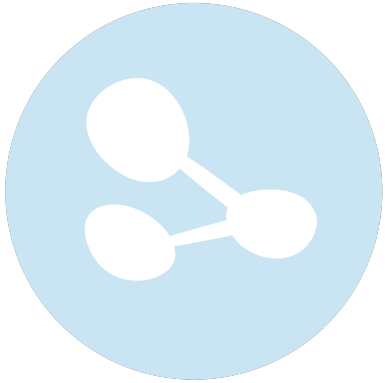

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MEETING SUMMARY
ASH ANNUAL MEETING 2021

Dr. Matthew J. Matasar, MD
Memorial Sloan Kettering Cancer Center
New York, NY, USA

HIGHLIGHTS FROM LYMPHOMA & MYELOMA CONNECT 2021
DECEMBER 2021

CONFLICT OF INTEREST AND FUNDING

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FIRST-LINE TREATMENT OF DLBCL

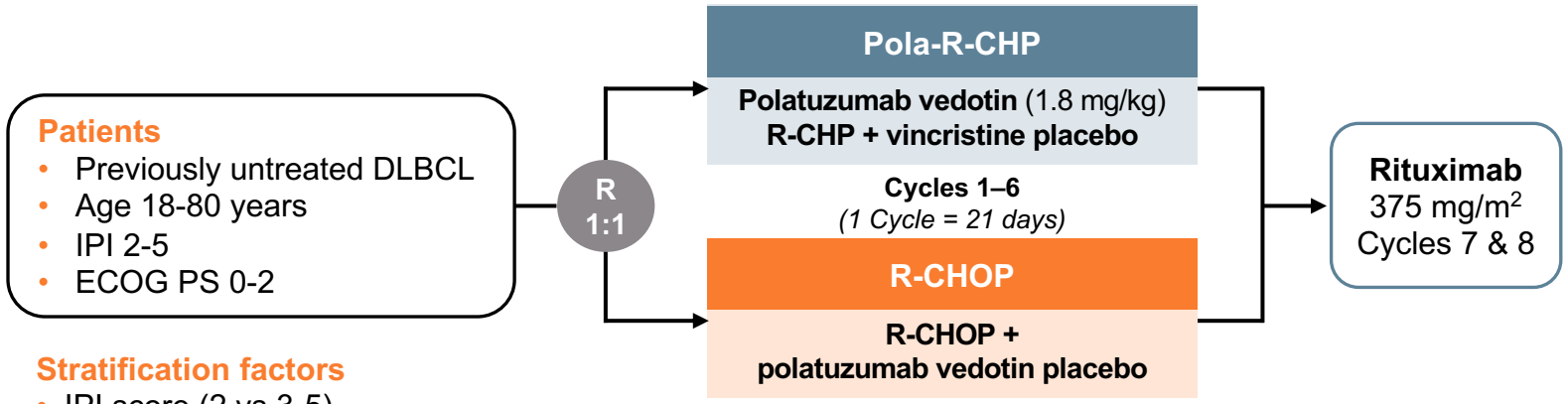
THE POLARIX STUDY: POLA-R-CHP VS R-CHOP THERAPY IN PTS WITH PREVIOUSLY UNTREATED DLBCL

Tilly H, et al.
ASH Annual Meeting 2021. Abstract #LBA-1. Oral presentation

DLBCL, diffuse large B-cell lymphoma; POLA-R-CHP, polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, prednisone; PTS, patients; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone

STUDY DESIGN

RANDOMISED, DOUBLE-BLIND PHASE 3 POLARIX TRIAL: POLA-R-CHP VS R-CHOP IN PREVIOUSLY UNTREATED DLBCL



Primary endpoint:
- Investigator-assessed PFS

Key secondary endpoints:
- EFS
- PET/CT-CR rate at end of treatment (IRC)
- OS
- DFS

Safety endpoints
- Incidence, nature, and severity of AEs

AE, adverse event; CR, complete response; DFS, disease-free survival; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; IPI, international prognostic index; IRC, Independent Review Committee; OS; overall survival; PET/CT, positron emission tomography/computed tomography; PFS, progression-free survival; (Pola-)R-CHP, (polatuzumab vedotin), rituximab, cyclophosphamide, doxorubicin, prednisone; R, randomised; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone

Tilly H, et al. ASH Annual Meeting 2021. Abstract #LBA-1. Oral presentation

RESULTS

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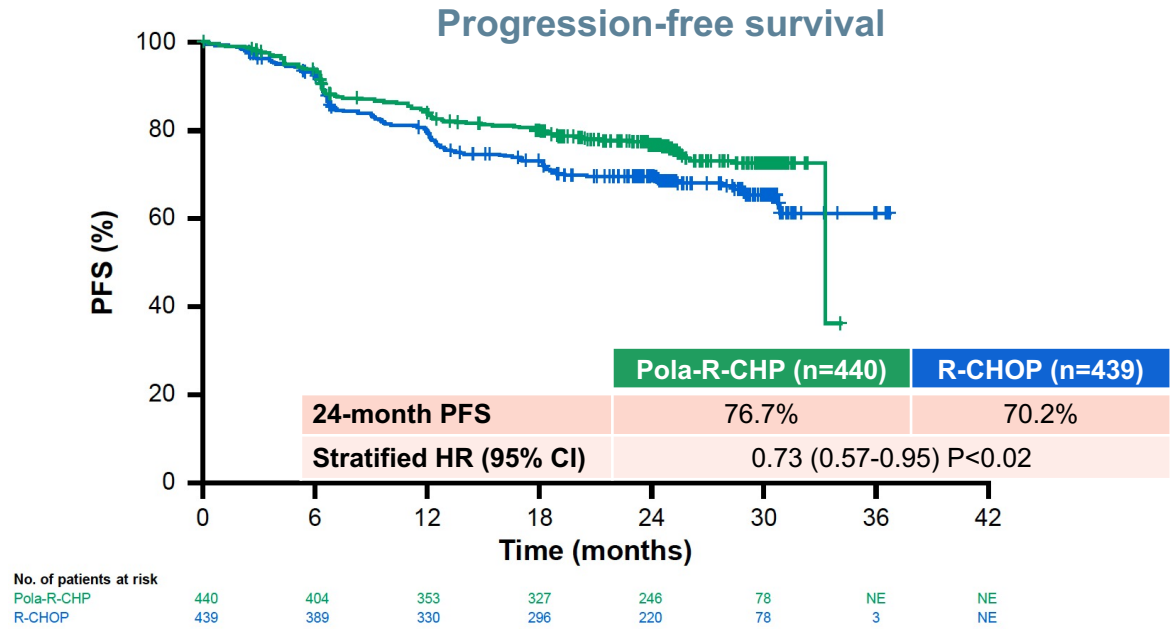
Efficacy

- Pola-R-CHP **significantly improved PFS** versus R-CHOP, with a 27% reduction in the relative risk of disease progression, relapse, or death and an absolute improvement of 6.5% at 24 months
- **EFS was improved** as well (HR 0.75, p=0.02)
- **OS was comparable** in both arms (HR 0.94, p=0.75); the final OS analysis is expected in 2022



Safety

- The safety profile was **comparable in both arms**, except an increased rate of diarrhoea and febrile neutropenia with Pola-R-CHP
- No difference in neuropathy or dose adjustments/discontinuations due to adverse events

CI, confidence interval; EFS, event-free survival; HR, hazard ratio; OS; overall survival; PFS, progression-free survival; Pola-R-CHP, polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, prednisone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone

Tilly H, et al. ASH Annual Meeting 2021. Abstract #LBA-1. Oral presentation

AUTHOR CONCLUSIONS AND CLINICAL INTERPRETATION

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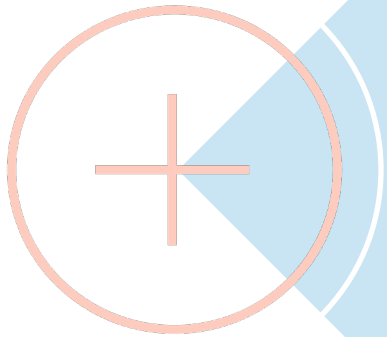
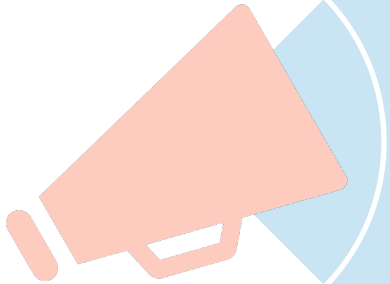


Pola-R-CHP significantly **prolongs PFS** vs R-CHOP in intermediate-and high-risk previously untreated DLBCL, with a **comparable safety profile**



These results **support Pola-R-CHP as initial treatment of DLBCL IPI 2+**

DLBCL, diffuse large B-cell lymphoma; IPI, international prognostic index; PFS, progression-free survival; Pola-R-CHP, polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, prednisone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone

Tilly H, et al. ASH Annual Meeting 2021. Abstract #LBA-1. Oral presentation

SECOND-LINE TREATMENT OF DLBCL

DATA ON CAR-T CELL THERAPY IN LBCL PRESENTED AT ASH 2021

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Three phase 3 trials

TRANSFORM[1]	ZUMA-7[2]	BELINDA[3]
• Liso-cel vs SOC with salvage CT followed by ASCT as 2L treatment in R/R LBCL • *Positive trial*	• Axi-cel vs SOC in R/R LBCL • *Positive trial*	• Tisa-cel vs SOC in primary refractory or relapsed aggressive B-cell NHL • *Negative trial: tisa-cel did not show a higher EFS vs SOC*

2L, second-line; ASCT, autologous stem cell transplantation; axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CT, chemotherapy; EFS, event-free survival; LBCL, large B-cell lymphoma; liso-cel, lisocabtagene maraleucel; NHL, non-Hodgkin lymphoma; R/R, relapsed or refractory; SOC, standard of care; tisa-cel, tisagenlecleucel

1. Kamdar M, et al. ASH Annual Meeting 2021. Abstract #91. Oral presentation; 2. Locke FL, et al. ASH Annual Meeting 2021. Abstract #2. Oral presentation; 3. Bishop MR, et al. ASH Annual Meeting 2021. Abstract #LBA-6

LISO-CEL, A CD19-DIRECTED CAR-T CELL THERAPY, VS SOC WITH SALVAGE CT FOLLOWED BY ASCT AS 2L TREATMENT IN PTS WITH R/R LBCL: RESULTS FROM THE RANDOMIZED PHASE 3 TRANSFORM STUDY

Kamdar M, et al.

ASH Annual Meeting 2021. Abstract #91. Oral presentation

2L, second-line; ASCT, autologous stem cell transplantation; CAR, chimeric antigen receptor; CT, chemotherapy; LBCL, large B-cell lymphoma; liso-cel, lisocabtagene maraleucel; PTS, patients; R/R, relapsed or refractory; SOC, standard of care

STUDY DESIGN

PHASE 3 TRANSFORM TRIAL: LISO-CEL VS SOC AS 2L THERAPY IN R/R LBCL

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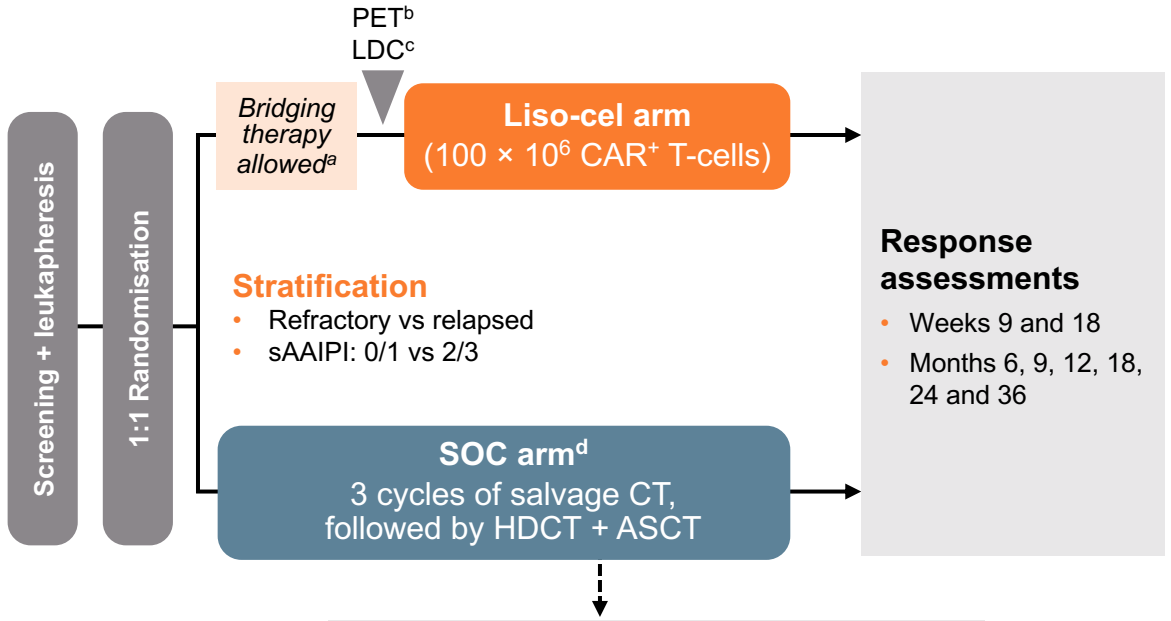
Key eligibility

- Age 18-75 years
- Aggressive NHL
  - DLBCL NOS (de novo or transformed from indolent NHL), HGBCL (double/triple hit) with DLBCL histology, FL3B, PMBCL, THRBCL
- R/R ≤12 months after 1L treatment containing an anthracycline and a CD20-targeted agent
- ECOG PS ≤1
- Eligible for HSCT
- Secondary CNS lymphoma allowed
- LVEF >40% for inclusion
- No minimum absolute lymphocyte count



Primary endpoint

- EFS (per IRC)

Key secondary endpoints

- CR rate, PFS, OS

Other secondary endpoints

- Duration of response, ORR, PFS on next line of treatment
- Safety, PROs

Exploratory endpoints

- Cellular kinetics
- B-cell aplasia

[a] Patients may have received a protocol-defined SOC regimen to stabilise their disease during liso-cel manufacturing
[b] Only for patients who received bridging therapy
[c] Lymphodepletion with fludarabine 30 mg/m^2 and cyclophosphamide 300 mg/m^2 for 3 days
[d] SOC was defined as physician's choice of R-DHAP, R-ICE, or R-GDP

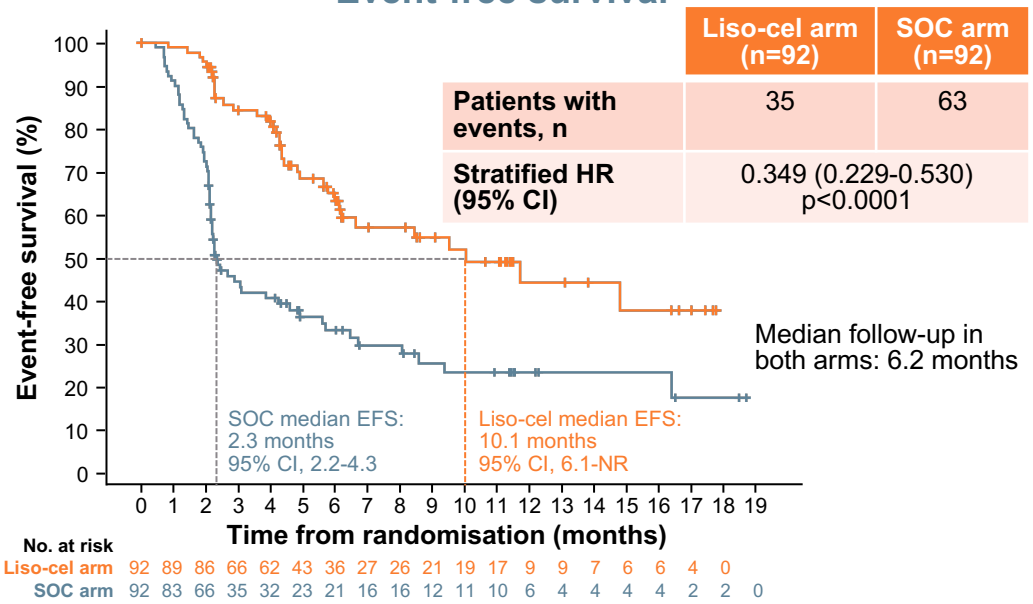
1L, first-line; 2L, second-line; ASCT, autologous stem cell transplantation; CAR, chimeric antigen receptor; CNS, central nervous system; CR, complete response; CT, computed tomography; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; FL3B, follicular lymphoma grade 3B; HDCT, high-dose chemotherapy; HGBCL, high-grade B-cell lymphoma; HSCT, haematopoietic stem cell transplantation; IRC, independent review committee; LBCL, large B-cell lymphoma; LDC, lymphodepleting chemotherapy; liso-cel, lisocabtagene maraleucel; LVEF, left ventricular ejection fraction; NHL, non-Hodgkin lymphoma; NOS, not otherwise specified; ORR, overall response rate; OS, overall survival; PD, progressive disease; PET, positron emission tomography; PFS, progression-free survival; PMBCL, primary mediastinal large B-cell lymphoma; PRO, patient-reported outcome; R-DHAP, rituximab, dexamethasone, cytarabine, cisplatin; R-GDP, rituximab, gemcitabine, dexamethasone, cisplatin; R-ICE, rituximab, ifosfamide, carboplatin, etoposide phosphate; R/R, relapsed or refractory; sAAIPI, secondary age-adjusted International Prognostic Index; SOC, standard of care; THRBCL, T-cell/histiocyte-rich large B-cell lymphoma; Kamdar M, et al. ASH Annual Meeting 2021. Abstract #91. Oral presentation

RESULTS

Efficacy

- **Liso-cel demonstrated superiority over SOC**, with highly statistically significant and clinically meaningful improvements in EFS, CR rate, and PFS
  - The primary EFS endpoint was met, representing a 65% reduction in risk of events
  - CR rate was 66% vs 39% (p<0.0001)
  - Median PFS was 14.8 vs 5.7 months (HR 0.406; p=0.0001
- The median OS was not reached with liso-cel vs 16.4 months for SOC (HR 0.509; p=0.0257)
  - Not significant per protocol statistics

Event-free survival



Safety

- Consistent with the safety profile in ≥3L LBCL
  - 1 case of grade 3 CRS; no grade 4/5 events
  - 12% neurological events (4% grade 3)

3L, third-line; CI, confidence interval; CR, complete response; CRS, cytokine release syndrome; EFS, event-free survival; HR, hazard ratio; LBCL, large B-cell lymphoma; NR, not reached; OS, overall survival; PFS, progression-free survival; SOC, standard of care

Kamdar M, et al. ASH Annual Meeting 2021. Abstract #91. Oral presentation

AUTHOR CONCLUSIONS

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Liso-cel improved outcomes versus salvage CT followed by HDCT and ASCT and exhibited a favourable safety profile

TRANSFORM data support liso-cel as a potential new 2L standard of care in early relapsing or refractory LBCL

2L, second-line; ASCT, autologous stem cell transplantation; CT, computed tomography; HDCT, high-dose chemotherapy; LBCL, large B-cell lymphoma

Kamdar M, et al. ASH Annual Meeting 2021. Abstract #91. Oral presentation

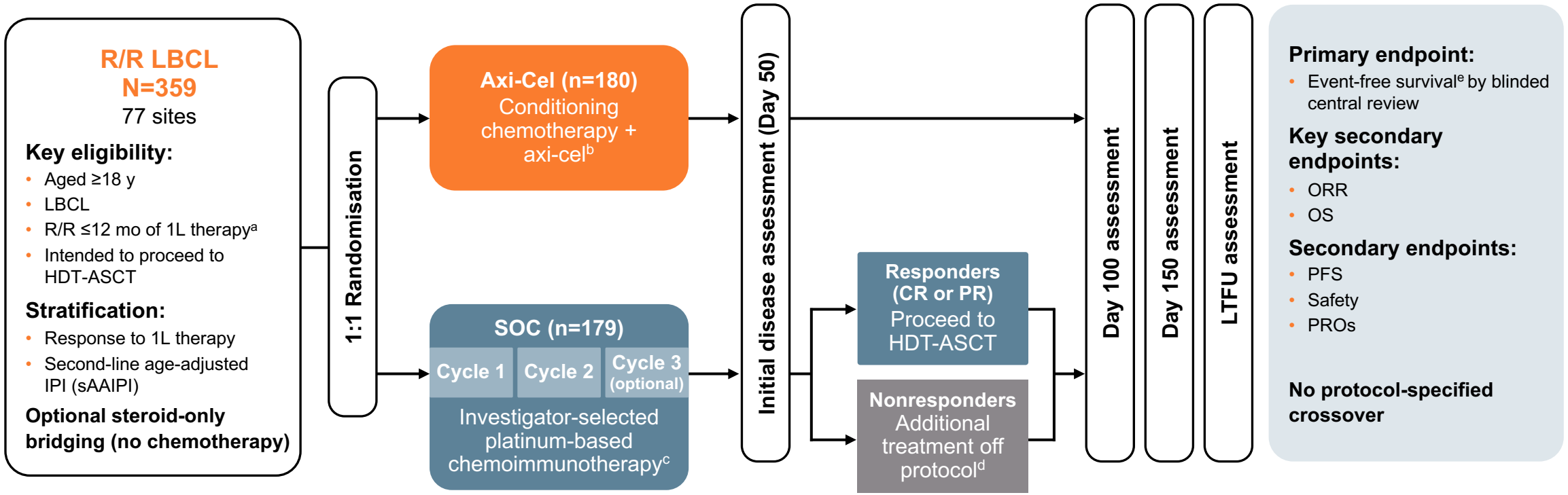
PRIMARY ANALYSIS OF ZUMA-7: A PHASE 3 RANDOMISED TRIAL OF AXI-CEL VS SOC THERAPY IN PTS WITH R/R LBCL

Locke FL, et al.
ASH Annual Meeting 2021. Abstract #2. Oral presentation

Axi-cel, axicabtagene ciloleucel; LBCL, large B-cell lymphoma; PTS, patients; R/R, relapsed or refractory; SOC, standard of care

STUDY DESIGN

PHASE 3 ZUMA-7 TRIAL: AXI-CEL VS SOC AS 2L THERAPY IN R/R LBCL



[a] Refractory disease was defined as no CR to 1L therapy; relapsed disease was defined as CR followed by biopsy-proven disease relapse ≤12 months from completion of 1L therapy
[b] Axi-cel patients underwent leukapheresis followed by conditioning chemotherapy with cyclophosphamide (500 mg/m^2/day) and fludarabine (30 mg/m^2/day) 5, 4, and 3 days before receiving a single axi-cel infusion (target intravenous dose, 2 × 10^6 CAR T cells/kg)
[c] Protocol-defined SOC regimens included R-GDP, R-DHAP, R-ICE, or R-ESHAP
[d] 56% of patients received subsequent cellular immunotherapy
[e] EFS was defined as time from randomisation to the earliest date of disease progression per Lugano Classification, commencement of new lymphoma therapy, or death from any cause

1L, first-line; 2L, second-line; ASCT, autologous stem cell transplantation; axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CR, complete response; EFS, event-free survival; HDT, high-dose therapy; LBCL, large B-cell lymphoma; LTFU, long-term follow-up; mo, month; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; PRO, patient-reported outcome; R/R, relapsed or refractory; SOC, standard of care; R-DHAP, rituximab, dexamethasone, cytarabine, cisplatin; R-ESHAP, rituximab, etoposide, methylprednisolone, cytarabine, cisplatin; R-GDP, rituximab, gemcitabine, dexamethasone, cisplatin; R-ICE, rituximab, ifosfamide, carboplatin, etoposide phosphate; sAAIPI, secondary age-adjusted International Prognostic Index

Locke FL, et al. ASH Annual Meeting 2021. Abstract #2. Oral presentation

RESULTS

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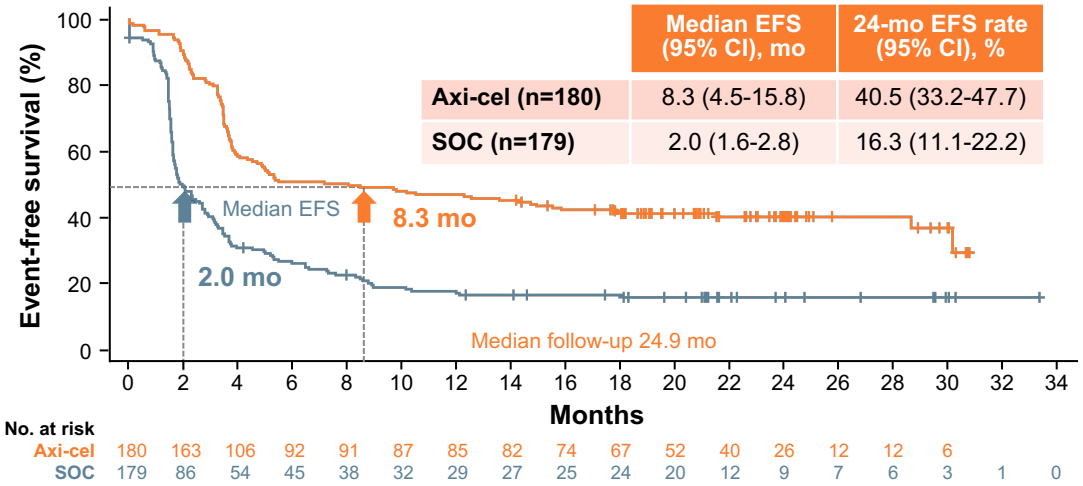
Efficacy

- Axi-cel showed superior efficacy versus 2L SOC
  - >4-fold greater median EFS (8.3 vs 2.0 months)
  - Nearly 2.5-fold greater 2-year EFS (40.5% vs 16.3%)
  - 33% higher ORR (83% vs 50%)
  - Double the CR rate (65% vs 32%)
- The median OS was not reached with axi-cel vs 35.1 months for SOC (HR 0.73; p=0.027)
- Nearly 3 times more patients in the axi-cel arm received definitive therapy vs the SOC arm

Event-free survival

HR 0.398 (95% CI, 0.308-0.514); p<0.0001



	Median EFS (95% CI), mo	24-mo EFS rate (95% CI), %
Axi-cel (n=180)	8.3 (4.5-15.8)	40.5 (33.2-47.7)
SOC (n=179)	2.0 (1.6-2.8)	16.3 (11.1-22.2)

Safety

- Consistent with the safety profile in previous studies
  - 92% CRS (6% grade 3/4) with axi-cel
  - 60% neurological events (21% grade 3/4) with axi-cel vs 20% (1% grade 3/4) with SOC

2L, second-line; CI, confidence interval; CR, complete response; CRS, cytokine release syndrome; EFS, event-free survival; HR, hazard ratio; mo, month; ORR, overall response rate; OS, overall survival; SOC, standard of care

Locke FL, et al. ASH Annual Meeting 2021. Abstract #2. Oral presentation

AUTHOR CONCLUSIONS

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ZUMA-7 represents a paradigm shift

Axi-cel should be the new standard in 2L treatment of early relapsing or refractory LBCL

2L, second-line; LBCL, large B-cell lymphoma
Locke FL, et al. ASH Annual Meeting 2021. Abstract #2. Oral presentation

CLINICAL INTERPRETATION

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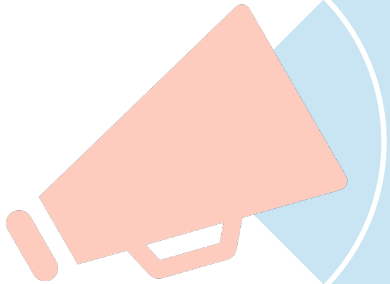

CAR-T therapy will become a standard of care in the treatment of high-risk, early relapsing or refractory LBCL

Trial design, as well as differences in costimulatory domains between the different cellular products, may have impacted the negative outcome of the BELINDA trial

CAR, chimeric antigen receptor; LBCL, large B-cell lymphoma; R/R, relapsed or refractory

FOLLICULAR LYMPHOMA

MOSUNETUZUMAB MONOTHERAPY IS AN EFFECTIVE AND WELL-TOLERATED TREATMENT OPTION FOR PTS WITH R/R FL WHO HAVE RECEIVED ≥ 2 PRIOR LINES OF THERAPY: PIVOTAL RESULTS FROM A PHASE I/II STUDY

Budde EL, et al.
ASH Annual Meeting 2021. Abstract #127. Oral presentation

FL, follicular lymphoma; PTS, patients; R/R, relapsed or refractory

STUDY DESIGN

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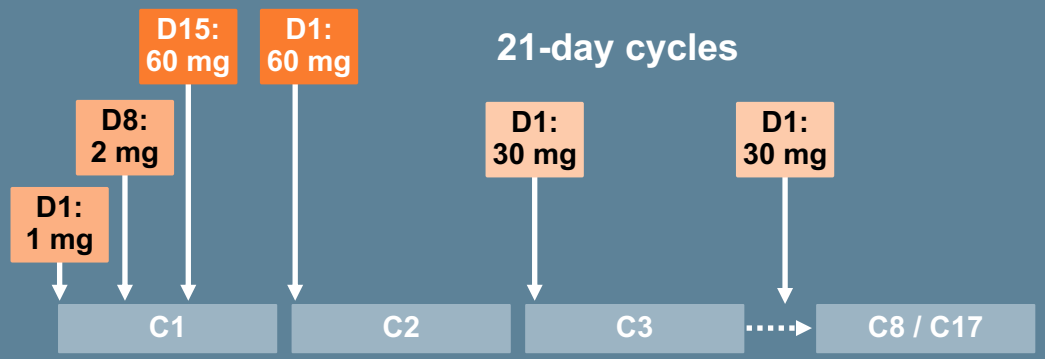
SINGLE-ARM PHASE 2 EXPANSION TRIAL OF MOSUNETUZUMAB MONOTHERAPY IN R/R FL AFTER ≥2 PRIOR THERAPIES

Key eligibility criteria:

- FL (Grade 1-3a)
- ECOG PS 0-1
- ≥2 prior regimens, incl:
  - ≥1 anti-CD20 Ab
  - ≥1 alkylating agent

Mosunetuzumab iv Q3W

C1 step-up dosing (CRS mitigation)
Fixed-duration treatment: 8 cycles if CR after C8 / 17 cycles if PR/SD after C8
No mandatory hospitalisation



Primary endpoint:

- CR (best response) rate by IRF[a] – assessed vs 14% historical control CR rate

Key secondary endpoints:

- ORR
- DoR
- PFS
- Safety and tolerability

[a] Assessed by CT and PET-CT using Cheson 2007 criteria

Ab, antibody; C, Cycle; CR, complete response; CRS, cytokine release syndrome; CT, computed tomography; D, Day; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; IRF, independent review facility; ORR, objective response rate; PET, positron emission tomography; PFS, progression-free survival; PR, partial response; Q3W, once every 3 weeks; R/R, relapsed or refractory; SD, stable disease

Budde EL, et al. ASH Annual Meeting 2021. Abstract #127. Oral presentation

RESULTS

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Baseline characteristics

- ~50% of the 90 patients included were double refractory to anti-CD20 and alkylator therapy
- ~50% were POD24

Efficacy

- The **primary endpoint was met**: the CR rate with mosunetuzumab was significantly greater than historical controls
  - **CR** rate: **60% vs 14%** in historical controls **(p<0.0001)**
- **ORR** rate: 80%
- Median **DoR**: 22.8 months (95% CI: 9.7, NE)
- Median **PFS**: 17.9 months (95% CI: 10.1, NE)

Safety

- 44% CRS (1.1% grade 3 and 1.1% grade 4); primarily occurring in Cycle 1. All events resolved
- 4.4% ICANS (all grade 1/2)

CI, confidence interval; CR, complete response; CRS, cytokine release syndrome; DoR, duration of response; NE, not estimable; ORR, objective response rate; PFS, progression-free survival; POD24, progression of disease within 2 years; ICANS, immune effector cell-associated neurotoxicity syndrome

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AUTHOR CONCLUSIONS AND CLINICAL INTERPRETATION

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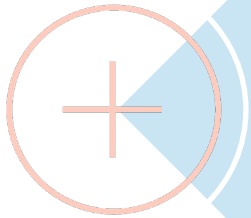
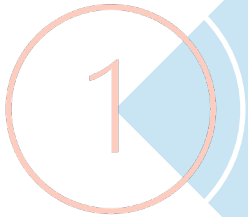
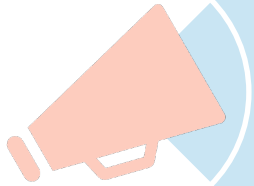


Fixed-duration mosunetuzumab monotherapy resulted in **deep and durable responses in heavily pre-treated/high-risk R/R FL**



Mosunetuzumab is the first T-cell-engaging bispecific antibody to demonstrate clinically meaningful phase 2 outcomes in R/R FL



Mosunetuzumab is a **potentially promising off-the-shelf, outpatient therapy**

FL, follicular lymphoma; R/R, relapsed or refractory

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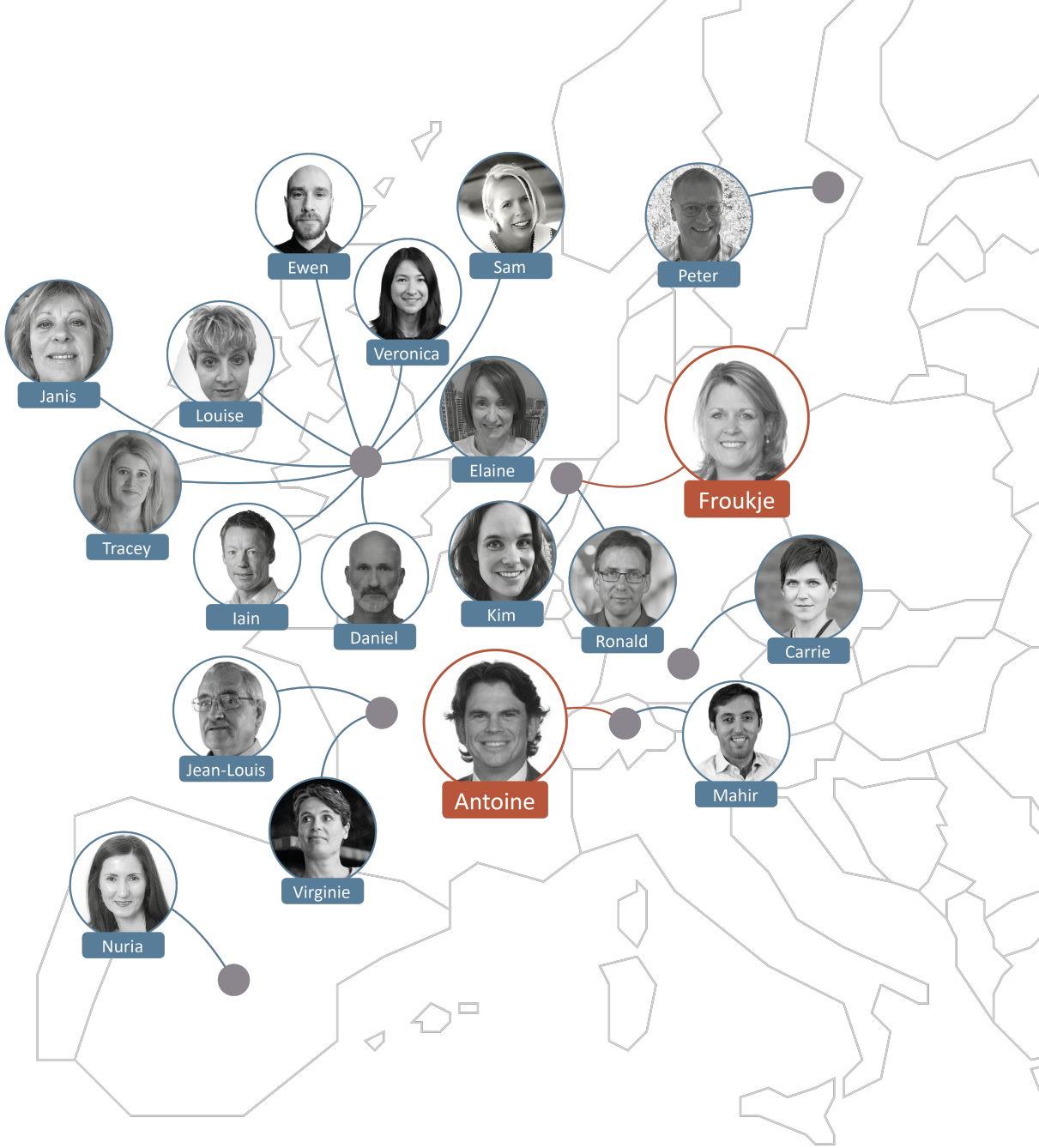

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