MAYO CLINIC

Non-Hodgkin and Hodgkin lymphomas

Mohamed A. Kharfan-Dabaja, MD, MBA, FACP
Blood and Marrow Transplantation and Cellular Therapies
Mayo Clinic, Jacksonville, FL

16th Annual Miami Cancer Meeting (MCM)
March 31st , 2019
Miami, FL

Off label presentation

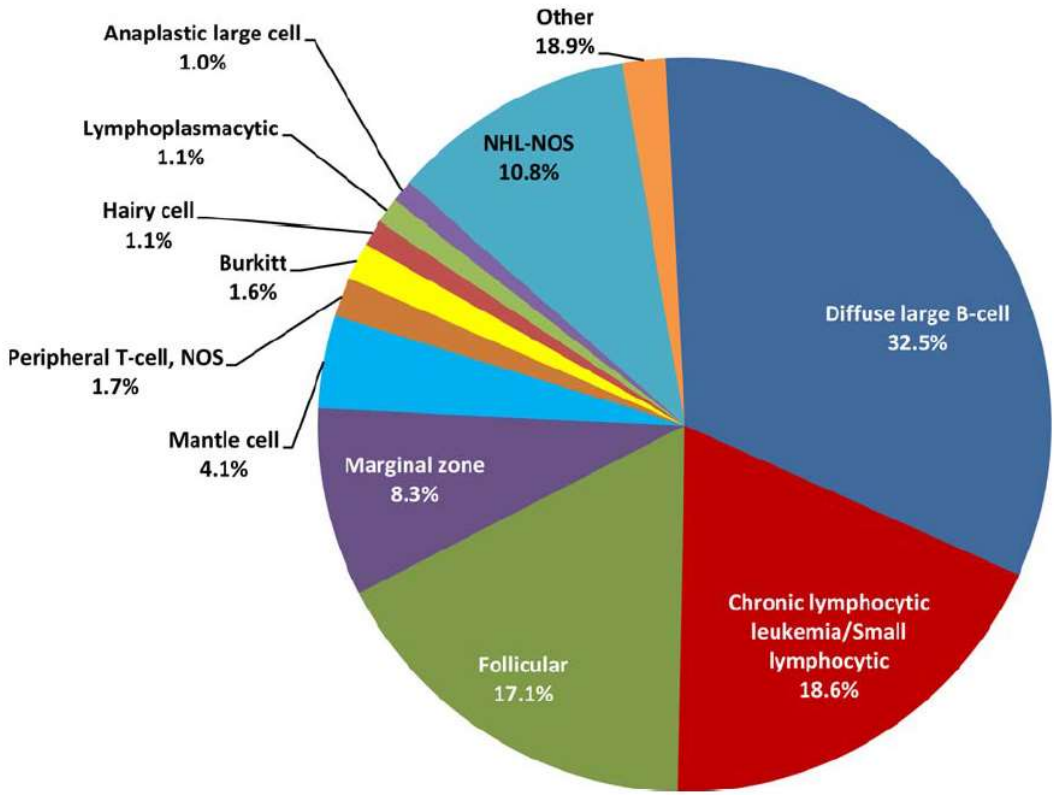
- **Lisocabtagene maraleucel (JCAR017)**
- **CD30 CAR-T therapy for Hodgkin lymphoma**

Outline

- Non-Hodgkin lymphoma (NHL)
  - What is new in the treatment of NHL
    - Diffuse large B cell lymphoma
      - Molecular and genetics
      - Update on CAR-T cell therapy

- Classical Hodgkin lymphoma
  - New therapies
  - Emerging data on CAR-T therapy

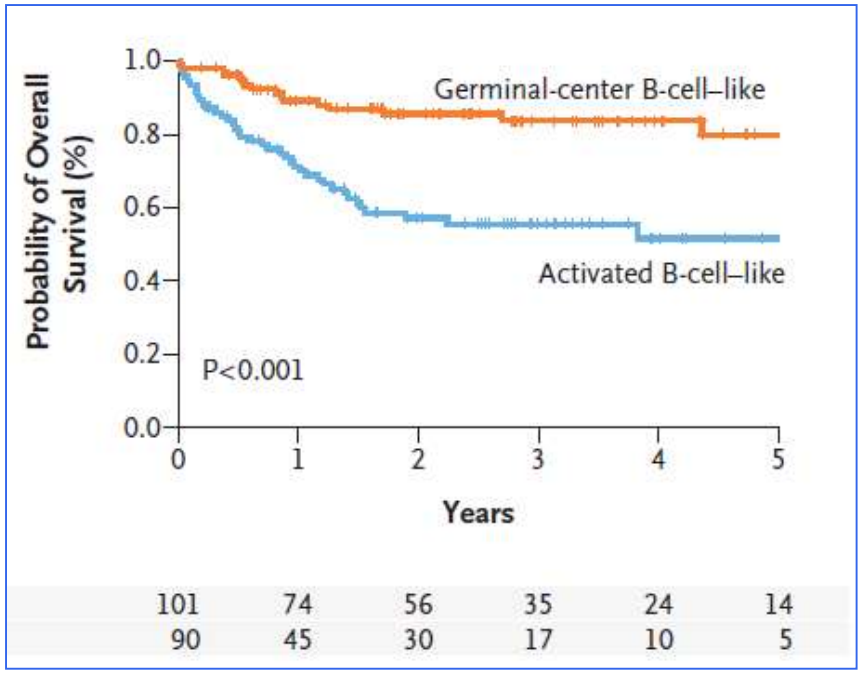
Distribution of NHL: 2009-2011 in the National Cancer Database



Al-Hamadani, et al. Am J Hematol. 2015; 90:790-95

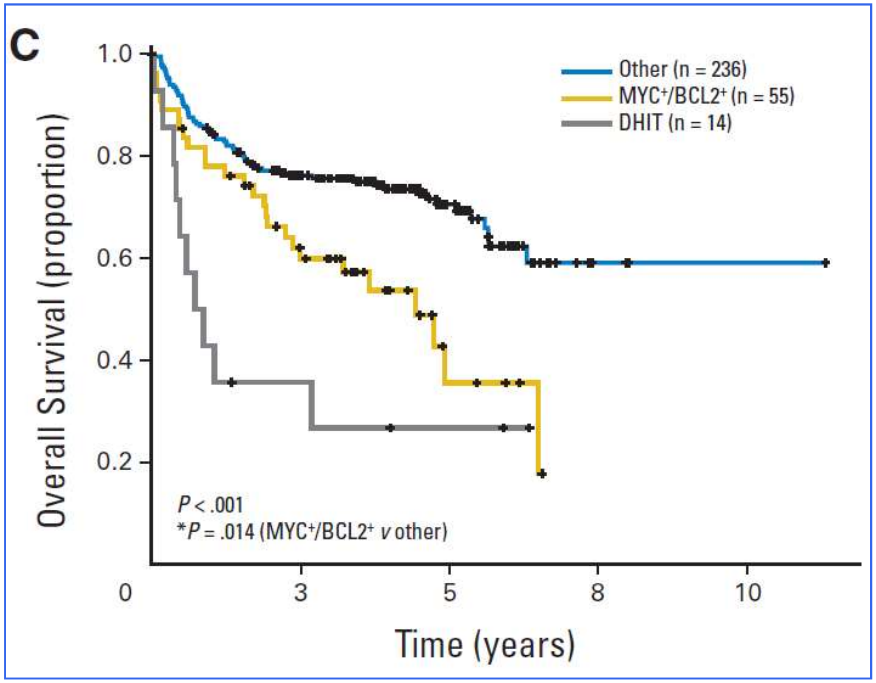
DLBCL is a molecularly heterogeneous disease with different prognosis

Patients with ABC DLBCL are less likely to be cured by R-CHOP



N Engl J Med. 2008 Nov 27;359(22):2313-23

"Double-Hit" (Myc + Bcl-2) carries poor prognosis



J Clin Oncol 2012 30:3452-3459.

Unmet Needs

- Primary refractory or first relapse within 12 months
- Transformed lymphoma
- Relapse post -autologous HCT or not autologous transplant eligible

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Genetics and Pathogenesis of Diffuse Large B-Cell Lymphoma

R. Schmitz, G.W. Wright, D.W. Huang, C.A. Johnson, J.D. Phelan, J.Q. Wang, S. Roulland, M. Kasbekar, R.M. Young, A.L. Shaffer, D.J. Hodson, W. Xiao, X. Yu, Y. Yang, H. Zhao, W. Xu, X. Liu, B. Zhou, W. Du, W.C. Chan, E.S. Jaffe, R.D. Gascoyne, J.M. Connors, E. Campo, A. Lopez-Guillermo, A. Rosenwald, G. Ott, J. Delabie, L.M. Rimsza, K. Tay Kuang Wei, A.D. Zelenetz, J.P. Leonard, N.L. Bartlett, B. Tran, J. Shetty, Y. Zhao, D.R. Soppet, S. Pittaluga, W.H. Wilson, and L.M. Staudt

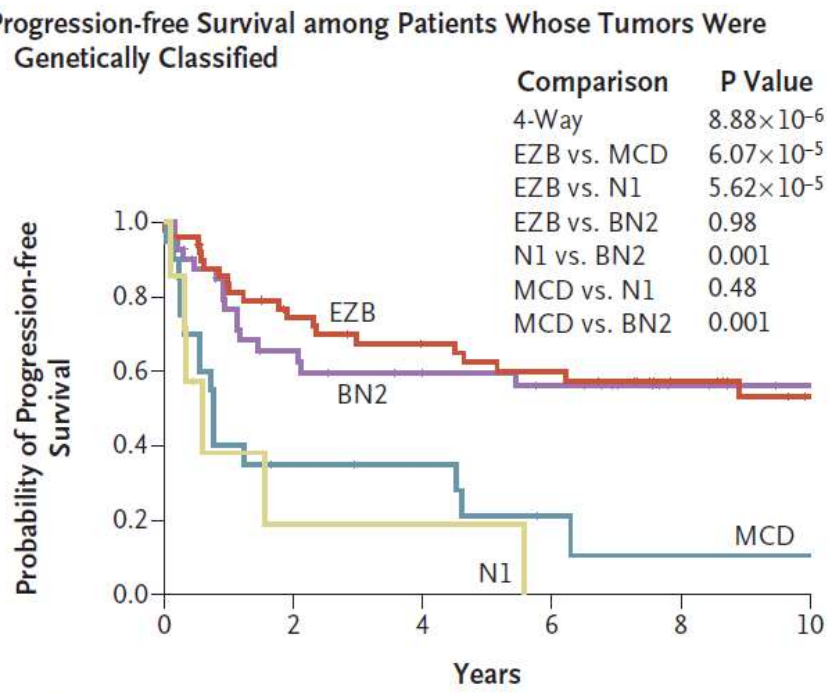
DLBCL genetic subtypes

- **MCD:** co-occurrence of *MYD88* and CD79B mutations
- **BN2:** *BCL6* fusions and *NOTCH2* mutations
- **N1:** based on NOTCH1 mutations
- **EZB:** based on *EZH2* mutations and *BCL2* translocations

Schmitz et al. N Engl J Med. 2018; 378: 1396-407

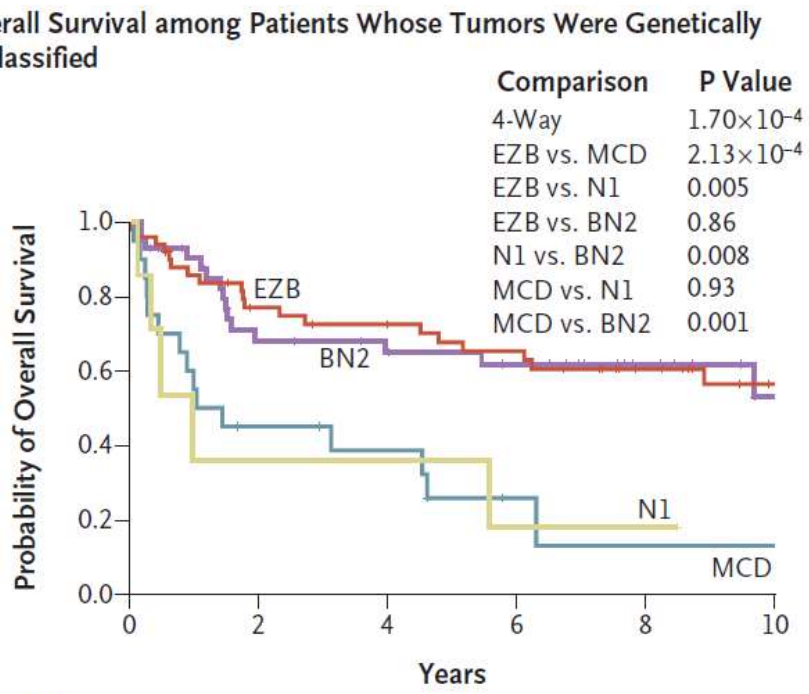
Genetic subtypes of DLBCL and survival

A Progression-free Survival among Patients Whose Tumors Were Genetically Classified



No. at Risk						
MCD	20	6	5	2	1	1
BN2	41	22	17	15	8	5
N1	7	1	1	0	0	0
EZB	49	32	27	24	17	11

B Overall Survival among Patients Whose Tumors Were Genetically Classified



No. at Risk						
MCD	20	8	6	2	1	1
BN2	42	24	20	18	11	5
N1	7	2	2	1	1	0
EZB	50	34	30	27	19	11

Schmitz et al. N Engl J Med. 2018; 378: 1396-407

Diffuse large B-cell lymphoma

- It is anticipated that 74,200 persons will develop non-Hodgkin lymphoma in the US in 2019[a]
  - Approx. 30-35% will be diffuse large B-cell (DLBCL) type
- First-line chemo-immunotherapy yields successful outcomes in two-third of cases[b]
- High-dose therapy and autologous HCT cures ~50% of chemosensitive-relapsed cases[c]
  - But outcomes are dismal for those who receive an auto-HCT with relapsed refractory disease (< 15% are cured)[d]

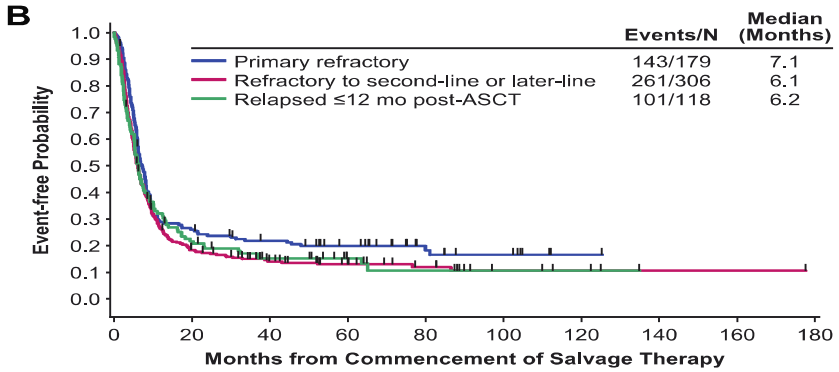
MAYO CLINIC

a. Siegel RL, et al. CA Cancer J Clin. 2019; 69:7-34
b. Feugier P, et al. J Clin Oncol 23:4117-26, 2005
c. Philip T, et al. N Engl J Med 333:1540-5, 1995
d. Philip T, et al. N Engl J Med 316:1493-8, 1987

Before availability of CAR-T

Table 2. Rate of response to chemotherapy after refractory disease

	MDACC (n = 165)	IA/MC (n = 82)	LY.12 (CCTG) (n = 219)	CORAL (LYSARC) (n = 170)	Pooled* (N = 636)
Patients evaluated for response, n†	165	82	106	170	523
Response rate, % (95% CI)	20	26	26	31	26 (21-31)
CR rate	7	7	2	15	7 (3-15)
PR rate	13	18	25	16	18 (13-23)
Response rate by refractory category, % (95% CI)					
Primary refractory					
RR	—	25	27	10	20 (11-34)
CR rate	—	10	1	2	3 (1-11)
Refractory to second-line or later-line therapy					
RR	20	21	20	40	26 (17-39)
CR rate	7	5	20	18	10 (5-20)
Relapse ≤12 mo post-ASCT					
RR	19	35	—	39	34 (24-45)
CR rate	6	10	—	25	15 (6-31)



Crump M, et al. Blood. 2017; 130 (16): 1800-09

Immunotherapy

Bone Marrow Transplantation (2017) **52,** 1487–1494

www.nature.com/bmt

REVIEW

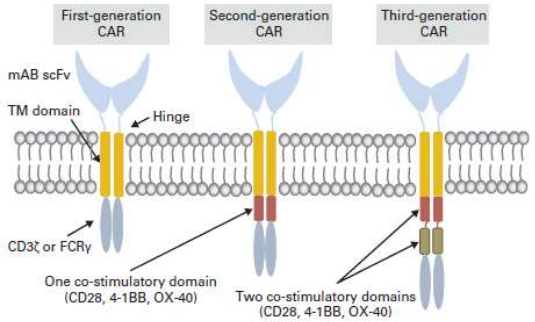
Is myeloablative dose intensity necessary in allogeneic hematopoietic cell transplantation for lymphomas?

MA Kharfan-Dabaja[1,2], N El-Jurdi[3], E Ayala[1,2], AS Kanate[4], BN Savani[5] and M Hamadani[6]

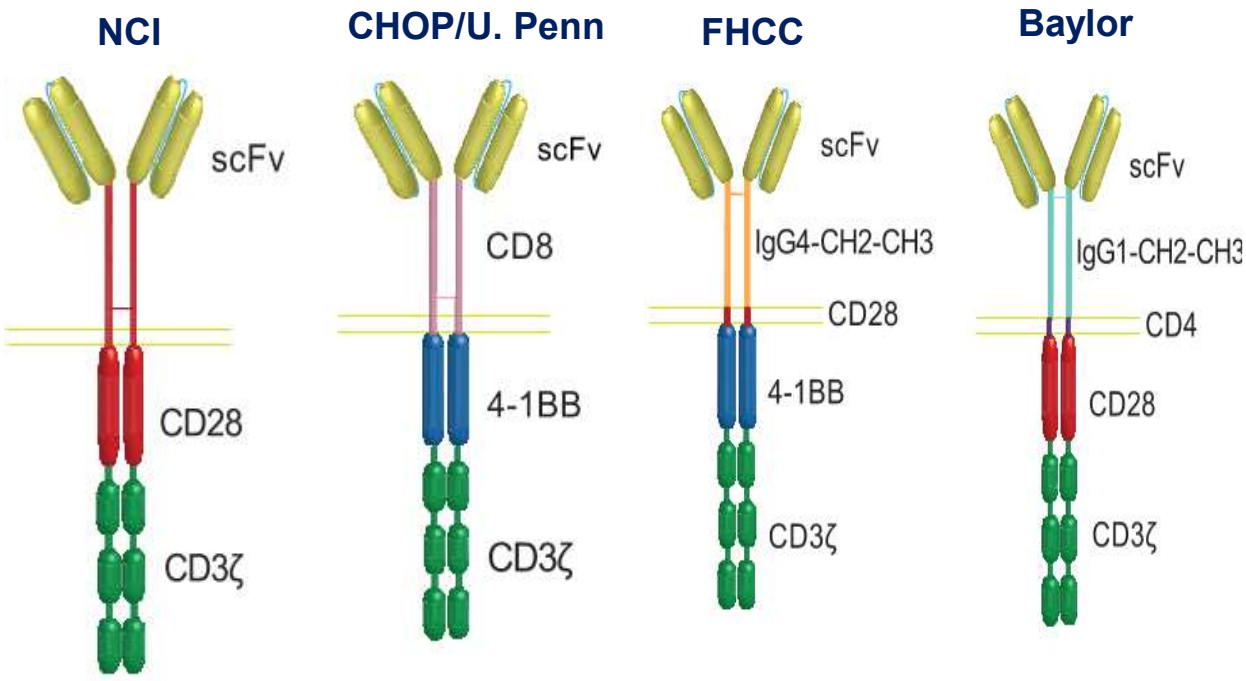
Table 3. Studies comparing MAC and RIC allo-HCT in patients with DLBCL

Author (ref)	*N*	*Conditioning regimen*	*NRM*	*PFS*	*OS*	*Comments*
Bacher *et al.*,[54] CIBMTR	396	MAC = 165 RIC = 143 NMA = 88	MAC = 56% RIC = 47% NMA = 36% (5-year) $P = 0.007$	MAC = 18% RIC = 15% NMA = 25% (5-year) $P = 0.309$	MAC = 18% RIC = 20% NMA = 26% (5-year) $P = 0.365$	ATG at conditioning regimen was used more often with RIC and NMA as compared to MAC KPS < 90, prior relapse resistant to therapy, and use of unrelated donors resulted in higher NRM
Fenske *et al.*,[55] CIBMTR	503	MAC = 127 RIC = 376	MAC resulted in worse NRM vs RIC ($\leqslant$10 months from allo-HCT) HR = 1.99 (95%CI = 1.34, 2.95) $P = 0.001$	MAC = 27% RIC = 30% (5-year) $P = 0.47$	MAC = 28% RIC = 37% (5-year) $P = 0.055$	Beyond 10 months from allo-HCT, the risk of NRM was similar between MAC and RIC (HR = 0.59 (95%CI = 0.25, 1.39), $P = 0.23$ At 1-year after allo-HCT, OS favored RIC (56% vs. 44%, $P = 0.01$)
van Kampen *et al.*,[56] EBMT	101	MAC = 37 RIC = 64	MAC = 41% RIC = 20% (3-year) $P = 0.05$	—	—	Patients undergoing RIC allo-HCT were significantly older (54 vs 43 years, $P < 0.001$) PBSC were more commonly used in RIC allo-HCT (84 vs 60%, $P < 0.001$) No difference in PFS and OS between RIC and MAC allo-HCT
Hamadani *et al.*,[57] CIBMTR	533[a]	MAC = 307 RIC/NMA = 226	MAC = 53% RIC/NMA = 42% (3-year) $P = 0.03$	MAC = 19% RIC/NMA = 23% (3-year) $P = 0.40$	MAC = 19% RIC = 28% (3-year) $P = 0.027$	On multivariate analysis, follicular histology was associated with better PFS and OS when compared with DLBCL
Robinson *et al.*,[58] EBMT	230[b]	MAC = 132 RIC = 98	MAC = 25%[c] RIC = 19%[c]	MAC = 28%[c] RIC = 28%[c]	MAC = 30%[c] RIC = 38%[c]	After adjusting for confounding factors NRM was significantly worse for patients undergoing allo-HCT (vs auto-HCT) without difference in incidence of relapse

CD19+ CARs



Park JH, et al. J Clin Oncol. 2015; 33: 651-53



CAR T-cell therapy in diffuse large B-cell lymphoma

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma

S.S. Neelapu, F.L. Locke, N.L. Bartlett, L.J. Lekakis, D.B. Miklos, C.A. Jacobson, I. Braunschweig, O.O. Oluwole, T. Siddiqi, Y. Lin, J.M. Timmerman, P.J. Stiff, J.W. Friedberg, I.W. Flinn, A. Goy, B.T. Hill, M.R. Smith, A. Deol, U. Farooq, P. McSweeney, J. Munoz, I. Avivi, J.E. Castro, J.R. Westin, J.C. Chavez, A. Ghobadi, K.V. Komanduri, R. Levy, E.D. Jacobsen, T.E. Witzig, P. Reagan, A. Bot, J. Rossi, L. Navale, Y. Jiang, J. Aycock, M. Elias, D. Chang, J. Wiezorek, and W.Y. Go

This article was published on December 10, 2017, at NEJM.org.

N Engl J Med 2017;377:2531-44.
DOI: 10.1056/NEJMoa1707447

N=111 patients

Table 1. Treatment Disposition and Baseline Characteristics of the Patients.*

Variable	Patients with DLBCL	Patients with PMBCL or TFL	All Patients
Treatment disposition			
No. of patients enrolled	81	30	111
Treatment with axi-cel — no. (%)			
Yes	77 (95)	24 (80)	101 (91)
No	4 (5)	6 (20)	10 (9)
Death before treatment†	1 (1)	2 (7)	3 (3)
Adverse event‡	3 (4)	2 (7)	5 (5)
Other§	0	2 (7)	2 (2)
Characteristics at baseline			
No. of patients	77	24	101
Disease type — no. (%)			
DLBCL	77 (100)	0	77 (76)
PMBCL	0	8 (33)	8 (8)
TFL	0	16 (67)	16 (16)
Age			
Median (range) — yr	58 (25–76)	57 (23–76)	58 (23–76)
≥65 yr — no. (%)	17 (22)	7 (29)	24 (24)
Male sex — no. (%)	50 (65)	18 (75)	68 (67)
ECOG performance-status score of 1 — no. (%)	49 (64)	10 (42)	59 (58)
Disease stage — no. (%)			
I or II	10 (13)	5 (21)	15 (15)
III or IV	67 (87)	19 (79)	86 (85)
International Prognostic Index score — no. (%)¶			
0–2	40 (52)	13 (54)	53 (52)
3 or 4	37 (48)	11 (46)	48 (48)
CD-19 status — no./total no. (%)‖			
Negative	7/63 (11)	1/19 (5)	8/82 (10)
Positive	56/63 (89)	18/19 (95)	74/82 (90)
Prior therapies — no. (%)			
≥Three prior lines of therapy	49 (64)	21 (88)	70 (69)
History of primary refractory disease**	23 (30)	3 (12)	26 (26)
History of resistance to two consecutive lines	39 (51)	15 (62)	54 (53)

Table 1. (Continued.)

Variable	Patients with DLBCL	Patients with PMBCL or TFL	All Patients
Refractory subgroup at study entry — no. (%)			
Primary refractory	2 (3)	0	2 (2)
Refractory to second-line or subsequent therapy	59 (77)	19 (79)	78 (77)
Relapse after autologous stem-cell transplantation	16 (21)	5 (21)	21 (21)

This article was published on December 10, 2017, at NEJM.org.

N Engl J Med 2017;377:2531-44.
DOI: 10.1056/NEJMoa1707447

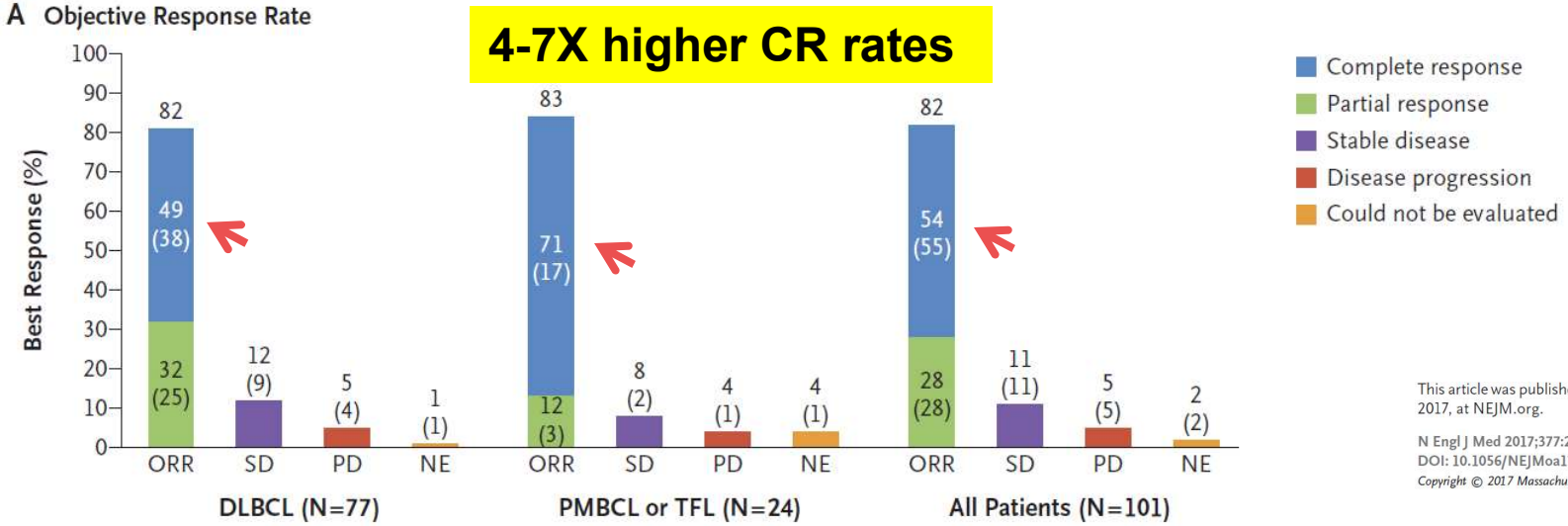
Before CAR-T

Table 2. Rate of response to chemotherapy after refractory disease

	MDACC (n = 165)	IA/MC (n = 82)	LY.12 (CCTG) (n = 219)	CORAL (LYSARC) (n = 170)	Pooled* (N = 636)
Patients evaluated for response, n†	165	82	106	170	523
Response rate, % (95% CI)	20	26	26	31	26 (21-31)
CR rate	7	7	2	15	7 (3-15)
PR rate	13	18	25	16	18 (13-23)
Response rate by refractory category, % (95% CI)					
Primary refractory					
RR	—	25	27	10	20 (11-34)
CR rate	—	10	1	2	3 (1-11)
Refractory to second-line or later-line therapy					
RR	20	21	20	40	26 (17-39)
CR rate	7	5	20	18	10 (5-20)
Relapse ≤12 mo post-ASCT					
RR	19	35	—	39	34 (24-45)
CR rate	6	10	—	25	15 (6-31)

Axicabtagene ciloleucel

4-7X higher CR rates



This article was published on December 10, 2017, at NEJM.org.

N Engl J Med 2017;377:2531-44.
DOI: 10.1056/NEJMoa1707447

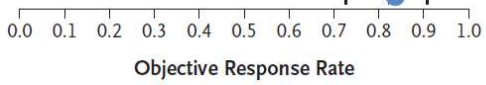
MAYO CLINIC

Crump M, et al. Blood. 2017; 130 (16): 1800-09

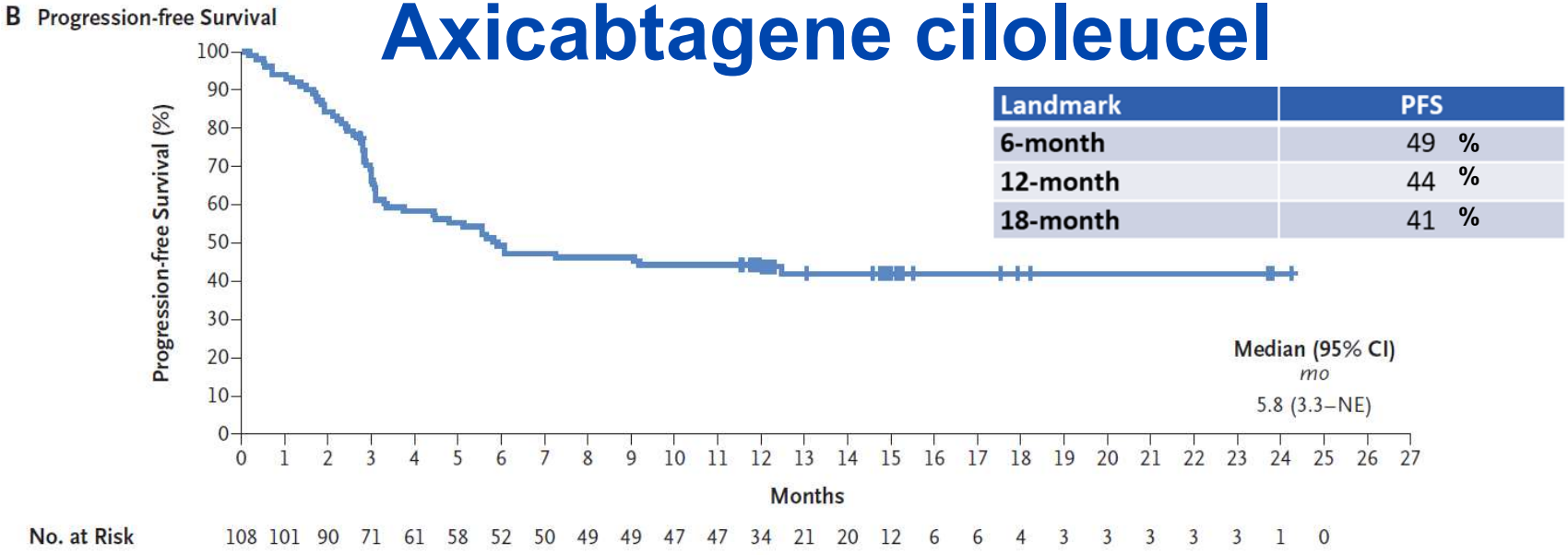
Neelapu SS, et al. N Engl J Med. 2017; 377:2531-44

B Subgroup Analysis

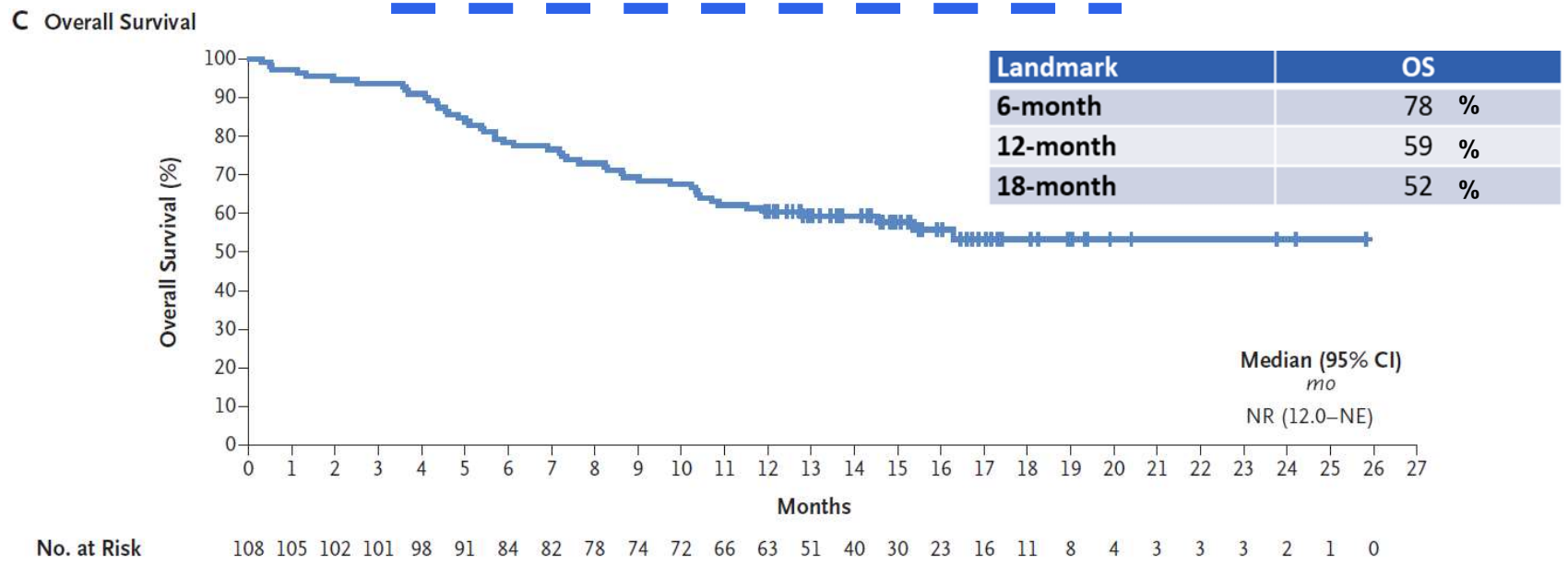
Subgroup	No. of Patients Who Could Be Evaluated	No. of Patients with Event	Objective Response Rate (95% CI)
Overall	101	83	0.82 (0.73–0.89)
Refractory subgroup			
Refractory to ≥second-line therapy	78	65	0.83 (0.73–0.91)
Relapse after ASCT	21	16	0.76 (0.53–0.92)
Age			
<65 yr	77	61	0.79 (0.68–0.88)
≥65 yr	24	22	0.92 (0.73–0.99)
Disease stage			
I or II	15	13	0.87 (0.60–0.98)
III or IV	86	70	0.81 (0.72–0.89)
IPI risk score			
0–2	53	46	0.87 (0.75–0.95)
3 or 4	48	37	0.77 (0.63–0.88)
Extranodal disease			
Yes	70	56	0.80 (0.69–0.89)
No	31	27	0.87 (0.70–0.96)
Bulky disease (≥10 cm)			
Yes	17	12	0.71 (0.44–0.90)
No	84	71	0.85 (0.75–0.91)
Treatment history			
Primary refractory disease	26	23	0.88 (0.70–0.98)
Refractory to two consecutive lines	54	42	0.78 (0.64–0.88)
CD19 status			
Positive	74	63	0.85 (0.75–0.92)
Negative	8	6	0.75 (0.35–0.97)
CD19 histologic score			
≤150	26	22	0.85 (0.65–0.96)
>150	56	47	0.84 (0.72–0.92)
Cell of origin			
Germinal center B-cell–like subtype	49	43	0.88 (0.75–0.95)
Activated B-cell–like subtype	17	13	0.76 (0.50–0.83)
CD4:CD8 ratio			
>1	47	41	0.87 (0.74–0.95)
≤1	52	40	0.77 (0.63–0.87)
Tocilizumab use			
Yes	43	36	0.84 (0.69–0.93)
No	58	47	0.81 (0.69–0.90)
Glucocorticoid use			
Yes	27	21	0.78 (0.58–0.91)
No	74	62	0.84 (0.73–0.91)



Axicabtagene ciloleucel



Landmark	PFS
6-month	49 %
12-month	44 %
18-month	41 %

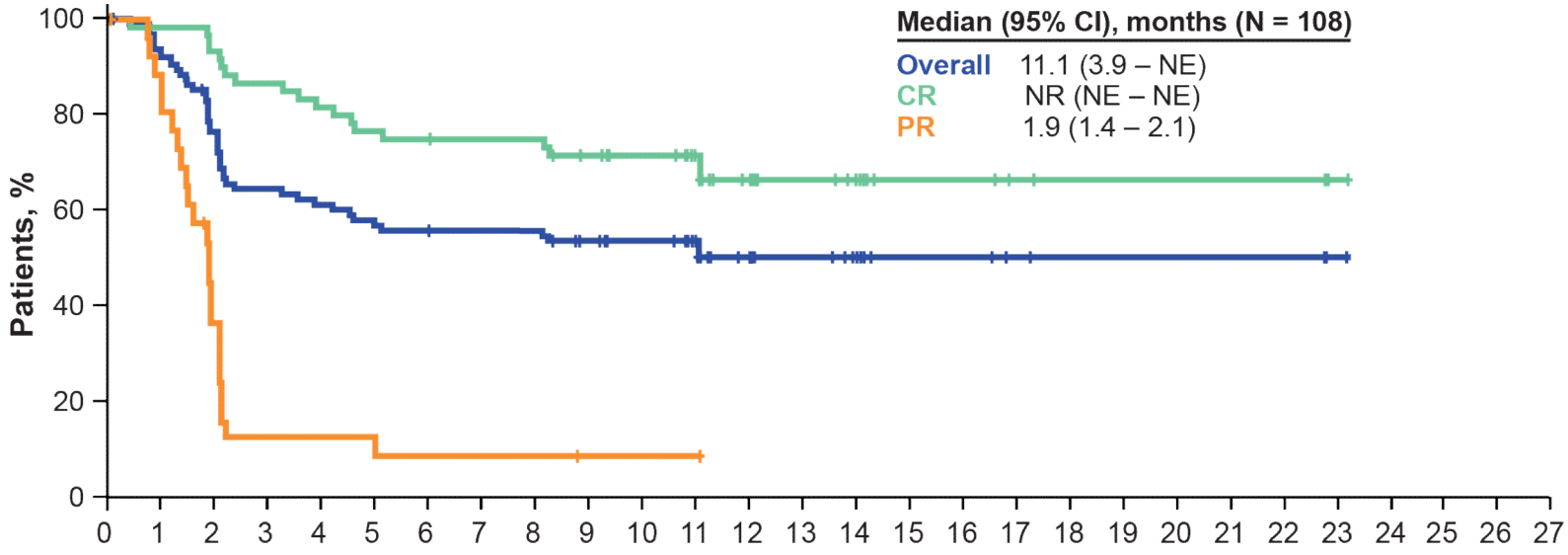


Landmark	OS
6-month	78 %
12-month	59 %
18-month	52 %

MAYO CLINIC

Neelapu SS, et al. N Engl J Med. 2017; 377:2531-44

DOR by best objective response (median F/U of 15.4 months)



Patients at Risk

Overall	89	82	67	56	53	49	48	47	47	42	38	31	19	16	12	6	6	4	3	3	3	3	3	1	0
CR	63	61	58	53	50	47	46	45	45	41	37	30	19	16	12	6	6	4	3	3	3	3	3	1	0
PR	26	21	9	3	3	2	2	2	2	1	1	1	0												

American Society *of* Hematology
Helping hematologists conquer blood diseases worldwide

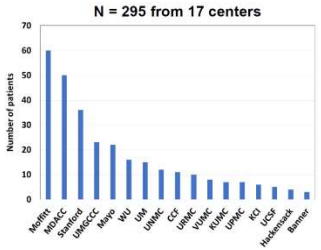
Axicabtagene Ciloleucel (Axi-cel) CD19 Chimeric Antigen Receptor (CAR) T-cell Therapy for Relapsed/Refractory Large B-cell Lymphoma: Real World Experience

Loretta J. Nastoupil*, Michael D. Jain*, Jay Yaakov Spiegel, Armin Ghobadi, Yi Lin, Saurabh Dahiya, Matthew Lunning, Lazaros Lekakis, Patrick Reagan, Olalekan Oluwole, Joseph McGuirk, Abhinav Deol, Alison R. Sehgal, Andre Goy, Brian T. Hill, Andreadis Charalambos, Javier Munoz, Jason Westin, Julio C. Chavez, Amanda Cashen, Nabil N. Bennani, Aaron Rapoport, Julie M. Vose, Lei Feng **David B. Miklos**, Sattva S. Neelapu**, Frederick L. Locke****

*LJN and MDJ are co-first authors
**DBM, SSN, and FLL are co-senior authors

ASH 2018 Abstract 91

- 17 US academic centers
- 165 patients infused Axicabtagene Ciloleucel
  - Data reported on 134 cases



MAYO CLINIC

Nastoupil LJ, et al. ASH 2018 (abs # 91)
Courtesy, Dr. Micheal Jain

Baseline Characteristics

Characteristic	SOC Axi-cel (N=293)	ZUMA-1[1] (N=108)
Number of patients Infused/Leukapheresed	274/295 (93%)	108/119 (91%)
Median age, years (range)	60 (21-83)	58 (23-76)
≥ 65yrs, N (%)	96 (33)	27 (25)
Male, N (%)	189 (65)	73 (68)
ECOG PS 0-1, N (%)	232 (81)	108 (100)
PS 2/3-4, N (%)	44 (15) / 12 (4)	0
Disease Stage III/IV, N (%)	240 (84)	90 (83)
DLBCL, N (%)	197 (68)	77 (76)
PMBCL/tFL, N (%)	17 (6) / 75 (26)	8 (7) /16 (15)
IPI ≥ 3, N (%)	158 (55)	48 (44)
> 3 prior therapies, N (%)	215 (75)	76 (70)
Primary refractory, N (%)	100 (35)	27 (25)
Refractory to second line or later, N (%)	121 (42)	80 (74)
Relapsed post-ASCT, N (%)	95 (33)	25 (23)

SOC: Standard of care; N: number; ECOG PS: Eastern Cooperative Oncology Group performance status; tFL: transformed FL; IPI: International Prognostic Index

[1]Neelapu, Locke et al. *NEJM*. 2017 Dec 28;377(26):2531-2544

Nastoupil LJ, et al. ASH 2018 (abs # 91)
Courtesy, Dr. Micheal Jain

Safety of Axi-Cel in the Real World

	SOC Axi-cel N = 274 (mITT)	ZUMA-1[1] N = 108
All Grades of CRS*, N (%)	240 (92%)	100 (93%)
Grade ≥ 3 CRS, N (%)	18 (7%)	14 (13%)
Median time to onset of CRS	3 days	2 days
All Grades of NT**, N (%)	181 (69%)	70 (65%)
Grade ≥ 3 NT, N (%)	85 (33%)	33 (31%)
Median time to onset of NT	6 days	5 days

* Lee criteria used for grading CRS

** CTCAE or CARTOX criteria used for grading neurotoxicity

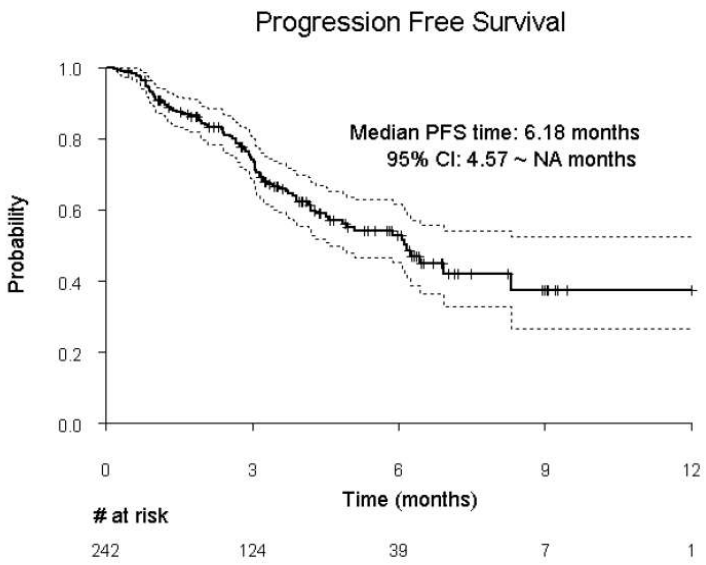
[1]Neelapu, Locke et al. *NEJM*. 2017 Dec 28;377(26):2531-2544

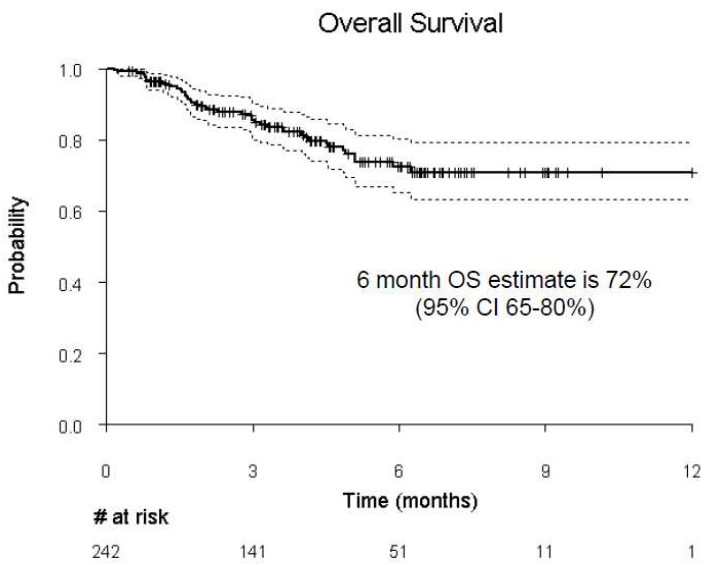
American Society *of* Hematology ASH 2018 Abstract 91

MAYO CLINIC

Nastoupil LJ, et al. ASH 2018 (abs # 91)
Courtesy, Dr. Micheal Jain

PFS and OS at Median F/U of 3.9 Months in the Real World





mITT population, OS calculated from time of CAR T infusion until death or last contact.

American Society *of* Hematology ASH 2018 Abstract 91

ZUMA 1: Median PFS= 5.8 months; Median OS= not reached

MAYO CLINIC

Nastoupil LJ, et al. ASH 2018 (abs # 91)
Courtesy, Dr. Micheal Jain

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Stephen J. Schuster, M.D., Michael R. Bishop, M.D., Constantine S. Tam, M.D., Edmund K. Waller, M.D., Ph.D., Peter Borchmann, M.D., Joseph P. McGuirk, D.O., Ulrich Jäger, M.D., Samantha Jaglowski, M.D., Charalambos Andreadis, M.D., Jason R. Westin, M.D., Isabelle Fleury, M.D., Veronika Bachanova, M.D., Ph.D., S. Ronan Foley, M.D., P. Joy Ho, M.B., B.S., D.Phil., Stephan Mielke, M.D., John M. Magenau, M.D., Harald Holte, M.D., Ph.D., Serafino Pantano, Ph.D., Lida B. Pacaud, M.D., Rakesh Awasthi, Ph.D., Jufen Chu, Ph.D., Özlem Anak, M.D., Gilles Salles, M.D., Ph.D., and Richard T. Maziarz, M.D., for the JULIET Investigators*

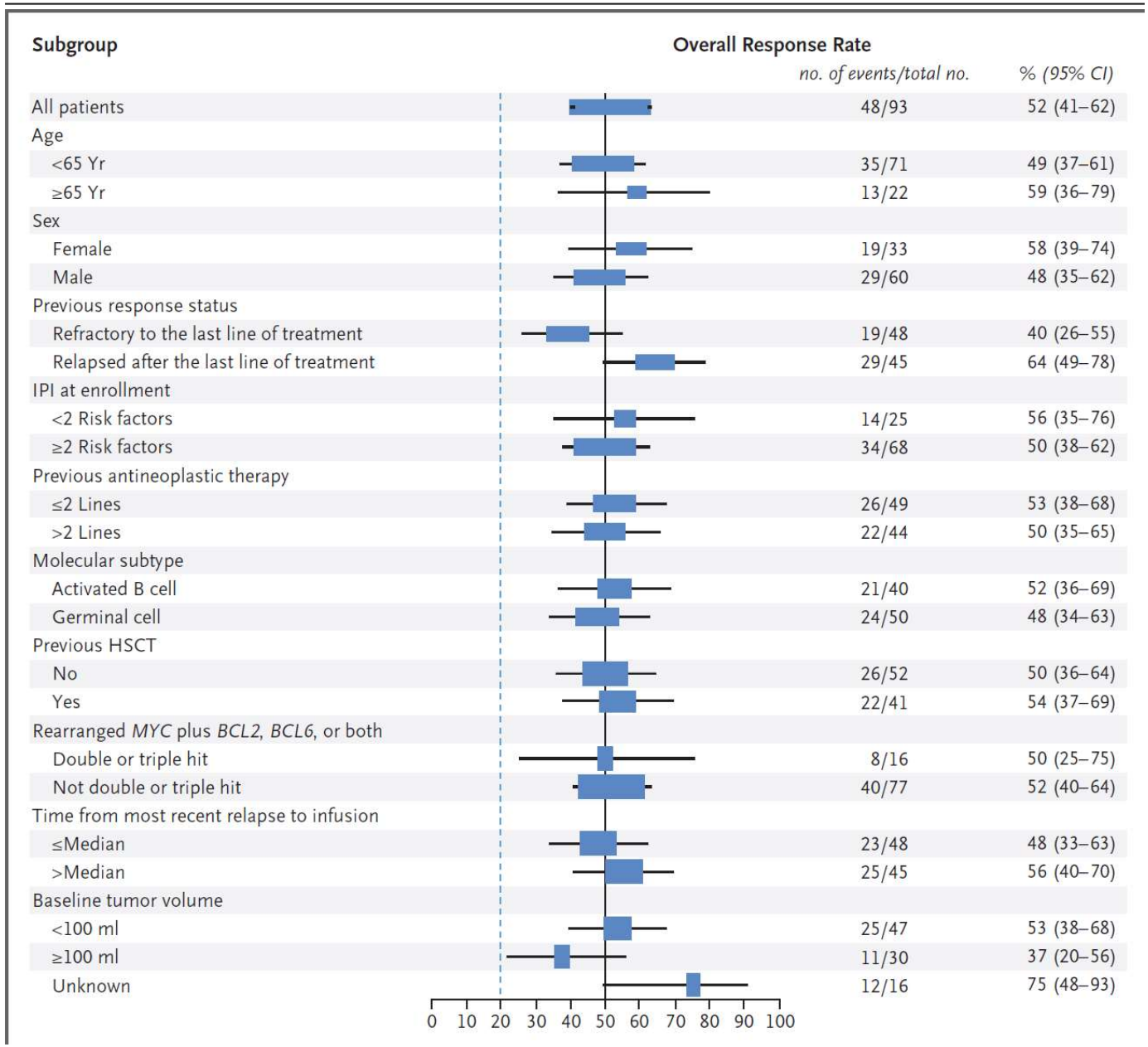
This article was published on December 1, 2018, at NEJM.org.

N Engl J Med 2019;380:45-56.
DOI: 10.1056/NEJMoa1804980

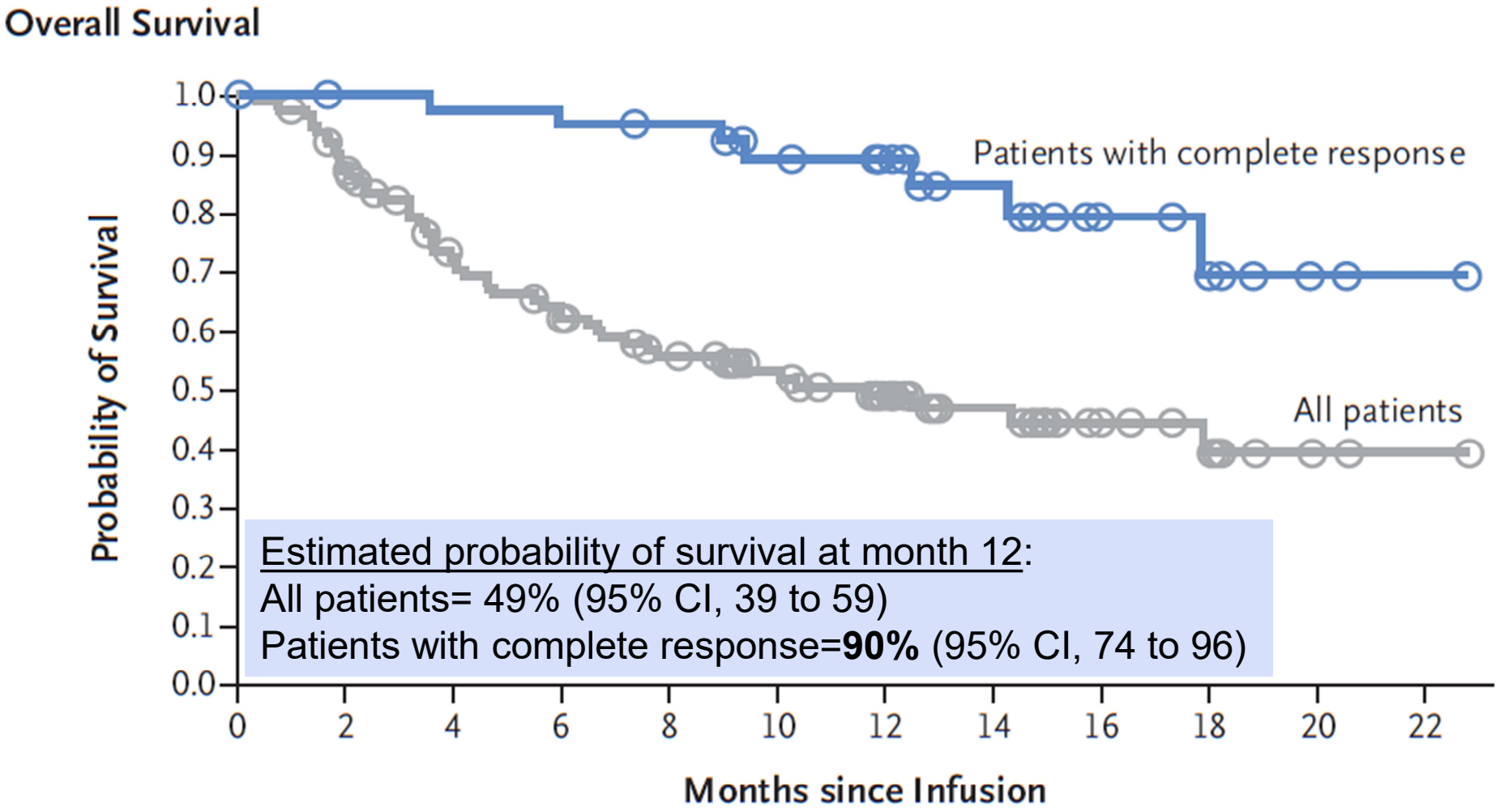
N=111 patients

Table 1. Demographic and Clinical Characteristics of the Patients in the Full Analysis Set at Baseline.*

Characteristic	Patients (N=111)
Median age (range) — yr	56 (22–76)
Age ≥65 yr — no. (%)	25 (23)
ECOG performance status — no. (%)†	
0	61 (55)
1	50 (45)
Disease stage at study entry — no. (%)‡	
Stage I	8 (7)
Stage II	19 (17)
Stage III	22 (20)
Stage IV	62 (56)
Bone marrow involvement at study entry — no. (%)	8 (7)
Diagnosis on central histologic review — no. (%)	
Diffuse large B-cell lymphoma, not otherwise specified	88 (79)
Transformed follicular lymphoma	21 (19)
Other	2 (2)
Double- or triple-hit rearrangement: *MYC* plus *BCL2*, *BCL6*, or both — no./total no. (%)§	19/70 (27)
Cell of origin of cancer — no. (%)	
Germinal center B-cell type	63 (57)
Non–germinal center B-cell type	45 (41)
Missing data	3 (3)
No. of previous lines of antineoplastic therapy — no. (%)¶	
1	5 (5)
2	49 (44)
3	34 (31)
4–6	23 (21)
Relapse after last therapy — no. (%)‖	50 (45)
Refractory diffuse large B-cell lymphoma — no. (%)**	61 (55)
Previous autologous hematopoietic stem-cell transplantation — no. (%)	54 (49)


Subgroup
Overall Response Rate
no. of events/total no.
% (95% CI)
All patients 48/93 52 (41–62)
Age
<65 Yr 35/71 49 (37–61)
≥65 Yr 13/22 59 (36–79)
Sex
Female 19/33 58 (39–74)
Male 29/60 48 (35–62)
Previous response status
Refractory to the last line of treatment 19/48 40 (26–55)
Relapsed after the last line of treatment 29/45 64 (49–78)
IPI at enrollment
<2 Risk factors 14/25 56 (35–76)
≥2 Risk factors 34/68 50 (38–62)
Previous antineoplastic therapy
≤2 Lines 26/49 53 (38–68)
>2 Lines 22/44 50 (35–65)
Molecular subtype
Activated B cell 21/40 52 (36–69)
Germinal cell 24/50 48 (34–63)
Previous HSCT
No 26/52 50 (36–64)
Yes 22/41 54 (37–69)
Rearranged MYC plus BCL2, BCL6, or both
Double or triple hit 8/16 50 (25–75)
Not double or triple hit 40/77 52 (40–64)
Time from most recent relapse to infusion
≤Median 23/48 48 (33–63)
>Median 25/45 56 (40–70)
Baseline tumor volume
<100 ml 25/47 53 (38–68)
≥100 ml 11/30 37 (20–56)
Unknown 12/16 75 (48–93)
0 10 20 30 40 50 60 70 80 90 100

JULIET study: Tisagencleucel



Estimated probability of survival at month 12:
All patients= 49% (95% CI, 39 to 59)
Patients with complete response=**90%** (95% CI, 74 to 96)

Schuster SJ, et al. N Engl J Med. 2019; 380:45-56

Long-term Follow-up of Tisagenlecleucel in Adult Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma: Updated Analysis of JULIET Study

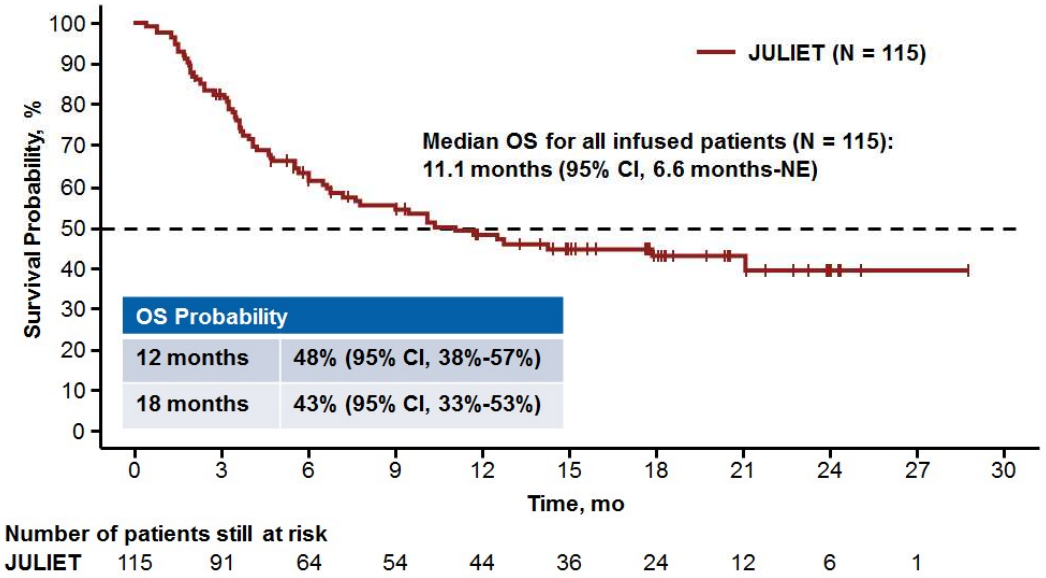
Stephen J. Schuster, Michael R. Bishop, Constantine Tam, Peter Borchmann, Ulrich Jaeger, Edmund K. Waller, Harald Holte, Joseph P. McGuirk, Samantha Jaglowski, Kensei Tobinai, Charalambos Andreadis, Isabelle Fleury, Stephan Mielke, Takanori Teshima, Jason R. Westin, Veronika Bachanova, Stephen Ronan Foley, P. Joy Ho, John M. Magenau, Nina D. Wagner-Johnston, Koji Kato, Marie Jose Kersten, Koen Van Besien, Jufen Chu,
Aline Jary, Özlem Anak, Gilles Salles, Richard T. Maziarz

Presentation at 2019 TCT meeting in Houston, TX
Courtesy Dr. R.T. Maziarz

Schuster SJ, et al. Biol Blood Marrow Transplant. 2019; vol 25 (3), Suppl, S20–S21

JULIET: Median Overall Survival

Median OS not reached (95% CI, 21 months-NE) in patients in CR



- No patients proceeded to allogeneic SCT or auto-SCT while in remission

Auto-SCT, autologous stem cell transplant; CI, confidence interval; CR, complete response; NE, not evaluable; OS, overall survival; SCT, stem cell transplant.
Median OS in CR patients: not reached (95% CI, 21 months-NE).

Presentation at 2019 TCT meeting in Houston, TX
Courtesy Dr. R.T. Maziarz

Schuster SJ, et al. Biol Blood Marrow Transplant. 2019; vol 25 (3), Suppl, S20–S21

JULIET: Safety Profile With Longer Follow-up Consistent With Prior Reports[1]

AESI[a]	All Patients (N = 115)		
	All Grades, n (%)	Grade 3, n (%)	Grade 4, n (%)
Cytokine release syndrome[b]	66 (57)	16 (14)	10 (9)
Prolonged cytopenia[c]	52 (45)	20 (17)	19 (17)
Infections	43 (37)	20 (17)	2 (2)
Neurological events[d]	23 (20)	8 (7)	5 (4)
Febrile neutropenia	17 (15)	15 (13)	2 (2)
Tumor lysis syndrome	2 (2)	1 (1)	1 (1)

- No new safety signals were detected
- No treatment-related mortality was reported

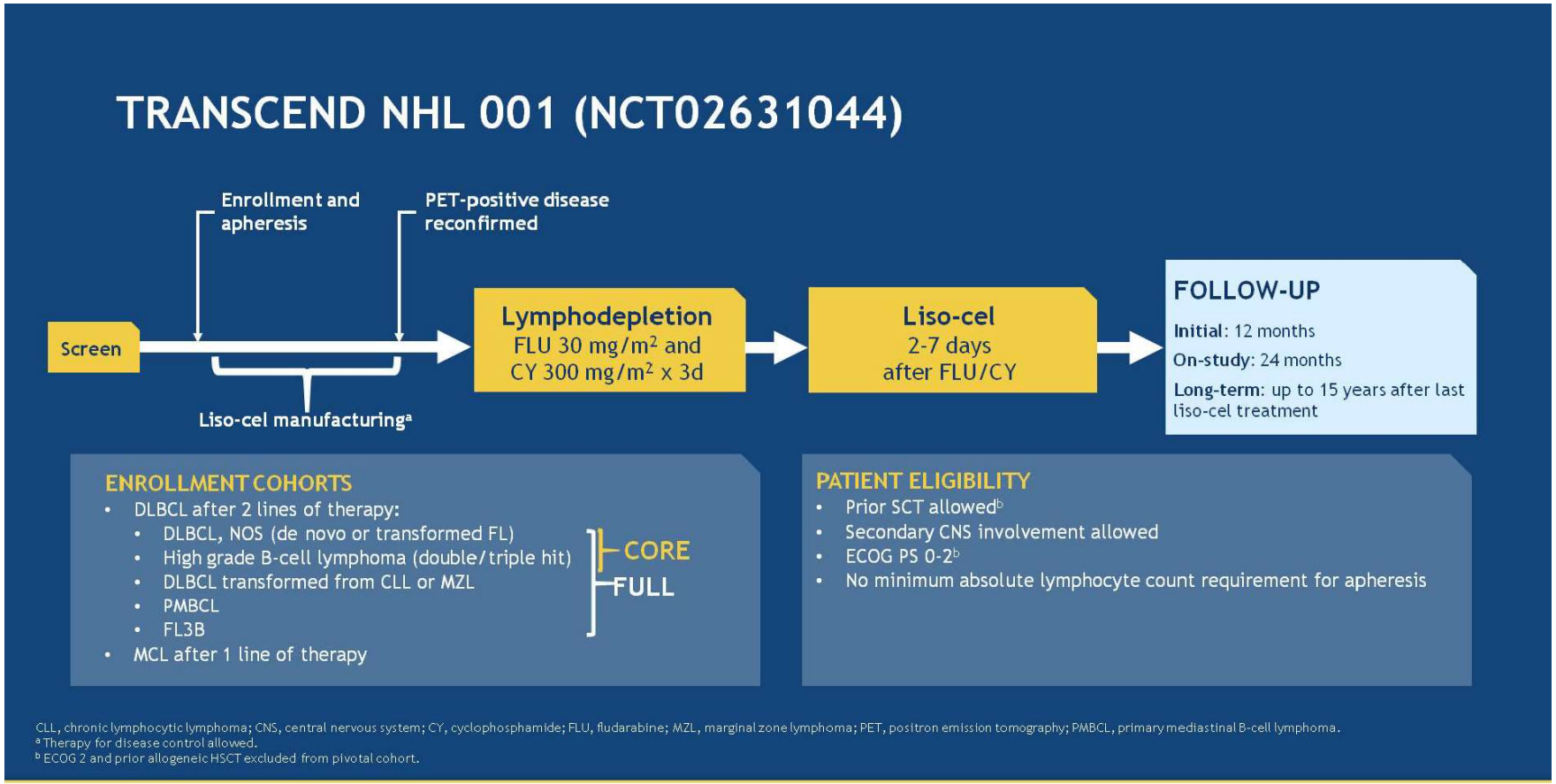
AESI, adverse event of special interest.
[a] Occurring within 8 weeks of tisagenlecleucel infusion; [b] Cytokine release syndrome was graded using the Penn scale; [c] Not resolved by Day 28; [d] A single case of grade 2 cerebral edema was reported as the finding of a computed tomography scan without contrast and suboptimal quality. Repeat scanning with contrast 24 hours later showed no cerebral edema.
1. Borchmann P, et al. Presented at: 23rd Congress of the European Hematology Association; June 16, 2018; Stockholm, Sweden. Abstract S799.

Presentation at 2019 TCT meeting in Houston, TX
Courtesy Dr. R.T. Maziarz

Schuster SJ, et al. Biol Blood Marrow Transplant. 2019; vol 25 (3), Suppl, S20–S21

Lisocabtagene maraleucel (JCAR017)
****not FDA approved****

TRANSCEND NHL 001, pivotal trial of lisocabtagene maraleucel (JCAR017)



Abramson JS, et al. J Clin Oncol 36, 2018 (suppl; abstr 7505)

TRANSCEND NHL 001, pivotal trial of lisocabtagene maraleucel (JCAR017)

- Best ORR
  - FULL=74% (65/88)
  - CORE=80% (52/65)
- Best CR
  - FULL= 52% (46/88)
  - CORE=55% (36/65)

Abramson JS, et al. J Clin Oncol 36, 2018 (suppl; abstr 7505)

TRANSCEND NHL 001, pivotal trial of lisocabtagene maraleucel (JCAR017)

High Response Rates in R/R DLBCL

Potential Dose Response Relationship in CORE Patient Population; DL2 Chosen for Pivotal Cohort

	FULL	CORE		
	All Dose Levels (n=102)	All Dose Levels[a] (n=73)	DL1S (n=33)	DL2S (n=37)
ORR (95% CI), %	75 (65-83)	80 (68-88)	79 (61-91)	78 (62-90)
CR (95% CI), %	55 (45-65)	59 (47-70)	55 (36-72)	62 (45-78)
3-mo ORR (95% CI), %	51 (41-61)	59 (47-70)	52 (34-69)	65 (48-80)
3-mo CR (95% CI), %	38 (29-48)	45 (34-57)	36 (20-55)	51 (34-68)
6-mo ORR (95% CI), %	40 (31-50)	47 (35-59)	42 (26-61)	49 (32-66)
6-mo CR (95% CI), %	34 (25-44)	41 (30-53)	33 (18-52)	46 (30-63)

Baseline high tumor burden well balanced between DL1 and DL2 (≈ 1/3)[b]

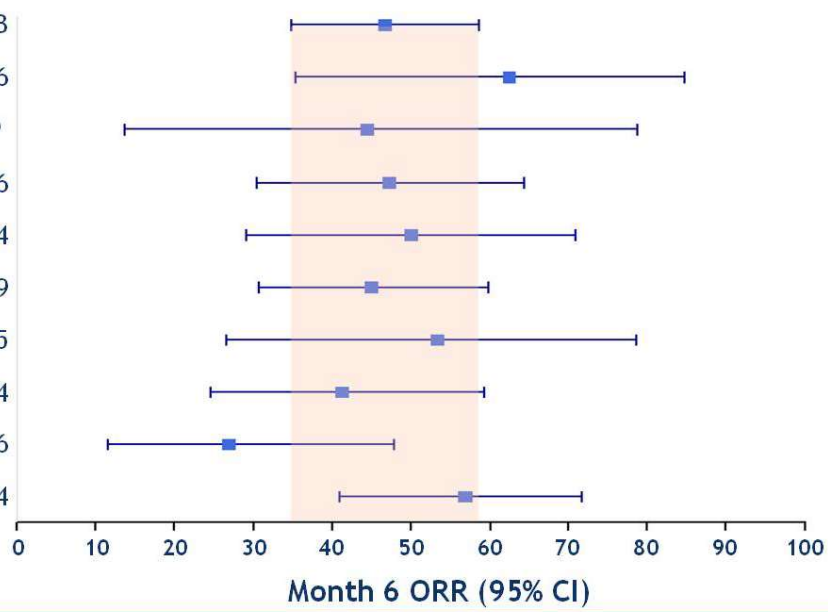
[a] Three patients treated on DL1D had similar outcomes.
[b] Defined as sum of the products of diameters (SPD) > 50 cm^2.

Abramson JS, et al. J Clin Oncol 36, 2018 (suppl; abstr 7505)

TRANSCEND NHL 001, pivotal trial of lisocabtagene maraleucel (JCAR017)

High Durable ORR in Poor-Risk DLBCL Subgroups

Population	ORR (95% CI)	n
CORE patient population[a]	46.6 (34.8-58.6)	73
Double/triple hit	62.5 (35.4-84.8)	16
Double expressor	44.4 (13.7-78.8)	9
Never in CR	47.2 (30.4-64.5)	36
Chemosensitive	50 (29.1-70.9)	24
Chemorefractory	44.9 (30.7-59.8)	49
Relapse < 12 mo from ASCT	53.3 (26.6-78.7)	15
SD/PD to last chemotherapy	41.2 (24.6-59.3)	34
IPI 3-5	26.9 (11.6-47.8)	26
IPI 0-2	56.8 (41-71.7)	44



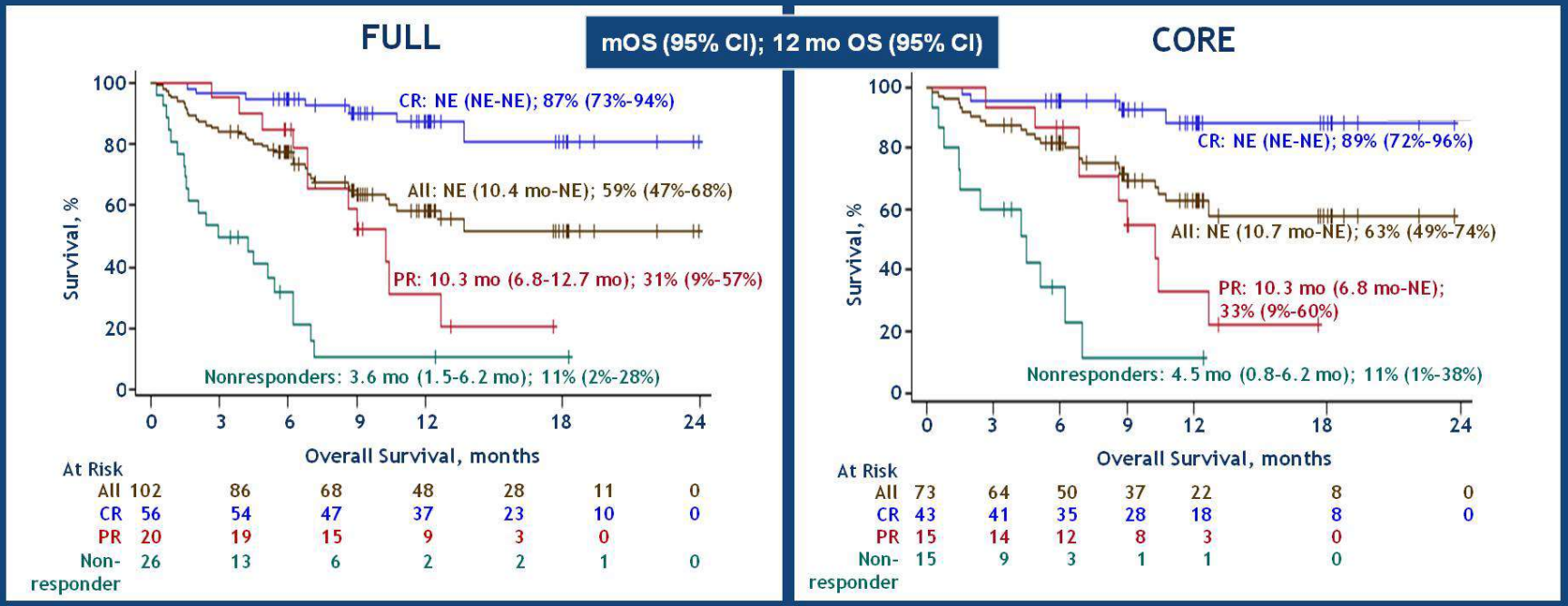
[a] Includes all DLBCL patients treated at all dose levels in CORE.

Abramson JS, et al. J Clin Oncol 36, 2018 (suppl; abstr 7505)

TRANSCEND NHL 001, pivotal trial of lisocabtagene maraleucel (JCAR017)

Overall Survival (OS)

Early OS Encouraging in High-Risk DLBCL Patient Population (Median Follow-up 12 Months)



NE, not estimable.

Abramson JS, et al. J Clin Oncol 36, 2018 (suppl; abstr 7505)

Summary of toxicities of various CD19 CAR T-cell therapies

CAR T product	Study	N	CRS any grade	CRS Grade 3-4	CRES any grade	CRES grade 3-4
Axicabtagene ciloleucel (Neelapu et al.)	ZUMA-1	101 (111)*	93%	13%	64%	28%
Tisagenlecleucel (Schuster et al. and Borchman et al.)	JULIET	111 (165)*	58%	22%	21%	13%
Lisocabtagene maraleucel (Abramson et al.)	TRANSCEND	175**	37%	1%	25%	15%

*** Enrolled**

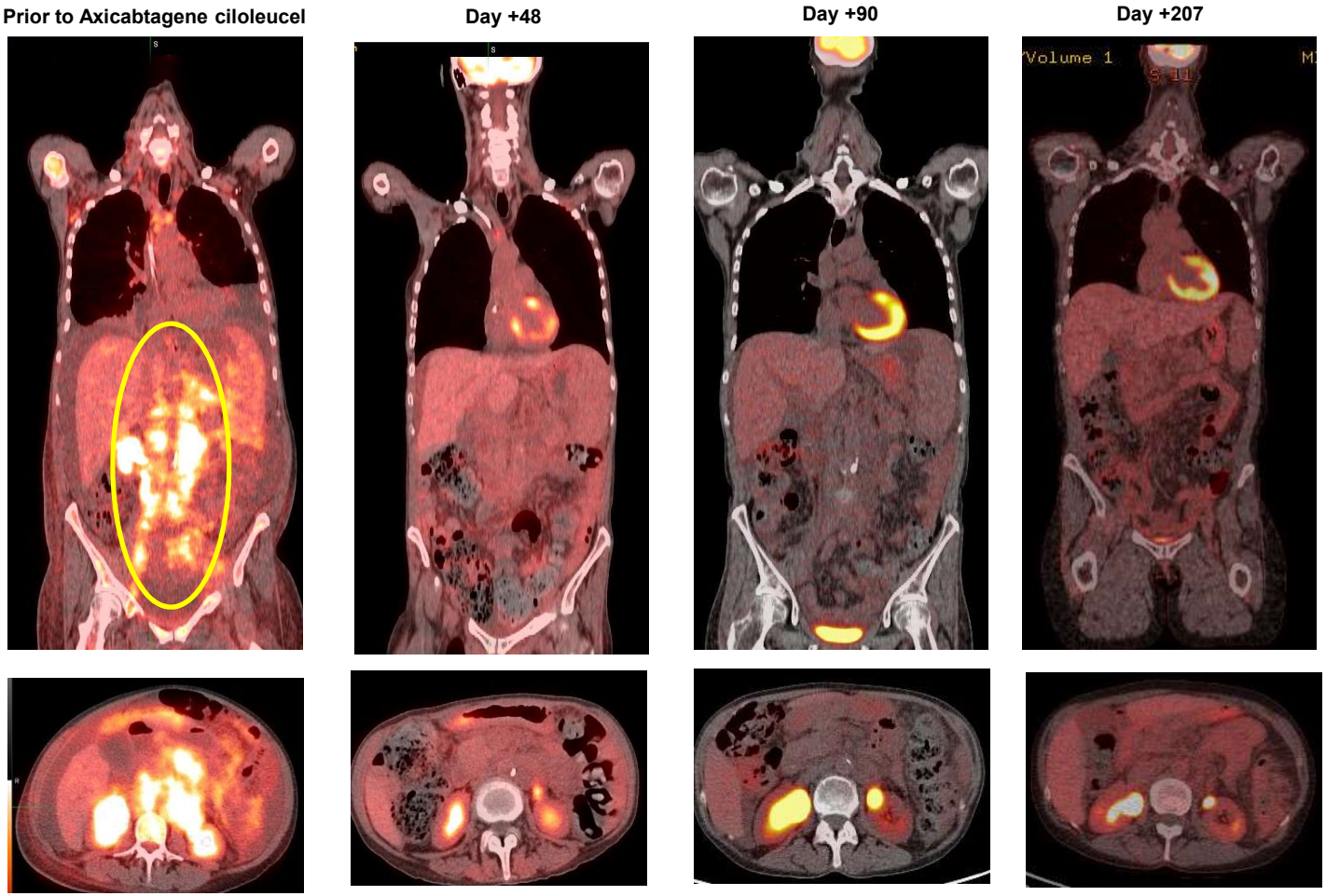
**** FULL=102; CORE=73**

Neelapu SS, et al. N Engl J Med. 2017; 377:2531-44;
Schuster SJ et al. ICML 2017
Borchmann P, et al (Abs S799). EHA; Stockholm, Sweden June 2018
Abramson JS, et al. J Clin Oncol 36, 2018 (suppl; abstr 7505)

Mayo Clinic Florida experience

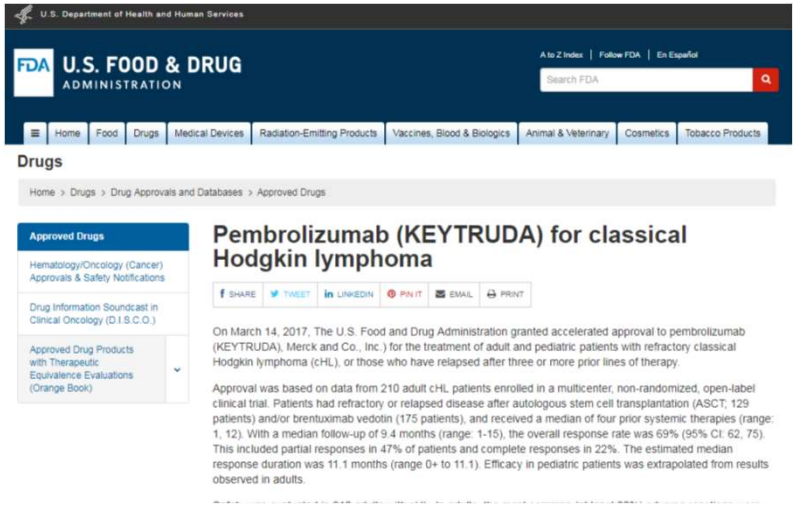
- 52 y. old woman
  - 2010: Follicular lymphoma (Stage 2)
    - XRT followed by maintenance rituximab x 2 years
    - 2014: Progression (+ BM involved)
      - Bendamustine-rituximab→ Ibritumomab tiuxetan (achieved CR)
    - 2016: Relapse
      - R-CHOP x 3 and 1 cycle of Ofatumumab-CHOP (achieved CR)
    - April 2017: relapse
      - Lenalidomide (rash), then O-CHOP x 2, then R-ICE x 2→ PR
    - July 2017: Progression
      - O-ICE (counts slow to recover)
    - Dec 2017: Transformation to high-grade lymphoma
      - GEMOX-R, referred to another center, unable to manufacture Axicabtagene ciloleucel (~80% circulating follicular lymphoma)
      - Obinutuzumab + GEMOX→ stable disease
        - Decrease in circulating follicular lymphoma cells (~1-8%)
        - BM still 80% involved with follicular lymphoma
    - June 2018– received Axicabtagene ciloleucel

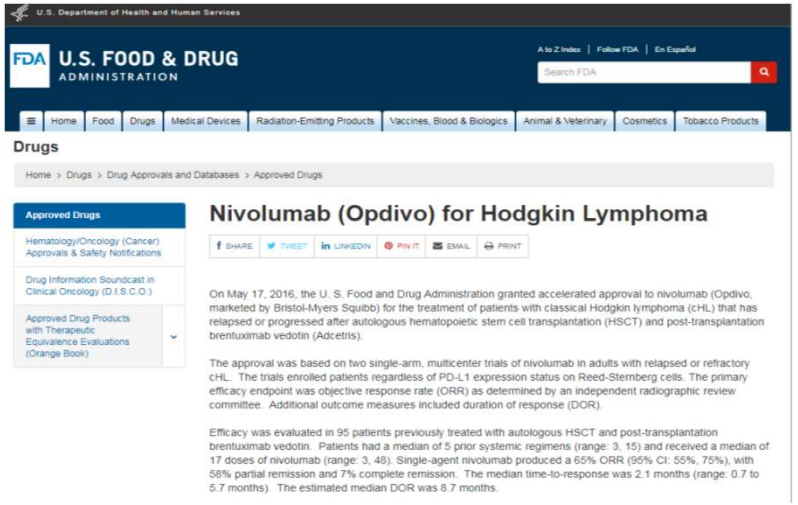
Mayo Clinic Florida experience



Courtesy Dr. Manoj Jain
Mayo Clinic, Florida

Hodgkin lymphoma





The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

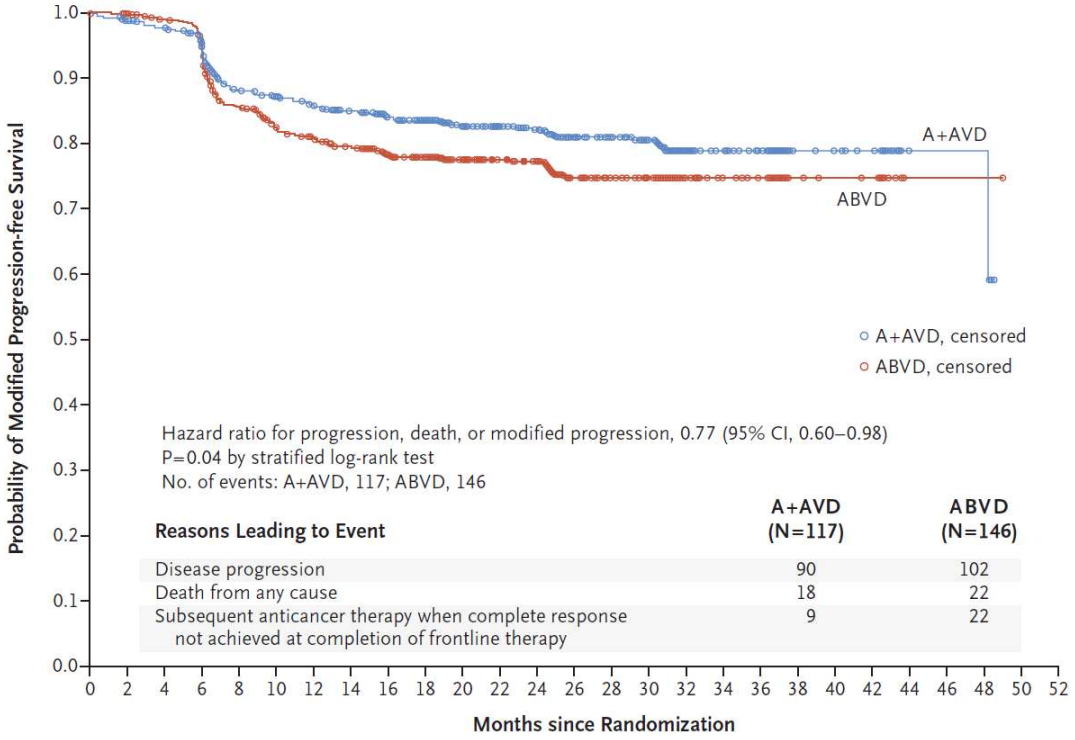
Brentuximab Vedotin with Chemotherapy for Stage III or IV Hodgkin's Lymphoma

J.M. Connors, W. Jurczak, D.J. Straus, S.M. Ansell, W.S. Kim, A. Gallamini, A. Younes, S. Alekseev, Á. Illés, M. Picardi, E. Lech-Maranda, Y. Oki, T. Feldman, P. Smolewski, K.J. Savage, N.L. Bartlett, J. Walewski, R. Chen, R. Ramchandren, P.L. Zinzani, D. Cunningham, A. Rosta, N.C. Josephson, E. Song, J. Sachs, R. Liu, H.A. Jolin, D. Huebner, and J. Radford, for the ECHELON-1 Study Group*

Table 1. Patient Demographic and Clinical Characteristics at Baseline (Intention-to-Treat Population).*

Characteristic	A+AVD (N=664)	ABVD (N=670)	Total (N=1334)
Male sex — no. (%)	378 (57)	398 (59)	776 (58)
Age — yr			
Median	35	37	36
Range	18–82	18–83	18–83
Age categories — no. (%)			
<45 yr	451 (68)	423 (63)	874 (66)
45–59 yr	129 (19)	145 (22)	274 (21)
60–64 yr	24 (4)	40 (6)	64 (5)
≥65 yr	60 (9)	62 (9)	122 (9)
Regions — no. (%)			
Americas	261 (39)	262 (39)	523 (39)
Europe	333 (50)	336 (50)	669 (50)
Asia	70 (11)	72 (11)	142 (11)
Ann Arbor stage at initial diagnosis — no. (%)†			
Stage II‡	1 (<1)	0	1 (<1)
Stage III	237 (36)	246 (37)	483 (36)
Stage IV	425 (64)	421 (63)	846 (64)
Not applicable, unknown, or missing	1 (<1)	3 (<1)	4 (<1)
International Prognostic Score — no. (%)§			
0 or 1	141 (21)	141 (21)	282 (21)
2 or 3	354 (53)	351 (52)	705 (53)
4 to 7	169 (25)	178 (27)	347 (26)
ECOG performance status — no. (%)¶			
0	376 (57)	378 (57)	754 (57)
1	260 (39)	263 (39)	523 (39)
2	28 (4)	27 (4)	55 (4)
Not obtained or missing	0	2 (<1)	2 (<1)
Extranodal involvement at diagnosis — no. (%)			
Yes	411 (62)	416 (62)	827 (62)
1 extranodal site	217 (33)	223 (33)	440 (33)
>1 extranodal sites	194 (29)	193 (29)	387 (29)
No	217 (33)	228 (34)	445 (33)
Unknown or missing	36 (5)	26 (4)	62 (5)
Patients with any B symptom — no. (%)‖	400 (60)	381 (57)	781 (59)

A Modified Progression-free Survival as Assessed by Independent Review Committee



Hazard ratio for progression, death, or modified progression, 0.77 (95% CI, 0.60–0.98)
P=0.04 by stratified log-rank test
No. of events: A+AVD, 117; ABVD, 146

Reasons Leading to Event	A+AVD (N=117)	ABVD (N=146)
Disease progression	90	102
Death from any cause	18	22
Subsequent anticancer therapy when complete response not achieved at completion of frontline therapy	9	22

No. at Risk

A+AVD	664	637	623	600	541	528	513	493	463	439	347	328	309	196	185	169	96	85	77	26	24	21	4	4	4	0	0
ABVD	670	636	626	593	521	490	474	459	432	413	326	306	292	177	164	153	76	66	62	16	13	12	1	1	1	0	0

CONCLUSIONS

A+AVD had superior efficacy to ABVD in the treatment of patients with advanced-stage Hodgkin's lymphoma, with a 4.9 percentage-point lower combined risk of progression, death, or noncomplete response and use of subsequent anticancer therapy at 2 years. (Funded by Millennium Pharmaceuticals and Seattle Genetics; ECHELON-1 ClinicalTrials.gov number, NCT01712490; EudraCT number, 2011-005450-60.)

MAYO CLINIC

Connors JM, et al. N Engl J Med. 2018; 378: 331

2900 Two-Year Follow-up of Keynote-087 Study: Pembrolizumab Monotherapy in Relapsed/Refractory Classic Hodgkin Lymphoma

Program: Oral and Poster Abstracts
Session: 624. Hodgkin Lymphoma and T/NK Cell Lymphoma—Clinical Studies: Poster II
Hematology Disease Topics & Pathways:
Therapies, Clinically relevant

Sunday, December 2, 2018, 6:00 PM-8:00 PM
Hall GH (San Diego Convention Center)

Pier Luigi Zinzani, MD[1], *Robert W. Chen, MD*[2], *Hun Ju Lee, MD*[3], *Philippe Armand, MD, PhD*[4], *Nathalie A Johnson, MD, PhD,*[5], *Pauline Brice, MD*[6*], *John Radford, MD, FRCP*[7*], *Vincent Ribrag, MD*[8], *Daniel Molin*[9*], *Theodoros P. Vassilakopoulos, MD, PhD*[10*], *Akihiro Tomita, MD, PhD*[11], *Bastian Von Tresckow, MD*[12*], *Margaret A. Shipp, MD*[4], *Eunhee Kim*[13*], *Akash Nahar, MD, MPH*[13*], *Arun Balakumaran, MD, PhD, SM*[13*] *and Craig H. Moskowitz, MD*[14]

- **Cohort 1**:
  R/R cHL progressed after auto-HCT and subsequent brentuximab vedotin (BV)
- **Cohort 2**:
  Salvage chemotherapy and BV
- **Cohort 3**:
  Auto-HCT but not treated with BV after auto-HCT

		Total population	Cohort 1	Cohort 2	Cohort 3
ORR % (95% CI)		71.9 (65.3-77.9)	76.8 (65.1-86.1)	66.7 (55.3-76.8)	73.3 (60.3-83.9)
Median DOR[a] (range), month	Patients with CR	NR (0.0+-27.0+)	25.0 (0.0+-26.0+)	19.2 (0.0+-27.0+)	NR (5.3-27.0+)
	Patients with PR	10.9 (0.0+-25.1+)	19.5 (0.0+-25.1+)	7.9 (0.0+-22.3+)	13.9 (0.0+-24.4)
	Patients with CR/PR	16.5 (0.0+-27.0+)	22.1 (0.0+-26.0+)	11.1 (0.0+-27.0+)	24.4 (0.0+-27.0+)
Median PFS[a] (95% CI), month	All patients	13.7 (11.1-17.0)	16.4 (11.3-27.6)	11.1 (7.6-13.8)	19.4 (10.8-22.1)
	Patients with CR	NR (21.7-NR)	27.6 (16.3-NR)	21.9 (11.1-NR)	NR (21.7-NR)
	Patients with PR	13.8 (12.0-22.1)	22.2 (13.6-NR)	13.4 (7.6-13.8)	19.4 (8.5-22.1)
24-month OS rate,[a] %		90.9	92.5	90.6	89.4

CR, complete response; DOR, duration of response; NR, not reached; ORR, overall response rate; PR, partial response; PFS, progression-free survival; OS, overall survival.
[a]From Kaplan-Meier method for censored data.
"+" indicates that there is no progressive disease by the time of last disease assessment.

680 CD30-Chimeric Antigen Receptor (CAR) T Cells for Therapy of Hodgkin Lymphoma (HL)

Program: Oral and Poster Abstracts
Type: Oral
Session: 624. Hodgkin Lymphoma and T/NK Cell Lymphoma—Clinical Studies: Immunotherapy and Targeted Strategies
Hematology Disease Topics & Pathways:
Adult, Biological, Diseases, Therapies, CAR-Ts, Hodgkin Lymphoma, Young Adult, Study Population, Clinically relevant, Lymphoid Malignancies

Monday, December 3, 2018: 10:45 AM
Room 6F (San Diego Convention Center)

Carlos A. Ramos, MD[1], *Mrinalini Bilgi*[1*], *Claudia P. Gerken*[1*], *Olga Dakhova*[1*], *Zhuyong Mei*[1*], *Bambi J. Grilley, RPh*[1*], *Adrian P. Gee, PhD*[1], *Cliona M. Rooney, PhD*[1*], *Gianpietro Dotti, MD*[2*], *Barbara Savoldo, MD, PhD*[2*], *Helen E. Heslop, MD, DSc*[1] *and Malcolm K. Brenner, MD, PhD*[1*]

[1]*Center for Cell and Gene Therapy, Baylor College of Medicine, Texas Children's Hospital, Houston Methodist Hospital, Houston, TX*
[2]*Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC*

- **Manufactured CD30.CARTs for 15 pts using retroviral transduction and containing a CD28 endodomain**
- **Culture duration was 15±3 days, with a final transduction efficiency of 97.6%±1.8%**
- **N=9**
  - **Lymphodepletion with Flu-CY**
  - **8 evaluated at 6 weeks after infusion**
    - **CR=6 (75%)**
    - **Disease progression=2 (25%)**

Conclusions

- **DLBCL**
  - CAR-T cell therapy represents the new standard of care for:
    - Adults with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy, including DLBCL-NOS, 1ry mediastinal large B-cell lymphoma (only axicabtagene ciloleucel) , high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma
  - Challenges for broader applicability
    - Cost of Axicabtagene ciloleucel= **$373,000**
    - Cost of Tisagencleucel= **$373,000**
    - Prompt referrals to CAR T certified centers
    - Logistically cumbersome
- **Hodgkin lymphoma**
  - Brentuximab vedotin plus AVD front-line
  - Checkpoint inhibitors integral components of Rx algorithms (relapsed)
  - CD30 CAR-T holds promise

Thank you
Gracias

MAYO CLINIC