Follicular Lymphoma: Updates and novel immune therapies

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Presenter Disclosure Information

Larry W. Kwak, M.D., Ph.D.

- The following relationships exist related to this presentation:
  - Xeme BioPharma, Inc. (founder equity, consultant)
  - Sellas (consultant)
  - Celltrion (consultant)
  - Antigenics/Agenus (equity)
Follicular NHL

- 2nd most common NHL
- 22,000 new cases/yr, median age 60
- Normal counterpart germinal center B cell
- Graded by # large cells
- Grade I, II, IIIa indolent
- Gr IIIb aggressive
  (Gr IIIb ≈ DLBCL)
Usual Clinical presentation

- Painless lymphadenopathy, waxing and waning
- B symptoms uncommon
- Abdominal, retroperitoneal masses
- Spleen involved (40%)
- Marrow frequently involved (>70%)
- Extranodal sites (except the marrow) uncommon.
- Elevated LDH uncommon
- Stage III/IV in over 80% of patients
Prognosis in follicular NHL - FLIPI

4167 patients

• Age > 60, Stage III/IV, > 4 nodal sites, LDH, Hgb < 12

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

• FLIPI2: B2M, BM involvement, LN > 6cm
Treatment Principles

- Early treatment not beneficial.
- Anthracyclines not clearly beneficial (CHOP not better than bendamustine).
- Remissions progressively shorten.
- Chemotherapy + anti-CD20 monoclonal antibody therapy (rituximab) has had an impact on BOTH remission duration and survival.
Watch and Wait Strategy

Overall survival

Time to first therapy
Why treat follicular NHL?

- Local symptoms due to progressive or bulky nodal disease.
- Compromised organ function due to progressive or bulky disease.
- B symptoms.
- Symptomatic extranodal disease, effusions.
- Cytopenias (BM infiltration, hypersplenism).
Early Stage Follicular Lymphoma

- 24 Gy IFRT is a potentially curative approach
- 10-yr PFS/OS: 45-60%/60-80%
- Median survival 15-20 years
Bendamustine-Rituximab (B-R) vs CHOP-R

StiL NHL 1-2003

Follicular
Waldenströms
Marginal zone
Small lymphocytic
Mantle cell

Bendamustine 90 mg/m² day 1+2 + R day 1, max 6 cycles, q 4 wks.

CHOP-R, max 6 cycles, q 3 wks.
Bendamustine-R v CHOP-R
follicular lymphoma

- No difference in overall survival
- BR less toxic than CHOP-R
Mechanism of Action of Tumor Targeting mAb

Obinutuzumab-Based Immunochemotherapy in Pts With Untreated FL (GALLIUM): Background

- Standard frontline treatment for advanced, symptomatic FL is rituximab-based induction and maintenance therapy
  - Median PFS: > 6 yrs\textsuperscript{[1]}
  - Despite advances, FL remains incurable due to eventual relapse

- Obinutuzumab: novel, type II anti-CD20 monoclonal antibody
  - Phase II GAUDI study demonstrated 93% to 96% response rates when combined with CHOP or FC for pts with R/R FL\textsuperscript{[2]}
  - Phase III GADOLIN study showed prolonged PFS when combined with bendamustine vs bendamustine alone for R/R iNHL\textsuperscript{[3]}

- Current phase III GALLIUM study compared safety, efficacy of obinutuzumab-based vs rituximab-based immunochemotherapy in pts with untreated iNHL\textsuperscript{[4]}

GALLIUM: Study Design

- International, randomized, open-label phase III study

**INDUCTION**

- **Obinutuzumab‡ + CHOP, CVP, or Bendamustine§**
  - (n = 601)

- **Rituximab‡ + CHOP, CVP, or Bendamustine§**
  - (n = 601)

**MAINTENANCE**

- **CR or PR at EOI visit¶**

- **Obinutuzumab §**
  - (n = 539)

- **Rituximab‖**
  - (n = 527)

**For 2 yrs or until PD**

- **Primary endpoint:** investigator-assessed PFS in FL pts

- **Secondary endpoints:** IRC-assessed PFS (confirmatory), OS, EFS, DFS, DoR, TTNT, CR/ORR at EOI (± FDG-PET), safety


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*All data presented for pts with FL though study also enrolled MZL pts (randomized separately). †Obinutuzumab dosing: 1000 mg IV, D1, 8, 15 of cycle 1 and D1 of cycles 2-8 (Q3W) or cycles 2-6 (Q4W). ‡Rituximab dosing: 375 mg/m² IV on D1 of cycles 1-8 (Q3W) or cycles 1-6 (Q4W). §Obinutuzumab dosing: 1000 mg IV every 2 mos. ¶Rituximab dosing: 375 mg/m² IV every 2 mos. #CHOP: Q3W, 6 cycles; CVP: Q3W, 8 cycles; bendamustine: Q4W, 6 cycles. #Pts with SD at EOI followed up to 2 yrs for PD.
# GALLIUM: Baseline Characteristics (FL)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Obinutuzumab + Chemotherapy (n = 601)</th>
<th>Rituximab + Chemotherapy (n = 601)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age, yrs (range)</strong></td>
<td>60 (26-88)</td>
<td>58 (23-85)</td>
</tr>
<tr>
<td><strong>Male, %</strong></td>
<td>47.1</td>
<td>46.6</td>
</tr>
<tr>
<td><strong>Ann Arbor disease stage at diagnosis, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I/II/III/IV</td>
<td>1.7/6.9/34.8/56.7*</td>
<td>1.3/7.4/35.0/56.3†</td>
</tr>
<tr>
<td><strong>FLIPI risk group, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (0-1)/intermediate (2)/high (≥ 3)</td>
<td>21.3/37.3/41.4</td>
<td>20.8/37.1/42.1</td>
</tr>
<tr>
<td><strong>B symptoms, %</strong></td>
<td>33.4</td>
<td>34.3‡</td>
</tr>
<tr>
<td><strong>Bone marrow involvement, %</strong></td>
<td>53.7§</td>
<td>49.3*</td>
</tr>
<tr>
<td><strong>Extranodal involvement, %</strong></td>
<td>65.2</td>
<td>65.9</td>
</tr>
<tr>
<td><strong>Bulky disease (≥ 7 cm), %</strong></td>
<td>42.5‡</td>
<td>45.2‡</td>
</tr>
<tr>
<td><strong>Median time from diagnosis to randomization, mos (range)</strong></td>
<td>1.5 (0.1-121.6)‖</td>
<td>1.4 (0-168.1)</td>
</tr>
</tbody>
</table>

*n = 598. †n = 597. ‡n = 600. §n = 592. ¶n = 598, value not determined in 3 pts.

GALLIUM: Pt Disposition

- Median follow-up: 34.5 mos
- Chemotherapy use:
  - Bendamustine, n = 827
  - CHOP, n = 433
  - CVP, n = 141
- 114 pts still on maintenance
  - Obinutuzumab arm, n = 60
  - Rituximab arm, n = 54

<table>
<thead>
<tr>
<th>FL Pt Disposition At Time of Current Analysis</th>
<th>Obinutuzumab + Chemotherapy (n = 601)</th>
<th>Rituximab + Chemotherapy (n = 601)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withdraw during induction, n</td>
<td>37</td>
<td>47</td>
</tr>
<tr>
<td>- AE</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>- PD</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>- Death</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>- Other</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>Withdraw during maintenance, n</td>
<td>118</td>
<td>132</td>
</tr>
<tr>
<td>- AE</td>
<td>51</td>
<td>64</td>
</tr>
<tr>
<td>- PD</td>
<td>37</td>
<td>38</td>
</tr>
<tr>
<td>- Death</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>- Other</td>
<td>27</td>
<td>26</td>
</tr>
</tbody>
</table>
## GALLIUM: Responses (FL)

<table>
<thead>
<tr>
<th>Responses at EOI*</th>
<th>Obinutuzumab + Chemotherapy (n = 601)</th>
<th>Rituximab + Chemotherapy (n = 601)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, % (95% CI)</td>
<td>88.5 (85.7-91.0)</td>
<td>86.9 (83.9-89.5)</td>
</tr>
<tr>
<td>CR, % (95% CI)</td>
<td>19.5 (16.4-22.9)</td>
<td>23.8 (20.4-27.4)</td>
</tr>
<tr>
<td>PR, %</td>
<td>69.1</td>
<td>63.1</td>
</tr>
<tr>
<td>SD, %</td>
<td>0.5</td>
<td>1.3</td>
</tr>
<tr>
<td>PD, %</td>
<td>2.3</td>
<td>4.0</td>
</tr>
<tr>
<td>Not evaluable/missing data, %</td>
<td>4.0/4.7</td>
<td>3.5/4.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Obinutuzumab + Chemotherapy (n = 601)</th>
<th>Rituximab + Chemotherapy (n = 601)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRC-assessed PFS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Pts with event, %</td>
<td>15.5</td>
<td>20.8</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>▪ 3-yr PFS, % (95% CI)</td>
<td>81.9 (77.9-85.2)</td>
<td>77.9 (73.8-81.4)</td>
<td>0.71 (0.54-0.93)</td>
<td>.0138</td>
</tr>
<tr>
<td>TTNT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Pts with event, %</td>
<td>13.3</td>
<td>18.5</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>▪ 3-yr TTNT, % (95% CI)</td>
<td>87.1 (84.0-89.6)</td>
<td>81.2 (77.6-84.2)</td>
<td>0.68 (0.51-0.91)</td>
<td>.0094</td>
</tr>
<tr>
<td>OS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Pts with event, %</td>
<td>5.8</td>
<td>7.7</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>▪ 3-yr OS, % (95% CI)</td>
<td>94.0 (91.6-95.7)</td>
<td>92.1 (89.5-94.1)</td>
<td>0.75 (0.49-1.17)</td>
<td>.21</td>
</tr>
</tbody>
</table>
## GALLIUM: Safety (FL)

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Obinutuzumab + Chemotherapy (n = 595)</th>
<th>Rituximab + Chemotherapy (n = 597)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE, %</td>
<td>99.5</td>
<td>98.3</td>
</tr>
<tr>
<td>Grade ≥ 3 AEs occurring in ≥ 5% pts, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Neutropenia</td>
<td>43.9</td>
<td>37.9</td>
</tr>
<tr>
<td>▪ Leukopenia</td>
<td>8.6</td>
<td>8.4</td>
</tr>
<tr>
<td>▪ Febrile neutropenia</td>
<td>6.9</td>
<td>4.9</td>
</tr>
<tr>
<td>▪ IRRs</td>
<td>6.7</td>
<td>3.7</td>
</tr>
<tr>
<td>▪ Thrombocytopenia</td>
<td>6.1</td>
<td>2.7</td>
</tr>
<tr>
<td>Selected grade ≥ 3 AEs of interest, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Infections/infestations</td>
<td>20.0</td>
<td>15.6</td>
</tr>
<tr>
<td>▪ IRRs*</td>
<td>12.4</td>
<td>6.7</td>
</tr>
<tr>
<td>▪ Second neoplasms†</td>
<td>4.7</td>
<td>2.7</td>
</tr>
<tr>
<td>Serious AEs/AE leading to discontinuation/grade 5 AEs, ‡ %</td>
<td>46.1/16.3/4.0 ‡</td>
<td>39.9/14.2/3.4 ‡</td>
</tr>
<tr>
<td>Median change in IgG levels from baseline to EOI, g/L (range)</td>
<td>-1.50 (-22.3 to 6.5) ‖</td>
<td>-1.46 (-16.4 to 9.1) ‖</td>
</tr>
</tbody>
</table>

* Any AE within 24 hrs of infusion considered to be related to drug. † Starting 6 mos post treatment. ‡ Most fatal AEs occurred in pts receiving bendamustine across treatment arms. § Includes pt who died after cutoff from on-treatment AE. †n = 462. ‖n = 472.

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GALLIUM: Conclusions

- In pts with untreated, advanced FL, obinutuzumab-based immunochemotherapy and maintenance decreased the risk of disease progression or death by 34% vs rituximab-based therapy
  - Study unblinded at planned interim analysis based on IDMC recommendation
- Selected AEs of grade 3/4 were more frequent with obinutuzumab
  - Infection/infestation, cytopenias, IRRs
- A higher incidence of deaths occurred in pts who received bendamustine
- Investigators concluded that obinutuzumab-based therapy should be considered as a frontline therapy option for FL

Newly Diagnosed, Follicular Lymphoma Stage I, II (non-bulky)

XRT feasible?

YES

IFRT alone (24 Gy) (Gr 1-2)

R-CHOP x 3 cycles + IFRT (24-30 Gy) (Gr 3A/B)

Gr 1-2: R-bendamustine x 6 cycles
Gr 3A/B: R-CHOP x 6 cycles

NO

City of Hope - Standard of Care 2017
Newly Diagnosed, Advanced Stage Follicular Lymphoma (III, IV, Stage II bulky)

Treatment indicated?

NO

Observation

YES

Rituximab alone +/- maintenance

• R-bendamustine x 6 cycles
• R-CHOP +/- maintenance (Grade 3A/B)

City of Hope - Standard of Care 2017
Relapsed or Refractory Follicular Lymphoma

low risk/durable response to prior rituximab monotherapy?

NO

1. Clinical trial
   2. R-CHOP or R-bendamustine (depending on upfront tx)
   3. Lenalidomide + rituximab
   4. Idelalisib (failed 2 lines)
   5. Stem cell transplantation (refractory)

YES

Rituximab alone

Response?

NO

Consider maintenance

YES
Novel Therapies

- Molecularly targeted
  bcl-2, B-cell kinase inhibitors (syk, btk, PI3K)
- New monoclonal antibodies
  humanized, different targets (e.g. BAFF-R)
- Novel immunotherapies
  CAR/Transduced T cells
  - PD-1/PD-L1 inhibition (checkpoint blockade)
  - Therapeutic vaccines
Pidilizumab (anti-PD1) + rituximab in relapsed follicular lymphoma (FL) patients

**Rituximab**

**Pidilizumab**

- Days 17 24 31 38
- Days 1 2 3 4
- n = 30

If SD/PR/CR continue 8 more infusions every 4 wks

Days
- 1 29 57 85 113

CT/PET/BM
- 0 57 113 q3mo

Core Bx
- 0 14 113

Blood/PBMC
- 1,2 14

**Pidilizumab (CT-011)** – iv infusion at 3.0 mg/kg/cycle q4 weeks for up to 12 cycles

**Rituximab** - iv infusion at a dose of 375 mg/m² weekly for 4 weeks
Pidilizumab + Rituximab – Best response
Summary of clinical results

• Pidilizumab + Rituximab therapy is well tolerated, there were no grade/4 or autoimmune adverse events noted.

• Highly effective in relapsed, rituximab-sensitive follicular lymphoma with an ORR of 66% and CR of 52%

• Compares favorably to previous rituximab retreatment data (e.g. ORR of 40% & CR of 11% - Davis et al, J Clin Oncol 2000)

Westin et al. [Neelapu, Kwak] Lancet Oncol, 2014
Positive controlled Phase III cancer vaccine clinical trials

• Sipuleucel-T (prostate cancer) *
  *NEJM* July 2010

• gp100 peptide (melanoma)
  *NEJM* June 2011

• B-cell idiotype protein (lymphoma)
  *J Clin Oncol* July 2011

* FDA approved
Bench-to-bedside development of a homegrown therapeutic agent from an academic laboratory

**Cancer vaccine strategy**

- **Lymphoma Tumor**
  - Preclinical
    - Addition of GM-CSF Adjuvant improves vaccine potency
      
      \[(\text{Proc Natl Acad Sci 1996})\]

- **“Idiotypic” protein**

**Phase I/II Clinical Trial**

\[\text{(Nat Med 1999):}\]

- Vaccine induces molecular remissions

**Phase III Controlled Clinical Trial**

\[\text{(J Clin Oncol 2011):}\]

- Vaccine prolongs DFS in patients in a chemotherapy-induced remission (n=117, \(p=0.045\))

\[\text{CD8+}\]
Conclusions: Id protein vaccine Phase III trial

- As a controlled clinical experiment, the positive lymphoma vaccine Phase III randomized trial has scientific value for its validation of the cancer vaccine concept (improved disease-free survival in 1st remission patients)

- Additional clinical trials are needed, combining this vaccine with anti-CD20 mAb (rituximab)-containing chemotherapy regimens in the U.S.

- Peptides derived from idiotypes are the most frequently presented neoantigens by human lymphomas to T cells (Alizadeh et al, *Nature 2017*, in press)

- re-visit idiotype vaccines?
2nd generation DNA Vaccine Strategy

• Maintain or improve efficacy

• Reduce Manufacturing Time
  – For Protein Vaccines: 3-6 months
  – For DNA Vaccines: 4-5 weeks
Next generation vaccines: targeting dendritic cells with genetic fusions

Antigen Presenting Cell (APC) Receptor Targeting

Biragyn et al. [Kwak]  Nature Biotech  1999; Science 2002
Personalized identification of lymphoma-associated $V_{H/L}$ gene from patient biopsy

BM

↓

Total RNA

↓

cDNA

↓

Touch down semi-qPCR

First step

- Isolation fragment
- Clone
- Transformation
- Pick random colonies
- DNA sequencing

Second step

Determine lymphoma associated VH/VL gene

<table>
<thead>
<tr>
<th>VH</th>
<th>Vk</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARR NY WW GS Y RF DY</td>
<td>Q SY D T S NV</td>
</tr>
<tr>
<td>ARR NY WW GS Y RF DY</td>
<td>Q SY D T S NV</td>
</tr>
<tr>
<td>ARR NY WW GS Y RF DY</td>
<td>Q SY D T S NV</td>
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<tr>
<td>ARR NY WW GS Y RF DY</td>
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<td>Q SY D T S NV</td>
</tr>
<tr>
<td>ARR NY WW GS Y RF DY</td>
<td>Q SY D T S NV</td>
</tr>
</tbody>
</table>

ScFc gene synthesis

Clone into DNA vaccine plasmid

Slide courtesy of Dr. Soung-Chul Cha

Origin: National Gene Vector Laboratory (licensed to Aldevron)
Phase I Study of an Active Immunotherapy for Asymptomatic Phase Lymphoplasmacytic Lymphoma with DNA Vaccines Encoding Antigen-Chemokine Fusion (activated March 2015)

• Formulation and Administration:
  – 0.5ml intramuscular injection rotated between thighs

• Dosing Cohorts:
  – Cohort 1: 500 µg
  – Cohort 2: 2500 µg

• Schedule of Administration:
  Wk 0
  Wk 4
  Wk 8

Multiple Myeloma SPORE (P50 CA142509)
Project 2 (Neelapu/Thomas)
Neoantigen load correlates with clinical benefit to checkpoint blockade immunotherapy.

Development of other *personalized* cancer vaccines
Future directions: Cancer vaccines

- Precision medicine approaches (genetic sequencing) to generate personalized vaccines

- Additional improvements in the vaccine delivery platforms (e.g. 2nd generation idiotype DNA fusion vaccines)

- Combine lymphoma vaccines with strategies for checkpoint blockade
Toni Stephenson Lymphoma Center (TSLC): Mission/Vision

The TSLC will become recognized as an international leader in translating breakthrough scientific discoveries in lymphoma biology into world-class clinical medicine standards of excellence.

Guiding principles
• Our goal is not only to practice the standard of care (SOC), but also to invent the SOC
• Every appropriate patient should be enrolled in a biologic protocol (Opt out re: consent interview)
• Identify and leverage synergistic capabilities across both discovery research and clinical care
Toni Stephenson Lymphoma Center (TSLC) at COH

Lymphoma Disease Team Faculty

Dr. Robert Chen (co-chair)
Dr. Leslie Popplewell (co-chair)
  Dr. Jasmine Zain
  Dr. Christiane Querfeld
  Dr. Steven Rosen
  Dr. Nademanee
  Dr. Tanya Siddiqi
  Dr. Alex Herrera
  Dr. Elizabeth Budde
  Dr. Alexandra Levine

  Pathology (4)
  Radiation Oncology (1)
  Radiology (3)
  Surgery (1)
  Biostatistics (1)

Clinical Research Nurses (9)
Clinical Research Coordinators (8)
Tissue Bank Staff (2)
Lab Trainees (17)