Overview Of European Clinical Trials In Follicular B-cell Lymphoma

SWG-EHA, Milan, June 12, 2014

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Follicular Lymphoma Treatment
First line

Staging evaluation

Localized
radiotherapy

Advanced indolent
W&W Rituximab

Advanced with symptoms
R-chemo
No Clear European Consensus To Define “Advanced FL With Symptoms”? 

<table>
<thead>
<tr>
<th>GELA criteria</th>
<th>BNLI criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ High tumor bulk defined by either:</td>
<td></td>
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<tr>
<td>- a tumor &gt; 7 cm</td>
<td></td>
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<tr>
<td>- 3 nodes in 3 distinct areas each &gt; 3 cm</td>
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<tr>
<td>- symptomatic splenic enlargement</td>
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<tr>
<td>- organ compression</td>
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<tr>
<td>- ascites or pleural effusion</td>
<td></td>
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<tr>
<td>✓ Presence of systemic symptoms</td>
<td></td>
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<tr>
<td>✓ Serum LDH or β2-microglobulin above normal values</td>
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<tr>
<td>✓ Rapid disease progression in the preceding 3 months</td>
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<tr>
<td>✓ Life threatening organ involvement</td>
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<tr>
<td>✓ Renal or liver infiltration</td>
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<tr>
<td>✓ Bone lesions</td>
<td></td>
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<tr>
<td>✓ Systemic symptoms or pruritus</td>
<td></td>
</tr>
<tr>
<td>✓ Hb&lt;10 g/dL or WBC&lt; 3.0×10⁹/L or Plat.&lt;100×10⁹/L ; related to marrow involvement</td>
<td></td>
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</tbody>
</table>
Proportion of patients with no new treatment initiated

% not requiring Rx at 3yr
- W+W=48%
- R4=80%
- R4+RM=91%

HR (Rituximab vs W+W) = 0.37, 95%CI = 0.25, 0.56, p<0.001
HR (Rituximab + M vs W+W) = 0.20, 95% CI = 0.13, 0.29, p<0.001
HR (Rituximab + M vs Rituximab) = 0.57, 95% CI = 0.29, 1.12, p=0.10
FLIRT Trial (advanced but asymptomatic)

SC route could improve anti-lymphoma immunity

Control arm

Experimental arm

Endpoint: PFS
Hypothesis: Control arm: median 23.5 m vs median 45 month in experimental arm:
Number of patients: 210
First patient: Q1-Q2 2014
Ancillary studies

- *FCGRT* and FcRn
- Rituximab PK and variability
- Immunity against FL Ag
- Prognostic value of t(14;18)
Conventional Treatment Options
In Advanced FL With Symptoms

6 – 8 x
R-CVP or R-CHOP
(or R-BENDA)

Consolidation with
ASCT is not a standard
anymore

Maintenance with
rituximab
PRIMA study

Consolidate with
RIT ?
FIT, SWOG study
Primary endpoint (PFS): 36 months follow-up

Stratified HR = 0.55
95% CI: 0.44–0.68
p < 0.0001

Rituximab maintenance

Observation

Event-free rate

Time (months)

Patients at risk

Salles et al., Lancet 2011
First-line R-CVP versus R-CHOP induction therapy and maintenance rituximab for indolent lymphoma

A multicenter phase III randomized study PLRG-4 by the Polish Lymphoma Research Group

Research grant from Roche Polska Ltd. [ML 19931]

ClinicalTrials.gov: NCT 00801281
PLRG-4 study design

Diagnosis of FL, MZL, SLL, LP L → Indication for treatment → Randomization → Induction

- R-CVP
- R-CHOP

Response assessment:
- CR
- PR
- NC
- PD

Off protocol

Maintenance

- R q 2 m x 12
- F/U 36 m

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>EFS – time to event: PD, relapse, change of therapy, patient withdrawal (SAE), patient refusal, death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statistical considerations</td>
<td>Assumed $\Delta$ median EFS 18 (30 vs. 48) m. 147 events needed to provide 80% power for two-sided log rank-test to detect a difference at 0.05 level of significance. Interim analyses planned after 37, 74 and 111 events. N = 250 patients.</td>
</tr>
</tbody>
</table>
## Patient outcome

<table>
<thead>
<tr>
<th></th>
<th>R-CHOP</th>
<th>R-CVP</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluable for response</td>
<td>105</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>41%</td>
<td>37%</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>52%</td>
<td>60%</td>
<td>NS</td>
</tr>
<tr>
<td>ORR</td>
<td>93%</td>
<td>97%</td>
<td></td>
</tr>
<tr>
<td>Evaluable for EFS</td>
<td>121</td>
<td>118</td>
<td></td>
</tr>
<tr>
<td>Median FU (95% C.I.)</td>
<td>38 (35, 42) months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-yr EFS (95% C.I.)</td>
<td>69% (59%, 76%)</td>
<td>65% (55%, 73%)</td>
<td>0.3</td>
</tr>
<tr>
<td>3 yr OS (95% C.I.)</td>
<td>92% (86%, 96%)</td>
<td>96% (90%, 98%)</td>
<td>0.6</td>
</tr>
</tbody>
</table>
Median follow up 38 (95% C.I. 35, 42) months

74 events of 147 needed
Bendamustine-Rituximab + 2 vs 4 yrs Rituximab

StiL NHL 7-2008 - MAINTAIN

Follicular Lymphoma → R

Bendamustine-Rituximab
+ 2 years Rituximab
q 2 months

Bendamustine-Rituximab
+ 4 years Rituximab
q 2 months

n = 611
FOLL12 study: A phase III multicenter, randomized study comparing standard treatment with rituximab maintenance versus response adapted post-induction treatment as first line treatment in advanced follicular lymphoma.
Primary objective

Evaluate whether a PET and MRD response-based maintenance therapy is more effective in terms of PFS than a standard maintenance therapy with R in patients with untreated, advanced FL.
56 sites authorized

109 patients

101 randomized

53 standard arm

48 experimental arm

5 screening

3 screening failure
Brief induction chemoimmunotherapy with Rituximab + Bendamustine + Mitoxantrone followed by Rituximab in elderly (65-80) patients with advanced stage previously untreated follicular lymphoma. PI Carola Boccomini

Vitolo et al, EHA 2013, oral
chemotherapy-free front-line treatment of follicular lymphoma: the SAKK trials

The Swiss Oncology Research Network
Study design SAKK 35/03

Stratification
- Untreated/pretreated
- Bulky disease
- Center

Registration

Induction
375 mg/m² weekly x 4
PR, CR

PD, SD
off study

R

Short-term maintenance
375 mg/m² every 2 months x 4

Long-term maintenance
375 mg/m² every 2 months for a maximum of 5 years or until progression, relapse or unacceptable toxicity

C. Taverna et al. ASH 2013
Event-Free Survival

Median (95% CI)  3.4 (2.1, 5.3) versus 5.3 (3.5, NA) years
p=0.14
Progression-Free Survival

Median (95% CI) \(3.5 (2.1, 5.9)\) versus \(7.4 (5.1, \text{NA})\) years

HR = 0.63 (0.41, 0.99), \(p=0.04\)

Long-term rituximab maintenance doubled the median PFS without increased undue toxicity.
EFS: retrospectively defined analysis

Only patients at risk after 8 months from randomization

<table>
<thead>
<tr>
<th>Time from 8 months after randomization (years)</th>
<th># at risk Short-term</th>
<th># at risk Long-term</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>77</td>
<td>69</td>
</tr>
<tr>
<td>1</td>
<td>55</td>
<td>55</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>53</td>
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<tr>
<td>3</td>
<td>32</td>
<td>48</td>
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<td>4</td>
<td>27</td>
<td>44</td>
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<td>5</td>
<td>17</td>
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<td>6</td>
<td>11</td>
<td>11</td>
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<tr>
<td>7</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
<td>2</td>
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</table>

Median (95% CI) 2.9 (1.8, 4.8) versus 7.1 (4.4, NA) years

p=0.004
Conclusions

• EFS, the primary endpoint was not met, which is mainly due to the unexpected early separation of the survival curves.

• Long-term rituximab maintenance significantly improved PFS without leading to increased undue toxicity.

• A retrospectively defined analysis considering only EFS events from the time when treatment was different in the 2 arms, shows a statistically significant increase in EFS with long-term maintenance.

• OS was similar in both arms.
How to improve on current results in FL?

Optimizing the mAb itself
- ↑ Affinity
- ↑ PCD
- Target a different epitope
- ↑ ADCC
- ↑ CDC
- FcRn Conjugates

Stimulating immune effector cells
- Mφ
- NK
- T

Optimization of Rituximab’s efficacy
GALLIUM (BO21223) Phase III: Study design

Previously untreated advanced indolent NHL (n=1400)

<table>
<thead>
<tr>
<th>GA101 1000 mg + chemotherapy* (n=700)</th>
<th>Maintenance GA101 q2m x 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab 375 mg/m² + chemotherapy* (n=700)</td>
<td>CR/PR</td>
</tr>
</tbody>
</table>

| Maintenance rituximab q2m x 2 years |

*FL: Each site to choose 1 of 3 chemotherapy regimens (CHOP, CVP, or bendamustine) which will then be administered to all patients
Non-FL: CHOP, CVP, or bendamustine selected on a patient-by-patient basis

Phase III

Open label study with induction and 2 years maintenance therapy
- Primary Endpoint: PFS; HR 0.74; ↑ median PFS from 72m to 97m
- Secondary Endpoints: OS, EFS, ORR, CR, TNLT, safety and other
- One futility analysis based on 33% PFS events; one IA based on 67% of PFS events
- 1200 patients from 250 sites, study duration approx. 6.1 years from FPI to final clinical data cutoff
- 200 additional patients with MZL, MALT, or SMZL
- Fully recruited

www.clinicaltrials.gov; NCT01332968
How to improve on current results in FL?

Stimulating immune effector cells

- Mφ
- NK
- T

Non-specific immune stimulation
- IMIDs: Lenalidomide
- Cytokines: IL2, IL12, IL21, IFNα, G-CSF, GM-CSF

Targeted-therapies
- DC: TLR9-agonists (CpG)
- Macrophages: Anti-CD47
- γδ T cells: BrHPP
- NK cells: - Anti-KIR
  - Anti-CD137
The “RELEVANCE” Trial

1st line FL N=1000

- **R**
- **R-Chemo**
- **R \(^2\)**

- CR, CRu, PR
- CR, CRu, PR
- CR, CRu, PR

**R \(^2\) maintenance**

(lenalidomide 1 yr + rituximab 2 yrs)

- **R \(2\) Regimen:**
  - **Rituximab** weekly x 4, then day 1 of each cycle 2 to cycle 6, 8 weeks later responding patients continue every 8 weeks for 12 cycles
  - **Lenalidomide** 20 mg x 6 cycles
    - CR-10 mg lenalidomide 10 mg for 12 cycles
    - PR- 20 mg lenalidomide 3-6 months then, 10 mg \(\leq 18\) cycle

**R-Chemo**

- Investigator choice of R-CHOP, R-CVP, or R-B

**Eligibility:**

- Patients who need treatment (GELF criteria)

**Stratification:**

- FLIPI (0-1 v 2 v 3-5), Age (\(>60\) v \(\leq 60\)), diameter of largest node (\(>6\) v \(\leq 6\) cm)

**Endpoints:**

- PFS, CR/CRu? At 30 months

**R \(^2\) maintenance**

(2 yrs)

6 mos. 

24 mos.
An open-label, multicentre, randomized, phase II study to compare the efficacy of \( R^2 \) (Rituximab+Revlimid) vs Rituximab to previously untreated patients with FL in need of therapy

Chairs: Emanuele Zucca
Eva Kimby
SAKK-Nordic 35/10 – Study Design
untreated FL in need of therapy

Arm A

1:1 Randomization

Rituximab 375mg/m²

Wks. -2 -1 1 3 5 7 9 11 13 16 22-24

No CR/PR (> 25% decrease of SPD)

Follow up

Second restaging

Final restaging

> 25% decrease of SPD

Arm B

Rituximab 375mg/m²

Lenalidomide daily

2 wks pre-phase

2 wks post-phase

Stratification factors:
grade 1/2 versus 3a
bulky disease versus no bulk
FLIPI score 1+2 versus ≥3
Center

Chair
Emanuele Zucca
Eva Kimby

Only FU
SAKK-Nordic 35/10 – untreated FL in need of therapy

Study Design
The calculation of the sample size was based on complete response (CR) rate at week 23 (primary endpoint). With 10% significance level (one-sided) and a power of 90% for the Z-test with unequal variance, based on a Rituximab monotherapy (control) CR rate of 50% and a Rituximab + Lenalidomide (experimental) CR rate of 70%, 76 evaluable patients per treatment arm were required. Therefore a total of 152 patients were needed.

Accrual completed in Q4 2013
Next SAKK-Nordic 35/10 trial for untreated FL in need of therapy

- Rituximab alone

\textit{vs}

- Rituximab-Ibrutinib
Trials in relapsed/refractory follicular lymphoma
A PHASE III MULTICENTER, RANDOMIZED STUDY COMPARING CONSOLIDATION WITH \textit{^{90}Yttrium}\textsuperscript{-}LABELED IBRITUMOMAB TIUXETAN (ZEVALIN\textsuperscript{®}) RADIOIMMUNOTHERAPY VS AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) IN PATIENTS WITH RELAPSED FOLLICULAR LYMPHOMA (FL) AGED 18-65 YEARS

3x R-chemo regimens

\[ CR, PR \]

Randomization

ARAC with R in vivo purging\hfill ARA-C with R in vivo purging

consolidation with RIT\hfill consolidation with ASCT (BEAM)

\[ R \text{ maintenance} \quad R \text{ maintenance} \]
A randomized phase III multicenter trial assessing efficacy and toxicity of a combination of rituximab and lenalidomide (R2) vs rituximab alone as maintenance after chemoimmunotherapy with rituximab-bendamustine for relapsed/refractory FL patients not eligible for autologous transplantation

**Primary Objective**
To evaluate in patients responsive to induction whether the R2-MANT program may improve PFS compared to patients treated with R-MANT
Relapsed FL not eligible for ASCT: Renoir study. PI Barbara Botto

PCR analysis for Bcl-2 rearrangement on PB/BM

REALPSED/REFRACTORY
FOLLICULAR LYMPHOMA
NEED TO THERAPY

R-Bendamustine x 4 once a month
Rituximab 375 mg/m² day 0 or 1 (day 8 on cycle 1)
Bendamustine 90 mg/m² iv days 1-2

Restaging and PCR analysis for Bcl-2 rearrangement on PB/BM

CR/PR

NR

OFF

Random

R2
Rituximab 375 mg/m² day 1 q 90 days (8 cycles for 2 years)
Lenalidomide (10 mg dd 1-21 q 28) (24 cycles for 2 years)

R alone

Rituximab 375 mg/m² day 1 q 90 days (8 cycles for 2 years)

Clinical and molecular follow-up
months 12, 18, 24 and 30 (end of study)
GALEN (GA101+lenalidomide) – Phase Ib/II

**Phase Ib**
- FL (n=20)
  - GA101 (1000 mg) x 8 + lenalidomide (10, 15, 20, or 25mg q21d)

**Phase II**
- FL (n=90)
  - GA101 (1000 mg) x 8 + lenalidomide RD
  - GA101 q2m x 2 years + lenamidomide 1 year
- R/R CD20+ NHL
  - GA101 (1000 mg) x 8 + lenalidomide RD
  - GA101 q2m x 2 years + lenamidomide 1 year
- anNHL (n=88)
  - GA101 (1000 mg) x 8 + lenalidomide RD
  - GA101 q2m x 2 years + lenamidomide 1 year
ReBeL trial: HOVON 110

a randomized phase I/II trial of lenalidomide and rituximab with or without bendamustine in patients with relapsed FL
## LBR dose escalation phase 1

### 3+3 design

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Lenalidomide mg</th>
<th>Bendamustine mg/m²</th>
<th>Rituximab mg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10 mg D3-21</td>
<td>70 mg/m² d1,2</td>
<td>375 d1</td>
</tr>
<tr>
<td>2</td>
<td>15 mg D3-21</td>
<td>70 mg/m² d1,2</td>
<td>375 d1</td>
</tr>
<tr>
<td>3</td>
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</tr>
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<td>4</td>
<td>20 mg D3-21</td>
<td>90 mg/m² d1,2</td>
<td>375 d1</td>
</tr>
</tbody>
</table>
lenalidomide rituximab

lenalidomide bendamustine rituximab

lenalidomide rituximab

lenalidomide bendamustine rituximab

rituximab maintenance

FL ≥18 max 3 prior regimens

SD/PR/CR

PR/CR

Part 2
n=150

Cycle 1-3

Cycle 4-6
New treatment targeted modalities

1 - Antibodies

- New targets: anti CD19, anti CD22, CD79, CD37, PD1, PDL1...

- New ADC or radioconjugates: MMAE (CD79,CD22), Lutetium (anti CD37)...

- Combinations
New treatment targeted modalities

2- Targets of signaling pathways

BCR signature:
- SYK: fostamatinib, GS?
- PI3K: idelalisib, Bay 86-6946, IPI-145
- PKC-β: sotrastaurine
- BTK: ibrutinib
- mTOR: everolimus

Apoptosis:
- BH3 mimetic: ABT-199

Epigenetic:
- HDACinh: Abexinostat

Efficacy tests

ASSOCIATIONS
THANK YOU!