Richter syndrome: pathogenesis and management

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Conflict of Interest Disclosure

I hereby declare the following potential conflicts of interest concerning my presentation:

• Consultancy: Hoffmann-La Roche, Celgene, Janssen, Gilead, Morphosys, Abbvie
• Research Funding: Hoffmann-La Roche, Celgene, Janssen, Gilead, Morphosys, Abbvie
• Honoraria: Hoffmann-La Roche, Celgene, Janssen, Gilead, Morphosys, Abbvie
• Patents and Royalties: none
• Membership on an Entity’s Board of Directors or Advisory Committees: none
• Discussion of off-label drug use: ibrutinib, pembrolizumab, venetoclax
Cumulative incidence of RS

Transformation of CLL to DLBCL

- Black line: from diagnosis (n=1641)
- Red dotted line: from first treatment (n=567)

0.5% per year of observation

Parikh et al Br J Haematol 2013
Diagnosis of RT

• When to suspect RT?
  ▪ Rapid growth of lymph nodes
  ▪ Rapid clinical deterioration
  ▪ Fever in the absence of infection
  ▪ Rising LDH

• Diagnostic test – PET scan
Survival by SUV_{max}

<table>
<thead>
<tr>
<th>Total</th>
<th>Died</th>
</tr>
</thead>
<tbody>
<tr>
<td>216</td>
<td>95</td>
</tr>
<tr>
<td>116</td>
<td>90</td>
</tr>
</tbody>
</table>

\[ p < 0.0001 \]
FNA is Inferior to Tissue Biopsy in Diagnosis of RT

In those with concurrent FNA and biopsy, FNA was non-diagnostic in 53% patients.
Differential diagnosis: prolymphocytoid evolution

After pathology revision, \(~20\%\) of ‘RS’ are downgraded to CLL in prolymphocytoid evolution

Soilleux et al, Histopathology 2016
Richter syndrome

95-99%

1-5%

Swerdlow SH. WHO classification of tumours of haematopoietic and lymphoid tissues 2008
Clonally related vs unrelated Richter syndrome

Rossi et al, Blood 2011
The genetic lesions of Richter syndrome can be detectable at subclonal levels in the initial CLL clone.

- **NOTCH 1 EX34:** c.7544_7545delCT p.P2515fs*4 (heterozygous)
- **TP53 EX7:** c.716A>C p.N239T (heterozygous)

### CLL and RS Comparison

- **CLL:**
  - 30 months
  - 5.6%
  - 58%
- **RS:**
  - 30 months
  - 43%

### CLL Progression

- **RS precursor**
- **CLL diagnosis**
- **CLL progression**
- **RS transformation**

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HL variant of Richter syndrome

**Median OS: 4 y**

- **40%** Clonally related
- **70%** EBV+

**Median OS: <1 y**

- **80%** Clonally related
- **5%** EBV+
The genetic profile of clonally unrelated RS differs from that of clonally related RS

- TP53 disruption: p = 0.018
- Stereotyped HCDR3: p = 0.009

Rossi et al, Blood 2011
The genetic profile of Richter syndrome (RS) differs from that of de novo DLBCL.

Lesions of **TP53**, **NOTCH1**, **MYC** and **CDKN2A/B** recapitulates 90% RS.
**TP53 abnormalities in Richter syndrome**

**Graph 1:**
- **No TP53 disruption** vs. **TP53 disruption**
- Cumulative probability of survival (%)
- Months: 0, 12, 24, 36, 48, 60, 72, 84, 96, 108
- **p < .001**

**Table 1:**
<table>
<thead>
<tr>
<th>Phase</th>
<th>Frequency</th>
<th>TP53 M</th>
<th>del17p13</th>
<th>TP53 M/del17p13</th>
</tr>
</thead>
<tbody>
<tr>
<td>MBL</td>
<td>N=1/63</td>
<td>(1.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early stage CLL</td>
<td>N=13/268</td>
<td>(4.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLL requiring treatment</td>
<td>N=30/318</td>
<td>(9.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F-refactory CLL</td>
<td>N=44/99</td>
<td>(44.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Richter syndrome</td>
<td>N=25/38</td>
<td>(65.7%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**DNA damage pathways:**
- p53
- p21
- cyclin B
- cdc2
- p53 (phosphorylated)
- p21 (phosphorylated)
- BAX
- Caspase 9
- DNA damage
- Cell cycle arrest
- Apoptosis

**References:**

**Statistical Analysis:**
- All RS (n=50)
- TP53 disr RS (n=21)
- TP53 wt RS (n=29)
- n of CNAs
- 12.5
- 21.1
- 6.3
- p < .001

**Abbreviations:**
- MBL
- CLL
- M
- TP53
CDKN2A/B abnormalities in Richter syndrome

N=14/59 (24%)

N=0/305 (0%)

N=0/144 (0%)

N=0/144 (0%)

Edelmann J et al, Blood 2012; 120: 4783-94
Chirginova et al, Blood 2013; 122: 2673-82

P= .0105
HR=3.6; 95% CI, 1.3-10.1

TP53 inactivation and/or CDKN2A loss

wt TP53 and wt CDKN2A
**MYC abnormalities in Richter syndrome**

**Mutation**
- Missense
- DNA-BINDING and DIMERIZATION with MAX

**Translocation**
- IgH → MYC

**Amplification**
- CASC11 → MYC, MYC, MYC

**Aberrant cell proliferation**
- Metabolic reprogramming
- Genomic instability

**Frequency (%)**
- N=7/27 (26%)
- N=6/161 (3%)

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**NOTCH1 mutations in Richter syndrome**

- **Cumulative probability of transformation (%)**
  - NOTCH1 wt
  - NOTCH1 M
  - p < .001

- **Frequency (%)**
  - N=2/63 (3%) de novo DLBCL
  - N=60/539 (11%) MBL
  - N=10/48 (20%) CLL diagnosis
  - N=18/58 (31%) F-ref CLL
  - N=18/58 (31%) Richter syndrome
  - *** P < 0.001
  - ** P < 0.05

**References**
Richter syndrome show biased usage of the BCR in the subset 8 (IGHV4-39) configuration

- BCR from subset 8 CLL display extreme antigen polyreactivity
- Subset 8 CLL clones respond avidly to stimulation by multiple antigens

Proliferation and apoptosis are the master cellular programs deregulated in Richter syndrome.

CLL

- MYC
- TP53
- BCR (subset 8)
- NOTCH1
- CDKN2A/B

DLBCL

- Transformation
- Chemoresistance
- Rapid disease kinetics

Driving forces
Type of prior treatment as risk factor for Richter’s transformation?
Risk of 2nd malignancies for FCR-based vs non-genotoxic regimens as initial therapy for CLL in patients >65 years

<table>
<thead>
<tr>
<th>Malignancy*</th>
<th>FCR-based (n=120)</th>
<th>Non-genotoxic* (n=170)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid tumors</td>
<td>13 (11%)</td>
<td>18 (11%)</td>
</tr>
<tr>
<td>Richter’s transformation</td>
<td>8 (7%)</td>
<td>2 (1%) (p = .02)</td>
</tr>
<tr>
<td>AL/MDS</td>
<td>10 (8%)</td>
<td>7 (4%)</td>
</tr>
</tbody>
</table>

*Antibody regimens (n=53), Lenalidomide regimens (n=68), BCR antagonist regimens (n=49)
Incidence of RS in various studies of Ibrutinib

<table>
<thead>
<tr>
<th>STUDY</th>
<th>PATIENTS</th>
<th>PROG _ CLL</th>
<th>PROG17 _ RS</th>
</tr>
</thead>
<tbody>
<tr>
<td>RESONATE-17 (DEL 17P/ TP53 MUTATED)</td>
<td>144</td>
<td>22 (15%)</td>
<td>17 (12%)</td>
</tr>
<tr>
<td>RESONATE PHASE 3 (VS OFATUMUMAB)</td>
<td>195</td>
<td>11 (6%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>OSU (MADDICKS) PRIOR RX (97%)</td>
<td>308</td>
<td>13 (4%)</td>
<td>18 (6%)</td>
</tr>
</tbody>
</table>
Ibrutinib: Patterns of Relapse, and Subsequent Survival

Maddocks, JAMA Oncology 2015, 1:80

Jain, Blood 2015, 125:2062
Richter syndrome after ibrutinib

Cumulative Incidence Estimates (95% CI)

<table>
<thead>
<tr>
<th>Event</th>
<th>At 12 months</th>
<th>At 18 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLL Progression</td>
<td>0.3% (0% to 1.0%)</td>
<td>2.4% (0.3% to 4.6%)</td>
</tr>
<tr>
<td>Richter’s</td>
<td>4.5% (2.0% to 7.0%)</td>
<td>6.5% (3.3% to 9.6%)</td>
</tr>
<tr>
<td>Other Event</td>
<td>13.5% (9.5% to 17.6%)</td>
<td>15.6% (11.1% to 20.0%)</td>
</tr>
</tbody>
</table>

* Not acquired at transformation
Richter’s Transformation under Treatment with Venetoclax (M13-982 Trial)
BAG Trial: Venetoclax plus Obinutuzumab

before  

after 3 weeks  

after 3 months  

14.12.2015  

04.01.2016  

23.03.2016
Venetoclax and Richter’s transformation

- 70 patients with relapsed / refractory CLL enrolled in venetoclax studies at Melbourne Health and Peter MacCallum Cancer Center (2011 – 2015)
  - M12-175 : Venetoclax Monotherapy (Phase I)
  - M13-365 : Venetoclax + Rituximab (Phase I)
  - M13-982 : Venetoclax Monotherapy (Phase II, del(17p) CLL)

- 28 patients discontinued venetoclax treatment:
  - 16 (57%) Richter Transformation
  - 7 (25%) CLL progression
  - 5 (18%) other reasons*

- Median 12 months (0 – 34) follow-up after discontinuation

*lung CA, oesophageal CA, strangulated hernia, poor ECOG status, personal choice
Survival After Discontinuation of Venetoclax

CLL (n=7), 1yOS 69%

RS (n=16), 1yOS 48%
Median OS 1 year

CLL vs RS, p=0.88

Others (n=5)
Treatment options for patients with Richter’s transformation
## Therapeutic Regimens in RT

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>OFAR1</th>
<th>OFAR2</th>
<th>Hyper CVAD+R</th>
<th>R-CHOP</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>18</td>
<td>31</td>
<td>35</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Age ≥ 60 yrs, %</td>
<td>61</td>
<td>74</td>
<td>37</td>
<td>17</td>
<td>0.001</td>
</tr>
<tr>
<td>PS &gt; 1, %</td>
<td>33</td>
<td>29</td>
<td>23</td>
<td>0</td>
<td>0.2</td>
</tr>
<tr>
<td>PLT &gt;= 100 x 10^9/L, %</td>
<td>56</td>
<td>48</td>
<td>63</td>
<td>50</td>
<td>0.7</td>
</tr>
<tr>
<td>Prior therapies &gt;1, %</td>
<td>72</td>
<td>71</td>
<td>71</td>
<td>33</td>
<td>0.08</td>
</tr>
<tr>
<td>Overall response, %</td>
<td>56</td>
<td>39</td>
<td>46</td>
<td>50</td>
<td>0.7</td>
</tr>
<tr>
<td>Median survival, mos</td>
<td>13.1</td>
<td>6.6</td>
<td>9.1</td>
<td>14.9</td>
<td>0.1</td>
</tr>
<tr>
<td>Median FFS, mos</td>
<td>6.8</td>
<td>3</td>
<td>6.5</td>
<td>9.2</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Poor efficacy and tolerability of R-CHOP in relapsed/refractory chronic lymphocytic leukemia and Richter transformation

Petra Langerbeins, Raymonde Busch, Nadine Anheier, Jan Dürrig, Manuela Bergmann, Maria-Elisabeth Goebeler, Hans-Jürgen Hurtz, Martina B. Stauch, Stephan Stilgenbauer, Hartmut Döhner, Anna-Maria Fink, Paula Cramer, Kirsten Fischer, Clemens-Martin Wendtner, Michael Hallek, Barbara Eichhorst

months, respectively, and median increase in hemoglobin was 3.4 g/L. RT patients responded in 67%, progression-free was 10 and overall survival 21 months. The most common adverse events were hematologic toxicities in 92%. Severe infections occurred in 28%. Treatment was discontinued early in 45% of all patients mainly as a result of toxicity. This trial shows that R-CHOP has no role in treating complicated CLL. R-CHOP is associated with significant toxicities and fairly low efficacy compared with almost every other CLL-regimen. In RT, it might still be used as an induction therapy before allogeneic stem cell transplantation. Am. J. Hematol. 89:E239–E243, 2014. © 2014 Wiley Periodicals, Inc.
Stem Cell Transplant in RT

20 pts with RT underwent SCT (17 allo, 3 auto)

Only ≈10% of pts with RT → SCT
Clinical Practice Recommendations for Use of Allogeneic Hematopoietic Cell Transplantation in Chronic Lymphocytic Leukemia on Behalf of the Guidelines Committee of the American Society for Blood and Marrow Transplantation


BCL-2 inhibitors, regardless of whether an objective response is achieved. For Richter transformation, we recommend allo-HCT upon demonstration of an objective response to anthracycline-based chemotherapy. A reduced-intensity conditioning regimen is recommended whenever indicated. These recommendations highlight the rapidly changing treatment landscape of CLL. Newer therapies have disrupted prior paradigms, and allo-HCT is now relegated to later stages of relapsed or refractory CLL.
Targeting the molecular programs that are altered in RS

- **TP53** independent cell death: **venetoclax**
- **BCR** signaling: **BTKi, PI3Ki**
- **MYC**: bromodomain inhibitors
- **NOTCH** signaling: **anti NNR antibodies**
- **Oncogene** deregulation: **XPO1 inhibitors**
A Phase 1 Study of Venetoclax (ABT-199 / GDC-0199) Monotherapy in Patients with Relapsed/Refractory Non-Hodgkin Lymphoma

John F. Gerecitano¹, Andrew W. Roberts²,³, John F. Seymour⁴, William G. Wierda⁵, Brad S. Kahl⁶, John M. Pagel⁷, Soham Puvvada⁸, Thomas J. Kipps⁹, Mary Ann Anderson²,³, Martin Dunbar¹⁰, Ming Zhu¹⁰, Lori Gressick¹⁰, Lindsay Wagner¹⁰, Su Young Kim¹⁰, Sari Heitner Enschede¹⁰, Rod Humerickhouse¹⁰, Matthew S. Davids¹¹

¹Memorial Sloan-Kettering Cancer Center, USA; ²Royal Melbourne Hospital, Australia; ³Walter and Eliza Hall Institute of Medical Research, Australia; ⁴Peter MacCallum Cancer Centre, Australia; ⁵University of Texas MD Anderson Cancer Center, Houston, TX; ⁶Washington University, USA; ⁷Swedish Medical Center, USA; ⁸University of Arizona, USA; ⁹University of California San Diego, USA; ¹⁰AbbVie, USA; ¹¹Dana-Farber Cancer Institute, USA
## Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic, n (%)</th>
<th>All N=106</th>
<th>MCL n=28</th>
<th>FL n=29</th>
<th>DLBCL n=41</th>
<th>Other n=8</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>66 (25–86)</td>
<td>72 (35–85)</td>
<td>64 (46–75)</td>
<td>67 (25–86)</td>
<td>63 (56–73)</td>
</tr>
<tr>
<td><strong>Prior therapies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>3 (1–10)</td>
<td>3 (1–7)</td>
<td>3 (1–10)</td>
<td>3 (1–8)</td>
<td>4 (2–6)</td>
</tr>
<tr>
<td>Rituximab-refractory</td>
<td>33 (31)</td>
<td>8 (29)</td>
<td>8 (28)</td>
<td>16 (39)</td>
<td>1 (33)</td>
</tr>
<tr>
<td><strong>Bulky nodes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;5 cm</td>
<td>49 (48)</td>
<td>16 (59)</td>
<td>8 (29)</td>
<td>22 (54)</td>
<td>3 (38)</td>
</tr>
<tr>
<td>&gt;10 cm</td>
<td>14 (14)</td>
<td>3 (11)</td>
<td>2 (7)</td>
<td>8 (20)</td>
<td>1 (13)</td>
</tr>
<tr>
<td><strong>LDH</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; Upper Limit of Normal</td>
<td>45 (44)</td>
<td>7 (27)</td>
<td>10 (35)</td>
<td>27 (68)</td>
<td>1 (13)</td>
</tr>
</tbody>
</table>

*a* Includes 7 patients DLBCL-Richter’s transformation

*b* Includes n=4 WM, n=3 MZL, n=1 MM
### Objective Responses by Histology – All Doses

<table>
<thead>
<tr>
<th>Best Objective Response, n (%)</th>
<th>All N=106</th>
<th>MCL n=28</th>
<th>FL n=29</th>
<th>DLBCL n=34</th>
<th>DLBCL-RT n=7</th>
<th>WM n=4</th>
<th>MZL n=3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response</td>
<td>47 (44)</td>
<td>21 (75)</td>
<td>11 (38)</td>
<td>6 (18)</td>
<td>3 (43)</td>
<td>4 (100)</td>
<td>2 (67)</td>
</tr>
<tr>
<td>CR</td>
<td>14 (13)</td>
<td>6 (21)</td>
<td>4 (14)</td>
<td>4 (12)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>33 (31)</td>
<td>15 (54)</td>
<td>7 (24)</td>
<td>2 (6)</td>
<td>3 (43)</td>
<td>4 (100)</td>
<td>2 (67)</td>
</tr>
<tr>
<td>SD</td>
<td>32 (30)</td>
<td>5 (18)</td>
<td>17 (59)</td>
<td>8 (24)</td>
<td>2 (29)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PD</td>
<td>23 (22)</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td>19 (56)</td>
<td>1 (14)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- 4 patients discontinued prior to assessment
- n=1 with MM had PD

As of September 15, 2015
Ibrutinib and rituximab induced rapid response in refractory Richter syndrome

Zanetta Lamar¹, LeAnne Kennedy², Brooke Kennedy¹, Mary Lynch¹, Amanda Goad¹, David Hurd¹ & Zachariah McIver¹

¹Comprehensive Cancer Center, Wake Forest University, Medical Center Boulevard, Winston-Salem, North Carolina 27157
²Department of Pharmacy, Wake Forest Baptist Health, Medical Center Boulevard, Winston-Salem, North Carolina 27157

He never developed ibrutinib-associated lymphocytosis. The response continued for 3 months. During evaluation for allogeneic transplant, he developed progressive disease and elected to forego further therapy and later died.

<table>
<thead>
<tr>
<th>Aug-12</th>
<th>Feb-13</th>
<th>May-13</th>
<th>Jun-13</th>
<th>Sep-13</th>
<th>Nov-13</th>
<th>Jan-14</th>
<th>Feb-14</th>
<th>Apr-14</th>
<th>May-14</th>
<th>Jun-14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosed with CLL</td>
<td>FCR × 6 cycles</td>
<td>CT scan demonstrated recurrence</td>
<td>Rituximab and Bendamustine × 5 cycles</td>
<td>Ofatumumab × 4 cycles</td>
<td>R-POCH × 4 cycles</td>
<td>Richter confirmed PET scan no response</td>
<td>R-ICE × 1 cycle; R-DHAC × 3</td>
<td>PET scan without response</td>
<td>Ibrutinib 420 mg daily and Rituximab weekly × 5</td>
<td>PET response – eligible for transplant</td>
</tr>
</tbody>
</table>

Clinical Case Reports 2015; 3(7): 615–617
The efficacy of **ibrutinib** in the treatment of Richter syndrome

Mazie Tsang, Tait D. Shanafelt, Timothy G. Call, Wei Ding, Asher Chanan-Khan, Jose F. Leis, Grzegorz S. Nowakowski, Deborah Bowen, Michael Conte, Susan M. Schwager, Susan L. Slager, Neil E. Kay, Curtis A. Hanson and Sameer A. Parikh

Table 1. Clinical characteristics of CLL patients diagnosed with RS

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At the time of CLL diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>51</td>
<td>69</td>
<td>65</td>
<td>71</td>
</tr>
<tr>
<td><strong>Subtype (GCB vs ABC)</strong></td>
<td>ABC</td>
<td>ABC</td>
<td>ABC</td>
<td>ABC</td>
</tr>
<tr>
<td><strong>MYC rearrangement by FISH</strong></td>
<td>Negative</td>
<td>Not done</td>
<td>Not done</td>
<td>Negative</td>
</tr>
<tr>
<td><strong>EBV status</strong></td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Negative</td>
</tr>
<tr>
<td><strong>Ibrutinib dose, mg per day</strong></td>
<td>420</td>
<td>140</td>
<td>420</td>
<td>420</td>
</tr>
<tr>
<td><strong>Concomitant therapy with ibritnib</strong></td>
<td>Methylprednisolone 1000 mg Intravenously (twice per wk for 1 mo, once per wk for 1 mo, and once every 2 wks for 1 mo)</td>
<td>Methylprednisolone 1000 mg Intravenously (twice per wk for 1 mo, once per wk for 1 mo, and once every 2 wks for 1 mo)</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td><strong>Duration of ibritinib therapy, months</strong></td>
<td>8.5</td>
<td>3.7</td>
<td>2.8</td>
<td>10.8</td>
</tr>
<tr>
<td><strong>Best response achieved</strong></td>
<td>PR</td>
<td>Clinical benefit*</td>
<td>CR</td>
<td>PR</td>
</tr>
<tr>
<td><strong>Status at most recent follow-up</strong></td>
<td>Progressive DLBCL</td>
<td>Death</td>
<td>Ongoing complete remission</td>
<td>Progressive CLL</td>
</tr>
</tbody>
</table>
Targeting MYC dependence in cancer by inhibiting BET bromodomains

Jennifer A. Mertz, Andrew R. Conery, Barbara M. Bryant, Peter Sandy, Srividya Balasubramanian, Deanna A. Mele, Louise Bergeron, and Robert J. Sims III

A

![Graph showing relative MYC and p21 expression over time with DMSO and (+)-JQ1 treatment.]

B

![Graph showing tumor volume over days of treatment with different treatments: Vehicle QD, Cytarabine 100 mpk, 5+/2-, (+)-JQ1 30 mpk, BID, (+)-JQ1 50 mpk, QD.]

PNAS 2011; 108: 16669-16674
Therapeutic antibody targeting of individual Notch receptors

Yan Wu1*, Carol Cain-Hom2*, Lisa Choy2, Thijs J. Hagenbeek2, Gladys P. de Leon7, Yongmei Chen1, David Finkle4, Rayna Venook4, Xiumin Wu5, John Ridgway5, Dorreyah Schahin-Reed6, Graham J. Dow2†, Amy Shelton2, Scott Stawicki1, Ryan J. Watts6, Jeff Zhang8, Robert Choy8, Peter Howard8, Lisa Kadyk8, Minhong Yan5, Jiping Zha3, Christopher A. Callahan3, Sarah G. Hymowitz7 & Christian W. Siebel2
**LYMPHOID NEOPLASIA**

*Selinexor is effective in acquiring with ibrutinib in chronic lymphocytic leukemia.*

Zachary A. Hing,1,2 Rose Mantel,2 Kyle A. Beckwith, Amy J. Johnson,2,3 Amy M. Lehman,4 John C. Byrd;1
1Medical Scientist Training Program, 2Division of Hematology, Department of Medicine, 3Division of Hematology, Department of Medicine, 4Center for Biostatistics, The Ohio State University, Columbus, OH

**Key Points**

- Selinexor exhibits synergy with ibrutinib in CLL.
- Selinexor is effective in vitro in ibrutinib-resistant CLL.

*B* $^*$

Selinexor = Selective inhibitor of nuclear export (SINE)
Selinexor in Initial or Relapsed/Refractory Richter’s Transformation (SIRRT)

This study has been terminated.
(Due to enrollment challenges in this rare disease. The termination is not a consequence of any safety concern.)

Sponsor:
Karyopharm Therapeutics, Inc

ClinicalTrials.gov Identifier: NCT02138786
First received: May 13, 2014
Last updated: October 3, 2016
Last verified: October 2016

Enrollment: 26
Study Start Date: November 2014
Estimated Study Completion Date: November 2016
Primary Completion Date: September 2016 (Final data collection date for primary outcome measure)
Randomized, Phase II Dose Optimization Study Of Chimeric Antigen Receptor Modified T Cells Directed Against CD19 (CTL019) In Patients With Relapsed, Refractory CLL

David L Porter, MD
University of Pennsylvania Medical Center
Abramson Cancer Center

ASH 2013, Abstract 873 and 4162
Optimizing the CAR Signaling Domain to Treat CD19+ Malignancy

- CD28 and 4-1BB (CD137-TNF family) signaling tested in vitro and in murine models
- CARs with 4-1BB or CD28 mediate potent antileukemic effects in NALM-6 xenograft model
- 4-1BBz more potent than CD28 in 3 different xenograft models with primary B ALL
- 4-1BB confers both antigen dependent and independent survival effects that promote T cell persistence
Summary

A patient with relapsed and refractory chronic lymphocytic leukaemia with Richter transformation was treated with chimeric antigen receptor (CAR)-modified T cells targeted for CD19 but later relapsed with a clonally related plasmablastic lymphoma. The loss of most routine markers of pre-plasma cell or B lymphoid differentiation (including CD19) highlights the ability of such mature lymphomas to evade lineage-specific targeted immunotherapy by differentiating along pathways comparable to their normal cellular counterparts. Molecular genetic evaluation demonstrated multiple independent lines of CD19-negative disease that eventually evolved in this single patient. Such plasticity represents potential challenges for antigen-directed CAR-T cell therapy, while serving as a testament to the selective pressure exerted by these engineered T cells over time.
Chimeric antigen receptor T cells targeting Fcμ receptor selectively eliminate CLL cells while sparing healthy B cells

Elena Faitschuk, Andreas A. Hombach, Lukas P. Frenzel, Clemens-Martin Wendtner, Hinrich Abken

Blood 2016 ;blood-2016-01-692046; doi:10.1182/blood-2016-01-692046

Key points

• FcμR is a more selective target for the CAR T cell therapy of CLL compared with currently used targets including CD19.
Anti-FcµR CAR T cells specifically lyse CLL cells but spare healthy B cells.
• Allo SCT is effective in RS
• Pembrolizumab signaled activity in RS
• RS lacks ‘immune escape’ genes mutations (no selective pressure)
• No info on the immune status of RS patients
834 PD-1 Blockade with Pembrolizumab (MK-3475) in Relapsed/Refractory CLL Including Richter Transformation: An Early Efficacy Report from a Phase 2 Trial (MC1485)

CLL: Therapy, excluding Transplantation:
Program: Oral and Poster Abstracts
Type: Oral
Session: 642. CLL: Therapy, excluding Transplantation: Relapsed/Refractory CLL Therapy Excluding Transplantation

Monday, December 7, 2015: 5:45 PM
Valencia BC (W415BC), Level 4 (Orange County Convention Center)

Wei Ding, MD, PhD1, Haidong Dong, MD, PhD2*, Timothy G. Call, MD1, Tait D. Shanafelt, MD3, Sameer A. Parikh, MD1, Jose F. Leis, MD, PhD4, Betsy R. Laplant, MS5*, Rong He, MD6*, Thomas E. Witzig, MD1, Yi Lin, MD, PhD1, Asher Chanan-Khan, MD7, Deborah A. Bowen, APRN, CNP1*, Michael Conte, PA-C1*, Thomas M. Habermann, MD1, David Viswanatha, MD6, Ivana Micallef, MD1, Neil E. Kay, MD1 and Stephen Ansell, MD, PhD8
Clinical Outcome

<table>
<thead>
<tr>
<th>Response status</th>
<th>Total Evaluable (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>PR</td>
<td>2 (14%)</td>
</tr>
<tr>
<td>SD</td>
<td>6 (43%)</td>
</tr>
<tr>
<td>PD (including UPD)</td>
<td>5 (36%)</td>
</tr>
<tr>
<td>ORR</td>
<td>3 (21%)</td>
</tr>
</tbody>
</table>

- All 3 patients with CR or PR are RS patients.
- No CR, PR was seen in CLL (N = 7 evaluable)
- Among 7 RS patients enrolled, 1 CR, 2 PR (RS-CR), 3 SD and 1 PD.
- Among the 5 RS pts with previous PD on ibrutinib, all 5 had either CR/PR or SD with nodal responses.
Duration of Therapy for RS Cohort

All RS patients are alive (last one enrolled July)

Patient 1
- CR

Patient 2
- PR due to CLL

Patient 3
- RS-CR

Patient 4
- SD

Patient 5
- PD

Patient 6
- responded to ibrutinib again

Patient 7
- No prior RS directed chemotherapy

Days on Therapy

0 50 100 150 200 250 300
A Phase 1/2, open label, multicenter study to assess the safety and tolerability of durvalumab (anti-PD-L1 antibody) as monotherapy and in combination therapy in subjects with lymphoma or chronic lymphocytic leukemia
SUMMARY

• RS occurs in 5% of chemo-immunotherapy frontline patients in 5 years.

• Especially common in del17p patients and salvage patients.

• Appears to be less common in targeted therapies but too early.

• Essential to get biopsies not FNA of PET positive nodes for accurate diagnosis, genomic studies with concurrent CLL cells.

• Standard treatment is an anthracycline-based induction chemo, followed by allogeneic transplantation, if possible.

• Potential new therapeutic approaches include venetoclax, ibrutinib, BET inhibitors, NOTCH receptor inhibitors, XPO inhibitors and immune approaches (CAR T cells, PD-1/PD-L1 inhibitors, etc.).
Thanks for your attention!