Year in Review

Chronic Lymphocytic Leukemia

BTK Inhibitors

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January 2021
The BTKi floodgates have opened...

Irreversible

Reversible

Courtesy of Matthew S Davids, MD, MMSc
Previously Untreated CLL (N = 529)
- Age < 70
- ECOG 0-2
- CrCl > 40
- Able to tolerate FCR
- No deletion 17p by FISH

Randomized 2:1
Ibrutinib + Rituximab (IR) → Ibrutinib until PD
FCR

Primary Endpoint
PFS


- IR was superior to FCR for IGHV unmutated patients
- AEs grade ≥ 3
  - IR, 80.1%
  - FCR, 79.7%
- Infectious complications of grade ≥ 3
  - IR, 10.5%
  - FCR, 20.3%
- April 21, 2020: FDA expanded the indication of ibrutinib to include its combination with rituximab for the initial treatment of adult patients with CLL/SLL

Courtesy of Matthew S Davids, MD, MMSc
Phase 3 RESONATE-2 Trial: 5-Year Update
Ibrutinib Provides Durable Response as Initial Therapy in Frail Pts

Efficacy

- Ibrutinib benefit was also consistent in patients with high prognostic risk (TP53 mutation, 11q deletion, and/or unmutated IGHV)

Safety

- Discontinuation due to AEs decreased over time, with 58% of ibrutinib pts continuing daily treatment

<table>
<thead>
<tr>
<th>Median PFS, mo</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibrutinib</td>
<td>NE</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>15.0</td>
</tr>
</tbody>
</table>

Conclusions

Impact on Patient Care and Treatment Algorithm
• Ibrutinib-based therapy is superior to FCR for young, fit patients with unmutated IGHV
• Ibrutinib provides long term benefit with reasonable tolerability for older patients
• Discontinuations due to toxicity do continue over time, esp. in older patients

Implications for Future Research
• Longer term follow-up needed to understand how to approach mutated-IGHV patients
• Ongoing studies are looking at ibrutinib + CIT (iFCR, iFCG, etc.)
• Ibrutinib will be a key comparator in the CLL17 study (I vs IV vs VO) and in combination with obin in the US cooperative group studies (vs IVO)

Courtesy of Matthew S Davids, MD, MMSc
Second Generation BTKi: Acalabrutinib: Agent Overview

- Highly-selective, potent kinase inhibitor
- Designed to minimize off-target activity with minimal effects on TEC, EGFR, or ITK signaling
- Dosing is 100 mg PO bid

Kinase selectivity profiling at 1 µM

<table>
<thead>
<tr>
<th>Kinase</th>
<th>Acalabrutinib IC₅₀ (nM)</th>
<th>Ibrutinib IC₅₀ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BTK</td>
<td>5.1</td>
<td>1.5</td>
</tr>
<tr>
<td>TEC</td>
<td>126</td>
<td>10</td>
</tr>
<tr>
<td>BMX</td>
<td>46</td>
<td>0.8</td>
</tr>
<tr>
<td>TXK</td>
<td>368</td>
<td>2.0</td>
</tr>
<tr>
<td>ERBB2</td>
<td>~1000</td>
<td>6.4</td>
</tr>
<tr>
<td>EGFR</td>
<td>&gt;1000</td>
<td>5.3</td>
</tr>
<tr>
<td>ITK</td>
<td>&gt;1000</td>
<td>4.9</td>
</tr>
<tr>
<td>JAK3</td>
<td>&gt;1000</td>
<td>32</td>
</tr>
<tr>
<td>BLK</td>
<td>&gt;1000</td>
<td>0.1</td>
</tr>
</tbody>
</table>

The size of the red circle is proportional to the degree of inhibition.


Courtesy of Matthew S Davids, MD, MMSc
Acalabrutinib is Highly Effective in Front-Line CLL

Phase 1/2 ACE-CL-001 Study in patients with previously untreated CLL requiring tx (N = 99)

Acalabrutinib
200 mg once daily
or
100 mg twice daily

• ORR 97% (7% CR, 90% PR)
• Median time to response 3.7 mo

ASCO/EHA 2020 Update: Acalabrutinib monotherapy demonstrated durable remissions and long-term tolerability (median follow-up of 53 months)

• 86% of patients remain on treatment
• Median DOR was not reached
  48-month DOR rate: 97% (95% CI, 90%–99%)
• Median EFS was not reached
  48-month EFS rate: 90% (95% CI, 82%–94%)

Acalabrutinib plus Obinutuzumab in Treatment-Naïve and Relapsed/Refractory Chronic Lymphocytic Leukemia

Jennifer A. Woyach1, James S. Blachly1, Kerry A. Rogers1, Seema A. Bhat1, Molgan Jianfar1, Gerard Lozanski1, David M. Weiss1, Barbara L. Andersen1, Michael Gudrajani1, Melanie M. Frigault2, Ahmed Hamdy3, Raquel Izumi3, Veerendra Munugaveladzla3, Cheng Quah3, Min-Hui Wang3, and John C. Byrd1

Peripheral blood

Bone marrow

TN (n = 19)

C4D1
C7D1
C15D1
C18D1
C21D1
C24D1
C27D1
C30D1
C36D1

C12D1

Patients (%)

Bone marrow

TN (n = 19)

Patients (%)

A

Treatment-naïve (n = 19)

Best response

MRD

IGHVmut

FISH_Del11q

FISH_Del17p

Seq_TP53mut

Seq_TP53_LoH

Response

Genetic alteration

PR

PRL

CR

Not available

Absent

Present

Not available

R/R 42-mo PFS rate (95% CI): 72.7% (43.8%–88.4%)

TN 39-mo PFS rate (95% CI): 94.4% (66.6%–99.2%)

Censored

Proportion progression-free

At risk

TN

R/R

0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45

39-mo PFS rate (95% CI): 94.4% (66.6%–99.2%)

72.7% (43.8%–88.4%)

Woyach et al, Cancer Discovery, 2020

Courtesy of Matthew S Davids, MD, MMSc
Phase 3 ELEVATE-CLL TN: Acalabrutinib is Superior to Obinutuzumab + Chlorambucil for Treatment-Naïve CLL

**Treatment-naive CLL (N=535)**

Age ≥65 or <65 years with coexisting conditions:
- CIRS score >6, or
- creatinine clearance <70 mL/min

**Stratification**
- del(17p), y vs n
- ECOG PS 0-1 vs 2
- Geographic region (N America, W Europe, or other)

**Primary endpoint**
- PFS (assessed by IRC) Acala-G vs G-Clb

**Crossover** from G-Clb to acalabrutinib was allowed after IRC-confirmed progression

- Median follow-up: 28.3 months
- 90% reduction in disease progression or death with acalabrutinib + obinutuzumab
- On November 21, 2019, the FDA approved acalabrutinib monotherapy for the treatment of adult patients with chronic CLL based on analyses from the ELEVATE-TN and ASCEND phase III trials.


(Courtesy of Matthew S Davids, MD, MMSc)
A Phase 2 Study of Acalabrutinib, Venetoclax and Obinutuzumab (AVO) for 1L CLL: Safety

**AEs (N=44), %**

<table>
<thead>
<tr>
<th>AEs (N=44), %</th>
<th>All Grades</th>
<th>Grade ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most frequent hematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>77</td>
<td>34</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>70</td>
<td>22</td>
</tr>
<tr>
<td>Anemia</td>
<td>52</td>
<td>5</td>
</tr>
<tr>
<td>Non-hematologic (≥20%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>80</td>
<td>2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>77</td>
<td>2</td>
</tr>
<tr>
<td>Bruising</td>
<td>57</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>45</td>
<td>0</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>34</td>
<td>2</td>
</tr>
<tr>
<td>Rash</td>
<td>32</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>27</td>
<td>0</td>
</tr>
<tr>
<td>GERD</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>IRR</td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td>Elevated creatinine</td>
<td>23</td>
<td>0</td>
</tr>
</tbody>
</table>

**SAEs**

- Grade 4 neutropenia (n=4), grade 4 hyperkalemia (n=1; in the setting of AKI just prior to C4D1 without TLS), grade 3 cardiac troponin I elevated (n=1; in the setting of O IRR), grade 3 lung infection (n=1)

**AEs of special interest**

- Grade ≥3 infections: 1 (2.3%, grade 3 lung infection)
- IRRs: 11 (25%, including 23% grade 1/2, 2% grade 3)
- Hypertension: 5 (11%; no grade ≥3)
- Afib: 1 grade 3
- Lab TLS: 2 grade 3 (both after O and prior to V)

A Phase 2 Study of Acalabrutinib, Venetoclax and Obinutuzumab (AVO) for 1L CLL: Efficacy and Summary

- 11 pts in BM-uMRD CR discontinued after 15 cycles, as per protocol
  - Median time off therapy: 4 months (range: 1-10)
- Median follow-up: 19 cycles (range, 6-26)
- No patients had progressed or had recurrent MRD to date

Summary
- AVO demonstrated efficacy and a favorable safety profile in patients with high-risk, TN CLL
- No TLS due to Ven was observed using a 4-week Ven ramp-up
- Accrual to a TP53-aberrant cohort is ongoing

Phase 3 ASCEND: Acalabrutinib Monotherapy Significantly Improves PFS in R/R CLL

**Adult patients with R/R CLL**

N = 310

- ≥ 1 prior systemic therapies (no prior exposure to a BCL-2 inhibitor or BCR-signalling inhibitor)
- ECOG PS 0-2
- Stratified by Del(17p), ECOG PS 0-1 vs 2, 1-3 vs ≥ 4 prior tx

**Randomization**

- Acalabrutinib vs Idelalisib + Rituximab or Bendamustine + Rituximab

**Primary endpoint:** IRC-assessed PFS

**Acalabrutinib vs IdR/BR**

- Median follow-up of 22.0 months
- Estimated 18-month PFS was 82% for acalabrutinib vs 48% for investigator’s choice
- Estimated 18-month OS was 88% for both treatment regimens
- ORR was 80% for acalabrutinib vs 84% for investigator's choice

**Courtesy of Matthew S Davids, MD, MMSc**
Conclusions

Impact on Patient Care and Treatment Algorithm

• Acalabrutinib is a well-tolerated BTKi with evolving long term efficacy data
• Safety profile of acala makes it a good option, especially for older patients
• Combining acala with obin can deepen response, improve PFS

Implications for Future Research

• Ongoing study is examining AVO vs AV vs CIT (CL-311 study)
• Future studies needed to compare AV-based therapy to VO

Courtesy of Matthew S Davids, MD, MMSc
MAIC: Acalabrutinib ± Obinutuzumab (G) Demonstrated Lower Rates of Several Clinically Important AEs vs Ibrutinib ± G in TN CLL

Acalabrutinib ± Obinutuzumab (G) Demonstrated Lower Rates of Several Clinically Important AEs vs Ibrutinib ± G in TN CLL

### AEs With Statistically Significant Differences After Matching

<table>
<thead>
<tr>
<th>Acalabrutinib vs Ibrutinib</th>
<th>Acalabrutinib + G vs Ibrutinib + G</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AE rate, %</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Acal ESS=79</strong></td>
<td><strong>Acal + G ESS=97</strong></td>
</tr>
<tr>
<td><strong>Ibr n=136</strong></td>
<td><strong>Ibr + G n=113</strong></td>
</tr>
<tr>
<td><strong>Rate difference % (95% CI)</strong></td>
<td><strong>Rate difference % (95% CI)</strong></td>
</tr>
<tr>
<td><strong>P-value</strong></td>
<td><strong>P-value</strong></td>
</tr>
<tr>
<td><strong>Grade 3/4 AEs</strong></td>
<td><strong>Grade 3/4 AEs</strong></td>
</tr>
<tr>
<td>Infections</td>
<td>Infections</td>
</tr>
<tr>
<td>12.4</td>
<td>24.0</td>
</tr>
<tr>
<td>-11.6 (−21.9,−1.0)</td>
<td>−11.4 (−17.5,−5.3)</td>
</tr>
<tr>
<td>&lt;0.05</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>0</td>
<td>4.0</td>
</tr>
<tr>
<td>−4.0 (−7.3,0.0)</td>
<td>−4.5 (−8.6,−0.4)</td>
</tr>
<tr>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>Grade 1-4 AEs</strong></td>
<td><strong>Grade 1-4 AEs</strong></td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>Peripheral edema</td>
</tr>
<tr>
<td>7.5</td>
<td>21.0</td>
</tr>
<tr>
<td>−13.5 (−21.7,−5.0)</td>
<td>−11.4 (−17.5,−5.3)</td>
</tr>
<tr>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>Pyrexia</td>
</tr>
<tr>
<td>6.2</td>
<td>20.0</td>
</tr>
<tr>
<td>−13.8 (−21.6,−6.0)</td>
<td>−15.3 (−26.8,−3.9)</td>
</tr>
<tr>
<td>&lt;0.001</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Hypertension</td>
</tr>
<tr>
<td>6.4</td>
<td>18.0</td>
</tr>
<tr>
<td>−11.6 (−19.9,−3.0)</td>
<td>−8.6 (−15.6,−1.7)</td>
</tr>
<tr>
<td>&lt;0.01</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Major hemorrhage</td>
<td>Major hemorrhage</td>
</tr>
<tr>
<td>1.8</td>
<td>7.0</td>
</tr>
<tr>
<td>−5.2 (−10.2,0.0)</td>
<td></td>
</tr>
<tr>
<td>&lt;0.05</td>
<td></td>
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</tbody>
</table>
MAIC: Acalabrutinib ± G Demonstrated a Trend Towards Improved PFS and OS vs Ibrutinib ± G in TN CLL

Acalabrutinib monotherapy significantly reduced risk of death compared with ibrutinib + G by 84% (P<0.001) after matching.
Conclusions

Impact on Patient Care and Treatment Algorithm
• The MAIC found that acalabrutinib (with or without obin) had lower rates of several AEs than ibrutinib (with or without obin) in treatment-naïve patients with CLL, without compromising efficacy
• Although not definitive, this study provides some initial insights into differences between these drugs

Implications for Future Research
• ELEVATE R/R will help define the differences between acala and ibrutinib
# Zanubrutinib (BGB-3111): High BTK Selectivity

<table>
<thead>
<tr>
<th>Targets</th>
<th>Assays</th>
<th>Ibrutinib IC$_{50}$ (nM)</th>
<th>Zanubrutinib IC$_{50}$ (nM)</th>
<th>Ratio (Zanubrutinib:Ibrutinib)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BTK</td>
<td>BTK-pY223 Cellular Assay</td>
<td>3.5</td>
<td>1.8</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>Rec-1 Proliferation</td>
<td>0.34</td>
<td>0.36</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>BTK Occupation Cellular Assay</td>
<td>2.3</td>
<td>2.2</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>BTK Biochemical Assay</td>
<td>0.20</td>
<td>0.22</td>
<td>1.1</td>
</tr>
<tr>
<td>EGFR</td>
<td>p-EGFR HTRF Cellular Assay</td>
<td>101</td>
<td>606</td>
<td>6.0</td>
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<tr>
<td></td>
<td>A431 Proliferation</td>
<td>323</td>
<td>3210</td>
<td>9.9</td>
</tr>
<tr>
<td>ITK</td>
<td>ITK Occupancy Cellular Assay</td>
<td>189</td>
<td>3265</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>p-PLC$_{v1}$ Cellular Assay</td>
<td>77</td>
<td>3433</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>IL-2 Production Cellular Assay</td>
<td>260</td>
<td>2536</td>
<td>9.8</td>
</tr>
<tr>
<td></td>
<td>ITK Biochemical Assay</td>
<td>0.9</td>
<td>30</td>
<td>33</td>
</tr>
<tr>
<td>JAK3</td>
<td>JAK3 Biochemical Assay</td>
<td>3.9</td>
<td>200</td>
<td>51</td>
</tr>
<tr>
<td>HER2</td>
<td>HER2 Biochemical Assay</td>
<td>9.4</td>
<td>661</td>
<td>70</td>
</tr>
<tr>
<td>TEC</td>
<td>TEC Biochemical Assay</td>
<td>0.8</td>
<td>1.9</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Results From Arm C of the Phase 3 SEQUOIA Trial of Zanubrutinib for Patients With TN del(17p) CLL/SLL: Efficacy

Best Overall Response

**ORR, 94.5%**
(95% CI, 88.4-98.0)

**Best Overall Response**

<table>
<thead>
<tr>
<th>Investigator Assessment</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>5.5%</td>
</tr>
<tr>
<td>CRi</td>
<td>0.9%</td>
</tr>
<tr>
<td>nPR</td>
<td>0.9%</td>
</tr>
<tr>
<td>PR</td>
<td>86.2%</td>
</tr>
<tr>
<td>PR-L</td>
<td>0.9%</td>
</tr>
<tr>
<td>SD</td>
<td>4.6%</td>
</tr>
<tr>
<td>PD</td>
<td>0.9%</td>
</tr>
</tbody>
</table>

**Progression-Free Survival**

18-mo PFS (95% CI)*:
90.6% (83.3, 94.9)

**Overall Survival**

18-mo OS (95% CI)*:
95.4% (89.3, 98.1)


Courtesy of Matthew S Davids, MD, MMSc

Median follow-up: 21.9 months (range, 5.0-30.2)
Conclusions

Impact on Patient Care and Treatment Algorithm
• Zanubrutinib is efficacious in patients with high risk TN CLL
• The toxicity profile looks more similar to acala than to ibrutinib
• Possible advantages of zanubrutinib include potential for daily dosing and no drug-drug interaction with PPIs

Implications for Future Research
• Awaiting registrational arm of the SEQUOIA study for zanubrutinib approval in CLL
• Other promising combinations with zanu under evaluation (e.g. BOVen)
Overall response rates to BTKi:

- BTKi naïve (n=44): 84%
- BTKi exposed (n=30): 53%
- PI3Ki (n=17): 47%
- CAR-T (n=18): 67%
BTK inhibitor therapy is effective in patients with CLL resistant to venetoclax

**ORR: 91%, CR: 18%**

**LYMPHOID NEOPLASIA**

Comment on Lin et al, page 2266

**Inverting the BTK-BCL2 order**

Jennifer R. Brown | Dana-Farber Cancer Institute

In this issue of Blood, Lin et al report the first long-term follow-up data showing that Bruton tyrosine kinase inhibitors (BTKi’s) are effective in chronic lymphocytic leukemia (CLL) after previous progression on venetoclax.¹

Lin VS et al., Blood, 2020

Courtesy of Matthew S Davids, MD, MMSc
Conclusions

Impact on Patient Care and Treatment Algorithm
• Several retrospective datasets have emerged suggesting that BTKis are active post-venetoclax
• For patients with prior BTKi progression, re-treatment with a BTKi is unlikely to be helpful
• PI3Kis are an option for patients who progress on both BTKi and BCL-2i, but initial data suggest responses are unlikely to be durable

Implications for Future Research
• Awaiting prospective data on this sequence (MURANO will provide some)
• Sequencing questions are important but it is challenging to incorporate the next line of therapy into a clinical trial
• Prospective registry-based studies are one way to capture this information
Resistance and Intolerance Limit Covalent BTK Inhibitor Outcomes

- Front line: Ibrutinib discontinuation rate at 5 years = 41%\(^1\)
- Relapsed/refractory: Predicted ibrutinib discontinuation rate at 5 years = 53.7% (4 sequential studies)\(^7\)
- The appearance of BTK C481 mutations is the dominant reason for progressive CLL after covalent BTK inhibitors\(^1-8\)
- BTK C481 mutations prevent covalent BTK inhibitors from effective target inhibition\(^1-6\)


Courtesy of Matthew S Davids, MD, MMSc

(Courtesy of A. Mato)
ARQ-531 (MK-1026) is active in high risk CLL patients including C481S BTK mut
Phase 1/2 BRUIN Study of LOXO-305 in Patients With R/R CLL/SLL: Safety

<table>
<thead>
<tr>
<th>Adverse Events, at All Doses and Patients (N=323), n (%)</th>
<th>Treatment-Emergent AEs, (≥10%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Treatment-Related AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>65 (20)</td>
<td>40 (12)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>55 (17)</td>
<td>45 (14)</td>
</tr>
<tr>
<td>Contusion</td>
<td>42 (13)</td>
<td>37 (12)</td>
</tr>
<tr>
<td>AEs of special interest, b, c</td>
<td>53 (16)</td>
<td>48 (15)</td>
</tr>
<tr>
<td>Bruising</td>
<td>35 (11)</td>
<td>30 (9)</td>
</tr>
<tr>
<td>Rash</td>
<td>16 (5)</td>
<td>13 (4)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>15 (5)</td>
<td>10 (3)</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>15 (5)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2 (&lt;1)</td>
<td>-</td>
</tr>
<tr>
<td>AFib/Flutter</td>
<td>2 (&lt;1)</td>
<td>-</td>
</tr>
</tbody>
</table>

- No DLTs reported and MTD not reached
- 5 (1.5%) discontinued due to treatment-related AEs
- 200 mg QD selected as recommended phase 2 dose

Data cutoff date of 27 September 2020.<sup>1</sup>The AEs listed are the most common that occurred at any grade in at least 10% of the patients, regardless of attribution.<sup>2</sup>AEs of special interest are those that were previously associated with covalent BTKi.<sup>3</sup>Bruising includes contusion, petechia, ecchymosis and increased tendency to bruise. Hemorrhage includes hematoma, epistaxis, rectal hemorrhage, subarachnoid hemorrhage, upper gastrointestinal hemorrhage, vitreous hemorrhage and wound hemorrhage. Rash includes rash maculo-papular, rash, rash macular, rash erythematous, rash popular, rash pruritic and rash pustular.<sup>4</sup>Subarachnoid bleed sustained during a bicycle accident, considered by investigator as unrelated to LOXO-305. Both events considered by investigators as unrelated to LOXO-305 due to a history of prior atrial fibrillation in each.


Courtesy of Matthew S Davids, MD, MMSc
Phase 1/2 BRUIN Study of LOXO-305 in Patients With R/R CLL/SLL: Efficacy

- ORR increased over time: PR/PR-L 63% to 86% from start of treatment to ≥10 months follow-up
- Median follow-up: 6 months (0.6-17.8+) for efficacy-evaluable\(^a\) pts
- 83 (94%) of responding patients with CLL/SLL are ongoing/in response
  - 5 responders discontinued: 4 for PD, 1 in PR electively underwent transplantation

\(^a\)Efficacy evaluable patients are those who had at least one evaluable post-baseline assessment or had discontinued treatment prior to first post-baseline assessment.


---

### Response Rates

<table>
<thead>
<tr>
<th></th>
<th>All Patients(^a) (N=139)</th>
<th>BTK Pre-Treated Patients(^a) (n=121)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR, % (95% CI)</strong></td>
<td>63 (55-71)</td>
<td>62 (53-71)</td>
</tr>
<tr>
<td><strong>Best response, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>69 (50)</td>
<td>57 (47)</td>
</tr>
<tr>
<td>PR-L</td>
<td>19 (14)</td>
<td>18 (15)</td>
</tr>
<tr>
<td>SD</td>
<td>45 (32)</td>
<td>41 (34)</td>
</tr>
</tbody>
</table>

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### Treatment Duration

![Treatment Duration Graph]

Data cut-off date 27 September 2020.

### PFS

![PFS Graph]

Number at risk

- 170
- 105
- 82
- 51
- 31
- 19
- 7
- 3
- 2

Months from start of treatment

- 0
- 2
- 4
- 6
- 8
- 10
- 12
- 14
- 16

Patients free from Progression (%)

Courtesy of Matthew S Davids, MD, MMSc

Conclusions

Impact on Patient Care and Treatment Algorithm
• Reversible, non-covalent BTKi appear to be active in both BTK wildtype and mutant patients
• Though early, the toxicity profile of these new drugs also appears to be favorable
• Once approved, these drugs will initially have a role in BTKi progressors

Implications for Future Research
• Studies are in development to compare the new BTKis to R/R SOC
• Frontline study of new BTKis vs. ibrutinib will also likely be pursued
• These drugs have the potential for broader use if these studies are positive

Courtesy of Matthew S Davids, MD, MMSc