Hairy Cell Leukemia
From Hairy Beginnings to a BRAF New World

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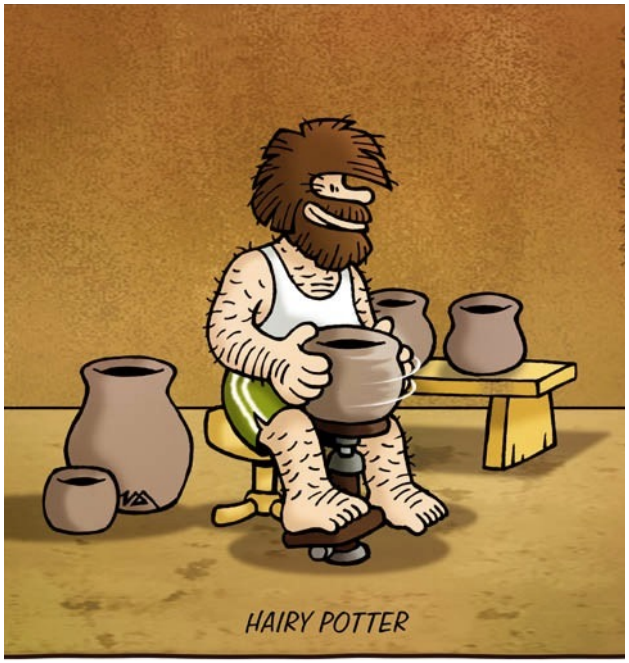
London

Getting the right information
Google: **Hairy**….?

Hairy Monster

Hairy Biker



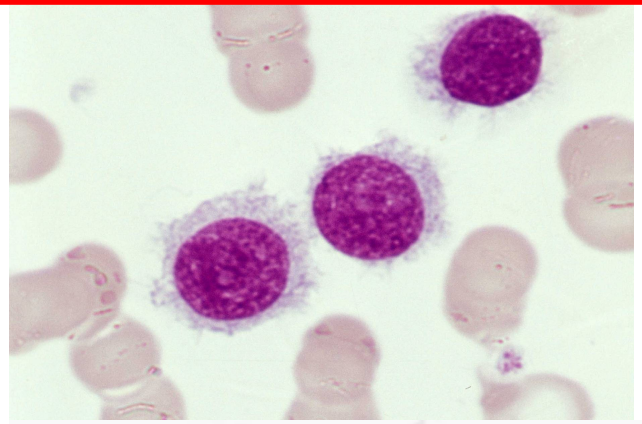
Hairy Potter

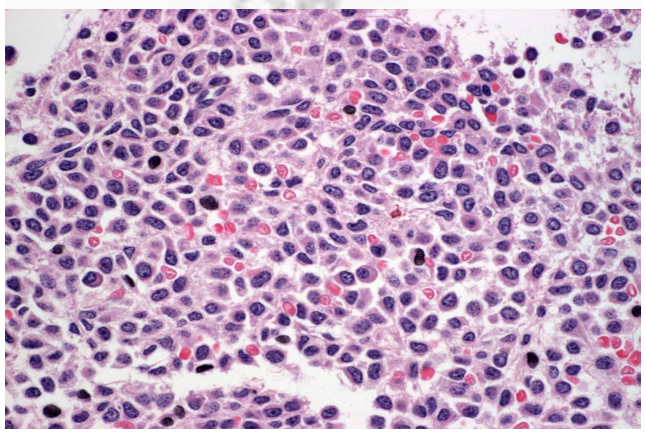
www.hairycellleukemia.org

Outline

- Definition
- History of HCL
- Treatment landmarks
- Clinical presentation and diagnosis
- Unusual clinical manifestations
  - Bone lesions
- Infection
- HCLv

Hairy Cell Leukaemia





- M:F= 4:1
- Median age 54 years
- Pancytopenia and splenomegaly
- Unusual infections
- Para-neoplastic phenomena
- CD25, CD103, CD123
- BRAF V600E mutations
- HCLv and HCL with VH 4-34 (both BRAF WT) have poorer outcome
- International consensus guidelines Blood 2017 (Grever et al)
- BCSH guidelines 2020

HCL : The last 60 years

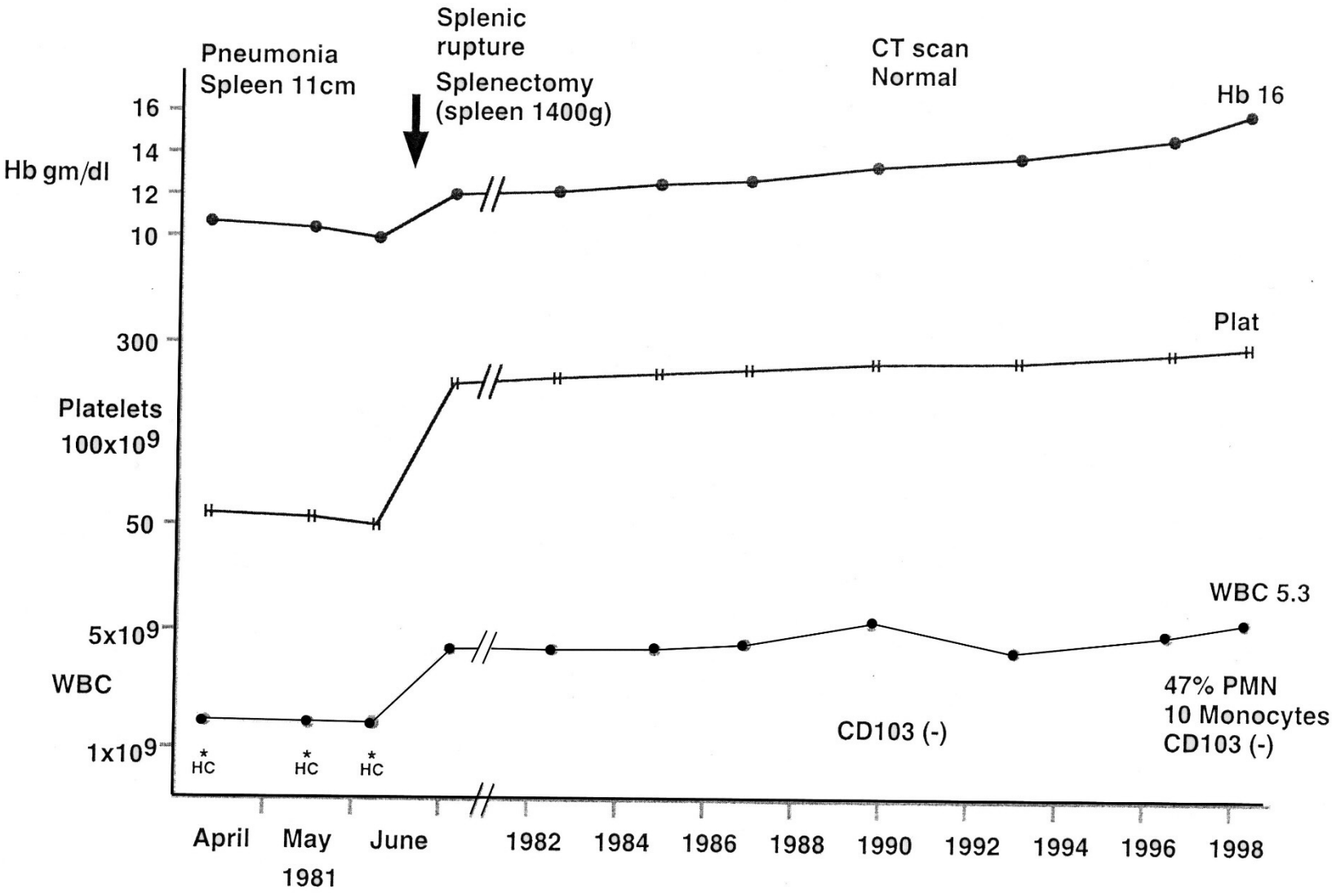
- 1958 First clinical description by Bouroncle
- 1966 First use of the term Hairy Cell Leukaemia
- 1979 Splenectomy
- 1984 Interferon
- 1987 Pentostatin
- 1990 Cladribine
- 1999 Long-term follow-up of PAs
- 2000 Development of Immunotoxins (moxetumumab pasudotox)
- 2011 Discovery of BRAF mutations in >90%
- 2014 Combination of PA with rituximab (obinutuzumab)
- 2015- 2020 Novel Agents: BRAFi (Vemurafenib,Dabrafenib) Moxetumumab, Ibrutinib

Dr. Bertha Bouroncle

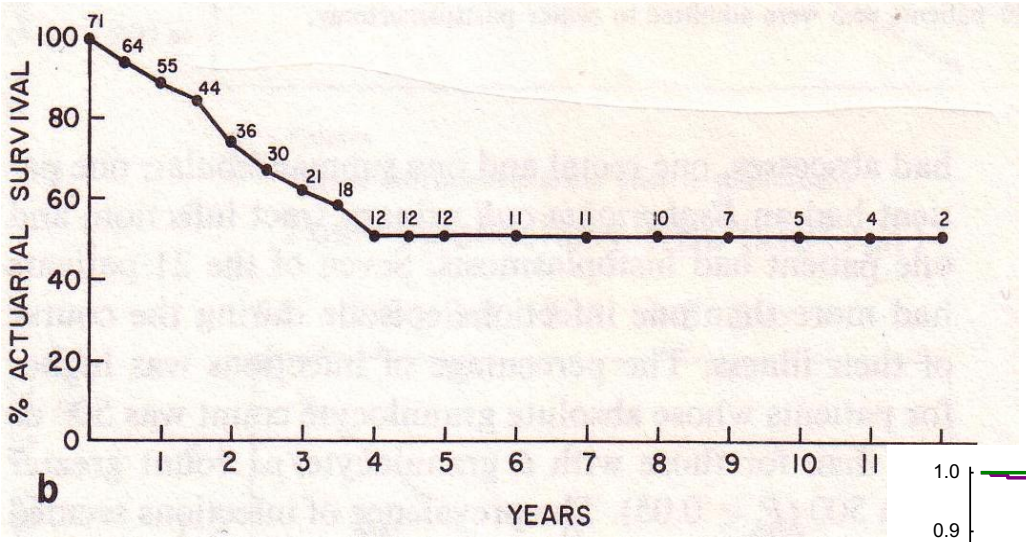
Natural History of HCL Prior to 1984

- Incurable and unresponsive to therapy
- Commonly employed treatments included:
  - Chemotherapy (minimal responses)
  - Splenectomy (some palliation with improvement of counts)
- Median survival of 4.5 years; deaths due to:
  - Infection
  - Cytopenias and bleeding
- Second malignancies in 3-10%

HCL: Splenectomy



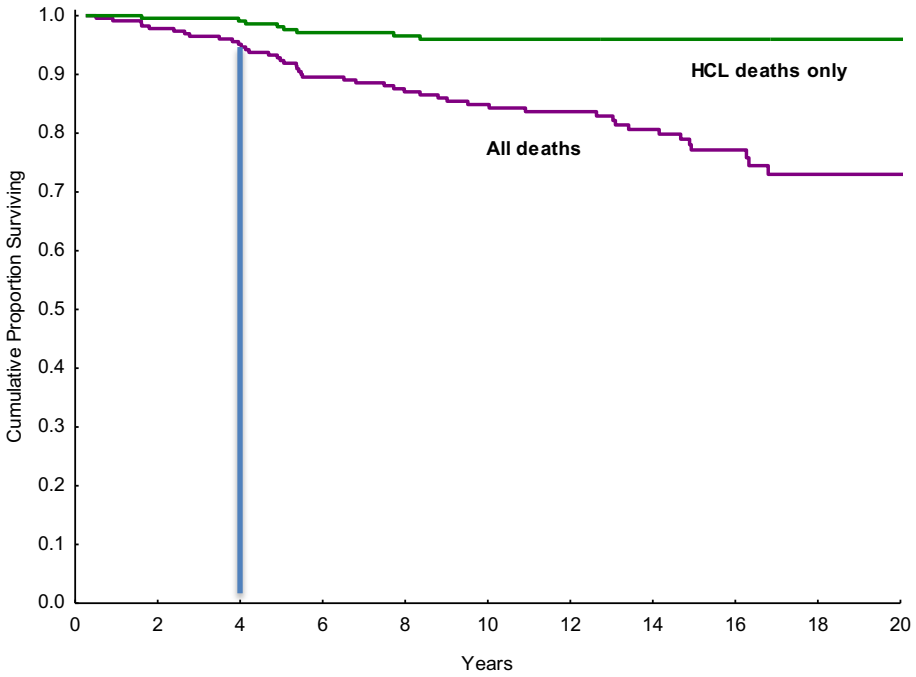
Overall Survival 1978- 2018



Median OS 4 years in 1978

- OS at 15 years 78%, same as age-matched population
- OS at 15 years 96% excluding non-HCL related deaths
- Currently only 8 HCL-related deaths (7 pre-1998)
- Patients still in CR at 5y have only 25% risk of relapse

RMH Series (n=250)



Golomb, Catovsky, Golde, *Annals of Internal Medicine* 89: 677 (1978)

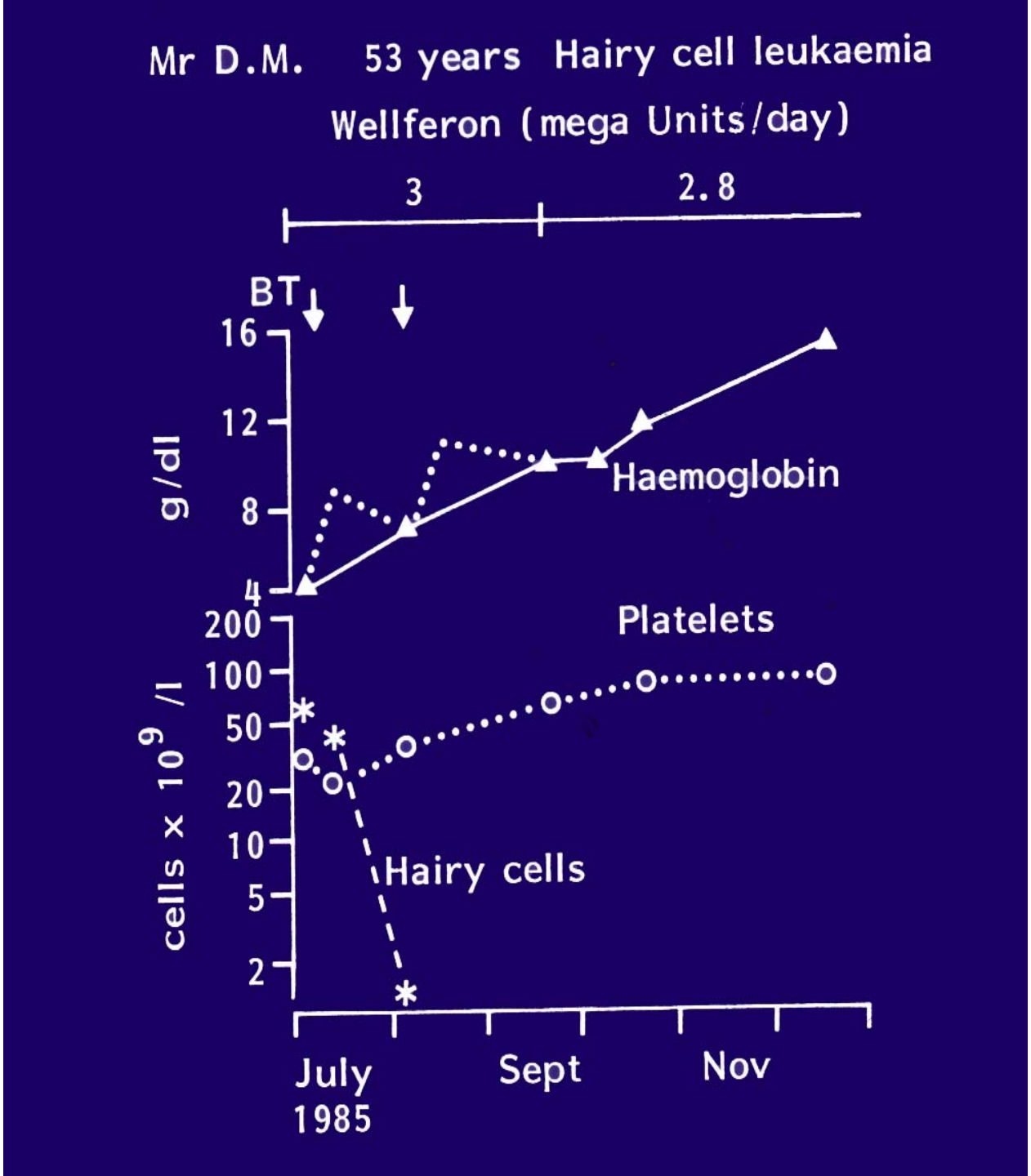
HCL: treatment landmarks

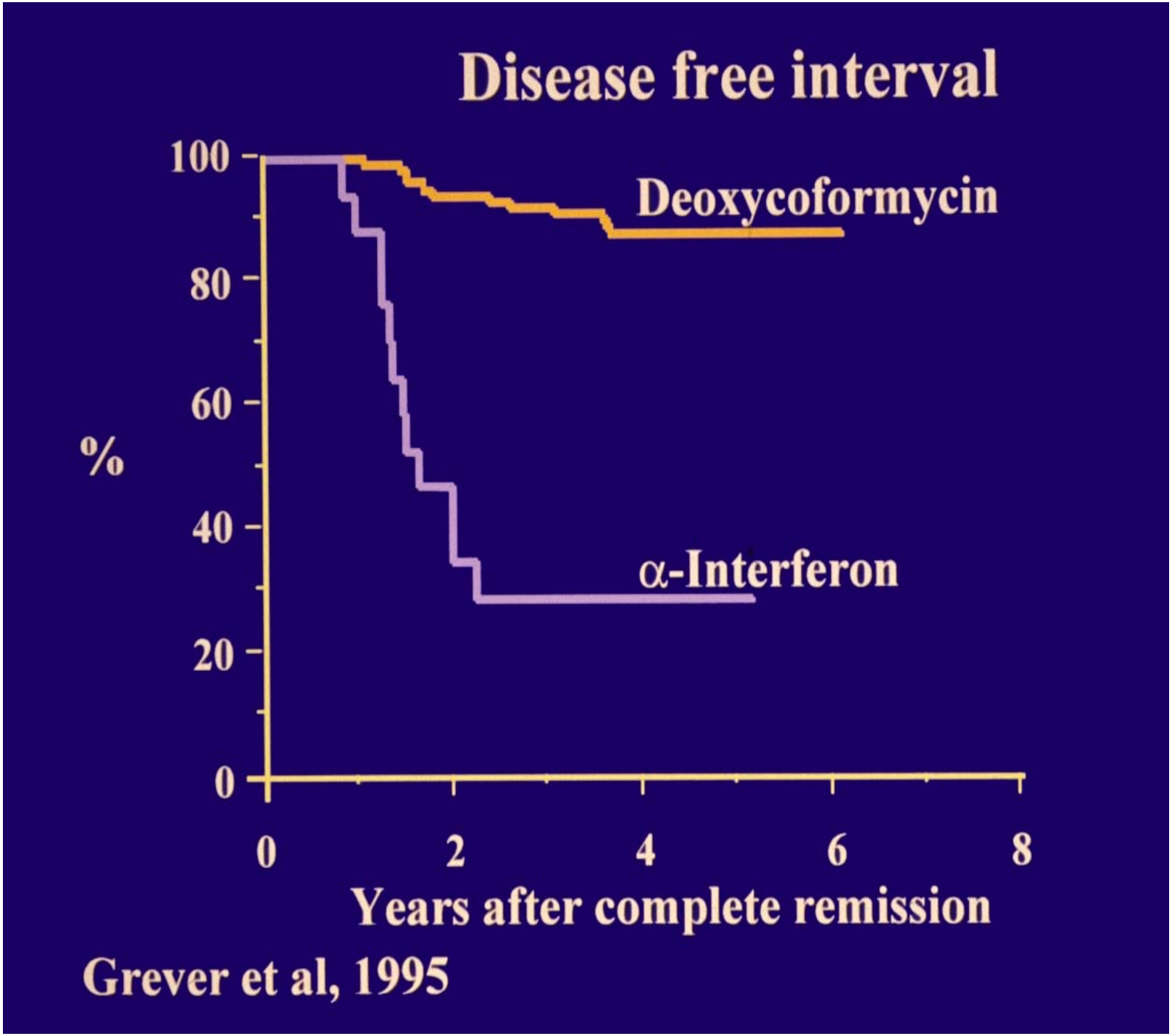
1984 – Interferon-alpha – 3/7 CR
*Quesada et al, NEJM **310**, 15-18*

1987 – DCF (Pentostatin) – 16/27 CR
*Spiers et al, NEJM **316**, 825-830*

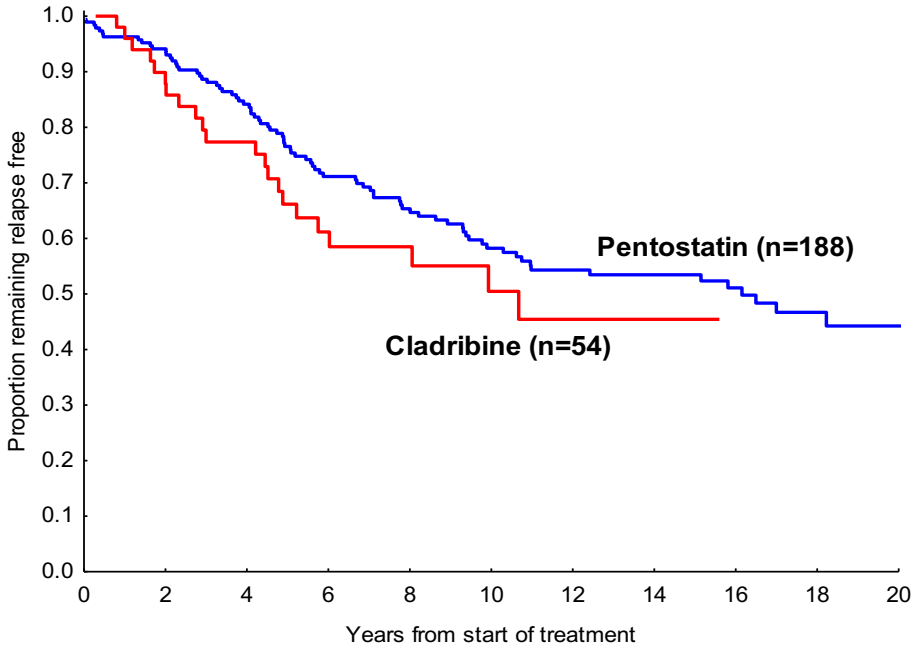
1990 – 2CDA (Cladribine) – 11/12 CR
*Piro et al, NEJM **322**, 1117-1121*

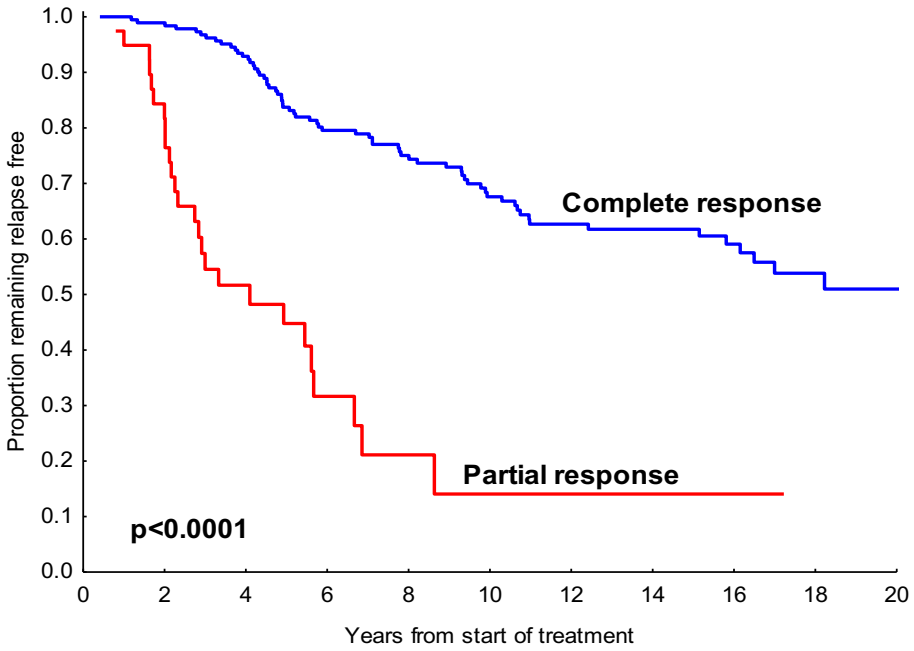
1995 First randomised trial Pentostatin vs Interferon, *Grever et al JCO , 1995*


Mr D.M. 53 years Hairy cell leukaemia
Wellferon (mega Units/day)
3
2.8
BT
16
12
8
4
g/dl
Haemoglobin
200
100
50
20
10
5
2
cells x 10^9 /l
Platelets
Hairy cells
July
1985
Sept
Nov


Disease free interval
100
80
60
40
20
0
%
Deoxycoformycin
α-Interferon
0
2
4
6
8
Years after complete remission
Grever et al, 1995

Relapse-Free Survival: RMH Series N= 250





Median RFS: 16y (Median PFS: 10.5y)

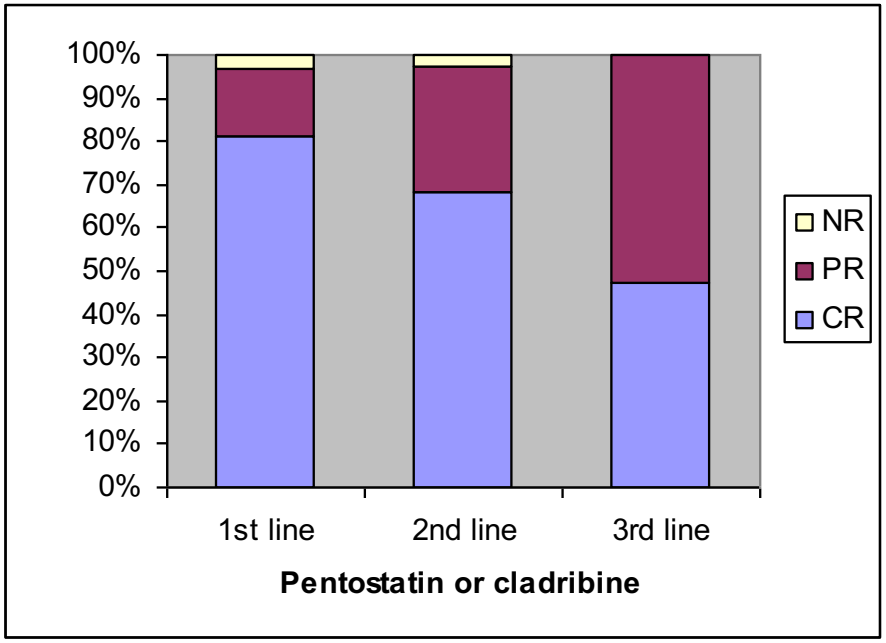
No difference between pentostatin or cladribine

Better if achieve CR vs PR (independent of line of therapy)

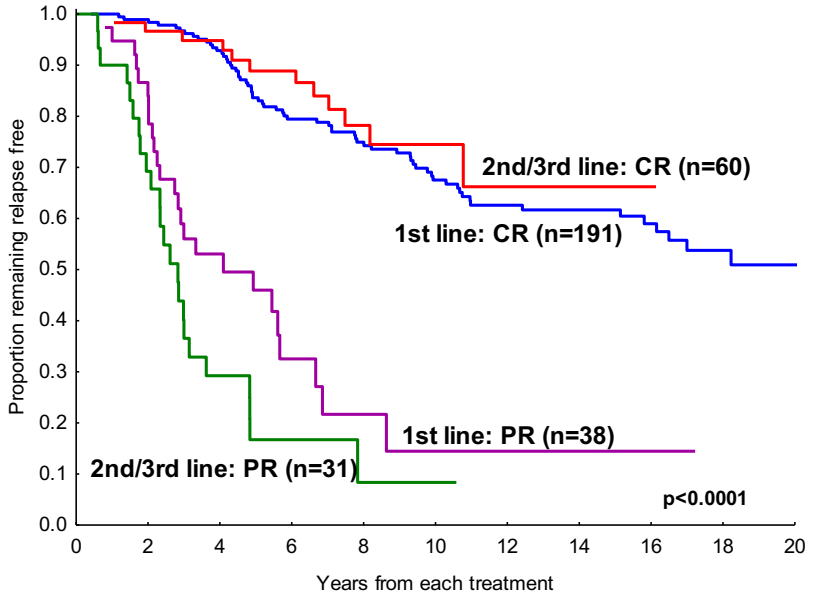
Else *et al*, *Cancer* 104: 2442 (2005) (updated 2010)

Outcome by Line of Treatment and Response

Response by line of treatment



Relapse-Free Survival

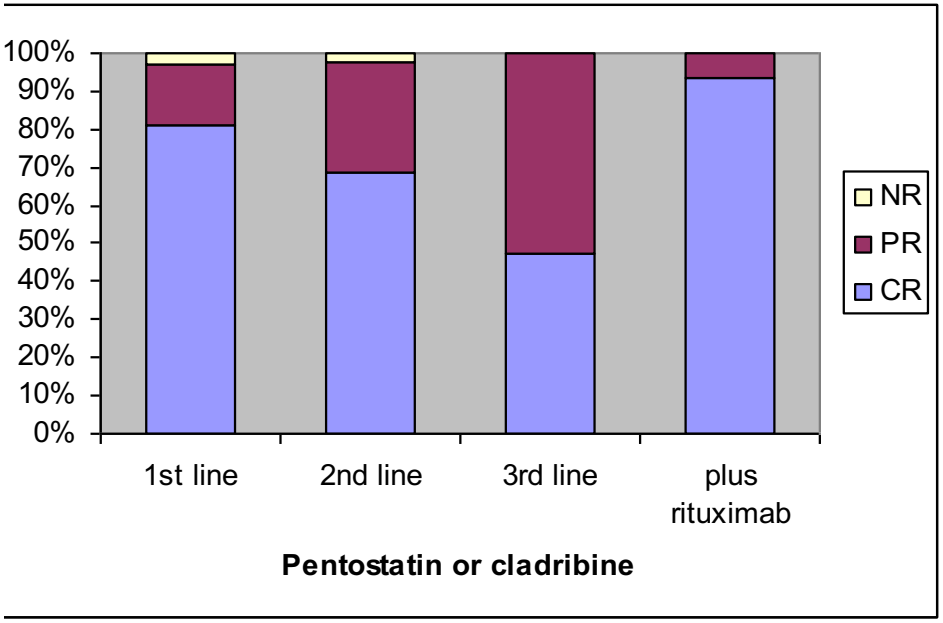


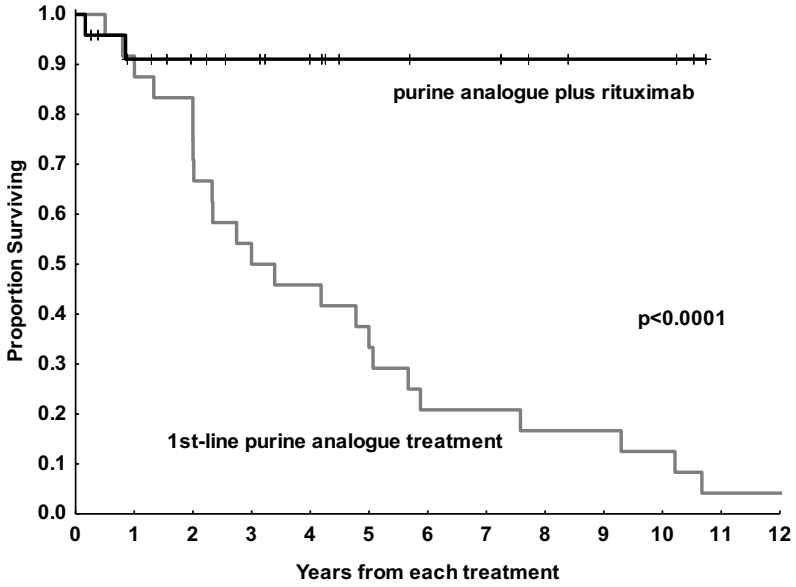
- Median RFS 16y (1st line), 11y (2nd line), 6.5y (3rd line)
- Median time to purine refractory disease ~ 34 years

Else *et al*, *Cancer* 104: 2442 (2005) (updated)

Else *et al*, *Br J Haem* 145: 733 (2009) (updated)

Outcome after combination PA + Rituximab for relapsed HCL





- Superior RR (95%) and Survival following addition of Rituximab to PA at relapse , even in heavily pre-treated patients
- BCSH guideline recommends combination PA+R at relapse
- Evidence from trials that concurrent CDA+R is superior as first-line therapy (Kreitman JCO 2020)

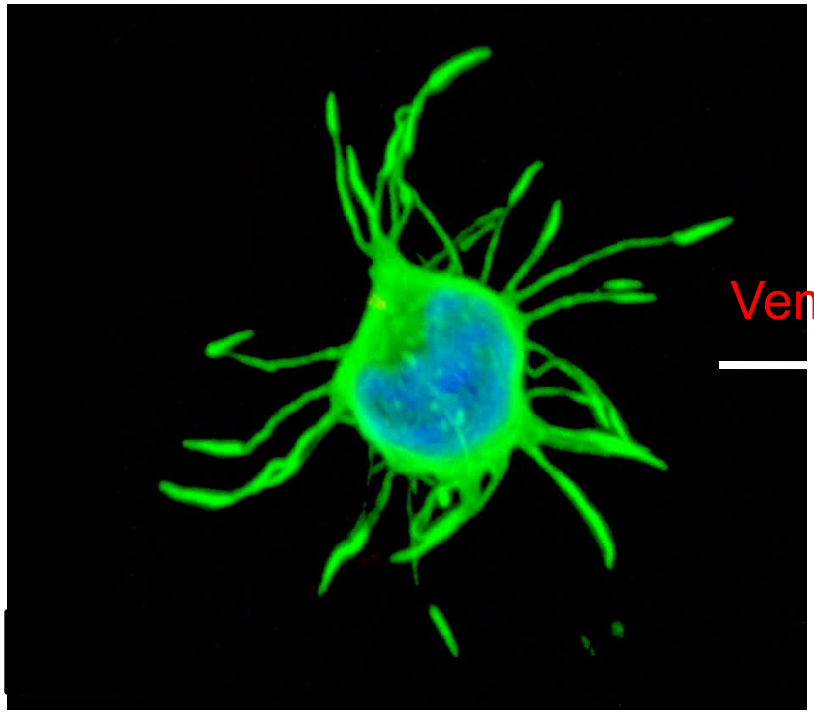
HCL: treatment landmarks

2011 – Tiacci et al demonstrated *BRAF V600* mutations in 100% of cases

2015- Vemurafenib reported as effective therapy

Effect of Vemurafenib on HCL cells

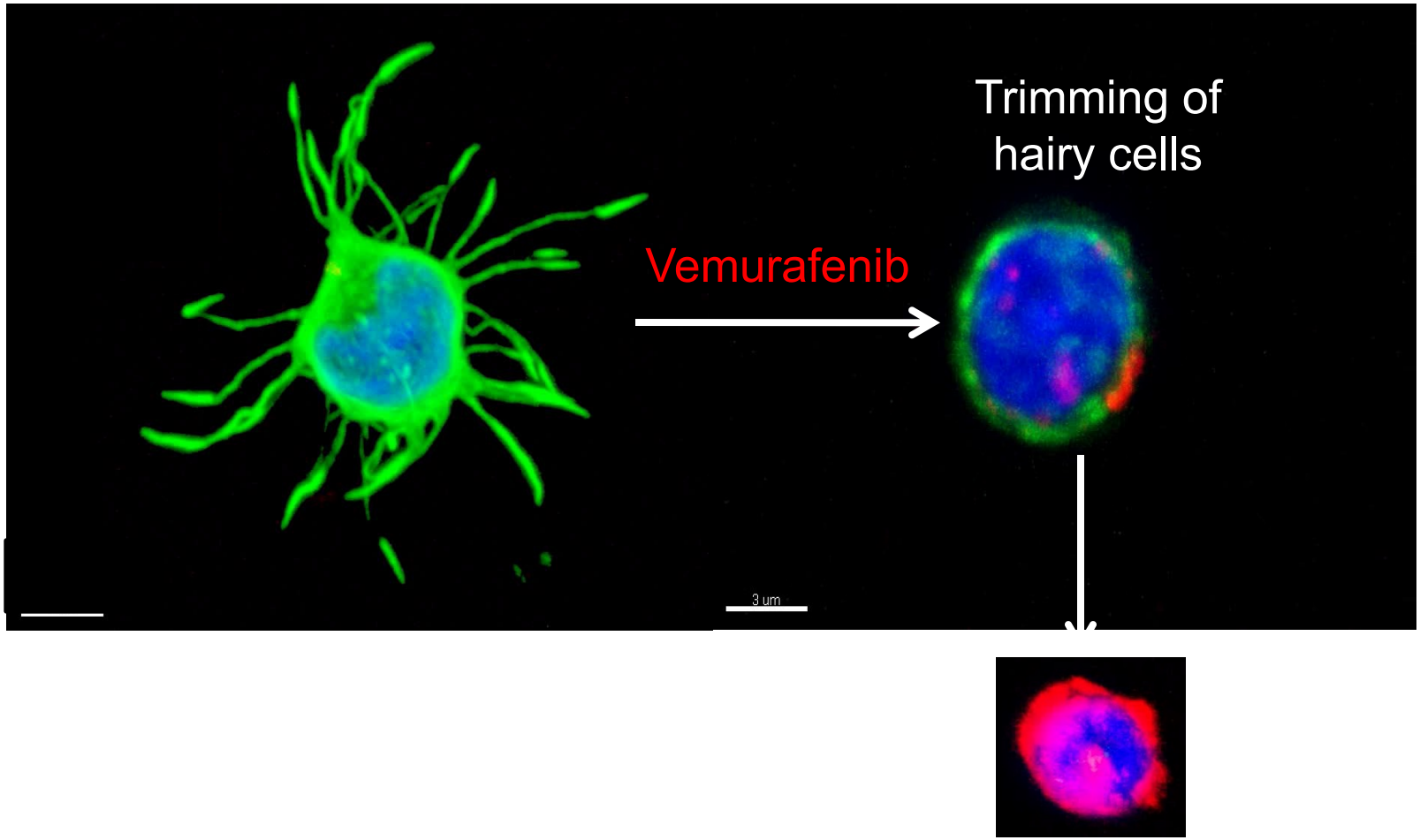
Hairy cell



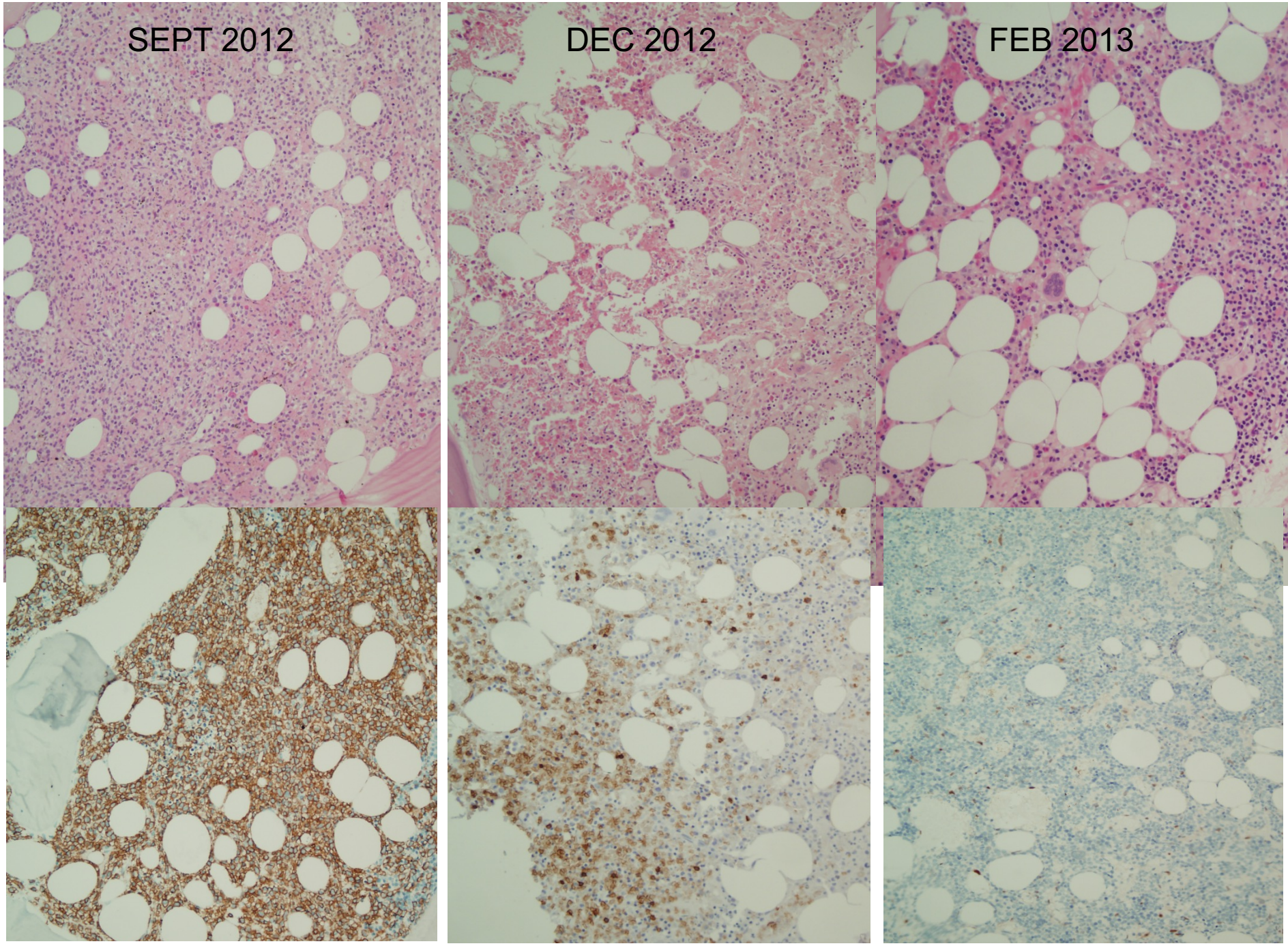
Vemurafenib

Courtesy H Tiacci

Effect of Vemurafenib on HCL cells

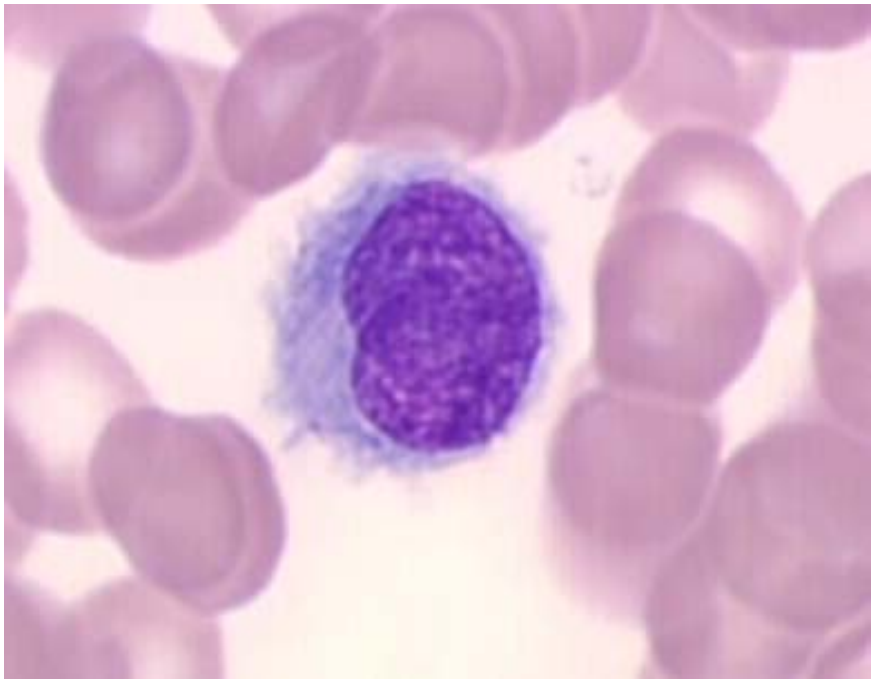


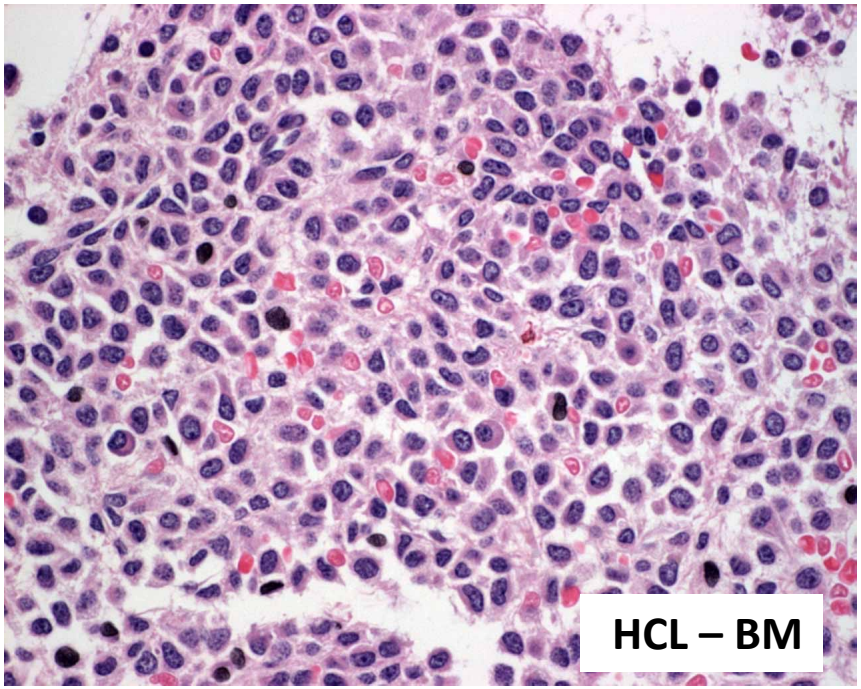
Courtesy H Tiacci

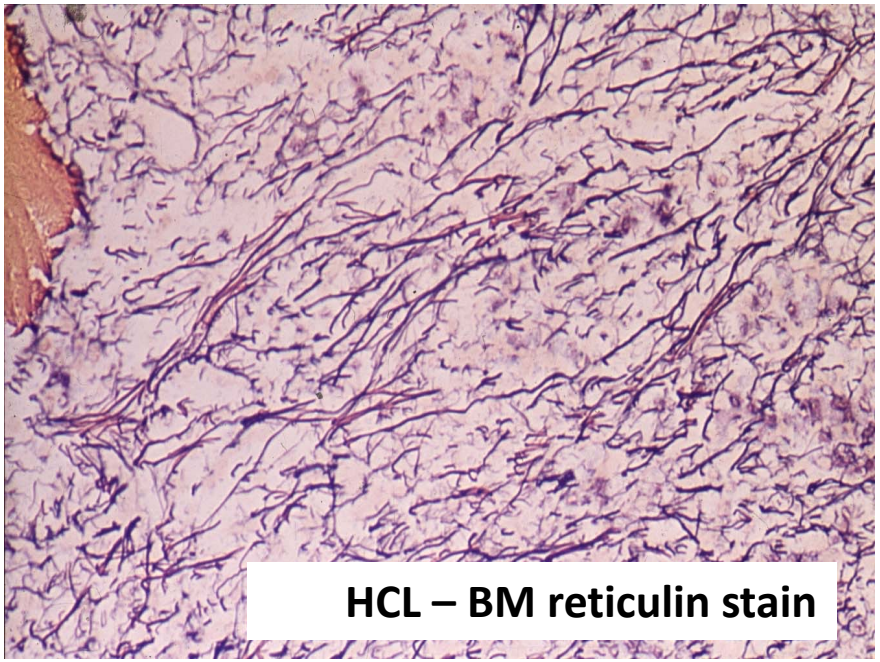

SEPT 2012
DEC 2012
FEB 2013

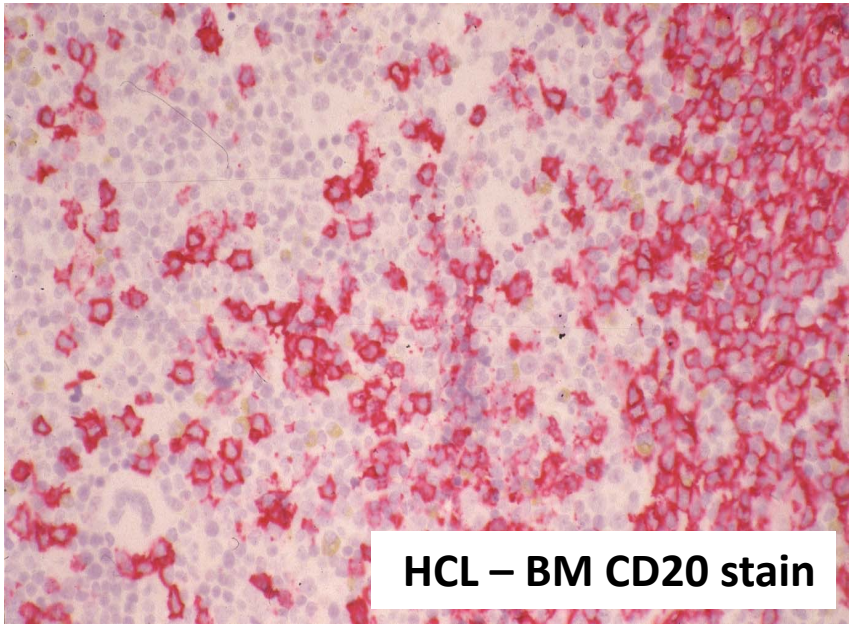
Clinical Presentation and Diagnosis of HCL

- Classical clinical features
  - cytopenia (monocytopenia)
  - splenomegaly
- Flow cytometry (PB/BM)
  - CD25, CD103, CD123
  - CD20, CD22, FMC7, CD11c
- Immunohistochemistry (BM/spleen)
  - Annexin A1, CD72 (DBA 44), CD20, TRAP
  - BRAF




HCL – BM


HCL – BM reticulin stain


HCL – BM CD20 stain

Initial Assessment

- Determine if diagnosis is correct (e.g. classic HCL is a different disease from HCL variant, misdiagnosis of aplastic anaemia)
- While 10% patients with HCL do not require immediate treatment, they require close follow-up.
- Patients with active infection require special treatment planning
- Need to assess kidney function and history of hepatitis exposure before treatment
- Bone marrow biopsies at initiation and following completion of therapy are important

When to Initiate Therapy

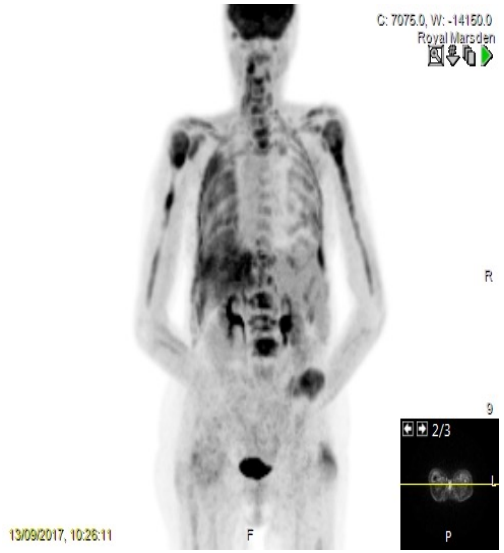
- Progressive decrease in blood counts, with absolute neutrophil count (ANC) <1,000, platelet count <100,000, or hemoglobin <11
- Symptoms associated with bone marrow failure, from an enlarged spleen, or other manifestations of disease

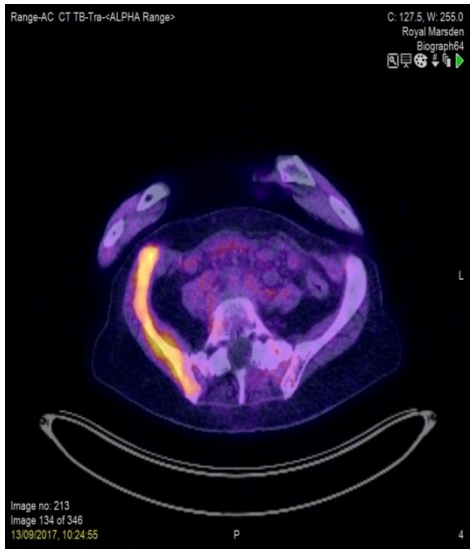
Grever et *al*: Consensus Guidelines for Diagnosis and Management of Hairy Cell Leukemia. *Blood* 129 (5): 553-560, 2017

Unusual Clinical Manifestations

- Lymphadenopathy
- Bone involvement
- Skin involvement (paraneoplastic eg erythema nodosum)
- Liver
- CNS
- Breast, pulmonary infiltration (case reports)
- Auto-immune disorders (Bechet's, vasculitis, AIHA/ITP, Sjogren's)
- Rare infections (atypical mycobacteria)
- Second malignancies

Focal bone lesions in HCL





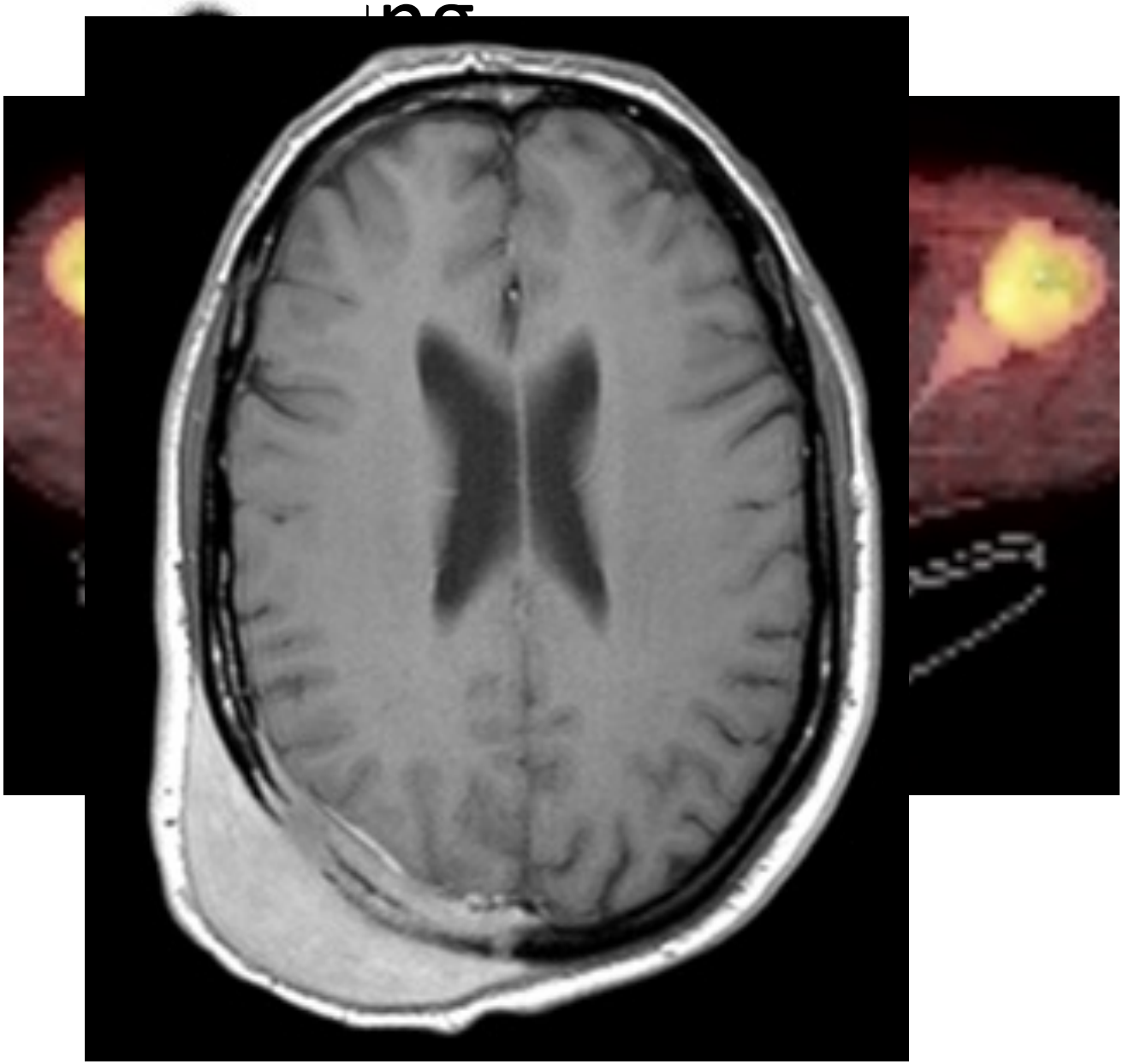
A rare presentation in HCL

- Incidence from the literature is ~3% (probably under reported)
- Rare as a first presentation usually seen later in disease
- Lesions are usually lytic
- Often associated with nodal or extranodal disease
- Involved site RT can be useful for symptom control
- Focal bone lesions generally respond to standard HCL treatment but can cause bone destruction that persists post- treatment

RV 42 year old male

- Presented with one month history of a right occipital swelling and scapula/rib pain
- Also 6-9 months of headache
- MRI showed a skull deficit with a soft tissue mass eroding the occipital bone with both intra and extra cranial disease
- Tissue and BM biopsy showed cHCL
- PET CT showed soft tissue masses to T1 paravertebral region, mediastinum, splenomegaly and widespread FDG avid lytic bone lesions
- MRI brain/spine showed leptomeningeal disease and CSF flow was +ve for HCL. T3 anatomical cord compression (asymptomatic)

imaging



RV: Treatment and responses

- Excellent response to:
  - Radiotherapy + Dexamethasone
  - Intrathecal chemotherapy with clearance of HCL from CSF
  - Cladribine
- MRI showed significant response at 1-2 months post treatment
- FBC showed haematologic response with normalisation of FBC including monocytes

RMH Cohort

- 4 male patients, 1 female patient
- 4 presented with focal bone lesions many years from diagnosis (average 21.25 years, range 11-26 years)
- 1 presented with focal bone lesions at diagnosis
- Average number of treatments before developing bone lesions = 5 (range 2-7)
- On developing bone lesions remissions either unachievable (1) or short duration of < 2 years (2)

Issues

- We have little experience of imaging techniques in HCL
- Imaging performed is very symptom lead which is appropriate but we may be missing asymptomatic disease

Matthew Cross, unpublished data

Infection in Hairy Cell Leukemia

- Approximately 17% of patients present with active infection complicated by pancytopenia.
- More than 50% will have infection at some point
- Before effective therapy, infection accounted for 55% of fatalities
- Infections are often with atypical organisms eg TB, fungi
- Compromised immune system with monocytopenia, defective T and NK cells, neutropenia risks **before** treatment
- Anti-leukaemic therapy further suppresses immune cells producing both prolonged immunosuppression and myelosuppression

Clinical Case

- Middle-aged man presented with fatigue and increasing headache
- Lab studies: WBC 8.9 with neutrophils 0.8; monocytes 0; hemoglobin 123; platelet 44; BMBx >80% hairy cells
- Immunophenotype classic hairy cell leukemia
- Treatment Cladribine 7 day IV with Fluconazole prophylaxis for a month
- Fluconazole stopped, then 10 days later developed fever & headache
- LP and brain biopsy showed Cryptococcus
- Treatment with antifungals for several months
- Achieved CR with normal blood count and MRI

Long-Term Consequences of Therapy for HCL

- Prolonged immunosuppression with reduced CD4 and CD8 T-cells
- Most common long-term infection is shingles (vaccination is appropriate)
- Risk for secondary malignancies is uncertain and unlikely to be related to therapy
- Bone marrow toxicity can result from excessive therapy

HCL: Summary

- Rare B cell leukaemia presenting with cytopenias and splenomegaly
- Diagnosis based on blood and bone marrow morpholgy and immunophenotype
- BRAF mutation status discriminates between classical and variant HCL
- Very high complete remission rate with purine analogues
- Very long remissions, especially for patients who achieve a CR
- Patients still in CR at 5y have only 25% risk of relapse
- Many novel treatments now available (to be presented next !))
- OS in RMH series is the same as an age-matched population

HCL Variant

HCL-V

- First recognised by Cawley *et al* in 1980
- Biologically distinct from classical HCL and 1:10 as common
- Since 2008 has been included in the "splenic B-cell leukaemias/lymphomas unclassifiable"
- Incidence 0.03/100,000 persons/year; 0.4% of all lymphoid malignancies
- RMH series of 39 patients*
  - M:F 2:1
  - Median age at diagnosis 73 years (range 42-92)

* Hockley et al Brit J Haem 2012; 158: 347-354

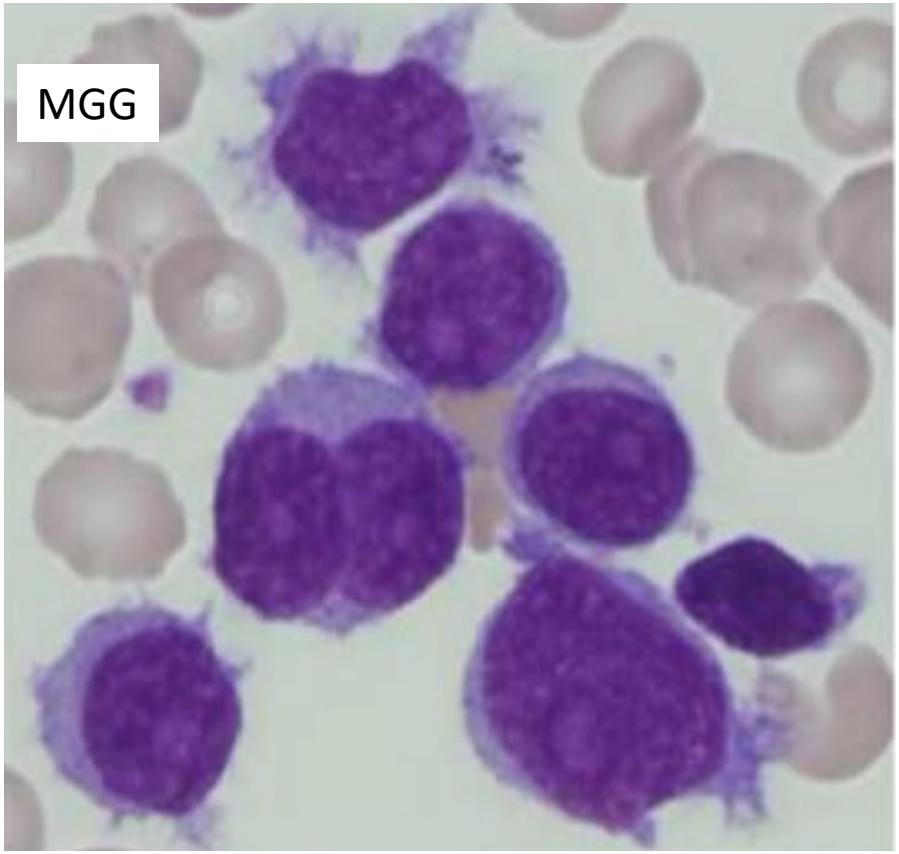
81 year old lady

- Presented aged 78 years with a 6 month history of fevers, one stone of weight loss, night sweats and abdominal distension
- She was otherwise fit and well with no other medical problems
- She had no significant travel history and did not smoke or drink alcohol
- On examination she had massive splenomegaly palpable to the level of the umbilicus
- The examination was otherwise normal and she had no palpable lymphadenopathy in the cervical, axillary or inguinal regions

81 year old lady

- FBC: haemoglobin 119 g/L, **WBC 68 $\times 10^9$cells/L,** lymphocytes 53 x10^9cells/L, neutrophils 4.1 x10^9cells/L, **monocytes 6.81 x10^9cells**/L, platelets 134 x10^9/L
- Urea, creatinine and liver function tests were normal
- Flow cytometry of peripheral blood showed: Clonal B cells representing 60% of total PB leucocytes **positive** for CD19, CD20, CD22, CD79b, CD11c, **CD103** and showed moderate expression of lambda. Cells were **negative** for CD5, CD10, CD23, **CD25 and CD123**
- BM infiltrate Annexin A1 negative
- **Negative for B-RAF V600E mutations**
- **Diagnosis HCL-variant**

HCL-V
Clinical and Laboratory features



PB: Cells 2 x size normal lymphocyte, round or bilobed nucleus, single nucleolus, basophilic cytoplasm with villi

- **Splenomegaly**, in 85% >10cm below costal margin
- Lymphadenopathy rare (14%)
- **Leucocytosis** (median 34 x10^9/l)
- Anemia 30%, thrombocytopenia 45%
- **Absence of moncytopenia**
- CD20 bright+, CD103+, CD27+, CD11c +
- CD25-, CD123-, CD200 -, Cyclin D1- , Annexin A1-
- ***BRAF V600E* not mutated**
- *MAP2K1* mutations in 50%
- *TP53* mutations in 30%

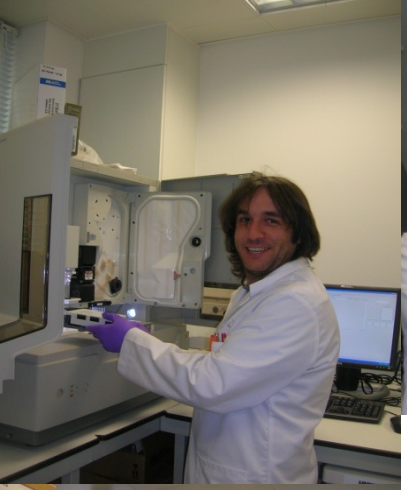
Hockley et al Brit J Haem 2012; 158: 347-354

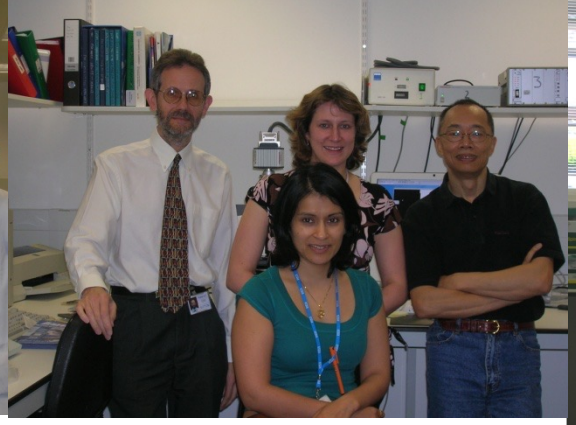
81 year old lady
Diagnosis HCLv

- The patient was treated with Cladribine daily x 5 and Rituximab weekly x 8 resulting in normalisation of her full blood count and regression of her splenomegaly
- She achieved a CR (BM and CT)
- Remains well and in continued remission 8 years later

HCLv Summary

- Rare splenic B cell malignancy characterised by splenomegaly and lymphocytosis
- Biologically distinct from HCL
- Typically resistant to PA monotherapy
- Median survival 9 years compared to >20 for HCL
- Standard first-line therapy CDA+Rituximab
- Novel therapies: Moxetumumab, Ibrutinib, MEK inhibitors effective in R/R disease






RMH/ICR

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Ricardo Morilla, Alison Morilla,
Sarah Hockley, John Swansbury,

David Gonzales, Ayoma Attygale,
Andrew Wotherspoon




Patients, HCL Foundation, SASS Foundation ARBIB Foundation, BRC, Charitable Donations