Understanding Hairy Cell Leukemia: Current and New Therapies

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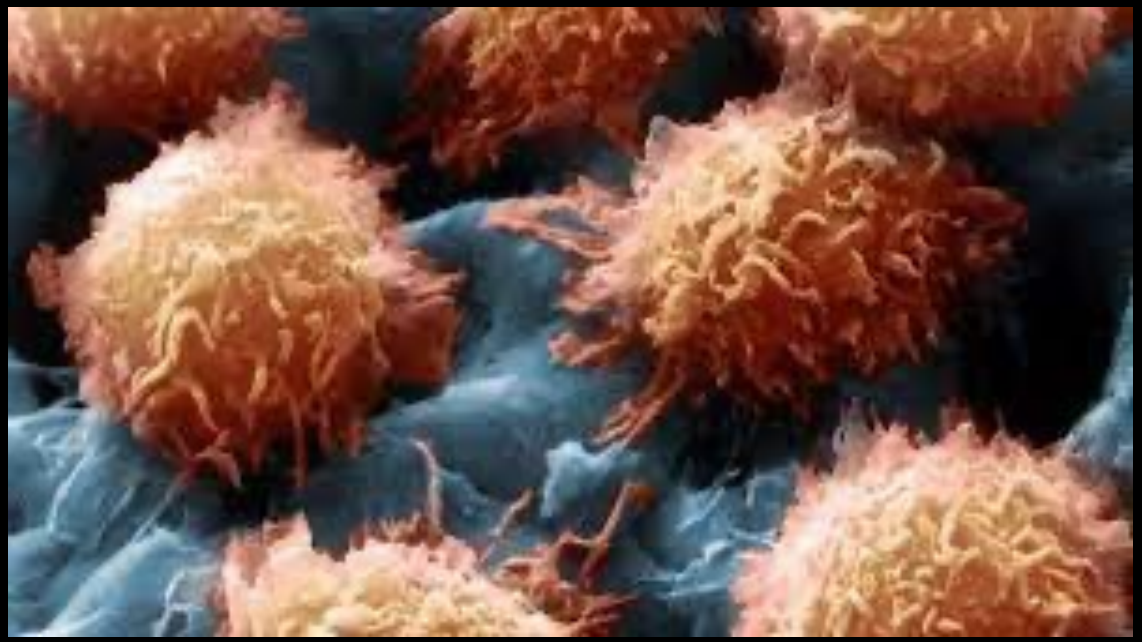
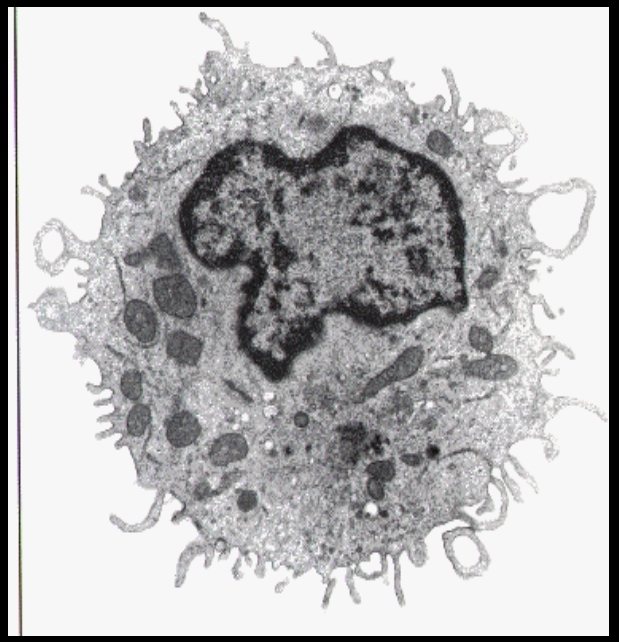
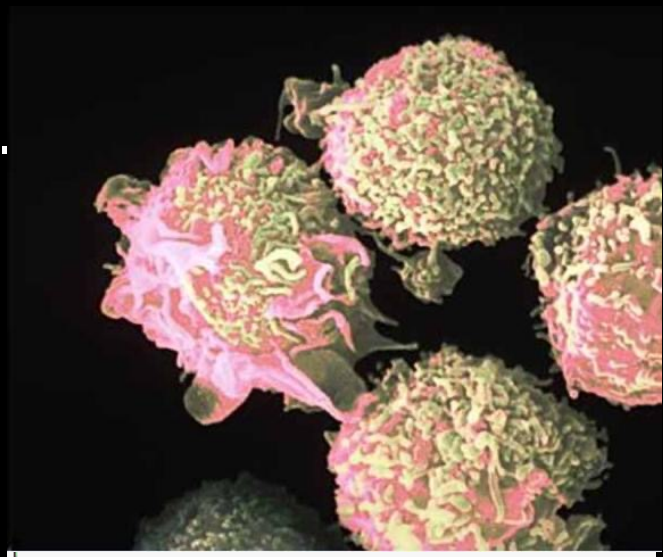


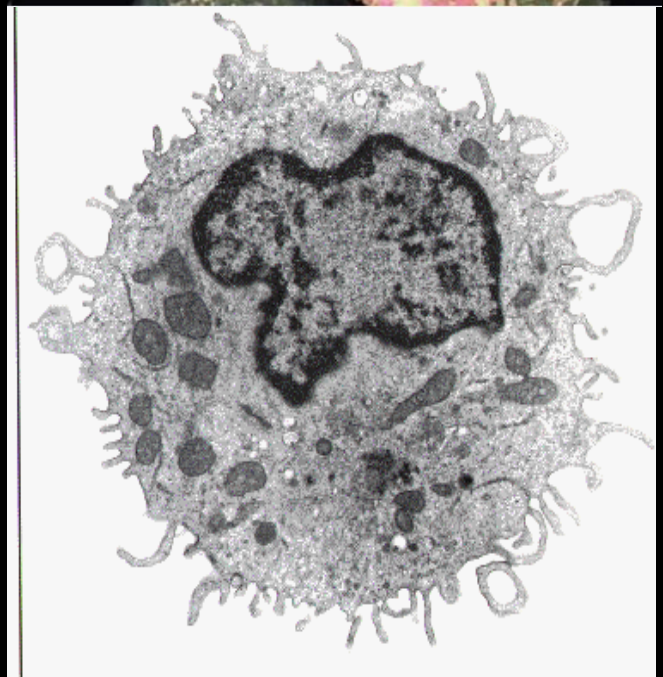


HAIRY CELL LEUKEMIA

- **Introduction**
  - B-cell, 2% of all leukemias. ~1200/year in 2023
  - Normal blood counts low, large spleen
  - Cytoplasmic projections, CD22+, CD20+, CD103.
  - Classic HCL: CD25+, driven by BRAF V600E



- **Treatment**
  - Purine analogs: Cladribine and Pentostatin can induce long term CRs but are not known to be curative and have decreased efficacy with each repeated course.
  - Variants of HCL lacking CD25 (HCLv) or expressing um-IGHV4-34 respond poorly.



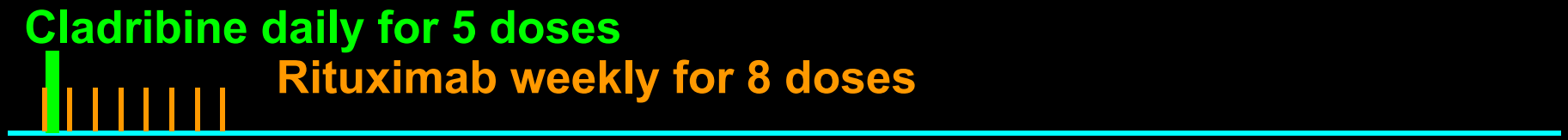
- **Diagnosis**
  - Flow cytometry of blood or bone marrow
  - Exclude other disorders
  - Determine if HCL or a variant

HCL vs HCLv

Type	HCL	HCLv	IGHV4-34+ HCL
% of HCL patients	~90%	~10%	2-5%
Spleen size enlargement	Mild	Severe	Severe
Lymph nodes	No	Yes	Yes
Normal blood counts	Low	Normal	Low
Leukemic cells in blood	Low	High	High
CD25	+	-	+
BRAF V600E mutation	+	-	-
Response to Cladribine or Pentostatin	Good	Poor	Poor

- Variant HCL tends to be more common among patients with relapsed or refractory HCL

Cladribine with Rituximab for HCLv

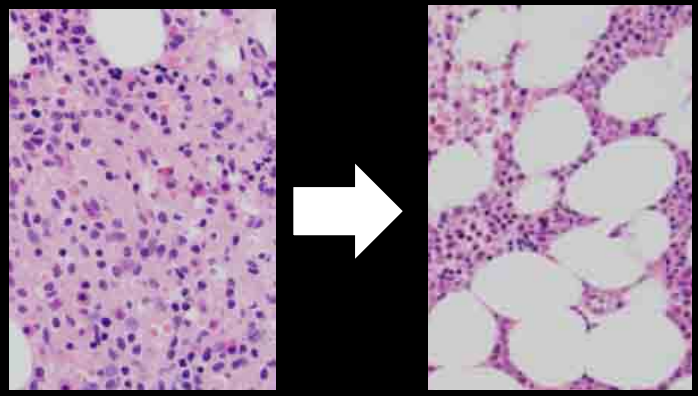


	Complete remission (CR)
• Cladribine alone for HCLv	7% of 42 patients
• Cladribine + Rituximab in HCLv	95% of 20 patients

Single agent Cladribine or Pentostatin should not be used for HCLv.

What does complete remission (CR) mean?

- No HCL visible by ‘standard’ stains (H/E, WS) of the bone marrow and blood



Resolution of:

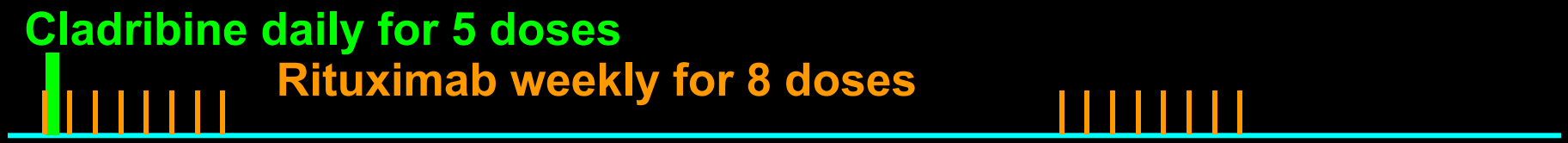
- Enlarged spleen, lymph nodes, high HCL counts
- Normal blood counts: ANC≥1.5, Hgb≥11, Plt≥100

- Need for treatment: ANC<1, Hgb<10, Plt<100
- Also, painful spleen, growing lymph nodes

CR with minimal residual disease (MRD)

- Special stains of the bone marrow biopsy
- Flow cytometry of the blood
- Flow cytometry of the bone marrow aspirate (most sensitive)
- Molecular studies: PCR
- Importance of MRD: CR may last longer if MRD is negative

Long term results of CDAR for HCLv

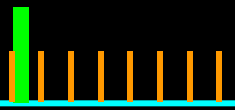


- 95% of 20 patients achieved CR and 80% achieved MRD-free CR.
- Achieving MRD-free CR at 1 or 6 months by bone marrow or just by blood flow cytometry was associated with longer overall survival.
- TP53 mutation was associated with shorter overall survival.
- Although 16 (80%) achieved MRD-free CR, only 5 (25%) stayed MRD-free so far, 1 died of Parkinson's still MRD-free.
- In patients with MRD-free CR who became MRD+, delayed rituximab was often successful in re-achieving MRD-free CR for many years so far.
- Since HCLv patients relapsing after CDAR may be more resistant to chemo, more intense 1st line treatment like pentostatin-rituximab or bendamustine rituximab has been tried.

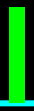
Cladribine with Rituximab for untreated HCL

Cladribine daily for 5 doses (CDAR)

Concurrent Rituximab weekly for 8 doses

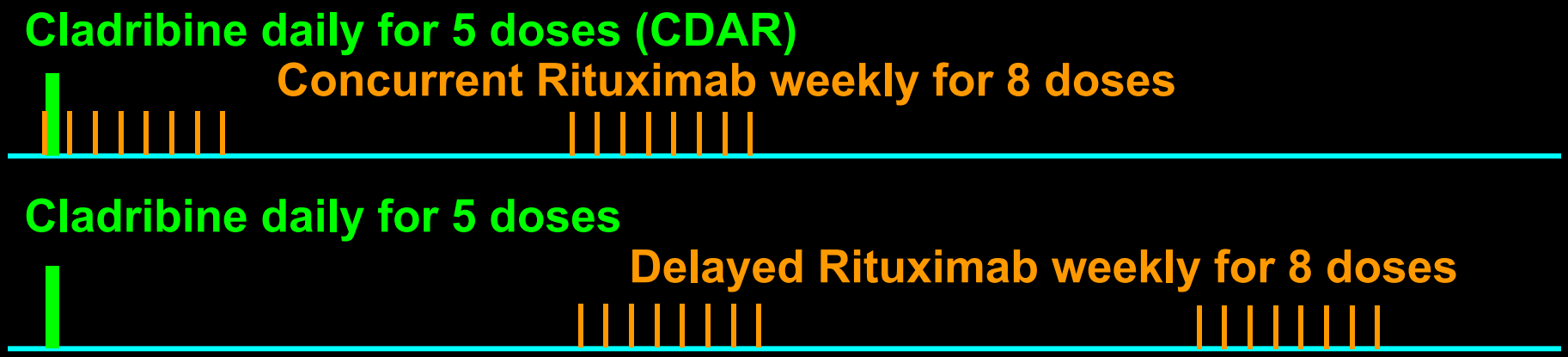


Cladribine daily for 5 doses



	Complete remission (CR) (by 6 mo)	MRD-free CR (6 mo)	MRD-free CR (6.5y)
• CDAR	100%	97%	94%
• Cladribine alone	88%	24%	12%

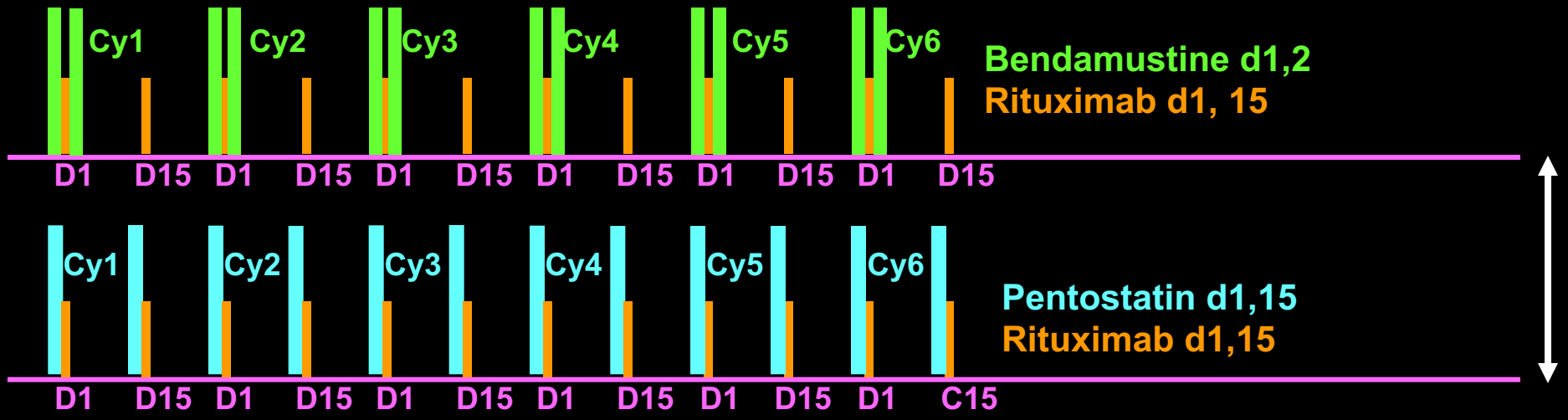
Cladribine with Rituximab for untreated HCL



	Complete remission (CR) (by 6 mo)	MRD-free CR (6 mo)	MRD-free CR (6.5y)
• CDAR	100%	97%	94%
• Cladribine alone	88%	24%	12%
• Cladribine + delayed rituximab			47%

- By either approach, 0-3% of patients needed more treatment by 6.5y, compared to 28% by 6.5y reported in 2009 after cladribine or pentostatin alone.

Rituximab with either Pentostatin or Bendamustine for multiply relapsed and refractory HCL

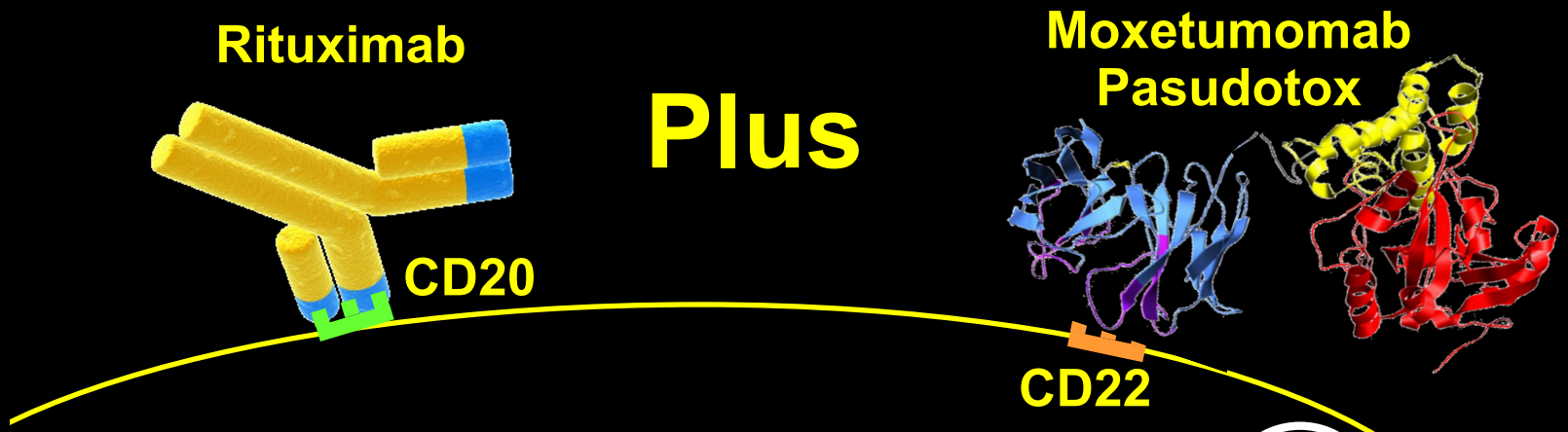


- 65-73% CR rate
- Most CRs MRD-free, also works for HCLv, especially 1st line
- While highly effective, this approach may be toxic due to chemo

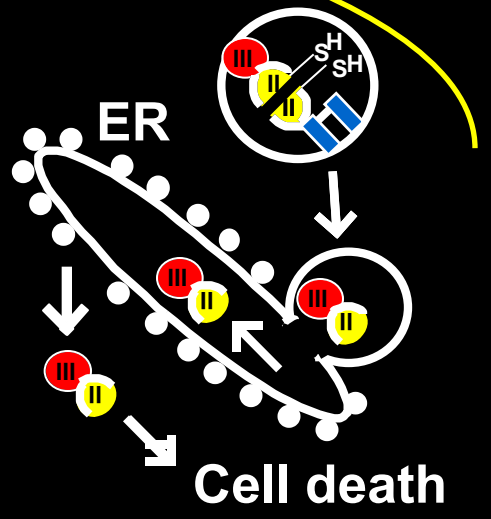
Questions:

- Can MRD-free CR be achieved without chemo?

Targeting both CD20 and CD22 in HCL with MoxeR

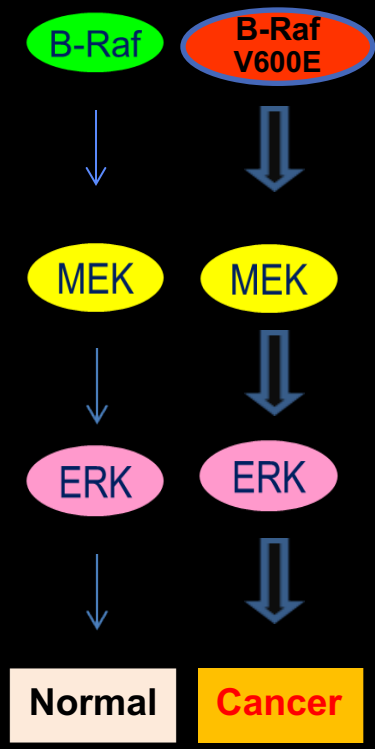


- Moxetumomab Pasudotox (Moxe) was a recombinant protein approved for relapsed HCL/HCLv that bound to CD22 and it contained a protein toxin which kills the cell.
- The protein toxin could cause antibodies which would prevent MRD-free CR.
- Adding rituximab to Moxe increased the MRD-free CR rate from <50% to >70% by lowing anti-drug antibodies and more rapidly achieving MRD-free CR.
- Moxe was taken off the market for business reasons and awaits a drug company making more drug and continuing development.



Targeting the BRAF pathway with oral drugs

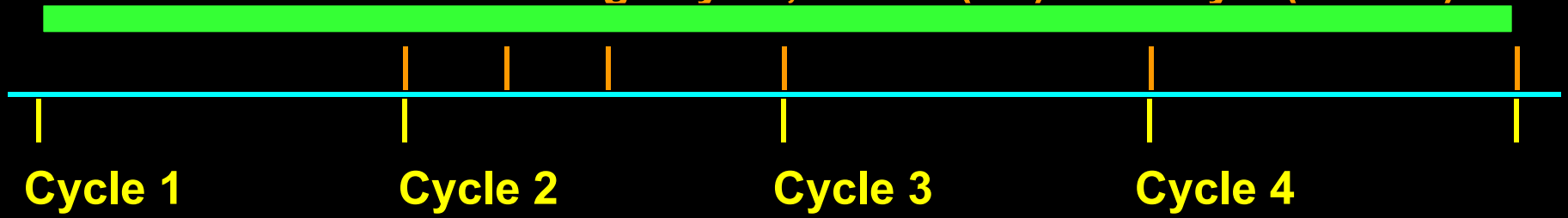
- In HCL, BRAF carrying the V600E mutation over-stimulates the BRAF→MEK→ERK pathway.
- Vemurafenib inhibits BRAF V600E and resulted in 35-45% CRs in HCL, all MRD+
- Dabrafenib inhibits BRAF V600E, Trametinib inhibits MEK.
- Dabrafenib alone achieves 30% CRs in HCL.
- Both drugs were more effective and less toxic than Vemurafenib in melanoma and are also effective in HCL, achieving CRs in 66% with long-term treatment.
- In Italy, Vemurafenib and Rituximab achieved 87% CRs and 57% MRD-free CRs in relapsed HCL.
- These agents can have side effects, including skin rashes/cancer for Vemurafenib, and fever/chills for Dabrafenib-Trametinib.
- BRAF inhibitor Encorafenib and MEK inhibitor Binimetinib are currently being tested at NIH. Encorafenib causes fever less often than Dabrafenib.
- On the Encorafenib-Binimetinib protocol, rituximab can be given to convert MRD+ CR to MRD-negative CR.



Chemo-free first-line treatment of HCL

Vemurafenib 960 mg 2x/day for four 28-day cycles

Obinutuzumab 1000 mg days 1, 8 & 15 (C2) and day 1 (C3 & 4)



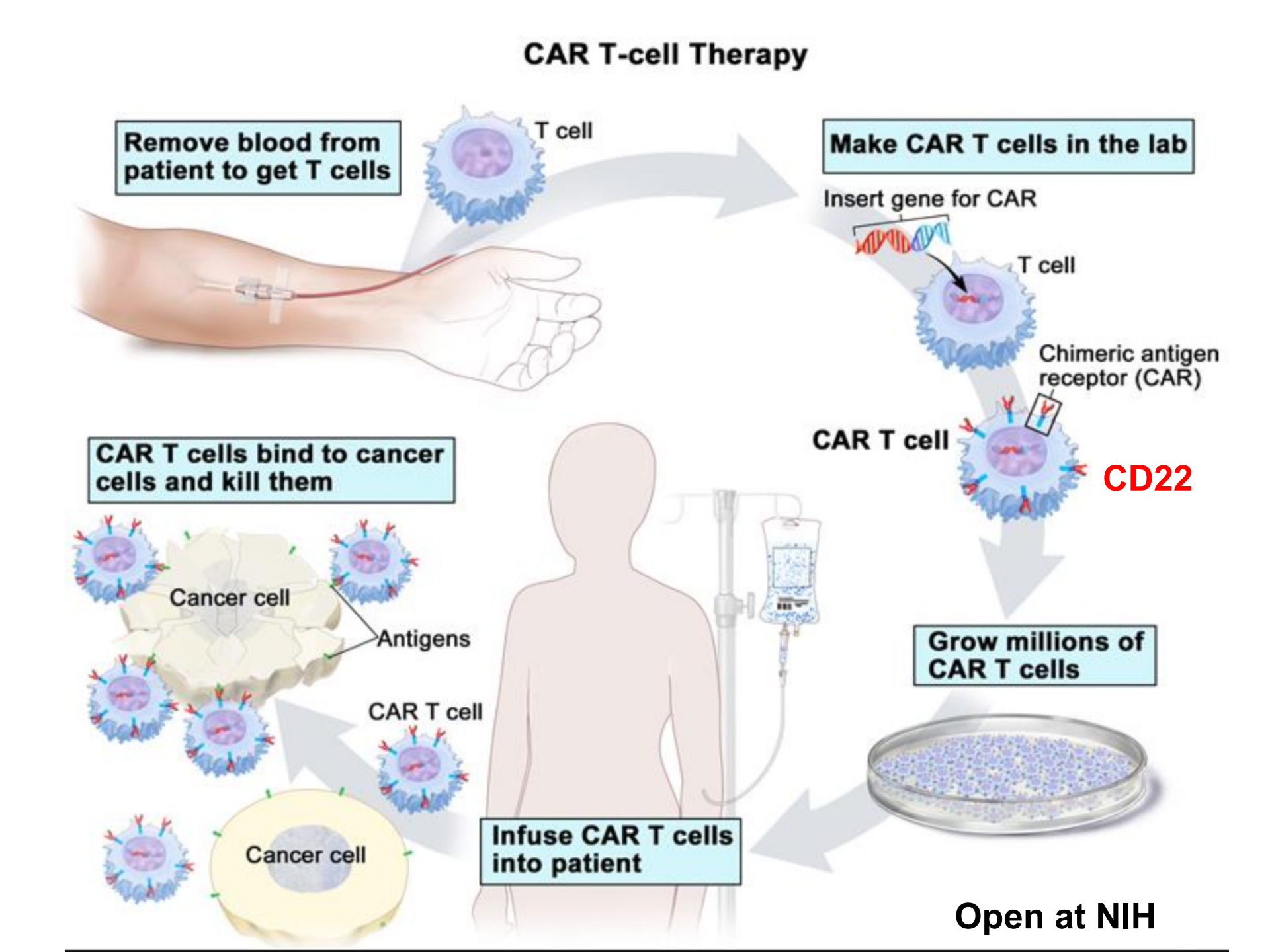
- Drs. Park and Tallman from MSKCC led a study testing Vemurafenib with anti-CD20 Mab Obinutuzumab starting on Cycle 2 day 1.
- Vemurafenib had a head start in minimizing HCL burden so that Obinutuzumab toxicity would be minimized, although 5 patients had reactions.
- Vemurafenib toxicity was usually mild-moderate and included rash (93%), joint pains (80%), itching (50%) and fatigue (43%).
- Of 30 patients enrolled, 3 stopped treatment because of toxicity, 27 completed treatment, all of whom achieved CR,
- Of the 30 enrolled 26 (87%) achieved MRD-free CR.
- At a median follow-up of 35 months, none of the 27 patients completing treatment relapsed.
- None of the 26 MRD-free CRs became MRD+, but bone marrows were not done after 1 year.
- An advantage to this approach is that T-cells, particularly CD4+, were spared

Oral drug Ibrutinib for HCL

- Ibrutinib, approved for chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL), inhibits Bruton's Tyrosine Kinase (BTK).
- Ibrutinib achieves 19% CRs, mostly MRD+.
- Ibrutinib is also effective in HCLv, unlike BRAF inhibitors.
- Ibrutinib can cause atrial fibrillation, increase the risk of bleeding and infections, but in general is better tolerated than the BRAF/MEK inhibitors.
- Ibrutinib can take many months and even years to work in HCL, so it should not be given to patients with severe low blood counts who need to respond quickly.

Venetoclax in HCL targeting BCL-2

- Tiacci et al. reported 6 patients who progressed 6, 18, 18, 25, 37, and 37 months after Vemurafenib-Rituximab, and 2 of 6 achieved MRD+ CR with Venetoclax 400 mg/day.
- Forconi et al. reported 1 patient treated with Venetoclax who achieved a CR.
- Three of the patients treated by Venetoclax by Tiacci et al. received Rituximab:
  - 1 with MRD+ CR to Venetoclax had a decrease in MRD
  - 1 with a marginal response to Venetoclax had MRD+ CR
  - 1 with no response to Venetoclax responded.
- A multicenter trial of Venetoclax in HCL will begin soon in the US, run by NCI-CTEP


CAR T-cell Therapy
Remove blood from patient to get T cells
T cell
Make CAR T cells in the lab
Insert gene for CAR
T cell
Chimeric antigen receptor (CAR)
CAR T cell
CD22
CAR T cells bind to cancer cells and kill them
Cancer cell
Antigens
CAR T cell
Cancer cell
Infuse CAR T cells into patient
Grow millions of CAR T cells
Open at NIH

Conclusions for treatment of HCL/HCLv

- 1st line treatment is purine analog +/- rituximab, although Vemurafenib-Obinutuzumab is a chemo-free option.
- Cladribine-rituximab eliminates MRD and decreases relapse long-term compared to cladribine alone.
- HCLv, which lacks CD25 and BRAF V600E, should not be treated with purine analog alone.
- Purine analogs including Cladribine, Pentostatin and Bendamustine can be combined with Rituximab to eliminate MRD in relapsed HCL, albeit with chemotherapy toxicity.
- BRAF and/or MEK oral inhibitors can rapidly achieve CR but usually need rituximab to eliminate MRD.
- BTK inhibitor Ibrutinib works very slowly in HCL but can also achieve CR, generally without eliminating MRD.
- Venetoclax +/- Rituximab is active in HCL.
- Participation in clinical trials is encouraged for all patients.

Treating HCL in the age of COVID-19

- COVID-19 vaccines produce antibodies and T-cells, which protect from infection, hospitalization, and death.
- Antibodies can be low or absent after purine analogs, Ibrutinib or Rituximab (12 mo or longer).
- HCL patients should have antibodies measured.
- Low/absent normal B-cells lead to poor antibodies response.
- HCL patients who have low/absent antibodies but since the last vaccine dose have had recovery of normal B-cells, should get another vaccine dose.
- HCL patients with persistently low normal B-cells may require drugs like Paxlovid, Remdesivir or MoInupiravir.
- Don't compromise HCL treatment due to COVID-19 but consider delaying to achieve the highest antibody level possible before starting treatment, particularly Rituximab.
- Patients without normal B-cells due to HCL/HCLv may be treated with BRAF inhibition to restore normal B-cells.

Clinical trials featured on the HCL Foundation Website

• Vemurafenib-Rituximab	Untreated	HCL	Scripps
• Cladribine & Rituximab	1 relapse	HCL	NIH
• Encorafenib-Binimetinib	≥1-2 relapses	HCL	NIH
• Binimetinib	≥1-2 relapses	HCL/HCLv	NIH
• CAR-T targeting CD22	≥2-3 relapses	HCL/HCLv	NIH
• CAR-T targeting CD19	≥2 relapses	HCL	Multi