The Evolving Treatment Landscape of Large B-cell Lymphoma

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Disclosures

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Outline

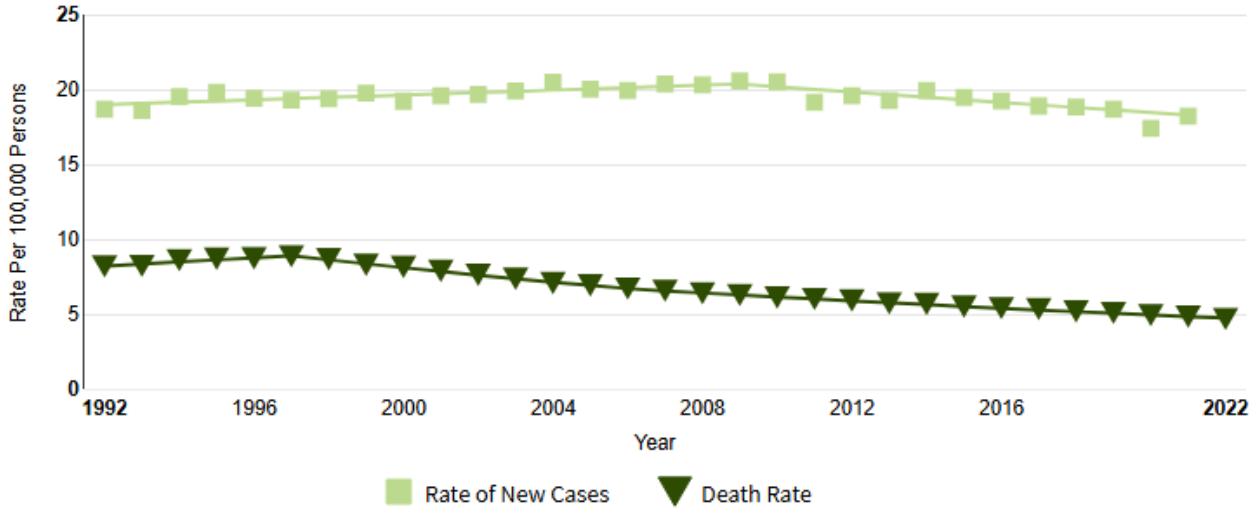
- Lymphoma overview
- Large B-cell lymphoma overview
- Initial treatment of large B-cell lymphoma
- Treatment of relapsed and refractory large B-cell lymphoma
  - Fit patients
  - Unfit or refractory patients
- Future directions

Non-Hodgkin Lymphoma Incidence

Estimated New Cases in 2024	80,620
% of All New Cancer Cases	4.0%

Estimated Deaths in 2024	20,140
% of All Cancer Deaths	3.3%

5-Year Relative Survival
74.3%
2014–2020



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https://seer.cancer.gov/statfacts/html/nhl.html

Evaluation and Diagnosis

- Complete blood count, chemistries including LDH
- Cross sectional imaging
  - CT versus PET CT
- Biopsy
  - Excisional/incisional biopsy preferred
  - Core needle biopsy is excisional/incisional biopsy is not feasible
  - Fine needle aspirate alone is not adequate

NHL Staging

Stage	Description
Stage I	Involvement of a single lymph node region or lymphoid structure (eg, spleen, thymus, Waldeyer's ring) or involvement of a single extralymphatic site (IE)
Stage II	Involvement of two or more lymph node regions on the same site of the diaphragm (II) or localized contiguous involvement of only one extranodal organ or side and its regional lymph nodes with or without other lymph node regions on the same side of the diaphragm (IIE)
	Note: The number of anatomic regions involved may be indicated by a subscript (eg, II3).
Stage III	Involvement of lymph node regions on both sides of the diaphragm (III), which also may be accompanied by involvement of the spleen (IIIS) or by localized contiguous involvement of only one extranodal organ side (IIIE) or both (IIISE)
Stage IV	Disseminated (multifocal) involvement of one or more extranodal organs or tissues, with or without associated lymph node involvement or isolated extralymphatic organ involvement with distant (nonregional) nodal involvement
Designations applicable to any disease stage	
A	No symptoms
B	Fever (temperature >38°C), night sweats, unexplained loss of more than 10% of body weight during the previous 6 months.
X	Bulky disease
E	Involvement of a single extranodal site that is contiguous or proximal to the known nodal site

Rademaker, J. Radiologic Clinics of North America, 2007-01-01, Volume 45, Issue 1, Pages 69-83

Large B-cell Lymphoma Overview, WHO 5th Edition

- Diffuse large B-cell lymphoma, NOS
  - Germinal center B-cell (GCB)-like
  - Activated B-cell (ABC)-like
- T-cell/histiocyte-rich large B-cell lymphoma
- High grade B-cell lymphoma with *MYC* and *BCL2* rearrangements ("double hit lymphoma")
- ALK-positive large B-cell lymphoma
- Large B-cell lymphoma with *IRF4* rearrangements
- High grade B-cell lymphoma with 11q aberration
- Lymphomatoid granulomatosis
- EBV-positive diffuse large B-cell lymphoma NOS
- Diffuse large B-cell lymphoma with chronic inflammation
- Fibrin associated large B-cell lymphoma
- Fluid overload-associated large B-cell lymphoma
- Plasmablastic lymphoma
- Primary large B-cell lymphoma of immune-privileged sites
- Primary cutaneous diffuse large B-cell lymphoma, leg type
- Intravascular large B-cell lymphoma
- Primary mediastinal B-cell lymphoma
- Mediastinal grey zone lymphoma
- High grade B-cell lymphoma NOS

Diffuse Large B-cell Lymphoma Incidence

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https://seer.cancer.gov/statfacts/html/dlbcl.html

MANAGEMENT OF EARLY STAGE DLBCL

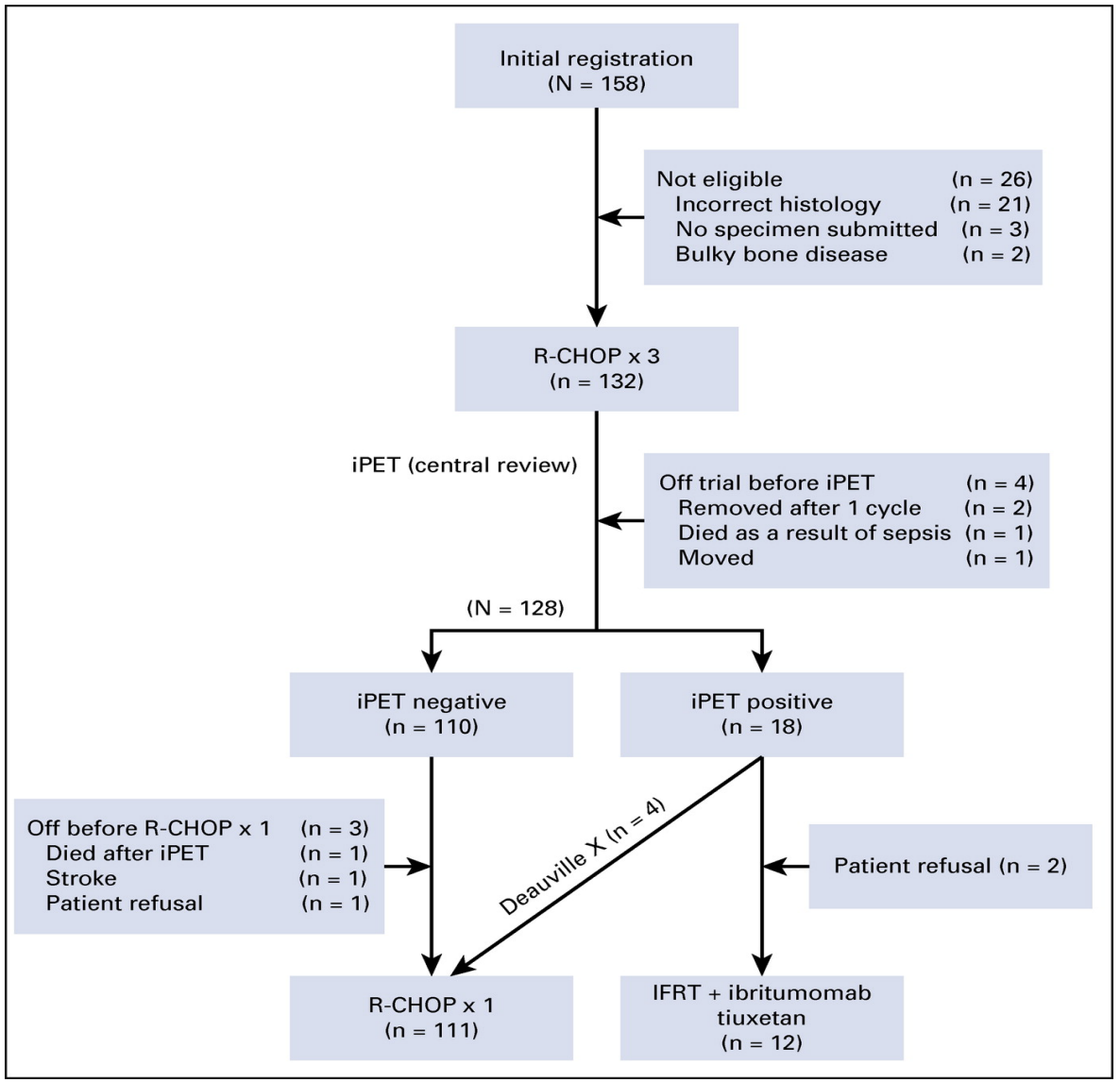
Do All Early Stage DLBCL Patients Need Radiation?

- Historically, patients were treated with combined modality therapy (radiation and chemotherapy)

- S1001 and the FLYER studies are supportive of a radiation free approach in patients with limited stage DLBCL
  - Excluded patients with bulky disease

- Radiation may continue to have a role for certain patients
  - No data with abbreviated schedules in patients receiving dose attenuated chemotherapy
  - Patient scenarios where local control is of particular importance (e.g. pathologic fracture)

S1001



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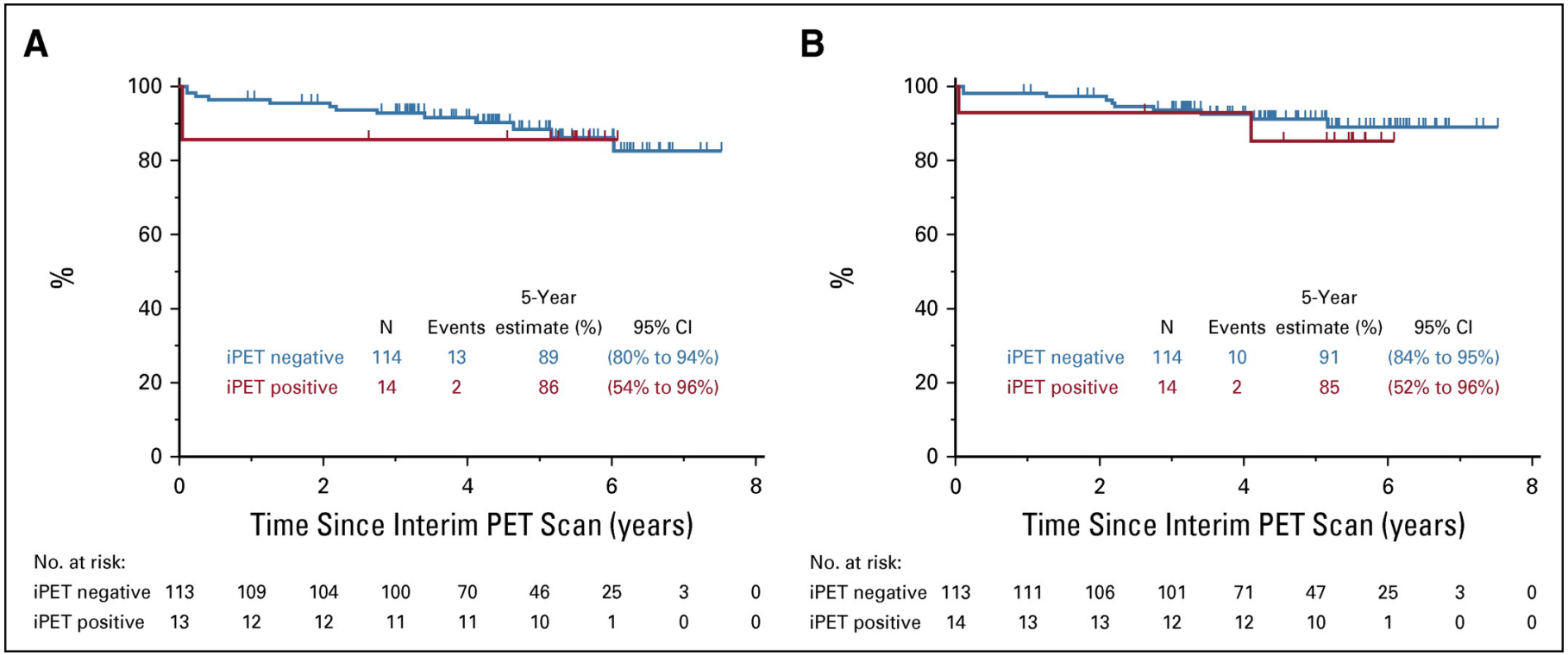
DO. Persky, et al. *Journal of Clinical Oncology* 2020 383003-3011.

S1001



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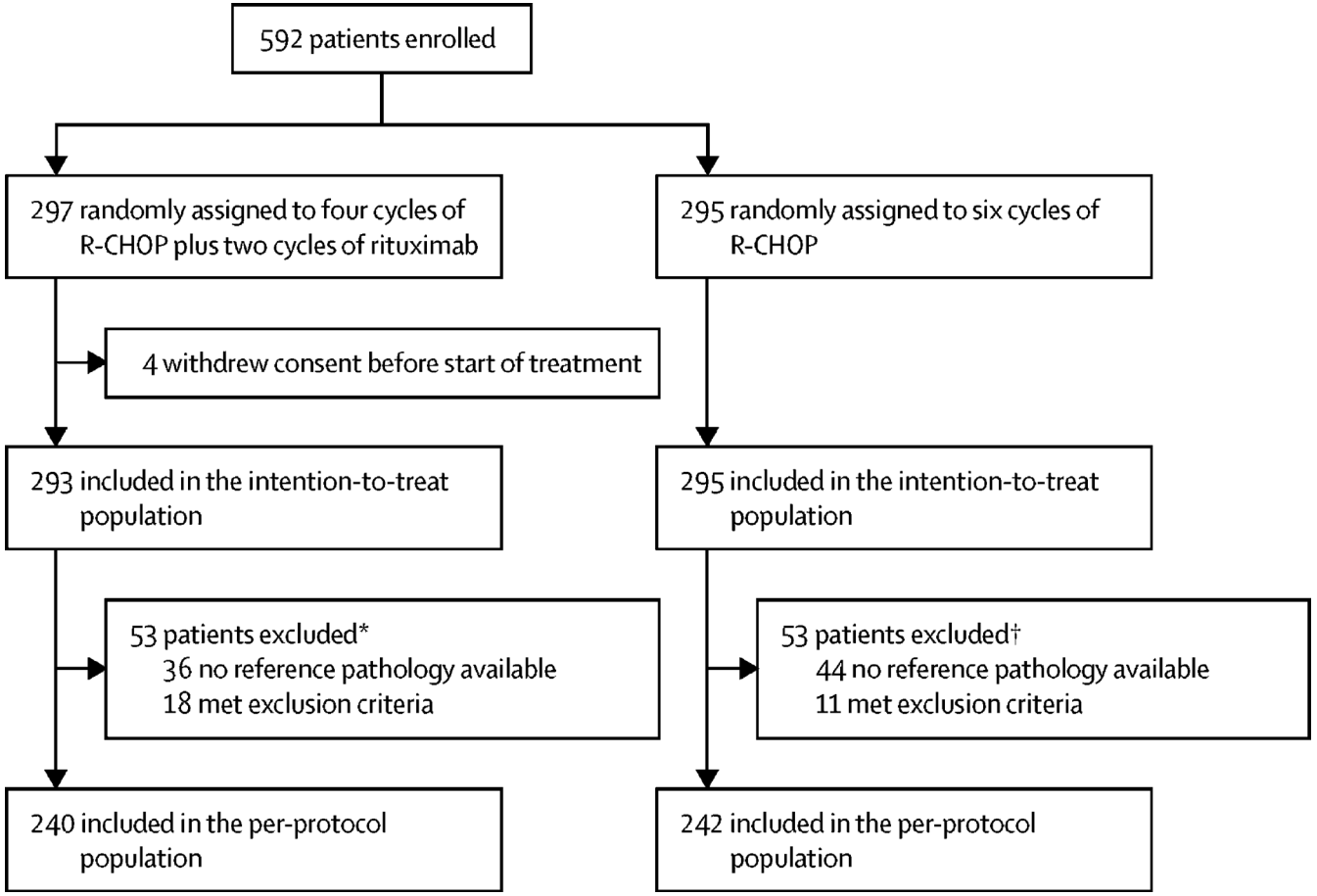
DO. Persky, et al. *Journal of Clinical Oncology* 2020 383003-3011.

FLYER



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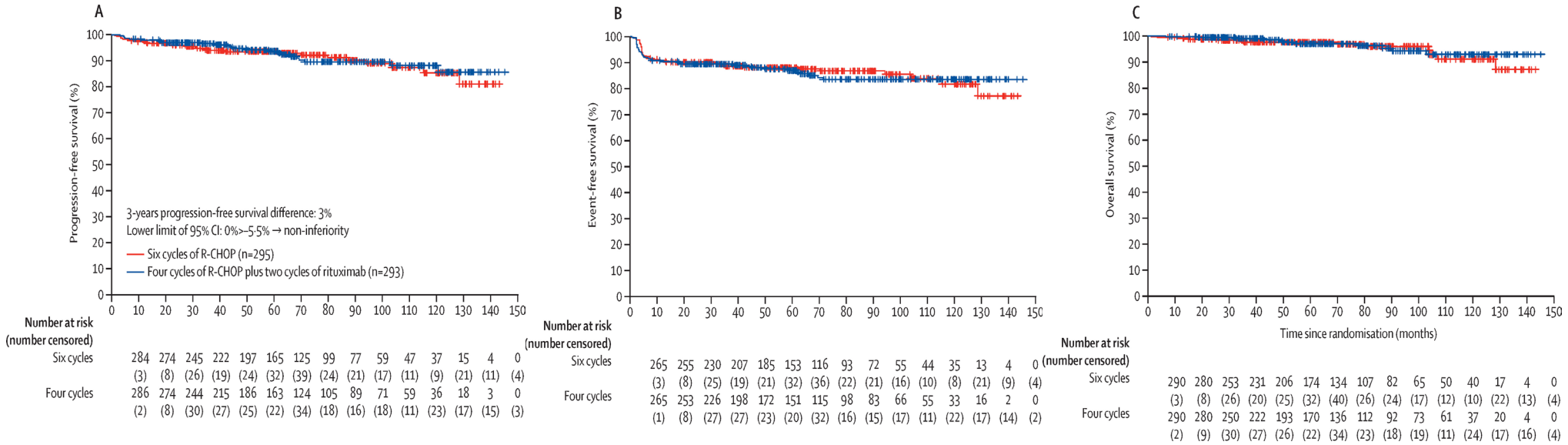
V. Poeschel, etal. *The Lancet* 2019 3942271-2281DOI: (10.1016/S0140-6736(19)33008-9)

FLYER



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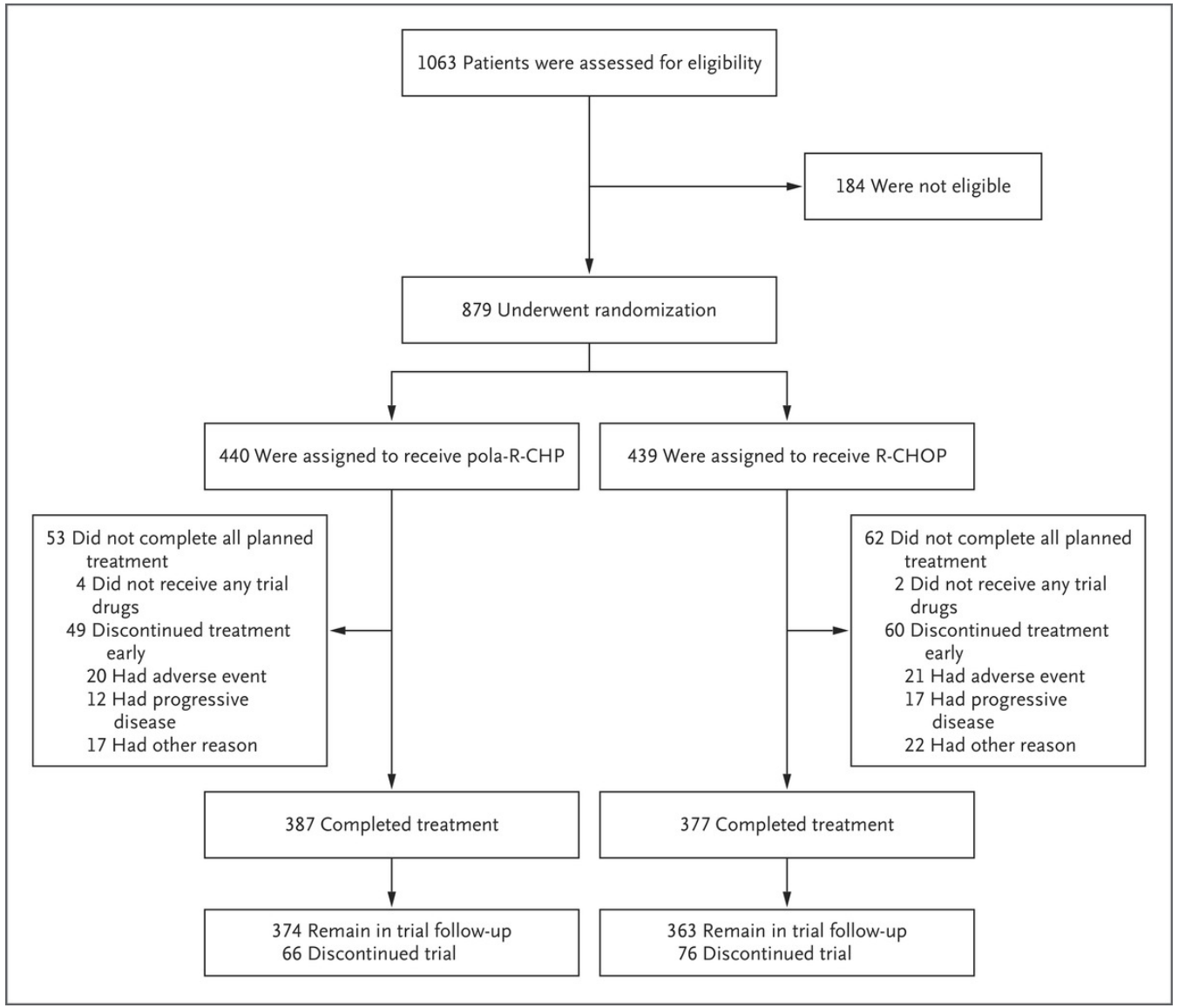
V. Poeschel, et al. *The Lancet* 2019 3942271-2281DOI: (10.1016/S0140-6736(19)33008-9)

FRONTLINE MANAGEMENT OF ADVANCED STAGE DLBCL AND TRANSFORMED LYMPHOMA

POLARIX: A New Standard of Care in DLBCL

- R-CHOP has been the standard of care for 2 decades for DLBCL
- Large, international, randomized controlled trial of R-CHP + polatuzumab vedotin versus R-CHOP + placebo
- Key inclusion criteria
  - DLBCL, regardless of cell of origin or double hit status
  - ECOG 0-2
  - IPI score of 2-5
- Key exclusion criteria
  - History of indolent lymphoma
  - Known CNS involvement

FDA approval 4/17/2023



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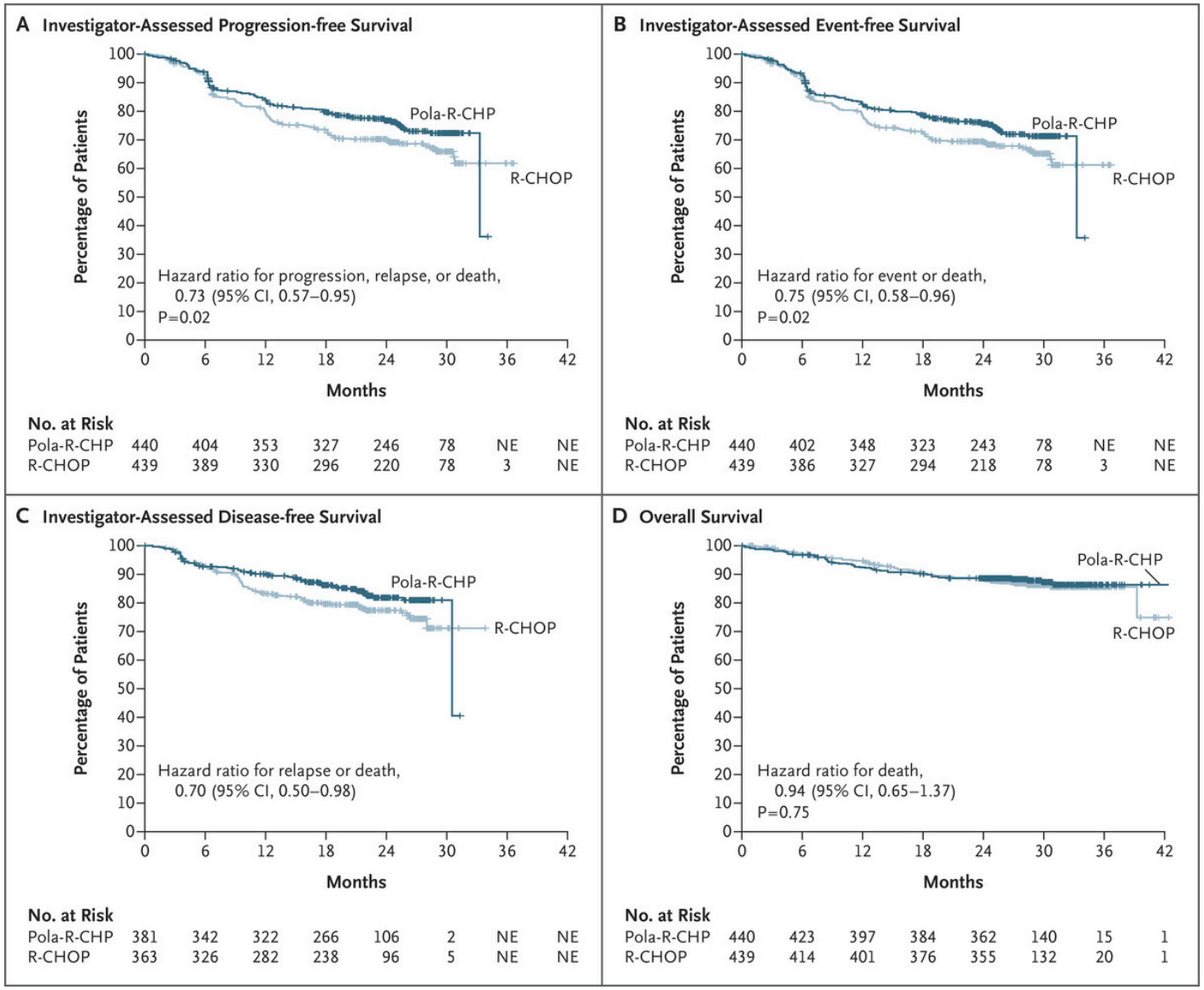
H Tilly et al. N Engl J Med 2022;386:351-363.



Benefits seen in patients with ABC-like DLBCL

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H Tilly et al. N Engl J Med 2022;386:351-363.

Table 3. Adverse Events during the Treatment Period (Safety Population).*

Adverse Event	Pola-R-CHP (N=435)		R-CHOP (N=438)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Peripheral neuropathy†	230 (52.9)	7 (1.6)	236 (53.9)	5 (1.1)
Nausea	181 (41.6)	5 (1.1)	161 (36.8)	2 (0.5)
Neutropenia	134 (30.8)	123 (28.3)	143 (32.6)	135 (30.8)
Diarrhea	134 (30.8)	17 (3.9)	88 (20.1)	8 (1.8)
Anemia	125 (28.7)	52 (12.0)	114 (26.0)	37 (8.4)
Constipation	125 (28.7)	5 (1.1)	127 (29.0)	1 (0.2)
Fatigue	112 (25.7)	4 (0.9)	116 (26.5)	11 (2.5)
Alopecia	106 (24.4)	0	105 (24.0)	1 (0.2)
Decreased appetite	71 (16.3)	5 (1.1)	62 (14.2)	3 (0.7)
Pyrexia	68 (15.6)	6 (1.4)	55 (12.6)	0
Vomiting	65 (14.9)	5 (1.1)	63 (14.4)	3 (0.7)
Febrile neutropenia	62 (14.3)	60 (13.8)	35 (8.0)	35 (8.0)
Headache	56 (12.9)	1 (0.2)	57 (13.0)	4 (0.9)
Cough	56 (12.9)	0	53 (12.1)	0
Decreased weight	55 (12.6)	4 (0.9)	52 (11.9)	1 (0.2)
Asthenia	53 (12.2)	7 (1.6)	53 (12.1)	2 (0.5)
Dysgeusia	49 (11.3)	0	57 (13.0)	0

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H Tilly et al. N Engl J Med 2022;386:351-363.

Transformed Indolent Lymphoma

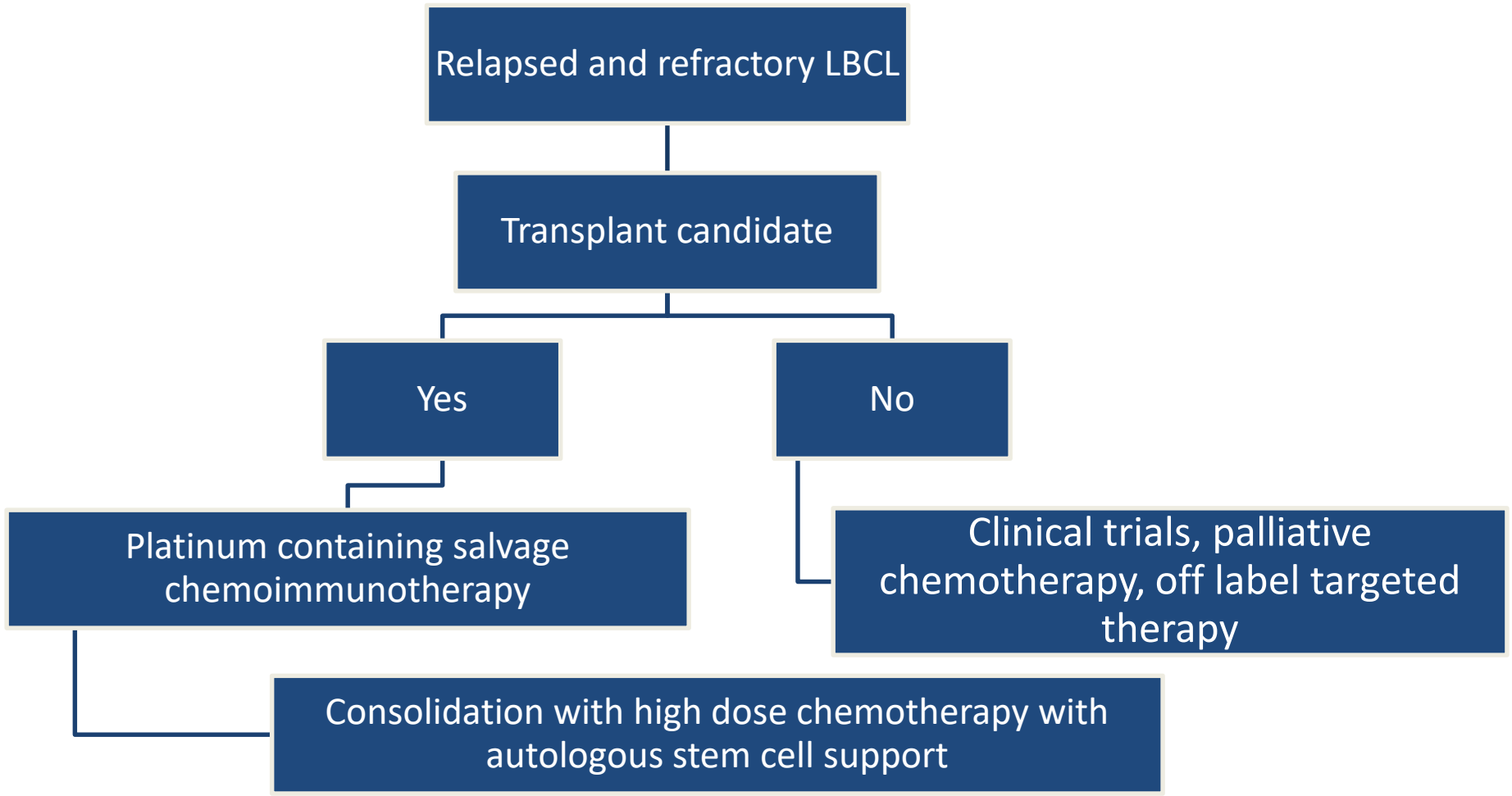
- Previously untreated patients
  - Patients who are anthracycline naïve have outcomes comparable to *de novo* DLBCL without ASCT

- Previously treated patients
  - Patients with histologic transformation treated with anthracyclines included in Canadian intergroup and PRIMA studies and appear to benefit from consolidative ASCT
  - POD24 after BR is associated with histologic transformation and 2-year OS is only ~40%

Link BK, et al. J Clin Oncol. 2013 Sep 10;31(26):3272-8; Wang Y, et al. Blood. 2019 ;134 (16):1289-1297; Freeman CL, et al. Blood. 2019;134(9):761-764; Kuruvilla J, et al. Blood. 2015;126(6):733-738; Sarkozy C, et al. J Clin Oncol. 2016;34(22):2575-2582.

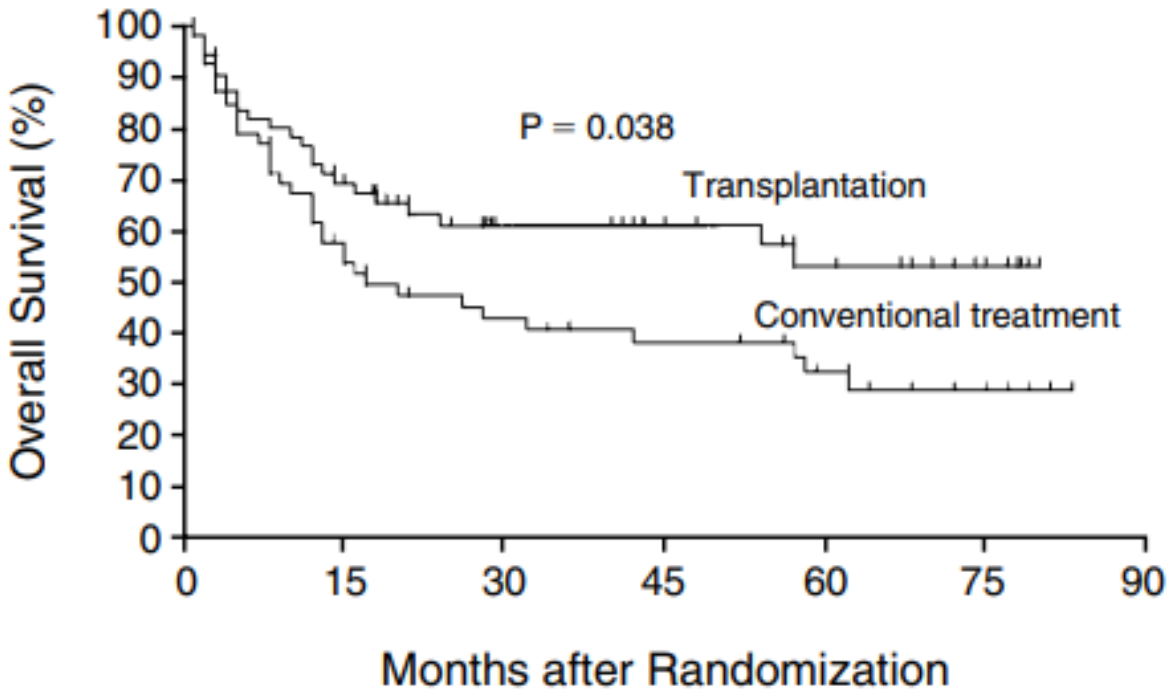
AUTOLOGOUS STEM CELL TRANSPLANT (ASCT) FOR RELAPSED AND REFRACTORY LARGE B-CELL LYMPHOMA (LBCL)

Relapsed LBLC Treatment Paradigm Circa 2017



ASCT in Relapsed and Refractory LBCL Patients

- Randomized controlled trial in patients with intermediate or high-grade NHL
- Patients received salvage therapy with DHAP for 2 cycles followed by randomization to consolidation with ASCT versus continued conventional therapy
- EFS and OS superior in the ASCT group



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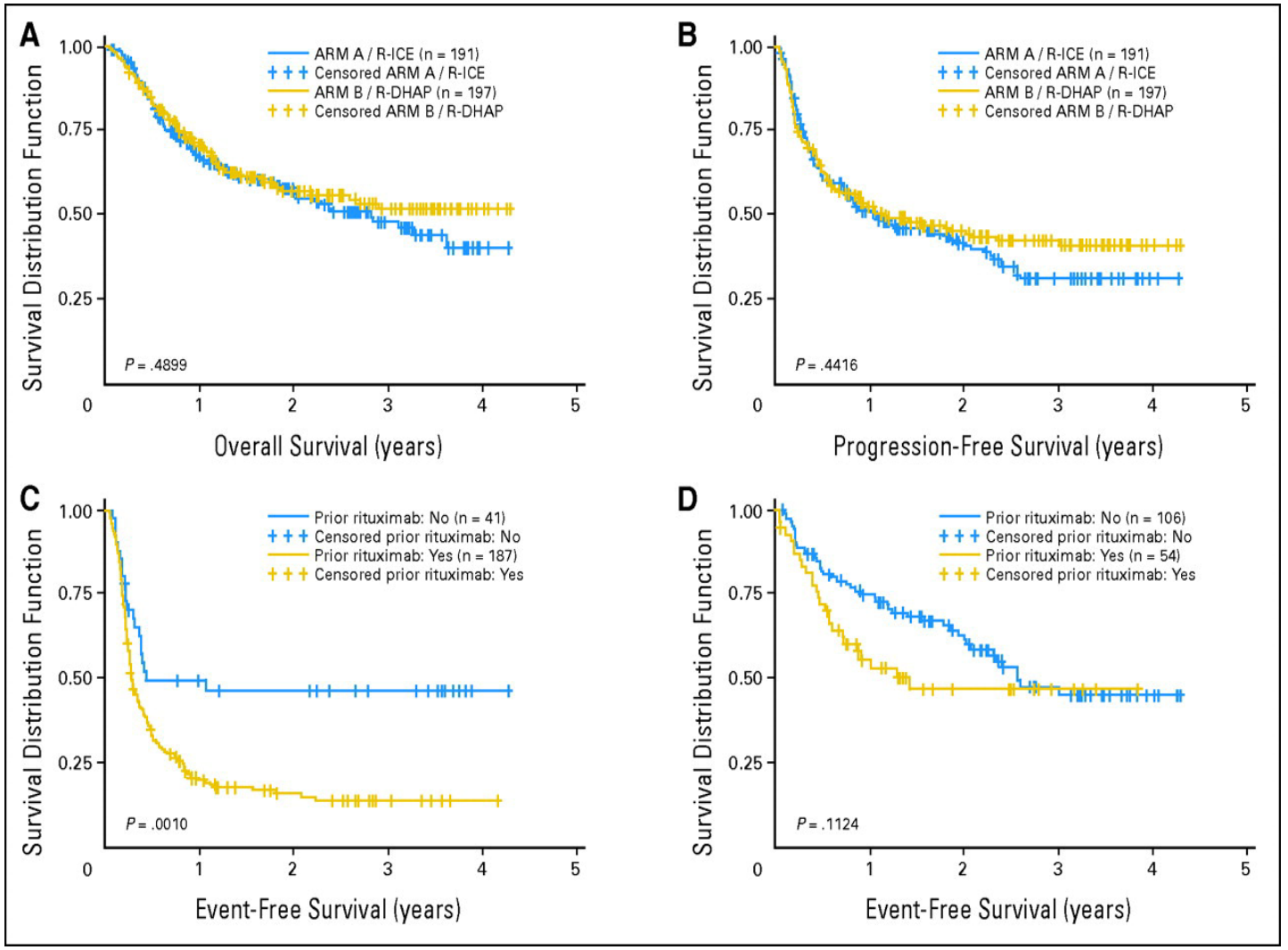
Philip T, et al. N Engl J Med. 1995 Dec 7;333(23):1540-5

ASCT for Relapsed and Refractory LBCL

- CORAL study was a randomized study of R-DHAP vs R-ICE followed by ASCT
- Median PFS and OS were similar between groups
- Patients with prior rituximab exposure and relapsed within 12 months had inferior EFS



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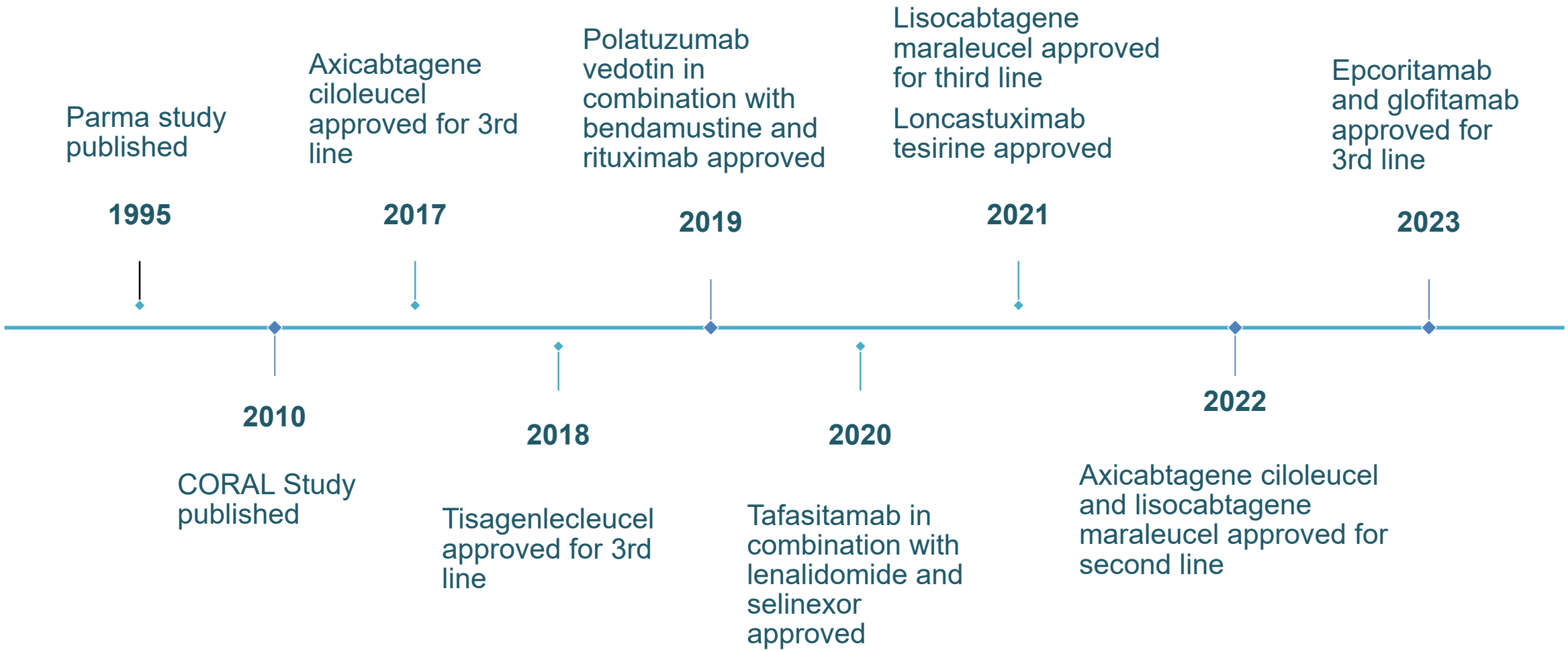
Gisselbrecht C, et al. *Journal of Clinical Oncology* 2010 28 4184-4190

TARGETED THERAPY FOR FIT PATIENTS WITH RELAPSED LBCL

Classes of Targeted Therapies for LBCL

- Chimeric antigen receptor (CAR) T-cells
  - Genetically modified autologous or allogeneic T-cells that target cell surface molecules
- Antibody-drug conjugates
  - Allow for delivery of chemotherapy or toxins more specifically to tumor cells
- Bispecific antibodies
  - Antibodies that target multiple antigens
  - Can engage T-cells

Timeline of Approvals in Relapsed LBCL



CAR T-cell therapy for Relapsed and Refractory LBCL

Anti-CD19 CAR T-cell	Patients apheresed	Patients dosed	ORR (CR)	2-year PFS	Median OS
Axicabtagene ciloleucel	111	101	83% (58%)	39%	25.8 months
Tisagenlecleucel	165	111	52% (40%)	38.2%	12 months
Lisocabtagene maraleucel	344	269	73% (53%)	40.6%	21.1 months

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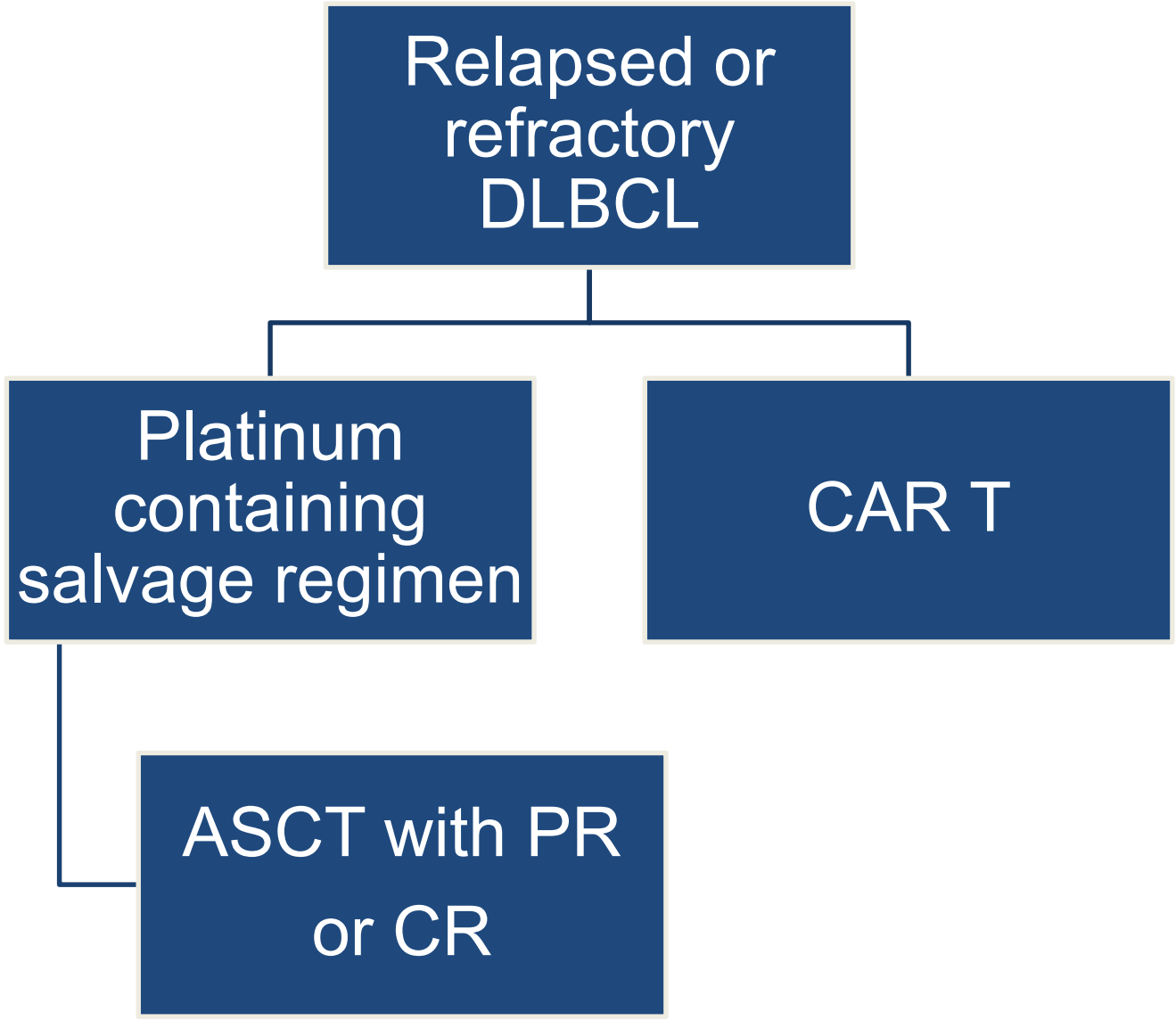
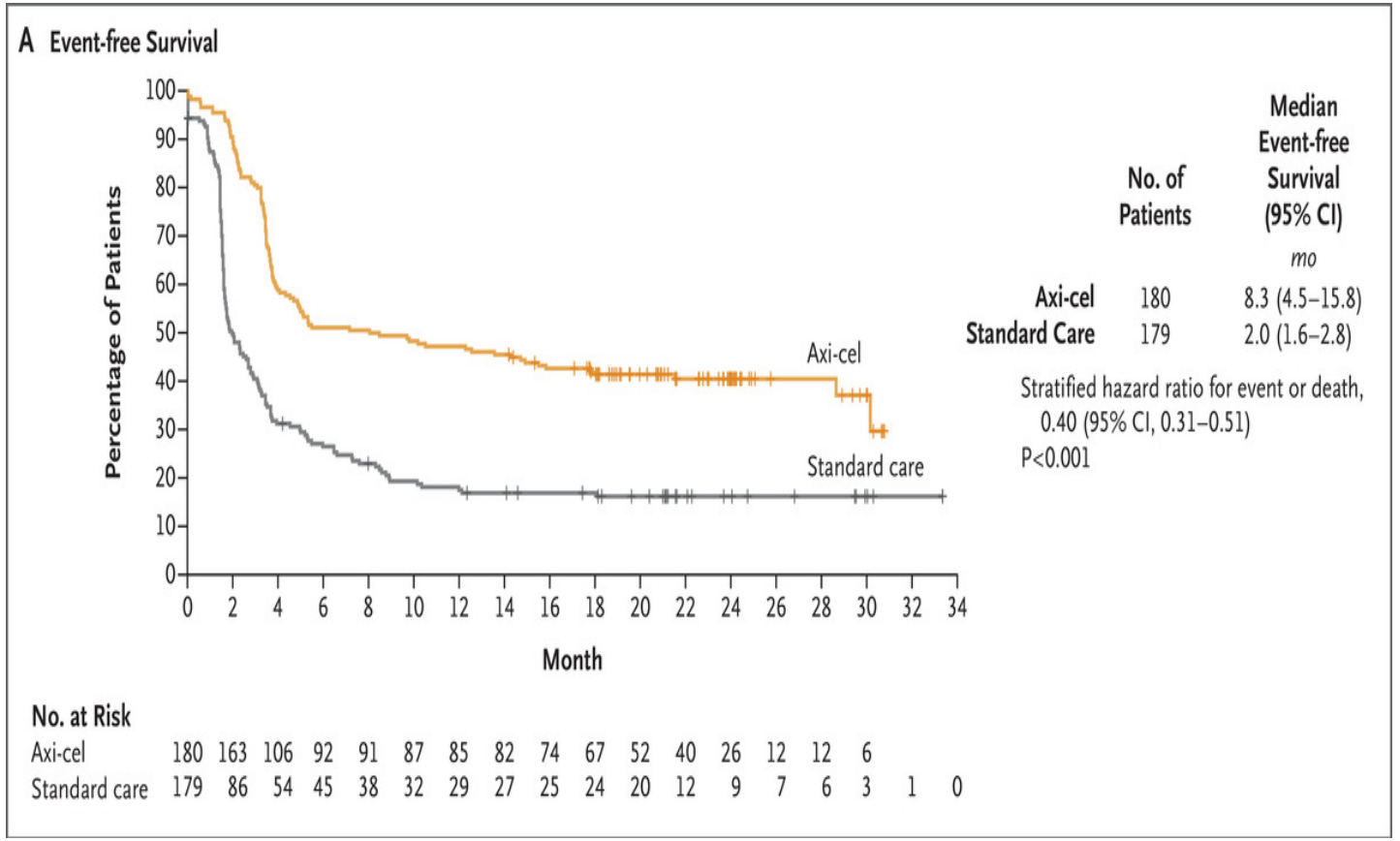
Neelapu SS et al. N Engl J Med 2017;377:2531-2544; Locke FL, et al. Lancet Oncol. 2019 Jan;20(1):31-42; SJ Schuster et al. N Engl J Med 2019;380:45-56; Abramson JS, et al.. The Lancet, Volume 396, Issue 10254, 839 – 852; JS. Abramson, et al. *Blood* 2021; 138 (Supplement 1): 2840


Relapsed or refractory DLBCL
Platinum containing salvage regimen
CAR T
ASCT with PR or CR

ZUMA-7: Axicabtagene Ciloleucel (axi-cel)

- Axi-cel vs platinum containing salvage followed by ASCT
- Patients with disease relapse within 12 months of diagnosis
- No bridging apart from corticosteroids
- No formal crossover
- 2- year EFS 41% vs 16%
- With longer term follow up, there is an OS benefit
- Label expanded on 4/1/2022 to include patients with relapse within 12 months of chemoimmunotherapy



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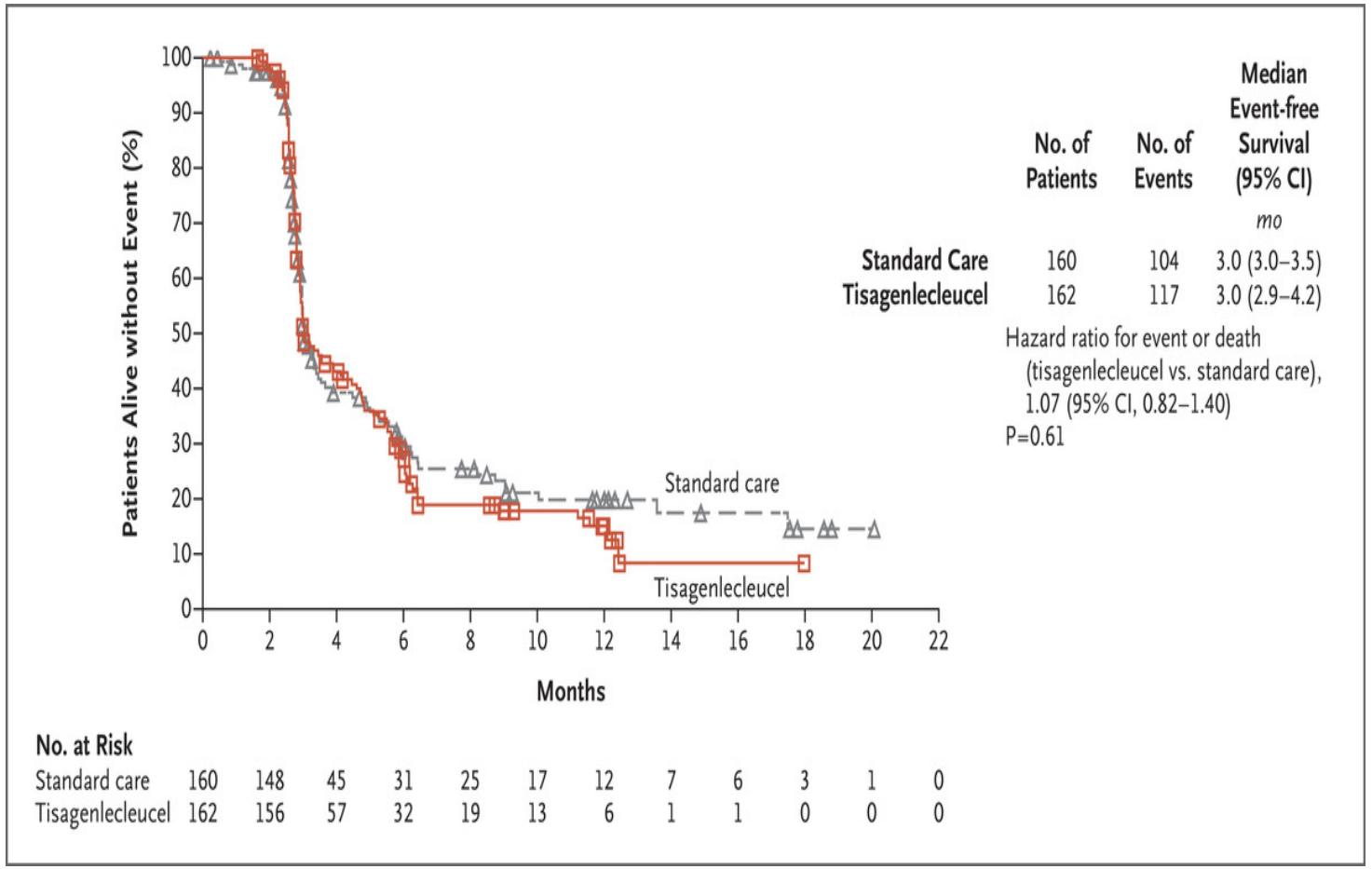
FL Locke et al. N Engl J Med 2022;386:640-654.

BELINDA: Tisagenlecleucel (tisa-cel)

- Tisa-cel vs platinum containing salvage followed by ASCT
- Patients with disease relapse within 12 months completion of therapy
- Bridging therapy with platinum containing salvage
- Crossover allowed
- Median EFS was 3 months in both groups



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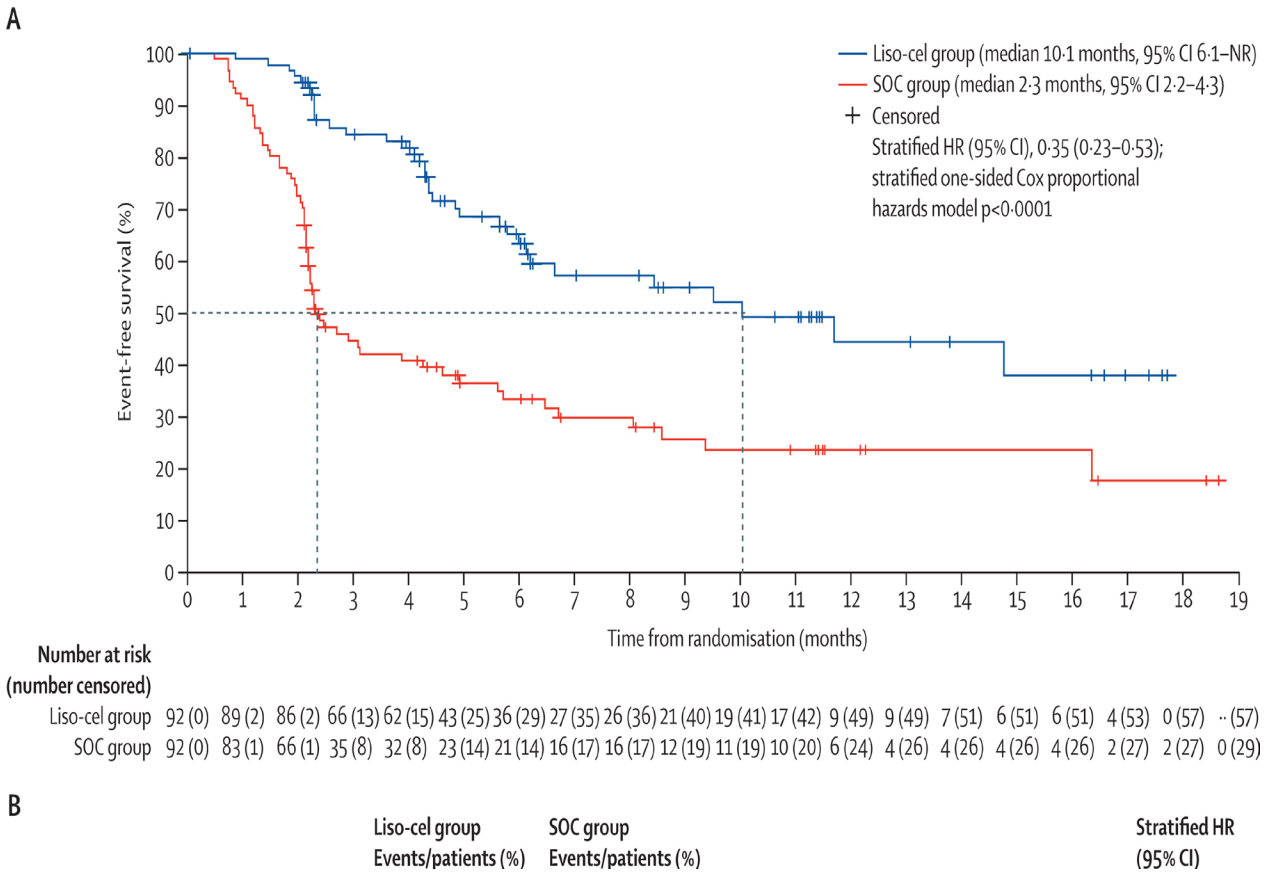
MR Bishop et al. N Engl J Med 2022;386:629-639.

TRANSFORM: Lisocabtagene Maraleucel (liso-cel)

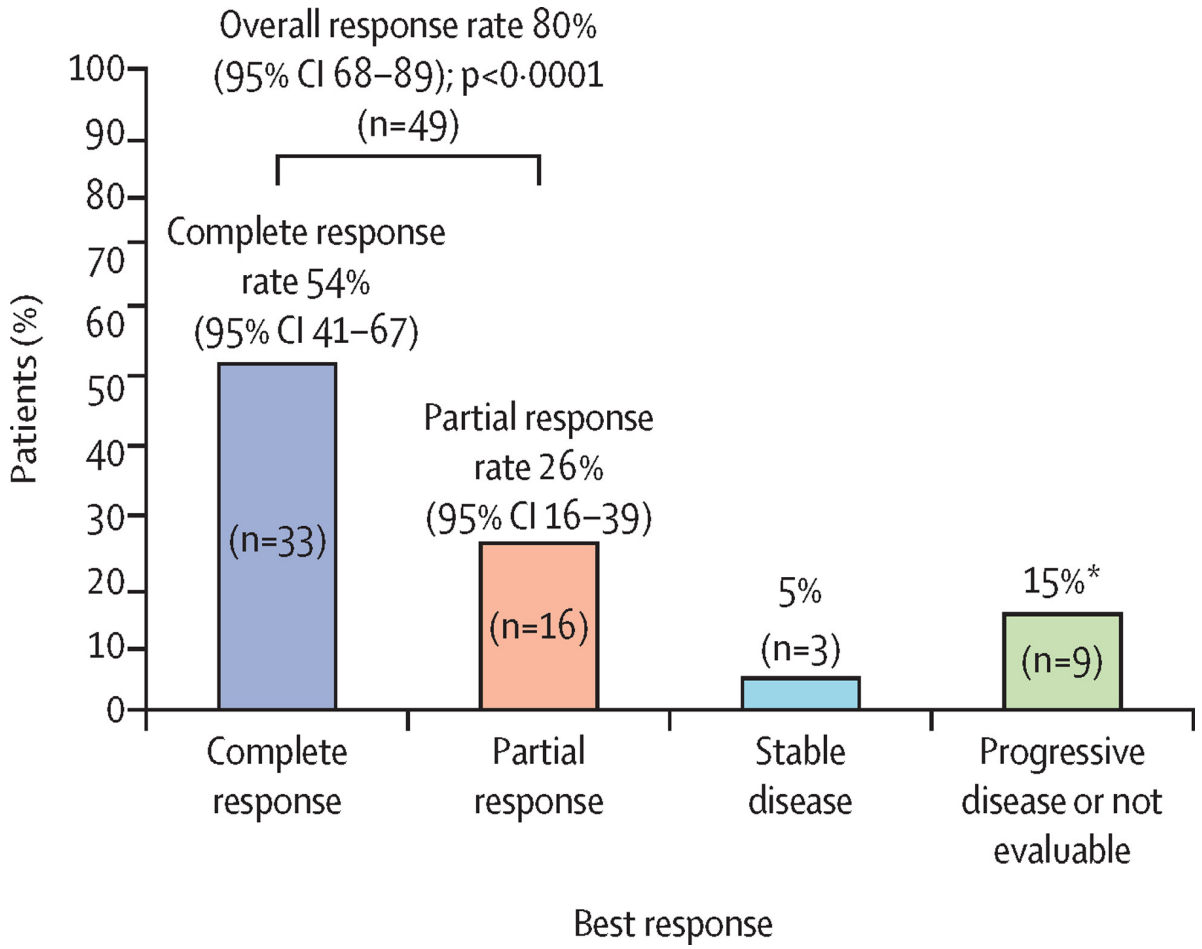
- Liso-cel vs platinum containing salvage followed by ASCT
- Patients with disease relapse within 12 months of treatment completion
- Cycle of platinum containing salvage allowed for bridging
- Crossover allowed
- Median EFS 10.1 vs 2.3 months
- Label expanded on 7/24/2022 to include patients with relapse within 12 months of chemoimmunotherapy



Kamdar M, et al. *The Lancet* 2022 399 2294-2308

PILOT (Liso-cel)

- Liso-cel as second line therapy for patients considered ineligible for ASCT
- Most common reason for ineligibility was age greater than 70
- High rates of response
- Median PFS 22.6 months
- Liso-cel now approved for second line therapy in transplant ineligible patients with LBCL



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Sehgal A, Lancet Oncol. 2022 Aug;23(8):1066-1077

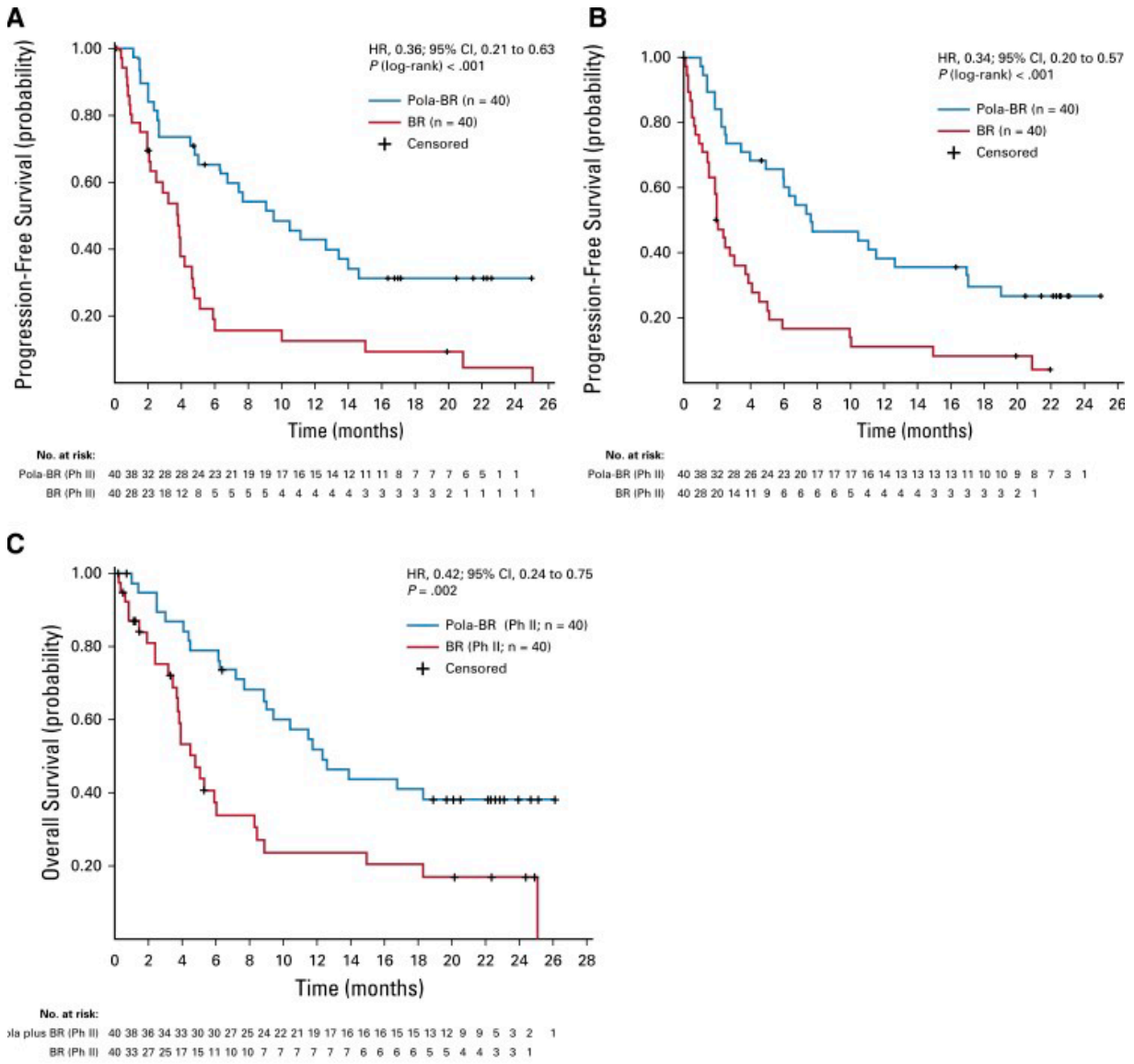
Summary CAR T-cells for LBCL

- CAR T-cells are active in patients with disease resistant to chemotherapy or relapsed after ASCT
- Axi-cel and liso-cel are superior to salvage chemotherapy followed by ASCT in patients with refractory disease or relapsed within 12 months. ASCT remains the standard in other patients
- CAR T-cells are feasible in transplant ineligible patients
- Disease relapse remains a concern

TARGETED THERAPY FOR UNFIT PATIENTS OR THOSE WITH RELAPSED/REFRACTORY LBCL

BR and Polatuzumab Vedotin (BR-pola)

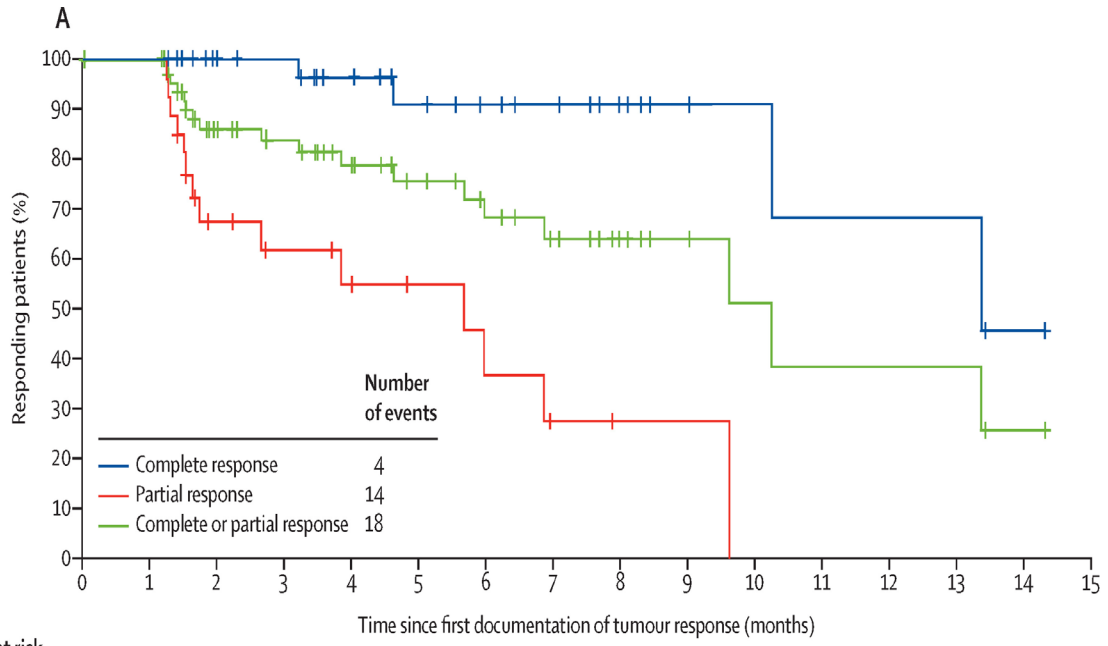
- Patients with relapsed and refractory DLBCL
- Phase 1b/2 trial with randomized cohort
- ORR BR-pola 45% vs BR 17.5%; CR BR-pola 40% vs BR 17.5%
- Median PFS, OS and DOR were superior in BR-pola arm
- Role of polatuzumab in relapsed setting will likely be reduced given results of POLARIX
- **Bendamustine should be avoided prior to CAR T collection**



Sehn LH, et al. J Clin Oncol. 2020 Jan 10;38(2):155-165

Loncastuximab Tesirine (lonca-t)

- Patients with relapsed and refractory DLBCL 2 or greater lines of therapy
- ORR 48.3%, CR 24%
- Median PFS 4.9 months, median OS 9.9 months, median DOR 10.3 months
- Grade ≥3 events mostly hematologic
- Peripheral edema common



Number at risk (number censored)																
Complete response	35 (0)	34 (1)	28 (7)	26 (9)	21 (13)	17 (16)	14 (19)	12 (21)	8 (25)	5 (28)	4 (29)	3 (29)	3 (29)	3 (29)	1 (30)	0 (31)
Partial response	35 (0)	28 (7)	13 (14)	10 (16)	8 (17)	6 (19)	4 (19)	2 (20)	1 (20)	1 (21)	0 (21)	0 (21)	0 (21)	0 (21)	0 (21)	0 (21)
Complete or partial response	70 (0)	62 (8)	41 (21)	36 (25)	29 (30)	23 (35)	18 (38)	14 (41)	9 (46)	6 (49)	4 (50)	3 (50)	3 (50)	3 (50)	1 (51)	0 (52)

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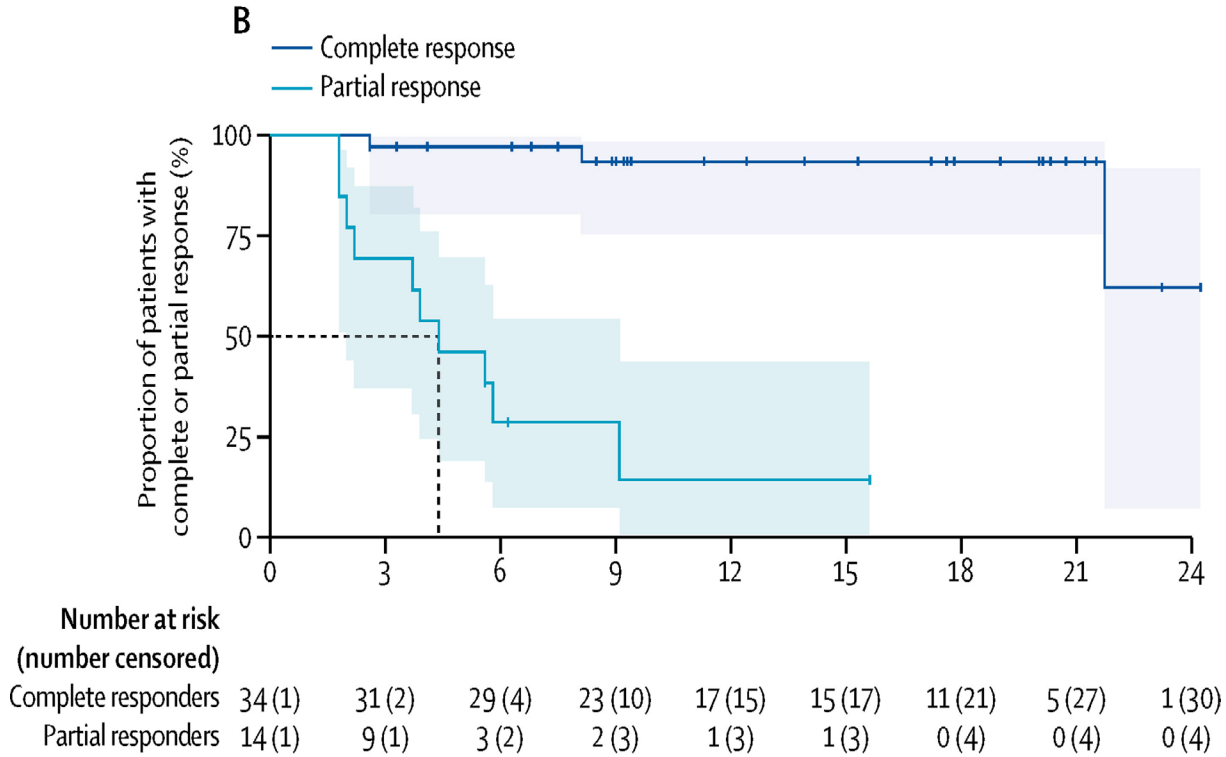
PF Caimi, et al. The Lancet Oncology 2021 22790-800

Lenalidomide and Tafasitamab

- Patients with relapsed DLBCL (>3 months from end of treatment)
- ORR 60%, CR 43%
- Median PFS 12.1 months, median DOR 21.7 months
- Grade ≥3 toxicities largely hematologic



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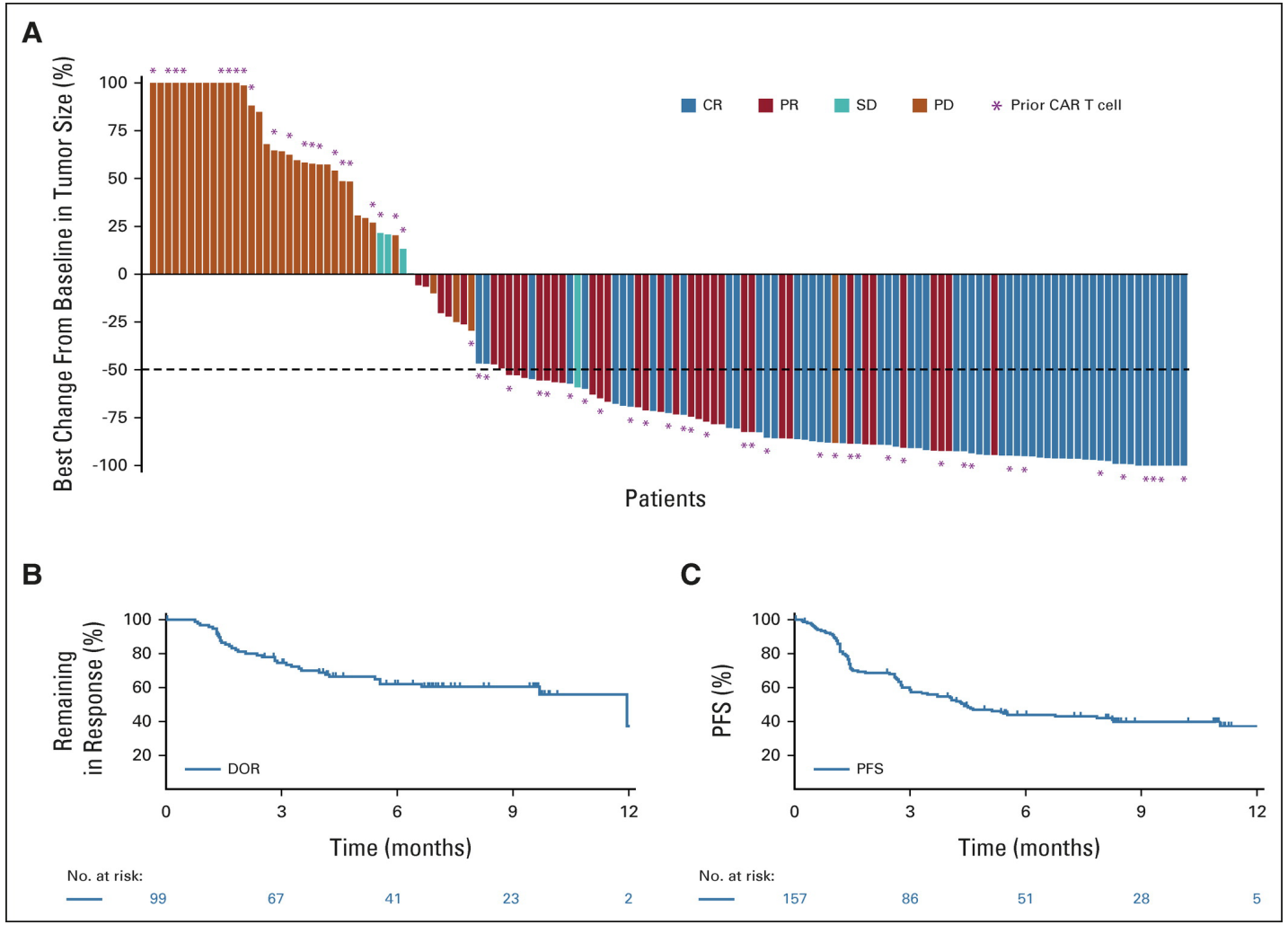
G Salles, et al. The Lancet Oncology 2020 21978-988

Epcoritamab

- Open-label phase 1-2 clinical trial
- Heavily pretreated with median 3 lines of therapy and 38.9% receiving prior CAR T
- ORR 63.1%, CR 38.9%
- Median PFS 4.4 months
- Median duration of response was 9.7 months and median duration of CR was not reached
- Grade ≥3 CRS in 2.5%, any grade ICANS 6.4% with one fatal event



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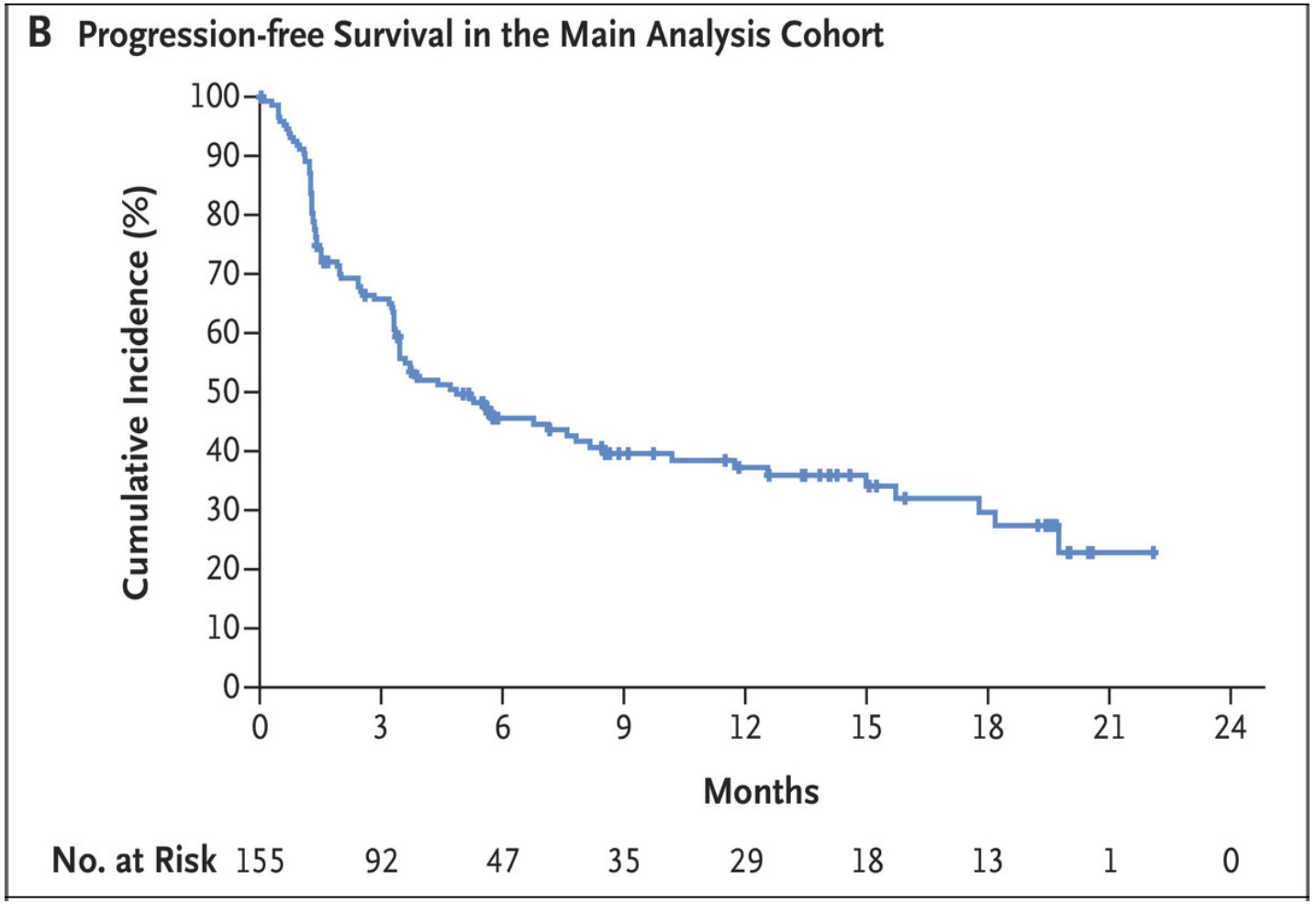
Thieblemont C, et al. *Journal of Clinical Oncology* 2023 412238-2247.

Glofitamab

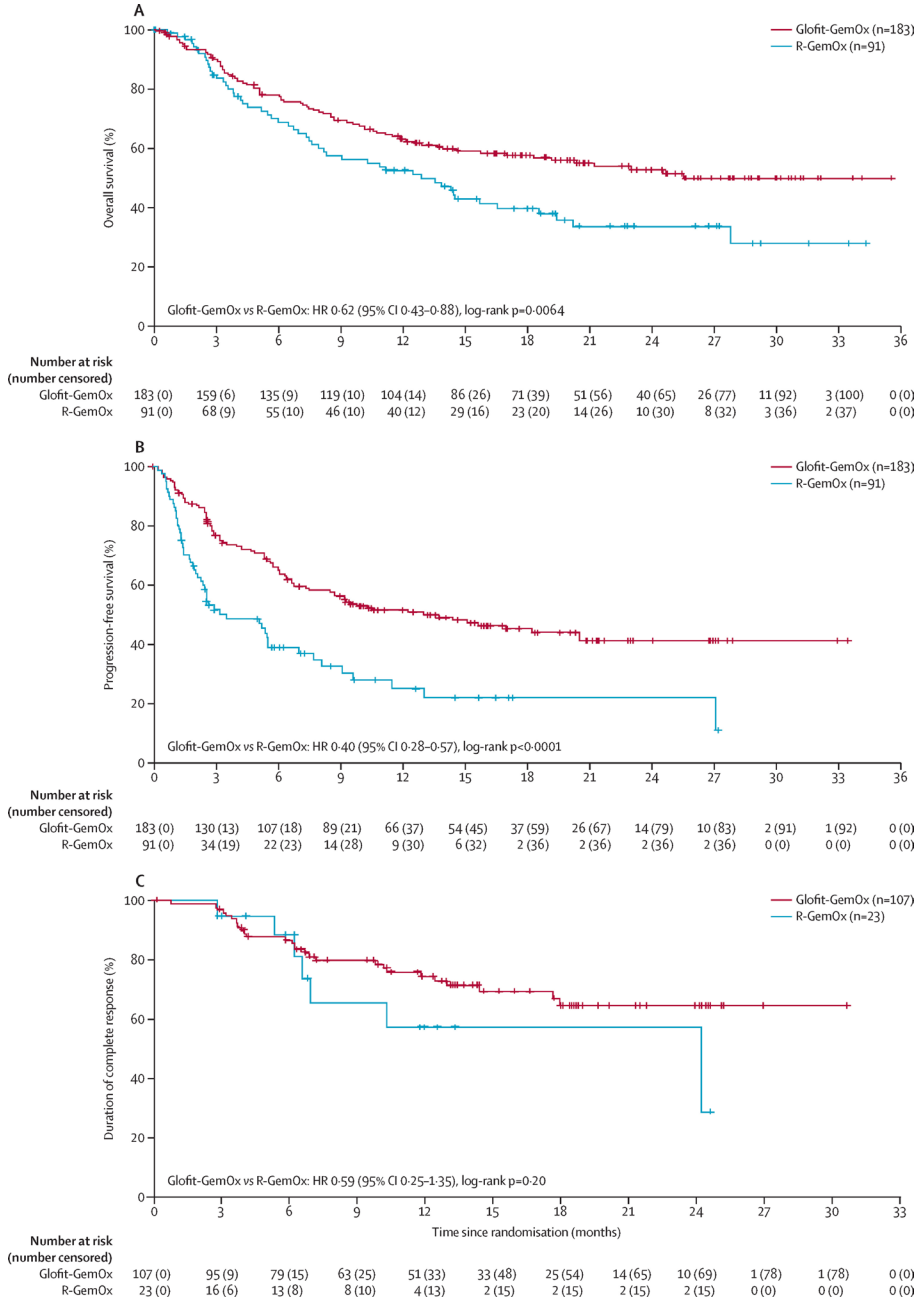
- Open-label phase 1-2 clinical trial
- Heavily pretreated with median 3 lines of prior therapy and 33% receiving prior CAR T.
- ORR 52%, CR 39%
- Median PFS 4.8 months
- Median duration of response was 18.4 months, median duration of CR was not reached
- Grade ≥3 CRS in 4%, grade ≥3 ICANS 3%



MJ Dickinson et al. N Engl J Med 2022;387:2220-2231.

STARGLO

- Randomized, controlled trial of glofitamab and gemcitabine oxaliplatin (GemOx) versus rituximab and GemOx
- The addition of glofitamab to GemOx improved overall survival
- This regimen is now part of guideline recommendations for patients who are ineligible for cellular therapy



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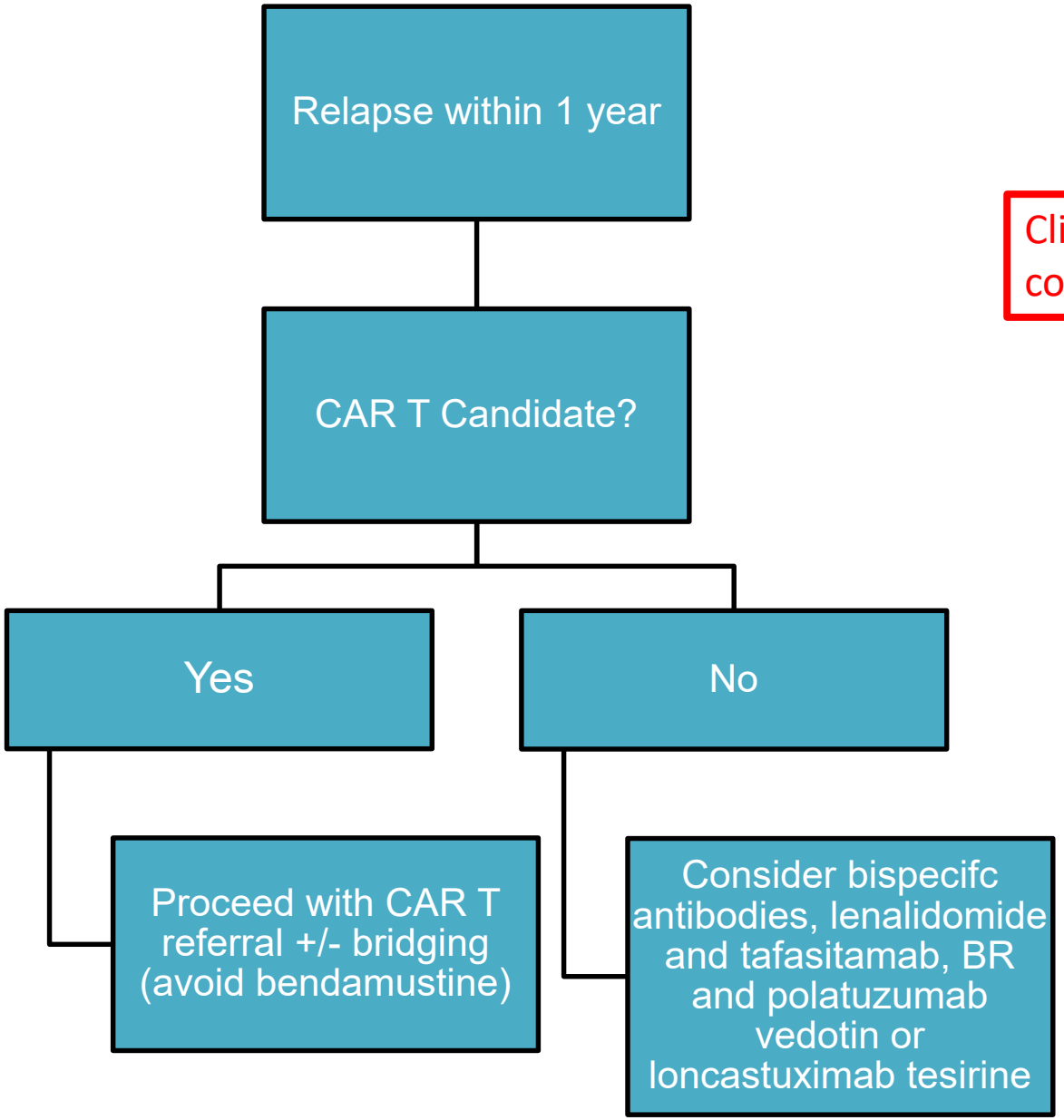
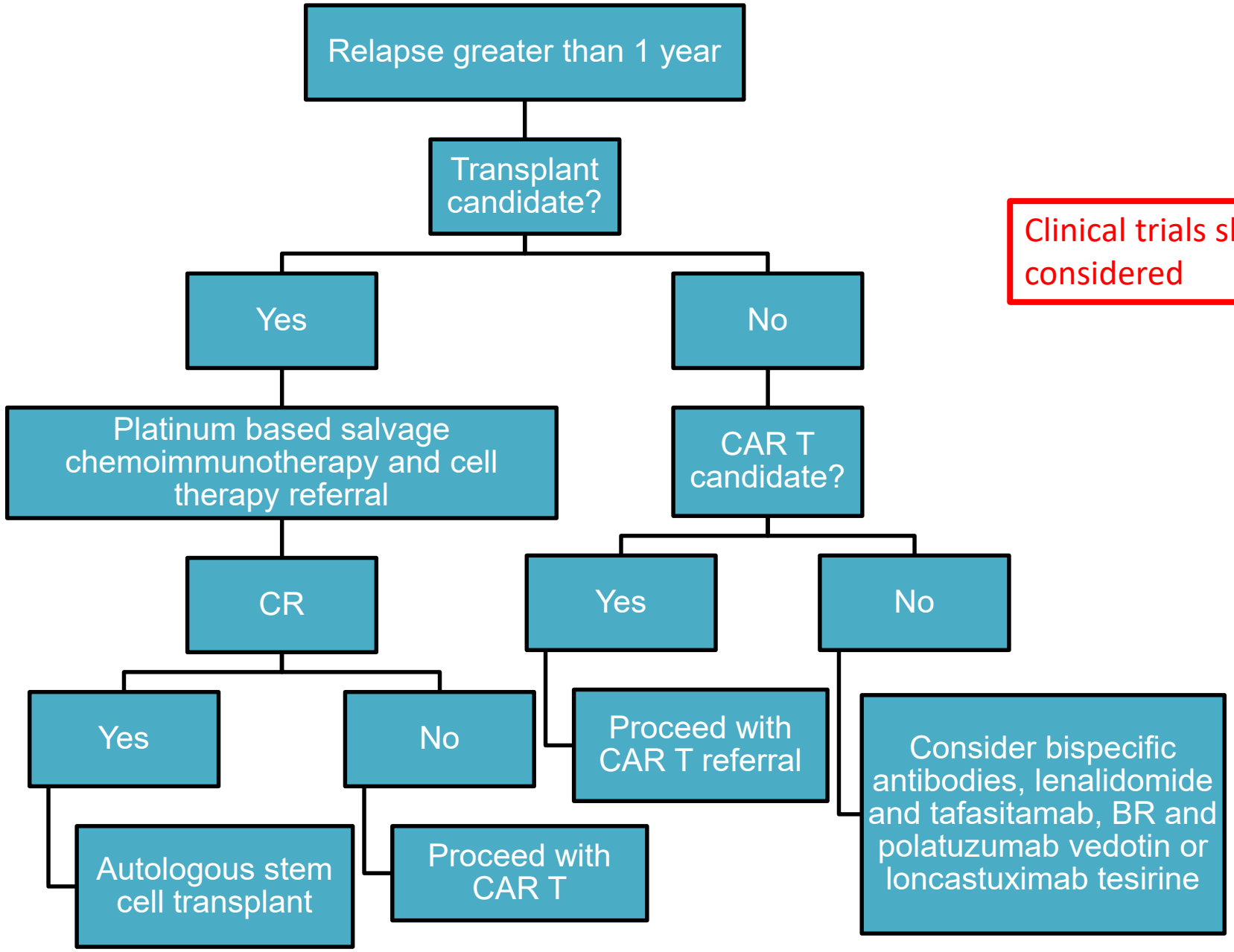
Abramson, Jeremy S et al. The Lancet, Volume 404, Issue 10466, 1940 - 1954



Clinical trials should be considered



Clinical trials should be considered

FUTURE OF THERAPY FOR FRONTLINE AND RELAPSED LBCL

Sequencing Therapy

- Should anti-CD19 agents be avoided prior to CAR T? Are they effective after CAR T?
- How to combine novel agents in the relapsed setting?
- How should patients be treated post CAR T? Is consolidation helpful in high-risk patients?
  - **S2114 (NCT05633615): A Randomized Phase II Trial of Consolidation Therapy Following CD19 CAR T-Cell Treatment for Relapsed/Refractory Diffuse Large B-Cell Lymphoma or Grade IIIB Follicular Lymphoma**

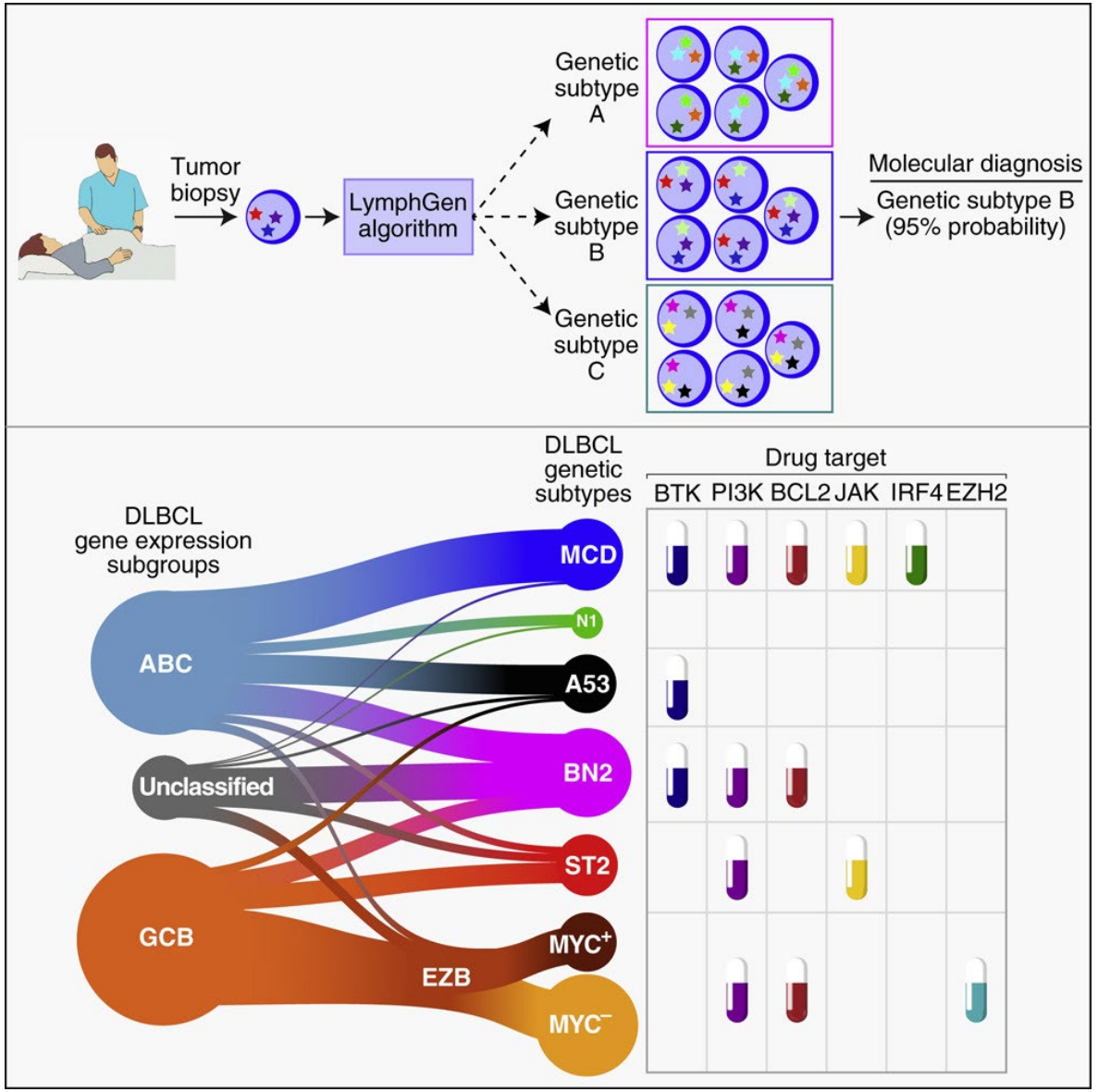
Personalizing Therapy

- Commercially available treatments can be recommended based on comorbidities, performance status, disease status, social support, distance from treatment center, prior therapy, etc.
- Tailor current and future therapies to disease biology
  - Activated B-cell subtype is associated with improved activity with both lenalidomide and tafasitamab as well as polatuzumab vedotin-based therapy
- Identify patients who are at high risk of disease progression

G Salles, et al. The Lancet Oncology 2020 21978-988; Sehn LH, et al. J Clin Oncol. 2020 Jan 10;38(2):155-165

Personalizing Therapy

- LBCL is biologically complex and targeted drugs will likely work in small subsets of patients
- Trials that assess efficacy based on tumor biology are needed
  - S2207 (NCT05890352): Randomized Phase II Study of the Addition of Targeted Therapeutic Agents to Tafasitamab-Based Therapy in Non-Transplant-Eligible Patients With Relapsed/Refractory Large B-Cell Lymphoma
- Ultimately, we aim to assign patients to therapy based on disease biology



Wright, GW, et al. Cancer Cell, Volume 37, Issue 4, 2020, Pages 551-568

QUESTIONS