Cases from the Community: Investigators Discuss Available Research Guiding the Care of Patients with Non-Hodgkin Lymphoma

Saturday, May 31, 2025 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Faculty

Joshua Brody, MD Christopher Flowers, MD, MS Ann LaCasce, MD, MMSc Tycel Phillips, MD, FASCO

Moderator Jeremy S Abramson, MD, MMSc



Faculty



Joshua Brody, MD

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Moderator

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Dr Brody — Disclosures Faculty

No relevant conflicts of interest to disclose.



Dr Flowers — Disclosures Faculty

| Consulting Agreements | AbbVie Inc, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, Celgene Corporation, Denovo Biopharma, Genentech, a member of the Roche Group, Genmab US Inc, Gilead Sciences Inc, Karyopharm Therapeutics |
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Dr LaCasce — Disclosures Faculty

| Advisory Committees | Genmab US Inc, Kite, A Gilead Company |
|-----------------------|---------------------------------------|
| Consulting Agreements | Pierre Fabre |



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| Nonrelevant Financial Relationships | Leukemia & Lymphoma Society (LLS) Scholar in Clinical Research |



Dr Abramson — Disclosures Moderator

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| Nonrelevant Financial Relationships | Foresight Diagnostics |



Dr Love — Disclosures

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This educational activity contains discussion of non-FDA-approved uses of agents and regimens. Please refer to official prescribing information for each product for approved indications.



| | Immunotherapy and Antibody-Drug Conjugates in Lung Cancer 11:15 AM - 12:45 PM CT (12:15 PM - 1:45 PM ET) |
|--------------------|---|
| Friday May 30 | Colorectal Cancer 6:30 PM - 8:30 PM CT (7:30 PM - 9:30 PM ET) |
| | EGFR Mutation-Positive Non-Small Cell Lung Cancer 6:30 PM - 8:30 PM CT (7:30 PM - 9:30 PM ET) |
| | Urothelial Bladder Cancer 6:45 AM - 7:45 AM CT (7:45 AM - 8:45 AM ET) |
| Saturday May 31 | Non-Hodgkin Lymphoma 7:00 PM - 9:00 PM CT (8:00 PM - 10:00 PM ET) |
| | Prostate Cancer 7:00 PM - 9:00 PM CT (8:00 PM - 10:00 PM ET) |
| | Chronic Lymphocytic Leukemia (Webinar) 7:00 AM - 8:00 AM CT (8:00 AM - 9:00 AM ET) |
| Sunday June 1 | HER2-Positive Gastrointestinal Cancers 7:00 PM - 8:30 PM CT (8:00 PM - 9:30 PM ET) |
| | Ovarian and Endometrial Cancer 7:00 PM - 9:00 PM CT (8:00 PM - 10:00 PM ET) |
| | Renal Cell Carcinoma (Webinar) 7:00 AM - 8:00 AM CT (8:00 AM - 9:00 AM ET) |
| Monday June 2 | Multiple Myeloma (Webinar) 6:00 PM - 7:00 PM CT (7:00 PM - 8:00 PM ET) |
| | Metastatic Breast Cancer 7:00 PM - 9:00 PM CT (8:00 PM - 10:00 PM ET) |
| Tuesday June 3 | Soft Tissue Sarcoma and Other Connective Tissue Neoplasms (Webinar) 7:00 AM - 8:00 AM CT (8:00 AM - 9:00 AM ET) |



Clinicians in the Meeting Room

Networked iPads are available.



Review Program Slides: Tap the Program Slides button to review speaker presentations and other program content.



Answer Survey Questions: Complete the pre- and postmeeting surveys.



Ask a Question: Tap Ask a Question to submit a challenging case or question for discussion. We will aim to address as many questions as possible during the program.



Clinicians Attending via Zoom



Review Program Slides: A link to the program slides will be posted in the chat room at the start of the program.



Answer Survey Questions: Complete the pre- and postmeeting surveys.



Ask a Question: Submit a challenging case or question for discussion using the Zoom chat room.



Get CME Credit: A CME credit link will be provided in the chat room at the conclusion of the program.



About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based program.
 An email will be sent to all attendees when the activity is available.



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Moderator Jeremy S Abramson, MD, MMSc



Contributing General Medical Oncologists



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Agenda

MODULE 1: Selection and Sequencing of Available Therapies for Diffuse Large B-Cell Lymphoma — Dr Flowers

MODULE 2: Evolving Management Paradigm for Mantle Cell Lymphoma — Dr Phillips

MODULE 3: Integration of Novel Therapies into the Management of Follicular Lymphoma — Dr LaCasce

MODULE 4: Integrating Bispecific Antibodies into the Management of NHL — Dr Brody

MODULE 5: Current Role of CAR T-Cell Therapy in Various Non-Hodgkin Lymphoma (NHL) Subtypes — Dr Abramson



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Advances in Treatment of
Diffuse Large B-Cell LymphomaDiffuse Large B-Cell LymphomaChristopher Flowers, MD, MS, FASCODivision Head
Chair, ProfessorDivision of Cancer Medicine
Department of Lymphoma/Myeloma

THE UNIVERSITY OF TEXAS MDAnderson Cancer Center

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Tilly et al. NEJM 2022

Primary endpoint: Progression-free survival *Pola-R-CHP significantly improved PFS vs R-CHOP*



HR 0.73 (P=0.02) 95% CI: 0.57, 0.95

- Pola-R-CHP demonstrated a 27% reduction in the relative risk of disease progression, relapse, or death vs R-CHOP
- 24-month PFS:

76.7% with Pola-R-CHP vs 70.2% with R-CHOP (Δ =6.5%)

Five-year analysis of the POLARIX study

<u>Gilles Salles</u>, Franck Morschhauser, Laurie H. Sehn, Alex F. Herrera, Jonathan W. Friedberg, Marek Trněný, Georg Lenz, Jeff P. Sharman, Charles Herbaux, John M. Burke, Matthew Matasar, Graham P. Collins, Yuqin Song, Antonio Pinto, Shinya Rai, Koji Izutsu, Calvin Lee, Saibah Chohan, Matthew Sugidono, Yanwen Jiang, Connie Lee Batlevi, Mark Yan, Jamie Hirata, Hervé Tilly, Christopher R. Flowers



At the 5-year follow up, Pola-R-CHP had a **sustained and significant PFS benefit**, confirming results from the primary analysis of PFS at 2 years of follow up (HR 0.73).¹

MD Anderson Department of Lymphoma/Myeloma

Presented at the 66th ASH Annual Meeting | December 7–10, 2024

Safety summary

Safety profiles were similar with Pola-R-CHP and R-CHOP



ITT population. Data cut-off: June 28, 2021; median 28.2 months' follow-up. CI, confidence interval; HR, hazard ratio; NE, not evaluable; PFS, progression-free survival.

Polatuzumab Vedotin Efficacy in DLBCL Subtypes by COO



| | | Pola (N | I=440) | R- (N | -CHOP I=439) | | | | |
|--|-------------------------|-------------------------|------------------------------|-------------------------|------------------------------|--------------------------|--|----------------------|------------------|
| Baseline Risk Factors | Total N | n | 2-year Rate | n | 2-year Rate | Hazard Ratio | 95% Wald Cl | Pola-R-CHP Better | R-CHOP Better |
| Age group ≤60 >60 | 271 608 | 140 300 | 74·1 77·9 | 131 308 | 71∙9 69∙5 | 0·9 0·7 | (0·6 to 1·5) (0·5 to 0·9) | | |
| Sex Male Female | 473 406 | 239 201 | 75·9 77·7 | 234 205 | 65·9 75·2 | 0·7 0·9 | (0·5 to 0·9) (0·6 to 1·4) | | |
| ECOG PS 0-1 2 | 737 141 | 374 66 | 78·4 67·2 | 363 75 | 71·2 65·0 | 0·8 0·8 | (0·6 to 1·0) (0·5 to 1·4) | , | |
| IPI score IPI 2 IPI 3–5 | 334 545 | 167 273 | 79∙3 75∙2 | 167 272 | 78·5 65·1 | 1∙0 0∙7 | (0·6 to 1·6) (0·5 to 0·9) | | |
| Bulky disease Absent Present | 494 385 | 247 193 | 82·7 69·0 | 247 192 | 70·7 69·7 | 0·6 1·0 | (0·4 to 0·8) (0·7 to 1·5) | ⊧ 8 4 | |
| Geographic region Western Europe, United States, Canada, and Australia | 603 | 302 | 78.6 | 301 | 72.0 | 0.8 | (0·6 to 1·1) | - | 4 |
| Asia Rest of world | 160 116 | 81 57 | 74.3 70.8 | 79 59 | 65.6 67.3 | 0.6 0.9 | (0·4 to 1·5) (0·6 to 1·5) | | |
| Ann Arbor stage I–II III IV | 99 232 548 | 47 124 269 | 89·1 80·7 72·6 | 52 108 279 | 85∙5 73∙6 66∙1 | 0·6 0·8 0·8 | (0·2 to 1·8) (0·5 to 1·3) (0·6 to 1·1) | | |
| Baseline LDH ≤ULN >ULN | 300 575 | 146 291 | 78·9 75·4 | 154 284 | 75∙6 67∙2 | 0·8 0·7 | (0·5 to 1·3) (0·5 to 1·0) | | |
| No. of extranodal sites 0–1 ≥2 | 453 426 | 227 213 | 80·2 73·0 | 226 213 | 74·5 65·8 | 0·8 0·7 | (0·5 to 1·1) (0·5 to 1·0) | | 4 |
| Cell-of-origin GCB ABC Unclassified Unknown | 352 221 95 211 | 184 102 44 110 | 75·1 83·9 73·0 73·8 | 168 119 51 101 | 76·9 58·8 86·2 64·3 | 1·0 0·4 1·9 0·7 | (0·7 to 1·5) (0·2 to 0·6) (0·8 to 4·5) (0·4 to 1·2) | | |
| Double expressor by IHC DEL Non DEL Unknown | 290 438 151 | 139 223 78 | 75·5 77·7 76·0 | 151 215 73 | 63·1 75·7 69·8 | 0·6 0·9 0·8 | (0·4 to 1·0) (0·6 to 1·3) (0·4 to 1·5) | | |
| Double- or triple-hit lymphoma Yes No Unknown | 45 620 214 | 26 305 109 | 69·0 76·8 78·5 | 19 315 105 | 88·9 70·3 66·4 | 3·8 0·7 0·6 | (0·8 to 17·6) (0·5 to 1·0) (0·4 to 1·1) | | |
| | | | | | | | (| r ⊡25 | 1 5 |

Palmer et al. NEJM 2023

Tilly et al. NEJM 2022

CAR T-cell vs. SOC in 2L for LBCL: EFS

ZUMA 7 / Axi-cel

TRANSFORM / Liso-cel





HHR 00 3375 Median f/u 373.9 mo

| | 3 year EFS estimates: | |
|--------------|-----------------------|--------------|
| Zuma 7: | | Transform: |
| Axi-cel: 41% | | Liso-cel 45% |
| SOC: 19% | | SOC: 19% |

Westin J et al, NEJM 2023 Kamdar et al, ASCO 2024, Abramson et al. Blood 2023

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Lymphoma Microenvironment Archetype Profiles (LymphoMAPs) FMAC enriched



FMAC enriched for CAFs and TAMs

LN enriched for supportive LN stroma (FRC/FDC) and healthy T-cells

TEX enriched for effector & exhausted T-cells and super-activated macrophages

Li et al, ASH 2024

Projection of LymphoMAPs onto ZUMA7





Phase 3 clinical trial comparing axi-cel to SOC in 2L rrLBCL

 Defines strategy for future CAR T development

| Subgroup | Axi-cel | Standard ca | re | HR (95% CI) |
|-----------------------|---------|-------------|---|------------------|
| All Patients | 134 | 122 | ⊢ • ¦ | 0.4 (0.3 to 0.5) |
| LymphoMAP | | | 1 | |
| FMAC | 51 | 47 | ⊢ •• । | 0.4 (0.2 to 0.6) |
| LN | 49 | 42 | ⊢ • ! | 0.2 (0.1 to 0.3) |
| TEX | 31 | 32 | ·● | 0.6 (0.4 to 1.2) |
| DLBCL histology | | | i | |
| DLBCL and other | 104 | 104 | ⊢ ● | 0.4 (0.3 to 0.5) |
| HGBCL | 30 | 18 | ·• | 0.4 (0.2 to 0.8) |
| Cell-of-origin subtyp | e | | i | |
| GCB | 99 | 96 | ⊢ •−• 1 | 0.4 (0.3 to 0.6) |
| ABC | 13 | 9 | • • · · · · · | 0.2 (0.1 to 0.7) |
| Unclassified | 16 | 12 | • · · · · · · · · · · · · · · · · · · · | 0.1 (0.1 to 0.4) |
| Tumor burden (SPD) | | | i | |
| < Median | 62 | 52 | ⊢_● ↓ ↓ | 0.3 (0.2 to 0.5) |
| > Median | 59 | 55 | ⊢ •−- | 0.3 (0.2 to 0.5) |
| | | | 0.1 0.3 1.0 | |
| | | | Axi-cel better SOC I | better |

Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma J Clin Oncol. 2020

Laurie H Sehn, Alex F Herrera, Christopher R Flowers, Manali Kamdar, Andrew McMillan, Mark Hertzberg, Sarit Assouline, Tae Min Kim, Won Seog Kim, Muhit Ozcan, Jamie Hirata, Elicia Penuel, Elicia Penuel, Ji Cheng, Joseph N. Paulson, Grace Ku, Matthew Matasar





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Pola-BR PFS and OS



- The significant survival benefit with Pola+BR persists with longer follow-up
- Response rates in the extension cohort consistent with the randomized Pola+BR arm
- The 2-year PFS 28.4% and the 2-year OS 38.2% for patients in the randomized Pola+BR cohort

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Sehn LH et al. Blood Adv. 2022.

Pola BR Safety Summary

| | Rando | omized | Extension | |
|----------------------|--------------|-------------------|------------------------------|------------------------------|
| AE summary, n (%) | BR (N=39) | Pola+BR (N=39) | Cohort Pola+BR (N=106) | Pooled Pola+BR (N=151) |
| Any Grade AEs | 38 (97.4) | 39 (100) | 105 (99.1) | 150 (99.3) |
| Grade 3–4 AEs | 28 (71.8) | 34 (87.2) | 83 (78.3) | 122 (80.8) |
| SAEs | 24 (61.5) | 26 (66.7) | 56 (52.8) | 86 (57.0) |
| Grade 5 AEs | 10 (25.6) | 11 (28.2) | 6 (5.7) | 17 (11.3) |

No new safety signals identified with longer follow-up in randomized arms + patients in the extension cohort

| | Pooled Pola+BR (N=151) | | |
|-----------------------------|------------------------|-----------|--|
| Common AEs, n (%) | Any grade | Grade 3–4 | |
| Hematological AEs | | | |
| Neutropenia | 56 (37.1) | 49 (32.5) | |
| Thrombocytopenia | 49 (32.5) | 31 (20.5) | |
| Anemia | 49 (32.5) | 19 (12.6) | |
| Non-hematological AEs | | | |
| Infections and infestations | 74 (49.0) | 33 (21.9) | |
| Diarrhea | 54 (35.8) | 6 (4.0) | |
| Nausea | 50 (33.1) | 1 (0.7) | |
| Pyrexia | 44 (29.1) | 2 (1.3) | |
| Fatigue | 40 (26.5) | 3 (2.0) | |
| Decreased appetite | 39 (25.8) | 4 (2.6) | |
| AEs of special interest | | | |
| Peripheral neuropathy | 47 (31.1) | 3 (2.0) | |

Selected Therapies Approved in R/R DLBCL

| | Pola-BR | Selinexor | Tafasitamab/Lenalidomide | Loncastuximab Tesirine |
|---------|----------------|-----------------|----------------------------------|---------------------------|
| MOA | Anti-CD79b ADC | XPO-1 inhibitor | Anti-CD19 mAb/Immunomodulator | Anti-CD19 ADC |
| ORR | 45% | 28% | 58% | 48% |
| CR rate | 40% | 12% | 40% | 24% |
| PFS | 9.2 m | 2.6 m | 11.6 m | 4.9 m |
| DOR | 12.6 m | 9.3 m | 43.9 m | 10.3 m |
| OS | 12.4 m | 9.1 m | 33.5 m | 9.9 m |

Novel salvage regimens may improve outcomes with ASCT

Sehn LH et al. *Blood Adv*. 2022;6(2):533-543. Kalakonda N et al. *Lancet Haematol*. 2020;7(7):e511-e522. Duell J et al. *Haematologica*. 2021;106(9):2417-2426. Caimi PF et al. *Lancet Oncol*. 2021;22(6):790-800.

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Tafasitamab + Lenalidomide: 5-year Outcomes

| Final 5-year data | N = 80 (%) |
|-------------------------|------------|
| Objective Response Rate | 46 (57.5) |
| Complete Response | 33 (41.3) |
| Partial Response | 13 (16.3) |



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Duell J et al. Haematologica. 2024

Tafasitamab + Lenalidomide: 5-year Safety Summary



| | All grades, N (%) | Grade ≥3, N (%) |
|---|--|---|
| Any TEAE | 74 (91.4) | 52 (64.2) |
| Hematologic Neutropenia Anemia Thrombocytopenia Febrile neutropenia Leukopenia | 40 (49.4) 30 (37.0) 23 (28.4) 10 (12.3) 10 (12.3) | 39 (48.1) 6 (7.4) 13 (16.0) 10 (12.3) 8 (9.9) |
| Non-hematologic Asthenia Peripheral edema Pyrexia Fatigue Diarrhea Constipation Nausea Vomiting Bronchitis Urinary tract infection Pneumonia Respiratory tract infection Decreased appetite Hypokalemia Cough Dyspnea Back pain Muscle spasms C-reactive protein increased | $\begin{array}{c} 21 \ (25.9) \\ 20 \ (24.7) \\ 19 \ (23.5) \\ 14 \ (17.3) \\ 30 \ (37.0) \\ 15 \ (18.5) \\ 12 \ (14.8) \\ 12 \ (14.8) \\ 13 \ (16.0) \\ 11 \ (13.6) \\ 10 \ (12.3) \\ 9 \ (11.1) \\ 18 \ (22.2) \\ 15 \ (18.5) \\ 24 \ (29.6) \\ 11 \ (13.6) \\ 16 \ (19.8) \\ 12 \ (14.8) \\ 9 \ (11.1) \end{array}$ | $\begin{array}{c} 2 \ (2.5) \\ 0 \\ 1 \ (1.2) \\ 2 \ (2.5) \\ 1 \ (1.2) \\ 0 \\ 0 \\ 0 \\ 1 \ (1.2) \\ 2 \ (2.4) \\ 8 \ (9.9) \\ 0 \\ 0 \\ 5 \ (6.2) \\ 1 \ (1.2) \\ 2 \ (2.5) \\ 3 \ (3.7) \\ 0 \\ 0 \\ 0 \end{array}$ |

TEAE: treatment-emergent adverse event.

Duell J et al. *Haematologica*. 2024

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Loncastuximab Tesirine: LOTIS-2 Trial Single Arm Open Label Phase 2 Study in DLBCL



Lonca, loncastuximab tesirine; ORR, overall response rate; Q3W, every 3 weeks; Q12W, every 12 weeks; R/R, relapsed/refractory.

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Caimi PF et al. Lancet Oncol. 2021

Loncastuximab Tesirine: Results



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Loncastuximab Tesirine: Adverse Events

| Adverse Event (AE) | Patients n (%) | | |
|--------------------------------|----------------|--|--|
| Any Treatment Emergent AE | 143 (98.6) | | |
| GGT increased | 61 (42.1) | | |
| Neutropenia | 58 (40.0) | | |
| Thrombocytopenia | 48 (33.1) | | |
| Fatigue | 40 (27.6) | | |
| Anemia | 38 (26.2) | | |
| Nausea | 34 (23.4) | | |
| Cough | 33 (22.8) | | |
| Alkaline phosphatase increased | 29 (20.0) | | |
| Peripheral Edema | 29 (20.0) | | |

GGT, gamma glutamyltransferase ; SAEs, serious adverse events; TEAE, treatment-emergent adverse event..

TEAE leading to treatment discontinuation: 24.8%

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Caimi PF et al. Haematologica. 2024.

ECHELON-3: Study Design

- Multicenter, double-blind, placebo-controlled, randomized phase 3 trial
- Primary endpoint: OS in ITT population



Stratification:

- CD30 status (≥1% vs <1%)
- Cell of origin (GCB vs non-GCB)
- Prior CAR T-cell therapy (yes vs no)
- Prior SCT (yes vs no)

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ECHELON-3: Outcomes



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Bartlett et al. J Clin Oncol 2025

ECHELON-3: AEs

| | BV + Len + R (n = 112), No. (%) | | Placebo + Len + R (n = 116), No. (%) | |
|----------------------------------|---------------------------------|----------|--------------------------------------|----------|
| AE | Any Grade | Grade ≥3 | Any Grade | Grade ≥3 |
| Any AE | 109 (97) | 99 (88) | 113 (97) | 89 (77) |
| Neutropenia | 52 (46) | 48 (43) | 37 (32) | 32 (28) |
| Thrombocytopenia | 36 (32) | 28 (25) | 25 (22) | 22 (19) |
| Diarrhea | 35 (31) | 5 (4) | 27 (23) | 2 (2) |
| Anemia | 32 (29) | 25 (22) | 31 (27) | 24 (21) |
| Fatigue | 27 (24) | 7 (6) | 20 (17) | 3 (3) |
| COVID-19 | 26 (23) | 8 (7) | 18 (16) | 6 (5) |
| Asthenia | 24 (21) | 4 (4) | 14 (12) | 3 (3) |
| Peripheral sensory neuropathy | 22 (20) | 5 (4) | 9 (8) | 0 |
| Pneumonia | 19 (17) | 12 (11) | 8 (7) | 6 (5) |
| Constipation | 19 (17) | 2 (2) | 21 (18) | 0 |
| Decreased appetite | 19 (17) | 1 (1) | 11 (9) | 0 |
| Nausea | 17 (15) | 1 (1) | 19 (16) | 1 (1) |
| Pyrexia | 17 (15) | 2 (2) | 17 (15) | 1 (1) |
| Hypokalemia | 15 (13) | 6 (5) | 9 (8) | 3 (3) |
| Febrile neutropenia | 10 (9) | 10 (9) | 11 (9) | 11 (9) |
| Neutropenia | 9 (8) | 9 (8) | 7 (6) | 7 (6) |
| COVID-19 pneumonia | 8 (7) | 8 (7) | 4 (3) | 4 (3) |

MD Anderson Department of Lymphoma/Myeloma

Bartlett et al. J Clin Oncol 2025

BTK Inhibitors Under Investigation for DLBCL





Phase III ESCALADE Study Design and Treatment Schedule



Patients eligible for randomization will be stratified by the following factors:

- R-IPI score (2 [good prognosis] vs 3–5 [poor prognosis])
- Geographic region (Asia vs United States/Canada/Western Europe/Oceania vs rest of world)

*Acalabrutinib 100 mg PO BID (C2 to C8); *R-CHOP (C2 to C6) then rituximab (C7 to C8); *Placebo PO BID (C2 to C8).



All treatment cycles are 21 days. All patients will receive primary prophylaxis with granulocyte colony-stimulating factors accompanying all R-CHOP cycles. #Baseline assessment will be obtained at screening *Assessments (PET-OT scans and dedicated OT scans with contrast) obtained up to 50 days before randomization (but within 30 days of cycle 1) and EOT, with a whole-body FDG PET-CT obtained mid-treatment (after cycle 4); 4n the follow-up period (beginning 4 months after the EOT response assessment), dagnostic CT scans (without PET scans) will be obtained overy 4 months through year 3 of follow-up (e, 3) years from EOT wist), then every 6 months through year 5 of follow-up (e, 5) years from EOT visit).



Sehn LH et al. ASCO 2021; Abstract TPS7572

Case Presentation: 51-year-old man with newly diagnosed GCB-type DLBCL (Stage IV) receives polatuzumab vedotin-R-CHP



Dr Victoria Giffi (Hagerstown, Maryland)



QUESTIONS FOR THE FACULTY

For which patients with newly diagnosed DLBCL are you prioritizing the use of polatuzumab vedotin/R-CHP?

Do you actively assess cell of origin for all of your patients with newly diagnosed DLBCL? Do you use cell of origin as a basis for selecting patients for treatment with polatuzumab vedotin/R-CHP? In your opinion, is the Hans algorithm that is used for molecular classification of DLBCL accurate enough to justify this practice?

Have you observed renal insufficiency in patients who have received polatuzumab vedotin/R-CHP as initial therapy? Are there any strategies to prevent its development?



QUESTIONS FOR THE FACULTY

What is your approach to the use of CNS prophylaxis for patients with DLBCL?

What other novel first-line strategies for DLBCL seem promising to you? In your opinion, is there a firm biologic rationale for the evaluation of BTK inhibitors as a component of first-line therapy for DLBCL, particularly for patients with non-GCB disease? When can we anticipate seeing results from the ESCALADE study, and do you have any predictions as to what they will show?



Case Presentation: 83-year-old woman with cardiac comorbidities and recurrent non-GCB DLBCL receives tafasitamab/lenalidomide



Dr Shachar Peles (Lake Worth, Florida)



QUESTIONS FOR THE FACULTY

How do you approach sequencing of polatuzumab vedotin/BR, tafasitamab/lenalidomide and loncastuximab tesirine relative to each other and to CAR T-cell therapy and bispecific antibodies in patients with R/R DLBCL? What factors do you consider when selecting among these regimens?

What has been your experience in terms of duration of response with tafasitamab/lenalidomide? How typical is this patient's experience? Are there any types of patients who might benefit more or less from treatment with tafasitamab/lenalidomide?



QUESTIONS FOR THE FACULTY

How do you approach patients who are having difficulty tolerating the lenalidomide component of tafasitamab/lenalidomide? Would you consider discontinuing therapy completely for this patient at some point, given her ongoing complete remission?



Case Presentation: 87-year-old woman with multiregimenrelapsed/refractory DLBCL receives loncastuximab tesirine with near CR but experiences fatigue and cutaneous toxicities



Dr Spencer Bachow (Boca Raton, Florida)



QUESTIONS FOR THE FACULTY

For which patients with R/R DLBCL would you prioritize the use of loncastuximab tesirine? Have you observed deep and durable responses with this agent in your own patients?

What are the most concerning tolerability issues you have encountered with loncastuximab tesirine? Have you encountered cutaneous toxicities as in this patient's case? Are there any prophylactic measures that can be taken to reduce the incidence of skin-related adverse events?

Would you consider discontinuing therapy with loncastuximab tesirine in patients who achieve a complete remission?



QUESTIONS FOR THE FACULTY

Do you believe it is reasonable to try multiple CD19-directed approaches for the same patient? Is there a minimum time you would wait after disease progression on one of these strategies before rechallenging with another CD19-targeted approach? Would you asses CD19 expression before doing so?



Agenda

MODULE 1: Selection and Sequencing of Available Therapies for Diffuse Large B-Cell Lymphoma — Dr Flowers

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MODULE 3: Integration of Novel Therapies into the Management of Follicular Lymphoma — Dr LaCasce

MODULE 4: Integrating Bispecific Antibodies into the Management of NHL — Dr Brody

MODULE 5: Current Role of CAR T-Cell Therapy in Various Non-Hodgkin Lymphoma (NHL) Subtypes — Dr Abramson





Evolving Landscape of Mantle Cell Lymphoma

Tycel Phillips, MD Associate Professor City of Hope

Outline

- Historical Treatment
- cBTKi in 1L MCL



Time to treatment amongst patients assigned to W&W

- 141 of 222 (64%) proceeded to treatment
- Only 13 (6%) received treatment within 6 months of diagnosis
- 49 (22%) remain under observation
- 32 (14%) did not proceed to treatment prior to death
- 116 (52%) were observed for over 2 years

Observation is Okay if patient asymptomatic...





Young/Fit.....Then



Age of Transplant



TRIANGLE Phase 3 Study of Ibrutinib + SOC as a Substitute for ASCT in Younger Patients With MCL: Study Design and Patients

Key Eligibility Criteria

- Previously untreated stage II-IV MCL
- Age <66 years
- Suitable for HA and ASCT
- ECOG PS 0-2



Primary endpoint: FFS Secondary endpoints: Response rates, PFS, RD, OS, safety

^a2 patients aged 66 & 68 years were randomized. ^b1 CLL, 1 FL. ^c1 NHL NOS, 1 HD, 2 MZL. ^d1 HCL, 1 DLBCL. Dreyling M, et al. ASH 2022. Abstract 1.

R maintenance (± I) was added in all 3 trial arms, following national guidelines. It was initiated in 168 (58%) patients in Arm A; 165 (57%) patients in Arm A+I; and 158 (54%) patients in Arm I



Failure Free Survival



-4-year FFS A+I: 82% 4-year FFS A: 70%

- p-value (overrunning, one-sided): p=0.0026
- •HR (A+I vs. A): HR=0.64





288 255 245 235 219 211 200 187 158 121 74 57 32 20 4 1 0

290 273 263 250 246 237 228 213 167 129 89 67 31 20 7 2 0



LMU KLINIKUM



Is Transplant needed when using a BTKi in 1L?





Dreyling M et al. Lancet 2024;403(10441):2293-2306.

Survival



| А | 288 270 260 255 243 238 233 222 | 186 145 92 | 73 | 41 23 | 5 | 1 |
|-----|---------------------------------|-------------|----|-------|---|---|
| A+I | 292 281 267 262 257 253 248 235 | 201 160 107 | 83 | 39 26 | 8 | 2 |
| Ĩ | 290 282 273 266 264 259 253 243 | 194 147 101 | 78 | 41 21 | 7 | 2 |

4-year OS:

- A: 81%
- (MCL Younger exp.: 80%)
- A+I: 88%
- I: 90%
- two-sided test, (α = 5%):
- A vs. I: p=0.0019, HR: 0.565
- A vs. A+I: p=0.0036, HR I: 0.587
- A+I vs. I: ongoing



Dreyling M et al. Lancet 2024;403(10441):2293-2306.

End of an ERA





Young/Fit.....Now



Older/Unfit.....Then





SHINE

SHINE: A Randomized, Double-Blind, Phase III Study



Induction: Bendamustine 90 mg/m2 Days 1 and 2, Rituximab 375 mg/m2 Day 1, Q4W. A cycle is defined as 28 days.

CR, complete response; ITT, intent-to-treat; MIPI, Mantle Cell Lymphoma International Prognostic Index; PD, progressive disease; PFS, progression-free survival; PR, partial response.



SHINE OS = Diminished SHINE....



| Cause of death | lbrutinib + BR (N = 261) | Placebo + BR (N = 262) |
|---|-----------------------------|---------------------------|
| Death due to PD and TEAE | 58 (22.2%) | 70 (26.7%) |
| Death due to PD | 30 (11.5%) | 54 (20.6%) |
| Death due to TEAEs* | 28 (10.7%) | 16 (6.1%) |
| Death during post- treatment follow-up excluding PD and TEAEs | 46 (17.6%) | 37 (14.1%) |
| Total deaths | 104 (39.8%) | 107 (40.8%) |

• Death due to Covid-19: 3 patients in the ibrutinib arm during the TEAE period and 2 patients in the placebo arm after the TEAE period

 Exploratory analysis of cause-specific survival including only deaths due to PD or TEAEs showed an HR of 0.88

*The most common grade 5 TEAE was infections in the ibrutinib and placebo arms: 9 versus 5 patients. Grade 5 TEAE of cardiac disorders occurred in 3 versus 5 patients, respectively. Cl, confidence interval; HR, hazard ratio; NR, not reached; PD, progressive disease; TEAE, treatment-emergent adverse event.











Lewis et al. ASH 2024

the MIRACLE of SCIENCE with SOUL M Cityof Hope



Progression-free survival

survival probability

Progression





Number at risk (number censored)



5-year PFS (95% CI) IR: 52.4% (40.0% to 68.6%) R-CHOP: 19.2% (10.6% to 35.1%)



ENRICH

Number at risk (number censored)



5-year PFS (95% CI) IR: 50.8% (42.8% to 60.4%) BR: 47.4% (39.5% to 56.9%)



Overall survival



ENRICH



IR: 59.4% (46.9% to 75.3%) R-CHOP: 46.3% (33.5% to 63.8%)

Acalabrutinib plus bendamustine and rituximab in untreated mantle cell lymphoma (MCL): Results from the phase 3, double-blind, placebo-controlled ECHO trial





Response

Best Overall Response and Complete Response Rates

An additional 13% of patients achieved CR with acalabrutinib + BR





> WANG et al. EHA 2024

PFS (primary endpoint) Was Significantly Improved With Acalabrutinib + BR



PBR, placebo + bendamustine + rituximab; PD, progressive disease; PFS, progression-free survival.

WANG et al. EHA 2024






WANG et al. EHA 2024



Older/Unfit.....Now





What to make of this

- Easy Answer
 - R-CHOP is a bad 1L regimen for most patients....has been demonstrated in several trials to be inferior to most regimens and needs a lot (ASCT or indefinite maintenance) to have equivalent efficacy to BR and in this case BTKi + R
- Harder Answer
 - Is 1L BTKi the right approach in older patients?
 - ECHO w/ improved PFS vs. BR while ENRICH was equivalent
 - Positive: not chemotherapy, better in p53 mutated patients
 - Negative: indefinite therapy vs. finite, likely not better than sequential therapy in non-p53 mutated patients (again indefinite vs finite).
 - Likely need a better but fixed non-chemo based regimen



Novel Combinations



Phase II Multicenter Study of BOVen

Key Eligibility Criteria:

- Previously untreated MCL (except localized RT prior)
- *TP₅₃* mutation (any variant allele frequency allowed)
- ECOG PS ≤2
- ANC >1, PLT >75, HGB ≥9 (unless if due to MCL)

Kumar et al. Blood 2023

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9** | 10** | 11* |
|-----------------------------------|---------------------------|-----------------------|------------------------------|-----------------------------------|-----------------------|---------------------|---|---|--|-------------------------|----------------|
| Zanubrutinib | | | | | | | | | | | |
| Obinutuzuma | ab 🎁 | | 1 | 1 | 1 | 1 | 1 | 1 | | | |
| Venetoclax | | | | | | | | | | | |
| MRD PBL Imaging | 1 T | | 1 T | | | | Ť | | | | 1 ît |
| Dosing: | | | | | | | | | | | |
| Zanubrutinib 1 Until EOT or in | .60 mg ora itolerance | al twice da ** | oily Obinu Cycle Cycle | ituzumal 1: day 1, 2-8: day | 8, 15 1000 mg 1 | g IVPB | Venetoci 5-week ra 100mg; 2 Until EO | ax 400mg amp-up: 1 oomg; 40 F or intole | g oral dail week eac o mg oral rance** | y h of 20mg daily |); 50mg; |
| Total # of cyc | les: 24 (2 | 2 years) | | | | | | | | | |
| After 24 cycle MRD pos | s, if CR a sitive, the | and MRI en contin | D undete ue zanu | ectable (brutinib | uMRD), and vene | then no etoclax. | further tx | . If <cr< td=""><td>and/or</td><td></td><td></td></cr<> | and/or | | |
| Pts with CR/u zanubruti | MRD wil | ll be moi venetocl | nitored fo ax. | or MRD | positivity | or recu | irrence ar | nd can re | start | | |

Aim to enroll 25 pts, if 11 or more alive and progression free at the end of the 2nd year, BOVen will be declared effective in this high-risk population.



Response timing and duration



Median follow up:23.3 months



- There were 9 events:
 - 5 progressions
 - 4 deaths
 - 2 COVID-related
 - 1 unknown
 - 1 PNA / respiratory failure
- The 4 deaths occurred in patients in ongoing response at time of death

Progression-Free and Overall Survival Outcomes



Primary PFS Endpoint is Met: 11 patients progression-free at 2 years

Acalabrutinib Venetoclax and Rituximab



PD, progressive disease; PET, positron emission tomography; PFS, progression-free survival; PR, partial response; pt, patient; sMIPI, simplified MCL International Prognostic Index; TN, treatment-naive; TTIR, time to initial resp

Conclusions

100% of pts responded to AVR; 90% achieved CR by PET/CT and 71% by Lugano



Treatment with AVR resulted in a high rate of complete molecular responses





Treatment and Outcome Summary

- Observation acceptable for most patients at diagnosis
- Several treatment options available for younger patients but intensive regimen followed by autologous stem cell transplant is practically dead at this time.....(Blastoid??)
 - TRIANGLE, ECHO (lite) preferred by most
- BR most utilized regimen for older patients deemed not ideal for intensive therapy but will this change w/ ECHO.....better question should it change??



Case Presentation: 80-year-old very symptomatic woman with newly diagnosed widespread MCL receives inpatient treatment with R-mini-CHOP



Dr Syed Zafar (Fort Myers, Florida)



QUESTIONS FOR THE FACULTY

Would you consider a BTK inhibitor-based regimen for this patient? Do you have a preference for a particular BTK inhibitor for your older patients with newly diagnosed MCL, and if so, which one? What would you partner it with? Given its recently FDA approval, are you preferentially using acalabrutinib/BR for your older patients?

Would you consider a BTK inhibitor in combination with venetoclax and obinutuzumab as initial therapy for a patient with MCL outside of a clinical trial? How are these triplet regimens tolerated?



QUESTIONS FOR THE FACULTY

What is your usual front-line treatment for younger patients with MCL with and without TP53 mutations? Are you generally prioritizing BTK inhibitor-containing regimens for your younger patients, and if so, which ones?

Is there still a role for transplant for younger patients with newly diagnosed MCL? If so, in what situations do you use it?



Case Presentation: 83-year-old man with R/R MCL and complicating psychosocial issues initiates treatment with acalabrutinib



Dr Neil Morganstein (Summit, New Jersey)



QUESTIONS FOR THE FACULTY

For a patient with R/R MCL to whom you're going to administer a covalent BTK inhibitor, how do you choose between acalabrutinib and zanubrutinib?

How, if at all, does your preference for a BTK inhibitor in the relapsed setting change based on age and comorbidities? How do the individual side-effect profiles weigh into this decision?

Do you still use ibrutinib for your patients with MCL under any circumstances? Is the risk of sudden cardiac death with ibrutinib real? Does this occur with other BTK inhibitors?



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Integration of Novel Therapies into the Management of Follicular Lymphoma

Ann S. LaCasce, MD, MMSc

May 31, 2025



Rationale for the combination of tafasitamab and lenalidomide in B-cell lymphoma



Cheson et al. Blood Cancer Journal 2021

Dana-Farber Cancer Institute

inMIND: Phase 3, Double-Blind, Placebo-Controlled, International, Multicenter Randomized Study



- Powered to assess PFS in the FL population, triggered when 174 investigator-assessed events occurred
- OS analysis planned after 5 years of follow-up

Sehn et al. ASH 2024

Baseline Characteristics

| | Tafasitamab + Len + R | Placebo + Len + R | Total |
|--|-----------------------|-------------------|---------------|
| Variable | (n=273) | (n=275) | (N=548) |
| Median age, years (range) | 64.0 (36, 88) | 64.0 (31, 85) | 64.0 (31, 88) |
| ≥75, n (%) | 54 (19.8) | 54 (19.6) | 108 (19.7) |
| Male sex, n (%) | 150 (54.9) | 149 (54.2) | 299 (54.6) |
| Median time since initial diagnosis of FL, years (range) | 5.2 (0, 34) | 5.5 (1, 33) | 5.3 (0, 34) |
| ECOG PS at screening, n (%) | | | |
| 0 | 181 (66.3) | 192 (69.8) | 373 (68.1) |
| 1-2 | 92 (33.7) | 83 (30.2) | 175 (31.9) |
| Ann Arbor stage, n (%) | | | |
| l or ll | 52 (19.0) | 50 (18.2) | 102 (18.6) |
| III or IV | 221 (81.0) | 225 (81.8) | 446 (81.4) |
| FL grade, n (%) | | | |
| 1 or 2 | 203 (74.4) | 203 (73.8) | 406 (74.1) |
| 3A | 67 (24.5) | 71 (25.8) | 138 (25.2) |
| B symptoms, n (%) | 63 (23.1) | 67 (24.4) | 130 (23.7) |
| FLIPI score, n (%) | | | |
| 0-1 | 57 (20.9) | 57 (20.7) | 114 (20.8) |
| 2 | 79 (28.9) | 67 (24.4) | 146 (26.6) |
| 3-5 | 137 (50.2) | 150 (54.5) | 287 (52.4) |
| GELF criteria, n (%) | 222 (81.3) | 232 (84.4) | 454 (82.8) |
| FL diagnosis confirmed by central pathology, n (%) | 256 (93.8) | 259 (90.5) | 505 (92.2) |

ITT population. ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; GELF, Groupe d'Etude des Lymphomes Folliculaires; ITT, intent-to-treat; Len, lenalidomide; R, rituximab.

Treatment History

| | Tafasitamab + Len + R | Placebo + Len + R | Total |
|---|-----------------------|-------------------|-------------|
| Variable | (n=273) | (n=275) | (N=548) |
| Median number of prior lines of therapy (range) | 1.0 (1, 7) | 1.0 (1, 10) | 1.0 (1, 10) |
| Number of prior lines of therapy, n (%) | | | |
| 1 | 147 (53.8) | 153 (55.6) | 300 (54.7) |
| 2 | 66 (24.2) | 71 (25.8) | 137 (25.0) |
| 3 | 39 (14.3) | 30 (10.9) | 69 (12.6) |
| ≥4 | 21 (7.7) | 21 (7.6) | 42 (7.7) |
| Time since last anti-lymphoma therapy, n (%) | | | |
| ≤2 years | 147 (53.8) | 157 (57.1) | 304 (55.5) |
| >2 years | 126 (46.2) | 118 (42.9) | 244 (44.5) |
| POD24, n (%) | 85 (31.1) | 88 (32.0) | 173 (31.6) |
| Relapsed/refractory status to last therapy, n (%) | | | |
| Relapsed | 148 (54.2) | 164 (59.6) | 312 (56.9) |
| Refractory | 112 (41.0) | 97 (35.2) | 209 (38.1) |
| Undetermined | 13 (4.8) | 14 (5.1) | 27 (4.9) |
| Refractory to prior anti-CD20 therapy, n (%) | 118 (43.2) | 115 (41.8) | 233 (42.5) |

ITT population. ITT, intent-to-treat; Len, lenalidomide; POD24, disease progression within 24 months of initial diagnosis; R, rituximab.

PFS by Independent Review Committee



Significant PFS benefit was confirmed by independent review committee

ITT population. *Estimated using Kaplan-Meier method. [†]Estimated using a stratified Cox proportional hazard model. [‡]Nominal *P* value; stratified log-rank test with a 2-sided significance level of 5%. CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; Len, lenalidomide; NE, not evaluable; NR, not reached; PFS, progression-free survival; R, rituximab.

PFS by POD24 Status and Refractoriness to Anti-CD20



Anti-CD20 Refractory: Yes





Anti-CD20 Refractory: No



ITT population. Subgroup analyses are based on stratification factor. Analysis by investigator assessment. CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; Len, lenalidomide; NE, not evaluable; PFS, progression-free survival; POD24, progression of disease within 24 months of initial diagnosis; R, rituximab.

Overall Survival



- OS was tested only for futility at the time of the primary analysis
- After a median follow-up of 15.3 months, the futility threshold was not crossed and a positive trend was observed

ITT population. Analysis by investigator assessment. *Estimated using Kaplan-Meier method. †Estimated using a stratified Cox proportional hazard model. CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; Len, lenalidomide; NE, not evaluable; NR, not reached; OS, overall survival; R, rituximab.

Grade 3 or 4 TEAEs and Dose Modifications

| | | Υ. | y 17 |
|----------------------------|--------------------------------------|--|------------------|
| Preferred Term, n (%) | Tafasitamab + Len + R (n=274)* | Placebo + Len + R (n=272) [†] | Total (n=546) |
| Neutropenia | 109 (39.8) | 102 (37.5) | 211 (38.6) |
| Pneumonia | 23 (8.4) | 14 (5.1) | 37 (6.8) |
| Thrombocytopenia | 17 (6.2) | 20 (7.4) | 37 (6.8) |
| Neutrophil count decreased | 16 (5.8) | 18 (6.6) | 34 (6.2) |
| Anemia | 12 (4.4) | 16 (5.9) | 28 (5.1) |
| COVID-19 | 16 (5.8) | 6 (2.2) | 22 (4.0) |
| COVID-19 pneumonia | 13 (4.7) | 3 (1.1) | 16 (2.9) |

- Most Common Grade 3 or 4 TEAEs (≥5% in Any Group)
- Tafasitamab and placebo dose interruptions or discontinuations due to TEAEs were similar between treatment arms, n (%):
 - Dose delay or interruption due to TEAEs:
 203 (74%) vs 190 (70%)
 - Discontinued study treatment due to TEAEs: 30 (11%) vs 18 (7%)
- Len discontinuations due to TEAEs were similar between tafasitamab and placebo arms, n (%):
 - 39 (14%) vs 31 (11%)
- Len dose reductions were similar between tafasitamab and placebo arms
 - Median relative dose intensity: 86% vs 87%

Safety population. *One patient randomized to the placebo + len + R group is included in the tafasitamab + len + R safety population because the patient erroneously received tafasitamab. [†]Three patients randomized to the placebo + len + R group are not included in the safety population because they erroneously received tafasitamab (n=1), or did not receive any study treatment due to confirmation of R hypersensitivity (n=1), or the patient withdrew from the study (n=1). COVID-19, coronavirus disease 2019; Len, lenalidomide; R, rituximab; TEAE, treatment-emergent adverse event.

FL Patient Population Comparison

| | inMIND Tafasitamab + Len + R | inMIND Placebo + Len + R | AUGMENT ¹ R + Len |
|-------------------------------------|---------------------------------|-----------------------------|---------------------------------|
| Variable | (n=273) | (n=275) | (n=147) |
| Median age, years | 64 | 64 | 62 |
| Male, % | 55 | 54 | 42 |
| Ann Arbor stage IV at enrollment, % | 55 | 59 | 30 |
| FL grade 3A, % | 25 | 26 | 12 |
| FLIPI high risk (score 3-5), % | 50 | 55 | 37 |
| ECOG PS 0, % | 66 | 70 | 67 |
| ECOG PS 1-2, % | 34 | 30 | 33 |
| B symptoms present, % | 23 | 24 | 8 |
| High tumor burden per GELF (yes), % | 81 | 84 | 52 |
| Refractory to last prior regimen, % | 41 | 35 | 18 |
| Refractory to anti-CD20, % | 43 | 42 | - |

1, Leonard JP, et al. J Clin Oncol. 2019;37:1188-1899.

ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; GELF, Groupe d'Etude des Lymphomes Folliculaires; Ien, Ienalidomide; R, rituximab.

Tazemetostat in relapsed/refractory FL (EZH2 mutant and wild type)



Oncogenic mutations in EZH2 "lock" B cells in the germinal center

~20% of patients with FL also have EZH2 gain of function mutations

Morchhauser et al. Lancet Onc 2019



| | EZH2 ^{mut} (n=45) | EZH2 ^{₩™} (n=54) |
|--|----------------------------|---------------------------|
| Age, years | 62 (57–68) | 61 (53-67) |
| Sex | | |
| Male | 19 (42%) | 34 (63%) |
| Female | 26 (58%) | 20 (37%) |
| ECOG performance status | | |
| 0 | 21 (47%) | 26 (48%) |
| 1 | 24 (53%) | 23 (43%) |
| 2 | 0 | 4 (7%) |
| Missing | 0 | 1 (2%) |
| Satisfied GELF criteria* | | |
| Yes | 31 (69%) | 40 (74%) |
| No | 14 (31%) | 14 (26%) |
| Time from initial diagnosis, years | 4.7 (1.7-6.4) | 6-3 (3-4-9-0) |
| Histology | | |
| Grade 1, 2, or 3a | 42 (93%) | 51 (94%)† |
| Grade 3b or transformed follicular lymphoma‡ | 3 (7%) | 6 (11%)† |
| Previous lines of anticancer therapy§ | | |
| One | 2 (4%) | 1 (2%) |
| Two | 22 (49%) | 16 (30%) |
| Three | 10 (22%) | 11 (20%) |
| Four | 4 (9%) | 10 (19%) |
| Five or more | 7 (16%) | 16 (30%) |
| Median | 2 (2-43) | 3 (2–5) |
| Refractory to last regimen¶ | 22 (49%) | 22 (41%) |
| Poor risk features | | |
| Refractory to a rituximab-containing regimen | 22 (49%) | 32 (59%) |
| Double refractory** | 9 (20%) | 15 (28%) |
| Previous haematopoietic stem-cell transplant | 4 (9%) | 21 (39%) |
| Disease progression within 24 months of disease diagnosis in patients treated with first-line immunochemotherapy (POD24) | 19 (42%) | 32 (59%) |

Despite higher response rates in EZH2 mutant patients, PFS similar in both groups

| | EZH2 ^{mut} (n=45) | | EZH2 ^{wr} (n=54) | |
|-------------------------------|----------------------------|---------------------------|---------------------------|---------------------------|
| | IRC-assessed | Investigator- assessed | IRC-assessed | Investigator- assessed |
| Objective response rate* | 31 (69%; 53-82) | 35 (78%; 63-89) | 19 (35%; 23-49) | 18 (33%; 21-48) |
| Overall disease control rate† | 44 (98%) | 45 (100%) | 37 (69%) | 34 (63%) |
| Best overall response | | | | |
| Complete response | 6 (13%) | 4 (9%) | 2 (4%) | 3 (6%) |
| Partial response | 25 (56%) | 31 (69%) | 17 (31%) | 15 (28%) |
| Stable disease | 13 (29%) | 10 (22%) | 18 (33%) | 16 (30%) |
| Progressive disease | 1 (2%) | 0 | 12 (22%) | 16 (30%) |
| Not estimable or unknown | 0 | 0 | 5 (9%) | 4 (7%) |

Data are n (%; 95% CI) or n (%). IRC=independent radiology committee. *Objective response rate includes patients with a complete or partial response. †Overall disease control rate includes patients with a complete response, partial response, or stable disease.

Table 2: Tumour response by EZH2 mutation status in the modified intention-to-treat population as assessed by the IRC and investigators

Morchhauser et al. Lancet Onc 2019

Dana-Farber Cancer Institute





Differences in outcome likely driven by patient selection



| | Before matching | | | | | After matching | | | | |
|--------------------------------------|------------------------|---------------------------|-----------------------|--------------------|---------|---------------------------|------------------------|-----------------------|--------------------|---------|
| Variable | Cohort | group ^a | Mean | Standardized | | Cohort group ^a | | Mean | Standardized | |
| | WT (<i>n</i> = 54) | MT (<i>n</i> = 45) | difference (MT-WT) | mean difference | P value | WT (<i>n</i> = 28) | MT (<i>n</i> = 28) | difference (MT–WT) | mean difference | P value |
| Matched | | | | | | | | | | |
| ECOG PS | | | | | | | | | | |
| 0 | 26 (48.2) | 21 (46.7) | -1.5 | | | 16 (57.1) | 15 (53.6) | -3.6 | | |
| 1 | 23 (42.6) | 24 (53.3) | 10.7 | | | 12 (42.9) | 13 (46.4) | 3.6 | | |
| 2 | 4 (7.4) | 0 (0) | -7.4 | | | 0 (0) | 0 (0) | 0 | | |
| Unknown | 1 (1.9) | 0 (0) | -1.9 | 0.47 | 0.18 | 0 (0) | 0 (0) | 0 | 0.07 | 1.00 |
| POD24 | 32 (59.3) | 19 (42.2) | -17.0 | 0.35 | 0.14 | 14 (50.0) | 12 (42.9) | -7.1 | 0.14 | 0.79 |
| Prior ASCT | 20 (37.0) | 4 (8.9) | -28.2 | 0.71 | < 0.01 | 3 (10.7) | 3 (10.7) | 0 | 0 | 1.00 |
| Line of anticancer therapy, <i>n</i> | 3.7 ± 1.7 | 3.0 ± 1.7 | -0.7 ± 0.3 | 0.40 | 0.05 | 3.1 ± 1.2 | 2.8 ± 1.4 | -0.3 ± 0.4 | 0.25 | 0.36 |
| Double refractory | 15 (27.8) | 9 (20.0) | -7.8 | 0.18 | 0.51 | 6 (21.4) | 8 (28.6) | 7.1 | 0.17 | 0.76 |
| Nonmatched | | | | | | | | | | |
| Age, mean ± SD, y | 61.1 ± 11.4 | $\boldsymbol{61.8\pm9.0}$ | 0.8 ± 2.1 | 0.08 | 0.71 | 64.9 ± 9.8 | 61.0 ± 9.2 | -4.0 ± 2.5 | 0.42 | 0.13 |
| Female sex | 20 (37.0) | 26 (57.8) | 20.7 | 0.43 | 0.06 | 10 (35.7) | 17 (60.7) | 25.0 | 0.52 | 0.11 |
| Grade 3b and transformed FL | 6 (11.1) | 3 (6.7) | -4.4 | 0.16 | 0.51 | 4 (14.3) | 2 (7.1) | -7.1 | 0.23 | 0.67 |
| Refractory to rituximab | 32 (59.3) | 22 (48.9) | -10.4 | 0.21 | 0.41 | 16 (57.1) | 14 (50.0) | -7.1 | 0.14 | 0.79 |
| Refractory to last therapy | 22 (40.7) | 22 (48.9) | 8.2 | 0.16 | 0.54 | 11 (39.3) | 12 (42.9) | 3.6 | 0.07 | 1.00 |

Table 1: Variables before and after matching

Table 2: Objective response rates before matching

| Population | Before matching (<i>n</i> = 99) (95% CI), % | After matching (<i>n</i> = 56) (95% CI), % | | | |
|---|--|---|--|--|--|
| WT EZH2 | 35 (22–48) | 50 (31–69) | | | |
| MT EZH2 | 69 (55–83) | 71 (54–88) | | | |
| Abbreviations: CI: confidence interval; MT: mutant type, WT: wild type. | | | | | |

Dana-Farber Cancer Institute

Proudman et al. Oncotarget 2022

Preclinical data suggest EZH2 inhibitors improve T-cell function and may improve efficacy of bi-specifics/CAR-T



Highlights

- Development of syngeneic models recapitulating human follicular lymphoma and DLBCL
- EZH2 inhibition increases immunogenicity of lymphoma cells and T cell interaction
- EZH2 inhibition sensitizes lymphoma to T cell immunotherapies
- EZH2 inhibition prevents T cell exhaustion by promoting a memory phenotype

Isshiki et al. Cancer Cell 2025

Rosewood study of obinutuzumab +/- zanubrutinib in relapsed/refractory follicular lymphoma

Key Eligibility Criteria

- Adults with grade 1-3a FL
- R/R disease, previously treated with ≥2 prior systemic treatments including an anti-CD20 antibody and an appropriate alkylatorbased combination therapy
- Measurable disease
- ECOG PS 0-2
- Adequate organ functions
- No prior BTK inhibitor

ARM A

Zanubrutiniba plus obinutuzumab Until PD/unacceptable toxicity N=145

Randomization 2:1

Stratification factors

- Number of prior lines
- Rituximab refractory status
- Geographic region

ARM B Obinutuzumab^b

Option to crossover to combination if PD/SD centrally confirmed at 12 months

Primary Endpoint

- ORR assessed by ICR according to Lugano classification¹
- Select Secondary Endpoints
- ORR assessed by investigator
- DOR and PFS determined by ICR review and investigator assessment
- Overall survival
- CR and CMR rate assessed by ICR and investigator assessment

| Patient Characteristic | ZO (n = 145) | 0 (n = 72) | Total (N = 217) |
|--|--------------------------|--------------------------|--------------------------|
| Age, years, median (range) | 63.0 (31-84) | 65.5 (32-88) | 64.0 (31-88) |
| Geographic region, No. (%) | | | |
| Mainland China | 21 (14) | 12 (17) | 33 (15) |
| Rest of the world | 124 (86) | 60 (83) | 184 (85) |
| Previous lines of therapy | | | |
| Median (range) | 3 (2-11) | 3 (2-9) | 3 (2-11) |
| 2-3, No. (%) | 104 (72) | 54 (75) | 158 (73) |
| >3, No. (%) | 41 (28) | 18 (25) | 59 (27) |
| ECOG PS 0-1, No. (%) | 140 (97) | 71 (99) | 211 (97) |
| High FLIPI score, No. (%) | 77 (53) | 37 (51) | 114 (53) |
| Ann Arbor stage III-IV, No. (%) | 119 (82) | 60 (83) | 179 (82) |
| Target lesion SPD by ICR, mm², median (Q1, Q3) | 1,614.0 (783.0, 3,344.0) | 1,727.0 (732.0, 3,504.0) | 1,655.0 (756.0, 3,351.5) |
| Bulky disease (≥7 cm), No. (%) | 23 (16) | 12 (17) | 35 (16) |
| High LDH level (>ULN), No. (%) | 49 (34) | 29 (40) | 78 (36) |
| High tumor burden per GELF criteria, No. (%) | 83 (57) | 40 (56) | 123 (57) |
| Refractory to rituximab, No. (%) | 78 (54) | 36 (50) | 114 (53) |
| Refractory to most recent line of therapy, No. (%) | 47 (32) | 29 (40) | 76 (35) |
| PD ≤24 months of starting first line of therapy, No. (%) | 50 (34) | 30 (42) | 80 (37) |
| | | | |

Zinzani et al. JCO 2023



Addition of Zanubrutinib associated with improved ORR/CR and PFS

| End Point | ZO (n = 145) | 0 (n = 72) |
|--|-------------------|--------------------|
| ORR by ICR, % (95% CI) | 69 (61 to 76) | 46 (34 to 58) |
| CR, No. (%) | 57 (39) | 14 (19) |
| PR, No. (%) | 43 (30) | 19 (26) |
| DOR by ICR, months, median (95% CI) | NE (25.3 to NE) | 14.0 (9.2 to 25.1) |
| 18-month rate, % | 69 (58 to 78) | 42 (23 to 60) |
| Duration of CR by ICR, months, median (95% CI) | NE (26.5 to NE) | 26.5 (2.7 to NE) |
| 18-month rate, % (95% CI) | 87 (74 to 94) | 51 (21 to 75) |
| PFS by ICR, months, median (95% CI) | 28.0 (16.1 to NE) | 10.4 (6.5 to 13.8) |

| Subgroup | o | zo | | Risk Differen % (95% CI) |
|---------------------------|------------------------|-------------------------|------------------------------|-----------------------------|
| All patients in ITT | 33/72 (46) | 100/145 (69) | | 23 (9 to 37 |
| Age, years | | | | |
| <65 | 14/32 (44) | 58/83 (70) | | 26 (6 to 46 |
| >65 | 19/40 (48) | 42/62 (68) | | 20 (1 to 40 |
| <75 | 30/60 (50) | 89/130 (68) | | - 18 (4 to 33 |
| >75 | 3/12 (25) | 11/15 (73) | | 48 (15 to 82 |
| Sex | | 1410 1101 | | |
| Male | 14/33 (42) | 53/75 (71) | | 28 (9 to 48 |
| Female | 19/39 (49) | 47/70 (67) | | 18 (_1 to 38 |
| Geographic region | 10/00 (40) | 4///0 (0// | | 101-110-00 |
| China | 5/12 (42) | 15/21 (71) | | 30 (.4 to 64 |
| Ex China | 29/60 (47) | 95/124 (60) | | 22 /7 to 27 |
| Provious lines of thereas | 20/00 (47) | 00/124 (00/ | | 22 (7 10 37 |
| Previous lines of therap | 9 | 77/100 (71) | | 21 (0 +- 27 |
| 2-3 | 27/54 (50) | ///108 (/1) | | 21 (6 to 37) |
| >3 | 6/18 (33) | 23/37 (62) | | 29 (2 to 56 |
| Baseline ECOG PS | | | | |
| 0 | 17/31 (55) | 64/86 (74) | | 20 (0 to 39 |
| 21 | 16/41 (39) | 36/59 (61) | | 22 (3 to 41) |
| Bulky disease: any targe | t lesion longest dian | neter ≥5 cm | | |
| Yes | 15/31 (48) | 31/57 (54) | | 6 (-16 to 28 |
| No | 18/41 (44) | 69/88 (78) | | |
| Bulky disease: any targe | t lesion longest dian | neter ≥7 cm | | |
| Yes | 3/12 (25) | 11/23 (48) | | 23 (-9 to 55 |
| No | 30/60 (50) | 89/122 (73) | | 23 (8 to 38 |
| Bulky disease: any targe | t lesion longest dian | neter ≥10 cm | | |
| Yes | 0/6 (0) | 1/5 (20) | | 20 (-15 to 55 |
| No | 33/66 (50) | 99/140 (71) | | - 21 (7 to 35 |
| FLIPI risk category | | | | |
| Low (0-1) | 3/9 (33) | 21/29 (72) | | |
| Intermediate (2) | 13/24 (54) | 26/34 (76) | | 22 (-2 to 47 |
| High (≥3) | 17/37 (46) | 49/77 (64) | | |
| Rituximab-refractory sta | itus | | | |
| Refractory | 14/36 (39) | 47/78 (60) | | 21 (2 to 41 |
| Not refractory | 19/36 (53) | 53/67 (79) | | 26 (7 to 45 |
| Refractory status to the | most recent line of th | herapy | | |
| Refractory | 11/29 (38) | 29/47 (62) | | 24 (1 to 46 |
| Not refractory | 21/42 (50) | 66/93 (71) | | 21 (3 to 39 |
| Progression of disease v | within 24 months of s | starting the first line | of therapy | |
| Yes | 14/30 (47) | 30/50 (60) | | 13 (-9 to 36 |
| No | 15/35 (43) | 55/74 (74) | | 32 (12 to 51 |
| Progression of disease y | within 24 months of a | starting the first line | of chemoimmunotherapy | |
| Voe | 0/22 (41) | 25/20 (64) | | 22/.2 to 49 |
| No | 14/31 (45) | 40/59 (68) | | 23 (1 to 44 |
| Programming of diseases | within 6 months of or | 40/59 (66) | t recent line of thereasy | 23 (110 44 |
| Ver. | 10/20 (21) | 42711 (EQ) | a recent mile of therapy | 29 /10 to 47 |
| Yes | 12/39 (31) | 42/71 (59) | | 28 (10 to 4/ |
| No Deservoires of dis- | 19/30 (03) | 53/67 (79) | at second line of the second | 10 (-4 to 36 |
| Progression of disease v | within 12 months of (| completion of the m | ost recent line of therapy | - |
| Yes | 17/52 (33) | 59/95 (62) | | 29 (13 to 46 |
| No | 14/17 (82) | 36/43 (84) | | 1 (-20 to 23 |



Zinzani et al. JCO 2023

Phase 2, single center study of loncastuximab tesirine with rituximab in relapsed/refractory follicular lymphoma



Dana-Farber Cancer Institute

Alderuccio et al. Lancet Hematology 2025

Majority of patients treated in 2nd line, though half were refractory and half were POD24

| | Enrolled patients (n=39) | |
|---|--------------------------|--|
| Age, years | 68 (58–77) | |
| Sex | | |
| Male | 21 (54%) | |
| Female | 18 (46%) | |
| Race | | |
| White | 37 (95%) | |
| Black or African American | 2 (5%) | |
| Ethnicity | | |
| Hispanic | 22 (56%) | |
| Non-Hispanic | 17 (44%) | |
| ECOG performance status | | |
| 0 | 29 (74%) | |
| 1 | 10 (26%) | |
| Follicular lymphoma grade * | | |
| Grade 1-2 | 28 (72%) | |
| Grade 3A | 11 (28%) | |
| Previous transformed or previous grade 3B * follicular lymphoma | 11 (28%) | |
| Ann Arbor stage | | |
| п | 7 (18%) | |
| III | 11 (28%) | |
| IV | 21 (54%) | |
| Bone marrow involvement | 13 (33%) | |
| Bulky disease (>7cm) | 9 (23%) | |
| Relapsed or refractory disease | | |
| Refractory | 20 (51%) | |
| Relapsed | 19 (49%) | |

| | Enrolled patients (n=39) | |
|---|--------------------------|--|
| FLIPI risk factors [†] | | |
| 0 or 1 | 9 (23%) | |
| 2 | 6 (15%) | |
| 3 | 15 (38%) | |
| 4 | 9 (23%) | |
| 5 | 0 | |
| β2 microglobulin | | |
| High (>2·3 mg/L) | 27 (69%) | |
| Normal (≤2·3 mg/L) | 12 (31%) | |
| ≥1 GELF criteria | 36 (92%) | |
| POD24 after the first line of treatment ‡ | 20 (51%) | |
| Number of previous lines of therapy | | |
| One | 26 (67%) | |
| Two | 2 (5%) | |
| Three to six | 11 (28%) | |
| First-line lymphoma therapy | | |
| R-CHOP | 22 (56%) | |
| Bendamustine with rituximab | 10 (26%) | |
| Single-agent rituximab | 6 (15%) | |
| Rituximab, fludarabine, mitoxantrone, and dexamethasone | 1 (3%) | |

Alderuccio et al. Lancet Hematology 2025

12-month PFS 95% with favorable toxicity profile



| | Grade 1–2 | Grade 3 | Grade 4 |
|--------------------------------------|-----------|----------|---------|
| Patients with any TEAEs | 37 (95%) | 18 (46%) | 5 (13%) |
| Haematological TEAEs | | | |
| Neutropenia | 10 (26%) | 4 (10%) | 1 (3%) |
| Anaemia | 14 (36%) | 0 | 0 |
| Lymphopenia | 5 (13%) | 5 (13%) | 3 (8%) |
| Platelet count decreased | 9 (23%) | 0 | 0 |
| Leukopenia | 2 (5%) | 1 (3%) | 0 |
| Febrile neutropenia | 0 | 1 (3%) | 0 |
| Non-haematological TEAEs | | | |
| Hyperglycaemia | 16 (41%) | 1 (3%) | 0 |
| Alkaline phosphatase increased | 16 (41%) | 0 | 0 |
| Alanine aminotransferase increased | 14 (36%) | 1 (3%) | 0 |
| Aspartate aminotransferase increased | 15 (38%) | 0 | 0 |
| Fatigue | 15 (38%) | 0 | 0 |
| Rash maculopapular | 14 (36%) | 0 | 0 |
| Creatinine increased | 8 (21%) | 0 | 0 |
| Hyponatraemia | 7 (18%) | 0 | 0 |
| Cough | 7 (18%) | 0 | 0 |
| Diarrhoea | 6 (15%) | 0 | 0 |
| Generalised oedema | 5 (13%) | 1 (3%) | 0 |
| Peripheral oedema | 5 (13%) | 1 (3%) | 0 |
| Photosensitivity | 6 (15%) | 0 | 0 |



Alderuccio et al. Lancet Hematology 2025

Golcadomide as a potential first-in-class oral CELMoD agent for NHL



Allosteric regulation of cereblon¹

Inactive/open cereblon No Ikaros/Aiolos bound



80% Lenalidomide 20%

0% Golcadomide 100%



Active/closed cereblon

Ikaros/Aiolos bound

- Recent cryo-EM data indicate that the cereblon complex has both an open, inactive state and a closed, active state¹
- Due to the unique binding modes of golcadomide, it is significantly more efficient than lenalidomide at driving the closed conformation,¹ leading to deeper and more rapid degradation of Ikaros/Aiolos

A Study to Compare the Efficacy and Safety of Golcadomide in Combination With Rituximab (Golca + R) vs Investigator's Choice in Relapsed/Refractory Follicular Lymphoma (GOLSEEK-4) A Study to Evaluate the Efficacy and Safety of Golcadomide in Combination With Rituximab in Newly Diagnosed Advanced Stage Follicular Lymphoma (GOLSEEK-2)



ROR1 and Zilovertamab Vedotin

- ROR1 is an oncofetal protein important for embryonic development
 - Physiologic expression disappears before birth¹
 - Pathologic expression of ROR1 often reappears in aggressive hematologic and solid tumor cancers²
- ROR1 is present on the tumor cell surface and amenable to targeting with antibody-based therapeutics¹
- Zilovertamab vedotin (MK-2140) is an ADC of:
 - The humanized monoclonal antibody, UC-961, with no normal tissue cross-reactivity
 - A cleavable linker and the anti-microtubule toxin, MMAE³
- Binding to tumor cell ROR1 causes rapid internalization and lysosomal trafficking to deliver MMAE



Borcherding N et al. Protein Cell. 2014;5:498-502; 2. Danesmanesh AH et al. Leuk Lymphoma. 2013;54:843-850.3. Vaisitti T et al. Blood. 2021;137:3365-3377.

A Study of Zilovertamab Vedotin (MK-2140) as Monotherapy and in Combination in Aggressive and Indolent B-cell Malignancies (MK-2140-006)


Case Presentation: 68-year-old man with recurrent FL and bulky disease receives mosunetuzumab



Dr Syed Zafar (Fort Myers, Florida)



QUESTIONS FOR THE FACULTY

How long do you continue mosunetuzumab in patients with R/R FL? If this patient achieves a complete response, would you discontinue mosunetuzumab in his case?

What other novel strategies are you excited about in R/R FL? Do you believe tafasitamab in combination with lenalidomide/ rituximab (R²) will receive FDA approval for R/R FL in the near future? If you were able to access tafasitamab/R², for which patients with R/R FL would you want to administer it? How would the availability of this regimen affect your sequencing of bispecific antibodies and CAR T-cell therapy?



Agenda

MODULE 1: Selection and Sequencing of Available Therapies for Diffuse Large B-Cell Lymphoma — Dr Flowers

MODULE 2: Evolving Management Paradigm for Mantle Cell Lymphoma — Dr Phillips

MODULE 3: Integration of Novel Therapies into the Management of Follicular Lymphoma — Dr LaCasce

MODULE 4: Integrating Bispecific Antibodies into the Management of NHL — Dr Brody

MODULE 5: Current Role of CAR T-Cell Therapy in Various Non-Hodgkin Lymphoma (NHL) Subtypes — Dr Abramson



Integrating Bispecific Antibodies into the management of NHL

Joshua Brody, MD







Sehn LH, et al. Blood. 2025;145:708-719.

Budde LE, et al. Lancet Oncol. 2022 Aug;23(8):1055-1065.

Efficacy/Safety: bsAbs for r/r Follicular Lymphoma – mosunetuzumab NCT02500407

Grade 1-2 Grade 3 Grade 4 Mosunetuzumab Cytokine release syndrome 1(1%) 38 (42%) 1(1%) Fatigue 33 (37%) 0 0 Headache 27 (30%) 1(1%) 0 Neutropenia or decreased 12 (13%) 12 (13%) 2 (2%) neutrophil count 25 (28%) Pyrexia 1(1%) 0 Hypophosphataemia 9 (10%) 15 (17%) 0 Pruritus 19 (21%) 0 0 Hypokalaemia 15 (17%) 2 (2%) 0 16 (18%) Cough 0 0 Constipation 16 (18%) 0 0 Diarrhoea 15 (17%) 0 0 Nausea 0 15 (17%) 0 Rash 13 (14%) 1(1%) 0

CD20

| | Grade 1-2 | Grade 3 | Grade 4 |
|------------------------------------|------------------------|---------|---------|
| Dry skin | 14 (16%) | 0 | 0 |
| Anaemia | 5 (6%) | 7 (8%) | 0 |
| Chills | 11 (12%) | 1 (1%) | 0 |
| Hypomagnesaemia | <mark>11 (1</mark> 2%) | 0 | 0 |
| Increased alanine aminotransferase | 6 (7%) | 4 (4%) | 1(1%) |
| Insomnia | 11 (12%) | 0 | 0 |
| Arthralgia | 10 (11%) | 0 | 0 |
| Peripheral oedema | 10 (11%) | 0 | 0 |
| Abdominal pain | 8 (9%) | 1 (1%) | 0 |
| Back pain | 8 (9%) | 1 (1%) | 0 |
| Dizziness | 9 (10%) | 0 | 0 |
| Urinary tract infection | 8 (9%) | 1 (1%) | 0 |
| Skin exfoliation | 9 (10%) | 0 | 0 |
| Thrombocytopenia | 5 (6%) | 0 | 4 (4%) |

Sehn LH, et al. Blood. 2025;145:708-719.

Budde LE, et al. Lancet Oncol. 2022 Aug;23(8):1055-1065.



Efficacy/Safety: bsAbs for r/r Follicular Lymphoma – epcoritamab EPCORE NHL-1



Linton KM, et al. Lancet Haematol. 2024; 11:e593-e605.

BsAbs in earlier settings and in combination therapies for FL: epcoritamab

Epcoritamab + R² in First-Line Therapy FL: EPCORE NHL-2 arm 6



BsAbs in earlier settings and in combination therapies for FL: mosunetuzumab

Mosunetuzumab w Response-Driven Lenalidomide Augmentation As 1st-Line Therapy for FL/MZL: (NCT04792502)



Efficacy/Safety: bsAbs for r/r DLBCL – epcoritamab EPCORE NHL-1



Efficacy/Safety: bsAbs for r/r DLBCL – glofitamab NCT02500407



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

Dickinson MJ et al. Blood (2024) 144 (Supplement 1): 865

BsAbs with chemo: Gem-Ox + CD20 x CD3 bsAbs for r/r DLBCL



Overall survival (%)

BsAbs with chemo: Gem-Ox + CD20 x CD3 bsAbs for r/r DLBCL





Abramson JS et al., Lancet 2024 Nov 16;404(10466):1940-1954.

BsAbs + chemo: Gem-Ox + CD20 x CD3 bsAbs for r/r DLBCL

Phase III STARGLO - Two-year follow-up

Overall survival with ~2 years of follow up



| Outcome | R-GemOx (n=91) | Glofit-GemOx (n=183) | | |
|---|--------------------------|--------------------------|--|--|
| 2-year follow up analysis (median follow up: 24.7 months) | | | | |
| OS, median (95% CI); months | 13.5 (7.9, 18.5) | NE (19.2, NE) | | |
| HR (95% CI) | 0.60 (0.42, 0.85) | | | |
| p-value* | 0.003 | | | |
| 24-month OS, % (95% CI) | 33.6 (22.9, 44.2) | 54.4 (46.8, 62.0) | | |

At data cut-off, 26.9% of Glofit-GemOx-treated patients and 57.1% of R-GemOx-treated patients had received ≥1 NALT

Abramson JS et al., Lancet 2024 Nov 16;404(10466):1940-1954.

Abramson JS et al., ASCO 2025 do not distribute

BsAbs + chemo: Gem-Ox + CD20 x CD3 bsAbs for r/r DLBCL

Phase III STARGLO - Two-year follow-up

Progression-free survival with extended follow up



| Outcome | R-GemOx (n=91) | Glofit-GemOx (n=183) |
|----------------------------------|--------------------------|--------------------------|
| PFS, median (95% CI); months | 3.6 (2.5, 7.1) | 13.8 (8.8, 30.0) |
| ORR, % (95% CI) | 40.7 (30.5, 51.5) | 68.3 (61.0, 75.0) |
| CR rate, % (95% CI) | 25.3 (16.8, 35.5) | 58.5 (51.0, 65.7) |
| DoCR, median (95% CI); months | 24.2 (6.9 <i>,</i> NE) | NE (27.2, NE) |
| Ongoing CR, % (n) | 17.6 (16) | 42.1 (77) |

Efficacy/Safety: bsAbs for other lymphomas - glofitamab in mantle cell lymphoma



Phillips TJ et al., J Clin Oncol. 2025 Jan 20;43(3):318-328.

Efficacy/Safety: bsAbs for other lymphomas - glofitamab in mantle cell lymphoma

| 1,000 mg Gpt CRS Event/Management Cohort (n = 16) | Glofitamab SUD, No. (%) | | | Glofitamab SUD, No. (%) | | | |
|--|---------------------------------|---------------------------------|--------------------------|--------------------------|---------------------------------|---------------------------------|--------------------------|
| | 1,000 mg Gpt Cohort (n = 16) | 2,000 mg Gpt Cohort (n = 44) | All Patients (N = 60) | CRS Event/Management | 1,000 mg Gpt Cohort (n = 16) | 2,000 mg Gpt Cohort (n = 44) | All Patients (N = 60) |
| Any CRS | 14 (87.5) | 28 (63.6) | 42 (70.0) | CRS management | | | |
| Grade 1 | 4 (25.0) | 18 (40.9) | 22 (36.7) | Tocilizumab | 11 (68.8) | 11 (25.0) | 22 (36.7) |
| Grade 2 | 6 (37.5) | 7 (15.9) | 13 (21.7) | Corticosteroid | 8 (50.0) | 10 (22.7) | 18 (30.0) |
| Grade 3 | 2 (12.5) | 3 (6.8) | 5 (8.3) | Tocilizumab and | 6 (37.5) | 7 (15.9) | 13 (21.7) |
| Grade 4 | 2 (12.5) | 0 | 2 (3.3) | corticosteroids | | | |
| Serious AF of CRS | 11 (68.8) | 12 (27 3) | 23 (38.3) | Low flow oxygen | 6 (37.5) | 4 (9.1) | 10 (16.7) |
| | | (, | | ICU stay | 5 (31.3) | 4 (9.1) | 9 (15.0) |
| Fatal CRS event | 0 | 0 | 0 | Fluid support | 4 (25.0) | 5 (11.4) | 9 (15.0) |
| | | | | Single-pressor therapy | 4 (25.0) | 3 (6.8) | 7 (11.7) |
| | | | | Multiple-pressor therapy | 2 (12.5) | 0 | 2 (3.3) |
| | | | | High-flow oxygen | 1 (6.3) | 0 | 1 (1.7) |

Phillips TJ et al., J Clin Oncol. 2025 Jan 20;43(3):318-328.

Mechanical ventilation

1 (6.3)

1 (1.7)

0

Efficacy/Safety: bsAbs beyond CD20 – AZD0486 CD19 x CD3



- N=114 (FL: n=56/DLBCL: n=58) 0.3-15 mg target dose
- No related AE leading to discontinuation
- No treatment-related deaths
- **CRS** Grade ≥ 3: **0%** (n=0/90) in 2SUD
- ICANS Grade ≥ 3: 2% (n=2/90) in 2SUD
 - Only in DLBCL patients; transient and reversible
- Majority of ICANS/CRS onset in Cycle 1 during SUD
- Grade <u>></u>3 TEAEs affecting <u>></u>15% of patients
 - Neutropenia (18%), lymphopenia (16%)

Case Presentation: 73-year-old man with history of cardiac issues and seizures and primary refractory DLBCL is considered for bispecific antibody therapy



Dr Shams Bufalino (Park Ridge, Illinois)



QUESTIONS FOR THE FACULTY

In general, for which patients with R/R DLBCL do you administer bispecific antibodies? How do you choose between glofitamab and epcoritamab?

For a patient with R/R DLBCL who has experienced disease progression on a bispecific antibody, would you offer another bispecific antibody as a later line of treatment? If so, at what point?



QUESTIONS FOR THE FACULTY

How long do you continue bispecific antibodies in patients with R/R DLBCL? Do you strictly adhere to the package insert recommendations regarding duration of therapy for glofitamab and epcoritamab?

Beyond CD20, what other targets for bispecific antibodies seem promising in NHL? Based on preliminary data, how does the CD19 x CD3 bispecific antibody AZD0486 seem to stack up against currently available agents?



Case Presentation: 86-year-old man with high-risk recurrent FL with EZH2 mutation and PD after tazemetostat receives mosunetuzumab



Dr Gigi Chen (Pleasant Hill, California)



QUESTIONS FOR THE FACULTY

How do you think through sequencing of bispecific antibodies and CAR T-cell therapy for patients with R/R FL? How do patient age/fitness and the pace of their disease affect your thinking?

What would you recommend for this man if he were to experience disease progression? Would you consider restarting mosunetuzumab, or would you move on to something else?

In your experience, are most patients receiving this therapy locally, or are they being referred to tertiary care centers? Do you anticipate that this dynamic may change as clinicians gain greater experience with bispecific antibodies?



QUESTIONS FOR THE FACULTY

What are the most important pearls you would offer a communitybased oncologist about monitoring for and mitigating CRS and neurotoxicity with bispecific antibodies?

Do you instruct patients to monitor their temperatures during step-up dosing of bispecific antibodies? Do you recommend that they obtain blood pressure cuffs and pulse oximeters for home testing? Do you provide some or all patients with a prescription for dexamethasone before starting bispecific antibody therapy?



Agenda

MODULE 1: Selection and Sequencing of Available Therapies for Diffuse Large B-Cell Lymphoma — Dr Flowers

MODULE 2: Evolving Management Paradigm for Mantle Cell Lymphoma — Dr Phillips

MODULE 3: Integration of Novel Therapies into the Management of Follicular Lymphoma — Dr LaCasce

MODULE 4: Integrating Bispecific Antibodies into the Management of NHL — Dr Brody

MODULE 5: Current Role of CAR T-Cell Therapy in Various Non-Hodgkin Lymphoma (NHL) Subtypes — Dr Abramson





Chimeric Antigen Receptor (CAR) T-Cell Therapy for Diffuse Large B-Cell Lymphoma (DLBCL)

Jeremy S. Abramson, MD, MMSc Massachusetts General Hospital Harvard Medical School



Major findings from phase III trials for 2nd line CAR in DLBCL



Three randomized trials of Chimeric Antigen Receptor (CAR) T-cell therapy versus SOC in transplant-eligible DLBCL with early relapse or primary refractory disease



Axi-cel vs. SOC as 2nd line therapy in primary refractory or early relapsed large B-cell lymphomas



Median Follow-up: 47.2 mo

| Toxicity | Grade | % |
|----------|-----------------------|----------|
| CRS | Any grade Grade ≥3 | 92 6 |
| Neurotox | Any grade Grade ≥3 | 60 21 |

Axi-cel associated with improved QOL by PRO

Locke, et al. NEJM 2021; Westin, et al. NEJM 2023

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Liso-cel vs. SOC as 2nd line therapy in primary refractory or early relapsed large B-cell lymphomas



Median Follow-up: 34 mo

Abramson, et al. Proc. EHA 2024; Abstract S272

| Toxicity | Grade | % |
|----------|----------------------|---------|
| CRS | Any grade Grade 3 | 49 1 |
| Neurotox | Any grade Grade 3 | 11 4 |

Liso-cel associated with improved QOL by PRO

Tisa-cel vs. SOC as 2nd line therapy in primary refractory or early relapsed large B-cell lymphomas



Median Follow-up: 10 mo

| Toxicity | % |
|---|---------|
| CRS Any grade Grade ≥3 | 61 5 |
| Neurotoxicity Any grade Grade ≥3 | 10 2 |

| Bishon. | et | al. | NFIM | 202 |
|---------|----|-----|------|------|
| bishop, | cι | aı. | | 202. |

Long term efficacy and safety for 3rd line+ CAR in DLBCL



CAR T-cells can CURE chemotherapy-refractory LBCL in the 3rd line or later setting

| | Axicabtagene Ciloleucel ZUMA-1 | Lisocabtagene Maraleucel TRANSCEND | Tisagenlecleucel JULIET |
|--|---|--|--|
| Construct | antiCD19-CD28tm-CD28-CD3z | antiCD19-CD28tm- 41BB -CD3z | antiCD19-CD8αtm- 41BB -CD3z |
| Med Age, y (range) | 58 (23–76) | 63 (18–86) | 56 (22–76) |
| ORR/CRR % (IRC) | 74/54 | 73/53 | 52/40 |
| Median PFS, mos | 5.9 | 6.8 | 2.9 |
| PFS (2y) % | 42 | 41 | 30 |
| Median OS, mos | 25.8 | 27.3 | 11.1 |
| CRS (Any/severe) % | 93/13 | 42/2 | 58/22 *different grading scale |
| NT (Any/severe) % | 64/28 | 30/10 | 21/12 |
| References | Neelapu, et al. NEJM 2017 Locke, et al. Lancet Onc 2019 | Abramson, et al. Lancet 2020 Abramson, et al. Blood 2024 | Schuster, et al. NEJM 2019 Schuster, et al. Lancet Onc. 2021 |
| Media 80- 80- 80- 80- 80- 80- 90- 80- 90- 80- 80- 90- 80- 90- 90- 90- 90- 90- 90- 90- 9 | PFS in PFS (95% Cl), months: 5.9 (3.3–15.0) 100 - PFS 80 | Median (95% Cl), 27.3 months (24.0-NR) Image: Clip of the second se | PFS 3 6 9 12 15 18 21 24 27 30 23 36 39 42 45 Time from infusion (months) 47(11) 38(13) 36(14) 31(16) 31(16) 20(17) 26(19) 24(21) 21(24) 21(24) 21(24) 11(32) 2(42) 1(43) 0(44) |

CAR T-cells can CURE Large B-cell Lymphomas as 3rd line or later therapy: 5-year Follow up From ZUMA-1 and TRANSCEND



- After day 91, 14 (6%) pts had grade \geq 3 infections (grade 5, n = 3, 2 of whom had additional anti-cancer therapies)
 - Nineteen (8%) pts had second primary malignancies (non-melanoma skin cancers [n = 7], MDS [n = 9]).

Long term safety from JULIET

| Prolonged cytopenias | Anemia | Thrombocytopenia | Neutropenia |
|---------------------------------|--------|------------------|-------------|
| Grade ≥3 cytopenia after day 90 | 3% | 8% | 8% |

| Infections | Any grade | Grade 3 | Grade 4 |
|-------------|-----------|---------|---------|
| <2 months | 33% | 14% | 0 |
| 2-12 months | 65% | 23% | 2% |
| >12 months | 40% | 13% | 35 |

| Malignancies | Incidence, n (%) | Prior ASCT, n | # prior lines |
|----------------|------------------|---------------|---------------|
| Any | 9 (8%) | 4 | 1-5 |
| Prostate | 3 (3%) | 1 | 2-5 |
| Basal cell | 2 (2%) | 1 | 1-2 |
| AML | 1 (1%) | 1 | 3 |
| Breast | 1 (1%) | 1 | 4 |
| MDS | 1 (1%) | 0 | 3 |
| Neuroendocrine | 1 (1%) | 0 | 2 |
Follicular lymphoma



Three CAR T-cell products for 3rd line + follicular lymphoma

| | Lisocabtagene Maraleucel TRANSCEND-FL | Tisagenlecleucel ELARA | Axicabtagene Ciloleucel ZUMA-5 |
|----------------------|---|--|---|
| n | 107 | 94 | 124 |
| Median # prior lines | 3 | 4 | 3 |
| Chemorefractory | 67% | 78% | 68% |
| POD24 | 54% | 60% | 55% |
| CR rate | 94% | 69% | 79% |
| Median PFS, m | NR | 53 mo | 57 mo |
| PFS | 73% at 24m | 50% at 60m | 50% at 60m |
| CRS (Any/severe) % | 58/1 | 49/0 | 82/7 |
| NT (Any/severe) % | 15/2 | 4/1 | 59/19 |
| References | Morschhauser, et al. Nature Med 2024 Nastoupil, et al. Proc ASH 2024 | Fowler, et al. Nat Med 2022. Thieblemont, et al.Proc ASH 2024 | Jacobson, et al. Lancet Onc 2022 Neelapu, et al. Proc ASH 2024 |

PFS for CAR T-cells in 3rd line or later FL



Nastoupil, et al. Proc ASH 2024; Neelapu, et al. Proc ASH 2024; Thieblemont, et al. Proc ASH 2024.

Mantle cell lymphoma



CAR T-cell for MCL post covalent BTK inhibition

| | Brexu-(Anti-CD19 CA | cel R T-cell | |
|-------------|--|------------------------|------------|
| | Endpoint | n=68 | |
| | ORR | 93% | |
| | CRR | 67% | |
| | Med PFS | 25 mo | |
| | Severe CRS/NT | 15%/43% | |
| 100- 80- | June of the second seco | | ssion-free |

Liso-cel Anti-CD19 CAR T-cell

| Endpoint | n=83 |
|---------------|-------|
| ORR | 83% |
| CRR | 72% |
| Med PFS | 12 mo |
| Severe CRS/NT | 1%/9% |



Marginal zone lymphoma



Liso-cel in Marginal Zone Lymphoma Press release: February 10, 2025

- The Phase 2 TRANSCEND FL trial evaluating liso-cel in adults with relapsed or refractory indolent B-cell non-Hodgkin lymphoma met its primary endpoint in the marginal zone lymphoma (MZL) cohort
- Results showed a statistically significant overall response rate (ORR) in these patients
- The study also met the key secondary endpoint of complete response rate (CRR).
- Liso-cel demonstrated durable responses and a consistent safety profile with no new safety signals observed
- Await data presentation at ICML 2025

Take home points

- CAR T-cells induce deep and durable remissions in DLBCL, follicular lymphoma, mantle cell lymphoma and marginal zone lymphoma (new data coming soon)
- Liso-cel and axi-cel are preferred 2nd line treatment for DLBCL which is primary refractory or relapsed within 12 months. Liso-cel also approved for 2nd line nontransplant eligible patients
- Liso-cel, axi-cel and tisa-cel also available in 3rd line and later DLBCL
- Liso-cel, tisa-cel or axi-cel available for 3rd line and later treatment of FL, but will likely be used after bispecific antibodies in most patients
- Liso-cel and brexu-cel are preferred for MCL after failure of covalent BTK inhibitors. Pirtobrutinib can serve as a valuable bridging therapy

Case Presentation: 81-year-old man with recurrent non-GCB type DLBCL and significant pulmonary involvement



Dr Warren Brenner (Boca Raton, Florida)



QUESTIONS FOR THE FACULTY

How do you choose between CAR T-cell therapy, bispecific antibodies and other available therapies for patients such as this who are older and have borderline performance status but are symptomatic from their disease?

What bridging strategy would you recommend prior to CAR T-cell therapy for a patient such as this?

Which patients with other NHL subtypes — FL and MCL represent ideal candidates for CAR T-cell therapy? Where in the treatment sequence do you typically recommend CAR T-cell therapy for these patients? Do you anticipate that CAR T-cell therapy may soon have a role in marginal zone lymphoma as well?



Case Presentation: 76-year-old man with transformed DLBCL and PD after R-CHOP receives bridging therapy with polatuzumab vedotin/rituximab followed by lisocabtagene maraleucel



Dr Spencer Bachow (Boca Raton, Florida)



QUESTIONS FOR THE FACULTY

If you saw this patient with primary refractory DLBCL today, is there anything you would have done differently? Would you recommend CAR T-cell therapy or another strategy? Would you bring up the idea of transplant?

How should oncologists in the community follow their patients who have received CAR T-cell therapy? How often should CBCs be assessed, and when should growth factors be administered?

Should these patients routinely be assessed for hypogammaglobulinemia and be infused with IVIG if they develop recurrent infections or low immunoglobulin levels?

How do you approach vaccination for patients who have received CAR T-cell therapy?



Contributing General Medical Oncologists



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Thank you

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Consensus or Controversy? Clinical Investigators Provide Perspectives on the Current and Future Care of Patients with Chronic Lymphocytic Leukemia

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> Faculty Catherine C Coombs, MD William G Wierda, MD, PhD

> > Moderator Neil Love, MD



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