Venetoclax for Treatment of Pediatric Patients with Relapsed/Refractory Cancers

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Medical Director
AbbVie Inc.
Venetoclax Agenda

- Regulatory history
- Mechanism of action
- Clinical trial experience in adults
- Proposed pediatric plan
- Pediatric trial challenges identified
# US Regulatory History of Venetoclax

<table>
<thead>
<tr>
<th>IND</th>
<th>Active</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orphan Drug Designation Granted</td>
<td>CLL</td>
<td>September 2012</td>
</tr>
<tr>
<td></td>
<td>DLBCL</td>
<td>March 2014</td>
</tr>
<tr>
<td></td>
<td>AML</td>
<td>February 2016</td>
</tr>
<tr>
<td>Breakthrough Therapy Designation Granted</td>
<td>R/R CLL with 17p del</td>
<td>April 2015</td>
</tr>
<tr>
<td></td>
<td>R/R CLL in combination with rituxumab</td>
<td>December 2015</td>
</tr>
<tr>
<td></td>
<td>Treatment-naïve AML in combination with HMAs</td>
<td>January 2016</td>
</tr>
<tr>
<td>Approval</td>
<td>R/R CLL with 17p del</td>
<td>April 2016</td>
</tr>
</tbody>
</table>
Venetoclax

- Novel, orally bioavailable, small-molecule B-cell lymphoma (BCL-2) inhibitor
- Selective high affinity binding to BCL-2
- Lower affinity to other anti-apoptotic proteins
- Overexpression of anti-apoptotic proteins with
  - Tumor initiation
  - Disease progression
  - Resistance to chemotherapy
Venetoclax: Restoration of Apoptosis Through BCL-2 Inhibition

- BCL-2 Overexpression, Cancer Cell Survival
  - Pro-apoptotic proteins
  - BCL-2

- Venetoclax Binds to BCL-2
  - Venetoclax

- Cancer Cell Death
  - Mitochondria
  - Apoptosis initiation
  - Caspase activation
Clinical Trial Experience in Adults
Current Trials in Adults

- Chronic lymphocytic leukemia (CLL)
  - Small lymphocytic leukemia (SLL)
- Acute myeloid leukemia (AML)
- Non-Hodgkin’s lymphoma (NHL)
- Multiple myeloma (MM)
Accelerated Approval Venetoclax for Patients with 17p Deletion CLL

<table>
<thead>
<tr>
<th></th>
<th>Venetoclax N=106 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate (ORR)</td>
<td>85 (80.2)</td>
</tr>
<tr>
<td>95% CI</td>
<td>(71.3, 87.3)</td>
</tr>
<tr>
<td>Complete remission (CR) + CRi</td>
<td>8 (7.5)</td>
</tr>
<tr>
<td>CR, n (%)</td>
<td>6 (5.7)</td>
</tr>
<tr>
<td>CRi, n (%)</td>
<td>2 (1.9)</td>
</tr>
<tr>
<td>nPR, n (%)</td>
<td>3 (2.8)</td>
</tr>
<tr>
<td>PR, n (%)</td>
<td>74 (69.8)</td>
</tr>
</tbody>
</table>

CRi = complete remission with incomplete marrow recovery
nPR = nodular partial response
USPI, April 2016.
### Activity in AML

<table>
<thead>
<tr>
<th></th>
<th>Venetoclax(^1) N=32 n (%)</th>
<th>Venetoclax + low-dose cytarabine(^2) N=18 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>6 (19)</td>
<td>8 (44)</td>
</tr>
<tr>
<td>CR</td>
<td>2 (6)</td>
<td>4 (22)</td>
</tr>
<tr>
<td>CRi</td>
<td>4 (13)</td>
<td>4 (22)</td>
</tr>
<tr>
<td>PR</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>20 (63)</td>
<td>10 (56)</td>
</tr>
</tbody>
</table>

## Activity in NHL

<table>
<thead>
<tr>
<th></th>
<th>DLBCL (N=34)</th>
<th>FL (N=29)</th>
<th>MCL (N=28)</th>
<th>DLBCL (N=16)</th>
<th>FL (N=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR</strong></td>
<td>6 (18)</td>
<td>11 (38)</td>
<td>21 (75)</td>
<td>6 (38)</td>
<td>21 (78)</td>
</tr>
<tr>
<td><strong>CR</strong></td>
<td>4 (12)</td>
<td>4 (14)</td>
<td>6 (21)</td>
<td>4 (25)</td>
<td>8 (30)</td>
</tr>
<tr>
<td><strong>PR</strong></td>
<td>2 (6)</td>
<td>7 (24)</td>
<td>15 (54)</td>
<td>2 (13)</td>
<td>13 (48)</td>
</tr>
<tr>
<td><strong>Stable disease</strong></td>
<td>8 (24)</td>
<td>17 (59)</td>
<td>5 (18)</td>
<td>2 (13)</td>
<td>1 (4)</td>
</tr>
<tr>
<td><strong>Progressive disease</strong></td>
<td>19 (56)</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td>6 (38)</td>
<td>2 (7)</td>
</tr>
</tbody>
</table>

DLBCL = diffuse large b-cell lymphoma, FL = follicular lymphoma, MCL = mantle cell lymphoma
Safety of Venetoclax
Venetoclax Exposure

Patients received venetoclax
N=1493

- CLL n=935
- MM n=110
- AML n=102
- NHL n=346

Combination therapy n=933
Monotherapy n=560

Duration on monotherapy
~50 patients >2 years
~200 patients >1 year
Overall Safety Profile in Adults

- Most common AEs
  - Mild GI toxicity
- Grade 3/4 AEs
  - Cytopenias
- Identified risks
  - Tumor lysis syndrome (TLS)
  - Neutropenia
### AEs in ≥ 20% of Patients Across All Monotherapy Studies

<table>
<thead>
<tr>
<th>MedDRA Preferred Term</th>
<th>Overall AE Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>41%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>41%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>30%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>29%</td>
</tr>
<tr>
<td>Anemia</td>
<td>22%</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>20%</td>
</tr>
</tbody>
</table>

Includes patients with CLL, AML, NHL and MM in ongoing clinical studies as of November 2015.
Grade 3/4 AEs in ≥ 5% of Patients Across All Monotherapy Studies

<table>
<thead>
<tr>
<th>MedDRA Preferred Term</th>
<th>Overall AE Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=560</td>
</tr>
<tr>
<td></td>
<td>%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>26</td>
</tr>
<tr>
<td>Anemia</td>
<td>14</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>11</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>6</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>5</td>
</tr>
<tr>
<td>Neutrophil count decrease</td>
<td>5</td>
</tr>
</tbody>
</table>

Includes patients with CLL, AML, NHL and MM in ongoing clinical studies as of November 2015
Tumor Lysis Syndrome (TLS)

- Potent activity of venetoclax → rapid reduction in tumor burden → risk of TLS
- Clinical TLS observed only in early dose finding studies in CLL
- Mitigated by more gradual dose ramp-up
- Standard prophylaxis measures recommended
- Since December 2012 no cases of clinical TLS observed
Neutropenia in Monotherapy

- Common grade 3/4 AE
- Managed with standard of care
- Improved over time on study
- No trend towards increased infection rate
Safety Considerations Evaluated Before Pediatric Trial

- Clinical adult safety data well-characterized
  - Mild GI events and cytopenias
  - Expected to be similar in children
  - No additional concerns with long-term use
- Relevant nonclinical finding in adult animals
  - Decreased spermatogenesis
    - Risk to humans unknown
- Nonclinical juvenile toxicity study to characterize potential safety profile in pediatrics
Proposed Pediatric Plan
## Mechanism Based Selection of Pediatric Tumor Types

<table>
<thead>
<tr>
<th>Pediatric Cancer</th>
<th>BCL-2 Overexpression</th>
<th>Cell Line Response</th>
<th>Murine Xenograft Response</th>
<th>Clinical Response in Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>NHL*</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>ALL</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Not tested</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Not tested</td>
</tr>
</tbody>
</table>

*Burkitt’s lymphoma cell lines did not respond to venetoclax*
Neuroblastoma: Preclinical Rationale
BCL-2 Dependent Model

Unmet Medical Need in Relapsed / Refractory Patients

- Newly diagnosed patients
  - ALL, NHL and neuroblastoma
    - OS rate >75%
  - AML
    - OS rate ~60%
- Relapsed / refractory setting
  - Prognosis remains dismal for all indications

SEER 2012.
Overview of Proposed Study

- Phase 1: dose escalation and cohort expansion study
- Multi center global study
  - ~40 sites in US, EU, Canada, Australia
- Proposed enrollment
  - ~150 patients
  - Age 1 to <18 years
Study Objectives

- Primary objectives
  - Safety (dose limiting toxicity)
  - Pharmacokinetics
- Secondary objectives
  - Efficacy (ORR, CR)
  - Safety in combination with chemotherapy
- Exploratory
  - Minimum residual disease (MRD) analysis
  - Biomarker analysis
Phase 1: Two Part Study Design

Part 1
Dose Escalation
N = 24-72

Using standard 3 + 3 + 3 design

Dose level 1
400 mg

Dose level 2
800 mg

Determines recommended dose for Part 2

Part 2
Cohort Expansion
N = 32-100

AML
ALL
NHL
Neuroblastoma
Part 1: Dose Escalation Scheme

- **AML, ALL ≥ 20kg**: Dose level 1 → Dose level 2
- **AML, ALL <20kg**: Dose level 1 → Dose level 2
- **NHL, NBL ≥ 20kg**: Dose level 1 → Dose level 2
- **NHL, NBL <20kg**: Dose level 1 → Dose level 2
Part 2: Cohort Expansion
Gehan 2-Stage Design

- Cohort 1: AML
- Cohort 2: ALL
- Cohort 3: NHL
- Cohort 4: Neuroblastoma

Stage 1
- Enroll
- Evaluate anti-tumor activity

Stage 2
- Enroll up to additional
- Depending on anti-tumor activity in Stage 1

- N = 8 - 25

Targeting a response rate of 20%
Venetoclax Pediatric Formulation

- Tablet formulation (recently approved)
  - 10 mg, 50 mg and 100 mg
- Rapidly disintegrating tablets
  - 2.5 mg, 10 mg and 25 mg
  - Used to make oral liquid suspension
Venetoclax Pediatric Dose Projections

- Impact on hepatic metabolism by CYP3A4 in patients <2 years
- Age band dosing: <2 years
- Weight band dosing: ≥ 2 years
Venetoclax Pediatric Dose Projections

Simulated AUC$_{ss}$ of Venetoclax Pediatric Doses

<table>
<thead>
<tr>
<th>Weight Range</th>
<th>Dose</th>
<th>AUC$_{ss}$ (μg*day/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 – &lt;2 yrs</td>
<td>80 mg</td>
<td>2</td>
</tr>
<tr>
<td>10 – &lt;20 kg</td>
<td>120 mg</td>
<td>2.5</td>
</tr>
<tr>
<td>20 – &lt;30 kg</td>
<td>180 mg</td>
<td>3</td>
</tr>
<tr>
<td>30 – &lt;45 kg</td>
<td>250 mg</td>
<td>3.5</td>
</tr>
<tr>
<td>≥ 45 kg</td>
<td>400 mg</td>
<td>4</td>
</tr>
</tbody>
</table>

Illustrative of dose level 1
Rationale for Venetoclax in Combination Therapy

- Acceptable safety profile first with monotherapy
- Meet efficacy endpoint
- Based on investigator discretion in best interest of the child
- Combination therapy may
  - Push tumor cell to apoptosis
  - Maintain response
  - Stop repeated progression
Allowed Combination Agents

- AML
  - Low dose cytarabine
- ALL
  - Dexamethasone and vincristine
- NHL
  - Rituximab
- Neuroblastoma
  - Cyclophosphamide
## Potential Pediatric Challenges

<table>
<thead>
<tr>
<th>Challenges</th>
<th>Mitigation</th>
</tr>
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<tbody>
<tr>
<td>Suspension formulation palatability</td>
<td>Taste studies and dosing vehicle evaluation ongoing</td>
</tr>
<tr>
<td>Number of tablets for high dose groups</td>
<td>Combination of tablets and liquid dosing</td>
</tr>
<tr>
<td>Food effect on pediatric formulation</td>
<td>Bioavailability study</td>
</tr>
<tr>
<td>Trial enrollment across tumor types</td>
<td>NHL / DLBCL: outreach to encourage screening</td>
</tr>
</tbody>
</table>
Venetoclax Summary

- Venetoclax
  - Showed activity in adults
  - Reasonable candidate for pediatric evaluation
- Morbidity and mortality in relapsed setting remains high
- Mechanistically venetoclax works differently than other therapies
  - May show response where other treatments failed
  - Will offer another treatment option
- Sponsors committed to continue development in pediatric oncology
Venetoclax for Treatment of Pediatric Patients with Relapsed/Refractory Cancers

Pediatric Subcommittee of the Oncologic Drugs Advisory Committee
June 28, 2016
AbbVie Figure 2: BCL-2/BCL-X<sub>L</sub> Expression Ratio Among Pediatric Tumor Types

CCSK = clear cell sarcoma of the kidney; NBL = neuroblastoma; AML = acute myeloid leukemia; ALL = acute lymphocytic leukemia; WT = Wilms tumor; OS = osteosarcoma; AMLIF = AML induction failure; RT = rhabdoid tumor

The ratio of BCL-2 mRNA expression relative to BCL-2L1 is plotted for pediatric tumor samples.