

Case #1—Chronic Lymphocytic Leukemia: New Advances in Research and Treatment

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Disclosures for Thorsten Zenz, MD

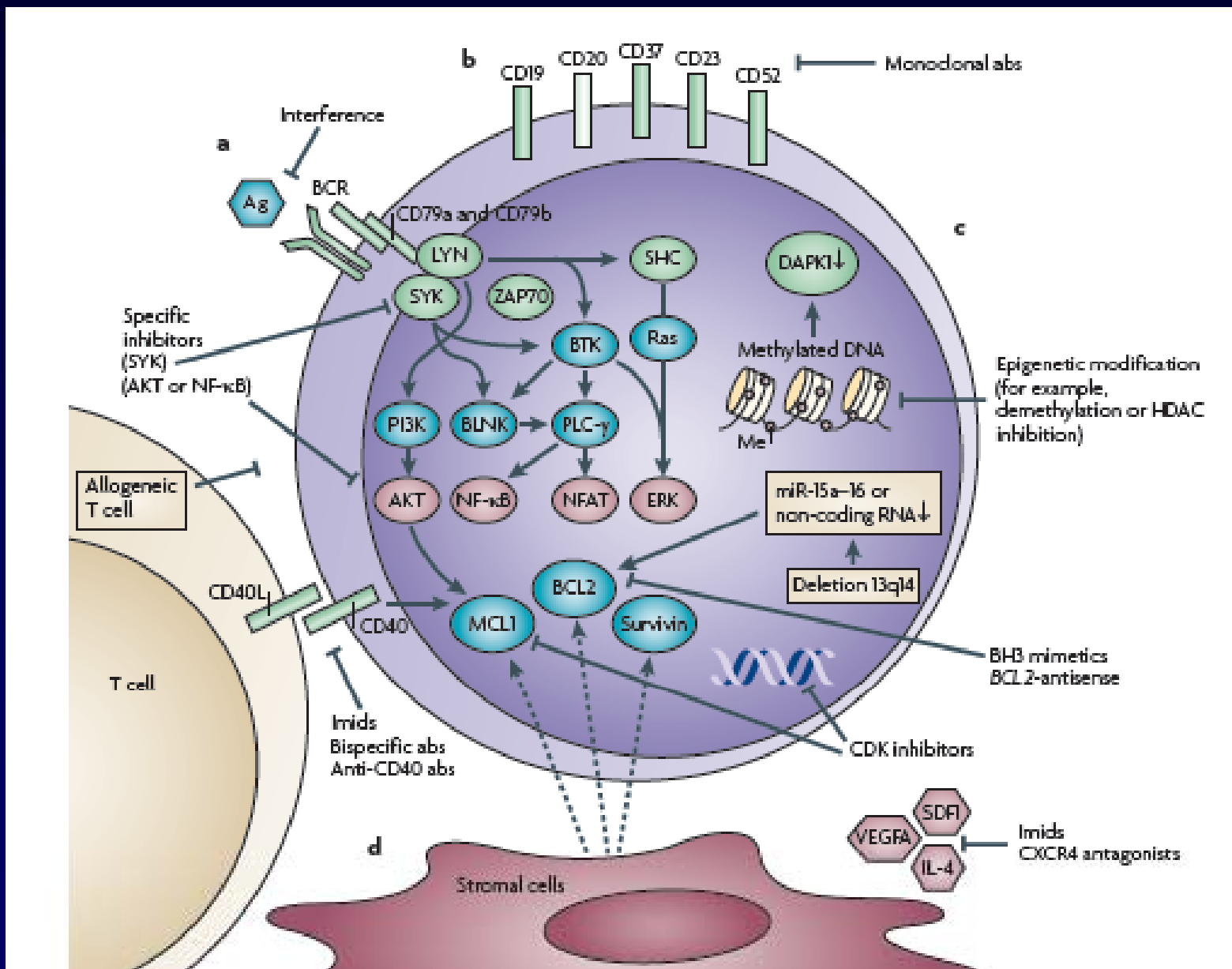
Grant / Research Support: Genmab, Roche Pharma

Consultant / Speaker's Bureau: GSK, Celgene, Trubion

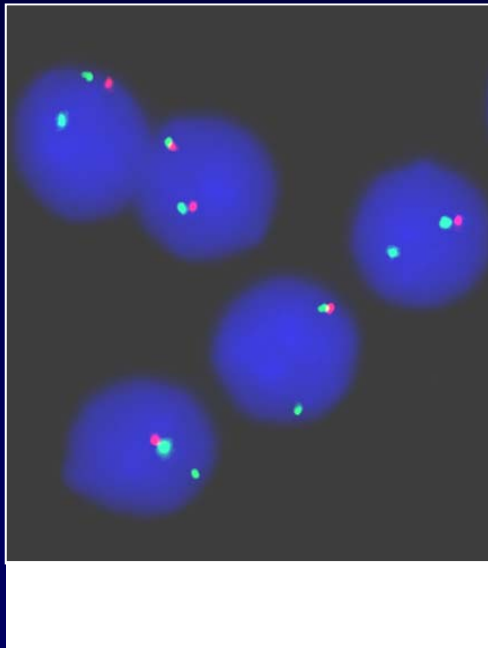
CLL—Diagnosis

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

Pathogenesis

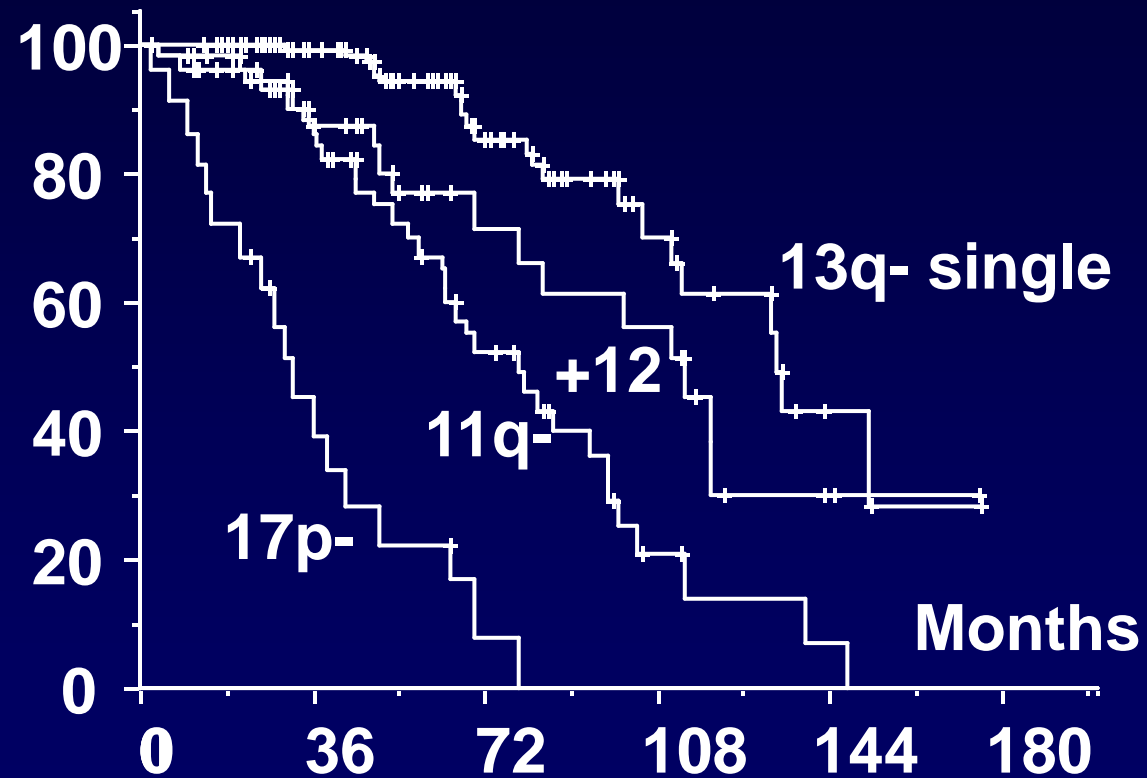


CLL: Genomic Aberrations



<u>Aberration</u>	<u>Incidence</u>	<u>Genes</u>
del 13q14	55%	miR15/16, ?
del 11q23	20%	ATM, ?
tris 12q13	16%	?
del 17p13	8%	TP53
t 14q32	4%	IgH

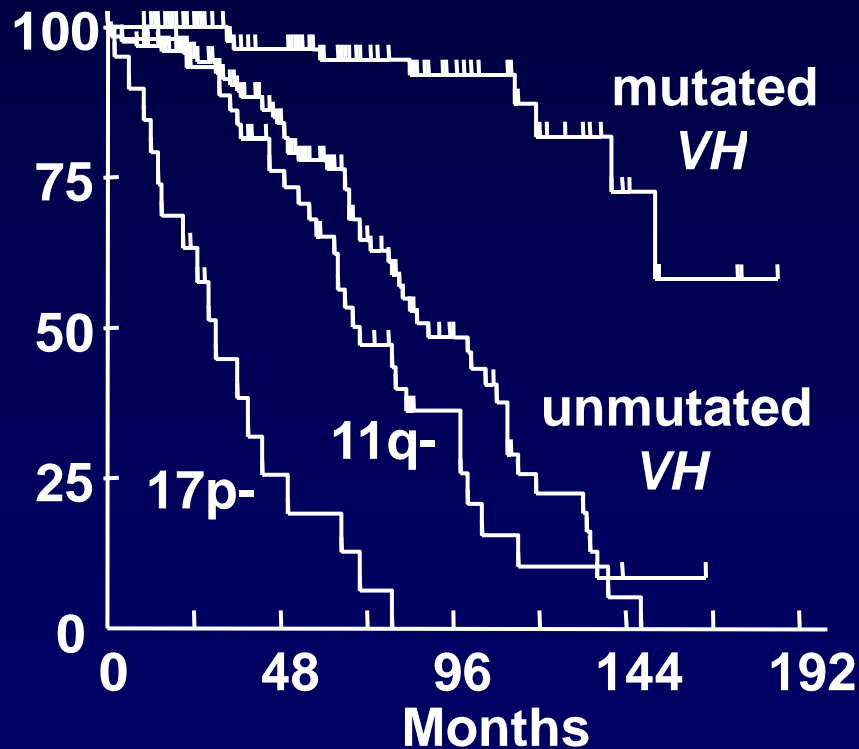
Prognosis and Genomic Aberrations



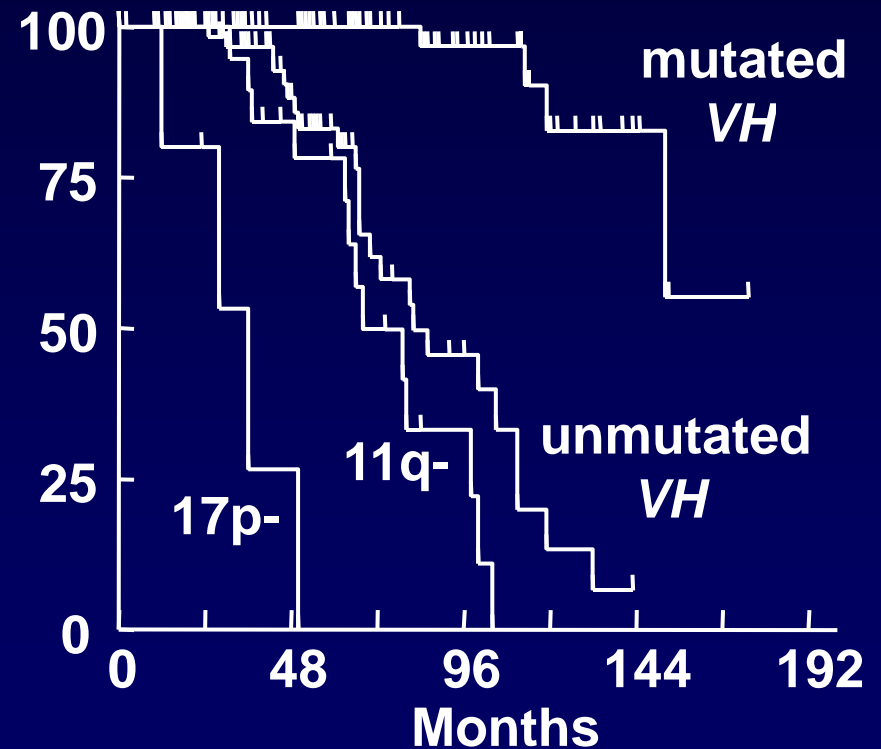
Overall Survival in CLL

VH Mutation Status and Genomic Aberrations

All Patients (n = 300)



Binet A (n = 189)



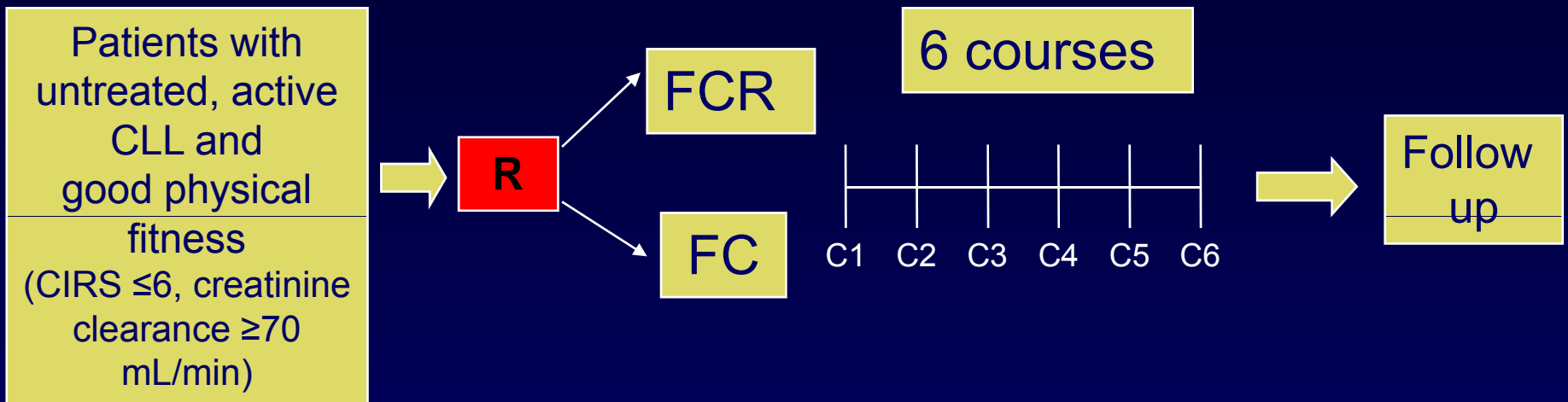
Recommended Initial Therapy for Asymptomatic Patients

- Continued observation
- Chlorambucil with or without prednisone
- Fludarabine alone
- Fludarabine + cyclophosphamide (FC)
- FC + rituximab (FCR)
- Fludarabine + rituximab
- Other

CLL—First-Line Treatment

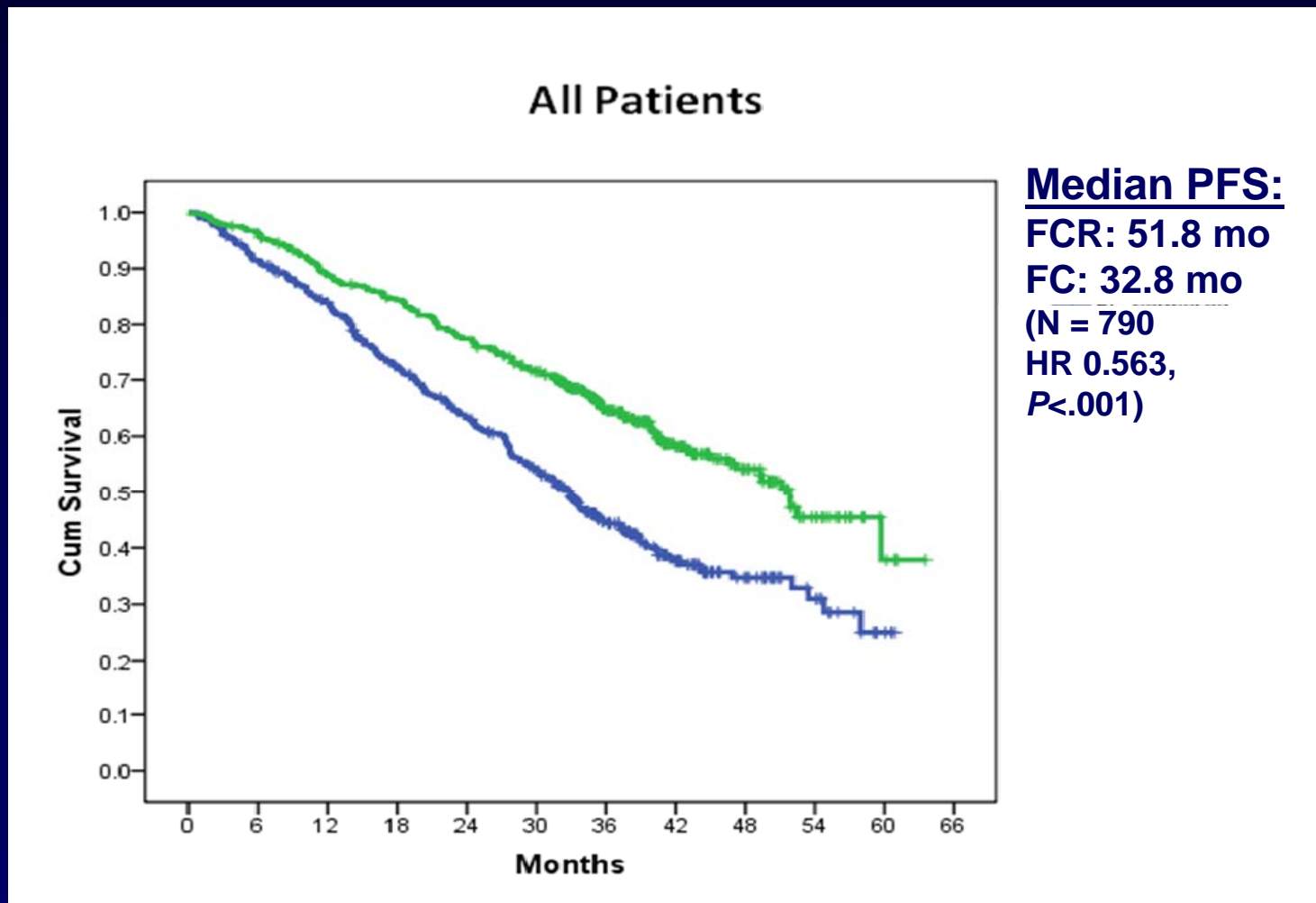
- **FCR**
- **Chlorambucil with or without prednisone**
- **Rituximab monotherapy**
- **Alemtuzumab**
- **Bendamustine**
- **CHOP with or without rituximab**

CLL8 Study Design

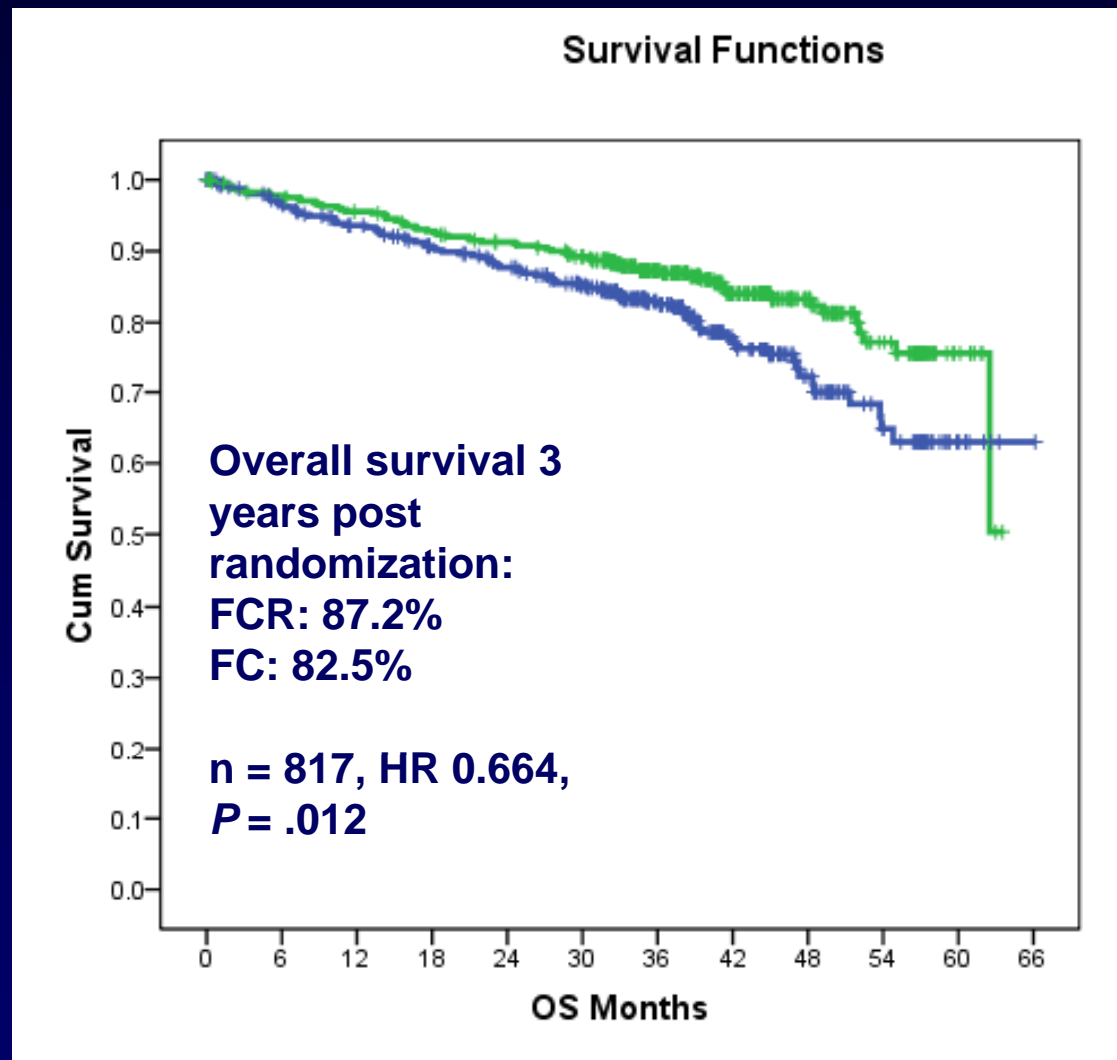


Updated results of the 2nd analysis
Median observation time 37.7 months

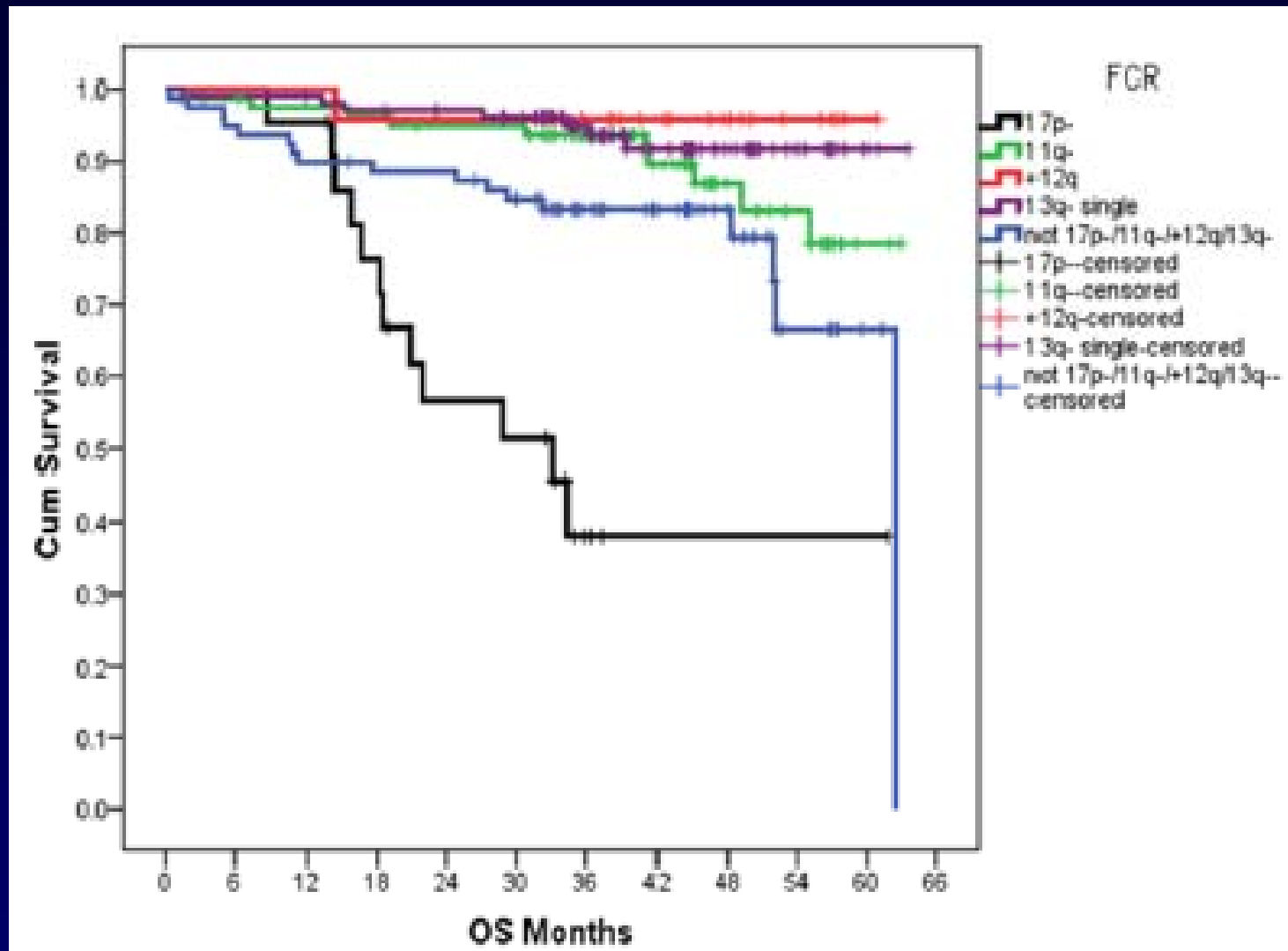
Progression-Free Survival



Overall Survival



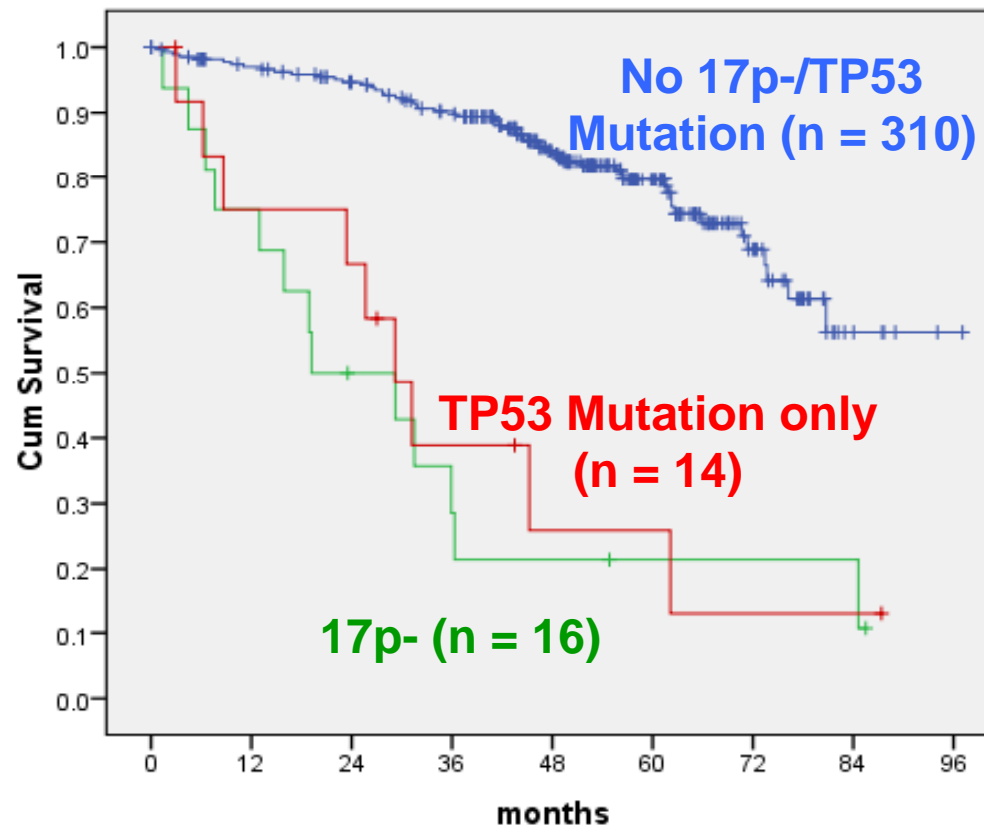
CLL8: Prognosis



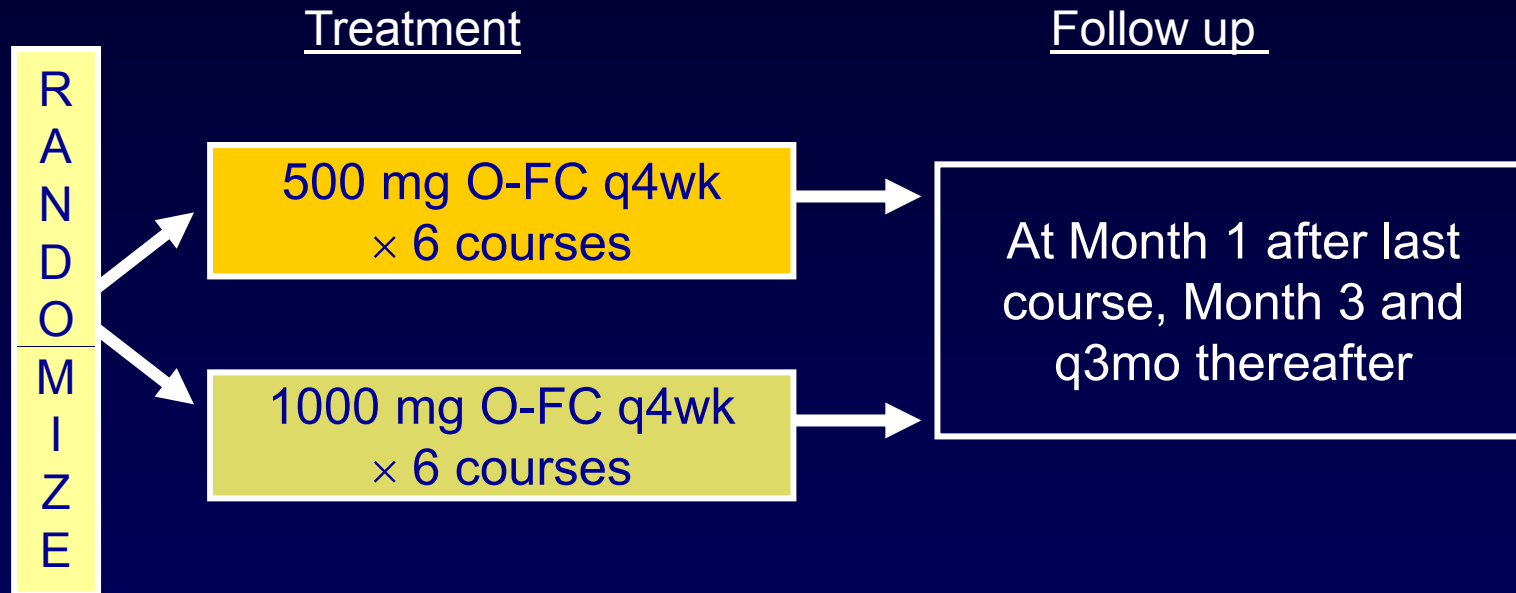
Hallek M, et al, *Blood*. 2009;114: Abstract 535.

TP53 Mutation / CLL4 (n = 340)

Overall Survival

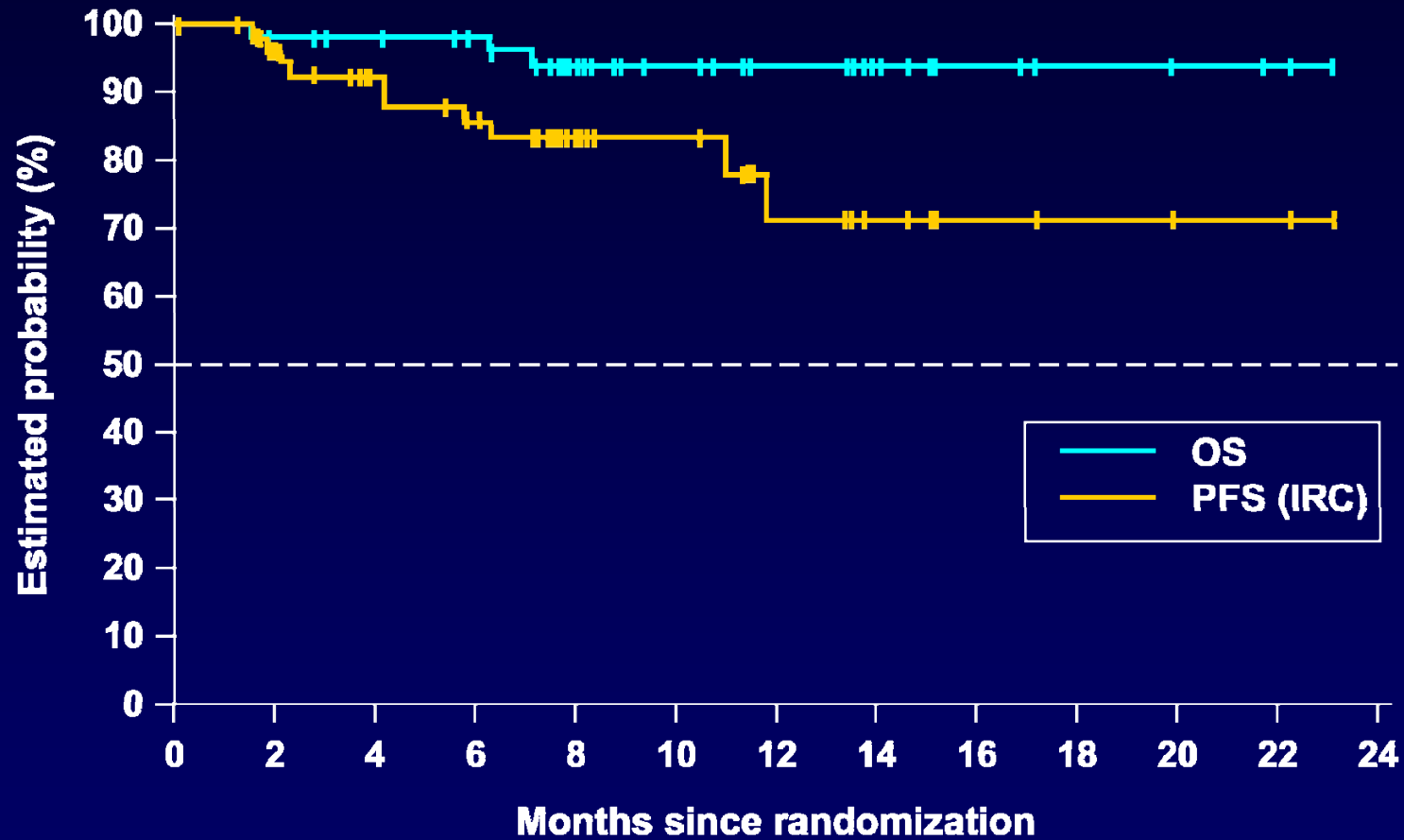


O-FC in CLL: 407 Study Schema



Course	Ofatumumab	Fludarabine	Cyclophosphamide
1	300 mg d1	25 mg/m ² IV d2–4	250 mg/m ² IV d2–4
2–6	500 or 1000 mg d1	25 mg/m ² IV d1–3	250 mg/m ² IV d1–3

O-FC in CLL: Survival Outcomes



N (PFS) 61
N (OS) 61

43
53

22
29

11
15

4
6

2
3

0
0

O-FC in CLL: Conclusions

- **O-FC is a highly active first-line regimen**
 - Trend for higher CR rate with ofatumumab 1000 mg
- **Ofatumumab safely combined with FC for previously untreated CLL**
 - Myelosuppression was most frequent adverse event with O-FC regimen
 - No unexpected toxicity
- **Continued follow-up ongoing for time-to-event endpoints**
- **Further studies of O-FC regimen with ofatumumab 1000 mg or higher dose**

Challenges in First-Line CLL

- **Treatment strategies for 17p-/p53 mutant CLL**
- **Early identification of poor responders**
- **Role of maintenance**
- **Role of allogeneic SCT in first line**

Refractory CLL

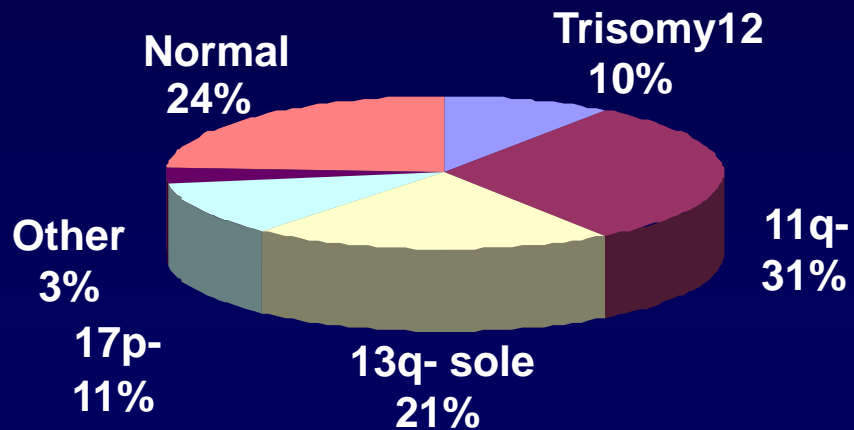
- **Lenalidomide monotherapy**
- **Alemtuzumab monotherapy**
- **Rituximab monotherapy**
- **Ofatumumab monotherapy**
- **Allogeneic SCT**

Refractory CLL

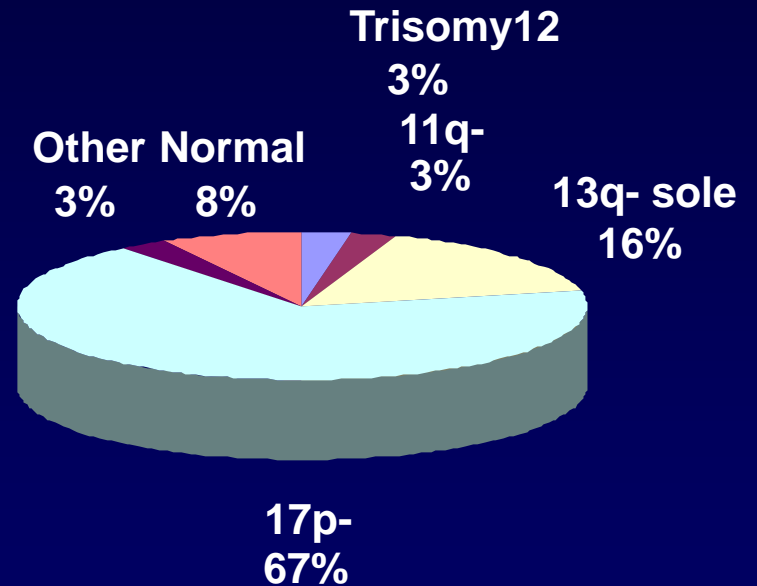
	Binet-A CLL1 n = 830	First-Line Rx (F vs FC) CLL4 n = 326	F-Refractory (Alemtuzumab) CLL2H n = 104
13q- single	48	33	22
+12q	12	14	12
11q-	9	21	25
17p-	3	5	31
Unmut. IGHV	39	65	78
TP53 mutation	?	8	37

F-Refractory CLL

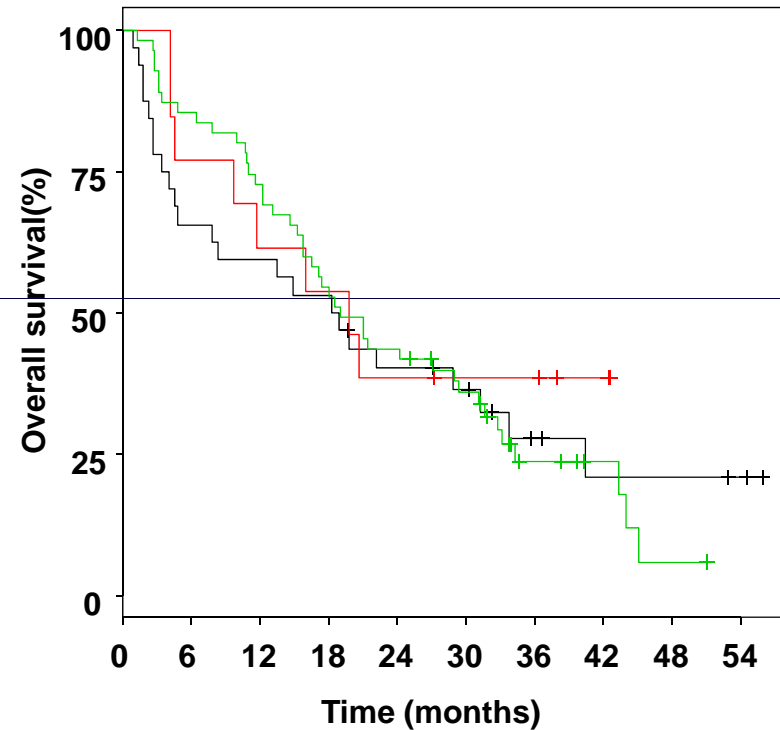
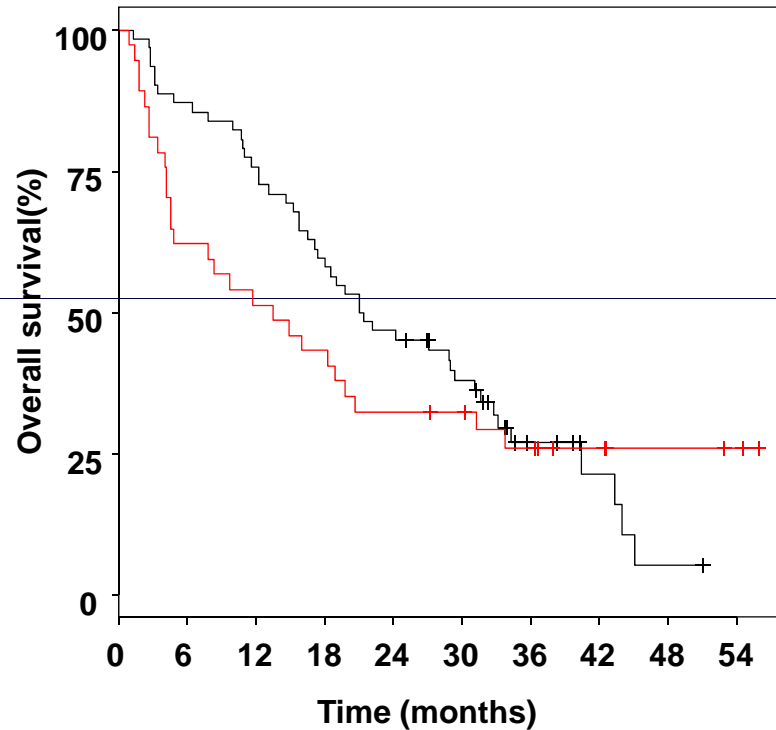
TP53 Wild Type
N = 62



TP53 Mutated
N = 37



F-Refractory CLL (Ab-Based Treatment—Alemtuzumab)



- TP53 mutation (n = 37)
- No TP53 mutation (n = 62)

- TP53 mutation no 17p- (n = 13)
- 17p- (n = 32)
- All others (n = 55)

Zenz T, et al. *Blood*.2009;114(13):2589-2597.

Ofatumumab in CLL Refractory to Both Fludarabine and Alemtuzumab

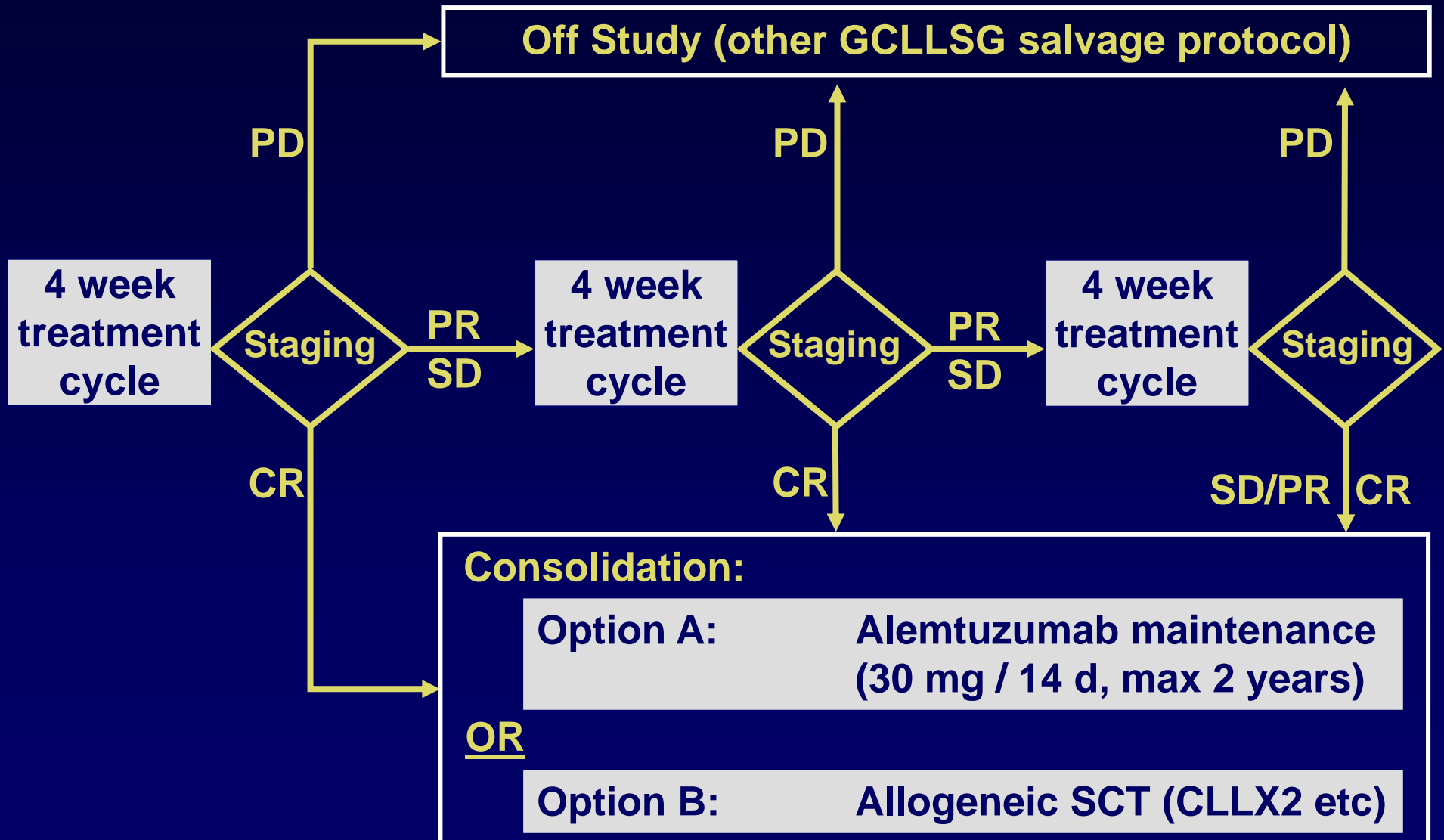
	DR (n = 59)	BFR (n = 79)
ORR, % (99% CI)	51 (34, 68)	44 (30, 59)
Complete response	0	1
Partial response	51	43
Stable disease	39	43
Progressive disease	3	10
Time to next CLL therapy, mo	9.0 (7.3, 10.7)	7.9 (7.1, 9.3)
Overall survival, mo	13.7 (9.4, NR)	15.4 (10.2, 20.2)

Treatments in Clinical Use Working Independent of p53

Alemtuzumab	Lozanski 04, Hillmen 07, Stilgenbauer 07	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	Österborg 08	42% (DR)

Allogeneic stem cell transplantation

CLL20: F-Refractory / 17p- CLL Alemtuzumab + Dexamethasone



Outlook CLL

