Brut force: the role of BTK-inhibitors in CLL and B-cell disorders

Hematology Fellows’ Conference
Stacey Shiovitz
September 13, 2013
Overview

• CLL/SLL
  o Overview
  o Current therapies

• BTK-inhibitors in CLL

• Other applications of BTK-inhibitors
CLL/SLL
Epidemiology

- Incidence: ~15,000 cases/year

- Median age diagnosis 71yo; death 79yo
  - 70% are >65yo at diagnosis; <2% are <45yo

- Male 2:1 Female

- White > Black >> Other

- 10% are familial
  - Female; younger (mean age dx = 58yo)
  - Increased incidence of LPD, MBL

refs: seer.cancer.gov, 8/1/13
Gribben, Blood 2010
Overall Survival

Mayo CLL clinic vs. age-matched Minnesota population

Kay, ASH-SAP 2010
Diagnostic Criteria

• Spectrum: CLL = peripheral leukemia / SLL = LN disease
  o Only 5% will have node-only disease

• Clonal expansion of abnormal B-cells in peripheral blood
  o ≥ 5000 B-lymphocytes/μL*
  o Lymphoid cells ≤ 55% atypical/immature
  o Low density of surface Ig (IgM/D) with κ or λ LC
  o B cell surface antigens (CD19, CD20_{dim}, CD23)
  o CD5 surface antigen

*If <5000, classified as monoclonal B-lymphocytosis (MBL)

iwCLL: Hallek, Blood 2008
Peripheral smear

- Smudge cell
- Increase in small, round B-cells

Image: UpToDate, 2013
Lymph node biopsy

Low power:
Pseudofollicular pattern (vaguely nodular proliferation centers)

Higher power:
Predominance of small lymphocytes with scattered larger prolymphocytes and paraimmunoblasts

Image: UpToDate, 2013
Bone marrow aspirate

Nodular, interstitial, or diffuse infiltrate of small round cells

Image: UpToDate, 2013
# Differential Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>sIg</th>
<th>CD20</th>
<th>CD5</th>
<th>CD23</th>
<th>CD10</th>
<th>CD103</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chronic lymphocytic leukemia</strong></td>
<td>Weak</td>
<td>Weak</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Lymphoplasmacytic lymphoma</strong></td>
<td>Mod</td>
<td>+</td>
<td>−/+</td>
<td>+/−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td><strong>Mantle cell lymphoma</strong></td>
<td>Mod</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>(partial)</td>
<td>−</td>
</tr>
<tr>
<td><strong>Marginal zone: nodal/MALT lymphoma</strong></td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−/+</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td><strong>Splenic marginal zone lymphoma</strong></td>
<td>+</td>
<td>+</td>
<td>−/+</td>
<td>−/+</td>
<td>−</td>
<td>−/+</td>
</tr>
<tr>
<td><strong>Follicular lymphoma</strong></td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−/+</td>
<td>+/−</td>
<td>−</td>
</tr>
<tr>
<td><strong>Hairy cell leukemia</strong></td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+</td>
</tr>
</tbody>
</table>

− or −/+ = negative or weak; MALT = mucosa-associated lymphoid tissue; sIg = surface immunoglobulin.

Kay, ASH-SAP 2010
## Staging

<table>
<thead>
<tr>
<th>System</th>
<th>Clinical features</th>
<th>Median survival, y</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rai stage (simplified 3-stage)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 (low risk)</td>
<td>Lymphocytosis in blood and marrow only</td>
<td>&gt; 10</td>
</tr>
<tr>
<td>I and II (intermediate risk)</td>
<td>Lymphadenopathy, splenomegaly +/- hepatomegaly</td>
<td>7</td>
</tr>
<tr>
<td>III and IV (high risk)</td>
<td>Anemia, thrombocytopenia</td>
<td>0.75-4</td>
</tr>
<tr>
<td><strong>Binet group</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Fewer than 3 areas of lymphadenopathy; no anemia or thrombocytopenia</td>
<td>12</td>
</tr>
<tr>
<td>B</td>
<td>More than 3 involved node areas; no anemia or thrombocytopenia</td>
<td>7</td>
</tr>
<tr>
<td>C</td>
<td>Hemoglobin &lt; 100 g/L; platelets &lt; 100 × 10 g/L</td>
<td>2-4</td>
</tr>
</tbody>
</table>

Gribben, Blood 2010
## Molecular characterization

<table>
<thead>
<tr>
<th>Testing</th>
<th>Good risk</th>
<th>Poor risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetics&lt;sup&gt;1&lt;/sup&gt;</td>
<td>del 13q, normal</td>
<td>del 11q (ATM), del 17p (p53), complex</td>
</tr>
<tr>
<td>IgVH mutation status&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Mutated</td>
<td>Unmutated (≤ 2% mutation)</td>
</tr>
<tr>
<td>ZAP70&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Low</td>
<td>High (&gt;30%)</td>
</tr>
<tr>
<td>CD38&lt;sup&gt;1,3&lt;/sup&gt;</td>
<td>Low</td>
<td>High (&gt;20%)</td>
</tr>
</tbody>
</table>

<sup>1</sup> Results may change over the course

<sup>2</sup> May be difficult to obtain in the community

<sup>3</sup> Testing can vary between labs
Cytogenetics are prognostic

Döhner, NEJM 2000

- del 17p
- del 11q
- trisomy 12q
- normal
- del 13q (only)
### Differential Diagnosis

<table>
<thead>
<tr>
<th>Neoplasm</th>
<th>Genetic abnormality (%)</th>
<th>IgVH genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLL</td>
<td>del13q (50); del 11q (20); trisomy 12 (20); del 17p (10)</td>
<td>50% unmutated</td>
</tr>
<tr>
<td>LPL</td>
<td>t(9;14)-PAX5R</td>
<td>Mutated</td>
</tr>
<tr>
<td>MCL</td>
<td>t(11;14)-BCL1R</td>
<td>Unmutated (rarely mutated)</td>
</tr>
<tr>
<td>FL</td>
<td>t(14;18)-BCL2R</td>
<td>Mutated, ongoing</td>
</tr>
<tr>
<td>Extranodal and nodal MZL</td>
<td>trisomy 3; t(11;18)-API2/MLT; t(1;14)-BCL10R</td>
<td>Mutated, ongoing</td>
</tr>
<tr>
<td>Splenic MZL</td>
<td>del 7q21-32 (40)</td>
<td>50% mutated</td>
</tr>
</tbody>
</table>

Gribben, Blood 2010
### Summary: poor prognostic factors

<table>
<thead>
<tr>
<th>Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced stage at diagnosis</td>
</tr>
<tr>
<td>Advanced age</td>
</tr>
<tr>
<td>Male sex</td>
</tr>
<tr>
<td>Diffuse pattern of bone marrow infiltration</td>
</tr>
<tr>
<td><strong>Short lymphocyte doubling time</strong></td>
</tr>
<tr>
<td><strong>High expression of Ki67, p27</strong></td>
</tr>
<tr>
<td><strong>High serum levels of β2-microglobulin, thymidine kinase, soluble CD23, and TNFα</strong></td>
</tr>
<tr>
<td>Poor-risk cytogenetics: 17p, 11q deletions, and complex cytogenetic abnormalities</td>
</tr>
<tr>
<td>IgVH unmutated mutational status</td>
</tr>
<tr>
<td>High level of CD38 expression</td>
</tr>
<tr>
<td>High level of ZAP70 expression</td>
</tr>
<tr>
<td><strong>High level of expression of lipoprotein lipase</strong></td>
</tr>
<tr>
<td>Altered microRNA expression</td>
</tr>
<tr>
<td>Poor response to therapy or short duration of response</td>
</tr>
</tbody>
</table>

Gribben, Blood 2010
CLL TREATMENT
Treatment initiation

Meta-analysis of >2000 cases of early CLL:

• Immediate vs. deferred therapy
• 10-yr OS: 44 vs. 47%
• Therefore, delay to onset of symptoms
  o Follow q3 months with H+P, labs
  o Trend lymphocyte doubling time (LDT)

CLL Trialists, JCNI 1999
Treatment indications

- Marrow failure / presence of cytopenias
- Bulky lymphadenopathy (>10cm) or splenomegaly (>6cm from CM)
- Rapid disease progression
  - Short Lymphocyte Doubling Time (LDT < 6 mos.)
- CLL-related complications (cytopenias, frequent infections)
  - AIHA alone: treat if steroid-refractory
- Constitutional symptoms

TREATMENT GOALS:
- Complete remission (CR)
- No minimal residual disease (MRD)

iwCLL: Hallek, Blood 2008
## Response criteria

<table>
<thead>
<tr>
<th></th>
<th>Clonal lymphs</th>
<th>LN*</th>
<th>HSM</th>
<th>B-symptom</th>
<th>ANC (#/µL)</th>
<th>Plt (#/µL)</th>
<th>Hgb (g/dL)</th>
<th>Marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CR</strong></td>
<td>Absent</td>
<td>Absent</td>
<td>None</td>
<td>Absent</td>
<td>≥1500</td>
<td>&gt;100K</td>
<td>&gt;11.0</td>
<td>&lt;30% lymph, no nodules</td>
</tr>
<tr>
<td><strong>CRI</strong></td>
<td>Absent</td>
<td>Absent</td>
<td>None</td>
<td>Absent</td>
<td>One of 3 cytopenias still present</td>
<td></td>
<td></td>
<td>Hypocellular</td>
</tr>
<tr>
<td><strong>PR</strong></td>
<td>≥ 50% decr.</td>
<td>≥ 50% decr.</td>
<td>≥ 50% decr.</td>
<td>≥ 50% decr.</td>
<td>≥1500</td>
<td>&gt;100K</td>
<td>&gt;11.0</td>
<td>50% decr. In infiltrate or 50% improved from baseline</td>
</tr>
</tbody>
</table>

*Sum of products of up to 6 LN

iwCLL: Hallek, Blood 2008
MRD

- Evaluation of second-line alemtuzumab with standard response criteria vs. MRD by serial BMBx/flow:

Moreton, JCO 2005
Treatment options

- Alkylating agents
  - Chlorambucil
  - Cyclophosphamide

- Purine nucleosides
  - Fludarabine
  - Pentostatin
  - Cladribine

- Purine nucleosides and alkylators

- Chemoimmunotherapy

Kay, Blood 2006
FCR

Fludarabine / Cyclophosphamide / Rituximab

- MDACC (phase II)$^1$: FCR
  - Response: overall 95%, CR 72%
  - OS 77%, PFS 51%

- GCLLSG CLL8 (phase III)$^{2,3}$: FCR (vs. FC)
  - PFS: 38% (vs. 27%), p<0.0001
  - OS: 69% (vs. 62%), p=0.001; median NR (vs. 86 mos.)

$^1$Tam, Blood 2008  $^2$Hallek, Lancet 2010  $^3$Fischer, ASH 2012
BR
Bendamustine / Rituximab

• GCLLSG (phase II): BR
  - Response: overall 88%, CR 23%
    - del 17p: 37.5%, del 11q 90%, unmutated IgVH 89%
  - Median follow-up 27 months
    - OS: 90.5%
    - Event-free: 34 months

• Phase III FCR vs. BR trial is underway
  (GCLLSG, recruitment complete)

1Fischer, JCO 2012
2clinicaltrials.gov
BTK inhibition

CLL
Bruton’s Tyrosine Kinase (BTK)

- Xq21.33-q22

- Gene mutations cause X-linked agammaglobulinemia type 1
  - Failure to produce mature B lymphocytes
  - Failure of Ig heavy chain rearrangement
  - Increased susceptibility to infections

- Key to B-cell development
  - Tec (protein tyrosine kinase) family kinase
  - Chemokine-mediated homing and adhesion of B cells through regulation of integrin proteins
  - Affect B-cell proliferation in response to antigen

Woyach, Blood 2012
B-cell receptor (BCR) signaling

Woyach, Blood 2012
Targeted therapies

Woyach, Blood 2012
Ibrutinib (PCI-32765)

• Small molecule covalent inhibitor of BTK (binds cysteine-481)
  o Potent: MIC$_{50}$ = 0.5nmol/L

• Inhibits BTK signaling
  o Including ERK, NFκB, PI3K
  o Dec. cell proliferation, tumor-cell migration
  o Inhibition is independent of BTK catalytic activity

Honigberg, PNAS 2010; Herman, Blood 2011; Ponader, Blood 2012
Preclinical studies

Ibrutinib is 1000X more selective for B-cells vs. T-cells

Honigberg, PNAS 2010
Preclinical studies

- In CLL cell lines, ibrutinib inhibited CLL cell migration and survival
- In CLL mouse model, ibrutinib inhibited CLL progression
- Treated 8 dogs with spontaneous NHL
  \[\Rightarrow 3\text{ PR} + 3\text{ SD}\]

- Honigberg, PNAS 2010; Herman, Blood 2011; Ponader, Blood 2012
Ibrutinib: Phase I

Bruton Tyrosine Kinase Inhibitor Ibrutinib (PCI-32765) Has Significant Activity in Patients With Relapsed/Refractory B-Cell Malignancies

Ibrutinib: Phase I

- 56 patients with CLL, NHL, or Waldenström's
  - 28 days on, 7 days off (5 cohorts: 1.25 to 12.5 mg/kg dose)
  - Daily continuous dosing (2 cohorts: 8.3 mg/kg or fixed dose 560 mg)

- Continue dose escalation until MTD or three dose levels above full BTK occupancy by ibrutinib
  - Response evaluated every 2 cycles, including CBC, T/B/NK counts, serum Ig, CT scans

- Eligibility criteria:
  - 1-4 prior therapies (not first-line)
  - ECOG PS 0-1
  - ANC ≥ 1.5 and plt ≥ 75 (unless marrow involvement)
  - Intact renal and hepatic function
  - No secondary malignancy

Advani, JCO 2013
Phase I: patient population

N = 56 patients
Median age 65
16 with CLL
Median 3 prior tx
- 93% had prior Rituxan

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No.</th>
<th>%</th>
</tr>
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<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>41-82</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>38</td>
<td>68</td>
</tr>
<tr>
<td>Female</td>
<td>18</td>
<td>32</td>
</tr>
<tr>
<td><strong>Histologic subtype</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follicular lymphoma</td>
<td>16</td>
<td>29</td>
</tr>
<tr>
<td>CLL/SLL</td>
<td>16</td>
<td>29</td>
</tr>
<tr>
<td>Mantle-cell lymphoma</td>
<td>9</td>
<td>16</td>
</tr>
<tr>
<td>DLBCL</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>Marginal zone/mucosal-associated lymphoid tissue lymphoma</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Waldenström macroglobulinemia</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td><strong>Prior therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median No.</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>1-10</td>
<td></td>
</tr>
<tr>
<td>Rituximab</td>
<td>52</td>
<td>93</td>
</tr>
<tr>
<td>Alkylator based</td>
<td>47</td>
<td>84</td>
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<tr>
<td>Anthracycline based</td>
<td>25</td>
<td>45</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>15</td>
<td>27</td>
</tr>
<tr>
<td>Autologous stem-cell transplantation</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>

Advani, JCO 2013
Phase I: PK studies

- Rapidly absorbed and eliminated
- Once daily dosing adequate
- Full saturation of BTK at 2.5mg/kg dosing level (2nd lowest)

Advani, JCO 2013
Phase I: results

Max % change in tumor burden (n = 48)

Change From Baseline SPD (%)

-100 -50 0 50 100 150 200

CLL/SLL  MCL  DLBCL  FL  Other indolent NHL

Advani, JCO 2013
Phase I: results

MTD not reached

2 DLT:
• Hypersensitivity gr3
• Transient gr2 neutropenia

Few grade 3/4 AE:
• Neutropenia (12.5%)
• Thrombocytopenia (7.2%)
• Anemia (7.1%)

No effect on Ig levels

Advani, JCO 2013
Efficacy

• Overall RR: 54%
  - CLL/SLL: 11 / 16, 2 CR
  - Follicular: 6 / 16, 3 CR
  - Mantle cell: 7 / 9, 3 CR
  - Large cell: 2 / 7
  - Waldenström's: 3 / 4
  - Marginal zone: 1 / 4

• Median PFS: 13.6 months
  - 20 still on ibrutinib with continued response

All CLL responders had rapid decline in LN with cycle 1 and developed a lymphocytosis (10/11 had later normalization of the lymphocyte count)

Advani, JCO 2013
Phase I: summary

- Ibrutinib orally available for once daily dosing
- Fixed dose effective
- Continuous schedule preferable
- Rare grade 3/4 toxicities
- Good response rate in variety of previously treated B-cell disorders
  - Especially CLL, mantle cell

Advani, JCO 2013
Targeting BTK with Ibrutinib in Relapsed Chronic Lymphocytic Leukemia

John C. Byrd, M.D., Richard R. Furman, M.D., Steven E. Coutre, M.D., Ian W. Flinn, M.D., Ph.D., Jan A. Burger, M.D., Ph.D., Kristie A. Blum, M.D., Barbara Grant, M.D., Jeff P. Sharman, M.D., Morton Coleman, M.D., William G. Wierda, M.D., Ph.D., Jeffrey A. Jones, M.D., M.P.H., Weiqiang Zhao, M.D., Ph.D., Nyla A. Heerema, Ph.D., Amy J. Johnson, Ph.D., Juthamas Sukbuntherng, Ph.D., Betty Y. Chang, Ph.D., Fong Clow, Sc.D., Eric Hedrick, M.D., Joseph J. Buggy, Ph.D., Danelle F. James, M.D., and Susan O’Brien, M.D.
Ibrutinib in CLL: Phase Ib/II

- 85 patients with relapsed/refractory CLL/SLL requiring treatment
  - Cohort 1 (n = 27): 420mg daily
  - Cohort 2 (n = 24): 840mg daily
  - High-risk* cohort 3 (n = 34): 420mg daily
    *Primary refractory or progressed < 24 months

- Endpoints: 1° = safety
  2° = RR, PFS

- Eligibility
  - ANC ≥750, platelets ≥50
  - At least 2 prior therapies (unless Cohort 3)
  - Adequate renal and hepatic function
  - Absence of active infection

Amended to allow 22 pt to enroll with cytopenias due to marrow involvement

Byrd, NEJM 2013
Ibrutinib in CLL: Phase Ib/II

• Assessment
  o Interphase cytogenetics, IgVH mutation analysis, \( \beta_2 \)-microglobulin levels
  o Interval radiology imaging

• Analysis:
  o Censored at progression, change in therapy, lost to follow-up
  o If persistent lymphocytosis but otherwise met criteria for PR, was deemed “PR with lymphocytosis”

Byrd, NEJM 2013
Phase Ib/II: patient population

- **N = 85 patients**
- **Median age 66**
- **65% high-risk (Rai III/IV)**
- **Median 4 prior tx**
  - 98% had prior Rituxan
- **81% IgVH unmutated**
- **33% del 17p**
- **36% del 11q**

**N = 85 patients**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N = 85)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>Median — yr</td>
<td>66</td>
</tr>
<tr>
<td>Range — yr</td>
<td>37–82</td>
</tr>
<tr>
<td>≥70 yr — no. (%)</td>
<td>30 (35)</td>
</tr>
<tr>
<td><strong>Sex</strong> — no. (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>65 (76)</td>
</tr>
<tr>
<td>Female</td>
<td>20 (24)</td>
</tr>
</tbody>
</table>

| Rai stage at treatment initiation — no. (%)pora |                |
| 0, I, or II                                       | 29 (34)        |
| III or IV                                          | 55 (65)        |
| Data missing                                       | 1 (1)          |

| No. of previous therapies                         |                |
| Median                                             | 4              |
| Range                                              | 1–12           |

| Previous therapy — no. (%)                        |                |
| Nucleoside analogue                                | 81 (95)        |
| Rituximab                                          | 83 (98)        |
| Alkylator                                          | 76 (89)        |
| Alemtuzumab                                        | 18 (21)        |
| Bendamustine                                       | 33 (39)        |
| Ofatumumab                                         | 22 (26)        |

**Unmutated immunoglobulin variable-region heavy-chain gene — no. (%)**

| Patients with data that could be evaluated       | 69 (81)        |
| Data missing                                      | 4 (5)          |

| Interphase cytogenetic abnormality — no. (%)pora2 |                |
| 17p13.1 deletion                                  | 28 (33)        |
| 11q22.3 deletion                                  | 31 (36)        |

| β2-microglobulin level — no. (%)                  |                |
| >3 mg/liter                                       | 39 (46)        |
| Data missing                                      | 5 (6)          |

modified from: Byrd, NEJM 2013
Phase Ib/II: results

Transient lymphocytosis seen in first 2-3 months of therapy

As lymphocytosis improves, ORR by traditional criteria increases

Byrd, NEJM 2013
Phase Ib/II: response rate

• Median follow-up 20.9 months
  o 54 patients (64%) still on treatment

• Overall response rate: 71%
  o Low-dose: 2 CR + 34 PR + [ 10 PR-lymph \(\rightarrow 91\%\) ]
  o High-dose: 0 CR + 24 PR + [ 5 PR-lymph \(\rightarrow 86\%\) ]

• Sub-groups for clinical/genomic risk factors:
  o Only IgVH was significant (RR: 77% unmutated vs. 33% mutated, \(p=0.005\))
    • But with PR-lymph: 75% vs. 90%, NS

Byrd, NEJM 2013
## Phase Ib/II: subgroup results

Byrd, NEJM 2013

### Table: Subgroup Results

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>Overall response rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>85</td>
<td>71 (60–80)</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>420 mg</td>
<td>51</td>
<td>71 (56–82)</td>
</tr>
<tr>
<td>840 mg</td>
<td>34</td>
<td>71 (52–85)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;70 yr</td>
<td>55</td>
<td>69 (55–81)</td>
</tr>
<tr>
<td>≥70 yr</td>
<td>30</td>
<td>73 (54–88)</td>
</tr>
<tr>
<td><strong>Rai stage at baseline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0, I, or II</td>
<td>29</td>
<td>69 (49–85)</td>
</tr>
<tr>
<td>III or IV</td>
<td>55</td>
<td>71 (57–82)</td>
</tr>
<tr>
<td><strong>Previous chemotherapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3 Regimens</td>
<td>27</td>
<td>74 (54–89)</td>
</tr>
<tr>
<td>≥3 Regimens</td>
<td>58</td>
<td>69 (56–81)</td>
</tr>
<tr>
<td><strong>17p13.1 deletion</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>28</td>
<td>68 (48–84)</td>
</tr>
<tr>
<td>Negative</td>
<td>52</td>
<td>71 (57–83)</td>
</tr>
<tr>
<td><strong>11q22.3 deletion</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>31</td>
<td>77 (59–90)</td>
</tr>
<tr>
<td>Negative</td>
<td>49</td>
<td>65 (50–78)</td>
</tr>
<tr>
<td><strong>IGHV</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutated</td>
<td>12</td>
<td>33 (10–65)</td>
</tr>
<tr>
<td>Unmutated</td>
<td>69</td>
<td>77 (65–86)</td>
</tr>
<tr>
<td><strong>β2-microglobulin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤3 mg/liter</td>
<td>39</td>
<td>72 (55–85)</td>
</tr>
<tr>
<td>&gt;3 mg/liter</td>
<td>41</td>
<td>68 (52–82)</td>
</tr>
</tbody>
</table>

**ORR (%)**

Byrd, NEJM 2013
Phase Ib/II results: survival

Progression-free survival

Overall survival

75%

83%

*Published results at 26 months

Byrd, NEJM 2013
Phase Ib/II results: survival

Progression-free survival

- No 17p or 11q deletions (n=29)
- 11q deletion (n=23)
- 17p deletion (n=28)

P=0.04 by log-rank test

Overall survival

- No 17p or 11q deletions (n=29)
- 11q deletion (n=23)
- 17p deletion (n=28)

P=0.15 by log-rank test

- Mutated IGHV (n=12)
- Unmutated IGHV (n=69)

P=0.67 by log-rank test

- Unmutated IGHV (n=69)
- Mutated IGHV (n=12)

P=0.86 by log-rank test

Byrd, NEJM 2013
### Phase Ib/II: adverse events

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Grade 1-2</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>0</td>
<td>15%</td>
</tr>
<tr>
<td>Anemia</td>
<td>NR</td>
<td>6%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>NR</td>
<td>6%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>47%</td>
<td>2%</td>
</tr>
<tr>
<td>Fever</td>
<td>22%</td>
<td>5%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>28%</td>
<td>4%</td>
</tr>
<tr>
<td>Cough</td>
<td>31%</td>
<td>0</td>
</tr>
<tr>
<td>URI</td>
<td>33%</td>
<td>0</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>13%</td>
<td>5%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>NR</td>
<td>12%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>13%</td>
<td>5%</td>
</tr>
</tbody>
</table>

NR = AE not reported

Byrd, NEJM 2013
Phase Ib/II: cytopenias

Majority had sustained improvement of cytopenias

Byrd, NEJM 2013
Phase Ib/II: summary

• Early lymphocytosis seen
  o Transient in most patients x 2-3 months
  o Correlated with response

• Response rate 71% (91% with PR-lymph)
  o IgVH-mutated is only subgroup with poor response, but no effect on survival
  o del 17p still poorly, but did see a response

• 26-month: median PFS 75%, OS 83%

• Most common gr 3/4 AE: neutropenia, pneumonia

Byrd, NEJM 2013
Ibrutinib combinations in CLL

- **Ibrutinib + rituximab\(^1\)**
  - Phase II: \(n = 40\); del 17p or PFS <36 mos. or relapsed with del 11q
  - At 3 months: ORR 85% (all PR) + 15% PR-lymph
    - Noted earlier and shorter peak of lymphocytosis

- **Ibrutinib + ofatumumab (PCYC 1108)\(^2\)**
  - Phase II: \(n=30\); relapsed/refractory CLL
    - Dose ibrutinib for 28 days prior to starting ofatumumab
  - At 5 months: ORR 90%, CR 10%

- **BR x 6 cycles + ibrutinib until PD (PCYC 1109)\(^3\)**
  - Phase II: \(n=27\); relapsed/refractory CLL/SLL/PLL, 3 with Richter’s
  - At 6 months: ORR 100% in CLL (2/3 Richter’s)

\(^1\)Burger, ASH 2012; \(^2\)O’Brien, ASCO 2012; \(^3\)Jaglowski, ASCO 2012
Ibrutinib resistance

• CLL patients that had progressed on ibrutinib
  o Pool of 246 patients from mono or dual therapy
  o Median 14 months of ibrutinib

• Evaluated CLL genome in 3 patients with at least a PR on therapy
  \(\rightarrow\) progressive disease without Richter’s
  o Overall, relative genomic stability

• Found single nucleotide variant in each conferring resistance
  o 2/3 at amino acid 481 (drug binding site)
  o 1/3 with wt BTK, but gain-of-function PLC-\(\gamma\) mutation (downstream of BTK)

Chang, ASCO 2013
BTK inhibition

Beyond CLL
Targeting BTK with Ibrutinib in Relapsed or Refractory Mantle-Cell Lymphoma

Michael L. Wang, M.D., Simon Rule, M.D., Peter Martin, M.D., Andre Goy, M.D., Rebecca Auer, M.D., Ph.D., Brad S. Kahl, M.D., Wojciech Jurczak, M.D., Ph.D., Ranjana H. Advani, M.D., Jorge E. Romaguera, M.D., Michael E. Williams, M.D., Jacqueline C. Barrientos, M.D., Ewa Chmielowska, M.D., John Radford, M.D., Stephan Stilgenbauer, M.D., Martin Dreyling, M.D., Wieslaw Wiktor Jedrzejczak, M.D., Peter Johnson, M.D., Stephen E. Spurgeon, M.D., Lei Li, Ph.D., Liang Zhang, M.D., Ph.D., Kate Newberry, Ph.D., Zhishuo Ou, M.D., Nancy Cheng, M.S., Bingliang Fang, Ph.D., Jesse McGreivy, M.D., Fong Clow, Sc.D., Joseph J. Buggy, Ph.D., Betty Y. Chang, Ph.D., Darrin M. Beaupre, M.D., Ph.D., Lori A. Kunkel, M.D., and Kristie A. Blum, M.D.

Wang, NEJM 2013
Ibrutinib in MCL: Phase II

• 111 patients with relapsed/refractory MCL and measurable disease
  o Cohort 1: ≥2 cycles of bortezomib (n = 48): 560 mg daily
  o Cohort 2: <2 cycles of bortezomib (n = 63): 560 mg daily

• Endpoints: 1° = ORR
  2° = duration response, PFS, OS, safety

• Eligibility
  o ANC ≥750, platelets ≥50 (unless marrow involvement)
  o 1-5 prior therapies
  o ECOG 0-2
  o Adequate renal and hepatic function

Wang, NEJM 2013
Ibrutinib in MCL: Phase II

• **Assessment**
  - CT at end of cycle 3, 5, 7 + q3 cycles until PD
  - Also: PET-CT, BMBx, GI bx (as indicated)
  - Lab correlate: trend lymphocytes, cytokine expression

• **Analysis: Simon’s two-stage design**
  - Check efficacy of sub-group prior to full enrollment
  - Interim analysis for each cohort for futility (not reached)

Wang, NEJM 2013
Phase II: patient population

N = 111 patients
Median age 68
Median 3 prior treatment
- 89% had prior rituximab
49% high-risk MIPI
45% refractory
72% advanced disease

Wang, NEJM 2013

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No Prior Treatment with Bortezomib (N=63)</th>
<th>Prior Treatment with Bortezomib (N=48)</th>
<th>All Patients (N=111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>66</td>
<td>69</td>
<td>68</td>
</tr>
<tr>
<td>Range</td>
<td>46–83</td>
<td>40–84</td>
<td>40–84</td>
</tr>
<tr>
<td>Sex — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>46 (73)</td>
<td>39 (81)</td>
<td>85 (77)</td>
</tr>
<tr>
<td>Female</td>
<td>17 (27)</td>
<td>9 (19)</td>
<td>26 (23)</td>
</tr>
<tr>
<td>ECOG performance status — no. (%)‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 or 1</td>
<td>53 (84)</td>
<td>46 (96)</td>
<td>99 (89)</td>
</tr>
<tr>
<td>2</td>
<td>9 (14)</td>
<td>2 (4)</td>
<td>11 (10)</td>
</tr>
<tr>
<td>&gt;2</td>
<td>1 (2)</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>No. of prior regimens</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Range</td>
<td>1–5</td>
<td>1–5</td>
<td>1–5</td>
</tr>
<tr>
<td>≥3 — no. (%)</td>
<td>31 (49)</td>
<td>30 (62)</td>
<td>61 (55)</td>
</tr>
<tr>
<td>Previous therapy — no. (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hyper-CVAD</td>
<td>18 (29)</td>
<td>15 (31)</td>
<td>33 (30)</td>
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<tr>
<td>Stem-cell transplantation</td>
<td>8 (13)</td>
<td>4 (8)</td>
<td>12 (11)</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>9 (14)</td>
<td>18 (38)</td>
<td>27 (24)</td>
</tr>
<tr>
<td>Rituximab or rituximab-containing regimen</td>
<td>56 (89)</td>
<td>43 (90)</td>
<td>99 (89)</td>
</tr>
<tr>
<td>Simplified MIPI — no. (%)§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>9 (14)</td>
<td>6 (12)</td>
<td>15 (14)</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>24 (38)</td>
<td>18 (38)</td>
<td>42 (38)</td>
</tr>
<tr>
<td>High risk</td>
<td>30 (48)</td>
<td>24 (50)</td>
<td>54 (49)</td>
</tr>
<tr>
<td>Bulky mass — no. (%)¶</td>
<td>6 (10)</td>
<td>3 (6)</td>
<td>9 (8)</td>
</tr>
<tr>
<td>At least one node ≥5 cm — no. (%)</td>
<td>26 (41)</td>
<td>17 (35)</td>
<td>43 (39)</td>
</tr>
<tr>
<td>Refractory disease — no. (%)</td>
<td></td>
<td></td>
<td>27 (43)</td>
</tr>
<tr>
<td>Advanced disease — no. (%)***</td>
<td>49 (78)</td>
<td>31 (65)</td>
<td>80 (72)</td>
</tr>
</tbody>
</table>
Phase II: results

- ORR: 68%
- Median 17.5 mos.
- CR: 21%
  - 19% no B
  - 23% prior B
- PFS: 13.9 months
  - 7.4 mo. no B
  - 16.6 mo. prior B
- Median OS: NR

<table>
<thead>
<tr>
<th>Variable</th>
<th>No Prior Treatment with Bortezomib (N=63)</th>
<th>Prior Treatment with Bortezomib (N=48)</th>
<th>All Patients (N=111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>43 (68)</td>
<td>32 (67)</td>
<td>75 (68)</td>
</tr>
<tr>
<td>Complete</td>
<td>12 (19)</td>
<td>11 (23)</td>
<td>23 (21)</td>
</tr>
<tr>
<td>Partial</td>
<td>31 (49)</td>
<td>21 (44)</td>
<td>52 (47)</td>
</tr>
<tr>
<td>None†</td>
<td>20 (32)</td>
<td>15 (31)</td>
<td>35 (32)</td>
</tr>
<tr>
<td>Response duration — mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>15.8</td>
<td>NR</td>
<td>17.5</td>
</tr>
<tr>
<td>95% CI</td>
<td>5.6–NR</td>
<td>NR–NR</td>
<td>15.8–NR</td>
</tr>
<tr>
<td>Progression-free survival — mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>7.4</td>
<td>16.6</td>
<td>13.9</td>
</tr>
<tr>
<td>95% CI</td>
<td>5.3–19.2</td>
<td>8.3–NR</td>
<td>7.0–NR</td>
</tr>
<tr>
<td>Overall survival — mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>95% CI</td>
<td>10.0–NR</td>
<td>11.9–NR</td>
<td>13.2–NR</td>
</tr>
</tbody>
</table>

Wang, NEJM 2013
Phase II: overall response

Response rate:
- ORR 68%
- CR 21%
- PR 47%

Duration: 17.5 mos.
Phase II: survival

Median PFS: 13.9 mos.
7.4 (no B) vs. 16.6 (B) mos.

Median OS: NR

Wang, NEJM 2013
Phase II: toxicities

- Similar to prior studies

- Major exception: 4 cases of subdural hemorrhage
  - 1 with concurrent low platelets
  - Since have excluded enrolling patients on warfarin (in case is a CYP effect)
  - However, thought to be an independent mechanism
Ibrutinib + bortezomib

- Co-administration → synergy
  - Increased mitochondrial injury and apoptosis in DLBCL and MCL cells
  - Inactivation of AKT, NF-κB; down-regulation of MCL1, BCL-XL, XIAP
  - Increased DNA damage with reactive oxygen species

- Results seen in primary cells and highly bortezomib-resistant DLBCL/MCL cells

Dasmahapatra, Br J Hem 2013
Future uses

Single agent in...

- First-line vs. chlorambucil in elderly CLL [RESONATE-2] [Open at FHCRC]
- Relapsed/refractory CLL/SLL/PLL with del 17p
- Follicular lymphoma
- Waldenström's
- Hairy cell leukemia
- Relapsed/refractory multiple myeloma [Open at FHCRC]
- Relapsed/refractory de novo DLBCL [Open at FHCRC]
- Second-line vs. temsirolimus in MCL
- Second-line vs. ofatumumab in relapsed/refractory CLL [Open at FHCRC]

clinicaltrials.gov, 8/7/13; core®FYI
Future uses

Combined with...

- FCR or BR in CLL/SLL
- R-CHOP in non-germinal center DLBCL, NHL
- BR vs. RI vs. I in first-line elderly CLL
- BR in relapsed DLBCL, MCL, indolent NHL; first-line MCL
- Lenalidomide in CLL/SLL
- Lenalidomide and rituximab in follicular lymphoma

clinicaltrials.gov, 8/7/13
Future uses

Evaluation of...
- Interaction with grapefruit juice (CYP hypothesis)
- Leukemic cell kinetics
- Patients with hepatic impairment
- Maintenance
- Post-HSCT

Outside of cancer...
- Autoimmune disorders (ex. inhibition of ITK = IL-2 Inducible kinase)
- Rheumatoid arthritis

clinicaltrials.gov, 8/7/13
Dubovsky, Blood 2013
Thank you!