# Sequencing treatment options in primary refractory DLBCL

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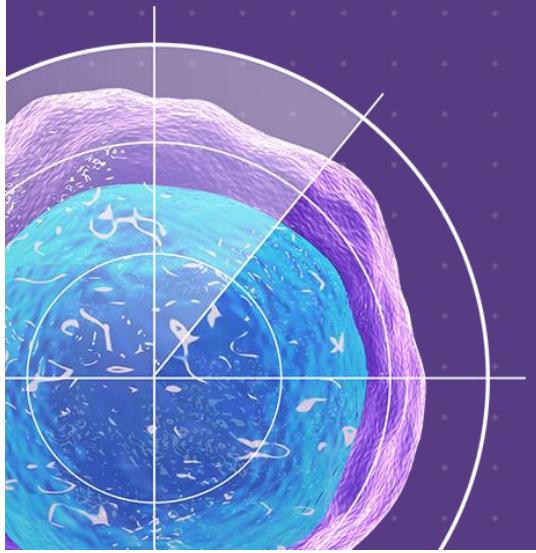


# Disclosures

| | Research funding | Consultancy |
|---|---|---|
| Celgene | √ | √ |
| Gilead–Kite | √ | √ |
| Acerta/AstraZeneca | √ | √ |
| GSK | √ | √ |
| Roche | √ | √ |
| Janssen | √ | √ |
| ADC Therapeutics | √ | √ |
| BioInvent | √ | √ |
| Takeda | √ | √ |
| Karyopharm Therapeutics | √ | √ |
| Incyte | | √ |

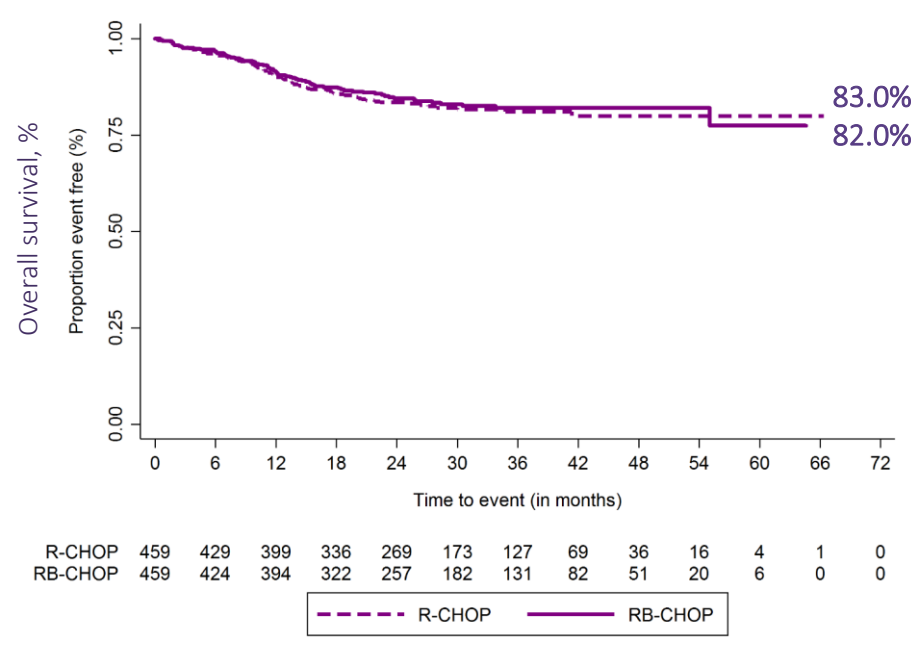
# Female aged 72

- Weight loss, palpable neck, inguinal adenopathy
- Diffuse large B-cell lymphoma (NOS). GCB phenotype. High Ki67 (80–90%)
- No translocation of *MYC*, *BCL2*, or *BCL6* by FISH. Not double expressor.
- Mutation panel: *BCL2*$^{mut}$, *CREBP*$^{mut}$
- Nodal disease above and below the diaphragm with BM involvement
- Increased LDH (×4.4 ULN)
- Stage IVB; high IPI

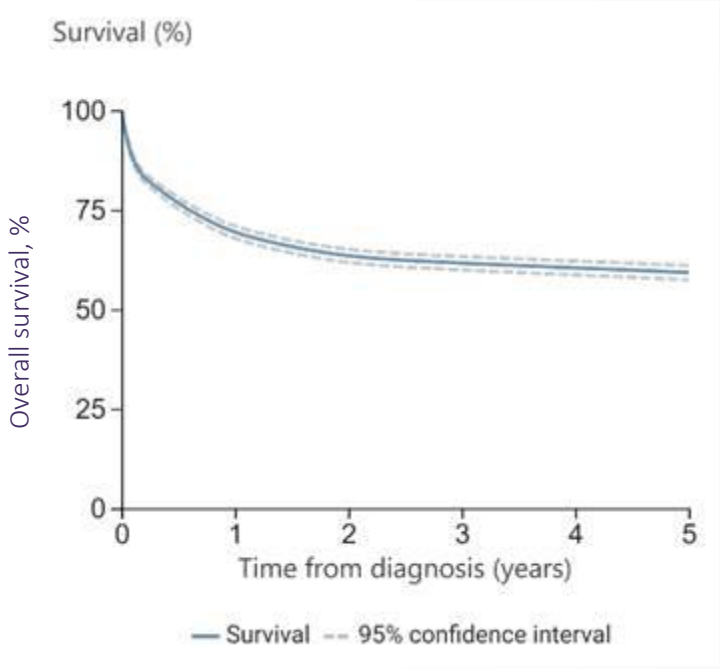
- R-CHOP ×4 with disease progression. Primary progressive disease
- BM remains positive; high LDH

BM, bone marrow; FISH, fluorescence *in situ* hybridisation; GCB, germinal centre B-cell; IPI, International Prognostic Index; LDH, lactate dehydrogenase; mut, mutated; NOS, not otherwise specified; R-CHOP, rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone; ULN, upper limit of normal.

# DLBCL is a curable disease… but many patients are failed by our current therapies



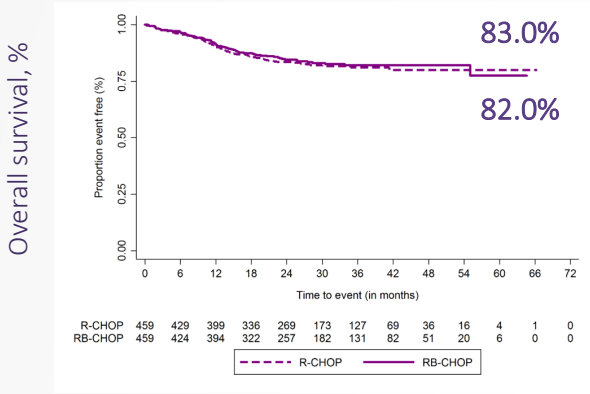

Davies A, et al. *Lancet Oncol.* 2019;20:649-62.



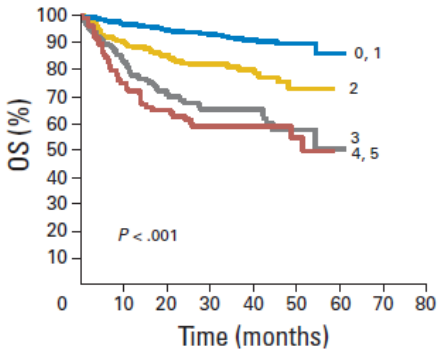

Haematological Malignancy Research Network (HMRN). Survival statistics. https://hmrn.org/statistics/survival.

DLBCL, diffuse large B-cell lymphoma; R-CHOP, rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone; RB-CHOP, rituximab + bendamustine + cyclophosphamide + doxorubicin + vincristine + prednisone.

# DLBCL is a curable disease… but many patients are failed by our current therapies

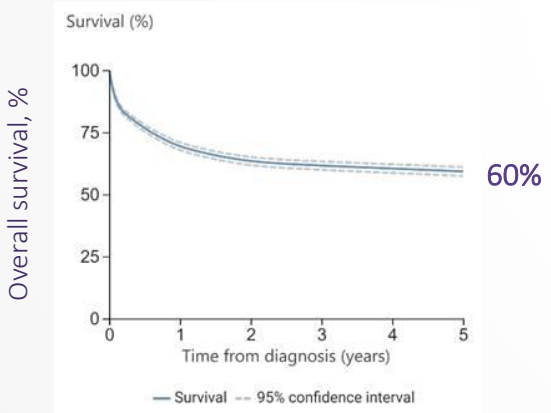



Davies A, et al. *Lancet Oncol.* 2019;20:649-62.

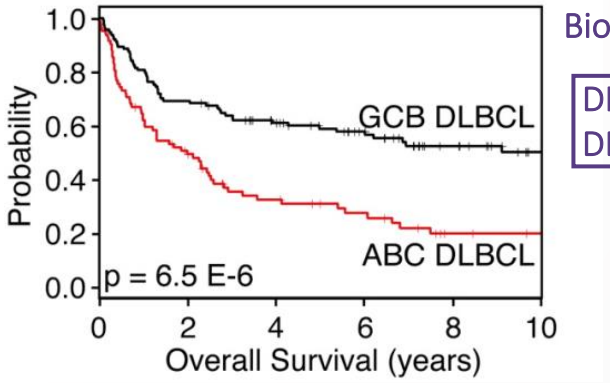



Clinical stratification

Ziepert M, et al. *J Clin Oncol.* 2010;28:2373-2380.




Haematological Malignancy Research Network (HMRN). Survival statistics. https://hmrn.org/statistics/survival.



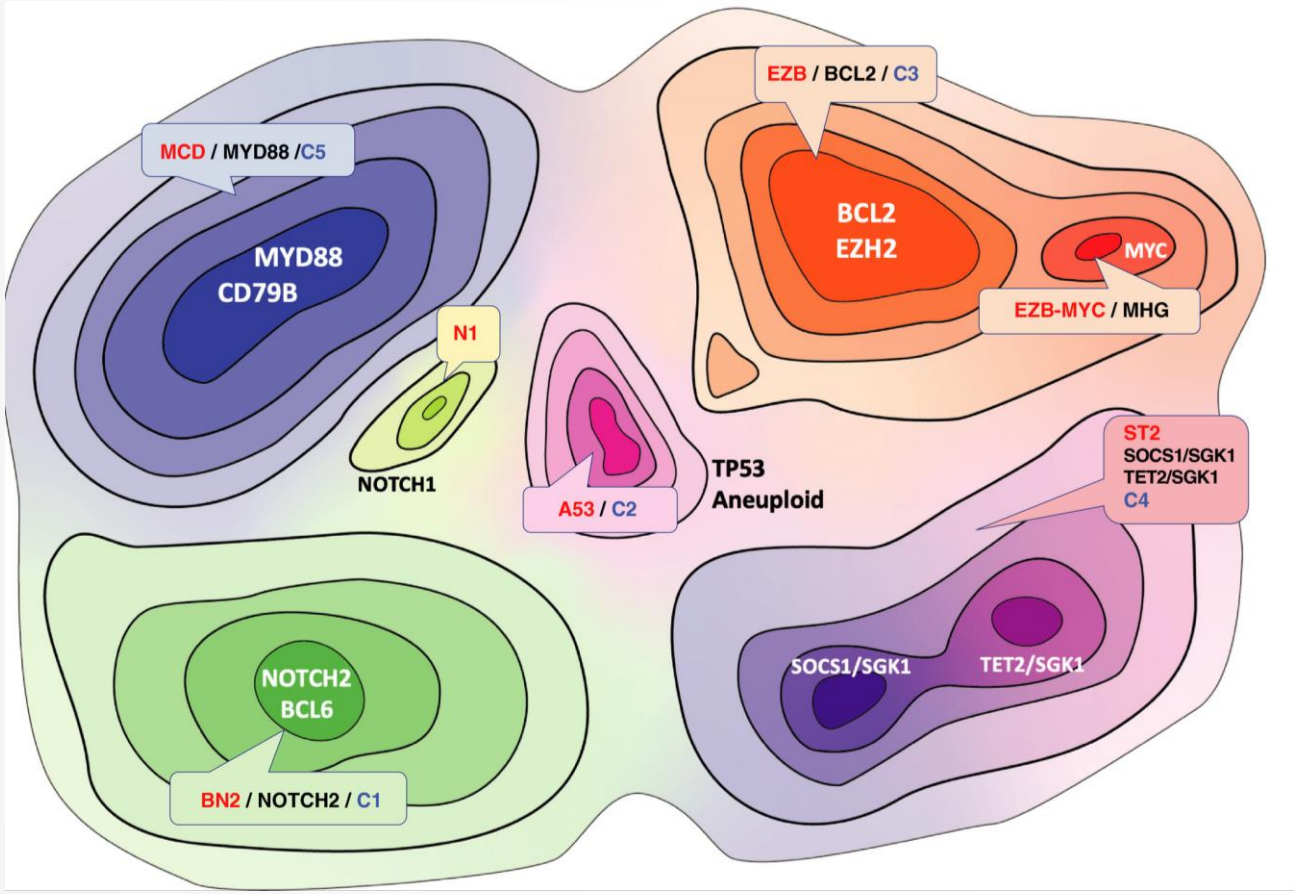

Biological stratification

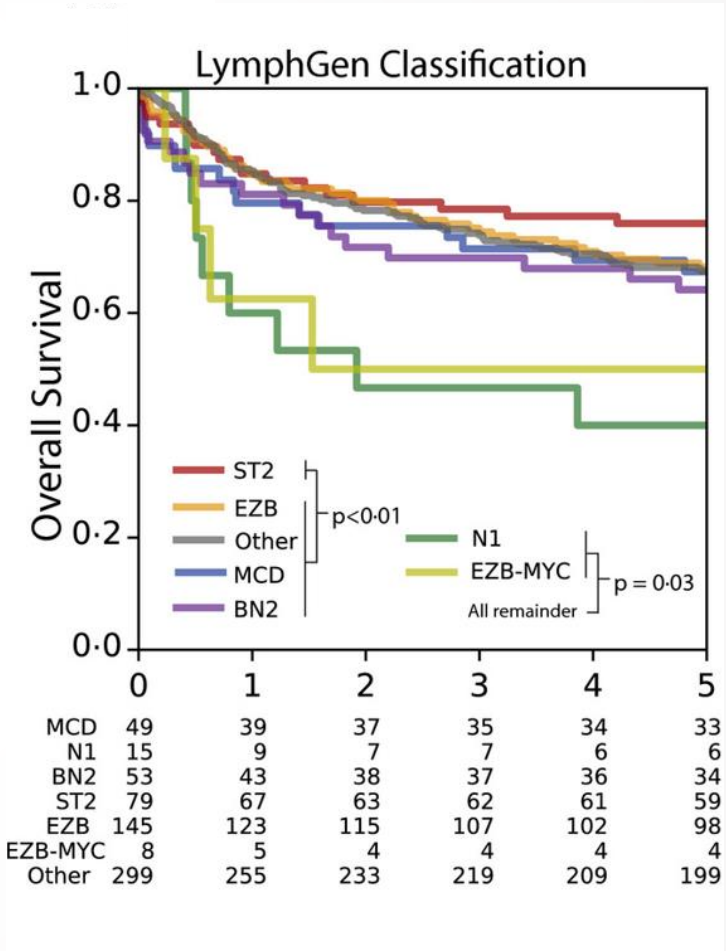
DHL/THL
DEL

Wright G, et al. *Proc Natl Acad Sci.* 2003;100(17):9991-9996.

ABC, activated B-cell; DEL, double-expressor lymphoma; DHL, double-hit lymphoma; DLBCL, diffuse large B-cell lymphoma; GCB, germinal centre B-cell; OS, overall survival; R-CHOP, rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone; RB-CHOP, rituximab + bendamustine + cyclophosphamide + doxorubicin + vincristine + prednisone; THL, triple-hit lymphoma.

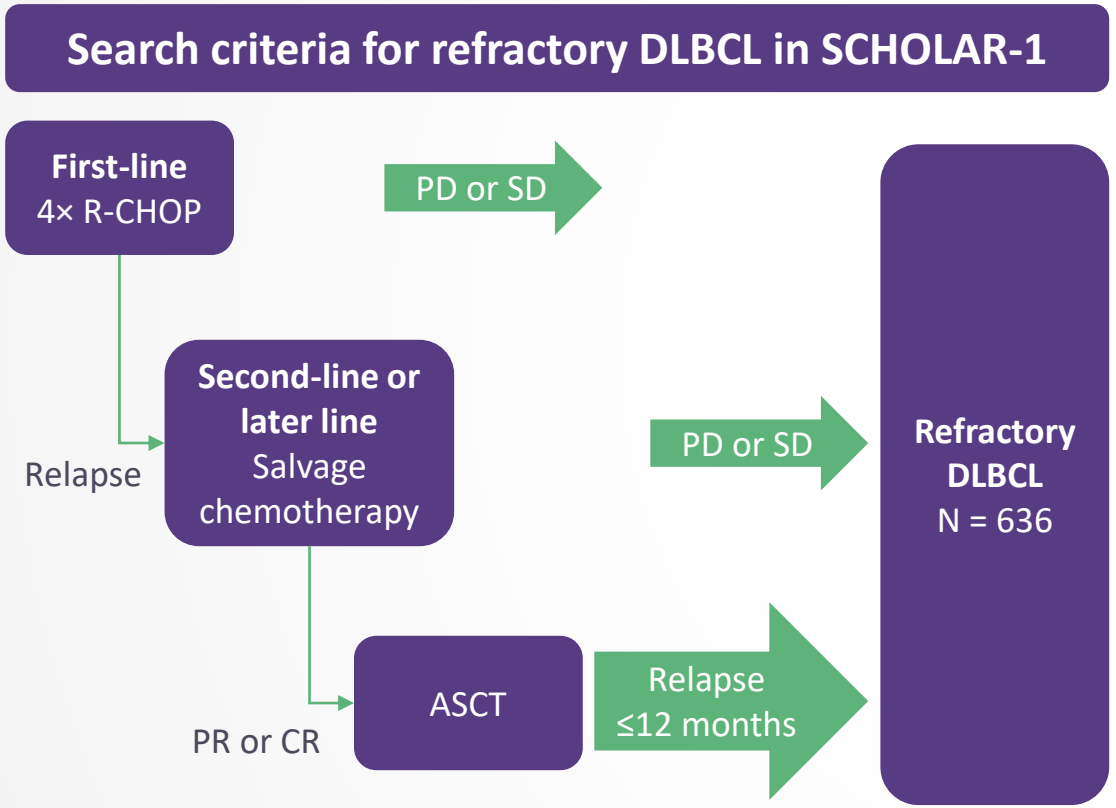
# Insights from molecular heterogeneity?

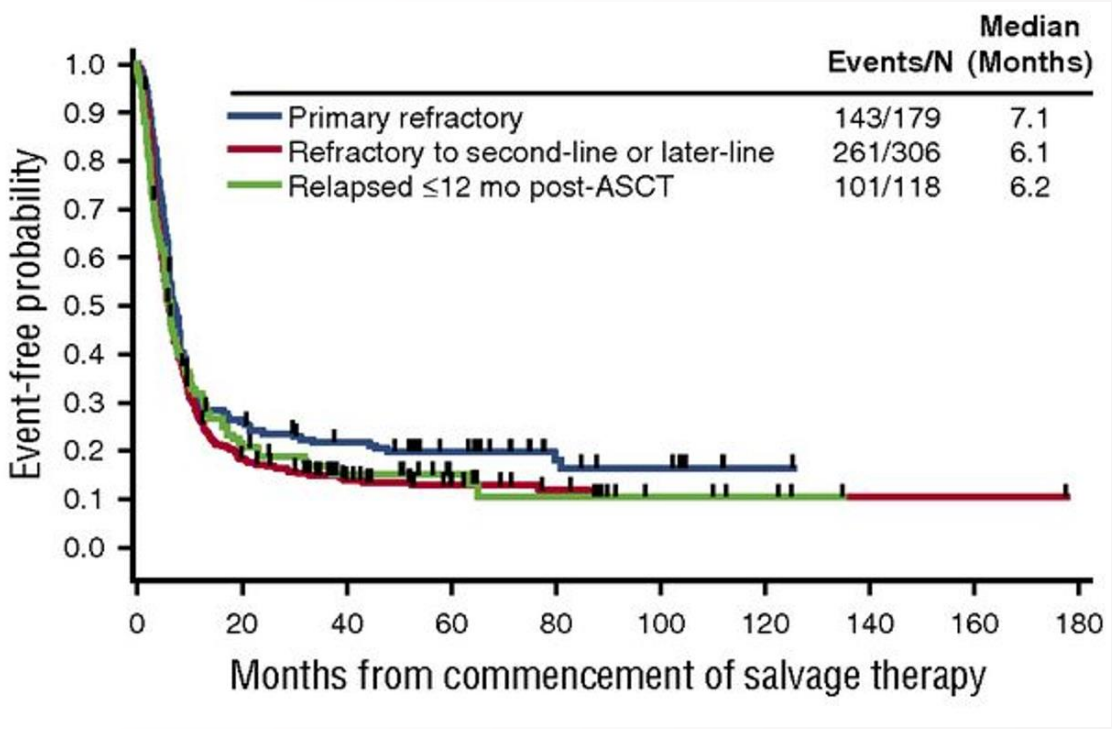



Runge HFP, et al. *Br J Haematol*. 2020;192:216-220.

# Outcomes in refractory DLBCL: results from the international SCHOLAR-1 study

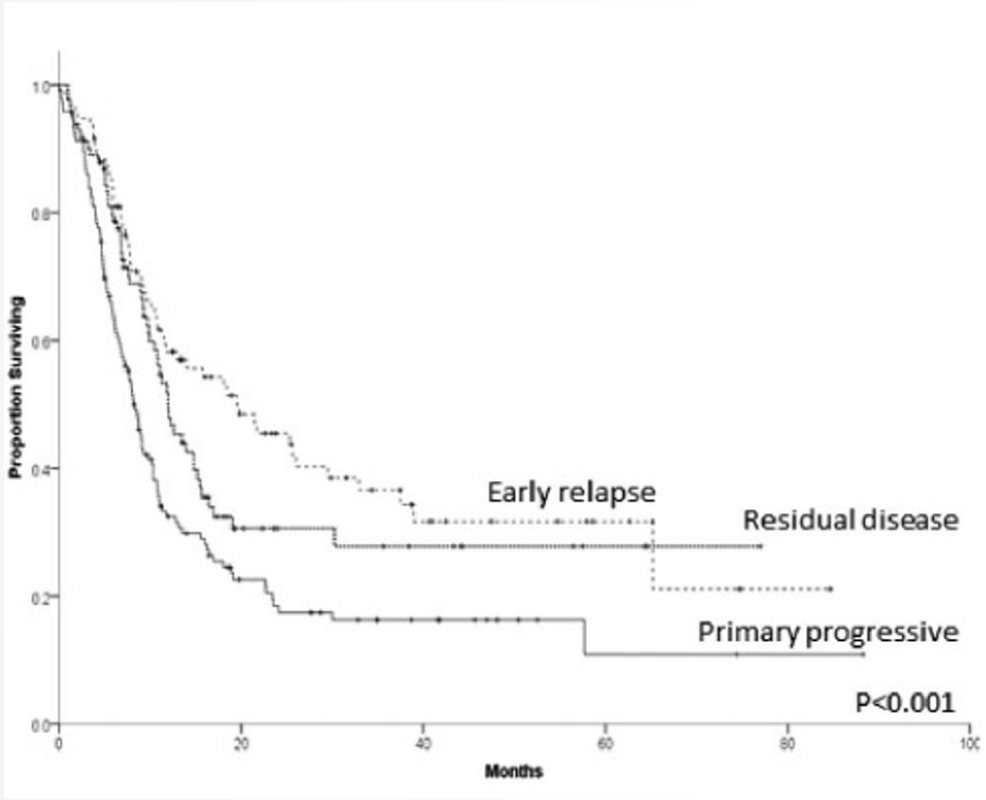



ASCT, autologous stem cell transplantation; CR, complete response; DLBCL, diffuse large B-cell lymphoma; PD, progressive disease; PR, partial response; R-CHOP, rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone; SD, stable disease.

Crump M, et al. *Blood.* 2017;130(16):1800-1808.

# Patterns of primary refractory disease




- In refractory disease, the tendency is to have the same treatment paradigm as relapsed DLBCL
- Data are from the same studies: R/R patients

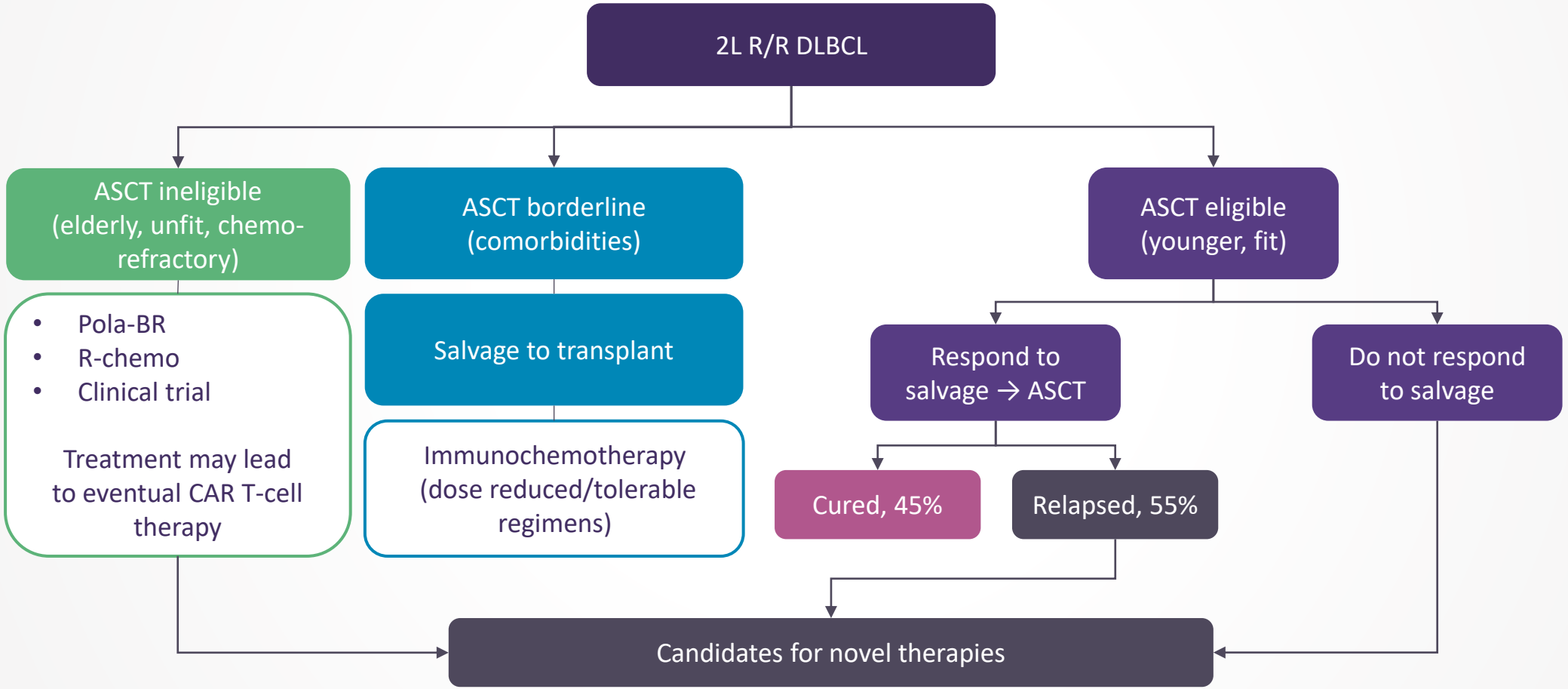
2-year OS

- Primary progressive (PD by or on Week 6 after completing CIT), 19%
- Residual disease (PR or SD after ≥5 cycles of CIT), 31%
- Early relapse (achieve a CR then PD <6 months following completion of CIT), 46%

CIT, chemoimmunotherapy; CR, complete response; DLBCL, diffuse large B-cell lymphoma; OS, overall survival; PD, progressive disease; PR, partial response; R/R, relapsed/refractory; SD, stable disease.

Costa L, et al. *Am J Hematol.* 2017;92(2):161-170.

# Current treatment algorithm: 2L setting[1,2]

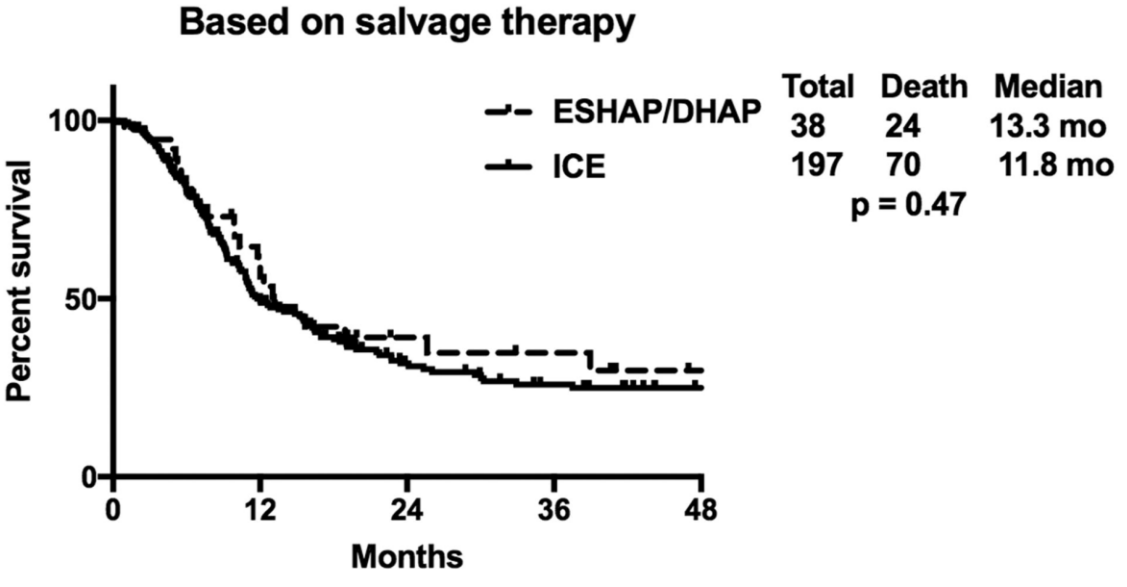



2L, second line; ASCT, autologous stem cell transplantation; CAR, chimeric antigen receptor; CR, complete response; DLBCL, diffuse large B-cell lymphoma; OS, overall survival; PD, progressive disease; Pola-BR, polatuzumab vedotin + bendamustine + rituximab; R-chemo, rituximab + chemotherapy; R/R, relapsed/refractory; SD, stable disease.

**1.** Sarkozy C, Sehn LH. *Ann Lymphoma.* 2019;3:10. **2.** Sehn L, Gascoyne RD. *Blood.* 2015;125:22-32.

# Response to reinduction therapy in primary refractory disease (REFINE study)

| Response | DHAP/ESHAP (n = 38) | ICE (n = 197) | p value |
|---|---|---|---|
| ORR (CR + PR) | 18 (47) | 99 (50) | 0.85 |
| CR | 9 (24) | 44 (22) | 0.67 |

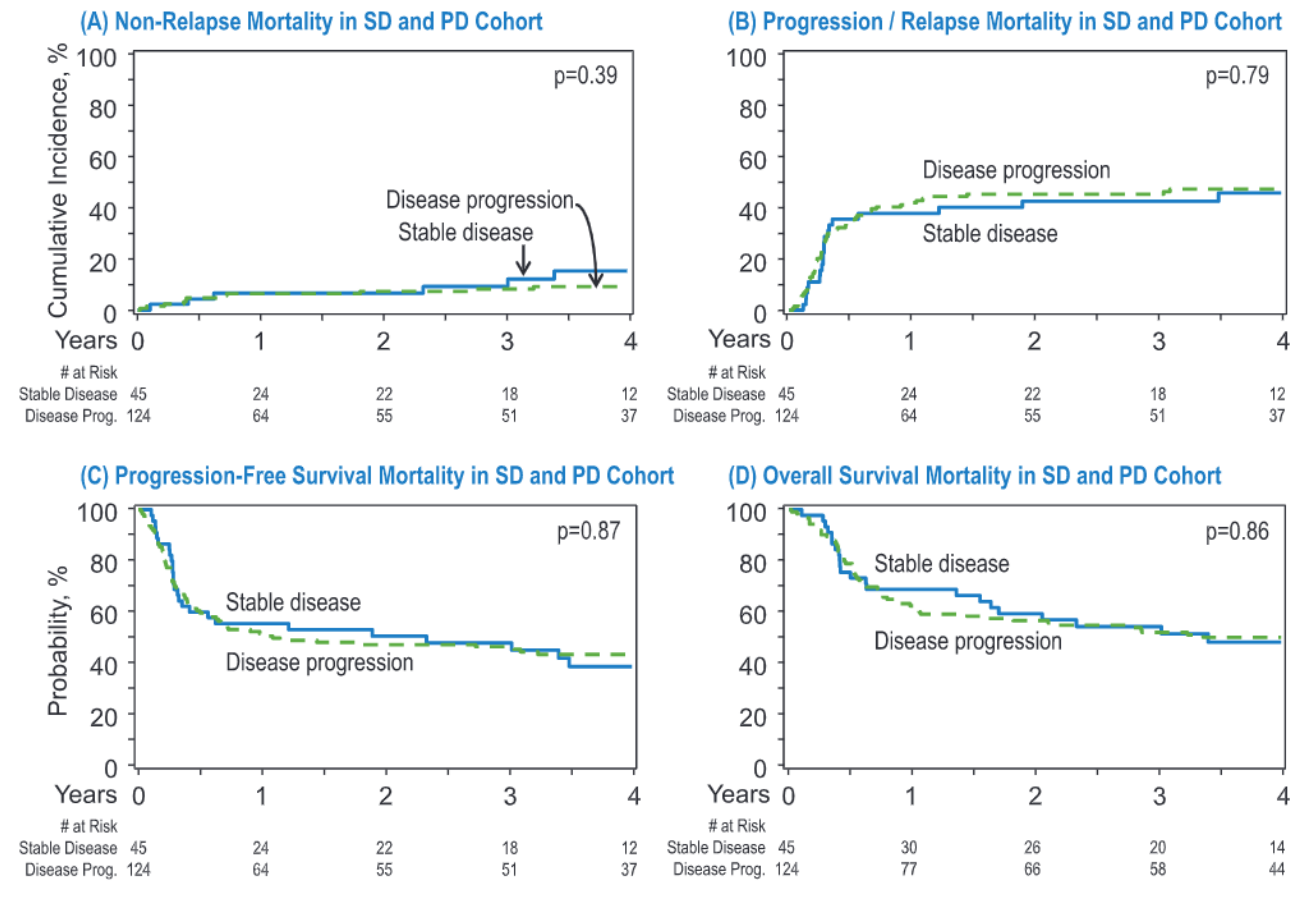



- Probably no difference in reinduction regimen in those with primary treatment failure
- Definition: Relapse within 6 months of upfront chemoimmunotherapy (R-CHOP), primary progressive disease, or stable disease as best response after upfront therapy

CR, complete response; DHAP, dexamethasone + high-dose cytarabine + cisplatin; ESHAP, etoposide methylprednisolone + high-dose cytarabine + cisplatin; ICE, ifosfamide + carboplatin + etoposide; mo, months; ORR, overall response rate; OS, overall survival; PD, progressive disease; Pola-BR, polatuzumab vedotin + bendamustine + rituximab; PR, partial response; R-chemo, rituximab + chemotherapy; R-CHOP, rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone; R/R, relapsed/refractory; SD, stable disease.

Badar T, et al. *Leuk Lymphoma.* 2019;60(4):940-946.

# Primary refractory disease: Durable control may be achieved with an ASCT if response to reinduction therapies




- CIBMTR (n = 169) either SD or PD with frontline
- All had response (CR/PR) to reinduction therapy

4-year

| | |
|---|---|
| PFS | 41.4% (95% CI, 38–50) |
| OS | 49.6% (95% CI, 44–56) |
| NRM | 10.8% (95% CI, 6–13) |

Response status at ASCT: PFS

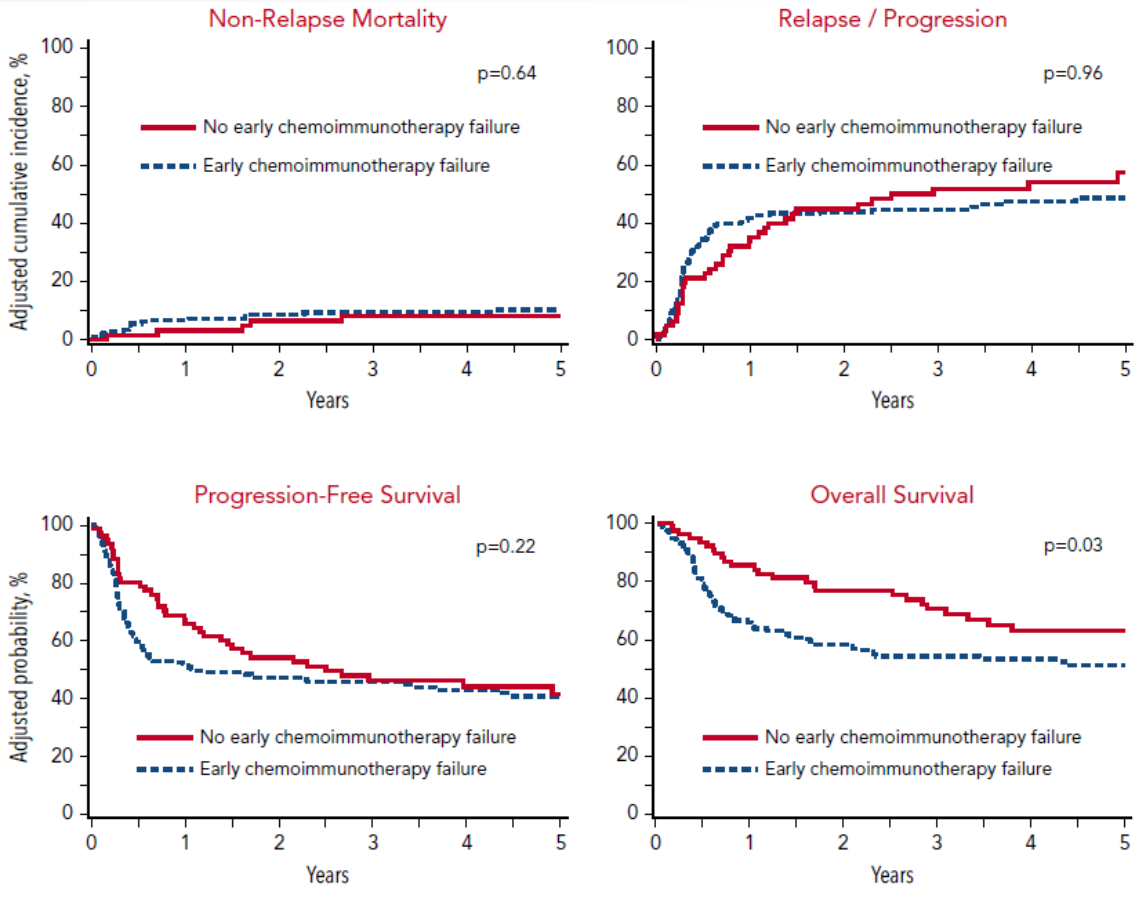
CR (35%) 39.3% (95% CI, 27–53)

PR (65%) 42.5% (95% CI, 33–52)

ASCT, autologous stem cell transplantation; CI, confidence interval; CIBMTR, Center for International Blood and Marrow Transplant Research; CR, complete response; NRM, non-relapse mortality; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

Bal S, et al. *Transplant Cell Ther.* 2021;27(1):55.e1-55.e7.

# Should ASCT be offered to patients in PET+ PR?[1,2]




- CIBMTR (n = 249) relapsed DLBCL PET+ PR
- Included early chemotherapy failures (relapse within 12 months; n = 182)
  - 79% were primary refractory

5-year

| | |
|---|---|
| PFS | 41% |
| OS | 51% |

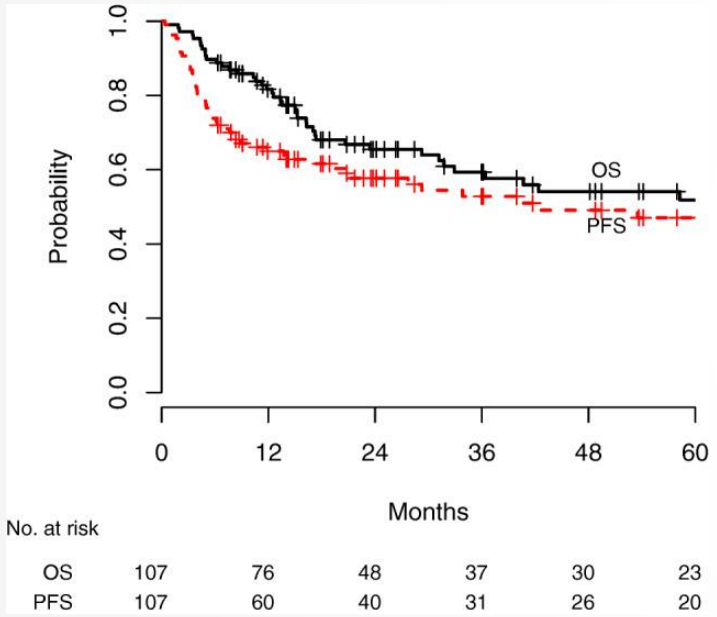
- Cures with low NRM/modest cost

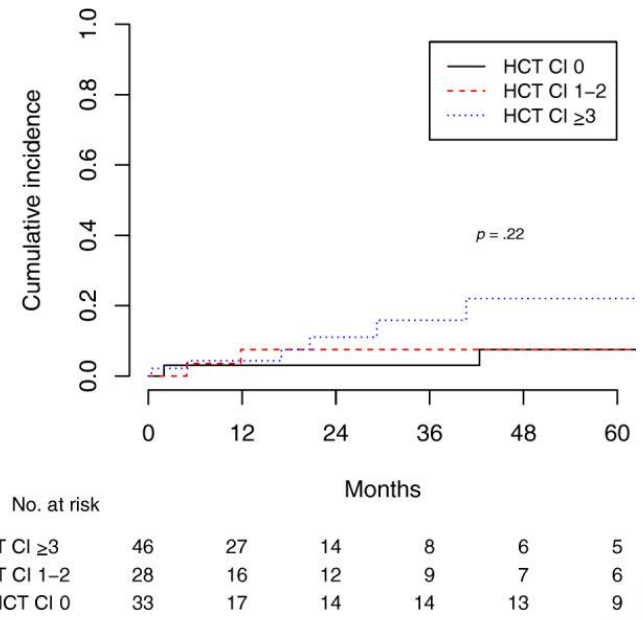
ASCT, autologous stem cell transplantation; CIBMTR, Center for International Blood and Marrow Transplant Research; DLBCL, diffuse large B-cell lymphoma; NRM, non-relapse mortality; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; PR, partial response; SD, stable disease.

**1.** Shah N, et al. *Blood.* 2021;137(10):1416-1423. **2.** *Oncologist*. 2020;25(Suppl 1):S10-S11.

# Should we challenge the assumption that ASCT is too toxic in the elderly?

- Outcomes for patients aged >70 receiving ASCT (DLBCL n = 63; 59%)



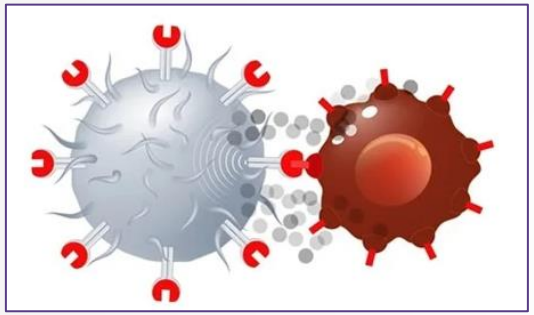

| | | | | |
|---|---|---|---|---|
| 2-year | PFS | 58% (95% CI, 48–67) | NRM | 7% (95% CI, 3–14) |
| | OS | 65% (95% CI, 55–74) | | |

- Patient selection
- Optimising supportive care
- Use of comprehensive geriatric assessment methodologies
- Trajectory of functional recovery
- Individualised choices/shared decisions

ASCT, autologous stem cell transplantation; CIBMTR, Center for International Blood and Marrow Transplant Research; DLBCL, diffuse large B-cell lymphoma; HCT CI, hematopoietic cell transplantation-specific comorbidity index; NRM, non-relapse mortality; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival.

Sun L, et al. *Oncologist*. 2018;23(5):624-630.

# Approved CD19-directed CAR T cells in DLBCL*



McKenzie S. CAR-T cell toxicity and safety profiles. https://www.news-medical.net/health/CAR-T-Cell-Toxicity-and-Safety-Profiles.aspx. 2019.

| | Axicabtagene ciloleucel[1] | Tisagenlecleucel[2] | Lisocabtagene maraleucel[3] |
|---|---|---|---|
| Construct | Anti-CD19-CD28-CD3z | Anti-CD19-41BB-CD3z | Anti-CD19-41BB-CD3z |
| Vector | Retrovirus | Lentivirus | Lentivirus |
| T-cell manufacturing | Bulk | Bulk | Defined doses CD4, CD8 |
| Dose | $2 \times 10^6$/kg (max. $2 \times 10^8$) | $0.1–6.0 \times 10^8$/kg | $1.0 \times 10^8$/kg |
| Bridging therapy | None allowed in pivotal trial | 92% | 59% |
| Lymphodepletion | Flu/Cy 30/500 mg/m$^2$/day ×3 days | Flu/Cy 25/250 mg/m$^2$/day ×3 days or bendamustine | Flu/Cy 30/300 mg/m$^2$/day ×3 days |
| Approval status | EMA approved<br>Adult: R/R DLBCL,† R/R PMBCL<br><br>FDA approved<br>Adult: R/R DLBCL, R/R HGBCL, R/R transformed FL, R/R PMBCL | EMA approved<br>Paediatric: R/R ALL<br>Adult: R/R DLBCL†<br><br>FDA approved<br>Paediatric: R/R ALL<br>Adult: R/R DLBCL, R/R HGBCL, R/R transformed FL | FDA approved<br>Adult R/R DLBCL (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma Grade 3B<br><br>Not EMA approved |

ALL, acute lymphocytic leukaemia; HGBCL, high-grade B-cell lymphoma; CAR, chimeric antigen receptor; Cy, cyclophosphamide; EMA, European Medicines Agency; FDA, U.S. Food and Drug Administration; FL, follicular lymphoma; Flu, fludarabine; PMBCL, primary mediastinal large B-cell lymphoma.

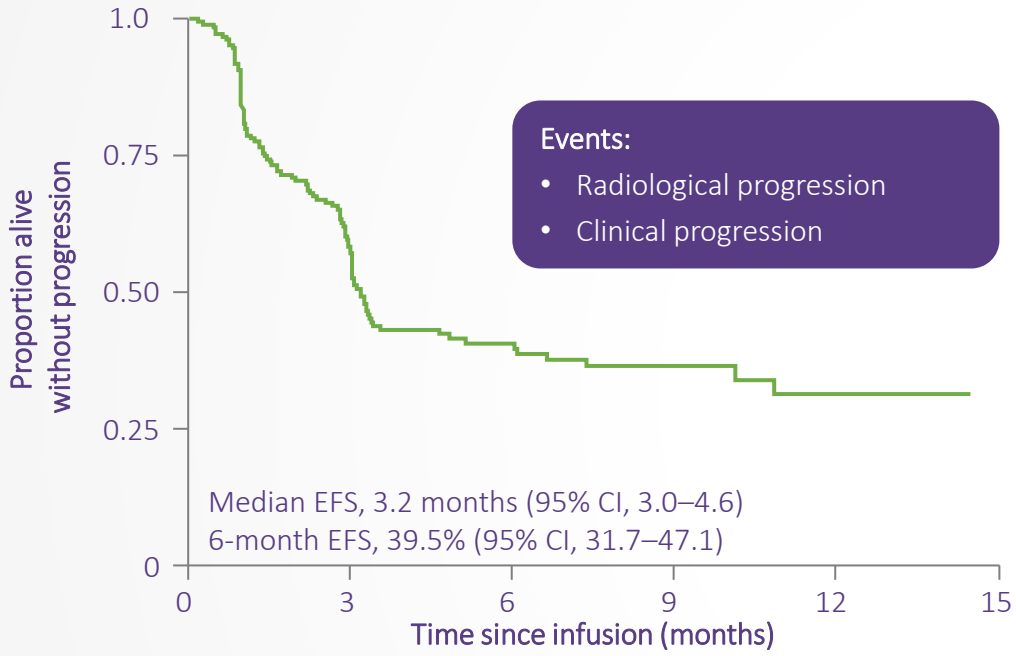
*The purpose of this slide is to summarise data; no comparison is intended.

†Including high-grade BCL and transformed FL.

**1.** Locke FL, et al. *Lancet Oncol.* 2019;20:31-42. **2.** Schuster SJ, et al. *N Engl J Med*. 2019;380:45-56. **3.** Abramson JS, et al. *Lancet.* 2020;396:839-852.

# UK NCCP: Achieving benefit in a real-world population

## EFS of infused patients



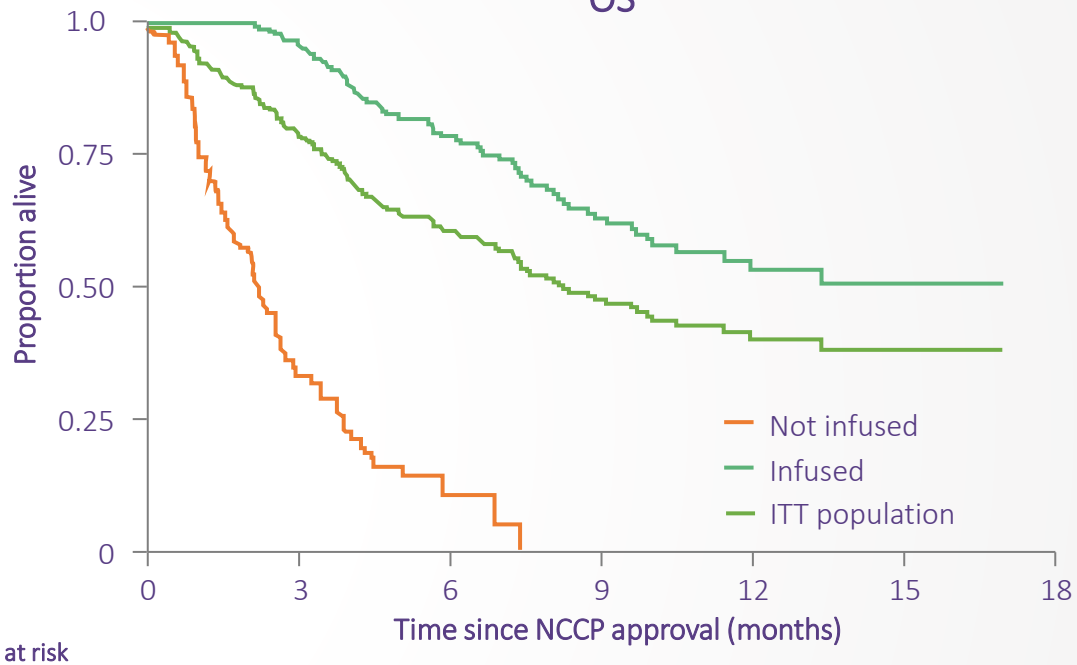

**Events:**
- Radiological progression
- Clinical progression

Number at risk

| | | | | | | |
|---|---|---|---|---|---|---|
| | 183 | 80 | 39 | 19 | 8 | 0 |

- Median follow-up (infused): 9.9 months
- 97/183 patients have progressed
- 39/97 are alive with a median of 137 days since progression (IQR, 63–248)

## OS




Number at risk

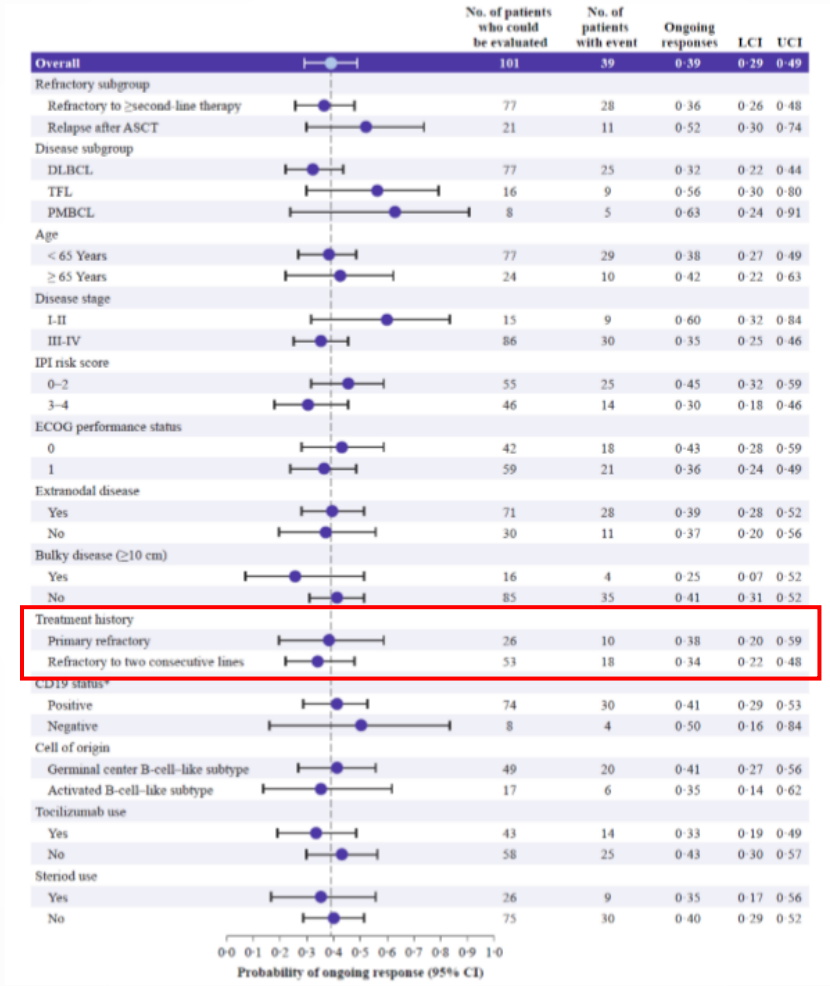
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Not infused | 70 | 23 | 3 | 0 | 0 | 0 | 0 |
| Infused | 183 | 175 | 112 | 64 | 29 | 6 | 0 |
| ITT population | 253 | 198 | 115 | 64 | 29 | 6 | 0 |

Median OS
- Infused: 13.4 months (95% CI, 9.7–NR)
- ITT population: 8.1 months (95% CI, 7.0–10.0)
- Not infused: 2.2 months (95% CI, 1.6–2.7)

CI, confidence interval; EFS, event-free survival; IQR, interquartile range; ITT, intent to treat; NCCP, National CAR-T Clinical Panel; NR, not reached; OS, overall survival.

Kuhnl A, et al. Abstract #S243; 25th EHA Annual Congress. Jun 12, 2020; Virtual.

# Long-term efficacy in refractory patients




ASCT, autologous stem cell transplant; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group performance status; IPI, International Prognostic Index; LCI, lower confidence interval; No., number; PMBCL, primary mediastinal large B-cell lymphoma; TFL, transformed follicular lymphoma; UCI, upper confidence interval.
*CD19 status was determined by histologic score for the 82 patients with available samples.
Locke et al. *Lancet Oncol.* 2019;20(1):31-42 [Supplementary data, Figure S4].

# Should we instead proceed to a CAR T-cell therapy?

- The superiority of CAR-T over ASCT has not been shown in those with relapsed chemosensitive DLBCL
- CAR-T clearly works at time of ASCT relapse, but the reverse sequence is not generally considered feasible
- Difficult to deliver further therapies for patients that relapse post CAR-T

Phase III second line studies

- ZUMA-7: Axi-cel (NCT03391466)
- BELINDA: Tisagen (NCT03570892)
- TRANSFORM: Liso-cel (NCT03570892)

ASCT, autologous stem cell transplantation; Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; Liso-cel, Lisocabtagene maraleucel; Tisagen, tisagenlecleucel.
Based on information available at ClinicalTrials.gov.

# CAR T-cell therapies in those with moderate impairment of physiology

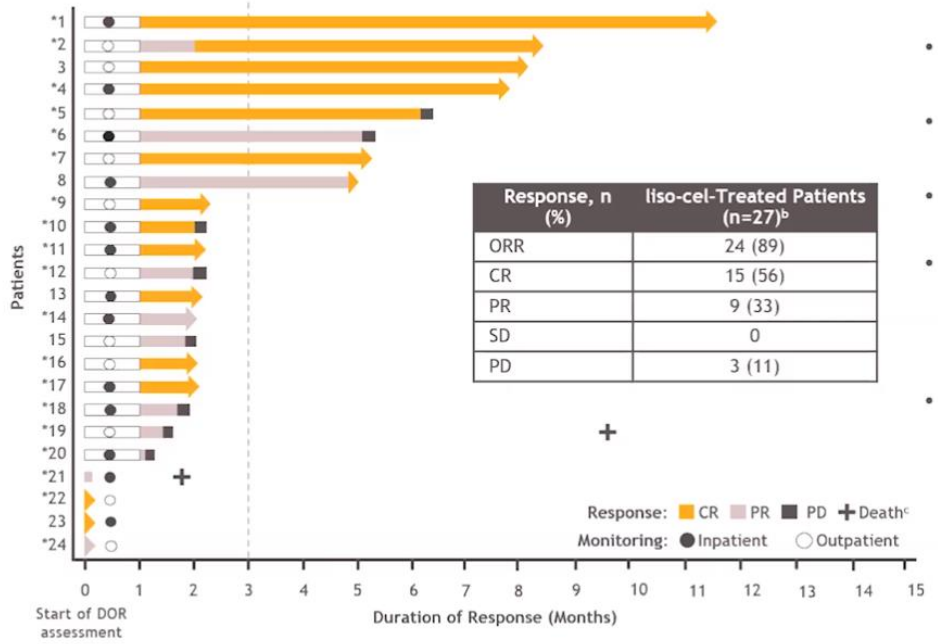
| | TRANSCEND NHL 001[1]<br>Lisocabtagene maraleucel | ZUMA-1[2,3]<br>Axicabtagene ciloleucel | JULIET[4]<br>Tisagenlecleucel |
|---|---|---|---|
| Creatinine clearance | >30 mL/min | >60 mL/min | ≥60 mL/min |
| LVEF | ≥40% | ≥50% | ≥45% |
| Secondary CNS involvement | Yes | No | No |
| ECOG | 0/1/2<br>(ECOG 2 added in 2017 protocol amendment) | 0/1 | 0/1 |
| Minimum ALC | No minimum | ≥100/µL | >300/mm$^3$ and absolute CD3+ T cells >150/mm$^3$ |

ALC, absolute lymphocyte count; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; LVEF, left-ventricular ejection fraction.

**1.** Abramson JS, et al. *Lancet.* 2020;396:839-852 (incl. suppl.) **2.** Neelapu SS, et al. *N Engl J Med.* 2017;377:2531-2544 (incl. suppl.) **3.** ClinicalTrials.gov. clinicaltrials.gov/ct2/show/NCT02348216. Updated Mar 23, 2021. Accessed Mar 2021. **4.** Schuster SJ, et al. *N Engl J Med.* 2019;380:45-56 (incl. suppl.).

# Pilot study: Patients ineligible for ASCT

- Age ≥70 years (68%)
- ECOG PS 2 (28%) or impaired organ function (24%)
- 24% ≥2 criteria
- 48% refractory to last therapy




| Response, n (%) | Iiso-cel-Treated Patients (n=27)[b] |
|---|---|
| ORR | 24 (89) |
| CR | 15 (56) |
| PR | 9 (33) |
| SD | 0 |
| PD | 3 (11) |

- All patients achieved an early objective response by Day 30
- 10 of 12 patients who had a CR with ≥1 follow-up assessment remain in CR
- Median follow-up for response was 5 months
- Kaplan-Meier-estimated probability of continued response:
  - 63% (95% CI, 37-81) at 3 months
  - 53% (95% CI, 25-75) at 6 months
- Treatments received after progression included:
  - Pembrolizumab (n=2)
  - Rituximab + chemotherapy (n=1)

CR, complete response; DOR, duration of response; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.
*Patients met ≥1 prognosis risk factor and ≥1 TNE criterion.
[a]n=24. [b]Responses were calculated based on patients who had Day 29 response assessment data entered in the clinical database or who died/discontinued study before Day 29 prior to the data cut. [c]The third death is not shown because the patient never responded.

11
Abstract S244

ASCT, autologous stem cell transplantation; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status.
Ghosh N, et al. Abstract #S244. 25th EHA Annual Congress; Dec 6, 2020; Virtual.

# Considered non-transplant eligible but perhaps CAR-T eligible?

## NCCN guidelines 2021[1]

**Second-line and subsequent therapy (non-candidates for transplant)**

**Preferred regimens (in alphabetical order)**

- GemOx ± rituximab
- Polatuzumab vedotin ± bendamustine ± rituximab

**Other recommended regimens (in alphabetical order)**

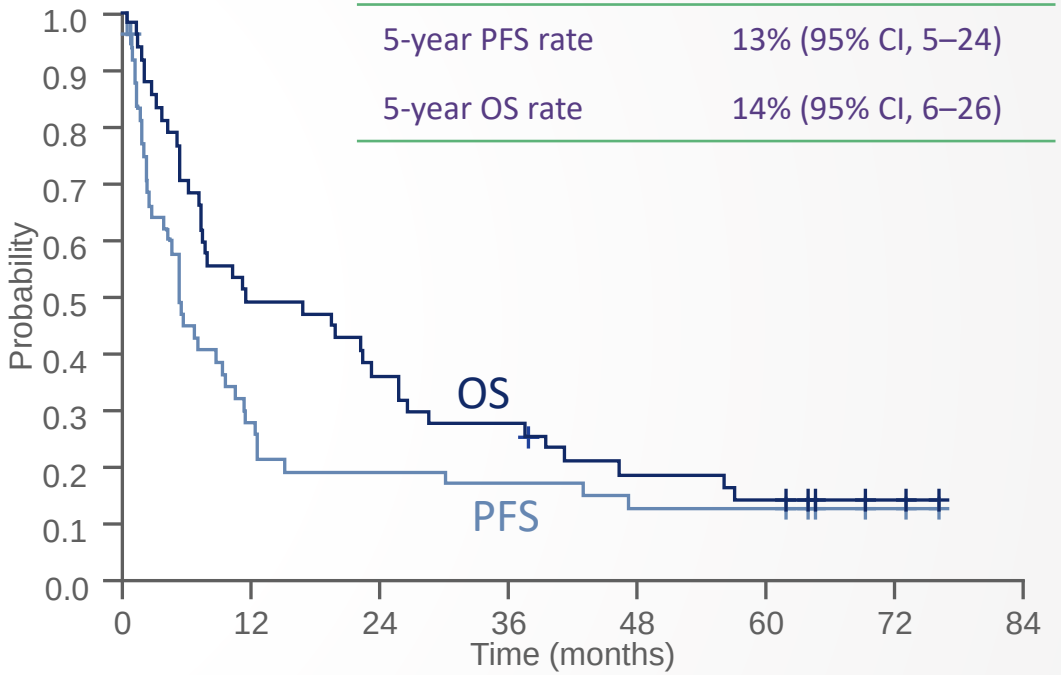
- CEPP (cyclophosphamide, etoposide, prednisone, procardazine) ± rituximab — PO and IV
- CEOP (cyclophosphamide, etoposide, vincristine, prednisone) ± rituximab
- DA-EPOCH ± rituximab
- GDP ± rituximab or (gemcitabine, dexamethasone, carboplatin) ± rituximab
- Gemcitabine, vinorelbine ± rituximab (category 3)
- Rituximab
- Tafasitamab + lenalidomide

**Useful in certain circumstances**

- Brentuximab vedotin for CD30+ disease
- Bendamustine ± rituximab (category 2B)
- Ibrutinib (non-GCB DLBCL)
- Lenalidomide ± rituximab (non-GCB DLBCL)

## R-GemOx efficacy[2]

| | |
|---|---|
| 5-year PFS rate | 13% (95% CI, 5–24) |
| 5-year OS rate | 14% (95% CI, 6–26) |

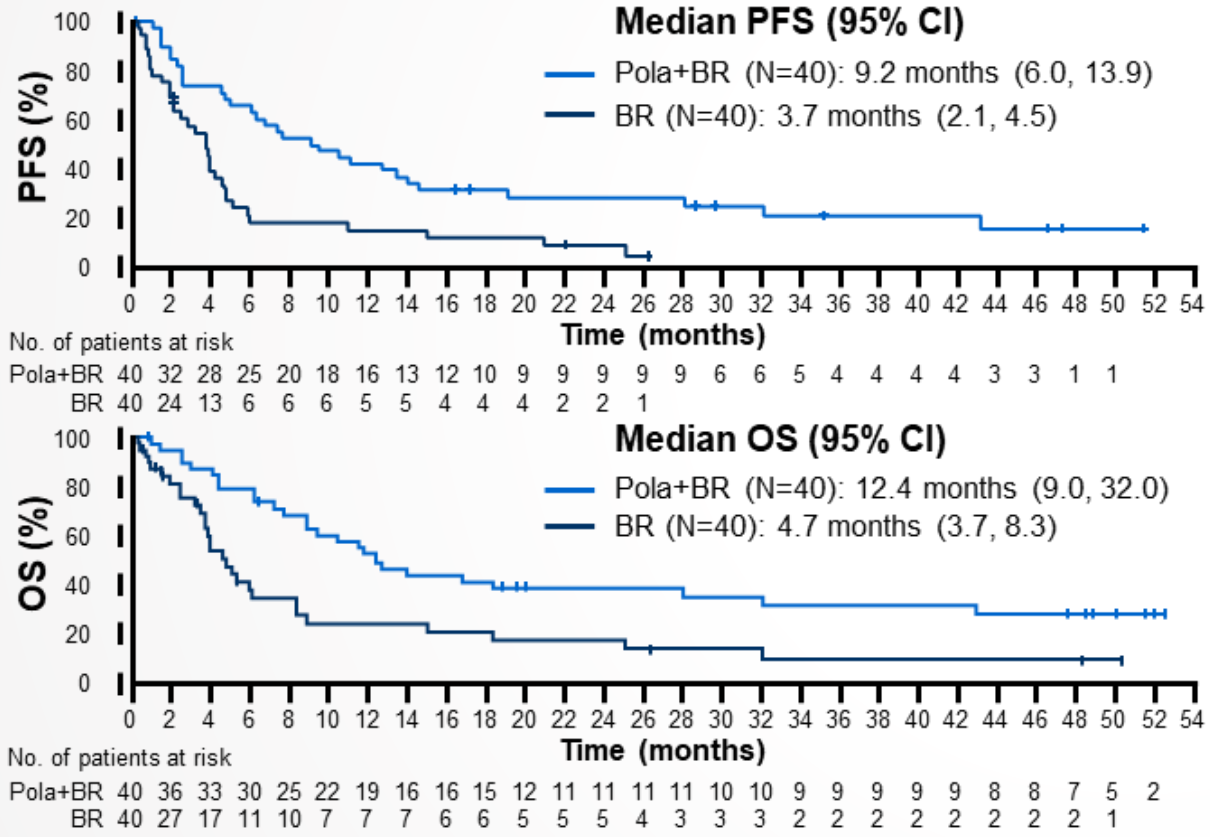



**ORR, 61%; CR/CRu rate, 44%**

CI, confidence interval; CR, complete response; CRu, unconfirmed complete response; DA-EPOCH, dose-adjusted etoposide phosphate + prednisone + vincristine sulfate + cyclophosphamide + doxorubicin hydrochloride; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; GCB, germinal centre B-cell; GemOx, gemcitabine + oxaliplatin; IV, intravenous; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PO, per os; PR, partial response; SD, stable disease.

**1.** NCCN Guidelines Version 4. 2021. Diffuse large B-cell lymphoma. Accessed May 2021. **2.** Mounier N, et al. *Haematologica.* 2013;98:1726-31.

# Polatuzumab plus rituximab and bendamustine

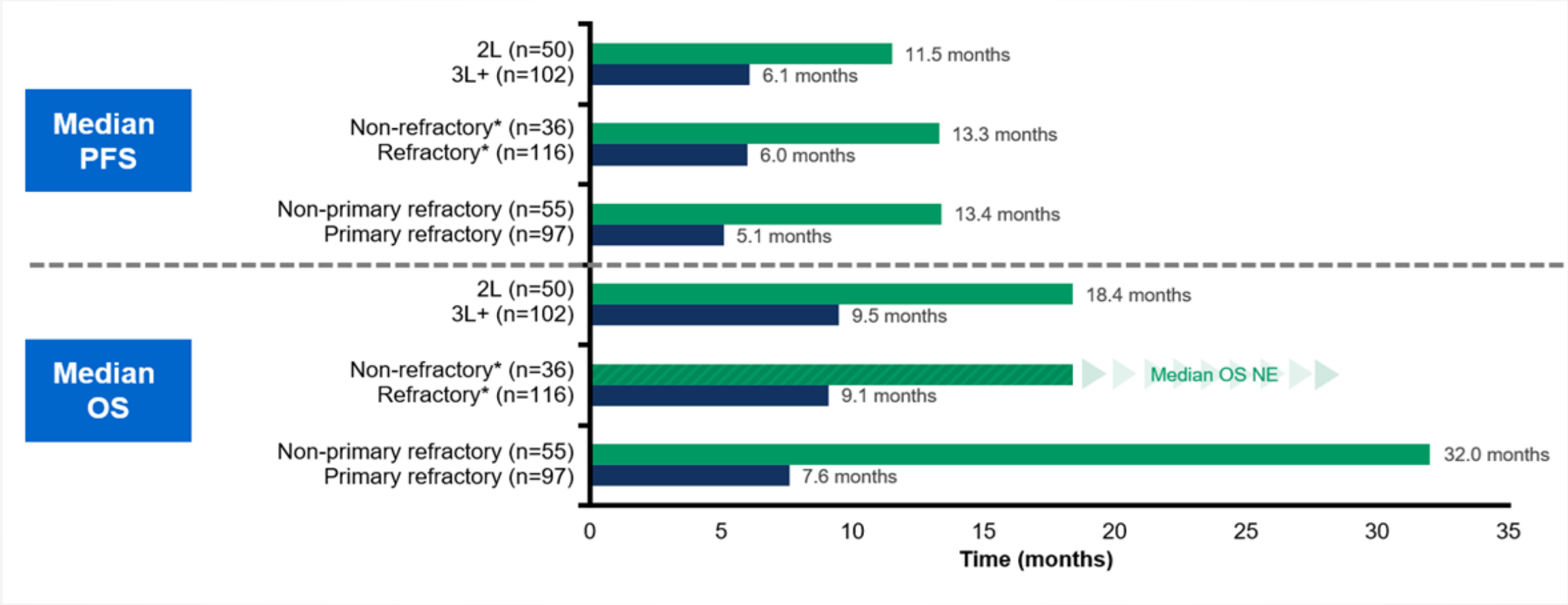



- Caution with bendamustine if CAR T-cell therapy is an option

BR, bendamustine + rituximab; CAR, chimeric antigen receptor; CI, confidence interval; OS, overall survival; PFS, progression-free survival; Pola, polatuzumab.

Sehn LH, et al. Poster #3020. 62nd ASH Annual Meeting and Exposition; Dec 2020; Virtual.

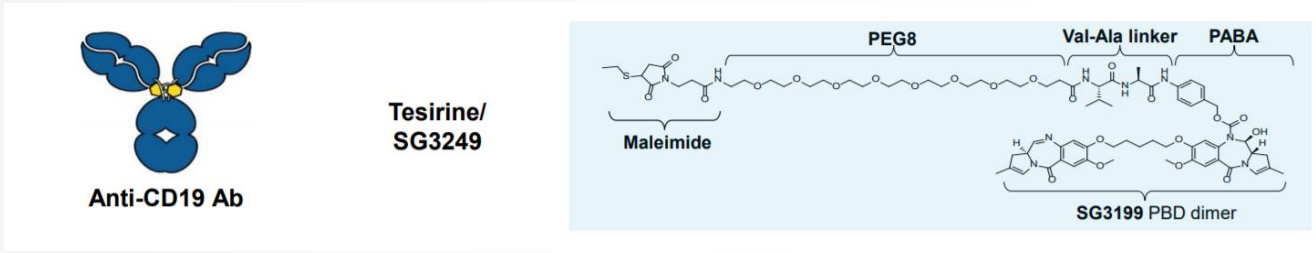
# Efficacy in patients with primary refractory disease

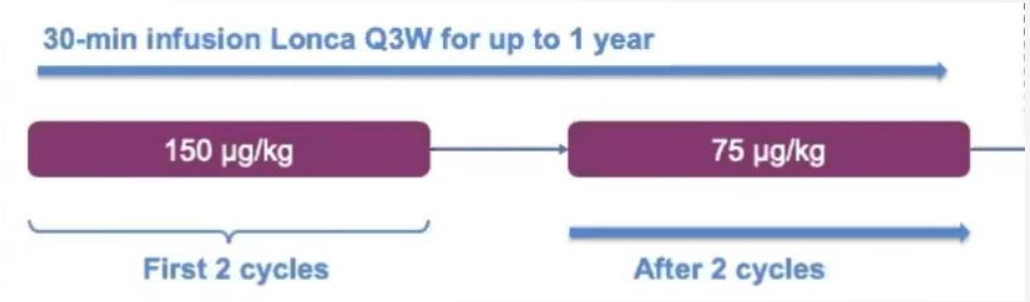



2L, second line; 3L, third line; NE, not evaluable; OS, overall survival; PFS, progression-free survival.

Sehn LH, et al. Poster #3020. 62nd ASH Annual Meeting and Exposition. Dec 2020; Virtual.

# Loncastuximab tesirine: CD19 ADC




- n = 145. 58% refractory to last therapy; median 3 (2–7) therapies

Eligibility criteria:

- R/R DLBCL (failed or intolerant to available standard therapy)
- ECOG PS 0–2
- If previous CD19-directed therapy received, must have a biopsy that shows CD19 expression after completion of the CD19-directed therapy

Exclusion criteria:

- Hypersensitivity to or positive serum human ADA to a CD19 antibody
- Previous therapy with ibrutinib (or other BTK inhibitors) or lonca
- Primary endpoint: CRR (Phase II)

ADA, adenosine deaminase; ADC, antibody–drug conjugate; BTK, Bruton's tyrosine kinase; CRR, complete response rate; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; Lonca; loncastuximab tesirine; R/R, relapsed/refractory.

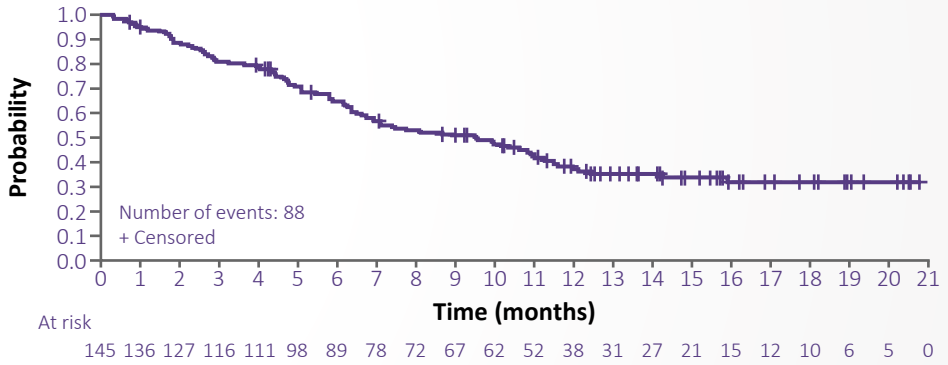
Caimi P, et al. Poster #1183. 62nd ASH Annual Meeting and Exposition; Dec 2020; Virtual.

# LOTIS-2 (Phase II single-arm study): Loncastuximab tesirine demonstrates promising clinical activity in 3L+ R/R DLBCL[1,2]

| **Safety** | |
|---|---|
| Any TEAE n (%) | 143 (99) |
| Most common Grade ≥3, % | |
| Neutropenia | 26 |
| Thrombocytopenia | 18 |
| GGT increased | 17 |
| Anaemia | 10 |

| **Efficacy outcomes** | **% (95% CI)** |
|---|---|
| ORR, % (95% CI) | 48 (40–57) |
| Double/triple-hit | 33 (12–62) |
| Transformed disease | 45 (27–64) |
| Primary refractory | 38 (21–58) |
| CRR, % (95% CI) | 25 (18–33) |
| Median DOR, months (95% CI) | 12.6 (6.9–NR) |
| In responders | 13.4 (12.6–NR) |

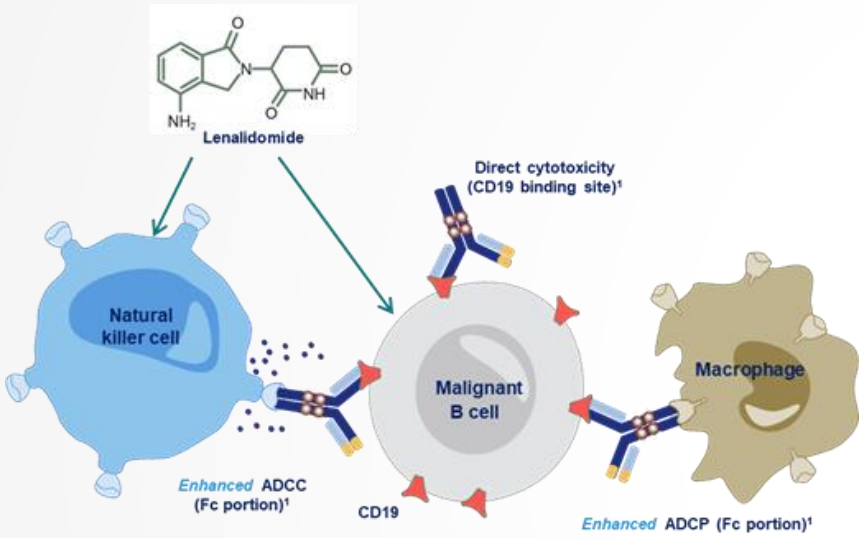
**Median OS, 9.53 months (95% CI, 6.93–11.24)**




3L, third line; CI, confidence interval; CRR, complete response rate; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; GGT, gamma-glutamyl transpeptidase; NR, not reached; ORR, overall response rate; OS, overall survival; R/R, relapsed/refractory; TEAE, treatment-emergent adverse event.

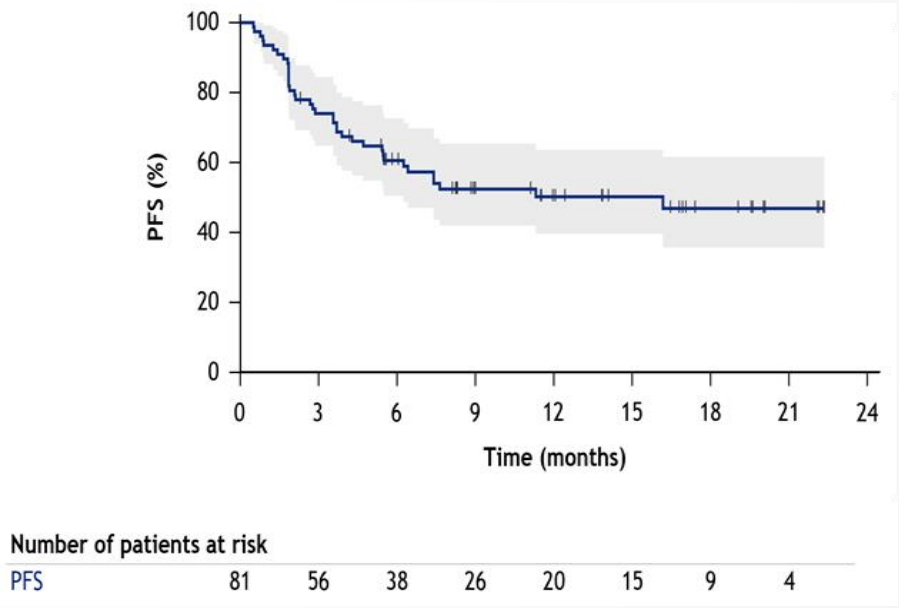
**1.** Caimi P, et al. Poster #1183. 62nd ASH Annual Meeting and Exposition. Dec 2020; Virtual. **2.** ClinicalTrial.gov. https://clinicaltrials.gov/ct2/show/NCT03589469. Updated Apr 1, 2021. Accessed May 2021.

# Tafasitamab and lenalidomide




- n = 81
- **Important:** Excluded primary refractory DLBCL, defined as no response to or PD during or within 6 months of frontline therapy; no DHL/THL

| PFS | |
|---|---|
| Median, months | 16.2 |
| 12-month PFS rate, % (range) | 50.1 (39.5–63.6) |




ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; DHL, double-hit lymphoma; PD, progressive disease; PFS, progression-free survival; THL, triple-hit lymphoma.

Salles G, et al. *Blood.* 2018;132(Suppl 1):227. Abstract and oral presentation. 60th ASH Annual Meeting and Exposition; Dec 2018; San Diego, US.

# CD19-directed ADC therapy does not preclude future CD19-directed CAR T-cell therapy

| | Patients (N = 14) |
|---|---|
| Age, median (range), y | 58.5 (27–86) |
| **Sex, n (%)** | |
| Male | 11 (79) |
| Female | 3 (21) |
| **Race, n (%)** | |
| White | 13 (93) |
| African American/Black | 1 (7) |
| **Lymphoma subtype** | |
| DLBCL* | 10 |
| Transformed DLBCL | 4 |
| **IPI at diagnosis, n (%)** | |
| Low (0, 1) | 3 (21) |
| Low-intermediate (2) | 3 (21) |
| High-intermediate (3) | 5 (36) |
| Unknown | 3 (21) |
| Advanced stage (III/IV) at diagnosis | 4 (29) |
| ***c-MYC* rearrangement, n (%)** | |
| Yes | 3 (21) |
| No | 8 (57) |
| Unknown | 3 (21) |
| Median interval between diagnosis and start of loncastuximab tesirine (range), mo | 21.5 (6.8–258) |
| **Best response to loncastuximab tesirine, n (%)** | |
| Complete response | 1 (7) |
| Partial response | 5 (36) |

Percentages may not add up to 100 due to rounding.
*One patient had mediastinal large B-cell lymphoma.

| | Patients (N = 14) |
|---|---|
| **CD19 expression on lymphoma cells after loncastuximab tesirine therapy, n (%)** | 10 (71) |
| Positive | 4 (29) |
| Not checked | |
| Median interval between loncastuximab tesirine and CAR T-cell therapy (range), | 120 (22–600) |
| **Additional therapy between loncastuximab tesirine and CAR T-cell therapy, n (%)** | |
| Yes* | 6 (43) |
| No | 8 (57) |
| **Disease status before CAR T-cell therapy, n (%)** | |
| Refractory disease | 5 (36) |
| Progressive disease | 8 (57) |
| Partial remission | 1 (7) |
| Flu/Cy lymphodepletion, n (%) | 14 (100) |
| **Type of CAR T-cell therapy, n (%)** | |
| Axicabtagene ciloleucel | 5 (36) |
| Tisagenlecleucel | 2 (14) |
| Investigational targeting CD19† | 4 (29) |
| JCAR017 | 3 (21) |
| **Best response to CAR T-cell therapy, n (%)** | |
| Complete response | 6 (43) |
| Partial response | 1 (7) |
| Refractory disease | 7 (50) |
| **CRS grade, n (%)** | |
| None | 6 (43) |
| 1 | 3 (21) |
| 2 | 4 (29) |
| 3 | 1 (7) |
| **ICANS grade, n (%)** | |
| None | 8 (57) |
| 1 | 4 (29) |
| 2 | 1 (7) |
| 3 | 0 (0) |
| 4 | 1 (7) |

*Additional therapy between loncastuximab tesirine and CAR T-cell therapy included radiation alone (n = 3), radiation, ifosphamide/vinblastine/etoposide (n = 1), radiation; rituximab/methotrexate (n = 1), lenalidomide, anti-CD47 antibody, ibrutinib (n = 1).
†One patient each received a CD19/CD22-directed CAR, and a CD19/CD20-directed CAR. Neither patient responded to CAR treatment.

ADC, antibody–drug conjugate; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; Flu/Cy, fludarabine/cyclophosphamide; ICANS; Immune effector cell-associated neurotoxicity syndrome; IPI, International Prognostic Index.
Thapa B, et al. *Blood Adv.* 2020;4(16):3850-3852.

# CD20xCD3 bispecific antibodies in early clinical development for DLBCL

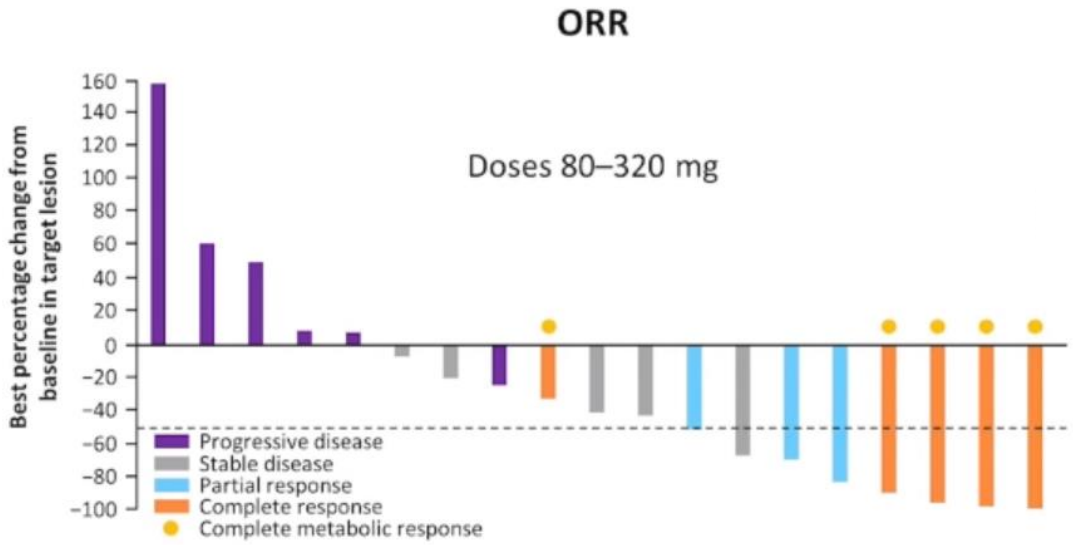
| | Bispecific antibody | Descriptor | Formulation | Development phase (disease) |
|---|---|---|---|---|
| **1:1 format**  | Mosunetuzumab[1,2,3] | Fully humanised, IgG1-like with modified Fc region | IV/SC | Phase I/II (R/R NHL, R/R FL) |
| | Odronextamab[2,4] | Hinge-stabilised, fully humanised, full-length IgG4 with a modified Fc region | IV | Phase I (R/R NHL, CLL, lymphoma); Phase II (R/R NHL) |
| | Epcoritamab[5] | DuoBody full-length, human IgG1 with a silent Fc region | SC | Phase I/II (R/R NHL) |
| | Plamotamab[6] | Humanised, IgG1-like with modified Fc region | IV | Phase I (R/R NHL, R/R CLL) |
| **2:1 format**  | Glofitamab[2,7,8] | Fully humanised, IgG1-like with modified Fc region | IV | Phase I/II (R/R NHL)<br>Phase III (R/R DLBCL) |

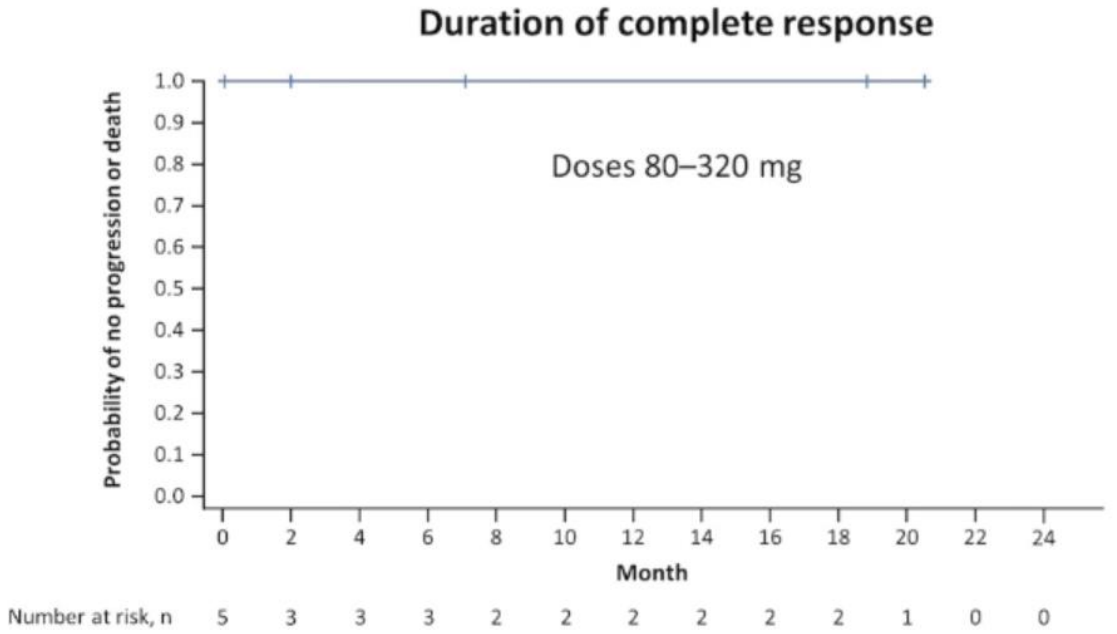
CLL, chronic lymphocytic leukaemia; DLBCL, diffuse large B-cell lymphoma; Fc, fragment crystallisable; FL, follicular lymphoma; IgG1, immunoglobulin G1; IgG4, immunoglobulin G4; IV, intravenous; NHL, non-Hodgkin lymphoma; R/R, relapsed/refractory; SC, subcutaneous.

**1.** Sun LL, et al. *Sci Transl Med.* 2015;7:287ra701. **2.** Bacac M, et al. *Oncoimmunol.* 2016;5:e1203498. **3.** Matasar M, et al. Poster #2096. 62nd ASH Annual Meeting and Exposition; Dec 2020; Virtual. **4.** Smith EJ, et al. *Sci Rep.* 2015;5:1. **5.** Lugtenburg P, et al. *Blood.* 2019;134(supplement_1):758. **6.** Patel K, et al. *Blood.* 2019;134 (Supplement_1):4079. **7.** Hutchings M, et al. Oral abstact #403. 62nd ASH Annual Meeting and Exposition; Dec 2020; Virtual. **8.** ClinicalTrials.gov. https://www.clinicaltrials.gov/ct2/show/NCT04408638. Updated Apr 28, 2021.

# Odronextamab in R/R DLBCL: Post CAR-T

**ORR**: **33%** (n=8/24); **CR rate**: **21%** (n=5/24)
**CRs appear durable; median DoCR not reached**
- **100%** of CRs are ongoing,* for up to **20 months**

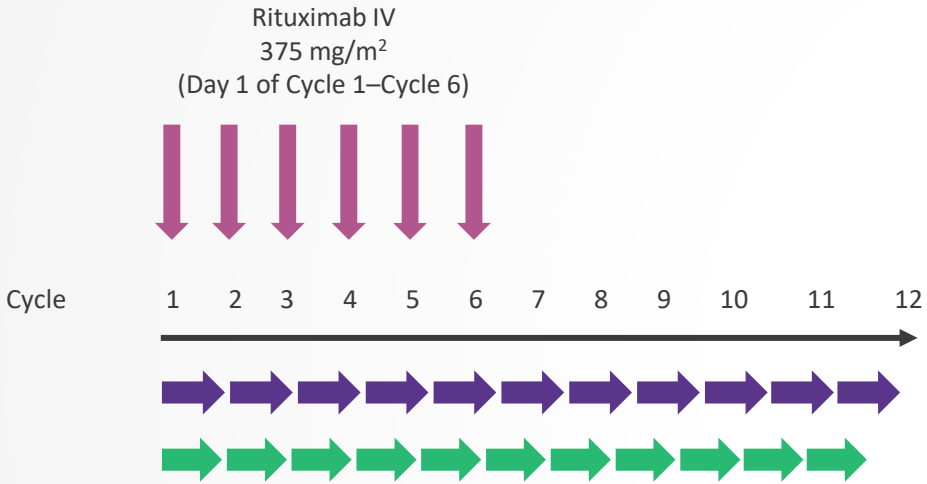



Data cut-off: Oct 14, 2020.
Response per investigator assessment according to Lugano criteria. Median duration of follow up is 3 months (range, 0–22).
*At time of last tumor assessment.

CAR, chimeric antigen receptor; CR, complete response; DoCR, duration of complete response; ORR, overall response rate.
Bannerji R, et al. Oral abstract #400. 62nd ASH Annual Meeting and Exposition; Dec 2020; Virtual.

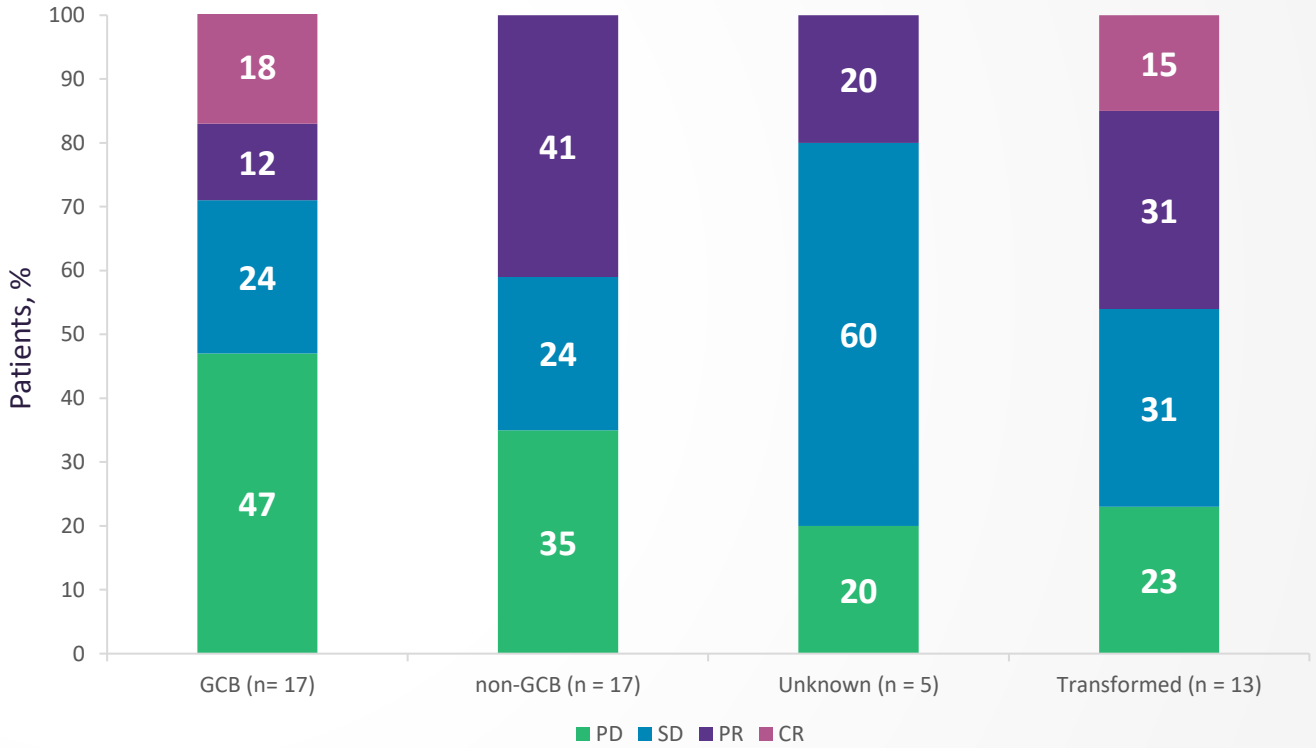
# Ibrutinib plus lenalidomide and rituximab: Activity in R/R non–GCB DLBCL




Ibrutinib 560 mg (4 capsules) PO continuous daily
(Days 1–28 of each cycle)

Lenalidomide PO (10, 15, 20, 25 mg)
(Days 1–21 of each cycle)

Response assessment every 3 months through Cycle 24; response assessment every 6 months after Cycle 25.




CR, complete response; DLBCL, diffuse large B-cell lymphoma; GCB, germinal centre B-cell-like; IV, intravenous; PD, progressive disease; PO, per os; PR, partial response; R/R, relapsed/refractory; SD, stable disease.

Goy A, et al. *Blood.* 2019;134(13):1024-1036.

# Selinexor (XPO1 inhibitor) in R/R DLBCL (SADAL study – NCT02227251)

**R/R DLBCL (N = 127)**

2–5 prior regimens

Not eligible for ASCT

Platelet count >75,000/mm$^3$

Excluded if CrCl <30 mL/min

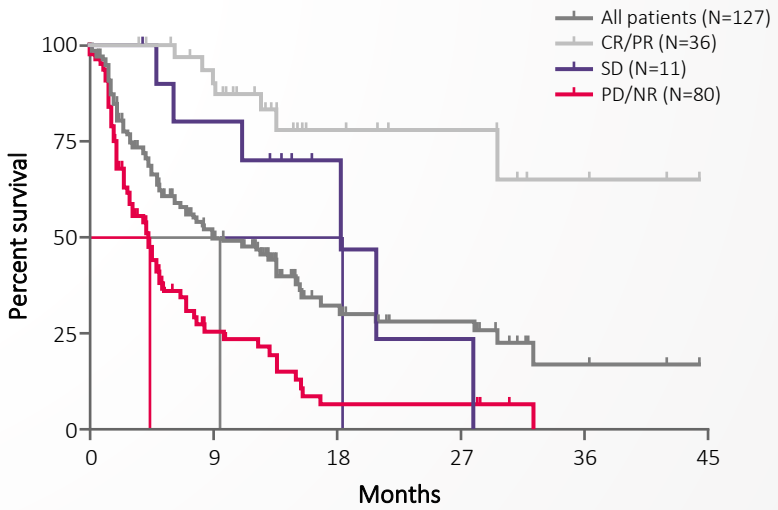
→

**Selinexor**
60 mg twice-weekly
(Days 1 and 3 of 28-day cycle)
until PD or intolerable toxicity

Primary endpoint: ORR

| Efficacy outcomes | N = 127 |
|---|---|
| ORR, % | 28 |
| CR, % | 12 |
| Median OS, months (95% CI) | 9.1 (6.6–15.1) |
| CR | NE (29.7–NE) |
| SD | 18.3 (11.1–28.0) |
| PD/NR | 4.3 (3.0–5.4) |

| N = 127 | Grade 1–2 | Grade 3 | Grade 4 |
|---|---|---|---|
| **Most common haematological AEs, %** | | | |
| Thrombocytopenia | 16 | 31 | 15 |
| Anaemia | 21 | 21 | 1 |
| Neutropenia | 6 | 16 | 9 |
| **Most common non-haematological AEs, %** | | | |
| Nausea | 52 | 6 | 0 |
| Fatigue | 36 | 11 | 0 |
| Decreased appetite | 33 | 4 | 0 |

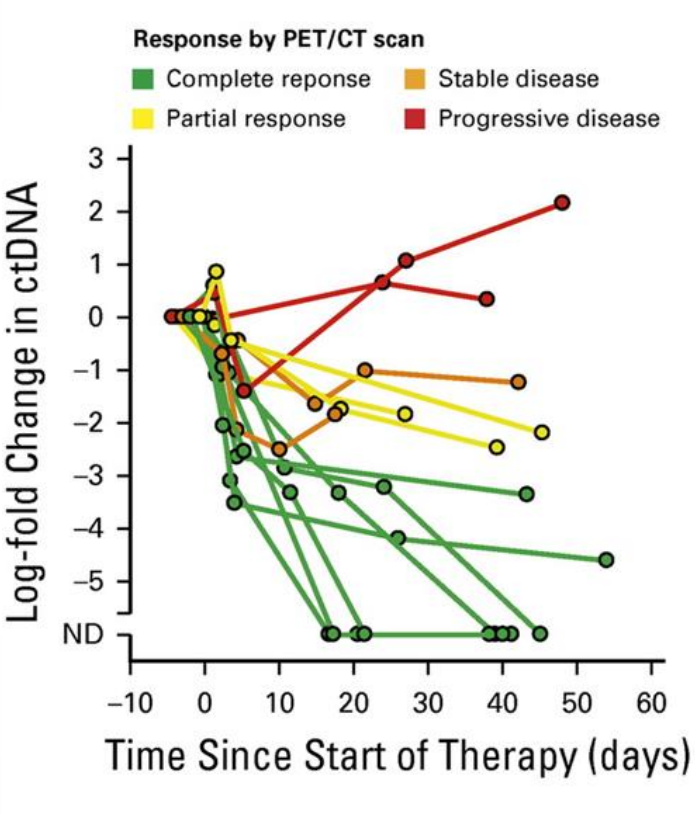



AE, adverse event; ASCT, autologous stem cell transplantation; CR, complete response; CrCl, creatinine clearance; DLBCL, diffuse large B-cell lymphoma; NE, not evaluable; NR, not reached; ORR, overall response rate; PD, progressive disease; R/R relapsed/refractory; SD, stable disease.

Kalakonda N, et al. *Lancet Haematol.* 2020;7:e511-22.

# Conclusions

- Outcomes for primary refractory DLBCL are poor in the rituximab era
- Early indicators of failure (ctDNA and PET) with effective interventions
- Results from conventional chemotherapeutic approaches are disappointing
- Cellular therapies may be of clear value in some
- ADC combine high specificity of a mAb with potent cytotoxic
- Ongoing design of new agents… multiple trials assessing combinations
- Much still to be understood regarding sequencing, bridging…




Kurtz DM, et al. *J Clin Oncol.* 2018;36(28):2845-2853.

ADC, antibody–drug conjugate; ctDNA, circulating tumor DNA; DLBCL, diffuse large B-cell lymphoma; mAb, monoclonal antibody; PET/CT, positron emission tomography–computed tomography; R/R relapsed/refractory.

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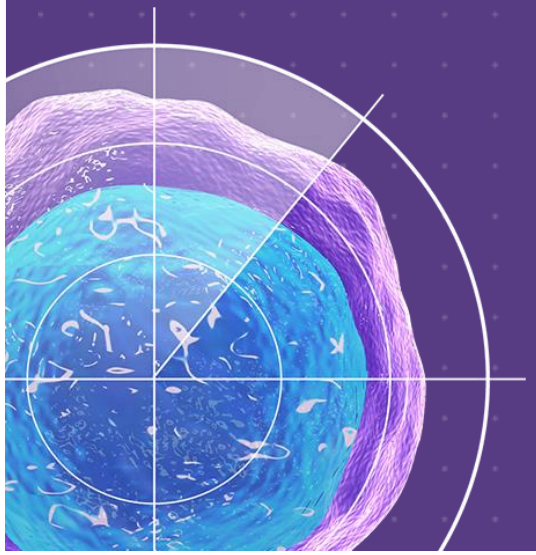
# Thank you



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