Role of autologous transplant and CART therapy for DLBCL

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Thank You!!!

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Outline

- When autologous transplant is NOT a good option in RR setting?
- Efforts to optimise autoSCT

- Place of CART in relapsed DLBL

Introduction…

- Standard treatment for relapsed DLBL is salvage chemotherapy followed by autologous transplant *(esp in pre-rituximab era)*.

- Question is – is this the algorithm in 2022 also?

IN WHICH CLINICAL SCENARIOS, OUTCOMES OF POST SALVAGE AUTO ARE SO INFERIOR, THAT ALTERNATIVE TREATMENT STRATEGIES NEED URGENT ATTENTION??

1. Early relapse and prior rituximab exposure

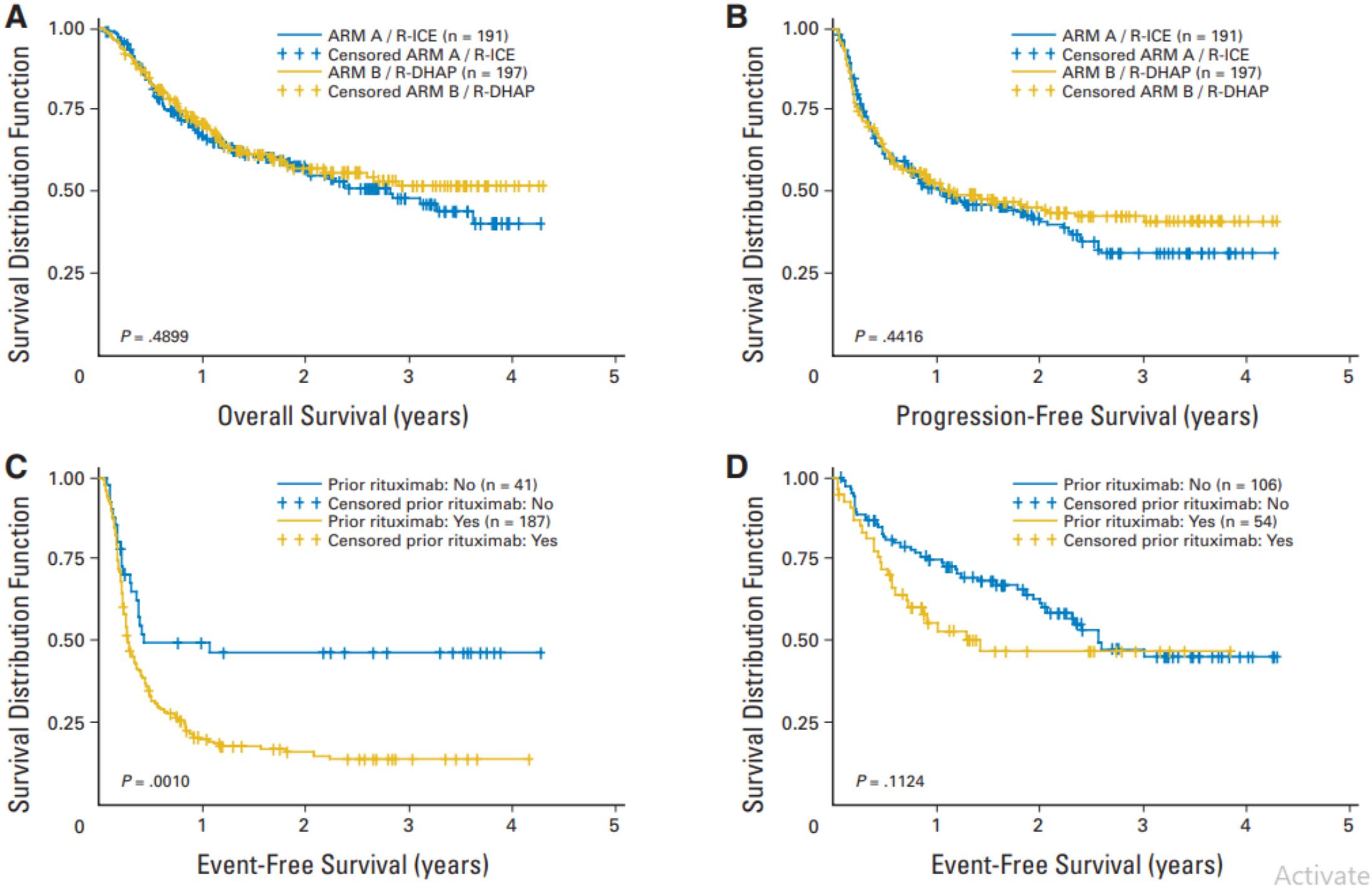
VOLUME 28 · NUMBER 27 · SEPTEMBER 20 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Salvage Regimens With Autologous Transplantation for Relapsed Large B-Cell Lymphoma in the Rituximab Era

Christian Gisselbrecht, Bertram Glass, Nicolas Mounier, Devinder Singh Gill, David C. Linch, Marek Trneny, Andre Bosly, Nicolas Ketterer, Ofer Shpilberg, Hans Hagberg, David Ma, Josette Brière, Craig H. Moskowitz, and Norbert Schmitz


A
Survival Distribution Function
1.00
0.75
0.50
0.25
0
1
2
3
4
5
ARM A / R-ICE (n = 191)
Censored ARM A / R-ICE
ARM B / R-DHAP (n = 197)
Censored ARM B / R-DHAP
P = .4899
Overall Survival (years)
B
Survival Distribution Function
ARM A / R-ICE (n = 191)
Censored ARM A / R-ICE
ARM B / R-DHAP (n = 197)
Censored ARM B / R-DHAP
P = .4416
Progression-Free Survival (years)
C
Survival Distribution Function
Prior rituximab: No (n = 41)
Censored prior rituximab: No
Prior rituximab: Yes (n = 187)
Censored prior rituximab: Yes
P = .0010
Event-Free Survival (years)
D
Survival Distribution Function
Prior rituximab: No (n = 106)
Censored prior rituximab: No
Prior rituximab: Yes (n = 54)
Censored prior rituximab: Yes
P = .1124
Event-Free Survival (years)

- Early relapse and prior rituximab treatment (n=187) defined a population with a poor response rate to the standard treatment; with 3-year PFS = 23%.

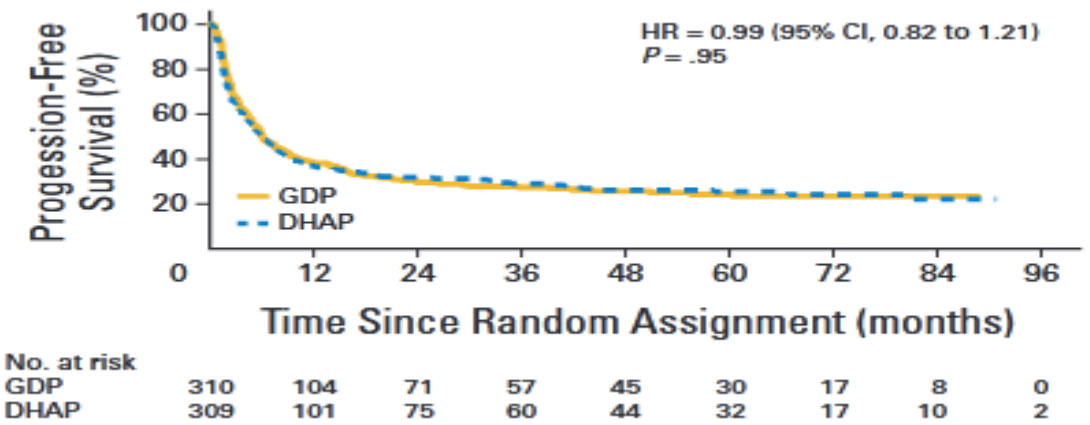
- For responding patients who underwent ASCT (n=68), 3-year PFS was 39%, compared with 14% for patients who did not receive transplantation (n=119; P= 0.001)

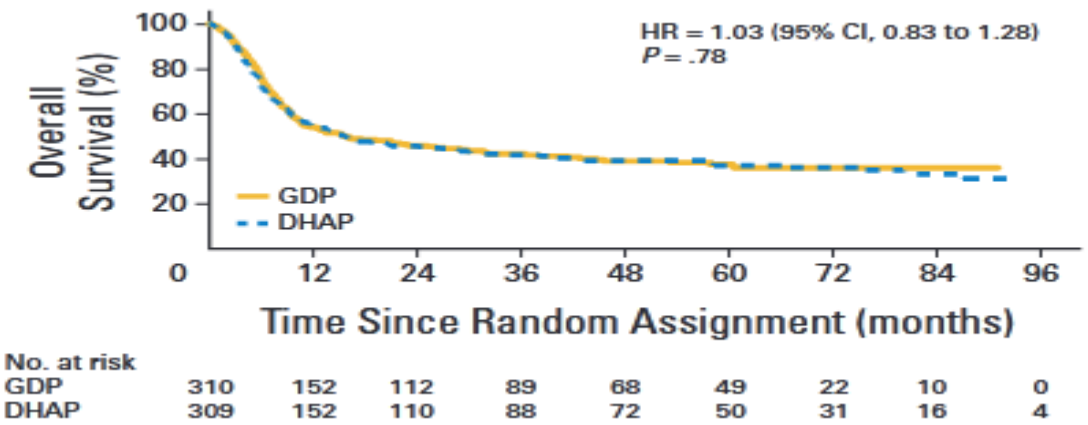
VOLUME 32 · NUMBER 31 · NOVEMBER 1 2014

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized Comparison of Gemcitabine, Dexamethasone, and Cisplatin Versus Dexamethasone, Cytarabine, and Cisplatin Chemotherapy Before Autologous Stem-Cell Transplantation for Relapsed and Refractory Aggressive Lymphomas: NCIC-CTG LY.12





- **Both the NCIC-CTG LY.12 and the CORAL study results show that the group of early relapse (< 1 year) and primary refractory patients have a failure rate >80% with salvage chemotherapy and autologous stem cell transplant.**

- **Patients who attain CR2 after salvage chemotherapy fare better after auto-HCT, than those with < CR**

2. Double hit lymphoma

In upfront setting:

- most important determinator of prognosis is intensity of 1st therapy, usually with dose-adjusted REPOCH, hyper-CVAD or Magrath regimen.
- RCHOP is inferior to these regimens even if followed by consolidation with auto-HCT.
- For patients treated with intensive induction, consolidation auto-HCT is not recommended.

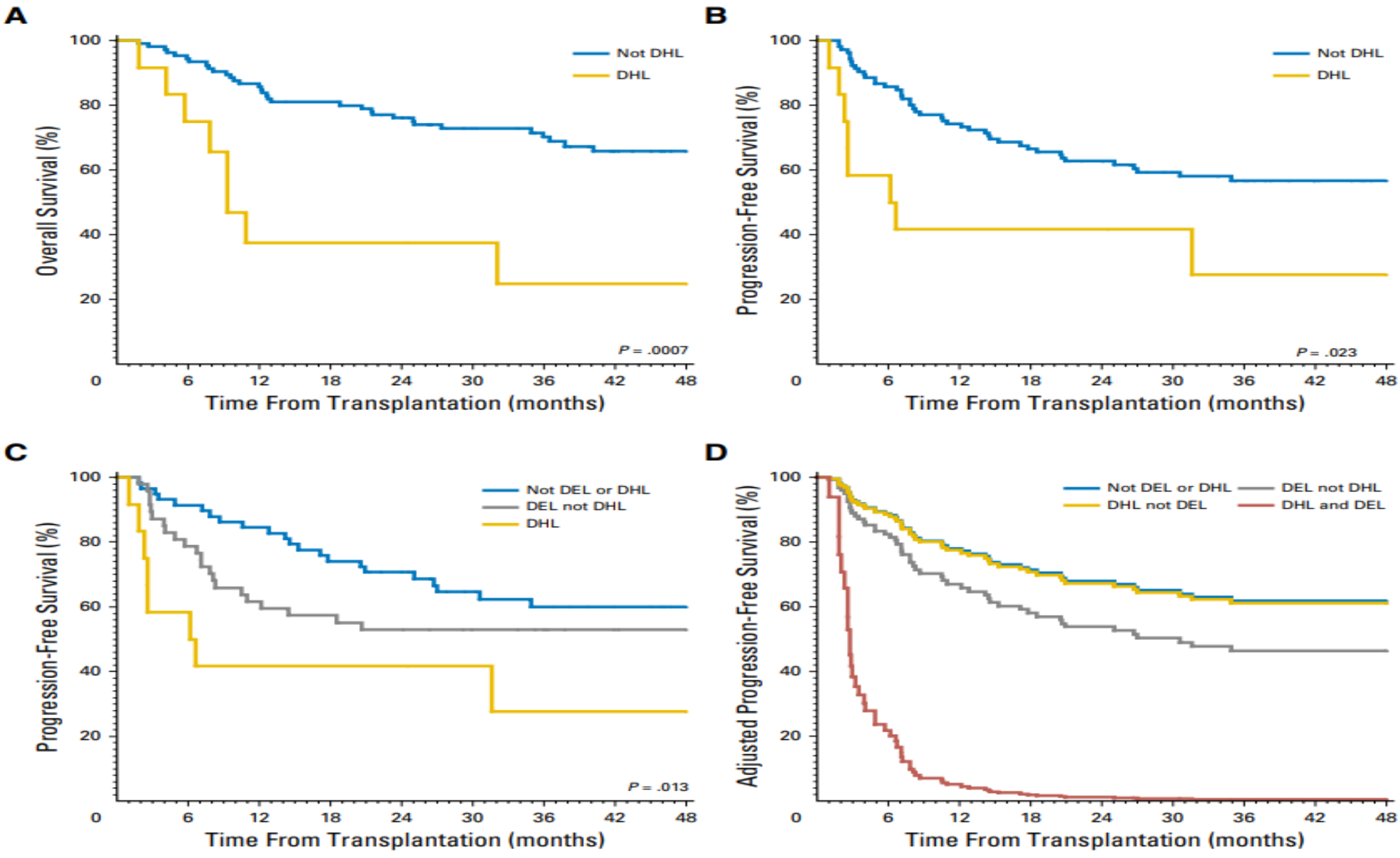
VOLUME 35 · NUMBER 1 · JANUARY 1, 2017

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Relapsed or Refractory Double-Expressor and Double-Hit Lymphomas Have Inferior Progression-Free Survival After Autologous Stem-Cell Transplantation

Alex F. Herrera, Matthew Mei, Lawrence Low, Haesook T. Kim, Gabriel K. Griffin, Joo Y. Song, Reid W. Merryman,


A
Overall Survival (%)
100
80
60
40
20
0
Not DHL
DHL
P = .0007
6
12
18
24
30
36
42
48
Time From Transplantation (months)
B
Progression-Free Survival (%)
Not DHL
DHL
P = .023
Time From Transplantation (months)
C
Progression-Free Survival (%)
Not DEL or DHL
DEL not DHL
DHL
P = .013
Time From Transplantation (months)
D
Adjusted Progression-Free Survival (%)
Not DEL or DHL
DEL not DHL
DHL not DEL
DHL and DEL
Time From Transplantation (months)

- **DEL and DHL are both associated with inferior outcomes after ASCT in patients with rel/ref DLBCL.**

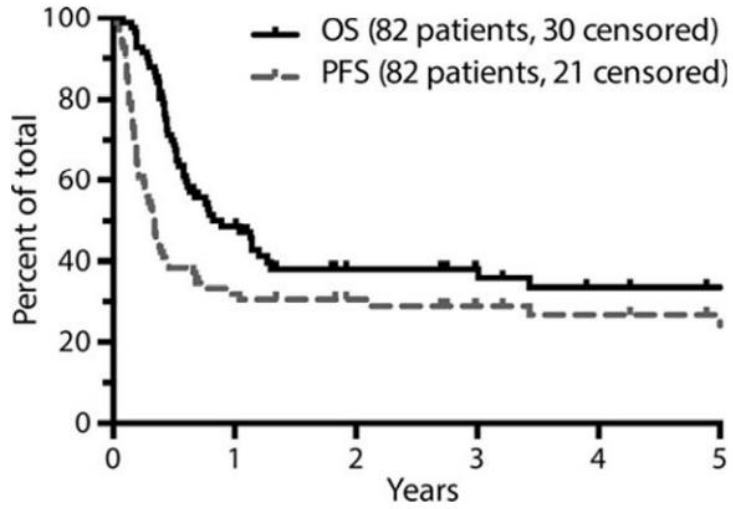
- **Although ASCT remains a potentially curative approach, these patients, particularly those with DHL, are a high-risk subset who should be targeted for investigational strategies other than standard ASCT.**

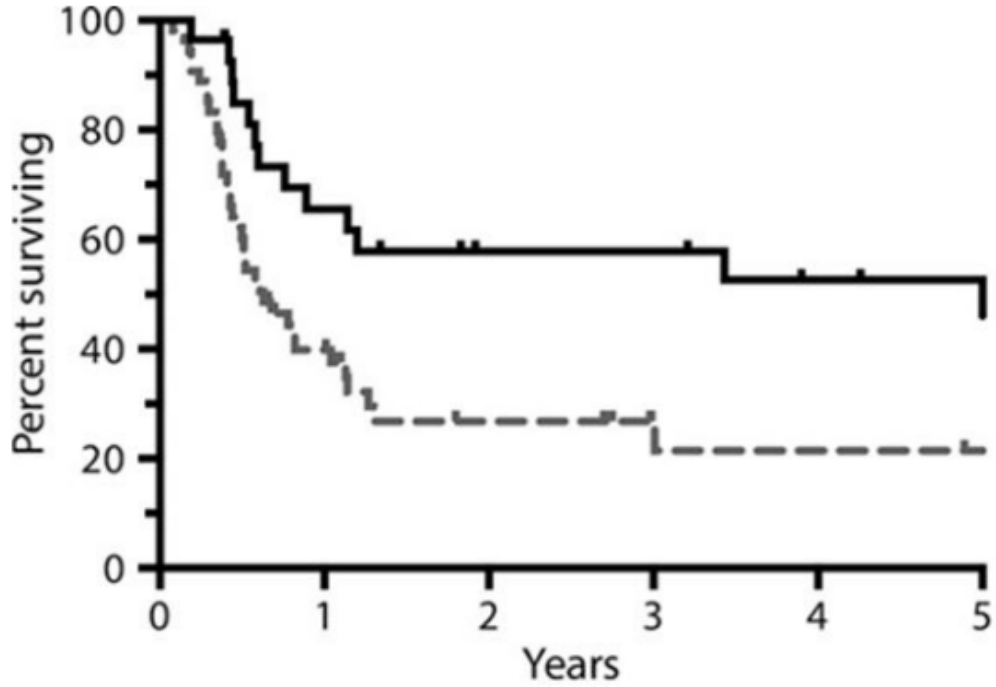
3. Primary refractory DLBCL…

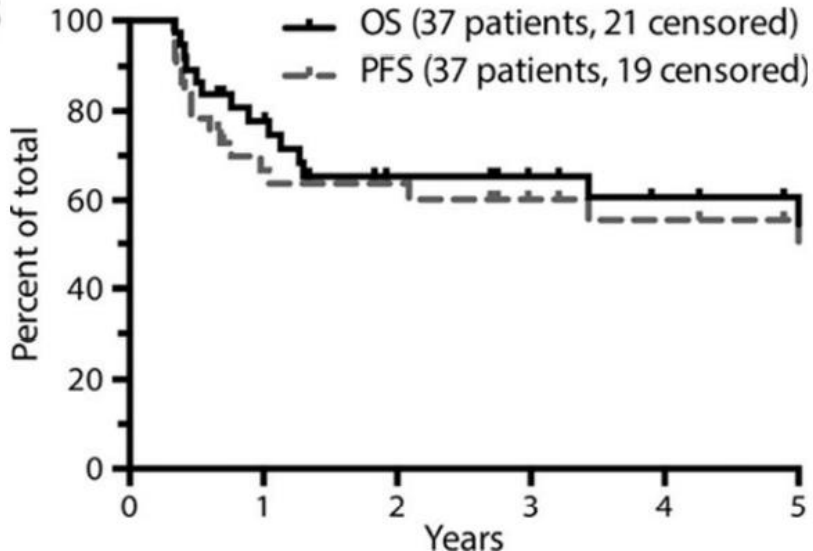
Br J Haematol. 2017 February ; 176(4): 591–599. doi:10.1111/bjh.14453.

Outcomes of primary refractory diffuse large B-cell lymphoma (DLBCL) treated with salvage chemotherapy and intention to transplant in the rituximab era

Santosha A. Vardhana[1], **Craig S. Sauter**[1], **Matthew J. Matasar**[1], **Andrew D. Zelenetz**[1], **Natasha Galasso**[2], **Kaitlin M. Woo**[2], **Zhigang Zhang**[2], and **Craig H. Moskowitz**[1]


OS (82 patients, 30 censored)
PFS (82 patients, 21 censored)
Percent of total
100
80
60
40
20
0
0
1
2
3
4
5
Years


Percent surviving
100
80
60
40
20
0
0
1
2
3
4
5
Years


OS (37 patients, 21 censored)
PFS (37 patients, 19 censored)
Percent of total
100
80
60
40
20
0
0
1
2
3
4
5
Years

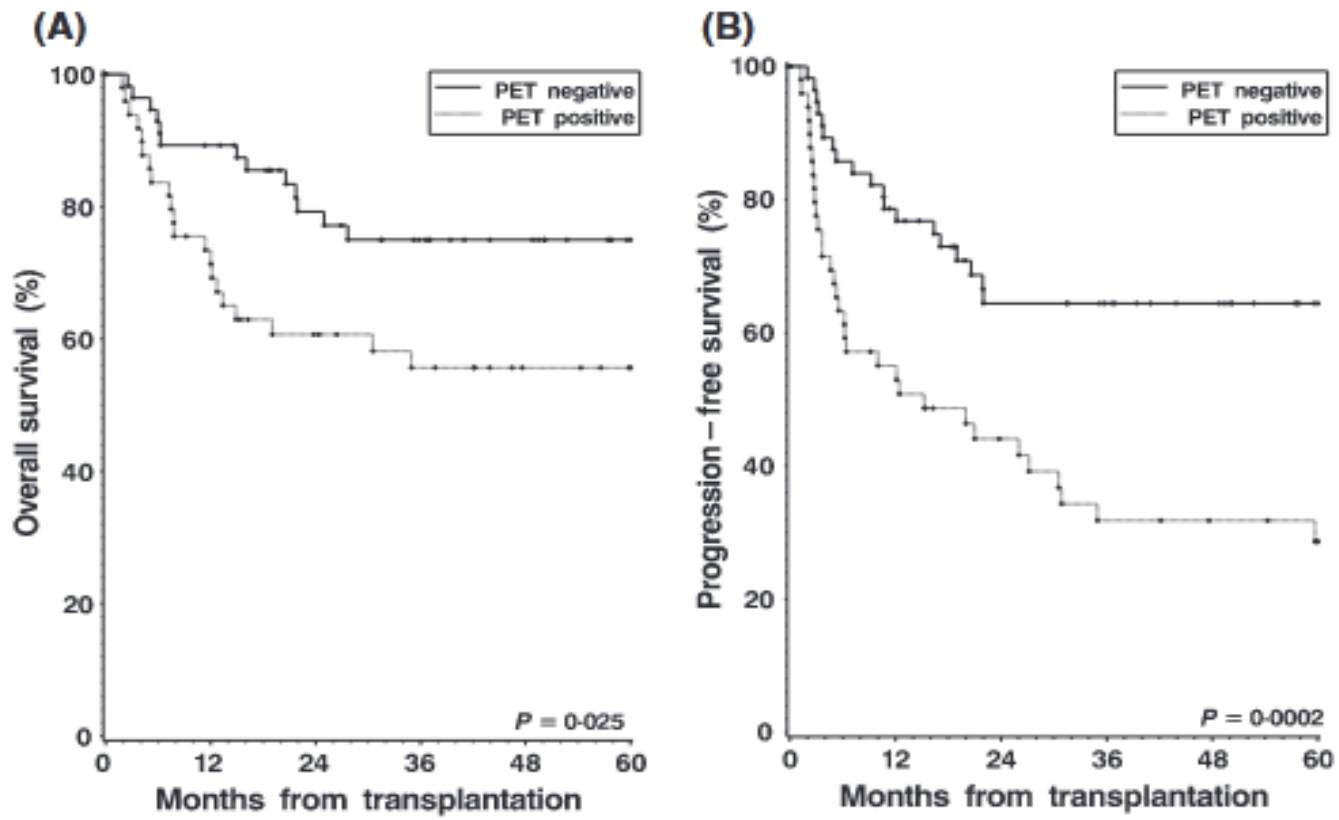
- **Salvage chemotherapy with intent of subsequent high-dose therapy and ASCT remains a feasible strategy in certain patients with primary refractory DLBCL, particularly for those achieving a PR to frontline therapy.**

- **Primary barrier to cure in primary refractory disease -- resistance to salvage → future studies should aim to improvise.**

4. Sub-optimal PET response to salvage…

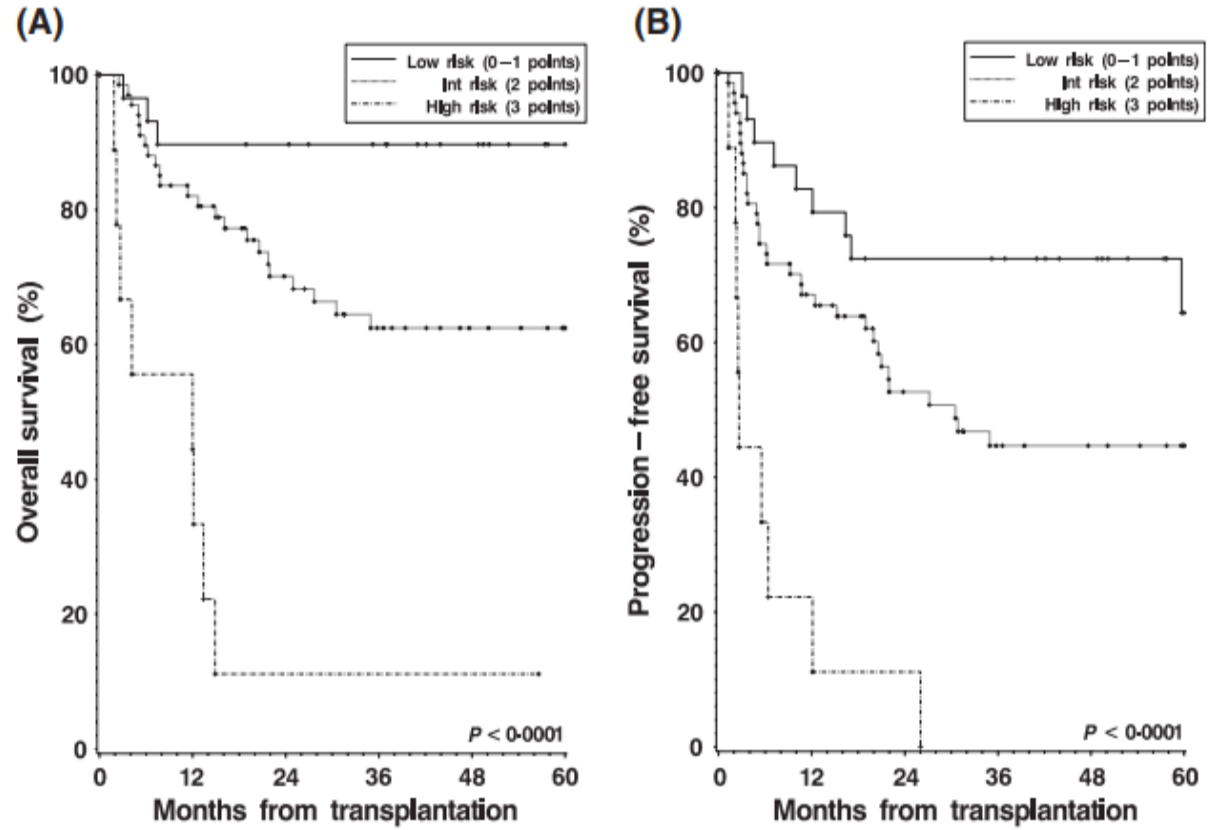
bjh research paper

Prognostic factors for patients with diffuse large B cell lymphoma and transformed indolent lymphoma undergoing autologous stem cell transplantation in the positron emission tomography era



	Univariate				Multivariate			
	OS		PFS		OS		PFS	
Variable	HR	*P*	HR	*P*	HR	*P*	HR	*P*
Age ≥60 years*	**2·4**	**0·011**	1·4	0·2	**3·6**	**0·004**	**2·1**	**0·012**
Male	1·5	0·3	1·4	0·3				
>2 lines of chemotherapy	0·9	0·9	1·3	0·5				
Radiotherapy								
None	Ref		Ref					
Pre-ASCT	1·9	0·18	**2·5**	**0·015**				
Post-ASCT	1·6	0·2	1·8	0·069				
Primary refractory disease	1·1	0·7	1·3	0·4				
Duration of remission < 6 months*†	1·7	0·3	0·9	0·8				
Time from relapse to ASCT ≥ 5 months*	0·6	0·2	0·8	0·6				
B symptoms at relapse	1·4	0·4	**2·1**	**0·012**				
Stage at relapse								
1	Ref		Ref					
2	1·2	0·8	1·0	1·0				
3	**3·8**	**0·040**	1·8	0·2				
4	**3·6**	**0·040**	1·9	0·12				
LDH elevated at relapse	1·1	0·9	1·1	0·8				
Extranodal sites at relapse								
Marrow	1·1	0·9	1·1	0·9				
Lung	1·0	1·0	1·3	0·5				
ECOG PS at relapse >1	0·5	0·3	0·5	0·3				
Bulky (≥10 cm) at relapse	1·3	0·6	1·5	0·4				
saa-IPI‡								
0	Ref		Ref					
1	2·1	0·4	1·6	0·5				
2–3	3·3	0·15	**3·8**	**0·026**				
Symptomatic relapse	**2·8**	**0·011**	**2·2**	**0·010**	**3·3**	**0·003**	**2·4**	**0·003**
Rituximab with induction	1·8	0·3	1·2	0·6				
Rituximab with salvage	1·4	0·4	2·1	0·052				
PET positive after salvage	**2·1**	**0·029**	**2·8**	**0·0003**	**3·0**	**0·002**	**3·4**	**<0·0001**
Albumin at SCT <36*·§	1·5	0·2	1·1	0·6				
Graft source								
BM or BM + PB	Ref		Ref					
PB	0·6	0·3	0·5	0·2				
CD34 > 3·0 $\times 10^6$/kg*	0·7	0·4	0·7	0·2				

Risk Group	Number of Points	# of patients (%)	4-year OS (95 CI) $P < 0·0001$	4-year PFS (95 CI) $P < 0·0001$
Low	0–1	48 (46)	84% (70–972)	67% (52–79)
Intermediate	2	47 (45)	59% (43–72)	41% (26–55)
High	3	10 (10)	10% (1–36)	0% (N/A)



- **Patients with Deauville score of 4 post-salvage are at high risk of auto failure.**

- **Chances are higher if early relapse or primary refractory disease or symptomatic relapse.**

LOOKING FORWARD, STARTEGIES TO IMPROVISE…

- Improvise salvage chemotherapy
- Incorporating BiTE/ADC to salvage
- Improvise autologous transplant
- Salvage allogeneic transplant
- CART

Improvise salvage chemotherapy

- Addition of Len to RICE (R2ICE) – a/w more cytopenia, uncertain benefit

- Addition of Ibr to RICE – P1 safe upto Ibr 840/d → PII recruiting

- Choice of second salvage

    - Benda-Gemcitabine-Vinorelbine and Ritux-Topotecan-Paclitaxel

Incorporating BiTE/ADCs

Variable	BR–Polatuzumab	Selinexor	Tafasitamab and Lenalidomide	Loncastuximab
Refractory to last treatment, %	75%	72%	44%	58%
Prior AHCT, %	25%	30%	11%	14%
Prior CAR T, %	0%	0%	0%	9%
Best ORR, %	63%	28%	58%	48%
Best CR, %	50%	12%	40%	24%
Follow-up, median (months)	22	15	34	Not reported
DOR, median (months)	13	9	44	10
PFS, median (months)	10	3	12	5
OS, median (months)	12	9	34	10
Neutropenia, G $\geq$ 3, %	46%	25%	49%	26%
Thrombocytopenia, G $\geq$ 3, %	41%	46%	17%	18%
Neutropenic fever, %	10%	3%	12%	3%
Adverse events of interest	Peripheral neuropathy 44% (G1, 28%; G2, 15%)	Hyponatremia (G3, 8%), nausea 58% (G3, 6%), vomiting 30%	Pneumonia 22%, tumor flare 4%, diarrhea 36% (G 3, 1%)	↑GGT (G $\geq$ 3, 17%), edema/effusion 31% (G $\geq$ 3, 5%), rash 43% (G $\geq$ 3, 4%)

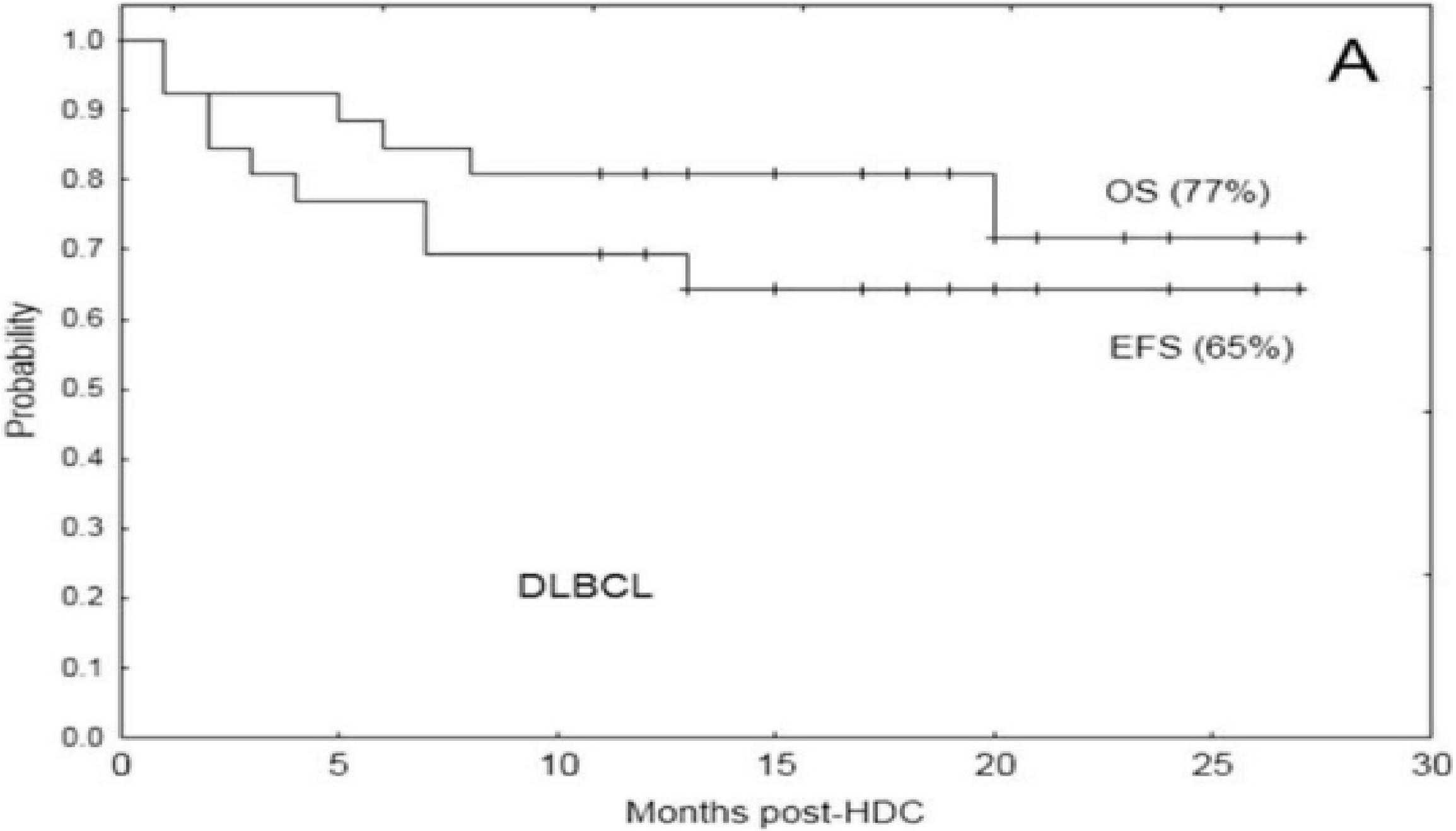
Improvise autologous transplant

Double Epigenetic Modulation of High-Dose Chemotherapy With Azacitidine and Vorinostat for Patients With Refractory or Poor-Risk Relapsed Lymphoma

Cancer. 2016 September 1; 122(17): 2680–2688

Yago Nieto, MD, PhD[1], Benigno C. Valdez, PhD[1], Peter F. Thall, PhD[2], Roy B. Jones, PhD,

- More active high-dose chemotherapy regimens needed for refractory lymphomas. Gem/Bu/Mel combined with vorinostat → facilitates chemotherapy access to DNA → vorinostat induced DNA methyltransferase upregulation --> preclinically abrogated by azacitidine.


A
OS (77%)
EFS (65%)
DLBCL
Probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
5
10
15
20
25
30
Months post-HDC

Salvage allogeneic transplant

- If POOR RISK DLBL patients go to allo-HCT with chemo-sensitive disease to allow time for Graft versus lymphoma, they have similar outcomes to patients with ‘generic’ DLBCL who underwent allo-HCT.

Biol Blood Marrow Transplant 24 (2018) 514–520

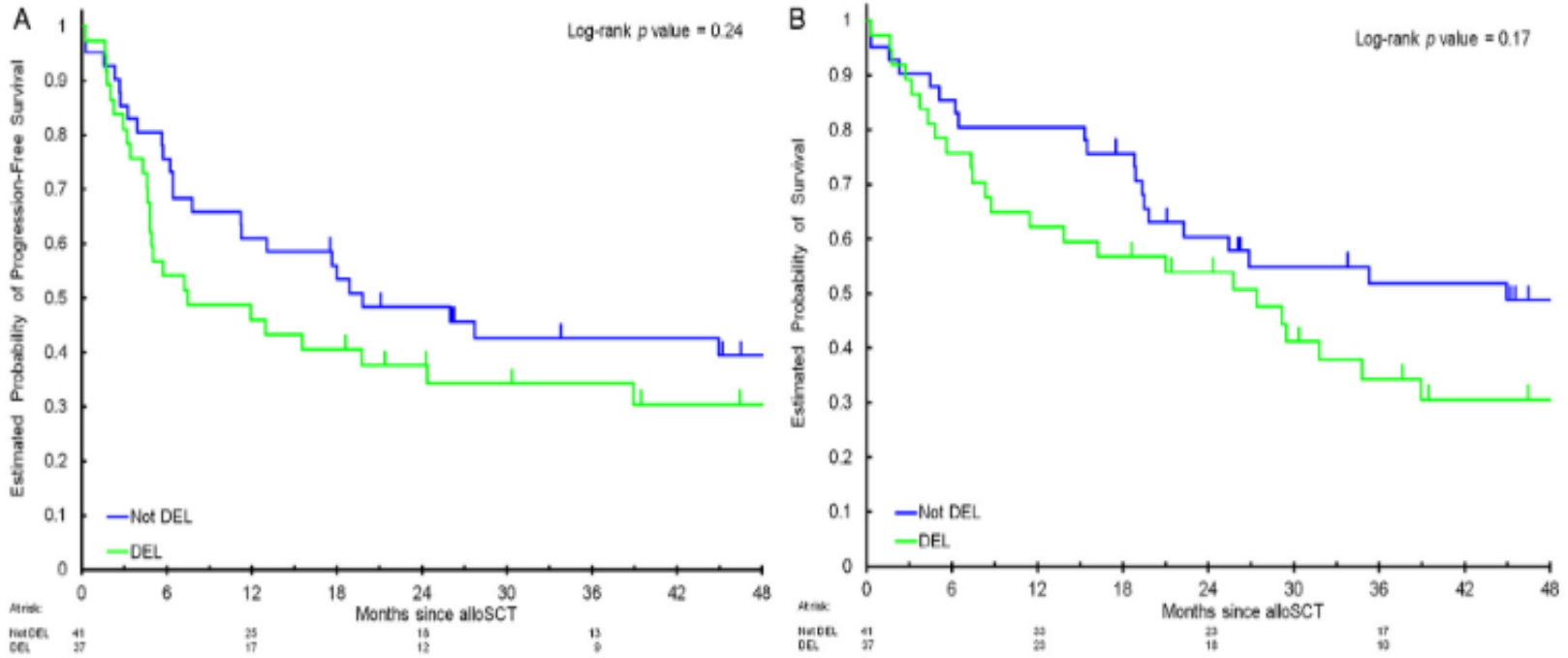
ELSEVIER

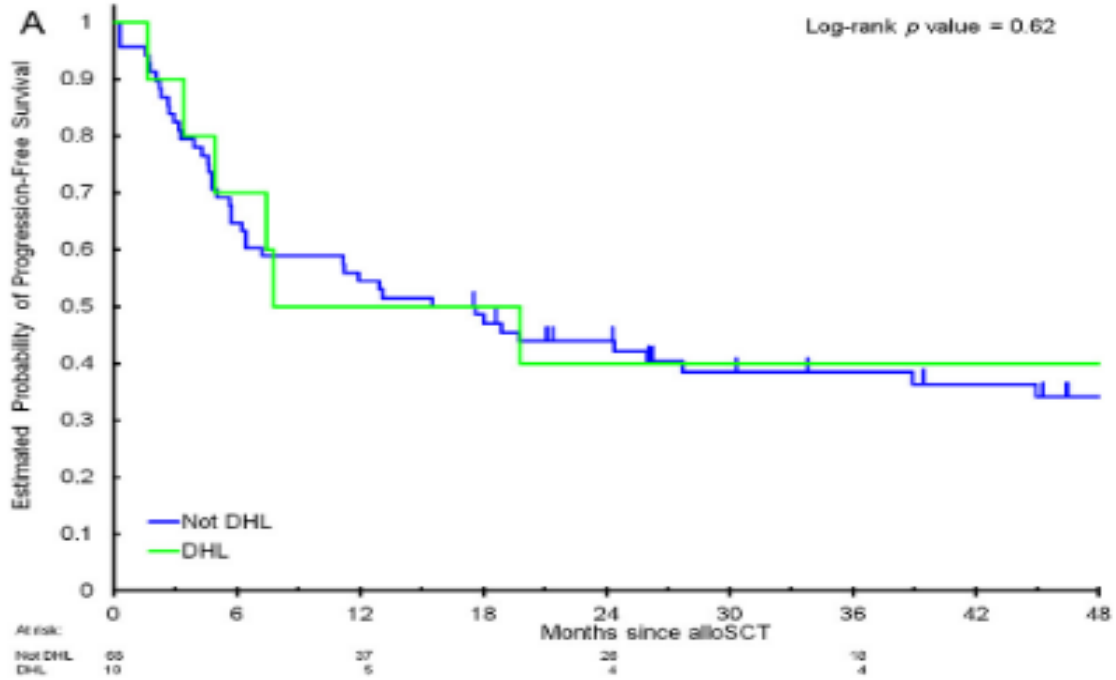
Biology of Blood and Marrow Transplantation

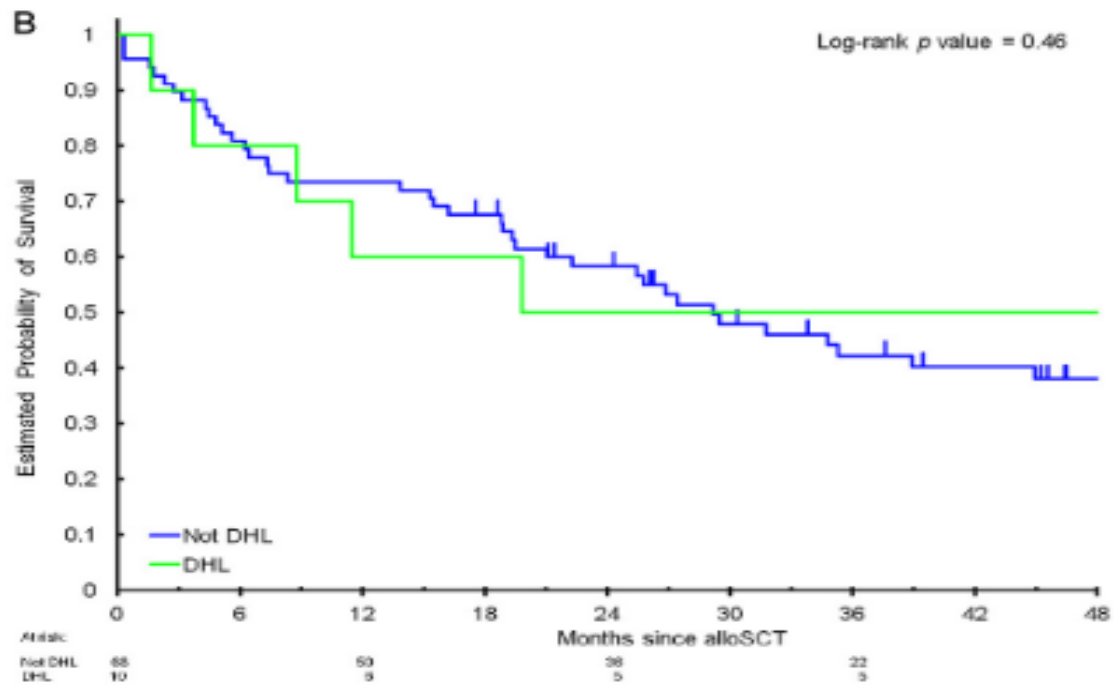
journal homepage: www.bbmt.org

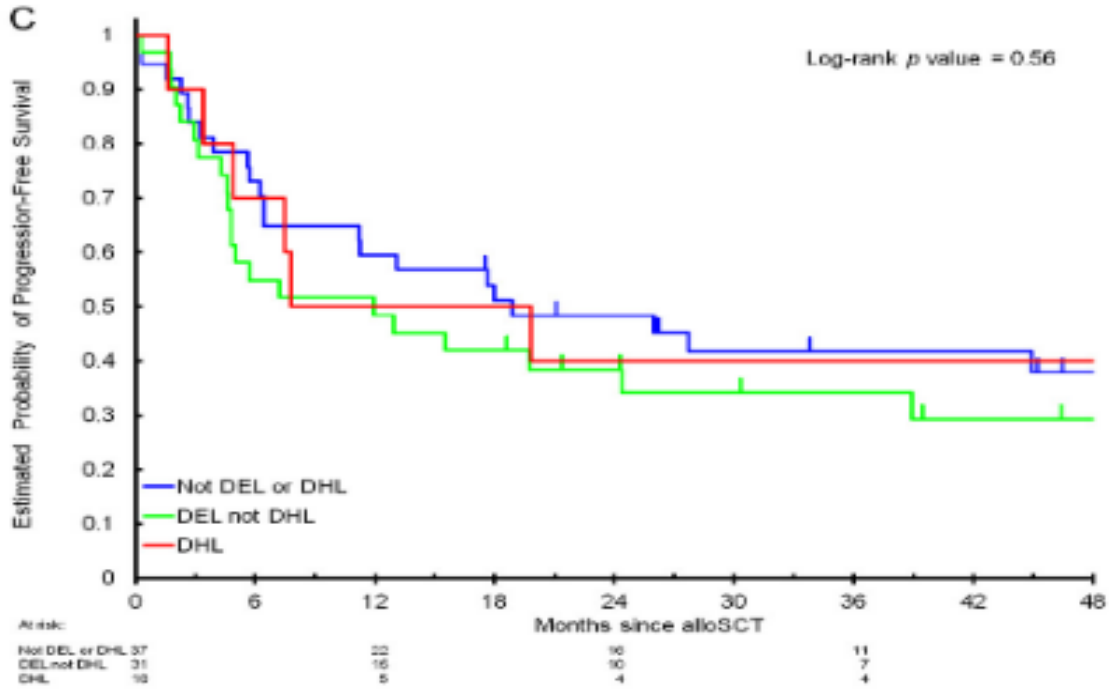
Outcomes after Allogeneic Stem Cell Transplantation in Patients with Double-Hit and Double-Expressor Lymphoma

N=88, >60% had failed auto SCT




A
Log-rank p value = 0.62
Estimated Probability of Progression-Free Survival
Not DHL
DHL
Months since alloSCT
At risk:
Not DHL 68 37 28 18
DHL 10 5 4 4


B
Log-rank p value = 0.46
Estimated Probability of Survival
Not DHL
DHL
Months since alloSCT
At risk:
Not DHL 68 30 18 12
DHL 10 5 3 3


C
Log-rank p value = 0.56
Estimated Probability of Progression-Free Survival
Not DEL or DHL
DEL not DHL
DHL
Months since alloSCT
At risk:
Not DEL or DHL 37 18 10 7
DEL not DHL 31 16 8 5
DHL 10 5 4 4

bjh research paper

Allogeneic transplantation provides durable remission in a subset of DLBCL patients relapsing after autologous transplantation

British Journal of Haematology, 2016,174,235–248

- RR DLBCL relapsing after auto-HCT 3year PFS → 31% after a subsequent allo-HCT → Response Predictors -- chemorefractory disease at the time of allo-HCT, suboptimal KPS (<80%) and interval after auto-HCT of <1 year

CART

Two FDA approved anti-CD19 CAR-Ts for aggressive DLBCL (including TFLs and high grade B-cell lymphomas)

The NEW ENGLAND JOURNAL of MEDICINE

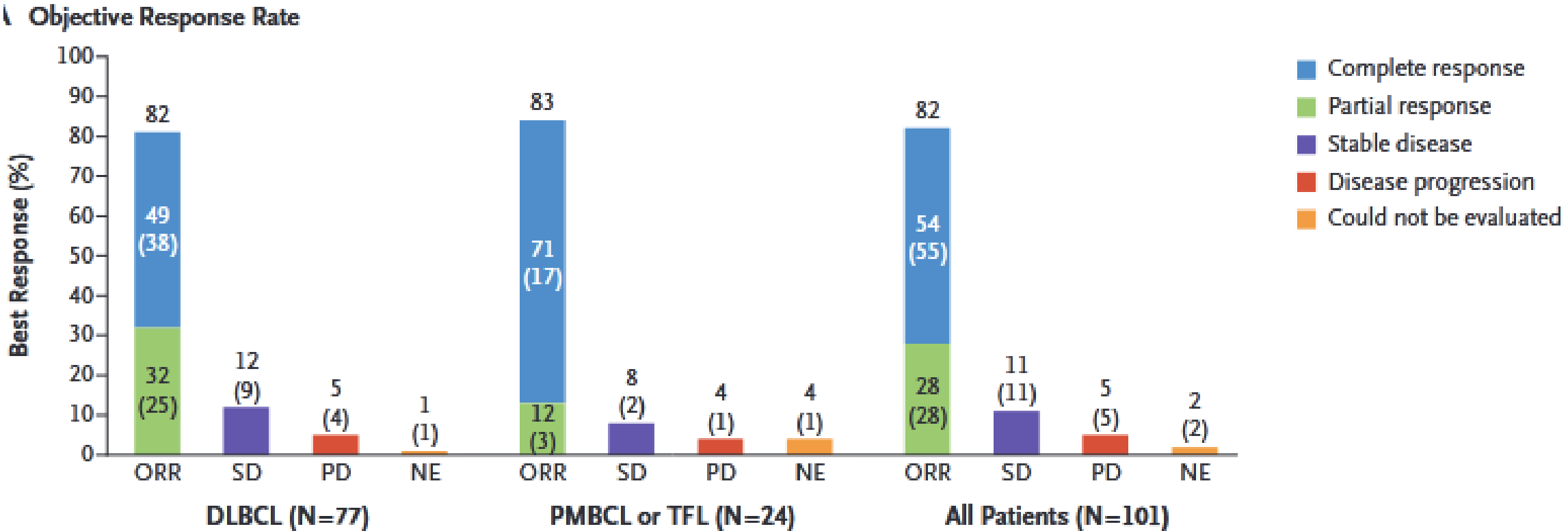
N Engl J Med 2017;377:2531-44

ORIGINAL ARTICLE

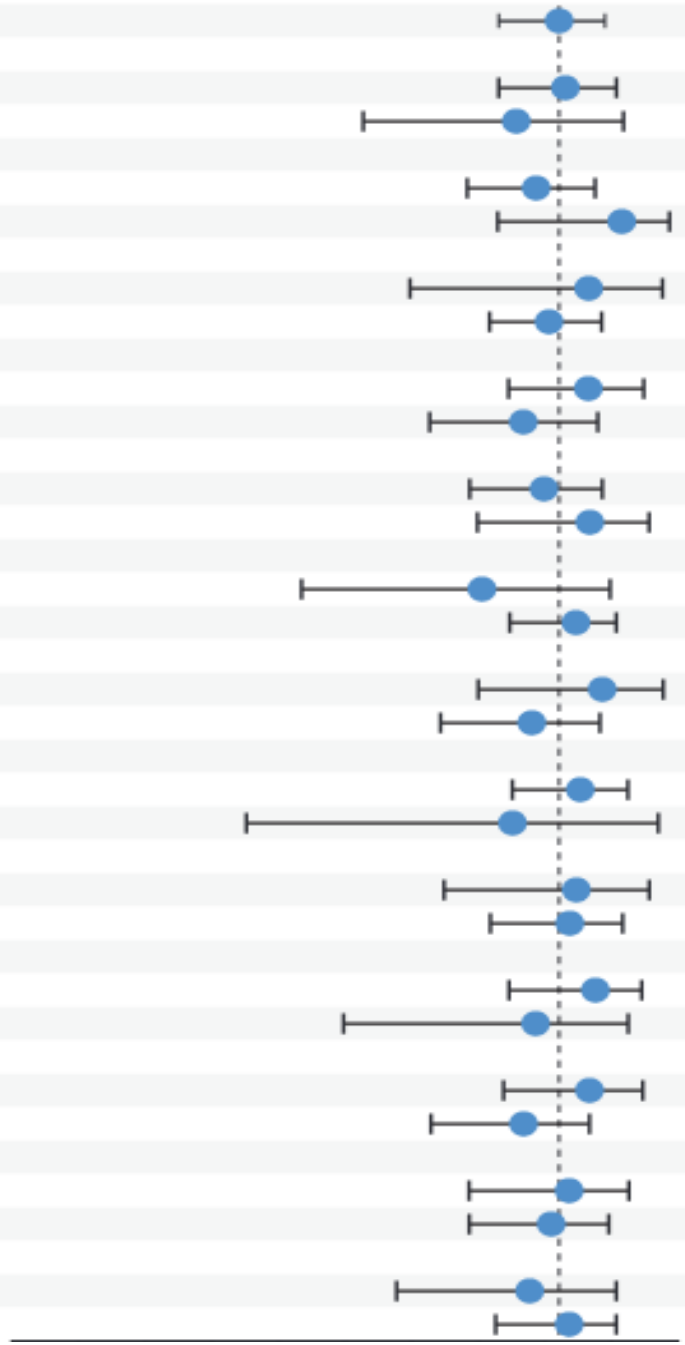
Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma

S.S. Neelapu, F.L. Locke, N.L. Bartlett, L.J. Lekakis, D.B. Miklos, C.A. Jacobson,

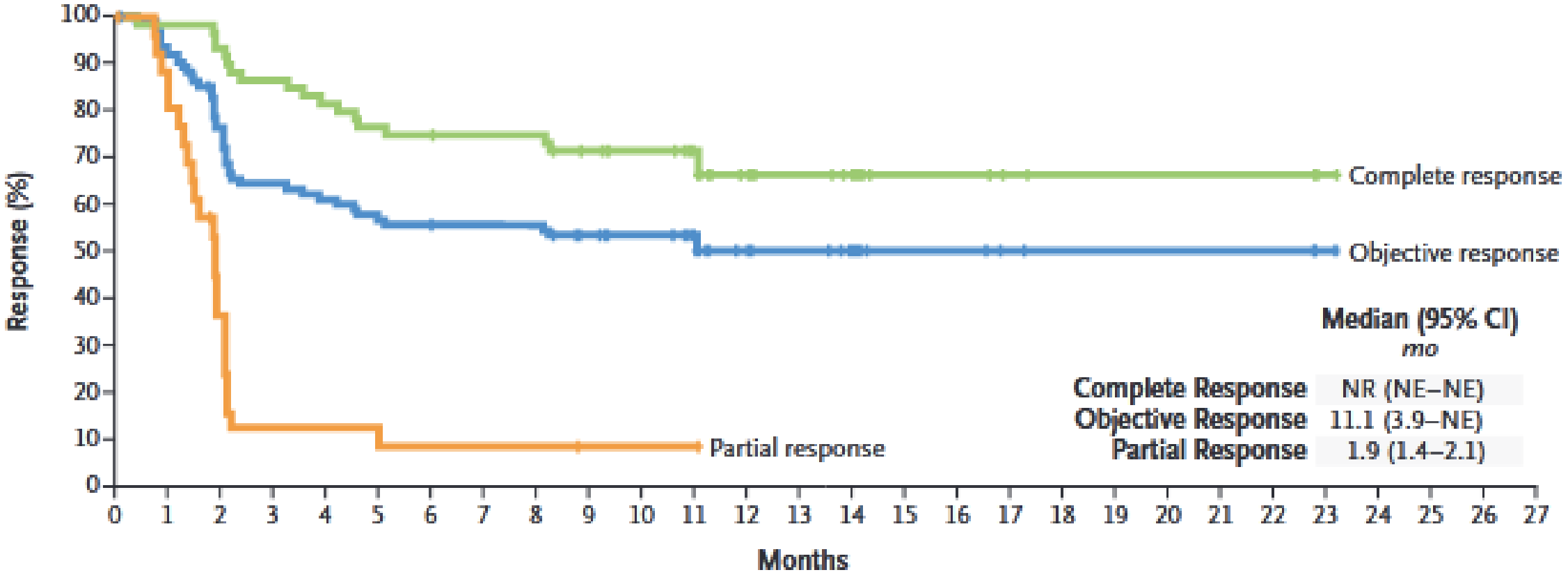
Yescarta, CD28 costimulatory molecule



Subgroup	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)



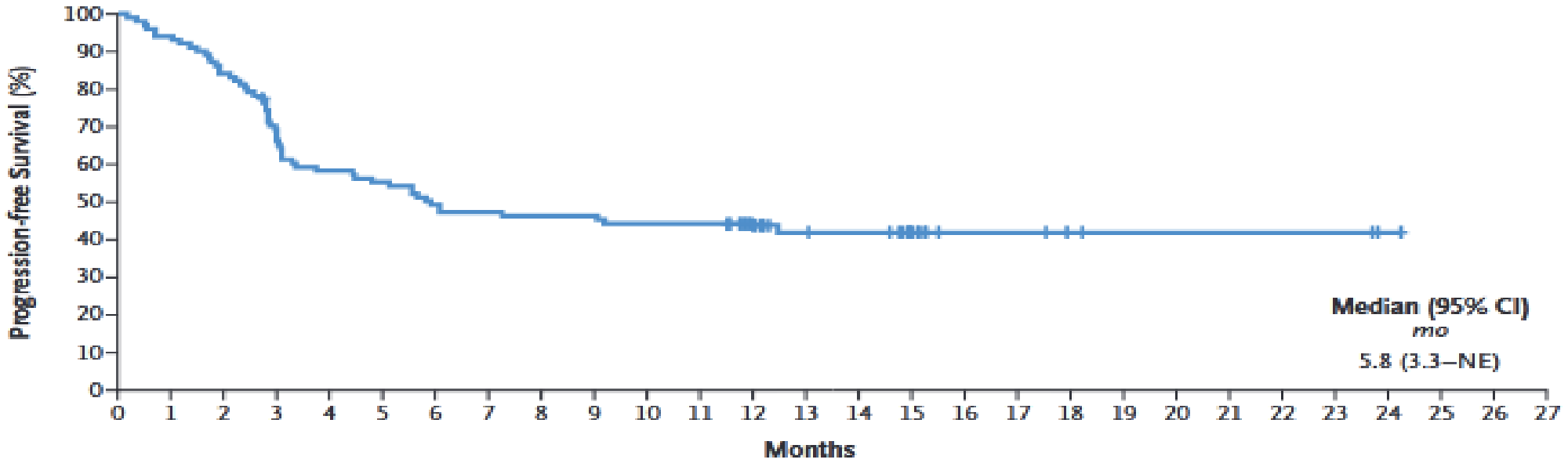
A Duration of Response



No. at Risk

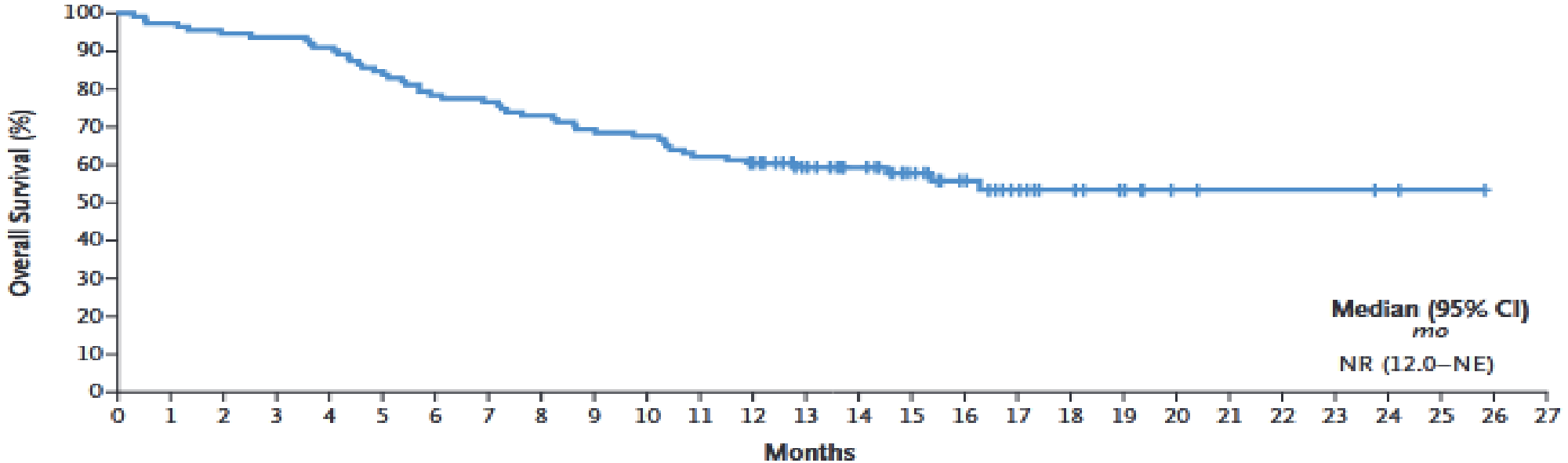
Complete response	63	61	58	53	50	47	46	45	45	41	37	30	19	16	12	6	6	4	3	3	3	3	3	1	0
Objective response	89	82	67	56	53	49	48	47	47	42	38	31	19	16	12	6	6	4	3	3	3	3	3	1	0
Partial response	26	21	9	3	3	2	2	2	2	1	1	1	0												

B Progression-free Survival



No. at Risk	108	101	90	71	61	58	52	50	49	49	47	47	34	21	20	12	6	6	4	3	3	3	3	3	1	0

C Overall Survival



No. at Risk	108	105	102	101	98	91	84	82	78	74	72	66	63	51	40	30	23	16	11	8	4	3	3	3	2	1	0

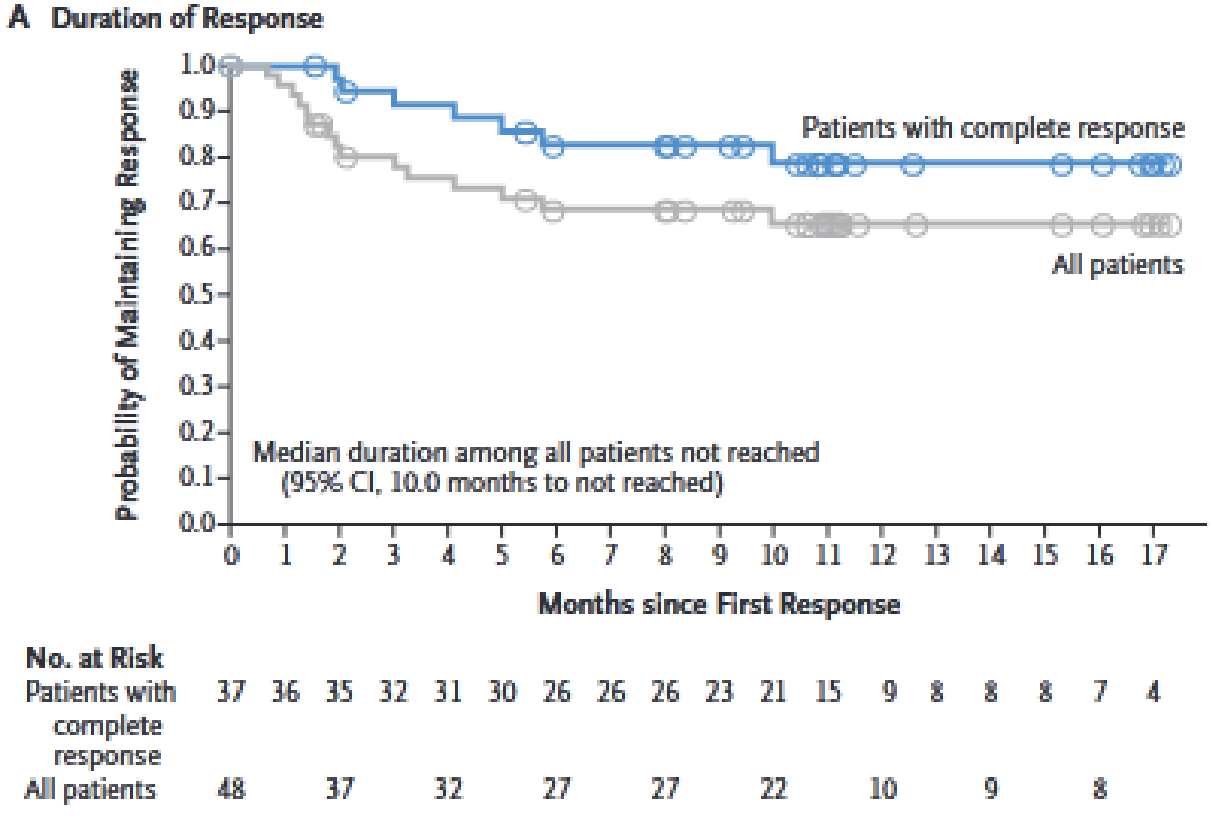
The NEW ENGLAND JOURNAL of MEDICINE

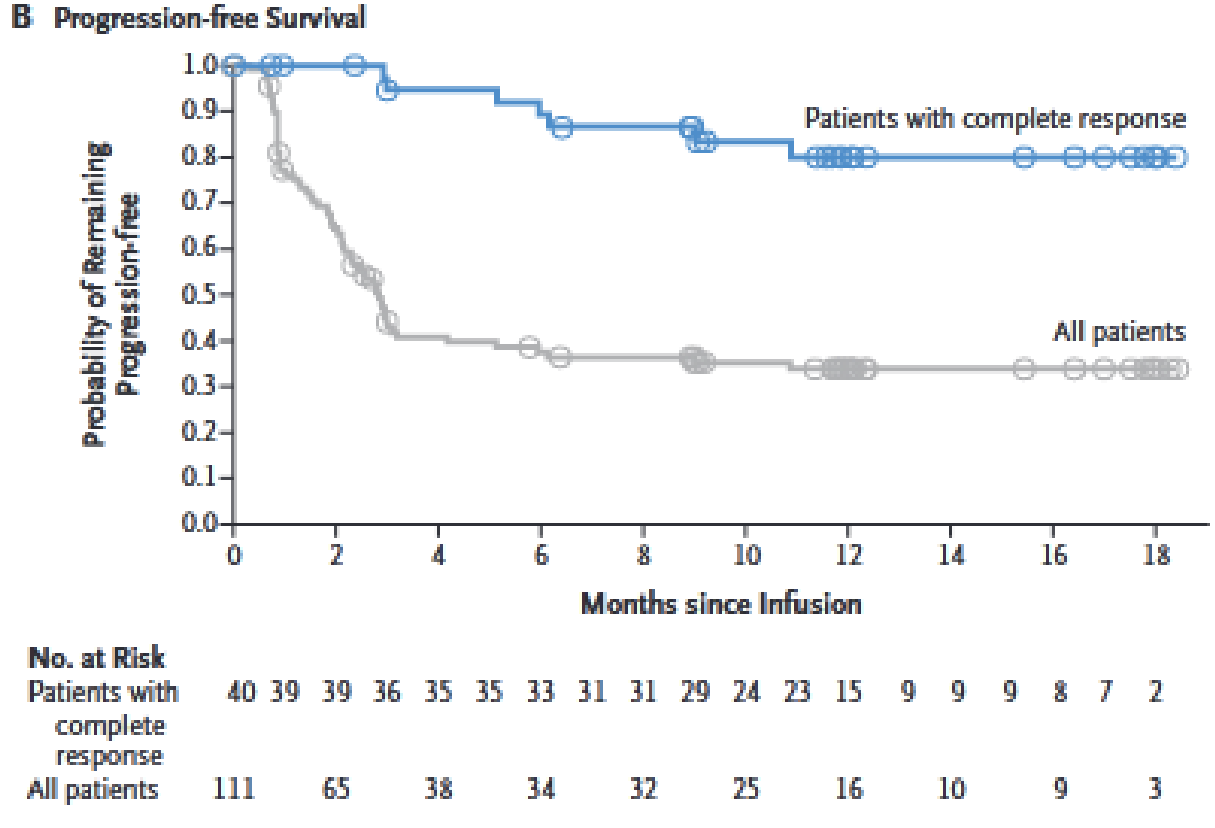
N Engl J Med 2019;380:45-56

ORIGINAL ARTICLE

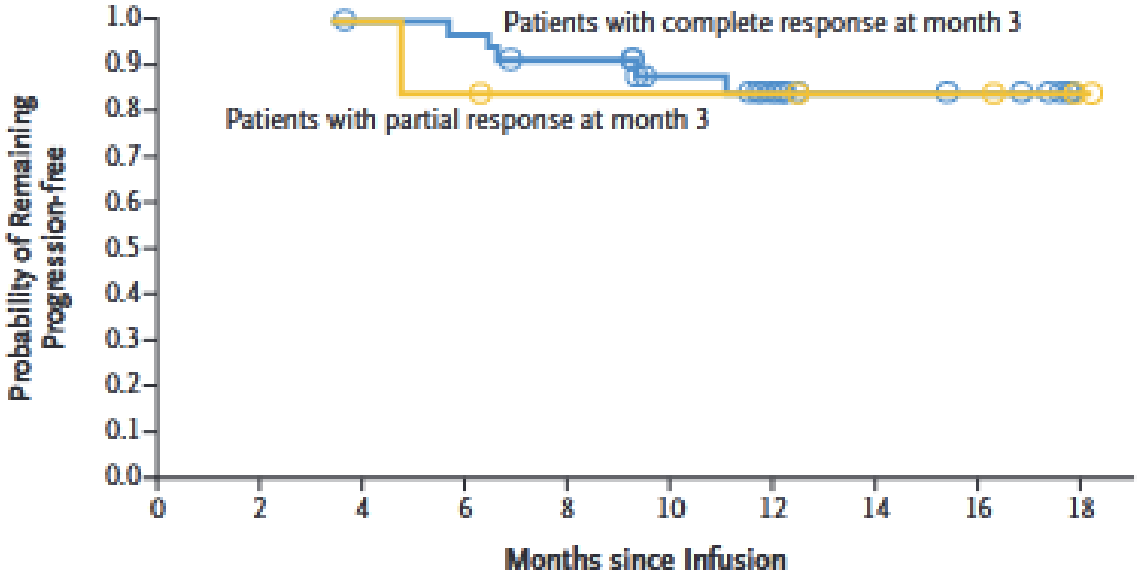
Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Kymriah, 4-1BB costimulatory molecule



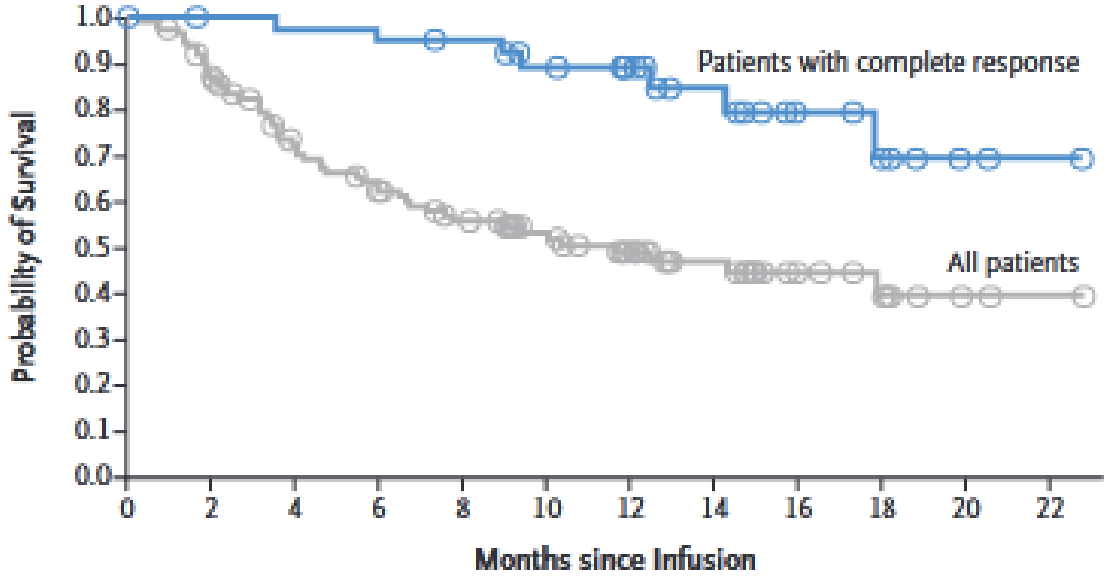


C **Progression-free Survival among Patients with a Response**



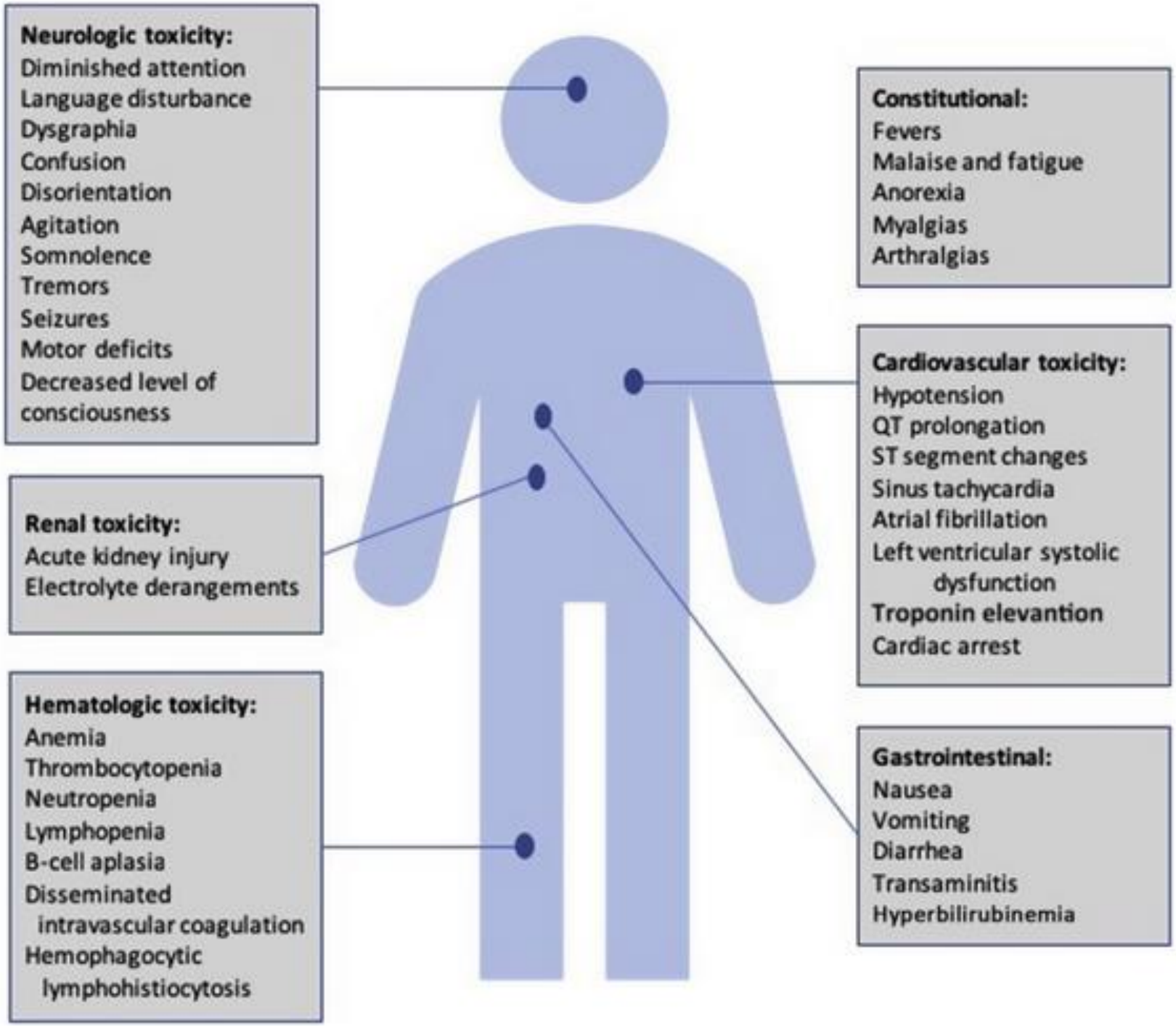
No. at Risk								
Patients with complete response	32	30	28	21	12	7	6	1
Patients with partial response	6	4	4	4	4	3	3	2

D **Overall Survival**



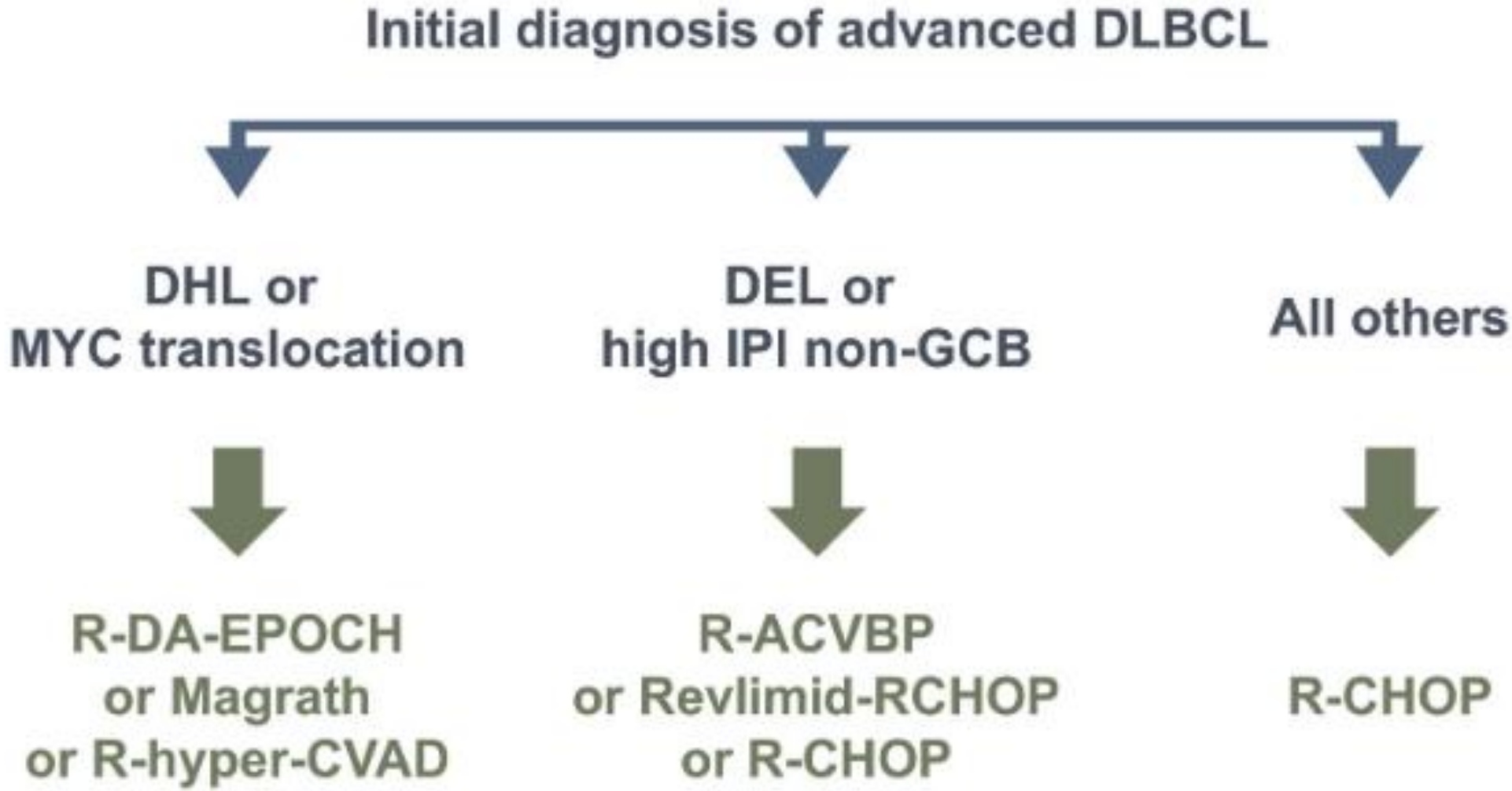
No. at Risk																					
Patients with complete response	40	40	40	40	39	39	38	38	37	36	30	29	23	16	16	12	9	9	7	3	2	1	1
All patients	111		94		71		60		50		40		28		19		11		8		2		1

- The costimulatory molecule 41BB is associated with longer persistence of the CAR-Ts but this translates to a higher incidence of persistent hypogammaglobulinemia and need to give monthly intravenous immunoglobulin.
  Initial responses (and complications) may be faster with Yescarta due to the CD28 costimulation however patients with Kymriah have been treated in the outpatient setting potentially due to lower incidence of dramatic side effects

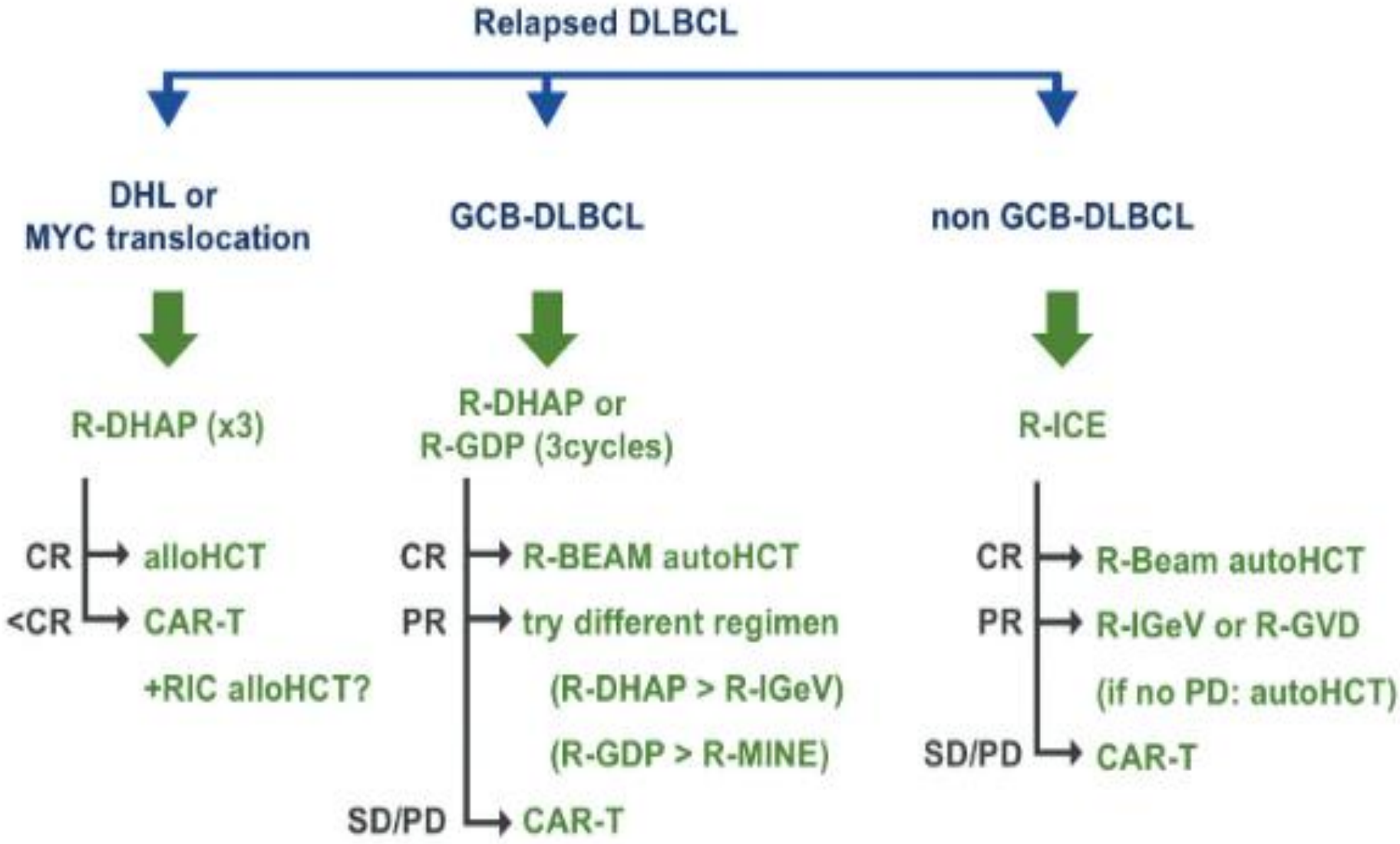

Neurologic toxicity:
Diminished attention
Language disturbance
Dysgraphia
Confusion
Disorientation
Agitation
Somnolence
Tremors
Seizures
Motor deficits
Decreased level of consciousness
Renal toxicity:
Acute kidney injury
Electrolyte derangements
Hematologic toxicity:
Anemia
Thrombocytopenia
Neutropenia
Lymphopenia
B-cell aplasia
Disseminated intravascular coagulation
Hemophagocytic lymphohistiocytosis
Constitutional:
Fevers
Malaise and fatigue
Anorexia
Myalgias
Arthralgias
Cardiovascular toxicity:
Hypotension
QT prolongation
ST segment changes
Sinus tachycardia
Atrial fibrillation
Left ventricular systolic dysfunction
Troponin elevantion
Cardiac arrest
Gastrointestinal:
Nausea
Vomiting
Diarrhea
Transaminitis
Hyperbilirubinemia

Evolving algorithms…

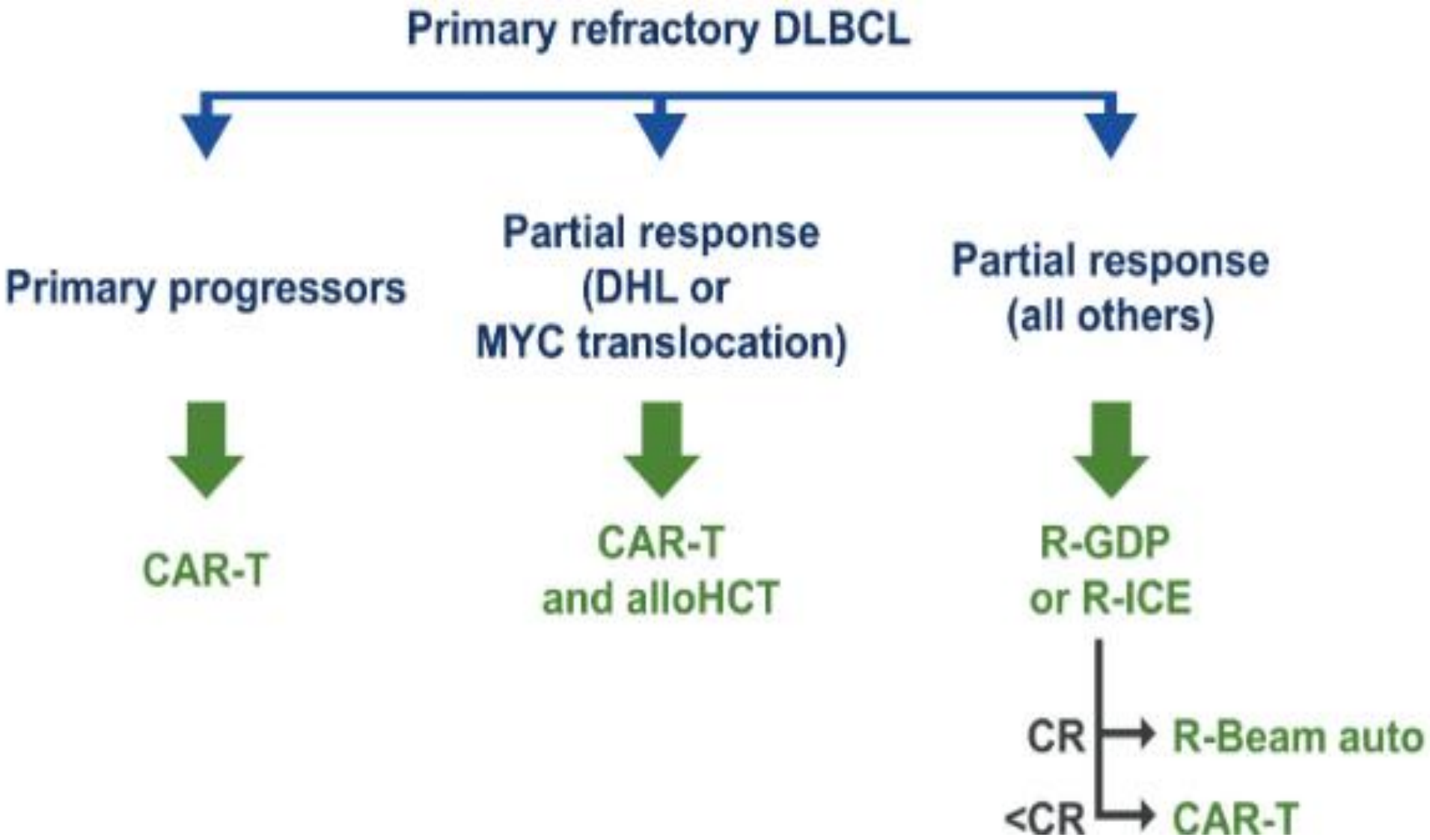
Newly diagnosed DLBL



Relapsed DLBL



Primary refractory DLBL



Post auto relapse

Take Home Message…

- Predictors of poor response to DLBL treatment include early relapse; DEL/DHL subtype; Primary refractory disease; sub-optimal PET response.

  . Lot of strategies being tried to improvise outcomes of these poor risk patients.

  . Increasing role of alloSCT being recognised in auto failure.

  . CART is a potential tool with great potential.

  . Sequencing of these therapies still need to be understood to improvise outcomes.

Thank You!!!