Novel Strategies Combining BTK and Bcl-2 Inhibitors in CLL

Matthew S. Davids, MD, MMSc
Director of Clinical Research, Division of Lymphoma
Dana-Farber Cancer Institute
Associate Professor of Medicine | Harvard Medical School
Boston, USA
BTK inhibition increases CLL cell dependence on Bcl-2
Frontline Ibrutinib + Venetoclax rapidly induces deep responses

Jain et al., *NEJM*, 2019

### A Study Schema

**Ibrutinib, 420 mg daily**

**Venetoclax, with dose escalated weekly to 400 mg once daily**

### B Response to Treatment over Time

<table>
<thead>
<tr>
<th>Patients with a Response (%)</th>
<th>After 3 Cycles of Ibrutinib Monotherapy (N=75)</th>
<th>After 3 Cycles of Venetoclax-Ibrutinib (N=72)</th>
<th>After 6 Cycles of Venetoclax-Ibrutinib (N=70)</th>
<th>After 9 Cycles of Venetoclax-Ibrutinib (N=60)</th>
<th>After 12 Cycles of Venetoclax-Ibrutinib (N=33)</th>
<th>After 18 Cycles of Venetoclax-Ibrutinib (N=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete remission, with or without normal blood count recovery</td>
<td>96, 43</td>
<td>73, 57</td>
<td>83, 60</td>
<td>88, 61</td>
<td>96, 69</td>
<td></td>
</tr>
<tr>
<td>Partial remission</td>
<td>0, 17</td>
<td>40, 17</td>
<td>27, 12</td>
<td>61, 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undetectable MRD in bone marrow</td>
<td>4, 0</td>
<td>4, 0</td>
<td>4, 0</td>
<td>4, 0</td>
<td>4, 0</td>
<td></td>
</tr>
</tbody>
</table>

### A Progression-free Survival

### B Overall Survival

Jain et al., *NEJM*, 2019
UK CLARITY: Ibrutinib + Venetoclax also leads to high rates of undetectable MRD in R/R CLL, which are translating into durable response.
CAPTIVATE (PCYC-1142) is an international, multicenter phase 2 study evaluating first-line treatment with 3 cycles of ibrutinib followed by 12 cycles of combined ibrutinib + venetoclax that comprises 2 cohorts: MRD and FD.

Results from the MRD cohort demonstrated uMRD in more than two-thirds of patients treated with 12 cycles of ibrutinib + venetoclax (PB, 75%; BM, 68%), and 30-month PFS rates of ≥95% irrespective of subsequent MRD-guided randomized treatment.

Primary analysis of results from the FD cohort of CAPTIVATE are presented.

BM, bone marrow; MRD, minimal residual disease; FD, fixed-duration; PB, peripheral blood; PFS, progression-free survival.

1. Wierda WG et al. ASH 2020, Abstract #123.
CAPTIVATE: Primary Endpoint of CR Rate\textsuperscript{a}: Fixed-Duration Treatment with Ibrutinib + Venetoclax Provides Deep, Durable Responses

- Median age: 60 (range 33-71)
- \textit{TP53} aberrance in 17%
- Primary endpoint was met: 56\% (95\% CI, 48–64) CR rate\textsuperscript{a} in patients without del(17p)
  - Significantly excludes 37\% minimum rate (\(P<0.0001\))
  - Meaningful improvement over 40\% rate of historical comparator of FCR in CLL\textsuperscript{10}

\textbf{Best Overall Response\textsuperscript{b}}

<table>
<thead>
<tr>
<th>Patients without del(17p)</th>
<th>N=136</th>
<th>All treated patients</th>
<th>N=159</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>39.0</td>
<td>PR</td>
<td>40.3</td>
</tr>
<tr>
<td>CR</td>
<td>54.4</td>
<td>CR</td>
<td>52.2</td>
</tr>
<tr>
<td>CRi</td>
<td>1.5</td>
<td>CRi</td>
<td>3.1</td>
</tr>
<tr>
<td>nPR</td>
<td>0.7</td>
<td>nPR</td>
<td>0.6</td>
</tr>
<tr>
<td>nPR</td>
<td>0.7</td>
<td>nPR</td>
<td>0.6</td>
</tr>
<tr>
<td>CR/CRi</td>
<td>55%</td>
<td>CR/CRi</td>
<td>55%</td>
</tr>
</tbody>
</table>

- DOCR \geq 12 cycles
  - \(66/76\) (87) vs \(78/88\) (89)\textsuperscript{*}

\textsuperscript{a}Proportion of patients with CR or CRi. \textsuperscript{b}Overall response was assessed at the end of Cycle 3, on Day 1 of Cycles 7, 10, 13, 19, 25, 28, and 31, and every 6 months thereafter.

\textsuperscript{1} Eichhorst B et al. \textit{Lancet Oncol.} 2016;17:928-942.

\textsuperscript{*}After achieving CR\textsuperscript{a}, 9 patients with <1 year of follow-up were not evaluable; 1 patient died 7 months after CR and completion of therapy.

\textsuperscript{10} ASCO 2021, CAPTIVATE-FD; Ghia et al.

nPR, nodular partial response; PR, partial response; DOCR, duration of complete response.
CAPTIVATE: FD Cohort: High Rates of Undetectable MRD\(^a\) in BM and PB

- High rates of uMRD were observed in both BM and PB, including in patients with high-risk disease features
- uMRD rates were similar between patients with and without bulky disease in BM (63% vs 59%) and PB (both 77%)
- uMRD rates were higher in patients with unmutated IGHV versus mutated IGHV in BM (64% vs 53%) and PB (84% vs 67%)

\(^a\)By 8-color flow cytometry (sensitivity, 10\(^{-4}\)).
## CAPTIVATE: Majority of AEs with Ibrutinib + Venetoclax Were Low Grade

<table>
<thead>
<tr>
<th>AEs, n (%)</th>
<th>All treated patients</th>
<th>Grade 1/2</th>
<th>Any grade</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Most frequent AEs (≥30%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>94 (59)</td>
<td>99 (62)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>66 (42)</td>
<td>68 (43)</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>14 (9)</td>
<td>66 (42)</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>51 (32)</td>
<td>53 (33)</td>
<td></td>
</tr>
<tr>
<td><strong>Grade 3/4 AEs (≥5%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>98 (62)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections&lt;sup&gt;a&lt;/sup&gt;</td>
<td>52 (33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>13 (8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>9 (6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>AEs of clinical interest (any grade)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>7 (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major hemorrhage&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3 (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Any serious AE</strong></td>
<td>36 (23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fatal AEs</strong></td>
<td>1 (1)&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Dose reduction in 21%, discontinuation due to AE in 5%

<sup>a</sup>Combined terms. <sup>b</sup>Sudden death in 1 patient during ibrutinib lead-in.
Phase 3 GLOW Study

Subjects N=211

Key inclusion criteria
- ≥65 years or
- 18–64 with CIRS score >6 or creatinine clearance <70 mL/min

Stratification
- IGHV mutation and del(11q) status

Primary endpoint:
- PFS (assessed by IRC)

Median age: 71 (range 47-93)

CIRS = cumulative illness rating scale; CLL = chronic lymphocytic leukemia; PFS = progression-free survival; R/R = relapsed/refractory; I = ibrutinib; V = Venetoclax; O = Obinutuzumab; Clb = Chlorambucil.

I+V was superior to Clb+O in PFS and consistent across predefined subgroups

<table>
<thead>
<tr>
<th></th>
<th>Median (mo)</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>I+V</td>
<td>106</td>
<td>0.216</td>
<td>0.131-0.357</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Clb+O</td>
<td>105</td>
<td>NR</td>
<td>21.0</td>
<td></td>
</tr>
</tbody>
</table>
GLOW: Undetectable MRD\(^a\) Rate with I+V was Significantly Higher

- Rate of uMRD at EOT+3 was significantly higher for I+V vs Clb+O, irrespective of compartment

- With I+V, PB/BM uMRD concordance\(^b\) was 92.9% (52/56)
  - Versus 43.6% (17/39) for Clb+O

- Best uMRD rates were higher for I+V (by flow cytometry)
  - I+V: 67.9% (BM) and 80.2% (PB)
  - Clb+O: 22.9% (BM) and 46.7% (PB)

\(^a\)All rates are reported with a cutoff of 10\(^{-4}\)

\(^b\)PB/BM uMRD concordance calculated for patients with uMRD in PB and a paired BM sample at 3 months after end of treatment (EOT+3); uMRD, undetectable minimal residual disease; EOT+3, 3 months post end of treatment; NGS, next-generation sequencing; ITT, intent to treat; BM, bone marrow; PB, peripheral blood

EHA 2021, Kater AP, et al.
**GLOW: Summary of Safety and TLS Risk Reduction**

### Grade 3 or Higher AEs in ≥5% of Patients

<table>
<thead>
<tr>
<th></th>
<th>I+V (N = 106)</th>
<th>Clb+O (N = 105)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median exposure, mos (range)</td>
<td>13.8 (0.7-19.5)</td>
<td>5.1 (1.8-7.9)</td>
</tr>
<tr>
<td>Any, %</td>
<td>75.5</td>
<td>69.5</td>
</tr>
<tr>
<td>Neutropenia(^a)</td>
<td>34.9</td>
<td>49.5</td>
</tr>
<tr>
<td>Infections(^b)</td>
<td>17.0</td>
<td>11.4</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5.7</td>
<td>20.0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10.4</td>
<td>1.0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7.5</td>
<td>1.9</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>6.6</td>
<td>0</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>5.7</td>
<td>0</td>
</tr>
<tr>
<td>TLS</td>
<td>0</td>
<td>5.7</td>
</tr>
</tbody>
</table>

\(^a\)Includes ‘neutrophil count decreased’; grade ≥3 febrile neutropenia: 1.9% for I+V vs 2.9% for Clb+O

\(^b\)Includes multiple preferred terms

- After 3 cycles of ibrutinib lead-in, <2% of patients remained at risk for TLS based on high tumor burden
- 2 (1.9%) patients in I+V arm discontinued ibrutinib due to atrial fibrillation
- SAEs in ≥5% of patients for I+V vs Clb+O: Infections (12.3% vs 8.6%) and atrial fibrillation (6.6% vs 0%)
- Rate of secondary malignancies at time of analysis: 8.5% for I+V vs 10.5% for Clb+O
  - NMSC: 3.8% vs 1.9%
  - Other: 4.7% vs 8.6%

--Discontinuation due to AE in 10%--
GLOW: Overall Survival

- HR (95% CI) for overall survival: 1.048 (0.454, 2.419), with 11 deaths in I+V arm and 12 in Clb+O arm (Table)
- Causes of death were generally similar in nature for both study arms, with infections (including COVID-19-related pneumonia) and cardiac events most common

<table>
<thead>
<tr>
<th>Death from Any Cause</th>
<th>During Treatment</th>
<th></th>
<th>During Follow-up</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I+V (N=106)</td>
<td>Clb+O (N=105)</td>
<td>I+V (N=106)</td>
<td>Clb+O (N=105)</td>
</tr>
<tr>
<td></td>
<td>Ibr lead-in</td>
<td>I+V</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total, n</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td>2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>General Disorders (Sudden Death)</td>
<td>-</td>
<td>2</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Neoplasm</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hepatobiliary Disorders</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Respiratory, Thoracic, Mediastinal Dis.</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Progressive Disease/Richter’s Transform.</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
</tbody>
</table>

Median treatment exposure 13.8 mos for I+V and 5.1 mos for Clb+O; overall median study follow up 27.7 months

<sup>a</sup> 1 patent listed as cardiac disorder had 3 causes of death: Tachy-brady syndrome, cardiac failure, pneumonia
Inhibiting 3 distinct targets may result in even greater efficacy
I+V+O (IVO) is highly active in 1L CLL, though tolerability is variable

Safety:

- Hypertension: 82%
- Infusion-related reactions: 74%
- Gr 3/4 neutropenia in 66%
- Arthralgias: 56%
- Headache: 52%
- Atrial fibrillation 10%

Rogers et al., J Clin Oncol., 2020
Triples with newer BTKis are also active and well-tolerated: AVO Study

Study schema (n=44)

Primary endpoint: BM-uMRD CR at C16D1

Safety

- 80% headache (2% Gr ≥3)
- 33% Gr ≥3 neutropenia
- 25% Infusion-related reactions
- 11% hypertension
- 2% Gr ≥3 infection, Afib, and infusion-related reactions (2% each)
- No major bleeding or febrile neutropenia

A = Acalabrutinib; V = Venetoclax; O = Obinutuzumab
Triplets with newer BTKis are also active and well-tolerated: BOVen Study

**BOVen treatment schema**

- **Efficacy**
  - First uMRD in peripheral blood: 2.7% (1/37)
  - Best uMRD: 91.9% (34/37)
  - 89.2% (33/37) have achieved uMRD in peripheral blood and bone marrow and stopped therapy after a median of 10 mo (8 mo of triplet)

- **Safety**
  - Hematologic Adverse Events:
    - Neutrophil count decreased: 43.6% (Grade ≥3: 5.1%)
    - Platelet count decreased: 23.1%
    - Anemia: 46.2%
  - Non-Hematologic Adverse Events:
    - Diarrhea: 25.6%
    - Brusing: 41% (Grade ≥3: 2.6%)
    - Infusion related reaction: 23.1%
    - Myalgia: 10.5%
    - Fatigue: 10.5%
    - Rash: 15.4%
    - Sinusitis: 12.8%
    - Constipation: 12.8%
    - Cough: 12.8%
    - Gastroesophageal reflux disease: 10.3%
    - Arthralgia: 10.3%
    - Nasal congestion: 10.3%
    - Weight loss: 10.3%

**BOVen Treatment = Zanubrutinib (Z), Obinutuzumab and Venetoclax**

Soumerai, JD, et al. ASH 2020
Where are we heading in 1L CLL?

Selected phase 3 trials:

- **UK NCRI FLAIR**: FCR vs. I vs. IV (vs. IR) (n=1,522)
- **CLL13/GAIA**: FCR/BR vs. VR, vs. VO, vs. IVO (n=920)
- **Alliance A041702**: IO vs. IVO (older pts, n=454)
- **ECOG EA9161**: IO vs. IVO (younger pts, n=720)
- **ACE-CL-311**: AVO vs. AV vs. CIT (non-TP53 aberrant, n=780)
- **CLL17**: I vs. IV vs. VO (all comers, n=882)
- **MAJIC**: AV vs. VO (all comers, n=600)
Conclusions: BTKi/BCL-2i in CLL

- Strong scientific rationale for combining BTKi/BCL-2i in CLL
- Early studies of Ibr/Ven showed excellent efficacy in 1L and R/R
- More mature studies of Ibr/Ven continue to show excellent efficacy but suggest better tolerability in younger patients
- Promising triplet therapies now in development with IVO, AVO, ZVO
- Active participation in clinical trials remains critical
Case 1

- A 78 y.o. man with distant h/o prostate cancer and appendiceal carcinoid both cured with surgical resection, 20-year history of SVT managed with diltiazem, as well as trisomy 12, unmutated IGHV CLL observed with his local oncologist since 2012. Gradual progression for the first few years, but by 2018 had more steady progression of CLL and saw me in 10/2018 for initial consultation.

- I repeated prognostic markers and he had acquired del(17p) and TP53 mutation. WBC count up to 233, Hgb 11.6, Plts 283. Lymph nodes 3-4 cm in max dimension, and developing progressive fatigue that was interfering with his daily activities.

- Patient enrolls in the AVO trial (Acala x 1 month, Acala/Obinu x 2 months, Acala/Ven/Obinu x 6 months, then Acala/Ven x 6 or 18 months depending on response). Tolerated therapy well and by C4D1, he achieved a PR, WBC count 3.6, Hgb 13.7, Plts 242. Underwent 4-week outpatient V ramp-up without TLS. At C16D1 had achieved CR with uMRD in the marrow by flow (10^-4) and discontinued Acala/Ven.

- Pt has been back on observation since that time and is now still in CR with uMRD about 20 months after completing all therapy.