Sequencing of Treatment in Indolent Lymphomas (CLL and FL)

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Learning Objectives

1. Implement a plan for monitoring patients with CLL for 17p deletion at diagnosis and throughout the course of the disease
2. Interpret emerging data supporting combination therapies in CLL
3. Evaluate clinical trial data for novel targeted therapies in the management of newly diagnosed and relapsed/refractory follicular lymphoma
Disclosures

- **Dr. Thompson**
  - Research funding: AbbVie, Pharmacyclics, Amgen, Adaptive Biotechnologies
  - Advisory board/honoraria: AbbVie, Pharmacyclics, Amgen, Genentech, Gilead

- **Ms. Nodzon**
  - Consulting fees from and served on speakers bureaus: AbbVie, Genentech, Gilead
Part I: Treatment of CLL

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Novel Targets in CLL: Approved Therapies

- Second generation CD20 monoclonal antibodies (mAb)
  - Ofatumumab
  - Obinutuzumab
- Bruton’s tyrosine kinase (BTK) inhibitor
  - Ibrutinib
- Phosphoinositide 3-delta kinase (PI3K) inhibitor
  - Idelalisib
  - Duvelisib
- B-cell lymphoma 2 (BCL2) inhibitor
  - Venetoclax
Targeting B-Cell Receptor Signaling in CLL

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Targeting BCL2 in CLL

Current First-Line Treatment of CLL

- Chemoimmunotherapy: FCR, BR, chlorambucil + obinutuzumab or chlorambucil + ofatumumab
- Ibrutinib monotherapy
What Do We Want From an Ideal First-Line CLL Treatment?

<table>
<thead>
<tr>
<th>Attribute</th>
<th>CIT</th>
<th>Ibrutinib monotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>High rate of complete remission, ideally with undetectable MRD</td>
<td>Subgroups, esp. with FCR</td>
<td>No</td>
</tr>
<tr>
<td>Limited duration, leading to durable remissions (and potentially “cure”)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Tolerable and effective in all patients, including:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Older patients and those with comorbidities</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>2. Those with unfavorable genomic characteristics</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Assessment of Fitness Critical in Treatment Choice

• CIRS score most frequently used; more important than chronologic age
• Patients with score <6 and adequate renal function (eGFR 70 or higher) generally considered “fit” for intensive regimens (e.g., FCR)
Chemoimmunotherapy Regimens in First-Line CLL

- FCR: Potent, high rates of CR and U-MRD\(^1\); first regimen to demonstrate improved overall survival\(^2\)
- Bendamustine and rituximab (BR): Similar PFS with less toxicity in the subgroup of fit patients aged >65\(^3\); however, inferior PFS for BR compared to FCR in patients ≤65 and no evidence of plateau on PFS curve
- Chlorambucil + obinutuzumab showed improved PFS and OS compared to chlorambucil alone; PFS approx. 2.5 years\(^4,5\)
- Chlorambucil + ofatumumab also improved PFS compared to chlorambucil alone; PFS approx. 22 months\(^6\)

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CLL10: FCR Achieves Superior PFS But BR Is Better Tolerated

- No PFS advantage (yet) for FCR vs. BR in patients >65

Eichhorst. Lancet Oncol 2016
IGHV-Mutated Patients Have Prolonged PFS After First-Line FCR

Patients With M-CLL and U-MRD Post-FCR Have Favorable PFS

Thompson et al, Leukemia 2018.
Subset With Highly Favorable Outcomes After FCR Is Relatively Small

- Note: Patients were only eligible for CLL8 if they had eGFR >70 and limited comorbidities (CIRS score of ≤6)
- Note median PFS for patients with UM-CLL receiving FCR have median survival of 3.5-4.5 years
- Del(17p) associated with median PFS ~1 year

TP53 Mutation Negatively Impacts Survival After FCR, Even If Sub-Clonal
Ibrutinib: Favorable PFS in R/R CLL With del(17p)

- Median PFS not reached at 2.5 years
- Compare this to ~1 year PFS seen in first-line patients with del(17p) or TP53 mutation treated with FCR
- Standard-of-care for del(17p) or TP53-mutated patients first line

Treatment Options for “Unfit” Patients
CLL11: Chlorambucil + Obinutuzumab

- Eligibility: CIRS >6 (median 8) or eGFR <70 (median 62)
- Median age 73

COMPLEMENT 1: Chlorambucil + Ofatumumab

- Eligibility: fludarabine-based treatment “inappropriate” (investigator judgement)
- Median age 69

RESONATE II: Ibrutinib vs. Chlorambucil

- Eligibility: patients ≥65 (median 73)
- 2-year PFS 89%; compare to median PFS of 29 months with G-Clb
A Suggested First-Line Treatment Algorithm

Del(17p) and/or TP53 mutation

Yes

Ibrutinib

No

Fit – CIRS ≤6

FISH, IGHV mutation status

Yes

IGHV-mutated, non-del(11q)

FCR§ or BR

§ FCR preferred in patients ≤65 years of age. BR or FCR for patients >65

No

IGHV-unmutated and/or del11q

Ibrutinib¶ or G-Clb or O-Clb

Ibrutinib*

*Note, no results of head-head comparison with CIT in first-line setting

¶Ibrutinib preferred unless contraindicated.

Adapted from Jain et al. ASCO Education Book 2018.
### Key Ongoing Studies in “Fit” First-Line Treatment of CLL

<table>
<thead>
<tr>
<th>Study</th>
<th>Age Range, Fitness</th>
<th>CIT Regimen</th>
<th>Comparator Regimen(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG E1912 (NCT02048813)</td>
<td>Fit; 18–70 yr; ECOG PS ≤2</td>
<td>FCR × 6</td>
<td>Ibr + R × 6, then Ibr</td>
</tr>
<tr>
<td>UK FLAIR study</td>
<td>Fit; 18–75 yr, ECOG PS ≤ 2</td>
<td>FCR × 6</td>
<td>Ibr + R × 6, then Ibr until U-MRD</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(max 6 y)</td>
</tr>
<tr>
<td>CLL13 (NCT02950051)</td>
<td>Fit; ≥18 yr; CIRS score ≤ 6; no individual organ score ≥ 4</td>
<td>FCR × 6 cycles if ≤65, BR × 6</td>
<td>1. V+R × 6 then V × 6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. V+G × 6 then V × 6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3. Ibr+V+G × 6, then Ibr + V × 6</td>
</tr>
</tbody>
</table>
# Key Ongoing Studies in First-Line CLL “Unfit” Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Age Range, Fitness</th>
<th>CIT Regimen</th>
<th>Comparator Regimen(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevate CLL TN</td>
<td>Unfit; ≥65 yr or CrCl 30–69 or CIRS score &gt;6</td>
<td>G-Clb x 6</td>
<td>1. Acalabrutinib</td>
</tr>
<tr>
<td>(NCT02475681)</td>
<td></td>
<td></td>
<td>2. Acalabrutinib + G x 6, then acalabrutinib</td>
</tr>
<tr>
<td>iLLUMINATE</td>
<td>≥ 65 yr or CrCl 30–69 or CIRS score &gt;6</td>
<td>G-Clb x 6</td>
<td>Ibr + G x 6 cycles then Ibr monotherapy</td>
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<tr>
<td>(NCT02264574)</td>
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</tr>
<tr>
<td>CLL14</td>
<td>Unfit; ≥ 18 yr; CIRS score ≥6</td>
<td>G-Clb x 6</td>
<td>V+G x 6 then V x 6</td>
</tr>
<tr>
<td>(NCT02242942)</td>
<td></td>
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</tr>
<tr>
<td>UNITY</td>
<td>≥ 18 yr, ECOG 0-2</td>
<td>G-Clb x 6</td>
<td>TGR-1202 (umbralisib) + ublituximab</td>
</tr>
<tr>
<td>(NCT02612311)</td>
<td></td>
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</tr>
</tbody>
</table>
Potential First-Line Approvals

- Ibrutinib + rituximab
- Ibrutinib + obinutuzumab
- Acalabrutinib +/- obinutuzumab
- Venetoclax + …
  - Rituximab
  - Obinutuzumab
  - Ibrutinib + obinutuzumab
- Umbralisib + ublituximab
Targeted Therapies in R/R CLL

• 4 approved agents in 3 classes:
  • BTK inhibitors: ibrutinib
  • PI3K inhibitors: idelalisib, duvelisib
  • Bcl-2 inhibitor: venetoclax

• No head-to-head data to guide which to use or which order to use them

• Data to show venetoclax is effective after failure of ibrutinib or idelalisib but no high-quality data to demonstrate the reverse
RESONATE I: R/R CLL

Hazard ratio for progression or death, 0.22 (95% CI, 0.15–0.32) P<0.001 by log-rank test

<table>
<thead>
<tr>
<th>Months</th>
<th>Ibrutinib</th>
<th>Ofatumumab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>3</td>
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<tr>
<td></td>
<td>6</td>
<td>6</td>
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<td></td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>15</td>
</tr>
</tbody>
</table>

No. at Risk
Ibrutinib: 195 183 116 38 7 0
Ofatumumab: 196 161 83 15 1 0
Long-Term Ibrutinib Phase II PFS Data

• R/R cohort median PFS 51 months (43 months for UM-CLL)

Idelalisib + Rituximab in R/R CLL

- Durable responses in R/R CLL
- Toxicity management more complex than Bcl-2 inhibitors and BTK inhibitors

Duvelisib vs. Ofatumumab (DUO)

Venetoclax in R/R Patients With del(17p)
Venetoclax + Rituximab in First Relapse

- U-MRD in PB 62%; not affected by pre-treatment genomic characteristics
- 90% with U-MRD in PB had U-MRD in BM
- Now approved for R/R CLL regardless of del(17p)

Venetoclax Post-Ibrutinib/Idelalisib Failure

- Median PFS 2 years in very high-risk patient group

How to Sequence Therapies in Relapsed CLL
Which Treatment to Give at Relapse

- No randomized data
- Nonrandomized data suggest superior PFS for ibrutinib compared to idelalisib
- No comparative data for ibrutinib vs. venetoclax or venetoclax + R

Approach to Treatment of R/R CLL

• BTKi and BCL-2 inhibitor naive → either ibrutinib or venetoclax +/- rituximab; no comparative data
• BTKi intolerant/refractory → venetoclax +/- rituximab; if BTKi intolerant, idelalisib + R or duvelisib could also be tried
• Venetoclax-refractory → limited data; trial of ibrutinib
• Double-refractory → clinical trials (e.g., CAR-T)
• Patients who are refractory to BTKi or venetoclax should be considered for allogeneic stem cell transplant if otherwise eligible
Part II: Recognition and Management of Toxicities From Targeted Agents in CLL

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Department of Malignant Hematology
Moffitt Cancer Center
Ofatumumab

• First fully humanized anti-CD20 mAb¹
• FDA approved indications:
  • 2009: refractory to fludarabine and alemtuzumab²
  • 2014 COMPLEMENT 1: with chlorambucil in treatment naïve³
  • 2016 COMPLEMENT 2: with fludarabine and cyclophosphamide⁴
  • 2016 PROLONG: maintenance therapy after two lines of therapy⁵
• Black box warning¹
  • Hepatitis B virus reactivation
  • Progressive multifocal leukoencephalopathy

Obinutuzumab

- Humanized anti-CD20 mAb with greater ADCC than rituximab\(^1\)
- FDA approved in 2013 for treatment naive CLL in combination with chlorambucil\(^2\)
- Black box warning\(^3\)
  - Hepatitis B virus reactivation
  - Progressive multifocal leukoencephalopathy

Anti-CD20 mAb-Related Toxicities

• Tumor lysis syndrome
• Infusion related reactions
  • Grade 3 ≥: obinutuzumab 21-31%\(^1\) and ofatumumab 10%\(^2\)
  • High tumor burden and/or ALC >25,000: ↑ risk
  • Hypotension, rigors, pyrexia, hypoxia, urticaria, bronchospasms, etc.
  • Premedication protocol per institution: acetaminophen, steroid and antihistamine
  • Frequently monitor patients with preexisting pulmonary/cardiac conditions
• Neutropenia: grade 3 ≥ 26%
• Bacterial, fungal, and reactivated viral infections (e.g., CMV, HSV, VZV)

Oral Targeted Therapies in CLL

• Ibrutinib inhibits BTK\(^1\)
  • RESONATE (2014) and RESONATE-2 (2016): broad approval regardless of Del 17p

• Idelalisib inhibits PI3K delta kinase\(^2\)
  • FDA approved in 2014 for R/R CLL in combination with rituximab or SLL after 2 prior therapies

• Duvelisib is a dual inhibitor of PI3K delta and gamma kinases\(^3\)
  • FDA approved in 2018 for R/R CLL after 2 prior therapies

• Venetoclax inhibits BCL-2\(^4\)
  • FDA approved in 2016 for R/R CLL harboring Del 17p and 2018 for R/R CLL with rituximab

Ibrutinib

- Binds covalently to BTK cysteine 481 with an initial half-life of 4-6 hours and 24-hour target inhibition
- Promotes apoptosis by inhibiting B-cell proliferation, migration and adhesion
  - Rapid reduction in lymphadenopathy
  - Redistribution lymphocytosis (class effect)
- Testing for BTK and PLCγ2 mutations in suspected progression
RESONATE and RESONATE-2
AEs of Interest in the Integrated Analysis

- Median 29 mos. of ibrutinib with 47 mos. follow-up
- 29% discontinued for AEs and 12% dose reductions, > first year
- Notable interest: atrial fibrillation, bleeding, hypertension, and infection (30%)

<table>
<thead>
<tr>
<th>Integrated Analysis (N=330)</th>
<th>Diarrhea</th>
<th>Arthralgia</th>
<th>HT</th>
<th>Rash*</th>
<th>Bleeding*</th>
<th>Fatigue</th>
<th>AFib</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEs of interest, n (%)</td>
<td>174 (53)</td>
<td>74 (22)</td>
<td>68 (21)</td>
<td>119 (36)</td>
<td>182 (55)</td>
<td>120 (36)</td>
<td>36 (11)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>116 (35)</td>
<td>45 (14)</td>
<td>11 (3)</td>
<td>72 (22)</td>
<td>130 (39)</td>
<td>66 (20)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>43 (13)</td>
<td>22 (7)</td>
<td>33 (10)</td>
<td>35 (11)</td>
<td>35 (11)</td>
<td>44 (13)</td>
<td>15 (5)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>15 (5)</td>
<td>7 (2)</td>
<td>24 (7)</td>
<td>12 (4)</td>
<td>14 (4)</td>
<td>10 (3)</td>
<td>16 (5)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Grade 5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dose reductions due to AEs of interest, n/N (%)</td>
<td>5/174 (3)</td>
<td>3/74 (4)</td>
<td>0</td>
<td>3/119 (3)</td>
<td>4/182 (2)</td>
<td>2/120 (2)</td>
<td>4/36 (11)</td>
</tr>
<tr>
<td>Discontinuation due to AEs of interest, n (%)</td>
<td>2/174 (1)</td>
<td>0</td>
<td>1/68 (1)</td>
<td>2/119 (2)</td>
<td>6/182 (3)</td>
<td>1/120 (1)</td>
<td>3/36 (8)</td>
</tr>
</tbody>
</table>

*Pooled terms.
Ibrutinib-Associated Bleeding

- BTK and TEC kinases play key roles in glycoprotein VI signaling necessary for collagen-mediated platelet aggregation
- Impact partially reversed after 2.5 days of withholding Ibrutinib and reversible within 1 week of discontinuation

Ibrutinib: Atrial Fibrillation

- Activation of PI3K-Akt pathway is a critical regulator of atrial rhythm under stress\(^1\)
  - Regulated by BTK and TEC kinases
- Standard rate/rhythm management
  - Avoid CYP3A4 inhibitors
  - Referral to cardio-oncologist
- CHA2DS2-VASc system based on risk: score of \(\geq 2\) recommend direct oral anticoagulant\(^2\)

Ibrutinib-Associated Bleeding: Patient Management

- Avoid vitamin K antagonists due to limited safety data\(^1\)
- Caution against concomitant NSAIDs, fish oils, vitamin E, and aspirin-containing products
- Direct oral anticoagulants may increase risk
  - Assess risks and benefits individually when making treatment decisions (e.g., CHA2DS2-VAS c and HAS-BLED)
  - Caution with CYP3A4 interacting therapy
- Hold pre/post surgical procedures for 3 days (minor) and 7 days (major)
- Transfuse platelets for serious bleeding events

Ibrutinib: Hypertension

- Mechanism under investigation
- Incidence of grade ≥3 hypertension increased over time to 26% after 46 months\(^1\)
- Standard management
  - Avoid CYP3A4 inhibitors and inducers
- Monitor blood pressure regularly as hypertension may be co-causal for the development of atrial fibrillation and cerebral hemorrhage

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Idelalisib

• Inhibitor of PI3K delta kinase isoform unique to leukocytes¹

• Inhibition of T regulatory cells increases risk for immune-mediated toxicities²
  • Not indicated for treatment naive CLL/SLL

• Black box warning: fatal and serious toxicities (hepatic, diarrhea, colitis, pneumonitis, infections and intestinal perforation)³

# Idelalisib Study 116: Select AEs in ≥20%

<table>
<thead>
<tr>
<th>Category</th>
<th>Term</th>
<th>IDELA+R</th>
<th>PBO+R</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Selected AEs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea/Colitis</td>
<td>⭐ 21/5</td>
<td>15/0</td>
<td></td>
</tr>
<tr>
<td>Bleeding</td>
<td>14/1</td>
<td>19/1</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>⭐ 10/8</td>
<td>13/9</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>10/1</td>
<td>5/0</td>
<td></td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>⭐ 6/4</td>
<td>1/1</td>
<td></td>
</tr>
<tr>
<td><strong>Selected lab values, abnormal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT/AST elevation</td>
<td>⭐ 40/8</td>
<td>20/1</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>60/37</td>
<td>51/27</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>29/7</td>
<td>32/17</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>19/11</td>
<td>32/18</td>
<td></td>
</tr>
</tbody>
</table>

Idelalisib: Diarrhea

- Exclude infectious etiology
- Early onset: median time 8 weeks
  - Typically grade 1-2
  - Supportive care and anti-motility agents
- Late onset: median time 8 months
  - Typically grade ≥ 3
  - Characteristic of immune-mediated colitis (assess for CMV-colonoscopy/biopsy)
  - Drug holding and corticosteroids (enteric, PO or IV)
    - Duration based on clinical response
    - Mean time to resolution with budesonide 9mg was 12.1 days versus 1 month for drug holding
  - 67% rechallenged and 58% without recurrence

Idelalisib: Pneumonitis vs. Pneumonia

**Pneumonitis**

- Rare, 4%¹
- Pulmonary symptoms (cough, dyspnea, hypoxia, interstitial infiltrates on a radiologic exam, or >5% decline in oxygen saturation)
  - Hold Idelalisib
  - Bronchoscopy with BAL?
- Time to onset < 1 to 15 months¹
- Corticosteroids and permanently discontinue¹,²

**Pneumonia**

- 8% grade 3¹
- Acute inflammation of lung caused by infection
- Bronchoscopy with BAL?
- *Pneumocystis jirovecii* pneumonia
  - Rare, 3%¹
  - Occurred in patients not receiving prophylaxis
  - NCCN recommends prophylaxis³

Idelalisib: Hepatotoxicity

• Typically occurs <12 weeks of initiation and reversible with dose interruption\(^1\)
• 74% of patients requiring treatment interruptions successfully resumed without recurrence\(^2\)
• Avoidance of hepatotoxic agents
• Monitor for viral reactivation (HSV, CMV, Hep)\(^1-3\)

Duvelisib

- Dual inhibitor of PI3K delta and gamma kinases\(^1,2\)
- Black box warnings: fatal and serious toxicities (infections, diarrhea or colitis, cutaneous reactions and pneumonitis)\(^2\)

DUO Study: Select AEs

- Median exposure: duvelisib 50 wks and ofa 12 doses (6 mos)
- Severe opportunistic infections (6%): bronchopulmonary aspergillosis (n=4), fungal (n=2), PJP (n=3), and CMV colitis (n=1)

<table>
<thead>
<tr>
<th>Select AEs ≥ 10%</th>
<th>All Grades (%)</th>
<th>≥ Grade 3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Duv (N=158)</td>
<td>Ofa (N=155)</td>
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<tr>
<td>Hematologic</td>
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<tr>
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<tr>
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<tr>
<td>URTI</td>
<td>16</td>
<td>8</td>
</tr>
</tbody>
</table>
Venetoclax

• Selective BCL-2 inhibitor that directly induces apoptosis independent of TP53 pathway\(^1,2\)
• FDA approved indications\(^3\):
  • 2016: monotherapy for R/R CLL with Del 17p\(^4\)
  • 2018 MURANO trial: +rituximab for R/R CLL\(^5\)
• Concomitant use with strong CYP3A inhibitors during ramp-up contraindicated\(^3\)

Venetoclax: AEs of Special Interest

- AIHA 7% as monotherapy
- Myelosuppression: managed with dose interruption/reduction
  - Grade ≥ 3 neutropenia 64% (+rituximab) and 63% (monotherapy); consider G-CSF and/or antibiotics
  - Thrombocytopenia 29% (any grade): monotherapy
- GI: Any grade, diarrhea 43% and nausea 42% in both trials
- Infection
  - Upper respiratory infection most common in ≥ 20% across both trials
  - Pneumonia 9% (grade 3) across both trials
- Grade ≥3 laboratory tumor lysis syndrome: 3% (+rituximab) and 6% (monotherapy)

Measures to Mitigate Tumor Lysis Risk

- Disease burden + anti-hyperuricemic agent + hydration
- Low-risk: nodal mass <5 cm AND ALC ≤25,000
  - Outpatient dosing at all levels
  - Post dose labs: 6-8 and 24 hours for first dose of 20 mg and 50 mg
- Medium risk: nodal mass 5 to <10 cm OR ALC ≥ 25,000
  - Outpatient. Consider hospitalization if CrCl <80 mL/min.
  - Post dose labs: 6-8 and 24 hours for first dose of 20 mg and 50 mg
- High risk: nodal mass ≥10 cm OR ALC ≥25,000 AND any node ≥5 cm
  - Hospitalized for first dose of 20 mg and 50 mg
  - Post dose labs: 4, 8, 12, and 24 hours for first dose of 20 mg and 50 mg then outpatient for ramp-up doses with post dose labs at 6-8 hours and 24 hours
Part II: Summary

- Infusion-related reactions are manageable events inherent to ofatumumab and obinutuzumab
- Patients receiving ibrutinib should be counseled and monitored for bleeding and cardiac-related events. Consider referral to cardio-oncologist
- Counsel patients receiving Idelalisib regarding diarrhea, infections, and hepatic toxicities
- Venetoclax has a favorable risk-benefit profile. Patient profiling required to mitigate risk of tumor lysis
- Concomitant medication monitoring with oral oncolytics
Part III: Treatment of FL

Philip A. Thompson, MB, BS (Hons.)
Assistant Professor, Department of Leukemia
University of Texas MD Anderson Cancer Center
Part III: Initial Treatment of Follicular Lymphoma

Stage I/II
- Life expectancy <15y: observation
- Life expectancy >15y: RT with curative intent

Stage III/IV
- Asymptomatic: observation
- Symptomatic: R-CHOP, R-CVP, R-benda

R maintenance
Watch and Wait vs. Immediate Treatment for Stage III/IV FL

- No survival benefit for early treatment in asymptomatic patients\(^1\)-\(^3\)
- GELF criteria for high disease burden suggesting need for treatment:
  1. Any nodal or extranodal tumor mass >7 cm in diameter
  2. Involvement of at least 3 nodal sites, each with diameter >3 cm
  3. Presence of systemic or B symptoms
  4. Splenic enlargement with inferior margin below the umbilical line
  5. Compression syndrome (ureteral, orbital, gastrointestinal)
  6. Pleural or peritoneal serous effusion (irrespective of cell content)
  7. Leukemic phase (>5.0 x 10\(^9\)/L circulating malignant cells)
  8. Cytopenia (granulocyte count < 1.0x10\(^9\)/L and/or platelets <100x10\(^9\)/L)

Choice of CIT

• STiL study¹ (BR vs R-CHOP in indolent and mantle cell lymphoma) showed:
  1. Superior PFS for BR vs R-CHOP, including when only FL analyzed
  2. BR associated with lower grade 3/4 neutropenia, infection rates, peripheral neuropathy and no alopecia

• Value of maintenance R more uncertain after BR therapy

• Additionally, post-hoc analysis of GALLIUM study showed higher rates of fatal AEs in older adults (>70) receiving bendamustine (in both R- and G-containing arms)

• Either remains a reasonable choice; R-CVP or R monotherapy for very elderly/unfit patients

¹ Rummel, Lancet Oncol 2013.
R vs. G: GALLIUM STUDY

- **R** (Treatment naive FL or MZL, n=1202)
  - **R-chemo** (bendamustine, CHOP or CVP)
  - **R maintenance** 2 monthly for 2 years

- **G** (bendamustine, CHOP or CVP)
  - **G-chemo** (bendamustine, CHOP or CVP)
  - **G maintenance** 2 monthly for 2 years

Obinutuzumab Improves PFS Compared With Rituximab


median follow-up 41 months

HR 0.68 (95% CI 0.54 to 0.87, \( P=0.0016 \))
G Superior PFS to R in Both Bendamustine and CHOP Groups

- Obinutuzumab arm associated with higher:
  1. IRRs (59 vs 49%)
  2. Febrile neutropenia per cycle (6.9 vs. 4.9%)
  3. Cumulative incidence of grade 3-4 infections (20 vs. 15.6%).

- Bendamustine arm associated with highest # fatal AEs; CHOP with highest # grade 3-5 AEs (esp. cytopenias)

GALLIUM: Risk of a POD24 Event by Treatment Arm

- POD24 an important milestone as patients who progress within 2 years have very poor outcomes
Factors Influencing Choice of Monoclonal Antibody

**Rituximab**
- Less grade ≥3 toxicity (infections/IRRs)
- Lower cost
- No OS advantage
- Can use G if rituximab refractory

**Obinutuzumab**
- More potent, more MRD negative patients
- Superior PFS
- 5% absolute reduction in POD24 events
PRIMA Study: PFS

- 2-year rituximab maintenance post-CIT (R-CHOP, R-CVP or R-FCM)
- No OS benefit

R Maintenance May Be Associated With Reduced Risk of Transformation

- Multi-center, retrospective analysis
- 2.6% absolute risk reduction for transformation at 10 years

Factors Influencing Decision to Give Maintenance

- Chemotherapy backbone: PRIMA study used R maintenance after R-CHOP or R-CVP; unclear if beneficial after BR
- Tolerability of induction
- Reduced risk of histologic transformation
- NB. No survival benefit from R maintenance
Approach to Relapsed/Refractory Follicular Lymphoma
Early Relapse Within 2 Years of R-CHOP Is Associated With Poor Outcome

**Overall Survival of Patients with FL by Time to Relapse After First-Line R-CHOP from NLCS**

<table>
<thead>
<tr>
<th>Time to Relapse</th>
<th>2-Year OS (95% CI), %</th>
<th>5-Year OS (95% CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference (no early POD)</td>
<td>97 (94.6-98.1)</td>
<td>90 (86.2-92.4)</td>
</tr>
<tr>
<td>Early progression (early POD)</td>
<td>68 (58.2-76.3)</td>
<td>50 (39.4-59.2)</td>
</tr>
</tbody>
</table>

Approach to First Relapse of Follicular Lymphoma

- Biopsy confirmed relapsed FL
  - In need of treatment? (yes/no)
  - Active surveillance

- Trial available? (yes/no)
  - Clinical trial

- POD24?
  - AutoSCT candidate? (yes/no)
    - AutoSCT
    - R or G-alkylator e.g. R-CHOP, BR, R-ICE (CR/PR <PR)
      - ASCT
      - Clinical trial/novel agents (e.g. idelalisib)
  - R or G-alkylator e.g. R-CHOP, R-ICE, R-benda (CR/PR)

Courtesy of Dr. Chan Cheah
Phase III GADOLIN Study: Obinutuzumab + Bendamustine vs. Bendamustine

Rituximab-refractory CD20+ iNHL (FL, MZL, SLL) N=413

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

Bendamustine
90 mg/m²/day IV D1 and D2 x 6 cycles (28D cycles)

Obinutuzumab
1000 mg IV D1, 8 and 15 Cycle 1; D1 cycles 2-6 (28D cycles)

Bendamustine + Obinutuzumab

Obinutuzumab Maintenance

Obinutuzumab
1000 mg IV every 2m for 2y or until progression

- Primary endpoint was progression-free survival (PFS)
- Responses monitored by CT post induction then every 3 months for 2 years then every 6 months

GADOLIN: Obinutuzumab Improves Progression-Free Survival

IRC assessed median PFS not reached
Obi +B vs 14.9 mos for B monotherapy

Phase II 101-09: Idelalisib Monotherapy in Refractory iNHL

**Rituxan + Alkylator Refractory iNHL**

**Single-Arm Study (N=125)**

- **Idelalisib 150 mg BID continuously**
- Therapy maintained until progression

**Disease assessments:**
- Weeks 0, 8, 16, 24
- Every 12 weeks thereafter
- Evaluated by Independent Review Committee

**Primary endpoint:**
- Overall response rate (ORR)

**Secondary endpoints:**
- Duration of response (DOR)
- PFS
- Overall survival (OS)
- Safety
- Quality of life

Tumor Response

- Follicular lymphoma (N=72): ORR 56%, 42% PR, and 14% CR

**Idelalisib: PFS**

**Median PFS = 11 months**

Phase II CHRONOS-1: Copanlisib in Relapsed/Refractory Follicular Lymphoma

- Inhibitor of PI3K alpha and delta isoforms

**Patient Characteristics**
- Prior treatment, n (range): 3 (2-8)
- Median time from last therapy until PD: 8.5m
- Prior Rituximab: 100%
- Refractory to last regimen: n (%)
  - Rituximab: 59 (56.7)
  - Alkylating agent: 39 (37.5)
  - Rituximab and alkylating agent: 43 (41.3)

**Primary endpoint:** ORR

Phase II CHRONOS-1: PFS

Results (N=104 FL):
- ORR 59%
  - 14% CR
  - 44% PR
- Median DOR 12.2 mos (range, 0-22.6)

Phase II DYNAMO Study: Duvelisib in Relapsed/Refractory iNHL

• Inhibitor of PI3K delta and gamma isoforms

R/R iNHL patients (N=129)

Duvelisib 25 mg BID continuously

Study Endpoints
• Primary: ORR
• Secondary:
  - Safety
  - DOR
  - PFS
  - OS

Inclusion Criteria:
• 3 iNHL disease subtypes
  - follicular lymphoma (FL)
  - small lymphocytic lymphoma (SLL)
  - marginal zone lymphoma (MZL)
• Double refractory to rituximab (monotherapy or in combination) and to chemotherapy or radioimmunotherapy
• No eligibility restrictions for cytopenias

Phase II DYNAMO Study: Duvelisib in Relapsed/Refractory iNHL

<table>
<thead>
<tr>
<th></th>
<th>FL N=83</th>
<th>SLL N=28</th>
<th>MZL N=18</th>
<th>Overall N=129</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, %</td>
<td>41</td>
<td>68</td>
<td>33</td>
<td>46</td>
</tr>
<tr>
<td>DoR (months), median</td>
<td>9.2</td>
<td>9.9</td>
<td>NE</td>
<td>9.9</td>
</tr>
<tr>
<td>PFS (months), median</td>
<td>8.3</td>
<td>11.3</td>
<td>NE</td>
<td>8.4</td>
</tr>
<tr>
<td>TTR (months), median</td>
<td>1.9</td>
<td>1.9</td>
<td>3.6</td>
<td>1.9</td>
</tr>
<tr>
<td>OS (months), median</td>
<td>18.4</td>
<td>NE</td>
<td>NE</td>
<td>18.4</td>
</tr>
</tbody>
</table>
Part III: Summary

- Approximately 20% of FL patients relapse within two years and are refractory to therapy resulting in 5-year OS <50%
- Patients refractory to or relapsed with two years after rituximab and alkylating agents have limited treatment options and should be enrolled in clinical trials or treated with novel agents
- Limited efficacy of BCL-2 inhibitors or BTK inhibitors (unlike CLL). Novel therapies (e.g., CAR-T) urgently needed
Part IV: Recognition and Management of AEs of Novel Agents in FL
### Copanlisib: AEs of Special Interest

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
</tr>
<tr>
<td>Any treatment-emergent adverse event</td>
<td>140 (99)</td>
</tr>
<tr>
<td>Nonhematologic toxicities</td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>71 (50)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>48 (34)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>43 (30)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>43 (30)</td>
</tr>
<tr>
<td>Fever</td>
<td>36 (25)</td>
</tr>
<tr>
<td>Nausea</td>
<td>33 (23)</td>
</tr>
<tr>
<td>Lung infection</td>
<td>30 (21)</td>
</tr>
<tr>
<td>Oral mucositis</td>
<td>29 (20)</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>26 (18)</td>
</tr>
<tr>
<td>Cough</td>
<td>23 (16)</td>
</tr>
<tr>
<td>Maculopapular rash</td>
<td>18 (13)</td>
</tr>
<tr>
<td>Constipation</td>
<td>17 (12)</td>
</tr>
<tr>
<td>Bronchial infection</td>
<td>16 (11)</td>
</tr>
<tr>
<td>Flu-like symptoms</td>
<td>16 (11)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>15 (11)</td>
</tr>
<tr>
<td>Skin infection</td>
<td>15 (11)</td>
</tr>
<tr>
<td>Hematologic toxicities</td>
<td></td>
</tr>
<tr>
<td>Decreased neutrophil count</td>
<td>42 (30)</td>
</tr>
<tr>
<td>Decreased platelet count</td>
<td>29 (20)</td>
</tr>
<tr>
<td>Anemia</td>
<td>22 (15)</td>
</tr>
<tr>
<td>Adverse events of special interest</td>
<td></td>
</tr>
<tr>
<td>Pneumonitis (noninfectious)</td>
<td>11 (8)</td>
</tr>
<tr>
<td>Colitis</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Laboratory toxicities</td>
<td></td>
</tr>
<tr>
<td>Elevated AST*</td>
<td>39 (28)</td>
</tr>
<tr>
<td>Elevated ALT*</td>
<td>32 (23)</td>
</tr>
</tbody>
</table>

- Hyperglycemia: 50%; grade ≥3 41%
- Hypertension: 30%; grade ≥3 24%
- Elevated AST: 28%
- Elevated ALT: 23%
- Other grade ≥3 events:
  - Decreased ANC 30%
  - Lung infection 21%; grade ≥3 13%
Acknowledgements

• Dr. Chan Cheah – follicular lymphoma insights and slides

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