

# Chronic Lymphocytic Leukemia: Improving Outcomes With Novel Treatments

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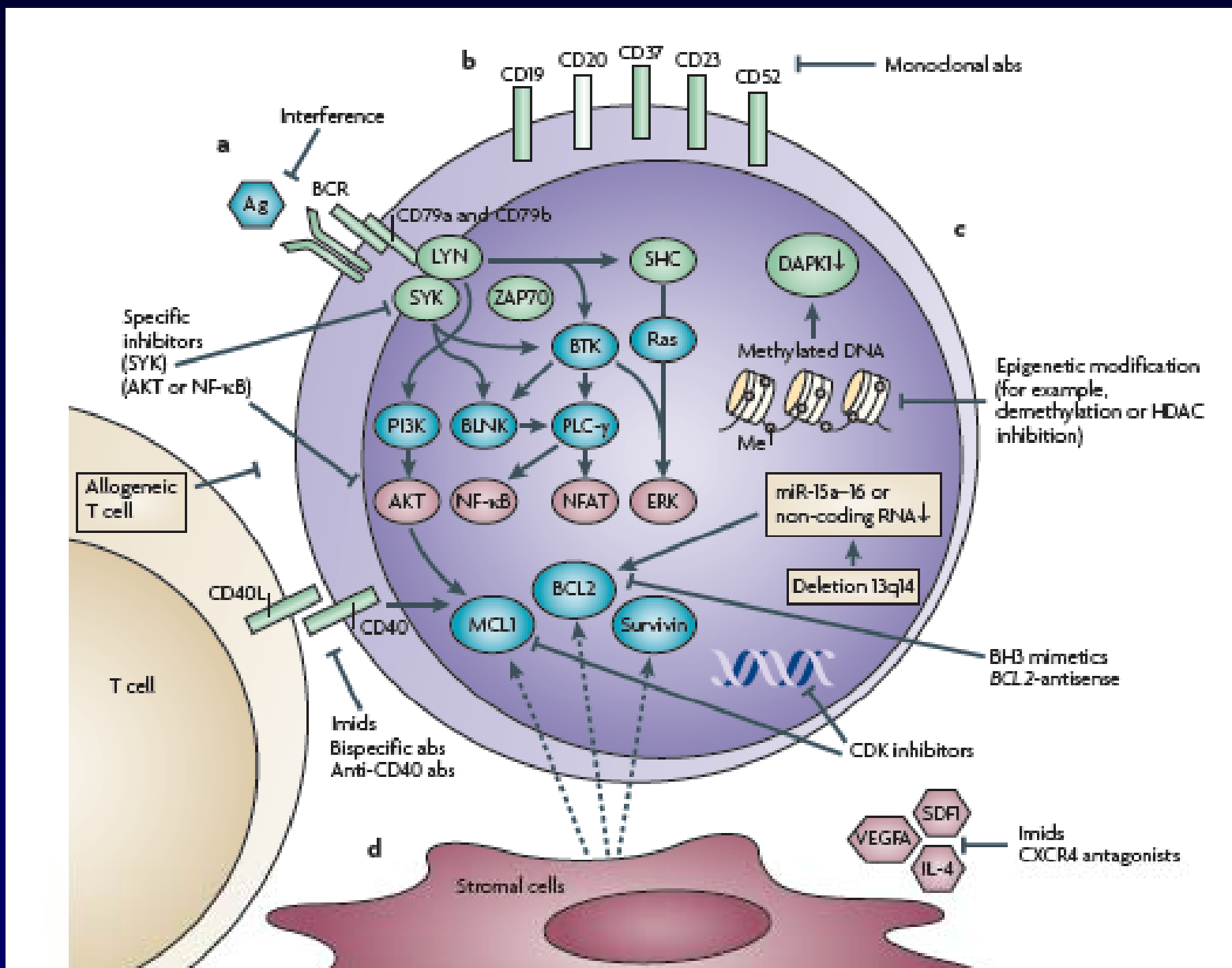
# **CLL: Practical Approach With Focus on Refractory CLL**

- **Prognostic factors**
- **First-line treatment**
- **Approach to F-refractory CLL**

# CLL: Diagnosis

- **CD19+, CD5+, CD23+, CD20 low**
- **Prognosis**
  - **IGHV**
  - **FISH**
  - **ZAP70**
  - **Serum markers**
  - **Stage**
- **Currently no benefit of early treatment (but important trial question)**

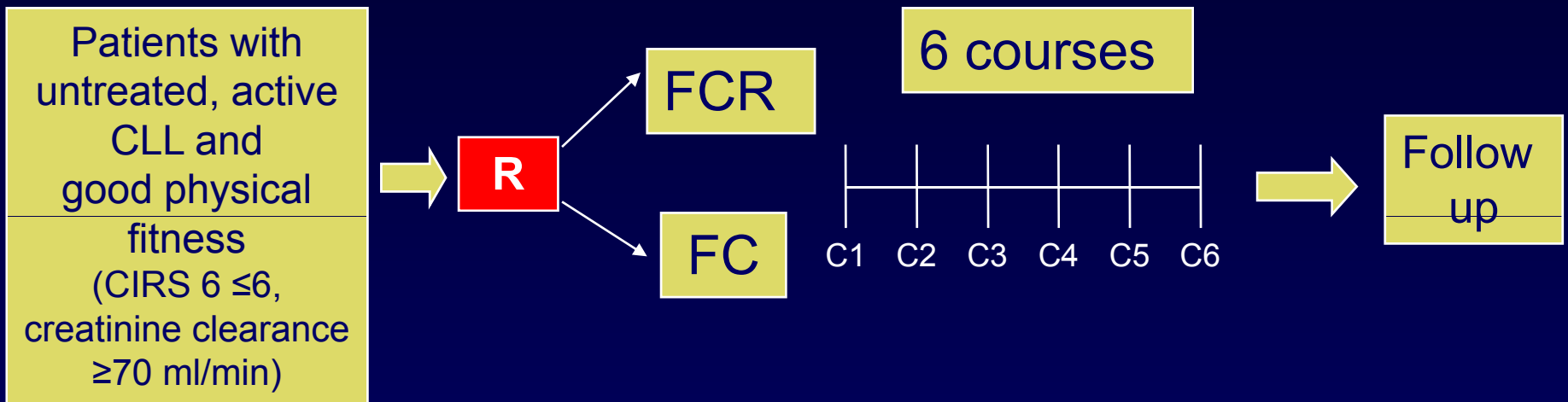
# Pathogenesis



# First-Line Treatment: Case

- **Treat with fludarabine + cyclophosphamide + rituximab (FCR)**
- **Chlorambucil with or without prednisone**
- **Rituximab weekly monotherapy**
- **Alemtuzumab**
- **Bendamustine**
- **CHOP with or without rituximab**

# CLL8 Study Design



Updated results of the 2nd analysis  
Median observation time 37.7 months.

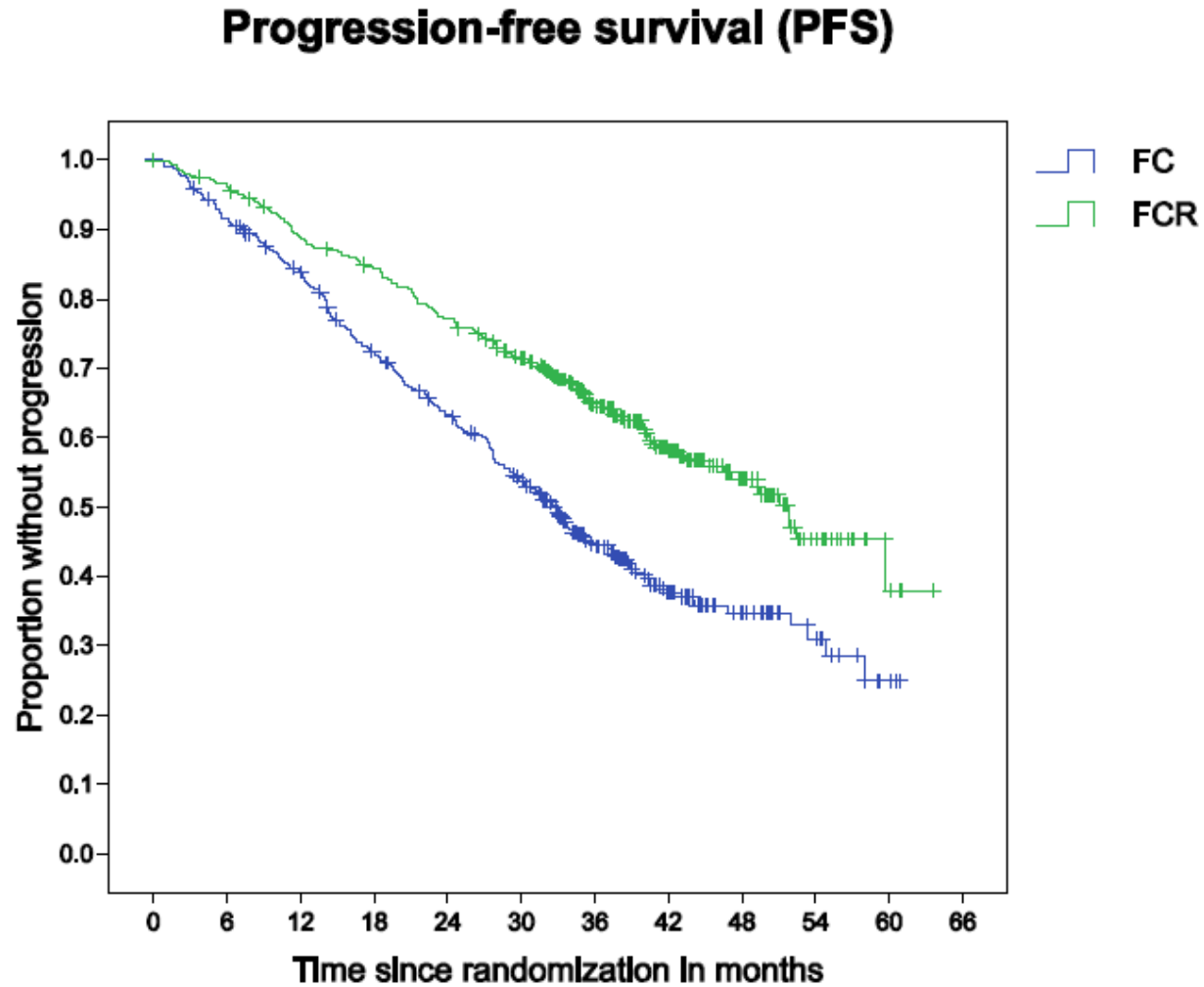
# CLL8: Best Response to Treatment

		FC	FCR
<b>CR*</b>		<b>21.8%</b>	<b>44.1%</b>
PR		66.6%	51.0%
<b>Overall response rate</b>		<b>88.4%</b>	<b>95.1%</b>
All included in PR	**CR <sub>u</sub>	4.6%	3.6%
	**CR <sub>i</sub>	1.9%	2.3%
	nPR	5.7%	3.4%
SD		<b>7.8%</b>	<b>3.9%</b>
PD		<b>3.8%</b>	<b>1.0%</b>

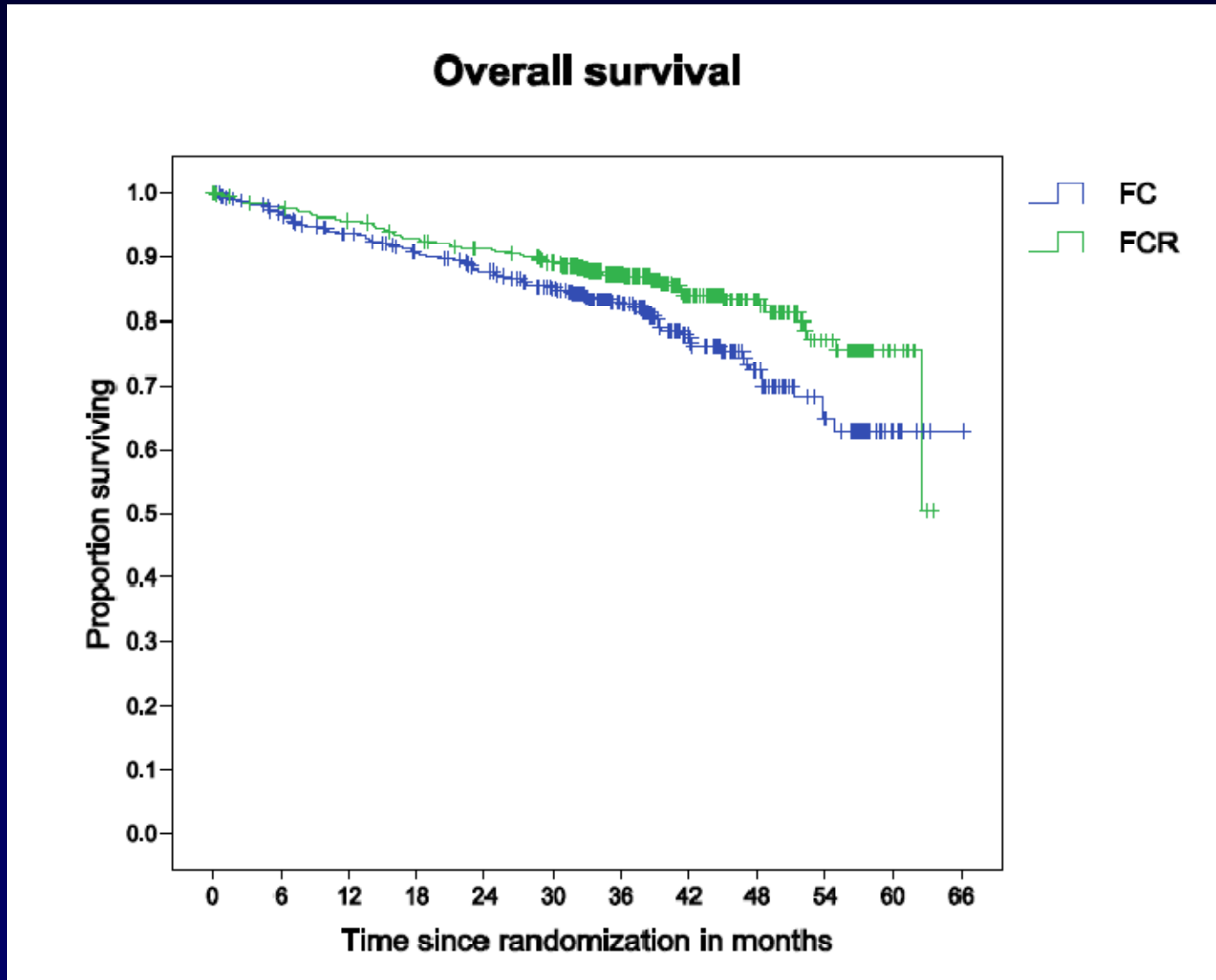
\*According NCI WG Criteria, confirmatory BM assessment performed up to 6 months after final restaging

**P<.01**

# CLL8: Progression-Free Survival

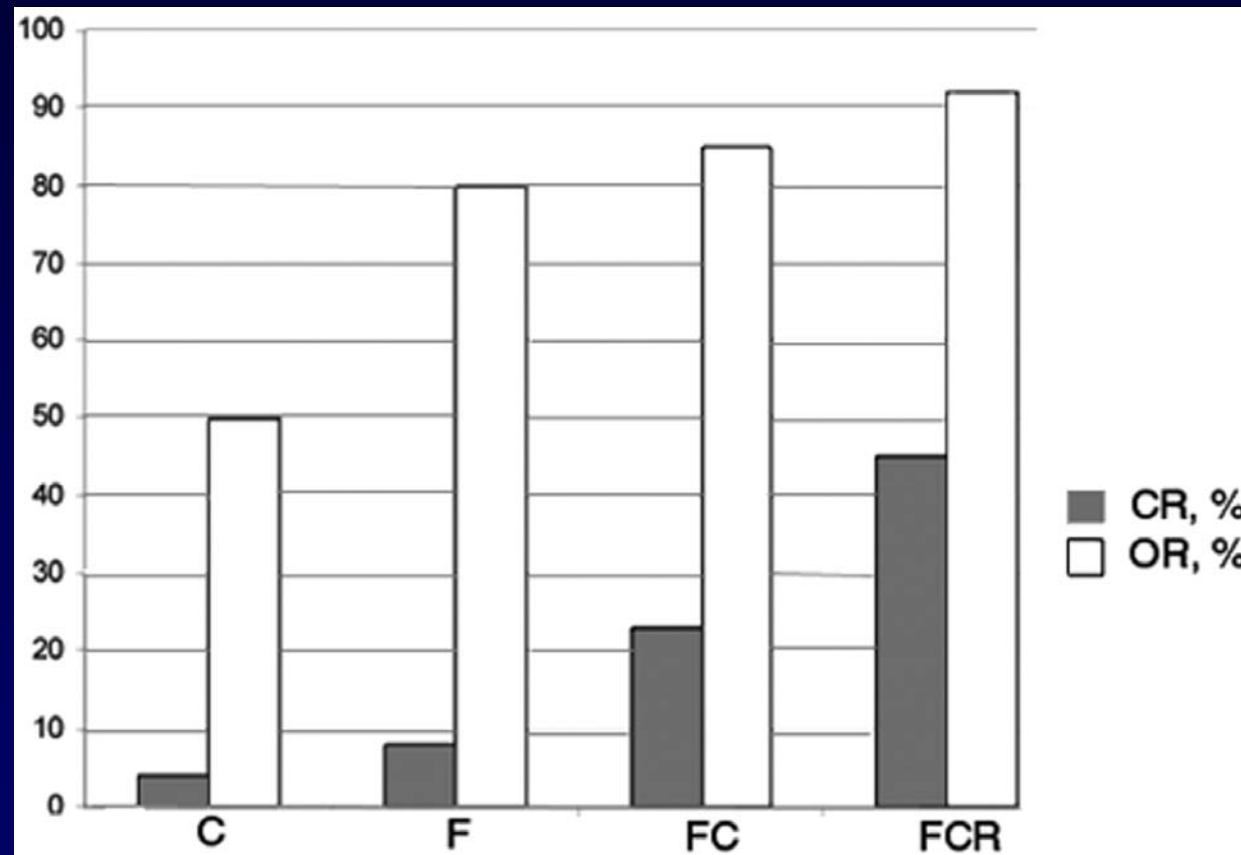


# CLL8: Overall Survival (OS)



Hallek M, et al. *Lancet*. 2010;376(9747):1164-1174.

# Treatment of CLL Over 20 Years

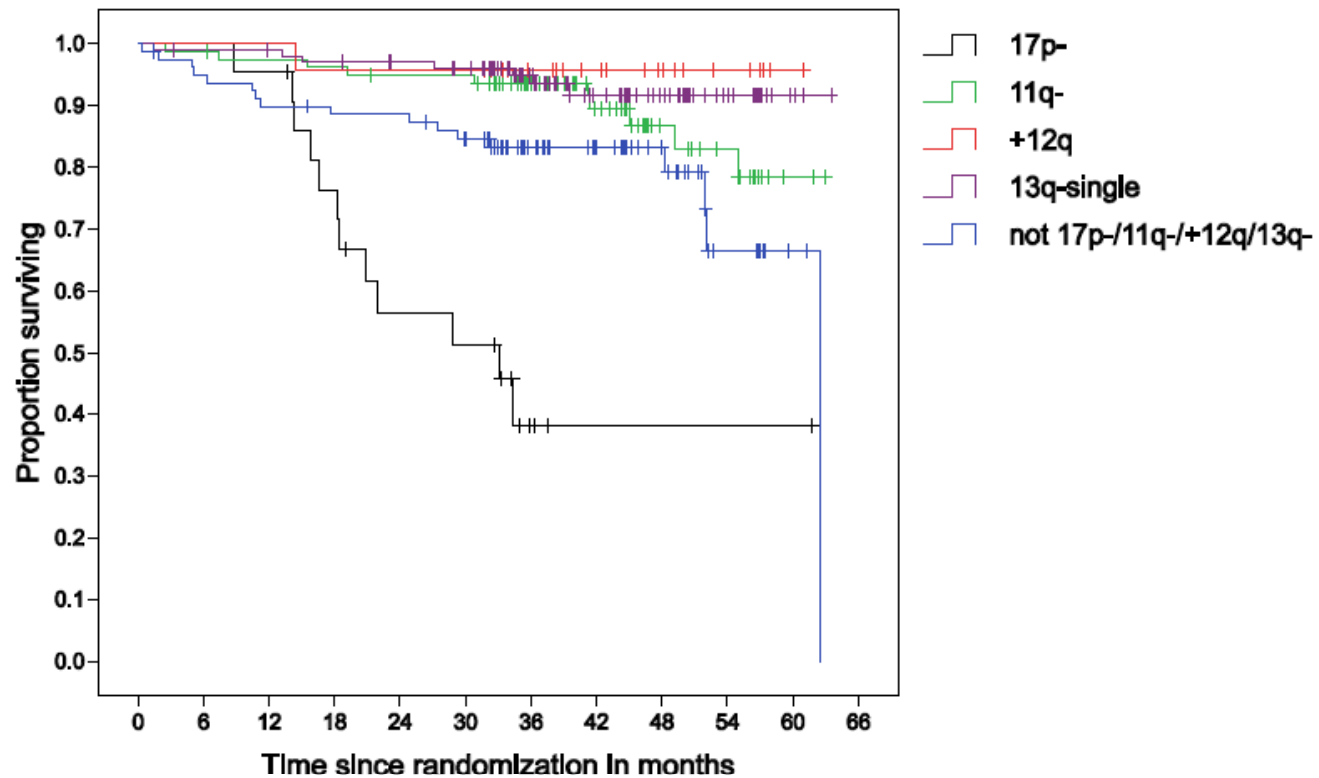


Overall survival



# CLL: Genetics

**FCR: Overall survival (FISH)**



# Cox Model (CLL8) OS

	HR	P
FCR arm	0.633	.019
<i>IGHV</i> unmutated	1.632	.035
<i>TP53</i> Mutation	2.634	.002
17p-	3.523	.0002

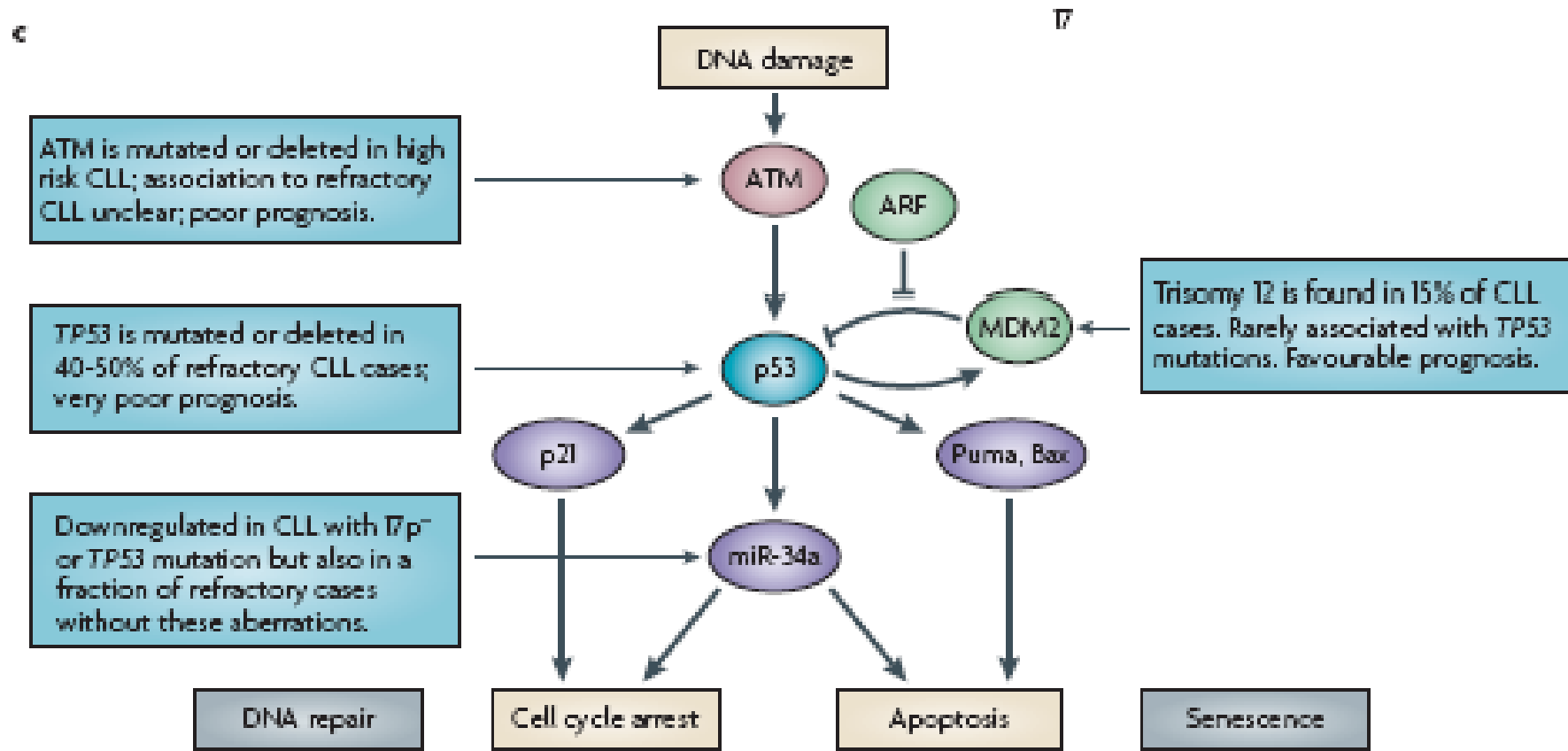
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Model including: FISH, age, Binet, treatment, *IGHV*, *TP53* mutation  
N = 580

# Alternatives to FCR First-Line

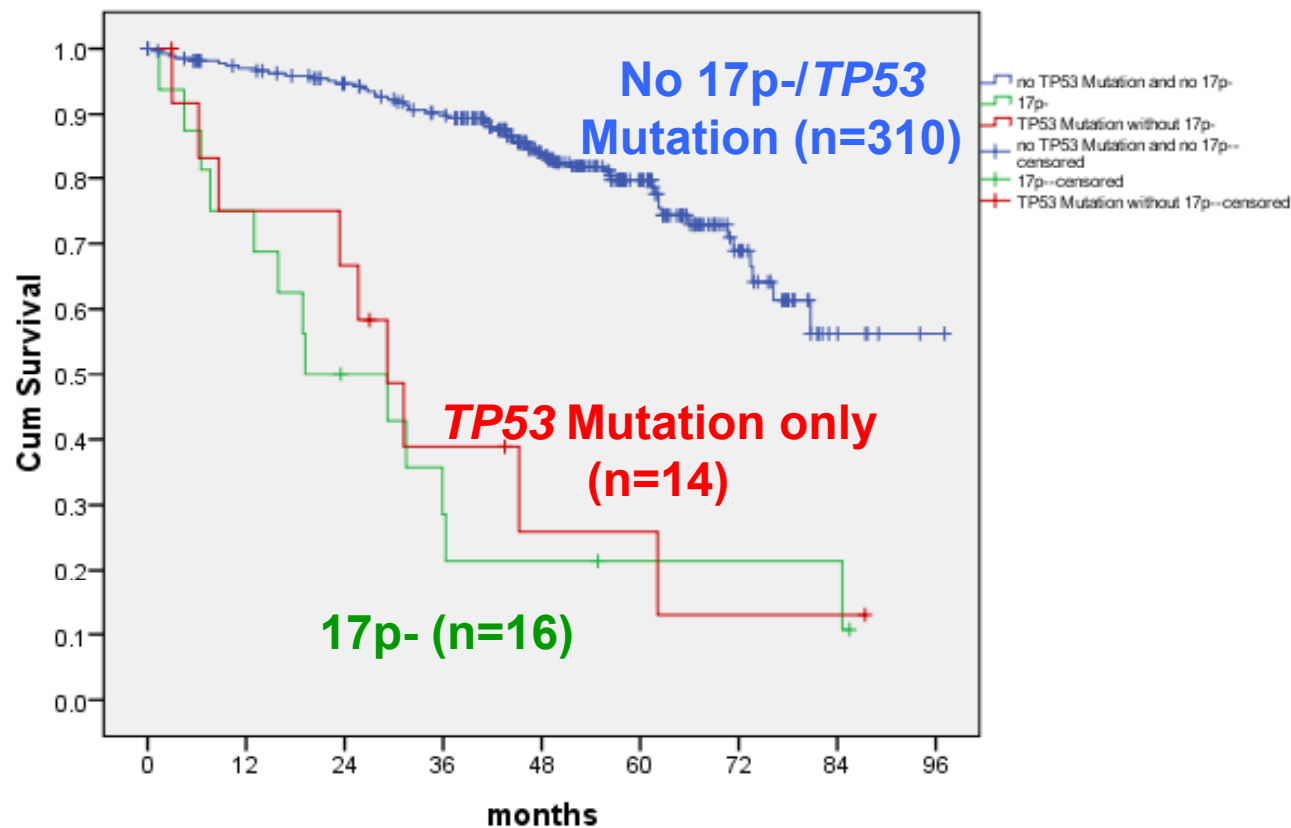
- **BR (Fischer et al, ASH 2009; CLL10)**
- **FCR-lite**
- **PCR**
- **R-Chlorambucil, Hillmen et al ASH 2009;  
CLL11 (Cbl; R-Cbl; GA101-Cbl)**

# Impaired p53 Pathway in CLL



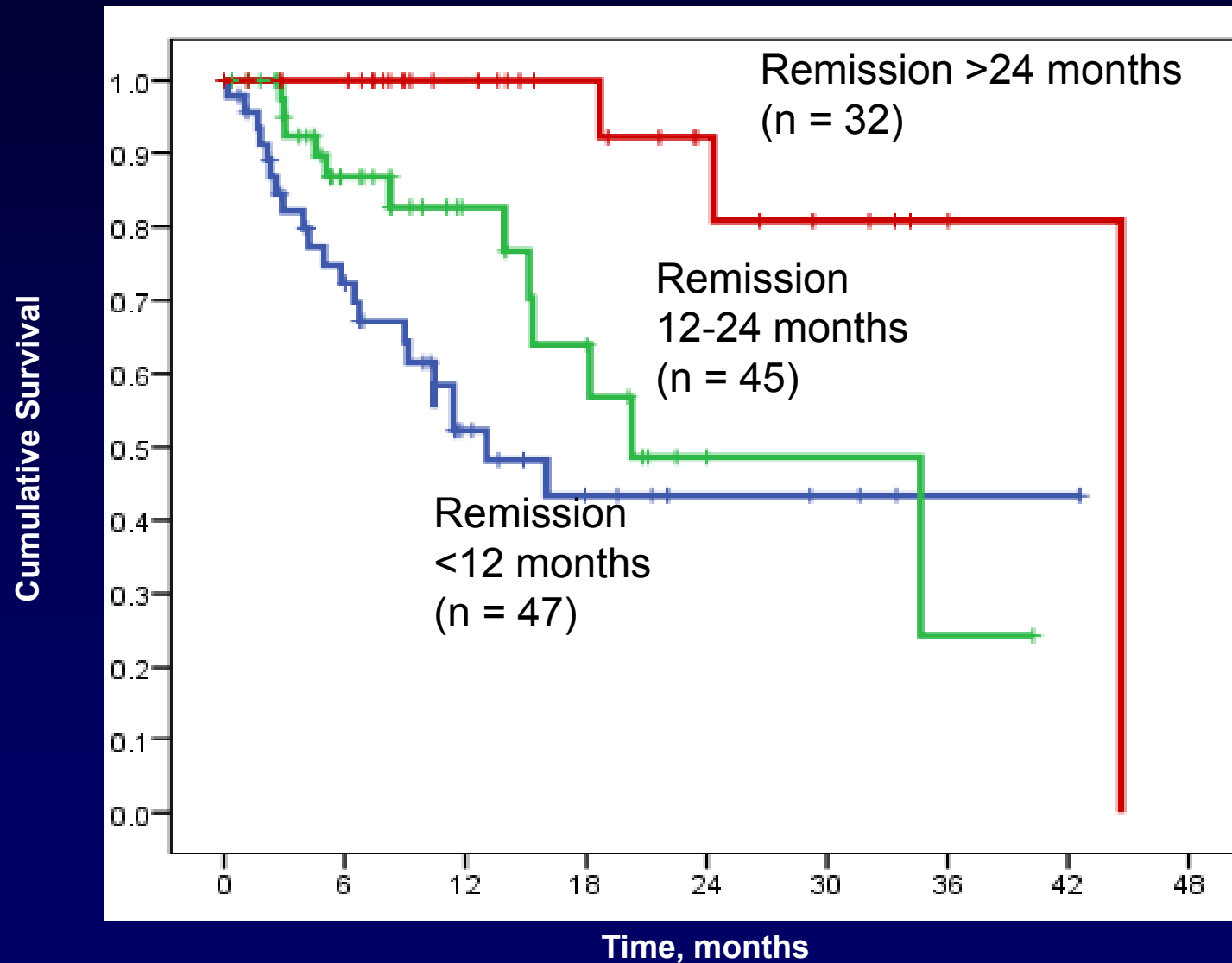
# Difficulties With First-Line Impact of *TP53* Mutation in CLL

## Overall survival CLL 4 (n=340)



# OS After Failure in CLL8

## Importance of PFS Length



Zenz T. Unpublished data, 2010.

Stilgenbauer S, Zenz T. *Hematology Am Soc Hematol Educ Program*. 2010; In press.

# F-Refractory CLL

	<b>Binet-A CLL1 n = 830</b>	<b>First-Line RX (F vs FC) CLL4 n = 326</b>	<b>F-Refractory CLL2H n = 104</b>
<b>13q- single</b>	<b>48</b>	<b>33</b>	<b>22</b>
<b>+12q</b>	<b>12</b>	<b>14</b>	<b>12</b>
<b>11q-</b>	<b>9</b>	<b>21</b>	<b>25</b>
<b>17p-</b>	<b>3</b>	<b>5</b>	<b>31</b>
<b>Unmutated IGHV</b>	<b>39</b>	<b>65</b>	<b>78</b>
<b>TP53 mutation</b>	<b>?</b>	<b>8</b>	<b>37</b>

# Treatments in Clinical Use Working Independent of p53

Alemtuzumab	Lozanski 04, Hillmen 07, Stilgenbauer 09	25% to 65%
Alemtuzumab + Steroids	Pettitt 06	5/6 response
Flavopiridol	Byrd 07	PR 9 of 19 patients (47%) with 17p-
Lenalidomide	Chanan Khan 07, Ferrajoli 08	50% PR, 13% ORR
Steroids	Thornton 03	5/10 response
Ofatumumab	Osterborg 08	44% (DR)

## **Allogeneic stem cell transplantation**

Lozanski G, et al. *Blood*. 2004;103(9):3278-3281. Hillmen P, et al. *J Clin Oncol*. 2007;25(35):5616-5623. Stilgenbauer S, et al. *J Clin Oncol*. 2009;27(24):3994-4001. Pettitt AR, et al. *Leukemia*. 2006;20(8):1441-1445. Byrd JC, et al. *Blood*. 2007;109(2):399-404. Chanan-Khan AA, et al. *Blood*. 2007;110: Abstract 3108. Ferrajoli A, et al. *Blood*. 2008;111(11):5291-5297. Thornton PD, et al. *Ann Hematol*. 2003;82(12):759-765. Osterborg A, et al. *Blood*. 2008;112: Abstract 328.

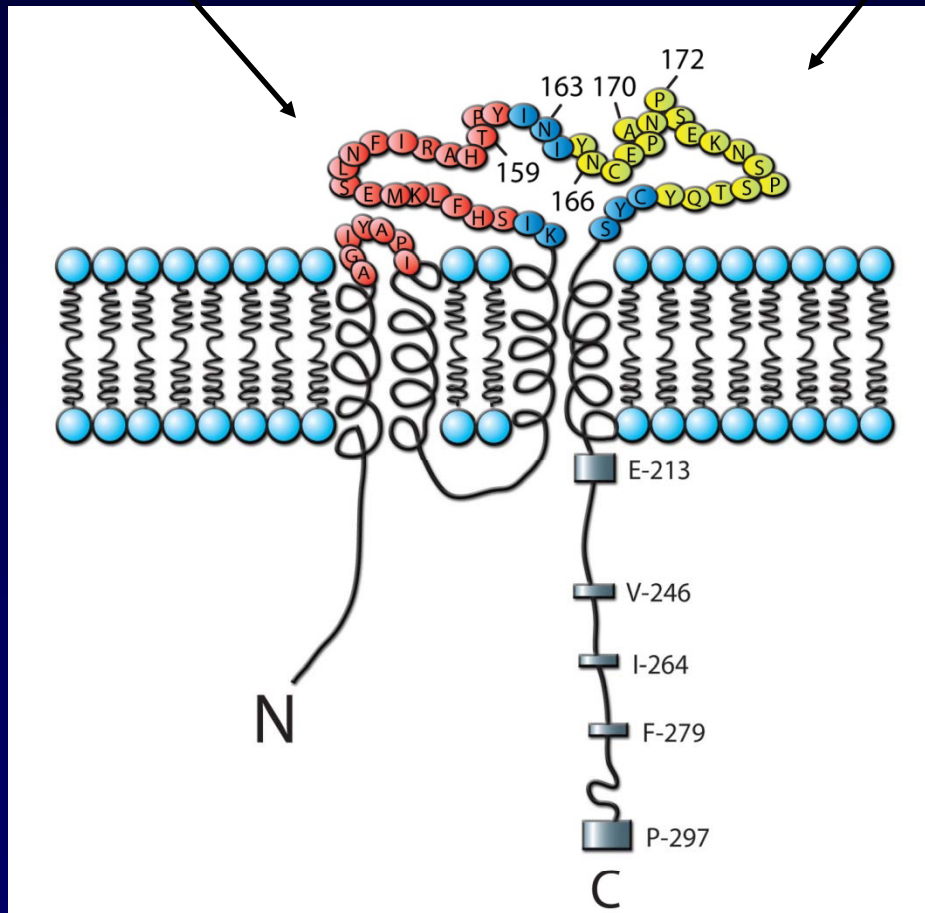
# **Single-Agent Ofatumumab, a Novel CD20 Monoclonal Antibody, Results in High Response Rates in Patients With Fludarabine-Refractory Chronic Lymphocytic Leukemia Also Refractory to Alemtuzumab or With Bulky Lymphadenopathy**

**A. Österborg, T. Kipps, J. Mayer, S. Stilgenbauer, C.D. Williams, A. Hellmann, T. Robak, R. Furman, P. Hillmen, M. Trneny, M.J. Dyer, S. Padmanabhan, M. Piotrowska, T. Kozak, G. Chan, R. Davis, N. Losic, J. Wilms, C. Russell and W.G. Wierda\* on behalf of the 406 Study Investigators**

# Ofatumumab: Characteristics<sup>1,2</sup>

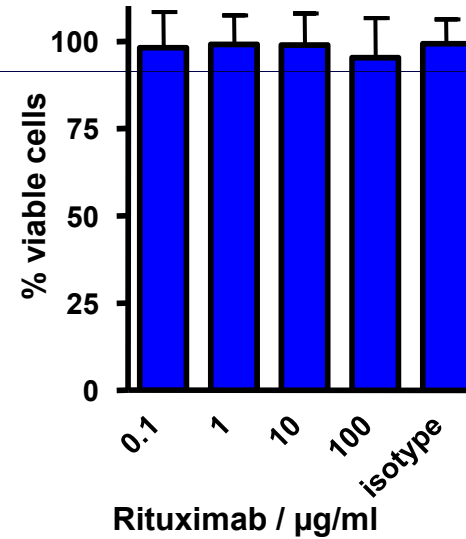
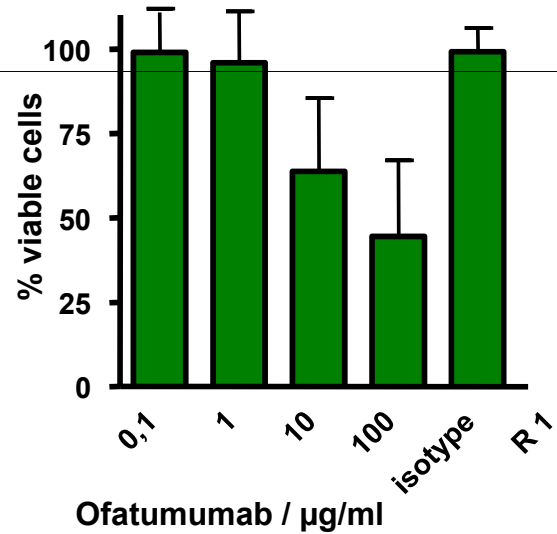
Ofatumumab  
binding site

Rituximab  
binding site



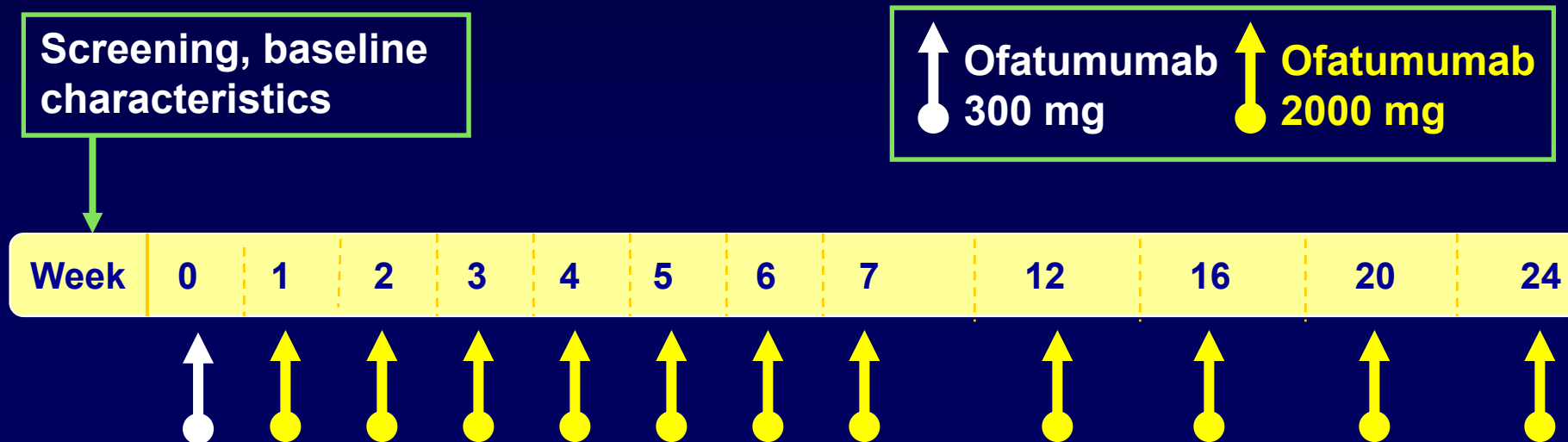
- Human CD20 monoclonal antibody (mAb)
- Binds to small loop of CD20
- Potent lysis of B cells
- More effective *in vitro* CDC versus rituximab
- Effective CDC of cells with low CD20 expression ( CLL cells)

# "New" CD20 Ab CDC Assay (n=18)



# Ofatumumab in Refractory CLL Study Design

- International, open-label, single-arm study conducted in Europe and the United States



# Ofatumumab in Refractory CLL Patient Population

## Fludarabine- and alemtuzumab-refractory (FA-ref)

- Refractory to fludarabine-containing regimen ( $\geq 2$  cycles)
- Refractory to alemtuzumab-containing regimen ( $\geq 12$  doses)

## Fludarabine-refractory with bulky lymph nodes (BF-ref)

- Refractory to fludarabine-containing regimen ( $\geq 2$  cycles)
- Less suitable for alemtuzumab due to bulky nodes ( $> 5$  cm)

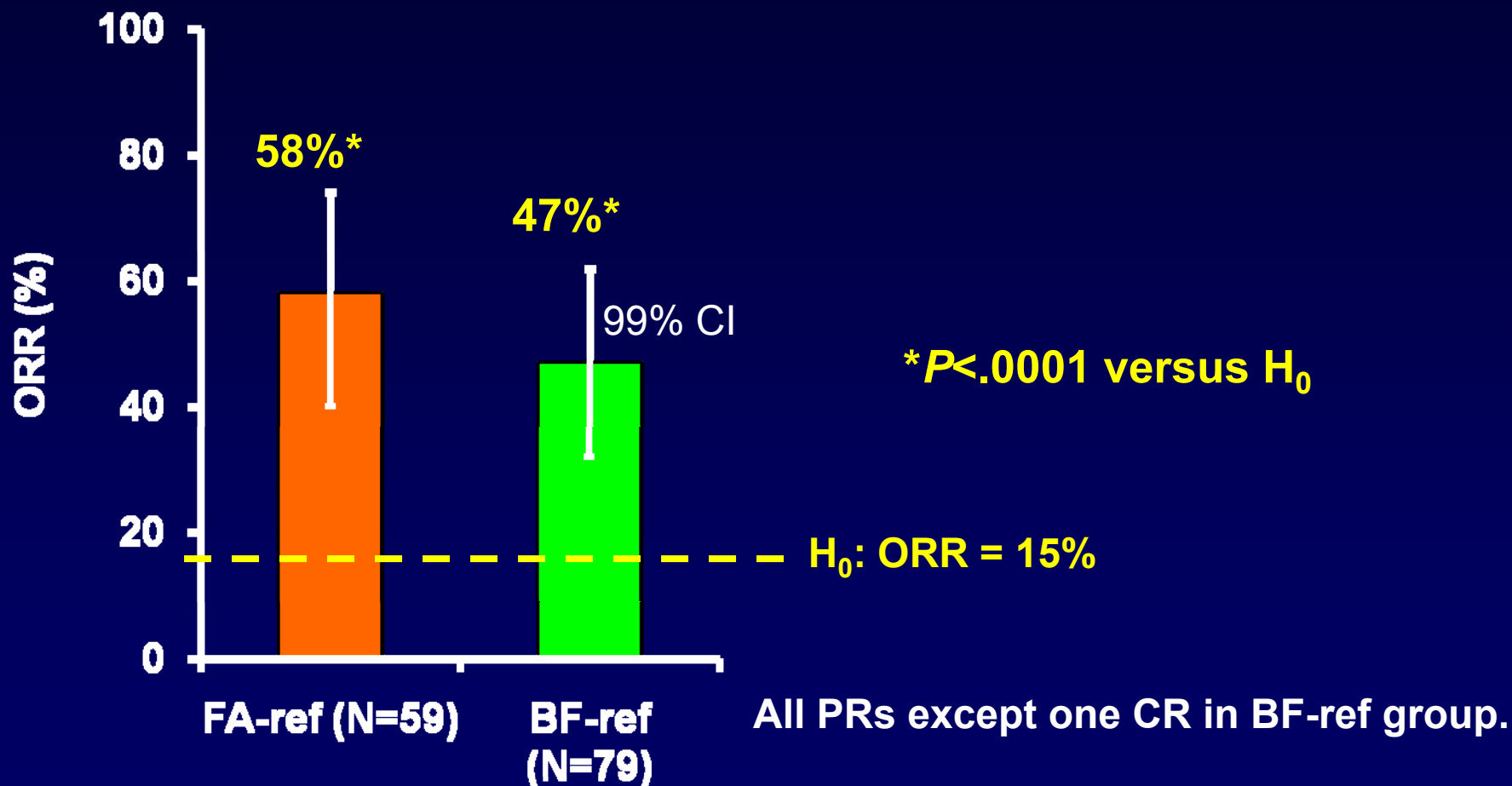
- No upper age limit ( $\geq 18$  years of age)
- ECOG performance status 0 to 2
- No exclusions for cytopenias

# Ofatumumab in CLL Refractory to Both Fludarabine and Alemtuzumab

	FA-ref (n = 59)	BF-ref (n = 79)
<b>ORR, % (99% CI)</b>	51 (34, 68)	44 (30, 59)
Complete response	0	1
Partial response	51	43
Stable disease	39	43
Progressive disease	3	10
<b>Time to next CLL therapy, mo</b>	9.0 (7.3, 10.7)	7.9 (7.1, 9.3)
<b>Overall survival, mo</b>	13.7 (9.4, NR)	15.4 (10.2, 20.2)

Osterborg, et al. *Blood*. 2008;112: Abstract 328. Wierda W, et al. *J Clin Oncol*.2010;28(10):1749-1755.

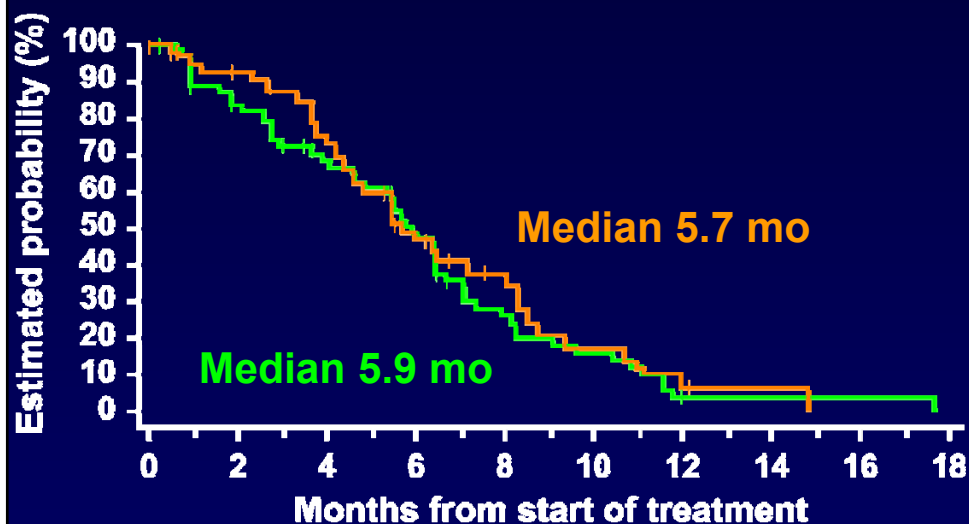
# Ofatumumab in Refractory CLL Overall Response Rate



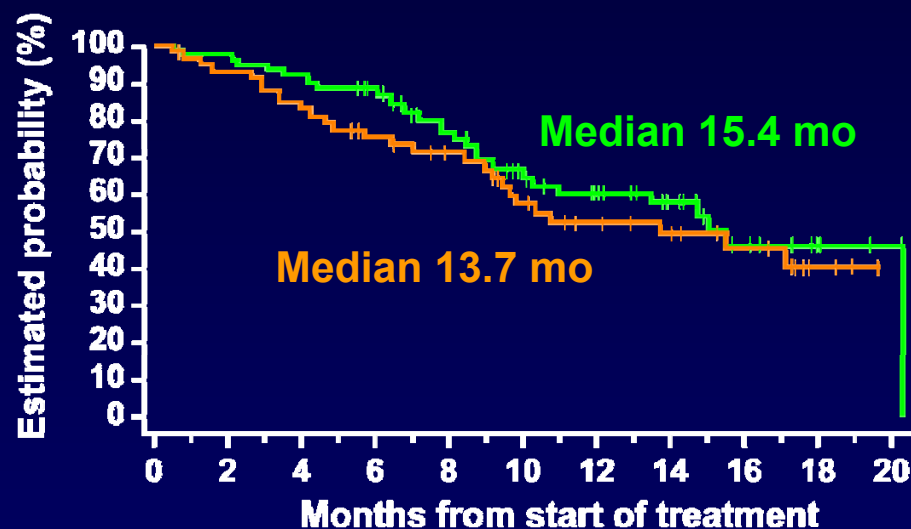
\*The null hypothesis of ORR = 15% was tested against the corresponding two-sided alternative hypothesis ORR $\neq$ 15% using an exact test.

# Ofatumumab in Refractory CLL Survival Outcomes

## Progression-free survival\*



## Overall survival\*\*



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

\*\*Time from start of treatment to death.

# Choice of Therapy and Why?

Chemotherapy “refractory”

Extensively enlarged lymph nodes

Does not desire any additional chemotherapy

Overall goal: palliation

**Lenalidomide monotherapy (ORR~20-30%)**

**Alemtuzumab monotherapy (ORR~33%)**

**Rituximab monotherapy (ORR~20%)**

**Ofatumumab monotherapy (ORR ~50%)**

**Allogeneic SCT (2<sup>nd</sup> step in younger patients)**

# Definitions and Corresponding Treatment Algorithms for Ultra High-Risk CLL

17p- / TP53 mutation  
(treatment indication,  
1st or > treatment line)  
**F-refractory CLL**

Refractory to  
fludarabine and  
alemtuzumab

Short PFS <24 (-36) months after FCR  
(or similar regimen, eg, PCR, FR, BR),  
and absence of 17p- / TP53 mutation  
(exclude clonal evolution by retesting)



## Option 1: Treatment in clinical trial

Clinical trial of novel agents / combinations with evidence for activity

## Option 2: Standard treatment (outside trial):

Alemtuzumab

Ofatumumab

Prior response to  
FCR: CR / nPR:  
→FCR  
(ORR ~ 70%)

Prior response to FCR  
(or similar) PR:  
**Alternative regimens**  
(ORR with FCR ~30%)



**Consolidation (if PR / CR achieved):**  
Fit patients: allo-SCT after reduced-intensity conditioning  
Patients not eligible for allo-SCT: consolidation therapy in clinical trial