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

A CME Hybrid Symposium Held in Conjunction with the 2022 ASCO Annual Meeting

Sunday, June 5, 2022
7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)

Faculty

Ian W Flinn, MD, PhD
Brian T Hill, MD, PhD
John P Leonard, MD

Matthew Lunning, DO
Laurie H Sehn, MD, MPH
Mitchell R Smith, MD, PhD

Moderator
Neil Love, MD
Faculty

Ian W Flinn, MD, PhD
Director of Lymphoma Research Program
Sarah Cannon Research Institute
Tennessee Oncology
Nashville, Tennessee

Brian T Hill, MD, PhD
Director, Lymphoid Malignancy Program
Cleveland Clinic Taussig Cancer Institute
Cleveland, Ohio

John P Leonard, MD
Richard T Silver Distinguished Professor of Hematology and Medical Oncology
Senior Associate Dean for Innovation and Initiatives
Executive Vice Chair, Joan and Sanford I Weill Department of Medicine
Weill Cornell Medicine
New York, New York

Matthew Lunning, DO
Associate Professor
Fred and Pamela Buffett Cancer Center
Associate Vice Chair of Research, Department of Medicine
Assistant Vice Chancellor of Clinical Research
University of Nebraska Medical Center
Omaha, Nebraska

Laurie H Sehn, MD, MPH
Chair, Lymphoma Tumour Group
BC Cancer Centre for Lymphoid Cancer
Clinical Professor of Medicine
Division of Medical Oncology
University of British Columbia
Associate Editor, Blood
Vancouver, British Columbia, Canada

Mitchell R Smith, MD, PhD
Clinical Professor of Medicine
George Washington University
Washington, DC

Moderator
Neil Love, MD
Research To Practice
Miami, Florida
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 premeeting survey before the meeting. Survey results will be presented and discussed throughout the meeting.

- 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.

- Complete Your Evaluation: Tap the CME Evaluation button to complete your evaluation electronically to receive credit for your participation.

For assistance, please raise your hand. Devices will be collected at the conclusion of the activity.
 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 premeeting survey before the meeting. Survey results will be presented and discussed throughout the meeting.

- **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 video/PowerPoint program. An email will be sent to all attendees when the activity is available.

• To learn more about our education programs, visit our website, www.ResearchToPractice.com
<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Friday</td>
<td><strong>Acute Myeloid Leukemia and Myelodysplastic Syndromes</strong>&lt;br&gt;11:45 AM – 12:45 PM CT (12:45 PM – 1:45 PM ET)</td>
</tr>
<tr>
<td></td>
<td><strong>Lung Cancer</strong>&lt;br&gt;6:30 PM – 9:00 PM CT (7:30 PM – 10:00 PM ET)</td>
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<tr>
<td>Saturday</td>
<td><strong>Prostate Cancer</strong>&lt;br&gt;6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)</td>
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<td></td>
<td><strong>Gastrointestinal Cancers</strong>&lt;br&gt;7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)</td>
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<td>Sunday</td>
<td><strong>Ovarian Cancer</strong>&lt;br&gt;6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)</td>
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<tr>
<td></td>
<td><strong>Chronic Lymphocytic Leukemia and Non-Hodgkin Lymphoma</strong>&lt;br&gt;7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)</td>
</tr>
<tr>
<td>Monday</td>
<td><strong>Urothelial Bladder Cancer</strong>&lt;br&gt;6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)</td>
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<tr>
<td></td>
<td><strong>Breast Cancer</strong>&lt;br&gt;7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)</td>
</tr>
<tr>
<td>Tuesday</td>
<td><strong>Multiple Myeloma</strong>&lt;br&gt;6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)</td>
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</table>
Exciting CME Events in Chicago You Do Not Want to Miss
A CME Hybrid Symposium Series Held in Conjunction with the 2022 ASCO Annual Meeting

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John P Leonard, MD
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Laurie H Sehn, MD, MPH
Mitchell R Smith, MD, PhD

Breast Cancer
Monday, June 6, 2022
7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)
Faculty
Javier Cortés, MD, PhD
Matthew P Goetz, MD
Erika Hamilton, MD
Ian E Krop, MD, PhD
Hope S Rugo, MD
Sara M Tolaney, MD, MPH

Urothelial Bladder Cancer
Monday, June 6, 2022
6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)
Faculty
Yohann Loriot, MD, PhD
Elizabeth R Plimack, MD, MS
Jonathan E Rosenberg, MD

Multiple Myeloma
Tuesday, June 7, 2022
6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)
Faculty
Ajai Chari, MD
Elizabeth O’Donnell, MD
Robert Z Orlowski, MD, PhD
Commercial Support

This activity is supported by educational grants from ADC Therapeutics, AstraZeneca Pharmaceuticals LP, Genentech, a member of the Roche Group, Incyte Corporation, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Kite, A Gilead Company, and Lilly.

Research To Practice CME Planning Committee Members, Staff and Reviewers

Planners, scientific staff and independent reviewers for Research To Practice have no relevant conflicts of interest to disclose.
Dr Love — Disclosures

**Dr Flinn — Disclosures**

<table>
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<tr>
<th>Consulting Agreements (to Sarah Cannon Research Institute)</th>
<th>AbbVie Inc, AstraZeneca Pharmaceuticals LP, BeiGene Ltd, Century Therapeutics, Genentech, a member of the Roche Group, Genmab, Gilead Sciences Inc, Great Point Partners LLC, Hutchison MediPharma, Iksuda Therapeutics, InnoCare Pharma, Janssen Biotech Inc, Juno Therapeutics, a Celgene Company, Kite, A Gilead Company, MorphoSys, Novartis, Nurix Therapeutics Inc, Pharmacyclics LLC, an AbbVie Company, Roche Laboratories Inc, Seagen Inc, Servier Pharmaceuticals LLC, Takeda Pharmaceuticals USA Inc, TG Therapeutics Inc, Unum Therapeutics, Verastem Inc, Vincerx Pharma, YL-Pharma Co Ltd</th>
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### Dr Hill — Disclosures

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<th>Advisory Committee and Consulting Agreements</th>
<th>AbbVie Inc, ADC Therapeutics, AstraZeneca Pharmaceuticals LP, BeiGene Ltd, Bristol-Myers Squibb Company, Epizyme Inc, Genentech, a member of the Roche Group, Kite, A Gilead Company, MorphoSys, Novartis</th>
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</table>
## Dr Leonard — Disclosures

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<td>Epizyme Inc, Genentech Foundation, Janssen Biotech Inc</td>
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<tr>
<td><strong>Data and Safety Monitoring Board/Committee</strong></td>
</tr>
<tr>
<td>AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Genentech, a member of the Roche Group</td>
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# Dr Lunning — Disclosures

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<tr>
<td>Contracted Research</td>
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**Dr Smith — Disclosures**

<table>
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<th>Janssen Biotech Inc</th>
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<tr>
<td>Speakers Bureau</td>
<td>Acrotech Biopharma</td>
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Mitchell R Smith, MD, PhD

Moderator
Neil Love, MD
Agenda

Module 1 – Newly Diagnosed Chronic Lymphocytic Leukemia (CLL) — Dr Flinn

Module 2 – Relapsed/Refractory (R/R) CLL; Novel Investigational Strategies — Dr Smith

Module 3 – Follicular Lymphoma (FL) — Dr Leonard

Module 4 – Mantle Cell Lymphoma (MCL) — Dr Lunning

Module 5 – Diffuse Large B-Cell Lymphoma (DLBCL) — Dr Sehn

Module 6 – Chimeric Antigen Receptor (CAR) T-Cell Therapy — Dr Hill
MODULE 1: Newly Diagnosed CLL – Dr Flinn
An 88-year-old woman with CLL, well controlled atrial fibrillation and a history of COPD and pneumonia

Dr Erik Rupard (West Reading, Pennsylvania)
A 73-year-old woman with CLL who developed severe basal cell carcinomas during ibrutinib therapy

Dr Zanetta Lamar (Naples, Florida)
An 80-year-old man with newly diagnosed del(13q) CLL and life-threatening anemia

Dr Namrata Peswani (Richardson, Texas)
Treatment Naïve CLL

Ian W. Flinn, MD, PhD
Sarah Cannon Research Institute
Tennessee Oncology
<table>
<thead>
<tr>
<th>Without Del(17p)/TP53 Mutation</th>
<th>With Del(17p)/TP53 Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preferred</strong></td>
<td><strong>Preferred</strong></td>
</tr>
</tbody>
</table>
| Patients age ≥65 years OR patients age <65 years with significant comorbidities (CrCl <70 mL/min) | Acalabrutinib ± obinutuzumab
• Ibrutinib
• Venetoclax + obinutuzumab
• Zanubrutinib |
| Other Regimens               | Other Regimens            |
| Patients age <65 years without significant comorbidities | Acalabrutinib ± obinutuzumab
• Ibrutinib
• Venetoclax + obinutuzumab
• Zanubrutinib |
| • Bendamustine + anti-CD20   | • Bendamustine + anti-CD20 |
| • Chlorambucil + obinutuzumab| • Fludarabine + cyclophosphamide + rituximab
• Ibrutinib + obinutuzumab
• Chlorambucil
• Rituximab
• Ibrutinib + rituximab
• Fludarabine + rituximab
• High-dose methylprednisolone + rituximab or obinutuzumab |

**a** Category 1 preferred regimen. **b** Preferred for patients with IGHV-mutated CLL.

NCCN Clinical Practice Guidelines® in Oncology for Chronic Lymphocytic Leukemia V.2.2022.
Up to 7 Years of Follow-Up in the RESONATE-2 Study of Ibrutinib for Patients With TN CLL: Treatment and Summary

Most common reason for discontinuation over 7 years was adverse event (23%); limited data available on next therapies

---

**Ibrutinib Treatment Disposition**

<table>
<thead>
<tr>
<th></th>
<th>Ibrutinib n=136</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (range) duration of ibrutinib treatment, years(^a)</td>
<td>6.2 (0.06-7.2)</td>
</tr>
<tr>
<td>Continuing ibrutinib on study, n (%)</td>
<td>64 (47)</td>
</tr>
<tr>
<td>Discontinued ibrutinib, n (%)</td>
<td></td>
</tr>
<tr>
<td>Adverse event</td>
<td>31 (23)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>16 (12)</td>
</tr>
<tr>
<td>Death</td>
<td>11 (8)</td>
</tr>
<tr>
<td>Withdrawal by patient</td>
<td>9 (7)</td>
</tr>
<tr>
<td>Investigator decision</td>
<td>4 (3)</td>
</tr>
</tbody>
</table>

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\(^a^{74.0 months (0.7-86.8).}
**ECOG 1912: IR vs FCR in Younger Patients With TN CLL**

- Phase 3 trial of 529 patients with TN CLL aged \(\leq 70\) years who received either ibrutinib + rituximab (IR, \(n=354\)) or FCR (\(n=175\))
- With a median follow-up of 48 months, 3-year PFS was 89% vs 71% in the IR and FCR arms, respectively (\(P<0.0001\))
  - In \(IGHV\)-mut patients, difference in PFS between the IR and FCR arms was not statistically significant
- 3-year OS was 99% vs 93% in the IR and FCR arms, respectively (\(P=0.009\))

4-Year Follow-Up of ELEVATE-TN: Acalabrutinib ± Obinutuzumab vs Obinutuzumab + Chlorambucil in TN CLL – Study Design and Patient Characteristics

### Key Eligibility Criteria
- Age ≥65 years or >18 to <65 years with comorbidities (defined as CrCl 30-69 mL/min and CIRS-G >6)
- Untreated CLL requiring treatment per iwCLL 2008 criteria
- ECOG PS ≤2
- No significant cardiovascular disease

### Patient Characteristics

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>A+O (n=179)</th>
<th>A (n=179)</th>
<th>O+Clb (n=177)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), years</td>
<td>70 (41-88)</td>
<td>70 (44-87)</td>
<td>71 (46-91)</td>
</tr>
<tr>
<td>ECOG PS, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>169 (94.4)</td>
<td>165 (92.2)</td>
<td>167 (94.4)</td>
</tr>
<tr>
<td>2</td>
<td>10 (5.6)</td>
<td>14 (7.8)</td>
<td>10 (5.6)</td>
</tr>
<tr>
<td>Bulky disease ≥5 cm, n (%)</td>
<td>46 (25.7)</td>
<td>68 (38.0)</td>
<td>54 (30.5)</td>
</tr>
<tr>
<td>Rai stage, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>47 (26.3)</td>
<td>51 (28.5)</td>
<td>40 (22.6)</td>
</tr>
<tr>
<td>IV</td>
<td>38 (21.2)</td>
<td>37 (20.7)</td>
<td>38 (21.5)</td>
</tr>
<tr>
<td>Cytogenetics, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>del(17p)</td>
<td>17 (9.5)</td>
<td>16 (8.9)</td>
<td>16 (9.0)</td>
</tr>
<tr>
<td>del(17p) and/or mut TP53</td>
<td>25 (14.0)</td>
<td>23 (12.8)</td>
<td>25 (14.1)</td>
</tr>
<tr>
<td>del(11q)</td>
<td>31 (17.3)</td>
<td>31 (17.3)</td>
<td>33 (18.6)</td>
</tr>
<tr>
<td>Complex karyotype&lt;sup&gt;a&lt;/sup&gt;</td>
<td>15 (8.4)</td>
<td>13 (7.3)</td>
<td>25 (14.1)</td>
</tr>
<tr>
<td>Mutated TP53, n (%)</td>
<td>21 (11.7)</td>
<td>19 (10.6)</td>
<td>21 (11.9)</td>
</tr>
<tr>
<td>Unmutated IGHV, n (%)</td>
<td>103 (57.5)</td>
<td>119 (66.5)</td>
<td>116 (65.5)</td>
</tr>
<tr>
<td>Treatment ongoing, n (%)</td>
<td>134 (74.9)</td>
<td>124 (69.3)</td>
<td>0</td>
</tr>
</tbody>
</table>

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<sup>a</sup> Patients with ≥3 chromosomal abnormalities.

4-Year Follow-Up of ELEVATE-TN: Acalabrutinib ± Obinutuzumab vs Obinutuzumab + Chlorambucil in TN CLL – PFS and OS

INV-Assessed PFS Overall

INV-Assessed PFS In Del(17p) and/or Mutated TP53

INV-Assessed PFS In Unmutated IGHV

4-Year Follow-Up of ELEVATE-TN: Acalabrutinib ± Obinutuzumab vs Obinutuzumab + Chlorambucil in TN CLL – Response

INV-Assessed ORR

MRD Status in Patients With CR/CRi

4-Year Follow-Up of ELEVATE-TN: Acalabrutinib ± Obinutuzumab vs Obinutuzumab + Chlorambucil in TN CLL – Safety

<table>
<thead>
<tr>
<th>AEs of Clinical Interest, n (%)</th>
<th>A+O (n=178)</th>
<th>A (n=179)</th>
<th>O+Clb (n=169)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade ≥3</td>
<td>Any Grade</td>
</tr>
<tr>
<td>Cardiac events</td>
<td>37 (20.8)</td>
<td>14 (7.9)</td>
<td>34 (19.0)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>7 (3.9)</td>
<td>1 (0.6)</td>
<td>11 (6.1)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>84 (47.2)</td>
<td>5 (2.8)</td>
<td>75 (41.9)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>7 (3.9)</td>
<td>5 (2.8)</td>
<td>7 (3.9)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>14 (7.9)</td>
<td>6 (3.4)</td>
<td>13 (7.3)</td>
</tr>
<tr>
<td>Infections</td>
<td>134 (75.3)</td>
<td>42 (23.6)</td>
<td>132 (73.7)</td>
</tr>
<tr>
<td>Secondary primary malignancies</td>
<td>28 (15.7)</td>
<td>13 (7.3)</td>
<td>24 (13.4)</td>
</tr>
<tr>
<td>Excluding nonmelanoma skin</td>
<td>15 (8.4)</td>
<td>10 (5.6)</td>
<td>11 (6.1)</td>
</tr>
</tbody>
</table>

# SEQUOIA: Phase 3 Open-Label Study of Zanubrutinib vs Bendamustine + Rituximab in TN CLL/SLL – Study Design and Efficacy

## Key Eligibility Criteria
- TN CLL/SLL
- Without del(17p)
- ≥65 years of age or unsuitable for FCR treatment

## Randomize

1:1

### Arm A
- Zanubrutinib
- 160 mg po bid
- n=241

### Arm B
- Bendamustine + rituximab<sup>a</sup>
- n=238

## Progression-Free Survival Probability

<table>
<thead>
<tr>
<th>No. of patients at risk</th>
<th>BR</th>
<th>Zanubrutinib</th>
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<tr>
<td></td>
<td>238</td>
<td>241</td>
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<table>
<thead>
<tr>
<th>Months</th>
<th>BR</th>
<th>Zanubrutinib</th>
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<tbody>
<tr>
<td>0</td>
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</tr>
<tr>
<td>3</td>
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<td>6</td>
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## IRC-assessed PFS

<table>
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<tr>
<th>HR (95% CI)</th>
<th>P value</th>
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<tr>
<td>0.42 (0.27 - 0.63)</td>
<td>&lt;0.0001</td>
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## 24-mo PFS, % (95% CI)

<table>
<thead>
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<th>Zanubrutinib (n=241)</th>
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<tr>
<td>85.5 (80.1–89.6)</td>
<td>69.5 (62.4–75.5)</td>
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## IRC-assessed ORR, % (95% CI)

<table>
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<th>Zanubrutinib (n=241)</th>
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</thead>
<tbody>
<tr>
<td>94.6 (91.0–97.1)</td>
<td>85.3 (80.1–89.5)</td>
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## CR, n (%)

<table>
<thead>
<tr>
<th>Zanubrutinib (n=241)</th>
<th>BR (n=238)</th>
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<tbody>
<tr>
<td>16 (6.6)</td>
<td>36 (15.1)</td>
</tr>
</tbody>
</table>

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<sup>a</sup> Bendamustine 90 mg/m² on day 1 and 2 and rituximab 375 mg/m² in cycle 1, 500 mg/m² in cycles 2-6 for 6 × 28-day cycles.

ELEVATE-RR: Phase 3 Study of Acalabrutinib vs Ibrutinib in Patients With R/R CLL – Study Design and Results

Key Eligibility Criteria
- Previously treated CLL
- Presence of del(17p) and/or del(11q)
- ECOG PS ≤2
- No significant CV disease, no concomitant treatment with warfarin or equivalent VKA
- No prior treatment with ibrutinib, a BCRi, or a BCL-2i

Primary Endpoint: Noninferiority on IRC-Assessed PFS

Secondary Endpoints: Incidence of any-grade atrial fibrillation/flutter, incidence of grade ≥3 infection, incidence of RT, OS

Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Acala (n=268)</th>
<th>Ibr (n=265)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>66 (41-89)</td>
<td>65 (28-88)</td>
</tr>
<tr>
<td>ECOG PS 0-1, n (%)</td>
<td>247 (92)</td>
<td>243 (92)</td>
</tr>
<tr>
<td>Bulky disease ≥5 cm, n (%)</td>
<td>128 (48)</td>
<td>136 (51)</td>
</tr>
<tr>
<td>Rai stage 3 or 4, n (%)</td>
<td>131 (49)</td>
<td>134 (51)</td>
</tr>
<tr>
<td>Cytogenetics, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>del(17p)</td>
<td>121 (45)</td>
<td>120 (45)</td>
</tr>
<tr>
<td>del(11q)</td>
<td>167 (62)</td>
<td>175 (66)</td>
</tr>
<tr>
<td>Complex karyotype</td>
<td>124 (46)</td>
<td>125 (47)</td>
</tr>
<tr>
<td>TP53 mutated</td>
<td>100 (37)</td>
<td>112 (42)</td>
</tr>
<tr>
<td>IGHV unmutated</td>
<td>220 (82)</td>
<td>237 (89)</td>
</tr>
<tr>
<td>Prior therapies, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>2 (1-9)</td>
<td>2 (1-12)</td>
</tr>
<tr>
<td>1-3</td>
<td>234 (87)</td>
<td>237 (89)</td>
</tr>
<tr>
<td>≥4</td>
<td>33 (12)</td>
<td>28 (11)</td>
</tr>
</tbody>
</table>

*Patients with ≥3 chromosomal abnormalities.
ELEVATE-RR: Phase 3 Study of Acalabrutinib vs Ibrutinib in Patients With R/R CLL – Post Hoc Safety Analysis

<table>
<thead>
<tr>
<th>Events of clinical interest</th>
<th>Incidence, %</th>
<th>Exposure-Adjusted Incidence&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Exposure-Adjusted Time With Event&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade ≥3</td>
<td>Any Grade</td>
</tr>
<tr>
<td></td>
<td>Acala&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Ibr&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Acala&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cardiac events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation/Flutter</td>
<td>24%</td>
<td>30%</td>
<td>9%</td>
</tr>
<tr>
<td>Hypertension&lt;sup&gt;e&lt;/sup&gt;</td>
<td>9%</td>
<td>16%*</td>
<td>5%</td>
</tr>
<tr>
<td>Bleeding events&lt;sup&gt;f&lt;/sup&gt;</td>
<td>38%</td>
<td>51%*</td>
<td>4%</td>
</tr>
<tr>
<td>Major bleeding events&lt;sup&gt;g&lt;/sup&gt;</td>
<td>5%&lt;sup&gt;i&lt;/sup&gt;</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Infections&lt;sup&gt;j&lt;/sup&gt;</td>
<td>78%</td>
<td>81%</td>
<td>31%</td>
</tr>
<tr>
<td>Selected common AEs&lt;sup&gt;k&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>35%</td>
<td>46%*</td>
<td>1%</td>
</tr>
<tr>
<td>Headache</td>
<td>35%*</td>
<td>20%</td>
<td>2%</td>
</tr>
<tr>
<td>Cough</td>
<td>29%&lt;sup&gt;k&lt;/sup&gt;</td>
<td>21%</td>
<td>1%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>20%</td>
<td>17%</td>
<td>3%*</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>16%</td>
<td>23%*</td>
<td>0</td>
</tr>
<tr>
<td>Back pain</td>
<td>8%</td>
<td>13%*</td>
<td>0</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>6%</td>
<td>13%*</td>
<td>0</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>4%</td>
<td>12%*</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup> Incidence, % exposure-adjusted.  
<sup>b</sup> Incidence, % exposure-adjusted time with event.  
<sup>c</sup> n=266.  
<sup>d</sup> n=263.  
<sup>e</sup> Includes hypertension, blood pressure increased, and blood pressure systolic increased.  
<sup>f</sup> Bleeding events occurring in ≥10% of patients in either treatment arm include contusion and epistaxis.  
<sup>g</sup> Any hemorrhagic event that was serious, grade ≥3, or a CNS hemorrhage (any grade).  
<sup>h</sup> Of 12 patients with major hemorrhage events in the Acala arm, CNS-related hemorrhage events were reported in 4 patients.  
<sup>i</sup> Of 14 patients with major hemorrhage events in the Ibrutinib arm, CNS-related hemorrhage events were reported in 1 patient who had 2 events.  
<sup>j</sup> Infections occurring in ≥10% of patients in either treatment arm include upper respiratory tract infection, pneumonia, bronchitis, nasopharyngitis, and urinary tract infection.  
<sup>k</sup> AEs occurring in ≥10% of patients in either treatment arm that are not already captured in the ECIs presented.  

* Two-sided P value <0.05 without multiplicity adjustment, for comparison of incidence based on Barnard’s exact test.  

- Median follow-up 40.9 months  
- Treatment ongoing 46% (Acala) and 41% (Ibr)  
- Most common reasons for discontinuation PD (31% Acala vs 26% Ibr), AEs (15% Acala vs 22 Ibr)  
- Median (range) treatment exposure 38.3 months (0.3-55.9) Acala vs 35.5 (0.2-57.7) Ibr
ALPINE: Phase 3 Study of Zanubrutinib vs Ibrutinib in Patients With R/R CLL/SLL – Study Design and Results

**Key Eligibility Criteria**
- R/R to ≥1 prior systemic therapy for CLL/SLL
- Measurable lymphadenopathy by CT or MRI
- No current or past RT, prior BTKi therapy, or warfarin/other VKA

**Primary endpoint:**
- ORR (CR+PR) noninferiority and INV-assessed superiority

**Secondary endpoints:**
- Any-grade atrial fibrillation
- DOR
- PFS
- OS
- Time to treatment failure
- PR-L or higher
- PROs
- Safety

**Select Patient Characteristics**
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Zanubrutinib (n=207)</th>
<th>Ibrutinib (n=208)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), y</td>
<td>67 (35-90)</td>
<td>67 (36-89)</td>
</tr>
<tr>
<td>Del(17p) and/or mut TP53</td>
<td>41 (19.8)</td>
<td>38 (18.3)</td>
</tr>
<tr>
<td>Del(11q)</td>
<td>61 (29.5)</td>
<td>55 (26.4)</td>
</tr>
</tbody>
</table>

**Efficacy, n (%)**

<table>
<thead>
<tr>
<th></th>
<th>Zanubrutinib (n=207)</th>
<th>Ibrutinib (n=208)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (CR+PR), 95% CI 162 (78.3), 72.0-83.7</td>
<td>130 (62.5), 55.5-69.1</td>
<td></td>
</tr>
<tr>
<td>CR/CRi</td>
<td>4 (1.9)</td>
<td>3 (1.4)</td>
</tr>
<tr>
<td>nPR</td>
<td>1 (0.5)</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>157 (77.1)</td>
<td>127 (61.1)</td>
</tr>
<tr>
<td>ORR (CR+PR+PR-L)</td>
<td>183 (84.4)</td>
<td>169 (81.3)</td>
</tr>
<tr>
<td>PR-L</td>
<td>21 (10.1)</td>
<td>39 (18.8)</td>
</tr>
<tr>
<td>SD</td>
<td>17 (8.2)</td>
<td>28 (13.5)</td>
</tr>
<tr>
<td>PD</td>
<td>1 (0.5)</td>
<td>2 (1.0)</td>
</tr>
</tbody>
</table>

**AEs of Special Interest**

<table>
<thead>
<tr>
<th>Category</th>
<th>Zanubrutinib (n=204)</th>
<th>Ibrutinib (n=207)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac disorders</td>
<td>28 (13.7)</td>
<td>52 (25.1)</td>
</tr>
<tr>
<td>Atrial fibrillation/flutter</td>
<td>5 (2.5)</td>
<td>21 (10.1)</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>73 (35.8)</td>
<td>75 (36.2)</td>
</tr>
<tr>
<td>Major hemorrhage</td>
<td>6 (2.9)</td>
<td>8 (3.9)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>34 (16.7)</td>
<td>34 (16.4)</td>
</tr>
<tr>
<td>Infections</td>
<td>122 (59.8)</td>
<td>131 (63.3)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>58 (28.4)</td>
<td>45 (21.7)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>19 (9.3)</td>
<td>26 (12.6)</td>
</tr>
<tr>
<td>Secondary primary malignancies</td>
<td>17 (8.3)</td>
<td>13 (6.3)</td>
</tr>
<tr>
<td>Skin cancer</td>
<td>7 (3.4)</td>
<td>10 (4.8)</td>
</tr>
</tbody>
</table>

**Notes:**
- 2 patients with missing values.
- In safety analysis population.
- Cardiac disorders leading to treatment discontinuation: 0 patients (zanubrutinib) vs 7 (3.4%) patients (ibrutinib).
- Includes hemorrhages that were serious or grade ≥3 or CNS hemorrhages of all grades.
- Pooled terms including neutropenia, neutrophil count decreased, and febrile neutropenia; thrombocytopenia and platelet count decreased.
Guidelines include zanubrutinib as an option in patients with relapsed/refractory CLL/SLL or frontline CLL with TP53 mutation and an intolerance or contraindication to other BTKis.
CLL14: 4-Year Follow-Up of Phase 3 Study of Venetoclax + Obinutuzumab vs Chlorambucil + Obinutuzumab – Study Design and Efficacy

Key Eligibility Criteria

- Patients with TN CLL and coexisting medical conditions
- CIRS >6 and/or CrCl <70 mL/min

Venetoclax-Obinutuzumab (Ven-G) (6 cycles) followed by venetoclax (6 cycles)

Chlorambucil-Obinutuzumab (Clb-G) (6 cycles) followed by chlorambucil (6 cycles)

Primary endpoint:
- PFS

Secondary endpoints:
- Response
- MRD
- OS

PFS (All Patients)

Median PFS
- Ven-G: NR
- Clb-G: 36.4 months

4-year PFS rate
- Ven-G: 74.0%
- Clb-G: 35.4%

HR 0.33, 95% CI [0.25-0.45] P<0.0001

CLL14: 4-Year Follow-Up of Phase 3 Study of Venetoclax + Obinutuzumab vs Chlorambucil + Obinutuzumab – PFS by Mutational Status

**PFS by TP53 Status**

**Median PFS**
- Ven-G & no TP53 del/mut: NR
- Ven-G & TP53 del/mut: 49.0 mo
- Clb-G & no TP53 del/mut: 38.9 mo
- Clb-G & TP53 del/mut: 20.8 mo

**PFS by IGHV Status**

**Median PFS**
- Ven-G & IGHV-mut: NR
- Ven-G & IGHV-unmut: 57.3 mo
- Clb-G & IGHV-mut: 54.5 mo
- Clb-G & IGHV-unmut: 26.9 mo

## CLL14: 4-Year Follow-Up of Phase 3 Study of Venetoclax + Obinutuzumab vs Chlorambucil + Obinutuzumab – Safety

<table>
<thead>
<tr>
<th>Most Frequent Grade ≥3 AEs,%</th>
<th>Ven-G (n=212)</th>
<th>Clb-G (n=214)</th>
<th>Secondary Primary Malignancies (SPM)</th>
<th>Ven-G (n=212)</th>
<th>Clb-G (n=214)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>During treatment</td>
<td>After treatment</td>
<td>During treatment</td>
<td>After treatment</td>
<td>Overall total number of events, n</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>51.9</td>
<td>4.0</td>
<td>47.2</td>
<td>1.9</td>
<td>47</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>13.7</td>
<td>0.5</td>
<td>15.0</td>
<td>0.0</td>
<td>42</td>
</tr>
<tr>
<td>Anemia</td>
<td>7.5</td>
<td>1.5</td>
<td>6.1</td>
<td>0.5</td>
<td>47</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>4.2</td>
<td>1.0</td>
<td>3.3</td>
<td>0.5</td>
<td>47</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>2.4</td>
<td>0.0</td>
<td>4.7</td>
<td>0.0</td>
<td>42</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3.3</td>
<td>3.0</td>
<td>2.8</td>
<td>1.4</td>
<td>47</td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td>9.0</td>
<td>0.0</td>
<td>9.8</td>
<td>0.5</td>
<td>47</td>
</tr>
<tr>
<td>Tumor lysis syndrome</td>
<td>1.4</td>
<td>0.0</td>
<td>3.3</td>
<td>0.0</td>
<td>42</td>
</tr>
</tbody>
</table>

GLOW: Phase 3 Study of Fixed-Duration Ibrutinib + Venetoclax vs Chlorambucil + Obinutuzumab in TN CLL – Study Design and Results

**Key Eligibility Criteria**

- Previously untreated CLL
- ≥65 years of age or <65 years with CIRS >6 or CrCl <70 mL/min
- No del(17p) or known TP53 mutation
- ECOG PS ≤2

**Randomize 1:1**

**Ibrutinib** 420 mg po qd lead-in (3 cycles) followed by Ibrutinib + Venetoclax (I+V) (12 cycles; venetoclax ramp-up 20-400 mg over 5 weeks beginning C4) n=106

**Chlorambucil (Clb)** 0.5 mg/kg on D1 & D15 x 6 cycles + **Obinutuzumab (O)** 1000 mg D1-2, D8, D15 of C1, and D1 of C2-6 n=105

**Primary endpoint:** IRC-assessed PFS

**Current MRD analysis**

- MRD reported with cutoffs of <10^-4 and <10^-5
- PB/BM concordance calculated for patients with uMRD in PB at EOT+3 who had paired BM sample
- PFS results updated with 34.1 months of follow-up

**Safety (Median Follow-Up of 27.7 Months)**

<table>
<thead>
<tr>
<th></th>
<th>I+V (N=106)</th>
<th>Clb+O (N=105)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median exposure, mo (range)</td>
<td>13.8 (0.7-19.5)</td>
<td>5.1 (1.8-7.9)</td>
</tr>
<tr>
<td>Grade 3 or Higher AEs in ≥5% of Patients, %</td>
<td>75.5</td>
<td>69.5</td>
</tr>
<tr>
<td>Neutropenia^a</td>
<td>34.9</td>
<td>49.5</td>
</tr>
<tr>
<td>Infections^b</td>
<td>17.0</td>
<td>11.4</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5.7</td>
<td>20.0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10.4</td>
<td>1.0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7.5</td>
<td>1.9</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>6.6</td>
<td>0</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>5.7</td>
<td>0</td>
</tr>
<tr>
<td>TLS</td>
<td>0</td>
<td>5.7</td>
</tr>
</tbody>
</table>

^a Includes neutrophil count decreased; grade ≥3 febrile neutropenia: 1.9% for I+V vs 2.9% for Clb+O. ^b Includes multiple preferred terms.

GLOW: Phase 3 Study of Fixed-Duration Ibrutinib + Venetoclax vs Chlorambucil + Obinutuzumab in TN CLL – MRD Response

- In the Ibr+Ven arm, most patients with uMRD <10^{-4} had deep responses of uMRD <10^{-5}

<table>
<thead>
<tr>
<th>uMRD concordance in PB/BM, %</th>
<th>Ibr + Ven</th>
<th>Clb + O</th>
</tr>
</thead>
<tbody>
<tr>
<td>At &lt;10^{-4}</td>
<td>92.9</td>
<td>43.6</td>
</tr>
<tr>
<td>At &lt;10^{-5}</td>
<td>90.9</td>
<td>36.8</td>
</tr>
</tbody>
</table>

- uMRD in patients with unmutated IGHV CLL
  - With Ibr+Ven, depth of MRD response was similar in BM and PB for patients with unmutated IGHV CLL
  - Among patients with mutated TP53, 5 of 7 achieved uMRD <10^{-5} in both BM and PB with Ibr+Ven

<table>
<thead>
<tr>
<th>Patients with sustained uMRD, %</th>
<th>Ibr+Ven</th>
<th>Clb+O</th>
</tr>
</thead>
<tbody>
<tr>
<td>uMRD &lt;10^{-4}</td>
<td>84.5</td>
<td>29.3</td>
</tr>
<tr>
<td>uMRD &lt;10^{-5}</td>
<td>80.4</td>
<td>26.3</td>
</tr>
</tbody>
</table>

- uMRD <10^{-4} rate decreased 6% with Ibr+Ven vs 27% with Clb+O
- Patients with detectable MRD ≥10^{-4} in the Ibr+Ven arm were less likely to convert to PD vs those in the Clb+O arm or have worsening of detectable MRD levels
Phase 2 CAPTIVATE Study

- CAPTIVATE (PCYC-1142) is an international, multicenter phase 2 study evaluating first-line treatment with 3 cycles of ibrutinib followed by 12 cycles of combined ibrutinib + venetoclax with 2 cohorts: MRD and FD

- Primary analyses of both cohorts have been previously reported\(^1\),\(^2\)
- Presented are updated results from the MRD cohort, with median time on study: 38.2 months (range, 15.0–47.9)
  - Median postrandomization follow-up: 24.0 months (range, 5.8–33.1)

MRD, minimal residual disease; FD, fixed-duration.
Enrolled to CAPTIVATE MRD Cohort
N=164

Eligible for randomization
n=149a

Confirmed uMRD defined as uMRD (<10^-4 by 8-color flow cytometry) over ≥2 assessments ≥3 months apart and in both PB and BM

Confirmed uMRD: 86/149 (58%)
uMRD Not Confirmedb: 63/149 (42%)

Randomize 1:1
Stratified by IGHV status

Placebo (n=43)
Median follow-up: 38.0 months

Ibrutinib (n=43)
Median follow-up: 39.6 months

Ibrutinib (n=31)
Median follow-up: 39.2 months

Ibrutinib + Venetoclax (n=32)
Median follow-up: 37.9 months

Not eligible for randomization (n=15)
• 5 patients discontinued during ibrutinib lead-in
• 10 patients discontinued during ibrutinib + venetoclax combination

Best MRD response after 12 cycles ibrutinib + venetoclax prerandomization
• 74% uMRD in PB
• 68% uMRD in BM

Includes 1 patient who discontinued venetoclax but completed planned treatment with ibrutinib. Did not meet criteria for uMRD because of detectable MRD in PB and/or BM or undetectable MRD in PB that was not confirmed at consecutive assessments.

BM, bone marrow; PB, peripheral blood.

ASH 2021, CAPTIVATE-MRD; Ghia et al.
3-Year PFS Rates Were ≥95% Across All Randomized Arms

- With an additional year of follow-up since the primary analysis, only 1 new PFS event occurred on study; a patient in the uMRD Not Confirmedibrutinib arm who had PD after 42 months
- 36-month OS was 99% overall (97%–100% across randomized treatment arms)

PFS, progression-free survival; Plb, placebo. Tick marks indicate patients with censored data.

Median follow-up = 38 months

ASH 2021, CAPTIVATE-MRD; Ghia et al.
MODULE 2: Relapsed/Refractory (R/R) CLL: Novel Investigational Strategies – Dr Smith
A 71-year-old man with CLL who received pirtobrutinib in combination with venetoclax/rituximab on a clinical trial

Dr Shaachi Gupta (Lake Worth, Florida)
Use of monoclonal antibody therapy for COVID-19 prevention and treatment

Dr Vignesh Narayanan (Lone Tree, Colorado)
Relapsed/Refractory (R/R) CLL; Novel Investigational Strategies

RTP Symposium
ASCO 2022

Mitchell R. Smith
NCCN CLL/SLL Guidelines: *Relapsed/Refractory Regimens*

<table>
<thead>
<tr>
<th>R/R without del(17p)/TP53 mutation</th>
<th>Preferred</th>
<th>Other recommended regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frail w/significant comorbidities OR ≥65 y and younger pts w/significant comorbidities</td>
<td>• Acalabrutinib (category 1) • Ibrutinib (category 1) • Venetoclax + rituximab (category 1) • Duvelisib • Idelalisib + rituximab</td>
<td>• Alemtuzumab ± rituximab • Chlorambucil + rituximab • Reduced-dose FCR • HDMP + rituximab • Idelalisib • Lenalidomide ± rituximab • Obinutuzumab • Venetoclax</td>
</tr>
<tr>
<td>&lt; 65 y without significant comorbidities</td>
<td>• Acalabrutinib (category 1) • Ibrutinib (category 1) • Venetoclax + rituximab (category 1) • Duvelisib • Idelalisib + rituximab</td>
<td>• Alemtuzumab ± rituximab • Bendamustine + rituximab • FC + ofatumumab • FCR • HDMP + rituximab • Idelalisib • Lenalidomide ± rituximab • Obinutuzumab • Ofatumumab • PCR • Venetoclax</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>R/R with del(17p)/TP53 mutation</th>
<th>Preferred</th>
<th>Other recommended regimens</th>
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<tbody>
<tr>
<td>• Acalabrutinib (category 1) • Ibrutinib (category 1) • Venetoclax + rituximab (category 1) • Duvelisib • Idelalisib + rituximab • Venetoclax</td>
<td>• Alemtuzumab ± rituximab • HDMP + rituximab • Idelalisib • Lenalidomide ± rituximab • Ofatumumab • Zanubrutinib (for patients with intolerance or contraindication to other BTKi)</td>
<td></td>
</tr>
</tbody>
</table>

Kinomes of BTK Inhibitors

Ibrutinib

Acalabrutinib

Zanubrutinib

BID vs QD Dosing

Efficacy depends on covalent, prolonged BTKi
Toxicity may depend on peak vs AUC?

RESONATE Final Analysis, 6-year F/U of PFS: Ibrutinib vs Ofatumumab in Previously Treated CLL/SLL

- ≥ 1 prior therapy (N=391)
- ECOG PS 0-1
- Measurable nodal disease by CT

ITT Population

Ibrutinib overcomes Unmutated IGHV, del11q and largely p53 as prognostic factors

Del17p/mutp53
Med PFS 40 mos

IGHV mutation status

Ibrutinib Outcome by Prior Lines of Therapy

- PFS rates at 5 years higher for ibrutinib treatment in earlier lines (first-line: 70%; 1-2 prior lines: 60%; ≥3 prior lines: 33%)
- Treatment in earlier lines resulted in better PFS for patients with high-risk prognostic features

- OS rates at 5 years higher for ibrutinib treatment in earlier lines (first-line: 83%; 1-2 prior lines: 72%; ≥3 prior lines: 58%)
- Median OS for overall population not reached for first-line and 1-2 prior, and was 67 months for ≥3 prior lines

BR ± Ibrutinib for R/R CLL/SLL

**Phase III HELIOS**

Pts with previously treated R/R CLL/SLL (N = 578)
- ECOG PS 0-1
- Measurable LN
- No del(17p)

Bendamustine-Rituximab (BR) + Ibrutinib
(starting Day 2, cycle 1)

Bendamustine-Rituximab + Placebo
(starting Day 2, cycle 1)

- ORR
  - Ibrutinib + BR, 82.7%
  - Placebo + BR, 67.8%
  - \( P < .0001 \)

- Similar toxicity in both arms except more mild bleeding events and atrial fibrillation with BR + I

**PFS**

<table>
<thead>
<tr>
<th>BR+I</th>
<th>BR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, mo</td>
<td>NR</td>
</tr>
</tbody>
</table>

HR (95% CI) 0.203 (0.150-0.276); \( P < .0001 \)

**OS**

<table>
<thead>
<tr>
<th>BR+I</th>
<th>BR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, mo</td>
<td>NR</td>
</tr>
</tbody>
</table>

HR (95% CI) 0.628 (0.385-1.024); \( P = .0598 \)

Acalabrutinib Monotherapy in R/R CLL (ASCEND)

R/R CLL (N=310)

Stratified by:
- Del(17p)
- ECOG PS 0-1 vs 2
- 1-3 vs ≥ 4 prior therapies

Randomized 1:1

Acalabrutinib

Idelalisib + Rituximab (IdR)
-OR-
Bendamustine + Rituximab (BR)

Primary Endpoint: PFS (IRC)

Crossover from IdR/BR allowed after confirmed PD

Ghia, P et al JCO 2020
ELEVATE-RR: PHASE III COMPARISON ACALABRUTINIB vs IBRUTINIB FOR RELAPSED/REFRACTORY CLL [with del(17p) or del(11q)]:
NON-INFERIORITY DESIGN AND SAFETY ENDPOINTS: Median follow-up: 41 months

EFFECTICACY
PFS-non-inferior

HR: 1.00 (95% CI: 0.79-1.27)

TOXICITY: ALL GRADES

<table>
<thead>
<tr>
<th></th>
<th>ACALABRUTINIB</th>
<th>IBRUTINIB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afib</td>
<td>N = 266</td>
<td>N = 263</td>
</tr>
<tr>
<td>Grade</td>
<td>All</td>
<td>≥ 3</td>
</tr>
<tr>
<td>Afib</td>
<td>9%</td>
<td>5%</td>
</tr>
<tr>
<td>HBP</td>
<td>9%</td>
<td>4%</td>
</tr>
<tr>
<td>AE to DC</td>
<td>15%</td>
<td>21%</td>
</tr>
</tbody>
</table>
**ALPINE: Phase 3 Rel/Ref CLL Comparing Zanubrutinib and Ibrutinib**

- ≥ 1 prior line; no prior BTKi
- Median age 67 yrs
- 19% del17p and/or mutp53
- Data cutoff 1 yr after 415th pt randomized

**TOXICITY**

<table>
<thead>
<tr>
<th>Grade</th>
<th>ZANUBRUTINIB</th>
<th>IBRUTINIB</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>N = 207</td>
<td>N = 208</td>
</tr>
<tr>
<td>≥ 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Afib</td>
<td>2.5%</td>
<td>1%</td>
</tr>
<tr>
<td>AEs</td>
<td>56%</td>
<td>51%</td>
</tr>
<tr>
<td>AE to DC</td>
<td>8%</td>
<td>13%</td>
</tr>
</tbody>
</table>

**PFS by Investigator Assessment**

- CR+PR 78 vs 63%
- PR-L 10 vs 18%

**DID PR-L COMPROMISE THIS RESULT?**

For del17p (N=50 total): ORR 83% vs 54%

*Hillman P et al EHA 2021*
MURANO Study Design  VR vs. BR

- **Primary endpoint**: investigator-assessed PFS
- **Secondary endpoint**: rates of clearance of MRD
- Clinical response and MRD\* in PB during Ven monotherapy and follow-up visits were assessed every 3 months for 3 years, then every 6 months thereafter, or until PD

---

*Undetectable MRD defined as <1 CLL cell/10,000 leukocytes, determined by ASO-PCR or flow cytometry per iwCLL recommendations for reporting of MRD. BR, bendamustine–rituximab; D1C1, day 1, cycle 1; D1C2-6, day 1, cycles 2-6; EOCT, end of combination treatment; EOT, end of treatment; MRD, minimal residual disease; PB, peripheral blood; PD, progressive disease/disease progression; R, randomization; R/R, relapsed/refractory VenR, venetoclax–rituximab

MURANO 5-Year Follow-Up: Overall and Progression-Free Survival (All Patients)

MURANO: PFS by Depth of Response (MRD) at End of Treatment

**MRD status at EOT (month 24; n = 130)**

- **uMRD (<10^{-4})**
  - n = 83
  - Status off-therapy, n (%)
    - Progression-free: 72 (86.7)
    - PD: 11 (13.3)

- **Low-MRD+ (10^{-4}-10^{-2})**
  - n = 23
  - Status off-therapy, n (%)
    - Progression-free: 14 (60.9)
    - PD: 9 (39.1)

- **High-MRD+ (>10^{-2})**
  - n = 14
  - Status off-therapy, n (%)
    - Progression-free: 1 (7.1)
    - PD: 13 (92.9)

- **Unknown**
  - n = 10
  - Status off-therapy, n (%)
    - Progression-free: 8 (80.0)
    - PD: 2 (20.0)

**Graph:**
- 18-month PFS:
  - uMRD: 80.3% (95% CI, 83.5% to 97.0%)
  - Low-MRD+: 64.4% (95% CI, 42.1% to 86.6%)
  - High-MRD+: 9.3% (95% CI, 0.0% to 24.0%)

**Legend:**
- VenR uMRD
- VenR low MRD positivity
- VenR high MRD positivity

Venetoclax Responses Durable in Patients with CLL Relapsed/Refractory After Prior Ibrutinib and/or Idelalisib

• In patients with CLL R/R to ibrutinib and/or idelalisib treated with venetoclax monotherapy, median PFS was 24.7 months
• Median DoR and median OS were not reached after 24 months of follow-up

Median number of prior therapies in all patients: 4 (1-15)

What About Treatment Post-Venetoclax?

MURANO: post-Ven-R treatment outcomes

<table>
<thead>
<tr>
<th></th>
<th>ALL</th>
<th>Novel Agents</th>
<th>BTKi</th>
<th>Ven-based</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>99</td>
<td>52</td>
<td>18</td>
<td>32</td>
</tr>
<tr>
<td>ORR</td>
<td>71%</td>
<td>79%</td>
<td>100%</td>
<td>72%</td>
</tr>
<tr>
<td>Median duration (mos)</td>
<td>6</td>
<td>14</td>
<td>22</td>
<td>11</td>
</tr>
</tbody>
</table>

Harrup RA et al. ASH 2020 A3139.

**Abbreviations:** CR: complete response, PR: partial response, SD: stable disease, PD: progression of disease

Thompson MC et al. 2020 ASH 2020, A3136.
Therapy Post-Venetoclax Discontinuation in CLL:
Multicenter, retrospective cohort study (31 centers internationally, UK CLL Forum and Collaborative Study of Real World Evidence (CORE)

<table>
<thead>
<tr>
<th>Post-Ven Therapy</th>
<th>BTKi-naïve</th>
<th>BTKi-exposed</th>
<th>BTKi-naïve</th>
<th>BTKi-exposed</th>
<th>BTKi-naïve</th>
<th>BTKi-exposed</th>
<th>CAR-T</th>
<th>Anti-CD20 abs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agents</td>
<td>Ibrutinib</td>
<td>Acalabrutinib</td>
<td>Ibrutinib</td>
<td>Acalabrutinib</td>
<td>Ibrutinib</td>
<td>Acalabrutinib</td>
<td>IDelalisib</td>
<td>Duvelisib</td>
</tr>
<tr>
<td>Pre-Ven Exposure</td>
<td>BTKi-naïve</td>
<td>BTKi-exposed</td>
<td>BTKi-naïve</td>
<td>BTKi-exposed</td>
<td>BTKi-naïve</td>
<td>BTKi-exposed</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>44</td>
<td>20</td>
<td>10</td>
<td>17</td>
<td>18</td>
<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>83.9%</td>
<td>53%</td>
<td>70%</td>
<td>46.9%</td>
<td>66.6%</td>
<td>32%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>9%</td>
<td>6.6%</td>
<td>20%</td>
<td>5.9%</td>
<td>33.3%</td>
<td>16%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>56.8%</td>
<td>26.4%</td>
<td>30%</td>
<td>35.2%</td>
<td>33.3%</td>
<td>16%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR-L</td>
<td>18.1%</td>
<td>20%</td>
<td>20%</td>
<td>5.8%</td>
<td>0%</td>
<td>0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>11.6%</td>
<td>20%</td>
<td>-</td>
<td>23.7%</td>
<td>5.7%</td>
<td>32%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>4.5%</td>
<td>27%</td>
<td>30%</td>
<td>29.4%</td>
<td>27.7%</td>
<td>37%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ven DC’d for:
- CLL PD 38%
- AE 14%
- Richter 14%
- Pt pref 8%
- alloSCT 6%

What about Combining BTKi + BCL2i? Already in 1\textsuperscript{st} Line
Ibrutinib-Venetoclax in R/R CLL: BM MRD4 Responses

### Treatment schema

<table>
<thead>
<tr>
<th>C1</th>
<th>C2</th>
<th>C3</th>
<th>C4→27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibrutinib</td>
<td>420mg daily</td>
<td>420mg daily</td>
<td>420mg daily</td>
</tr>
<tr>
<td>Venetoclax</td>
<td>-</td>
<td>-</td>
<td>20mg daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 week;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>50mg daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 week;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>100mg daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 week;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>200mg daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 week;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>400mg daily</td>
</tr>
</tbody>
</table>

**Duration of therapy:** 24 cycles of combination treatment
- If BM MRD+ at 24 cycles, ibrutinib alone continues until PD

74 patients initiated combination
- 5 patients off-study during ibrutinib monotherapy

Median follow-up 27 months

---

# Summary of Approved PI3K Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Idelalisib</th>
<th>Copanlisib</th>
<th>Duvelisib</th>
<th>Umbralisib</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Isoform</strong></td>
<td>δ</td>
<td>αδ</td>
<td>γδ</td>
<td>δ (and CK1-epsilon)</td>
</tr>
<tr>
<td><strong>FDA-approved indications</strong></td>
<td>• R CLL (w/rituximab)</td>
<td>• R FL (≥2 prior systemic tx)</td>
<td>• R/R CLL (≥2 prior systemic tx)</td>
<td>• R/R MZL (≥1 prior anti-CD20–based tx)</td>
</tr>
<tr>
<td>• R SLL (≥2 prior systemic tx)</td>
<td></td>
<td></td>
<td>• R/R SLL (≥2 prior systemic tx)</td>
<td>• R/R FL (≥2 prior systemic tx)</td>
</tr>
<tr>
<td>• R FL (≥2 prior systemic tx)</td>
<td></td>
<td></td>
<td>• R/R FL (≥2 prior systemic tx)</td>
<td>• R/R FL (≥3 prior systemic tx)</td>
</tr>
<tr>
<td><strong>Use w/o rituximab</strong></td>
<td>No—CLL</td>
<td>Yes—SLL</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Method of administration</td>
<td>Oral</td>
<td>IV</td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>150 mg twice daily</td>
<td>60 mg as a 1-hour intravenous infusion on Days 1, 8, and 15 of a 28-day treatment cycle</td>
<td>25 mg twice daily</td>
<td>800 mg orally once daily with food</td>
</tr>
<tr>
<td><strong>Black box Warnings</strong></td>
<td>Hepatotoxicity, diarrhea or colitis, pneumonitis, infection, intestinal perforation</td>
<td>None</td>
<td>Infection, diarrhea or colitis, cutaneous reactions, pneumonitis</td>
<td>None</td>
</tr>
</tbody>
</table>

What’s on the Horizon?

• New BTKi: non-covalent
• New BCL2i: which members of BCL2 family need to be affected
• New PI3Ki: dosing/scheduling being re-evaluated
• New antibody-based therapy: Targets (ROR1); ADC; Bispecifics
• Immune modulatory agents
• CART
• COMBINATIONS/SEQUENCES
• What do we do when everything has been used in initial therapy?
  • CLONAL DYNAMICS/Mechanisms of Resistance to personalize therapy
Non-Covalent BTK Inhibitors

• Resistance to covalent BTKi often due to mutation in binding site
• Non-covalent BTKi are not inhibited by such mutations
• Pirtobrutinib (LOXO-305) blocks the ATP binding site in BTK, with minimal off-target inhibition
  • ARQ-531 hydrogen binds to amino acids 475&476, may block downstream of PLCgamma2 (another mechanism of BTKi resistance)
• In Phase 1/2 BRUIN trial no MTD was reached, RP2D is 200 mg/d
  >100 mg/d inhibited BTK at > IC90 throughout the dosing interval
• Most common Gr 3-4 AE neutropenia (10%); well tolerated
• In CLL/SLL (N=121) with prior BTKi, ORR = 62%
  • Prior BTKi resistance 67%
  • Prior BTKi intolerance 52%
  • C481 mutant 71%/BTK wt 66%

Mato AR et al. BRUIN Trial. Lancet 2021
BRUIN: Updated Pirtobrutinib Efficacy Findings

Mato AR et al. ASH 2021;Abstract 391.
### BRUIN: Updated Pirtobrutinib Safety Findings

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>All doses and patients (n=618)</th>
<th>Treatment-emergent AEs, (≥15%), %</th>
<th>Treatment-related AEs, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1</td>
<td>Grade 2</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>13%</td>
<td>8%</td>
<td>1%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15%</td>
<td>4%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Neutropenia*</td>
<td>1%</td>
<td>2%</td>
<td>8%</td>
</tr>
<tr>
<td>Contusion</td>
<td>15%</td>
<td>2%</td>
<td>-</td>
</tr>
<tr>
<td>AEs of special interest b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bruising c</td>
<td>20%</td>
<td>2%</td>
<td>-</td>
</tr>
<tr>
<td>Rash d</td>
<td>9%</td>
<td>2%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>8%</td>
<td>3%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Hemorrhage e</td>
<td>5%</td>
<td>2%</td>
<td>1%&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1%</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Atrial fibrillation/flutter f</td>
<td>-</td>
<td>1%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

No DLTs reported and MTD not reached
96% of patients received ≥1 pirtobrutinib dose at or above RP2D of 200 mg daily
1% (n=6) of patients permanently discontinued due to treatment-related AEs

Mato AR et al. ASH 2021;Abstract 391.
Will Other BH3 Mimetics Be Useful?
Lisaftoclax (APG-2575), efficacy in patients with CLL/SLL (ORR = 80%)

**Median (range) treatment of 9 cycles** (Range 5-24 cycles)

12 of 15 evaluable R/R CLL/SLL patients achieved partial response (PR) by 2008 iwCLL definition, for an **objective response rate of 80%**

**Median time to response of 2 cycles** (Range 2-8 cycles)

---

*Presented By: Sikander Ailawadhi, MD*  
*Source: Company data  SLIDE COURTESY OF DR> ASHER CHANAN_KHAN*
Anti-ROR1 Cirmtuzumab in CLL

“Naked” Antibody Phase 1, Choi MY et al Cell Stem Cell 22:951-959, 2018

Zilovertamab vedotin (ZV; previously VLS-101), ADC of cirmtuzumab, Phase I Wang M et al NEJM 2021

7/15 ORR MCL, not very active in CLL but N = 7
MODULE 3: Follicular Lymphoma (FL) – Dr Leonard
A 76-year-old woman with Stage III, Grade 1/2 FL now requiring treatment

Dr Shams Bufalino (Park Ridge, Illinois)
A 77-year-old man with newly diagnosed Grade I to II/III FL and a Ki-67 score of 80%

Dr Philip Brooks (Brewer, Maine)
A 77-year-old woman with EZH2 wild-type R/R FL who received tazemetostat

Dr Spencer Bachow (Boca Raton, Florida)
Updates in follicular lymphoma

John P Leonard, MD
Richard T Silver Distinguished Professor of Hematology and Medical Oncology
Senior Associate Dean for Innovation and Initiatives
Executive Vice Chair, Joan and Sanford I Weill Department of Medicine
Weill Cornell Medicine
New York, New York
How to treat advanced stage, high tumor burden FL?
One approach: Bendamustine-Rituximab vs R-CHOP

PFS (StiL)
Median (IQR, months)
Not reached (22.1–not reached)
40.9 (15.2–not reached)

HR 0.61 (95% CI 0.42–0.87)
p = 0.0072

OS for FL patients

Median for R-CHOP+ observation: 40.9 mo

PRIMA: Maintenance R after R-CHOP/R-CVP improves PFS but not OS

Salles G, et al, ASH 2017
GALLIUM: Obinutuzumab vs Rituximab with chemotherapy (and as maintenance)

GALLIUM: Obinutuzumab vs Rituximab with chemotherapy (and as maintenance) improves PFS but not OS

Can we give Obinutuzumab short infusions?
Gazelle study

- Phase IV study of Obinutuzumab administered in 90 min infusion in upfront FL patients from cycle 2 onwards
  - Cycle 1 day 1, 8, 15 standard rate, if no G3 IRR, onward 90 min
- 113 patients, only one had grade 3 tox with subsequent 90 min infusion rate
- > 90% pts completed infusions in under 2 hours
- Now FDA approved regimen

Hubel et al, ICML 2021
Trask et al, ASH 2021
RELEVANCE: Lenalidomide-Rituximab (R2) vs Chemo-R

Previously untreated patients with advanced FL requiring treatment per GEFL\(^{1,2}\) (N = 1,030)

Treatment period 1 (28 weeks)  Treatment period 2 (48 weeks)  Treatment period 3 (44 weeks)

R\(^2\)  R\(^2\)  Rituximab

R-chemo  Rituximab

Total treatment duration: 120 weeks

Morschhauser F, et al, NEJM 2018
RELEVANCE: Lenalidomide-Rituximab (R2) vs Chemo-R
Similar ORR and CR as initial therapy for FL

Morschhauser F, et al, NEJM 2018
RELEVANCE: Lenalidomide-Rituximab (R2) vs Chemo-R
Similar PFS and OS as initial therapy for FL

Morschhauser F, et al, NEJM 2018
Long term f/u of RELEVANCE study

- Median f/u 6 years
- 6 year PFS 60% R2 vs 59% R chemo
- Transformation rates similar (2% range)
- Similar ORR and OS with subsequent therapy in both groups
- Similar rates of second primary malignancies
- 6 year OS 89% in both groups

Morschhauser et al, ASH 2021
Key agents for recurrent FL

- Rituximab retreatment
- Obinutuzumab combination
- Radioimmunotherapy
- Lenalidomide + rituximab
- PI3K inhibitors
- EZH2 inhibitors
- Auto/Allo SCT
- CAR-T
- Novel agents
AUGMENT: $R^2$ vs rituximab monotherapy in R/R iNHL

- Primary endpoint: PFS by IRC (2007 IWG criteria w/o PET)

**Relapsed/refractory FL and MZL (N = 358)**

1:1

**R-lenalidomide ($R^2$)**
- Rituximab: 375 mg/m² d1, 8, 15, 22 of cycle 1; d1 of cycles 2-5
- Lenalidomide: 20 mg/d*, d1-21/28 (12 cycles)
  *10 mg if CrCl between 30 to 59 mL/min.

**R-placebo**
- Rituximab: 375 mg/m² d1, 8, 15, 22 of cycle 1; d1 of cycles 2-5
- Placebo: matched capsules (12 cycles)
  - Prophylactic anticoagulation / antiplatelet Rx recommended for at risk patients
  - Growth factor use was allowed per ASCO/ESMO guidelines¹,²

**Stratification**
- Prior rituximab (yes vs no)
- Time since last therapy (≤ 2 vs > 2 y)
- Histology (FL vs MZL)

**Key eligibility criteria**
- MZL or FL (grades 1-3a) in need of treatment
- ≥ 1 prior chemotherapy, immunotherapy or chemoimmunotherapy
- Not rituximab refractory

**5-year follow-up for OS, SPMs, subsequent treatment, and histological transformations**

NCT01938001

AUGMENT primary endpoint: Progression-free survival (ITT, IRC)

*Censoring rules based on FDA guidance.
Data cutoff June 22, 2018.

Leonard et al. JCO 2019

**Median PFS**

<table>
<thead>
<tr>
<th></th>
<th>R² (n = 178)</th>
<th>R-placebo (n = 180)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>By IRC, mo (95% CI)</td>
<td>39.4 (22.9-NE)</td>
<td>14.1 (11.4-16.7)</td>
<td>0.46 (0.34-0.62)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>By investigator, mo (95% CI)</td>
<td>25.3 (21.2-NE)</td>
<td>14.3 (12.4-17.7)</td>
<td>0.51 (0.38-0.69)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>
**GADOLIN study: bendamustine vs bendamustine + obinutuzumab in rituximab-refractory iNHL**

**Rituximab-refractory CD20 + iNHL**
- (including FL, MZL, and SLL), n = 413

**Stratification factors**
- NHL subtype (FL vs other)
- Prior therapies (≤ 2 vs > 2)
- Refractory type (R-mono vs R-chemo)
- Geographic region

**Obinutuzumab**
- 1,000 mg i.v. Days 1, 8, and 15 Cycle 1;
  - Day 1 Cycles 2–6 (28-day cycles)

**Bendamustine**
- 90 mg/m²/day i.v. Days 1 and 2
  - Cycles 1–6 (28-day cycles)

CR/PR/SD

**Obinutuzumab maintenance**
- 1,000 mg i.v. q2mo for 2 years or until progression

Response monitored by CT scan post-induction, then every 3 months for 2 years, then every 6 months

GADOLIN study: obinutuzumab improves PFS and OS in recurrent iNHL when added to bendamustine

The addition of obinutuzumab also improved PFS in patients who were refractory to both alkylators and rituximab

- HR 0.56 (0.40–0.78)

Final analysis: Median OS was 88.3 months with the addition of obinutuzumab vs 65.6 months

- HR 0.77; p = 0.0810

PI3K inhibitors with FL FDA indications withdrawn from market

- **Idelalisib** (Gopal NEJM 2014)
  - ORR in iNHL 59%, median duration 11.2 mo

- **Duvelisib** (Zinzani ICML 2017)
  - ORR iNHL 46%, median duration 9.9 mo

- **Umbralisib** (FDA 2021)
  - ORR FL 43%, median duration 11.1 mo
PFS of Copanlisib in R/R Indolent Lymphoma


<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>142</th>
<th>54</th>
<th>14</th>
<th>8</th>
<th>1</th>
<th>0</th>
</tr>
</thead>
</table>

Median, mo | 11.2 |
Range | 0.2-24.0 |
95% CI | 8.1-24.0 |

ORR 59% (12% CR)
Chronos-3 study (Copanlisib + Rituximab vs Placebo + Rituximab)

- Randomized trial of Copanlisib/R vs Placebo/R (Lancet Oncol 2021)
  - 307 pts, recurrent indolent lymphoma
  - 79% ORR/34% CR in C/R arm, 20.4 months DoR
  - Favored C/R vs P/R by primary endpoint
  - Followup analysis (ASH 2021) – longer response for those remaining on therapy vs d/c for toxicity but some durable responses after early discontinuation

Matasar et al, Lancet Oncol 2021
**Follicular Lymphoma and EZH2**

- **EZH2** an epigenetic regulator of gene expression and cell fate decisions\(^1\)

- **EZH2** is required for normal B-cell biology and germinal center formation\(^2\)
  - Oncogenic mutations in **EZH2** suppress exit from germinal state and "lock" B cells in this state thereby transforming into a cancer\(^2\)

- **EZH2** biology relevant in both mutant (MT) and wild-type (WT) **EZH2** FL
  - \(~20\%\) of patients with FL also have **EZH2** gain of function mutations\(^3\)

---

## Tazemetostat ORR in EZH2 mutant and wild type populations (recurrent FL)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Investigator (n=45)</th>
<th>IRC (n=54)</th>
<th>Investigator (n=54)</th>
<th>IRC (n=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n (%)</td>
<td>35 (78)</td>
<td>31 (69)</td>
<td>18 (33)</td>
<td>19 (35)</td>
</tr>
<tr>
<td>CR, n (%)</td>
<td>4 (9)</td>
<td>6 (13)</td>
<td>3 (6)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>PR, n (%)</td>
<td>31 (69)</td>
<td>25 (56)</td>
<td>15 (28)</td>
<td>17 (31)</td>
</tr>
<tr>
<td>SD, n (%)</td>
<td>10 (22)</td>
<td>13 (29)</td>
<td>16 (30)</td>
<td>18 (33)</td>
</tr>
<tr>
<td>PD, n (%)</td>
<td>0</td>
<td>1 (2)c</td>
<td>16 (30)</td>
<td>12 (22)</td>
</tr>
<tr>
<td>DOR, months, median (95% CI)</td>
<td>8.3 (5.5–13.8)</td>
<td>10.9 (7.2–NE)</td>
<td>14.7 (7.6–NE)</td>
<td>13.0 (5.6–NE)</td>
</tr>
</tbody>
</table>

Morschhauser, ICML 2019
## Structure of selected BITE and bispecific antibodies

<table>
<thead>
<tr>
<th>Bispecific Antibody</th>
<th>Targets</th>
<th>Design</th>
<th>Ig Fragment Formats</th>
<th>Ref.</th>
</tr>
</thead>
</table>
| blinatumomab        | CD19 x CD3 | • two murine scFv joined by a glycine-serine linker  
                      • monovalent CD19 and monovalent CD3 binding  
                      • cloned from anti-CD19 (clone H1D3) and anti-CD3 (clone L2K G7) murine mAbs | 1, 2, 3 |
| mosunetuzumab       | CD20 x CD3 | • humanized mouse heterodimeric IgG1-based antibody  
                      • monovalent CD20 and monovalent CD3c binding  
                      • modified Fc devoid of FcyRI and complement binding | 4 |
| glofitamab          | (CD20)2 x CD3 | • humanized mouse IgG1-based antibody  
                      • blivalent CD20 and monovalent CD3c binding  
                      • modified Fc devoid of FcyRI and complement binding | 5 |
| odrnextamab         | CD20 x CD3 | • fully human IgG4 based heterodimeric antibody  
                      • monovalent CD20 and monovalent CD3c binding  
                      • Fc-dependent effector function-mimimized antibody with Fc of the anti-CD3c heavy chain modified to reduce Protein A binding  
                      • common x light chain from anti-CD3c mAb | 6 |
| epocritamab         | CD20 x CD3 | • humanized mouse IgG1-based heterodimeric antibody  
                      • monovalent CD20 and monovalent CD3c binding  
                      • IgG1Fc modified to minimize Fc-dependent effector functions and to control Fab-arm exchange of mAb half-molecules, resulting in high bispecific product yield | 7 |

Ig, immunoglobulin; scFv, single chain variable fragment; mAb, monoclonal antibody; Fc, fragment crystallizable; FcyRI, Fc gamma receptor


Schuster et al, ICML 2021
Single-Agent Mosunetuzumab Shows Durable Complete Responses in Patients With Relapsed or Refractory B-Cell Lymphomas: Phase I Dose-Escalation Study

Lihua E. Budde, MD¹; Sarit Assouline, MD²; Laurie H. Sehn, MD³; Stephen J. Schuster, MD⁴; Sung-Soo Yoon, MD, PhD⁵; Dok Hyun Yoon, MD, PhD⁶; Matthew J. Matasar, MD⁷; Francesc Bosch, MD, PhD⁸; Won Seog Kim, MD, PhD⁹; Loretta J. Nastoupil, MD¹⁰; Ian W. Flinn, MD, PhD¹¹; Mazyar Shadman, MD, MPH¹²; Catherine Diefenbach, MD¹³; Carol O’Hear, MD, PhD¹⁴; Huang Huang, MSc¹⁵; Antonia Kwan, MBBS, PhD¹⁴; Chi-Chung Li, PhD¹⁴; Emily C. Piccione, PhD¹⁴; Michael C. Wei, MD, PhD¹⁴; Shen Yin, PhD¹⁴; and Nancy L. Bartlett, MD¹⁶

Best Percentage Change from Baseline in Indolent NHL, Including Grade 1-3a FL

ORR: 66.2%
Median duration of response: 16.8 mos
Median PFS: 11.8 mos
Adverse Events with Incidence ≥ 10%

All AEs AEs Related to Mosunetuzumab

- Cytokine Release Syndrome
- Hypophosphatemia
- Fatigue
- Neutropenia
- Diarrhea
- Anemia
- Headache
- Back Pain
- Nausea
- Pyrexia
- Constipation
- Cough
- Upper Respiratory Tract Infection
- Hypokalemia
- Malignant Neoplasm Progression
- Edema Peripheral
- Hypomagnesemia
- Rash
- Insomnia
- Chills
- Decreased Appetite
- Dizziness
- Pneumonia
- Sepsis
- Candida Sepsis

Frequency (%) Frequency (%)

Grade
1
2
3
4
5

Glofitamab, a Novel, Bivalent CD20-Targeting T-Cell–Engaging Bispecific Antibody, Induces Durable Complete Remissions in Relapsed or Refractory B-Cell Lymphoma: A Phase I Trial

Martin Hutchings, PhD1; Franck Morschhauser, MD, PhD2; Gloria Iacoboni, MD3,4; Carmelo Carlo-Stella, MD5; Fritz C. Offner, MD, PhD6; Anna Sureda, MD, PhD7; Gilles Salles, MD8; Joaquín Martínez-Lopez, MD, PhD, MBA9; Michael Crump, MD10; Denise N. Thomas, MSc11; Peter N. Morcos, PharmD11; Cristiano Ferlini, MD11; Ann-Marie E. Bröske, PhD12; Anton Bélousov, PhD13; Marina Bacac, PhD13; Natalie Dimier, PhD14; David J. Carlile, PhD14; Linda Lundberg, PhD15; David Perez-Callejo, MD, PhD15; Pablo Umaña, PhD13; Tom Moore, MD12; Martin Weisser, MD12; and Michael J. Dickinson, MBBS, DMedSci16

Response to Glofitamab in Patients with R/R B-Cell Lymphomas

ORR (transformed FL, N = 29): 55.2%
ORR (Grade 1-3A FL, N = 44): 70.5%

Glofitamab as Monotherapy and in Combination with Obinutuzumab Induces High Complete Response Rates in Patients with Multiple Relapsed or Refractory (R/R) Follicular Lymphoma (FL)

Franck Morschhauser,1 Carmelo Carlo-Stella,2 Michael Dickinson,3 Tycey Phillips,4 Roch Houot,5 Fritz Offner,6 Corinne Haioun,7 Paolo Corradini,8 Martin Hutchings,9 Anna Sureda,10 Joaquin Martinez-Lopez,11 Tomasz Wróbel,12 Shang-Ju Wu,13 Linda Lundberg,14 Estefania Mulvihill,14 David Perez-Callejo,14 James Reif,15 Anesh Panchal,16 Kathryn Humphrey,15 Emmanuel Bach16

1CHU Lille, Service des Maladies du Sang, F-59000 Lille, France; 2Humanitas University and Humanitas Research Hospital, Milan, Italy; 3Peter MacCallum Cancer Centre, Royal Melbourne Hospital and The University of Melbourne, Melbourne, Australia; 4University of Michigan Medical School, Ann Arbor, Michigan, USA; 5CHU de Rennes, Université de Rennes, INSERM U1236, EFS, Rennes, France; 6University Ziekenhuis Gent, Ghent, Belgium; 7Hotel Henri Mondor, AP-HP, Créteil, France; 8University of Milan, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; 9Rigshospitalet, Copenhagen, Denmark; 10Hospital Universitario 12 de Octubre (H12O), Centro Nacional de Investigaciones Oncológicas (CNO) and Universidad Complutense de Madrid, Madrid, Spain; 11Wroclaw Medical University, Wroclaw, Poland; 12National Taiwan University Hospital, Taipei, Taiwan; 13Hoffmann-La Roche Ltd, Basel, Switzerland; 14Roche Products Ltd, Welwyn Garden City, United Kingdom; 15Hopices Civils de Lyon and Université Claude Bernard, Pierre-Bénite, France.

Accepted as an Oral Presentation at the 63rd ASH Annual Meeting and Exposition
Phase I/II Study of Glofitamab as Monotherapy or in Combination with Obinutuzumab for R/R FL

- Myelosuppression was more common with the combination
- CRS rates were high and comparable, and cases were mainly low grade

Morschhauser F et al. ASH 2021;Abstract 128.
Key challenges in management of follicular lymphoma

- What will it take to “dislodge” watch and wait as a standard option?
  - Randomized trial with OS benefit? Clear QOL benefit? Evidence of “cure”?
- How will we ever define a “cure”?
  - Potentially “cured” patients can relapse 15+ years later
  - Should “functional cure” be the goal and how is that defined?
- How can we better choose individualized “QOL targeted” rx?
  - For regimens with similar OS, value of PFS benefit vs QOL
- Can we move to risk-adapted rx (induction, consolidation, maintenance)?
  - Prognostic scores, tumor/patient profiling, PET, MRD, ctDNA
MODULE 4: Mantle Cell Lymphoma (MCL) – Dr Lunning
A 77-year-old woman with newly diagnosed asymptomatic MCL with extranodal involvement

A 56-year-old man with blastoid variant MCL with a TP53 mutation
An 83-year-old man with MCL and disease progression on acalabrutinib

Dr Shams Bufalino (Park Ridge, Illinois)
Mantle Cell Lymphoma

Wrestle Mania

Matthew Lunning D.O. FACP
Associate Professor
Objectives

- Discuss current use of Bruton Tyrosine Kinase (BTK) inhibitors (i) in 1st line and relapsed/refractory (rel/ref) mantle cell lymphoma (MCL)
- Discuss results from studies presented at ASCO 2022 in MCL
- Discuss trial outcomes with BTK in combination with other systemic therapies for patients with MCL
- Discuss the outcomes of pirtobrutinib in patients with rel/ref MCL
- Discuss new agents and strategies in MCL
BTK Cage Match
BTK Cage Match

**Ibrutinib**
Median prior txs = 2
- mPFS = 14.6 months
- mPFS = 8.6 months

**Acalabrutinib**
Median prior txs = 2

**Zanubrutinib**
Median prior txs = 1
- mPFS = 21 months

p< 0.0001

Entering the Cage Match

Ibrutinib

Progression-free survival (% patients)

Median 25.4 mo
(95% CI: 17.5-57.5)

Median 10.3 mo
(95% CI: 8.1-12.5)

Patients at risk
1 prior line
>1 prior line

Rule et al. Haematologica 2019
Starting The Cage Match

Ibrutinib

![Graph showing PFS (probability) over time (months) for Ibrutinib with different Ki-67% values.](image)

No. at risk (events):

| Ki-67% <30 | 38 (1) 37 (1) 35 (1) 33 (0) 29 (0) 23 (0) 22 (0) 20 (1) 14 (0) 11 (0) 6 (0) 0 |
| Ki-67% ≥30 | 12 (0) 11 (1) 10 (1) 9 (0) 8 (0) 8 (1) 7 (0) 5 (0) 4 (0) 3 (0) 2 (0) 0 |

No. (events) HR (95% CI):

- Ki-67% <30: 38 (4)
- Ki-67% ≥30: 12 (3) 2.62 (0.57 to 11.73) P = .208
Elimination Chamber
Elimination Chamber

AS  R²  BR  R-CHOP  R-CHOP + cytarabine  Hyper-CVAD

Intensity
Where Does BTKi Fit?
Shine 2022
## Shine 2022

<table>
<thead>
<tr>
<th></th>
<th>Ibrutinib + BR (N = 261)</th>
<th>Placebo + BR (N = 262)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), years</td>
<td>71 (65-86)</td>
<td>71 (65-87)</td>
</tr>
<tr>
<td>≥ 75 years, n (%)</td>
<td>74 (28.4)</td>
<td>82 (31.3)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>178 (68.2)</td>
<td>186 (71.0)</td>
</tr>
<tr>
<td>ECOG PS 1, n (%)</td>
<td>127 (48.7)</td>
<td>118 (45.0)</td>
</tr>
<tr>
<td>Simplified MIPI, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>44 (16.9)</td>
<td>46 (17.6)</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>124 (47.5)</td>
<td>129 (49.2)</td>
</tr>
<tr>
<td>High risk</td>
<td>93 (35.6)</td>
<td>87 (33.2)</td>
</tr>
<tr>
<td>Bone marrow involvement, n (%)</td>
<td>198 (75.9)</td>
<td>200 (76.3)</td>
</tr>
<tr>
<td>Blastoid/pleomorphic histology, n (%)</td>
<td>19 (7.3)</td>
<td>26 (9.9)</td>
</tr>
<tr>
<td>Extranodal, n (%)</td>
<td>234 (89.7)</td>
<td>226 (86.3)</td>
</tr>
<tr>
<td>Bulky (≥ 5 cm), n (%)</td>
<td>95 (36.4)</td>
<td>98 (37.4)</td>
</tr>
<tr>
<td>TP53 mutated, n (%)</td>
<td>26 (10.0)</td>
<td>24 (9.2)</td>
</tr>
<tr>
<td>TP53 mutation status unknown, n (%)</td>
<td>121 (46.4)</td>
<td>133 (50.8)</td>
</tr>
</tbody>
</table>
Shine 2022

Wang et al. ASCO 2022 LBA 7502
### Shine 2022

<table>
<thead>
<tr>
<th></th>
<th>Ibrutinib + BR (N = 259)</th>
<th>Placebo + BR (N = 260)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3 or 4</td>
</tr>
<tr>
<td>Any bleeding*</td>
<td>42.9%</td>
<td>3.5%</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>5.8%</td>
<td>-</td>
</tr>
<tr>
<td>Atrial fibrillation*</td>
<td>13.9%</td>
<td>3.9%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>13.5%</td>
<td>8.5%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>17.4%</td>
<td>1.2%</td>
</tr>
</tbody>
</table>
Tag Teaming MCL

Legion of Doom
Tag Teaming MCL: Ibrutinib + R²

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>69 (45–85)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>14 (28%)</td>
</tr>
<tr>
<td>Male</td>
<td>36 (72%)</td>
</tr>
<tr>
<td>ECOG performance status score 0–1</td>
<td>45 (90%)</td>
</tr>
<tr>
<td>MIPI score</td>
<td></td>
</tr>
<tr>
<td>Low risk (≤5.7)</td>
<td>8 (16%)</td>
</tr>
<tr>
<td>Intermediate risk (5.7–6.1)</td>
<td>15 (30%)</td>
</tr>
<tr>
<td>High risk (≥6.2)</td>
<td>23 (46%)</td>
</tr>
<tr>
<td>Missing</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Ann Arbor stage IV disease</td>
<td>42 (84%)</td>
</tr>
<tr>
<td>Bone marrow involvement</td>
<td>34 (68%)</td>
</tr>
<tr>
<td>Refractory disease</td>
<td>8 (16%)</td>
</tr>
<tr>
<td>Number of previous therapies</td>
<td>2 (1-7)</td>
</tr>
<tr>
<td>Previous therapy</td>
<td></td>
</tr>
<tr>
<td>Autologous stem-cell transplantation</td>
<td>21 (42%)</td>
</tr>
<tr>
<td>Allogeneic stem-cell transplantation</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Ibrutinib</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

mPFS = 16 months

Jerkeman et al. Lancet Haematology 2018
Tag Teaming MCL: Venetoclax + Ibrutinib

Tam C et al. NEJM 2018

CR=62%
Tag Teaming MCL: 3-year Follow-up

mPFS = 29 months

4 of 5 MRD neg at 18 months remains off tx

Handunnetti et al. ASH 2019
# New Opponent: Pirtobrutinib

**Wang M, et al. ASH 2021, Abstr 381**

## Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>MCL (n=134)</th>
<th>BTK Pre-Treated MCL Patientsa (n=100)</th>
<th>BTK Naive MCL Patientsa (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age (range), years</strong></td>
<td>70 (46, 88)</td>
<td>Overall Response Rate, % (95% CI)</td>
<td>51% (41-61)</td>
</tr>
<tr>
<td><strong>Female / Male, n (%)</strong></td>
<td>30 (22) / 104 (78)</td>
<td>Best Response</td>
<td></td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classic</td>
<td>108 (81)</td>
<td>CR, n (%)</td>
<td>25 (25)</td>
</tr>
<tr>
<td>Pleomorphic/Blastoid</td>
<td>26 (19)</td>
<td>PR, n (%)</td>
<td>26 (26)</td>
</tr>
<tr>
<td><strong>ECOG PS, n (%)</strong></td>
<td></td>
<td>SD, n (%)</td>
<td>16 (16)</td>
</tr>
<tr>
<td>0</td>
<td>82 (61)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>50 (37)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2 (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Median number prior lines of systemic therapy (range)</strong></td>
<td>3 (1, 9)</td>
<td>Overall Response Rate, % (95% CI)</td>
<td>82% (48-98)</td>
</tr>
<tr>
<td><strong>Prior therapy, n (%)</strong></td>
<td></td>
<td>Best Response</td>
<td></td>
</tr>
<tr>
<td>BTK inhibitor</td>
<td>120 (90)</td>
<td>CR, n (%)</td>
<td>2 (18)</td>
</tr>
<tr>
<td>Anti-CD20 antibody</td>
<td>130 (97)</td>
<td>PR, n (%)</td>
<td>7 (64)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>122 (91)</td>
<td>SD, n (%)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>Stem cell transplantb</td>
<td>30 (22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMID</td>
<td>23 (17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCL2 Inhibitor</td>
<td>20 (15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteasome inhibitor</td>
<td>17 (13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAR-T</td>
<td>7 (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI3K inhibitor</td>
<td>5 (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Reason discontinued prior BTKa</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>100 (83)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxicity/Other</td>
<td>20 (17)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

**Figure:**

- Median duration of response: 18 months (95% CI: 4-6, Not Estimable)

*Asham Healthcare
december 2021*
New Opponent: Glofitamab

Hutchings et al. JCO 2021
Put Into Retirement in MCL: Lenalidomide post BTK

Wang M et al. J Hema & Onc 2017
Put Into Retirement in MCL: Venetoclax Post BTKi

<table>
<thead>
<tr>
<th>Gender</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>17 (85%)</td>
</tr>
<tr>
<td>Female</td>
<td>3 (15%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>First-line therapy</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHOP = R or CHOP-like</td>
<td>6</td>
</tr>
<tr>
<td>Fludarabine-based ± R</td>
<td>4*</td>
</tr>
<tr>
<td>Maxi-CHOP/HDAC ± R</td>
<td>8</td>
</tr>
<tr>
<td>Other</td>
<td>2*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ASCT consolidation in first remission</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>6 (30%)</td>
</tr>
<tr>
<td>No</td>
<td>14 (70%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rituximab maintenance in first remission</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>After immunochemotherapy</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>After ASCT</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Neither</td>
<td>18 (90%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Duration of exposure to BTK inhibitor</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4.77 months</td>
<td>0.66 – 34.85 months</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Response to prior BTK inhibitor</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response</td>
<td>11/20 (55%)</td>
</tr>
<tr>
<td>Complete response</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>Partial response</td>
<td>8 (40%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>4 (20%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>5 (25%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reason for BTK inhibitor discontinuation (n = 20)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressive disease</td>
<td>17</td>
</tr>
<tr>
<td>Stable disease</td>
<td>1</td>
</tr>
<tr>
<td>Toxicity</td>
<td>2</td>
</tr>
</tbody>
</table>

Eyre et al. Haematologica 2019
Elephant in The Ring
TP53 Matters

N=183 from MCL2 & MCL3 trials

Eskelund C et al. Blood 2017
CIRLL Study

- Zilovertamab + Ibrutinib
- MCL or CLL
- ORR of 81%
  - Historic ORR of 66%, the addition of zilovertamab to ibrutinib was favorable.
- CR rate observed in the MCL cohort was 35% compared with the historic ibrutinib monotherapy CR rate of 20%.
- Zilo and ibrutinib median PFS of 35.9 months in patients with MCL who were followed for a median of 14.4 months
  - Compared with 12.8 months with ibrutinib alone.
- ZILO-301 (Ibrutinib +/- Zilo) in MCL
- ZILO-302 (ZILO + Ibrutinib) with POD to ibrutinib
MODULE 5: Diffuse Large B-Cell Lymphoma (DLBCL) – Dr Sehn
A 23-year-old man with limited-stage DLBCL, germinal center B-cell (GCB) subtype

Dr Zametta Lamar
Naples, Florida

A 72-year-old man with pleural effusion and tamponade who is diagnosed with large B-cell lymphoma

Dr Shams Bufalino
Park Ridge, Illinois
An 88-year-old woman with newly diagnosed DLBCL who developed pneumonia after the first dose of R-CHOP

Dr Erik Rupard (West Reading, Pennsylvania)
Diffuse Large B-Cell Lymphoma (DLBCL)

Laurie H. Sehn, MD, MPH
Chair, Lymphoma Tumour Group
BC Cancer Centre for Lymphoid Cancer
Vancouver, Canada
## Novel Agents Recently Approved in R/R DLBCL

<table>
<thead>
<tr>
<th>MOA</th>
<th>Pola-BR</th>
<th>Selinexor</th>
<th>Tafasitamab/ Lenalidomide</th>
<th>Loncastuximab Tesirine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MOA</strong></td>
<td>Anti-CD79b ADC</td>
<td>XPO-1 inhibitor</td>
<td>Anti-CD19 MAb/Immunomodulator</td>
<td>Anti-CD19 ADC</td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td>45%</td>
<td>28%</td>
<td>58%</td>
<td>48%</td>
</tr>
<tr>
<td><strong>CR rate</strong></td>
<td>40%</td>
<td>10%</td>
<td>40%</td>
<td>24%</td>
</tr>
<tr>
<td><strong>PFS</strong></td>
<td>9.2m</td>
<td>2.6m</td>
<td>11.6m</td>
<td>4.9m</td>
</tr>
<tr>
<td><strong>DOR</strong></td>
<td>12.6m</td>
<td>9.3m</td>
<td>43.9m</td>
<td>10.3m</td>
</tr>
<tr>
<td><strong>OS</strong></td>
<td>12.4m</td>
<td>NR</td>
<td>33.5m</td>
<td>9.9m</td>
</tr>
</tbody>
</table>
GO29365 Phase 1b/2 Study: Pola-BR in ASCT-Ineligible DLBCL

**Inclusion:** transplant-ineligible DLBCL, ≥1 line of therapy

**Exclusion:** prior allo-SCT; history of transformation; current grade >1 PN

*Pola 1.8 mg/kg on D1 of each cycle of BR; up to 6 cycles at 3-weekly interval*
**Randomized cohort:**
- Survival benefit persists with longer follow-up
- 2-y PFS: 28.4%, 2-y OS was 38.2%

**Extension cohort:**

**Pooled cohort:**
- Non-primary refractory patients:
  Median PFS: 13.4 m, median OS: 32 m

Sehn et al, Blood Advances 2022
Median PFS and OS in the Pooled Pola+BR cohort according to line of therapy and refractory status

Sehn et al, Blood Advances 2022
**Tafasitamab and Lenalidomide: L-MIND Study**

Phase 2, single-arm, open-label, multicenter study (NCT02399085)

- **Sample size suitable to detect ≥15% absolute increase in ORR for Tafasitamab/LEN combination vs. LEN monotherapy at 85% power, 2-sided alpha of 5%**
- **Mature Data: Primary Endpoint Analysis with data cut-off 30 Nov 2018; minimum Follow-Up 12 months, median Follow-Up 17.3 months**

---

**Primary endpoint**
- ORR (Central read)

**Secondary endpoints**
- PFS
- DoR
- OS
- Safety of the Tafasitamab + LEN combination
- Exploratory and biomarker-based analyses

---

*Salles G et al, Lancet Oncology 2020*
L-MIND: Efficacy (n=80)

- ORR 60%, CR rate 43% by IRC
- Median follow-up 33.9 months
- Median PFS: 11.6 mos (95% CI: 6.3 - 45.7 mos)

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

Patient population:
Patients with R/R DLBCL following ≥2 lines of prior systemic therapy

Primary objective:
Evaluate efficacy, using ORR (central review), and safety of the full Phase 2 study population

30-min infusion Lonca Q3W for up to 1 year

First 2 cycles
150 µg/kg

After 2 cycles
75 µg/kg

Q12W for up to 3 years
Follow-up

Caimi et al, Lancet Oncology 2021
Efficacy Results – OR

ORR 48.2%

Complete response
Partial response

24.8
23.4

All patients (N=145)

PFS

Number of events: 73
Median (95% CI) PFS:
4.9 (2.9–8.3) months

Caimi et al, Lancet Oncology 2021; Kahl et al, SOHO 2021
### Glofitamab Pivotal Phase II Trial: Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>N=154†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>66.0 (21–90)</td>
</tr>
<tr>
<td>Male</td>
<td>100 (64.9)</td>
</tr>
<tr>
<td>ECOG PS‡</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>69 (44.8)</td>
</tr>
<tr>
<td>1</td>
<td>84 (54.5)</td>
</tr>
<tr>
<td>Ann Arbor stage</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>10 (6.5)</td>
</tr>
<tr>
<td>II</td>
<td>25 (16.2)</td>
</tr>
<tr>
<td>III</td>
<td>31 (20.1)</td>
</tr>
<tr>
<td>IV</td>
<td>85 (55.2)</td>
</tr>
<tr>
<td>NHL subtype</td>
<td></td>
</tr>
<tr>
<td>DLBCL</td>
<td>110 (71.4)</td>
</tr>
<tr>
<td>trFL</td>
<td>27 (17.5)</td>
</tr>
<tr>
<td>HGBCL</td>
<td>11 (7.1)</td>
</tr>
<tr>
<td>PMBCL</td>
<td>6 (3.9)</td>
</tr>
<tr>
<td>Bulky disease</td>
<td></td>
</tr>
<tr>
<td>&gt;6cm</td>
<td>64 (41.6)</td>
</tr>
<tr>
<td>&gt;10cm</td>
<td>18 (11.7)</td>
</tr>
<tr>
<td>Prior anti-CD20 Ab</td>
<td>154 (100.0)</td>
</tr>
<tr>
<td>Prior anthracycline</td>
<td>149 (96.8)</td>
</tr>
<tr>
<td>Prior CAR-T</td>
<td>51 (33.1)</td>
</tr>
<tr>
<td>Prior ASCT</td>
<td>28 (18.2)</td>
</tr>
<tr>
<td>Refractory to any prior therapy</td>
<td>139 (90.3)</td>
</tr>
<tr>
<td>Refractory to last prior therapy</td>
<td>132 (85.7)</td>
</tr>
<tr>
<td>Primary refractory</td>
<td>90 (58.4)</td>
</tr>
<tr>
<td>Refractory to prior CAR-T</td>
<td>46 (29.9)</td>
</tr>
<tr>
<td>Refractory to any prior anti-CD20</td>
<td>128 (83.1)</td>
</tr>
</tbody>
</table>

- **Heavily pre-treated, highly refractory population**

Clinical cut-off date: March 14, 2022; †unless otherwise specified; ‡safety-evaluable population (all treated patients); ‡ECOG PS 2, n=1 (0.6%); Ab, antibody; ASCT, autologous stem cell transplant; trFL, transformed follicular lymphoma.

Dickinson et al, ASCO 2022
### Response rates – primary endpoint met

<table>
<thead>
<tr>
<th>Efficacy endpoint</th>
<th>Glofitamab 2.5/10/30mg (n=155)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CR rate</strong>*</td>
<td>61 (39.4%)</td>
</tr>
<tr>
<td></td>
<td>[95% CI: 31.6%, 47.5%]</td>
</tr>
<tr>
<td><strong>ORR</strong>*</td>
<td>80 (51.6%)</td>
</tr>
<tr>
<td></td>
<td>[95% CI: 43.5%, 59.7%]</td>
</tr>
</tbody>
</table>

- Median duration of follow-up: 12.6 months (range: 0–22)
- Responses were achieved early: median time to first CR was 42 days (95% CI: 42, 44)
  - At time of primary analysis, primary endpoint met in the primary efficacy population (n=108)†:
    - 35.2% CR rate by IRC significantly greater (p<0.0001) than 20% historical control CR rate‡

*best response by intent-to-treat population; †the pivotal expansion cohort population; ‡the historical control CR rate was pre-specified based on a meta-analysis in patients with R/R DLBCL (where most [≥50%] had received ≥2 prior therapies) and compared with the CR rate in the primary efficacy-evaluable population using an exact binomial test (2-sided alpha level: 5%).

**Dickinson et al, ASCO 2022**
# Time-to-event endpoints

## Progression-free survival by IRC

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Pts at risk</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>155</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>92</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>47</td>
<td>60</td>
</tr>
<tr>
<td>9</td>
<td>35</td>
<td>40</td>
</tr>
<tr>
<td>12</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td>15</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>18</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

**N=155**

- Median PFS follow-up, mo (range): 12.6 (0–22)
- Median PFS, months (95% CI): 4.9 (3.4, 8.1)
- 6-month event-free rate, % (95% CI): 45.5 (37.2, 53.8)
- 12-month event-free rate, % (95% CI): 37.1 (28.5, 45.8)

* Clinically significant freedom from progression at 12 months and long-term overall survival

## Overall survival

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Pts at risk</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>155</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>97</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>58</td>
<td>60</td>
</tr>
<tr>
<td>9</td>
<td>49</td>
<td>40</td>
</tr>
<tr>
<td>12</td>
<td>33</td>
<td>20</td>
</tr>
<tr>
<td>15</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>18</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

**N=155**

- Median OS, months (95% CI): 11.5 (7.9, 15.7)
- 12-month OS rate, % (95% CI): 49.8 (41.1, 58.5)

Median DOR 18.4 m (13.7,NE)

*Dickinson et al, ASCO 2022*

---

- *including five deaths due to COVID-19; †KM estimates*
### Glofitamab safety profile

| Category                                      | N (%) | Data | Median no. of cycles received (range) | Median relative dose intensity, % (range) | AE 154 (98.7) | Related AE 140 (90.9) | Grade 3–4 AE 87 (56.5) | Related AE 64 (41.6) | Serious AE 73 (47.4) | Related AE 46 (29.9) | Grade 5 (fatal AE) 8 (5.2) | Related AE 0 | AE leading to treatment discontinuation 14 (9.1) | Related AE 5 (3.2) |
|-----------------------------------------------|-------|------|--------------------------------------|-------------------------------------------|---------------|------------------------|------------------------|------------------------|----------------------|------------------------|----------------------|------------------------|---------------------|

- Glofitamab was well tolerated, with a favorable safety profile

*unless otherwise specified; †COVID-19/COVID-19 pneumonia (n=5); sepsis (n=2); delirium (n=1); ‡includes neutrophil count decreased; §includes platelet count decreased; ¶pyrexia events separate from CRS

---

**Dickinson et al, ASCO 2022**
POLARIX: A randomized double-blinded study

Patients
- Previously untreated DLBCL
- Age 18–80 years
- IPI 2–5
- ECOG PS 0–2

Stratification factors
- IPI score (2 vs 3–5)
- Bulky disease (<7.5 vs ≥7.5cm)
- Geographic region (Western Europe, US, Canada, & Australia vs Asia vs rest of world)

R 1:1

R-CHOP
- R-CHOP† + polatuzumab vedotin placebo

R-CHOP
- R-CHOP† + polatuzumab vedotin placebo

Pola-R-CHP
- Polatuzumab vedotin (1.8mg/kg)*
- R-CHP + vincristine placebo

Rituximab
- 375mg/m²

Cycles 1–6
- (1 cycle=21 days)

Cycles 7 & 8

*Tilly H et al, NEJM 2022

*IV on Day 1; †R-CHOP: IV rituximab 375mg/m², cyclophosphamide 750mg/m², doxorubicin 50mg/m², and vincristine 1.4mg/m² (max. 2mg) on Day 1, plus oral prednisone 100mg once daily on Days 1–5.
IPI, International prognostic index; ECOG PS, Eastern Cooperative Oncology Group performance status; R, randomized.
## Baseline characteristics

<table>
<thead>
<tr>
<th>ITT population</th>
<th>Pola-R-CHP (N=440)</th>
<th>R-CHOP (N=439)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Median (range), years</td>
<td>65.0 (19–80)</td>
</tr>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td>Male</td>
<td>239 (54)</td>
</tr>
<tr>
<td><strong>ECOG PS, n (%)</strong></td>
<td>0–1</td>
<td>374 (85)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>66 (15)</td>
</tr>
<tr>
<td><strong>Bulky disease (≥7.5cm), n (%)</strong></td>
<td>Present</td>
<td>193 (44)</td>
</tr>
<tr>
<td><strong>Elevated LDH, n (%)</strong></td>
<td>Yes</td>
<td>291 (66)</td>
</tr>
<tr>
<td><strong>Time from diagnosis to treatment initiation</strong></td>
<td>Median, days</td>
<td>26</td>
</tr>
<tr>
<td><strong>Ann Arbor Stage, n (%)</strong></td>
<td>III–IV</td>
<td>393 (89)</td>
</tr>
<tr>
<td><strong>Extranodal sites, n (%)</strong></td>
<td>≥2</td>
<td>213 (48)</td>
</tr>
<tr>
<td><strong>IPI score, n (%)</strong></td>
<td>2</td>
<td>167 (38)</td>
</tr>
<tr>
<td></td>
<td>3–5</td>
<td>273 (62)</td>
</tr>
<tr>
<td><strong>Cell-of-origin, (%)</strong></td>
<td>ABC</td>
<td>102 (31)</td>
</tr>
<tr>
<td></td>
<td>GCB</td>
<td>184 (56)</td>
</tr>
<tr>
<td></td>
<td>Unclassified</td>
<td>44 (13)</td>
</tr>
<tr>
<td><strong>MYC/BCL2 expression, n (%)</strong></td>
<td>Double expression</td>
<td>139 (38)</td>
</tr>
<tr>
<td><strong>MYC/BCL2/BCL6 rearrangement, n (%)</strong></td>
<td>Double-/triple-hit</td>
<td>26 (8)</td>
</tr>
</tbody>
</table>
Primary endpoint: Progression-free survival
Pola-R-CHP significantly improved PFS versus R-CHOP

ITT population. Data cut-off: June 28, 2021; median 28.2 months' follow-up.
NE, not evaluable.

- Pola-R-CHP demonstrated a 27% reduction in the relative risk of disease progression, relapse, or death versus R-CHOP
- 24-month PFS: 76.7% with Pola-R-CHP versus 70.2% with R-CHOP (Δ=6.5%)

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

Tilly H et al, NEJM 2022
### Baseline Risk Factors

<table>
<thead>
<tr>
<th>Benefit</th>
<th>Younger ≤ 60y</th>
<th>Females</th>
<th>IPI = 2</th>
<th>Bulk ≥ 7.5 cm</th>
<th>GCB Subtype</th>
<th>DH/TH lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group</td>
<td>&lt;60</td>
<td>&gt;60</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG PS</td>
<td>0–1</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPI score</td>
<td>IPI 1</td>
<td>IPI 2</td>
<td>IPI 3–5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bulky disease</td>
<td>Absent</td>
<td>Present</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geographic region</td>
<td>Western Europe, United States, Canada, and Australia</td>
<td>Asia</td>
<td>Rest of world</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ann Arbor stage</td>
<td>I–II</td>
<td>III</td>
<td>IV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline LDH</td>
<td>&lt;ULN</td>
<td>&gt;ULN</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of extranodal sites</td>
<td>0–1</td>
<td>≥2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cell-of-origin</td>
<td>GCB</td>
<td>ABC</td>
<td>Unclassified</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Double expression by IHC</td>
<td>DFL</td>
<td>Non-DFL</td>
<td>Unknown</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Double-or triple-hit lymphoma</td>
<td>Yes</td>
<td>No</td>
<td>Unknown</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Tilly H et al, NEJM 2022**
Overall survival

HR 0.94 (95% CI 0.65, 1.37); P=0.75

Tilly H et al, NEJM 2022
Data cut-off: June 28, 2021. *Subsequent lymphoma treatment was defined as non-protocol anti-lymphoma therapy; †Includes any monotherapy, multi-drug, or cell-based regimen.
### Common adverse events

Data cut-off: June 28, 2021. Adverse events are Medical Dictionary for Regulatory Activities version 24.0 preferred terms; shown are all-grade adverse events occurring in ≥12% of patients in any treatment arm. *Peripheral neuropathy is defined by standard organ class group of preferred terms.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Pola-R-CHP</th>
<th>R-CHOP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral neuropathy</td>
<td></td>
<td>*</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Decreased weight</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Asthenia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Tilly H et al, NEJM 2022
Ongoing/Planned Trials in Upfront DLBCL

- BTK-inhibitor R-CHOP trials
  - Escalade (acala); UK trial; zanubrutinib
- First-Mind Trial
  - Tafasitamab/Lenalidomide + R-CHOP
- Bispecific antibodies + R-CHOP
- Biology-driven trials
- Response-adapted trials (ctDNA, quantitative PET/CT)
Glofit + R-CHOP shows encouraging clinical activity in R/R NHL

- In efficacy-evaluable patients (n=31), after a median 9.0 months’ (range: 0–29) follow-up, the ORR was 90% (n=28); the CMR rate was 81% (n=25).

- Median duration of response was not reached in the R/R NHL cohort (range: 1–993 based on censored observation).

- Across all dose levels and histologies, Glofit + R-CHOP demonstrated encouraging anti-tumour activity in patients with R/R NHL.

**Best % change in SPD from baseline by Glofit dose and histology in the dose-escalation phase†**

<table>
<thead>
<tr>
<th>Best % change in SPD</th>
<th>Gpt + 70µg</th>
<th>Gpt + 1800µg</th>
<th>Rpt + 2.5/10/10mg</th>
<th>Gpt + 2.5/10/30mg</th>
<th>Rpt + 2.5/10/30mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>FL (Grade) 1–3A</td>
<td>FL (Grade) 1–3A</td>
<td>FL (Grade) 1–3A</td>
<td>FL (Grade) 1–3A</td>
<td>FL (Grade) 1–3A</td>
<td>FL (Grade) 1–3A</td>
</tr>
<tr>
<td>DLBCL (trFL)</td>
<td>DLBCL (trFL)</td>
<td>DLBCL (trFL)</td>
<td>DLBCL (trFL)</td>
<td>DLBCL (trFL)</td>
<td>DLBCL (trFL)</td>
</tr>
</tbody>
</table>

**INV-assessed BOR rate (unconfirmed)**

<table>
<thead>
<tr>
<th>R/R NHL</th>
<th>ORR</th>
<th>CMR</th>
<th>PMR</th>
<th>NMR</th>
<th>PMD</th>
<th>Missing/NE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose-escalation phase (N=31)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indolent NHL (FL + MZL) (n=24)</td>
<td>22 (91.6)</td>
<td>20 (83.3)</td>
<td>2 (8.3)</td>
<td>0</td>
<td>1 (4.2)</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Aggressive NHL (trFL + MCL) (n=7)</td>
<td>6 (85.7)</td>
<td>5 (71.4)</td>
<td>1 (14.3)</td>
<td>0</td>
<td>1 (14.3)</td>
<td>0</td>
</tr>
</tbody>
</table>

**Ghosh et al, ASH 2021**
First-line treatment (Tx) with subcutaneous (SC) epcoritamab (epco) + R-CHOP in patients (pts) with high-risk diffuse large B-cell lymphoma (DLBCL): phase 1/2 data update

Falchi et al, ASCO 2022

**Objectives**

- The EPCORE NHL-2 trial (phase 1/2, NCT04683347) is evaluating epcoritamab combined with different standard of care therapies in patients with B-cell NHL.
- To present data from arm 1, which is investigating epcoritamab + R-CHOP in patients with previously untreated high-risk DLBCL.

**Conclusions**

- Epcoritamab + R-CHOP showed encouraging responses:
  - ORR 100%, CMR 77%
- Epcoritamab + R-CHOP has a manageable safety profile, no new safety signals were detected
  - CRS was predictable and generally low grade
  - All CRS events resolved
- These updated data support further exploration of epcoritamab + R-CHOP in first-line DLBCL

**Best Overall Responses**

<table>
<thead>
<tr>
<th>Response, n (%)</th>
<th>Total n=31</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response</td>
<td>31 (100)</td>
</tr>
<tr>
<td>CMR</td>
<td>24 (77)</td>
</tr>
<tr>
<td>PMR</td>
<td>7 (23)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>0</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>0</td>
</tr>
</tbody>
</table>

Data cutoff: March 25, 2022. *Based on modified response-evaluable population, defined as patients with ≥1 target lesion at baseline and ≥1 post-onset response evaluation and patients who died within 60 d of first dose.*
MODULE 6: Chimeric Antigen Receptor (CAR) T-Cell Therapy – Dr Hill
A 75-year-old woman with recurrent DLBCL and significant cardiac comorbidity

Dr Vignesh Narayanan
(Lone Tree, Colorado)

A 57-year-old man with double-hit DLBCL
An 84-year-old man with recurrent DLBCL

Dr Namrata Peswani (Richardson, Texas)
A 59-year-old man with R/R MCL and multiple comorbidities

Dr Spencer Bachow (Boca Raton, Florida)
Chimeric Antigen Receptor (CAR) T-Cell Therapy

Brian T. Hill, M.D., Ph.D.
Director, Lymphoid Malignancies Program

Research To Practice
ASCO Update
June 5, 2022
Long-Term Survival and Gradual Recovery of B Cells in Patients With Refractory Large B-Cell Lymphoma Treated With Axicabtagene Ciloleucel

- Caron A. Jacobson, MD, MMSc
- Fredrick L. Locke, MD
- Armin Ghobadi, MD
- David B. Miklos, MD, PhD
- Lazaros J. Lekakis, MD
- Olalekan O. Oluwole, MD, MPH, MBBS
- Yi Lin, MD, PhD
- Ira Braunschweig, MD
- Brian T. Hill, MD, PhD
- John M. Timmerman, MD
- Abhinav Deol, MD
- Patrick M. Reagan, MD
- Patrick Stiff, MD
- Ian W. Flinn, MD, PhD
- Umar Farooq, MD
- Andre H. Goy, MD
- Peter A. McSweeney, MB, ChB
- Javier Muñoz, MD, MS, FACP
- Tanya Siddiqi, MD
- John M. Rossi, MS
- Adrian A. Bot, MD, PhD
- Lianqing Zheng, PhD
- Remus Vezan, MD, PhD
- Zahid Bashir, MBBS, MS
- Jenny J. Kim, MD, MS
- Rong Chu, PhD
- and Sattva S. Neelapu, MD

1Dana-Farber Cancer Institute, Boston, MA, USA; 2Moffitt Cancer Center, Tampa, FL, USA; 3Washington University School of Medicine, St Louis, MO, USA; 4Stanford University School of Medicine, Stanford, CA, USA; 5Sylvester Comprehensive Cancer Center, University of Miami Health System, Miami, FL, USA; 6Vanderbilt-Ingram Cancer Center, Nashville, TN, USA; 7Mayo Clinic, Rochester, MN, USA; 8Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY, USA; 9Cleveland Clinic Foundation, Cleveland, OH, USA; 10UCLA David Geffen School of Medicine, Los Angeles, CA, USA; 11Karmanos Cancer Center, Wayne State University, Detroit, MI, USA; 12University of Rochester School of Medicine, Rochester, NY, USA; 13Loyola University Chicago Stritch School of Medicine, Maywood, IL, USA; 14Sarah Cannon Research Institute and Tennessee Oncology, Nashville, TN, USA; 15University of Iowa, Iowa City, IA, USA; 16John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ, USA; 17Colorado Blood Cancer Institute, Denver, CO, USA; 18Banner MD Anderson Cancer Center, Gilbert, AZ, USA; 19City of Hope National Medical Center, Duarte, CA, USA; 20Kite, a Gilead Company, Santa Monica, CA, USA; and 21The University of Texas MD Anderson Cancer Center, Houston, TX, USA
Overall Survival At 4 Years (mITT, n=101)

- Among axi-cel–treated patients (mITT, n=101), with ≥4 years of follow-up (median, 51.1 months), median OS was 25.8 months, and the KM estimate of the 4-year OS rate was 44%.
- Among the entire enrolled population (ITT, n=111), median OS was 17.4 months, and the KM estimate of the 4-year OS rate was 41%.

Axi-cel, axicabtagene ciloleucel; KM, Kaplan-Meier; mITT, modified intent-to-treat; NE, not estimable; OS, overall survival.
CAR T-Cell and B-Cell Detection in Blood

• As previously reported, patients in ongoing response after 2 years had significantly greater peak CAR T-cell expansion in blood 7–14 days after axi-cel infusion than did patients with relapse ($P=.014$) or no response ($P=.0003$)\(^1\)

• Blood samples from 21 patients in ongoing response (per institutional standard of care) at ≥3 years were available for analysis of CAR T cells and evaluation of B-cell presence
  - All evaluable patients had detectable B cells in blood at 3 years after axi-cel treatment
  - 67% of patients (n=14/21) had detectable CAR gene-marked cells and polyclonal B cells in blood at 3 years


Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor.
Second Line CAR-T vs. Standard of Care

3 Randomized Phase III Trials*
1. ZUMA-7 – Axi-cel
2. TRANSFORM – Liso-cel
3. BELINDA - Tisa-cel

*All required patients to have relapsed <12 months of completion of frontline treatment
94% of patients received axi-cel, whereas 36% of patients received HDT-ASCT.
94% of patients received axi-cel, whereas 36% of patients received HDT-ASCT.
ZUMA-7: Axi-cel vs. Standard of Care

Event-free Survival

Stratified hazard ratio for event or death,
0.40 (95% CI, 0.31–0.51)
P<0.001

Overall Survival

Stratified hazard ratio for death,
0.73 (95% CI, 0.53–1.01)

Locke FL et al. NEJM 2022
TRANSFORM: Liso-cel vs. Standard of Care

Kamdar et al. ASH 2021
TRANSFORM: Liso-cel vs. Standard of Care

Kamdar et al. ASH 2021
TRANSFORM: Liso-cel vs. Standard of Care

Kamdar et al. ASH 2021
Possible reasons for negative trial:
1. Standard-of-care arm allowed to get 2 salvage regimens without being counted as an event.
2. Less effective CAR-T product for refractory disease
Confused?
Favorable Outcomes of ASCT in Complete Remission: Prognostic Value of Chemosensitivity

Registry Comparison of patients in PR after ≤2 Lines of Prior Therapy

2A: Progression-Free Survival
- CAR-T therapy
- Auto HCT

2D: Overall Survival
- Auto HCT
- CAR-T therapy

Proposed Approach

Refractory DLBCL
(Positive end-of-treatment PET scan after frontline treatment)

\[ \rightarrow \]

CAR-T cell
Proposed Approach

Refractory DLBCL
(Positive end-of-treatment PET scan after frontline treatment)

- CAR-T cell

Relapsed DLBCL
(Relapse after prior CR)

- Chemosensitive to Second Line Treatment (i.e. R-ICE or similar)
  - yes
  - no

- Autologous Stem Cell Transplant (ASCT)
Axicabtagene ciloleucel as first-line therapy in high-risk large B-cell lymphoma: the phase 2 ZUMA-12 trial

Sattva S. Neelapu, Michael Dickinson, Javier Munoz, Matthew L. Ulrickson, Catherine Thieblemont, Olalekan O. Oluwole, Alex F. Herrera, Chaitra S. Ujjani, Yi Lin, Peter A. Riedell, Natasha Kekre, Sven de Vos, Christine Lui, Francesca Milletti, Jinghui Dong, Hairong Xu and Julio C. Chavez

ZUMA-12 Study Design

Phase 2

High-Risk LBCL
- High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 translocations, or
- LBCL with IPI score ≥3 any time before enrollment

Systemic Therapy
- 2 Cycles of an anti-CD20 mAb plus anthracycline-containing regimen

Dynamic Risk Assessment
- Positive interim PET (DS 4 or 5)

Additional Key Inclusion Criteria
- Age ≥18 years
- ECOG 0–1

Enrollment/Leukapheresis

Optional Nonchemotherapy Bridging Therapy

Conditioning Chemotherapy + Axi-Cel Infusion
- **Conditioning:**
  - Fludarabine 30 mg/m² IV and cyclophosphamide 500 mg/m² IV on Days −5, −4, and −3
- **Axi-Cel:**
  - Single IV infusion of 2×10^6 CAR T cells/kg on Day 0

Primary Endpoint
- CR (investigator-assessed per Lugano classification)

Key Secondary Endpoints
- ORR
- DOR
- EFS
- PFS
- OS
- Safety
- CAR T cells in blood and cytokine levels in serum

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Neelapu et al  TCT 2021  Abstract 4

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* Administered after leukapheresis and completed prior to initiating conditioning chemotherapy; PET-CT was required after bridging.
Axi-cell, axicabtagene ciloleucel; BCL, B-cell lymphoma; CAR, chimeric antigen receptor; CR, complete response; CT, computed tomography; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; DS, Deauville score; ECOG, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; IPI, International Prognostic Index; IV, intravenous; LBCL, large B-cell lymphoma; mAb, monoclonal antibody; ORR, overall response rate; OS, overall survival; PET, positron-emission tomography; PFS, progression-free survival.
Caveat: Need prospective randomized control trial, as value of interim PET scan during R-CHOP has not been demonstrated. Continuation of R-CHOP may have resulted in favorable outcomes in a significant proportion of patients.
Outcomes with KTE-X19 in patients (pts) with relapsed/refractory (R/R) mantle cell lymphoma (MCL) in ZUMA-2 who had progression of disease within 24 months of diagnosis (POD24).

Michael Wang, Javier Munoz, Andre Goy, Frederick Lundry Locke, Caron A. Jacobson, Brian T. Hill, John Timmerman, Houston Holmes, Samantha Jaglowski, Ian Flinn, Peter A. McSweeney, David Bernard Miklos, Marie José Kersten, Krimo Bouabdallah, Max S. Topp, Rhine Shen, Ioana Kloos, Weimin Peng, Xiang Fang, Patrick M. Reagan
The University of Texas MD Anderson Cancer Center, Houston, TX; Banner MD Anderson Cancer Center, Gilbert, AZ; John Theurer Cancer Center, Hackensack, NJ; Moffitt Cancer Center, Tampa, FL; Dana-Farber Cancer Institute, Boston, MA; Cleveland Clinic Foundation, Cleveland, OH; UCLA David Geffen School of Medicine, Los Angeles, CA; Texas Oncology, Dallas, TX; The Ohio State University Comprehensive Cancer Center, Division of Hematology, Columbus, OH; Sarah Cannon Research Institute and Tennessee Oncology, Nashville, TN; Colorado Blood Cancer Institute, Denver, CO; Stanford University School of Medicine, Stanford, CA; Amsterdam UMC, University of Amsterdam, and on behalf of HOVON/LLPC, Amsterdam, Netherlands; CHU Bordeaux, Service d’Hématologie et Thérapie Cellulaire, Bordeaux, France; Medizinische Klinik und Poliklinik II, Universitätshospital Würzburg, Würzburg, Germany; Kite, A Gilead Company, Santa Monica, CA; University of Rochester Medical Center, Rochester, NY
CAR-T for Mantle Cell Lymphoma: Brexu-Cel

**Figure 2. ORR by IRRC Assessment in Patients With and Without POD24**

- **With POD24 (n=28):**
  - CR: 61% (n=17)
  - PR: 32% (n=9)
  - SD: 4% (n=1)
  - PD: 4% (n=1)

- **Without POD24 (n=32):**
  - CR: 72% (n=23)
  - PR: 19% (n=6)
  - SD: 3% (n=1)
  - PD: 3% (n=1)

- The ORR was similar among patients with and without POD24, with a slightly higher CR rate in patients without POD24 (Figure 2).
- Similar rates of MRD-negativity were also observed among patients with (82%; n=9/11) and without (79%; n=15/19) POD24.

**Progression-Free Survival**

- **With POD24:**
  - Median (95% CI): 11.3 (6.0–NE) mo
  - 15-mo Rate (95% CI): 48.5 (28.2–66.1)%

- **Without POD24:**
  - Median (95% CI): 29.3 (14.5–NE) mo
  - 15-mo Rate (95% CI): 66.9 (44.3–82.0)%

Wang, et al. EHA 2021
Safety and Preliminary Efficacy in Patients with Relapsed/Refractory Mantle Cell Lymphoma Receiving Lisocabtagene Maraleucel in TRANSCEND NHL 001

M. Lia Palomba,1 Leo I. Gordon,2 Tanya Siddiqi,3 Jeremy Abramson,4 Manali Kamdar,5 Matthew Lunning,6 David G. Maloney,7 Charalambos Andreadis,8 Jon E. Arnason,9 Nilanjana Ghosh,10 Amitkumar Mehta,11 Scott R. Solomon,12 Thalia Farazi,13 Jacob Garcia,13 Christine Dehner,13 Ken Ogawara,14 Jie Gao,13 Michael Wang15

1Memorial Sloan Kettering Cancer Center, New York, NY, USA; 2Northwestern University Feinberg School of Medicine, Robert H. Lurie Comprehensive Cancer Center, Chicago, IL, USA; 3City of Hope National Medical Center, Duarte, CA, USA; 4Massachusetts General Hospital Cancer Center, Boston, MA, USA; 5University of Colorado Cancer Center, Aurora, CO, USA; 6University of Nebraska Medical Center, Omaha, NE, USA; 7Fred Hutchinson Cancer Research Center, Seattle, WA, USA; 8Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, San Francisco, CA, USA; 9Beth Israel Deaconess Medical Center, Boston, MA, USA; 10Levine Cancer Institute, Atrium Health, Charlotte, NC, USA; 11University of Alabama at Birmingham, Birmingham, AL, USA; 12Immunotherapy Program, Northside Hospital Cancer Institute, Atlanta, GA, USA; 13Bristol Myers Squibb, Seattle, WA, USA; 14Bristol Myers Squibb, Princeton, NJ, USA; 15University of Texas MD Anderson Cancer Center, Houston, TX, USA
CAR-T for Mantle Cell Lymphoma: Liso-Cel

Best Overall Response by Investigator Assessment

- ORR and CR rate, respectively, for patients with high-risk features:
  - Ki67 ≥30% (n = 23): 83% and 65%
  - Blastoid morphology (n = 13): 77% and 54%
  - TP53 mutations (n = 7): 100% and 57%

*Based on 32 patients treated; one patient was not evaluable and is not shown in the figure.

- Median on-study follow-up: 5.9 (range, 0.4–24.8) months
- Median time to first CR or PR: 0.95 (range, 0.9–2.0) months

Palomba, et al ASH 2020
CAR-T for Mantle Cell Lymphoma: Liso-Cel

Patient Responses over Time

- Median duration of response: not reached
- Median follow-up: 3.9 (range, 0.0–21.3) months

Palomba, et al. ASH 2020
Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (ZUMA-5): a single-arm, multicentre, phase 2 trial

Caron A Jacobson, Julio C Chavez, Alison R Sehgal, Basem M William, Javier Munoz, Gilles Salles, Pashna N Munshi, Carla Casulo, David G Maloney, Sven de Vos, Ran Reshef, Lori A Leslie, Ibrahim Yakoub-Agha, Olalekan O Oluwole, Henry Chi Hang Fung, Joseph Rosenblatt, John M Rossi, Lovely Goyal, Vicki Plaks, Yin Yang, Remus Vezan, Mauro P Avanzi, Sattva S Neelapu
CAR-T for Indolent Lymphoma: Axi-cel

FDA Approves Tisagenlecleucel for Relapsed or Refractory Follicular Lymphoma
Press Release: May 27, 2022

“On May 27, 2022, the Food and Drug Administration granted accelerated approval to tisagenlecleucel for adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.

The approval was based on the ELARA trial (NCT03568461), a multicenter, single-arm, open-label trial evaluating tisagenlecleucel, a CD19-directed chimeric antigen receptor (CAR) T cell therapy, in adult patients who were refractory or relapsed within 6 months after completion of two or more lines of systemic therapy (including an anti-CD20 antibody and an alkylating agent) or relapsed after autologous hematopoietic stem cell transplant.”

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-tisagenlecleucel-relapsed-or-refractory-follicular-lymphoma
TRANSCEND CLL 004: Phase 1 Cohort of Lisocabtagene Maraleucel (liso-cel) in Combination with Ibrutinib for Patients with Relapsed/Refractory (R/R) Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)

William G. Wierda,¹ Kathleen A. Dorritie,² Javier Munoz,³ Deborah M. Stephens,⁴ Scott Solomon,⁵ Heidi H. Gillenwater,⁶ Lucy Gong,⁶ Lin Yang,⁶ Ken Ogasawara,⁷ Jerill Thorpe,⁶ Tanya Siddiqi⁸

¹The University of Texas MD Anderson Cancer Center, Houston, TX, USA; ²UPMC Hillman Cancer Center, University of Pittsburgh, Pittsburgh, PA, USA; ³Banner MD Anderson Cancer Center, Gilbert, AZ, USA; ⁴Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA; ⁵Immunotherapy Program, Northside Hospital Cancer Institute, Atlanta, GA, USA; ⁶Bristol Myers Squibb, Seattle, WA, USA; ⁷Bristol Myers Squibb, Princeton, NJ, USA; ⁸City of Hope National Medical Center, Duarte, CA, USA
CAR-T for CLL: Liso-Cel

TRANSCEDELL 004 Phase 1/2 Study Design\(^1\) of liso-cel, a CD19-Directed, Defined Composition, CART Cell Product

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**Key Eligibility for Combination Cohort**
- R/R CLL/SLL, and
- Progressing on ibritinib at enrollment, \(^b\) or
- High-risk features\(^c\) and received ibritinib for ≥6 months with less than a CR, or
- BTK or PLC\(^2\) mutations, \(^d\) or
- Prior ibritinib with no contraindication to reinitiating ibritinib

---

**Dose Escalation:** mTP-2 Design\(^2\)
- 28-day dose-limiting toxicity period

Primary Objectives
- Safety
- Determine recommended dose

Exploratory Objectives
- Antitumor activity (ivCLL 2018)\(^3\)
  - Testing for MRD\(^4\)
- Cellular kinetic profile (qPCR)

---

\(^{a}\) No patient in the combination phase 1 cohort received nonconforming product. \(^{b}\) Defined as SD or PD as best response, or PD after previous response. \(^{c}\) Complex cytogenetic abnormalities, del(17p), TP53 mutated, or unmutated IGVR, \(^d\) BTK or PLC\(^2\) gene mutation, with or without progression on ibritinib. \(^e\) Lower dose was used if prior dose reduction was necessary to manage toxicity. MRD was assessed in blood by flow cytometry and/or in bone marrow by next generation sequencing (both with a sensitivity of ≤10\(^{-5}\)).

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Wierda, et al. ASH 2020

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Ooral presentation (Abs 546)
Siddiqi et al.
Phase I monotherapy update
dec 7, 2020, 8:00 am (PST)
CAR-T for CLL: Liso-Cel

Best Overall Response and uMRD (≤10^{-4}) at 10-Month Follow-Up

- No patients had PD during the first month after liso-cel
- One patient at DL1 had SD for 6 months but later progressed

*Evaluated according to iv CLL 2018 criteria. Assessed in blood by flow cytometry and/or in bone marrow by NGS. CRI, CR with incomplete blood count recovery; NGS, next-generation sequencing.

Wierda, et al. ASH 2020
CAR-T for CLL: Liso-Cel

**Cellular Kinetics—Expansion and Persistence**

### Liso-cel

- **Parameter**: $C_{\text{max}}$ (copies/μg) (Q1–Q3: 67,000 (25,000–119,000))
- **Parameter**: $T_{\text{max}}$ (day) (Q1–Q3: 15 (14–21))
- **Parameter**: AUC$_{0-\text{inf}}$ (day x copies/μg) (Q1–Q3: 470,000 (17,400–7,400,000))

*Median (interquartile range, Q1–Q3). *Evaluated using qPCR. *Defined as patients whose disease progressed on ETN and failed remission due to progression, intolerance, or failure to respond after at least 3 months of therapy.

- **Long-term persistence**
  - 50% of patients (n = 6/12) at 12 months
  - 18% of patients (n = 2/11) at 18 months

### Liso-cel + ibrutinib

- **Parameter**: $C_{\text{max}}$ (copies/μg) (Q1–Q3: 128,000 (47,000–344,000))
- **Parameter**: $T_{\text{max}}$ (day) (Q1–Q3: 11 (10–15))
- **Parameter**: AUC$_{0-\text{inf}}$ (day x copies/μg) (Q1–Q3: 482,000 (310,000–2,720,000))

*Median (interquartile range, Q1–Q3). *Evaluated using qPCR.

- **Long-term persistence**
  - 38% of patients (n = 6/16) at 6 months
  - 20% of patients (n = 1/5) at 12 months

Siddiqi et al., ASH 2020
Wierda, et al. ASH 2020
CAR-T for CLL: Liso-Cel

Cellular Kinetics—Expansion and Persistence

**Liso-cel**

**Liso-cel + ibrutinib**

Siddiqi et al, ASH 2020
Wierda, et al. ASH 2020
Breakfast with the Investigators: Urothelial Bladder Cancer
A CME Hybrid Symposium Held in Conjunction with the 2022 ASCO Annual Meeting
Monday, June 6, 2022
6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)

Faculty
Yohann Loriot, MD, PhD
Elizabeth R Plimack, MD, MS
Jonathan E Rosenberg, MD

Moderator
Neil Love, MD
Thank you for joining us!

CME links will be posted in the chat (Zoom participants only) and emailed to all participants within 24 hours of the program.