Risikoprofil-gesteuerte, individualisierte Therapiestrategien bei der CLL

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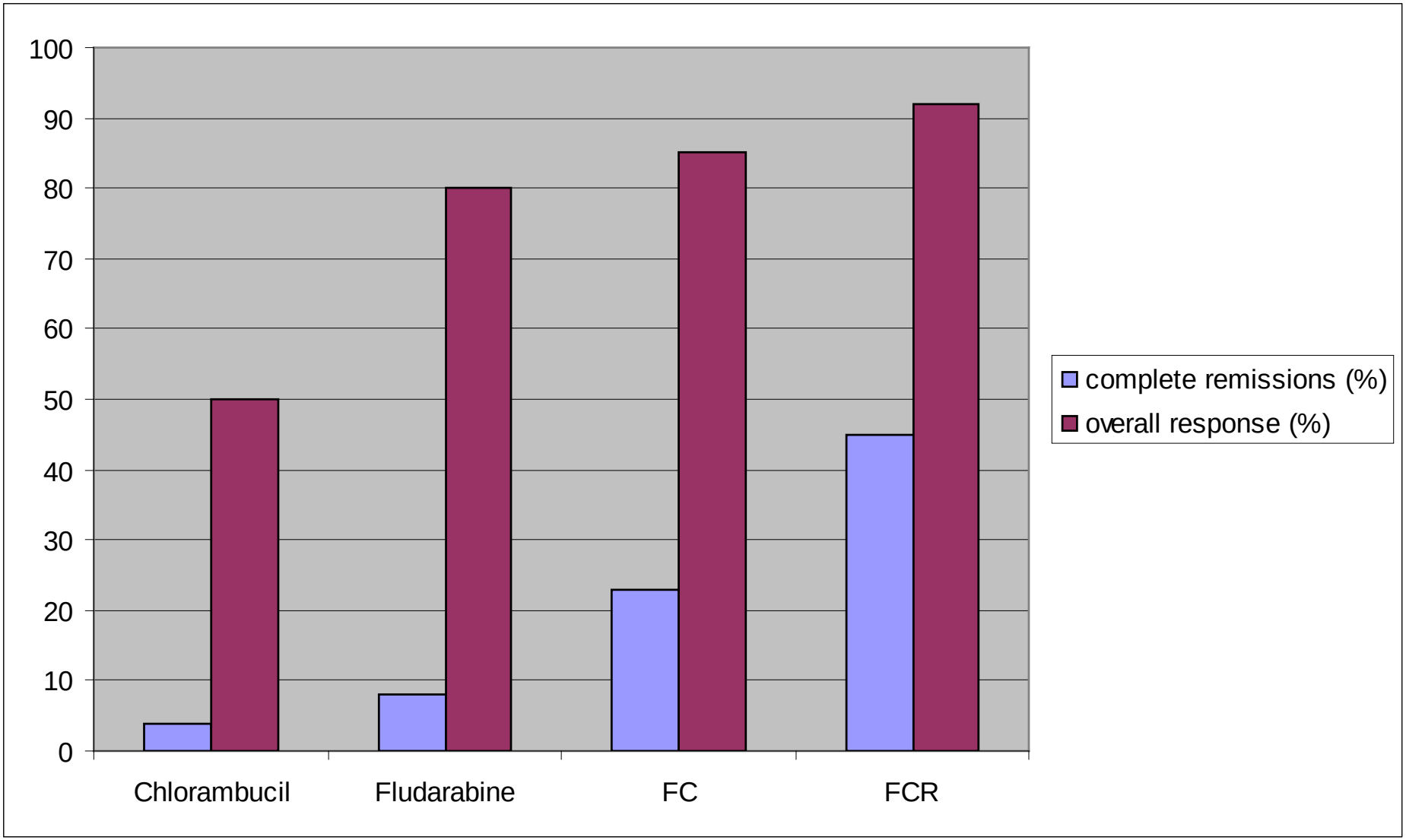
DEUTSCHE
STUDIENGRUPPE

Substantial progress in CLL therapy in one decade



How do I assess the prognosis of my CLL patient...

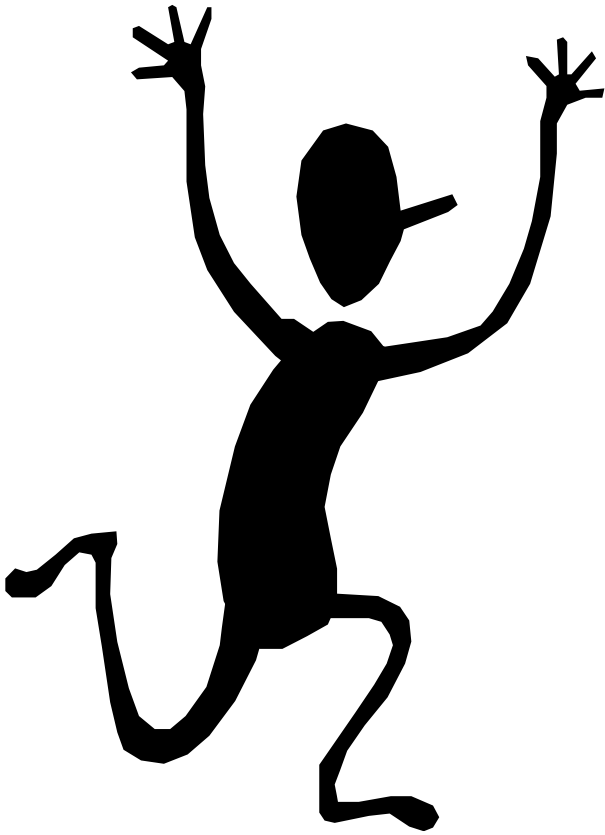
...the toolbox might need some cleaning up...

ZAP70 – sCD23 – staging – CT scan – hemoglobin – serum thymidine kinase – serum ß2-microglobulin – LDH – age – sex – CD38 – lymphocyte doubling time – B symptoms – response to treatment – MRD – immunoglobulin mutation status (IgVH) – absolute lymphocyte count – marrow infiltration pattern – PET scan – MRI – family history – lipoprotein lipase (LPL) A – gene expression microarray – del(17p) – FISH – del(11q) – conventional cytogenetics – complex karyotype abnormalites - V3.21 expression – VEGF - CD20, CD49d - Thrombopoietin - Telomere length - Telomerase activity - MCL-1 expression - Activation induced cytidine deaminase (AID) - Lipoprotein lipase A expression - ADAM29 expression - HS1 protein expression - Micro RNA genetic signature - CLLU1 expression???

Only 5 prognostic factors for CLL management

(Cramer & Hallek, Nat. Rev. Clin. Oncol. In press)

1. Staging
2. Lymphocyte doubling time
3. Response to treatment
4. Molecular cytogenetics (FISH)
5. Physical fitness



Frühe Stadien, keine Krankheits-Aktivität → keine Therapie

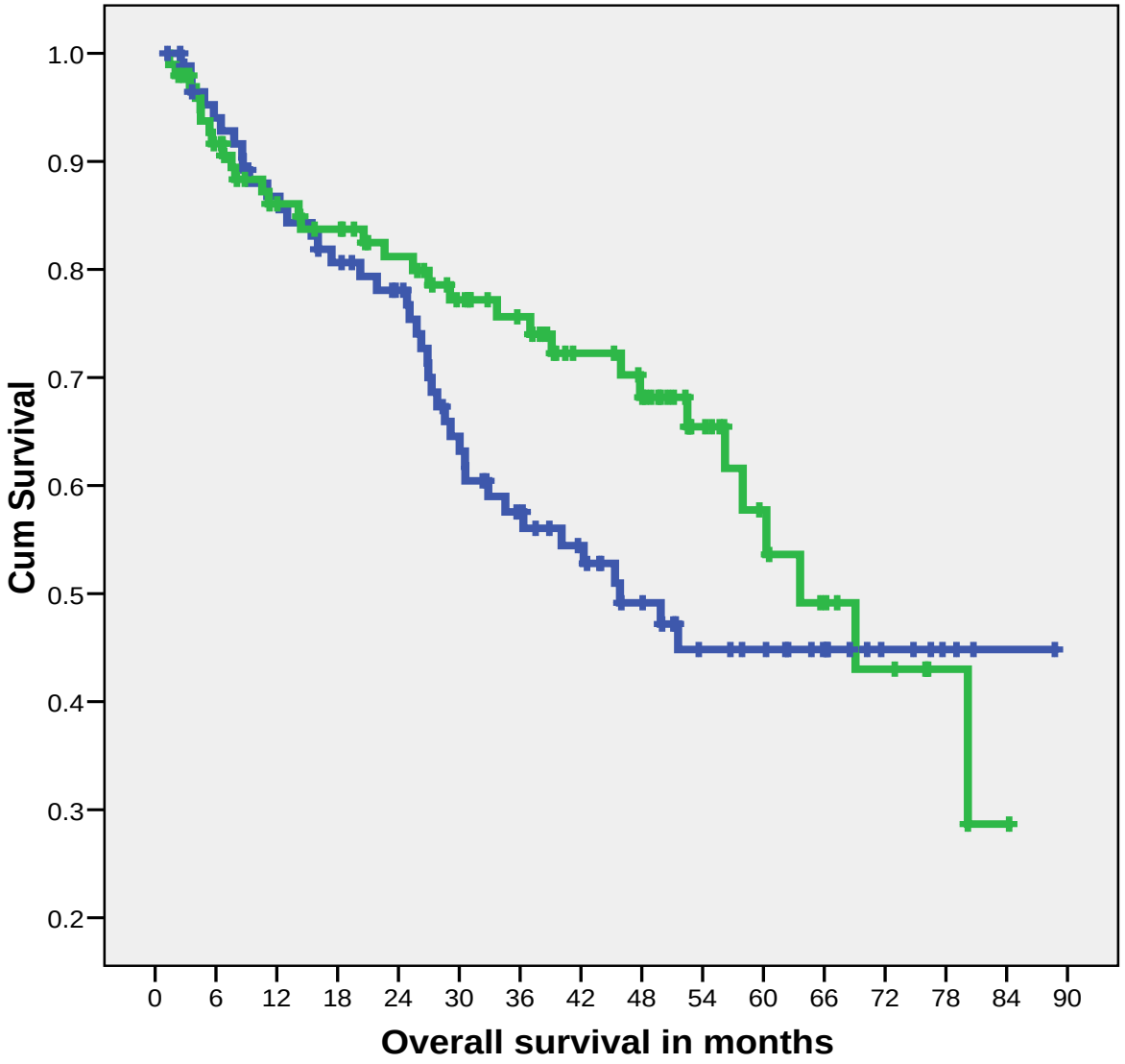
Fortgeschrittene Stadien, reduzierte Fitness → Chlorambucil

Comparison of fludarabine, bendamustine, alemtuzumab and chlorambucil as single agents

	Rai 2000[1]		Hillmen 2007[2]		Knauf 2009[3]	
Regimen N	F 179	Chl 193	Al 149	Chl 148	Ben 162	Chl 157
Median age, years	64	62	59	60	63	66
Rai Stage III-IV or Binet C, %	39	41	34	33	29	29
Grade 3/4 ↓ ANC, %	27	19	41	25	23	10.6
CR, %	20	4	24	2	31	2
OR, %	63	37	83	55	68	31
Med. PFS (mo)	20	14	14.6	11.7	21.6	8.3

1. Rai KR, *et al. N Engl J Med*. 2000; 343:1750–1757. 2. Hillmen P, *et al. J Clin Oncol.* 2007; 25:5616–5623.
3. Knauf WU, *et al. J Clin Oncol* 2009; 27:4378-4384

CLL5 protocol, patients > 65 years (median 70)



Median OS:

F 45.8 months;

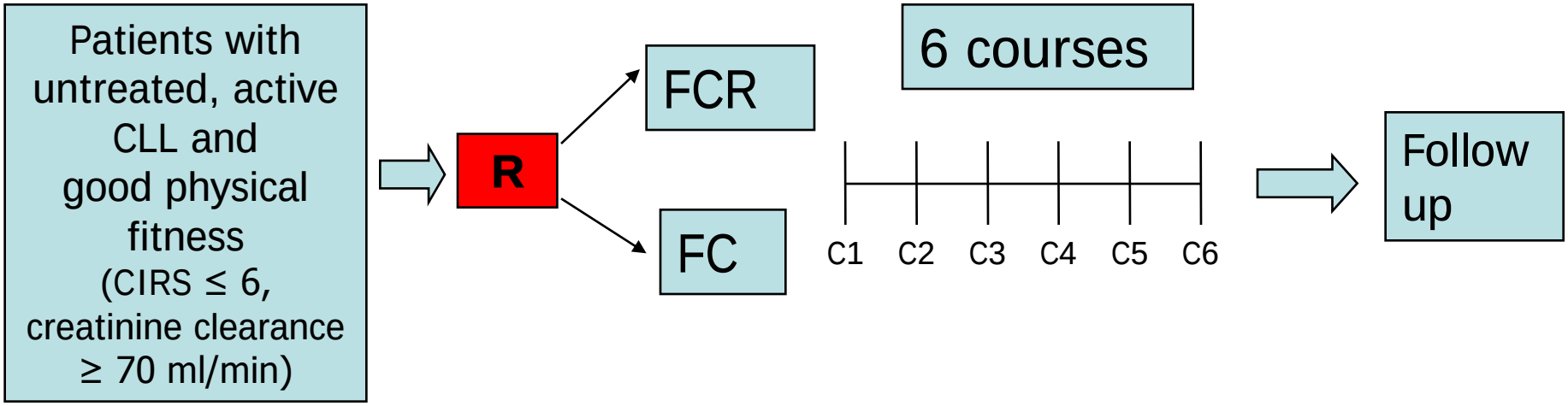
Clb 63.6 months

p = **0.15**

Fortgeschrittene Stadien, gute Fitness → FCR

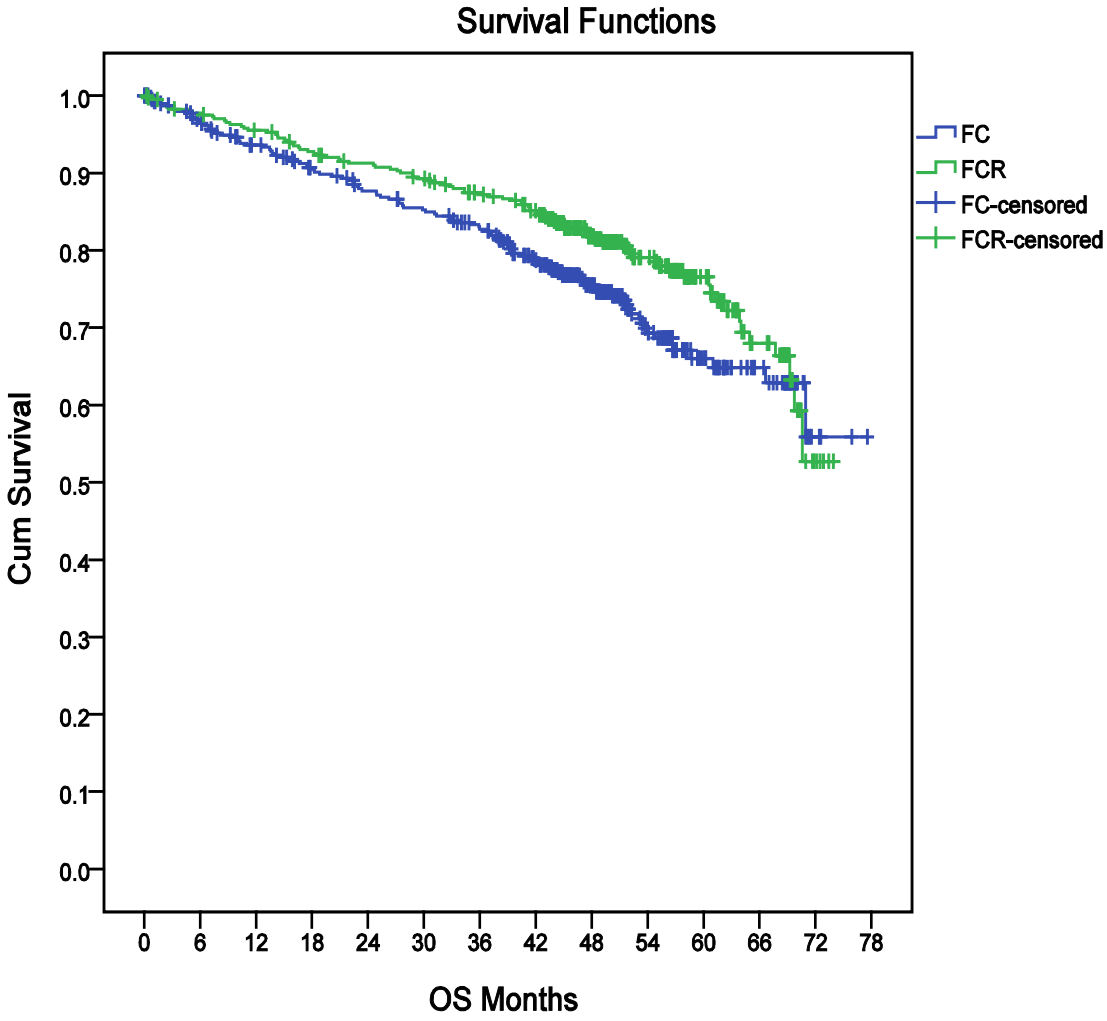
CLL8 Study Design

Hallek et al, Lancet 2010



Updated results of the 3rd analysis
Median observation time ca 48 months.

CLL8 UPDATE 2010: OVERALL SURVIVAL



N=817
Median OS not reached for both arms
75% OS:
FC: 48.4 months,
FCR: 60.7 months,
Hazard rate: 0.75;
95%CI:0.563-0.986;
p=0.039.

At 4 years post randomisation
75,5% were alive in the FC and
81,8% in the FCR arm.

Key lessons from the CLL8 study

- FCR improves outcome
  - Response rates (CR, ORR, MRD)
  - Progression-free survival
  - Overall survival
- Achieving a good response (CR) produces longer survival.
- Choice of first line therapy improves the natural course of CLL.

Für die Praxis

Classification of patients by a comprehensive geriatric assessment (CGA)

Group 1	Group 2	Group 3
• Completely independent • No comorbidity • Normal, age-matched life expectancy	• Somewhat impaired	• Severely handicapped • High comorbidity • Reduced life expectancy
„Go go“ Intensive therapy: FCR, Tx → long lasting remissions! Cure?	„Slow go“ Mild therapy: CLB, F mono → control of symptoms	„No go“ Palliative care

Balducci L & Extermann M, *Oncologist* 2000; 5:224–237.

Emergence of a „personalized“ approach in CLL management

Diagnostics	→ Therapy
• Molecular cytogenetics (FISH)	• Del(17p)/TP53mut → Alemtuzumab or FCR → alloTx • Del(13q), Trisomy 12 → FR or FCR • Del(11q) → FCR
• MRD	• Intensify therapy if MRD+? • Maintenance therapy?
• Clinical assessment of fitness	• Slow go → Monotherapy (CLB) + antibody? • Go go → FCR

CLL 2010: first line treatment

Stage	Fitness	Therapy	
		Standard	Alternatives (trials)
Binet A-B, Rai 0-II, inactive	Irrelevant	None	Treat high risk patients
Active disease or Binet C or Rai III-IV	Go go	• FCR • del(17p): FCR, A, FA → AlloSCT	FR, BR, FA
	Slow go	• CLB • del(17p): A	• Dose-reduced F, FC, B, FCR • CLB+R or CLB+O or CLB+GA101 • MAb monotherapy

CLL 2010: second line treatment

Response to therapy	Fitness	Therapy	
		Standard	Alternatives (trials)
Refractory or progression within 1-2 years	Go go	A, FA, FCR→Allo SCT	flavopiridol, lenalidomide, BR
	Slow go	Trial! A	F (unless del(17p)), FCRlite, BR, Bendamustine Lenalidomide, Ofatumumab, HD Rituximab
Progression after 1-2 years	all	Repeat first line	

Third-generation of trials of the GCLLSG: Risk, stage and fitness adapted