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

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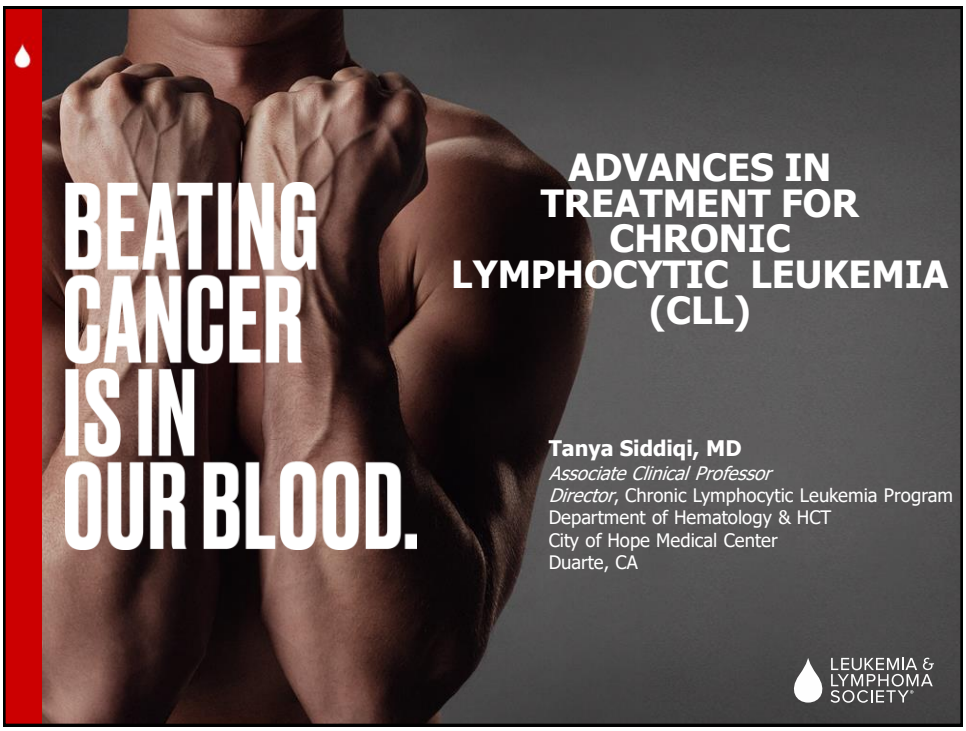

ADVANCES IN TREATMENT FOR CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

Tanya Siddiqi, MD
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Duarte, CA

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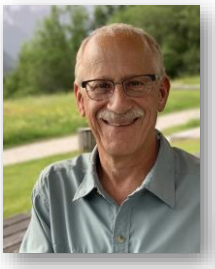
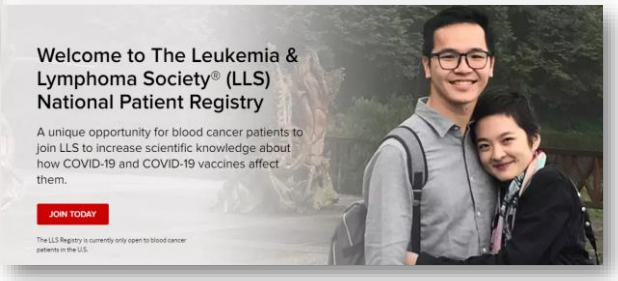
WELCOMING REMARKS

Advances in Treatment for Chronic Lymphocytic Leukemia (CLL)



Larry Saltzman, MD
Executive Research Director, LLS



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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.

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ADVANCES IN TREATMENT FOR CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

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The Leukemia & Lymphoma Society virtual educational program – 4/7/2021

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Objectives

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

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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

Muller-Hermlink HK, et al. In: Jaffe ES, Harris NL, Stein H, Vardiman JW, eds. World Health Organization Classification of Tumours: Pathology and Genetics of Tumours in Haematopoietic and Lymphoid Tissues. Lyon, France. IARC press, 2001: 195-6.

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Epidemiology (cont.)

- Male predominance
- Higher in Caucasians
- ~10% patients with a family history of some lymphoma
- Exact etiology is unknown

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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 ≥5000 monoclonal B-cells/uL is required
  - CD5/19/23 positive by flow; CD20 dim
- Bone marrow biopsy not needed for diagnosis

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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

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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

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CLL Staging

Rai stage	Risk category	Clinical features
0	Low	Lymphocytosis alone
1	Intermediate	Lymphadenopathy
2	Intermediate	Hepato/splenomegaly
3	High	Anemia (<11g/dl)
4	High	Thrombocytopenia (<100,000/L)

Binet stage	Clinical features
A	HGB≥10 g/dl, platelets ≥100/L, <3 areas of lymphadenopathy/ organomegaly*
B	HGB≥10 g/dl, platelets ≥100/L, ≥3 areas of lymphadenopathy/ organomegaly*
C	Anemia (<10g/dl), thrombocytopenia (<100,000/L), or both

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

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Who needs treatment?

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

Hallek M, et al. Blood 2018. 131: 2745-2760.

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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 (≥10cm 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 6months
  - (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

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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

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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

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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?

Eichhorst BF, et al. Hematol J 2006; 107: 885-91.
Hallek M, et al. Lancet 2010; 376: 1164-74.
Eichhorst B, et al. Blood 2014; 124: abs.19.

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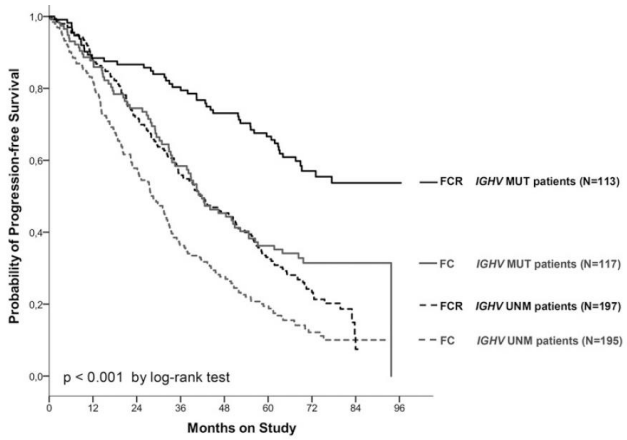
CLL8 study: FCR vs. FC



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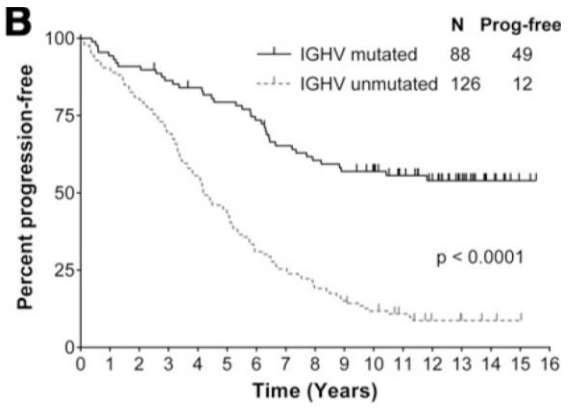
ASH2016 MDACC experience with FCR



Thompson et al., *Blood*, 2016.

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German CLL study group (GCLLSG): frontline treatment

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  - 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

Eichhorst BF, et al. Hematol J 2006; 107: 885-91.
Hallek M, et al. Lancet 2010; 376: 1164-74.
Eichhorst B, et al. Blood 2014; 124: abs.19.

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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

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

Eichhorst B, et al. Lancet Oncol 2016; 17: 928-42.

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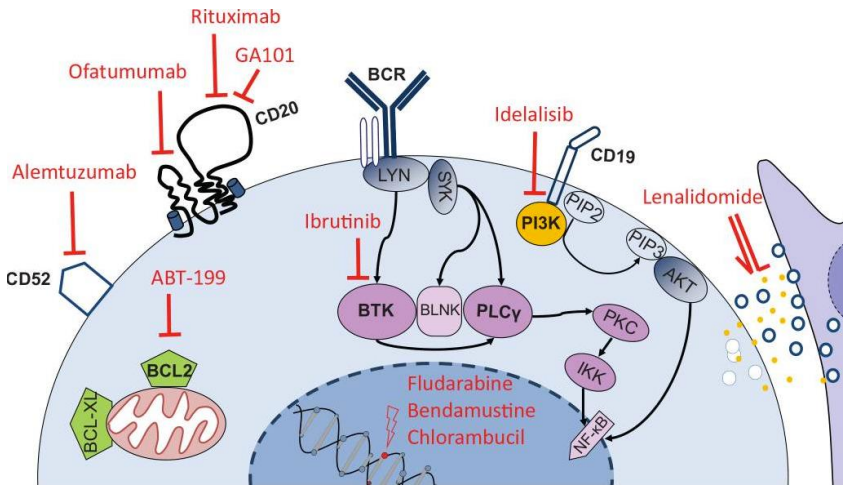
Targeted therapy in CLL



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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

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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)
- iLLUMINATE (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

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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 x6 yrs vs. FCR

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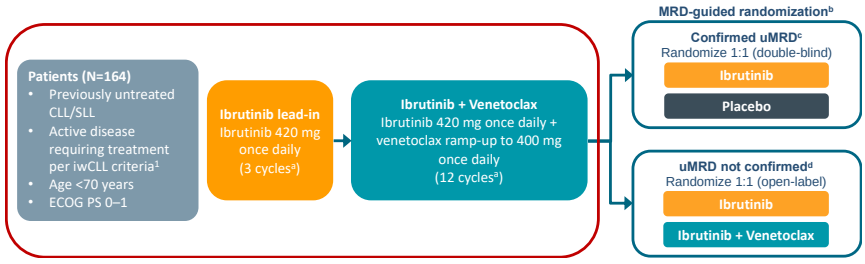
CAPTIVATE MRD Cohort: Study Design



- 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)

[a]1 cycle = 28 days; patients may have received 1 additional cycle while awaiting confirmation of undetectable MRD for randomization. [b]Stratified by IGHV mutation status. [c]Confirmed as having undetectable MRD ($<10^{-4}$ by 8-color flow cytometry) serially over at least 3 cycles in PB, and undetectable MRD in both PB and BM. [d]Defined as having detectable MRD or undetectable MRD not confirmed serially or not confirmed in both PB and BM.

1. Hallek M et al. *Blood*. 2008;111:5446-5456.

EHA 2020, CAPTIVATE-MRD; Siddiqi et al.

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High Rates of Undetectable MRD Achieved in PB and BM With Up to 12 Cycles of I + V Combination

	Peripheral Blood n=163	Bone Marrow[a] n=155
Best response of undetectable MRD in evaluable patients[b] (95% CI)	**75%** (68–82)	**72%** (64–79)

- 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

[a]BM MRD assessment was scheduled after completion of 12 cycles of combination treatment.
[b]Patients with undetectable MRD at any postbaseline assessment; evaluable patients are those who had at least 1 MRD sample taken postbaseline.

EHA 2020, CAPTIVATE-MRD; Siddiqi et al.

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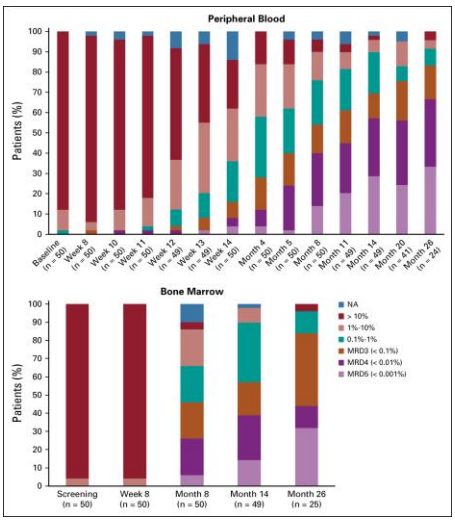
CLARITY Ph2 trial (up to 2 yrs of treatment)



Hillmen P, et al. J Clin Oncol 2019; 37:2722-2729.

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Novel BTKi/Bcl-2i combinations

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

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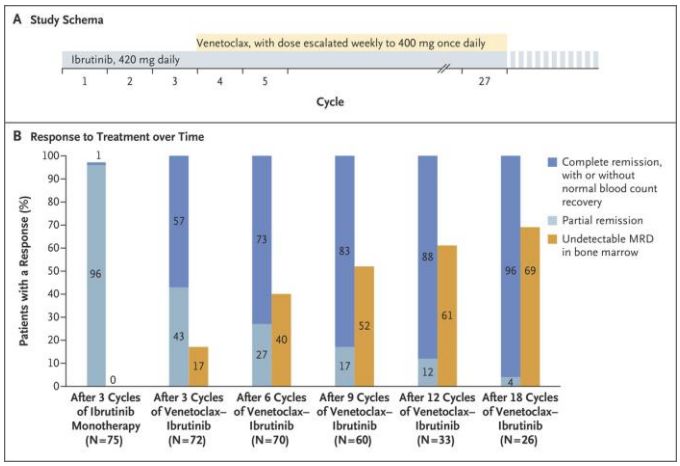
MDACC: IIT, Ph2, frontline high risk and older CLL pts, I+V for 24 cycles

Study Schema and Response to Treatment.



N Jain et al. N Engl J Med 2019;380:2095-2103.

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Novel BTKi/Bcl-2i combinations

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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

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Adverse event management

- **BTKi:**
  - Atrial fibrillation
  - Hemorrhage
  - Arthralgias
  - HTN
  - Rash
  - Infections
- **Ven:**
  - Tumor lysis syndrome
  - Infections

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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. Wierda[10]

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

ASH annual meeting 2020
Presentation 546

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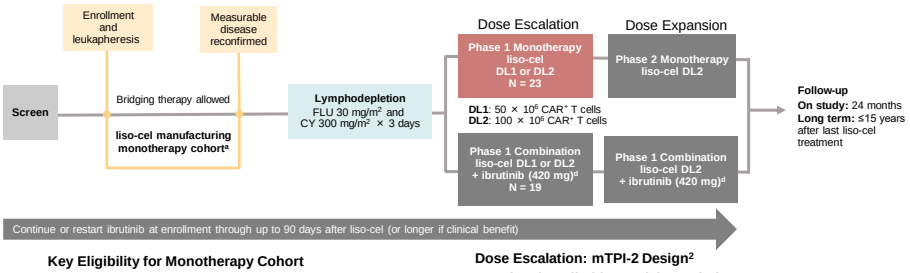
TRANSCEND CLL 004 Phase 1/2 Study Design[1] of liso-cel, a CD19-Directed, Defined Composition, CAR T Cell Product



Key Eligibility for Monotherapy Cohort

- R/R CLL/SLL
- Ineligible for BTKi or prior BTKi failure[b]
- High-risk disease[c]: ≥2 prior therapies failed
- Standard-risk disease: ≥3 prior therapies failed
- ECOG PS of 0—1

Dose Escalation: mTPI-2 Design[2]

28-day dose-limiting toxicity period

Primary objectives

- Safety
- Determine recommended dose

Exploratory objectives

- Antitumor activity (iwCLL 2018)[3]
  - Testing for MRD[e]
- Cellular kinetic profile (qPCR)

[a]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). [b]Defined as patients whose disease progressed on BTKi. [c]Complex cytogenetic abnormalities, del(17p), *TP53* mutated, or unmutated *IGHV*. [d]Lower dose was used if prior dose reduction was necessary to manage toxicity. [e]MRD was assessed in blood by flow cytometry and/or in bone marrow by next-generation sequencing (both with a sensitivity of $\leq 10^{-4}$).

1. ClinicalTrials.gov. NCT03331198; 2. Guo W, et al. *Contemp Clin Trials*. 2017;58:23–33; 3. Hallek M, et al. *Blood*. 2018;131:2745–2760.

Siddiqi T, et al. ASH annual mtg 2020.

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Demographic and Baseline Disease Characteristics

Characteristic	Monotherapy Cohort (N = 23)	BTKi Progression/Venetoclax Failure Subgroup[c] (n = 11)
Median age, y (range)	66 (50–80)	68 (59–76)
Male, n (%)	11 (48)	6 (55)
Median time since diagnosis, mo (range)	87.5 (30–209)	106 (30–209)
Bulky disease ≥5 cm, n (%)[a]	8 (35)	4 (36)
Median SPD, cm² (range)	25 (2–197)	41 (2—197)
Median BALL risk score[1] (range)	2 (0–3)	2 (0–3)
Median LDH, U/L (range)	235 (1–1956)	240 (1–1956)
Stage, n (%)		
Rai stage III/IV	15 (65)	7 (64)
Binet stage C	16 (70)	8 (73)
High-risk feature (any), n (%)	19 (83)	10 (91)
Del(17p)	8 (35)	4 (36)
TP53 mutated	14 (61)	8 (73)
Complex karyotype[b]	11 (48)	5 (45)
Median no. of lines of prior therapy (range)	4 (2–11)	5 (4–10)
Ibrutinib progression, n (%)	17 (74)	11 (100)
Ibrutinib intolerant, n (%)	6 (26)	0
Received bridging therapy, n (%)	17 (74)	8 (73)

[a]Defined as ≥1 lesion with longest diameter of >5 cm. [b]At least 3 chromosomal aberrations. [c]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. BALL, β_2 microglobulin, anemia, LDH, last therapy; SPD, sum of the product of perpendicular diameters.

1. Soumerai JD, et al. *Lancet Haematol*. 2019;6:e366-e374.

Siddiqi T, et al. ASH annual mtg 2020.

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

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

- 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

[a]No grade 4 or 5 CRS events were reported. [b]NEs were not mutually exclusive: encephalopathy (n = 3), aphasia (n = 1), confusional state (n = 1), muscular weakness (n = 1), and somnolence (n = 1). [c]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. [d]Based on Lee criteria (Lee et al, *Blood.* 2014;124:188–195).

Siddiqi T, et al. ASH annual mtg 2020.

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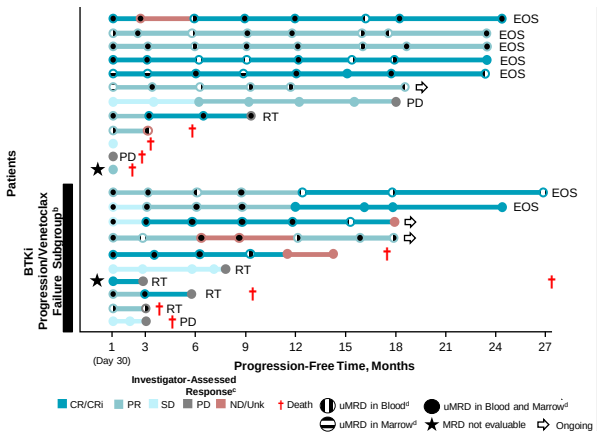
Patient Response at 24-Month Median Follow-Up



- ORR was 82% (CR/CRi, 46%; PR, 36%), with 68% (n = 15/22)[a] 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

[a]One patient had RT before lymphodepleting chemotherapy and was excluded from the efficacy analysis. [b]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. [c]Evaluated according to iwCLL 2018 criteria. [d]Assessed in blood by flow cytometry and/or in bone marrow by next-generation sequencing (both with a sensitivity of ≤10^{-4}). CRi, CR with incomplete blood count recovery; EOS, end of study; ND, not done; Unk, unknown.

Siddiqi T, et al. ASH annual mtg 2020.

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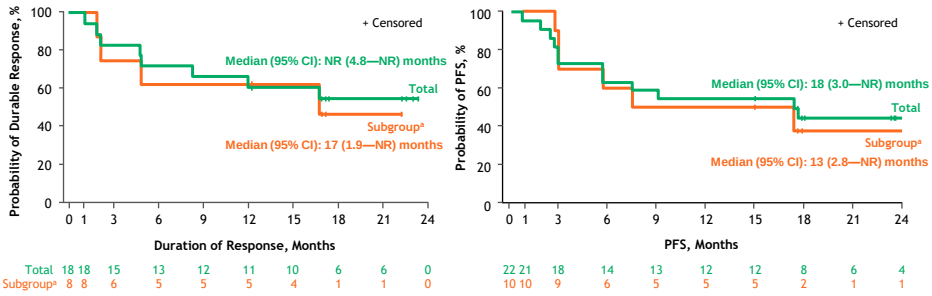
Duration of Response and PFS at 24-Month Median Follow-Up



[a]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.

Siddiqi T, et al. ASH annual mtg 2020.

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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)

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

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

[a]Based on Lee criteria (Lee et al, *Blood.* 2014;124:188–195). [b]NEs 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

Wierda W, et al. ASH annual mtg 2020.

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Ibrutinib-Related TEAEs Rarely Resulted in Dose Reduction or Discontinuation

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

[a]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

Wierda W, et al. ASH annual mtg 2020.

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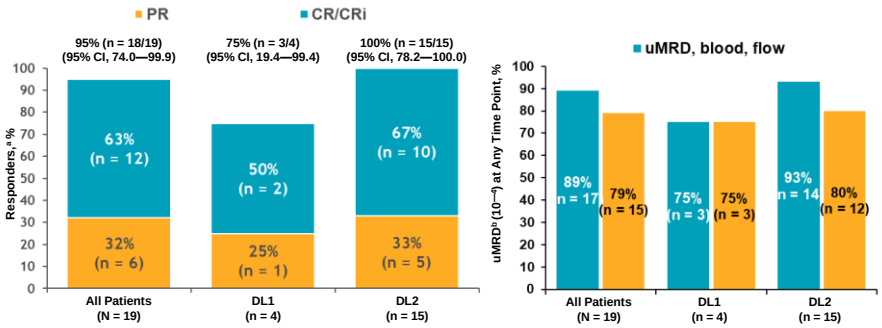
Best Overall Response and uMRD (≤10^{-4}) at 10-Month Follow-Up



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

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

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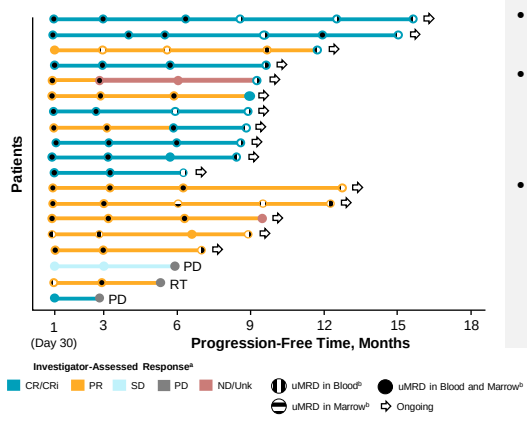
Patient Responses over Time at 10-Month Follow-Up



- 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)

[a]Evaluated according to iwCLL 2018 criteria. [b]Assessed in blood by flow cytometry and/or in bone marrow by NGS.
ND, not done; Unk, unknown.

Wierda W, et al. ASH annual mtg 2020.

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Other ongoing CAR T-cell trials in CLL

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

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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

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Questions?

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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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LLS EDUCATION & SUPPORT RESOURCES

HOW TO CONTACT US:

To contact an **Information Specialist** about disease, treatment and support information, resources and clinical trials:

Call: (800) 955-4572
Monday to Friday, 9 a.m. to 9 p.m. ET
Chat live online: www.LLS.org/InformationSpecialists
Monday to Friday, 10 a.m. to 7 p.m. ET
Email: infocenter@LLS.org
All email messages are answered within one business day.

CLINICAL TRIAL SUPPORT CENTER
Work one-on-one with an LLS Clinical Trial Nurse Navigator who will help you find clinical trials and personally assist you throughout the entire clinical-trial process.
www.LLS.org/Navigation

NUTRITION CONSULTATIONS
Our registered dietitian has expertise in oncology nutrition and provides free one-on-one consultations by phone or email.
www.LLS.org/Consult.

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LLS EDUCATION & SUPPORT RESOURCES

Online Chats
Online Chats are free, live sessions, **moderated by oncology social workers**. To register for one of the chats below, or for more information, please visit **www.LLS.org/Chat**.

Education Videos
View our free education videos on disease, treatment, and survivorship. To view all patient videos, please visit **www.LLS.org/EducationVideos**.

Patient Podcast
The Bloodline with LLS is here to remind you that after a diagnosis comes hope. To listen to an episode, please visit **www.TheBloodline.org**.

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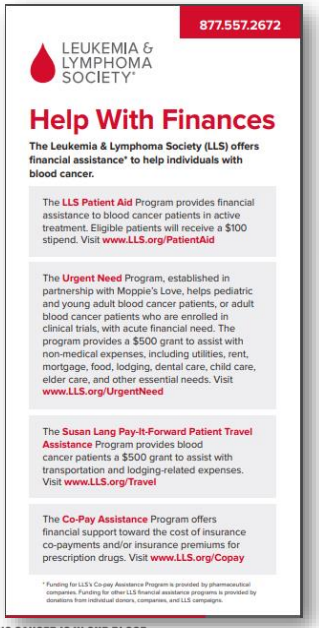

The Leukemia & Lymphoma Society (LLS) offers the following financial assistance programs to help individuals with blood cancer: **www.LLS.org/Finances**

To order free materials: **www.LLS.org/Booklets**

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