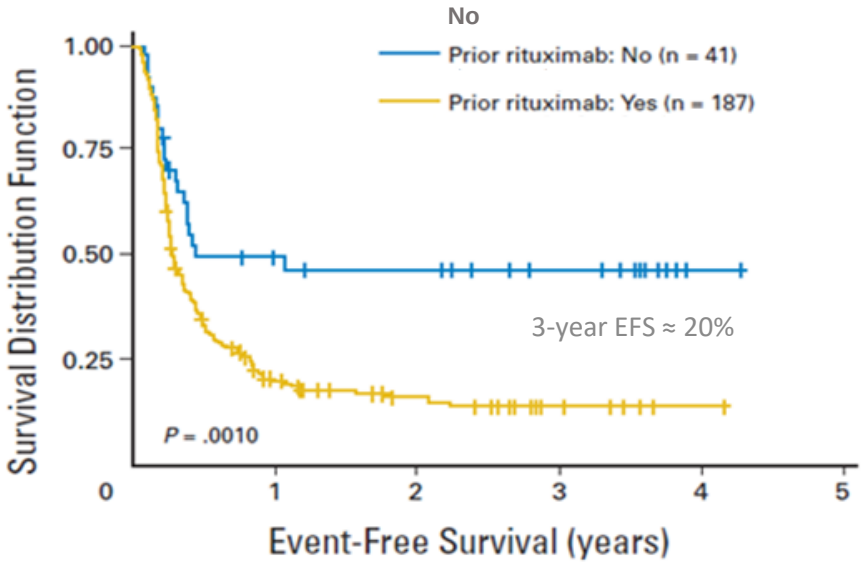
DLBCL, diffuse large B-cell lymphoma
DFS, disease-free survival
EFS, event-free survival
ASCT, autologous stem cell transplant

Diminishing Role of AutoSCT in the Rituximab Era: CORAL study

HD chemo + autoSCT: all patients (intent to treat)



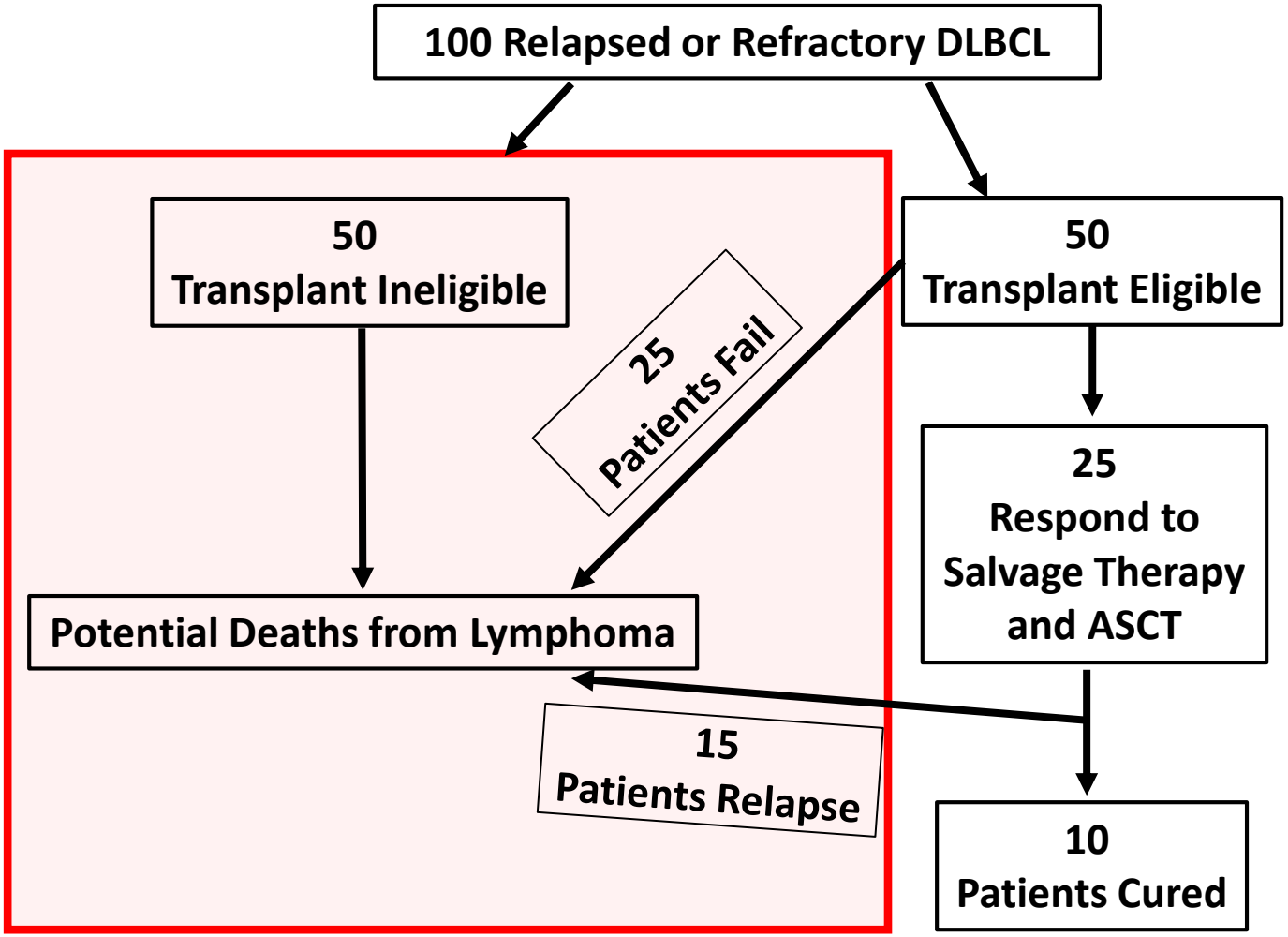
EFS for rituximab treatment + relapse <12 months after diagnosis



EFS = event-free survival, time from start of treatment to progression, relapse, new treatment, or death (irrespective of cause), whichever event occurred first.
HD = high dose; autoSCT = autologous stem cell transplant

Gisselbrecht et al, 2010.

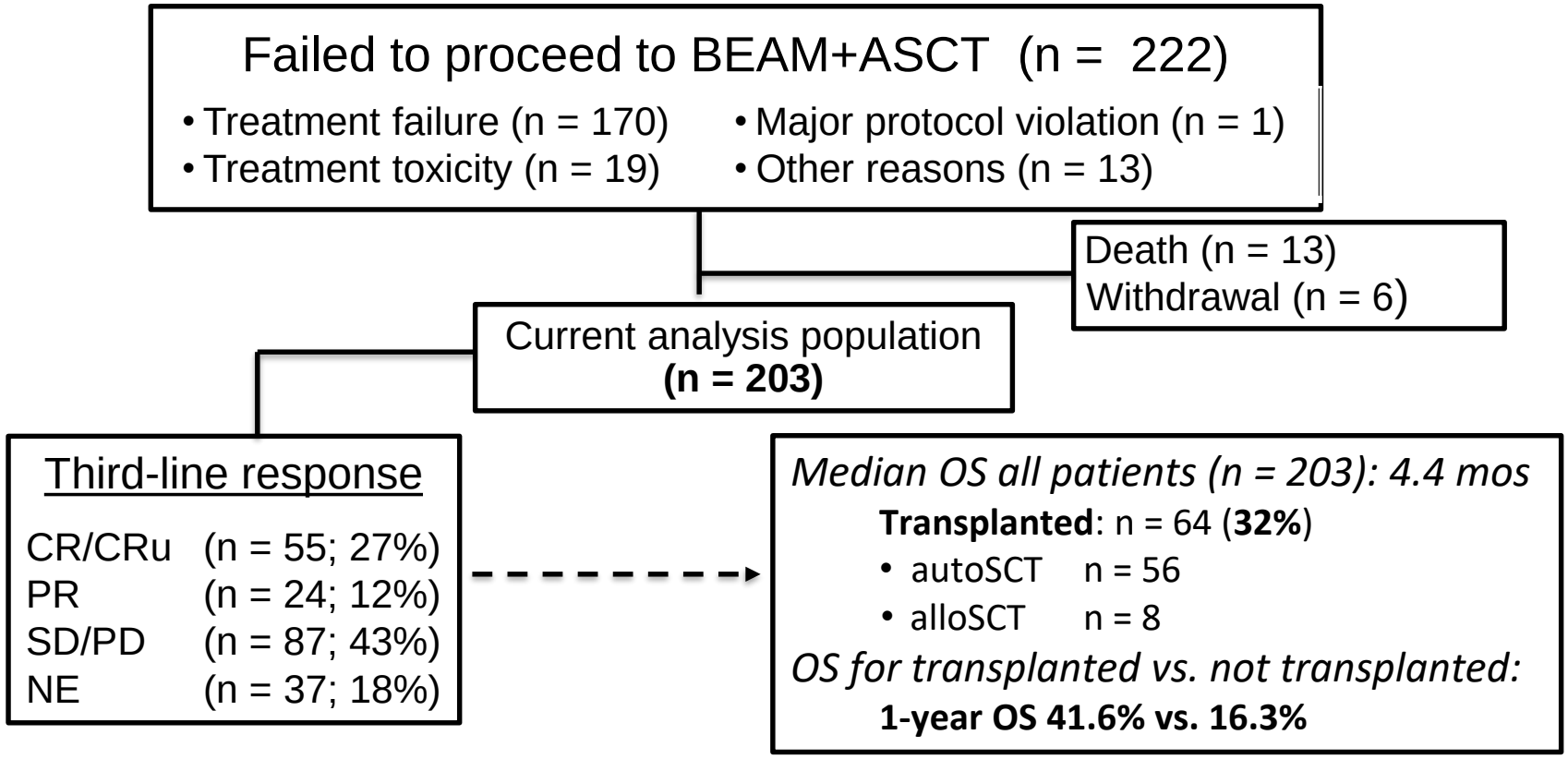
What does AutoSCT achieve as second line therapy in the rituximab era*?



*Estimates based on Gisselbrecht et al. J Clin Onc 2010 28:27, 4184-4190.
*Assumes all patients received rituximab as part of primary therapy

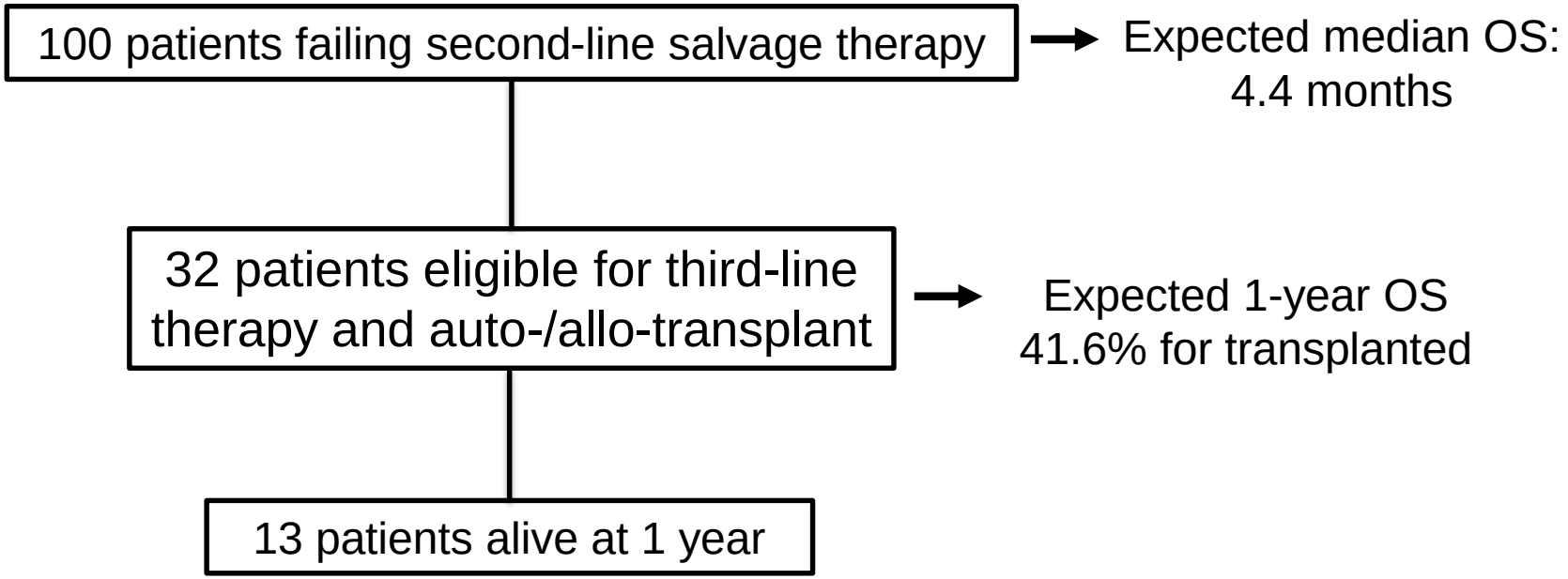
Outcomes for Relapsed DLBCL Failing Second-line Salvage Regimens: CORAL study

(Third Line Therapy or "*the third space*")



Van Den Neste, et al. Bone Marrow Transplantation 2016 51; 51

Outcomes for Relapsed DLBCL Receiving Third-line Salvage Regimens and Allo- or Auto- Transplant



Calculations based on Van Den Neste, et al. Bone Marrow Transplantation 2016 51; 51

Commercially approved CD19-directed CAR-T

Approved as Third Line Therapy (or **for "*the third space*")**

- **YESCARTA™ (axicabtagene ciloleucel): Package insert**

  2017 Adult patients with ***relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy***, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

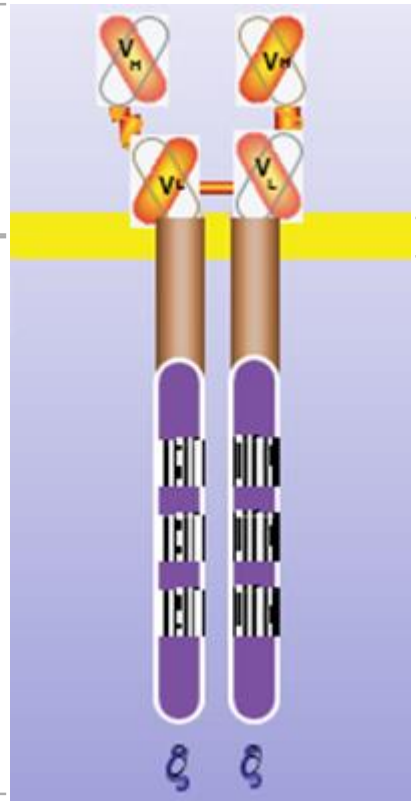
- **KYMRIAH™ (tisagenlecleucel): Package insert May 2018**

  Adult patients **with *relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy*** including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.

Generic Chimeric Antigen Receptor (CAR)

Extracellular domain

- scFv: monoclonal antibody derivative
- determines receptor specificity



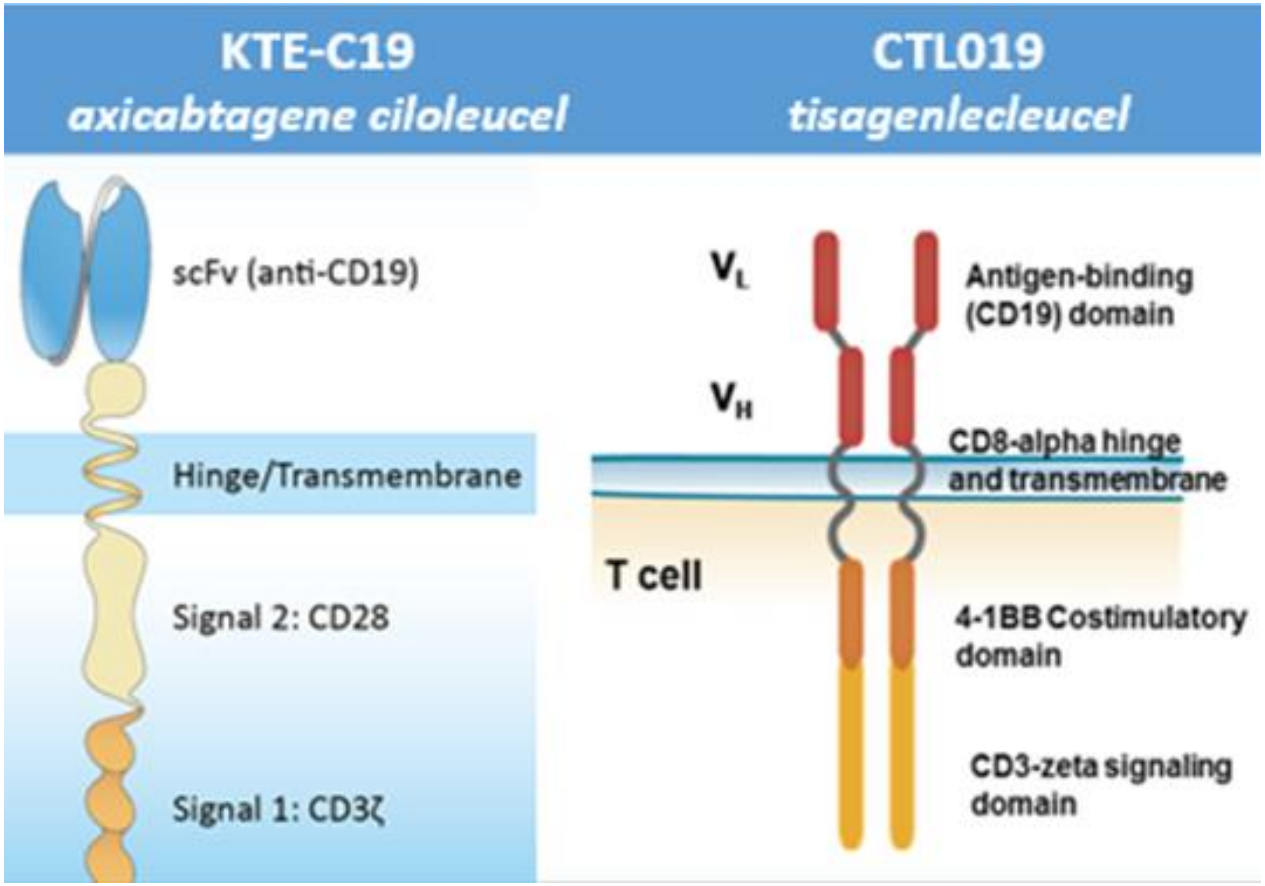
Transmembrane domain

- has an extracellular spacer / hinge region

Intracellular domain

- fusion protein comprised of a T-cell costimulatory receptor signaling domain + a TCRζ activation domain

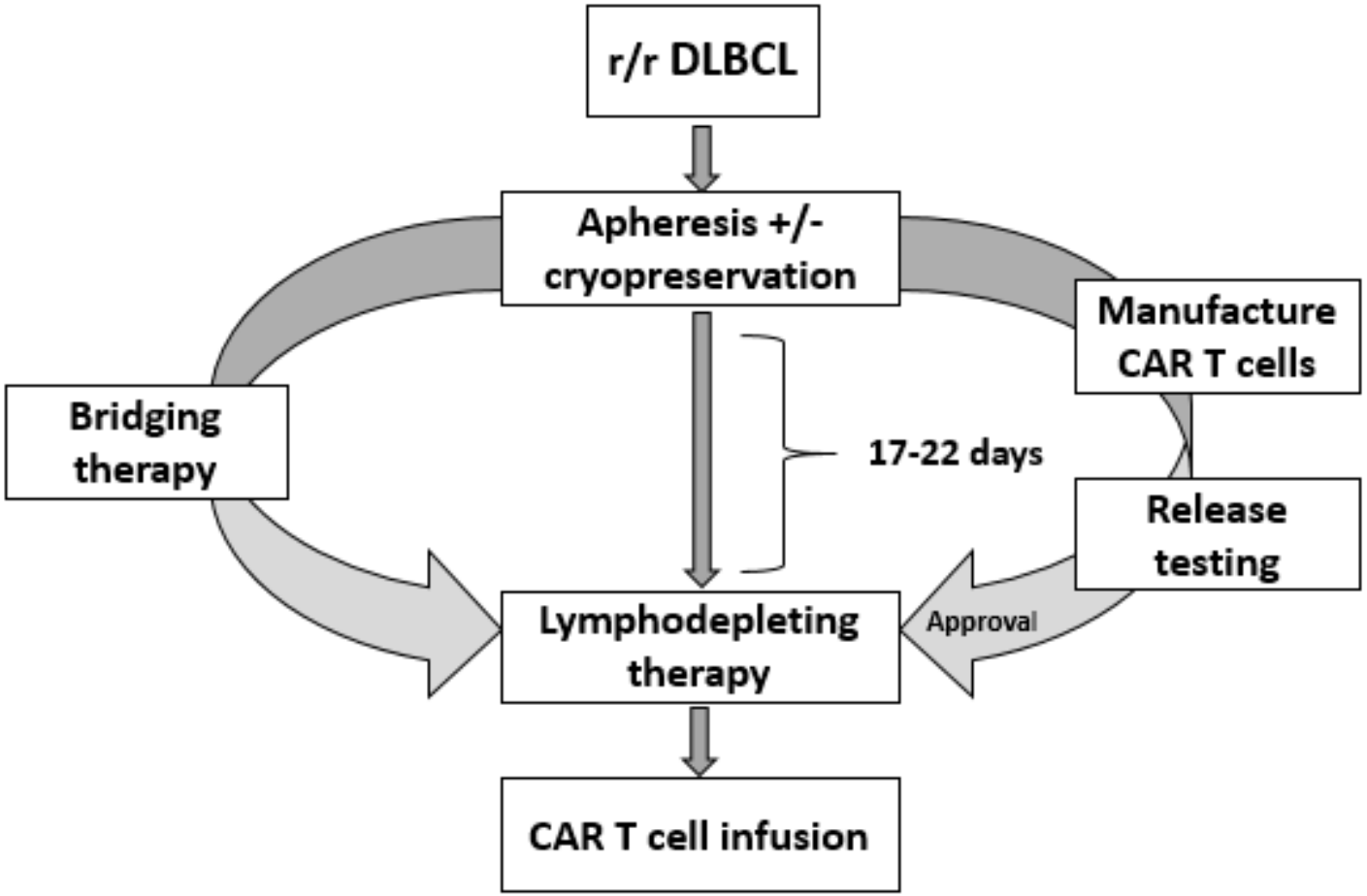
Approved CD19-directed CAR T Cells



Kite Pharma

Novartis

The CAR T Cell Process



S. J. Schuster, 2017

CTL019 Penn Study: UPCC13413, DLBCL

Key eligibility criteria

- **Adult histologically proven CD19+ relapsed/refractory DLBCL after ASCT or ineligible for ASCT, including primary refractory patients with PD or SD; transformed FL allowed; measurable disease; ECOG PS 0/1**

DLBCL Patient Characteristics
(N = 14)

Age, median	57.5 yr (range 25-77)
Female sex	3 (21%)
Prior therapies, median	3 (range 1-8)
Advanced Stage (III-IV)	9 (64%)
Bone marrow involved	3/14 (21%)
Elevated LDH	8 (57%)
ECOG PS, median	1 (range 0-1)
Refractory DLBCL*	12 (86%)
Prior autologous SCT	7 (50%)

*Refractory DLBCL is defined as: 1) progressive or stable disease as best response to chemotherapy (stable disease is < 12 month duration after at least 4 cycles of first line or 2 cycles of later line therapy), or 2) relapse ≤ 12 months after autoSCT. Patients must have received an anti-CD20 monoclonal antibody unless CD20 negative and an anthracycline as one of their prior regimens.

Schuster SJ, *et al*. N Engl J Med. 2017 Dec 28;377(26):2545-2554.

CTL019 Penn Study: UPCC13413, DLBCL

- Single-center, phase II study at the University of Pennsylvania showed durable remissions with a single infusion of CTL019 in r/r DLBCL (Cohort A)
  - No patient in CR at 6 months had relapsed at median follow-up, 28.6 months **(as of May 31,2017)**

Response Rates (N = 14)

	Month 3	Month 6
ORR	**50%**	**50%**
CR	**36%**	**43%**
PR	**14%**	**7%**

CR, complete response; ORR, overall response rate; PR, partial response

Response Duration: (n = 7; 6 CR + 1 PR)

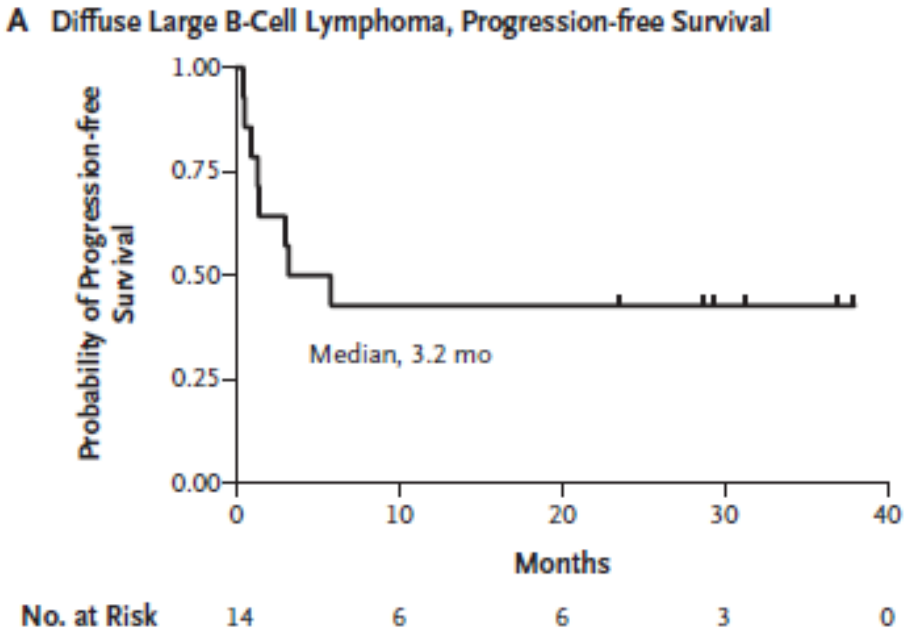
- Median response duration: not reached
- 86% responding at median follow-up of 28.6 months*

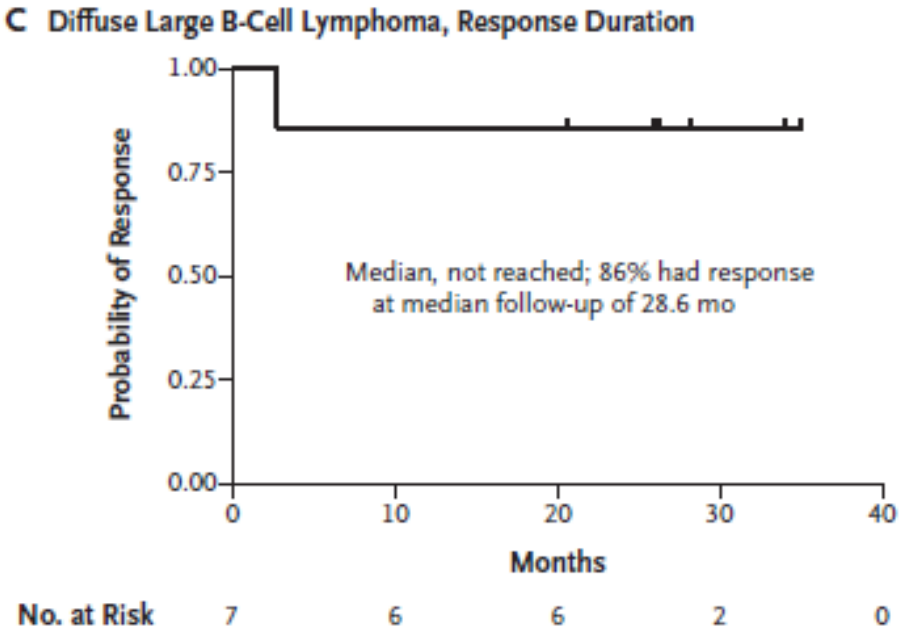
DLBCL: Lymphodepleting therapy (n = 14)	
(n)	**Regimen**
6	**Hyperfractionated /m^2 (1.8 gm/m^2)**
2	**Modified EPOCH (doxorubicin 10 mg/m^2 and etoposide 50 mg/m^2 daily x 4 by continuous infusion, cyclophosphamide 750 mg/m^2; no prednisone, no vincristine)**
2	**cyclophosphamide (1.0 gm/m^2)**
2	**bendamustine (90 mg/m^2 daily x 2)**
1	**Radiation therapy (4000 cGy) + cyclophosphamide (750 mg/m^2)**
1	**Infusional etoposide (etoposide 50 mg/m^2 daily x 4 by continuous infusion) + bolus cyclophosphamide (750 mg/m^2)**

*Schuster SJ, *et al*. N Engl J Med. 2017 Dec 28;377(26):2545-2554.

CTL019 Penn Study: UPCC13413, DLBCL

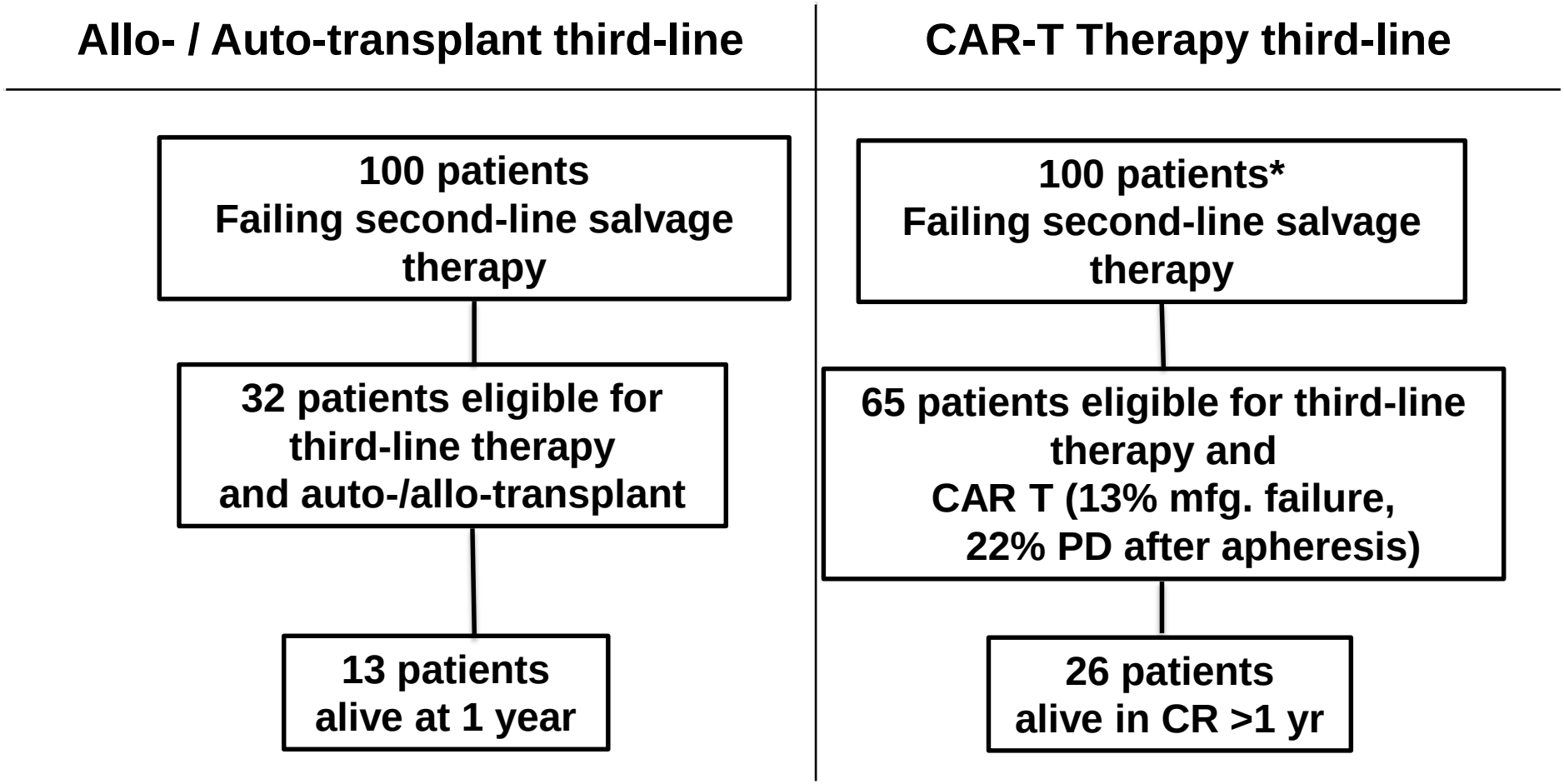
Remarkably durable response duration





Schuster SJ, *et al*. N Engl J Med. 2017 Dec 28;377(26):2545-2554.

Outcomes for Relapsed DLBCL Receiving Third-line Allo- or Auto- Transplant vs. CAR-T Therapy



*Biased since ½ of CAR T patients already had a transplant

Calculations based on Van Den Neste, et al. BMT 2016 and Schuster SJ, et al. NEJM 2017

JULIET Trial: Eligibility and endpoints

- *tisagenlecleucel (CTL019)*

N = 111; Median follow-up, 14 mo (max, 23 mo)

Key eligibility criteria

- **≥ 18 years of age**
- **Central confirmation of histology**
- **≥ 2 prior lines of therapy for DLBCL**
- **PD after or ineligible for auto-SCT**
- **No prior anti-CD19 therapy**
- **No active CNS involvement**

Endpoints

- **Primary endpoint: best overall response rate (ORR: CR + PR)**
  - Lugano criteria used for response assessment by IRC[1]
- **Secondary endpoints: DOR, OS, safety**

auto-SCT, autologous stem cell transplant; CNS, central nervous system; CR, complete response; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; IRC, Independent Review Committee; ORR, overall response rate; OS, overall survival; PD, progressive disease; PR, partial response.

1. Cheson BD, et al. *J Clin Oncol.* 2014;32(27):3059-3068.

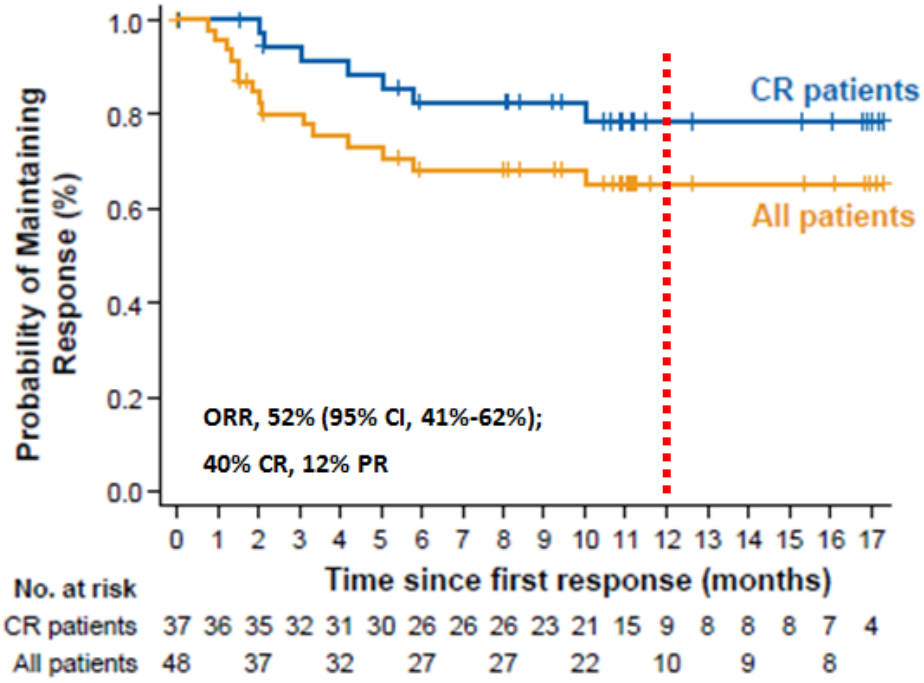
JULIET: Patient characteristics

	Patients (N = 111)
Age, median (range), years	56 (22-76)
≥ 65 years, %	23
ECOG performance status 0/1, %	55/45
Central histology review	
Diffuse large B-cell lymphoma, %	**79**
Transformed follicular lymphoma, %	**19**
Double/triple hits in CMYC/BCL2/BCL6 genes, %	**17**
Cell of origin[b]	
Germinal/Nongerminal center B-cell type, %	57/41
# of prior lines of antineoplastic therapy, %	
2/3 / 4-6	44/31 / 21
IPI ≥ 2 at study entry, %	72
Refractory/relapsed to last therapy, %	**55/45**
Prior auto-SCT, %	**49**
Bridging chemotherapy, n	102
Lymphodepleting chemotherapy, n	103

* *from* Borchmann et al. EHA 2018

JULIET Trial: Tisagenlecleucel in r/r DLBCL

Response Duration by Best ORR w/in 3 months of infusion



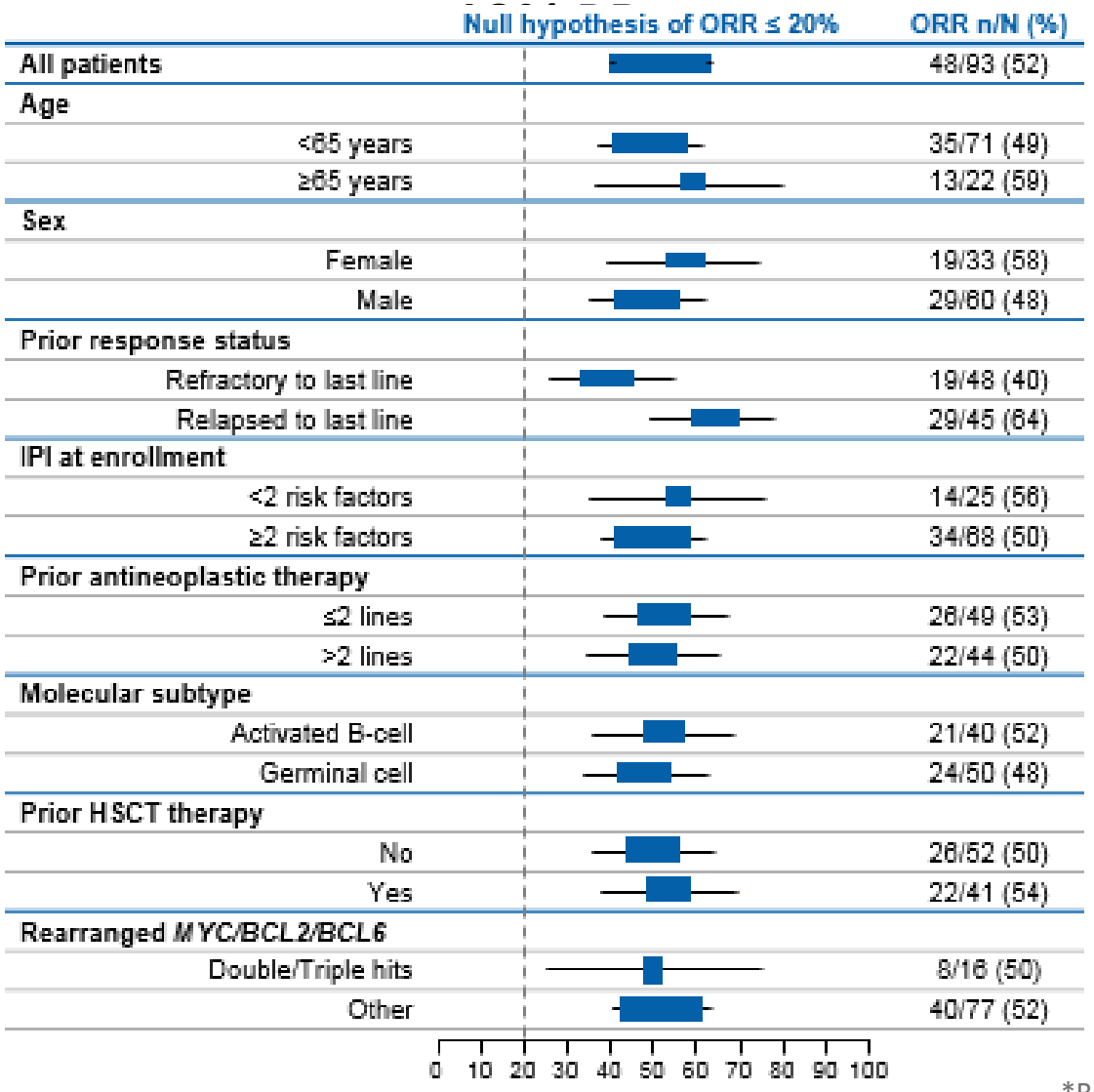
- **n = 93*; ORR / CR = 52% / 40%**
  *efficacy evaluable set with ≥ 3 months follow up
- **Median DOR not reached at 14 month median follow up**
- **12-mo relapse-free survival rates**
  CR = 78.5% (95% CI, 60%-89%)
  CR + PR = 65% (95% CI, 49%-78%)

ORR = overall response rate; CR = complete response; PR = partial response
r/r DLBCL = relapsed or refractory diffuse large B cell lymphoma

* from Borchmann et al. EHA 2018

JULIET: Response rates

Best ORR w/in 3 months of infusion, 52% (95% CI, 41%-62%): 40% CR,



*Borchmann et al. EHA 2018

ZUMA-1 Trial: Eligibility and endpoints

- *axicabtagene ciloleucel (KTE-C19)*

Key eligibility criteria

- **ZUMA-1 phase II portion**
  - **Cohort 1: patients with refractory DLBCL (n = 77)**
  - **Cohort 2: patients with refractory PMBCL or transformed FL (n = 24)**
- **Key inclusion criteria**
  - **No response to last CT or relapsed within 12 mos of ASCT**
  - **Prior treatment with anthracycline and anti-CD20 monoclonal antibody**

Secondary Endpoints

- **Assess TTR for patients with both objective response and CR**
- **Assess PR and CR at Month 3 as PFS prognostic factor**

TTR, time to response

Locke, et al. ASCO 2018

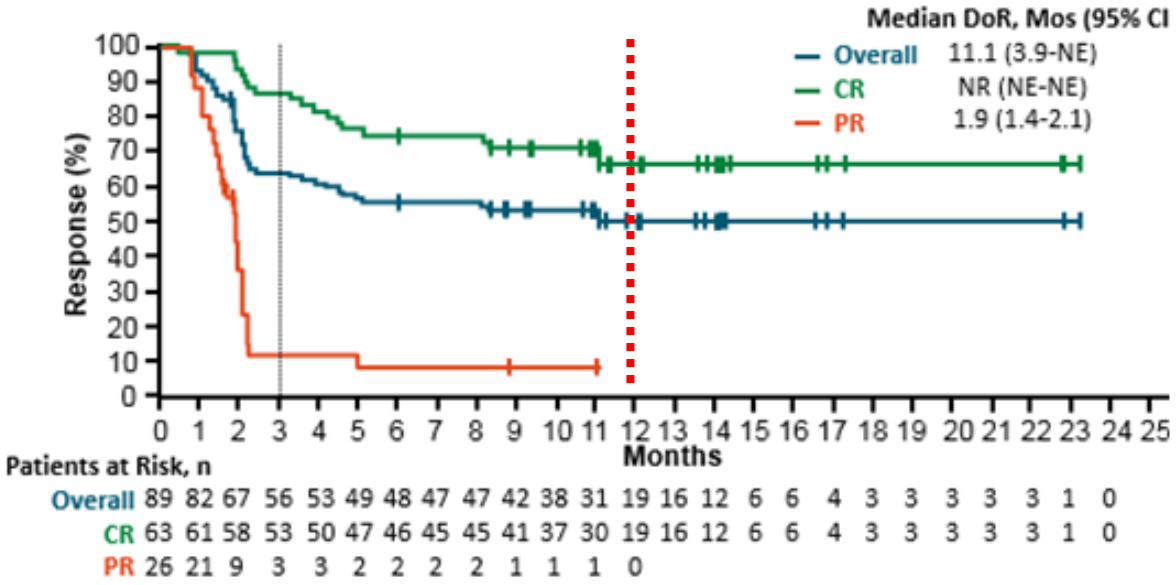
ZUMA-1: Patient Characteristics

Characteristic	Overall (N = 101)
Median age, yrs (range)	58 (23-76)
Male, n (%)	68 (67)
ECOG PS 1, n (%)	59 (58)
Disease stage III/IV, n (%)	86 (85)
IPI score 3-4, n (%)	46 (46)
≥ 3 prior therapies, n (%)	70 (69)
Median SPD of index lesions, mm^2 (range)	3721 (171-23,297)
Refractory Subgroup Prior to Enrollment	
Refractory to ≥ 2 lines of therapy, n (%) ▪ **Best response as PD to last therapy, n (%)**	**77 (76)** **67 (66)**
Relapse post-ASCT, n (%)	**21 (21)**

Locke, et al. ASCO 2018

ZUMA-1: Axicabtagene Ciloleucel in r/r DLBCL

Response Duration by Best Objective Response (ZUMA-1)



- **n = 101**
- **ORR/CR 82% / 54% [best]**
- more than half of patients with PR progressed by month 3
- **12 mo PFS for CR/PR @ month 3**
  CR = 79% (95% CI, 63-88);
  PR = 78% (95% CI, 36-94)

CR = complete response; PR = partial response; PFS = progression free survival

r/r DLBCL = relapsed or refractory diffuse large B cell lymphoma

Neelapu SS, et al. NEJM. 2017;377:2531; Locke FL, et al. ASCO 2018.

CD19-CAR T Cell Therapy Summary: DLBCL

	CTL019 * tisagenlecleucel		KTE-C19 ** axicabtagene ciloleucel	
Disease state	r/r DLBCL	r/r tFL	r/r DLBCL	r/r tFL/PMBCL
Response evaluable pts, n	89	22	77	24
Follow-up, median	14 months		15.4 months	
Efficacy	n = 93		n = 101	
ORR / CR	52% / 40% [w/in 3 mo]		82% / 54% [best]	
% PFS for CR @ 12 mos	78.5%		79%	
DOR (CR + PR; median)	not reached		11.1 months	
DOR (CR; median)	not reached		not reached	
Safety	n = 111		n = 101	
CRS	22% grade 3/4*		13% grade ≥ 3**	
Neurotoxicity	12% grade 3/4		28% grade ≥ 3	

*Borchmann et al. EHA 2018;

**Locke, et al. ASCO 2018;
Neelapau, et al. *NEJM*. 2017.

**** Penn scale; ** Lee scale***

Calculations based on Van Den Neste, et al. BMT 2016
and Schuster SJ, et al. NEJM 2017

CD19-directed CAR T cells: What's next?

Proof of Concept: Follicular Lymphoma UPCC13413

Key eligibility criteria

- **Adult histologically proven CD19+ relapsed/refractory FL with measurable disease <2 years after second or higher line of immunochemotherapy (not counting single agent monoclonal antibody therapy); measurable disease; ECOG PS 0/1**

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)**

Proof of Concept: Follicular Lymphoma UPCC13414

- Single-center, phase 2 study at the University of Pennsylvania showed durable remissions with a single infusion of CTL019 in r/r FL
  - No patient in CR at 6 months had relapsed at median follow-up, 28.6 months*

Response Rates[1] (N = 14)

	Month 3	Month 6
ORR	79%	78%
CR	50%	71%
PR	29%	7%

CR, complete response; ORR, overall response rate; PR, partial response

Response Duration (n = 11; CR + PR)

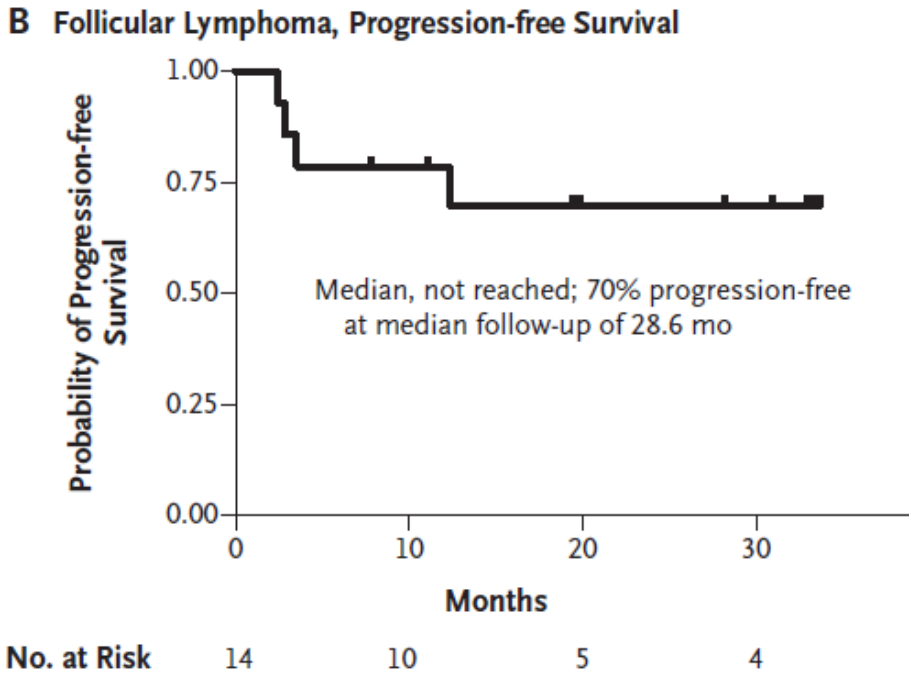
- **Median response duration: not reached**
- **88.9% responding at median follow-up of 28.6 months***

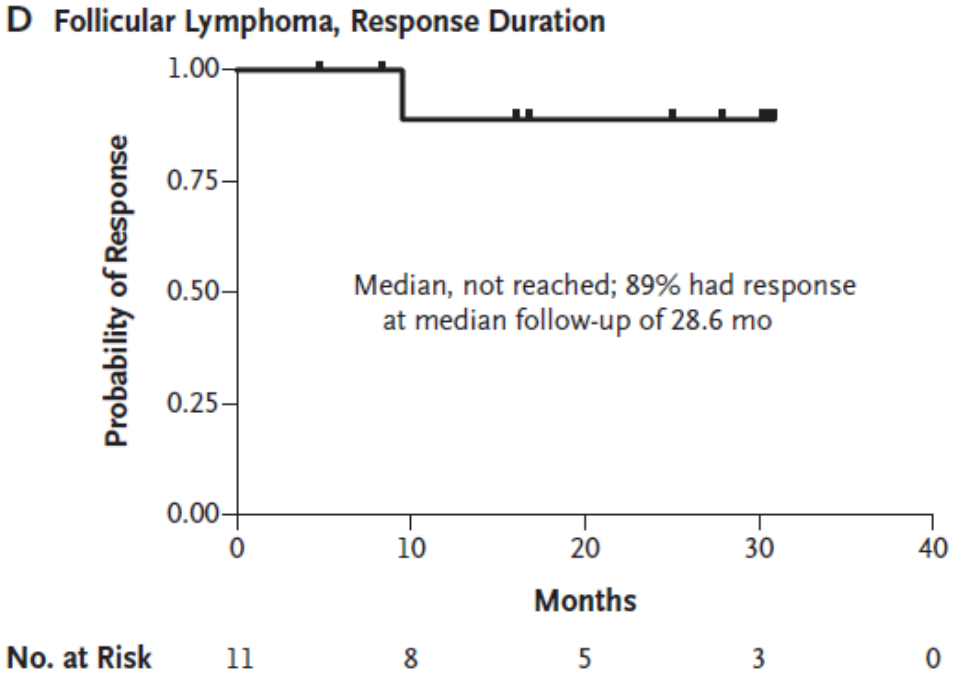
FL: Lymphodepleting therapy (n = 14)

(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

1. Chong, *et al*. ASH 2016. Abstract 1100.
2. Schuster SJ, *et al*. N Engl J Med. 2017 Dec 28;377(26):2545-2554.

CTL019 in Follicular Lymphoma UPCC13413

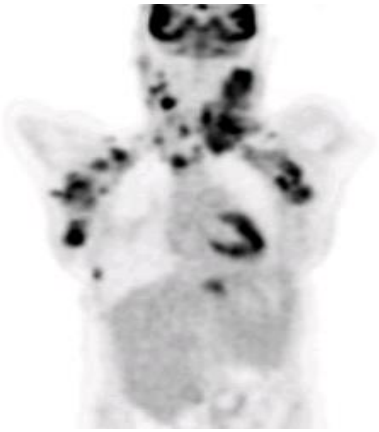


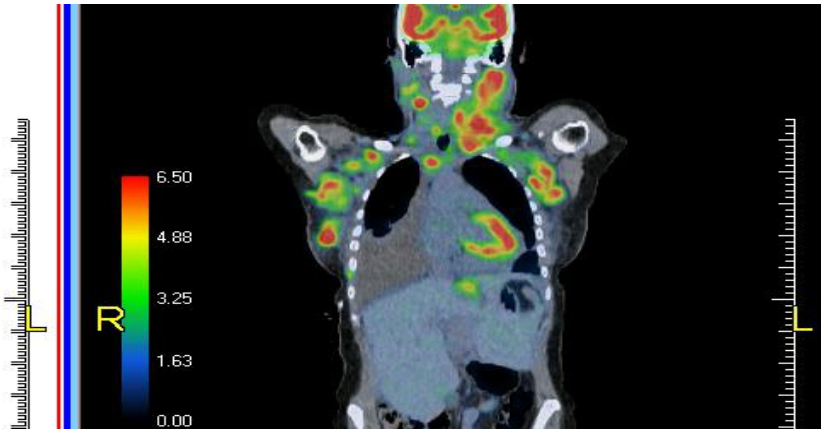


Schuster SJ, *et al*. N Engl J Med. 2017 Dec 28;377(26):2545-2554.

Follicular Lymphoma: 13413-19

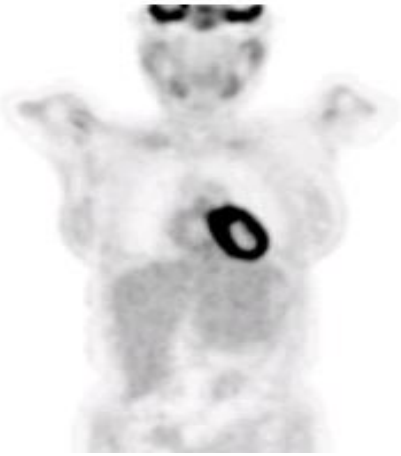
10/15/2014

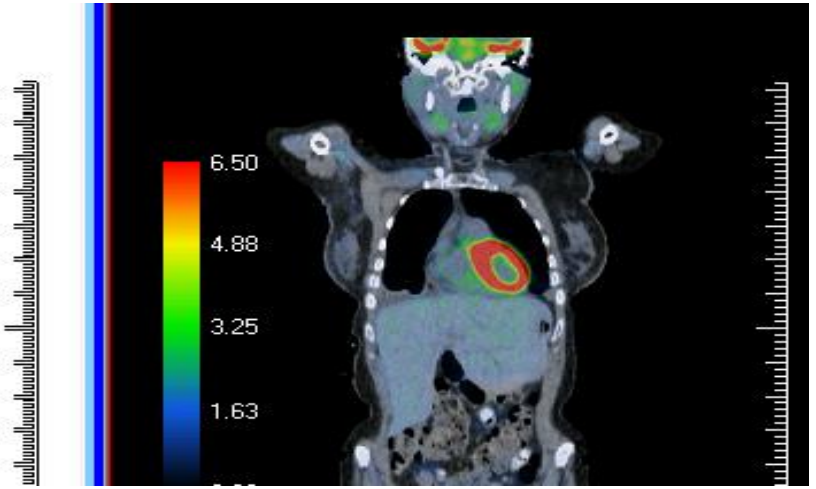




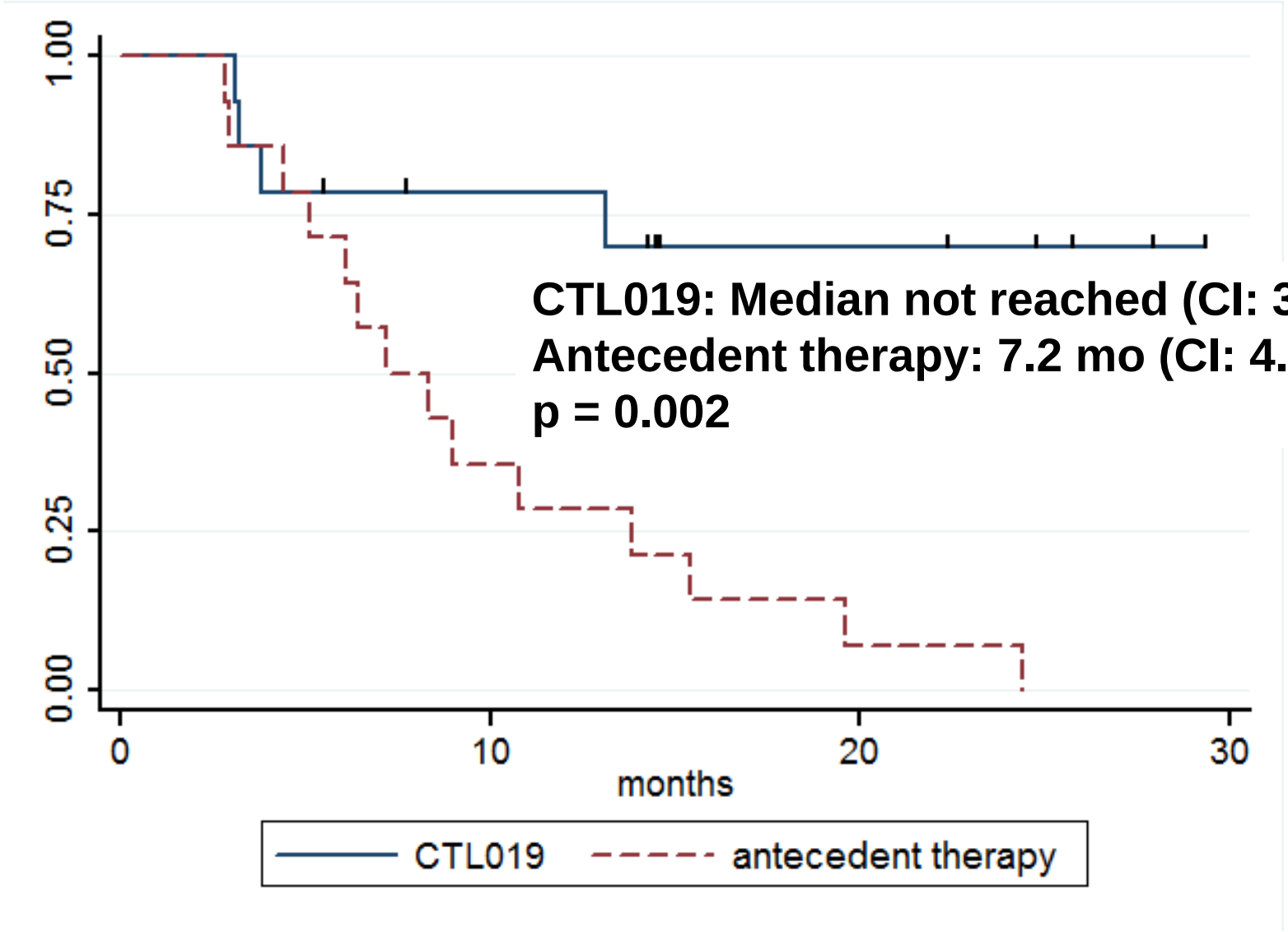
CTL019: 11/04/2014

12/03/2014





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.

CD19-directed CAR T Cell: Folklore

- **CAR T cells directed against CD19 result in profound and prolonged humoral immunodeficiency. UPCC13413 observations:**

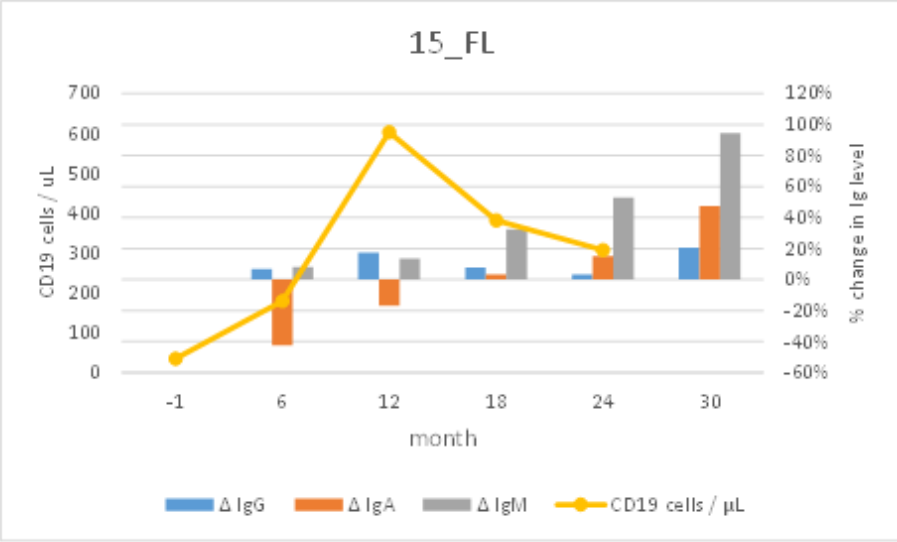
- 16 patients in CR ≥ 6 months: 8 had sustained polyclonal B-cell recovery

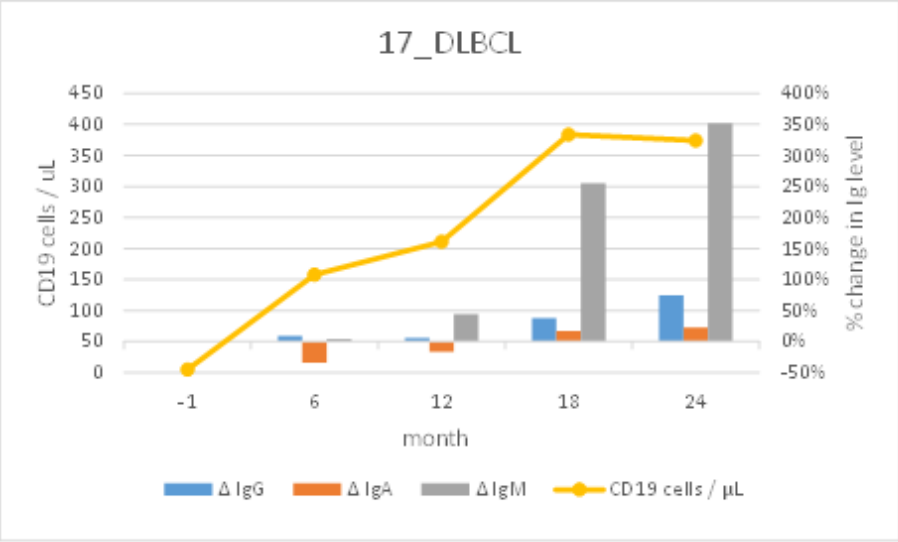
- 12 patients in CR ≥ 6 months did not receive prophylactic IVIG

- **2 patients required IVIG for recurrent infections at 12 and 22 months**

- 10 patients (5 DLBCL; 5 FL) at median follow-up 22.5 months (range, 11-34):

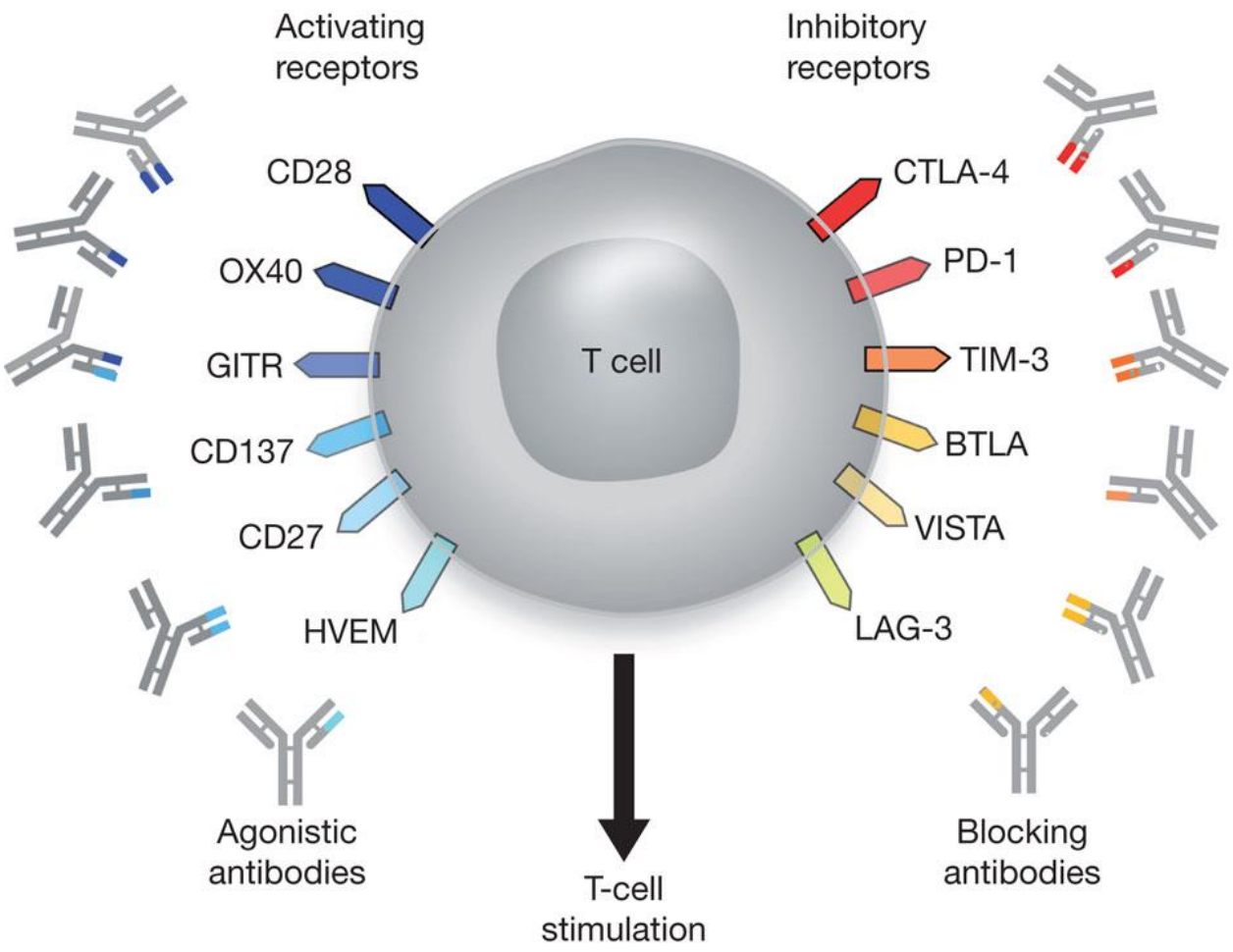
- **3/10 patients had increases in IgG levels by 18 months (2 to normal)**
- **4/10 patients reached normal IgM between 12 and 24 months**
- **3/10 patients had increases in IgA levels between 24 and 30 months (2 to normal)**





CTL019 CAR T Cells + ?

T Cell Targets for Immunoregulatory Therapy



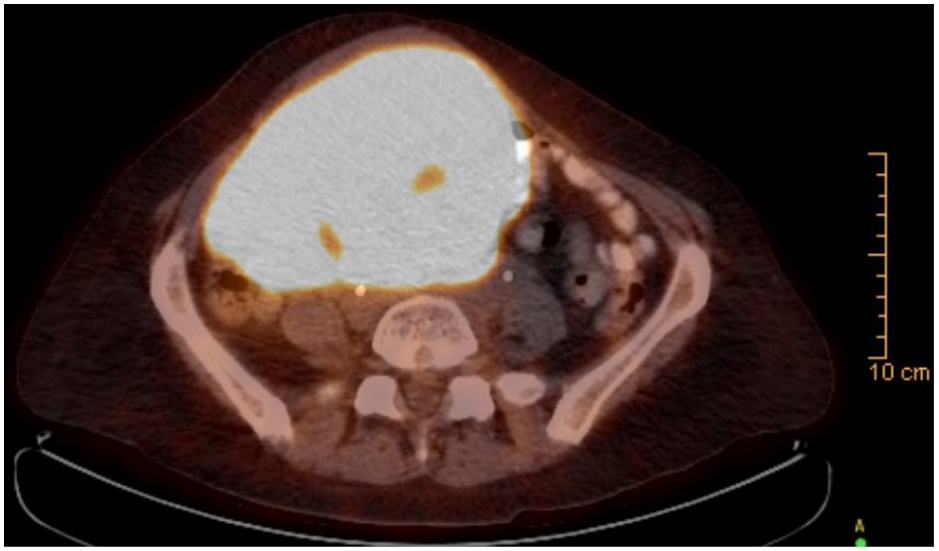
[1] Mellman *et al. Nature* 480, 480-489 (2011) doi:10.1038/nature10673

13413-34: FL

- 34 year old woman with FL, grade 2
- Past therapies included:
  - rituximab - CVP + maintenance rituximab
  - rituximab - chlorambucil - prednisone
  - Zevalin
  - R-CHOP
  - cyclophosphamide - etoposide
  - R-EPOCH
  - allogeneic bone marrow transplant
  - lenalidomide - rituximab
  - Ibrutinib
  - carboplatin - gemcitabine
- Lymphodepleting chemotherapy: 7/20/15
  - carboplatin - gemcitabine
- CTL019 infusion: 7/29/15

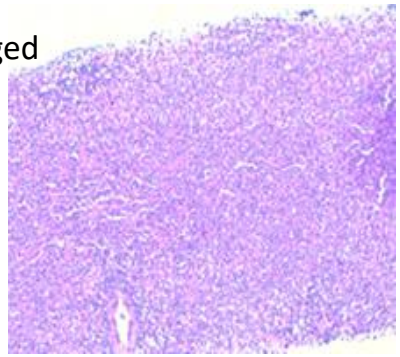
13413-34: FL Transformed to “Double Hit” DLBCL

October 15, 2015: Day +78 CTL019



Biopsy: October 23, 2015

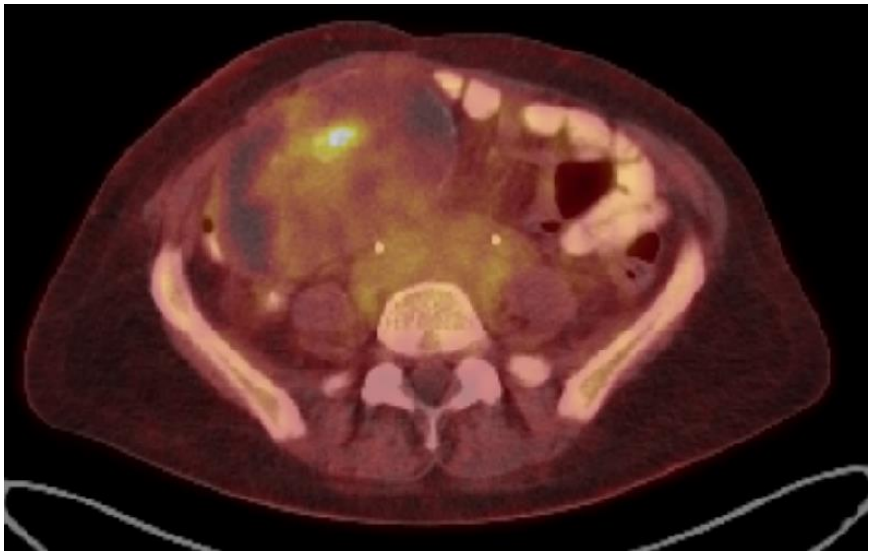
- Flow: kappa LC, CD10+, CD19+
- IHC: large PAX5+ B cells; PDL1+
- FISH: c-MYC and BCL-2 rearranged



→ **Nov. 2 & 3: radiation therapy (1400 cGy)**

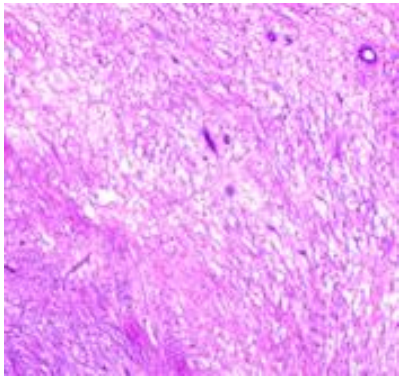
→ **Nov. 19 & Dec. 9: nivolumab**

December 30, 2015



Biopsy: March 6, 2016

- Extensive necrosis
- No tumor seen



CAR T Cells and PD-1 Blockade: Studies in Progress

- Phase I/II study of pembrolizumab in patients failing to respond to or relapsing after anti-CD19 chimeric antigen receptor modified T cell therapy for relapsed or refractory CD19+ lymphomas
  - NCT02650999
  - **Accrual is complete**
- Correlative studies in progress:
  - Study modulation of tumor immunophenotype and microenvironment and their effects on CAR T cells in patients failing CTL019, as well as effects of PD-1 blockade on CAR T cells, tumor and microenvironment

CTL019 CAR T Cells: Pros and Cons

Pros	Cons
• Serves an unmet need in DLBCL (already approved therapy in US / EU)	• Cost (expensive)
• Will be applicable to other CD19+ NHLs	• Production time (4weeks)
• Amenable to modulation of T cell function to improve efficacy	• Efficacy < 100%
• Amenable to modulation of T cell function to reduce toxicity	• Cytokine release syndrome
• Saves lives!	• Neurotoxicity
	• Requires apheresis and adequate lymphocyte count and function

Questions & Discussion