All presenters were independently selected by the organizing committee. Those presenters who disclosed affiliations or financial interests with the commercial organizations involved with products, to which they may refer, are listed below.

- Received an honorarium from the following:
  - Novartis
  - Celgene
  - Spectrum
Goals

- This presentation will be about therapy
- What Rx are available and when?
- Low tumor burden – watch and wait or immunotherapy
- High tumor burden – chemoimmunotherapy
- Relapse
Principles for Dealing with FL

- Adequate Tissue… Adequate Diagnosis
- Age of the Patient
  - Patients who develop FL after the age of 60 have a normal life expectancy
- Comorbidities?
- Any symptoms from the lymphoma?
  - “Patients who feel normal cannot feel better with treatment”
- Any organs or risk?
- Pace of the disease
What Tools?

What therapies do you have to sequence?
Watch and Wait

- Observation
- Rituximab
- Radioimmunotherapy
High Tumor Burden

- Bendamustine/rituximab
- Lenalidomide/rituximab (R2)
- R-CHOP
Relapsed

- Salvage chemotherapy w/wo SCT
  - R-ICE/R-DHAP/Gemcitidine-Dex-Plat (GDP)
- Radioimmunotherapy
- Lenalidomide or Ibrutinib
- Novel agent
  - To be covered by Dr. de Vos
What Do You Need to Know?

Before You Start the Sequence

• You’ll know a lot in 24 months
Age Matters in FL

Maurer M et al Blood 2014;124(24):1664
Early Progression in FL


R-CHOP

R-CHOP


Rituximab maintenance

R-CHOP
EFS12 for Follicular Lymphoma

Maurer M et al Blood 2014;124(24):1664

Group that needs attention
Early Relapse of Follicular Lymphoma After Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone Defines Patients at High Risk for Death: An Analysis From the National LymphoCare Study

Carla Casulo, Michelle Byrtok, Keith L. Dawson, Xiaolei Zhou, Charles M. Farber, Christopher R. Flowers, John D. Hainsworth, Matthew J. Maurer, James R. Cerhan, Brian K. Link, Andrew D. Zelenetz, and Jonathan W. Friedberg
Early POD = Prog <2 yrs from Dx

**Graph:**
- **Survival (probability)**
- **Time From Risk-Defining Events (months)**
- **No. at risk**
  - Early POD: 110, 82, 66, 56, 50, 42, 32, 14, 3
  - Reference: 420, 408, 387, 363, 344, 253, 145, 34, 0

*J Clin Oncol. 2015 Aug 10;33(23):2516-22*
I Need Foresight

How to find out who those 20% will be?
Integration of gene mutations in risk prognostication for patients receiving first-line immunocombination therapy for follicular lymphoma: a retrospective analysis of a prospective clinical trial and validation in a population-based registry

Pastore, A et al Lancet Oncol. 2015 Aug 6
Summary so far

- At the time of diagnosis:
  - FLIPI-2 score helps
  - B2M and LDH help
  - Age helps

- After 12 or 24 months:
  - You can predict likelihood of early death

- Will m7-FLIPI help choose those 20%?

- Will you be able to do anything about it?
  - We’ll see
Treatment

It Depends….on Low vs High Burden
Old definition…still relevant
Low Tumor Burden per ECOG

- < 3 nodal masses each greater than 3 cm in diameter.
- No systemic or B symptoms from NHL
- No splenomegaly >16 cm by CT
- No risk of compression of a vital organ
  - Epidural; Ureter; SVC etc
- No leukemic phase with >5000/mm3 circulating malignant cells
- No cytopenias as defined by:
  - Hgb < 10g/dL
  - Platelet count <100,000/mm3
  - ANC <1500/mm3
Individualize management; No survival advantage for any therapy

Acceptable options are:

- Observation
- Rituximab x 4 without maintenance
  
  Based on NCCTG, Ardesheha (LO 2014) and ECOG RESORT
- Radioimmunotherapy
  
  - *J Clin Oncol* 2013 Jan 20; 31(3): 308-313
  - Br J Haematol. 2013. Epub 2013/12/19
Ibritumomab Treatment Schema

Rituximab (250 mg/m²)

Followed by $^{90}$Y IBR
(0.4 or 0.3 mCi/kg*; max dose 32 mCi)

Day 1 2 3 4 5 6 7 8

*0.4 mCi/kg in patients with a platelet count ≥150,000/µL or 0.3 mCi/kg with a platelet count 100,000–149,000/µL.
Advantages of Radioimmunotherapy

- All treatment completed in 1 week (1 day) and 1 dose
- Outpatient - minimal loss of work
- No hair loss - others will not know the patient was treated
  - Only significant side effect is reversible myelosuppression
- Targeted therapy - treats the lymphoma but leaves normal organs alone
- Very good for extranodal sites; no collateral damage
- High response rate
- Usually given once; however, it can be repeated
$^{131}$I-Tositumomab Initial Treatment Trial

- 76 untreated pts follicular NHL stages III/IV
- Single dose of $^{131}$I-tositumomab (Bexxar) calculated to deliver 75 cGy to the whole body
- 95% overall response rate; 75% CR
- 59% were progression-free at 5 years
- Median PFS was 6.1 years
  - Median follow-up is 5 years

Progression-free and Overall Survival for All Patients

High Burden

- Patients who meet GELF criteria
- FLIPI-2 = 3-5 risk factors
- Rituximab/chemotherapy
  - R-CVP x 6
  - R-CHOP x 6
  - R-bendamustine x 4 – 6
- Protocol treatment – no current national trial
  - E2408 completed; BR based with 2 years of R-maintenance
Figure 3  Progression-free survival in histological subtypes of follicular lymphoma (A), mantle-cell lymphoma (B), marginal-zone lymphoma (C), and Waldenstrom’s macroglobulinaemia (D)  B-R=bendamustine plus rituximab. R-CHOP=CHOP plus rituximab.
Overall survival

Lancet 2013, online http://dx.doi.org/10.1016/S0140-6736(12)61763-2
ECOG 2408

Schema

Step 1 - INDUCTION

Arm A - BR treatment
Rituximab IV 375 mg/m² Day1
Bendamustine IV 90 mg/m² Day1 & 2
x 6 cycles

Arm B - BVR treatment
Bortezomib IV 1.3mg/m² Days 1,4,8,11
Rituximab IV 375 mg/m² Day1
Bendamustine IV 90 mg/m² Days 1 & 4
x 6 cycles

Arm C - BR treatment
Rituximab IV 375 mg/m² Day1
Bendamustine IV 90 mg/m² Day1 & 2
x 6 cycles

Step 2 - CONTINUATION

Arm D - Rituximab
Odd Cycles (1,3,5,...,23) - no Rituximab treatment
Even Cycles (2,4,6,...,24): Rituximab IV 375 mg/m² Day1

Arm E - Rituximab
Odd Cycles (1,3,5,...,23) - no Rituximab treatment
Even Cycles (2,4,6,...,24): Rituximab IV 375 mg/m² Day1

Arm F - Lenalidomide and Rituximab
Cycles 1-13: Lenalidomide 20 mg po Days 1-21
Odd Cycles (1,3,5,...,23) - no Rituximab treatment
Even Cycles (2,4,6,...,24): Rituximab IV 375 mg/m² Day1

Stratification
High Risk
Follicular Lymphoma (FLIP 1 score 3-5 OR GELF high tumor burden)

Randomization
1. FLIP 1 STATUS
   - Score 1-2*
   - Score 3
   - Score 4-5
2. GELF Criteria
   - Low tumor burden**
   - High tumor burden

Accrual goal = 250 total patients
Cycle length is 28 days (4 weeks)
*Requires High tumor burden per GELF criteria (see section 3)
**Requires FLIP 1 Status of 3 or higher (per FLIP 1 criteria)

286 enrolled; closed
R²-Lenalidomide/Rituximab

- Upfront therapy; Phase II; Single-Institution
- **Lenalidomide 20 mg days 1-21 q 28**
- **Rituximab 375 mg/m² each cycle**
- 6 cycles; response assessment; optional 12 total
  - No rituximab maintenance
- 110 patients enrolled over 3 years (2008-11)
  - *Follicular lymphoma* – 50
  - Marginal zone – 30
  - SLL - 30

*Fowler et al Lancet Oncol. 2014;15(12):1311-8*
R²-Lenalidomide/Rituximab

- **All patients**
  - ORR 90% (93/103 evaluable)
  - CR 63% (65/103) and PR 27% (28/103)

- **Follicular patients**
  - ORR 98% (45/46 evaluable)
  - CR 87% (40/46) and PR 11% (5/46)

*Fowler et al Lancet Oncol. 2014;15(12):1311-8*
### Table 1: Baseline clinical characteristics of patients with indolent non-Hodgkin lymphomas

<table>
<thead>
<tr>
<th></th>
<th>Follicular lymphoma (n=50)</th>
<th>Marginal zone lymphoma (n=30)</th>
<th>Small lymphocytic lymphoma (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years; median, range)</td>
<td>56 (35-84)</td>
<td>59 (36-77)</td>
<td>59 (34-76)</td>
</tr>
<tr>
<td>Sex, female</td>
<td>22 (44%)</td>
<td>18 (60%)</td>
<td>12 (40%)</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>23 (46%)</td>
<td>9 (30%)</td>
<td>0</td>
</tr>
<tr>
<td>IV</td>
<td>27 (54%)</td>
<td>21 (70%)</td>
<td>30 (100%)</td>
</tr>
<tr>
<td>High tumour burden (as per GELF)</td>
<td>27 (54%)</td>
<td>13 (43%)</td>
<td>14 (47%)</td>
</tr>
<tr>
<td>FLIPI score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>11 (22%)</td>
<td>..</td>
<td>..</td>
</tr>
<tr>
<td>2</td>
<td>25 (50%)</td>
<td>..</td>
<td>..</td>
</tr>
<tr>
<td>3-5</td>
<td>14 (28%)</td>
<td>..</td>
<td>..</td>
</tr>
</tbody>
</table>

Data are number (%), unless otherwise indicated. GELF=Groupe d’Etudes des Lymphomes Folliculaires. FLIPI=Follicular Lymphoma International Prognostic Index.
R²-Lenalidomide/Rituximab

Arms

Experimental: Lenalidomide + Rituximab

- Lenalidomide dose 20-mg on days 2-22 every 28 days for 6 cycles, if CR then 10-mg on days 2-22 every 28 days for 12 cycles. PR after 6 cycles, continue 20 mg for 3~6 cycles and then 10 mg on days 2-22 every 28-day cycles for up to 18 cycles.
- Rituximab, 375 mg/m2 on days 1, 8, 15 and 22 of cycle 1, day 1 of cycles 2 to 6; 8 weeks later responding patients continue with 375 mg/m2 rituximab every 8 weeks for 12 cycles.

Active Comparator: Control

- ONE of the following: Rituximab-CHOP, Rituximab-CVP, Rituximab-Bendamustine. 7 to 8 weeks later responding patients will continue with 375 mg/m2 rituximab every 8 weeks for 12 cycles.
Questions

- Answered questions
  - R-chemo is the standard for pts needing chemoRx
  - BR as good or better than RCHOP without OS benefit
  - Rituximab maintenance x 2 years as consolidation (per PRIMA) or RIT (per FIT) are FDA approved options but do not impact survival and are waning

- Unanswered questions
  - Is R2 maintenance better than R? – E2408
  - Can upfront RIT “cure” some patients? LS138D
  - Can R2 beat chemoimmunotherapy? RELEVANCE
Relapsed

- Salvage chemotherapy w/wo SCT
  - R-ICE/R-DHAP/Gemcitidine-Dex-Plat (GDP)
- Radioimmunotherapy
- Lenalidomide or Ibrutinib
- Novel agent
  - To be covered by Dr. de Vos
Follicular Lymphoma Relapse

**Aggressive Relapse**
- High bulk
- Symptoms
- TTP <6 months
- Transformed
- High LDH

↓
Salvage chemoRx

↓
Auto SCT

↓
Inadequate response or Relapse

↓
Allo SCT

**Indolent Relapse**
- Low bulk
- No symptoms
- Long TTP
- No transformation
- Normal LDH

↓
- Radioimmunotherapy
- Repeat chemoRx
- New chemotherapy
- Rituximab w/wo maintenance

**Auto SCT**
Inadequate response or Relapse

**Allo SCT**
Other Options?

New Drugs….New Targets
New Protocols

- Idelalisib
- Ibrutinib
- Vaccine
- Lenalidomide (BRR)
- Anti-PD1
Summary

- Know your patient
- Don’t overtreat
- RIT is an important niche agent for the early pt or first relapse
- EFS12/24; m7FLIPI are important new markers
- New trials will use these and molecular markers at diagnosis to try and cull out the 20% pts with an adverse prognosis
  - But will different Rx bring better results?