WELCOME & INTRODUCTIONS

Advances in Treatment for Chronic Lymphocytic Leukemia (CLL)

Welcome to LLS Community
We are a community of blood cancer patients, survivors and caregivers. We’re here to support you, give you trusted information and resources, and help you feel connected. No one should have to face a blood cancer diagnosis alone.

To join LLS Community, visit www.LLS.org/Community.

Program will begin shortly

BEATING CANCER IS IN OUR BLOOD.

ADVANCES IN TREATMENT FOR CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

Tanya Siddiqi, MD
Associate Clinical Professor
Director, Chronic Lymphocytic Leukemia Program
Department of Hematology & HCT
City of Hope Medical Center
Duarte, CA

BEATING CANCER IS IN OUR BLOOD.
WELCOMING REMARKS
Advances in Treatment for Chronic Lymphocytic Leukemia (CLL)

Larry Saltzman, MD
Executive Research Director, LLS

Welcome to The Leukemia & Lymphoma Society® (LLS) National Patient Registry
A unique opportunity for blood cancer patients to join LLS to increase scientific knowledge about how COVID-19 and COVID-19 vaccines affect them.

DISCLOSURES
Advances in Treatment for Chronic Lymphocytic Leukemia (CLL)

Tanya Siddiqi, MD has affiliations with: AstraZeneca, Bristol Myers Squibb, BeiGene, Kite Pharma, Pharmacyclics, and Research to Practice.
Objectives

- Epidemiology
- Diagnosis and workup
- Monoclonal B-lymphocytosis
- Prognostic markers
- Staging
- Treatment initiation guidelines
- Frontline therapeutic options
- Relapsed/refractory therapeutic options
Epidemiology

- Chronic lymphocytic leukemia (CLL) is a low grade leukemic lymphocytic lymphoma; small lymphocytic lymphoma (SLL) is a nodal form of the same disease

- CLL/SLL is the most common hematological malignancy in the Western world; incidence is ~5/100,000 persons per year in the US

- Median age at diagnosis ~72 years


Epidemiology (cont.)

- Male predominance

- Higher in Caucasians

- ~10% patients with a family history of some lymphoma

- Exact etiology is unknown
Diagnosis and workup

- Rule out masquerading other lymphoma

- History and physical examination; trend of CBCs; B symptoms (fever, night sweats, unexplained weight loss); severe fatigue

- Review CBC/differential, peripheral blood smear, flow cytometry/immunophenotyping: peripheral blood lymphocytosis with the presence of $\geq 5000$ monoclonal B-cells/uL is required
  - CD5/19/23 positive by flow; CD20 dim

- Bone marrow biopsy not needed for diagnosis

Monoclonal B-lymphocytosis (MBL)

- Presence of monoclonal lymphocytosis but with $<5000$ B-cells/uL in the peripheral blood and no accompanying lymphadenopathy or organomegaly by physical examination or radiographical imaging, cytopenias or disease-related symptoms is defined as MBL

- Incidence in the US is 3%

- Progression to CLL/SLL can occur @ 1-2% per year
Prognostic markers in CLL/SLL

- Cytogenetics:
  - Del13q
  - Trisomy 12
  - Normal
  - Del11q
  - Del17p
  - Del6q
  - TP53 mutations
  - Notch1 mutations
  - SF3B1 mutations

- IGHV mutation status
- ZAP70
- CD38
- Lymphocyte doubling time (LDT)
- β2 microglobulin
- Stage of disease by Rai or Binet staging

CLL Staging

<table>
<thead>
<tr>
<th>Rai stage</th>
<th>Risk category</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Low</td>
<td>Lymphocytosis alone</td>
</tr>
<tr>
<td>1</td>
<td>Intermediate</td>
<td>Lymphadenopathy</td>
</tr>
<tr>
<td>2</td>
<td>Intermediate</td>
<td>Hepato/splenomegaly</td>
</tr>
<tr>
<td>3</td>
<td>High</td>
<td>Anemia (&lt;11g/dl)</td>
</tr>
<tr>
<td>4</td>
<td>High</td>
<td>Thrombocytopenia (&lt;100,000/L)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Binet stage</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>HGB≥10 g/dl, platelets ≥100/L, &lt;3 areas of lymphadenopathy/organomegaly*</td>
</tr>
<tr>
<td>B</td>
<td>HGB≥10 g/dl, platelets ≥100/L, ≥3 areas of lymphadenopathy/organomegaly*</td>
</tr>
<tr>
<td>C</td>
<td>Anemia (&lt;10g/dl), thrombocytopenia (&lt;100,000/L), or both</td>
</tr>
</tbody>
</table>

*nodal areas: cervical [head and neck], axillary, inguinal (including femoral lymph nodes), spleen, liver
Who needs treatment?

- International workshop on CLL (iwCLL) guidelines for treatment initiation

iwCLL guidelines for treatment initiation

- progressive marrow failure as manifested by the development of, or worsening of, anemia and/or thrombocytopenia
- massive (≥6cm below left subcostal margin), progressive, or symptomatic splenomegaly
- massive (≥10 cm in longest diameter), progressive, or symptomatic lymphadenopathy
- progressive lymphocytosis with an increase of >50% over a 2 month period or LDT of <6 months
- autoimmune hemolytic anemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy
- constitutional symptoms defined as ≥1 of the following:
  (i) unintentional weight loss of ≥10% within the previous 6 months
  (ii) significant fatigue (ECOG PS ≥2; inability to work or perform usual activities)
  (iii) fevers >100.5F or 38C for ≥2 weeks without other evidence of infection
  (iv) night sweats for >1 month without evidence of infection
High risk, previously untreated CLL

- **CLL12 trial**
  - Ph3
  - Early stage (Binet A)
  - Double blind
  - Ibru vs. placebo

- **EVOLVE CLL/SLL study**
  - Ph3
  - Within 1 year of diagnosis
  - Early vs. delayed ven/obin

How to pick the right treatment?

- iwCLL guidelines for treatment initiation
- Stage of disease
- Lymphocyte doubling time and symptoms
- Cytogenetic risk
- Fitness of patient
- Response to prior therapy
German CLL study group (GCLLSG): frontline treatment

- CLL4 study: FC vs. fludarabine alone

- CLL8 study: FCR vs. FC
  - Subgroup with exceptionally good outcome has right age/fitness, mutated IGHV genes and no del17p/del11q
  - plateau after 4 yrs; MRD neg ≥10 yrs later – cure?


CLL8 study: FCR vs. FC

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Probability of Progression-free Survival

- FCR (IGHV MUT patients N=113)
- FC (IGHV MUT patients N=117)
- FCR (IGHV UNM patients N=197)
- FC (IGHV UNM patients N=195)

p < 0.001 by log-rank test

Months on Study

17
ASH2016 MDACC experience with FCR

German CLL study group (GCLLSG): frontline treatment

- CLL4 study: FC vs. fludarabine alone

- CLL8 study: FCR vs. FC
  - Subgroup with exceptionally good outcome has right age/fitness, mutated IGHV genes and no del17p/del11q
  - plateau after 4 yrs; MRD neg ≥10 yrs later – cure?

- CLL10 study: FCR vs. BR

Thompson et al., Blood, 2016.

**FCR vs. BR**

- Phase 3 randomized trial, fit CLL patients (ages 33-81 yrs) with advanced stage disease, previously untreated, no 17p deletion
- N = 564; 6 cycles of either regimen; median followup 37.1 months

<table>
<thead>
<tr>
<th></th>
<th>FCR</th>
<th>BR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>95%</td>
<td>96%</td>
<td>1.0</td>
</tr>
<tr>
<td>CR</td>
<td>40%</td>
<td>31%</td>
<td>0.034</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>[higher MRD negative CRs in FCR arm]</td>
</tr>
<tr>
<td>Median PFS</td>
<td>55.2 months</td>
<td>41.7 months</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>[better in &lt;65 years old]</td>
</tr>
<tr>
<td>OS at 3 years</td>
<td>91%</td>
<td>92%</td>
<td>0.897</td>
</tr>
<tr>
<td>Severe neutropenia</td>
<td>84%</td>
<td>59%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>[especially in older pts]</td>
</tr>
<tr>
<td>Severe infections</td>
<td>39%</td>
<td>25%</td>
<td>0.001</td>
</tr>
</tbody>
</table>


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**Targeted therapy in CLL**

![Targeted therapy in CLL diagram](image)
### Targeted therapies

- **Venetoclax** – BCL2i; FDA approved for CLL
- **APG2575** – BCL2i; in clinical trials
- **Ibrutinib** – BTKi; FDA approved for CLL
- **Acalabrutinib** – BTKi; FDA approved for CLL
- **Zanubrutinib** – BTKi; FDA approved for MCL; in clinical trials for CLL
- **LOXO305** – BTKi (non-covalent); in clinical trials
- **Idelalisib** – PI3Kδi; FDA approved for rel/ref CLL but further trials halted due to toxicities
- **Duvelisib** - PI3Kδ and γ inhibitor; FDA approved for rel/ref CLL
- **Umbralisib** – PI3Kδi; FDA approved for FL and MZL; in clinical trials for CLL

### Single agent and combination trials with targeted therapies

#### Frontline
- RESONATE2 (ibru vs. clb)
- CLL14 (ven/obin vs. clb/obin)
- E1912 (ibru/R vs. FCR)
- Alliance (ibru vs. ibru/R vs. BR)
- iLUMINATE (ibru/obin vs. clb/obin)
- ELEVATE-TN (acala vs. acala/obin vs. clb/obin)
- UNITY CLL (umbralisib/ublituximab vs. clb/obin)

#### Relapsed/refractory
- RESONATE
- MURANO (ven/R vs. BR)
- ASCEND (acala vs. idelalisib/R vs. BR)
- UNITY CLL (umbralisib/ublituximab vs. clb/obin)

By and large, the novel agent containing arm patients had better results than the chemotherapy containing arm patients in all these trials
Novel BTKi/Bcl-2i combinations

- **Frontline I+V trials:**
  - CAPTIVATE Ph2 trial
    - MRD and fixed duration cohorts
  - UK CLARITY Ph2 trial
  - UK FLAIR trial: ibrutinib alone vs. [ibrutinib] vs. I+V x6 yrs vs. FCR

- **Relapsed/refractory I+V trials**
  - MDACC trial
  - Stanford/COH trial

- **Ongoing Ph3 trials**
  - Alliance: ibrutinib vs. ibrutinib/obin, age more than 70 yrs
  - ECOG-ACRIN: ibrutinib vs. ibrutinib/obin, age less than or equal to 70 yrs
  - UK FLAIR trial: ibrutinib alone vs. [ibrutinib] vs. I+V x6 yrs vs. FCR

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CAPTIVATE MRD Cohort: Study Design

- Results are presented for pre-randomization phase of the CAPTIVATE MRD cohort (N=164) with 12 cycles of ibrutinib + venetoclax prior to MRD-guided randomization
- Time-limited therapy with 12 cycles of ibrutinib + venetoclax to be evaluated in a separate fixed-duration cohort (N=159)


EHA 2020, CAPTIVATE-MRD; Siddiqi et al.
```
High Rates of Undetectable MRD Achieved in PB and BM With Up to 12 Cycles of I + V Combination

EHA 2020, CAPTIVATE-MRD; Siddiqi et al.

<table>
<thead>
<tr>
<th>Best response of undetectable MRD in evaluable patients^a</th>
<th>Peripheral Blood n=163</th>
<th>Bone Marrow^b n=155</th>
</tr>
</thead>
<tbody>
<tr>
<td>(95% CI)</td>
<td>75% (68–82)</td>
<td>72% (64–79)</td>
</tr>
</tbody>
</table>

- Rates of undetectable MRD in peripheral blood and bone marrow were highly concordant at Cycle 16 (91%)
- In the all-treated population (N=164), undetectable MRD was achieved in 75% of patients in peripheral blood and in 68% of patients in bone marrow with up to 12 cycles of combination
- Proportion of patients with undetectable MRD in peripheral blood increased over the 12 cycles of combination therapy
- At 15 months, 98% of patients were progression free with no deaths

^aBM MRD assessment was scheduled after completion of 12 cycles of combination treatment.
^bPatients with undetectable MRD at any postbaseline assessment; evaluable patients are those who had at least 1 MRD sample taken postbaseline.

CLARITY Ph2 trial (up to 2 yrs of treatment)

Novel BTKi/Bcl-2i combinations

- Frontline I+V trials:
  - CAPTIVATE Ph2 trial
  - MRD and fixed duration cohorts
  - UK CLARITY Ph2 trial

- Relapsed/refractory I+V trials
  - MDACC trial
  - Stanford/COH trial

- Ongoing Ph3 trials
  - Alliance: ibru/obin vs. ibru/ven/obin, age more than 70 yrs
  - ECOG-ACRIN: ibru/obin vs. ibru/ven/obin, age less than or equal to 70 yrs
  - UK FLAIR trial: ibru alone vs. [ibruR] vs. I+V x 6 yrs vs. FCR

MDACC: IIT, Ph2, frontline high risk and older CLL pts, I+V for 24 cycles

Study Schema and Response to Treatment.

- After 3 Cycles of Ibrutinib Monotherapy (N=75): 100%
- After 1 Cycle of Venetoclax-Ibrutinib (N=72): 96%
- After 3 Cycles of Venetoclax-Ibrutinib (N=70): 83%
- After 6 Cycles of Venetoclax-Ibrutinib (N=60): 81%
- After 9 Cycles of Venetoclax-Ibrutinib (N=51): 80%
- After 12 Cycles of Venetoclax-Ibrutinib (N=33): 80%
- After 18 Cycles of Venetoclax-Ibrutinib (N=23): 80%

- Complete remission, with or without normal blood count recovery
- Partial remission
- Undetectable MRD in bone marrow

Novel BTKi/Bcl-2i combinations

- Frontline I+V trials:
  - CAPTIVATE Ph2 trial
    - MRD and fixed duration cohorts
  - UK CLARITY Ph2 trial

- Relapsed/refractory I+V trials
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  - UK FLAIR trial: ibru alone vs. [ibruR] vs. I+V x6 yrs vs. FCR

Choice Between BTKi and VenR As First Novel Agent

**Favors BTKi:**
- Longer follow-up data (only with ibrutinib)
- Use of newer BTKi improves toxicity profile
- High ORR with ven after BTKi vs less data on the reverse
- Intense early monitoring with ven

**Favors VenR:**
- High CR and undetectable MRD
- Fewer long term side effects
- Time-limited therapy, avoid selection pressure for resistance
- Patient preference
- Less cost
Adverse event management

- **BTKi:**
  - Atrial fibrillation
  - Hemorrhage
  - Arthralgias
  - HTN
  - Rash
  - Infections

- **Ven:**
  - Tumor lysis syndrome
  - Infections

Updated Follow-Up of Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Treated with Lisocabtagene Maraleucel in the Phase 1 Monotherapy Cohort of TRANSCEND CLL 004, Including High-Risk and Ibrutinib-Treated Patients

Tanya Siddiqi,1 Jacob D. Soumerai,2 Kathleen A. Dorritie,3 Deborah M. Stephens,4 Peter A. Riedell,5 Jon Arnason,6 Thomas J. Kipps,7 Heidi H. Gillenwater,8 Lucy Gong,8 Lin Yang,8 Ken Ogasawara,9 William G. Wierda10

1City of Hope National Medical Center, Duarte, CA, USA; 2Center for Lymphoma, Massachusetts General Hospital Cancer Center, Boston, MA, USA; 3UPMC Hillman Cancer Center, University of Pittsburgh, Pittsburgh, PA, USA; 4Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA; 5University of Chicago Medical Center, Chicago, IL, USA; 6Beth Israel Deaconess Medical Center, Boston, MA, USA;
7Moores Cancer Center, University of California San Diego Health, San Diego, CA, USA; 8Bristol Myers Squibb, Seattle, WA, USA; 9Bristol Myers Squibb, Princeton, NJ, USA; 10The University of Texas MD Anderson Cancer Center, Houston, TX, USA

ASH annual meeting 2020
Presentation 546
4. Liso-cel conforming product was successfully manufactured for 23 of 24 patients in the monotherapy phase 1 cohort; one patient who received nonconforming product was excluded from the safety evaluable population (N = 23). 5. Defined as patients whose disease progressed on BTKi. Complex cytogenetic abnormalities, del(17p), TP53 mutated, or unmutated IGHV. 6. Lower dose was used if prior dose reduction was necessary to manage toxicity. 7. MRD was assessed in blood by flow cytometry and/or in bone marrow by next generation sequencing (both with a sensitivity of ≤10⁻⁴).


Treatment-Emergent AEs, Cytokine Release Syndrome, and Neurological Events

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Monotherapy Cohort (N = 23)</th>
<th>BTKi Progression/Venetoclax Failure Subgroup (n = 11)</th>
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<tbody>
<tr>
<td>Common grade 3/4 treatment-emergent AEs (TEAEs), n (%))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>17 (74)</td>
<td>7 (64)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>16 (70)</td>
<td>6 (55)</td>
</tr>
<tr>
<td>Neutropenia/neutrophil count decrease</td>
<td>16 (70)</td>
<td>8 (73)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>10 (43)</td>
<td>2 (18)</td>
</tr>
<tr>
<td>Cytokine release syndrome (CRS)§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-grade CRS, n (%)</td>
<td>17 (74)</td>
<td>7 (64)</td>
</tr>
<tr>
<td>Median time to CRS onset, days (range)</td>
<td>3 (1–10)</td>
<td>1 (1–10)</td>
</tr>
<tr>
<td>Median duration of CRS, days (range)</td>
<td>12 (2–50)</td>
<td>15 (5–50)</td>
</tr>
<tr>
<td>Grade 3 CRS, n (%)</td>
<td>2 (9)</td>
<td>2 (18)</td>
</tr>
<tr>
<td>Neurological events (NEs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-grade NEs, n (%)</td>
<td>9 (39)</td>
<td>5 (46)</td>
</tr>
<tr>
<td>Median time to NE onset, days (range)</td>
<td>4 (2–21)</td>
<td>4 (2–21)</td>
</tr>
<tr>
<td>Median duration of NE, days (range)</td>
<td>20.5 (6–50)</td>
<td>38 (6–50)</td>
</tr>
<tr>
<td>Grade 23 NEs, n (%)</td>
<td>5 (22)</td>
<td>3 (27)</td>
</tr>
<tr>
<td>Management of CRS and/or NEs, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tocilizumab only</td>
<td>6 (26)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>Corticosteroids only</td>
<td>1 (4)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>Tocilizumab and corticosteroids</td>
<td>8 (35)</td>
<td>4 (36)</td>
</tr>
</tbody>
</table>

• Dose-limiting toxicities were reported for 2 patients at DL2, which resolved
• No late or delayed AEs of concern have emerged with longer follow-up

*No grade 4 or 5 CRS events were reported. *NEs were not mutually exclusive: encephalopathy (n = 3), aphasia (n = 1), confusional state (n = 1), muscular weakness (n = 1), and somnolence (n = 1). *Defined as patients whose disease progressed on BTKi and failed venetoclax due to progression, intolerance, or failure to respond after at least 3 months of therapy. *Based on Lee criteria (Lee et al, Blood. 2014;124:188–195).

Patient Response at 24-Month Median Follow-Up

• ORR was 82% (CR/CRi, 46%; PR, 36%), with 68% (n = 15/22)* of patients achieving a rapid response within 30 days
• 27% (n = 6/22) of patients had a deepening of response
• Response was durable. At 12 months, 50% (n = 11/22) were in response and only 2 of these responders progressed beyond 12 months
• Four of the 15 patients with uMRD (blood) response (CR or PR) have progressed, with 3 due to Richter transformation (RT)
• The subgroup also demonstrated rapid and durable responses
• Four of 6 progression events in the subgroup were due to RT

*One patient had RT before lymphodepleting chemotherapy and was excluded from the efficacy analysis. *Defined as patients whose disease progressed on BTKi and failed venetoclax due to progression, intolerance, or failure to respond after at least 3 months of therapy. *Evaluated according to iwCLL 2018 criteria. *Assessed in blood by flow cytometry and/or in bone marrow by next-generation sequencing (both with a sensitivity of ≤10−4). CR, CRi, CR with incomplete blood count recovery; EOS, end of study; ND, not done; Unk, unknown.
**Duration of Response and PFS at 24-Month Median Follow-Up**

![Graph showing duration of response and PFS at 24-month median follow-up.]

<table>
<thead>
<tr>
<th>Duration of Response, Months</th>
<th>Probability of Durable Response, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 1 3 6 9 12 15 18 21 24</td>
<td>100 80 60 40 20 0 0 0 0 0</td>
</tr>
</tbody>
</table>

+ Censored

Median (95% CI): NR (4.8—NR) months

Subgroup

Median (95% CI): 17 (1.9—NR) months

Total

Median (95% CI): 13 (2.8—NR) months

Subgroup

Median (95% CI): 18 (3.0—NR) months

Total

Subgroup

Median (95% CI): 17 (1.9—NR) months

Total

Subgroup

Median (95% CI): NR (4.8—NR) months

Total

- Defined as patients whose disease progressed on BTKi and failed venetoclax due to progression, intolerance, or failure to respond after at least 3 months of therapy.

NR, not reached.


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**TRANSCEND CLL 004: Phase 1 Cohort of Lisocabtagene Maraleucel (liso-cel) in Combination with Ibrutinib for Patients with Relapsed/Refractory (R/R) Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)**

William G. Wierda,¹ Kathleen A. Dorritie,² Javier Munoz,³ Deborah M. Stephens,⁴ Scott Solomon,⁵ Heidi H. Gillenwater,⁶ Lucy Gong,⁶ Lin Yang,⁶ Ken Ogasawara,⁷ Jerill Thorpe,⁶ Tanya Siddiqi⁸

- ¹The University of Texas MD Anderson Cancer Center, Houston, TX, USA; ²UPMC Hillman Cancer Center, University of Pittsburgh, Pittsburgh, PA, USA; ³Banner MD Anderson Cancer Center, Gilbert, AZ, USA; ⁴Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA; ⁵Immunotherapy Program, Northside Hospital Cancer Institute, Atlanta, GA, USA; ⁶Bristol Myers Squibb, Seattle, WA, USA; ⁷Bristol Myers Squibb, Princeton, NJ, USA; ⁸City of Hope National Medical Center, Duarte, CA, USA

ASH annual meeting 2020
Presentation 544
Treatment-Emergent AEs, Cytokine Release Syndrome, and Neurological Events

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Combination Cohort (N = 19)</th>
<th>DL1 + Ibrutinib (n = 4)</th>
<th>DL2 + Ibrutinib (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common grade 3/4 treatment-emergent AEs (TEAEs), n (%)</td>
<td>18 (95)</td>
<td>4 (100)</td>
<td>14 (93)</td>
</tr>
<tr>
<td>Neutropenia/neutrophil count decrease</td>
<td>17 (89)</td>
<td>3 (75)</td>
<td>14 (93)</td>
</tr>
<tr>
<td>Anemia</td>
<td>9 (47)</td>
<td>3 (75)</td>
<td>6 (40)</td>
</tr>
<tr>
<td>Fever and neutropenia</td>
<td>5 (26)</td>
<td>1 (25)</td>
<td>4 (27)</td>
</tr>
<tr>
<td>Cytokine release syndrome (CRS)†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-grade CRS, n (%)</td>
<td>14 (74)</td>
<td>4 (100)</td>
<td>10 (67)</td>
</tr>
<tr>
<td>Median time to CRS onset, days (range)</td>
<td>6.5 (1—13)</td>
<td>8 (6—13)</td>
<td>5.5 (1—8)</td>
</tr>
<tr>
<td>Median duration of CRS, days (range)</td>
<td>6 (3—13)</td>
<td>6.5 (4—7)</td>
<td>5.5 (3—13)</td>
</tr>
<tr>
<td>Grade 3 CRS, n (%)</td>
<td>1 (5)</td>
<td>1 (25)</td>
<td>0</td>
</tr>
<tr>
<td>Neurological events (NEs)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-grade NEs, n (%)</td>
<td>6 (32)</td>
<td>2 (50)</td>
<td>4 (27)</td>
</tr>
<tr>
<td>Median time to NE onset, days (range)</td>
<td>8 (5—12)</td>
<td>9 (6—12)</td>
<td>8 (5—10)</td>
</tr>
<tr>
<td>Median duration of NE, days (range)</td>
<td>6.5 (1—8)</td>
<td>8 (9—8)</td>
<td>5 (1—7)</td>
</tr>
<tr>
<td>Grade 3 NEs, n (%)</td>
<td>3 (16)</td>
<td>0</td>
<td>3 (20)</td>
</tr>
<tr>
<td>Management of CRS and/or NEs, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tocilizumab only</td>
<td>2 (11)</td>
<td>0</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Corticosteroids only</td>
<td>3 (16)</td>
<td>2 (50)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Tocilizumab and corticosteroids</td>
<td>3 (16)</td>
<td>1 (25)</td>
<td>2 (13)</td>
</tr>
</tbody>
</table>

†Based on Lee criteria (Lee et al., Blood. 2014;124:188–195). †NeEs were not mutually exclusive: aphasia (n = 1); ataxia (n = 1); and encephalopathy (n = 1).

- The combination of liso-cel and ibrutinib was well tolerated, with no reported dose-limiting toxicities
- No grade 5 AEs or grade 4 CRS or NEs were reported


Ibrutinib-Related TEAEs Rarely Resulted in Dose Reduction or Discontinuation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Combination Cohort (N = 19)</th>
<th>DL1 + Ibrutinib (n = 4)</th>
<th>DL2 + Ibrutinib (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibrutinib-related TEAEs, n (%)</td>
<td>15 (79)</td>
<td>3 (75)</td>
<td>12 (80)</td>
</tr>
<tr>
<td>Grade 3/4 ibrutinib-related TEAEs</td>
<td>7 (37)</td>
<td>2 (50)</td>
<td>5 (33)</td>
</tr>
<tr>
<td>Ibrutinib dose reduced due to TEAE, n (%)</td>
<td>2 (11)</td>
<td>0</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Ibrutinib discontinued due to TEAE, n (%)</td>
<td>4 (21)</td>
<td>1 (25)</td>
<td>3 (20)</td>
</tr>
<tr>
<td>Received ≥90 days of ibrutinib after liso-cel, n (%)</td>
<td>14 (74)</td>
<td>3 (75)</td>
<td>11 (73)</td>
</tr>
<tr>
<td>Median total duration of ibrutinib therapy, days (range)</td>
<td>141 (65—421)</td>
<td>161.5 (94—285)</td>
<td>141 (65—421)</td>
</tr>
<tr>
<td>Median duration of ibrutinib therapy after liso-cel infusion, days (range)</td>
<td>97 (14—388)</td>
<td>132 (59—197)</td>
<td>97 (14—388)</td>
</tr>
</tbody>
</table>

*Four patients were still receiving ibrutinib.

- Grade 3/4 ibrutinib-related TEAEs included: anemia (n = 4), neutropenia/neutrophil count decrease (n = 4), atrial fibrillation (n = 1), hypertension (n = 1), lung infection (n = 1), staphylococcal infection (n = 1), and thrombocytopenia (n = 1)
- TEAEs/toxicities leading to ibrutinib dose reduction (all resolved):
  - Grade 2 atrial fibrillation and grade 2 fatigue
  - TEAEs leading to ibrutinib discontinuation (all resolved):
    - Grade 3 atrial fibrillation, grade 2 red blood cell aplasia (related to liso-cel), grade 2 fatigue, and grade 1 palpitations

Best Overall Response and uMRD ($\leq 10^{-4}$) at 10-Month Follow-Up

- No patients had PD during the first month after liso-cel
- One patient at DL1 had SD for 6 months but later progressed

*Evaluated according to iwCLL 2018 criteria. 3Assessed in blood by flow cytometry and/or in bone marrow by NGS. CRi, CR with incomplete blood count recovery; NGS, next-generation sequencing.

Patient Responses over Time at 10-Month Follow-Up

- All responders (n = 18/19) achieved a response by Day 30 after liso-cel
- Among 18 patients with ≥6 months of follow-up, 89% (n = 16/18) maintained or improved response from Day 30
- Of 17 patients who achieved uMRD in blood:
  - All achieved this response by Day 30
  - Only 1 later progressed due to Richter transformation (RT)

*Evaluated according to iwCLL 2018 criteria. 3Assessed in blood by flow cytometry and/or in bone marrow by NGS. ND, not done; Unk, unknown.
Other ongoing CAR T-cell trials in CLL

- ZUMA-8 (axi-cel)
- JCAR014 + ibrutinib (University of Washington, Seattle)
- CTL019 + ibrutinib (University of Pennsylvania)
- Novel CAR T targets like ROR1 and CD22
- Off-the-shelf allogeneic CAR T-cell trials
- Bispecific antibodies

Overall Conclusions

- Explosion of novel therapies for CLL in recent years, including monoclonal antibodies (like obinutuzumab), small molecule inhibitors of various kinases (like BTK and PI3K) and the antiapoptotic pathway (especially Bcl2), and CD19-specific CAR-T cells
- These novel, non-chemotherapeutic agents seem to have done away with the need for standard chemoimmunotherapy in CLL
- Combination studies are underway to improve outcomes further and find a cure
Q&A SESSION
Advances in Treatment for Chronic Lymphocytic Leukemia (CLL)

• Ask a question by phone:
  – Press star (*) then the number 1 on your keypad.

• Ask a question by web:
  – Click “Ask a question”
  – Type your question
  – Click “Submit”

Due to time constraints, we can only take one question per person. Once you've asked your question, the operator will transfer you back into the audience line.
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Thank you