# Biomarkers and patient eligibility for CAR T-cell therapies in multiple myeloma and DLBCL

## The ins and outs of CAR T cells in the real world

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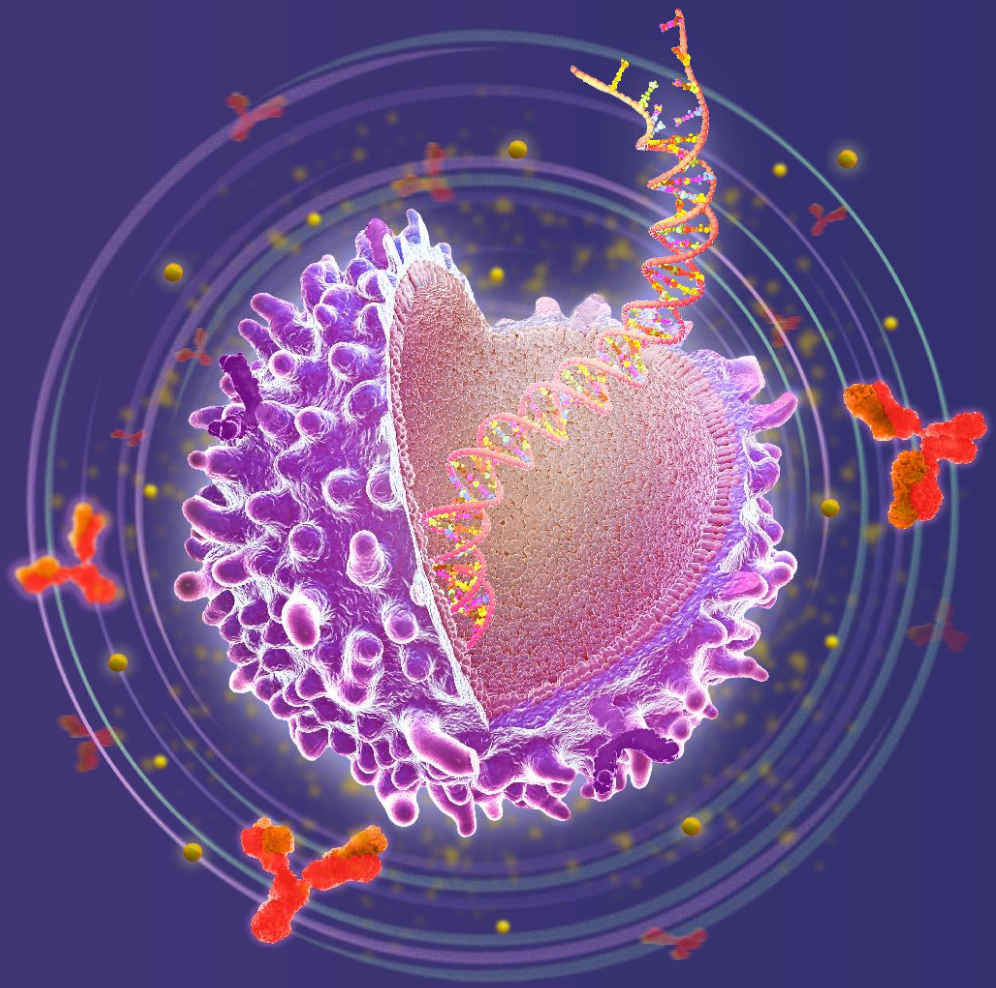
Kieron Dunleavy



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# Disclosures

- The following declarations are made for the last 3 years and the following 12 months (where arrangements have already been made):
  - Research grant(s)/in kind support: None
  - Participation in accredited CME/CPD: None
  - Consultant/strategic advisor: Astra Zeneca, Abbvie, Beigene, Amgen, Genentech, Genmab, Morphosys, Janssen, Daiichi Sankyo, Pharmacyclics, Incyte, ONO Pharmaceuticals
  - Patents/shares or stocks related or unrelated to this presentation: None
  - Non-financial interests: None

# Approved CD19 CAR T-cell therapies in LBCL

## FDA approvals

| CAR T-cell therapy approved | Date of approval | Target | Co-stimulatory domain | Pivotal trial |
|---|---|---|---|---|
| Axicabtagene ciloleucel | Oct 2017 | CD19 | CD28-CD3zeta | ZUMA-1[1,2] |
| Tisagenlecleucel | May 2018 | CD19 | 41BB-CD3zeta | JULIET[3] |
| Lisocabtagene maraleucel | Feb 2021 | CD19 | 41BB-CD3zeta | TRANSCEND[4] |

## EMA approvals

| CAR T-cell therapy approved | Date of approval | Target | Co-stimulatory domain | Pivotal trial |
|---|---|---|---|---|
| Axicabtagene ciloleucel | Aug 2018 | CD19 | CD28-CD3zeta | ZUMA-1[1,2] |
| Tisagenlecleucel | Aug 2018 | CD19 | 41BB-CD3zeta | JULIET[3] |
| Lisocabtagene maraleucel | May 2023 | CD19 | 41BB-CD3zeta | TRANSFORM[5] |

CAR, chimeric antigen receptor; EMA, European Medicines Agency; FDA, U.S. Food and Drug Administration; LBCL, large B-cell lymphoma.

**1.** Neelapu SS, et al. *N Engl J Med.* 2017;377(26):2531-2544. **2.** Locke FL, et al. *Lancet Oncol.* 2019;20(1):31-42. **3.** Schuster SJ, et al. *N Engl J Med.* 2019;380(1):45-56. **4.** Abramson JS, et al. *Lancet*. 2020;396(10254):839-852. **5.** Abramson JS, et al. *Blood*. 2023;141(14):1675-1684.

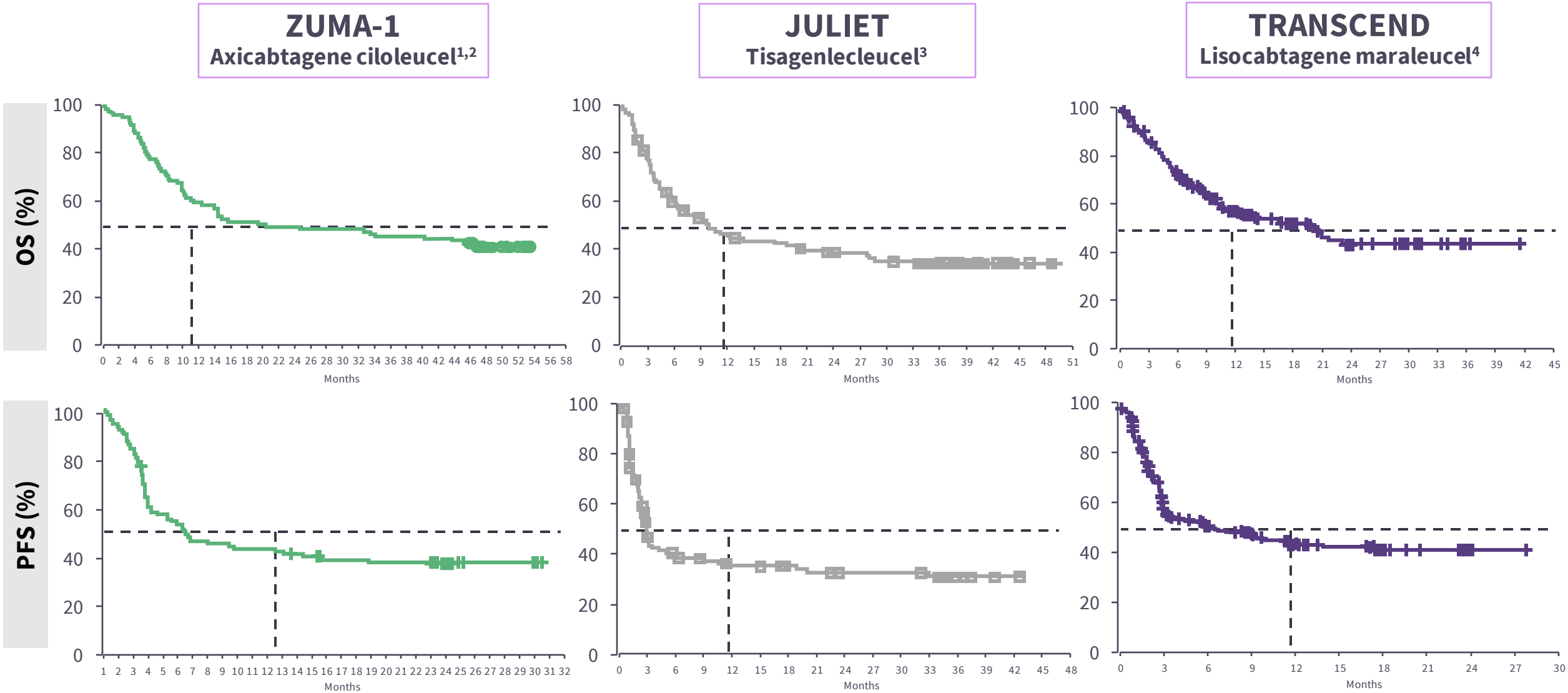
# Pivotal anti-CD19 CAR T-cell trials in LBCL

| Approved products | | | |
|---|---|---|---|
| | **Axicabtagene ciloleucel[1,2,3] (KTE-C19)** | **Tisagenlecleucel[4,5] (CTL019)** | **Lisocabtagene maraleucel[6] (JCAR017)** |
| Pivotal trial | **ZUMA-1** NCT02348216 | **JULIET** NCT02445248 | **TRANSCEND NHL 001** NCT02631044 |
| Phase | Phase I/II | Phase IIa | Phase I |
| Dose level | $2 \times 10^6$ cells | $3.1 \times 10^8$ cells | Dose Level 1: $5 \times 10^7$ cells<br>Dose Level 2: $1 \times 10^8$ cells |
| Conditioning chemotherapy | FLU 30 mg/m$^2$ and CY 500 mg/m$^2$ ×3 days | FLU 25 mg/m$^2$ + CY 250 mg/m$^2$ ×3 days (73%) or bendamustine 90 mg/m$^2$ ×2 days (20%) | FLU 30 mg/m$^2$ and CY 300 mg/m$^2$ ×3 days |
| Evaluable patients (N) | DLBCL/PMBCL/tFL (N = 101) | DLBCL (N = 93) | DLBCL (N = 256) |
| Selection criteria | R/R disease after ≥2 lines of systemic therapy | R/R disease after ≥2 lines of chemotherapy | R/R disease after ≥2 lines of systemic therapy or after auto-HSCT |
| Response rates | ORR = 83%<br>CR = 58% | ORR = 53%<br>CR = 39% | ORR = 73%<br>CR = 53% |

Auto-HSCT, autologous hematopoietic stem cell transplantation CAR, chimeric antigen receptor; CR, complete response; CY, cyclophosphamide; DLBCL, diffuse large B-cell lymphoma; FLU, fludarabine; ORR, overall response rate; PMBCL, primary mediastinal large B-cell lymphoma; R/R, relapsed/refractory; tFL, transformed follicular lymphoma.

**1.** Neelapu SS, et al. *N Engl J Med.* 2017;377(26):2531-2544. **2.** Locke FL, et al. *Lancet Oncol.* 2019;20(1):31-42. **3.** Neelapu SS, et al. *Blood.* 2023;141(19):2307-2315. **4.** Schuster SJ, et al. *N Engl J Med.* 2019;380(1):45-56. **5.** Schuster SJ, et al. *Lancet Oncol.* 2021;22(10):1403-1415. **6.** Abramson JS, et al. *Lancet.* 2020;396(10254):839-852.

# Pivotal anti-CD19 CAR T-cell trials in LBCL




CAR, chimeric antigen receptor; LBCL, large B-cell lymphoma; OS, overall survival; PFS, progression-free survival.

**1.** Neelapu SS, et al. *N Engl J Med.* 2017;377(26):2531-2544. **2.** Locke FL, et al. *Lancet Oncol*. 2019;20(1):31-42. **3.** Schuster SJ, et al. *N Engl J Med.* 2019;380(1):45-56. **4.** Abramson JS, et al. *Lancet*. 2020;396(10254):839-852.

# Will CD19-CAR T-cell therapy replace AUTO?

**ZUMA-7**
**Axicabtagene ciloleucel**

**BELINDA**
**Tisagenlecleucel**

**TRANSFORM**
**Lisocabtagene maraleucel**

High-risk LBCL
- Refractory to first-line therapy
- Relapsed after first-line therapy

**CAR-T**

**Salvage therapy + AUTO**

CAR, chimeric antigen receptor; LBCL, large B-cell lymphoma.

# Anti-CD19 CAR T-cell therapy for aggressive second-line LBCL

| | Approved products | | Not approved |
|---|---|---|---|
| | **Axicabtagene ciloleucel[1] (KTE-C19)** | **Lisocabtagene maraleucel[2] (JCAR017)** | **Tisagenlecleucel[3] (CTL019)** |
| Pivotal trial | **ZUMA-7** NCT03391466 | **TRANSFORM** NCT03575351 | **BELINDA** NCT03570892 |
| Phase | Phase III | Phase III | Phase III |
| Dose level | $2 \times 10^6$ cells | $1 \times 10^8$ cells | $2.9 \times 10^8$ cells |
| Conditioning chemotherapy | FLU 30 mg/m$^2$ and CY 500 mg/m$^2$ ×3 days | FLU 30 mg/m$^2$ and CY 300 mg/m$^2$ ×3 days | FLU 25 mg/m$^2$ + CY 250 mg/m$^2$ ×3 days or bendamustine 90 mg/m$^2$ ×2 days |
| Evaluable patients (N) | DLBCL (N = 180) | DLBCL (N = 92) | DLBCL (N = 162) |
| Response Rates | ORR = 83% CR = 65% | ORR = 86% CR = 66% | Tisagenlecleucel was not superior to standard salvage therapy |
| Primary endpoint – median EFS | 8.3 months vs 2 months | 10 months vs 2.3 months | 3 months for both arms |

CAR, chimeric antigen receptor; CR, complete response; CY, cyclophosphamide; DLBCL, diffuse large B-cell lymphoma; FLU, fludarabine; ORR, overall response rate.

**1.** YESCARTA. Package insert. Kite Pharma, Inc; 2022. **2.** Kamdar M, et al. *Lancet.* 2022;399(10343):2294-2308. **3.** Bishop MR, et al. *N Engl J Med.* 2022;386(7):629-639.

# What matters in CAR T-cell response?

**Clinical characteristics**

**Tumor biological characteristics**

**Tumor microenvironment**

**Interval response**
PET imaging
MRD dynamics

CAR, chimeric antigen receptor; MRD, minimal residual disease; PET, positron emission tomography.
Kieron Dunleavy. Personal communication. Jun 9, 2023.

# What matters in CAR T-cell response?

**Clinical characteristics**

Tumor bulk?
LDH?
Lines of therapy?
IPI characteristics?

**Tumor biological characteristics**

**Tumor microenvironment**

**Interval response**
PET imaging
MRD dynamics

CAR, chimeric antigen receptor; IPI, International Prognostic Index; LDH, lactate dehydrogenase; MRD, minimal residual disease; PET, positron emission tomography.
Kieron Dunleavy. Personal communication. Jun 9, 2023.

# What matters in CAR T-cell response?

**Clinical characteristics**

**Tumor biological characteristics**

GCB versus ABC?
PMBCL?
HGBCL?

**Tumor microenvironment**

**Interval response**
PET imaging
MRD dynamics

ABC, activated B-cell; CAR, chimeric antigen receptor; GCB, germinal center B-cell; HGBCL, high-grade B-cell lymphoma; MRD, minimal residual disease; PET, positron emission tomography; PMBCL, primary mediastinal large B-cell lymphoma.
Kieron Dunleavy. Personal communication. Jun 9, 2023.

# What matters in CAR T-cell response?

**Clinical characteristics**

**Tumor biological characteristics**

**Tumor microenvironment**

???

**Interval response**
PET imaging
MRD dynamics

???

CAR, chimeric antigen receptor; MRD, minimal residual disease; PET, positron emission tomography.
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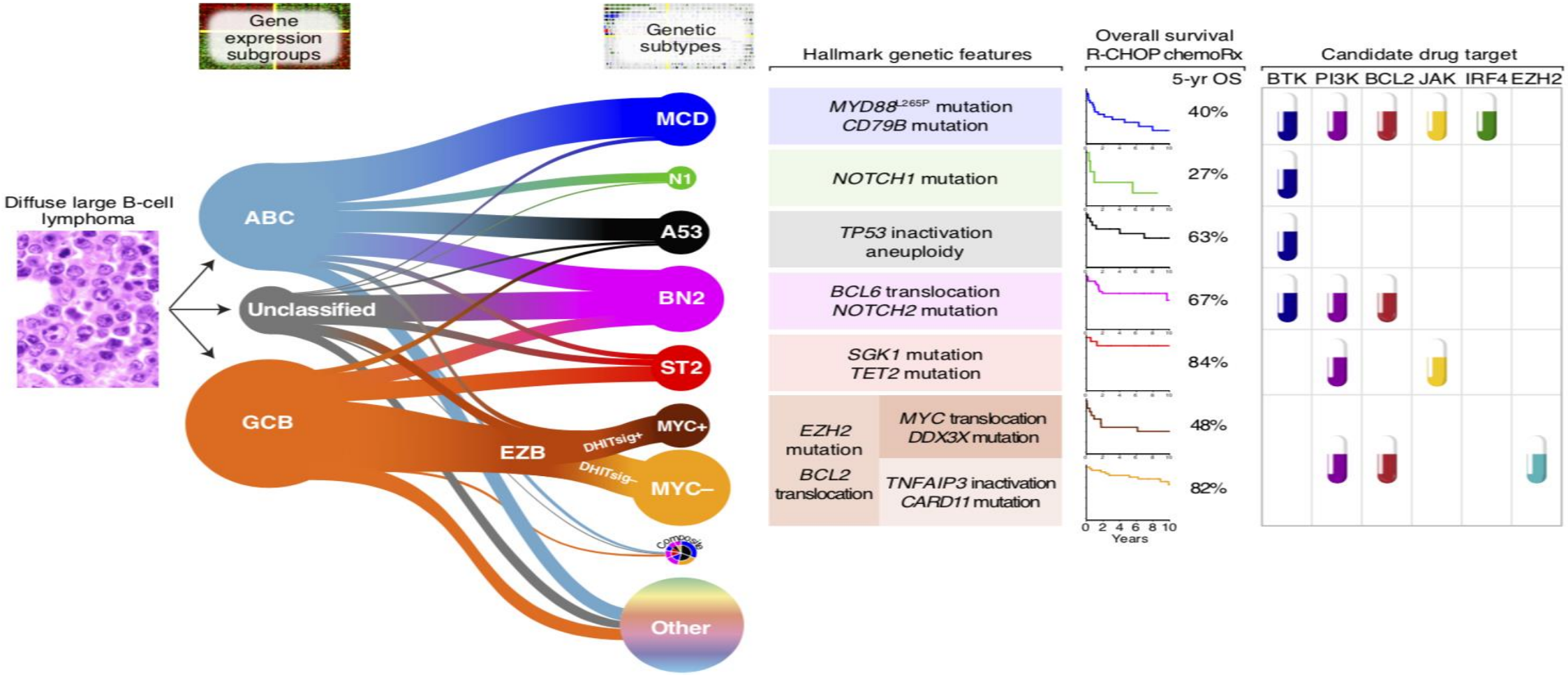
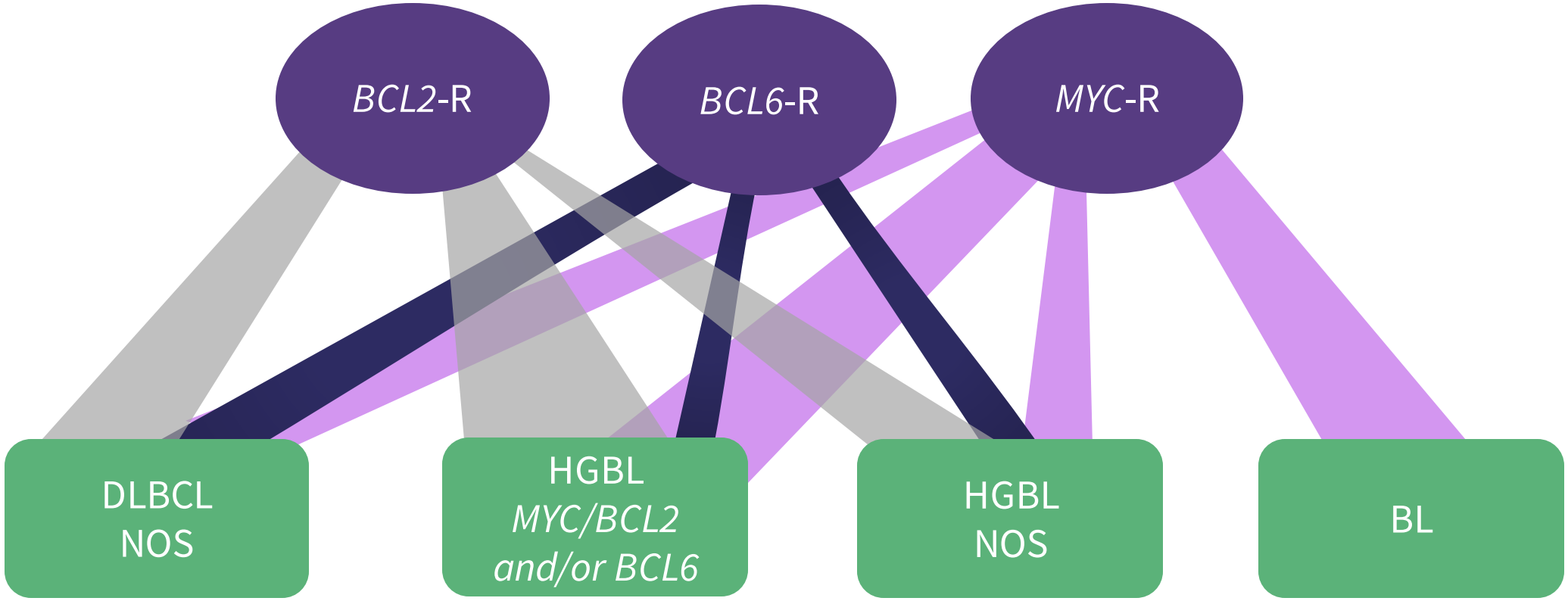
# Molecular biology of DLBCL[1]




ABC, activated B-cell; DLBCL, diffuse large B-cell lymphoma; GCB, germinal center B-cell; R-CHOP, cyclophosphamide, doxorubicin, prednisone, rituximab, and vincristine.

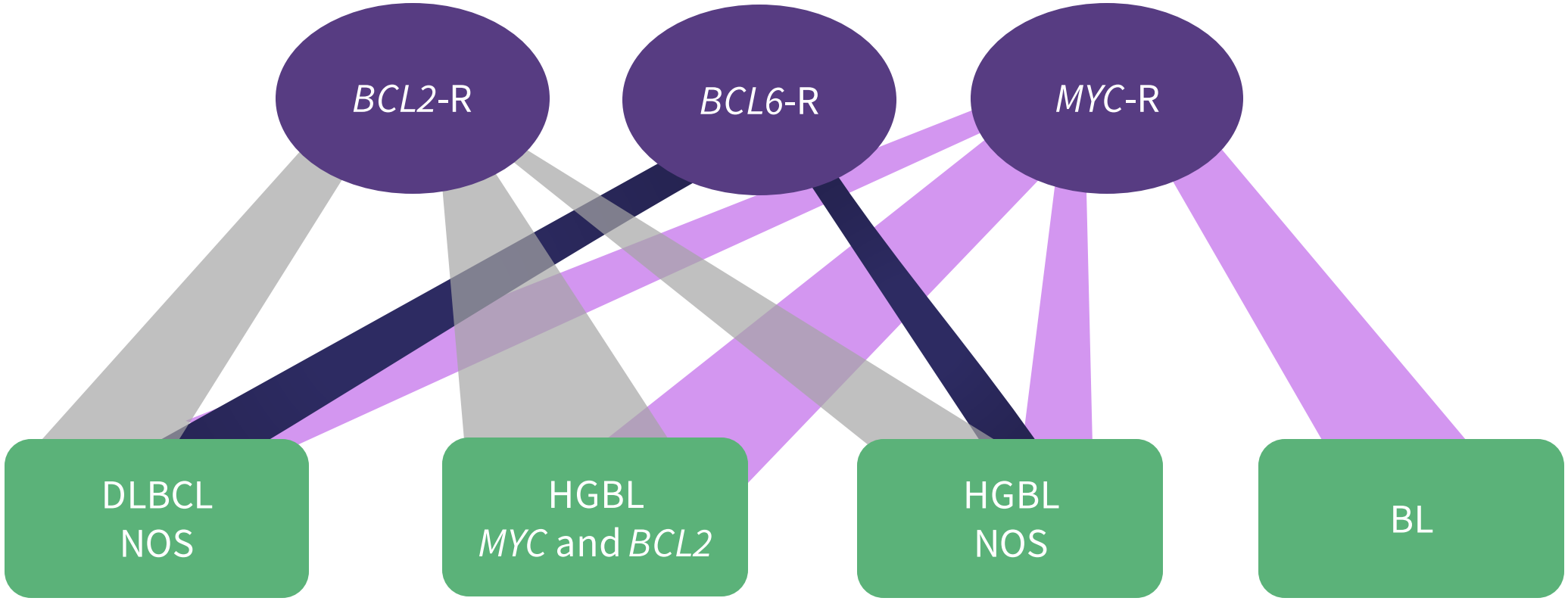
**1.** Level LD, et al. *Blood.* 2022;140(21):2193-2227.

# Aggressive B-cell lymphomas




ABC, activated B-cell; BL, Burkitt lymphoma; DLBCL, diffuse large B-cell lymphoma; GBC, germinal center B-cell; HGBL, high grade B-cell lymphoma; NOS, not otherwise specified; WHO, World Health Organization.

# Aggressive B-cell lymphomas

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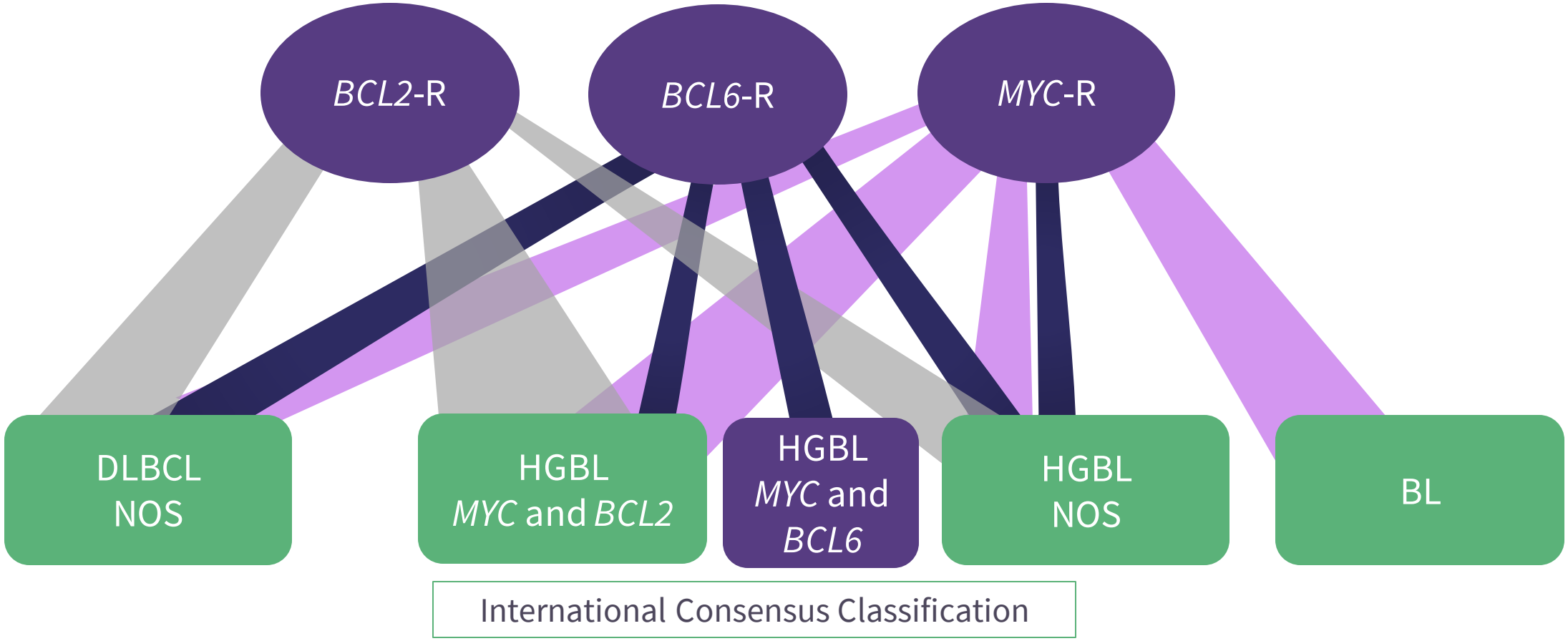


ABC, activated B-cell; BL, Burkitt lymphoma; DLBCL, diffuse large B-cell lymphoma; GBC, germinal center B-cell; HGBL, high grade B-cell lymphoma; NOS, not otherwise specified; WHO, World Health Organization.

# ZUMA-7: Impact of biomarkers on outcome[1]

| Subgroup | Axi-cel | Standard care | HR (95% CI) |
|---|---|---|---|
| Overall | 108/180 | 144/179 | 0.40 (0.31–0.51) |
| Age | | | |
| <65 years | 81/129 | 96/121 | 0.49 (0.36–0.67) |
| ≥65 years | 27/51 | 48/58 | 0.28 (0.16–0.46) |
| Response to first-line therapy | | | |
| Primary refractory disease | 85/133 | 106/131 | 0.43 (0.32–0.57) |
| Relapse ≤12 months after initiation or completion of first-line therapy | 23/47 | 28/48 | 0.34 (0.20–0.58) |
| Second line age-adjusted IPI | | | |
| 0 or 1 | 54/98 | 73/100 | 0.41 (0.28–0.58) |
| 2 or 3 | 54/82 | 71/79 | 0.39 (0.27–0.56) |
| Prognostic marker according to central laboratory | | | |
| HGBL, double- or triple-hit | 15/31 | 21/25 | 0.28 (0.14–0.59) |
| Doble-expressor lymphoma | 35/57 | 50/62 | 0.42 (0.27–0.67) |
| Molecular subgroup according to central laboratory | | | |
| Germinal center B-like | 64/109 | 80/99 | 0.41 (0.29–0.57) |
| Activated B-cell-like | 11/16 | 9/9 | 0.18 (0.05–0.72) |
| Unclassified | 8/17 | 12/14 | — |
| Disease type according to investigator | | | |
| DLBCL, not otherwise specified | 68/110 | 97/116 | 0.37 (0.27–0.52) |
| Large-cell transformation from follicular lymphoma | 10/19 | 24/27 | 0.35 (0.16–0.77) |
| HGBL, including rearrangement of *MYC* with *BCL2* or *BCL6* or both | 24/43 | 18/27 | 0.47 (0.24–0.90) |
| Disease type according to central laboratory | | | |
| DLBCL | 79/126 | 95/120 | 0.44 (0.32–0.60) |
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axi-cel, axicabtagene ciloleucel; CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; HGBL, high grade B-cell lymphoma; HR, hazard ratio.

**1.** Locke FL, et al. *N Engl J Med.* 2022;386(7):640-654.

# High metabolic tumor volume: Decreased efficacy of axi-cel in LBCL[1]

Tumor burden, measured by MTV on baseline $^{18}$F-FDG PET/CT scan, is associated with PFS and OS in axi-cel–treated LBCL patients (N = 48)

| | Low vs High MTV* | p value | Multivariate analysis, High vs Low MTV* | p value |
|---|---|---|---|---|
| PFS | HR, 0.40 (95% CI, 0.18–0.89) | 0.02 | OR, 0.30 (95% CI, 0.12–0.72) | 0.007 |
| OS | HR, 0.25 (95% CI, 0.10–0.66) | 0.005 | OR, 0.20 (95% CI, 0.07–0.57) | 0.002 |

axi-cel, axicabtagene ciloleucel; LBCL, large B-cell lymphoma; OR, odds ratio; PFS, progression-free survival.
*Median MTV cutoff value of 147.5 mL.
**1.** Dean EA, et al. *Blood Adv*. 2020;4(14):3268-3276.

# ZUMA-7: Impact of biomarkers on outcome[1]

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WHAT ABOUT TRANSFORM AND BELINDA?

DID THESE MARKERS DIFFER?

**1.** Locke FL, et al. *N Engl J Med.* 2022;386(7):640-654.

# CAR T-cell therapy outcomes in DLBCL vs HGBL

# Clinical trial CAR T-cell data[1]

| | ZUMA-1<br>Locke, *et al.*<br>*Lancet Oncol* 2019 | JULIET<br>Schuster, *et al.*<br>*NEJM* 2019 | TRANSCEND<br>Abramson, *et al.*<br>*Lancet* 2020 | ZUMA-7<br>Locke, *et al.*<br>*NEJM* 2021 | | BELINDA<br>Bishop, *et al.*<br>*NEJM* 2021 | | ZUMA-12<br>Neelapu ,*et al.*<br>*Nat Med* 2022 |
|---|---|---|---|---|---|---|---|---|
| | **Axi-cel** | **Tisa-cel** | **Liso-cel** | **Axi-cel** | **SOC** | **Tisa-cel** | **SOC** | **Axi-cel** |
| Phase | I/II | II | Seamless | III | | III | | II |
| Primary endpoint | ORR | ORR | ORR | EFS | | EFS after Week 12 | | CR |
| Patients, n | 101 | 111 | 256 | 180 | 179 | 162 | 160 | 40 |
| HGBL, n | 7 | 19 | 36 | 31 | 26 | 32 | 19 | 10 |
| **ALL** | | | | | | | | |
| ORR, % | 82 | 52 | 72.7 | 83 | 50 | 46.3 | 42.5 | 90 |
| CR, % | 54 | 40 | 53.1 | 65 | 32 | 28.4 (3.mo) | 27.5 | 80 |
| EFS, HR | — | — | — | 0.40 | — | 1.07 | — | NR |
| **HGBL** | | | | | | | | |
| ORR, % | 100 | 50 | 75.8 | 81 | 42 | NR | NR | — |
| CR, % | 67 | 25 | 60.6 | — | — | — | — | — |
| EFS, HR | — | — | — | 0.47 | — | — | — | — |
| Median Follow-up, months | 27.1 | 28.6 | 18.8 | 24.9 | | 10 | | 15.9 |

axi-cel, axicabtagene ciloleucel; CR, complete response; EFS, event-free survival; HGBL, high grade B-cell lymphoma; HR, hazard ratio; liso-cel, lisocabtagene maraleucel; mo, months; ORR, overall response rate; SOC, standard of care; tisa-cel, tisagenlecleucel.

**1.** Ali A , et al. *Blood*. 2022;140(13)1461-1469.

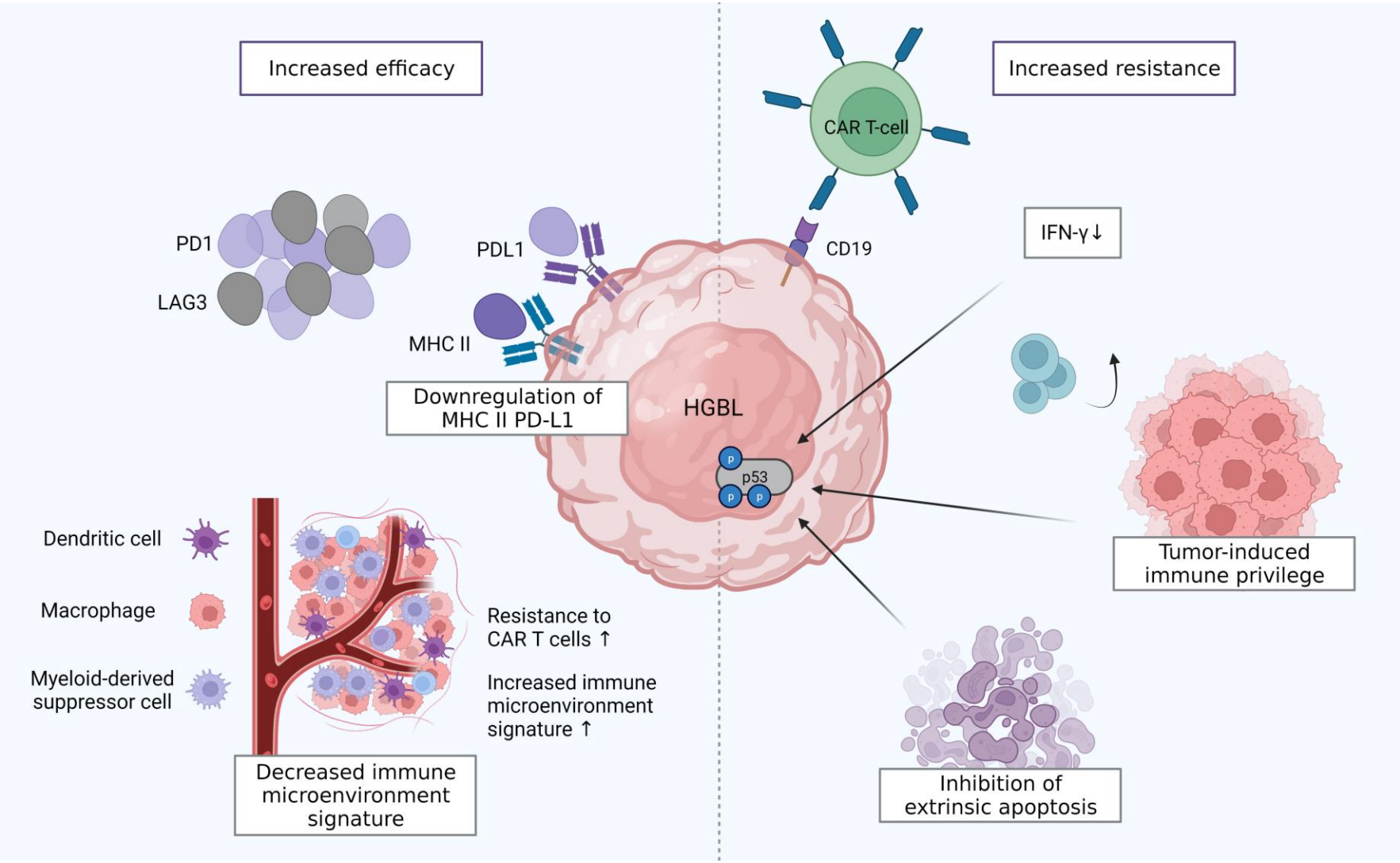
# Real-world CAR T-cell data[1]

| | Nastoupil, *et al.* *JCO* 2020 | Jacobson, *et al.* *JCO* 2020 | Iacoboni, *et al.* *Cancer Medicine* 2021 |
|---|---|---|---|
| Centers, n | 17 | 7 | 10 |
| Product | Axi-cel | Axi-cel | Tisa-cel |
| Patients, n | 275 | 122 | 75 |
| HGBL, n | 64 | 47 | 11 |
| **Total cohort** | | | |
| ORR | 82 | 70 | 60 |
| CR | 63 | — | — |
| PFS | 48 | — | — |
| OS | 68 | — | — |
| **HGBL** | | | |
| ORR | NR | 86 | 63.6 |
| CR | 64 | — | — |
| PFS | 39 | — | — |
| OS | 69 | — | — |

axi-cel, axicabtagene ciloleucel; CR, complete response; HGBL, high-grade B-cell lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; tisa-cel, tisagenlecleucel.

**1.** Ali A , et al. Blood. 2022;140(13)1461-1469.

# Impact of HGBL biology on efficacy of CAR T-cells[1]




Created using BioRender.com.

CAR, chimeric antigen receptor; HGBL, high grade B-cell lymphoma.

**1.** Ali A , et al. *Blood*. 2022;140(13)1461-1469.


- Which patients should get CAR T-cell therapy in first relapse?

- Clinical versus molecular biomarkers
    - IPI characteristics
    - Cell of origin/genomic characteristics

- Should HGBL be approached differently?

- Which groups may benefit from up-front novel CAR T-cell therapy?

-Where will MRD fit into the landscape of CAR T-cell therapeutics?

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Questions

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References