Year in Review — Clinical Investigators Provide Perspectives on the Most Relevant New Publications, Data Sets and Advances in Oncology: Chronic Lymphocytic Leukemia

Thursday, January 21, 2021
5:00 PM – 6:00 PM ET

Faculty
Matthew S Davids, MD, MMSc
Jennifer Woyach, MD

Moderator
Neil Love, MD
YiR Chronic Lymphocytic Leukemia Faculty

Matthew S Davids, MD, MMSc
Associate Professor of Medicine
Harvard Medical School
Director of Clinical Research, Division of Lymphoma
Dana-Farber Cancer Institute
Boston, Massachusetts

Jennifer Woyach, MD
Professor
Section Head, CLL and Hairy Cell Leukemia
Associate Division Director for Clinical Research
Division of Hematology
Department of Internal Medicine
The Ohio State University Comprehensive Cancer Center
Columbus, Ohio
Commercial Support

This activity is supported by educational grants from Adaptive Biotechnologies Corporation, AstraZeneca Pharmaceuticals LP, Lilly, and Pharmacyclics LLC, an AbbVie Company and Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC.
Research To Practice CME Planning Committee Members, Staff and Reviewers

Planners, scientific staff and independent reviewers for Research To Practice have no relevant conflicts of interest to disclose.
## Dr Davids — Disclosures

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advisory Committee</strong></td>
<td>AbbVie Inc, Ascentage Pharma, AstraZeneca Pharmaceuticals LP, Genentech, a member of the Roche Group, Janssen Biotech Inc, Lilly, Pharmacyclics LLC, an AbbVie Company, TG Therapeutics Inc</td>
</tr>
<tr>
<td><strong>Consulting Agreements</strong></td>
<td>AbbVie Inc, Adaptive Biotechnologies Corporation, AstraZeneca Pharmaceuticals LP, BeiGene, Genentech, a member of the Roche Group, Janssen Biotech Inc, Lilly, MEI Pharma Inc, Merck, Novartis, Pharmacyclics LLC, an AbbVie Company, Verastem Inc, Zentalis Pharmaceuticals</td>
</tr>
<tr>
<td><strong>Contracted Research</strong></td>
<td>AbbVie Inc, Ascentage Pharma, AstraZeneca Pharmaceuticals LP, Genentech, a member of the Roche Group, MEI Pharma Inc, Novartis, Pharmacyclics LLC, an AbbVie Company, Surface Oncology, TG Therapeutics Inc, Verastem Inc</td>
</tr>
<tr>
<td>Disclosure Type</td>
<td>Companies</td>
</tr>
<tr>
<td>------------------------------</td>
<td>------------------------------------------------------------------</td>
</tr>
<tr>
<td>Advisory Committee</td>
<td>AbbVie Inc, ArQule Inc, Janssen Biotech Inc</td>
</tr>
<tr>
<td>Consulting Agreements</td>
<td>AbbVie Inc, ArQule Inc, AstraZeneca Pharmaceuticals LP, Janssen Biotech Inc, Pharmacyclics LLC, an AbbVie Company</td>
</tr>
<tr>
<td>Contracted Research</td>
<td>AbbVie Inc, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly &amp; Company</td>
</tr>
<tr>
<td>Data and Safety Monitoring Board/Committee</td>
<td>Gilead Sciences Inc</td>
</tr>
</tbody>
</table>
We Encourage Clinicians in Practice to Submit Questions

You may submit questions using the Zoom Chat option below.

Feel free to submit questions now before the program begins and throughout the program.
Familiarizing Yourself with the Zoom Interface

How to answer poll questions

When a poll question pops up, click your answer choice from the available options. Results will be shown after everyone has answered.
ONCOLOGY TODAY
WITH DR NEIL LOVE

FRONT-LINE TREATMENT OF CHRONIC LYMPHOCYTIC LEUKEMIA

DR JOHN PAGEL
SWEDISH CANCER INSTITUTE
SEATTLE, WASHINGTON
Meet The Professor
Management of Ovarian Cancer

Friday, January 22, 2021
1:15 PM – 2:15 PM ET

Faculty
Professor Jonathan A Ledermann, MD

Moderator
Neil Love, MD
Cancer Conference Update: What Happened at the 2020 San Antonio Breast Cancer Symposium®

Management of HER2-Positive Breast Cancer

Monday, January 25, 2021
5:00 PM – 6:00 PM ET

Faculty
Erika Hamilton, MD

Moderator
Neil Love, MD
Year in Review — Clinical Investigators Provide Perspectives on the Most Relevant New Publications, Data Sets and Advances in Oncology: Targeted Therapy for Lung Cancer

Tuesday, January 26, 2021
5:00 PM – 6:00 PM ET

Faculty
Joel W Neal, MD, PhD
Paul K Paik, MD

Moderator
Neil Love, MD
Cases from the Community: Investigators Discuss Emerging Research and Actual Patients with Hepatocellular Carcinoma (Part 1 of a 3-Part Series)

Wednesday, January 27, 2021
5:00 PM – 6:30 PM ET

Faculty
Richard S Finn, MD
Tim Greten, MD
James J Harding, MD
Ahmed Omar Kaseb, MD, CMQ

Moderator
Neil Love, MD
Year in Review — Clinical Investigators Provide Perspectives on the Most Relevant New Publications, Data Sets and Advances in Oncology:

Multiple Myeloma

Thursday, January 28, 2021
5:00 PM – 6:00 PM ET

Faculty
Rafael Fonseca, MD
Jonathan L Kaufman, MD

Moderator
Neil Love, MD
Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 5 business days.
- 2019: PLTs 75k, Hb 9.2 mg/dl with increasing cancer margin.
- Repeat FISH del(13q14) & NGS. No evidence of TPS3 mutation.
Year in Review — Clinical Investigators Provide Perspectives on the Most Relevant New Publications, Data Sets and Advances in Oncology: Chronic Lymphocytic Leukemia

Thursday, January 21, 2021
5:00 PM – 6:00 PM ET

Faculty
Matthew S Davids, MD, MMSc
Jennifer Woyach, MD

Moderator
Neil Love, MD
YiR Chronic Lymphocytic Leukemia Faculty

Matthew S Davids, MD, MMSc
Associate Professor of Medicine
Harvard Medical School
Director of Clinical Research, Division of Lymphoma
Dana-Farber Cancer Institute
Boston, Massachusetts

Jennifer Woyach, MD
Professor
Section Head, CLL and Hairy Cell Leukemia
Associate Division Director for Clinical Research
Division of Hematology
Department of Internal Medicine
The Ohio State University Comprehensive Cancer Center
Columbus, Ohio
We Encourage Clinicians in Practice to Submit Questions

Feel free to submit questions now before the program begins and throughout the program.
Familiarizing Yourself with the Zoom Interface

How to answer poll questions

When a poll question pops up, click your answer choice from the available options. Results will be shown after everyone has answered.
ONCOLOGY TODAY
WITH DR NEIL LOVE
FRONT-LINE TREATMENT OF
CHRONIC LYMPHOCYTIC LEUKEMIA

DR JOHN PAGEL
SWEDISH CANCER INSTITUTE
SEATTLE, WASHINGTON

Listen on Apple Podcasts
Listen on Spotify
Listen on Google Podcasts
Meet The Professor
Management of Ovarian Cancer

Friday, January 22, 2021
1:15 PM – 2:15 PM ET

Faculty
Professor Jonathan A Ledermann, MD

Moderator
Neil Love, MD
Cancer Conference Update: What Happened at the 2020 San Antonio Breast Cancer Symposium®

Management of HER2-Positive Breast Cancer

Monday, January 25, 2021
5:00 PM – 6:00 PM ET

Faculty
Erika Hamilton, MD

Moderator
Neil Love, MD
Year in Review — Clinical Investigators Provide Perspectives on the Most Relevant New Publications, Data Sets and Advances in Oncology:

Targeted Therapy for Lung Cancer

Tuesday, January 26, 2021
5:00 PM – 6:00 PM ET

Faculty
Joel W Neal, MD, PhD
Paul K Paik, MD

Moderator
Neil Love, MD
Cases from the Community: Investigators Discuss Emerging Research and Actual Patients with Hepatocellular Carcinoma (Part 1 of a 3-Part Series)

Wednesday, January 27, 2021
5:00 PM – 6:30 PM ET

Faculty
Richard S Finn, MD
Tim Greten, MD
James J Harding, MD
Ahmed Omar Kaseb, MD, CMQ

Moderator
Neil Love, MD
Year in Review — Clinical Investigators Provide Perspectives on the Most Relevant New Publications, Data Sets and Advances in Oncology: Multiple Myeloma

Thursday, January 28, 2021
5:00 PM – 6:00 PM ET

Faculty
Rafael Fonseca, MD
Jonathan L Kaufman, MD

Moderator
Neil Love, MD
Year in Review — Clinical Investigators Provide Perspectives on the Most Relevant New Publications, Data Sets and Advances in Oncology: Chronic Lymphocytic Leukemia

Thursday, January 21, 2021
5:00 PM – 6:00 PM ET

Faculty
Matthew S Davids, MD, MMSc
Jennifer Woyach, MD

Moderator
Neil Love, MD
Agenda

Module 1: Venetoclax combinations — Azacitidine, decitabine, LDAC, pracinostat
Module 2: FLT3 inhibitors — Midostaurin, gilteritinib, quizartinib
Module 3: IDH inhibitors — Ivosidenib, enasidenib
Module 4: Oral azacitidine (CC-486)
Module 5: Secondary AML — CPX-351
Module 6: Novel agents and strategies — Gemtuzumab ozogamicin, glasdegib, magrolimab
Vladimir ...... Therapy for younger patient with AML very fit and eligible for chemotherapy who has TP53 mutation and complex karyotype. Chemotherapy or AZA VEN? Other combo? If CR proceed to Tx or not at all. Tx only for molecular CR? TP53 VAF < 5%? Is there any future for Tx for TP53mut AML? Please, honest response outside a trial and simple answer: What do you do 21 January 2020 in such a patient?
Agenda

Module 1: BTK Inhibitors

Module 2: Bcl-2 Inhibitors

Module 3: Novel Strategies – U2 Regimen (Umbralisib, Ublituximab)
CAR T-Cell Therapy
Agenda

Module 1: BTK Inhibitors

Module 2: Bcl-2 Inhibitors

Module 3: Novel Strategies – U2 Regimen (Umbralisib, Ublituximab)
CAR T-Cell Therapy
To what extent do issues related to COVID-19 (social distancing, avoiding lymphopenia, etc) affect your first-line therapy recommendation for a patient with CLL in their mid-70s with minor comorbidities and moderate disease burden who requires treatment?

1. Minimal or no effect
2. Now more likely to use BTK inhibitors
3. Now more likely to use venetoclax/obinutuzumab
In general, what first-line therapy do you recommend for a patient with CLL in their mid-70s with minor comorbidities and moderate disease burden and no IGHV, del(17p) or TP53 mutation who requires treatment?

1. Ibrutinib
2. Ibrutinib/anti-CD20 antibody
3. Acalabrutinib
4. Acalabrutinib/anti-CD20 antibody
5. Venetoclax/obinutuzumab
6. BR
7. Other
Module 1: BTK Inhibitors

- **Key Relevant Data Sets**
  - ECOG-E1912: Extended follow-up
  - RESONATE-2: Five-year update of first-line ibrutinib
  - ACE-CL-001: Acalabrutinib for treatment-naïve CLL
  - ELEVATE-TN: Acalabrutinib +/- obinutuzumab
  - AVO: Acalabrutinib/venetoclax/obinutuzumab
  - MAIC: Acalabrutinib +/- obinutuzumab
  - SEQUOIA: Zanubrutinib for treatment-naïve del(17p) CLL
  - BTK inhibition for venetoclax-refractory CLL
  - BRUIN: Next-generation BTK inhibitor LOXO-305
The BTKi floodgates have opened...

Irreversible

Reversible

Courtesy of Matthew S Davids, MD, MMSc
Phase 3 E1912: IR vs FCR
IR Effective as Initial Treatment for CLL

Previously Untreated CLL (N = 529)
- Age < 70
- ECOG 0-2
- CrCl > 40
- Able to tolerate FCR
- No deletion 17p by FISH

IR vs FCR
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

PFS-All Patients

OS

Courtesy of Matthew S Davids, MD, MMSc
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>Patients at Risk</th>
<th>Median PFS, mo</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibrutinib</td>
<td>NE</td>
<td>0.146 (0.098-0.218)</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>15.0</td>
<td></td>
</tr>
</tbody>
</table>

Phase 3 RESONATE-2 Trial: 5-Year Update
Ibrutinib Provides Durable Response as Initial Therapy in Frail Pts

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**

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

**Kinase Inhibition IC\(_{50}\) (nM)**

<table>
<thead>
<tr>
<th>Kinase</th>
<th>Acalabrutinib</th>
<th>Ibrutinib</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>


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)

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

Acalabrutinib
200 mg once daily
or
100 mg twice daily

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%)

Courtesy of Matthew S Davids, MD, MMSc

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 Munugalavadla³, Cheng Quah³, Min-Hui Wang³, and John C. Byrd³

A

Treatment-naïve (n = 19)

Best response
IGHVMut
FISH_Del11q
FISH_Del17p
Seq_TP53mut
Seq_TP53_LoH
MRD

Response
Genetic alteration
PR
Present
CR
Absent
Not available

Peripheral blood

Patients (%)

Bone marrow

Patients (%)

TN (n = 19)

C4D1 C7D1 C10D1 C13D1 C16D1 C19D1 C22D1 C25D1 C28D1 C31D1 C34D1

C4D1 C7D1 C10D1 C13D1 C16D1 C19D1 C22D1 C25D1 C28D1 C31D1 C34D1

Progression-free survival

Proportion progression-free

At risk

TN 19 19 18 18 19 18 18 17 17 17 17 15 4 4 0
R/R 26 26 26 26 26 26 26 25 23 23 23 22 10 9 1

39-mo PFS rate (95% CI): 94.4% (66.6%–99.2%)
42-mo PFS rate (95% CI): 72.7% (43.8%–88.4%)

TNA 42% 21% 4% 5% Not available
Low MRD (0.01%–1%)
MRD (≤0.01%)
MRD (≥1%)
Discontinuation
Not available

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

Treatment-naïve 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>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>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>

**Most frequent hematologic**

- Neutropenia: 77 (34%)
- Thrombocytopenia: 70 (22%)
- Anemia: 52 (5%)

**Non-hematologic (≥20%)**

- Headache: 80 (2%)
- Fatigue: 77 (2%)
- Bruising: 57 (0%)
- Nausea: 45 (0%)
- Hypocalcemia: 34 (2%)
- Rash: 32 (0%)
- Diarrhea: 27 (0%)
- GERD: 25 (0%)
- IRR: 25 (2%)
- Elevated creatinine: 23 (0%)

**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)


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

Acalabrutinib ± Obinutuzumab (G) vs Ibrutinib ± Obinutuzumab (G) in TN CLL

<table>
<thead>
<tr>
<th>AE rate, %</th>
<th>Acala ESS=79</th>
<th>Ibr n=136</th>
<th>Rate difference % (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3/4 AEs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td>12.4</td>
<td>24.0</td>
<td>-11.6 (-21.9, -1.0)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0</td>
<td>4.0</td>
<td>-4.0 (-7.3, 0.0)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Grade 1-4 AEs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>7.5</td>
<td>21.0</td>
<td>-13.5 (-21.7, -5.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>6.2</td>
<td>20.0</td>
<td>-13.8 (-21.6, -6.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6.4</td>
<td>18.0</td>
<td>-11.6 (-19.9, -3.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Major hemorrhage</td>
<td>1.8</td>
<td>7.0</td>
<td>-5.2 (-10.2, 0.0)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AE rate, %</th>
<th>Acala + G ESS=97</th>
<th>Ibr + G n=113</th>
<th>Rate difference % (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3/4 AEs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>0.6</td>
<td>12.0</td>
<td>-11.4 (-17.5, -5.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>0.5</td>
<td>5.0</td>
<td>-4.5 (-8.6, -0.4)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Grade 1-4 AEs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>32.1</td>
<td>8.0</td>
<td>+24.1 (+14.6, +33.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>20.7</td>
<td>36.0</td>
<td>-15.3 (-26.8, -3.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>3.4</td>
<td>12.0</td>
<td>-8.6 (-15.6, -1.7)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Courtesy of Matthew S Davids, MD, MMSc
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.
# 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>1.0</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>
</tr>
<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$_{y1}$ 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>


Courtesy of Matthew S Davids, MD, MMSc
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)

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

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

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

Courtesy of Matthew S Davids, MD, MMSc
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
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%) a</th>
<th>Treatment-Related AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Any Grade) (Grade 1) (Grade 2) (Grade 3) (Any Grade) (Grade 3/4)</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>Bruising</td>
<td>53 (16)</td>
<td>48 (15)</td>
</tr>
<tr>
<td>Rash</td>
<td>35 (11)</td>
<td>30 (9)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>16 (5)</td>
<td>13 (4)</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>15 (5)</td>
<td>10 (3)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15 (5)</td>
<td>2 (&lt;1)</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. aThe AEs listed are the most common that occurred at any grade in at least 10% of the patients, regardless of attribution. bAEs of special interest are those that were previously associated with covalent BTKi. cBruising 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 erythematosus, rash popular, rash pruritic and rash purpular. dSubarachnoid bleed sustained during a bicycle accident, considered by investigator as unrelated to LOXO-305. eBoth 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

<table>
<thead>
<tr>
<th>Best response, n (%)</th>
<th>All Patients(^a) (N=139)</th>
<th>BTK Pre-Treated Patients(^a) (n=121)</th>
</tr>
</thead>
<tbody>
<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>

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


PFS

Courtesy of Matthew S Davids, MD, MMSc
What is your usual preferred initial regimen for a 60-year-old patient with CLL with IGHV mutation but without del(17p) or TP53 mutation who requires treatment?

1. FCR (fludarabine/cyclophosphamide/rituximab)
2. BR (bendamustine/rituximab)
3. Ibrutinib
4. Ibrutinib + rituximab
5. Acalabrutinib
6. Acalabrutinib + obinutuzumab
7. Venetoclax + obinutuzumab
8. Other
What is your usual preferred initial regimen for a 60-year-old patient with del(17p) CLL who requires treatment?

1. FCR
2. BR
3. Ibrutinib
4. Ibrutinib + rituximab
5. Acalabrutinib
6. Acalabrutinib + obinutuzumab
7. Venetoclax + obinutuzumab
8. Other
Which second-line systemic therapy would you recommend for a 60-year-old patient with CLL with IGHV mutation but without del(17p) or TP53 mutation who responds to FCR and then experiences disease progression 3 years later?

1. Ibrutinib
2. Ibrutinib + rituximab
3. Acalabrutinib
4. Acalabrutinib + obinutuzumab
5. Venetoclax + rituximab
6. Venetoclax + obinutuzumab
7. Idelalisib
8. Duvelisib
9. Other
Agenda

Module 1: BTK Inhibitors

Module 2: Bcl-2 Inhibitors

Module 3: Novel Strategies – U2 Regimen (Umbralisib, Ublituximab)
CAR T-Cell Therapy
Module 2: Bcl-2 Inhibitors

- Key Relevant Data Sets
  - CLL14: Follow-up results with front-line venetoclax/obinutuzumab
  - MURANO: Five-year analysis of fixed-duration venetoclax/rituximab
  - CAPTIVATE: First-line ibrutinib + venetoclax
  - Phase II trial of ibrutinib/venetoclax/obinutuzumab: Three-year follow-up
  - CLARITY: Long-term responses to ibrutinib/venetoclax
  - MRD-driven, time-limited therapy with zanubrutinib, obinutuzumab, venetoclax
Phase 3 CLL14 Follow-Up

Untreated patients with CIRS>6 or CrCI <70

Stratify

Randomize

Chlorambucil 0.5 mg/kg d1 and 15 of cycles 1-6
Obinutuzumab 100 mg c1d1, 900 mg c1d2, 1000 mg c1d8 and 15, then 1000 mg day 1 of cycles 2-6

Venetoclax weekly ramp-up to 400 mg starting c1d22+
Obinutuzumab 100 mg c1d1, 900 mg c1d2, 1000 mg c1d8 and 15, then 1000 mg day 1 of cycles 2-6

Stratification
- Binet stage
- Geographic region

Key Points
- Median age 72
- 7-9% del(17p), 8-11% TP53 mutated
- 60% IGHV unmutated

Al-Sawaf O et al, Lancet Oncol 2020

Courtesy of Jennifer Woyach, MD
Phase 3 CLL14 Follow-Up

36 month PFS: 82% vs 50%

OS: no difference

uMRD peripheral blood 76% 3 months post-tx; 47% 18 months post-tx

Hazard ratio 0.31 (95% CI 0.22 – 0.44), $P < 0.0001$

39.6 months median follow-up

Al-Sawaf O et al, Lancet Oncol 2020
MURANO study design

R/R CLL (N=389)

Stratified by:
- Del(17p) by local labs
- Responsiveness to prior therapy
- Geographic region

\[ \text{Ven 400 mg orally once daily to PD, cessation for toxicity, or max 2 yrs from C1D1} \]

\[ \text{R} \]

\[ \text{R} 1:1 \]

\[ \text{Ven 5-week ramp-up} \]

\[ \text{Rituximab} \]

\[ 375 \text{ mg/m}^2 \text{ D1C1; } 500 \text{ mg/m}^2 \text{ D1C2–6} \]

\[ \text{Bendamustine} \]

\[ 70 \text{ mg/m}^2 \text{ D1,2 C1–6} + \text{Rituximab} \]

- Primary endpoint: investigator-assessed PFS; secondary endpoints include rate of undetectable MRD (uMRD)

Kater et al, ASH 2020

The James

Courtesy of Jennifer Woyach, MD
Phase 3 MURANO Study 5 Year Follow-Up

- Median PFS for VenR 53.6 months
- 5 year OS 82%
- Of 83 pts with uMRD at EOT, 38.5% remained uMRD. Unmutated IGHV and del17p were risk factors
- 25 months was average time from MRD conversion to requirement for therapy

Figure 1: Landmark OS by PB MRD status in pts that completed Ven Tx without PD.

Kater et al, ASH 2020

The James

Courtesy of Jennifer Woyach, MD
Phase 2 CAPTIVATE MRD Cohort

MRD Cohort
N=164
3 cycles ibr, then 12 cycles combination

Fixed Duration Cohort
3 cycles ibr, then 12 cycles combination

MRD +
Ibr Maintenance
Ibr/Ven Maintenance

MRD -
Placebo
Ibr maintenance

Randomization

Treatment-Naïve CLL, <70 yo

Wierda et al, ASH 2020
Siddiqi et al, EHA 2020

Courtesy of Jennifer Woyach, MD

The James
Phase 2 CAPTIVATE MRD Cohort

### Confirmed uMRD 30 month PFS
- 95.3% placebo
- 100% ibrutinib

### Without confirmed uMRD 30 month PFS
- 95.2% ibrutinib
- 96.7% ibr/ven

*Courtesy of Jennifer Woyach, MD*

---

**Figure. DFS by Randomized Treatment Arm in Confirmed uMRD Group**

- **Ibrutinib**
- **Placebo**

<table>
<thead>
<tr>
<th>Patients at Risk</th>
<th>Placebo</th>
<th>Ibrutinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>43</td>
<td>43</td>
</tr>
<tr>
<td>Ibrutinib</td>
<td>43</td>
<td>43</td>
</tr>
</tbody>
</table>

1-Year DFS rate (%)
- Placebo: 95.3 (95% CI: 82.7-98.8)
- Ibrutinib: 100.0 (100.0-100.0)

*P-value: 0.1475*

---

*The 3 DFS events in placebo arm were disease progression in 2 patients and MRD relapse in 1 patient.*
Phase 2 Ibrutinib/Venetoclax/Obinutuzumab 3 year follow-up

- Phase 2 study of 1 year fixed duration ibr/ven/obin
- 25 treatment-naïve and 25 relapsed/refractory patients
Phase 2 Ibrutinib/Venetoclax/Obinutuzumab 3 year follow-up

- 67% of TN and 50% RR patients developed uMRD in blood and marrow
- At approximately 2 years post-completion of therapy, one patient in TN cohort died of infection, and one in RR cohort relapsed
- T and NK cells remain suppressed 1 year after completion of therapy

Rogers et al, J Clin Oncol 2020

Courtesy of Jennifer Woyach, MD
Phase 2 CLARITY Trial

- 50 patients with relapsed/refractory CLL
- MRD in blood/marrow determined duration of therapy

Hillmen et al, J Clin Oncol 2019
Hillmen et al, ASH 2020

Courtesy of Jennifer Woyach, MD
Phase 2 CLARITY Trial

- 4 patients discontinued ibr in first 8 weeks and were replaced
- 23 pts stopped both treatments at or before M38, 17/23 were in uMRD4
- 40% achieved uMRD at month 14 and 48% at M26

Hillmen et al, J Clin Oncol 2019
Hillmen et al, ASH 2020

Courtesy of Jennifer Woyach, MD
Phase 2 BOVen in TN CLL

- 39 patients
- 72% high or very-high CLL-IPI

**Treatment Cycle:** C1 C2 C3 C4 C5 C6 C7 C8 C9+ (if needed)

- **Venetoclax:** Ramp-Up to Target 400 mg QD
- **Zanubrutinib:** 160 mg BID
- **Obinutuzumab:** 1000 mg on Cycle 1 D1\(^{b}/8/15\), and Cycles 2-8 D1

**PB MRD:** X X X X X X
**BM MRD:** X X X\(^{c}\) X\(^{c}\)
**CT imaging:** X X X\(^{c}\) X\(^{c}\)

---

*a-* Once peripheral blood (PB) uMRD is determined and confirmed in bone marrow (BM), patients complete 2 additional cycles followed by confirmatory MRD peripheral blood testing; if PB uMRD x 2 and BM uMRD x 1, therapy is discontinued.

*b-* Obinutuzumab split over days 1-2 of cycle 1 if ALC >25,000.

*c-* BM biopsy obtained at Screening and C3D1; thereafter BM is only obtained if PB-uMRD. CT imaging obtained at Screening, C3D1, C7D1, EOT, then every 6 months during post-treatment surveillance.
Phase 2 BOV en in TN CLL

- Median follow-up 14 months
  - 92% have achieved uMRD in peripheral blood and 84% in marrow
  - Median time to BM uMRD is 6 months
  - 77% of patients discontinued therapy at median 10 months
  - No recurrent MRD or progression has been observed

Soumerai et al, ASH 2020
What would be your most likely approach for a patient with newly diagnosed CLL to whom you decide to administer up-front venetoclax/obinutuzumab and who has detectable MRD ("MRD high") after completing 1 year of treatment?

1. Continue treatment
2. Discontinue treatment
Agenda

Module 1: BTK Inhibitors

Module 2: Bcl-2 Inhibitors

Module 3: Novel Strategies – U2 Regimen (Umbralisib, Ublituximab), CAR T-Cell Therapy
Module 3: Novel Strategies – U2 Regimen (Umbralisib, Ublituximab), CAR T-Cell Therapy

- **Key Relevant Data Sets**
  - UNITY-CLL: Umbralisib + ublituximab (U2)
  - TRANSCEND CLL 004: Lisocabtagene maraleucel (liso-cel) + ibrutinib
Phase 3 UNITY-CLL Study

- 421 total patients
- 57% TN
- 56% IGHV unmutated
- 10% del17p

Stratify

Chlorambucil 0.5 mg/kg d1 and 15 of cycles 1-6
Obinutuzumab 100 mg c1d1, 900 mg c1d2, 1000 mg c1d8 and 15, then 1000 mg day 1 of cycles 2-6
Umbralisib 800 mg daily C1D1 ongoing
Ublituximab C1 D1/2, 8, and 15, D1 of C2-6, and then D1 every 3 cycles following

Stratification
- TN vs RR
- del17p

Courtesy of Jennifer Woyach, MD
Phase 3 UNITY-CLL Study

- Median follow-up 36 months
- Median PFS U2 31.9 mo vs 17.9 mo overall
- In TN, U2 PFS 38.5 mo vs 26.1 mo
- In RR, U2 PFS 19.5 mo vs 12.9 mo
- G3+ Colitis in 3.4%, Transaminitis G3+ in 8.3%, G3+ pneumonitis in 2.9%

Courtesy of Jennifer Woyach, MD
Phase 1 TRANSCEND CLL 004 Study: Liso-Cel Plus Ibrutinib

- Liso-Cel is 4-1BB CAR-T product with equal CD4/CD8
- In this cohort patients had to have previously received ibrutinib, reinitiated or continued at study start and continued at least 90 days post CAR-T
- Lymphodepletion with Flu/Cy

Wierda et al, ASH 2020 Abstract 544

Courtesy of Jennifer Woyach, MD
Phase 1 TRANSCEND CLL 004 Study: Liso-Cel Plus Ibrutinib

- 19 patients included
- Median 4 prior therapies
- 74% had BTKi as last therapy and 53% had also received venetoclax
- 74% CRS, 1 grade 3; 16% G3+ neurologic events
- ORR 95%, 47% CR/CRi
- 83% maintained response at 3 months
- 79% had uMRD in marrow

Wierda et al, ASH 2020 Abstract 544

Courtesy of Jennifer Woyach, MD
Phase 1 TRANSCEND CLL 004 Study: Liso-cel monotherapy

- Study schema same as previous, but without ibrutinib
- 23 pts evaluable for safety, 22 for efficacy
- Median 6 prior therapies, all with prior ibr and 48% with ven too
- ORR 82%, CR/CRi 45%
- Median PFS 18 months, 5/8 progressions were RT
- G3+ CRS 9%, G3+ neuro events 22%

Siddiqi et al, ASH 2020 Abstract 546
Meet The Professor
Management of Ovarian Cancer

Friday, January 22, 2021
1:15 PM – 2:15 PM ET

Faculty
Professor Jonathan A Ledermann, MD

Moderator
Neil Love, MD
Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 5 business days.