Bcl-2 inhibition in NHL

Jonathan W. Friedberg M.D., M.M.Sc.
BCL-2, BH3 and apoptosis: Rational therapeutic targets in NHL

Antiapoptotic proteins, prevent activation of Bax and Bak, thus inhibiting apoptosis.

Pure BH3 mimetics, such as AT-101, allow activation of Bax and Bak, enhancing apoptosis.

Friedberg *Blood* 111:5263 2008
BCL-2 and Myc in DLBCL

BET inhibitors

MYC overexpression

BCL2 overexpression

BCL2 inhibitors

Mottok A, and Gascoyne R. Clin Cancer Res 2015;21:4-6
Oblimersen Sodium (bcl-2 antisense) and Rituximab for NHL

- Single arm nonrandomized trial.
- 70% prior rituximab
- 42 evaluable pts:
  - FL ORR 60%; 8CR
  - MCL ORR 20%
  - DLBCL ORR 28%
- Myelosuppression main toxicity
- Drug developed in melanoma and CLL; not approved.

Pro et al, British Journal Haematology 143:355  2008
Venetoclax, a small molecule Bcl-2 inhibitor, tips balance toward apoptosis

- High affinity for Bcl-2
- Low affinity for Bcl-XL, MCL-1, Bcl-W
- Activates apoptosis by disrupting Bcl-2 and BH3 interactions, leading to BH3 death signals in cell.
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
Venetoclax Phase 1 Strategy

- 70 patients with R/R NHL were enrolled in dose-escalation cohorts (target daily dose: 200 – 1200mg)

- 15 patients with FL and 21 with DLBCL were enrolled in a safety expansion cohort (target daily dose: 1200 mg)

Patients with NHL other than MCL:

- Week 1: 400 mg
- Week 2: 800 mg
- Week 3: 1200 mg

Step-up dosing used to avoid tumor lysis; more prolonged step-up for MCL
# 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>Median (range)</td>
<td>66 (25–86)</td>
<td>72 (35–85)</td>
<td>64 (46–75)</td>
<td>67 (25–86)</td>
</tr>
<tr>
<td><strong>Prior therapies</strong></td>
<td>Median (range)</td>
<td>3 (1–10)</td>
<td>3 (1–7)</td>
<td>3 (1–10)</td>
<td>3 (1–8)</td>
</tr>
<tr>
<td>Rituximab-refractory</td>
<td></td>
<td>33 (31)</td>
<td>8 (29)</td>
<td>8 (28)</td>
<td>16 (39)</td>
</tr>
<tr>
<td><strong>Bulky nodes</strong></td>
<td>&gt;5 cm</td>
<td>49 (48)</td>
<td>16 (59)</td>
<td>8 (29)</td>
<td>22 (54)</td>
</tr>
<tr>
<td></td>
<td>&gt;10 cm</td>
<td>14 (14)</td>
<td>3 (11)</td>
<td>2 (7)</td>
<td>8 (20)</td>
</tr>
<tr>
<td><strong>LDH</strong></td>
<td>&gt; Upper Limit of Normal</td>
<td>45 (44)</td>
<td>7 (27)</td>
<td>10 (35)</td>
<td>27 (68)</td>
</tr>
</tbody>
</table>

\[a\] Includes 7 patients DLBCL-Richter’s transformation

\[b\] Includes n=4 WM, n=3 MZL, n=1 MM
## Phase 1 venetoclax in NHL: Adverse Events

### All Grade AEs (in ≥ 15% patients), n (%)

<table>
<thead>
<tr>
<th>EventType</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>103</td>
<td>97</td>
</tr>
<tr>
<td>Nausea</td>
<td>51</td>
<td>48</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>47</td>
<td>44</td>
</tr>
<tr>
<td>Fatigue</td>
<td>43</td>
<td>41</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>22</td>
<td>21</td>
</tr>
<tr>
<td>Vomiting</td>
<td>22</td>
<td>21</td>
</tr>
<tr>
<td>Anemia</td>
<td>19</td>
<td>18</td>
</tr>
<tr>
<td>Constipation</td>
<td>19</td>
<td>18</td>
</tr>
<tr>
<td>Headache</td>
<td>19</td>
<td>18</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>19</td>
<td>18</td>
</tr>
<tr>
<td>Cough</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>Back pain</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>16</td>
<td>15</td>
</tr>
</tbody>
</table>

### Grade 3/4 AEs (in ≥ 5% patients), n (%)

<table>
<thead>
<tr>
<th>EventType</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Grade 3/4 AE</td>
<td>57</td>
<td>54</td>
</tr>
<tr>
<td>Anemia</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>

Two SAEs (600mg): both febrile neutropenia.

Two laboratory tumor lysis syndrome, both in patients with high tumor-burden disease; no clinical sequelae.
Phase 1 venetoclax: Waterfall plot by histology
Outcomes: Phase 1 venetoclax study

MCL: Objective responses observed across all dose cohorts.

FL: Objective responses more common at higher doses, including the 1200 mg expansion cohort.

82/106 (77%) patients have discontinued
- 69 due to PD
- 7 due AE\(^a\)
- 3 proceed to transplant \(^b\)
- 2 withdrew consent
- 1 noncompliance
Progression-Free Survival by Histology Subtype

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Median PFS, Months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All, n=106</td>
<td>17 (14, 22)</td>
</tr>
<tr>
<td>MCL, n=28</td>
<td>14 (ND)</td>
</tr>
<tr>
<td>FL, n=29</td>
<td>11 (6, 19)</td>
</tr>
<tr>
<td>DLBCL, n=34</td>
<td>1 (1, 3)</td>
</tr>
</tbody>
</table>

MCL: 28 16 12 4 1
FL: 29 17 7 4 2 1 1
DLBCL: 34 2
Conclusions: Phase 1 venetoclax

- Venetoclax given in step up approach is safe in R/R NHL
  - MTD not reached with doses up to 1200 mg evaluated
  - Lab TLS was observed in 2 pts; no clinical sequelae
- The ORR was 75% in MCL, 38% in FL, and 18% in DLBCL
  - Complete responses in patients with FL and MCL had durability
- Next steps: chemotherapy combinations.
A Dose-Escalation Study of Venetoclax (ABT-199/GDC-0199) in Combination with Bendamustine and Rituximab in Patients with Relapsed or Refractory Non-Hodgkin’s Lymphoma

Sven de Vos¹, Lode Swinnen², Mark Kozloff³, Ding Wang⁴, Erin Reid⁵, Loretta Nastoupil⁶, Nathan Fowler⁶, Jaclyn Cordero⁷, Diane D’Amico⁷, Susan Diehl⁷, Martin Dunbar⁷, Ming Zhu⁷, Shekman Wong⁷, Sari Heitner Enschede⁷, David Chien⁷, Rod Humerickhouse⁷, Christopher R. Flowers⁹
Synergy of venetoclax with bendamustine and rituximab

Xenograft experiments:
- Vehicle control
- Venetoclax
- Bendamustine/rituximab
- Benda/rituximab + venetoclax

Dosing Schedule: BR + Venetoclax

- **Dose-escalation portion**
  - Patients were treated on a 28-day cycle with daily VEN on 3 dosing schedules (3-, 7-, and 28-day).
  - BR regimen was 6 Cycles: B (90 mg/m² x 2) and R (375 mg/m²)

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**Venetoclax**

- **3/28 days**
  - Cohort 1 = 50 mg
  - Cohort 2 = 100 mg
  - Days 2 - 4

- **7/28 days**
  - Cohort 3 = 100 mg
  - Cohort 6 = 200 mg
  - Cohort 7 = 400 mg
  - Days 2 - 8

- **28/28 days**
  - Cohort 4 = 100 mg
  - Cohort 5 = 200 mg
  - Days 2 - 28

**Venetoclax monotherapy**

- Cohort 6 = 200 mg
  - Days 3 - 4

- Cohort 7 = 400 mg
  - Days 2 - 8

---

Venetoclax plus bendamustine and rituximab
Patient Characteristics: BR + venetoclax

- 48 patients were enrolled in 10 dose escalation cohorts
  - Median age was 62.5 years (range: 29–90 years)
  - 31 (65%) patients were male

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=48</td>
</tr>
<tr>
<td>Histology, n (%) FL</td>
<td></td>
</tr>
<tr>
<td>DLBCL</td>
<td>27 (56)</td>
</tr>
<tr>
<td>MZL</td>
<td>16 (33)</td>
</tr>
<tr>
<td></td>
<td>5 (10)</td>
</tr>
<tr>
<td>Prior therapy</td>
<td></td>
</tr>
<tr>
<td>R or R-based chemo, n (%)</td>
<td>48 (100)</td>
</tr>
<tr>
<td>B or BR, n (%)</td>
<td>11 (23)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>3 (1-8)</td>
</tr>
</tbody>
</table>
Following cohort 5 (200 mg; 28/28d), a protocol amendment was filed in order to:

- strongly encourage G-CSF prophylaxis during venetoclax administration, particularly in heavily pretreated patients
- refine the DLT definition in the context of known BR toxicities

<table>
<thead>
<tr>
<th>Cohort</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose-Limiting Toxicities during cycle 1, n (%)</td>
<td>50 mg 3/28d n=4</td>
<td>100 mg 3/28d n=4</td>
<td>100 mg 7/28d n=4</td>
<td>100 mg 28/28d n=3</td>
<td>200 mg 28/28d n=3</td>
<td>200 mg 7/28d n=4</td>
<td>400 mg 7/28d n=5</td>
<td>400 mg 28/28d n=8</td>
<td>600 mg 28/28d n=8</td>
<td>800 mg 28/28d n=5</td>
<td>N=48</td>
</tr>
<tr>
<td>Thrombocytopeniaa</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>2 (4)</td>
<td></td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Stevens-Johnson Syndromeb</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td>1 (2)</td>
<td></td>
</tr>
</tbody>
</table>

Venetoclax plus bendamustine and
Preliminary Efficacy: BR + Venetoclax

<table>
<thead>
<tr>
<th>Response, n (%)</th>
<th>DLBCL n=16</th>
<th>Follicular Lymphoma n=27</th>
<th>Marginal Zone B-Cell Lymphoma n=5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response</td>
<td>6 (38)</td>
<td>21 (78)</td>
<td>4 (80)</td>
</tr>
<tr>
<td>Complete response, CR</td>
<td>4 (25)</td>
<td>8 (30)</td>
<td>1 (20)</td>
</tr>
<tr>
<td>Partial response, PR</td>
<td>2 (13)</td>
<td>13 (48)</td>
<td>3 (60)</td>
</tr>
<tr>
<td>Stable disease, SD</td>
<td>2 (13)</td>
<td>1 (4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Progressive disease, PD</td>
<td>6 (38)</td>
<td>2 (7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Discontinued without assessment</td>
<td>1 (6)</td>
<td>3 (11)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Active (awaiting first assessment)</td>
<td>1 (6)</td>
<td>0 (0)</td>
<td>1 (20)</td>
</tr>
</tbody>
</table>

Partial response; SD, stable disease.
Ongoing enrollment: Phase 2 trial

- **R/R FL Grade 1-3a N=156 (planned)**
- **Chemo vs No Chemo Investigator’s Discretion**
- **Chemotherapy Free**
  - **Arm A**
    - Venetoclax 1 year, 800 mg daily
    - Rituximab cycles 1, 4, 6, 8, 10, 12
  - **Arm B**
    - Venetoclax 1 year, defined daily dose
    - Rituximab cycles 1-6
    - Bendamustine cycles 1-6
  - **Arm C**
    - Rituximab cycles 1-6
    - Bendamustine cycles 1-6

Phase Ib/II in 1L DLBCL evaluating the safety of venetoclax + R-CHOP or G-CHOP; expansion cohort evaluating the efficacy of venetoclax + R-CHOP in Bcl-2 high/low, cell of origin (ABC/GCB), and double-hit (Bcl-2/Myc)
Intergroup Trial in Development: Phase II-III

Untreated DHL/DPL

DA-EPOCH-R

DA-EPOCH-R + Venetoclax (ABT199)
DA-EPOCH-R +/- Venetoclax in DHL/DPL

• Primary Objective
  – Determine efficacy of venetoclax plus DA-EPOCH-R in MYC/BCL2 double-hit and double protein expressing lymphomas.

• Secondary Objectives
  – Evaluate safety of the combination of venetoclax with DA-EPOCH-R
  – Correlate outcome with MYC and BCL2 translocation status, cell of origin, and intensity of MYC and BCL2 protein expression
Endpoints

• Primary
  – Phase 2: Event-free survival at 12 months (EFS12)
  – Phase 3: Event-free survival at 24 months (EFS24)

• Secondary
  – Phase 2: Response rate (CR and PR), EFS24, progression-free survival, overall survival, incidence of adverse events and treatment discontinuation
  – Phase 3: Response rate, progression-free survival, overall survival, incidence of adverse events and treatment discontinuation

• Correlative
  – Correlate outcome with MYC and BCL2 translocation status, cell of origin, and intensity of MYC and BCL2 protein expression
Eligibility

- Age ≥ 18 years
- No prior systemic therapy
- Histologic diagnosis of DLBCL or BCLu
- Double hit lymphoma defined as dual translocations of MYC and BCL2, OR, Double protein expressing lymphoma defined as MYC IHC expression ≥ 40% and BCL2 ≥ 70%.*
- Ann Arbor stage II-IV
- Adequate organ and marrow function

* Registration will be based on local interpretation but all pathology will be centrally reviewed
Study Treatment

- Venetoclax at chosen dose on days 1-10 of each 21 day cycle
- DA-EPOCH R to be administered per routine on days 1-5 of a 21 day cycle for up to 6 total cycles
- Routine GCSF and prophylactic antibiotic support
- Restaging PETCT following cycle 2 and at end of treatment
Statistics

- **Phase 2**
  - 67 subjects will be required per arm to show an EFS12 of 75% compared to 60% with an alpha error 0.2 and 80% power
  - If this pre-specified endpoint is met, the study will convert to phase 3
  - Total accrual goal of 140 includes an additional 5% for dropouts and ineligible subjects

- **Phase 3**
  - 100 total subjects will be required per arm to show EFS24 of 60% compared to 40% using EFS24 with an alpha error of 0.05 and 82% power
  - Total accrual goal for phase 3: n= 210 (includes additional 5%). This is inclusive of patients enrolled on phase 2.

- **Stratify on IPI score**
Correlative studies

- Correlation of outcome with MYC and BCL2 translocation status
- Correlation of outcome based on COO using IHC and Nanostring
- Correlation of outcome based on DLBCL vs. BCLu histology
- Correlation with intensity of MYC and BCL2 expression
Phase I protocol in development
Venetoclax plus DA-EPOCH-R in aggressive B-cell lymphoma

• Phase I study at 4-5 sites

• Primary objective: Determine MTS/RP2D of venetoclax with DA-EPOCH-R

• Secondary objectives:
  – Evaluate toxicity of the combination
  – Preliminary estimation of efficacy based on response rate and EFS12
Eligibility

- Histologically confirmed chemo-naïve DLBCL or BCLu
- Transformed iNHL eligible if no prior anthracycline
- Age $\geq 18$ years
- ECOG PS 0-2
- Adequate marrow and organ function
- No known CNS involvement, active uncontrolled infection, other active malignancies
Design

Phase 3+3 design (Bayesian designs also under review)

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Venetoclax (mg po daily)</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1</td>
<td>400</td>
<td>1-5</td>
</tr>
<tr>
<td>0 (starting level)</td>
<td>400</td>
<td>1-10</td>
</tr>
<tr>
<td>1</td>
<td>600</td>
<td>1-10</td>
</tr>
<tr>
<td>2</td>
<td>800</td>
<td>1-10</td>
</tr>
</tbody>
</table>

MTD/RP2D is highest dose level at which fever than 2/6 subjects experience DLT
Dose-limiting toxicity

- Grade 4 neutropenia or thrombocytopenia lasting >7 days and/or fails to resolve to grade 1 by cycle 2
- Grade 3 thrombocytopenia with bleeding
- Grade 4 neutropenic fever
- Grade 3 or greater non-hematologic toxicity related to study treatment, except alopecia, reversible grade 3 infusion reactions, nausea/vomiting lasting <7 days
- Any grade 5 toxicity
Thank you!
Discussion