

Case #4 Chronic Lymphocytic Leukemia: New Advances in Research and Treatment

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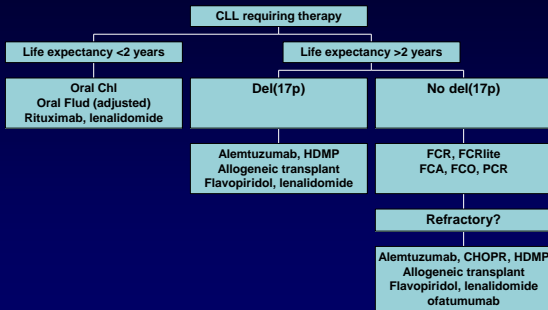


Indications for Treatment in Chronic Lymphocytic Leukemia (CLL)

- Progressive marrow failure: Development of, or worsening of, anemia and/or thrombocytopenia
- Massive/progressive/symptomatic splenomegaly or lymphadenopathy
- Progressive lymphocytosis: LDT <6 months
- Autoimmune cytopenia unresponsive to steroids
- Constitutional symptoms

Hallek M, et al. *Blood*. 2008;111(12):5446-5456.

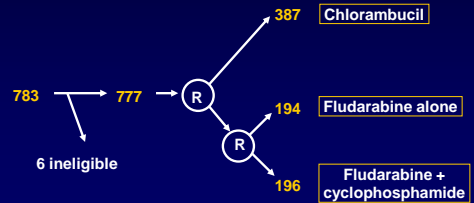
Treatment of CLL



Adapted from Kay NE, et al. *ASH Education Program Book* 2007:324-331.

LRF CLL4 Trial Design

- Randomized phase III trial in untreated CLL
 - Requiring therapy
 - Binet's progressive stage A, stage B, or stage C
- Recruitment between Feb 1999 and Oct 2004



Catovsky D, et al. *Lancet*. 2007;370(9583):230-239.

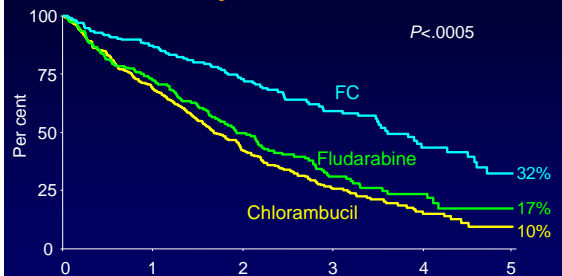
CLL4: Response by Treatment

	CR/nPR	PR	(ORR)	NR/PD	No. pts
ChI	29%	46%	(74%)	25%	305
F/FC	55%	35%	(90%)	10%	326
<i>P</i> < .001					
F	45%	37%	(82%)	18%	163
FC	64%	33%	(97%)	3%	163
<i>P</i> < .001					

Median follow-up: 32 months

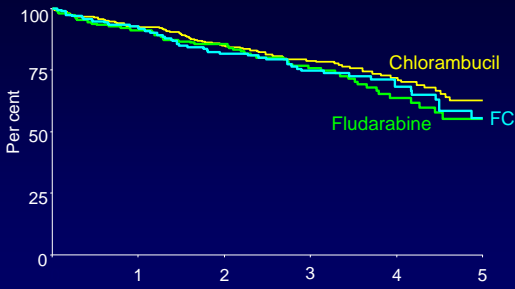
Catovsky D, et al. *Lancet*. 2007;370(9583):230-239.

CLL4: Progression-Free Survival by Treatment



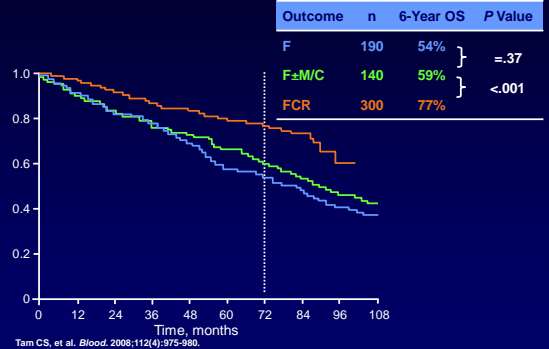
Catovsky D, et al. *Lancet*. 2007;370(9583):230-239.

CLL4: Overall Survival by Treatment



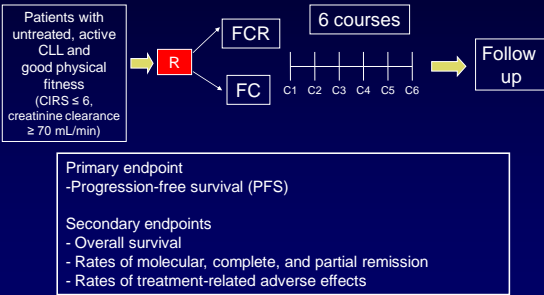
Catovsky D, et al. *Lancet*. 2007;370(9583):230-239.

Improved Efficacy of FCR (OS)



Tam CS, et al. *Blood*. 2008;112(4):975-980.

FCR: CLL8 Study Design



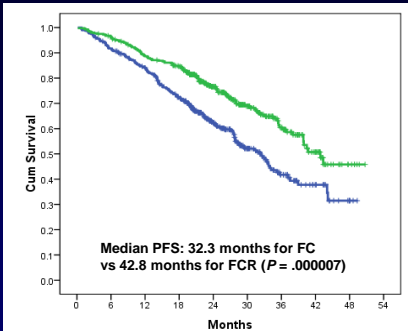
Hallek M, et al. *Blood*. 2008;112: Abstract 325.

CLL8: Response to Treatment

	FC	FCR	P
CR	22.9%	44.5%	<.01
CR _u	5.1%	3.3%	.22
CR _i	1.9%	2.6%	.52
nPR	4.9%	2.8%	.15
PR	50.4%	39.6%	<.01
SD	6.7%	3.9%	.08
PD	8.1%	3.3%	<.01

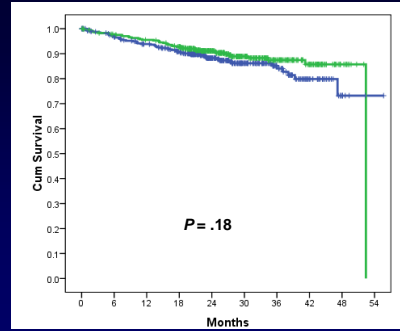
Hallek M, et al. *Blood*. 2008;112: Abstract 325.

CLL8: PFS (FCR vs FC)



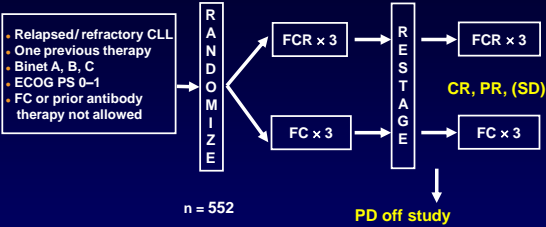
Hallek M, et al. *Blood*. 2008;112: Abstract 325.

CLL8: OS (FCR vs FC)



Hallek M, et al. *Blood*. 2008;112: Abstract 325.

REACH: FCR vs FC



Rituximab	Fludarabine	Cyclophosphamide
#1: 375 mg/m ² day 0		
#2-6: 500 mg/m ² day 1	25 mg/m ² , days 1-3	250mg/m ² , days 1-3

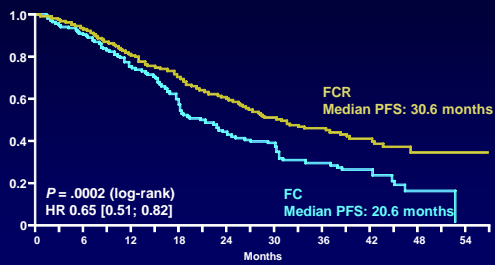
Robak T, et al. *Blood*. 2008;112: Abstract 1.

REACH: Response Rates

	FC, % n = 276	FCR, % n = 276	P
CR	13.0	24.3	.0007
PR/nPR	44.9	45.7	.8642
ORR	58.0	69.9	.0034
SD	22.1	17.0	n.d.
PD	5.4	2.5	n.d.
Not evaluable*	14.5	10.5	n.d.

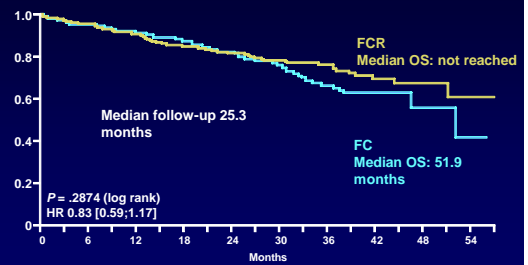
Robak T, et al. *Blood*. 2008;112: Abstract 1.

REACH: Progression-Free Survival



Robak T, et al. *Blood*. 2008;112: Abstract 1.

REACH: Overall Survival



Robak T, et al. *Blood*. 2008;112: Abstract 1.

CLL: Treatment of High-Risk Patients

“Patients with high-risk disease are those who can expect a significant reduction of life expectancy.”

EBMT criteria for allogeneic transplantation:

- Refractory to fludarabine combinations
- Early relapse following autologous transplantation
- Patients with p53 abnormalities requiring therapy

EBMT, European Group for Blood & Marrow Transplantation

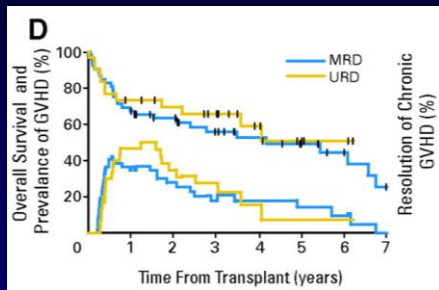
Dreger P, et al. *Leukemia*. 2007;21(1):12-17.

Reduced-Intensity Conditioning Allogeneic HCT

- Associated with 10% to 30% transplant-related mortality, but a 34% to 67% long-term progression-free survival in patients with high-risk disease
- Patients with high-risk CLL are prone to several transplant-related complications due to:
 - Old age
 - Frequent marrow involvement
 - Pre-existing immune suppression

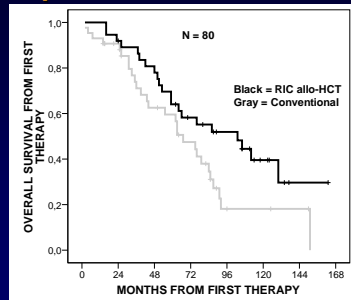
HCT, hematopoietic cell transplantation
 Delgado J, et al. *Blood*. 2009;114(13):2581-2588.

Reduced-Intensity Conditioning (RIC) Allogeneic HCT: Overall Survival



Sorror ML, et al. *J Clin Oncol*. 2009;26(30):4912-4920.

RIC Allo-HCT vs Conventional Therapies: OS From First Therapy



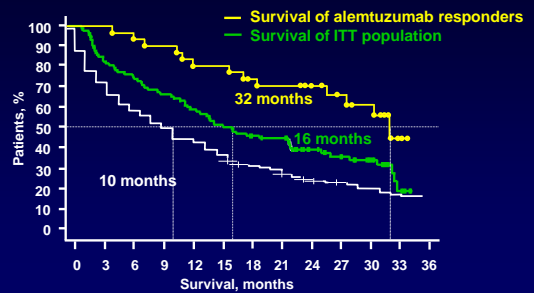
Delgado J, et al. *Ann Oncol* 2009 Jul 12. [Epub ahead of print]

Alternatives for Patients Not Eligible for Transplantation

- Alemtuzumab
- New monoclonal antibodies (ofatumumab, GA101)
- Lenalidomide
- Alvocidib (flavopiridol)
- High-dose methylprednisolone
- Bendamustine
- BCL-2 inhibitors (ABT-737, ABT-263.)

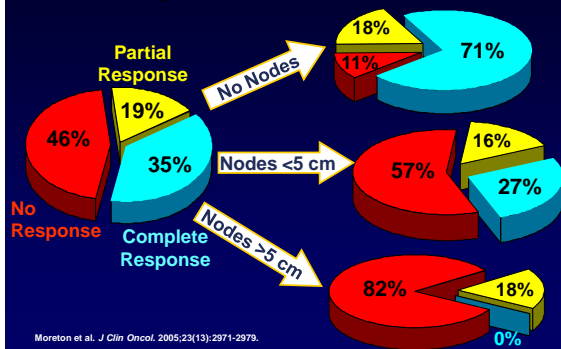
Delgado J, et al. *Blood Rev*. 2009;23(5):217-224.

Alemtuzumab Pivotal Trial: OS



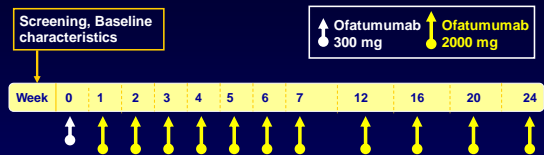
Keating MJ, et al. *Blood*. 2002;99(10):3554-3561.

Lymphadenopathy Predicts Poor Response to Alemtuzumab



Moreton et al. *J Clin Oncol*. 2005;23(13):2971-2979.

Ofatumumab in Refractory CLL: Treatment Schedule

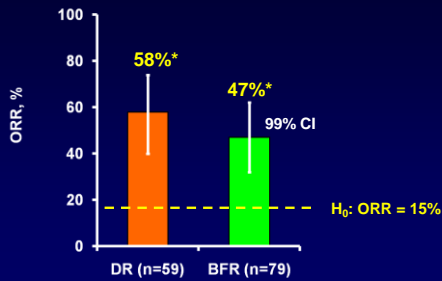


- Premedication:
 - Paracetamol (acetaminophen) 1 g PO or eq.
 - Antihistamine (cetirizine) 10 mg PO or eq.
 - Glucocorticoid (prednisolone) 100 mg IV or eq.

Median no. of infusions: 12 (range, 1-12) for both groups

Österborg A, et al. *Blood*. 2008;112: Abstract 328.

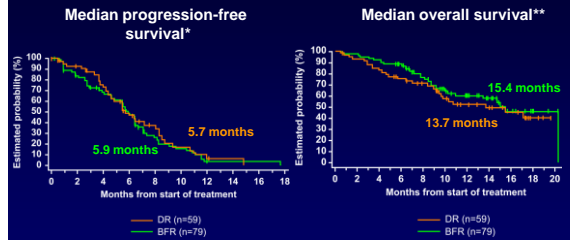
Ofatumumab in Refractory CLL: Objective Responses



*P<.0001 versus H₀ (two-sided exact test)

Österborg A, et al. *Blood*. 2008;112: Abstract 328.

Ofatumumab in Refractory CLL: Survival Outcomes



*Time from start of treatment to progression (assessed by IRC) or death
**Time from start of treatment to death

Österborg A, et al. *Blood*. 2008;112: Abstract 328.

Conclusions

- For patients with standard risk disease, the management should be tailored:
 - In elderly patients with significant comorbid conditions, the goal of therapy should be palliation of symptoms while minimizing toxicities
 - Younger patients should be offered modern chemoimmunotherapy combinations in order to achieve the best possible response
- High-risk patients should be referred for allo-HCT if they are eligible and have a donor. If not, a myriad of new compounds are quickly emerging, which can only lead to further improvements in outcome for such patients

Delgado J, et al. *Blood Rev*. 2009(5):217-224.

Research Agenda

- Development of less toxic therapeutic regimens for younger patients with standard-risk disease
- Development of more effective regimens for elderly patients with standard-risk disease
- Reduction of nonrelapse-mortality in patients undergoing allogeneic HCT
- Development of more effective therapies for patients with high-risk disease not eligible for allogeneic HCT

Delgado J, et al. *Blood Rev*. 2009(5):217-224.

Choice of therapy for this patient?

- Ofatumumab would be the preferred treatment, as it has proven efficacy in this clinical situation.
- Lenalidomide would be my second choice, but its efficacy is unknown in this context.
- Allogeneic SCT inappropriate due to old age.
- Alemtuzumab not advisable due to enlarged lymph nodes.
- Rituximab monotherapy unlikely to be effective in this clinical situation.