Venetoclax in MCL

Prof. Le Gouill
Nantes Medical University, France
Evasion of Apoptosis, or Cell Death, is One Hallmark of Cancer

1. **Resisting Cell Death**
2. Sustained angiogenesis for growth and survival (primarily solid tumors)
3. Self-sufficiency in growth signals
4. Insensitivity to anti-growth signals
5. Tissue invasion and metastasis
6. Limitless replication potential

Others: Evasion of immune system

The BCL-2 Family of Proteins Regulate the Apoptotic Process

The BCL-2 family consists of pro- and anti-apoptotic proteins that function cooperatively to regulate the intrinsic pathway of apoptosis\(^1\text{-}^2\).

The dynamic balance between pro- and anti-apoptotic members determines whether a cell will live or die\(^2\).

Venetoclax is a Selective Inhibitor of BCL-2

Venetoclax is a selective, orally available small-molecule BCL-2 inhibitor which helps restore apoptosis independent of TP53 functional status.1,2

Venetoclax is structurally designed to bind to BCL-2, in a manner analogous to native pro-apoptotic factors.1

Venetoclax Restores Apoptosis by Helping Release Sequestered Pro-apoptotic Proteins\textsuperscript{1-4}

Venetoclax inhibits BCL-2 and can contribute to releasing the store of pro-apoptotic proteins, helping tip the balance in favor of cell death\textsuperscript{1-3}.

Venetoclax can induce cell death irrespective of TP53 function as the effects of BCL-2 inhibition are thought to be independent of this pathway\textsuperscript{4}.

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Venetoclax is developed in a range of hematologic malignancies.

<table>
<thead>
<tr>
<th>Combination (study name)</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLL</strong></td>
<td></td>
</tr>
<tr>
<td>+Rituxan (MURANO)</td>
<td>r/r CLL</td>
</tr>
<tr>
<td>+Gazyva (CLL14)</td>
<td>CLL</td>
</tr>
<tr>
<td>monotherapy</td>
<td>r/r CLL 17p</td>
</tr>
<tr>
<td>+Rituxan</td>
<td>r/r CLL after BCRi</td>
</tr>
<tr>
<td>+BR</td>
<td>r/r CLL &amp; SLL</td>
</tr>
<tr>
<td>+Gazyva</td>
<td>r/r CLL &amp; CLL</td>
</tr>
<tr>
<td>+Gazyva/Imbruvica (CLL13)</td>
<td>1L CLL</td>
</tr>
<tr>
<td>+Rituxan vs BR (CONTRALTO)</td>
<td>r/r FL</td>
</tr>
<tr>
<td>+R-CHOP vs R-CHOP (CAVALLI)</td>
<td>1L DLBCL</td>
</tr>
<tr>
<td>+BR</td>
<td>r/r NHL</td>
</tr>
<tr>
<td>+Gazyva/polatuzumab</td>
<td>r/r CLL &amp; r/r NHL</td>
</tr>
<tr>
<td>+Gazyva/polatuzumab</td>
<td>DLBCL &amp; FL</td>
</tr>
<tr>
<td><strong>NHL</strong></td>
<td></td>
</tr>
<tr>
<td>monotherapy</td>
<td>r/r MM</td>
</tr>
<tr>
<td>+bortezomib/dex</td>
<td>r/r MM</td>
</tr>
<tr>
<td>+bortezomib/dex (a)</td>
<td>r/r MM</td>
</tr>
<tr>
<td><strong>MM</strong></td>
<td></td>
</tr>
<tr>
<td>+dec / +aza (a)</td>
<td>AML</td>
</tr>
<tr>
<td>monotherapy</td>
<td>AML</td>
</tr>
<tr>
<td>+dec / +aza</td>
<td>AML</td>
</tr>
<tr>
<td>+Ara-C</td>
<td>AML</td>
</tr>
<tr>
<td><strong>AML</strong></td>
<td></td>
</tr>
</tbody>
</table>

* indicates Phase 1 trials

Slide provided by Abbvie
Venetoclax: Rational in MCL
MCL: a Bcl-2-dependent tumor

VENETOCLAX, ABT-199 Affinity

BCL2 < 0.01 nM
BCLXL = 48nM
MCL1 > 444nM

Souers et al Nature Medicine 2013

MCL sensitivity to venetoclax correlates with BCL2 / (BCLXL + MCL1) mRNA ratio

Chiron et al Oncotarget 2015
Venetoclax in monotherapy in MCL
Davids MS et al. J Clin Oncol 2017
Phase I First-in-Human Study of Venetoclax in Patients With Relapsed or Refractory Non-Hodgkin Lymphoma

<table>
<thead>
<tr>
<th>Best response</th>
<th>All (106)</th>
<th>MCL (28)</th>
<th>FL (29)</th>
<th>DLBCL (34)</th>
<th>RT (7)</th>
<th>WM (4)</th>
<th>MZL (3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (%)</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>8 (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>24 (23)</td>
<td>2 (7)</td>
<td>1 (3)</td>
<td>19 (56)</td>
<td>1 (14)</td>
<td>0</td>
<td>1 (33)</td>
</tr>
</tbody>
</table>
Venetoclax in combo in MCL
Initial Report of a Multi-Institution Phase I/Ib study of Ibrutinib with Venetoclax in relapsed or refractory Mantle Cell Lymphoma.

2-stages study
Until progression or unacceptable toxicity

**STUDY TYPE**
- Phase: 1/1b
- Accrual: 28(target)
- Location: USA
- Start enrollment: 10/2015

**SPONSOR**
- Graig Portell, University of Virginia, USA

**STATUS**
- Open, recruiting

**KEY INCLUSION CRITERIA**
- Confirmed diagnosis of MCL with at least one prior line of Tx
- Measurable disease
- No previous ibrutinib or BTK inhibitors

**KEY ENDPOINTS**
- DLT (30 d post initiation)
- Toxicity (AE/SAE)
- ORR; CR;
- PFS; OS;
- Completing 4, 16, 28, 40, 56 wks Tx

**STUDY DESIGN**

<table>
<thead>
<tr>
<th>Venetoclax (mg per day)</th>
<th>Ibrutinib (mg per day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>400 (week 3+)</td>
<td>Zone 2 / Arm C</td>
</tr>
<tr>
<td>200 (week 2)</td>
<td>Zone 3 / Arm E</td>
</tr>
<tr>
<td>100 (week 1)</td>
<td>Zone 4 / Arm F</td>
</tr>
<tr>
<td>200 (week 3+)</td>
<td>Zone 1 / Arm A</td>
</tr>
<tr>
<td>200 (week 2)</td>
<td>Zone 2 / Arm B</td>
</tr>
<tr>
<td>100 (week 1)</td>
<td>Zone 3 / Arm D</td>
</tr>
</tbody>
</table>

**CLINICAL UPDATE [ASH 2016, Abstr # 2958]**

- 8 pts reported and finished stage I (Arms A to E)
- Mean age = 63 y (49-81). M / F = 7/1. 5 pts refractory / 3 pts relapsed after ASCT
- 7/8 evaluable for AE. 15 AE (14 grade ½). No TLS, 1 DLT (grade 4 neutropenia),
- 3 pts evaluable for response: 3 PR (1 pt achieving CR at 4 Mo)
Ibrutinib + ABT-199 for MCL (AIM Study)

Con Tam
Victorian Comprehensive Cancer Center
AIM: ABT-199 & Ibrutinib Study

- ABT-199 400mg daily
- Ibrutinib 560mg daily until PD or intolerance

Primary EP

CT, BM & MRD assessments

Plasma DNA

Con tam et al.
# Baseline Characteristics (n=8 eval)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (median, range)</td>
<td>72 (53 – 77)</td>
</tr>
<tr>
<td>Male / Female</td>
<td>7 / 1</td>
</tr>
<tr>
<td>Performance Status (ECOG) ≥ 1</td>
<td>6</td>
</tr>
<tr>
<td>MIPI High / Intermediate Blastic Morphology</td>
<td>6 / 2</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Prior Lines of Therapy (median)</td>
<td>2 (1 – 7)</td>
</tr>
<tr>
<td>- Chemorefractory (%)</td>
<td>63</td>
</tr>
<tr>
<td>- Prev hyperCVAD or autoSCT (%)</td>
<td>25</td>
</tr>
<tr>
<td>Current Status</td>
<td></td>
</tr>
<tr>
<td>- Died of progressive disease</td>
<td>1</td>
</tr>
<tr>
<td>- Alive and continuing therapy</td>
<td>7</td>
</tr>
<tr>
<td>- Time on therapy (days)</td>
<td>120 (54 – 285)</td>
</tr>
</tbody>
</table>

Con tam et al.
Complete remissions in 5 (62.5%) patients - 4 had marrow involvement at baseline, all 4 were MRD-negative at <0.01% by flow cytometry* in the marrow at wk 16.

Con tam et al.
CONCLUSIONS

• The combination of ibrutinib and staggered introduction of venetoclax is safe and deliverable without unexpected toxicities.

• The major toxicities are gastrointestinal.

• Achievement of deep responses of <0.01% MRD opens up possibilities for treatment cessation.
Mechanisms of resistance to venetoclax in MCL

MCL sensitivity to venetoclax correlates with BCL2 / (BCLXL + MCL1) mRNA ratio

Chiron et al Oncotarget 2015
lymphoma ecosystem protect against venetoclax-induced apoptosis

Peripheral Blood MCL cells

Coculture (CD40L+Ck)

Cell cycle activation Bcl2 family modulation

Drug Test D7 to D12

Venetoclax

% of live cells

PB Coculture

Bcl-xL

Mcl1

Bcl2

Bim

Pt#1 Pt#2 Pt#3

Chiron et al Blood Oct 2016
Indirectly targeting BCLXL in lymphoma

Egress from lymph nodes using a BTKi (neutralization of BCR and CXCR4 axis)

Lymph Nodes
BCLXL \(^{\text{high}}\)
Venetoclax Resistance

Blood
BCLXL \(^{\text{low}}\)
Venetoclax Sensitivity

Rapid loss of BCLXL expression in PB

Lymphocytosis
Homing

Chiron et al. Oncotarget 2015

Clinical Trial
Oasis Trial
PI: Pr. S Le Gouill
NTC#02558816

BTK-i (Ibrutinib) // anti-CD20 (GA101) // Venetoclax
A PHASE I/II TRIAL OF OBINUTUZUMAB, ABT-199 (GDC-0199) PLUS IBRUTINIB IN RELAPSED / REFRACTORY MANTLE CELL LYMPHOMA PATIENTS

**STUDY TYPE**
- Phase: 1/2
- Accrual: 33 (target)
- Location: France; UK

**STATUS**
- Open

**SPONSOR**
- J&J/Janssen; Roche; Nantes University Hospital

**KEY INCLUSION CRITERIA**
- Mantle cell lymphoma expressing CD5, CD20 and cyclin D1 or t(11,14) translocation
- Relapsed/refractory after at least one line of Tx
- ECOG PS 0-2

**KEY ENDPOINTS**
- DLT/MTD
- ORR; CRR, PRR; OS; TTP
- AE/Serious AE incidence
- Laboratory abnormalities incidence
- Tumor lysis syndrome incidence, severity
- Bio-bank for biomarker analysis

**CLINICAL UPDATE**
- No clinical update

### STUDY DESIGN

**Step A (9 pts)**
- Ibrutinib 560 mg QD d2-28 c1; d1-28 c2-6
- Obinutuzumab 1000 mg d1/2,8,15 c1; d1 c2-6

**Step B (24 pts)**
- Venetoclax QD: 100 mg w1, 200 mg w2, 400 mg w3, 400 – 1000 mg w3
- Ibrutinib and Obinutuzumab as in Step A

**Maintenance (c7+, 18 mos)**
- Ibrutinib 560 mg QD d1 - 28
- Obinutuzumab 1000 mg d1 c8+ (every 2 cycles)

**CLINICAL UPDATE**
- No clinical update
Conclusion

• There is a strong rational to use Venetoclax in MCL
• The tumor niche may protect against Venetoclax-induced apoptosis
• Ibrutinib + Venetoclax trial is ongoing (AIM)
• Ibrutinib + Venetoclax+Obinutuzumab trial is ongoing (Oasis)
• Venetoclax is probably one of the most promising new drug in MCL
Basic Research
M. Amiot (PhD)
C. Pellat-Deceunynck (PhD)
A. Moreau-Aubry (PhD)
D. Chiron (PhD)

C. Bellanger
C. Dousset
S. Maïga
B. Tessoulin
A. Papin

Translational Research
S. Le Gouill (MD PhD)
C. Touzeau (MD PhD)

Collaborations
Cornell University

Micronit