Realizing the Promise of Novel Therapeutics in NHL

A MasterClass and Tumor Board on Clinical Decision-Making in FL, MCL, and DLBCL

Friday Satellite Symposium preceding the 61st ASH Annual Meeting and Exposition
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Disclosures

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Introduction & Tumor Board Preview—
How Innovative Treatments Have Changed NHL Management

John P. Leonard, MD
The Richard T. Silver Distinguished Professor of Hematology and Medical Oncology
Professor of Medicine
Associate Dean for Clinical Research
Weill Cornell Medicine
New York, New York

PeerView Live
B-Cell Malignancies: A Spectrum of Challenging Cancers\textsuperscript{1-3}

... with many new treatment choices available

A Flurry of New Therapeutic Developments With Innovative Therapies in NHL

2013-2014
• Initial approvals of lenalidomide, idelalisib, and ibrutinib (MCL, CLL)  

2016-2018
• Initial approval of venetoclax and acalabrutinib (CLL, MCL)
• Approvals of copanlisib and duvelisib (FL, CLL)
• CAR T therapy (DLBCL)

2019
• Approval of R² (AUGMENT; R/R FL)
• Approval of venetoclax + obinutuzumab (CLL 14)
• Approval of acalabrutinib (CLL) and zanubrutinib (MCL)
• Evidence on CAR T therapy beyond DLBCL (eg, in MCL)

Unprecedented changes in the field, which, until recently, was characterized by chemoimmunotherapy
This Morning’s Agenda

MasterClass and Tumor Board Sessions

- **FL:** moving beyond immunochemotherapy—a look at the latest evidence

- **MCL:** continuing progress with newer therapeutics, from targeted agents to IMiDs and CAR T therapy

- **DLBCL:** understanding the shape of modern care and the potential of cell therapy beyond pretreated disease

*Be prepared for additional polling during each presentation*
Michael, an older patient with newly diagnosed, symptomatic FL on therapy with R-chemotherapy

What We’ll Explore

1. The experience of a patient receiving upfront immuno-CT, including safety considerations
2. Alternative, novel options at relapse and for subsequent therapy
3. Weighing treatment history, toxicity profile, and patient preferences when selecting and sequencing multiple lines of therapy
Tumor Board Preview: MCL

Multiple scenarios
- A patient presenting with MCL post-SCT
- An elderly patient unresponsive to immuno-CT

What We’ll Explore
The role of novel therapeutics in relapsed MCL, including in different age groups/patient presentations
A patient with DLBCL refractory to R-CHOP considering ASCT or clinical trial–based options

What We’ll Explore

1. ASCT vs clinical trials testing CAR T therapy
2. Standard second-line therapy in the absence of a trial
3. Cell therapy as an option after additional relapse
MasterClass & Tumor Board Sessions
Beyond Immunochemotherapy in Newly Diagnosed and Relapsed FL
What’s the Evidence?

Nathan H. Fowler, MD
Professor of Medicine,
Department of Lymphoma/Myeloma
The University of Texas
MD Anderson Cancer Center
Houston, Texas

PeerView Live
Tumor Board
Exploring Chemo-Sparing Treatment in FL
Michael, a Man With Relapsed FL After Upfront Immunochemotherapy

Michael is diagnosed with symptomatic FL at age 70 y
- CD10+, CD20+, and BCL-2+
- B symptoms
- Lymphadenopathy, with one tumor mass of 7 cm
- Treatment recommended (GELF)

Receives R-CHOP + R maintenance (2 years)
- Michael achieves a response and is disease free
- However, he has disease progression roughly 2 years after maintenance therapy

While receiving R-CHOP, Michael had difficulty with several R-chemo AEs, including neutropenia, febrile neutropenia, neuropathy, and alopecia
When discussing additional options with Michael, he brought up his prior experience with treatment.

R-chemo–related events: neutropenia, febrile neutropenia (GFS use), and neuropathy.

Based on the phase 3 AUGMENT trial, the $R^2$ regimen is an option that addresses some of the patient’s concerns about toxicity.

Michael achieves a response with $R^2$ and remains in remission (>2 years).

Be aware of the differences in AE profiles and discuss them with your patients.
Key Points From Michael’s Case ...

... and implications for modern therapy selection

1. This patient could have been treated with BR instead of R-CHOP; while the AE profile may be different between these two options, it is still substantial

2. When this patient was treated, R maintenance was common, but now R maintenance is used less frequently

3. Relapse is common; it’s important to include considerations such as cumulative toxicities

4. Many emerging new therapy options are available
Moving Beyond Immunochemotherapy in FL
Guidance for FL Treatment Decisions

1. Patient comorbidities
2. Aggressiveness/grade of disease
3. Goals of treatment/patient preference
4. GELF criteria

<table>
<thead>
<tr>
<th>GELF Criteria (Indications for Treatment in FL)¹</th>
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<tr>
<td>- Any nodal or extranodal tumor mass ≥7 cm</td>
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<td>- ≥3 nodal sites, each &gt;3 cm</td>
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<td>- Presence of B symptoms</td>
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<td>- Splenomegaly</td>
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<td>- Compression or vital organs compromised</td>
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<td>- Significant serous effusions; lymphocyte count &gt;5.0 x 10⁹/L</td>
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<td>- Cytopenia (granulocyte count &lt;1.0 x 10⁹/L and/or platelets &lt;100 x 10⁹/L)</td>
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Many Novel Agent Classes Are Now Included in Recommendations for FL Therapy (NCCN)¹

**First-Line Options in FL (NCCN)**

**Preferred**
- Bendamustine + **obinutuzumab** or rituximab
- R-CHOP or G-CHOP
- R-CVP or G-CVP

**Other Recommended**
- **Lenalidomide** + rituximab (**R²**)
- Rituximab (**R**)
- Alternative strategies are available for elderly or infirm patients if the above therapies are unlikely to be tolerable

**First-Line Consolidation or Extended Dosing**

- **Rituximab**
- **Obinutuzumab**
- Radiolabeled antibody 90-yttrium-ibritumomab tiuxetan

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Early Explorations of $R^2$ in Untreated FL

Lenalidomide + Rituximab vs Rituximab Monotherapy: First Analysis of Survival Endpoints of the Randomized Phase 2 Trial SAKK 35/10

$R^2$

**Rituximab:** 375 mg/m$^2$ at wk 1, 2, 3, 4, 12, 13, 14, and 15

**Lenalidomide:** 15 mg/d from 14 d before the first rituximab administration until 14 d after the last rituximab administration

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RELEVANCE: \( R^2 \) vs Rituximab-Chemotherapy (R-Chemo) in Previously Untreated Advanced FL

- Previously untreated patients with advanced FL requiring treatment per GELF
- \( N = 1,030 \)
- Coprimary endpoints (superiority)\(^a\)
  - CR/CRu at 120 wk
  - PFS
- Stratification
  - FLIPI score (0-1 vs 2 vs 3-5)
  - Age (>60 vs ≤60 y)
  - Lesion size (>6 vs ≤6 cm)

\(^a\) Per central (IRC) review by 1999 IWG with CT.


\( R^2 \) vs Rituximab-Chemotherapy (R-Chemo)

**Total Treatment Duration: 120 wk**

- \( R^2 \) Lenalidomide: 20 mg/d for 6 cycles and 10 mg/d for the next 12 cycles
- Rituximab: 375 mg/m\(^2\) on d 1, 8, 15, 22 of cycle 1 and d 1 of cycles 2-6; every 8 wk for next 12 cycles
3-y DOR was 77% for R² vs 74% for R-chemo (IRC); investigator results were consistent with IRC.

RELEVANCE: PFS and OS\textsuperscript{1,a}

<table>
<thead>
<tr>
<th>Events, n (%)</th>
<th>( R^2 ) (n = 513)</th>
<th>R-Chemo (n = 517)</th>
</tr>
</thead>
<tbody>
<tr>
<td>119 (23)</td>
<td>111 (21)</td>
<td></td>
</tr>
</tbody>
</table>

3-y PFS (95% CI) 77\% (72\%-80\%) 78\% (74\%-82\%)

HR (95\% CI); \( P \) \( 1.10 \) (0.85-1.43); .48

<table>
<thead>
<tr>
<th>Events, n (%)</th>
<th>( R^2 ) (n = 513)</th>
<th>R-Chemo (n = 517)</th>
</tr>
</thead>
<tbody>
<tr>
<td>38 (7)</td>
<td>31 (6)</td>
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</tbody>
</table>

3-y OS (95\% CI) 94\% (91\%-96\%) 94\% (91\%-96\%)

HR (95\% CI) \( 1.16 \) (0.72-1.86)

\textsuperscript{1} Data cutoff: May 31, 2017.
Safety of $R^2$ Regimen in Newly Diagnosed Patients\textsuperscript{1}

**R-chemo:** more frequent neutropenia, febrile neutropenia, growth factor usage, nausea, vomiting, neuropathy, and alopecia

**$R^2$:** more frequent cutaneous reactions, tumor flare, and diarrhea

There are safety differences for the two treatment arms in the RELEVANCE trial; discuss therapeutic preferences with patients

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R² is not superior to R-chemo (based on PFS and mature CR data at 120 wk)
  – Similar efficacy results with R² and R-chemo

There are safety differences between the treatment arms; weigh risks and benefits, as well as the effect of each on the patient’s quality of life

R² is a potential first-line option in patients with FL who require treatment

Rational combination: combining obinutuzumab with lenalidomide is anticipated to be synergistic in augmenting the innate and adaptive immune response in FL.

Phase 2 study tested O-len in previously untreated, stage II, III, or IV, high tumor burden (defined by GELF) FL (grade 1, 2, or 3a).

O-len was associated with very high CR rates and 2-year PFS estimates in untreated, high tumor burden FL.

- ORR of 98% (85 CR, 1 PR)
- 92% achieved a CR at the first assessment (cycle 4, day 1)

Progression-Free Survival

- Updated oral abstract 125; Saturday, December 7, 2019: 10:30 AM

Many Novel Agent Classes Are Now Included in Recommendations for FL Therapy (NCCN)\(^1\)

**Preferred**
- Bendamustine + obinutuzumab or rituximab
- R-CHOP or G-CHOP
- R-CVP or G-CVP
- Lenalidomide ± rituximab
- Rituximab

**Other Recommended**
- Ibritumomab tiuxetan
- Idelalisib
- Copanlisib
- Duvelisib

Second-Line Consolidation or Extended Dosing
- Rituximab, obinutuzumab, HDT + autoSCT, and alloSCT for selected patients

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AUGMENT Trial Design: R² vs R in R/R NHL¹

Multicenter, Double-Blind, Placebo-Controlled, Randomized Phase 3 Trial

- Patients with R/R grade 1-3a FL or MZL requiring treatment with prior use of ≥1 chemotherapy, immunotherapy, or chemoimmunotherapy
- Not refractory to rituximab
- N = 358

Rituximab 375 mg/m² on d 1, 8, 15, 22 of cycle 1; d 1 of cycles 2-5
Lenalidomide 20 mg/dᵃ on d 1-21/28 for 12 cycles (n = 178)
Note: anticoagulation/antiplatelet therapy recommended for patients at risk

≤12 cycles or until relapse, progression, or intolerability; 5-y follow-up for OS, SPMs, subsequent therapy, and histologic transformation

R + placeboᵇ
Matched capsules for 12 cycles (n = 180)

Stratification for prior rituximab (yes vs no); time since last therapy (≤2 y vs >2 y); FL vs MZL
- **Primary endpoint:** IRC-assessed PFS in ITT population
- **Secondary endpoints:** ORR, OS, histologic transformation, and safety

ᵃ 10 mg if CrCl is 30-59 mL/min. ᵇ Growth factor use in line with ASCO/ESMO guidelines permitted.

In this study, 82% of patients had FL; results showed that $R^2$ was associated with improved PFS in R/R FL vs rituximab alone.

**AUGMENT: PFS**

- $R^2$ median PFS: 39.4 mo (95% CI, 22.9-NE)
- R + placebo median PFS: 14.1 mo (95% CI, 11.4-16.7)

$P < .001$

$HR = 0.46$ (95% CI, 0.34-0.62)

## AUGMENT: Response and OS Outcomes

### R² Improved ORR/CR Rates and OS Compared With R + Placebo

<table>
<thead>
<tr>
<th>N (%)</th>
<th>R²</th>
<th>R</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>138 (78)</td>
<td>96 (53)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>CR</td>
<td>60 (34)</td>
<td>33 (18)</td>
<td>.001</td>
</tr>
</tbody>
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![Graph showing OS, Probability over Time Since Randomization, mo](image)

- **HR = 0.61 (95% CI, 0.33-1.13)**

- **No. at Risk**
  - R²: 178, 167, 155, 143, 122, 80, 44, 15, 1, 0
  - R + placebo: 180, 176, 167, 145, 116, 79, 40, 14, 3, 0

More patients receiving R + placebo discontinued due to disease progression
  - 30% vs 12%

More patients receiving R² discontinued due to AEs
  - 8% vs 4%

\[ \geq 10\% \text{ difference.} \]

R² showed superior efficacy vs R monotherapy for PFS, ORR, and CR irrespective of age
- PFS: HR = 0.46 (95% CI, 0.34-0.62); P < .0001
- Older patients treated with R² vs R-placebo had superior mPFS (24.9 vs 14.3 mo)
- R² maintained efficacy improvements vs R-placebo in pts aged ≥70 y, despite higher unfit status and lower overall lenalidomide treatment/exposure

### AUGMENT: Efficacy by Age Group¹

<table>
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<tr>
<th></th>
<th>≥70 y</th>
<th>&lt;70 y</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>R² (n = 47)</td>
<td>R-Placebo (n = 44)</td>
<td>R² (n = 131)</td>
</tr>
<tr>
<td>mPFS, mo (95% CI)</td>
<td>24.9 (16.4-NE)</td>
<td>14.3 (11.3-27.7)</td>
<td>39.4 (22.9-NE)</td>
</tr>
<tr>
<td>ORR, n (%)</td>
<td>38 (81)</td>
<td>26 (59)</td>
<td>100 (76)</td>
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<tr>
<td>CR, n (%)</td>
<td>12 (26)</td>
<td>7 (16)</td>
<td>48 (37)</td>
</tr>
<tr>
<td>mTTNLT, mo (95% CI)</td>
<td>NE (22.9-NE)</td>
<td>NE (20.8-NE)</td>
<td>NE (NE-NE)</td>
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</tbody>
</table>

• R² is a new chemo-sparing treatment option for patients with previously treated FL
• R² has meaningful advantages over single-agent rituximab
• AEs were common in the R² group, largely because of higher rates of grade 3/4 neutropenia, but the neutropenia was managed successfully with dose modifications and GFS
• May 2019: R² is FDA-approved for use in R/R FL²

Several common tactics can be used when managing patients with B-cell cancers on therapy with lenalidomide.

Dosing in FL/MZL: 20 mg/d orally on d 1-21 of repeated 28-d cycles for up to 12 cycles (based on AUGMENT).

**Important Safety Considerations**

- Exclude pregnancy: patients must use two reliable forms of contraception.
- Hematologic toxicity: monitor blood counts.
- Venous and arterial thromboembolism (risk for deep venous thrombosis, pulmonary embolism, myocardial infarction, and stroke): antithrombotic prophylaxis recommended.

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Tumor Board
Sequencing With Novel Therapeutics in Relapsed FL
After 3 years, Michael shows clinical signs of relapse; progressive disease is confirmed after a recent clinic visit.

Rechallenge with R-chemo? Consider transitioning to another chemo-free regimen?

A chemo-free option is a PI3K inhibitor, such as idelalisib (oral), duvelisib (oral), or copanlisib (IV).

Michael initiates therapy with duvelisib 25 mg twice a day.
Targeting PI3K is an option in FL, in which serial retreatment over several relapses can lead to disease resistance, which reduces options for patients with multiple treatment failures.

PI3K Inhibitors Have a Treatment Role in NHL/CLL

- Idelalisib: first PI3Ki approved based on evidence for R/R CLL and indolent NHL\textsuperscript{1,2}
  - Monotherapy for FL; in combination with rituximab for CLL

Recently, two next-generation PI3K inhibitors were approved
  - Duvelisib (CLL/SLL and FL)
  - Copanlisib (FL)

Duvelisib: Early Activity in iNHL

<table>
<thead>
<tr>
<th></th>
<th>25 mg BID (n = 14)</th>
<th>75 mg BID (n = 15)</th>
<th>All Doses (n = 31)</th>
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<tbody>
<tr>
<td>ORR, n (%)</td>
<td>9 (64.3)</td>
<td>7 (46.7)</td>
<td>18 (58.1)</td>
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<tr>
<td>95% CI</td>
<td>35.1-87.2</td>
<td>21.3-73.4</td>
<td>39.1-75.5</td>
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<td>Best overall response, n (%)</td>
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<tr>
<td>CR</td>
<td>4 (28.6)</td>
<td>1 (6.7)</td>
<td>6 (19.4)</td>
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<tr>
<td>PR</td>
<td>4 (28.6)</td>
<td>6 (40.0)</td>
<td>11 (35.5)</td>
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<tr>
<td>Minor response</td>
<td>1 (7.1)</td>
<td>0</td>
<td>1 (3.2)</td>
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<td>SD</td>
<td>3 (21.4)</td>
<td>7 (46.7)</td>
<td>10 (32.3)</td>
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<td>PD</td>
<td>1 (7.1)</td>
<td>1 (6.7)</td>
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<td>Unknown</td>
<td>1 (7.1)</td>
<td>0</td>
<td>1 (3.2)</td>
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PFS, Probability

<table>
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<tr>
<th>Time, mo</th>
<th>No. at Risk</th>
<th>Total</th>
<th>75 mg BID</th>
<th>25 mg BID</th>
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Median (95% CI), mo
- Total: 14.7 (5.4-30.2)
- 75 mg BID: 5.5 (2.8-22.0)
- 25 mg BID: 14.7 (5.4-NE)

DYNAMO: Study Design

A Phase 2 Study of Duvelisib Monotherapy in Double-Refractory iNHL Populations

Key Eligibility Criteria
- Patients with double-refractory iNHL
- Heavily pretreated
  - Median number of prior treatments = 3
- Refractory to both rituximab and a chemotherapy regimen or radioimmunotherapy
- N = 129

Primary endpoint: ORR by IRC

Key secondary endpoints: safety, DOR, PFS, and OS

Duvelisib 25 mg twice daily

DYNAMO: Efficacy of Duvelisib in Double-Refractory iNHL

- ORR of 47.3%
- Estimated median DOR was 10 months

Six patients who had ≥50% reduction in the target lesion did not meet the IRC’s assessment for response per IWG criteria because of extranodal disease and/or new lesions.

DYNAMO: PFS and OS Outcomes

Median PFS of 9.5 months; median OS of 28.9 months

CHRONOS-1: Copanlisib in Patients With Relapsed, Indolent NHL

**Phase 2 study**
- 142 patients with R/R indolent lymphoma after ≥2 lines of therapy

**Copanlisib 60 mg IV on d 1, 8, and 15 of a 28-d cycle**

- Copanlisib is active in R/R iNHL
  - ORR = 59% (84/142 patients)
  - CR = 12%
- Activity confirmed in updated analysis
  - ORR = 58.5%
  - Median DOR = >1 y
  - Median PFS = 11.3 mo

**Primary endpoint:** ORR  
**Secondary endpoints:** DOR, PFS, and OS

Copanlisib in R/R Indolent Lymphoma: PFS and OS

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

Median, mo NR
Range 0-30.3
95% CI —

Another PI3K Option: Umbralisib in R/R NHL

- Early-phase study in patients with R/R NHL, CLL, HL, or T-cell NHL (≥1 prior treatment regimen)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Objective Response, n (%)</th>
</tr>
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<tbody>
<tr>
<td>CLL (n = 20)</td>
<td>17 (85)</td>
</tr>
<tr>
<td>CLL, del17p/del11q (n = 8)</td>
<td>6 (75)</td>
</tr>
<tr>
<td>FL (n = 17)</td>
<td>9 (53)</td>
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<tr>
<td>DLBCL (n = 13)</td>
<td>4 (31)</td>
</tr>
</tbody>
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## The Safety Experience With PI3K Inhibitors

<table>
<thead>
<tr>
<th>Monitoring</th>
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<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>• GI events</td>
<td>• Hepatic function</td>
<td>• Infections</td>
</tr>
<tr>
<td>• Hepatotoxicity</td>
<td>• Blood counts</td>
<td>• Hyperglycemia</td>
</tr>
<tr>
<td>• Pneumonitis</td>
<td>• GI events</td>
<td>• Hypertension</td>
</tr>
<tr>
<td>• Anaphylaxis</td>
<td>• Pneumonitis</td>
<td>• Blood counts</td>
</tr>
<tr>
<td>• Intestinal perforation</td>
<td>• Infection</td>
<td>• Rash</td>
</tr>
<tr>
<td>• Opportunistic infections, such as CMV and PJP</td>
<td>• Rash</td>
<td>• Pneumonitis</td>
</tr>
</tbody>
</table>

### Tactics for addressing safety considerations with PI3K inhibitors

- Monitoring
  - GI events
  - Hepatotoxicity
  - Pneumonitis
  - Anaphylaxis
  - Intestinal perforation
  - Opportunistic infections, such as CMV and PJP

### Management for AEs can include

- **Idelalisib**
  - Dose interruption and/or discontinuation (eg, for hepatotoxicity or pneumonitis)

- **Duvelisib**
  - Dose interruption and therapeutic interventions (eg, antidiarrheal or steroid for GI events, depending on grade)

- **Copanlisib**
  - Dose reduction and withholding or discontinuing treatment among the potential interventions (eg, for cutaneous reactions)

---

Take-Homes on Therapeutic Sequencing in FL

- Regardless of first-line therapy, many patients still relapse and will require subsequent therapy.

- Choice and sequencing of first and subsequent therapy should (more or less...in this order) be based upon:
  - Comorbidities, patient’s ability to tolerate therapy.
  - Goals of therapy (prolongation of remission, side effects, disease control, etc.).
  - Cost, length of therapy, patient convenience.
Options beyond immunochemotherapy are now available for the management of patients with FL

- Include chemotherapy-sparing treatments (eg, R² and PI3K inhibitors)
- A greater number of options allows for flexible therapeutic sequencing over several lines of therapy

Pay attention to cumulative toxicities, differing safety profiles of chemotherapy, and nonchemotherapy options when selecting treatment
Where Novel Agent Classes Fit and Future Directions in the Management of MCL

Professor Simon Rule, MD, PhD
Professor of Clinical Haematology
Plymouth University Medical School
Plymouth, England, United Kingdom
Outline

• Background
• Prognostic factors
• Indolent MCL
• Management
  – Younger/older
• Relapse
• Where next?
What Risk Factors Do We Know?
Clinical Risk Factors: MIPI


(PALL: PS, age, LDH, leucocyte count)

Molecular Assay for Proliferation Signature in Routine FFPE MCL Samples

Progression of Disease

Impact of TP53 in Nordic Trials


Overall Survival

No TP53 mut (n = 156)

TP53 mut (n = 20)

\[ P < .0001 \]
## PFS and OS: Univariate and Multivariate Cox Regression Analysis


<table>
<thead>
<tr>
<th>Genes</th>
<th>Progression-Free Survival</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate</td>
<td>Multivariate (MIPI-c and Blastoid Variant Adjusted)</td>
</tr>
<tr>
<td>ATM mut</td>
<td>1.29</td>
<td>1.19</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.84-1.97</td>
<td>0.77-1.83</td>
</tr>
<tr>
<td>P</td>
<td>.245</td>
<td>.432</td>
</tr>
<tr>
<td>WHSC1 mut</td>
<td>1.53</td>
<td>1.51</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.90-2.60</td>
<td>0.87-2.61</td>
</tr>
<tr>
<td>P</td>
<td>.119</td>
<td>.140</td>
</tr>
<tr>
<td>CCND1 mut</td>
<td>0.83</td>
<td>0.94</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.41-1.66</td>
<td>0.46-1.92</td>
</tr>
<tr>
<td>P</td>
<td>.595</td>
<td>.860</td>
</tr>
<tr>
<td>KMT2D mut</td>
<td>2.59</td>
<td>2.74</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.50-4.48</td>
<td>1.55-4.84</td>
</tr>
<tr>
<td>P</td>
<td>.001</td>
<td>.001</td>
</tr>
<tr>
<td>TP53 mut</td>
<td>2.84</td>
<td>2.55</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.57-5.13</td>
<td>1.36-4.78</td>
</tr>
<tr>
<td>P</td>
<td>.001</td>
<td>.003</td>
</tr>
<tr>
<td>NOTCH1 mut</td>
<td>1.86</td>
<td>1.57</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.93-3.72</td>
<td>0.76-3.24</td>
</tr>
<tr>
<td>P</td>
<td>.078</td>
<td>.226</td>
</tr>
<tr>
<td>BIRC3 mut</td>
<td>0.88</td>
<td>0.70</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.32-2.41</td>
<td>0.25-1.96</td>
</tr>
<tr>
<td>P</td>
<td>.807</td>
<td>.500</td>
</tr>
<tr>
<td>TP53 del</td>
<td>3.51</td>
<td>3.13</td>
</tr>
<tr>
<td>95% CI</td>
<td>2.09-5.88</td>
<td>1.73-5.68</td>
</tr>
<tr>
<td>P</td>
<td>&lt; .0001</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>TP53 dis</td>
<td>3.39</td>
<td>3.17</td>
</tr>
<tr>
<td>95% CI</td>
<td>2.10-5.45</td>
<td>1.87-5.38</td>
</tr>
<tr>
<td>P</td>
<td>&lt; .0001</td>
<td>&lt; .0001</td>
</tr>
</tbody>
</table>

# MIPI-g Score

<table>
<thead>
<tr>
<th>Variables</th>
<th>Beta-Coefficients</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>KMT2D</em> mutations</td>
<td>1,035,607</td>
<td>2</td>
</tr>
<tr>
<td><em>TP53</em> disruption</td>
<td>1,113,875</td>
<td>2</td>
</tr>
</tbody>
</table>

**MIPI-c**

<table>
<thead>
<tr>
<th>Category</th>
<th>Beta-Coefficients</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>–</td>
<td>0</td>
</tr>
<tr>
<td>Low-intermediate</td>
<td>–</td>
<td>0</td>
</tr>
<tr>
<td>Intermediate-high</td>
<td>–</td>
<td>0</td>
</tr>
<tr>
<td>High</td>
<td>0.6847757</td>
<td>1</td>
</tr>
</tbody>
</table>

---

MIPI-g¹

MCL Treatment Algorithm

1. Adapted from Campo, Rule S. Blood. 2015;125:48-55.
Indolent MCL Exists
Observation vs Early Treatment

Initially observed (n = 75)

Early treatment (n = 355)

P = .041

Pathogenesis of MCL

Courtesy of E Campo.
Impact of SOX11

![Survival graph](image)

Survival, %

OS

- SOX11+
- SOX11-

\[ P = .63 \]

Watch-and-Wait for Newly Diagnosed MCL

Management of Newly Diagnosed MCL in the United Kingdom 2015-2017 (N = 222)

High intensity = high-dose cytarabine based therapy +/- BEAM autoSCT;
intermediate intensity = R-CHOP, R-bendamustine, or R-ibrutinib all with R maintenance;
low intensity = R-chlorambucil or dexamethasone monotherapy.

* Palliation = 2.3%.
MCL Treatment Algorithm

Patients Fit for Autograft

1. Adapted from Campo, Rule S. Blood. 2015;125:48-55.
Role of High-Dose Cytarabine

- Inclusion of HD cytarabine improves PFS
- Not OS
- If going “intensive,” you need to include HD cytarabine
- Many ways to achieve that, but try to minimize toxicity

LyMa Trial

**R-CHOP**

**R-DEHAP**

**R-DEHAP**

**R-DEHAP**

**R-DEHAP**

**R-BEAM**

**R-BEAM**

**R-BEAM**

**R-BEAM**

**Observation**

**Rituximab maintenance**
Every 2 mo during 3 y

**If > VGPR**

**If < VGPR**

**R-BEAM:** rituximab 500 mg/m² d 8, BCNU 300 mg/m² d-7, etoposide 400 mg/m² per day d-6 to d-3, aracytine 400 mg/m² per day d-6 to d-3, melphalan 140 mg/m² d-2

**R-DHAP:** rituximab 375 mg/m², aracytine 2 g/m² x 2 IV 3 hours injection 12 hours interval, dexamethasone 40 mg d1-4, cisplatin 100 mg/m² d1 (or oxaliplatin or carboplatin)

**OS From Randomization**

**mFU: 50.2 mo (46.4-54.2)**

<table>
<thead>
<tr>
<th>Survival Probability</th>
<th>Observation (95%CI)</th>
<th>Rituximab (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS 24m: 93.3 % (87.0-96.6)</td>
<td>93.3 % (87.1-96.6)</td>
<td></td>
</tr>
<tr>
<td>36m: 85.4 % (77.5-90.7)</td>
<td>93.3 % (87.1-96.6)</td>
<td></td>
</tr>
<tr>
<td>48m: 81.4 % (72.3-87.7)</td>
<td>88.7 % (80.7-93.5)</td>
<td></td>
</tr>
</tbody>
</table>

**OS From Randomization, mo**

PFS According to MRD Status After Treatment (ASCT)\(^1,2\)

Nordic MCL-2
R-maxi-CHOP/R-HA + ASCT

Nordic MCL-3
R-maxi-CHOP/R-HA + ASCT + Z

Step 0

- Any induction regimen
- Enroll before, during, or after induction

Submit diagnostic tissue for molecular testing

Clonal marker present?

Yes

Postinduction restaging + submission of blood for MRD assessment

MRD-neg CR

MRD-neg PR or MRD-pos CR

No

No informative marker: MRD indeterminate

MRD-neg PR or MRD indeterminate

REGISTRATION

Step 1

Randomization

Arm A
Auto-HCT + rituximab x 3 y

Arm B
Rituximab x 3 y

Arm C
Auto-HCT + rituximab x 3 y

Arm D
Auto-HCT + rituximab x 3 y

Stratify
- MIPI-c
- Intensive vs nonintensive induction

BUT ...
Cytology

OS According to Cytology

PFS According to Cytology

MIPI-B-miR

OS

PFS

Impact of TP53 in Nordic Trials\(^1\)

**Overall Survival**

![Graph showing overall survival](image)

- **No TP53 mut (n = 156)**
- **TP53 mut (n = 20)**

\[ P < .0001 \]

Ibrutinib Outcomes by TP53 Mutational Status

Patients With Mutated vs Wild-Type TP53

<table>
<thead>
<tr>
<th>Mutational Status</th>
<th>Median PFS, mo (95% CI)</th>
<th>Median OS, mo (95% CI)</th>
<th>ORR, %</th>
<th>CR, %</th>
<th>PR, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutated TP53 (n = 20)(^a)</td>
<td>4.0 (2.1-8.3)</td>
<td>10.3 (2.5-12.6)</td>
<td>55.0</td>
<td>0</td>
<td>55.0</td>
</tr>
<tr>
<td>Wild-type TP53 (n = 124)</td>
<td>12.0 (7.1-15.6)</td>
<td>33.6 (18.3-NE)</td>
<td>70.2</td>
<td>25.0</td>
<td>45.2</td>
</tr>
</tbody>
</table>

- Responses to ibrutinib were less favorable in patients with mutated versus wild-type TP53

\(^a\) Response data missing for three patients.

Allogeneic HSCT Effects on Outcomes of MCL With TP53 Alterations

MCL Treatment Algorithm

Patients Unfit for Autograft

1. Adapted from Campo, Rule S. Blood. 2015;125:48-55.
### Summary of Nonintensive Induction Regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>N</th>
<th>Age, y</th>
<th>ORR</th>
<th>CR</th>
<th>mPFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-CHOP</td>
<td>244</td>
<td>66</td>
<td>89%</td>
<td>42% (CT)</td>
<td>14.4 mo</td>
</tr>
<tr>
<td>VR-CAP</td>
<td>243</td>
<td>65</td>
<td>92%</td>
<td>53% (CT)</td>
<td>24.7 mo</td>
</tr>
<tr>
<td>BR(^b)</td>
<td>188</td>
<td>70</td>
<td>≈90%</td>
<td>≈45% (CT)</td>
<td>35-48 mo</td>
</tr>
<tr>
<td>RBAC500</td>
<td>57</td>
<td>71</td>
<td>91%</td>
<td>91% (PET)</td>
<td>Not reached</td>
</tr>
</tbody>
</table>

\(^a\) No maintenance therapy. \(^b\) Pooled data from three trials.

No difference in OS

VR-CAP was more effective than R-CHOP in patients with newly diagnosed MCL but at the cost of increased hemotoxicity
Final OS Analysis (ITT)
Median Follow-Up of 82.0 Months

HR = 0.66
95% CI (0.51-0.85)
P = .001

No. at Risk (No. Censored)
R-CHOP group
VR-CAP group

0 6 12 18 24 30 36 42 48 54 60 66 72 78 84 90 96 102 108
Time Since Randomization, mo

Overall Survival, %

VR-CAP
R-CHOP

Lenalidomide + Rituximab as Initial Treatment for MCL

Rates of Best Response at the Median Follow-Up of 30 mo

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>ITT Population (n = 38), %</th>
<th>Evaluable Patients (n = 36), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>33</td>
<td>87</td>
<td>92</td>
</tr>
<tr>
<td>CR&lt;sup&gt;a&lt;/sup&gt;</td>
<td>23</td>
<td>61</td>
<td>64</td>
</tr>
<tr>
<td>PR</td>
<td>10</td>
<td>26</td>
<td>28</td>
</tr>
<tr>
<td>SD</td>
<td>1</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>PD&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>NE&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2</td>
<td>5</td>
<td>–</td>
</tr>
</tbody>
</table>

<sup>a</sup> A CR was confirmed by means of combined PET and CT and, when indicated, by means of a bone marrow biopsy. <sup>b</sup> Although eight patients had PD, two had primary PD; six other patients had either SD, partial remission, or complete remission before PD developed. <sup>c</sup> Treatment was discontinued because an inflammatory syndrome (tumor flare) without disease progression occurred before the response assessment was performed.

5-Year Follow-Up of Lenalidomide + Rituximab as Initial Treatment for MCL


- Probability of OS
- Time Since Treatment, mo
- 5-y OS estimate: 77%

**OS by MIPI Score**
- P = .04 by log-rank test
- MIPI ≤6.2
- MIPI >6.2

RBAC500 as Induction Therapy for Elderly Patients

- Rituximab 375 mg/m² on d 1, bendamustine 70 mg/m² d 2 and 3, cytarabine (dose reduced) 500 mg/m² d 2-4
- Included previously untreated patients aged >65 y or 60-65 y unfit for ASCT with no history of indolent disease (non-nodal leukemic disease)
- Primary objectives: CR rate and safety

### End of Treatment PET/CT

<table>
<thead>
<tr>
<th></th>
<th>N = 57</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>52</td>
<td>91</td>
</tr>
<tr>
<td>CR</td>
<td>52</td>
<td>91</td>
</tr>
<tr>
<td>PD</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>NA</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>

### MRD by n-PCR (N = 45, 79%)

<table>
<thead>
<tr>
<th>Timepoints</th>
<th>n</th>
<th>MRD: BM/PB</th>
</tr>
</thead>
<tbody>
<tr>
<td>After cycle 2</td>
<td>45</td>
<td>54/62</td>
</tr>
<tr>
<td>End of therapy</td>
<td>45</td>
<td>55/79</td>
</tr>
<tr>
<td>+12 mo</td>
<td>28</td>
<td>57/75</td>
</tr>
</tbody>
</table>

Tumor Board

A Patient With MCL, Post-SCT

George, a fit man aged 65 years

- Presents to PCP for a scheduled assessment
- 3 years post–stem cell transplant
- Patient is fit (ECOG PS 0)

Investigations

- CT shows SOL
- Biopsy = classical MCL
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Study or Literature Reference</th>
<th>N</th>
<th>ORR</th>
<th>CR</th>
<th>Median DOR, mo</th>
<th>Median PFS, mo</th>
<th>Median OS, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibrutinib</td>
<td>PCYC-1104-CA</td>
<td>111</td>
<td>68%</td>
<td>21%</td>
<td>17.5</td>
<td>13.9</td>
<td>NR</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>Fischer 2006, Goy 2009</td>
<td>155a</td>
<td>33%</td>
<td>8%</td>
<td>9.2</td>
<td>6.5</td>
<td>23.5</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>Goy 2012</td>
<td>134</td>
<td>28%</td>
<td>8%</td>
<td>16.6</td>
<td>4.0</td>
<td>19.0</td>
</tr>
<tr>
<td>Temsirolimusb</td>
<td>Hess 2009</td>
<td>54</td>
<td>22%</td>
<td>2%</td>
<td>7.1</td>
<td>4.8</td>
<td>12.8</td>
</tr>
<tr>
<td>Acalabrutinib</td>
<td>Wang 2017</td>
<td>124</td>
<td>81%</td>
<td>40%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

a Of the 155 patients enrolled, 141 were assessable for response. b Results are presented for temsirolimus 175/75 mg dose group.
PFS and OS by Prior Line of Therapy

- Median PFS was just over 2 y in patients with 1 prior line of therapy

**PFS**
- Median 25.4 mo (17.5-57.5)
- Median 10.3 mo (8.1-12.5)

**OS**
- Median NR (36.0-NE)
- Median 22.5 mo (16.2-26.7)

Patients at risk

<table>
<thead>
<tr>
<th></th>
<th>1 prior</th>
<th>&gt; 1 prior</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 prior</td>
<td>99</td>
<td>81</td>
</tr>
<tr>
<td>&gt; 1 prior</td>
<td>271</td>
<td>193</td>
</tr>
</tbody>
</table>

Patients at risk

<table>
<thead>
<tr>
<th></th>
<th>1 prior</th>
<th>&gt; 1 prior</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 prior</td>
<td>99</td>
<td>88</td>
</tr>
</tbody>
</table>

Median PFS overall (95% CI): 12.5 (9.8-16.6) mo

Median OS overall (95% CI): 26.7 (22.5-38.4) mo
Ibrutinib in MCL: DOR by Best Response and Line of Therapy\(^1\)

- Median DOR was 4.5 y in patients achieving a CR
- Patients with 1 prior line had 2 x longer DOR than patients with >1 prior line

<table>
<thead>
<tr>
<th>Median DOR, mo (Range)</th>
<th>Overall (n = 258)</th>
<th>Prior Lines of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 258)</td>
<td>1 (n = 77)</td>
</tr>
<tr>
<td>Overall (N = 258)</td>
<td>22.2 (16.5-28.8)</td>
<td>34.4 (23.1-NE)</td>
</tr>
<tr>
<td>CR (n = 98)</td>
<td>55.7 (55.7-NE)</td>
<td>55.7 (33.1-NE)</td>
</tr>
<tr>
<td>PR (n = 160)</td>
<td>10.4 (7.7-14.9)</td>
<td>22.1 (10.6-34.4)</td>
</tr>
</tbody>
</table>

Line of Therapy and Outcome

Line 1 (n = 386)
Line 2 (n = 204)
Line 3 (n = 113)
Line 4 (n = 72)
Line 5-9 (n = 88)

**OS, %**

**PFS, %**

* OS and PFS after treatment with line 1, line 2, line 3, line 4, and lines 5-9.
**Median PFS With Second-Line Ibrutinib**

**Data From a Pooled Clinical Trial Cohort in R/R MCL¹**

---

**Graph: Data From a Pooled Clinical Trial Cohort in R/R MCL**

- **All patients treated with second-line ibrutinib (n = 99)**
  - First-line CIT, median TTNT: NR (95% CI: 17.5-57.5)
  - Second-line ibrutinib, median PFS: 25.4 (95% CI: 17.5-57.5)

- **Durable responders treated with second-line ibrutinib (n = 55)**
  - First-line CIT, median TTNT: NR (95% CI: 17.5-57.5)
  - Second-line ibrutinib, median PFS: 57.5 (95% CI: 25.2-NE)

- **56% of patients were durable responders**

---

**Definition:**

- **TTNT:** Time to next treatment, defined as time from start of frontline chemoimmunotherapy to start of ibrutinib second-line therapy.

---


---

**Note:**

This is the right reference instead.

---

**Table: Durable Responders**

<table>
<thead>
<tr>
<th>Category</th>
<th>Time, mo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-line CIT</td>
<td>NR (95% CI: 17.5-57.5)</td>
</tr>
<tr>
<td>Second-line ibrutinib</td>
<td>25.4 (95% CI: 17.5-57.5)</td>
</tr>
<tr>
<td>Durable responders</td>
<td>57.5 (95% CI: 25.2-NE)</td>
</tr>
</tbody>
</table>

---

**Legend:**

- NR: Not reported
- NE: Not estimable
Ibrutinib for CNS MCL
4-Year Follow-Up of Ibrutinib + Rituximab in R/R MCL

- **EFS**
  - Median EFS = 16 mo
  - Events/total = 37/50

- **DOR**
  - Median DOR = 46 mo
  - Lost response/total = 19/47

- **PFS**
  - Median PFS = 43 mo
  - Progressed/total = 23/50

- **OS**
  - Median OS = NR
  - Deaths/total = 18/50

---

Ibrutinib + Lenalidomide + Rituximab: The PHILEMON Study Design

- R² induction schedule adapted from Ruan et al. *N Engl J Med.* 2015
- Lenalidomide 15 mg d 1-21, 28-day cycle, up to 12 mo
- Eligible: R/R MCL, ≥1 rituximab regimen, no age limit
- Primary endpoint: ORR
- Aim: to improve ORR in R/R MC, compared with single-agent ibrutinib

## Ibrutinib + Lenalidomide + Rituximab: Response

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N = 42</strong></td>
<td>(n = 39)</td>
<td>(n = 3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td>37 (88%)</td>
<td>35 (90%)</td>
<td>2 (67%)</td>
<td>68</td>
</tr>
<tr>
<td><strong>CR</strong></td>
<td>27 (64%)</td>
<td>27 (69%)</td>
<td>0 (0%)</td>
<td>21</td>
</tr>
<tr>
<td><strong>PR</strong></td>
<td>10 (24%)</td>
<td>8 (21%)</td>
<td>2 (67%)</td>
<td>47</td>
</tr>
<tr>
<td><strong>No response</strong></td>
<td>5 (12%)</td>
<td>4 (10%)</td>
<td>1 (33%)</td>
<td>20</td>
</tr>
</tbody>
</table>

**After median follow-up of 17.8 months:**

ORR of 76%, CR of 28%

---

Maximal Responses to Treatment in All Patients and According to Presence of *TP53* Mutation

**Ibrutinib + Lenalidomide + Rituximab**

<table>
<thead>
<tr>
<th></th>
<th>All Patients (N = 50)</th>
<th><em>TP53</em> Wild Type (n = 38)</th>
<th><em>TP53</em> Mutated (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response</td>
<td>38 (76%, 63-86)</td>
<td>30 (79%, 64-89)</td>
<td>8 (73%, 43-90)</td>
</tr>
<tr>
<td>Complete remission</td>
<td>28 (56%, 42-69)</td>
<td>21 (55%, 40-70)</td>
<td>7 (64%, 35-85)</td>
</tr>
<tr>
<td>Partial remission</td>
<td>10 (20%, 11-33)</td>
<td>9 (24%, 13-39)</td>
<td>1 (9%, 2-38)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>1 (2%, 0-1)</td>
<td>1 (3%, 0-14)</td>
<td>0 (0%, 0-0)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>5 (10%, 4-21)</td>
<td>3 (8%, 3-21)</td>
<td>2 (18%, 5-48)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>6 (12%, 6-24)</td>
<td>4 (11%, 4-24)</td>
<td>1 (9%, 2-38)</td>
</tr>
</tbody>
</table>

Bill, a man aged 91 years

- January 2015: presents with B symptoms, leukocytosis, and bulky lymphadenopathy
- Commenced rituximab + chlorambucil
- Does not respond after two cycles with significant cytopenias
Bill initiated BTKi therapy

- June 2015: commenced BTKi
- Partial remission with leukocytosis within 1 mo—excellent clinical response
- Significant bruising—aspirin stopped
- PET-negative PR on imaging with residual marrow involvement at 9 mo
- VGPR at 12 mo
Alternative BTK Inhibitors

- Tirabrutinib
- Acalabrutinib
- Zanubrutinib
- M 7583
Acalabrutinib (ACP-196)\textsuperscript{1,2}

Acalabrutinib is more selective for BTK with less off-target kinase inhibition compared with ibrutinib in vitro.

## Kinase Inhibition

Average $IC_{50}$ (nM)

<table>
<thead>
<tr>
<th>Kinase</th>
<th>Acalabrutinib</th>
<th>Ibrutinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>BTK</td>
<td>5.1</td>
<td>1.5</td>
</tr>
<tr>
<td>TEC</td>
<td>126.0</td>
<td>10</td>
</tr>
<tr>
<td>ITK</td>
<td>$&gt;1,000$</td>
<td>4.9</td>
</tr>
<tr>
<td>BMX</td>
<td>46.0</td>
<td>0.8</td>
</tr>
<tr>
<td>TXK</td>
<td>368.0</td>
<td>2.0</td>
</tr>
<tr>
<td>EGFR</td>
<td>$&gt;1,000$</td>
<td>5.3</td>
</tr>
<tr>
<td>ERBB2</td>
<td>$≈1,000$</td>
<td>6.4</td>
</tr>
<tr>
<td>ERBB4</td>
<td>16.0</td>
<td>3.4</td>
</tr>
<tr>
<td>BLK</td>
<td>$&gt;1,000$</td>
<td>0.1</td>
</tr>
<tr>
<td>JAK3</td>
<td>$&gt;1,000$</td>
<td>32.0</td>
</tr>
</tbody>
</table>

# BTK Inhibitors for R/R MCL

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Study or Literature Reference</th>
<th>N</th>
<th>ORR</th>
<th>CR</th>
<th>Median DOR, mo</th>
<th>Median PFS, mo</th>
<th>Median Prior Lines of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibrutinib</td>
<td>Wang 2013</td>
<td>111</td>
<td>68%</td>
<td>21%</td>
<td>17.5</td>
<td>13.9</td>
<td>3</td>
</tr>
<tr>
<td>Acalabrutinib</td>
<td>Wang 2018</td>
<td>124</td>
<td>81%</td>
<td>40%</td>
<td>26</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>Tirabrutinib</td>
<td>Rule 2020&lt;sup&gt;a&lt;/sup&gt;</td>
<td>16</td>
<td>92%</td>
<td>46%</td>
<td>NR</td>
<td>NR</td>
<td>3</td>
</tr>
<tr>
<td>Zanubrutinib&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Tam 2019</td>
<td>48</td>
<td>87%</td>
<td>30%</td>
<td>15.4</td>
<td>NR</td>
<td>1</td>
</tr>
<tr>
<td>Zanubrutinib&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Song 2019</td>
<td>85</td>
<td>84%</td>
<td>59%</td>
<td>NR</td>
<td>24 wk, 83%</td>
<td>2</td>
</tr>
</tbody>
</table>

<sup>a</sup> In press.  
<sup>b</sup> Phase 1.  
<sup>c</sup> Chinese only phase 2.  
Nothing Works After Ibrutinib?
Venetoclax
PFS by Histology Subtype

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Median PFS, mo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (N = 106)</td>
<td>17 (14-22)</td>
</tr>
<tr>
<td>MCL (n = 28)</td>
<td>14 (ND)</td>
</tr>
<tr>
<td>FL (n = 29)</td>
<td>11 (6-19)</td>
</tr>
<tr>
<td>DLBCL (n = 34)</td>
<td>1 (1-3)</td>
</tr>
</tbody>
</table>

Percent Survival, %

Time, mo

MCL: 28 16 12 4 1
FL: 29 17 7 4 2 1 1
DLBCL: 34 2

Venetoclax Monotherapy After BTK Inhibitor\textsuperscript{1}

Survival Outcomes of Patients With R/R MCL on Venetoclax Monotherapy

- **PFS, Probability**
  - Median 3.2 mo (95% CI, 1.2-11.3 mo)

- **OS, Probability**
  - Median 9.4 mo (95% CI, 1.5 mo-NR)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Treatment Used</th>
<th>N</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheah et al</td>
<td>Assorted</td>
<td>31</td>
<td>ORR, 32%; median DOR, 6 mo; median OS, 8.4 mo</td>
</tr>
<tr>
<td>Martin et al</td>
<td>Assorted</td>
<td>73</td>
<td>ORR, 29%; median PFS 1.9 mo; median OS 5.8 mo</td>
</tr>
<tr>
<td>Wang et al</td>
<td>Lenalidomide ± other treatment</td>
<td>58</td>
<td>ORR, 29%; median DOR, 5 mo</td>
</tr>
<tr>
<td>Eyre et al</td>
<td>Venetoclax monotherapy</td>
<td>22</td>
<td>ORR, 53%; median PFS, 3.2 mo; median OS, 9.4 mo</td>
</tr>
<tr>
<td><strong>This study</strong></td>
<td><strong>R-BAC</strong></td>
<td><strong>29</strong></td>
<td><strong>ORR, 89.3%; median PFS, 8.6 mo; median OS, 12.2 mo</strong></td>
</tr>
</tbody>
</table>

Where Are We Going?
Window I/II Study: The Best Response Rate\textsuperscript{1}

Four patients had progressed after 10, 33, 13, and 4 mo of treatment (three patients had transformed to blastoid/pleomorphic variant), two had Ki-67% ≥30%, one was *TP53*-mutated, and another had *FAT1* and *SF3B1* mutations.

Two patients died after being on ibrutinib for 1 (discontinued due to bleeding) and 13 mo (transformed); both had Ki-67% ≥30%.
ENRICH: Phase 3 Trial of Rituximab + Ibrutinib vs Rituximab + Chemotherapy in Elderly MCL Pts

IR/R Intervention

R-CHEMO/R Standard care

R-CHEMO (every 21 d) for 6-8 cycles

Rituximab (every 56 d) for 2 y

Follow-up until disease progression

Rituximab (every 56 d) for 2 y

Ibrutinib daily + rituximab (every 21 d) for 8 cycles

Ibrutinib daily + rituximab (every 56 d) for 2 y

Ibrutinib to continue until disease progression

A:
R-CHOP/R-DHAP x 6 → ASCT → Observation

A + I:
R-CHOP/R-DHAP x 6 + I → ASCT → 2 y I-maintenance → Observation

I:
R-CHOP/R-DHAP x 6 + I → 2 y I-maintenance → Observation

Superiority/noninferiority: time to treatment failure
HR = 0.60; 65% vs 77% vs 49% at 5 y
AIM (ABT-199 & Ibrutinib in MCL) Study Schema

- **Primary endpoint**

  - ABT-199 400 mg daily
  - Ibrutinib 560 mg daily

- **CT, BM, and MRD assessments**

  - until PD or intolerance

- **Plasma DNA**

  - 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56 weeks

AIM Study: Response Rates (PET)¹

- Patients were restaged at wk 16 using CT, PET, double endoscopy (if baseline involvement), and BMAT with MRD studies

- Patients were not evaluable due to early death (n = 1) and target lesions judged on central review to be too small and poorly FDG-avid for reproducible measurement (n = 1)

<table>
<thead>
<tr>
<th></th>
<th>Wk 16, CT Only</th>
<th>Wk 16, PET/CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>10 (42%)</td>
<td>15 (63%)</td>
</tr>
<tr>
<td>CR, unconfirmed</td>
<td>4 (17%)</td>
<td>–</td>
</tr>
<tr>
<td>PR</td>
<td>4 (17%)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>SD</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>PD</td>
<td>3 (13%)</td>
<td>4 (17%)</td>
</tr>
<tr>
<td>NE</td>
<td>2 (8%)</td>
<td>2 (8%)</td>
</tr>
</tbody>
</table>

Wk 16
OR = 71%; CR = 63%
50% TP53 aberrations, 50% achieved CR

A Phase 1 Trial of Obinutuzumab + Venetoclax + Ibrutinib in R/R and Untreated MCL Patients

- PI (UK): Pr Simon Rule
- PI (France): Pr Steven Le Gouill
- Countries: France and UK

N = 33
- Step A: 9 patients
- Step B: 24 patients
- Step C upfront: 15 patients

Updated poster abstract 1530; Saturday, December 7, 2019, 5:30-7:30 PM
CAR T Cells?
Summary

- Treat when clinically indicated
- Young patients
  - Cytarabine is the key drug
  - What you add to it is not clear
- Older patients
  - CHOP- or bendamustine-based treatment appropriate
- New agents are rapidly moving into the frontline
  - Likely to be part of the standard of care soon
- Clinical trials are how we improve outcomes
Possible Future Algorithm for MCL

MCL

Require Therapy?

Yes

Young

BTKi combination

MRD

+ Cellular therapy

- BTKi maintenance

Yes

Older

BTKi combination

MRD

+ To progression

No

Frail elderly

BTKi (+ antibody)

STOP

Watch and wait

S Rule personal communication.
Achieving Better Outcomes in DLBCL With Innovative Therapy

Are We Rising to the Challenge?

Matthew A. Lunning, DO, FACP
Medical Director Lymphoma Research
Associate Professor, Division of Hematology/Oncology
Department of Medicine
University of Nebraska Medical Center
Omaha, Nebraska
Tumor Board
Assessing a Patient With DLBCL
Martha, a 63-year-old female, presents to PCP for a scheduled assessment:

- Bilateral axillary lymph nodes noted on screening mammogram.
- Comparison of prior images notes no lymph nodes seen.
- Physical exam noted lymph nodes in 2- to 3-cm lymph nodes in axilla and inguinal regions.
- Handheld ultrasound confirmed 2 to 3-cm abnormal size and echotexture.
Further Consultation Recommended

**Surgical & Pathology Consults**

1. Desire an excisional biopsy given location on exam.

2. Excisional biopsy of inguinal lymph node demonstrated large atypical lymphocytes with effacement of the lymph node architecture.

**Diagnosis:** Diffuse large B-cell lymphoma—not otherwise specified (DLBCL-NOS); see comments below
Comments Below DLBCL

Essential Immunophenotyping

- **IHC panel:** CD20, CD3, CD5, CD10, CD45, BCL-2, BCL-6, Ki-67 (70%), IRF4/MUM1, MYC (50%) with/without:

- **Cell surface marker analysis:**
  - kappa/lambda, CD45, CD3, CD5, CD19, CD10, CD20

Essential Workup<sup>a</sup>

- Physical exam, Performance Status, B symptoms
- CBC, CMP, LDH, uric acid, HBV testing, ± BM biopsy
- PET/CT
- Calculation of International Prognostic Index (IPI)

---

<sup>a</sup> ECG or MUGA scan if anthracycline- or anthracenedione-based regimen indicated. Pregnancy testing if chemo or RT planned.

Assessment Results

- CBC and CMP were unremarkable
- LDH was elevated
- PS = 0
- PET/CT demonstrated avid abnormal lymph nodes above and below diaphragm (stage 3)
  - No concern for extranodal disease or bone lesions
- IPI score = 3 (age, LDH, stage)
CBC and CMP were unremarkable
LDH was elevated
PS = 0
PET/CT demonstrated avid abnormal lymph nodes above and below diaphragm (stage 3)
  – No concern for extranodal disease or bone lesions
IPI score = 3 (age, LDH, stage)
FISH– t(14;18); MYC not altered
Dx: DLBCL-NOS; GCB subtype
The most common NHL in the United States

- Accounts for ≈24% of new cases of NHL
- Roughly 18,000 cases anticipated in 2019

Typically aggressive, presents with

- Rapidly enlarging lymphadenopathy and constitutional symptoms
- High frequency of extranodal disease
- Need for treatment within days to weeks of diagnosis

The Spectrum of DLBCL Subtypes

GCB

Non-GCB: unclassifiable

Non-GCB:

HGBL

DEL

DEL= Double Expressor Lymphoma; HGBL = High Grade B-cell Lymphoma
Treatment Landscape of DLBCL

- Frontline Therapy: approximately 60% cured
- Salvage Therapy: approximately 40% R/R
  - Chemosensitive
    - ASCT
  - Chemoresistant
    - CAR-T

R/R = Relapsed/Refractory; ASCT = Autologous Stem Cell Transplantation
First-Line Options in DLBCL

**First-line therapy**

- **R-CHOP-21**

**Alternate 1L Regimens**

- DA-EPOCH-R (HGBL)
- R-CHOP-14

**Special Populations**

- Anthracycline-sparing regimens for pts with poor LVEF
- >80 y of age with comorbidities
  - R-CDOP, R-mini-CHOP, others

**Lenalidomide maintenance** in pts 60-80 y of age after R-CHOP
Martha’s Treatment Experience

Tolerates R-CHOP therapy without issues, but end of treatment PET/CT demonstrates a Deauville 5

New lesion at left supraclavicular region (mSUV 18)
Scattered bone avidity without cortical destruction

Core needle biopsy of avid node lymph node
DLBCL-NOS

BM biopsy: Paratrabeckular CD10+ small lymphocytes consistent with involvement of follicular lymphoma
Second Attempt at Cure Vs Palliative Intent

Second-line therapy largely based on patient candidacy for ASCT

**ASCT Candidates**
- ICE, DHAP, GDP, and others
- Clinical trials

**Non-ASCT Candidates**
- Gemcitabine/Oxaliplatin
- Brentuximab vedotin (CD30+)
- Ibrutinib (non-GCB disease)
- Lenalidomide ± rituximab

- CAR T therapy approved in R/R DLBCL after ≥2 prior systemic therapies
- Axicabtagene ciloleucel (Axi-cel) and tisagenlecleucel approved
- Lisocabtagene maraleucel (TRANSCEND)—Pending approval

In My Mind & Try To Convey: SCHOLAR-1

- N = 636
  - Retrospective review
- ORR: 26%; CR rate: 7%
  - CT based response
- Median OS: 6.3 mo

<table>
<thead>
<tr>
<th></th>
<th>Events/N</th>
<th>Median, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary refractory</td>
<td>143/179</td>
<td>7.1</td>
</tr>
<tr>
<td>Refractory to second line or later</td>
<td>261/306</td>
<td>6.1</td>
</tr>
<tr>
<td>Relapse ≤12 mo of ASCT</td>
<td>101/118</td>
<td>6.2</td>
</tr>
</tbody>
</table>

Discussing Clinical Trials

**Head-to-Head Comparisons vs ASCT**

**BELINDA** (NCT03570892)
- Phase 3, R/R DLBCL
- Primary endpoint: EFS

**ZUMA-7** (NCT03391466)
- Phase 3, R/R DLBCL
- Primary endpoint: EFS

**TRANSFORM** (NCT03575351)
- Phase 3, R/R DLBCL
- Primary endpoint: EFS
Initially enrolled into a CAR-T vs ASCT trial, but unable to continue due to insurance constraints.

Received R-ICE as second-line therapy with evidence of Deauville 5 (residual avid sites 3 x > liver).

ASCT deferred and she remained relatively asymptomatic.

Moved toward insurance approval for commercially available CAR-T cell therapy (no clinical trials available).

The CLOCK STARTS …..
The Clock Starts
Getting Martha To \textit{CAR T Cell}

\textbf{Brain to Vein}

\textbf{Vein to Vein}

\begin{itemize}
\item 1. Leukapheresis
\item 2. T-cell activation/transduction
\item 3. Modified T-cell expansion
\item 4. Chemotherapy
\item 5. Modified T-cell infusion
\end{itemize}

\textbf{Mian et al. Abs 4452. Intent to Treat (CAR-T) Outcomes}
Entering Into ASH 2019: Where Is CAR-T?
## All CAR-T Cell Constructs Are Not The Same

<table>
<thead>
<tr>
<th>Study</th>
<th>ZUMA-1&lt;sup&gt;1&lt;/sup&gt;</th>
<th>JULIET&lt;sup&gt;2&lt;/sup&gt;</th>
<th>TRANSCEND&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAR-T dose</td>
<td>2 x 10&lt;sup&gt;6&lt;/sup&gt;/kg</td>
<td>0.6 to 6 x 10&lt;sup&gt;8&lt;/sup&gt;</td>
<td>0.5-1 x 10&lt;sup&gt;8&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>(max 2 x 10&lt;sup&gt;8&lt;/sup&gt;)</td>
<td></td>
<td>(CD4:CD8 = 1:1)</td>
</tr>
<tr>
<td>Relapsed/refractory</td>
<td>Refractory</td>
<td>Relapsed or refractory</td>
<td>Relapsed or refractory</td>
</tr>
<tr>
<td>Relapsed post ASCT</td>
<td>23%</td>
<td>49%</td>
<td>40%</td>
</tr>
<tr>
<td>Bridging therapy</td>
<td>None</td>
<td>Allowed</td>
<td>Allowed</td>
</tr>
<tr>
<td>Treated/apheresed</td>
<td>108/119 (91%)</td>
<td>111/147 (76%)</td>
<td>114/134 (85%)</td>
</tr>
</tbody>
</table>

---

ZUMA-1: Axi-Cel in Refractory Large B-Cell Lymphoma

Phase 1 (N = 7)

• Refractory DLBCL; PMBCL; tFL (n = 7)

Key eligibility criteria
• No response to last chemotherapy or relapse ≥12 mo post ASCT
• Prior anti-CD20 mAb and anthracycline

N = 108
Data cutoff: August 11, 2017
Median follow-up: 15.4 mo

Phase 2 (N = 101)

Cohort 1
Refractory DLBCL (n = 77)

Cohort 2
Refractory PMBCL/tFL (n = 24)

Conditioning regimen
• Cyclophosphamide 500 mg/m² + fludarabine 30 mg/m² for 3 days
• Axi-cel: 2 x 10⁶ CAR⁺ cells/kg

• 99% enrolled were successfully manufactured
• 91% enrolled were dosed

# ZUMA-1: Response Outcomes

## ORR With Axicabtagene Ciloleucel

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n</th>
<th>ORR, %</th>
<th>CR, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLBCL</td>
<td>77</td>
<td>82</td>
<td>49</td>
</tr>
<tr>
<td>tFL/PMBCL</td>
<td>24</td>
<td>83</td>
<td>71</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>101</td>
<td>82&lt;sup&gt;a&lt;/sup&gt;</td>
<td>54</td>
</tr>
</tbody>
</table>

At median follow-up of 15.4 mo

<table>
<thead>
<tr>
<th>n</th>
<th>ORR, %</th>
<th>CR, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>42</td>
<td>40</td>
<td></td>
</tr>
</tbody>
</table>

- Higher CAR-T cell levels in blood associated with response
- Overall rate of survival at 18 mo: 52%

---

ZUMA-1: Duration of Response

Median follow-up: 15.4 mo

Median (95% CI) mo
- Complete response: NR (NE-NE)
- Objective response: 11.1 (3.9-NE)
- Partial response: 1.9 (1.4-2.1)

No. at Risk
- Complete response: 63 61 58 53 50 47 46 45 45 41 37 30 19 16 12 6 6 4 3 3 3 3 3 1 0
- Objective response: 89 82 67 56 53 49 48 47 47 42 38 31 19 16 12 6 6 4 3 3 3 3 3 1 0
- Partial response: 26 22 21 9 3 3 2 2 2 2 1 1 1 0
ZUMA-1: 2-Year OS Follow-Up

CR at 3 months was a surrogate for CR at 2 years

Long-term efficacy
- IRC-assessed: n = 101
- ORR: 74% (n = 75)
- CR: 54% (n = 55)
- PR: 20% (n = 20)

OS Rate Overall, %
12-mo 60
18-mo 53
24-mo 51
# Axi-Cel: Real-World Data in DLBCL

<table>
<thead>
<tr>
<th></th>
<th>ZUMA-1</th>
<th>Real-World Data From 17 Centers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infused patients, N</td>
<td>108</td>
<td>293</td>
</tr>
<tr>
<td>Meeting ZUMA-1 eligibility criteria, %</td>
<td>100</td>
<td>57</td>
</tr>
<tr>
<td>Age, median (range)</td>
<td>58 (23-76)</td>
<td>60</td>
</tr>
<tr>
<td>ECOG 0 or 1, %</td>
<td>100</td>
<td>81</td>
</tr>
<tr>
<td>Prior autologous transplant, %</td>
<td>23</td>
<td>33</td>
</tr>
<tr>
<td>DLBCL, including HGBCL, not tFL or PMBCL, %</td>
<td>78</td>
<td>68</td>
</tr>
<tr>
<td>Best ORR/CR, %</td>
<td>82/58</td>
<td>81/57</td>
</tr>
<tr>
<td>Grade 3 or higher toxicity, %</td>
<td>CRS 13 / NEs 31</td>
<td>CRS 7 / NEs 33</td>
</tr>
</tbody>
</table>

Axi-Cel Update

Update from ZUMA-1 to SCHOLAR-1\(^1\)
- Axi-cel tx resulted in 11.5-fold higher odds of achieving CR compared to SCHOLAR-1.
- 2-year survival was 50% (ZUMA-1) compared to 12% (SCHOLAR-1) translating to a 73% reduction in the risk of death in ZUMA-1 compared to SCHOLAR-1.

Real-world evidence on cell therapy in DLBCL (data from 8 US academic centers)\(^2\)
- Axi-cel pts (N=120): D+90 CR was 39%.
- Tisagenleucel pts (N=32): D+90 was 39%.
- Efficacy appears to correlate with evidence from clinical trials

JULIET Trial: Phase 2 Global Trial of Tisagenlecleucel in R/R DLBCL

Eligibility
- Aged ≥18 years
- ≥2 prior lines of therapy for DLBCL
- Failed or ineligible for auto-SCT (no prior allo-SCT)
- ECOG PS: 0-1
- No active CNS involvement

Tisagenlecleucel cell dose: range of 0.6 to 6 x 10^8

Tisagenlecleucel in B-Cell NHL: JULIET Trial

Relapsed/Refractory DLBCL and Transformed FL

N = 93 infused and evaluated for efficacy
Median time from infusion to data cutoff was 14 months (range, 0.1-26)

- Best ORR: 52%
- CR rate: 40%
- RFS rate: 65% at 12 mo after initial response (79% among patients with CR)
JULIET: PFS

Probability of PFS vs. Time Since Infusion, mo

- Patients with CR
- All patients

No. at Risk
Patients with CR
40  39  39  36  35  35  33  31  29  24  23  15  9  9  8  7  2
All patients
111  65  38  34  32  25  16  10  9  3

JULIET: OS

Probability of OS vs Time Since Infusion, mo

No. at Risk
Patients with CR: 40 40 40 39 39 38 38 37 36 30 29 23 16 16 12 9 9 7 3 2 1 1
All patients: 111 94 71 60 50 40 28 19 11 8 2 1 1

CIBMTR Registry (real-world outcomes)

- Efficacy and safety in the real-world setting demonstrate similar efficacy and safety compared with the JULIET trial.

<table>
<thead>
<tr>
<th>Best Overall Response</th>
<th>Viability ≥80% (n = 23)</th>
<th>Viability 60%-80% (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>9 (39)</td>
<td>8 (38)</td>
</tr>
<tr>
<td>PR</td>
<td>5 (22)</td>
<td>4 (19)</td>
</tr>
<tr>
<td>Overall response (CR + PR)</td>
<td>14 (61)</td>
<td>12 (57)</td>
</tr>
<tr>
<td>No response/SD</td>
<td>2 (9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>PD</td>
<td>7 (30)</td>
<td>7 (33)</td>
</tr>
<tr>
<td>Not assessed</td>
<td>0 (0)</td>
<td>2 (10)</td>
</tr>
</tbody>
</table>

Updated oral abstract 766; Monday, December 9, 2019: 3:30 PM

Lisocabtagene Maraleucel (Liso-Cel; JCAR017): CD19-TargetedDefined Cell Product

- Immunomagnetic selection
- Lentiviral transduction
- Expansion
- CD4+ and CD8+ CAR T cells formulated separately
- Administered at precise doses of CD4+ and CD8+ CAR T cells

Patient’s PBMCs

- CD8+ (targets tumor)
- CD4+ (targets tumor, supports persistence)
- Other PBMC cell types

Phase 1 TRANSCEND-NHL-001: Patient Characteristics

Leukapheresed (N = 134)

- Product unavailable (n = 2)
- Product available (n = 18)
  - Withdrew (n = 5)
  - Progressed or died (n = 13)

Liso-cell treated (n = 114)

- Received nonconforming liso-cell (n = 12)
- Evaluable (n = 102)

<table>
<thead>
<tr>
<th></th>
<th>FULL (n = 102)</th>
<th>CORE (n = 73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, y (range)</td>
<td>61 (20-82)</td>
<td>60 (20-82)</td>
</tr>
<tr>
<td>≥65 y, n (%)</td>
<td>37 (36)</td>
<td>24 (33)</td>
</tr>
<tr>
<td>B-cell NHL subtype, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DLBCL, NOS de novo</td>
<td>63 (62)</td>
<td>53 (73)</td>
</tr>
<tr>
<td>Transformed from FL (tFL)</td>
<td>23 (23)</td>
<td>20 (27)</td>
</tr>
<tr>
<td>Transformed from MZL (tMZL) / CLL (tICLL)</td>
<td>6 (6) / 6 (6)</td>
<td>0</td>
</tr>
<tr>
<td>Follicular, grade 3B/PMBCL</td>
<td>1 (1) / 3 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Molecular subtype, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Double/triple-hit</td>
<td>19 (19)</td>
<td>16 (22)</td>
</tr>
<tr>
<td>Patient characteristics, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG PS 0-1</td>
<td>93 (91)</td>
<td>73 (100)</td>
</tr>
<tr>
<td>IPI 3-5</td>
<td>43 (42)</td>
<td>26 (36)</td>
</tr>
<tr>
<td>CNS involvement</td>
<td>2 (2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Chemorefractory</td>
<td>71 (70)</td>
<td>49 (67)</td>
</tr>
<tr>
<td>Prior lines of therapy, median (range)</td>
<td>3 (1-8)</td>
<td>3 (2-8)</td>
</tr>
<tr>
<td>Never achieved CR</td>
<td>49 (48)</td>
<td>36 (49)</td>
</tr>
<tr>
<td>Any HSCT</td>
<td>41 (40)</td>
<td>28 (38)</td>
</tr>
<tr>
<td>Prior autologous</td>
<td>38 (37)</td>
<td>28 (38)</td>
</tr>
<tr>
<td>Prior allogeneic</td>
<td>5 (5)</td>
<td>0</td>
</tr>
</tbody>
</table>

- 99% of patients apheresed in DLBCL cohort had available product
- 7 pts with MCL treated at DL1S
- 8 pts in DF and DE cohorts treated in outpatient setting

**TRANSCEND-NHL-001: Response Rates**

*Potential Dose Response Relationship in CORE Patient Population; DL2 Chosen for Pivotal Cohort*

<table>
<thead>
<tr>
<th></th>
<th>FULL All Dose Levels (N = 102)</th>
<th>CORE DL1S (n = 33)</th>
<th>CORE DL2S (n = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR (95% CI), %</strong></td>
<td>75 (65-83)</td>
<td>79 (61-91)</td>
<td>78 (62-90)</td>
</tr>
<tr>
<td><strong>CR (95% CI), %</strong></td>
<td>55 (45-65)</td>
<td>55 (36-72)</td>
<td>62 (45-78)</td>
</tr>
<tr>
<td><strong>3-mo ORR (95% CI), %</strong></td>
<td>51 (41-61)</td>
<td>52 (34-69)</td>
<td>65 (48-80)</td>
</tr>
<tr>
<td><strong>3-mo CR (95% CI), %</strong></td>
<td>38 (29-48)</td>
<td>36 (20-55)</td>
<td>51 (34-68)</td>
</tr>
<tr>
<td><strong>6-mo ORR (95% CI), %</strong></td>
<td>40 (31-50)</td>
<td>42 (26-61)</td>
<td>49 (32-66)</td>
</tr>
<tr>
<td><strong>6-mo CR (95% CI), %</strong></td>
<td>34 (25-44)</td>
<td>33 (18-52)</td>
<td>46 (30-63)</td>
</tr>
</tbody>
</table>

Baseline high tumor burden was well balanced between DL1 and DL2 (≈1/3)

TRANSCEND-NHL-001: Duration of Response

Median Follow-Up: 8 Months

MEDIAN FOLLOW-UP: 8 MONTHS

- In CORE population, 88% of patients with CR at 3 months stayed in CR at 6 months
- 93% of patients in CR at 6 months had ongoing response

TRANSCEND-NHL-001: Overall Survival

Median Follow-Up: 12 Months

**FULL**

- **CR:** NE (NE-NE); 87% (73%-49%)
- **All:** NE (10.4 mo-NE); 59% (47%-68%)
- **PR:** 10.3 mo (6.8-12.7 mo); 31% (9%-57%)
- **Nonresponders:** 3.6 mo (1.5-6.2 mo); 11% (2%-28%)

**CORE**

- **CR:** NE (NE-NE); 89% (72%-96%)
- **All:** NE (10.7 mo-NE); 63% (49%-74%)
- **PR:** 10.3 mo (6.8-NE); 33% (9%-60%)
- **Nonresponders:** 4.5 mo (0.8-6.2 mo); 11% (1%-38%)

Median Follow-Up: 12 Months

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>CR</th>
<th>PR</th>
<th>Nonresponders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FULL</strong></td>
<td>102</td>
<td>56</td>
<td>20</td>
<td>26</td>
</tr>
<tr>
<td><strong>CORE</strong></td>
<td>73</td>
<td>43</td>
<td>15</td>
<td>15</td>
</tr>
</tbody>
</table>

Data at ASH 19

Liso-Cel Updates
From TRANSCEND-NHL-001

Health-Related QoL outcomes¹
- Pts in the DLBCL cohort experienced an improvement in HRQoL and health utility through month 12
- A notable proportion of pts demonstrated clinically meaningful improvements at months 6 and 12

Long-term efficacy follow-up from the DLBCL cohort²
- ORR of 73%, CR rate of 53%; median DOR for pts in CR was not reached
- Median PFS was 6.8 mo
- Median OS was 19.9 mo

Updated oral abstract 66
Saturday, December 7, 2019: 8:45 AM

Updated oral abstract 241
Saturday, December 7, 2019: 2:00 PM

Martha’s Experience on CAR-T Therapy

- Martha proceeded to commercial CAR-T cell therapy.
- Lymphodepleting Cy/Flu was administered before infusion.
- Achieves a rapid response, D+4 had a fever and was hypotensive, but responsive to intravenous fluids. No evidence of hypoxia.
- Subsequently confirmed as grade 2 CRS.
# Summary of CRS and Neurotoxicity From Major CAR-T Cell Trials in DLBCL

<table>
<thead>
<tr>
<th>Study</th>
<th>CRS All Grades</th>
<th>CRS Grade ≥3</th>
<th>Neurotoxicity All Grades</th>
<th>Neurotoxicity Grade ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZUMA-1¹</td>
<td>93%</td>
<td>13%</td>
<td>65%</td>
<td>31%</td>
</tr>
<tr>
<td>JULIET²</td>
<td>58%</td>
<td>22%</td>
<td>21%</td>
<td>12%</td>
</tr>
<tr>
<td>TRANSCEND³</td>
<td>37%</td>
<td>1%</td>
<td>23%</td>
<td>13%</td>
</tr>
</tbody>
</table>

**Notes**

1. Lee criteria used for CRS grading on ZUMA-1 and TRANSCEND
2. U Penn criteria used for CRS grading on JULIET
3. CTCAE criteria for neurotoxicity grading

---

ASTCT CRS Consensus Grading

<table>
<thead>
<tr>
<th>CRS Parameter</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever(^a)</td>
<td>≥38° C</td>
<td>≥38° C</td>
<td>≥38° C</td>
<td>≥38° C</td>
</tr>
</tbody>
</table>

With

| Hypotension   | None         | Not requiring vasopressors | Requiring a vasopressor with/without vasopressin | Requiring multiple vasopressors (excluding vasopressin) |

And/or\(^b\)

| Hypoxia       | None         | Requiring low-flow nasal cannula\(^c\) or blow-by | Requiring high-flow nasal cannula,\(^c\) face mask, nonrebreather mask, or Venturi mask | Requiring positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation) |

\(^a\) Fever is defined as temperature ≥38° C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia. \(^b\) CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5° C, hypotension requiring one vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS. \(^c\) Low-flow nasal cannula is defined as oxygen delivered at 6 L/min. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/min.

### ASTCT ICANS Consensus Grading for Adults\(^1, a\)

<table>
<thead>
<tr>
<th>Neurotoxicity Domain</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICE score(^b)</td>
<td>7-9</td>
<td>3-6</td>
<td>0-2</td>
<td>0 (patient is unarousable and unable to perform ICE)</td>
</tr>
<tr>
<td>Depressed level of consciousness(^c)</td>
<td>Awakens spontaneously</td>
<td>Awakens to voice</td>
<td>Awakens only to tactile stimulus</td>
<td>Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse; stupor or coma</td>
</tr>
<tr>
<td>Seizure</td>
<td>NA</td>
<td>NA</td>
<td>Any clinical seizure, focal or generalized, that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention</td>
<td>Life-threatening prolonged seizure (&gt;5 min); or repetitive clinical or electrical seizures without return to baseline in between</td>
</tr>
<tr>
<td>Motor findings(^d)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Deep focal motor weakness, such as hemiparesis or paraparesis</td>
</tr>
<tr>
<td>Elevated ICP/cerebral edema</td>
<td>NA</td>
<td>NA</td>
<td>Focal/local edema on neuroimaging(^e)</td>
<td>Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve V1 palsy; or papilledema; or Cushing’s triad</td>
</tr>
</tbody>
</table>

---

a Grading for pediatric patients is also available.  
b A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.  
c Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).  
d Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.  
e Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

Summary of CRS Management Recommendations
Per the NCCN Guidelines

**Grade 1**
- **Tocilizumab** only for prolonged CRS (>3 d) in patients with significant symptoms or comorbidities
- **Supportive care** (eg, empiric antibiotics, IV fluids, symptomatic management of organ toxicity)

**Grade 2**
- **Tocilizumab** 8 mg/kg IV (not to exceed 800 mg/dose); repeat in 8 h if no improvement; do not exceed 3 doses in 24 h, max 4 doses total
- **Corticosteroids for persistent refractory hypotension**
- **Supportive care**
  - Vasopressors, transfer to ICU for hemodynamic monitoring for persistent refractory hypotension

**Grade 3**
- **Tocilizumab** as per grade 2
- **Dexamethasone** 10 mg IV every 6 hours; if refractory, manage as grade 4
- **Transfer to ICU; obtain ECG, hemodynamic monitoring**
- **Supportive care**
  - Vasopressors as needed

**Grade 4**
- **Tocilizumab** as per grade 2
- **Dexamethasone** 10 mg IV every 6 hours; if refractory, methylprednisolone 1,000 mg/d IV
- **ICU care and hemodynamic monitoring**
- **Mechanical ventilation as needed**
- **Supportive care**
  - Vasopressors as needed

Summary: R/R DLBCL

- CD19 CAR-T induces durable remissions in $\approx 40\%$ of relapsed or refractory DLBCL patients.
- CRS and neurotoxicity are the major toxicities, but they are generally reversible.
Summary and Next Steps With CAR-T Therapy

- CAR-T cell therapies are an option in R/R large cell lymphoma patients
- Promising data in CLL and emerging data in other lymphoid cancers (MCL)

Wang et al. Abs # 754

- Assessment of CAR-T therapy in other treatment settings, including
  - Head-to-head comparisons vs ASCT in second line
    - BELINDA (NCT03570892)
    - ZUMA-7 (NCT03391466)
    - TRANSFORM (NCT03575351)
  - Post CAR-T maintenance
    - BTK inhibitors
    - Checkpoint inhibitors
    - IMiDS
Symposium Summary and Audience Q&A

John P. Leonard, MD
The Richard T. Silver Distinguished Professor of Hematology and Medical Oncology
Professor of Medicine
Associate Dean for Clinical Research
Weill Cornell Medicine
New York, New York

Nathan H. Fowler, MD
Professor of Medicine,
Department of Lymphoma/Myeloma
The University of Texas MD Anderson Cancer Center
Houston, Texas

Matthew A. Lunning, DO, FACP
Medical Director Lymphoma Research
Associate Professor, Division of Hematology/Oncology
Department of Medicine
University of Nebraska Medical Center
Omaha, Nebraska

Professor Simon Rule, MD, PhD
Professor of Clinical Haematology
Plymouth University Medical School
Plymouth, England, United Kingdom

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*Thank you, and good day.*
Ab: antibody
ABC: activated B-cell like
ALL: acute lymphocytic leukemia
AraC: arabinofuranosyl cytidine
ASCT: autologous stem cell transplant
ASTCT: American Society for Blood and Marrow Transplantation
BID: twice a day
BiPAP: bilevel positive airway pressure
BLK: B lymphocyte kinase
BM: bone marrow
BMAT: bone marrow aspiration and trephine
BMX: bone marrow tyrosine kinase gene in chromosome X
BR: bendamustine + rituximab
BTK: Bruton tyrosine kinase
CAR: chimeric antigen receptor
CD: cluster of differentiation
CHOP: cyclophosphamide + doxorubicin hydrochloride + vincristine sulfate + prednisone
CIBMTR: Center for International Blood and Marrow Transplant Research
CLL: chronic lymphocytic leukemia
CMP: comprehensive metabolic panel
CPAP: continuous positive airway pressure
CR: complete response
CRS: cytokine release syndrome
CRu: complete remission, unconfirmed
CT: chemotherapy
CTCAE: Common Terminology Criteria for Adverse Events
DA-EPOCH-R: dose-adjusted etoposide + prednisone + vincristine + cyclophosphamide + doxorubicin, and rituximab
DE: dose expansion
del: deleted
DEL: double expresser
DF: dose finding
dis: disrupted
DL: dose level
DLBCL: diffuse large B-cell lymphoma
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOR</td>
<td>duration of response</td>
</tr>
<tr>
<td>ECOG</td>
<td>Eastern Cooperative Oncology Group</td>
</tr>
<tr>
<td>EFS</td>
<td>event-free survival</td>
</tr>
<tr>
<td>EGFR</td>
<td>epidermal growth factor receptor</td>
</tr>
<tr>
<td>ERBB2</td>
<td>erb-b2 receptor tyrosine kinase</td>
</tr>
<tr>
<td>ERBB4</td>
<td>erb-b4 receptor tyrosine kinase</td>
</tr>
<tr>
<td>FDG</td>
<td>F-18-Fluorodeoxyglucose</td>
</tr>
<tr>
<td>FISH</td>
<td>fluorescence in situ hybridization</td>
</tr>
<tr>
<td>FL</td>
<td>follicular lymphoma</td>
</tr>
<tr>
<td>FLIPI</td>
<td>Follicular Lymphoma International Prognostic Index</td>
</tr>
<tr>
<td>GCB</td>
<td>germinal center B-cell like</td>
</tr>
<tr>
<td>G-CHOP</td>
<td>obinutuzumab + cyclophosphamide + doxorubicin + vincristine + prednisone</td>
</tr>
<tr>
<td>G-CVP</td>
<td>obinutuzumab + cyclophosphamide + prednisone + vincristine</td>
</tr>
<tr>
<td>GELF</td>
<td>Groupe d’Etude des Lymphomes Folliculaires</td>
</tr>
<tr>
<td>GF</td>
<td>growth factor</td>
</tr>
<tr>
<td>HD</td>
<td>high dose</td>
</tr>
<tr>
<td>HDT</td>
<td>high-dose chemotherapy</td>
</tr>
<tr>
<td>HGBCL</td>
<td>high-grade B-cell lymphoma</td>
</tr>
<tr>
<td>HL</td>
<td>Hodgkin lymphoma</td>
</tr>
<tr>
<td>HR</td>
<td>hazard ratio / high risk</td>
</tr>
<tr>
<td>HRQoL</td>
<td>health-related quality of life</td>
</tr>
<tr>
<td>HSCT</td>
<td>hematopoietic stem cell transplantation</td>
</tr>
<tr>
<td>huEGFRt</td>
<td>truncated human EGFR</td>
</tr>
<tr>
<td>IC50</td>
<td>inhibitory concentration of 50%</td>
</tr>
<tr>
<td>ICANS</td>
<td>immune cell–associated neurologic syndrome</td>
</tr>
<tr>
<td>ICE</td>
<td>ifosfamide + carboplatin + etoposide + mesna</td>
</tr>
<tr>
<td>ICML</td>
<td>International Conference on Malignant Lymphoma</td>
</tr>
<tr>
<td>ICP</td>
<td>intracranial pressure</td>
</tr>
<tr>
<td>IHC</td>
<td>immunohistochemistry</td>
</tr>
<tr>
<td>IMiD</td>
<td>immunomodulatory drug</td>
</tr>
<tr>
<td>iNHL</td>
<td>indolent non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>IPI</td>
<td>International Prognostic Index</td>
</tr>
<tr>
<td>IR</td>
<td>intermediate risk</td>
</tr>
<tr>
<td>IRC</td>
<td>independent review committee</td>
</tr>
</tbody>
</table>
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITK</td>
<td>interleukin-2-inducible T-cell kinase</td>
</tr>
<tr>
<td>IWG</td>
<td>International Working Group</td>
</tr>
<tr>
<td>JAK3</td>
<td>Janus kinase 3</td>
</tr>
<tr>
<td>LBL</td>
<td>lymphoblastic lymphoma</td>
</tr>
<tr>
<td>LDH</td>
<td>lactate dehydrogenase</td>
</tr>
<tr>
<td>LPL</td>
<td>lymphoplasmacytic lymphoma</td>
</tr>
<tr>
<td>LR</td>
<td>low risk</td>
</tr>
<tr>
<td>LTR</td>
<td>long terminal repeat</td>
</tr>
<tr>
<td>mAb</td>
<td>monoclonal antibody</td>
</tr>
<tr>
<td>MCL</td>
<td>mantle cell lymphoma</td>
</tr>
<tr>
<td>mFU</td>
<td>median follow-up</td>
</tr>
<tr>
<td>MIPI</td>
<td>Mantle Cell Lymphoma International Prognostic Index</td>
</tr>
<tr>
<td>MIPI-B-miR</td>
<td>biological Mantle Cell Lymphoma International Prognostic Index</td>
</tr>
<tr>
<td>MIPI-c</td>
<td>Combined Mantle Cell International Prognostic Index</td>
</tr>
<tr>
<td>MIPI-g</td>
<td>genetic Mantle Cell Lymphoma International Prognostic Index</td>
</tr>
<tr>
<td>MM</td>
<td>multiple myeloma</td>
</tr>
<tr>
<td>mPFS</td>
<td>median progression-free survival</td>
</tr>
<tr>
<td>MRD</td>
<td>minimal residual disease</td>
</tr>
<tr>
<td>mTTNLT</td>
<td>median time to next anti-lymphoma treatment</td>
</tr>
<tr>
<td>MUGA</td>
<td>multiple gated acquisition</td>
</tr>
<tr>
<td>MZL</td>
<td>marginal zone lymphoma</td>
</tr>
<tr>
<td>NA</td>
<td>not applicable</td>
</tr>
<tr>
<td>NCCN</td>
<td>National Comprehensive Cancer Network</td>
</tr>
<tr>
<td>ND</td>
<td>no drug</td>
</tr>
<tr>
<td>NE</td>
<td>not evaluable</td>
</tr>
<tr>
<td>NHL</td>
<td>non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>NOS</td>
<td>not otherwise specified</td>
</tr>
<tr>
<td>NR</td>
<td>not reached/reported</td>
</tr>
<tr>
<td>NRM</td>
<td>nonrelapse mortality</td>
</tr>
<tr>
<td>obs</td>
<td>observation</td>
</tr>
<tr>
<td>O-len</td>
<td>obinutuzumab + lenalidomide</td>
</tr>
<tr>
<td>OR</td>
<td>overall response</td>
</tr>
<tr>
<td>ORR</td>
<td>overall response rate</td>
</tr>
<tr>
<td>PB</td>
<td>peripheral blood</td>
</tr>
<tr>
<td>PBMC</td>
<td>peripheral blood mononuclear cell</td>
</tr>
</tbody>
</table>
Abbreviations

PD: progressive disease
PI3K: phosphatidylinositol-4,5-bisphosphate 3-kinase
PI3Ki: PI3K inhibitor
PJP: Pneumocystis jirovecii pneumonia
PMBCL: primary mediastinal large B-cell lymphoma
POD: progression of disease
PR: partial response
PS: performance status
R/R: relapsed/refractory
R: rituximab
R2: lenalidomide + rituximab
RBAC: rituximab + bendamustine + cytarabine
R-ICE: rituximab and ifosfamide + carboplatin + etoposide + mesna
R2: lenalidomide + rituximab
RBAC: rituximab + bendamustine + cytarabine
R-ICE: rituximab and ifosfamide + carboplatin + etoposide + mesna
scFv: single-chain variable fragment
SCT: stem cell transplant
SD: stable disease
SLL: small lymphocytic lymphoma
SOL: space-occupying lesion
SPD: sum of the products of diameters
SPM: second primary malignancy
tCLL: transformed from CLL
TEAE: treatment-emergent adverse event
TEC: tyrosine kinase expressed in hepatocellular carcinoma
tFL: transformed from follicular lymphoma
tMZL: transformed from marginal zone lymphoma
TP53: tumor protein 53
TTNT: time to next treatment
TTT: time to treatment
TXK: T and X cell expressed kinase
URTI: upper respiratory tract infection
Abbreviations

VGPR: very good partial remission
VR-CAP: bortezomib + rituximab and cyclophosphamide + doxorubicin + prednisone
WM: Waldenström macroglobulinemia