

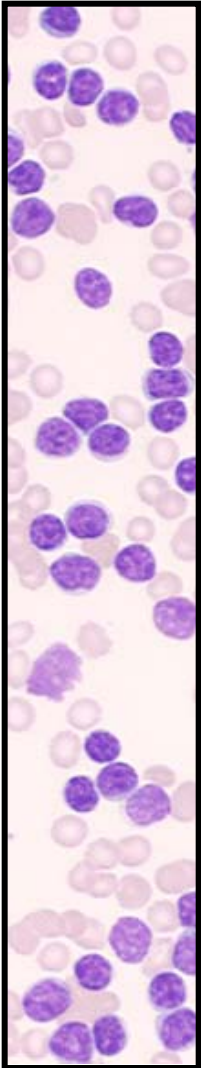
# **Molecular Markers to Guide Therapy**

## **- Chronic Lymphocytic Leukaemia -**

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**Ulm University**

# Chronic Lymphocytic Leukaemia (CLL)



- **Most common leukaemia in adults**
- **Diagnosis straightforward**
  - **CD19+/CD5+/CD23+ lymphocytosis**
- **Molecular pathogenesis unresolved**
  - **Microenvironment, B cell receptor, Genetics**
- **Clinical course highly variable**
  - **Survival times ranging from months to decades**
  - **Wide range of treatments (watch & wait – SCT)**

# Prognostic Factors

1. Age
2. Gender
3. Stage (Rai, Binet)
4. Comorbidity
5. Performance Status
6. LDT
7. BM-Pattern
8. WBC
9. LDH
10.  $\beta$ 2-MG
11. Thymidine Kinase
12. sCD23
13. Genomic Aberrations
14. IGHV Mutation Status
15. V3-21 Usage
16. SNPs (BCL2, MDM2)
17. CD38
18. ZAP-70
19. LPL
20. ADAM29
21. MRD
22. ...

# Treatment Options

1. Watch and wait
2. Chlorambucil
3. COP, CHOP
4. Fludarabine (F)
5. Bendamustine (B)
6. F-combinations (FC, FCM)
7. Alemtuzumab (Alem)
8. Rituximab (R)
9. Ofatumumab (O)
10. GA-101 (G)
11. Chemo+Ab (FCR, BR, etc.)
12. Thalidomide
13. Lenalidomide
14. Flavopiridol
15. Depsipeptide
16. Forodesine
17. Oblimersen
18. ABT263
19. CAL101
20. Allogeneic SCT
21. Blinatumomab
22. ...

# IWCLL Guidelines

Hallek et al. Blood 2008

**Table 1. Pretreatment evaluation of patients with CLL**

Diagnostic test	General practice*	Clinical trial
<b>Tests to establish the diagnosis</b>		
Complete blood count and differential count	Always	Always
Immunophenotyping of lymphocytes	Always	Always
<b>Assessment before treatment</b>		
History and physical, performance status	Always	Always
Complete blood count and differential	Always	Always
Marrow aspirate and biopsy	Desirable	Desirable
Serum chemistry, serum immunoglobulin, direct antiglobulin test	Always	Always
Chest radiograph	Always	Always
Infectious disease status	Always	Always
<b>Additional tests before treatment</b>		
Cytogenetics (FISH) for del(13q), del(11q), del(17p), trisomy 12, del(6q) in the peripheral blood lymphocytes	Desirable	Always
IgVH mutational status, ZAP-70, and CD38	NGI	Always
CT scan of chest, abdomen, and pelvis	NGI	Desirable
MRI, lymphangiogram, gallium scan, PET scans	NGI	NGI
Abdominal ultrasound*	Possible	NGI

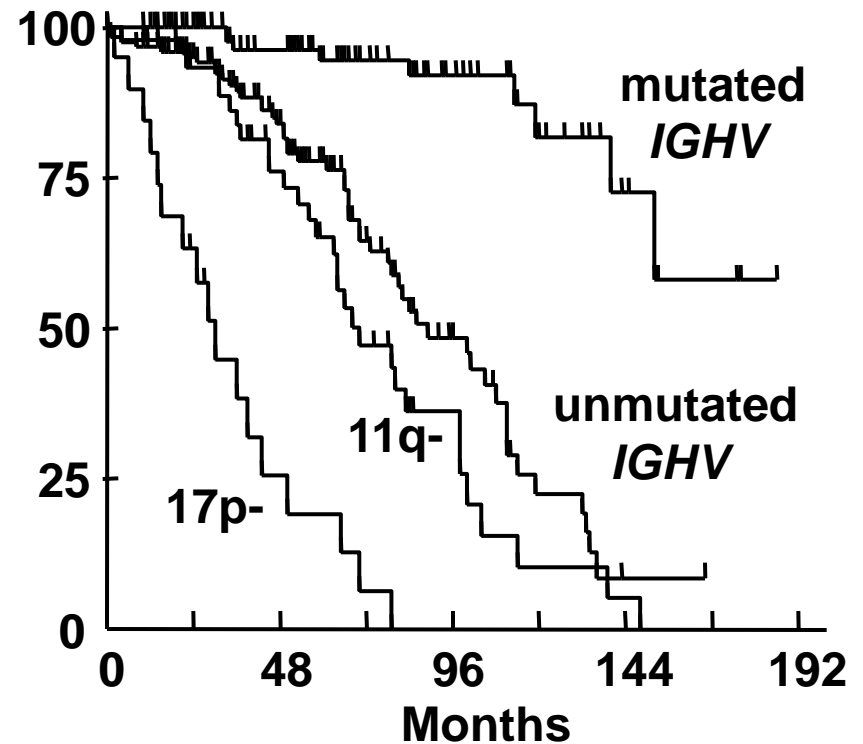
# Genotype, Phenotype and Outcome

11q Deletion and  
Lymphadenopathy



*Stilgenbauer et al. PNAS 1996;*  
*Döhner et al. Blood 1997*

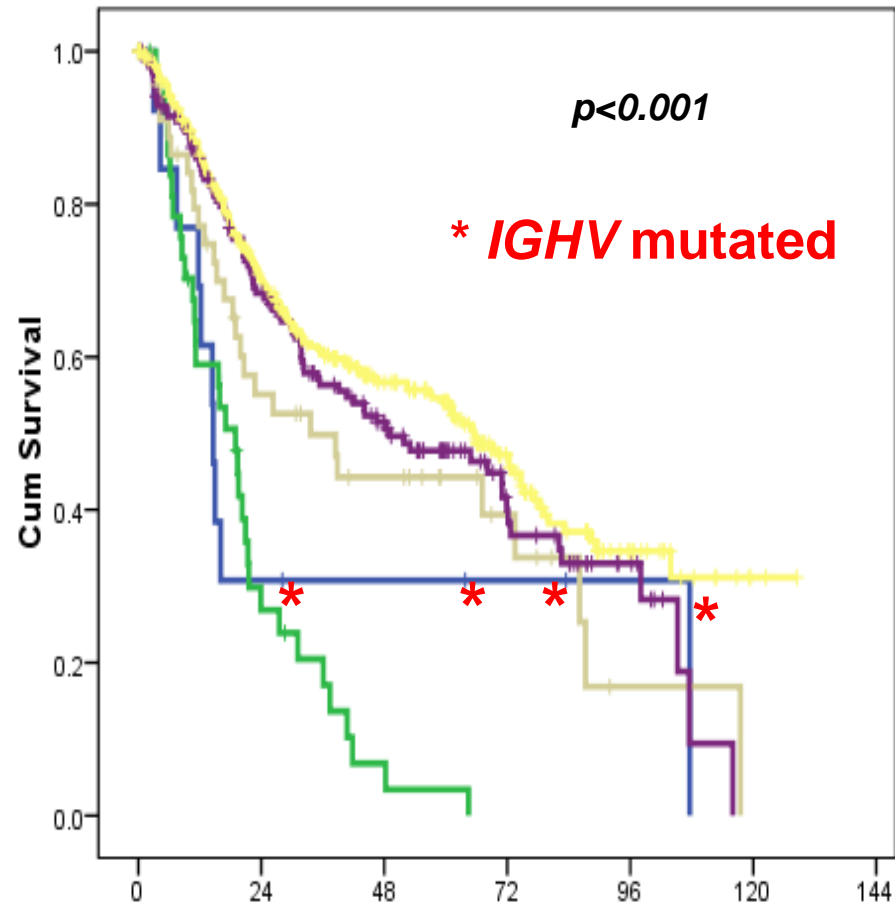
Overall survival (n=300)



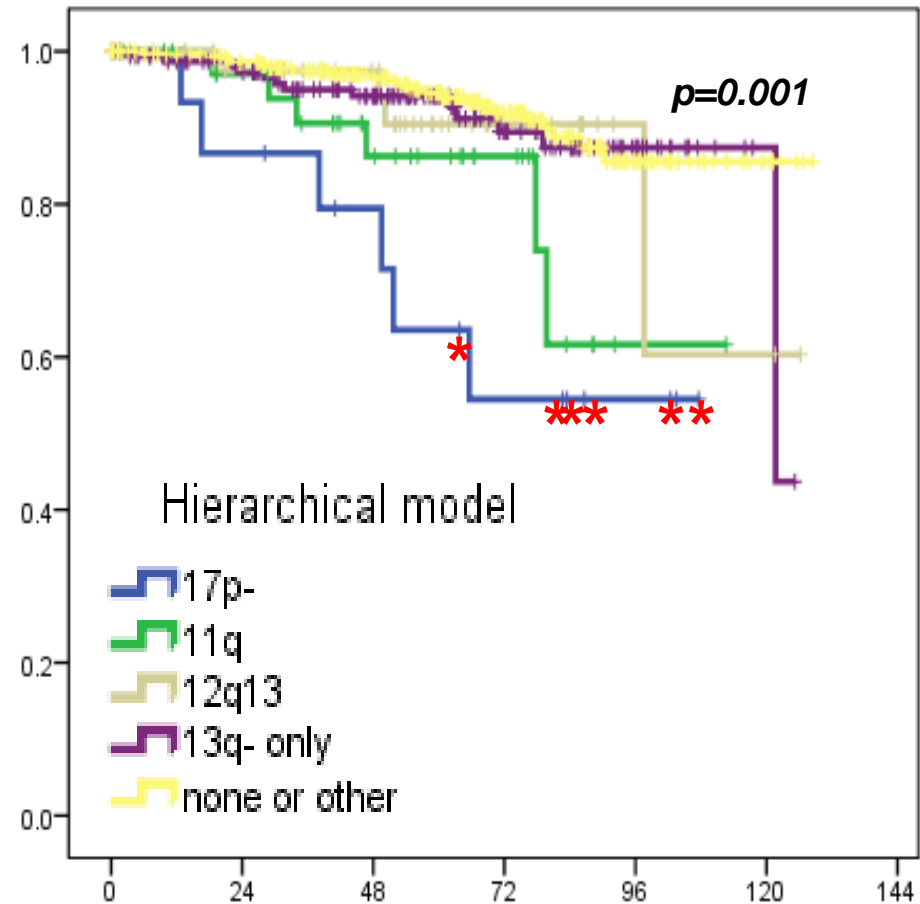
*Kröber et al. Blood 2002*

# Binet-A: CLL1 Trial of the GCLLSG Genomic Aberrations

## PFS

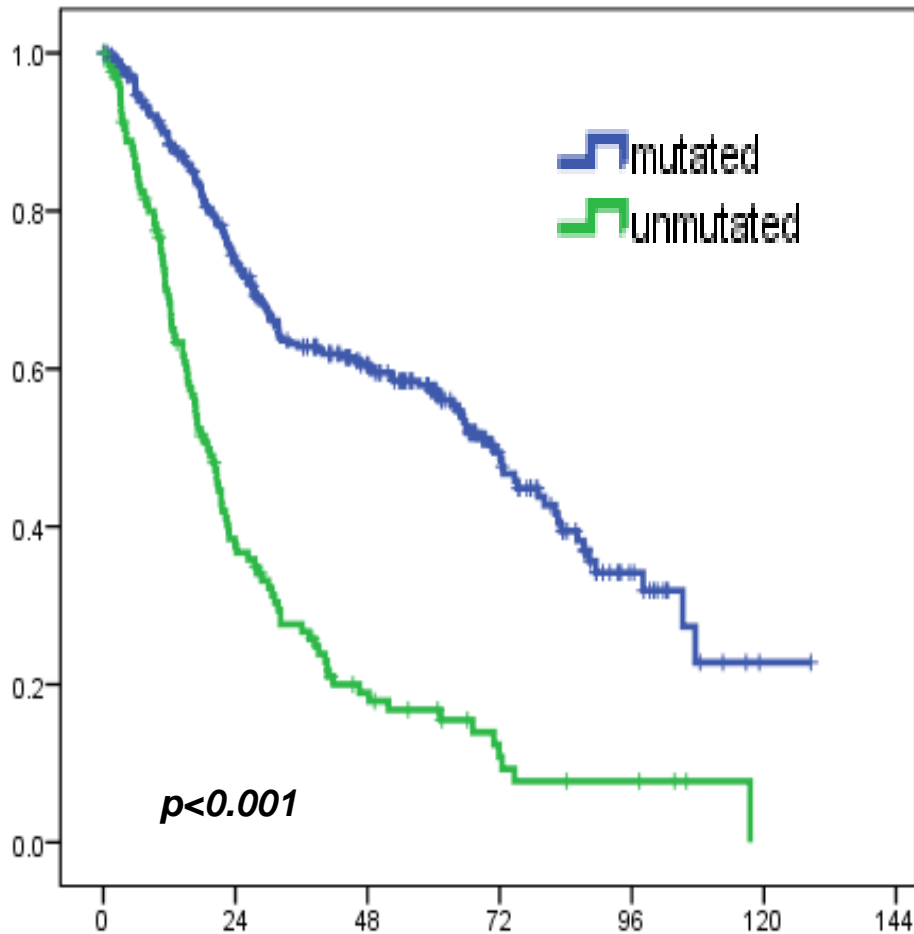


## OS

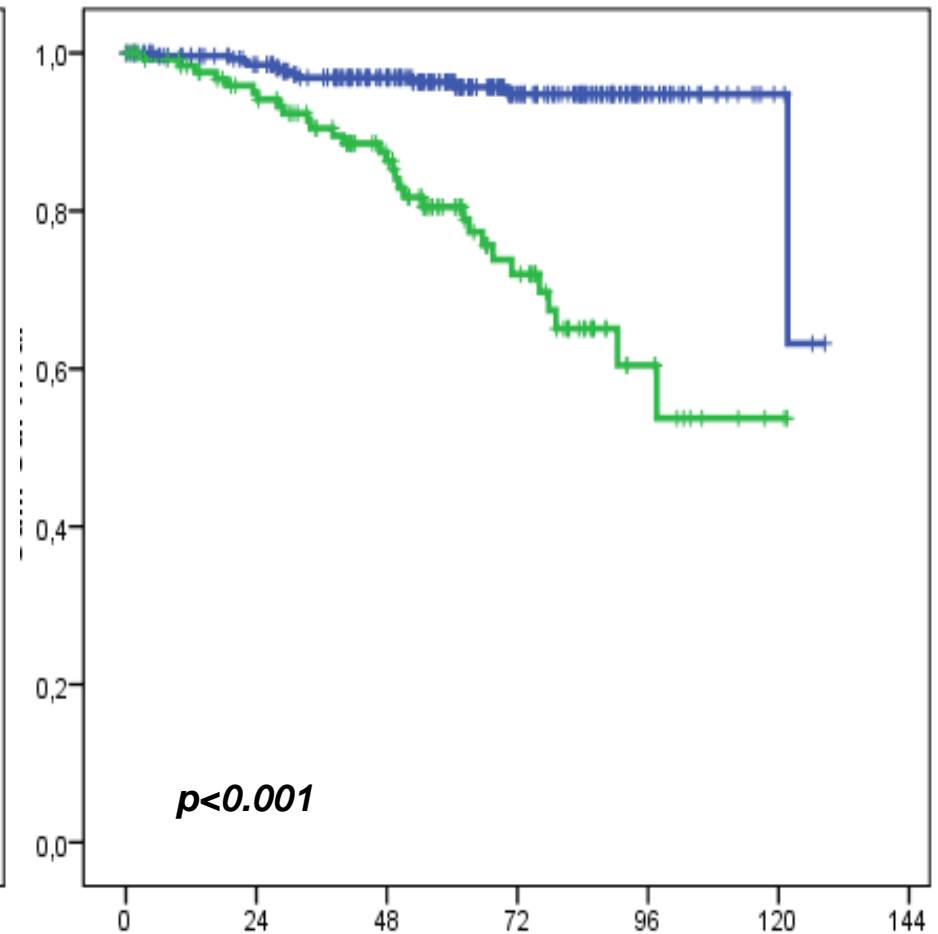


# Binet-A: CLL1 Trial of the GCLLSG IGHV Mutation Status

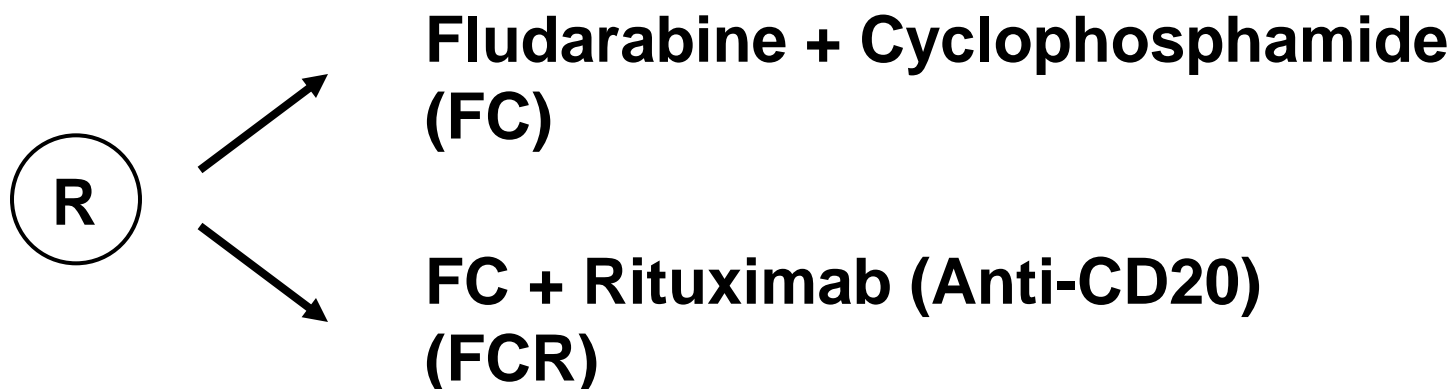
## PFS



## OS



# International CLL8 Trial (n=817) First-line Treatment (Binet B and C)



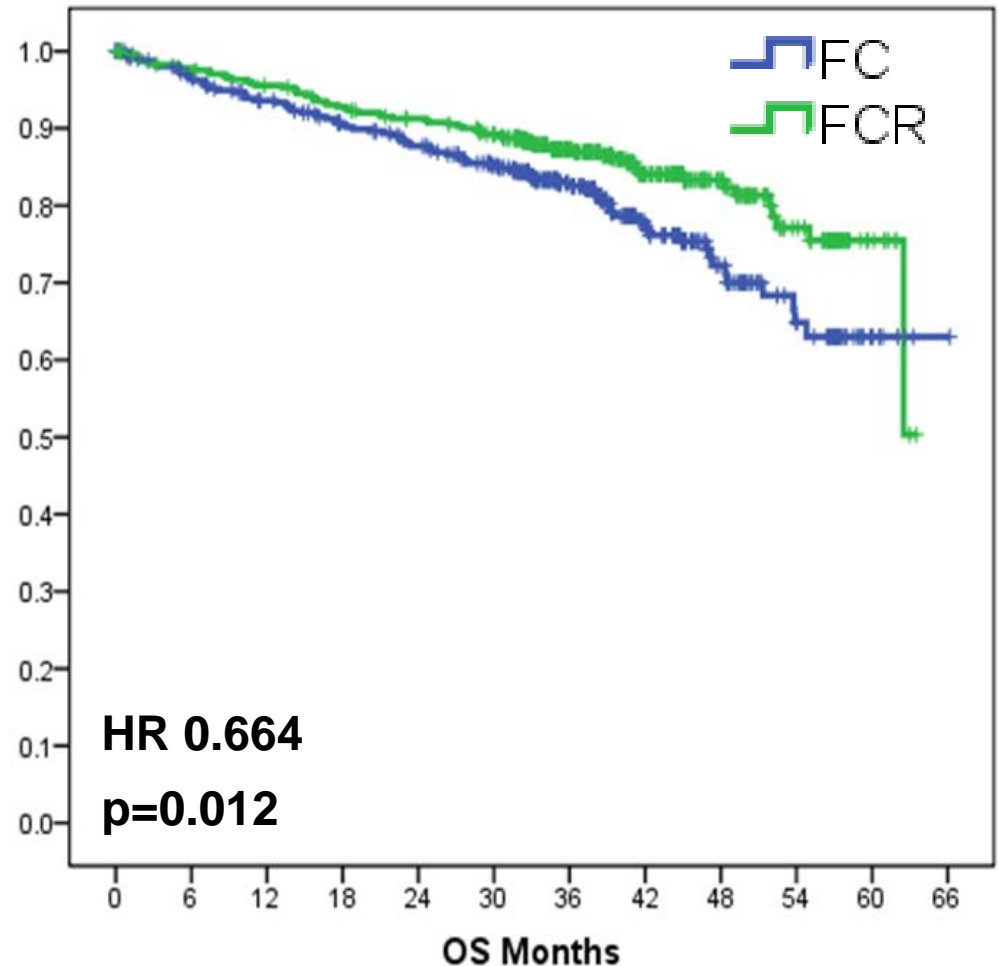
## Integrated Scientific Projects:

**Genomic Aberrations, *IGHV*, *TP53* and *ATM* Mutation, SNP Chip, CD38, ZAP-70, Serum Markers, mRNA & miR Profiling, Methylation, ...**

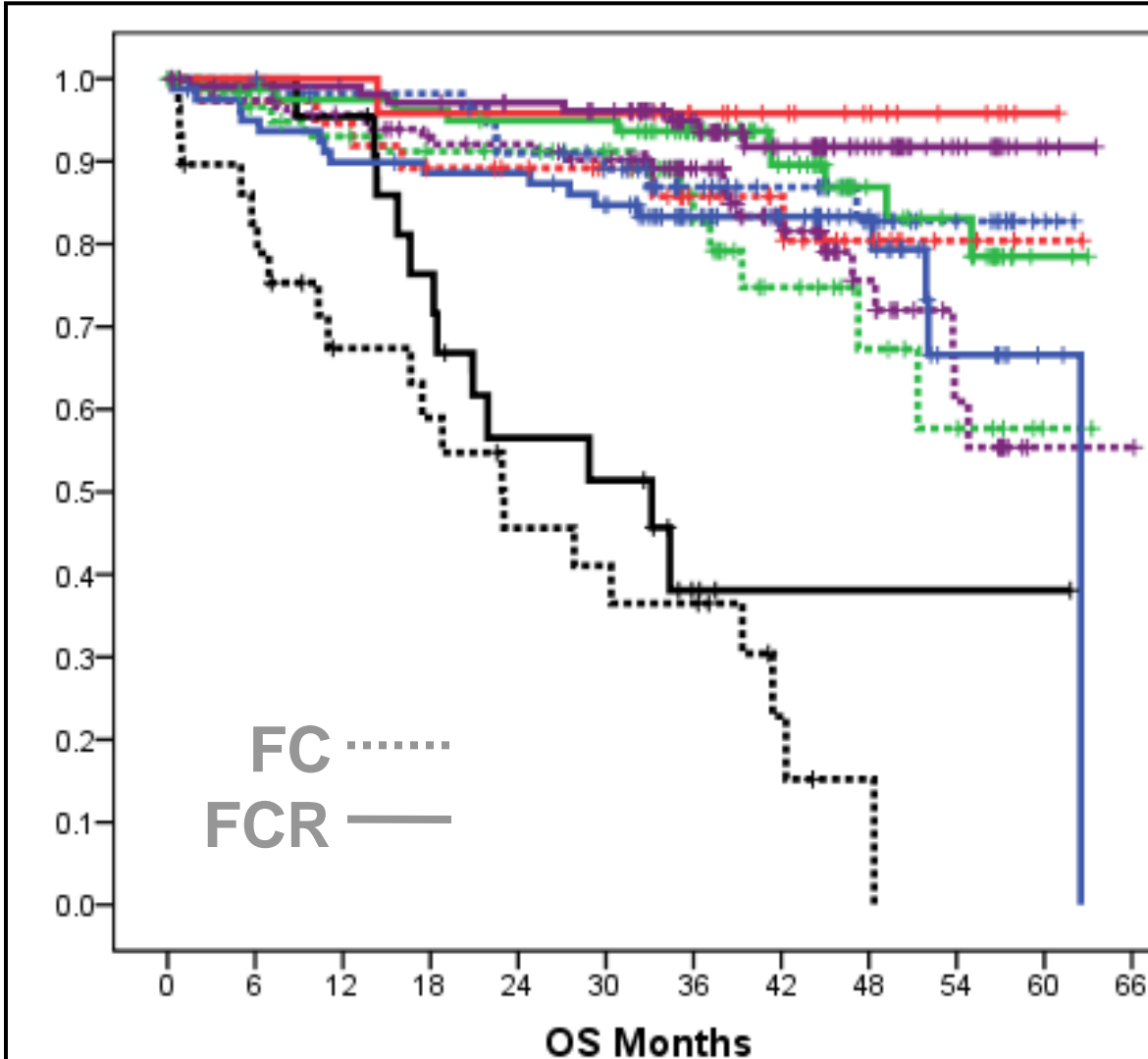


# CLL8: Overall Survival (Median follow-up 37.6 months)

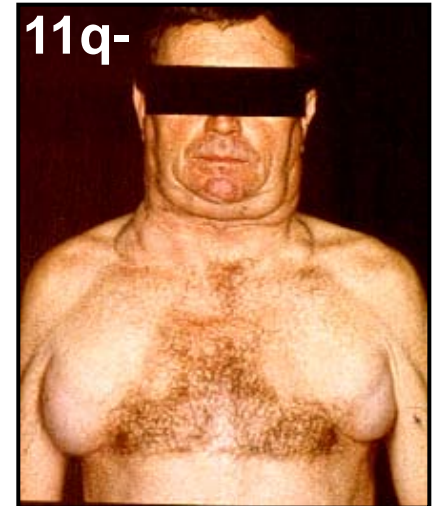
“FCR improves  
response rates,  
progression-free,  
and overall survival  
in untreated patients  
with CLL”



# CLL8 Treatment Effect: OS



17p-  
11q-  
+12q  
13q- single  
normal



# CLL2M: Bendamustine plus Rituximab Response by Genetics

Response	N=	ORR	(%)	CR	(%)
+12	19	17	89.5	3	15.8
11q-	21	19	90.5	9	42.9
17p-	7	3	42.9	-	-
IGHV unmutated	63	56	88.9	25	39.7

*Fischer et al. ASH, 2009*

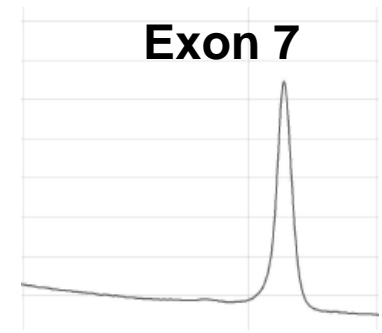
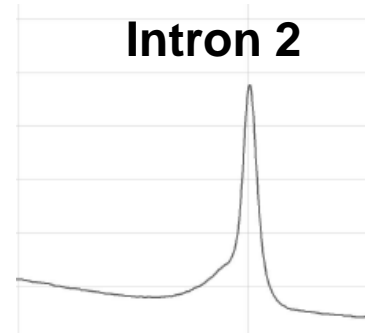
# Selection of p53 Deficient Clone

## Case Report:

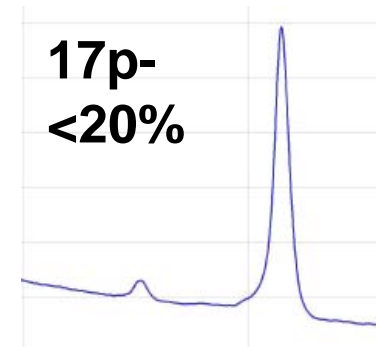
10/2002: Diagnosis CLL

07/2004: Progression →  
4 x FC / 3 x R

11/2004: No Response →  
entry CLL2H trial

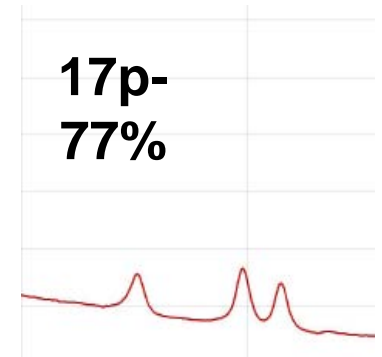
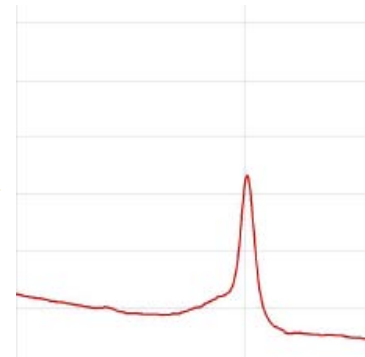


Control



17p-  
<20%

Before FC



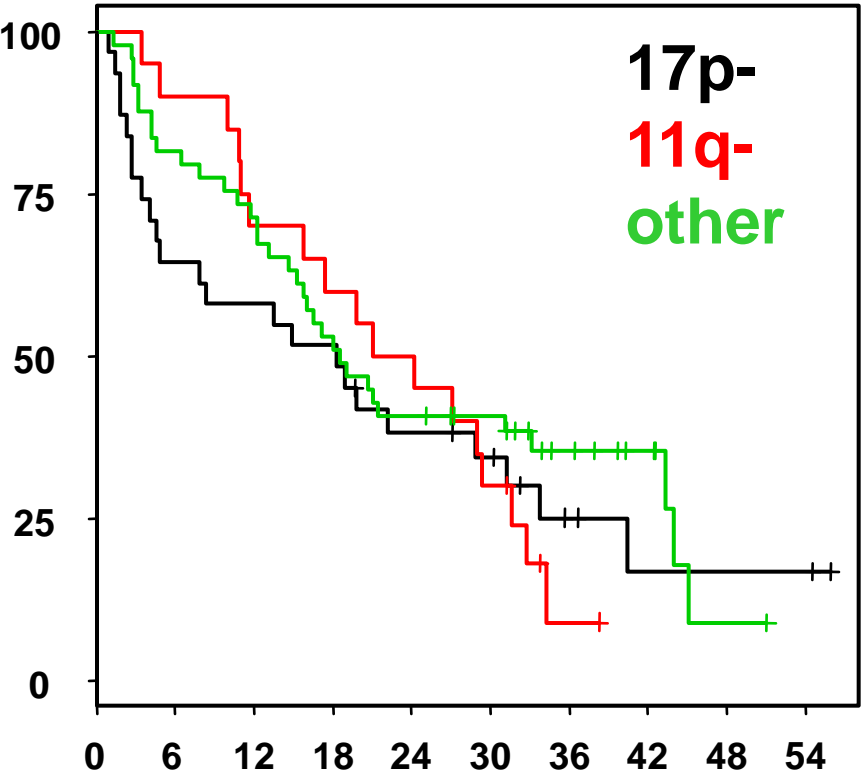
17p-  
77%

After FC

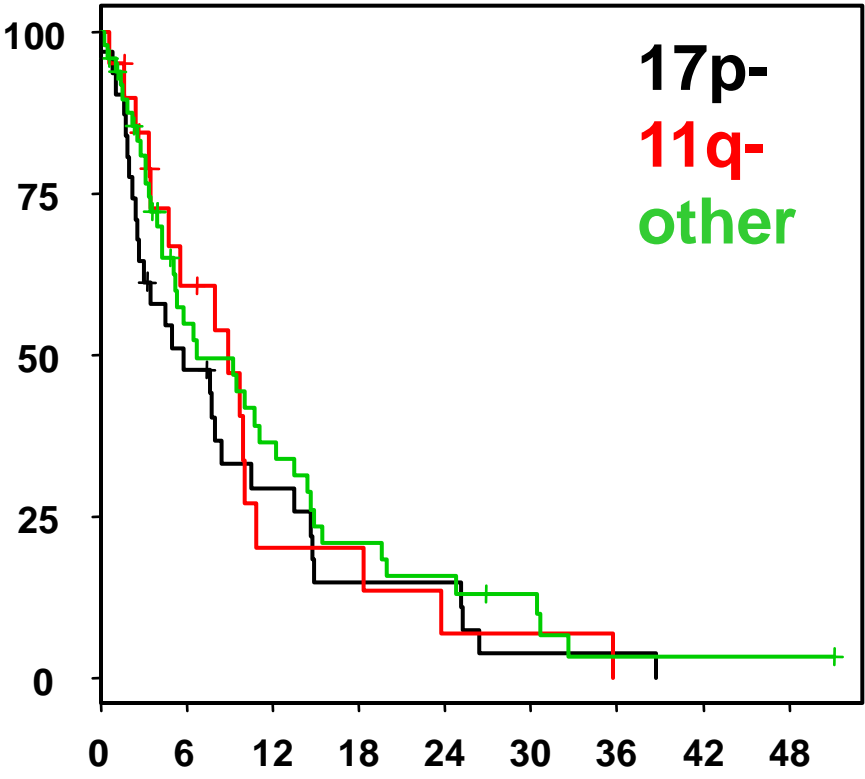
# CLL2H: Alectuzumab in Refractory CLL

## Survival by Genomic Subgroups

**OS**



**PFS**



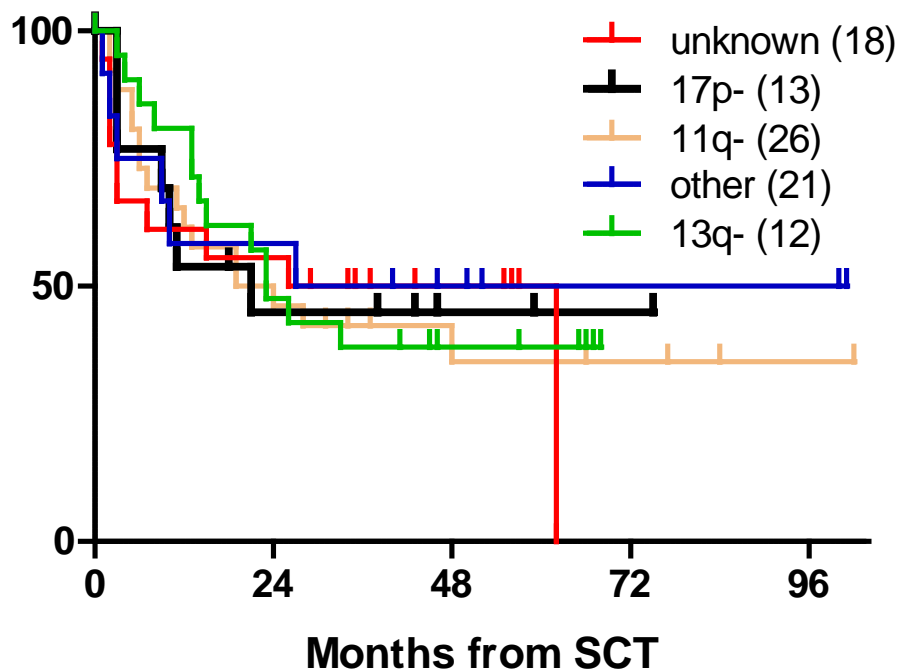
**Time (months)**

**Time (months)**

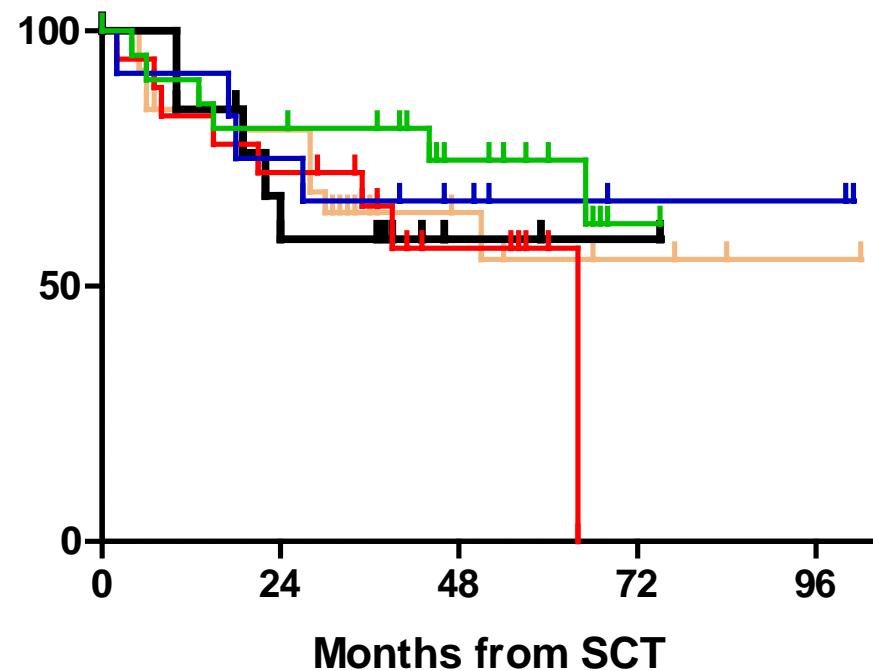
*Stilgenbauer et al. J Clin Oncol, 2009*

# CLL3X Trial: RIC Allo-SCT Outcome in Genetic Subgroups

## EFS

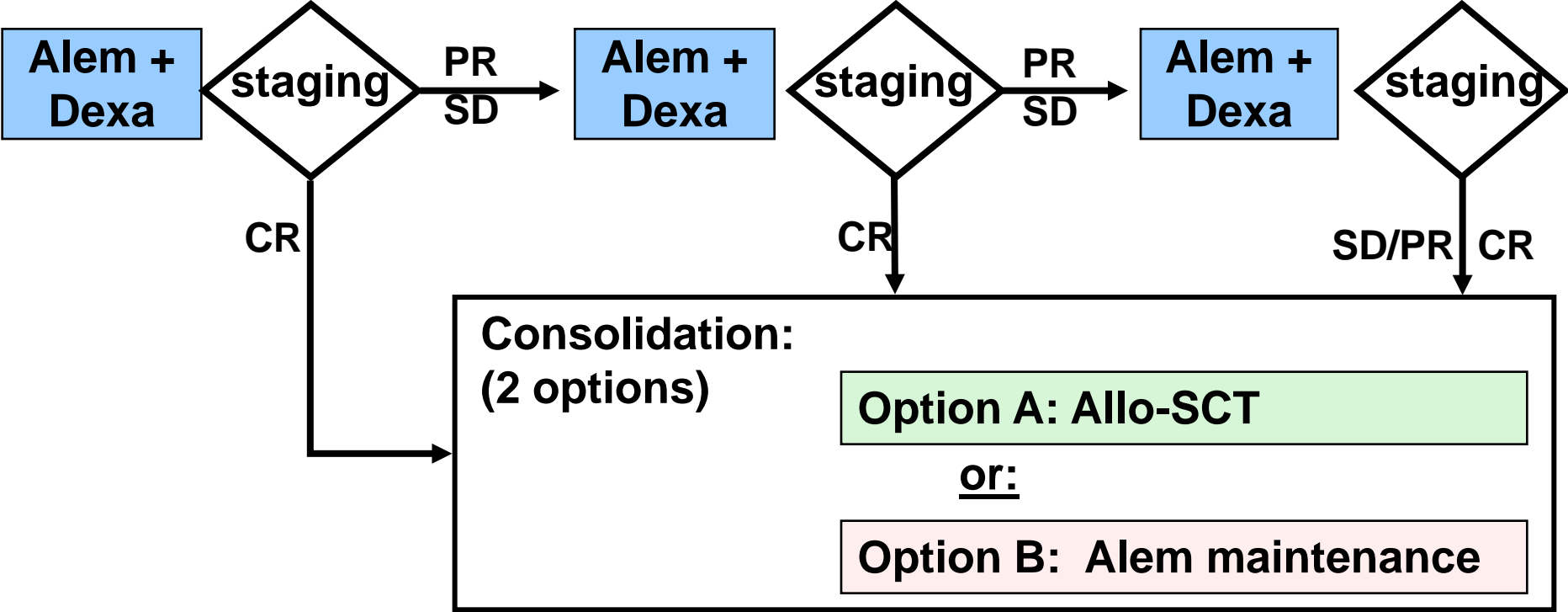


## OS



# CLL20 Trial (GCLLSG, FCLLSG)

Population: 17p- (first line) and Chemo-refractory CLL

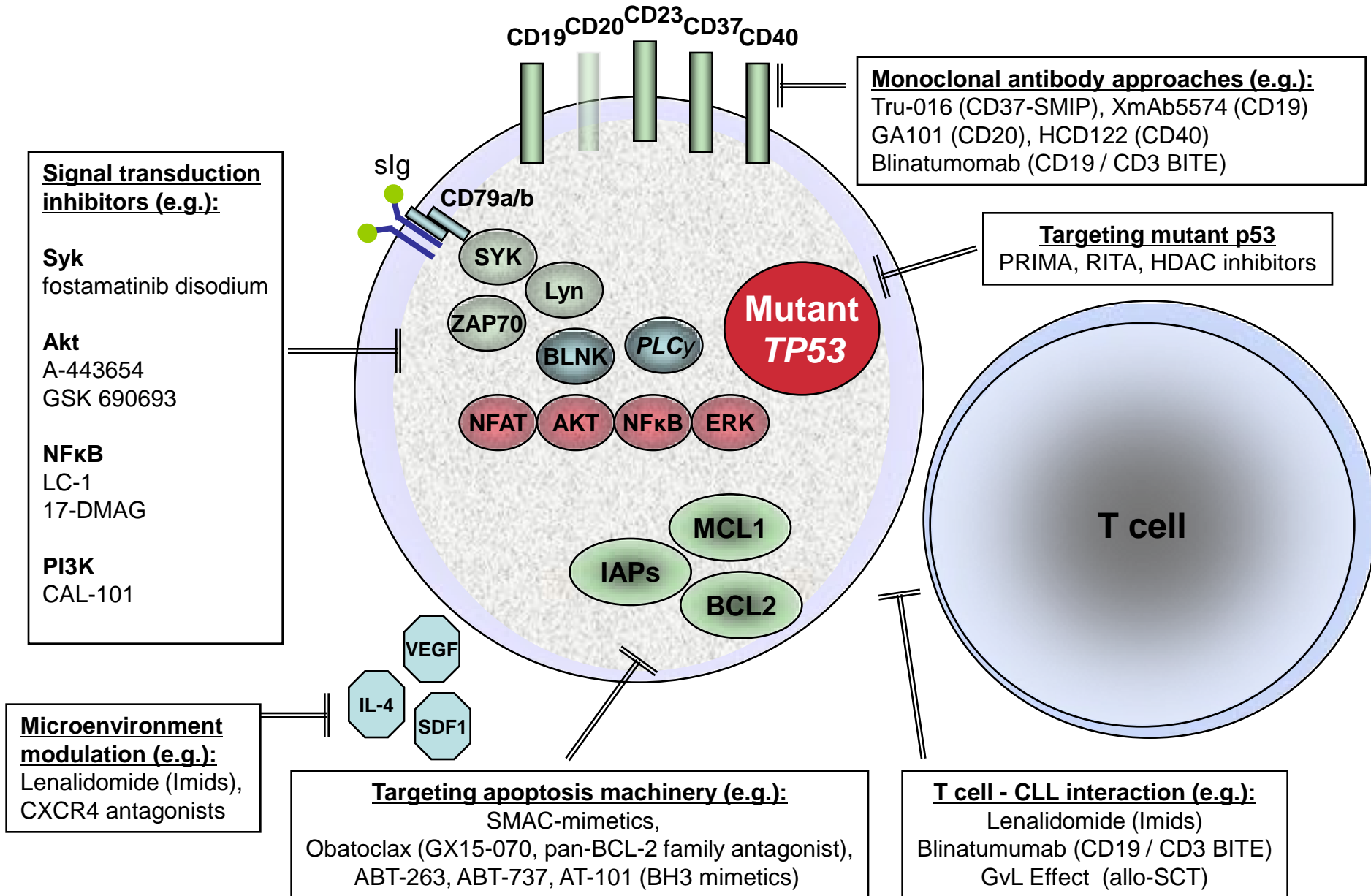


# Current GCLLSG Trials

Trial	Population	Stratification	Therapy
CLL7	Binet-A	TK, LDT, IGHV, 17p-, 11q-, +12	W&W vs FCR
CLL10	Binet B, C	excl. 17p-	FCR vs BR
CLL20	F-refr., 17p-	prior ther., 17p-	Alem + Dex, Maint. vs SCT
CLLX2	F-failure, 17p-	prior ther., 17p-	Allo-SCT



# Future Treatment Approaches



**Internal Medicine III, Ulm**

**Johannes Bloehdorn**

**Andreas Bühler**

**Jennifer Edelmann**

**Silja Groner**

**Andrea Schnaiter**

**Christof Schneider**

**Dirk Winkler**

**Thorsten Zenz**

**Hartmut Döhner**

**German CLL Study Group**

**Manuela Bergmann**

**Sebastian Böttcher**

**Raymonde Busch**

**Peter Dreger**

**Barbara Eichhorst**

**Anna Maria Fink**

**Kirsten Fischer**

**Michael Kneba**

**Clemens Wendtner**

**Michael Hallek**

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