Understanding Hairy Cell Leukemia

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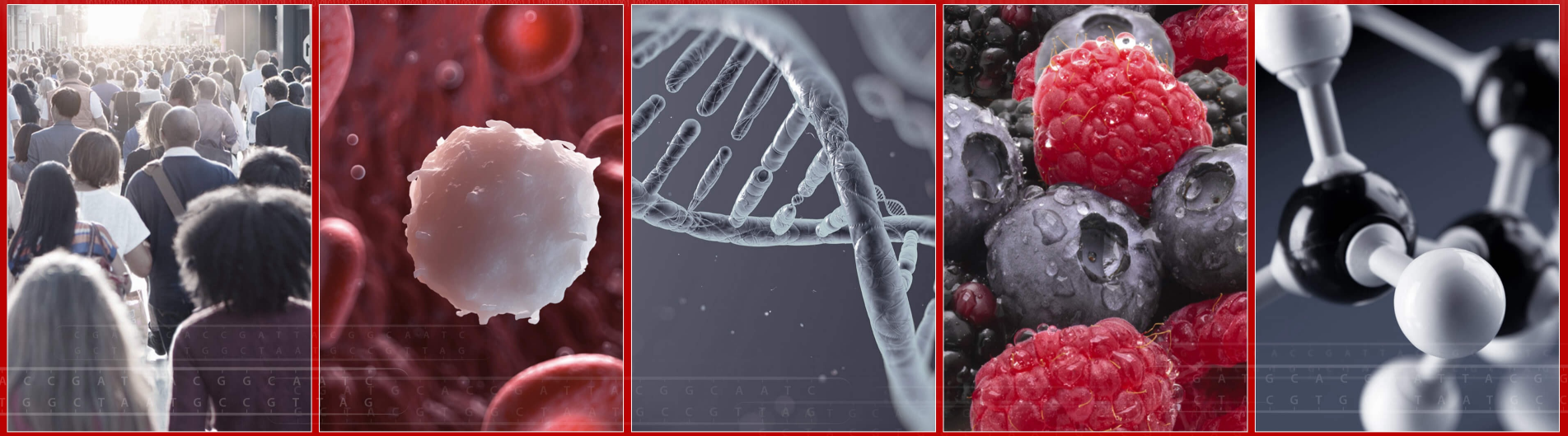

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Hairy Cell Leukemia

- Type of chronic blood cancer
- The cells that become cancer cells are white blood cells called B-lymphocytes
- B-lymphocytes are immune system cells
- Described by two different groups as “leukemic reticuloendotheliosis”

1. Gosselin GR, Hanlon DG, Pease GL. Leukaemic reticuloendotheliosis. Can Med Assoc J. 1956;74(11):886-891.
2. Bouroncle BA, Wiseman BK, Doan CA. Leukemic reticuloendotheliosis. Blood. 1958;13(7):609-6

Dr. Bertha Bouroncle

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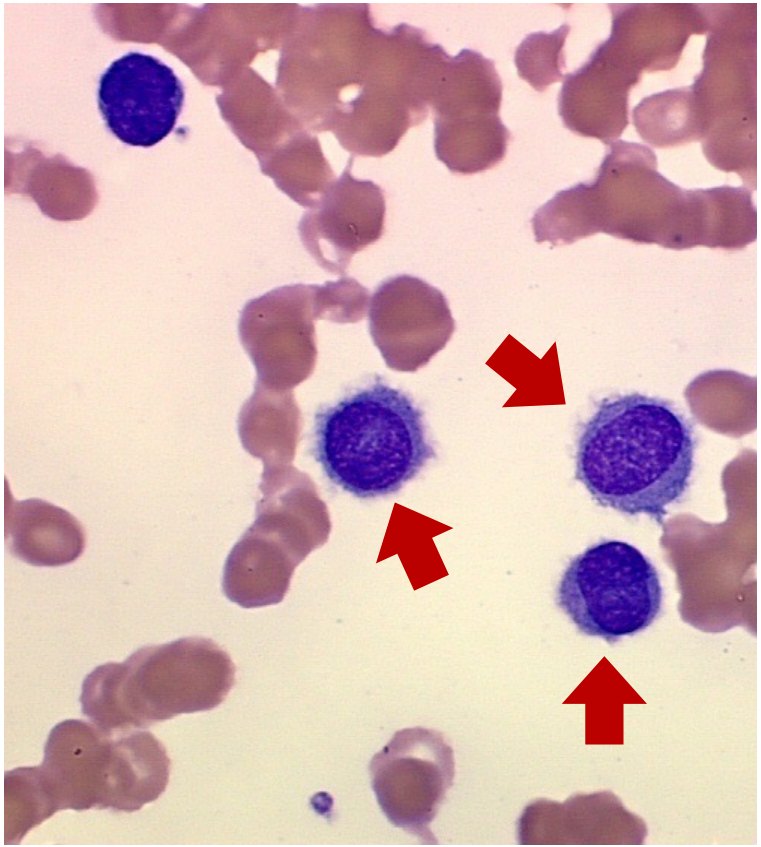
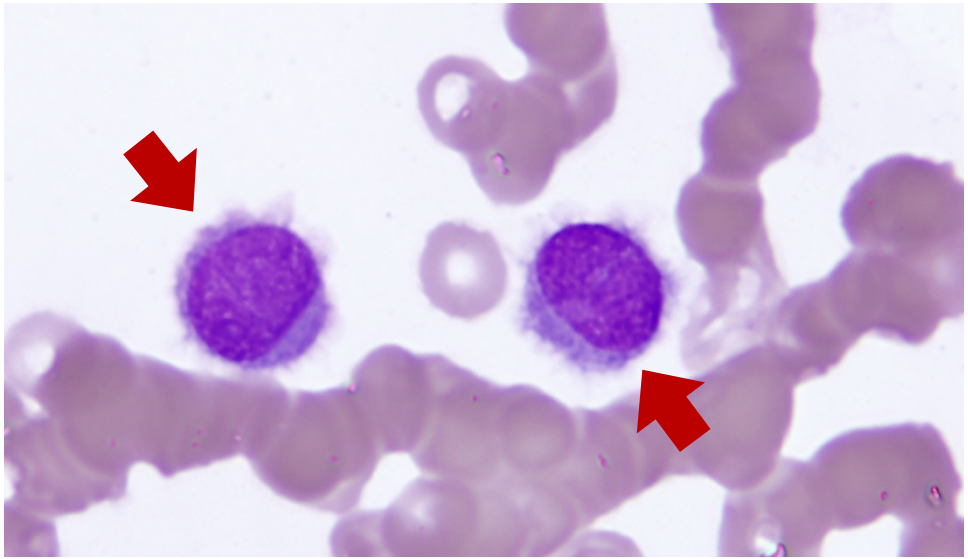
Diagnosis of Hairy Cell Leukemia

- Diagnoses requires verifying the presences of the leukemia cells
  - Usually requires a bone marrow biopsy
  - Leukemia cells are in the blood, bone marrow, lymph nodes, and spleen – *they can be elsewhere too*
- Leukemia cells identified by:
  - Morphology: appear as mature lymphocytes with cytoplasmic projections that look like hairs
  - Cell markers: CD19, CD20, CD11c, CD25, CD103,and CD123
- BRAF V600E mutation is found in classic hairy cell leukemia
- There is a variant form has a slightly different markers and mutations – *this has been recently reclassified*

Grever et al., Blood 2017; Grever et al., Blood Rev. 2014; Venkataraman et at., Am J Clin Pathol. 2011

Hairy Cell Leukemia in the Blood





Arrows show leukemia cells with hairy projections

Dr. Gerard Lozanski, The Ohio State University

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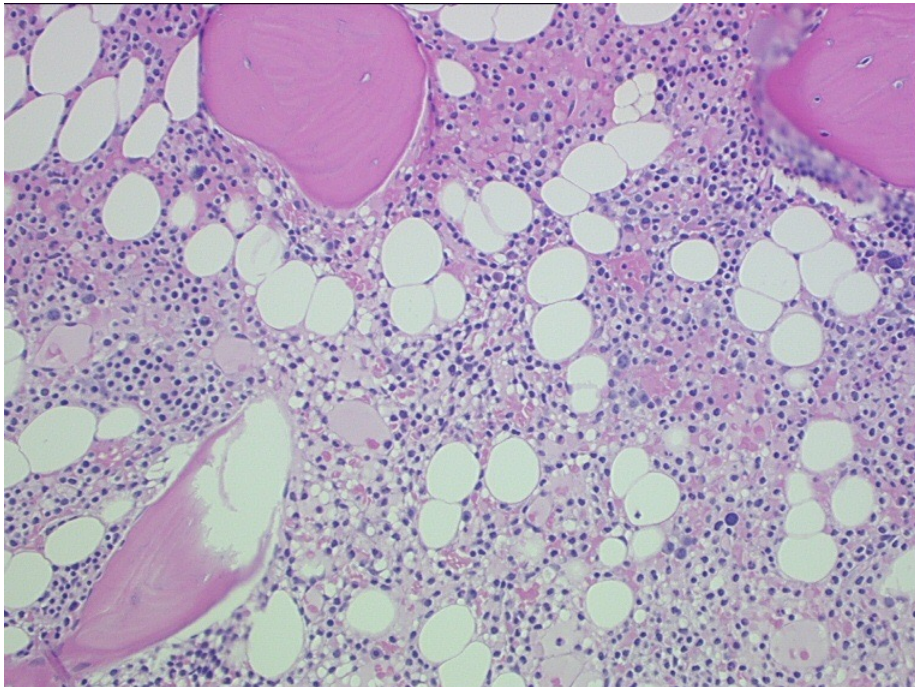
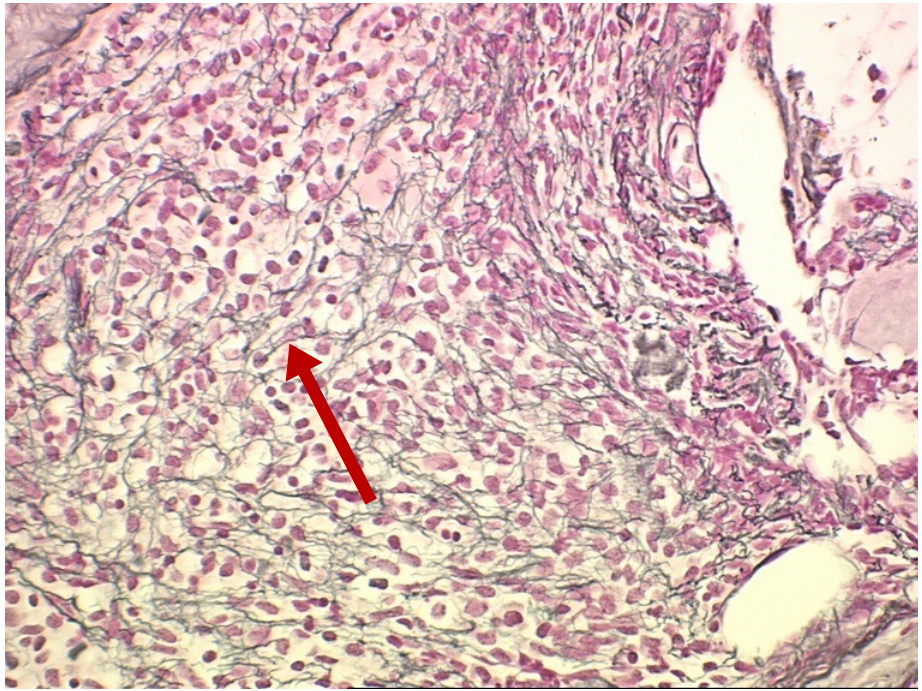
Hairy Cell Leukemia in the Bone Marrow





Arrow shows reticulin fibrosis common in hairy cell leukemia

Dr. Gerard Lozanski, The Ohio State University

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Facts About Hairy Cell Leukemia

- Rare leukemia
  - ~2% of adult leukemias
  - ~1,100 new cases per year in the US
  - 0.3 new cases per 100,000 people/year
- Demographic of those experiencing hairy cell leukemia
  - Median age at diagnosis is 55 years
  - More common in men (4:1)
  - More common in white people
- Expected survival is decades and in most cases it does not shorten the natural lifespan

Teras et al., CA Cancer J Clin. 2016

Clinical Features of Hairy Cell Leukemia

- Many people are diagnosed with no symptoms (asymptomatic)
- Causes low blood counts (cytopenias) due to marrow replacement with leukemia or marrow fibrosis
  - Low platelets (thrombocytopenia), RBCs (anemia), white blood cells (leukopenia), and/or neutrophils (neutropenia)
  - Particularly causes low monocyte counts (monocytopenia)
- Enlarged spleen, sometimes massively
- Enlarged lymph nodes or bone lesions
- Fatigue that limits usual activities
- Many people have an infection at time of diagnosis

When to Treat Hairy Cell Leukemia

- Treatment is only needed when there is something to improve
  - ~ 10% of people do not need treatment at diagnosis
  - Early treatment has side effects with no known benefit
- Standard treatment indications:
  1) Low blood counts
     - Absolute neutrophil count <1,000 /uL
     - Hemoglobin <10-11 g/dL
     - Platelet count <100,000 u/L
  2) Spleen enlargement that is massive or symptomatic
  3) Enlarged lymph nodes or bone lesions that are causing issues
  4) Constitutional symptoms interfering with daily life

Grever et al., Blood 2017

Considerations When Starting Treatment

- Bone marrow biopsy is helpful to determine baseline
- Assessment of general health, kidney, and other organ function
- Presence of infection
  - Active or chronic infection or history of opportunistic infection
  - Special planning is required when treating people with infection
- Disease symptoms or features (e.g. need for transfusions)
- Patient preferences about treatment
  - Administration schedule and duration
  - Side effects

Treatment Options for Hairy Cell Leukemia

- Purine nucleoside analogs (cladribine and pentostatin)
  - Most commonly used treatment
  - Can be given multiple times
  - Sometimes used with anti-CD20 antibodies
- Treatments beyond purine analogs
  - BRAF inhibitors: Vemurafenib, dabrafenib
  - BTK inhibitors: Ibrutinib, acalabrutinib, zanubrutinib
  - Moxetumomab Pasudotox (not currently available)
- Older treatments with value in select cases
  - Interferon
  - Splenectomy

Purine Nucleoside Analogs

- Drugs that interfere with DNA synthesis
- Two agents used in HCL with similar disease outcomes
- Different administration schedules

Cladribine	Pentostatin
• 0.1 mg/kg CIV daily x7 days • 0.14 mg/kg IV daily x5 days	• 4 mg/m^2 IV q2 weeks until remission

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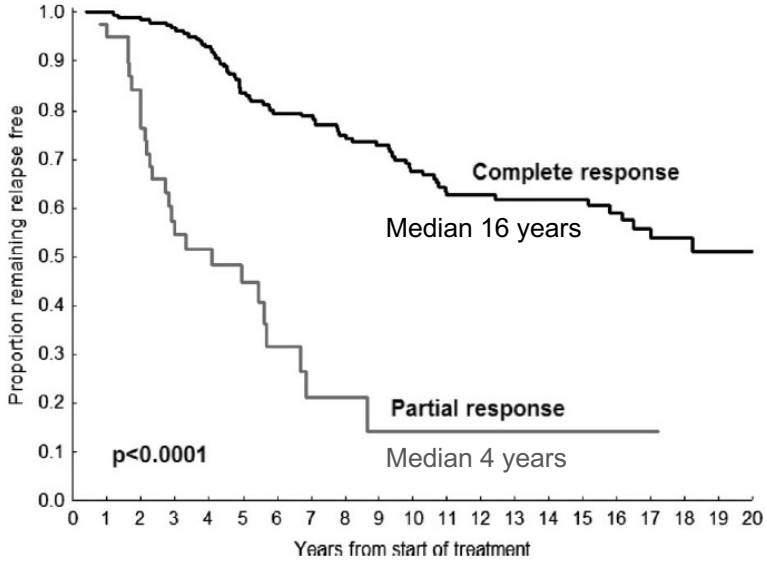
Grever et al., Blood 2017

Outcomes with Purine Nucleoside Analogs

- High remission rates (~80% complete remission)
- Results in 2-10+ years of remission
- Median time to next treatment is 7-8 years
- No major differences in outcomes between cladribine and pentostatin
- *Changed survival from ~4 years to near normal life expectancy*

Relapse-Free Survival After Initial Treatment with Cladribine or Pentostatin



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Dearden et al., Leuk. & Lymph. 2011

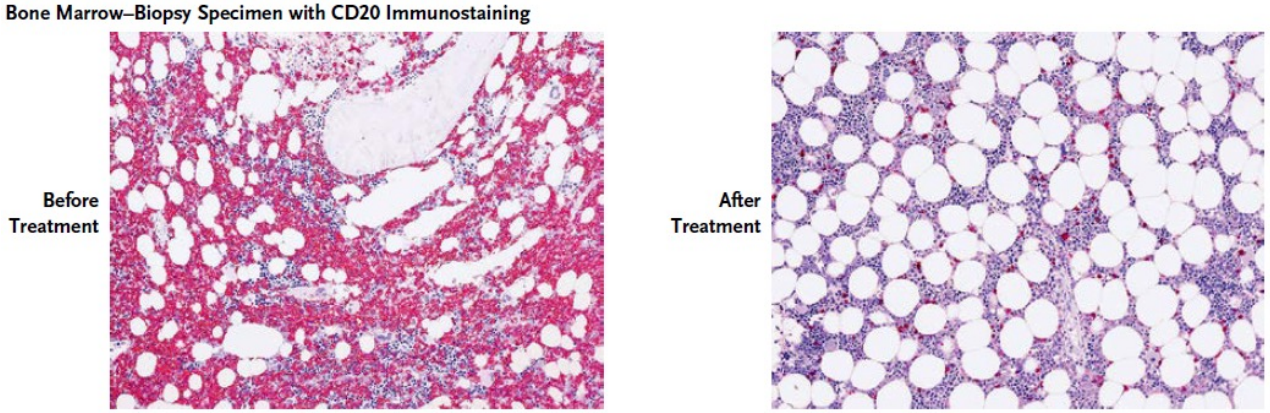
CDAR: Cladribine and Rituximab

- Randomized phase 2 study comparing cladribine with rituximab to cladribine with delayed rituximab
  - Same 5 day cladribine dose
  - Rituximab given weekly for 8 weeks starting with cladribine
- Higher rates of complete response and undetectable leukemia were seen with CDAR (100% vs 88% and 97% vs 24%)
- At 96 months median follow-up, 94% versus 12% had undetectable leukemia
- So far no differences in clinical relapses or survival were seen as patients all did well for a long time

Chihara et al., JCO 2020

Vemurafenib

- Rapidly clears disease in classic hairy cell leukemia
- Given as a pill for less than 6 months (usually)
- ORR high (96-100%), relapse-free survival short (median 9 months)
- Very useful in cases of infection when treatment is needed

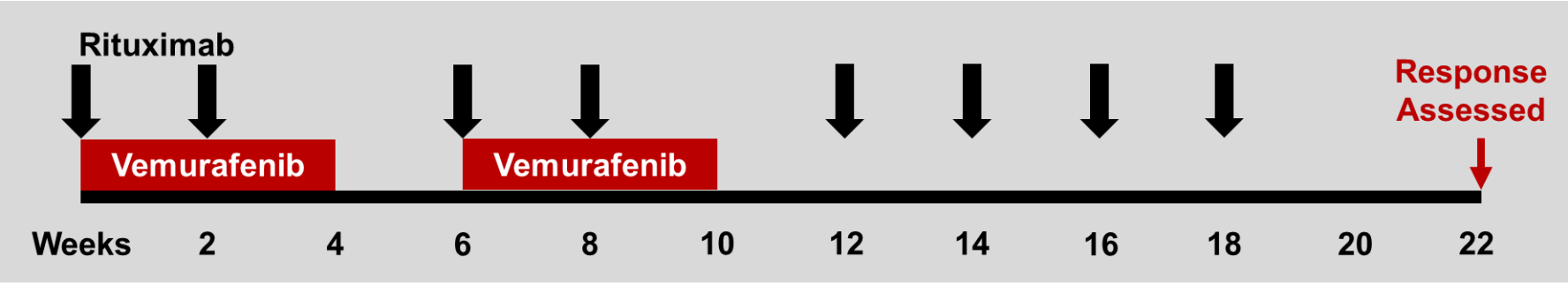


Tiacci et al., NEJM 2015; Shenoi et al., Blood Adv. 2019

Vemurafenib and Rituximab

- Phase 2 study aimed at improving durability of remissions
- Vemurafenib given in 2 short courses
- Rituximab given with and after vemurafenib

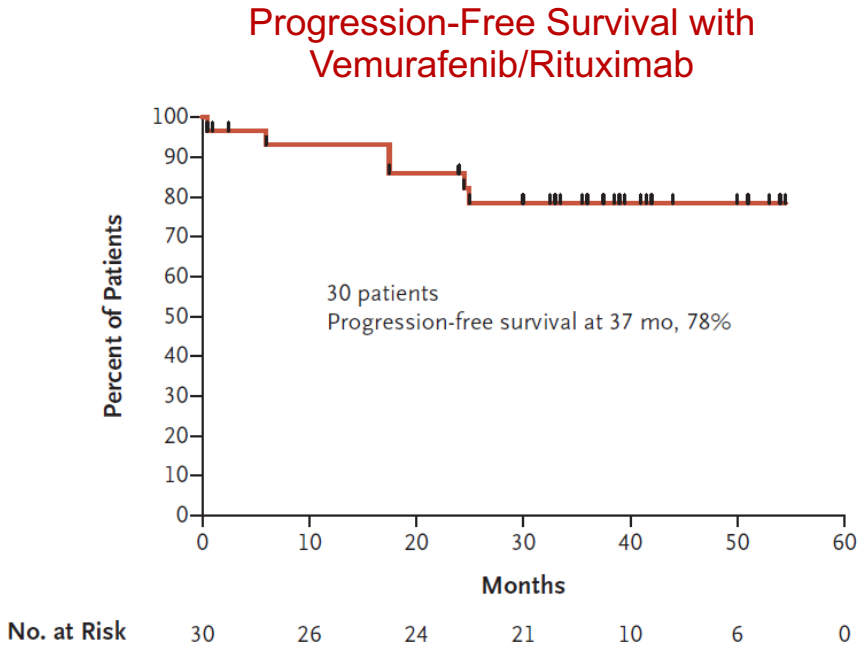
Study Treatment Diagram



Tiacci et al., NEJM 2021

Remissions with Vemurafenib and Rituximab are Durable

- 87% of patients had a response
- Rapid improvement in blood counts
  - Platelets 2 weeks
  - Neutrophils 4 weeks
- Longer remissions were seen if:
  - Leukemia was not detectable after treatment
  - Patients had not had prior BRAF inhibitor treatment



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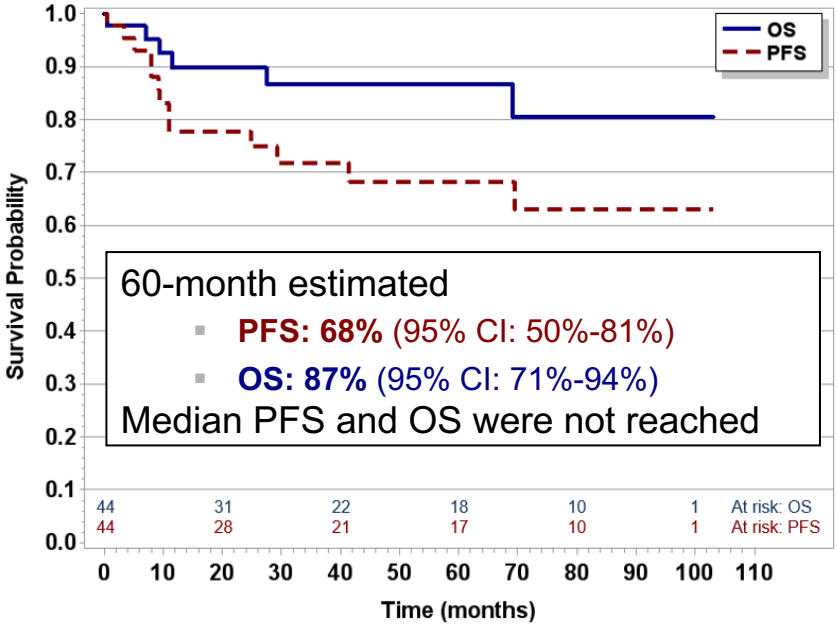
Tiacci et al., NEJM 2021

Ibrutinib

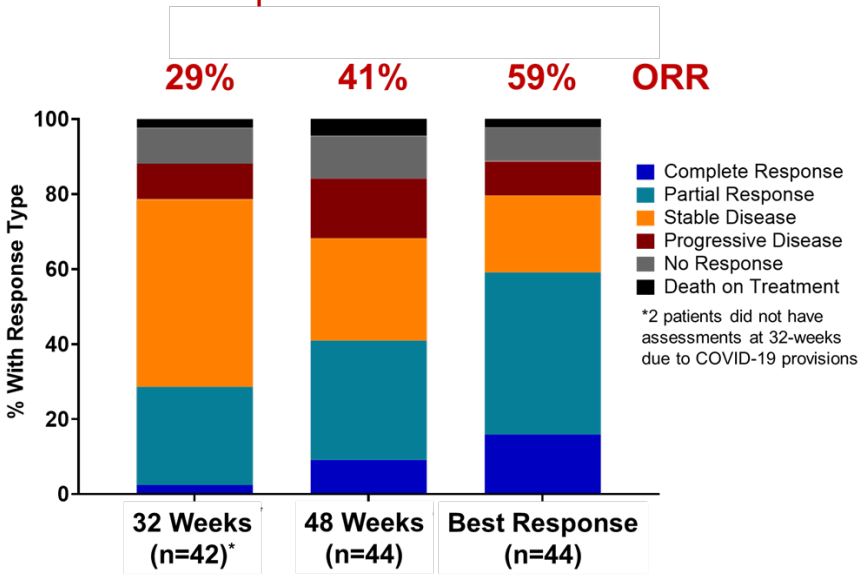
- Targets and inhibits Bruton's Tyrosine Kinase (BTK) in B-cells
- Effective in several B-cell cancers (CLL, MCL, MZL, WM)
- Oral agent (pill) given indefinitely
- Tested in a multisite NCI/CTEP sponsored phase 2 study
- Not approved in hairy cell leukemia but can be used "off-label"
- Good amount of experience in variant HCL (27% of patients)

Outcomes with Ibrutinib

Progression-Free and Overall Survival with Ibrutinib



Response to Ibrutinib



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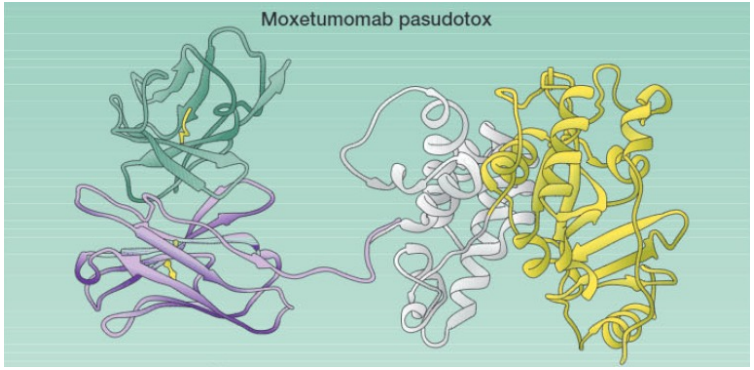
Rogers et al., ASH 2022

Moxetumomab Pasudotox

- Antibody-drug conjugate with CD22 immunoglobulin fused with a truncated *Pseudomonas* endotoxin
- IV therapy given 3 days (M,W,F) one week a month for 6 month
- Was FDA Approved for treatment of HCL after ≥2 prior treatments
- Removed from market by AstraZeneca for business reasons

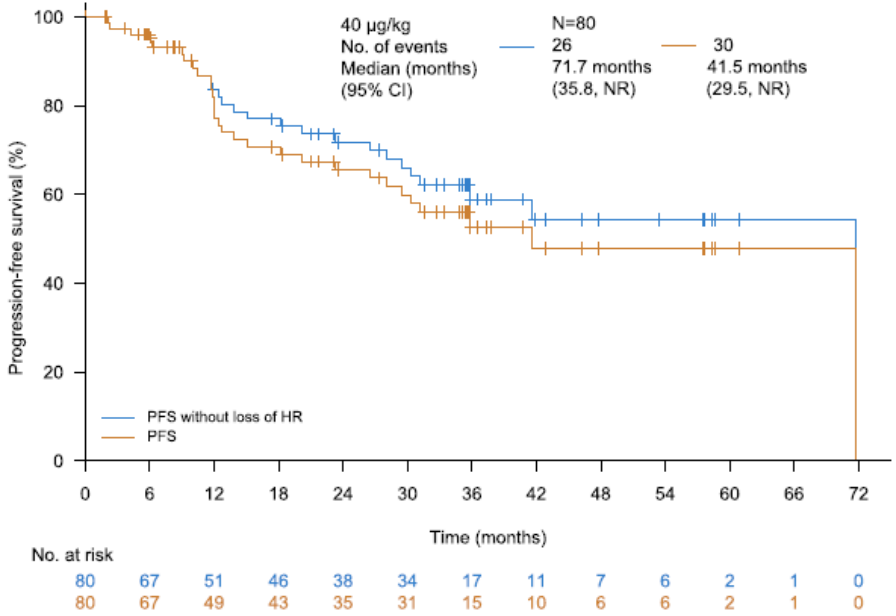


Kreitman et al., Clinical Cancer Resch. 2011

Outcomes with Moxetumomab Pasudotox

- 75% of patients had a response
  - 41% complete remission
  - 36% complete remission lasting >180 days
  - 33% complete remission lasting ≥360 days
- Can cause capillary leak syndrome (CLS) & hemolytic uremic syndrome (HUS)

Progression-Free Survival after Moxetumomab



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Kreitman et al., Leukemia 2018; Kreitman et al. J Hematol Oncol 2021

Treatment of Hairy Cell Leukemia in 2023

- Purine analogs remain the standard initial therapy HCL
  - May consider adding rituximab (with initial or repeat treatment)
  - Can be repeated at relapse/next treatment
- Good options exist for patients where purine analogs are unsuitable

Agent	Mechanism	ORR	Durability	Special Considerations
Moxetumomab pasudotox	Antibody-drug Conjugate	75%	MRD dependent	Unusual toxicities
Vemurafenib +Rituximab	BRAF inhibitor (anti-CD20 antibody)	96-100% 87%	1 year PFS = 73% 37 mo PFS = 78%	Requires BRAF p.V600E mutation
Ibrutinib	BTK inhibitor	54%	36 mo PFS = 73%	Useful in the variant

Kreitman et al., Leukemia 2018; Tiacci et al., NEJM 2021; Rogers et al., Blood 2021

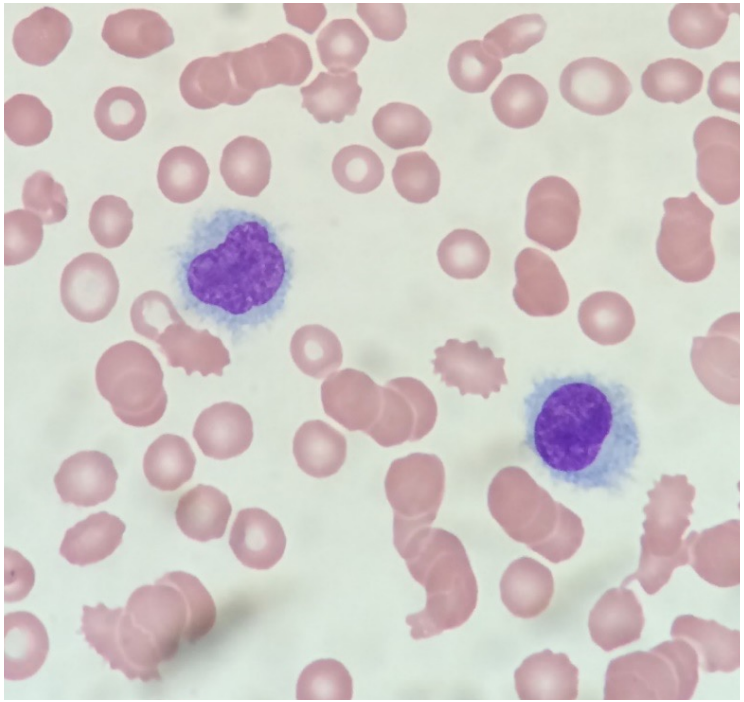
Health Maintenance for People with Hairy Cell Leukemia

- Higher risk of infections and second cancers
  - Recommend all age and risk appropriate cancer screenings
  - Skin cancer screening is important
  - Vaccination for pneumococcal pneumonia, influenza, COVID-19, RSV, and other infections (avoid live vaccines)
- Long-term side effects from treatment
  - Immunosuppression (particularly with purine analogues)
  - Neurotoxicity
  - Side effects from newer targeted agents
- As leukemia survival is good and other health risks matter!

Current Clinical and Research Questions

- What is the optimal treatment of classic hairy cell leukemia?
  - Should anti-CD20 antibodies (e.g. rituximab) be used concurrently with cladribine as initial treatment?
  - Is chemotherapy necessary? For which patients?
- What about the variant of hairy cell leukemia?
  - How should it be classified?
  - What are the best treatments?
- How should other aspects of health be supported?
- How does living with hairy cell leukemia impact quality of life?

Thank you for your attention!
Questions?



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