CHRONISCHE LYMPHATISCHE LEUKÄMIE

NEUE ENTWICKLUNGEN UND EMPFEHLUNGEN FÜR DIE THERAPIE

Wolfgang Knauf
Onkologische Gemeinschaftspraxis
Bethanien Krankenhaus der Frankfurter Diakonie Kliniken
Frankfurt / Main

UMBRUCH IN DER THERAPIE ?

BENDAMUSTIN

RITUXIMAB

FCR

LENALIDOMIDE (?)

REMISSION INDUCTION IN CLL

Consensus (?) practice in Europe

Alkylators	**Chlorambucil**
	Cyclophosphamide
Purine analogues	**Fludarabine**
	Cladribine (Poland, Sweden)
Other	**CHOP (France, Spain)**
	Bendamustine (Germany)
For younger (?) pts:	**FC (R)**

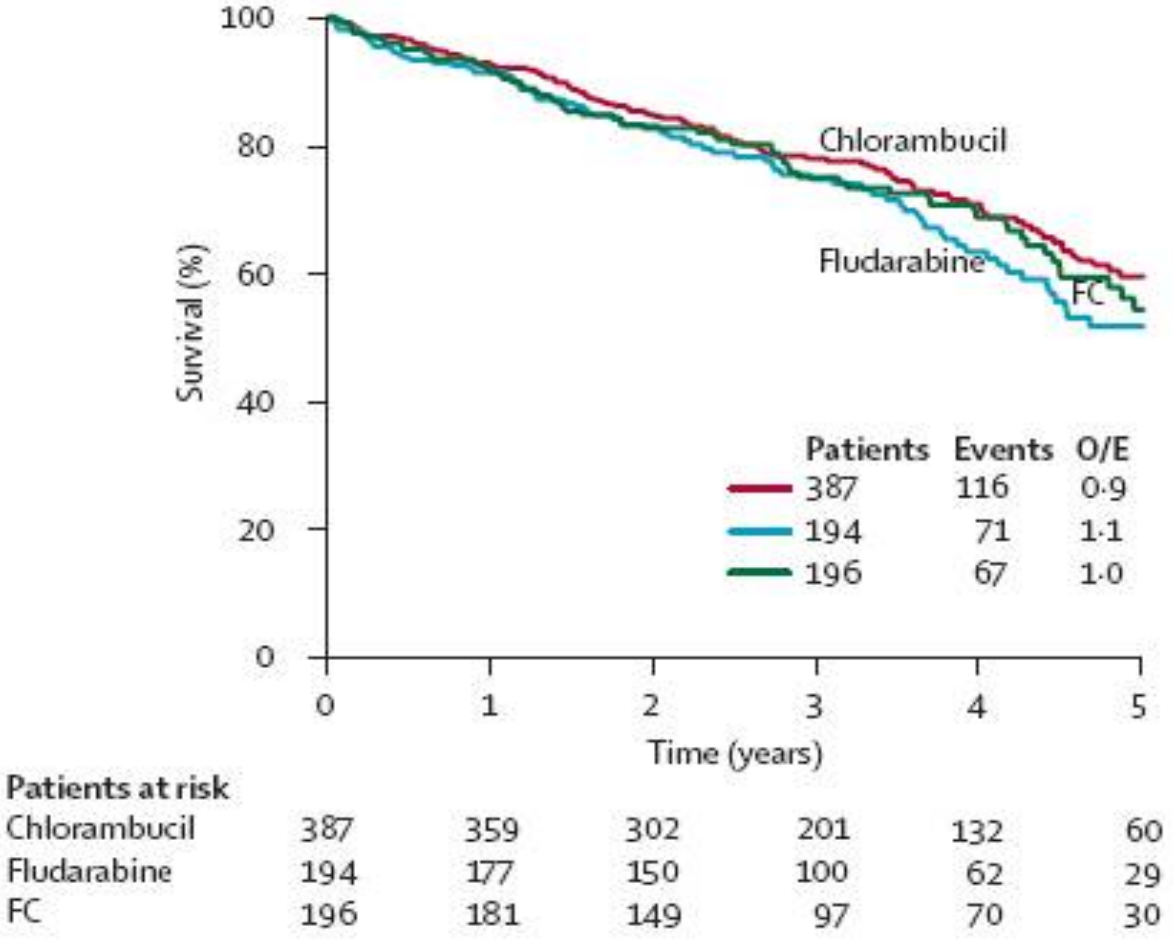
(Recommendations from UK/Germany study groups)

MoAbs	**Alemtuzumab (antiCD52)**

(Particularly recommended in 17p deleted CLL)

CBL versus F versus FC as 1st line treatment for CLL (LRF CLL4 Trial)

Catovsky D et al., Lancet 2007; 370: 230-39



Survival by treatment group

Still a role for Chlorambucil in first-line treatment of CLL ?

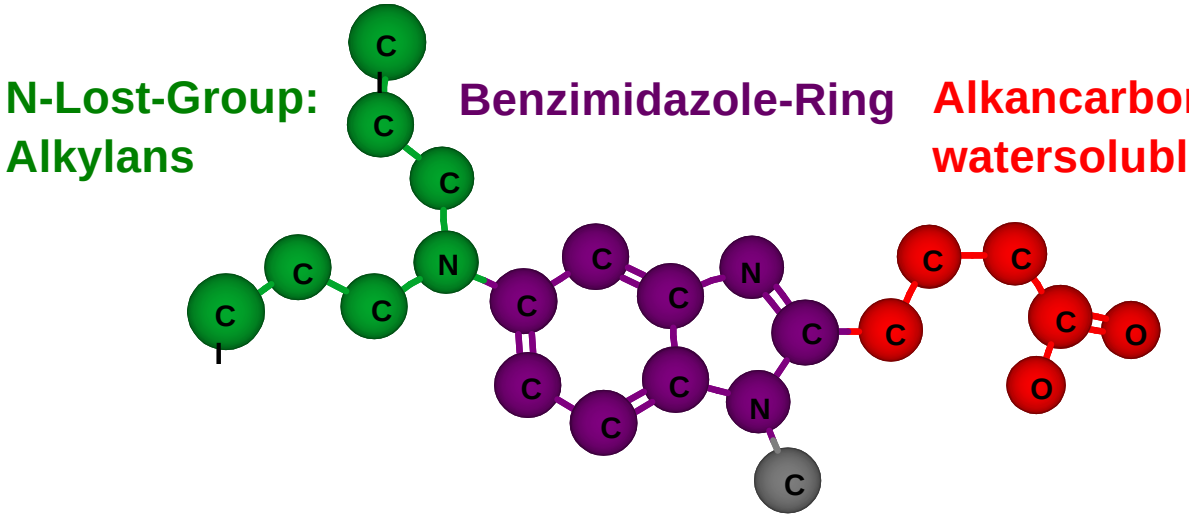
	Clb dose	Clb cycles	Median age	Early stage	Response	PFS	OS	Toxicity
Rai et al.	40mg/m^2	?	64	60% (Rai I/ II)	Clb < F 37 vs 63%	Clb < F 14 vs 20 mo	Clb = F 56 vs 66 mo	Clb < F
Eichhorst et al.	70mg/ month (incremental increase)	6.5	71	60% (Binet A+B)	Clb < F 59 vs 86%	Clb = F 18 vs 19 mo	Clb = F 64 vs 46 mo	Clb < F
Catovsky et al.	70mg/m^2	?	65	69% (Binet A+B)	Clb < F 72 vs 80%	Clb = F 20 vs 21	Clb = F *(median n.r.)*	Clb < F
Hillmen et al.	40mg/m^2	7	60	65% (Rai I/II)	Clb < Cam 55 vs 83%	Clb < Cam 12 vs 15 mo	*no data*	Clb<Cam
Knauf et al.	60 mg/m2	5	63	Binet B+C (no Binet A)	Clb < B 39 vs 68%	Clb < B 9 vs 21 mo	*Clb = B* *median not reached*	Clb < B

Bendamustine versus Chlorambucil as First-line Treatment in B Cell Chronic Lymphocytic Leukemia: Updated Analysis from an International Phase III Study

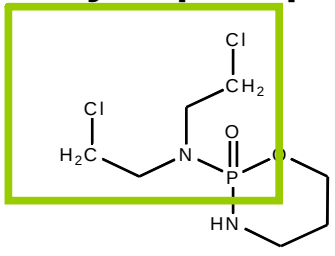
Wolfgang U. Knauf, M.D.[1], Toshko Lissichkov, M.D.[2], Ali Aldaoud, M.D.[3], Anna Liberati, M.D.[4], Javier Loscertales, M.D.[5] , Raoul Herbrecht, M.D.[6], Gunnar Juliusson, M.D.[7], Gerhard Postner, M.D.[8], Liana Gercheva M.D.[9], Stefan Goranov, M.D.[10], Martin Becker, M.D.[11], Klaus Hoeffken, M.D.[12] , Francoise Huguet, M.D.[13], Robin Foa, M.D.[14], Karlheinz Merkle, M.D.[15] and Marco Montillo, M.D.[16]

[1]Dept.of Hem./Oncol., Onkologische Praxis, Frankfurt, Germany, D-60389; [2]Hematology & Transfusion Medicine, National Hematological Center, Sofia, Bulgaria, BG-1756; [3]Onkologische Gemeinschaftspraxis, Leipzig, Germany, D-04289, [4]Dept. Oncology, Universita degli Studi, Perugia, Italy, I-6122, [5]Dept.Hematology, Hopital de la Princesa, Madrid, Spain, E-28006, [6]Hematology & Oncology, Hopital Universitaire Hautepierre, Strasbourg, France, F-67098, [7]Dept. Hematology, University Hospital, Lund, Sweden, S-22185, [8]Med.Oncology, Kaiser Franz Josef Spital, Vienna, Austria, A-10100, [9]Dept. Hematology, University Hospital, Varna, Bulgaria, BG-9010, [10]Dept. Hematology, University Hospital, Plovdiv,Bulgaria,BG-4000; [11]Onkologische Schwerpunktpraxis, Minden, Germany, D-32423, [12]Dept. Hematology, University Hospital, Jena, Germany, D-07747; [13]Dept. Hematology, Hopital Purpan, Toulouse, France, F-31059; [14]Ematologia, Universita “La Sapienza”, Roma, Italy, I-00161; [15]Oncol. Consulting, Miesbach, Germany, D-83714, [16]Ematologia, Ospedale Niguarda Ca’Granda, Milano, Italy, I-20162

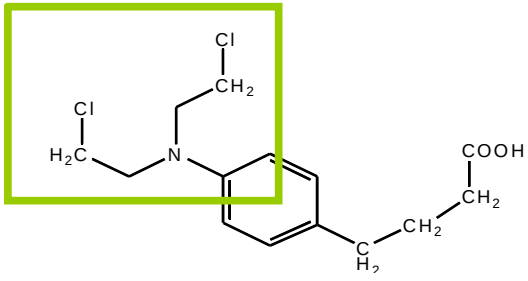
Chemical structure of bendamustine



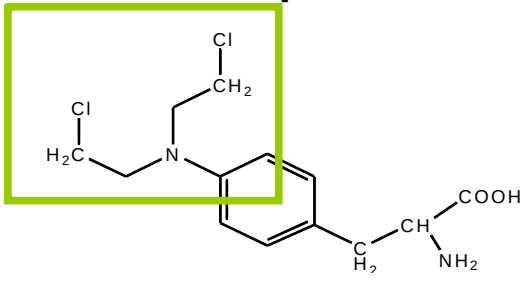
Cyclophosphamide



Chlorambucil



Melphalan



OBJECTIVES

- Compare the overall response rate (ORR) and progression free survival (PFS) of bendamustine and chlorambucil as primary therapy for patients with B-CLL Binet stage B/C

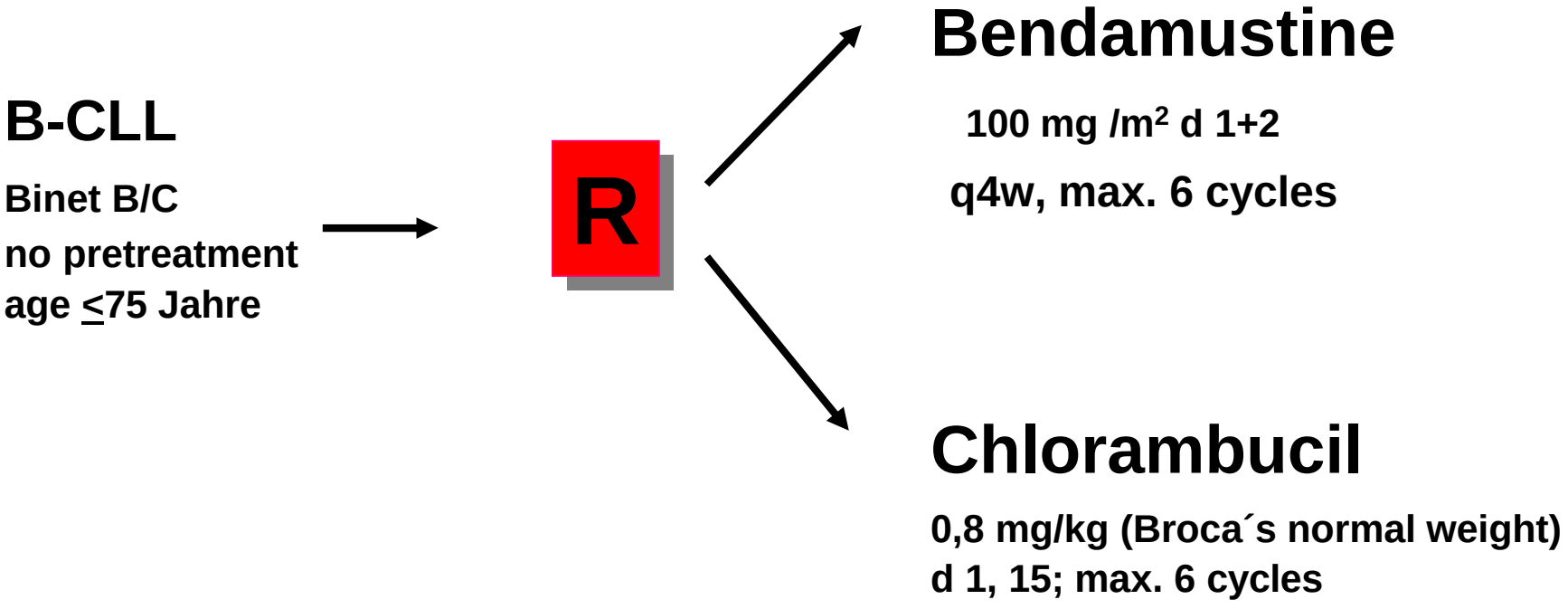
- Secondary endpoints included time to progression (TTP), duration of response (DoR) or remission, overall (OS) survival, and quality of life (QoL)

PATIENTS AND METHODS

- The study was a randomized, open-label, parallel-group, phase III trial conducted at 45 centers in Austria, Bulgaria, France, Germany, Italy, Spain, Sweden, and the United Kingdom

- Patients were randomized in a 1:1 ratio to receive bendamustine or chlorambucil with stratification by center and Binet stage

Bendamustine vs Chlorambucil
European „intergroup“ CLL Study



Calculated total doses of chlorambucil for an average patient (70kg / 1.75m / 1.85m²)

	Regimen	Total dose/cycle (mg)	Dose per m^2/cycle (mg)	Median cumulative dose (mg)
02CLLIII	0.8mg/kg d1 + 15	112	60	518
Eichhorst et al.	0.4 – 0.8 (Ø 0.5) mg/kg d1+15	56-112 (Ø 70)	30-60 (Ø 38)	455
Hillmen et al.	40mg/m^2 q d28	74	40	515
Rai et al.	40mg/m^2 q d28	74	40	n.a.
Catovsky et al.	10mg/m^2 d1 - 7	130	70	n.a.

n.a.: not available

1: Eichhorst et al. Blood 110 (11), Abstract 921, 2007

2: Hillmen et al. Blood 108 (11), Abstract 301, 2006

3: Rai et al. N Engl J Med 343:1750–1757, 2000

4: Catovsky et al. Lancet 370:230–239, 2007

RESULTS

- A total of 319 patients were randomized (162 bendamustine, 157 chlorambucil), of whom all were included in the efficacy analysis and 312 were evaluable for safety.

- The mean (± SD) number of treatment cycles was 4.8±1.7 in the bendamustine group and 4.6±1.7 in the chlorambucil group

- The median duration of follow-up was 29.2 months (29.8 bendamustine, 27.8 chlorambucil)

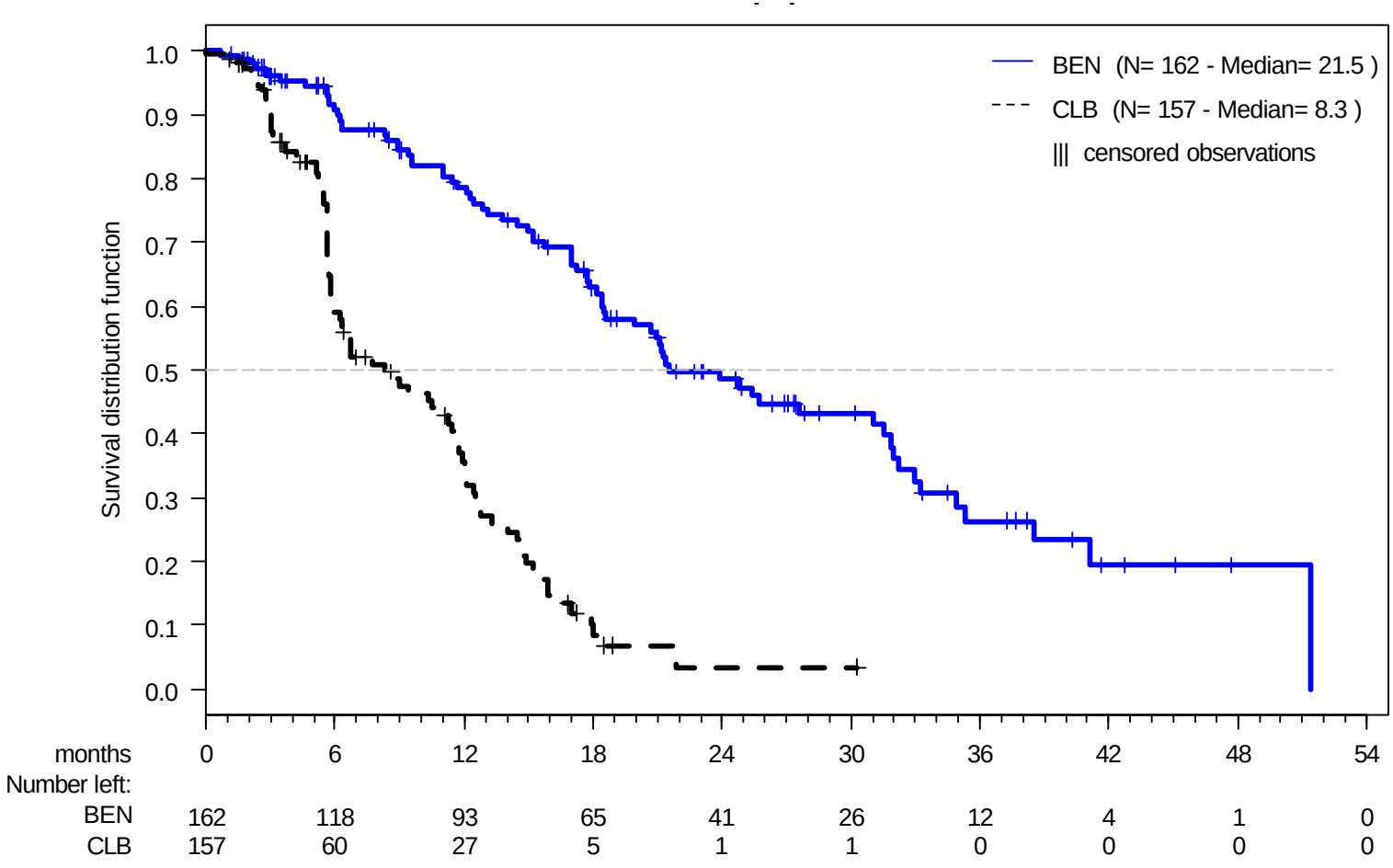
Quality of response (ITT population) by ICRA

	Bendamustine (n=162)	Chlorambucil (n=157)
Overall response	108 (67%)	47 (30%)
Complete response	51 (32%)	3 (2%)
Nodular partial response	16 (10%)	4 (3%)
Partial response	41 (25%)	40 (26%)
Unconfirmed response	6 (4%)	6 (4%)
Stable disease	20 (12%)	32 (20%)
Progressive disease	14 (9%)	53 (34%)
Not examined	14 (9%)	19 (12%)

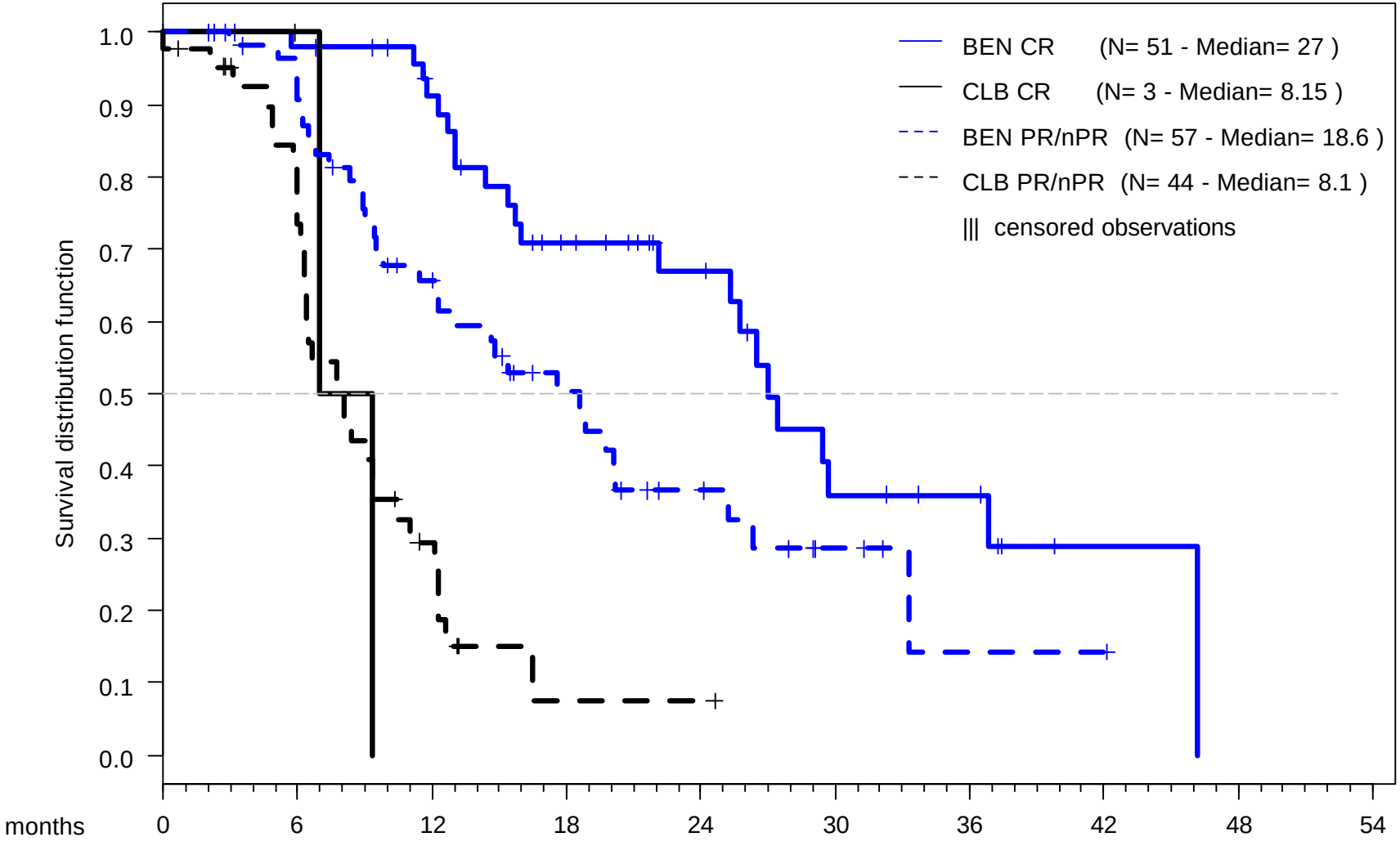
Clinical responses according to Binet stage (ITT population by ICRA assessment)

Binet stage	BEN (n=162)	CLB (n=157)
Binet B	80 (69,0%)	37 (33,0%)
Binet C	28 (60,9%)	10 (22,2%)

Kaplan-Meyer plot of progression-free survival (ICRA)



Duration of complete and partial response (ICRA)



Bendamustine + Rituximab

Phase II trial in pts. with relapsed CLL

Pts	No. #	ORR	CR	PR
62	4.5	77.4	14.5	62.9

Preliminary data, only 62 / 81 pts evaluated for response

Fischer K; ASH 2008

Chemoimmunotherapy with Fludarabine (F), Cyclophosphamide (C), and Rituximab (R) (FCR) versus Fludarabine and Cyclophosphamide (FC) improves response rates and progression-free survival (PFS) in previously untreated patients (pts) with advanced chronic lymphocytic leukemia (CLL)

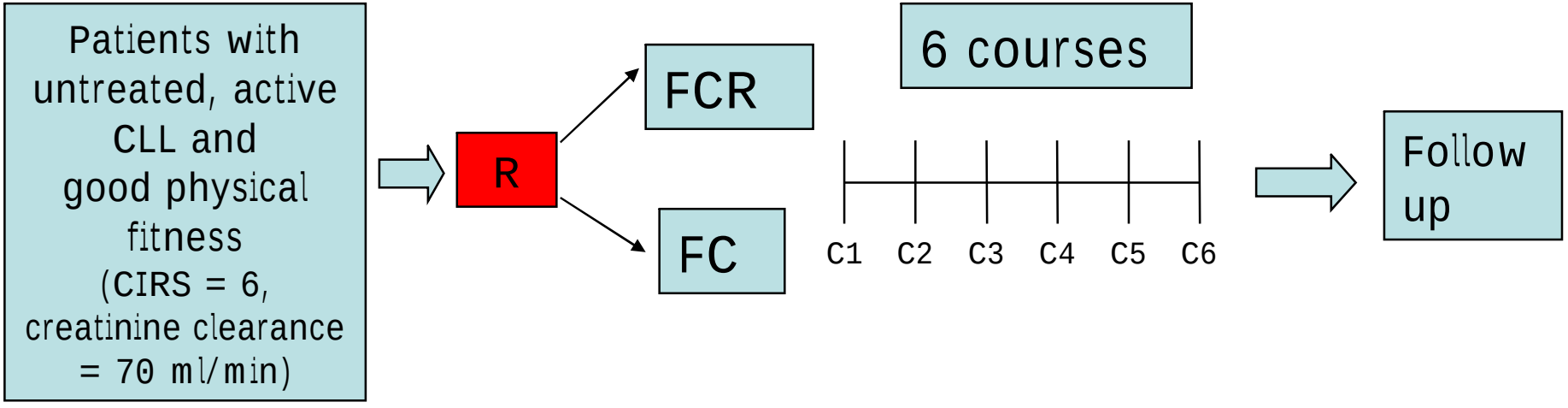
Hallek M*, Fingerle-Rowson G, Fink A-M, Busch R, Mayer J, Hensel M, Hopfinger G, Hess G, von Grünhagen U, Bergmann M, Catalano J, Zinzani PL, Caligaris Cappio F, Seymour J, Berrebi A, Jäger U, Cazin B, Trneny M, Westermann A, Wendtner C-M, Eichhorst BF, Staib P, Boettcher S, Ritgen M, Stilgenbauer S, Mendila M, Kneba M, Döhner H, Fischer K on behalf of an international group of investigators and of the German CLL Study Group (GCLLSG).

*University of Cologne, Germany

ASH 2008

DEUTSCHE CLL STUDIENGRUPPE

CLL8 Study Design



Primary endpoint

-Progression-free survival (PFS)

Secondary endpoints

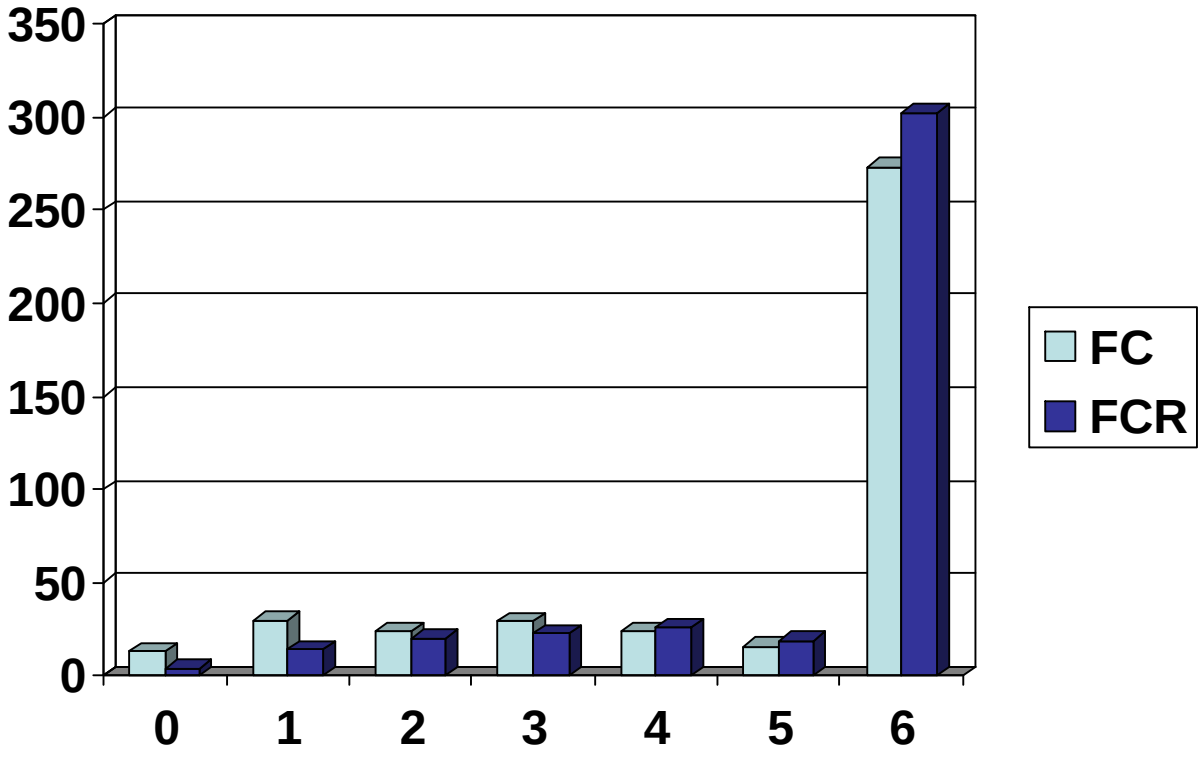
- Overall survival
- Rates of molecular, complete and partial remission
- Rates of treatment-related adverse effects

Patients: ITT population (n=817) of the CLL8 protocol

	FC (n = 409)	FCR (n = 408)
Female	105 (26%)	105 (26%)
Male	304 (74%)	303 (74%)
Median age	61 (range 36-81)	61 (range 30-80)
Binet A	22 (5.4%)	18 (4.4%)
Binet B	259 (63.6%)	263 (64.6%)
Binet C	126 (31%)	126 (31%)
B symptoms*	197 (48%)	167 (41%)
Median cumulative illness rating scale (CIRS)	1 (range 0-8)	1 (range 0-7)
Trisomy 12	14.4%	9.6%
Del(13q)	59.9%	53.7%
Del(11q23)	22.5%	26.7%
Del(17p13)	9.5%	7.0%

*P<0,05

Number of treatment courses applied

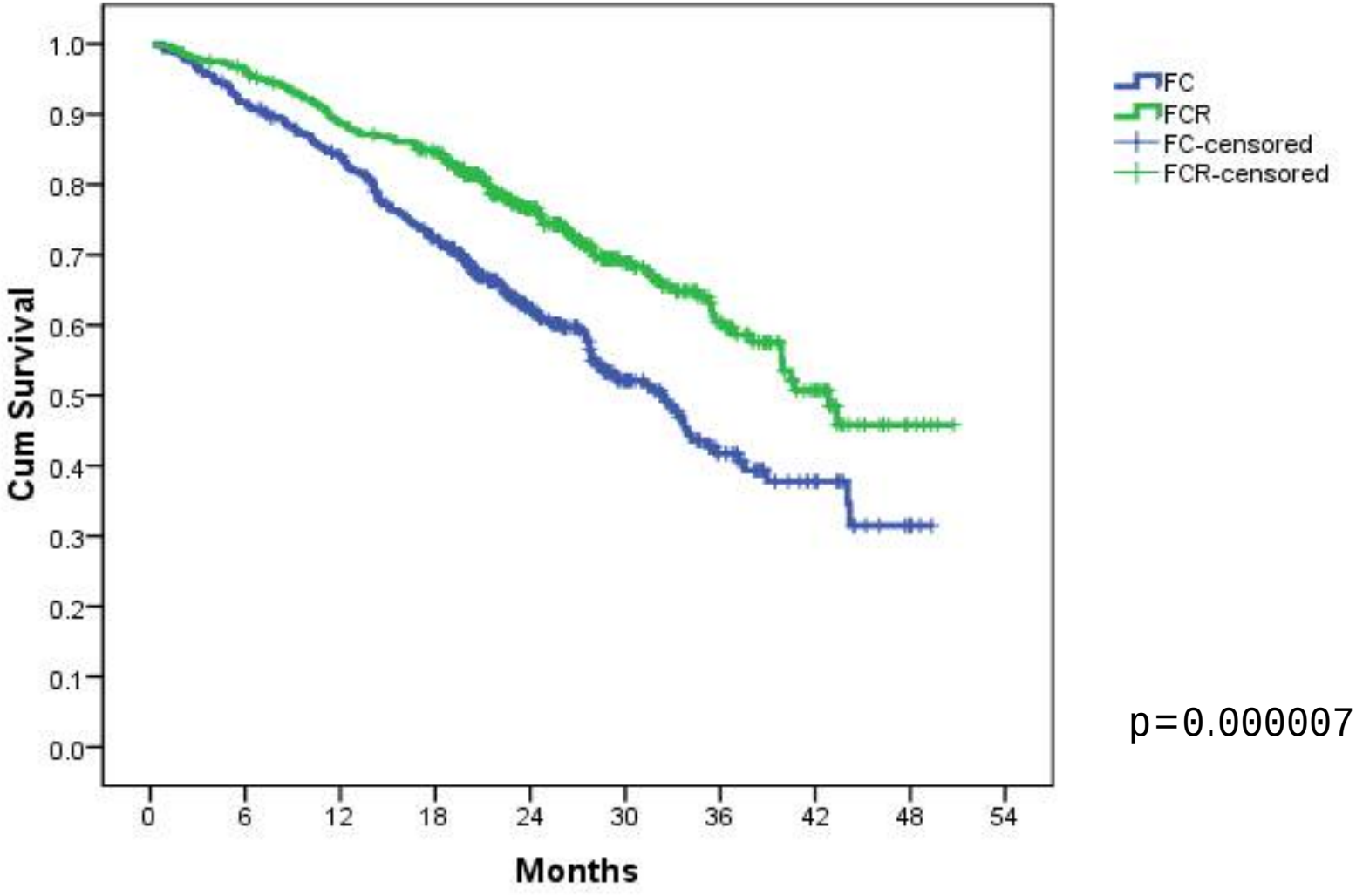


Response to treatment

	FC	FCR	p
CR	22.9%	44.5%	<0. 01
CR_u	5.1%	3.3%	0.22
CR_i	1.9%	2.6%	0.52
nPR	4.9%	2.8%	0.15
PR	50.4%	39.6%	<0.01
SD	6.7%	3.9%	0.08
PD	8.1%	3.3%	<0.01

Progression free survival: FCR versus FC

Median observation time 25.5 months

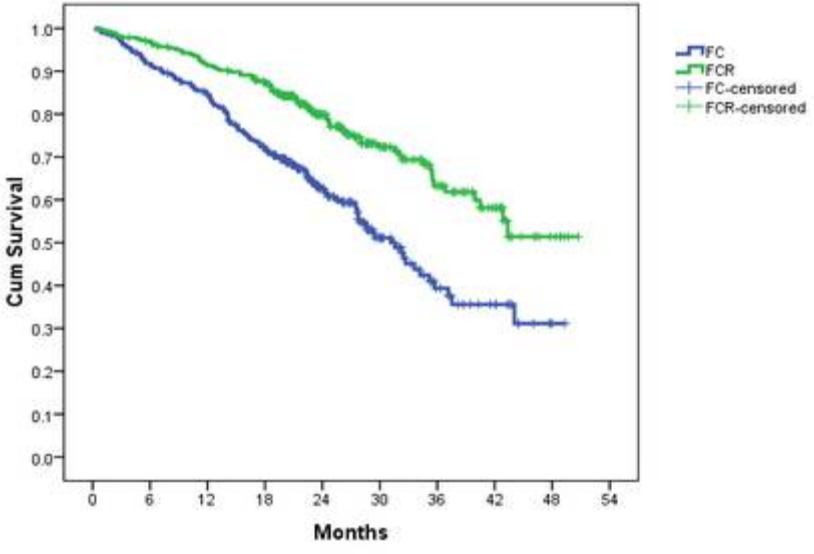


p=0.000007

Median PFS: 32.3 months for FC vs 42.8 months for FCR

Number of complete responses decreases with stage

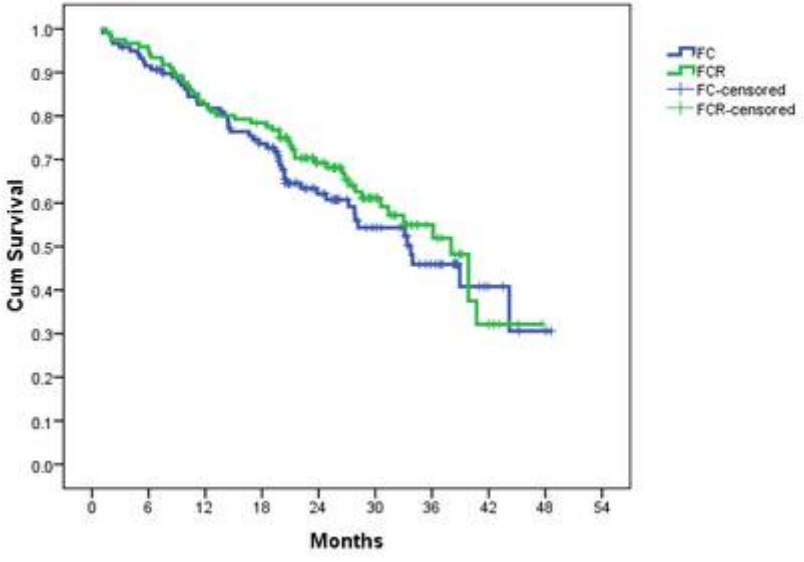
Binet stages A+B



p<0.000001

ORR 93,3%

Binet stage C



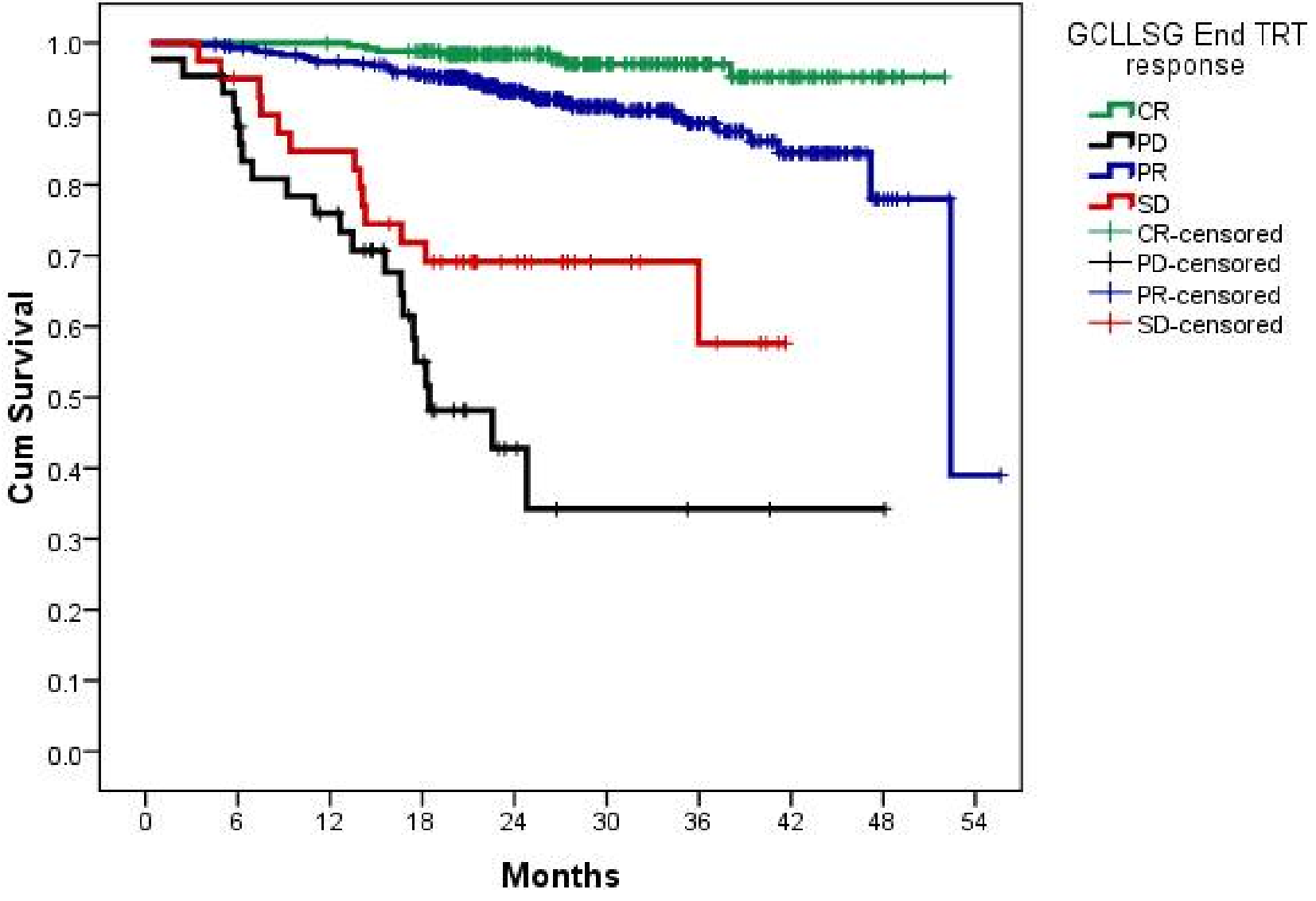
p=0.44

ORR 88,0%

Number of complete responses decreases with stage

Binet stage	CR Rate (%)
A	57,1
B	43,2
C	29,3

Overall survival and type of response



Rituximab plus Fludarabine and Cyclophosphamide (R-FC) vs. FC alone in Relapsed / Refractory CLL: Final Results of the REACH BO17072 trial

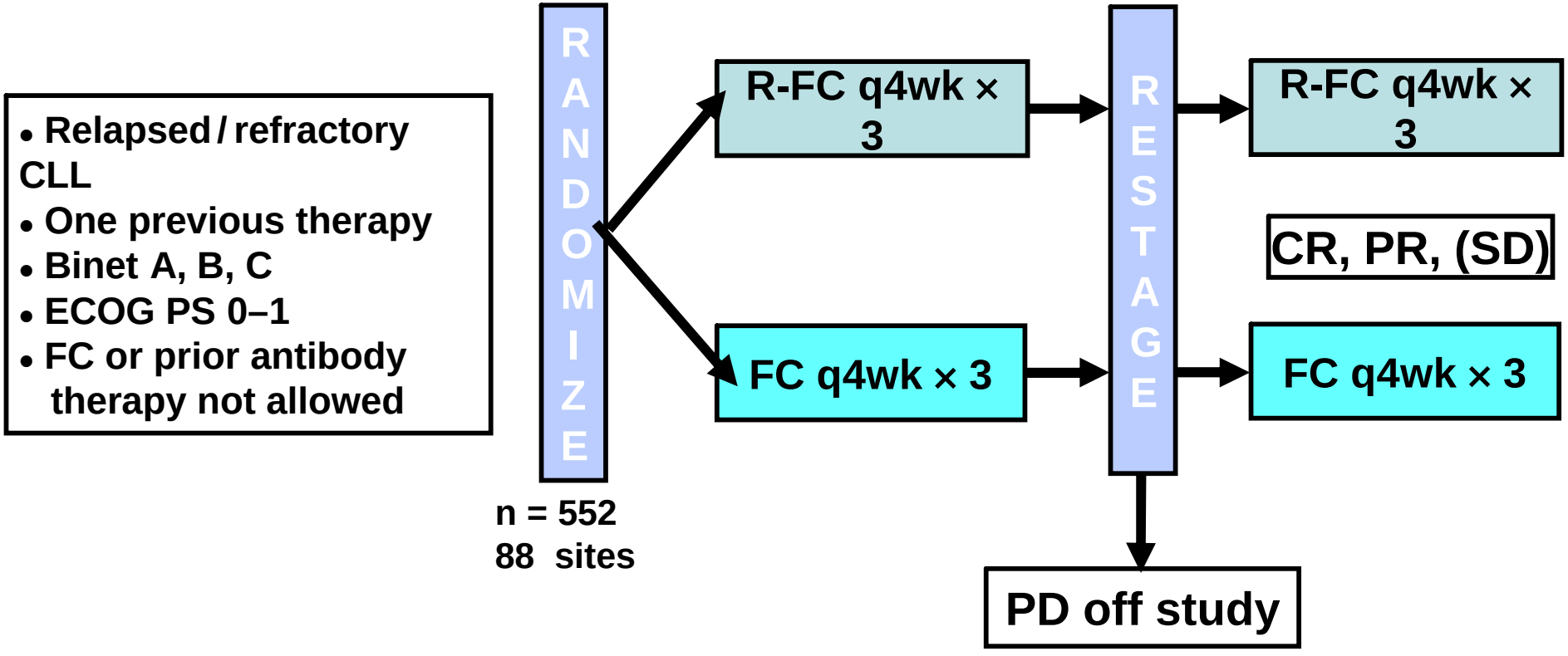
Tadeusz Robak, et al.

(multicentre, international, Europe, USA)

This study was sponsored by F. Hoffmann-La Roche Ltd.

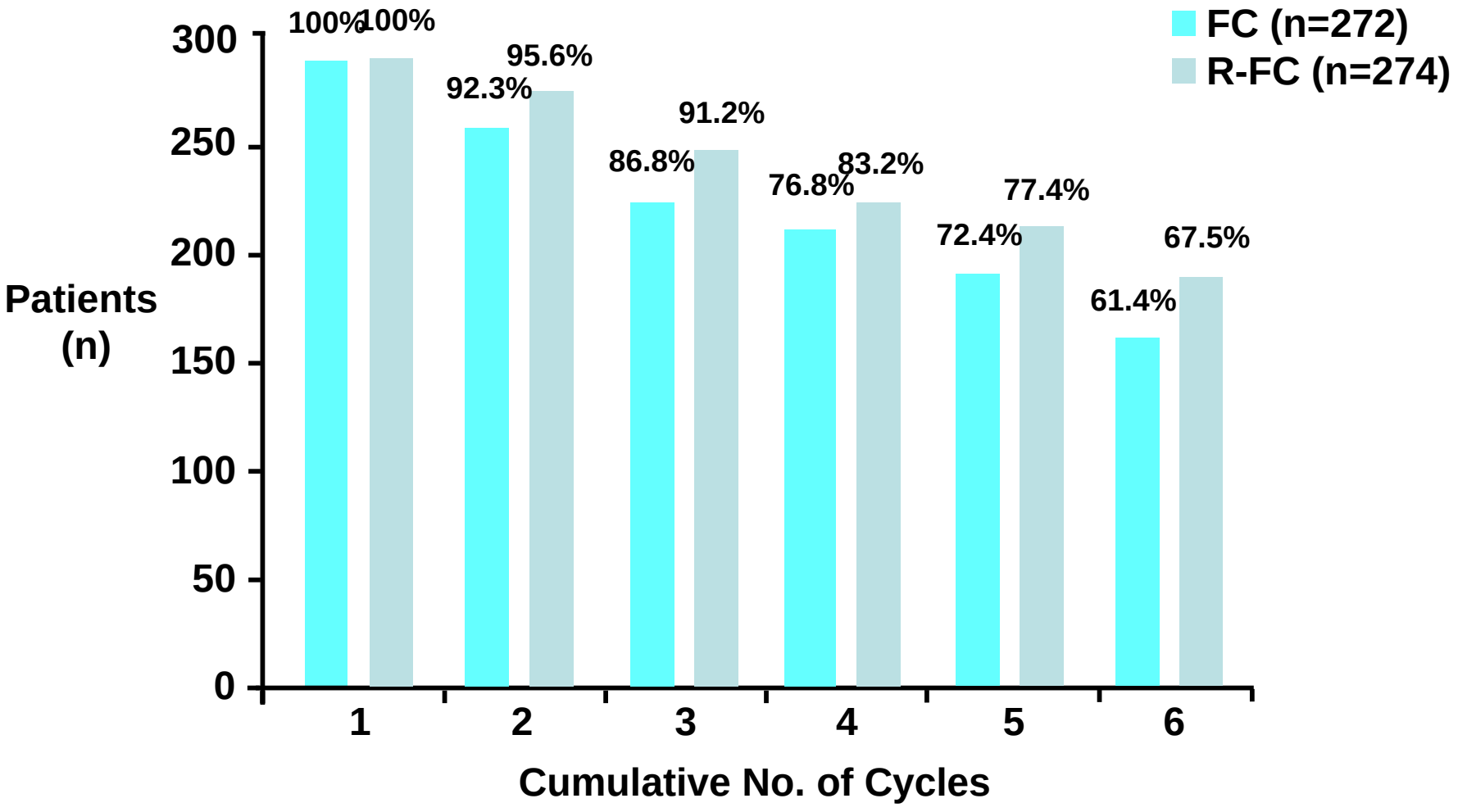
ASH 2008

REACH: Study Design – R-FC vs FC



Rituximab		Fludarabine	Cyclophosphamide
Cycle 1	375 mg/m^2 day 0	25 mg/m^2 iv, day 1–3	250mg/m^2 iv, day 1–3
Cycles 2–6	500 mg/m^2 day 1		

REACH: Treatment Cycles Received

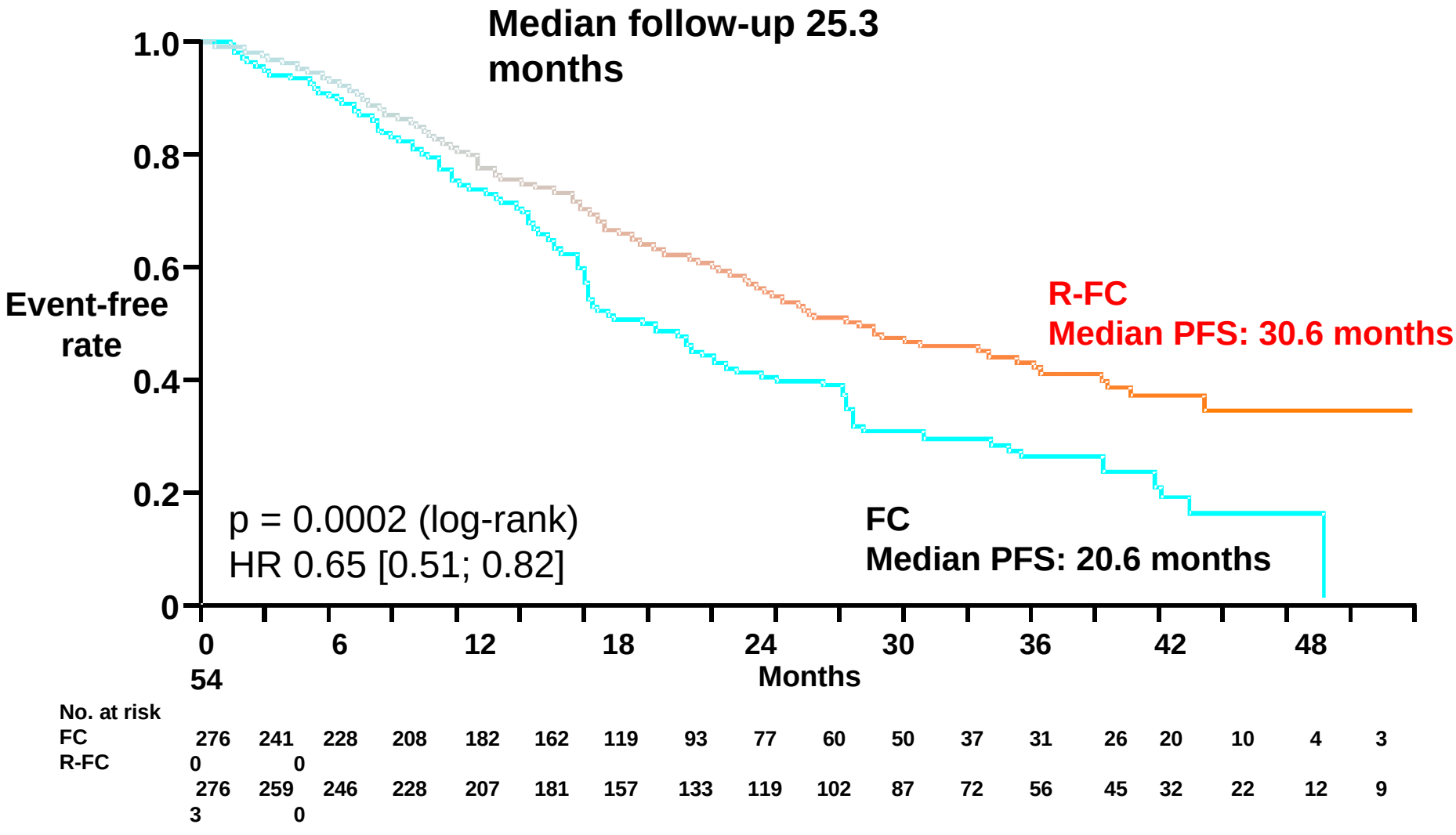


REACH: Response Rates

	FC (%) n = 276	R-FC (%) n = 276	*p*
CR	13.0	24.3	0.0007
PR/nPR	44.9	45.7	0.8642
ORR	58.0	69.9	0.0034
SD	22.1	17.0	n.d.
PD	5.4	2.5	n.d.
not evaluable*	14.5	10.5	n.d.

*Mainly patients with response that was not confirmed through a second assessment
n.d.: not done

REACH: Primary Endpoint PFS – ITT



FAZIT

Benda > CBL	**(ORR, CR, PFS)**
F > CBL	**(ORR, CR)**
FC > F	**(ORR, CR, PFS)**
FCR > FC	**(ORR, CR, PFS in Binet A/B)**
Campath > CBL	**(ORR, CR, PFS)**

Aber: CBL ohne Nachteil für OS

Konsequenzen

FCR versus BR

CBL versus CBL + R

Lenalidomide als neuer Partner ?

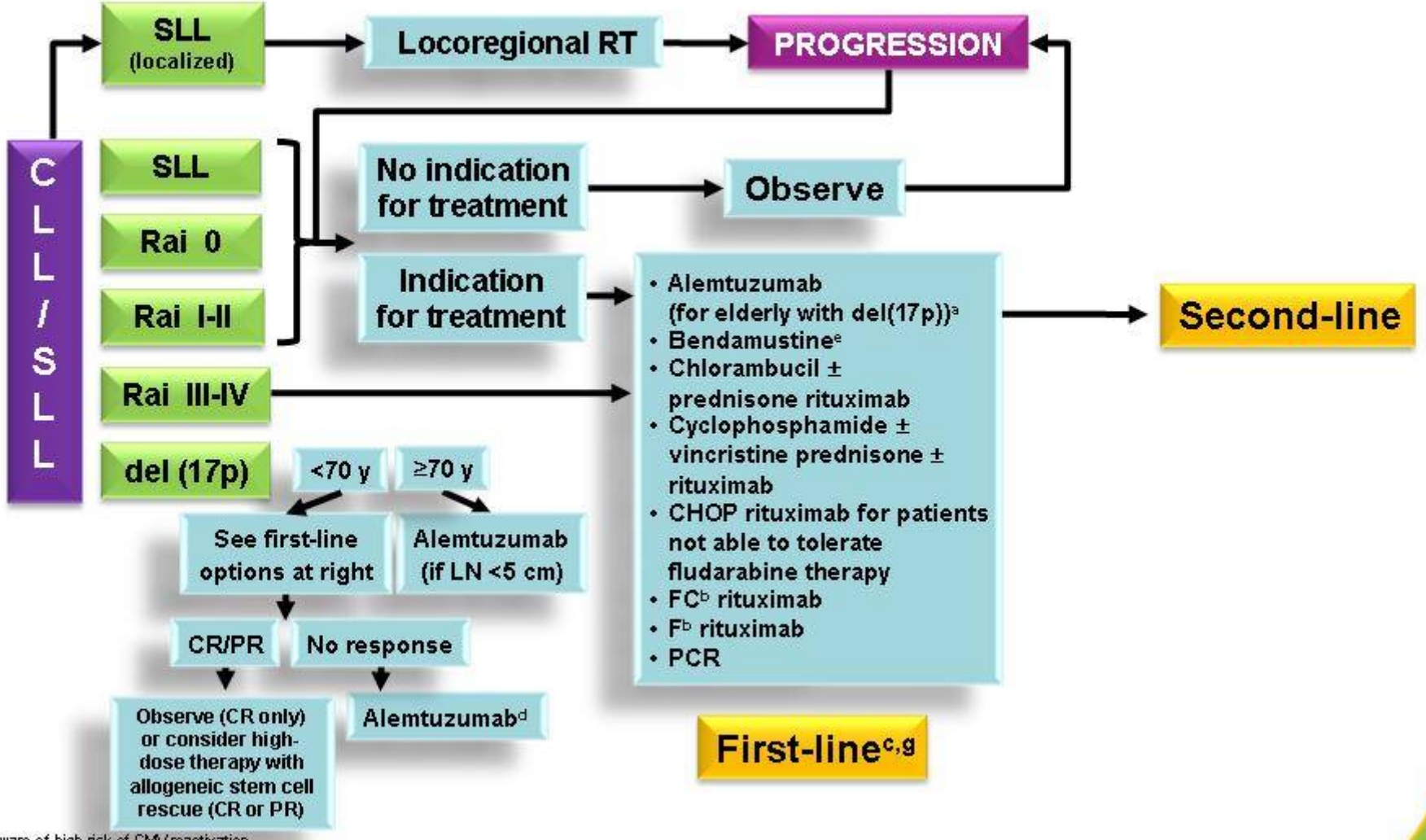
Objektivierung der physischen Verfassung (Monotherapie ? Kombination ?)

% Infections CTC grade 3-4

Author	CBL	Benda	BR	FC	FCR
Robak				19	17
Hallek				14.9	18.8
Knauf	3	7			
Fischer			5		

NCCN Practice Guidelines for CLL Updated in 2008

Use of specific drugs is reflective of NCCN guidelines, but not necessarily approved indications



[a] Must be aware of high risk of CMV reactivation.
[b] Autoimmune hemolytic anemia (AIHA) should not preclude the use of combination therapy containing fludarabine and patients should be observed carefully.
[c] Consider prophylaxis for tumor lysis syndrome.
[d] If response, consider high dose therapy with allogeneic stem cell rescue
[e] NCCN Drugs and Biologics Compendium. 2008.
[f] Rituximab and alemtuzumab should be used in combination only when there is existing literature to support its use in combination.
[g] Prophylactic therapy for shingles and pneumocystis should be considered in purine analog-based combination therapy
NCCN Clinical Practice Guidelines in Oncology. *Non-Hodgkin's Lymphomas*. V.3.2008.