UNIKLINIK KÖLN

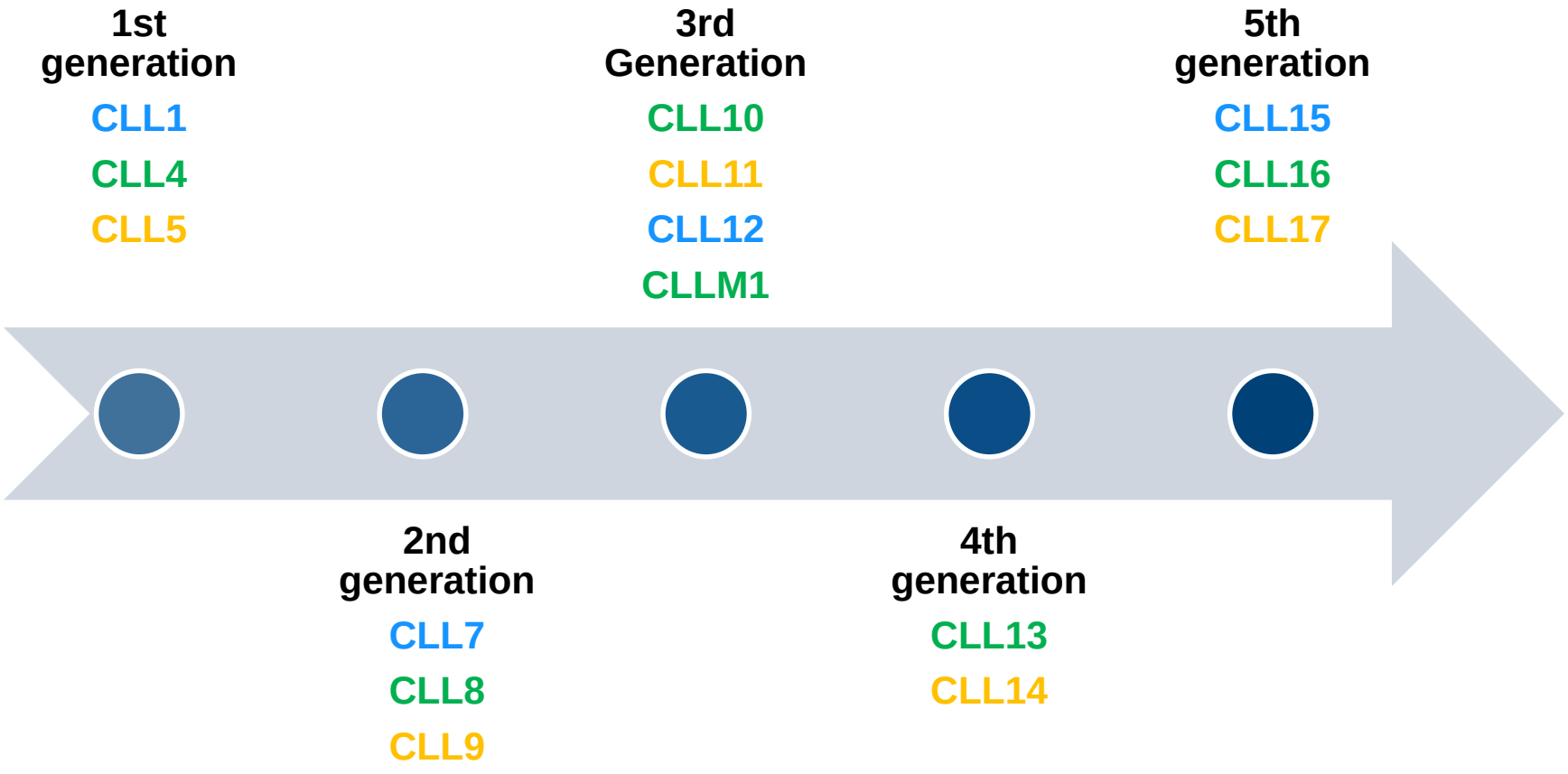
DEUTSCHE STUDIENGRUPPE

Behandlungsstrategien bei der CLL und Studien der DCLLSG

Frankfurt
22. März 2019
Barbara Eichhorst

Wissenschaftliches Studienkonzept der DCLLSG

DEUTSCHE STUDIENGRUPPE



Early stage disease Advanced stge + fit Advnced stage + less fit

Frühes Stadium

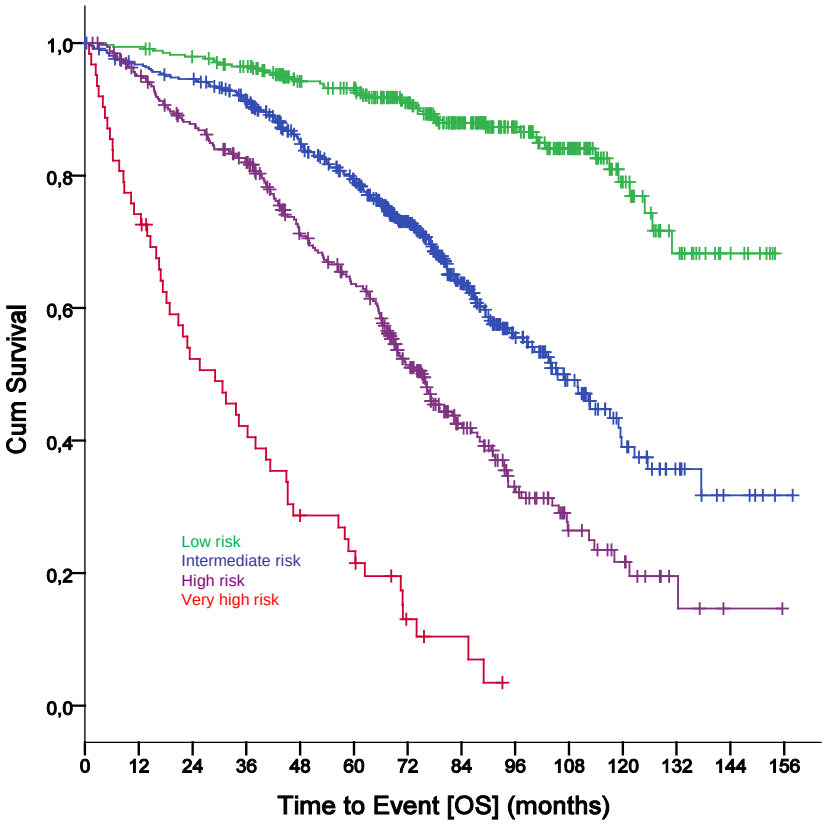
CLL INTERNATIONAL PROGNOSTIC INDEX

3472 patients from 5 study groups in US and Europe

Additional validation cohorts from US and Scandinavian groups.

Variable	Adverse factor	Coeff.	HR	Grading
TP53 (17p)	deleted and/or mutated	1.442	4.2	4
IGHV status	Unmutated	0.941	2.6	2
B2M, mg/L	> 3.5	0.665	2.0	2
Clinical stage	Binet B/C **or** Rai I-IV	0.499	1.6	1
Age	> 65 years	0.555	1.7	1

Prognostic Score					0 – 10
Risk group	Score	Patients N (%)	5-year OS, %	HR (95% CI)	*p* value
Low	0 – 1	340 (29)	93.2		
Intermediate	2 – 3	464 (39)	79.4	3.5 (2.5 - 4.8)	< 0.001
High	4 – 6	326 (27)	63.6	1.9 (1.5 - 2.3)	< 0.001
Very High	7 – 10	62 (5)	23.3	3.6 (2.6 - 4.8)	< 0.001

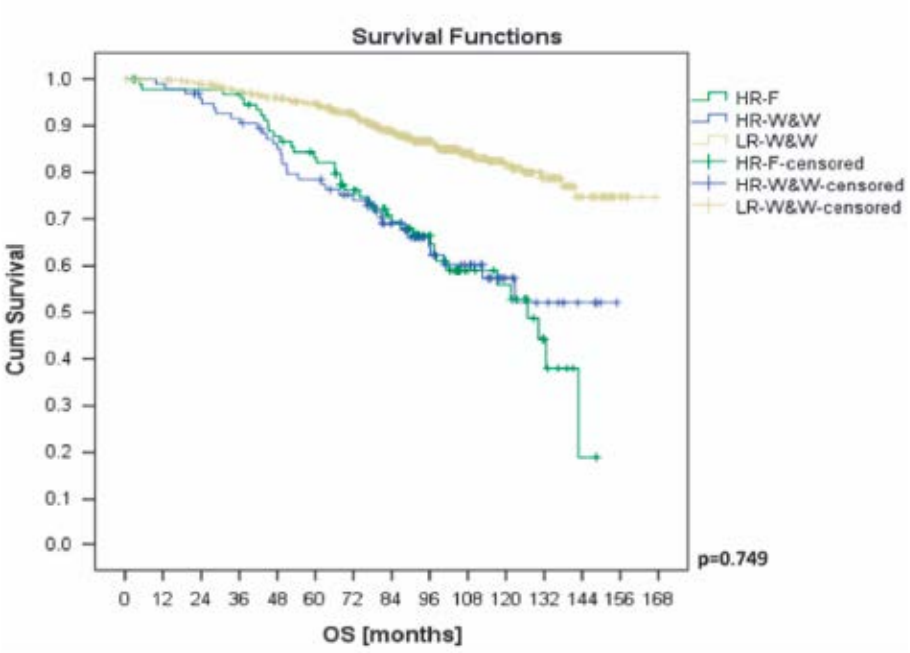


CLL-IPI Working Group ,
Lancet Oncol 2016

Chemo/Chemoimmuntherapie im Binetstadium A ohne Vorteil für das Überleben

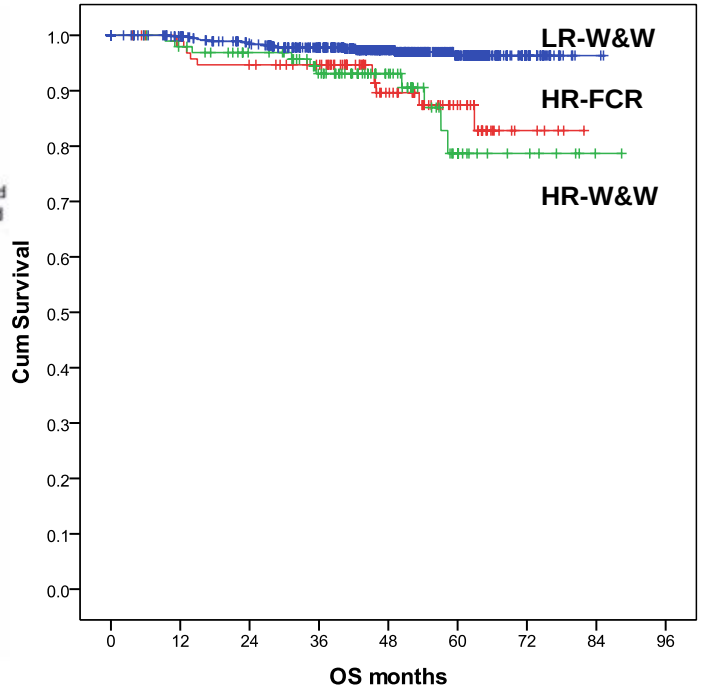
Gesamtübereleben

CLL1



Hoechstetter et al., Leukemia 2017

CLL7

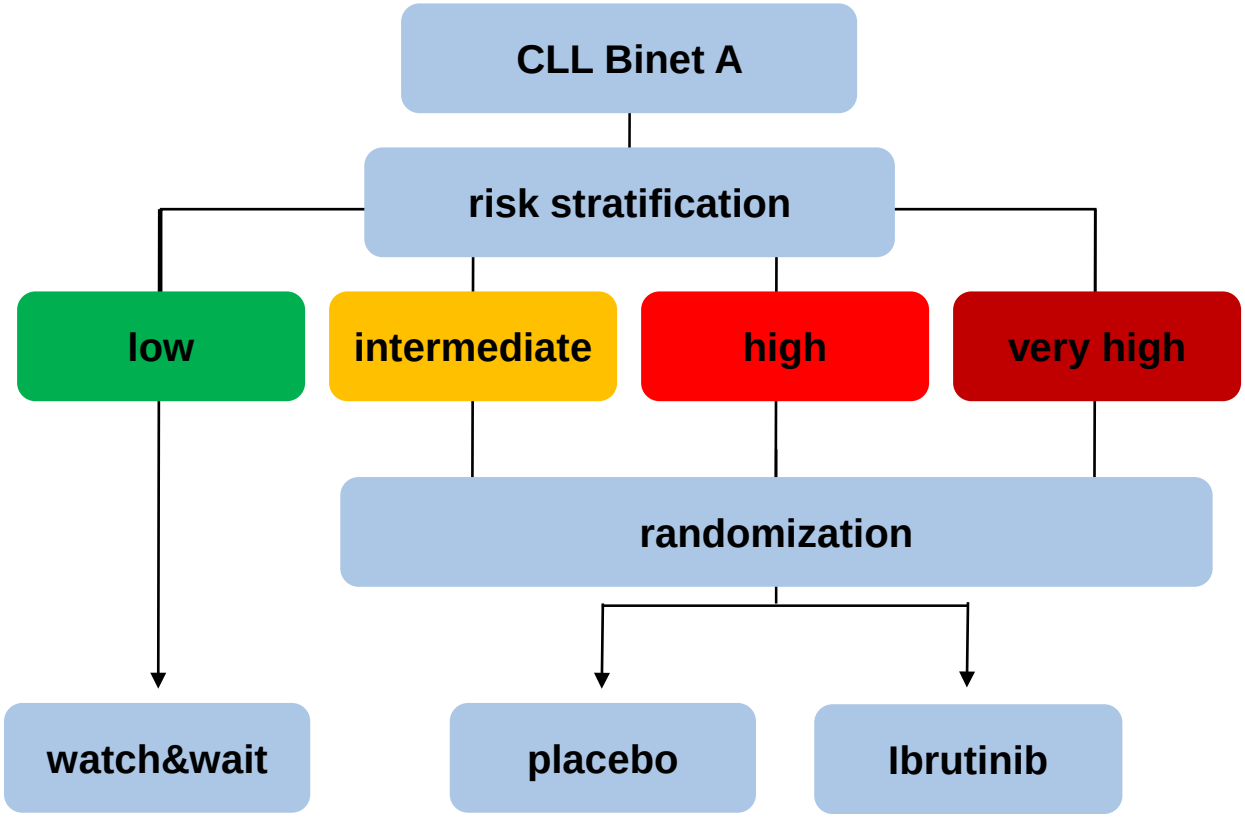


Log rank *P* < 0.001

Schweighofer et al., submitted

Sollte die Risiko-CLL im frühen Stadium mit Ibrutinib behandelt werden ?

CLL12 STUDIEN DESIGN



Phase III, placebo-controlled, double-blind, multicenter trial
Primary endpoint: EFS
Secondary endpoints: survival, PFS, TFS, TTNT, ORR, safety

Fortgeschrittenes Stadium

Therapieempfehlungen der DCLLSG 2018

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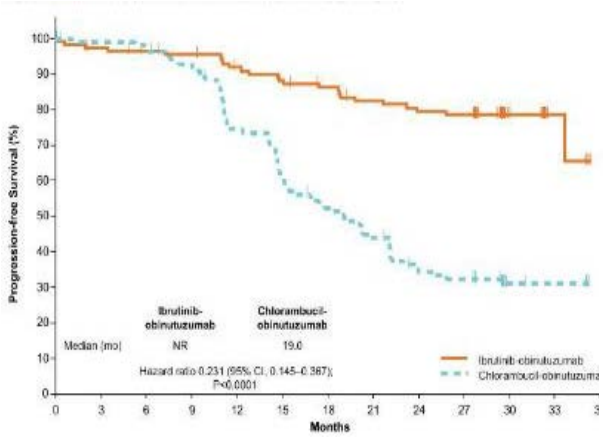
Binet Stadium	Fitness	Genetische TP53-Veränderungen	Erstlinientherapie
A/B ohne Symptome	irrelevant	irrelevant	keine
C, A/B mit Symptomen	go go	nein	FCR (BR ≥ 65 Jahre)
		ja	Ibrutinib, Bei Kontraindikationen bzgl. Ibrutinib: Venetoclax, Idelalisib + R, (allo HCTx)
	slow go	ja	
		nein	Chlorambucil + CD20-Antikörper (Obinutuzumab, Ofatumumab, Rituximab) oder Ibrutinib

Phase III Studien: Erstlinie Ibrutinib vs CIT

Trial	Arms	N Patients	Median age	% TP53mut /del
iLLUMINATE	Clb + Obinutuzumab	116	72	20%
	Ibrutinib+Obinutuzumab	113	70	16%
Alliance	BR	183	70	9%
	Ibrutinib	182	71	12%
	Ibrutinib + Rituximab	182	71	12%
ECOG-ACRIN E1912	FCR	175	58	0%
	Ibrutinib + Rituximab	345	57	0%

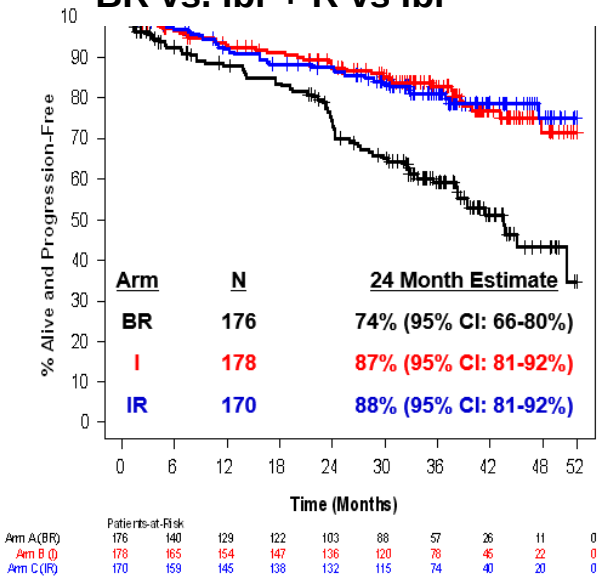
Ibrutinib verlängert gegenüber CIT das PFS

CLB+Obin vs. Ibr + Obin



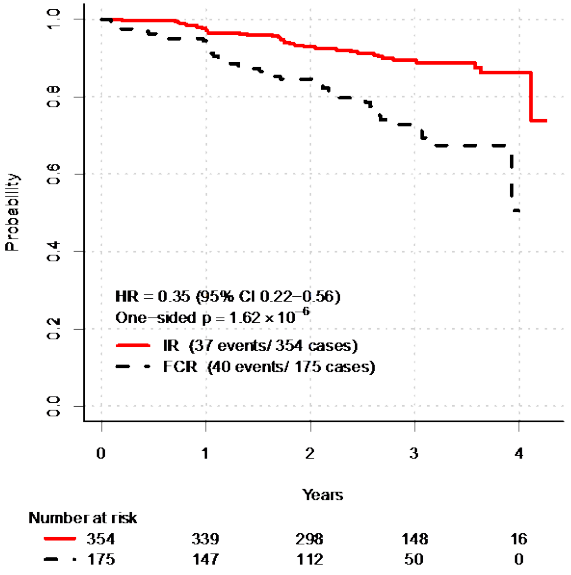
C. Moreno et al., Lancet Oncol 2018

BR vs. Ibr + R vs Ibr



J. Woyach et al., NEJM 2018

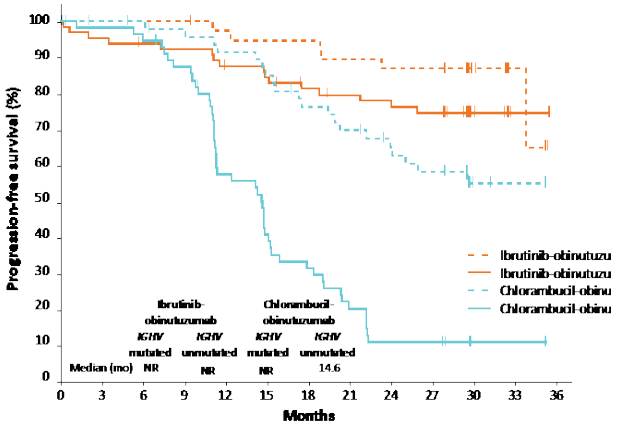
FCR vs Ibr+R



T. Shanafelt et al., ASH 2018

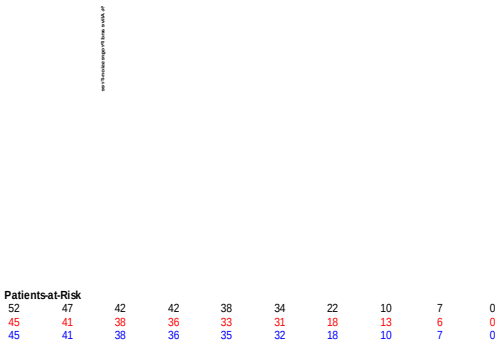
Ibrutinib verlängert gegenüber CIT das PFS – vor allem bei unmutiertem IGHV und weniger deutlich bei mutiertem IGHV

CLB+Obin vs. Ibr + Obin



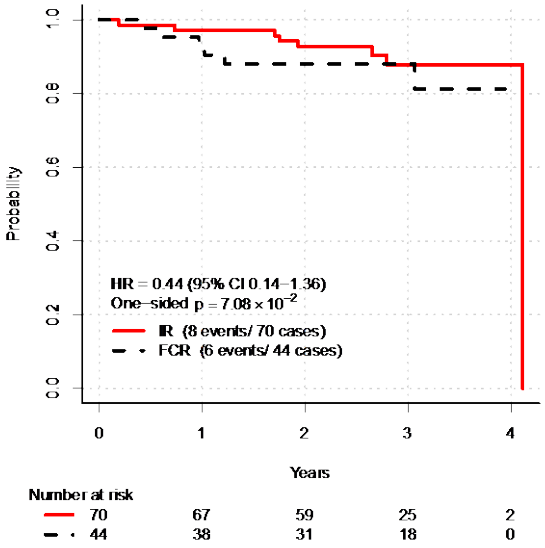
C. Moreno et al., Lancet Oncol 2018

BR vs. Ibr + R vs Ibr - nur mutierter IGHV



J. Woyach et al., NEJM 2018

FCR vs Ibr+R - nur mutierter IGHV



T. Shanafelt et al., ASH 2018

CLL Erstlinientherapie 2019

DEUTSCHE STUDIENGRUPPE

Stage	Fitness	del(17p) or p53mut	IGVH	Therapy
Binet A-B, Rai 0-II, inactive disease	Irrelevant	Irrelevant	irrelevant	None
Active disease or Binet C or Rai III-IV	Go go	No	M	FCR (BR above 65 years) or ibrutinib*
			U	Ibrutinib or FCR (BR above 65 years)*
		Yes	irrelevant	Ibrutinib, Venetoclax or Idelalisib+Rituximab (if contraindications for ibrutinib)
	Slow go	No	M	Chlorambucil + Obinutuzumab or Ibrutinib*
			U	Ibrutinib or Chlorambucil + Obinutuzumab*
		Yes	irrelevant	Ibrutinib or Venetoclax (+ Obinutuzumab) or Idelalisib+Rituximab (if contraindications for ibrutinib)

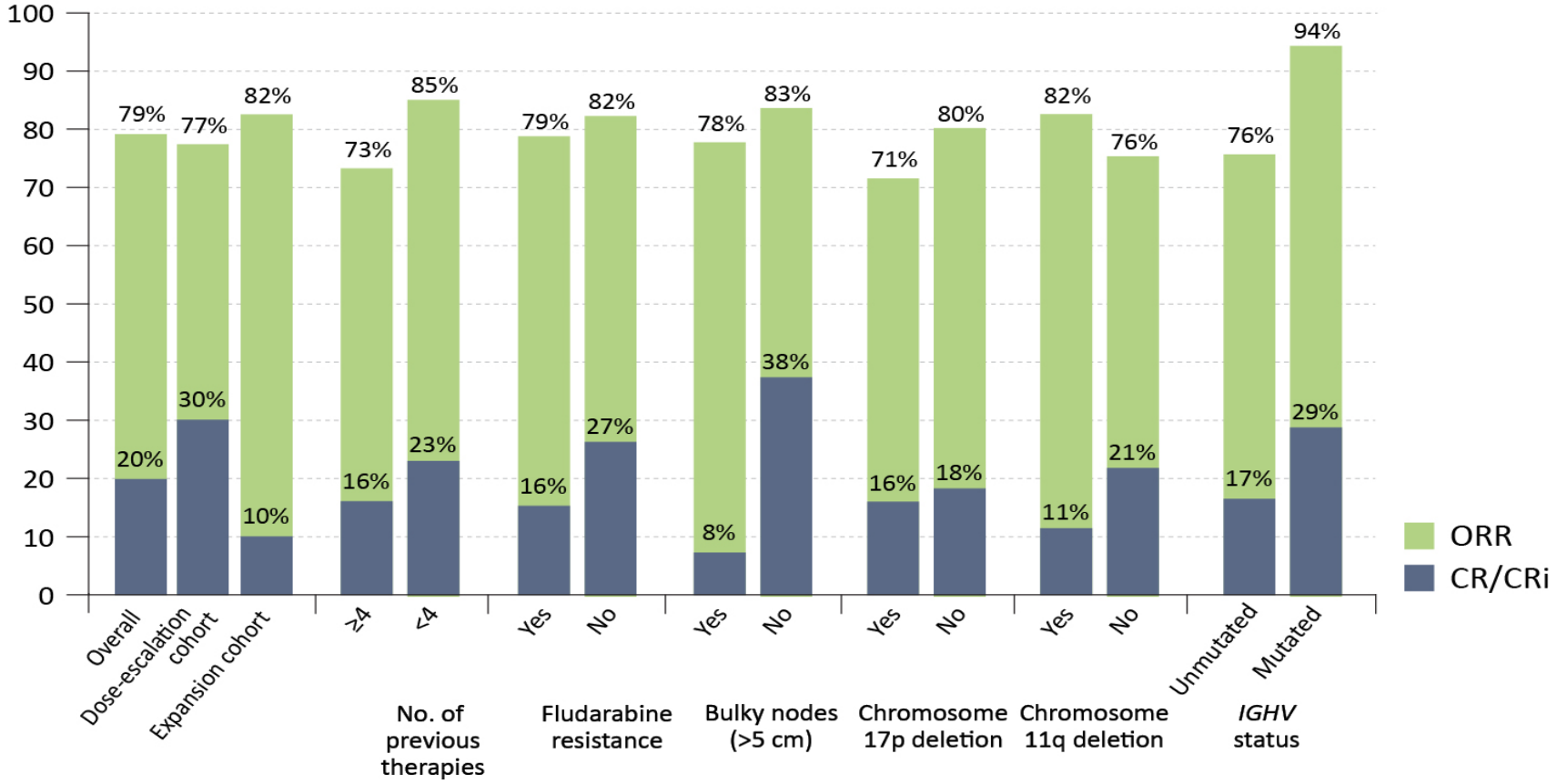
* Consider and discuss with patient: long-term vs fixed (6 m) duration therapy, lack of convincing evidence of overall survival differences, specific side effects of each therapeutic option (myelosuppression, infections, secondary malignancies (?) for CIT; cardiac toxicity, bleeding and autoimmune disease for Ibru)

CRs sind selten mit Ibrutinib – daher bisher keine Absetzstrategien mit Ibrutinib Monotherapie

Trial	N pts Ibr	Observation time	ORR best	CR
RESONATE II Burger et al., NEJM 2015	**136**	**18 mo**	**86%**	**4%**
RESONATE I Brown et al., Leukemia 2018	**195**	**19 mo**	**90%**	**7%**
Phase II O`Brien et al., Blood 2018	**132**	**60 mo**	**89%**	**29% in TN 10% in RR**

Venetoclax in der Therapie der R/R CLL

Phase II Studie in 116 Patienten



Roberts AW. *New England Journal of Medicine*. 2016;374:311–322.

CLL 14 DESIGN

Patients with untreated active CLL &
with coexisting medical conditions*

Safety Run-In Phase: Obinutuzumab + Venetoclax

Independent Data Monitoring Commitee (iDMC)

Obinutuzumab + Chlorambucil 6 x Obinutuzumab + Chlorambucil + 6 x Chlorambucil	Obinutuzumab + Venetoclax 6 x Obinutuzumab + Venetoclax + 6 x Venetoclax

Follow-up Phase

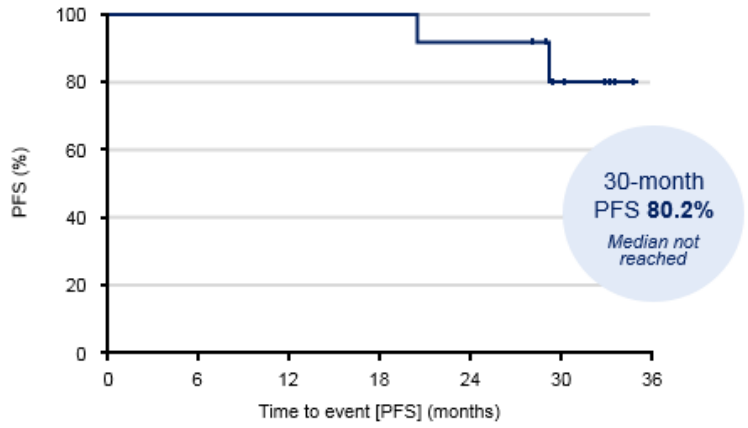
*CIRS > 6
and/ or
CrCl < 70mL/min

Fischer K et al. Blood 2017

Venetoclax + Obinutuzumab Erstlinie bei 12 Patienten in Safety Run-in: PFS & OS

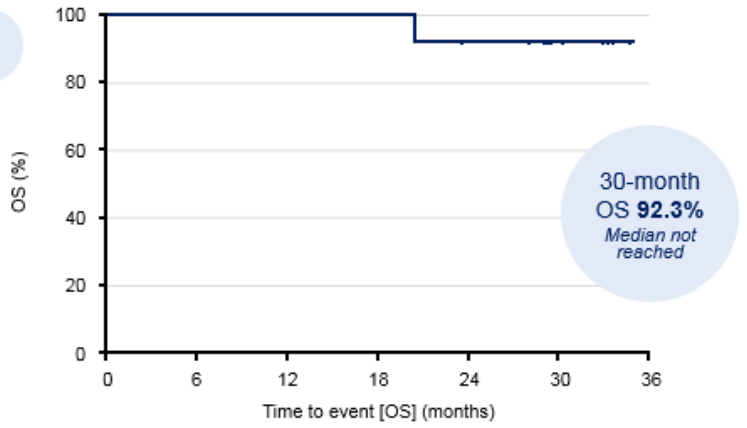
PROGRESSION-FREE SURVIVAL

A



OVERALL SURVIVAL

B



PFS, progression-free survival; OS, overall survival

Fischer K et al. EHA 2018

MEDIA

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Media Inquiries
(650) 467-6800

Wednesday, Oct 31, 2018

Phase III Data Showed That Venclexta Plus Gazyva Reduced The Risk Of Disease Worsening Or Death In People With Previously Untreated Chronic Lymphocytic Leukemia With Co-Morbidities

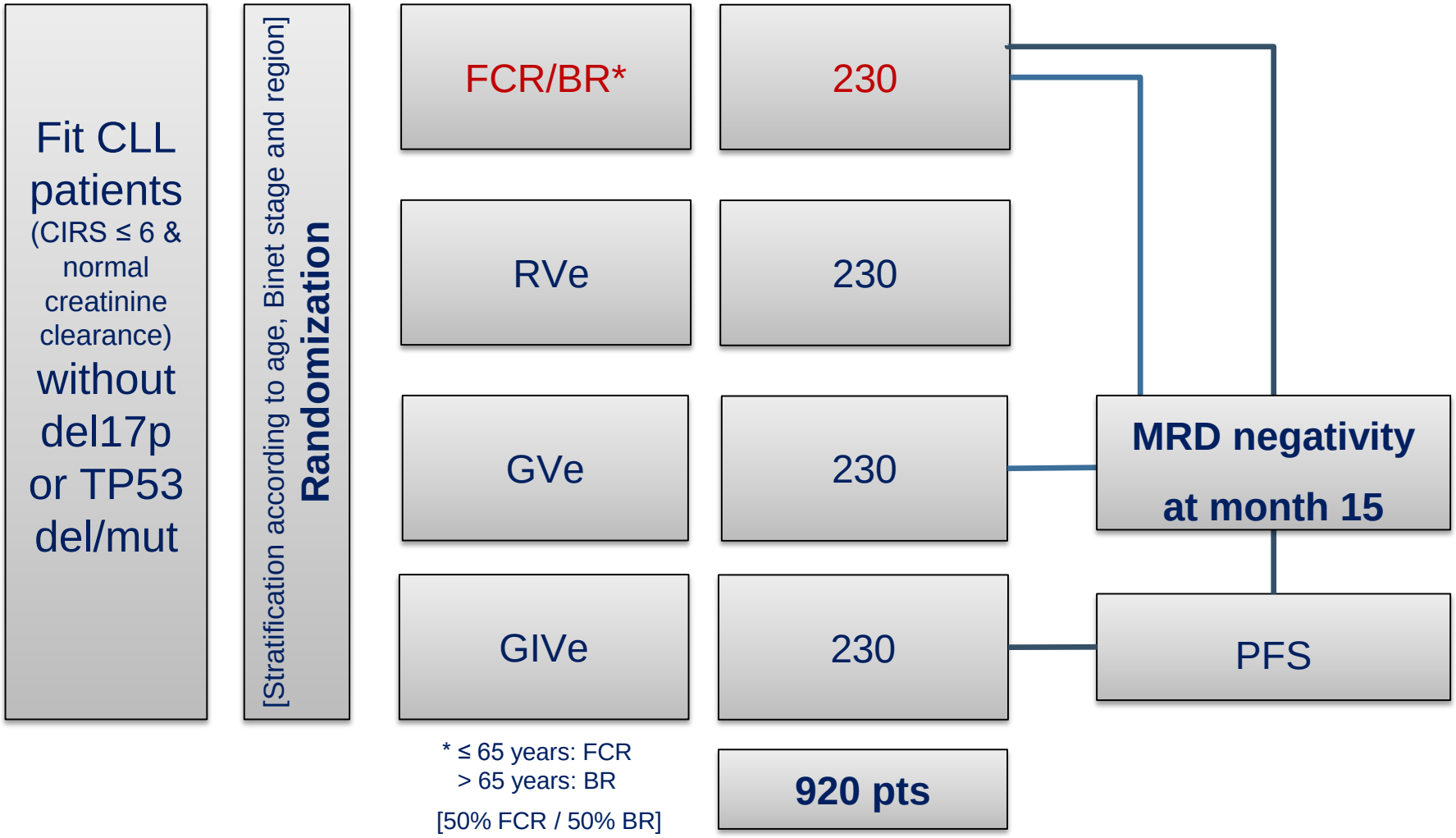
The Phase III CLL14 study compared Venclexta in combination with Gazyva to standard-of-care Gazyva plus chlorambucil

Data will be submitted to health authorities and presented at an upcoming medical meeting

South San Francisco, CA -- October 31, 2018 --

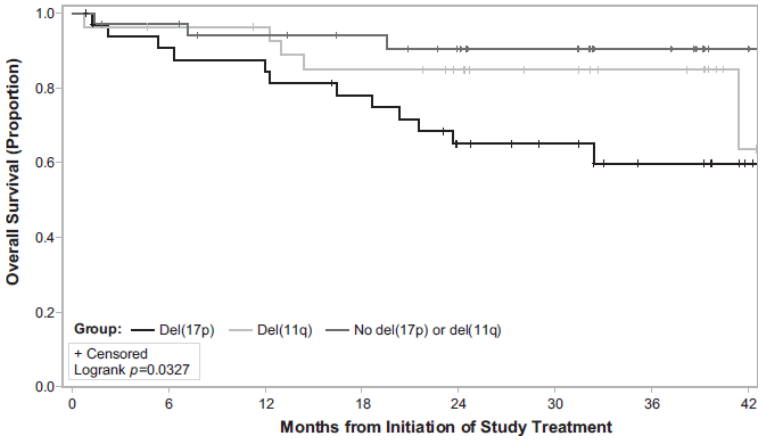
CLL13/GAIA

Standard chemoimmunotherapy vs. Venetoclax + Rituximab vs. Venetoclax + Obinutuzumab (GA101) vs. Venetoclax + Ibrutinib + Obinutzumab

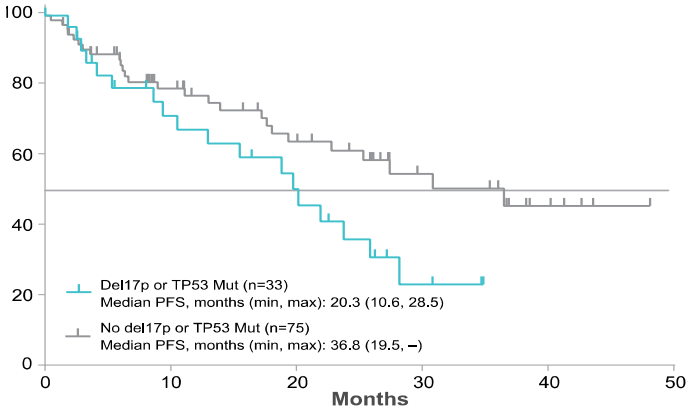


Auch mit neuen Substanzen ist die Prognose bei TP53 Mut/Del immer noch schlecht

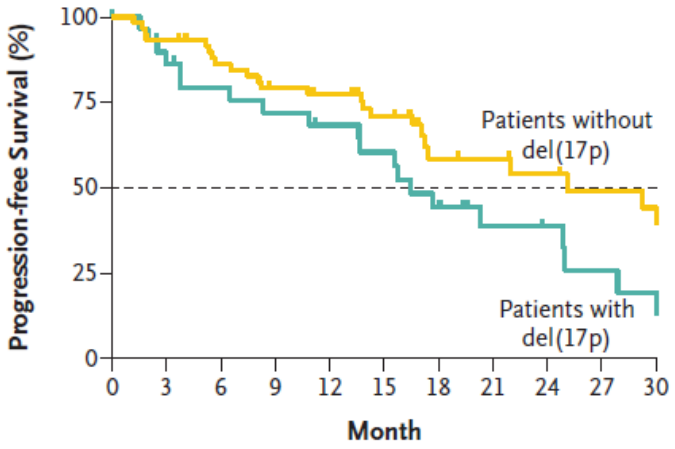
132 CLL patients 1st line and R/R receiving ibrutinib



114 CLL patients R/R receiving idela+ CIT



56 R/R CLL patients receiving venetoclax

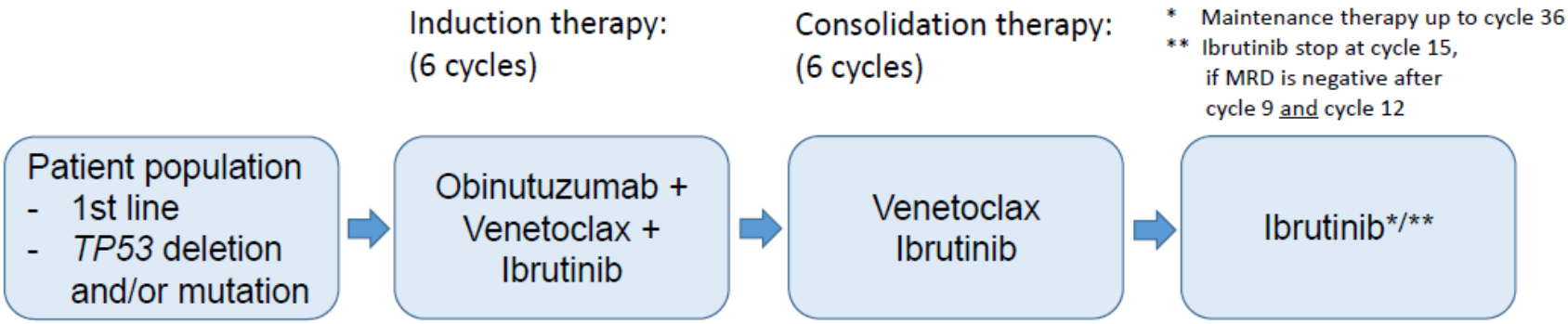


Byrd J et al., Blood 2015
Barrientos J et al., ASCO 2015
Roberts A et al., NEJM 2015

17p-/Tp53mut CLL Erstlinie: CLL2 GIVE-Studie (LKP Stilgenbauer)

DEUTSCHE STUDIENGRUPPE

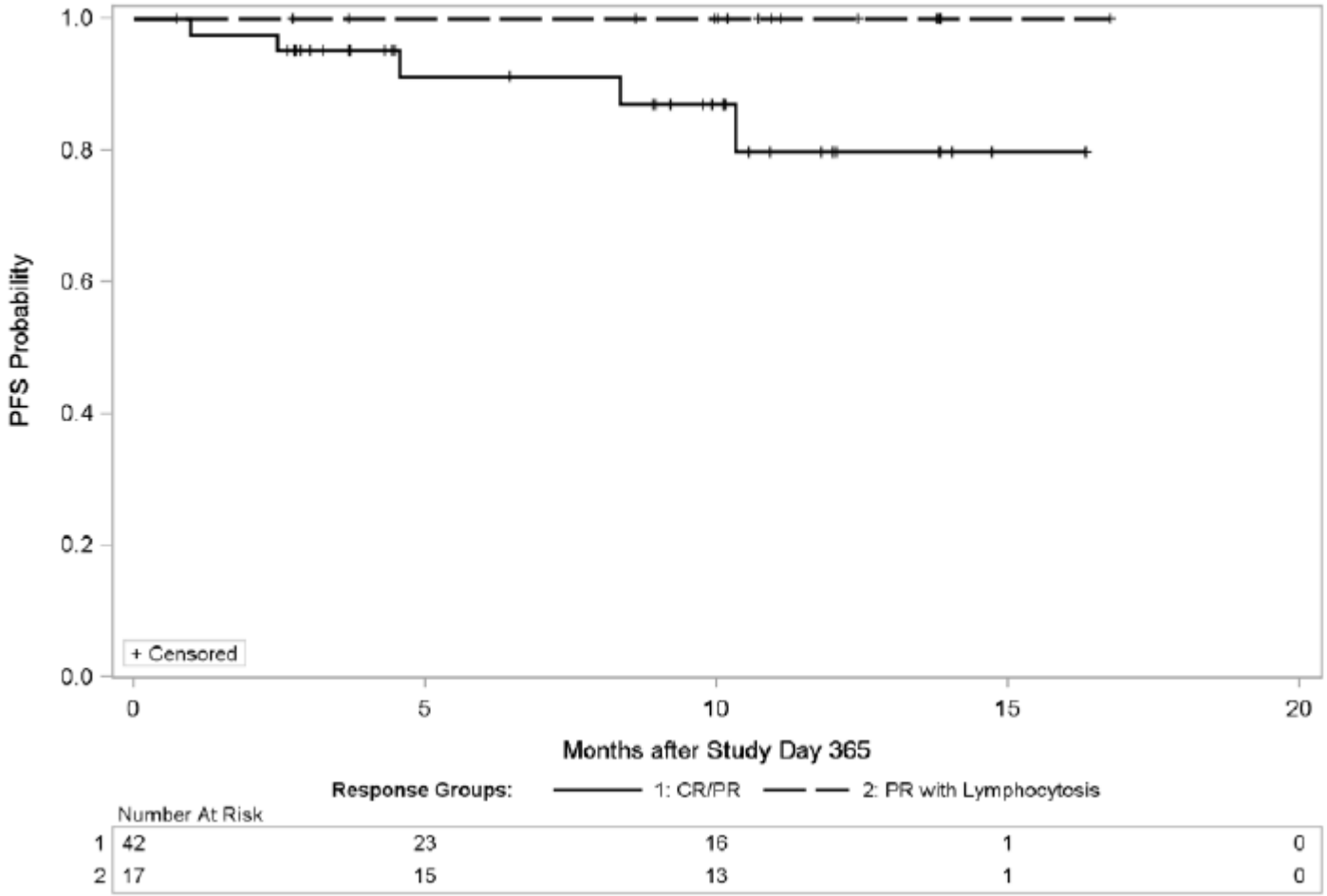
Phase II Studie: Obinutuzumab + Ibrutinib + Venetoclax bei 40 Patients



Primary endpoint:
Rate of patients free from progression at 12 months

…aber ist die Eradikation der CLL überhaupt notwendig ?

17 of 59 patients with persisting lymhocytosis after 12 months of ibruitnib



Woyach et al., Blood 2014

Rezidiv

CLL Zweitlinientherapie 2019

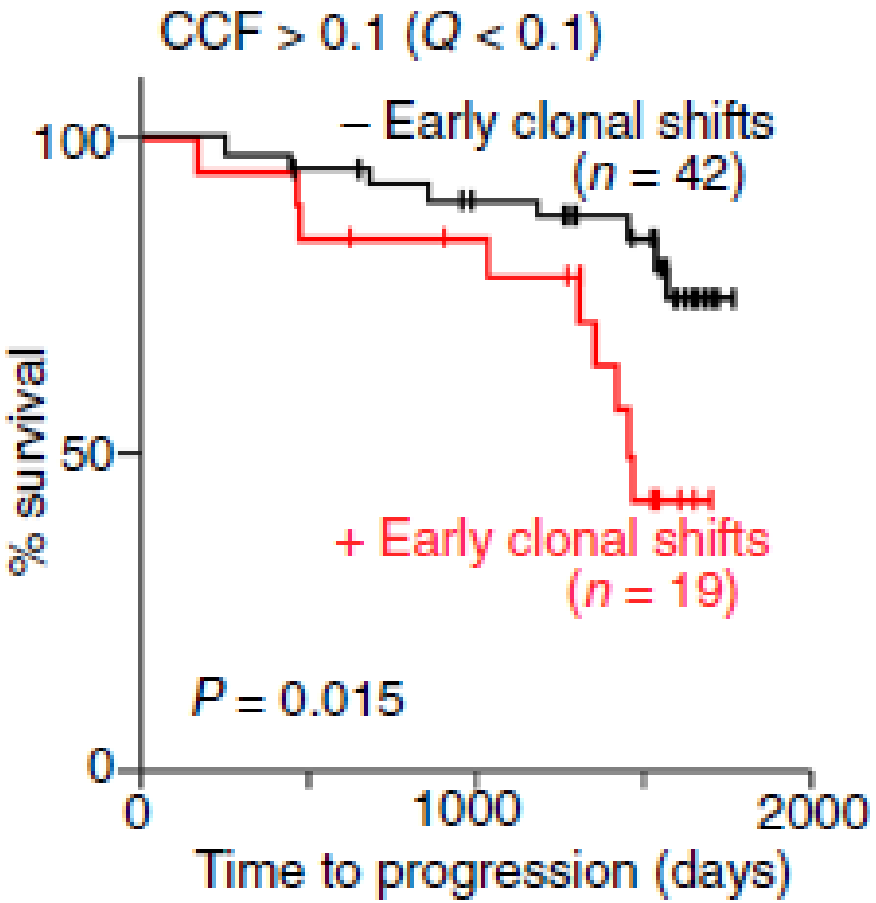
Response to 1L Therapy	Fitness	Therapy*
Refractory or progress within 3 years	Go go	Change to one of the following options: **Ibrutinib, Idelalisib + R, Venetoclax (+Rituximab),** FCR (after BR), A or A-Dex**, Lenalidomide (+ R), BR (after FCR). Discuss consolidation with allogeneic SCT.
	Slow go	Change to one of the following options: **Ibrutinib, Idelalisib + R, Venetoclax (+Rituximab),** A or A-Dex**, FCR-lite, BR, Lenalidomide (+R), Ofatumumab**, HD Rituximab.
Progress after 3 years	All	Repetition of 1L therapy is possible.

***Recommendations are based on evidence, not approval or availability in the market.**

**** Alemtuzumab or Ofatumumab are no longer marketed.**

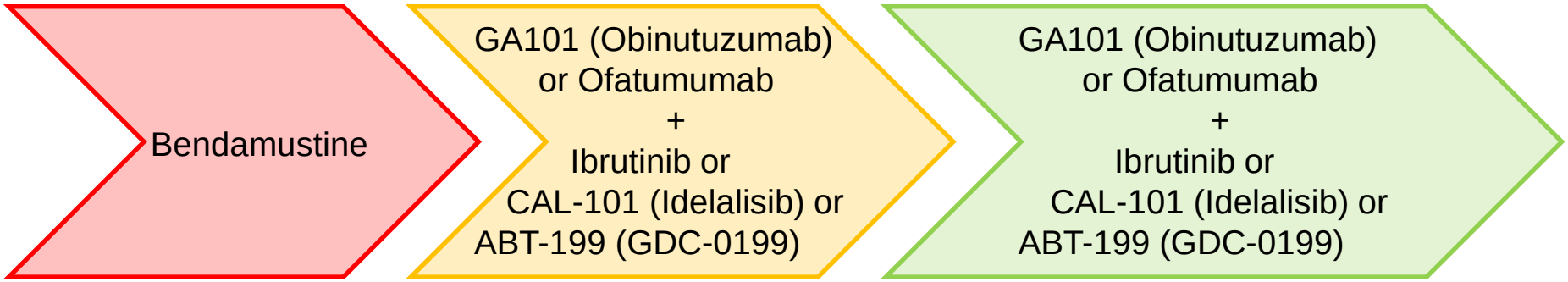
Klonaler Shift Auch Unter Targeted Agents

Exom und Transcriptom Sequencing bei 61 Patienten unter Ibrutinibtherapie



Landau et al., Nature Comm 2017

MRD-gesteuerte Kombinationstherapie mit targeted Agents & Antikörper



CLL2-BIG: Bendamustin, **I**brutinib, **G**A101 (Obinutuzumab)
CLL2-BAG: Bendamustin, **A**BT-199 (GDC-0199), **G**A101 (Obinutuzumab)
CLL2-BCG: Bendamustin, **C**AL-101 (Idelalisib), **G**A101 (Obinutuzumab)
CLL2-BIO: Bendamustin, **I**brutinib, **O**fatumumab

Cramer et al. Lancet Oncology 2018

Ansprechraten Kombinationstherapien BXX in 3 Phase II Studien:

BIO VS BIG VS BAG

	CLL2-BIO (n=66) submitted	CLL2-BIG (n=66) v. Tresckow, J. et al, Leukemia 2018	CLL2-BAG (n=66) Cramer, P. et al, Lancet Oncol. 2018
PATIENT COLLECTIVE			
Age: median (range) [yrs]	**61** (32-81)	**66** (36-83)	**59** (28-77)
Previously treated,	**26** pts (40%)	**31** pts (51%)	**29** pts (46%)
Del(17p)/TP53 mutation	**32%**	**21%**	**28%**
IGHV unmutated	**69%**	**70%**	**74%**
SAFETY			
SAEs	**85** (1.3 per pt)	**63** (1.0 per pt)	**89** (1.3 per pt)
SAEs in induction treatment	**46** (0.7 per pt)	**29** (0.5 per pt)	**59** (0.9 per pt)
EFFICACY			
ORR	**92%**	**100%**	**95%**
MRD negativity in PB ($< 10^{-4}$)	**14%**	**48%**	**87%**

CART-Zellen: Phase I/II Studien bei der CLL ASH 2018

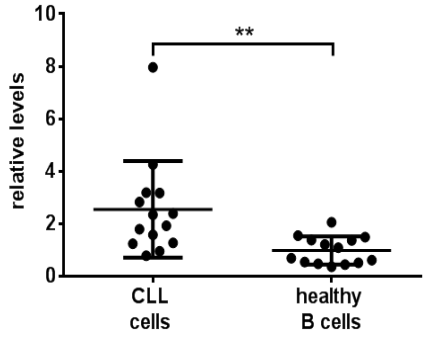
Abstract	Treatment/Product	N Pts	CR	Tox
298 by S. Gill (U. of Pennsylvenia)	1-5 x 10^8 CTL19	19	17/18	1 lethal cardiac arrh.
299 by J. Gauthier (Fred H., Seattle)	2 x 10^6/kg KG JCAR014 + Ibrutibnib	19	13/18	1 lethal cardiac arrh.
300 by T. Siddiqi (City of Hope, CA)	D1: 5 x 10^7 D2: 1 x 10^8 JCAR014	10	4/8	No grade 5

CLL^{Y}1:

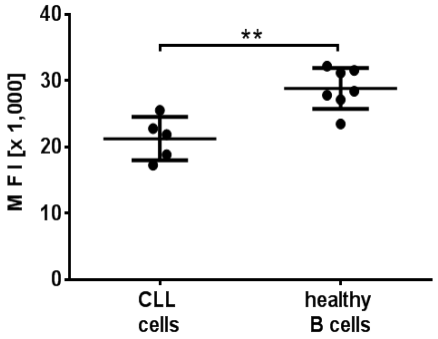
Geplante Phase I mit gegen FcµR gerichteten CART-Zellen

FcµR-Expression im Vergleich zu CD19

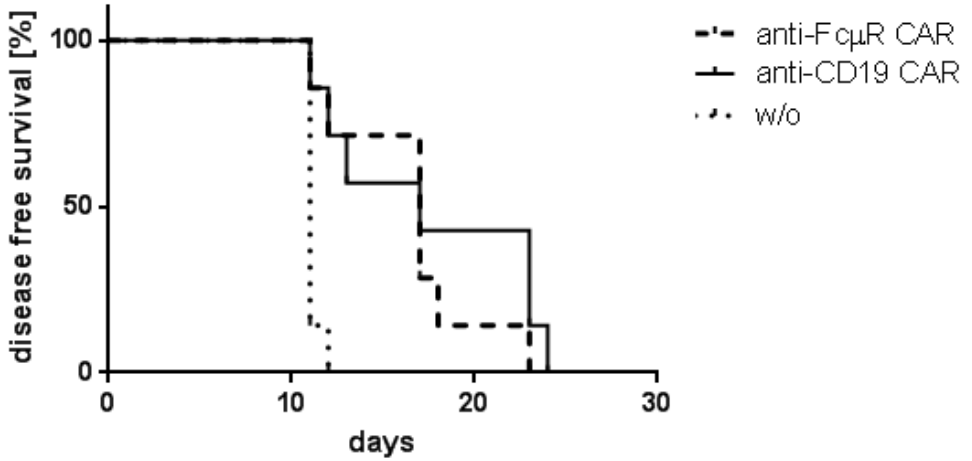
FcµR



CD19



Xenogenes Mausmodel mit anti-FcµR CAR und anti-CD19 CAR



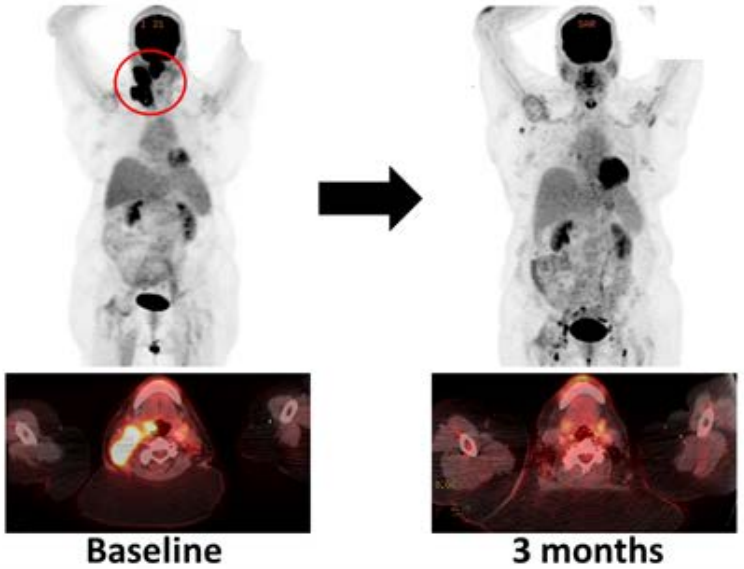
Faitschuk et al., Blood, 2016

Richter Transformation

Anti–PD1 Antikörper Nivolumab plus Ibrutinib bei R/R CLL oder RT

Phase II trial

- **Cohort 1: Patients with R/R CLL or RT**
  - **9 patients: 5 with R/R CLL, 4 with RT**
  - **Response: 3 PRs (R/R CLL) and 2 PRs (RT)**
- **Cohort 2: PR after 9 months Irbutinib**
  - **3 patients**
  - **Response: Ongoing**



PET Response in a Patient with Richter Transformation

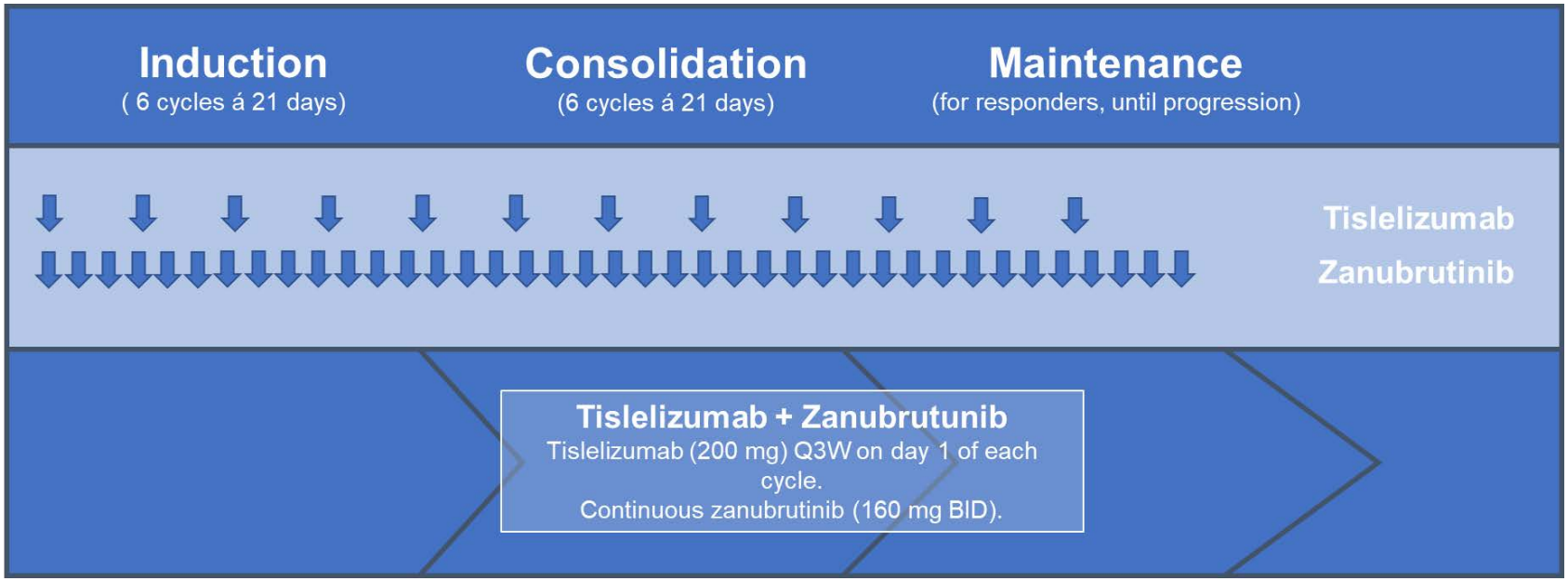
RT, Richter's transformation

Jain N, et al. *Blood.* 2016;128: Abstract 59.

CLL-RT1-STUDIE

Kombination Btk-Inhibitor (Zanubrutinib) + PD1-Inhibitor (Tislelizumab)

Treatment regimen



DCLLSG-STUDIEN 2019

DEUTSCHE STUDIENGRUPPE

Early stage Binet A, asymptomatic

CLL12

Risk of Early Progression
Ibru vs.
Placebo

Low Risk
Watch&Wait

Firstline, treatment requiring disease

CLL17*

Q4/2019

?

Ibru mono
vs
(Ibru+Ven)
vs
Obi+Ven

CLL13

Go Go
FCR/BR
vs
Ven-R
vs
Ven-Obi
vs
Ven-Obi-Ibru

CLL14#

Slow Go

Ven-Obi
vs
CLB-Obi

2GIVe

High Risk
17p(del)+ TP53 mut:

Ven-Obi-Ibru

*In planning or preparation
recruitment completed

Relapse/Refractory

CLL2-BCG

Relapse 17pdel, TP53mut
Benda Debulking,
Idela+Obi Induction,
Idela+Obi Maintenance

CLL2-BZAG*

Q2/2019

Relapse

Benda Debulking,
Obi-Ven-ZAnunrutinib
Induction,
Obi-Ven-Z Maintenance

CLL2-BAAG*

Q4/2018

Relapse

Benda Debulking,
Obi-Ven-Acalabrutinib
Induction,
Obi-Ven-A Maintenance

CLL2-BIV*

Q1/2019

Relapse

Benda Debulking,
Ibru-Ven-Induction,
Ibru-Ven Maintenance

Registry

Register

Long Term Follow up

CLL, SLL, B-PLL, T-PLL,
LGL, Richter's Syndrome,
HCL

Richter's Transformation

RT1*

Q1/2019

Richter's Transformation

Zanubutinib plus
Tislelizumab

CAR-T

CLLY1

Q1/2020

Relapse

CAR-T (-Anti-FcμR
CAR-T cells)