Results of E4402 (RESORT): A Randomized Phase III Study Comparing Two Different Rituximab Dosing Strategies for Low Tumor Burden Indolent B-Cell Lymphoma

Michael Williams, Fangxin Hong, Brad Kahl, Randy Gascoyne, Lynne Wagner, John Krauss, Sandra Horning
Is Watch & Wait, until high tumor burden develops, the best strategy in the rituximab era?

- Single agent R is active and well tolerated in frontline CLL/SLL
  - Hainsworth et al, J Clin Oncol 2003
- Single agent R is active and well tolerated in frontline low tumor burden Follicular Lymphoma
  - Colombat et al, Blood 2001

Can rituximab provide a low-risk treatment strategy which could delay the time to first chemotherapy?
Hypothesis:
- After initial rituximab therapy, extended scheduled dosing (Maintenance Rituximab - MR) will prolong disease control compared to retreatment dosing administered upon disease progression (Rituximab Retreatment - RR)

Study rationale:
- Previously untreated, low tumor burden, indolent B-cell lymphoma is an ideal patient population to test this hypothesis

Primary endpoint:
- Time to Treatment (Rituximab) Failure
ECOG 4402 (RESORT): A phase III randomized trial of rituximab in patients with low-tumor burden indolent NHL

**Induction**

- **Rituximab**
  - 375 mg/m² q wk × 4

**Randomize**

- Restage, wk 12

- CR or PR

**Maintenance**

- **Rituximab**
  - 375 mg/m² q 3 mo

**Rituximab Retreatment at progression**

- 375 mg/m² q wk × 4

*Continue until treatment failure: (exam q 3 mo, CT q 6 mo)*

- No response to retreatment, or disease progression within 6 mo of R
- Initiation of cytotoxic therapy, or inability to complete therapy
E4402 Major Eligibility

- **Indolent NHL**
  - Follicular grade 1 or 2
  - Small Lymphocytic
  - MALT
  - Marginal Zone nodal
  - Marginal Zone splenic

- **No prior lymphoma therapy**

- **Stage III or IV disease**

- **Measurable disease**

- **Low tumor burden as defined by GELF**
  - No tumor mass $\geq 7\text{cm}$
  - Fewer than 3 nodal masses $> 3\text{ cm}$
  - No system symptoms or B symptoms
  - No splenomegaly greater than $16\text{ cm}$ by CT scan
  - No risk of organ compression
  - No leukemic phase
  - No cytopenias
E4402 (RESORT) Objectives

- **Primary**
  - To compare the Time to Treatment Failure (TTF) between the MR and the RR arms

- **Secondary**
  - To compare time to first cytotoxic therapy (chemotherapy or radiation therapy) between the MR and the RR arms
  - To compare QOL between the arms
  - To compare toxicities between arms
E4402 (RESORT) Statistical Considerations

- 81% power to detect 36% reduction in the TTF hazard rate in FL patients
  - Type I error 5% (two sided)
- Required 270 randomized FL patients
- The study included non-FL patients
- Stratification factors
  - Age (< 60 vs ≥ 60)
  - Time from diagnosis (< 1 year vs ≥ 1 year)
- DMC recommended release of study results at a planned interim analysis in Sept 2011
**E4402 (RESORT) Results**

- Activated Nov 2003 – Closed to accrual Sep 2008
- 384 Follicular lymphoma
  - Kahl et al, ASH 2011; ASCO/ASH Joint Session 2012
- 129 non-Follicular lymphoma
  - 55 Small lymphocytic (SLL)
  - 71 Marginal zone (MZL)
  - 3 Other
- 50 (39%) of non-FL responded to Induction rituximab
  - 21 assigned to Retreatment Rituximab (RR)
  - 29 assigned to Maintenance Rituximab (MR)
E4402 RESORT Trial: Response to Induction Rituximab by lymphoma subtype

<table>
<thead>
<tr>
<th></th>
<th>SLL</th>
<th>Splenic MZL</th>
<th>Extranodal MZL</th>
<th>Nodal MZL</th>
<th>Other B-cell</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>55</td>
<td>5</td>
<td>38</td>
<td>28</td>
<td>3</td>
<td>129</td>
</tr>
<tr>
<td>ORR</td>
<td>12 (22%)</td>
<td>5 (100%)</td>
<td>14 (37%)</td>
<td>17 (61%)</td>
<td>2 (66%)</td>
<td>50 (39%)^1</td>
</tr>
<tr>
<td>CR/CRu</td>
<td>0</td>
<td>2</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>9 (7%)</td>
</tr>
<tr>
<td>PR</td>
<td>12</td>
<td>3</td>
<td>9</td>
<td>16</td>
<td>1</td>
<td>41 (32%)</td>
</tr>
<tr>
<td>SD</td>
<td>40</td>
<td>0</td>
<td>19</td>
<td>11</td>
<td>1</td>
<td>71 (59%)</td>
</tr>
<tr>
<td>PD</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>3 (2%)</td>
</tr>
</tbody>
</table>

^1 ORR in FL = 70% (p < .001)
Baseline Characteristics at Randomization

<table>
<thead>
<tr>
<th></th>
<th>RR (N=21)</th>
<th>MR (N=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>63 (47-86)</td>
<td>65 (39-85)</td>
</tr>
<tr>
<td><strong>Gender (M/F)</strong></td>
<td>32/68%</td>
<td>52/48%</td>
</tr>
<tr>
<td><strong>PS (0/1)</strong></td>
<td>86/14%</td>
<td>93/7%</td>
</tr>
<tr>
<td><strong>Stage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• III</td>
<td>27%</td>
<td>24%</td>
</tr>
<tr>
<td>• IV</td>
<td>73%</td>
<td>76%</td>
</tr>
<tr>
<td><strong>B2M elevated</strong></td>
<td>64%</td>
<td>69%</td>
</tr>
</tbody>
</table>
### Disease status at randomization

<table>
<thead>
<tr>
<th></th>
<th>RR (N=21)</th>
<th>MR (N=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/CRu</td>
<td>19%</td>
<td>17%</td>
</tr>
<tr>
<td>PR</td>
<td>81%</td>
<td>83%</td>
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</tbody>
</table>

Median follow up for time to event data: 4.3 years
Primary Endpoint: Time to Treatment Failure

HR = 4.77, 95% CI, (1.78, 12.79)
## Breakdown of Treatment Failure by Type

<table>
<thead>
<tr>
<th>Failure Type</th>
<th>RR</th>
<th>MR</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No response to R retreatment</td>
<td>2</td>
<td>NA</td>
<td>2</td>
</tr>
<tr>
<td>Disease progression &lt;6mo</td>
<td>5</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Alternative therapy</td>
<td>5</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Adverse event</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Complicating disease</td>
<td>1</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Patient withdrawal</td>
<td>3</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>16</td>
<td>15</td>
<td>31</td>
</tr>
</tbody>
</table>
Time to First Cytotoxic Therapy

Two-sided Log-rank p=0.002

- Retreatment
- Maintenance
## Treatment Information

- Analysis of # doses rituximab received, including the 4 induction doses

<table>
<thead>
<tr>
<th></th>
<th>Min</th>
<th>Max</th>
<th>Median</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR (n = 21)</td>
<td>4</td>
<td>12</td>
<td>4</td>
<td>6.0</td>
</tr>
<tr>
<td>MR (n = 29)</td>
<td>5</td>
<td>30</td>
<td>17</td>
<td>17.6</td>
</tr>
</tbody>
</table>
Toxicity

- **Second malignancies**
  - 4 in RR arm
  - 2 in MR arm (1 basal cell cancer)
  - 6 (2 basal cell) among the non-randomized pts who received Rx x 4 only

- **Two Grade 4 toxicities in MR arm**
  - Encephalopathy
  - Neutropenia

- **Deaths**
  - None
RESORT: Different Outcomes Observed for Follicular versus non-Follicular Subtypes

- Higher response rates to R x 4 induction in FL vs non-FL
  - CR/PR = 70% vs 39% (p < .001)
    - ORR for non-FL: MZL = 51% vs SLL = 22%

- No TTF benefit was observed with MR in FL vs a significant benefit in non-FL

- A time to cytotoxic chemotherapy benefit was observed for MR in both FL and non-FL subtypes, with a greater difference for the non-FL

* Kahl et al, ASH 2011 Late-Breaking Abstract #6; ASCO/ASH Joint Session, 2012
Time to Treatment Failure: *Follicular Lymphoma vs Non-FL Subtypes*

Kahl et al, ASH 2011 LBA #6; ASCO/ASH Joint Session 2012
Time to First Cytotoxic Therapy: Follicular Lymphoma vs Non FL Subtypes

Kahl et al, ASH 2011 LBA #6; ASCO/ASH Joint Session 2012
In this study of previously untreated, low tumor burden non-Follicular indolent B-cell lymphoma patients who achieved CR or PR to Rituximab x 4:

- Maintenance rituximab was superior to retreatment rituximab for the primary endpoint of time to treatment failure

- MR was also superior to RR for time to cytotoxic therapy
  - At 3 years, no MR patient (vs 30% of RR) had received cytotoxic therapy
  - MR patients received 3 x more R doses than RR
Conclusions

- If opting for Rituximab monotherapy in low-tumor burden indolent B-cell lymphoma patients:

  - Follicular lymphoma
    - Rituximab Retreatment is our recommended strategy in responding patients*

  - Non-Follicular indolent lymphoma
    - Maintenance Rituximab is an acceptable strategy in responding patients, although larger studies of the non-FL subtypes will be needed to verify these results

* Kahl et al, ASH 2011 Late-Breaking Abstract #6; ASCO/ASH Joint Session, 2012
Future Directions

- Continuing to follow for endpoints of
  - Overall survival
  - Risk for transformation

- In depth quality of life analysis

- Biomarker analysis
  - PKs
  - Fc Receptor polymorphisms
  - Microenvironment analysis via TMAs
  - Gene expression profiling
Acknowledgements

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- Co-investigators
- Patients