Debate No. 2: Treatment of Follicular Lymphoma Without Chemotherapy

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Treatment of Follicular Lymphoma without Chemotherapy

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Disclosures

1 HONORARIUM
   Celgene, Genentech, Gilead, Janssen, Juno, Novartis

2 RESEARCH SUPPORT
   Celgene, Genentech, Janssen, Juno
Objectives

• Review the pathogenesis of FL and potential therapeutic exploitation
• Current management of untreated follicular lymphoma
• Review the RELEVANCE study
Follicular Lymphoma

• The most frequent indolent NHL
• Often an incidental finding
• Patients are frequently asymptomatic
• Prolonged natural history
• Heterogeneous treatment options
• Treatable, but incurable with standard therapy
Early Steps of Follicular Lymphomagenesis

**Bone marrow**
- VDJ recombination
- t(14;18)
- Pre-B cell
- Immature B cell
- Other initiating events?

**Secondary lymphoid organs**
- GC reaction
- Ag encounter
- t(14;18)-bearing slgM memory B cell
- Ag recall?
- FL

**Events**
- Selection
- CSR
- Proliferation
- SHM
- slgM selection
- Clonal expansion
- Developmental arrest
- Dissemination
- BCL-2 constitutive expression
- Survival
- BCL-6 deregulation and ongoing AID activity
- Genomic instability

Huet. *Nature*. April 2018
Influences of the Microenvironment on FL cells

Recurrent genetic alterations allow immune escape, shifting immune and stromal cells towards a supportive phenotype.

Interactive loop between FL cells and macrophages in FL tissue provides a persistent low-level signal essential for survival.
Current Management of Untreated Follicular Lymphoma
The Natural History of FL

Stanford Experience

A

Median OS
Era 1: 11.0 yrs
Era 2: 11.0 yrs
Era 3: 18.5 yrs
Era 4: Not reached
Overall: 13.6 yrs

Survival Probability

Time (years)

0.0
0.2
0.4
0.6
0.8
1.0

P<0.001

Era 1
Era 2
Era 3
Era 4

Overall Survival

Years from Event

0
2
4
6
8
10
12

MER Survival
Expected MER Survival
Lyon Survival
Expected Lyon Survival

Maurer. AJH. 2016
Observation in an Untreated US Population of FL

Overall Survival

(A) Survival probability

(B) Survival probability

Nastoupil et. al. BJH 2016
BR vs. RCHOP for Untreated, Advanced Stage FL

**PFS (StiL)**

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

HR 0.61 (95% CI 0.42–0.87)

**OS for FL patients**

- Median for R-CHOP+ observation: 40.9 mo

Maintenance after Frontline Chemoimmunotherapy

Salles G, et al, ASH 2017
GALLIUM: Obinutuzumab vs. Rituximab with Chemotherapy followed by Maintenance

First-line iNHL CD20-positive (N = 1,400)

**Induction**
- G + CHOP, CVP, or bendamustine
- R + CHOP, CVP, or bendamustine

**Randomize**
- CR, PR

**Maintenance**
- G-maintenance q2mo x 2 years
- R-maintenance q2mo x 2 years

MRD assessments during maintenance and FU

Bendamustine n = 827, CHOP n = 433, CVP n = 1413

GALLIUM: Obinutuzumab vs. Rituximab with chemotherapy and maintenance: High grade adverse events

### Table: Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>R-chemo (N = 597)</th>
<th>G-chemo (N = 596)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE, %</td>
<td>98.3</td>
<td>99.5</td>
</tr>
<tr>
<td>Grade ≥ 3 AEs (&gt; 5% in either arm)</td>
<td>67.8</td>
<td>74.6</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>37.9</td>
<td>43.9</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>8.4</td>
<td>8.6</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>4.9</td>
<td>6.9</td>
</tr>
<tr>
<td>IRRs</td>
<td>3.7</td>
<td>6.7</td>
</tr>
<tr>
<td>Thrombosis</td>
<td></td>
<td>6.1</td>
</tr>
<tr>
<td>Grade 5 AEs by category</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td>9 (2.7)</td>
<td>20.0</td>
</tr>
<tr>
<td>IRRs</td>
<td>2 (0.6)</td>
<td>12.4</td>
</tr>
<tr>
<td>Secondary</td>
<td></td>
<td>4.7</td>
</tr>
<tr>
<td>SAEs (any)</td>
<td>G-CHOP N = 191</td>
<td>3 (1.6)</td>
</tr>
<tr>
<td>Infections</td>
<td>1 (0.5)</td>
<td>46.1</td>
</tr>
<tr>
<td>AEs cause</td>
<td>R-CHOP N = 201</td>
<td>4 (2.0)</td>
</tr>
<tr>
<td>discontinuation</td>
<td>G-CVP N = 61</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Grade 5 AEs</td>
<td>R-CVP N = 56</td>
<td>1 (1.8)</td>
</tr>
<tr>
<td>Median baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>induction</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Graph: Grade 5 (Fatal) AEs by treatment (FL)*

Maintenance Rituximab Following Frontline BR

PFS associated with response to BR
A Chemotherapy Free Option in Untreated FL
Mechanisms of Action of Lenalidomide

**T-Cell Effects**
- Activation and proliferation
- IMMUNE SYNAPSE FORMATION
- CD8+ T-effector cell activity
- Stimulation of cytotoxic CD8+ and helper CD4+ T cells
- Dendritic cell antigen presentation

**NK-Cell Effects**
- Number and activity of NK cells
- Enhanced ADCC
- Immune synapse formation and direct NK killing

**Microenvironment Effects**
- Anti-inflammatory cytokines: IL-2, IL-8, IL-10, IFN-γ, TNF-α
- Inflammatory cytokines: IL-1, IL-6, IL-12, TNF-α

**Malignant B-Cell Effects**
- p21^nFk-1, AP-1
- CDK2, CDK4, CDK6, Rb
- Akt, Gab1 phosphorylation
- G0/G1 arrest; proliferation

**T-cell activation and proliferation**
- IL-2
- IL-8

**Immune synapse formation**

**Microenvironment**
- NLC
- Stromal cell

Gribben et al. **JCO** 2015.
Lenalidomide + Rituximab (R²) in Untreated iNHL

MDACC, Phase II Study of R²

- Lanalidomide 20mg Days 1-21 Cycles 1-6
- Lanalidomide 20mg Days 1-21 Cycles 7-12
- Rituximab 375mg/M² Day 1 of Cycles 1-6
- Rituximab 375mg/M² Day 1 of Cycles 7-12

If clinical benefit, can proceed to 12 cycles

R, Restaging; *, SLL patients: Dose escalation of Lenalidomide starting with cycle 1: (10mg, 15mg, 20mg)
- No patients received maintenance therapy


FL, MZL, SLL

- PR
- SD
- CR

Fowler. Lancet Onc. 2014
RELEVANCE: $R^2$ vs. R-Chemo Study Design

Previously untreated patients with advanced FL requiring treatment per GELF$^{1,2}$ (N = 1030)

- FLIPI score (0-1 vs 2 vs 3-5)
- Age (> 60 vs ≤ 60 years)
- Lesion size (> 6 vs ≤ 6 cm)

Stratification

Treatment Period 1
(~6 months)

Treatment Period 2
(~1 year)

Treatment Period 3
(~1 year)

R$^2$

R$^2$

Rituximab

R-chemo
(R-CHOP, R-B, R-CVP)

Rituximab

Total Treatment Duration: 120 weeks

Primary endpoint: complete response (CR/CRu) rate at 120 weeks and PFS (co-primary)

NCT01476787; NCT01650701; EUDRA 2011-002792-42. Per central (IRC) review by 1999 IWG with CT.
### RELEVANCE: BASELINE CHARACTERISTICS (ITT)

<table>
<thead>
<tr>
<th>Characteristics, n (%)</th>
<th>R² (n = 513)</th>
<th>R-chemo (n = 517)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>59 (30-89)</td>
<td>59 (23-83)</td>
</tr>
<tr>
<td>Age &gt; 70 years</td>
<td>80 (16)</td>
<td>78 (15)</td>
</tr>
<tr>
<td>Male</td>
<td>251 (49)</td>
<td>251 (49)</td>
</tr>
<tr>
<td>0</td>
<td>341 (66)</td>
<td>345 (67)</td>
</tr>
<tr>
<td>1</td>
<td>157 (31)</td>
<td>157 (30)</td>
</tr>
<tr>
<td>2</td>
<td>13 (3)</td>
<td>14 (3)</td>
</tr>
<tr>
<td>Not evaluated</td>
<td>2 (&lt; 1)</td>
<td>1 (&lt; 1)</td>
</tr>
<tr>
<td>Ann Arbor stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I/II</td>
<td>30 (6)</td>
<td>40 (8)</td>
</tr>
<tr>
<td>III/IV</td>
<td>483 (94)</td>
<td>477 (92)</td>
</tr>
<tr>
<td>Bulky disease (&gt; 7 cm)</td>
<td>218 (42)</td>
<td>199 (38)</td>
</tr>
<tr>
<td>FL grade*</td>
<td>437 (85)</td>
<td>443 (86)</td>
</tr>
<tr>
<td>1 or 2</td>
<td>156 (30)</td>
<td>137 (26)</td>
</tr>
<tr>
<td>FLIPI score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk (0-1)</td>
<td>77 (15)</td>
<td>76 (15)</td>
</tr>
<tr>
<td>Intermediate risk (2)</td>
<td>183 (36)</td>
<td>191 (37)</td>
</tr>
<tr>
<td>High risk (3-5)</td>
<td>253 (49)</td>
<td>250 (48)</td>
</tr>
<tr>
<td>Lactate dehydrogenase (&gt; ULN)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B-symptoms - yes</td>
<td>141 (27)</td>
<td>134 (26)</td>
</tr>
</tbody>
</table>

Data cut-off 31 May 2017. *FL grade was unspecified or not FL grade 1-3a for 11 patients in each arm.
ECOG PS, Eastern Cooperative Oncology Group performance status; FLIPI, FL International Prognostic Index; ULN, upper limit of normal.
RELEVANCE: RESPONSE BY IRC (ITT)


Co-Primary Endpoint: CR/CRu at 120 weeks

Best CR/CRu

Best ORR

- 3-year DOR was 77% for $R^2$ vs 74% R-chemo (IRC)
- Investigator results were consistent with IRC
At a median follow-up of 37.9 months, interim PFS was similar in both arms.
### RELEVANCE: PRESPECIFIED SUBGROUP ANALYSIS OF INTERIM PFS (IRC)

<table>
<thead>
<tr>
<th></th>
<th>R², n/N</th>
<th>R-chemo, n/N</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>119/513</td>
<td>115/517</td>
<td>1.10 (0.85-1.43)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 60</td>
<td>58/281</td>
<td>55/282</td>
<td>1.15 (0.79-1.66)</td>
</tr>
<tr>
<td>&gt; 60</td>
<td>61/232</td>
<td>56/235</td>
<td>1.06 (0.74-1.53)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>61/251</td>
<td>59/251</td>
<td>1.02 (0.71-1.46)</td>
</tr>
<tr>
<td>Female</td>
<td>58/262</td>
<td>52/266</td>
<td>1.23 (0.85-1.79)</td>
</tr>
<tr>
<td><strong>Disease stage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I/II</td>
<td>6/30</td>
<td>5/40</td>
<td>2.23 (0.66-7.55)</td>
</tr>
<tr>
<td>III/IV</td>
<td>113/483</td>
<td>106/477</td>
<td>1.06 (0.82-1.39)</td>
</tr>
<tr>
<td><strong>Longest diameter of the longest node</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 6 cm</td>
<td>62/253</td>
<td>58/271</td>
<td>1.19 (0.83-1.71)</td>
</tr>
<tr>
<td>&gt; 6 cm</td>
<td>57/260</td>
<td>53/246</td>
<td>1.04 (0.71-1.51)</td>
</tr>
<tr>
<td><strong>FLIPI score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>14/77</td>
<td>9/76</td>
<td>2.06 (0.88-4.80)</td>
</tr>
<tr>
<td>2</td>
<td>37/183</td>
<td>35/191</td>
<td>1.12 (0.70-1.78)</td>
</tr>
<tr>
<td>3-5</td>
<td>68/253</td>
<td>67/250</td>
<td>1.00 (0.72-1.41)</td>
</tr>
<tr>
<td><strong>Country</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ex-North America</td>
<td>93/384</td>
<td>92/379</td>
<td>1.03 (0.77-1.38)</td>
</tr>
<tr>
<td>North America</td>
<td>26/129</td>
<td>19/138</td>
<td>1.53 (0.84-2.76)</td>
</tr>
</tbody>
</table>

*Post-hoc analysis showed no differences between R² and the three R-chemo regimens.*
**RELEVANCE: OVERALL SURVIVAL (IMMATURE; ITT)**


- **Events, n (%)**
  - R-chemo: 38 (7)
  - R2: 31 (6)

- **3-year OS (95% CI)**
  - R-chemo: 94% (91%-96%)
  - R2: 94% (91%-96%)

- **HR (95% CI)**
  - R-chemo: 1.16 (0.72-1.86)
  - R2: 1.16 (0.72-1.86)
RELEVANCE: Treatment-Emergent Adverse Events

Data cutoff 31May2017. Includes any-grade TEAEs (≥15%) and select AEs of interest as assessed per NCI CTCAE v4.03.

*Hematologic AEs were based on laboratory tests; all anemia events were grade 1. Cutaneous reactions included preferred terms from skin and subcutaneous tissue disorders (including rash), gastrointestinal disorders, general disorders and administration site conditions, infections and infestations, and reproductive system and breast disorders.
RELEVANCE: OTHER SAFETY RESULTS

• Second primary malignancies (SPMs) were similar between arms
  – All SPMs
    • $R^2$: 38 (7%)
    • R-chemo: 48 (10%)
  – Invasive SPMs
    • $R^2$: 25 (5%)
    • R-chemo: 27 (5%)

• Grade 5 TEAEs: 4 (1%) $R^2$ and 5 (1%) R-chemo patients

• Deaths related to study treatment occurred in 2 patients (1 per arm)
RELEVANCE: CONCLUSIONS

• R\textsuperscript{2} was not superior to R-chemo based on mature CR/CRu at 120 weeks and interim PFS
  – R\textsuperscript{2} and R-chemo showed similar efficacy results
  – Treatment effects on PFS were consistent across prespecified subgroups
  – Continued follow-up for more mature PFS and OS results is ongoing

• Important differences in safety profiles were observed between arms
  – R-chemo: More frequent neutropenia (grade 3/4), febrile neutropenia, growth factor usage, nausea, vomiting, neuropathy, and alopecia
  – R\textsuperscript{2}: More frequent cutaneous reactions, tumor flare, and diarrhea

• These results show that R\textsuperscript{2}, a novel immunomodulatory approach, is a potential first-line option for patients with FL requiring treatment
Can We Optimize Frontline Therapy in FL?

- Chemoimmunotherapy is still valid
- Need to enhance our understanding of FL biology to inform the next generation of trials
- Considering the toxicity and impact on QOL is imperative.
- Utilize the available tools to adapt treatment strategies
  - Low to intermediate risk FLIPI/M7FLIPI
    - Start with BR. Is it possible to incorporate CtDNA and PET/CT to inform duration of therapy?
  - High risk FLIPI/M7FLIPI
    - Enrich prospective trials with this population, ideally a non-chemotherapy backbone
AUGMENT STUDY DESIGN: RANDOMIZED DOUBLE BLIND PHASE III

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

1:1

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

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

**≤ 12 cycles or until PD, relapse, or intolerability**

**R-lenalidomide (R²)**
- Rituximab: 375 mg/m² d1, 8, 15, 22 of cycle 1; d1 of cycles 2-5
- Lenalidomide: 20 mg/d*, d1-21/28 (12 cycles)

*10 mg if CrCl between 30 to 59 mL/min.

**R-placebo**
- Rituximab: 375 mg/m² d1, 8, 15, 22 of cycle 1; d1 of cycles 2-5
- Placebo: matched capsules (12 cycles)

- Prophylactic anticoagulation / antiplatelet Rx recommended for at risk patients
- Growth factor use was allowed per ASCO/ESMO guidelines¹,²

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

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

NCT01938001
PRIMARY ENDPOINT: PROGRESSION-FREE SURVIVAL (ITT, IRC)

Data cutoff: June 22, 2018.

Censoring rules based on FDA guidance.

### PFS by IRC

<table>
<thead>
<tr>
<th>Time (mo)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>By IRC, mo</td>
<td>0.46 (0.34-0.62)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>By investigator, mo</td>
<td>0.51 (0.38-0.69)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

*Median follow up: 28.3 months

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>R² Placebo</th>
<th>R² Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>R²</td>
<td>180</td>
<td>178</td>
</tr>
<tr>
<td>R-Placebo</td>
<td>132</td>
<td>124</td>
</tr>
<tr>
<td></td>
<td>92</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td>58</td>
<td>59</td>
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<tr>
<td></td>
<td>40</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>26</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

*HR in the table is calculated as the ratio of the treatment group to the placebo group, with the 95% confidence interval (CI) provided for each time point.
Conclusions/Future Directions

Outcomes for patients with FL continue to improve, we need better risk stratifying tools.

The treatment landscape is rapidly expanding, and we lack predictive biomarkers to guide therapy.

Optimal sequencing of therapy in FL is unknown.

There is a need for better understanding of the toxicity profiles associated with available therapies as QOL and quality remissions are the primary goals of therapy.
Acknowledgements

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