Follicular Lymphoma

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Disclosures

1 HONORARIUM

Bayer, Celgene, Genentech, Gilead/KITE, Janssen, Juno, Merck, Novartis, Spectrum, TG Therapeutics

2 RESEARCH SUPPORT

Celgene, Genentech, Janssen, Karus, Merck, TG Therapeutics
Clinical Presentation of Follicular Lymphoma
Initial Presentation

50 year old M with no significant PMH presents with 2 month history of L neck adenopathy (11/2014). After a brief decrease in size following a course of oral antibiotics, with recurrence of adenopathy he was referred to ENT for further eval.

Otherwise asymptomatic, no B symptoms.
Initial Presentation Continued

Biopsy of the L neck adenopathy revealed:

Follicular lymphoma, grade 1

We performed immunohistochemical stains using fixed, paraffin-embedded tissue of this specimen. The neoplastic cells are positive for PAX-5, BCL-2, Bcl-6 (weak), and are negative for pan cytokeratin. Anti-Cd21 antibody highlights follicular dendritic meshwork within neoplastic follicles. Ki-67 immunostain demonstrates proliferative index of approximately 5-10%.

We performed flow cytometry immunophenotypic studies using cell suspension of the concurrent FNA specimen (see our pathology report C-14-224315) and detected an aberrant B-cell population that is immunophenotypically positive for CD10, CD19, CD20, CD22, CD23 partial, CD38 bright, CD44, CD45, CD79b, and surface immunoglobulin lambda light chain and negative for CD3, CD4, CD5, CD8, CD11c, CD30, CD34, CD43, CD56, and CD200.
Initial Staging/Work Up

Bone marrow biopsy results: Follicular Lymphoma present 5-10%

*Stage IV*

LDH is > ULN

CBC is normal

PET/CT results:

Hypermetabolic adenopathy above and below the diaphragm
Early Steps of Follicular Lymphomagenesis

Bone marrow
VDJ recombination

Secondary lymphoid organs
GC reaction

Ag encounter
- Selection
- CSR

Apoptosis

Differentiation

Dissemination

Ag recall?

ISFN

PFL

FL

Dissemination

FLLCs

Committed precursors

Additional genetic events?

BCL-2 constitutive expression
Survival

BCL-6 deregulation and ongoing AID activity
Genomic instability

Increasing genomic alterations

Huet. Nature. April 2018
# Common Genetic Alterations in FL

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Gene</th>
<th>Function</th>
<th>Frequency (%)*</th>
<th>Oncogenic alteration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epigenetic and transcriptional regulation</td>
<td><strong>KMT2D</strong></td>
<td>Histone H3K4 methyltransferase</td>
<td>70–90</td>
<td>Loss of function</td>
</tr>
<tr>
<td></td>
<td><strong>CREBBP</strong></td>
<td>Histone H3K27 and H3K18 acetyltransferase</td>
<td>50–70</td>
<td>Loss of function</td>
</tr>
<tr>
<td>Histone-encoding genes</td>
<td>Histone linkers and core histones</td>
<td>20–30</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>EZH2</strong></td>
<td>Histone H3K27 methyltransferase</td>
<td>10–30</td>
<td>Gain of function</td>
</tr>
<tr>
<td></td>
<td><strong>EP300</strong></td>
<td>Histone H3K27 and H3K18 acetyltransferase</td>
<td>10–20</td>
<td>Loss of function</td>
</tr>
<tr>
<td></td>
<td><strong>MEF2B</strong></td>
<td>Transcription factor</td>
<td>10–20</td>
<td>Gain of function</td>
</tr>
<tr>
<td>BCR signalling</td>
<td><strong>IGH and IGL variable domains</strong></td>
<td>Promotes N-glycosylation</td>
<td>~80</td>
<td>Gain of function</td>
</tr>
<tr>
<td></td>
<td><strong>CARD11</strong></td>
<td>BCR–NF-κB signalling pathway</td>
<td>10–15</td>
<td>Gain of function</td>
</tr>
<tr>
<td>Survival</td>
<td><strong>BCL2</strong></td>
<td>Anti-apoptosis</td>
<td>Translocations, ~85</td>
<td>Gain of function</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mutations, ~50</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td><strong>SOCS1, STAT6 and STAT3</strong></td>
<td>JAK–STAT signalling</td>
<td>20</td>
<td>Gain of function</td>
</tr>
<tr>
<td></td>
<td><strong>NOTCH1, NOTCH2, NOTCH3, NOTCH4, DTX1 and SPEN</strong></td>
<td>NOTCH pathway</td>
<td>18</td>
<td>Unknown</td>
</tr>
<tr>
<td>Immune escape</td>
<td><strong>HVEM</strong></td>
<td>Receptor</td>
<td>~50*</td>
<td>Loss of function</td>
</tr>
<tr>
<td></td>
<td><strong>EPHA7</strong></td>
<td>Ephrin receptor</td>
<td>70*</td>
<td>Loss of function</td>
</tr>
</tbody>
</table>

Clinical Presentation

- Lymphadenopathy
- Palpable mass, edema
- Splenomegaly
- Abnormal blood counts
- Skin lesions
- Endoscopy findings
- Abnormal imaging findings
Prognostic Tools for Newly Diagnosed Follicular Lymphoma
Cause of Death in FL in the Rituximab Era

Sarkozy. JCO 2018
Follicular Lymphoma International Prognostic Index (FLIPI)

Risk factors:

Nodal sites > 4
Stage III/IV
LDH > ULN
Hgb < 12 g/dL
Age > 60 y

Low risk – 0-1
Intermediate – 2
High – 3-5

Follicular Lymphoma International Prognostic Index 2 (FLIPI-2)

Risk factors:

- B2M > ULN
- Mass > 6 cm
- BM involved
- Hgb < 12 g/dL
- Age > 60 y

Low risk – 0
Intermediate – 1-2
High – 3-5

M7-FLIPI: Incorporation of Molecular Features

Indications for Treatment

**GELF criteria**

- High tumour bulk defined by either
  - Tumour > 7 cm
  - 3 nodes in 3 distinct areas each > 3 cm
  - Symptomatic splenic enlargement
  - Organ compression
  - Ascites or pleural effusion

- Presence of systemic symptoms

- Serum LDH or β2-microglobulin above normal values

**BNLI criteria**

- Rapid disease progression in the preceding 3 months
- Life-threatening organ involvement
- Renal or liver infiltration
- Bone lesions
- Systemic symptoms or pruritus
- Hb < 10 g/dL or WBC < 3.0 × 10^9/L or platelet count < 100 × 10^9/L; related to marrow involvement

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Initial Therapy for Newly Diagnosed Follicular Lymphoma
General Approach to Initial Therapy for FL

- **Localized**
  - W&W: Watch and Wait
  - W&W Radiotherapy

- **Advanced indolent**
  - W&W: Watch and Wait
  - R: Rituximab

- **Advanced with symptoms**
  - R: Rituximab
  - C: Chemo (G: Obinutuzumab)
  - R+L: Rituximab + Lenalidomide

W&W: watch and wait; R: rituximab; G: obinutuzumab
Rituximab vs. Watch and Wait for Low Tumor Burden FL

RESORT Trial: Rituximab x 4 Followed by Maintenance vs. Retreatment

**Treatment failure-free survival**

Two-sided log-rank p = 0.54  
Median FU 4.5 years

<table>
<thead>
<tr>
<th>Time since random assignment (years)</th>
<th>At risk</th>
<th>Failure</th>
<th>3-year (%)</th>
<th>5-year (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintenance</td>
<td>146</td>
<td>78</td>
<td>73</td>
<td>53</td>
</tr>
<tr>
<td>Retreatment</td>
<td>143</td>
<td>80</td>
<td>65</td>
<td>50</td>
</tr>
</tbody>
</table>

Approach to Indolent/Low Tumor Burden, Advanced Stage FL

Watch and wait acceptable (encouraged)

- Allows the opportunity to assess the pace of the disease
- Spare patients side effects of therapy

Rituximab x 4 if observation is undesirable/minimal symptoms

- No maintenance, re-treatment when appropriate
Initial Treatment Course – Clinical Vignette

50 y/o patient opts for W&W given he is asymptomatic

- Within 6 months, he experiences progression in size of lymph nodes
- Biopsy confirms no evidence of transformation, still grade 1/2 FL
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)

OS for FL patients

HR 0.61 (95% CI 0.42–0.87)
p = 0.0072

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 × 2 years
- R-maintenance q2mo × 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>
<thead>
<tr>
<th>% (n)</th>
<th>R-chemo (N = 597)</th>
<th>G-chemo (N = 596)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE, %</td>
<td>90.3</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>Thromboembolism</td>
<td></td>
<td>6.1</td>
</tr>
</tbody>
</table>

Grade 5 (fatal) AEs by treatment (FL)*

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.

Huet. Nature. April 2018

Kuppers & Stevenson. Blood. May 2018
RELEVANCE: Lenalidomide + Rituximab (R2) vs. Chemo-R

Previously untreated patients with advanced FL requiring treatment per GELF1,2 (N = 1,030)

- Treatment period 1 (28 weeks)
  - R2
  - n = 513

- Treatment period 2 (48 weeks)
  - R2
  - n = 517

- Treatment period 3 (44 weeks)
  - Rituximab

Total treatment duration: 120 weeks

Morschhauser F, et al, NEJM 2018
RELEVANCE: Lenalidomide-Rituximab (R2) vs Chemo-R
Similar Response and PFS

Interim PFS by IRC

Morschhauser F, et al, NEJM 2018
RELEVANCE: Lenalidomide-Rituximab (R2) vs Chemo-R

Safety comparisons

<table>
<thead>
<tr>
<th></th>
<th>R2</th>
<th>R-chemo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 4 neutropenia, %</td>
<td>32</td>
<td>50</td>
</tr>
<tr>
<td>Time to grade 3/4 neutropenia, months</td>
<td>3.7</td>
<td>0.6</td>
</tr>
<tr>
<td>Febrile neutropenia, %</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Range of grade ≥ 3 TEAEs, %</td>
<td>~60</td>
<td>~70</td>
</tr>
<tr>
<td>Grade 3/4 infections, %</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Grade ≥ 3 rash, %</td>
<td>7</td>
<td>1</td>
</tr>
</tbody>
</table>

- R-chemo was associated with more febrile neutropenia, growth factor usage, nausea, vomiting, neuropathy, and alopecia
- R² was associated with more frequent cutaneous reactions, tumour flare, and diarrhoea

Morschhauser F, et al, NEJM 2018
Tools to Inform Maintenance Therapy: PET/CT

**PFS according to PET status (cut-off ≥ 4) in IWC responders**

- PET negative: 205 subjects, 40% (81) censored, 74 median survival
- PET positive: 41 subjects, 78% (31) censored, 19 median survival

HR 3.9 (95% CI 2.5–5.9); p < 0.0001
Median PFS: **16.9** (10.8–31.4) vs **74.0** months (54.7–NR)

**OS according to PET status (cut-off ≥ 4) in IWC responders**

- PET negative: 205 subjects, 9% (7) censored, NR median survival
- PET positive: 41 subjects, 20% (8) censored, 81 months (81–95)

HR 6.7 (95% CI 2.4–18.5); p = 0.0002
Median OS: **79** months vs NR

PET, positron emission tomography; CET, computed tomography.
Maintenance R after Frontline BR is more impactful among those achieving a PR

Patients who achieved a CR following ≥ 4 cycles of BR

Patients who achieved a PR following ≥ 4 cycles of BR
**Approach to High Tumor Burden, Advanced Stage FL**

- **Bendamustine + Rituximab induction**
  - potential for less toxicity, greater/similar efficacy to R-CHOP
  - (PFS but no OS advantage)
  - If concern for occult transformation, consider R-CHOP

- **Obinutuzumab + chemo** (PFS but no OS advantage)
  - No subcutaneous option
  - Perhaps “commits” to maintenance based on GALLIUM
  - Potentially more infection with maintenance after bendamustine

- **Lenalidomide + Rituximab** (No PFS or OS advantage)
  - Potential for less toxicity

- **Maintenance Rituximab** (PFS but no OS advantage)
  - Not routine, offered/acceptable
Beyond frontline therapy, how do we approach relapsed FL?
Early Relapse of FL (<24 months) Defines Poor Risk Group

Stage 2-4 FL
N = 588

R-CHOP

Early progression of disease (POD)
No POD within 2 years of diagnosis

A
Survival (probability)
Time From Risk-Defining Events (months)

B
Survival (probability)
Time From Risk-Defining Events (months)

Casulo et. al. JCO 2015
**PET, Transformation, and Risk of Early POD in Therapy of FL**

Transformation is a significant contribution to early death in patients with early progression.

![Graph showing risk over time](image)

<table>
<thead>
<tr>
<th>Event rates at 3 years</th>
<th>Progression within 1 year (n=44)</th>
<th>Progression between 1-2 year (n=54)</th>
<th>PFS24 achievers (n=248)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of tFL,%</td>
<td>42.4</td>
<td>22.7</td>
<td>3.4</td>
</tr>
<tr>
<td>Risk of death due to tFL,%</td>
<td>18.6</td>
<td>9.8</td>
<td>0.9</td>
</tr>
<tr>
<td>Risk of death without tFL,%</td>
<td>14.4</td>
<td>12.0</td>
<td>2.5</td>
</tr>
<tr>
<td>Cumulative death rate,%</td>
<td>33.0</td>
<td>21.8</td>
<td>3.4</td>
</tr>
</tbody>
</table>

*Batlevi et al. ICML 15, 2019, Abst 103.*
Probability of Progression-Free Survival After Multiple Treatments

<table>
<thead>
<tr>
<th>Treatment Line</th>
<th>Median PFS Years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>6.62 (6.10-7.20)</td>
</tr>
<tr>
<td>Second</td>
<td>1.50 (1.35-1.70)</td>
</tr>
<tr>
<td>R-mono</td>
<td>1.50 (1.26-2.11)</td>
</tr>
<tr>
<td>R-chemo</td>
<td>1.48 (1.08-1.77)</td>
</tr>
<tr>
<td>Third</td>
<td>0.83 (0.68-1.09)</td>
</tr>
<tr>
<td>Fourth</td>
<td>0.69 (0.50-0.97)</td>
</tr>
<tr>
<td>Fifth</td>
<td>0.68 (0.43-0.88)</td>
</tr>
</tbody>
</table>

Link et al, 2018.
Lenalidomide + Rituximab in R/R FL

AUGMENT

- **Primary endpoint:**
  - Progression-free survival (PFS)
    - 90% power, 60% improvement in PFS (median 17.6 vs 11 months)
    - HR = 0.625
    - Final analysis at 193 events, IRC-assessed

- **Secondary endpoints:**
  - ORR, CR, DOR, safety

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**Treatment: 1 year**

- **Lenalidomide** 20 mg/day, d1-21/28, for up to 12 cycles +
  - **Rituximab** weekly x 4, then monthly x 4

- **Placebo** po qd, d1-21/28 for up to 12 cycles +
  - **Rituximab** weekly x 4, then monthly x 4

**Stratification Factors:**
- Previous R treatment (yes/no)
- Time since last lymphoma therapy (≤ 2 yrs/> 2 yrs)
- FL/MZL

Leonard. ASH 2018 Abstract
Lenalidomide + Rituximab Improves PFS compared with Rituximab Alone in R/R FL

Figure 1. Primary Endpoint PFS per IRC Assessment

Leonard. ASH abstract #445, 2018
Targeting Signaling Pathways in R/R FL
# PI3K Isoforms in B cell Malignancies

<table>
<thead>
<tr>
<th>Class I PI3K Isoform</th>
<th>Cellular Expression</th>
<th>Primary Physiological Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delta (δ)</td>
<td>Leukocytes</td>
<td>• B-cell signaling, development, and survival</td>
</tr>
</tbody>
</table>
| Alpha (α)            | Broad               | • Insulin signaling and angiogenesis  
|                      |                     | • Resistance mechanism in at least some lymphomas |
| Beta (β)             | Broad               | • Platelet function        |
| Gamma (γ)            | Leukocytes          | • Neutrophil and T-cell function |

Emerging Role of PI3K inhibitors for R/R FL

Idelalisib (PI3Kδi) in R/R FL

- 90% had improvement in lymphadenopathy
- 57% had ≥50% decrease from baseline

Enrolled April 2011 to October 2012

Idelalisib 150 mg BID

Therapy maintained until progression

Gopal. NEJM, 2014
Idelalisib is Active in Early Relapse FL

POD24 Ad Hoc Subgroup Efficacy Results

Safety Profile of Idelalisib

<table>
<thead>
<tr>
<th>AEs</th>
<th>Any grade N, %</th>
<th>Grade ≥3 N, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>54 (43%)</td>
<td>16 (13%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>37 (30%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>37 (30%)</td>
<td>2 (2%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Transaminases, n (%)</th>
<th>Grade 1-2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Any grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT or AST elevated</td>
<td>44 (35%)</td>
<td>13 (10%)</td>
<td>3 (2%)</td>
<td>60 (48%)</td>
</tr>
</tbody>
</table>

Emerging Role of PI3K inhibitors for R/R FL

Copanlisib (pan-PI3Ki) in R/R FL

Phase IIA study
Single-arm study (N = 33)

iNHL or CLL
≥2 prior lines of therapy

Copanlisib 60 mg IV
Days 1, 8, 15 of a 28 day cycle

Therapy maintained until progression or unacceptable toxicity

ORR 59%, 14% CR in R/R FL

Best overall response

CR
PR
SD
Unconfirmed SD
PD

*Patient was assessed as having SD by independent review

*1 patient classified by the investigator as having FL but who was reclassified by independent assessment as having diffuse large B-cell lymphoma, is not shown in the plot (change in lesions: increase of 250%)

SD, stable disease
Hyperglycemia Associated with Copanlisib

Measurement of blood glucose for patients (n=27) from the 0.8 mg/kg dose cohort during the first treatment cycle

- Hyperglycemia was transient
- Maximum change from baseline observed 5 hours post-infusion
- Plasma glucose approached baseline levels 24 hours post-infusion, and prior to subsequent infusions (eg, Day 8)

Efficacy

<table>
<thead>
<tr>
<th></th>
<th>Diabetic (n=20)</th>
<th>Non-diabetic (n=122)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Best Response, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>2 (10)</td>
<td>22 (18)</td>
</tr>
<tr>
<td>PR</td>
<td>6 (30)</td>
<td>56 (46)</td>
</tr>
<tr>
<td>ORR</td>
<td>8 (40)</td>
<td>78 (64)</td>
</tr>
<tr>
<td>SD</td>
<td>8 (40)</td>
<td>32 (26)</td>
</tr>
<tr>
<td>PD</td>
<td>1 (5)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>NA/NE</td>
<td>2 (10)</td>
<td>10 (8)</td>
</tr>
<tr>
<td><strong>Median PFS, months</strong></td>
<td>7.2</td>
<td>13.8</td>
</tr>
<tr>
<td><strong>Median DOR, months</strong></td>
<td>7.1</td>
<td>14.9</td>
</tr>
</tbody>
</table>
Hypertension Associated with Copanlisib

Measurement of systolic blood pressure for patients from the 0.8 mg/kg dose cohort during the first treatment cycle:

- Hypertension was transient.
- No patients experienced Grade 4 hypertension.
- The percent of patients with new or worsening G3 hypertension per cycle was relatively constant over the course of treatment.

**Best Response, n (%)**

<table>
<thead>
<tr>
<th></th>
<th>Hypertensives (n=41)</th>
<th>Non-Hypertensives (n=101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>11 (27)</td>
<td>13 (13)</td>
</tr>
<tr>
<td>PR</td>
<td>14 (34)</td>
<td>48 (48)</td>
</tr>
<tr>
<td>ORR</td>
<td>25 (61)</td>
<td>61 (60)</td>
</tr>
<tr>
<td>SD</td>
<td>10 (24)</td>
<td>30 (30)</td>
</tr>
<tr>
<td>PD</td>
<td>2 (5)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>NA/NE</td>
<td>4 (10)</td>
<td>8 (8)</td>
</tr>
</tbody>
</table>

**Median PFS, months**

- Hypertensives: 19.0
- Non-Hypertensives: 11.3

**Median DoR, months**

- Hypertensives: 22.6
- Non-Hypertensives: 10.9


Hypertensives (n=41) Non-Hypertensives (n=101)

**Hypertension Associated with Copanlisib**

Measurement of systolic blood pressure for patients from the 0.8 mg/kg dose cohort during the first treatment cycle.
Emerging Role of PI3K inhibitors for R/R FL

**Copanlisib has Activity in R/R FL**

- There were 140 patients that were evaluable based on their progression of disease (POD) from first-line treatment
- Principal histologies in the POD24 subset analysis were FL (102 patients) and MZL (23 patients)

**First-line treatments in the POD24 subgroup analysis**

- 85% of FL patients received some form of R-chemotherapy as first-line treatment

**CHRONOS-1**

<table>
<thead>
<tr>
<th></th>
<th>POD &lt;24 mo.</th>
<th>POD &gt;24 mo.</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=140</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>34%</td>
<td>21%</td>
</tr>
<tr>
<td>R-containing therapies 80%</td>
<td>23%</td>
<td>2%</td>
</tr>
<tr>
<td>R-CVP</td>
<td>18%</td>
<td>23%</td>
</tr>
<tr>
<td>R-CVP</td>
<td>21%</td>
<td>21%</td>
</tr>
<tr>
<td>R-CHOP</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Other</td>
<td>2%</td>
<td>2%</td>
</tr>
</tbody>
</table>

- Progressed in <24 mo.
- Progressed in ≥24 mo.

**Median time, months**

| From 1st line of treatment | 11.0 | 35.3 |
| To progression for most recent prior therapy | 7.0 (65.6% refractory) | 15.7 (48.9% refractory) |

CHOP, cyclophosphamide, hydroxydaunorubicin, oncovin, prednisone/prednisolone; CVP, cyclophosphamide, vincristine, prednisone/prednisolone; FL, follicular lymphoma; MZL, marginal zone lymphoma; R, rituximab. Santoro A et al. Presented at: American Society of Hematology Annual Meeting 2018; December 1-4, 2018; San Diego, CA. Abstract 395.
Emerging Role of PI3K inhibitors for R/R FL

**Duvelisib (PI3K γδ i) in R/R FL**

- **Phase 2, Single arm, n=129**
  - Duvelisib 25 mg BID Continuously
  - Treatment until progression or unacceptable toxicity

**Accrual Complete; Analysis as of April 2016 (last pt enrolled + 6 mo.)

**Best % change in nodal target lesions**

**Table: ORR per IRC, %**

<table>
<thead>
<tr>
<th></th>
<th>OVERALL N = 129</th>
<th>FL N = 83</th>
<th>SLL N = 28</th>
<th>MZL N = 18</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR per IRC, %</strong></td>
<td>46</td>
<td>41</td>
<td>68</td>
<td>33</td>
</tr>
<tr>
<td><strong>P-value</strong></td>
<td>p=0.0001*</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
<td>(37-55)</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Complete Response</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial Response</td>
<td>46</td>
<td>41</td>
<td>68</td>
<td>33</td>
</tr>
<tr>
<td><strong>ORR per Investigator, %</strong></td>
<td>58</td>
<td>53</td>
<td>79</td>
<td>50</td>
</tr>
<tr>
<td>Complete Response</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Partial Response</td>
<td>57</td>
<td>52</td>
<td>75</td>
<td>50</td>
</tr>
</tbody>
</table>

* The study met the primary endpoint (p=0.0001 against null hypothesis that ORR was ≤ 30% per IRC)

- **83% of pts had reduction in target lymph nodes (per IRC)**
# Toxicity Profile of Duvelisib

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>All Grades</th>
<th>Gr 3</th>
<th>Gr 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Diarrhea *</td>
<td>44</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Neutropenia *</td>
<td>32</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>Nausea</td>
<td>29</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>24</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue *</td>
<td>24</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Anemia *</td>
<td>23</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Thrombocytopenia *</td>
<td>21</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>21</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>18</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>15</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>15</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>15</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Other Common ≥ Gr 3 AEs (≥ 5% of pts)**

<table>
<thead>
<tr>
<th></th>
<th>%</th>
<th>%</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile neutropenia</td>
<td>9</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Lipase increased</td>
<td>9</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>ALT increased</td>
<td>14</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>
S1608: Randomized phase II trial in early progressing or refractory FL

FL progressing within 2 years or refractory to bendamustine based therapy

Stratify:
- maintenance therapy
- lack of CR / early POD

Mandatory specimen submission

TGR-1202 + Obinutuzumab
N = 45

Lenalidomide + Obinutuzumab
N = 45

CHOP + Obinutuzumab
N = 45

Primary clinical objective: CR by PET/CT
Primary translational objective: Validation of m7-FLIPI in this high-risk population
Novel Therapies Under Development
Mosunetuzumab: a Bispecific Antibody Targeting CD3 and CD20

**Mechanism of action**
- Redirects T-cells to engage and eliminate malignant B-cells
- Conditional agonist: T-cell activation dependent on B-cell engagement
- Amino-acid substitution (N297G) to inactivate ADCC and avoid destruction of engaged T cells

**Full-length humanized IgG1 antibody**
- Longer half-life than fragment-based drug formats
- PK properties enable QW to Q3W dosing
- Does not require ex-vivo T-cell manipulation
- Off the shelf, readily available treatment

ADCC, antibody-dependent cell-mediated cytotoxicity

Mosunetuzumab investigator brochure
Efficacy of Mosunetuzumab in R/R FL
Early evidence of durable CR; no relapses observed to date

Data cut-off date: 17 August 2018

- Median duration of CR: not reached
- Median duration of follow-up for CR: 330 days (range 54–788 days)

Change in SPD from baseline (%)

ORR 21/35 (60.0%)
CR 12/35 (34.3%)
5F9 is a First-in-class Macrophage Immune Checkpoint Inhibitor Targeting CD47

- 5F9 is a humanized IgG4 antibody against CD47, a don’t eat me signal, that induces tumor cell phagocytosis.
- 5F9 eliminates cancer cells through blockade of CD47 to its binding partner SIRP-alpha on macrophages.
- Cancer cells express pro-phagocytic (eat me) signals while most normal cells do not; this allows 5F9 to selectively eliminate cancer cells.
- 5F9/CD47 blockade induces anti-tumor activity in over 25 tumor models.
Anti-tumor Activity is Observed with 5F9 and Rituximab in Relapsed or Refractory NHL

<table>
<thead>
<tr>
<th>Response</th>
<th>All patients n=22</th>
<th>DLBCL n=15</th>
<th>Follicular Lymphoma n=7</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective Response Rate (ORR)</strong></td>
<td>11 (50%)</td>
<td>6 (40%)</td>
<td>5 (71%)</td>
</tr>
<tr>
<td><strong>Partial Response (PR)</strong></td>
<td>3 (14%)</td>
<td>1 (7%)</td>
<td>2 (29%)</td>
</tr>
<tr>
<td><strong>Complete Response (CR)</strong></td>
<td>8 (36%)</td>
<td>5 (33%)</td>
<td>3 (43%)</td>
</tr>
<tr>
<td><strong>Disease control rate (CR+PR+SD)</strong></td>
<td>14 (64%)</td>
<td>9 (60%)</td>
<td>5 (71%)</td>
</tr>
</tbody>
</table>

Data cutoff April 2018

- The objective response rate across all patients is 50% according to Lugano criteria
- Multiple CRs have been observed in both DLBCL and FL Phase 1b populations
- Efficacy is observed in rituximab-refractory patients

5F9 Dose (mg/kg)
- o = FL
- * = DLBCL

Progressive Disease (Lugano)
Partial Response (Lugano)

Patient 22 had PD but tumor measurements not available
CD19 CAR T-cell Products in Pivotal Trials in R/R FL

- **NCI**
  - Retrovirus
  - Kite Pharma
    - KTE-C19
    - Axicabtagene ciloleucel
    - Axi-cel

- **U Penn**
  - Lentivirus
  - Novartis
    - CTL-019
    - Tisagenlecleucel

- **FHCRC / SCH**
  - Lentivirus
  - Juno Therapeutics
    - JCAR017 (CD4:CD8 = 1:1)
    - Lisocabtagene maraleucel
    - Liso-cel

Adapted from van der Steegen et al. Nat Rev Drug Discov, 2015
Conclusions

With technological advances, our evolving understanding of FL biology will likely inform new therapies.

- Still aiming for cure

Given there are numerous treatment options, risk stratification is key.

As the majority of patients with FL can anticipate a normal life span, consideration of the impact of treatment options on QOL is imperative.
Acknowledgements

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R. Eric Davis
Nathan Fowler