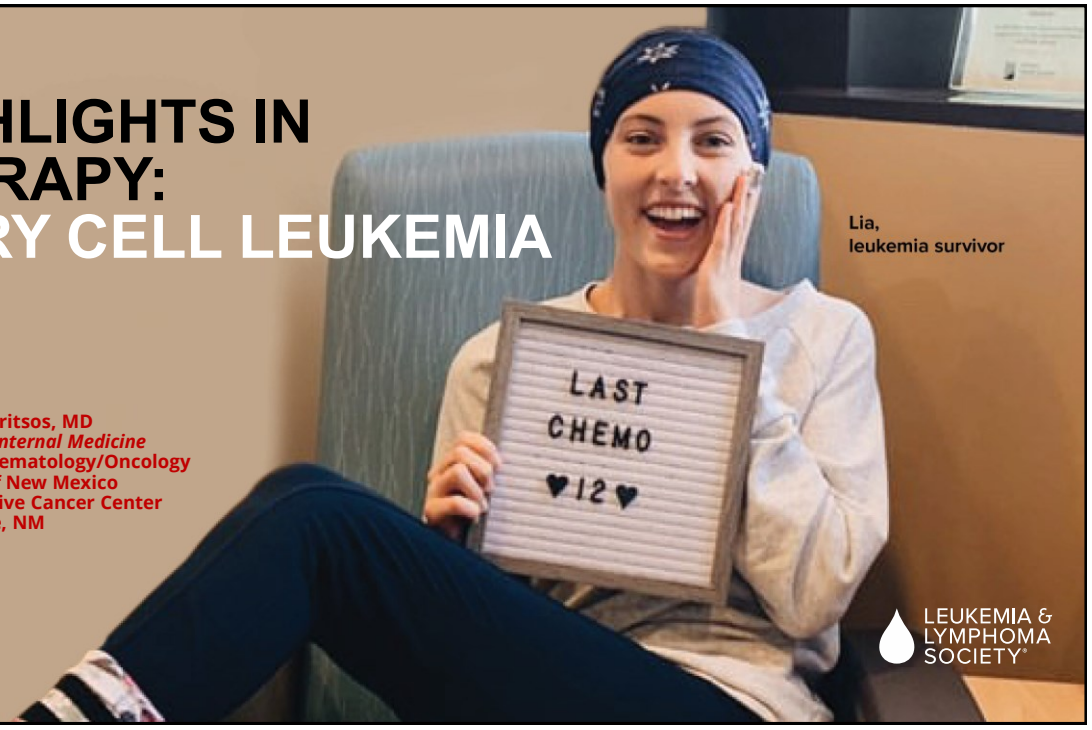
# HIGHLIGHTS IN THERAPY: HAIRY CELL LEUKEMIA




**Leslie A. Andritsos, MD**
***Professor of Internal Medicine***
**Division of Hematology/Oncology**
**University of New Mexico**
**Comprehensive Cancer Center**
**Albuquerque, NM**

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## WELCOMING REMARKS

**HIGHLIGHTS IN THERAPY: HAIRY CELL LEUKEMIA**

**Lizette Figueroa-Rivera, MA**
*Senior Director, Education & Support*
The Leukemia & Lymphoma Society
Rye Brook, NY

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## PRESENTATION

HIGHLIGHTS IN THERAPY: HAIRY CELL LEUKEMIA

**Leslie A. Andritsos, MD**
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## DISCLOSURES

HIGHLIGHTS IN THERAPY: HAIRY CELL LEUKEMIA

- Research support from the Hairy Cell Leukemia Foundation
- Discussing off-label use of:
  - Vemurafenib, Dabrafenib
  - Rituximab, Obinutuzumab
  - Ibrutinib, additional BTK inhibitors
  - MEK inhibitors
  - Chimeric antigen receptor therapy (CAR T)



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## OVERVIEW

- HCL epidemiology
- Diagnostic criteria
- Consensus guidelines for treatment and response assessments
- Highlights of therapy
- Complications
- Clinical trials
- Patient resources

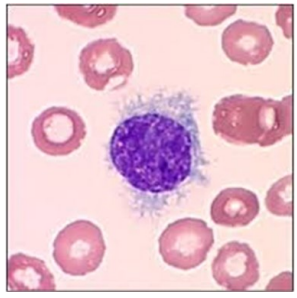

Photo courtesy of Gerard Lozanski, MD.

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## A BRIEF HISTORY OF HCL

- 1923: HCL-like cells first observed
- First termed “leukemic reticuloendotheliosis”
- Further characterized by Dr. B. Bouroncle in 1958[1]
- Uniformly fatal until development of interferon alfa in 1984
- Cladribine and Pentostatin in 1980s/1990s – transformed HCL into a chronic disease with near normal life expectancy[2]

6 [1]Bouroncle B et al. *Blood* 1958; [2]Else et al. *Br J Haematol* 2006.

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The New York Times

# New Drug Found Helpful in Treating Rare Cancer

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By Sandra Blakeslee

April 19, 1990

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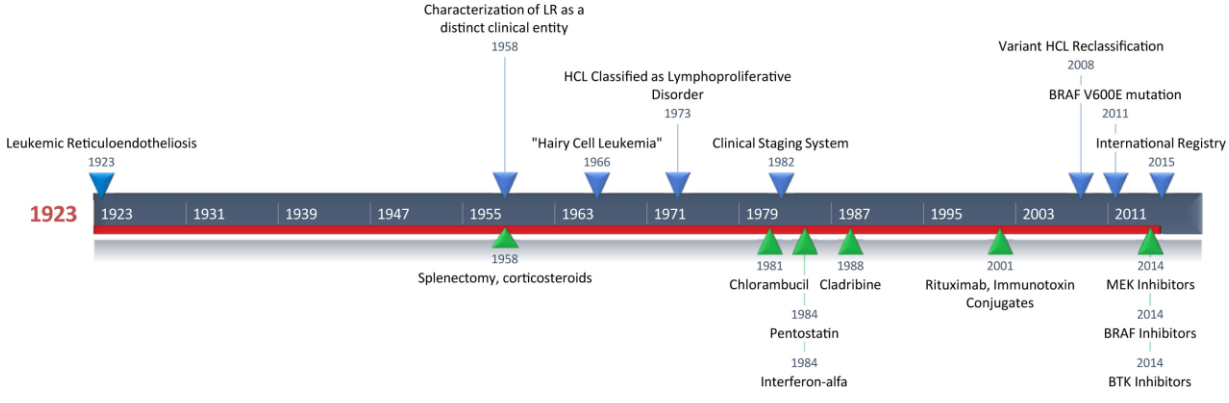


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8 Andritsos G. *Best Pract Res Clin Haematol* 2015.

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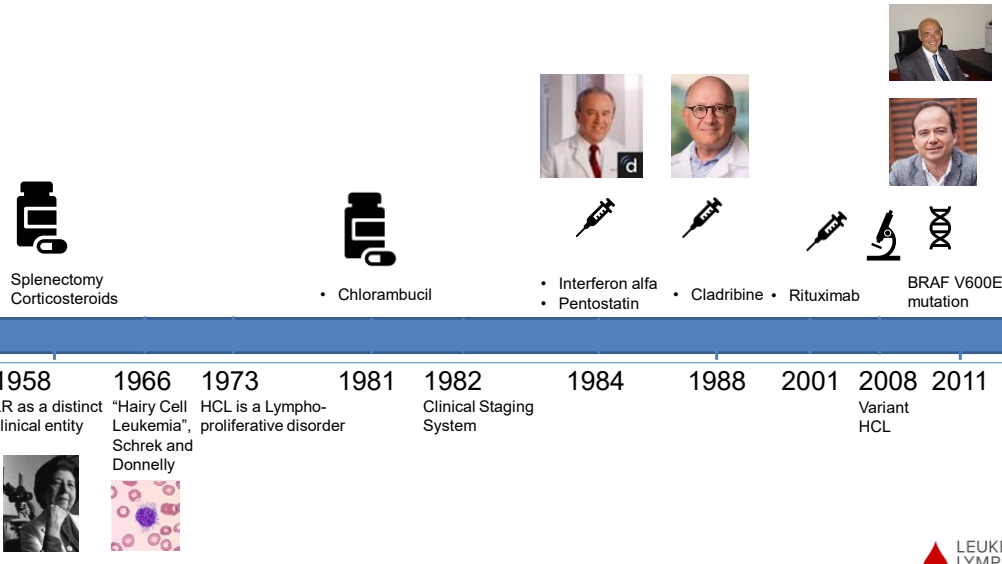
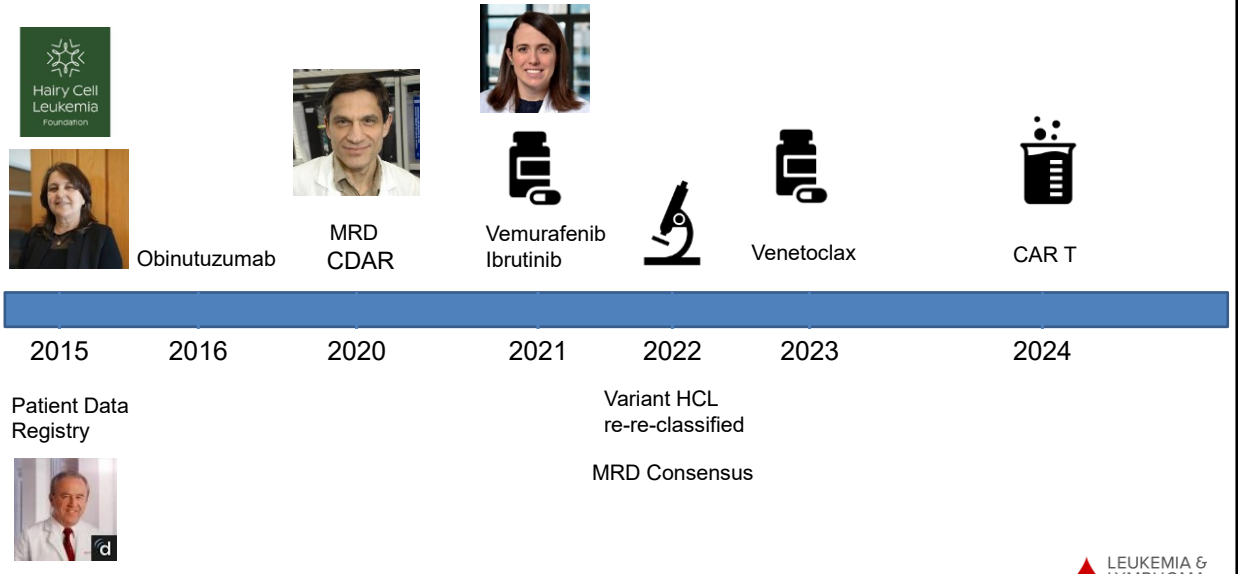
## HISTORICAL TIMELINE OF HCL: DIAGNOSIS AND THERAPIES








## HISTORICAL TIMELINE OF HCL: DIAGNOSIS AND THERAPIES




 CDAR, cladribine/rituximab; MRD, measurable residual disease.

## EPIDEMIOLOGY

- ~2% of all lymphomas
- Median age at diagnosis ~55–60 years of age
- ~4:1 male predominance
- Higher incidence among Caucasians[1]
- Lower incidence among Asian, African, and Arab populations[1]
- Higher incidence in first degree relatives of patients with HCL[2]
- Improved progression-free survival in women after treatment[3]
- Possible associations:
  - Farming[4,5]
  - Exposures to pesticides and herbicides[6,7]
  - Diesel exposure[5,6]
  - Exposure to ionizing radiation[6]

11 [1]Bernstein L et al. *Cancer Res* 1990;50:3605–9; [2]Sud A et al. *Blood* 201919;134(12):960–9; [3]Titmarsh GJ et al. *Am J Hematol* 2023;98(5);E116–8; [4]Monnereau A et al. *J Natl Cancer Inst Monogr* 2014;48:115–24; [5]Clavel J et al. *Br J Haematol* 1995;91(1):154–61; [6]Hardell L et al. *Leuk Lymphoma* 2002;43(5):1043–9; [7]*Federal Register* 2010.

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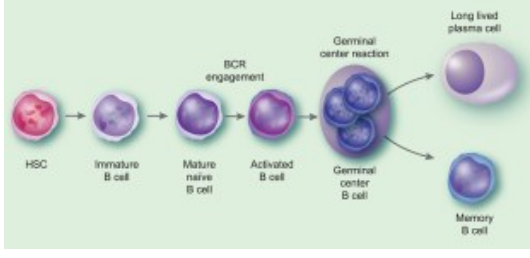
## HCL BIOLOGY

- Lymphoproliferative disorder, circulates in the blood in 10%–15% of patients (“leukemia”)
- Characterized by the accumulation of clonal B cells with surface hairy projections
- Cell of origin felt to be a late-activated memory B cell
- However, BRAF mutant stem cells have been identified in the bone marrow of some patients[1]

**B-cell development**




12 [1]Chung SS et al. *Sci Transl Med* 2014;28;6(238):238ra71.

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## HCL BIOLOGY

- Majority of classic HCL cases have common BRAF V600E mutation
- Acquired driver mutation
- Present in the entire tumor clone, with high stability at relapse
- Alternative mutations may act as driver mutations
  - Alternative BRAF mutations
  - MAP2K1 mutations
  - Others
- Consider next-generation sequencing if clinical course is more aggressive

13 Tiacci E et al. *N Engl J Med* 2011.

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## GENOMIC ALTERATIONS

**TABLE 1** Genomic alterations in hairy cell leukemia (HCL), hairy cell leukemia-variant (HCL-V), splenic diffuse red pulp lymphoma (SDRPL) and splenic marginal zone lymphoma (SMZL)

| | HCL | HCL-V | SDRPL | SMZL |
|---|---|---|---|---|
| MAPK pathway | | | | |
| BRAF V600E | **70%**[21]-**100%**[22–25] | 0%[22,23,25] | 0%[26,27]-2% (G469A)[24] | 0%[25]-2%[24] |
| MAP2K1[a] | 0%[22,23,24]-22%[21] | **38%**[23]-**42%**[21] | 7% (VH4–34+)[24]-12%[26] | 0%[24] |
| Cell cycle | | | | |
| CDKN1B (p27) | **11%**[23]-**16%**[22] | 0%[22,23] | 4%[26] | |
| CCND3 | 0%[23] | 13%[23] | **21%**[24]-**24%**[26] | 13%[24] |
| NFKB pathway | | | | |
| MYD88 | 0%[24] | | 0%[24] | 9%[24] |
| TNFAIP3 | 0%[24] | | 0%[24] | 20%[24] |
| Spliceosome | | | | |
| U2AF1 | 0%[21,23] | 13%[21,23] | | |
| TP53 | | 8%[21]-38%[23] | 0%[27] | |
| Notch pathway | | | | |
| NOTCH1 | 4%[23]-13%[24] | 0%[23] | 2%[24] | 9%[24] |
| NOTCH2 | 0%[24,28]-4%[23] | 0%[23] | 10%[24] | 17%[24]-25%[28] |
| Epigenetic regulators | | | | |
| KMT2C (histone methyltransferase) | 15%[23] | 25%[23] | | |
| ARID1A (SWI/SNF family) | 4%[21] | 4%[21] | 8%[26] | |
| Transcription factors (TF) | | | | |
| TTN | 4%[21] | 4%[21] | 8%[26] | |
| KLF2 | 13%[24]-16%[29] | 0%[29] | 2%[24] | 20%[29]-30%[24] |
| TF repressor | | | | |
| BCOR | 0%[24] | | **24%**[24] | 2%[24] |

[a]MAP2K1 mutations in 6/7 VH4–34+ HCL patients and in 4/10 VH4–34+ HCL-V patients.[21]

14 Waterfall JJ et al. *Nat Genet* 2014;46:8–10.

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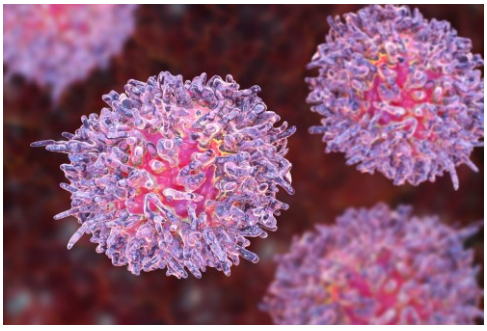
## WHY ARE THEY HAIRY?

- Cells develop membrane ruffling and microvilli formation
- Early clue into biology of HCL with constitutive activation of RAF-MEK-ERK pathway[1]
- Indication of ongoing cellular activation
- External portion of the cell is in a state of constant reorganization



www.HairyCellLeukemia.org

15 [1]Kamiguti AS et al. *Oncogene* 2003;17;22(15):2272–84.

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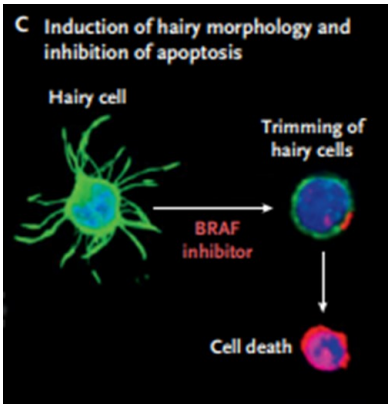
## HAIR LOSS PRECEDES CELL DEATH




16 Falini B and Tiacci E. *N Engl J Med* 2024;391;14.

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# DIAGNOSIS



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## INDICATORS OF POSSIBLE HCL

- Pancytopenia
- Monocytopenia
- Splenomegaly
- Presence of infection, especially unusual infection
- Constitutional symptoms (fevers, unintentional weight loss)
- Circulating hairy cells (less common)
- Need a bone marrow biopsy for definitive diagnosis



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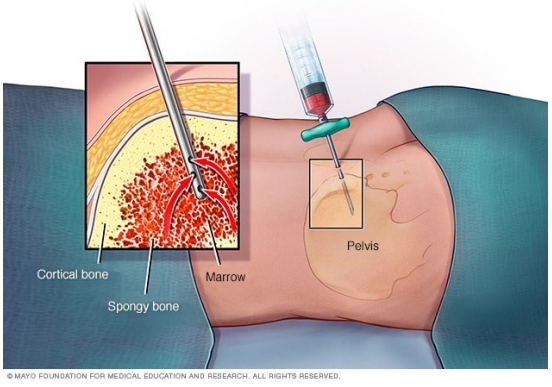
## BONE MARROW CORE BIOPSY AND ASPIRATE FOR MORPHOLOGY, IMMUNOPHENOTYPE, AND CYTOGENETICS



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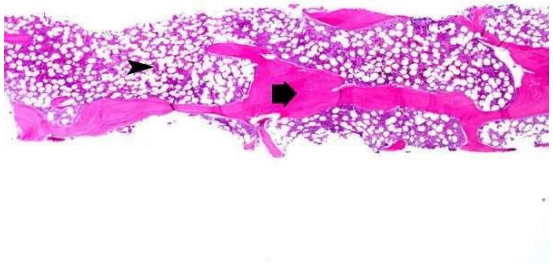
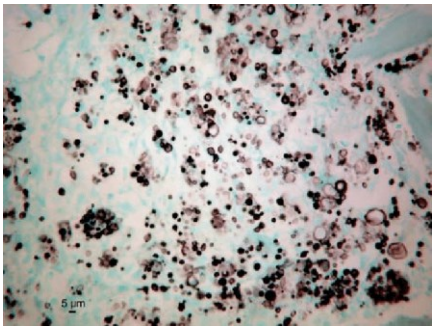
## BONE MARROW BIOPSY CORE AND STAINS





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## CONSENSUS GUIDELINES FOR DIAGNOSIS, RESPONSE ASSESSMENT, AND TREATMENT OF HCL

Review Article

blood

**Consensus guidelines for the diagnosis and management of patients with classic hairy cell leukemia**

Michael R. Grever,[1] Omar Abdel-Wahab,[2] Leslie A. Andritsos,[1] Versha Banerji,[3] Jacqueline Barrientos,[4] James S. Blachly,[1] Timothy G. Call,[5] Daniel Catovsky,[6] Claire Dearden,[7] Judit Demeter,[8] Monica Else,[6] Francesco Forconi,[9] Alessandro Gozzetti,[10] Anthony D. Ho,[11] James B. Johnston,[3] Jeffrey Jones,[1] Gunnar Juliusson,[12] Eric Kraut,[1] Robert J. Kreitman,[13] Loree Larratt,[14] Francesco Lauria,[10] Gerard Lozanski,[15] Emili Montserrat,[16] Sameer A. Parikh,[5] Jae H. Park,[2] Aaron Polliack,[17] Graeme R. Quest,[18] Kanti R. Rai,[4] Farhad Ravandi,[19] Tadeusz Robak,[20] Alan Saven,[21] John F. Seymour,[22] Tamar Tadmor,[23] Martin S. Tallman,[2] Constantine Tam,[22] Enrico Tiacci,[24] Xavier Troussard,[25] Clive S. Zent,[26] Thorsten Zenz,[27] Pier Luigi Zinzani,[28] and Brunangelo Falini[24]

- Established first standards for:
  - Diagnosis
  - Indications for treatment
  - Response assessments
  - Recommendations for first-line therapy
  - Treatment at relapse

21 Grever MR et al. *Blood* 2017;129(5):553–60.

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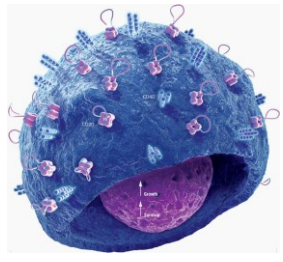
## CONSENSUS GUIDELINES FOR DIAGNOSIS

### Immunophenotype:

Clonal B cells positive for CD19, CD20, CD22, PAX5, CD79a, CD11c, CD25, CD103, CD123, CD200, DBA44, FMC7



### Immunohistochemical stains:

Annexin-1, VE1 (BRAF)

### BRAF testing:

BRAF V600E mutation positive by PCR or IHC (VE1/BRAF)

**In the case of an atypical phenotype, diagnosis is based on the most diagnostic features**

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## IMAGING NOT REQUIRED BUT USEFUL IN SOME CIRCUMSTANCES

- Ultrasound of spleen to obtain measurements
- CT scans to evaluate for presence of enlarged lymph nodes and/or enlarged spleen
- PET/CT scan to look for involvement in extranodal areas; currently no consensus on standard features in HCL
- Imaging would be recommended prior to starting treatment



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## VARIANT HCL

- Now termed splenic B-cell lymphoma/leukemia with prominent nucleoli[1]
- Typically has a more aggressive clinical course than cHCL
- By definition BRAF-V600E negative
- Originally felt to always be CD25 negative
- Considered a separate disease from HCL
- Treatment will not be addressed in this discussion; however, there is a great deal of overlap



[1]WHO Classification 2022.

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## INDICATIONS FOR TREATMENT

- Most HCL patients need treatment at the time of diagnosis
- Around 10% of patients can be monitored on observation at the time of diagnosis[1]
- Consider treatment when:
  - Hemoglobin <11 g/dL
  - Platelet count <100,000/μL
  - Absolute neutrophil count <1,000/μL
  - Splenomegaly, especially if symptomatic

25 [1]Golomb HM. *J Clin Oncol* 1983;1(10):652–6.

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# TREATMENT

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## TOWARD A CHEMOTHERAPY-FREE FUTURE

***EXCEPT***

- In HCL, chemotherapy still provides the longest progression-free survival
- Remains backbone of therapy in majority of patients

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## CHEMOTHERAPY ALONE

- Cladribine or pentostatin
- Highly effective in both the upfront and relapsed setting
- Equivalent response and long-term outcomes[1]
- Up front ~100% overall response rates, 70%–90% complete response rates
- Identification of residual disease more sophisticated but remissions remain the same
- 5-year progression-free survival around 70%
- Has resulted in near normalization of life expectancy[2]
- Still ~40% of patients relapse

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[1]Else et al. *BJH* 1999; [2]Yazan et al. *Clin Lymph Myel* 2017.

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## CLADRIBINE

- A purine nucleoside analog chemotherapy
- Multiple ways to administer:
  - 0.1 mg/kg/day continuous IV infusion for 7 days
  - 0.14 mg/kg/day IV over 2 hours for 5 days
  - 0.1–0.14 mg/kg/day subcutaneously daily for 5 days
  - 0.15 mg/kg/day IV once weekly for 6 weeks
- Route and duration of administration may depend on available facilities and patient preference
- No significant differences observed in responses based on regimen
- May have less neutropenia with weekly dosing

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## PENTOSTATIN

- Purine nucleoside analog chemotherapy
- Administered 4 mg/m$^2$ IV every two weeks × 12 doses
- Two additional doses if CR achieved after 12 doses
- Dose can be reduced
- Treatment interval can be lengthened
- Treatment can be held if complications arise
- Previously unavailable due to manufacturing delays, currently listed as available

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## PENTOSTATIN VS CLADRIBINE

**Long-term results for pentostatin and cladribine treatment of hairy cell leukemia**

CLAIRE E. DEARDEN, MONICA ELSE, & DANIEL CATOVSKY

*The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, UK*

**Abstract**

Over the past 25 years we have collected data at our institution from 242 patients with hairy cell leukemia (HCL), treated with pentostatin ($n = 188$) or cladribine ($n = 54$), with a median follow-up of 16 years. From this we have been able to conclude that there is no significant difference in outcome between the two agents either at first or subsequent lines of therapy. Overall, the complete response (CR) rate is 81% and the median disease-free survival (DFS) is 16 years. After relapse or non-response patients can be successfully retreated with pentostatin or cladribine achieving a lower rate of CRs with each line of therapy, although these remain equally durable. Complete response and pretreatment counts of hemoglobin > 10 g/dL together with platelets > $100 \times 10^9$/L are associated with the longest DFS. Importantly, for patients achieving a CR the DFS is five times as long as for those achieving a partial response (PR). Patients still in CR at 5 years have only a 25% risk of relapse by 15 years. Outcomes for patients with recurrent disease have improved with the addition of rituximab to either purine analog. Overall, only eight patients have died of HCL-related causes. Patients with HCL who achieve a CR can expect a normal lifespan.

**Keywords:** *Hairy cell leukemia, pentostatin, cladribine*

31 Dearden CE et al. *Leuk Lymphoma* 2011;52(S2):21–4.

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## COMPARISON OF RESPONSES

Table I. Single-agent cladribine and pentostatin treatment of 242 patients with hairy cell leukemia: response and disease-free survival by line of treatment.

| | No. of patients | CR | PR | NR | DFS at 5 years |
|---|---|---|---|---|---|
| First line | | | | | |
| Pentostatin | 188 | 82% | 14% | 4% | 77% |
| Cladribine | 54 | 76% | 24% | 0% | |
| Second line | | | | | |
| Pentostatin | 28 | 59% | 33% | 8% | 68% |
| Cladribine | 60 | 69% | 31% | 0% | |
| Third line | | | | | |
| Pentostatin | 4* | 100% | 0% | 0% | 58% |
| Cladribine | 18* | 38% | 62% | 0% | |

*Only 16/22 patients were evaluable for response (three pentostatin, 13 cladribine).
CR, complete response; PR, partial response; NR, no response; DFS, disease-free survival.

32 Dearden CE et al. *Leuk Lymphoma* 2011;52(S2):21–4.

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## DISEASE-FREE SURVIVAL ACCORDING TO RESPONSE

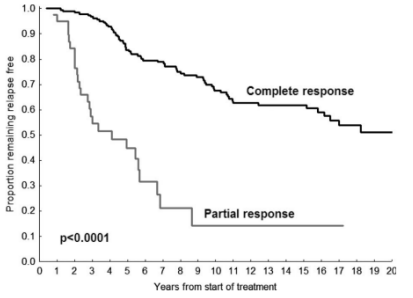


Figure 1. Disease-free survival by response to first-line single-agent treatment with either pentostatin or cladribine, showing a significant difference between patients achieving a complete response (CR) versus a partial response (PR). The median disease-free survival was 16 years overall: 20+ years (not reached) for patients attaining a CR and 4 years after a PR ($p < 0.0001$). There was no difference in DFS by type of treatment (pentostatin or cladribine).

33 Dearden CE et al. *Leuk Lymphoma* 2011;52(S2):21–4.

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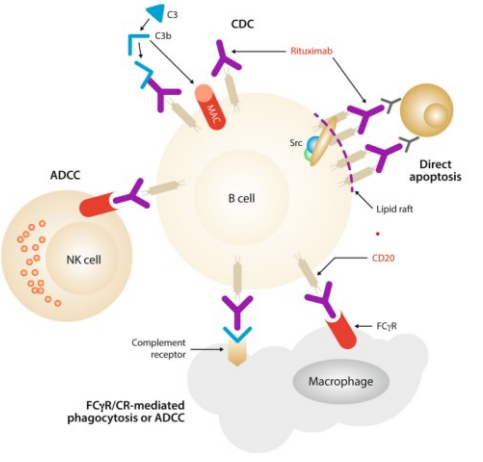
## RITUXIMAB

- Anti-CD20 immunotherapy
- Limited data for use in up-front setting as a single agent
- Multiple studies for use during relapse




34 Salles G et al. *Adv Ther* 2017;34:2232–73.

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**TO THE EDITOR:**

# Single-agent rituximab is an effective salvage therapy in pretreated patients with hairy cell leukemia

Alessandro Broccoli,[1,2] Lisa Argnani,[2] Laura Nanni,[1,2] Vittorio Stefoni,[1,2] Cinzia Pellegrini,[1] Beatrice Casadei,[1] Gabriele Gugliotta,[1] Matteo Carella,[1,2] Paolo Elia Coppola,[1,2] Gianmarco Bagnato,[1,2] and Pier Luigi Zinzani[1,2]

[1]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli," Bologna, Italy; and [2]Dipartimento di Scienze Mediche e Chirurgiche, Università di Bologna, Bologna, Italy

35 Broccoli A et al. *Blood Adv* 2023;7:6762–6.

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## RITUXIMAB ONCE WEEKLY × 4 WEEKS

**Table 1. Clinical details and outcomes by line of treatment**

| | Second line | Third line | Fourth line | Fifth line | Sixth line | Seventh line | Eighth line |
|---|---|---|---|---|---|---|---|
| Patients, n | 12 | 9 | 7 | 5 | 4 | 1 | 1 |
| Male, n | 12/12 | 8/9 | 6/7 | 5/5 | 4/4 | 1/1 | 1/1 |
| Leukocytes ($mm^{-3}$) | 2 250 | 1 740 | 2 600 | 1 800 | 2 950 | 1 600 | 5 900 |
| Neutrophils ($mm^{-3}$) | 660 | 1 160 | 1 300 | 740 | 1 350 | 1 072 | 2 000 |
| Hemoglobin (g/dL) | 13.4 | 11.3 | 13.1 | 11.6 | 12.7 | 11.7 | 7.6 |
| Platelets ($mm^{-3}$) | 72 000 | 89 000 | 56 000 | 100 000 | 97 000 | 77 000 | 21 000 |
| Splenomegaly | 33% | 33% | 0 | 20% | 0 | 0 | 0 |
| Last therapy before rituximab | Cladribine (100%) | Cladribine (89%)<br>Rituximab (11%) | Cladribine (86%)<br>Interferon (14%) | Cladribine (60%)<br>Interferon (40%) | Rituximab (50%)<br>Cladribine (25%)<br>Pentostatin (25%) | Rituximab (100%) | Cladribine (100%) |
| Early interruption of rituximab, n | 1 (death) | None | 1 (cytopenia) | None | 1 (cytopenia)<br>1 (infusion reaction) | None | None |
| Next therapy after rituximab | Cladribine (50%)<br>Rituximab (25%)<br>Vemurafenib (25%) | Cladribine (60%)<br>Interferon (20%)<br>Rituximab + vemurafenib (20%) | Vemurafenib (20%)<br>Pentostatin (40%)<br>Chlorambucil (20%)<br>Cladribine (20%) | Rituximab (50%)<br>Cladribine (25%)<br>Interferon (25%) | Interferon (50%)<br>Cladribine (25%)<br>Rituximab (25%) | None | None |
| Overall response | 75.0% | 88.9% | 57.1% | 80.0% | 50.0% | 100% | 0 |
| Complete response | 41.7% | 33.3% | 0 | 20.0% | 25.0% | 100% | 0 |
| Further treatment | 36.4% | 55.6% | 71.4% | 80.0% | 100% | 0 | 0* |
| Month to relapse, range | 2.6-24.9 | 2.5-109.0 | 1.2-28.8 | 10.0-37.5 | 1.5-193.7 | N/A | N/A* |

N/A, not assessable.
*Patient deceased in the post-rituximab follow-up.

36 *Blood Adv* 2023;7:6762–6.

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## TIME TO NEXT TREATMENT AND SURVIVAL ANALYSIS

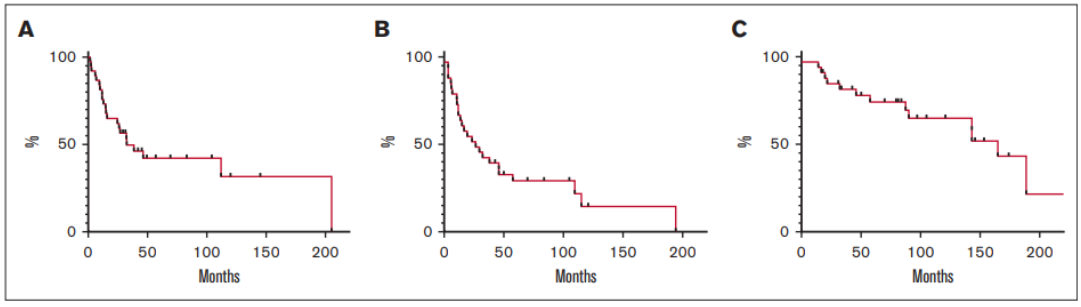


**Figure 1. Time to next treatment and survival analysis.** (A) TTNT calculated on each treatment received (it includes also patients who received rituximab more than once). (B) Progression-free survival determined on 33 patients from the initiation of the (first) treatment with rituximab to the date of progression, death, or last follow-up. (C) Overall survival determined on 33 patients from the initiation of the (first) treatment with rituximab to the date of death or last follow-up.

6764 RESEARCH LETTER 14 NOVEMBER 2023 • VOLUME 7, NUMBER 21 blood advances

37 Broccoli A et al. *Blood Adv* 2023;7(21):6762–6.

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## OBINUTUZUMAB

- Anti-CD20 monoclonal antibody
- Similar mechanism of action as rituximab
- Fully humanized
- Developed to be more potent than rituximab
- Better responses when given with chemotherapy than rituximab in other indolent lymphomas[1]

38 [1]Townsend W et al. *HemaSphere* 2023;7(7):e919.

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## OBINUTUZUMAB

**Efficacy and Safety of Obinutuzumab in Relapsed or Refractory Hairy Cell Leukemia (R/R HCL): An Italian Multicenter Phase-2 Academic Trial (HCL-PG04)**

Enrico Tiacci, Luca De Carolis, Monia Capponi, Flavio Falcinelli, Francesco Zaja, Alessandro Pulsoni, Edoardo Simonetti, Elisa Montechiarello, Alessandra Romano, Jacopo Olivieri, Alessandro Mancini, Gianna Maria D'Elia, Robin Foa, Maurizio Frezzato, Brunangelo Falini



*Blood* (2023) 142 (Supplement 1): 4398.

https://doi.org/10.1182/blood-2023-180035



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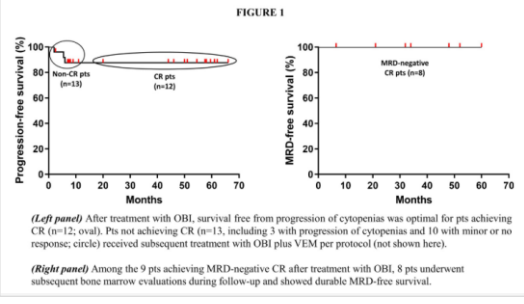
## OBINUTUZUMAB – RELAPSED HCL




***(Left panel)*** After treatment with OBI, survival free from progression of cytopenias was optimal for pts achieving CR (n=12; oval). Pts not achieving CR (n=13, including 3 with progression of cytopenias and 10 with minor or no response; circle) received subsequent treatment with OBI plus VEM per protocol (not shown here).

***(Right panel)*** Among the 9 pts achieving MRD-negative CR after treatment with OBI, 8 pts underwent subsequent bone marrow evaluations during follow-up and showed durable MRD-free survival.

- Phase 2 multicenter trial in relapsed HCL
- Schedule:
  - 1000 mg IV days 1, 8, and 15 of cycle 1 and on day 1, cycles 2–6 (1 cycle = 28 days)
- 26 patients treated
- 12 of 25 achieved a CR
- In CR patients, OS and PFS were 100% at 56 months
- In non-CR patients, vemurafenib was added at time of progression

 Tiacci E et al. *Blood* 2023;142(Suppl_1):4398.

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## CHEMO-IMMUNOTHERAPY

# Randomized Phase II Study of First-Line Cladribine With Concurrent or Delayed Rituximab in Patients With Hairy Cell Leukemia

Dai Chihara, MD, PhD[1]; Evgeny Arons, PhD[2]; Maryalice Stetler-Stevenson, MD, PhD[3]; Constance M. Yuan, MD, PhD[3]; Hao-Wei Wang, MD, PhD[3]; Hong Zhou, BS[2]; Mark Raffeld, MD[3]; Liqiang Xi, MD[3]; Seth M. Steinberg, PhD[4]; Julie Feurtado, RN[5]; Lacey James, CRNP[2]; Wyndham Wilson, MD, PhD[6]; Raul C. Braylan, MD[7]; Katherine R. Calvo, MD, PhD[7]; Irina Maric, MD[7]; Alina Dulau-Florea, MD[7]; and Robert J. Kreitman, MD[1,2]

41 Chihara D et al. *J Clin Oncol* 38:1527–38. © 2020.

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## RANDOMIZATION

- 68 patients randomly assigned 1:1 to concurrent cladribine plus rituximab vs cladribine followed by delayed rituximab
- Concurrent: Cladribine 0.15 mg/kg/day IV days 1–5
  PLUS rituximab 375 mg/m$^2$ beginning day 1 × 8 weekly doses
- Delayed: Cladribine 0.15 mg/kg/day IV days 1–5
  followed by rituximab 375 mg/m$^2$ × 8 weekly doses if MRD detected

42 Chihara D et al. *J Clin Oncol* 38:1527–38. © 2020.

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## CDAR RESULTS

- 6 months posttreatment:
  - CDAR: 100% CR; MRD negative 97%
  - Cladribine alone: 88% CR; MRD negative 24%
  - Statistically significant differences in MRD negativity
- 96 months median follow-up posttreatment:
  - CDAR: MRD negative 94%
  - Cladribine alone: MRD negative 12%
  - Delayed rituximab led to lower rate and durability of MRD negativity
- CDAR associated with higher rates of thrombocytopenia and need for platelet transfusions but faster blood count recovery overall

43 Chihara D et al. *J Clin Oncol* 38:1527–38. © 2020.

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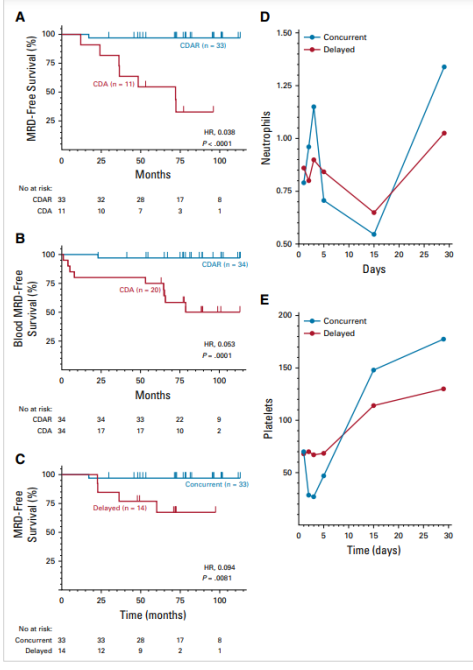
## CDAR RESULTS




44 Chihara D et al. *J Clin Oncol* 38:1527–38. © 2020.

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## CONCLUSIONS

- No unexpected toxicities
- Concurrent cladribine plus rituximab significantly increased MRD-negative remissions
- Delayed rituximab can also lead to MRD, but to a lesser extent
- MRD negativity increases progression-free survival



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## USE OF MRD IN TREATMENT ASSESSMENT

- Minimal/measurable residual disease (MRD)
  - The lowest level of HCL cells that can be detected accurately and reproducibly using validated methods
  - Can be measured in bone marrow or peripheral blood; marrow most accurate
- Methods for measuring MRD:
  - Immunohistochemical analysis
  - Multiparameter flow cytometry
  - Allele-specific PCR for BRAF
  - Currently no standardization for testing in HCL[1]
  - Future clinical practice guidelines will likely contain recommendations for MRD testing



[1]Ravandi F et al. *Blood Cancer J* 2022;12:165.

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# TARGETED THERAPIES

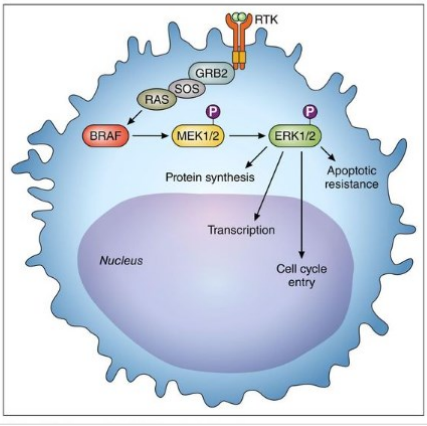






## BRAF INHIBITORS

The activated BRAF pathway provides oncogenic signaling to the leukemic hairy cell through the MEK-ERK cascade.






Grever MR et al. *Blood* 2016;127:2784–5.

## BRAF INHIBITORS GIVEN AS SINGLE AGENTS

- Vemurafenib and Dabrafenib
- Four phase 2 trials evaluating BRAFi as single agents
- Duration of therapy 3–5 months
- Overall response rates across studies: 90%
- Complete response rates: 30%–35%
- Duration of responses: median 1.5 years

49 Tiacci E et al. *Leukemia* 2021;35:3314–8; Tiacci E et al. *N Engl J Med* 2015;373:1733–47; Handa S et al. *Blood* 2022;140:2663–71; Blay JY et al. *ESMO Open* 2023;8:102038.

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## VEMURAFENIB WITH RITUXIMAB

- No established dose of vemurafenib in treating HCL
- Has been studied in combination with rituximab
- Phase 2 study of 30 patients with relapsed HCL
- Vemurafenib 960 mg twice daily plus rituximab IV × 8 doses over 18 weeks
- 26 patients (87%) achieved a complete response, 17 (65%) were MRD negative
- Median time to count recovery was 2 weeks for platelets and 4 weeks for neutropenia
- 78% of all patients were still in remission at 37 months after therapy
- Early results comparable to single-agent chemotherapy

50 Tiacci E et al. *N Engl J Med* 2021;384:1810–23.

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## VEMURAFENIB WITH RITUXIMAB

ORIGINAL ARTICLE

# Vemurafenib and Obinutuzumab as Frontline Therapy for Hairy Cell Leukemia

Jae H. Park, M.D.,[1,2] Sean Devlin, Ph.D.,[3] Benjamin H. Durham, M.D.,[4] Eric S. Winer, M.D.,[5] Scott Huntington, M.D.,[6] Gottfried von Keudell, M.D.,[6,7] Shreya Vemuri, M.P.H.,[8] Madhulika Shukla, B.A.,[8] Victoria Falco, R.N.,[8] Bernadette Cuello, N.P.,[1] Steven Gore, M.D.,[6,9] Richard Stone, M.D.,[5] Omar Abdel-Wahab, M.D.,[1,10] and Martin S. Tallman, M.D.[1,11,12]

51 Park JH et al. *NEJM Evid* 2023;2(10):EVIDoa2300074.

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## STUDY

- Phase 2 single-arm, multicenter study
- A total of 30 patients were enrolled
- All had indications for treatment per guidelines
- Treatment regimen:
  - Oral vemurafenib 960 mg twice daily × four 28-day cycles
  - Obinutuzumab beginning cycle 2
    - 1000 mg IV days 1, 8, and 15 of cycle 2
    - 1000 mg IV day 1 of cycles 3 and 4
  - Vemurafenib dose reductions allowed

52 Park JH et al. *NEJM Evid* 2023;2(10):EVIDoa2300074.

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## RESULTS

- Responses assessed at end of cycle 4
- MRD assessed with multiparameter flow cytometry
- 27 patients achieved a CR (90%)
- 96% of CRs were MRD negative
- Median duration of remission >2 years
- 3 patients withdrew due to toxicities
- 26 patients required dose reductions of vemurafenib
- Most common toxicities: rash, joint pain, fatigue
- Only 7% developed febrile neutropenia

53 Park JH et al. *NEJM Evid* 2023;2(10):EVIDoa2300074.

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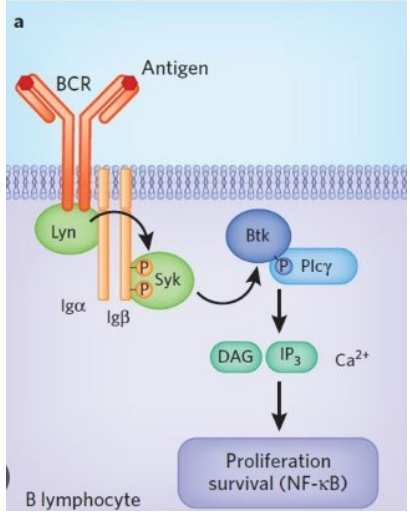
## BTK INHIBITORS

- Ibrutinib
- Acalabrutinib
- Zanabrutinib
- Pirtobrutinib




54 Hendriks RW. *Nat Chem Biol* 2011;7:4–5.

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## IBRUTINIB

- Oral BTK inhibitor
- Used extensively in CLL with excellent results
- Multicenter, phase 2 study of single-agent ibruitinib in relapsed/refractory HCL
- 37 patients were enrolled
  - 24 received 420 mg po qd
  - 13 received 840 mg po qd
- Overall response rate at 32 weeks was 24%; increased to 36% at 48 weeks
- Best overall response rate was 54%
- 36-month progression-free survival was 73% with overall survival of 85%
- Higher dose did not improve response
- Ibrutinib can lead to significant clinical benefit
- Other BTK inhibitors under investigation in HCL

55 Rogers KA et al. *Blood* 2021;137(25):3473–83.

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## VENETOCLAX

- Oral BH3 mimetic that induces apoptosis
- Widely studied in both leukemias and lymphomas
- In vitro data showing death of hairy cells prompted this study
- Studied in 6 patients with relapsed/refractory HCL
- Treatment:
  - 400 mg orally daily
  - Up to twelve 28-day cycles
  - Rituximab added in patients with poor response

56 Gounder M et al. *N Engl J Med* 2023;388(10):898–912.

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## RESPONSES

- Patients assessed at 6 and 12 months of therapy
  - 2 patients had a complete remission with MRD+
  - 1 patient had a partial remission
  - Remaining 3 patients had a minor response
  - Median time to response 2–3 months
  - Median time to improvement of neutropenia 4 weeks
- Rituximab added in 3 patients
  - Improved to CR with MRD+ in one patient
  - Hematological remission in patient with previously no response
  - Improvement in MRD in patient who had CR with MRD+
- Progression-free survival between 23–53 months in responders

57 Gounder M et al. *N Engl J Med* 2023;388(10):898–912.

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## PROPOSED ALGORITHM FOR INITIAL TREATMENT

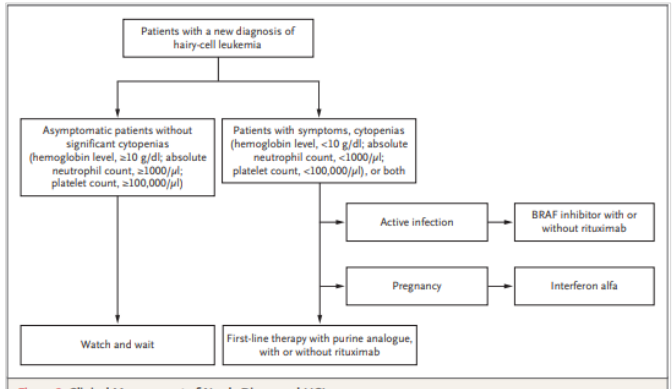


**Figure 3. Clinical Management of Newly Diagnosed HCL.**
In patients with newly diagnosed HCL, a watch-and-wait approach is indicated if there are no significant disease-related symptoms or cytopenias. Otherwise, purine analogue chemotherapy with or without rituximab is the usual standard-of-care first-line therapy. However, chemotherapy-free strategies are preferred in patients with an active infection (BRAF inhibitor with or without rituximab) and in those who are pregnant (interferon alfa).

58 Tiacci E et al. *N Engl J Med* 2024;391:1328–41.

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## PROPOSED ALGORITHM FOR TREATMENT AT RELAPSE

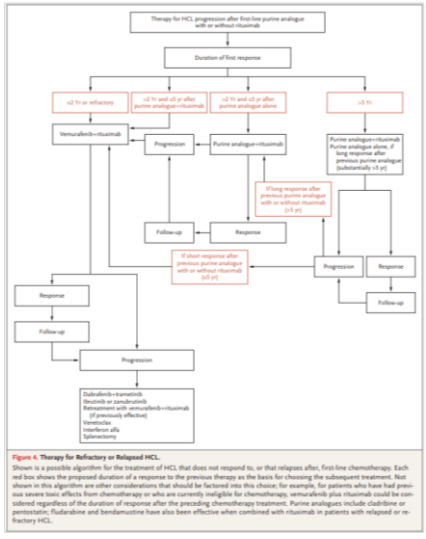


**Figure 4. Therapy for Refractory or Relapsed HCL.**

Shown is a possible algorithm for the treatment of HCL that does not respond to, or that relapses after, first-line chemotherapy. Each red box shows the proposed duration of a response to the previous therapy as the basis for choosing the subsequent treatment. Not shown in this algorithm are other considerations that should be factored into this choice; for example, for patients who have had previous severe toxic effects from chemotherapy or who are currently ineligible for chemotherapy, vemurafenib plus rituximab could be considered regardless of the duration of response after the preceding chemotherapy treatment. Purine analogues include cladribine or pentostatin; fludarabine and bendamustine have also been effective when combined with rituximab in patients with relapsed or refractory HCL.

59 Tiacci E et al. *N Engl J Med* 2024;391:1328–41.

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# IMMUNOTHERAPY IN HCL

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## CAR T

- Chimeric Antigen Receptor Therapy (CAR T)
- Patient's own lymphocytes are trained to target and kill tumor cells
- HCL potential targets for CAR T
  - CD19
  - CD22
  - BAFF
  - IGHV4-34
- Phase 1 study of CAR T (PI Robert Kreitman) currently enrolling patients who have relapsed/refractory hairy cell or variant hairy cell leukemia
- HCL2025 Projects: Early studies of BAFF CAR T at Case Western Reserve (PI Reshmi Parameswaran) and IGHV4-34 CAR T (PI Marco Ruella at Penn)

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## CONCLUSIONS

- Highly effective therapies available in HCL
- Chemotherapy likely still leads to longest progression-free survival especially when combined with anti-CD20
- Multiple nonchemotherapy options available if needed both in the up-front and relapsed setting
- Specific situations may warrant avoidance of chemotherapy; alternatively, some patients may not tolerate targeted therapies
- Careful consideration of patient's overall health, treatment goals, and community rates of infection should all factor into treatment decision
- Thank you!

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## HCL2025 guidelines

Expanding Research in Hairy Cell Leukemia to Better Characterize Its Biology, Develop New Therapies, and Optimize Outcomes for Patients.

# A NOTE OF THANKS TO LLS

Hairy Cell Leukemia Foundation

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"The Hairy Cell Leukemia Foundation (HCLF) and The Leukemia & Lymphoma Society (LLS) have joined forces to launch HCL2025, a 5-year, $10 million research initiative. HCL2025 supports studies of innovative treatments and novel management strategies in HCL. Through HCL2025, we will fund about $2,000,000 per year in HCL research, with a portion of the funds dedicated to the registry.

To launch HCL2025, we issued an open RFP. A review committee composed of leading HCL experts reviewed and made funding recommendations. We have now awarded multi-year grants to eight investigators at some of the world's best cancer research and treatment centers."

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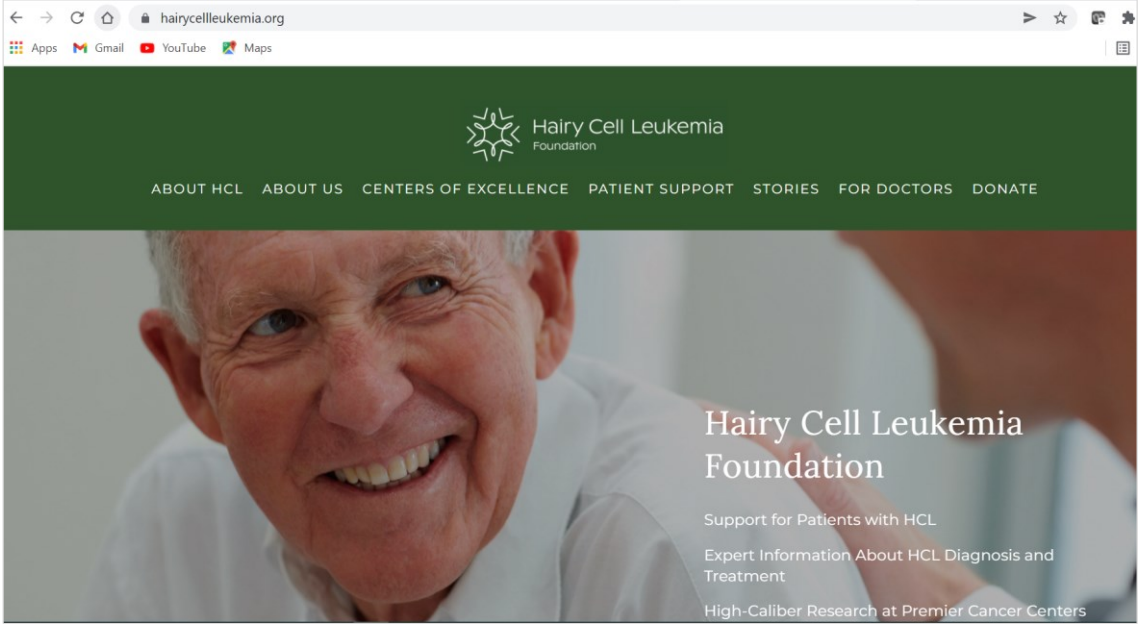


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## ASK A QUESTION

## HIGHLIGHTS IN THERAPY: HAIRY CELL LEUKEMIA

**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:**

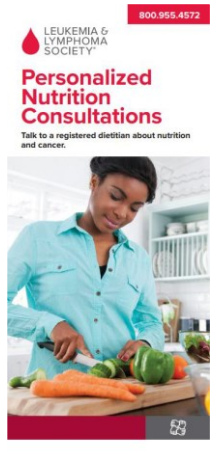
To contact an **Information Specialist** about disease, treatment and support information, resources and clinical trials:

**Call: (800) 955-4572**
Monday to Friday, 9 a.m. to 9 p.m. ET

**Chat live online: www.LLS.org/InformationSpecialist**
Monday to Friday, 10 a.m. to 7 p.m. ET

**Email: www.LLS.org/ContactUs**

**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**

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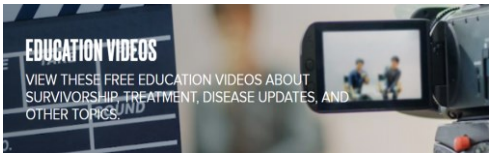
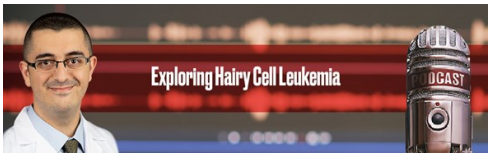
**Online Chats**

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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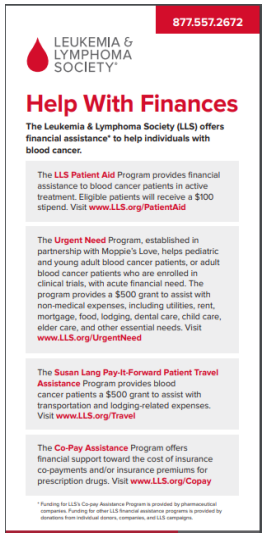
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**Help With Finances**

**The Leukemia & Lymphoma Society (LLS) offers financial assistance* to help individuals with blood cancer.**

The **LLS Patient Aid** Program provides financial assistance to blood cancer patients in active treatment. Eligible patients will receive a $100 stipend. Visit **www.LLS.org/PatientAid**

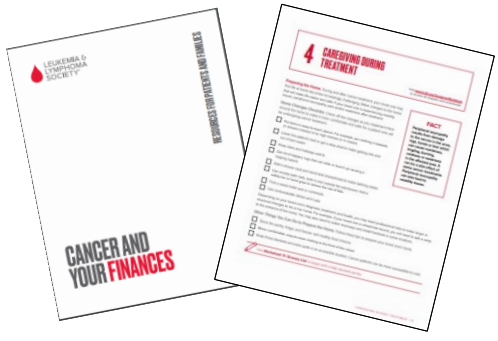
The **Urgent Need** Program, established in partnership with Moppie's Love, helps pediatric and young adult blood cancer patients, or adult blood cancer patients who are enrolled in clinical trials, with acute financial need. The program provides a $500 grant to assist with non-medical expenses, including utilities, rent, mortgage, food, lodging, dental care, child care, elder care, and other essential needs. Visit **www.LLS.org/UrgentNeed**

The **Susan Lang Pay-It-Forward Patient Travel Assistance** Program provides blood cancer patients a $500 grant to assist with transportation and lodging-related expenses. Visit **www.LLS.org/Travel**

The **Co-Pay Assistance** Program offers financial support toward the cost of insurance co-payments and/or insurance premiums for prescription drugs. Visit **www.LLS.org/Copay**

* Funding for LLS's Co-pay Assistance Program is provided by pharmaceutical companies. Funding for other LLS financial assistance programs is provided by donations from individual donors, companies, and LLS campaigns.

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




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

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We have one goal: A world without blood cancers