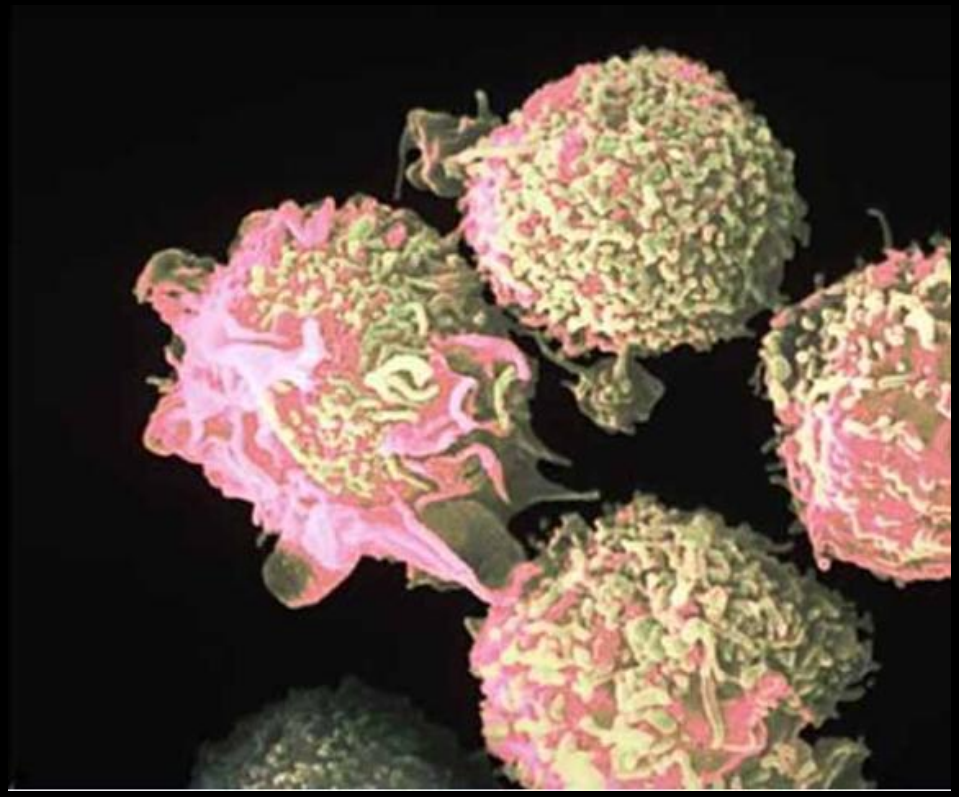
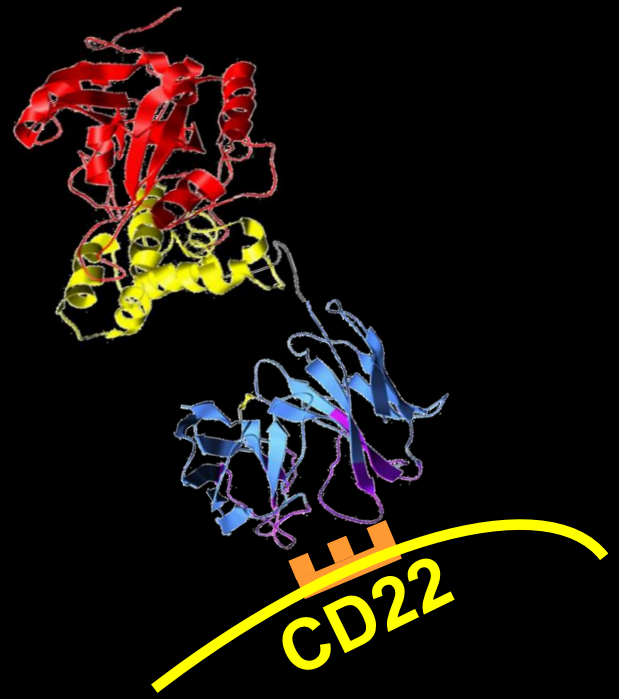
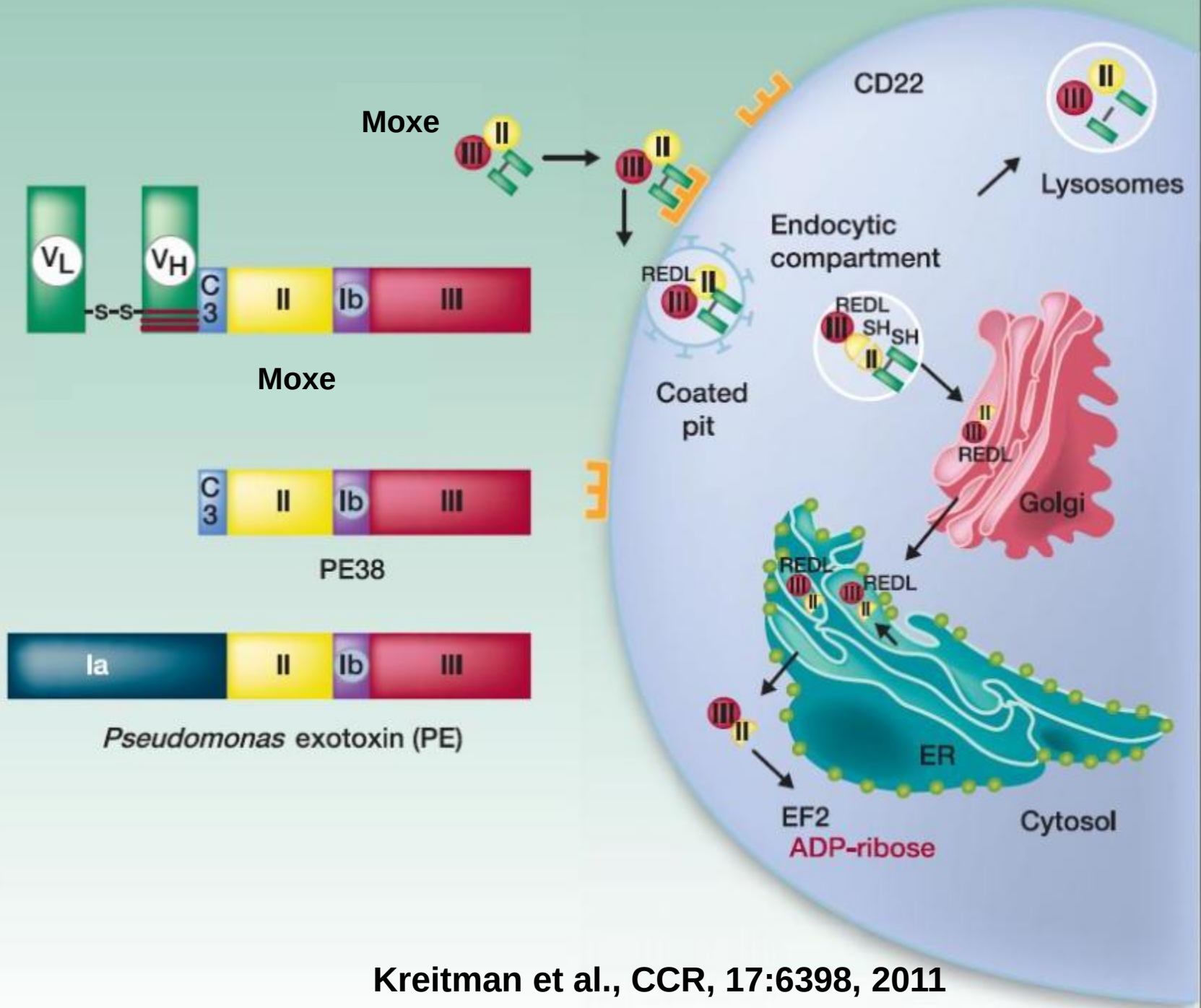
Moxetumomab Pasudotox
Robert J. Kreitman, M.D.





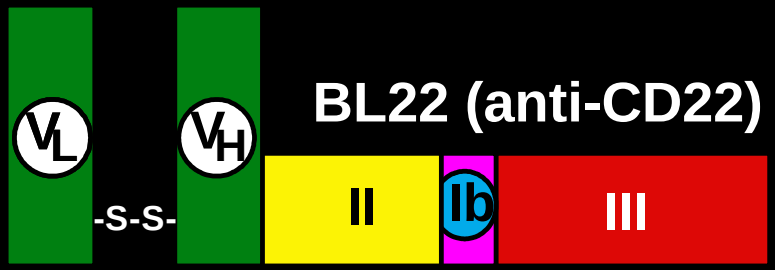


Kreitman et al., CCR, 17:6398, 2011

EFFICACY OF THE ANTI-CD22 RECOMBINANT IMMUNOTOXIN BL22 IN CHEMOTHERAPY-RESISTANT HAIRY-CELL LEUKEMIA

ROBERT J. KREITMAN, M.D., WYNDHAM H. WILSON, M.D., PH.D., KAREN BERGERON, R.N., MIRANDA RAGGIO, R.N., MARYALICE STETLER-STEVENSON, M.D., DAVID J. FITZGERALD, PH.D., AND IRA PASTAN, M.D.

NEJM (2001) 345:241 11/16 CR, 2/16 PR



Complete remissions: Phase 1: 19 (58%)
Phase 2: 17 (47%)

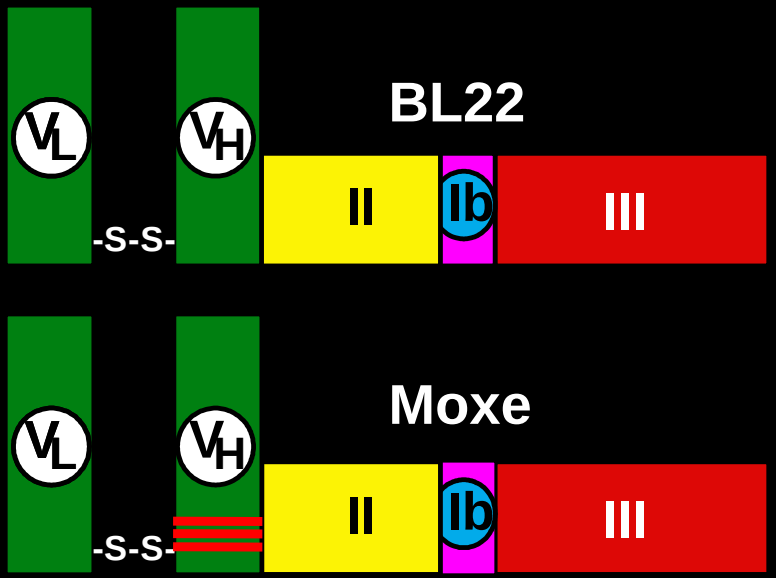
6 still in CR after 12-18 years

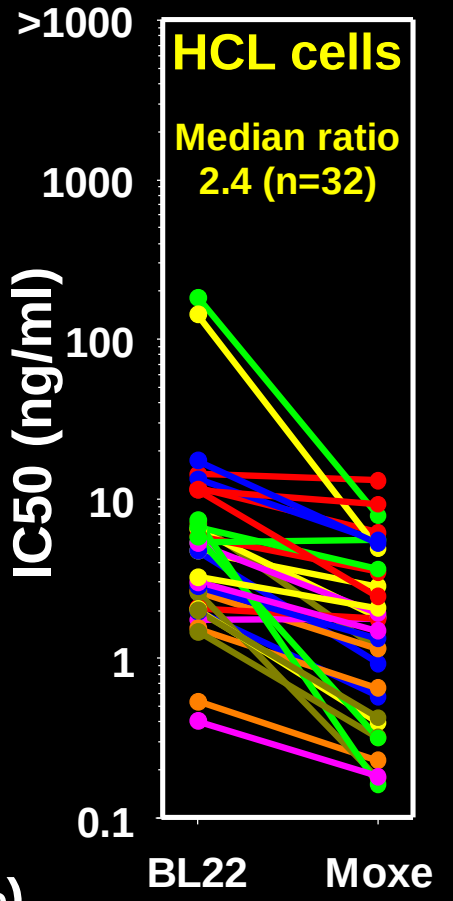
2 MRD-free, 1 at 16.5 and one at 20.5 years

Grd 3-4 Toxicity: HUS (6-12%), CLS (0-3%)

Kreitman et al., JCO, 23:6719, 2005
Kreitman et al., JCO, 27:2983, 2009

Moxetumomab Pasudotox
High affinity mutant of BL22





- 3 mutations in VH increase affinity 14-fold
- HA22 renamed CAT-8015 & moxetumomab pasudotox
- Phase 1: 28 complete remissions (57%), Grd 2 HUS (4%)

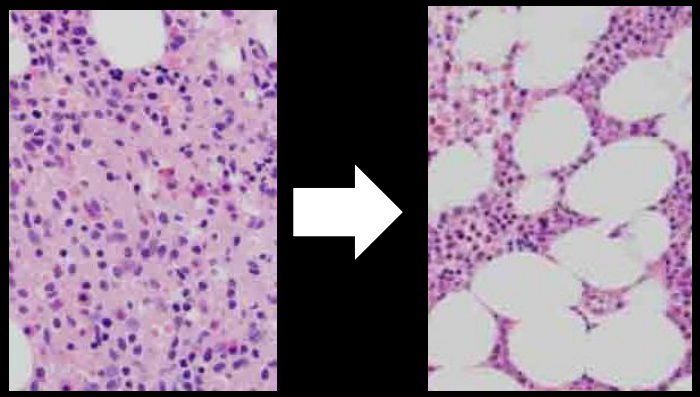
Kreitman et al., NEJM, 345, 241, 2001
Salvatore et al., CCR, 8:995, 2002
Kreitman et al., Blood, 131:2331, 2018

What is a response or remission in HCL?

- Improved normal blood counts
- Smaller spleen and lymph nodes if large before

What does complete remission (CR) mean?

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



- Normal blood counts: ANC≥1.5, Hgb≥11, Plt≥100

Definitions of CR and minimal residual disease (MRD)

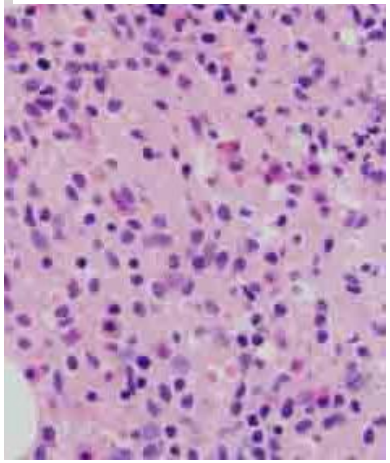
BMBx H/E

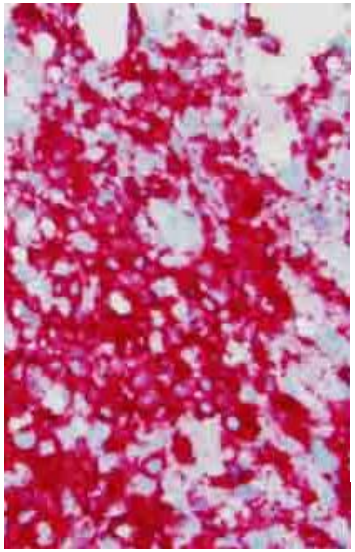
BMBx IHC

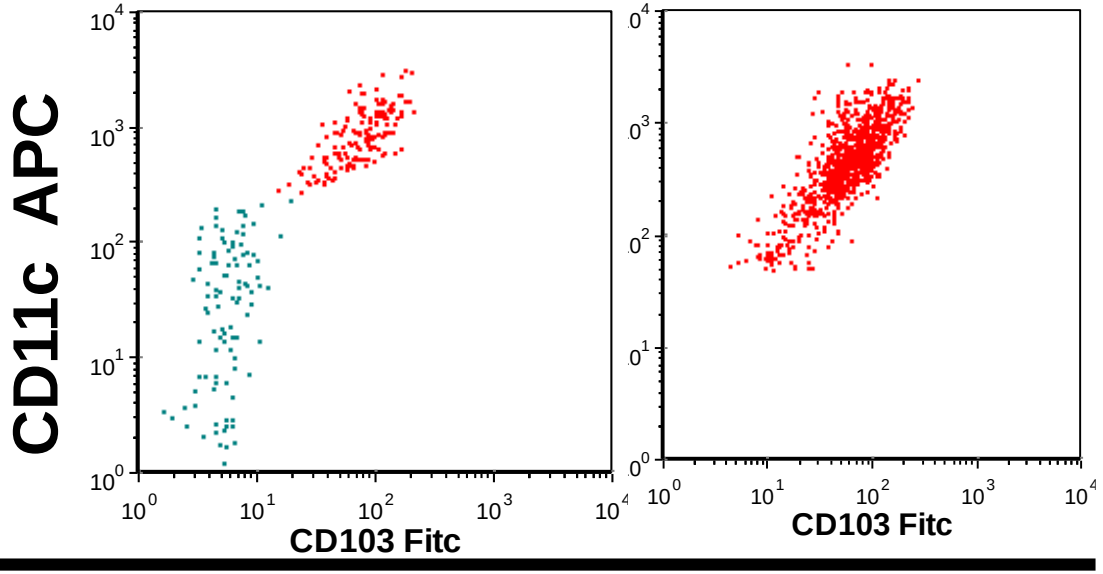
Blood Flow
(3 cells in 10^4)

BMA Flow
(most sensitive)

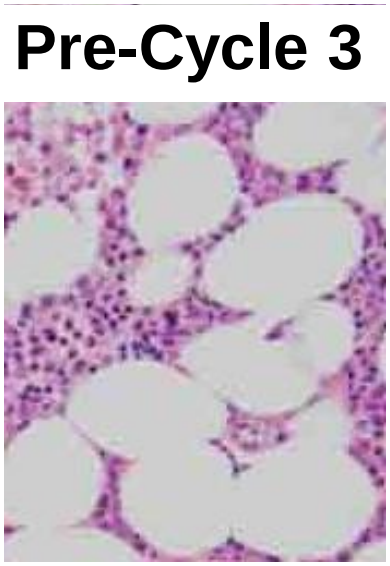
Pre-Cycle 1

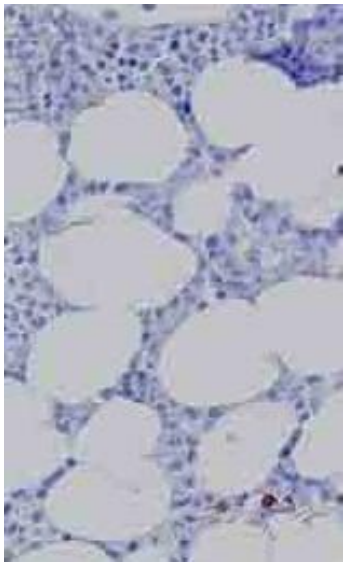


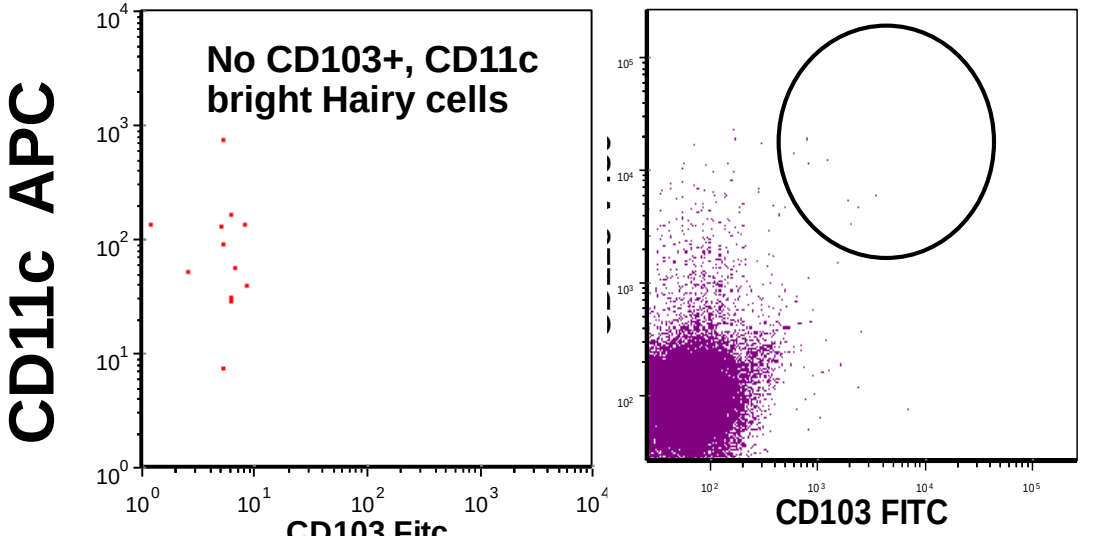




Pre-Cycle 3

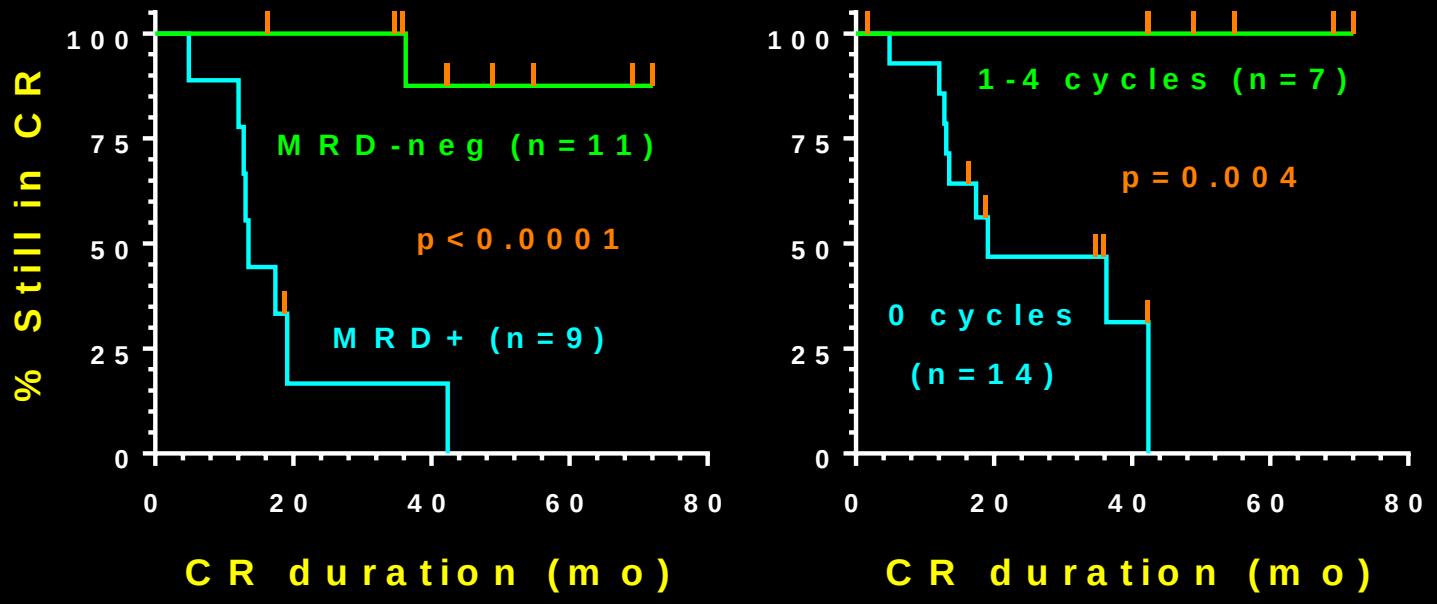






HH21 still MRD- 8.5y later

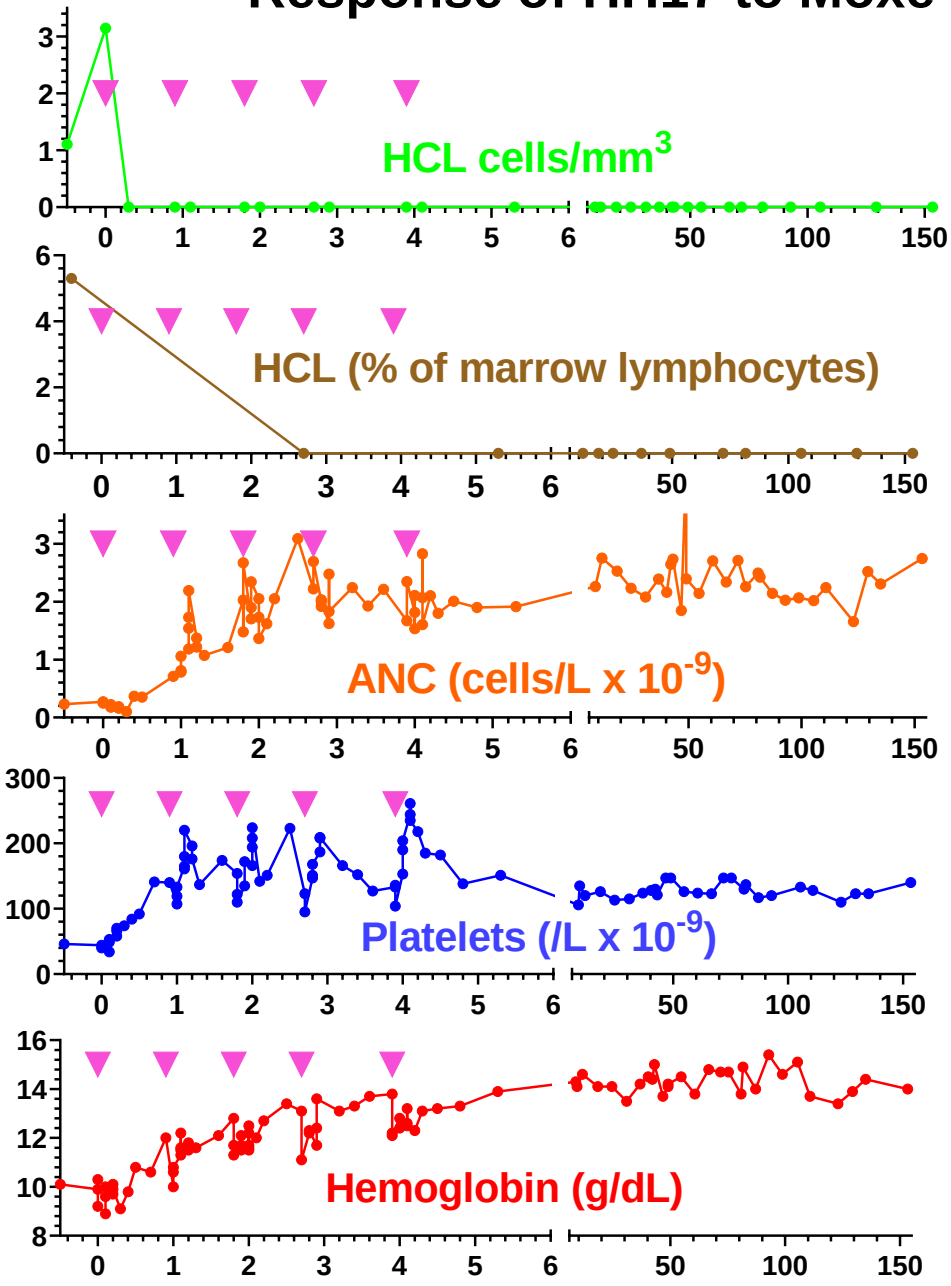
Importance of MRD-free CR from Moxe

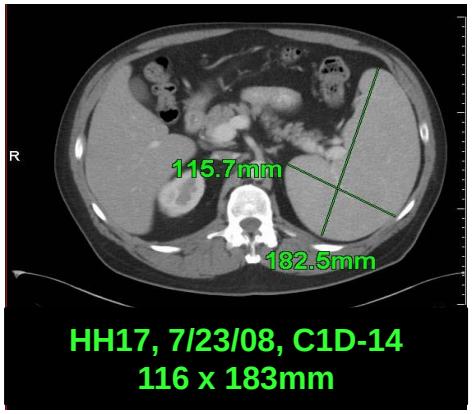


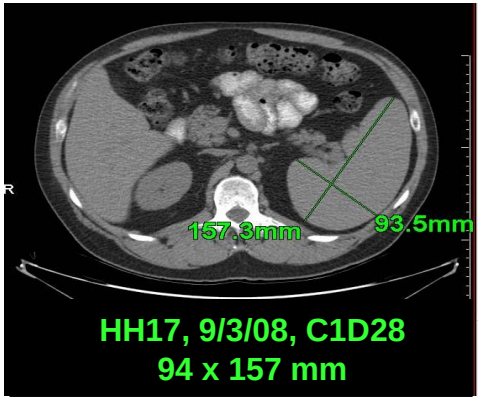
- In the phase 1 trial of Moxe, 11 patients had MRD-free CR and only 1 relapsed, while 9 had MRD+ CR and 8 relapsed.
- Seven patients who got 1-4 extra cycles after CR did not relapse.
- Of 14 patients who did not get extra cycles, most relapsed.
- CR duration is longer if Moxe can clear MRD, which requires extra cycles.

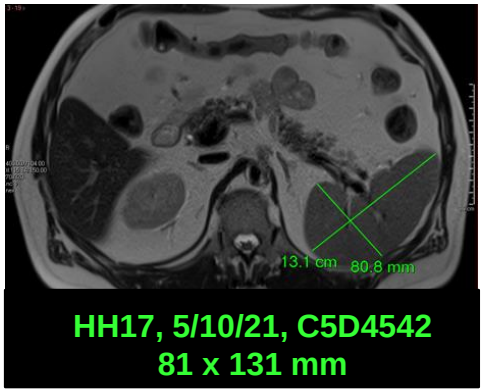
Kreitman et al. Blood, 131:2331, 2018

Response of HH17 to Moxe over 12.5 years









Kreitman et al., Blood Rev, 51:100888, 2022

Phase 3 Study Design and Treatment

- Pivotal, multicenter, single-arm, open-label study (NCT01829711) conducted at 34 centers in 14 countries
- Moxetumomab pasudotox treatment
  - 40 µg/kg IV on days 1, 3, and 5 of 28-day treatment cycles
  - Up to 6 treatment cycles
  - Discontinued if disease progression, start of alternate therapy, or unacceptable toxicity
  - Option to discontinue with <6 cycles if patient achieved MRD-negative CR (investigator assessed, by flow cytometry)
- Disease response and IHC MRD assessed by blinded independent review
- Primary endpoint: CR followed by normalized blood counts for ≥6 months

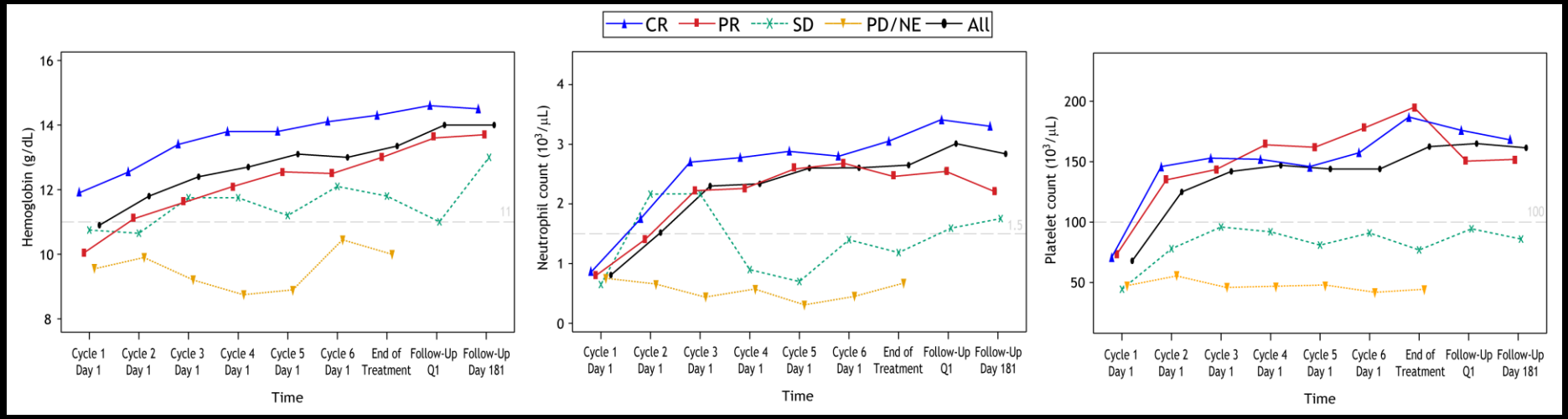
CR, complete response; IHC, immunohistochemistry; IV, intravenously; MRD, minimal residual disease.

Kreitman et al., Leukemia, 32:1768, 2018

Changes in Hematologic Parameters

- 80% of patients (64/80) achieved hematologic remission, with median onset of 1.1 months

Hemoglobin | Neutrophil Count | Platelet Count



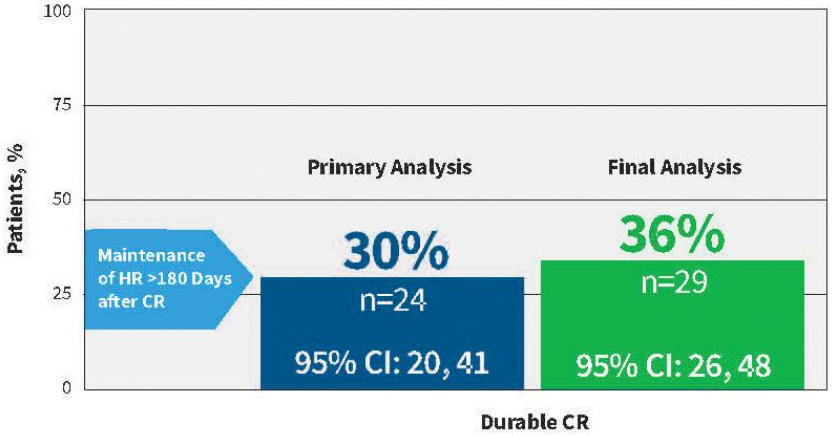
- Median immunoglobulin (IgA, IgG, and IgM) levels remained unchanged after treatment
- Median CD4 T-cell counts were stable or increased following a transient decrease on day 8

CR, complete response; PD/NE, progressive disease or not evaluable; PR, partial response; SD, stable disease.

Kreitman et al., Leukemia, 32:1768, 2018

Study 1053 Efficacy Results

LUMOXITI Demonstrated Durable Responses Among Patients With r/r HCL Who Had Received Prior Treatment With at Least 2 Systemic Therapies, Including 1 PNA[1,4]

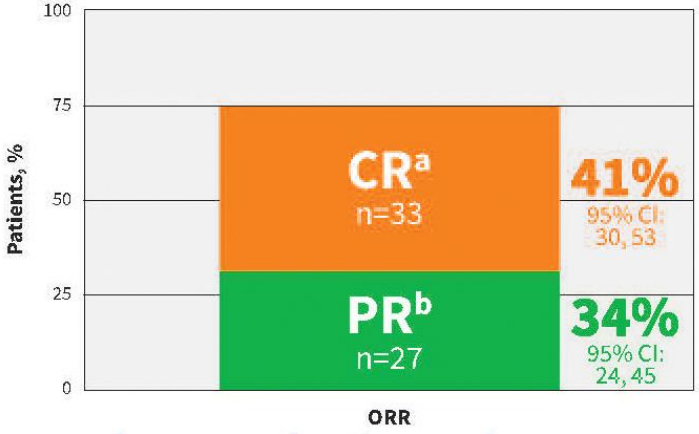


Primary Endpoint: Durable CR

32% of all patients (26/80) maintained CR with HR (95% CI: 22%, 44%) at their respective 360-day evaluation[4]

- The median duration of follow-up was 16.7 months (range: 2 to 49) at the primary analysis and was 24.6 months (range: 1.2-71.1) at the final analysis
- The median DoR was not reached (range: 0+ to 43+) at the primary analysis and was 66.7 months (range: 0 + to 66.7) at the final analysis

The ORR (Secondary Endpoint) Was 75% (95% CI: 64, 84)[1,2]



[a]CR was defined as clearing of the bone marrow of hairy cells by routine H&E stain, radiologic resolution of pre-existing lymphadenopathy and/or organomegaly, and HR.[2] [b]PR was defined as ≥50% decrease or normalization (<500/mm^3) in peripheral blood lymphocyte count, reduction of pre-existing lymphadenopathy and/or organomegaly, and HR.[2]

PR, partial response.

9 CRs not Durable

- **5 had CR later than EOT time point**
- **2 went traveling and stopped f/u**
- **2 lost HR**

Kreitman et al., Leukemia, 32:1768, 2018
Kreitman et al., J Hemat Oncol, 14:1, 2021

Prevention of CLS and HUS after Moxe

- Phase 3: CLS 5%, HUS 7.5%
- HUS is likely due to exposure of Moxe to glomerular endothelium, increased by CLS-related hypovolemia, and resolves in 1-2 weeks.
- Goal: keep the intravascular volume replete but prevent overload by using oral rather than IV fluid.
- Nausea or headache after Moxe responds rapidly to Dexamethasone 4 mg po.
- Before precautions: grade 3 HUS 3/9 (33%)
- After precautions: grade 1 HUS 1/17 (6%), (p=0.032 for grade 3 HUS)

Kreitman et al., Blood Rev, 51:100888, 2022

Duration of CR by IHC MRD Status

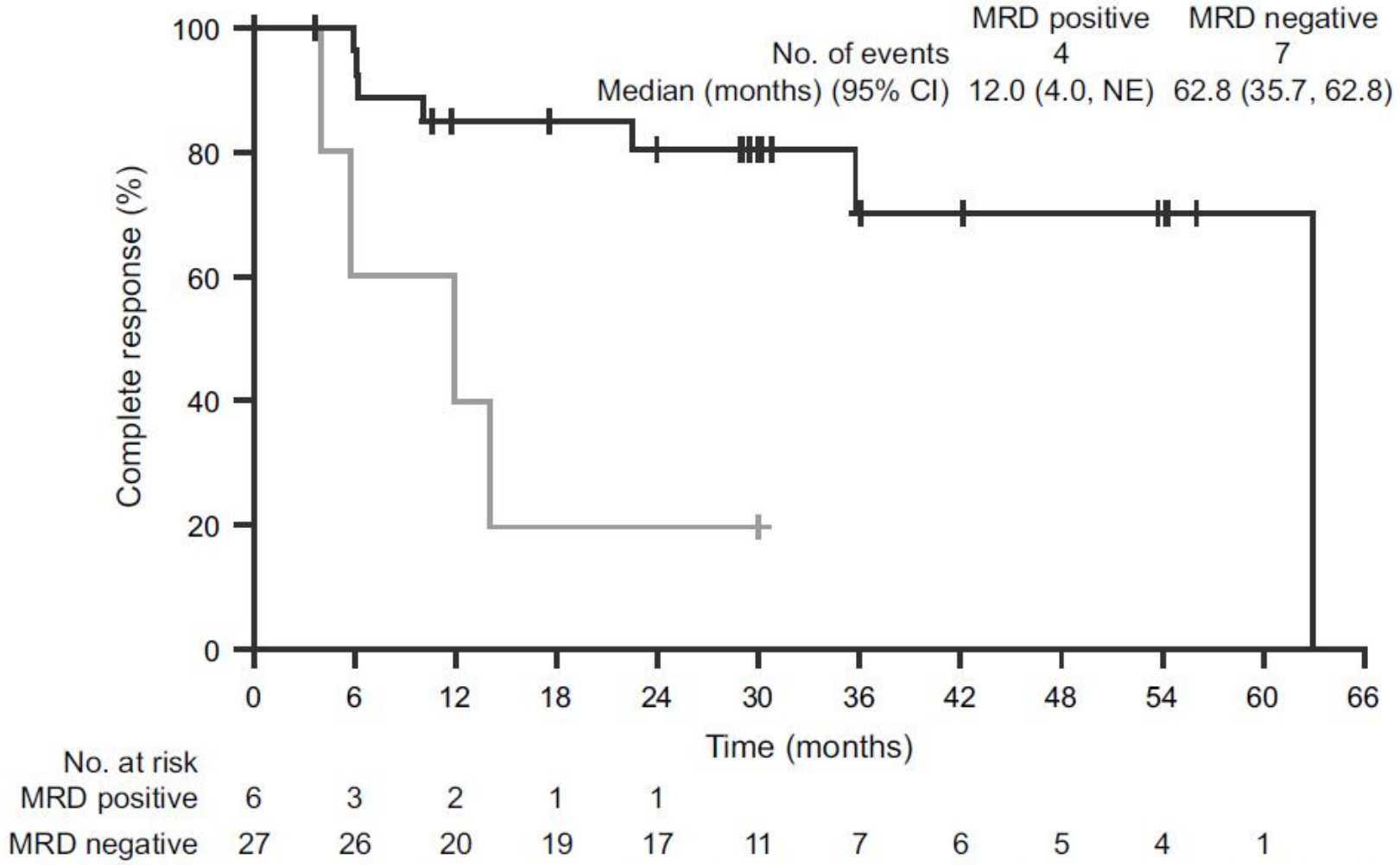
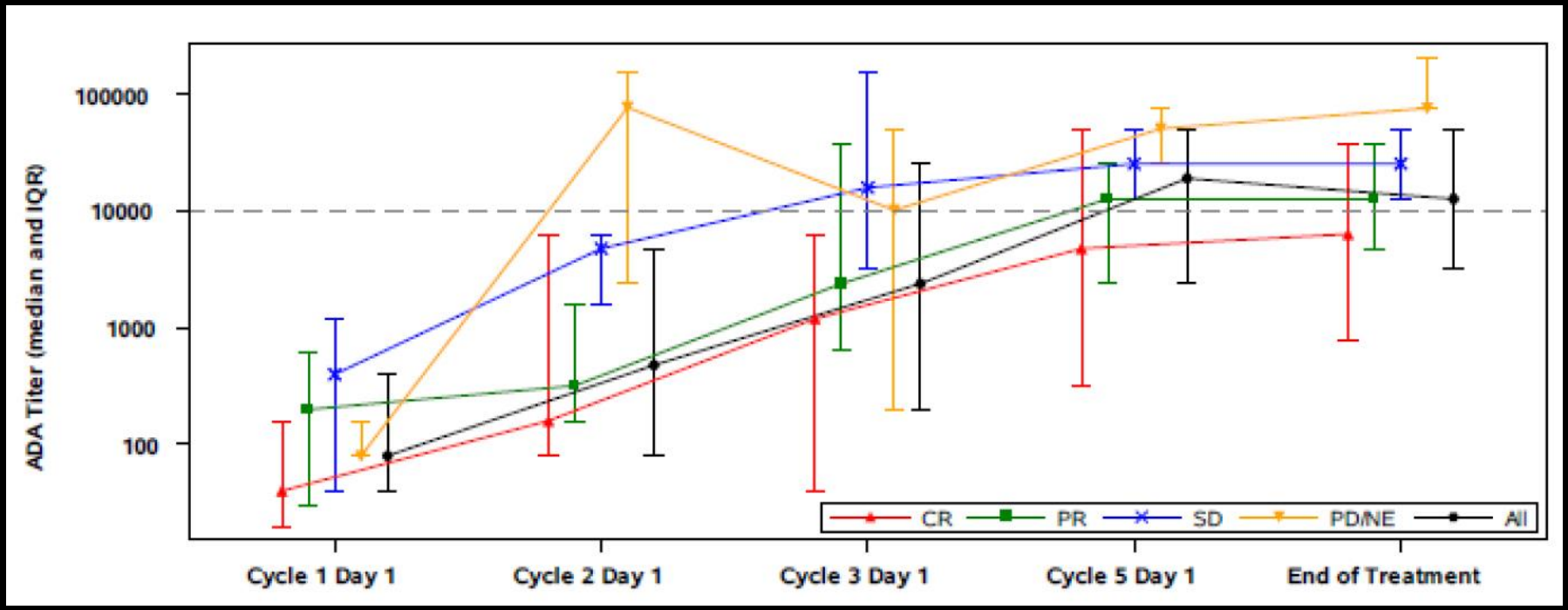


Fig. 2 MRD negativity was associated with durable CR. Kaplan–Meier plot for the patients with a complete response in the ITT population, as assessed by BICR ($n = 33$). The starting point of the observation was from the onset of CR and MRD testing. *BICR* blinded independent central review, *CI* confidence interval, *CR* complete response, *ITT* intent-to-treat, *MRD* minimal residual disease, *NE* not evaluable

Kreitman et al., J Hemat Oncol, 14:1, 2021

Moxe Phase 3 best response vs ADA titer

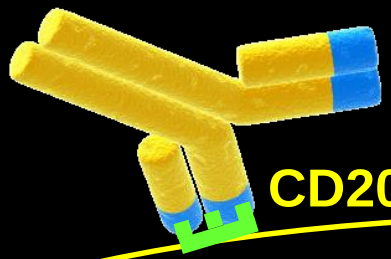


- ADA titer was lower in patients with CR vs PR vs SD.
- Prevention of ADA to Moxe remains an important goal.
- Higher HCL burden requires more cycles for MRD-free CR.
- More cycles of Moxe may be associated with higher risk of ADA.
- Prevention of ADA and reducing HCL tumor burden are useful goals.

Kreitman et al., Leukemia, 32, 1768, 2018

Targeting both CD20 and CD22 in HCL with MoxeR

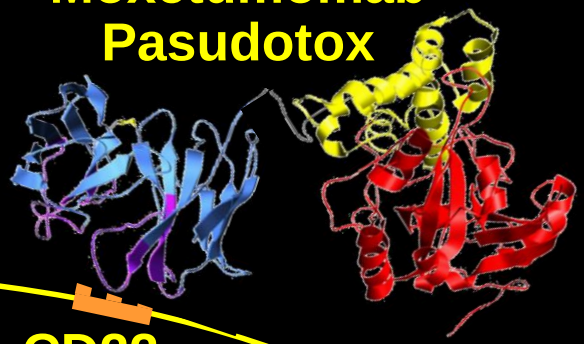
Rituximab



CD20

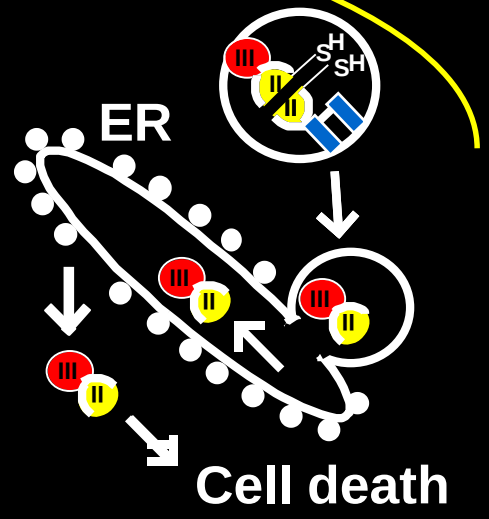
Plus

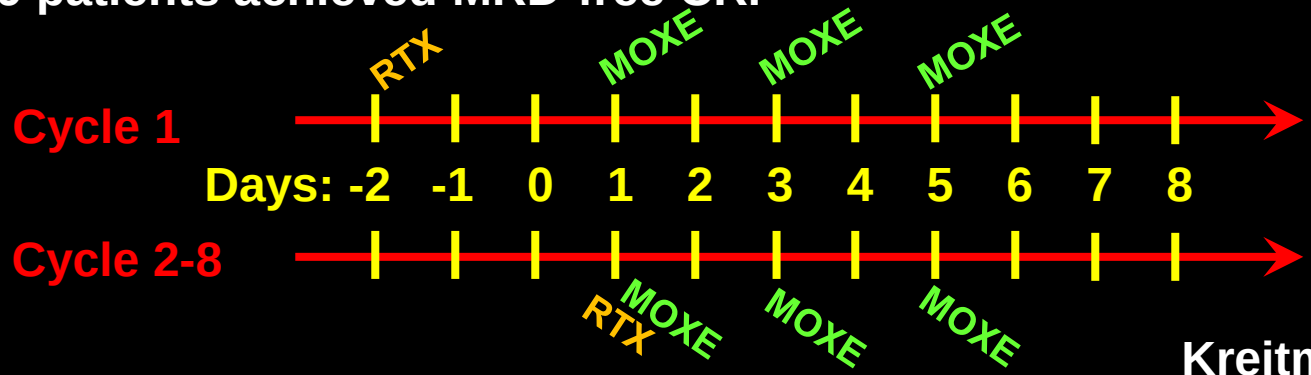
Moxetumomab Pasudotox



CD22

- 1st goal: Reduce normal B-cells, prevent ADA.
- 2nd goal: Reduce the amount of HCL so that Moxe can achieve CR more quickly.
- Test MoxeR first in multiply relapsed HCL.
- Give 4 cycles past MRD-free CR, maximum 8.
- Phase 1 trial results: 14 patients enrolled, 78% of 1st 9 patients achieved MRD-free CR.





Kreitman et al., ASCO, 2021

Conclusions

- Anti-CD22 recombinant immunotoxins including Moxe can achieve lifesaving complete remissions in patients with relapsed/refractory HCL.
- Minimal residual disease (MRD), which can lead to relapse, can be eliminated using consolidation cycles of Moxe
- Rituximab can be used to prevent immunogenicity and facilitate antitumor activity of Moxe.
- MoxeR is a chemo-free regimen which is highly active in multiply relapsed HCL, spares normal T-cells, and eliminates MRD.
- Moxe combined with anti-CD20 Mab could be tested earlier than 3rd-line, and in hematologic disorders other than HCL.

Immunotoxin development team

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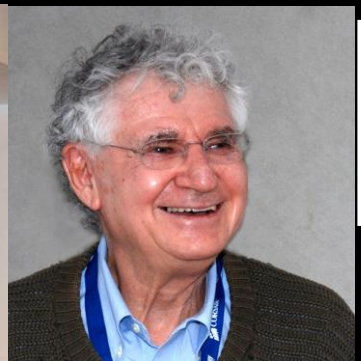

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