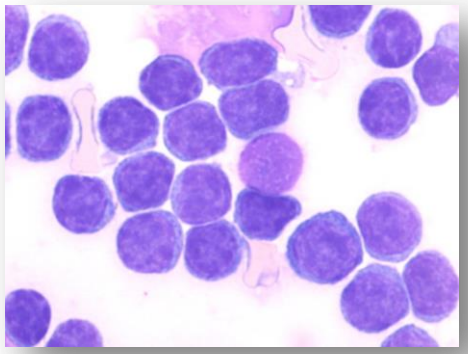
CLL – Trends in 2015



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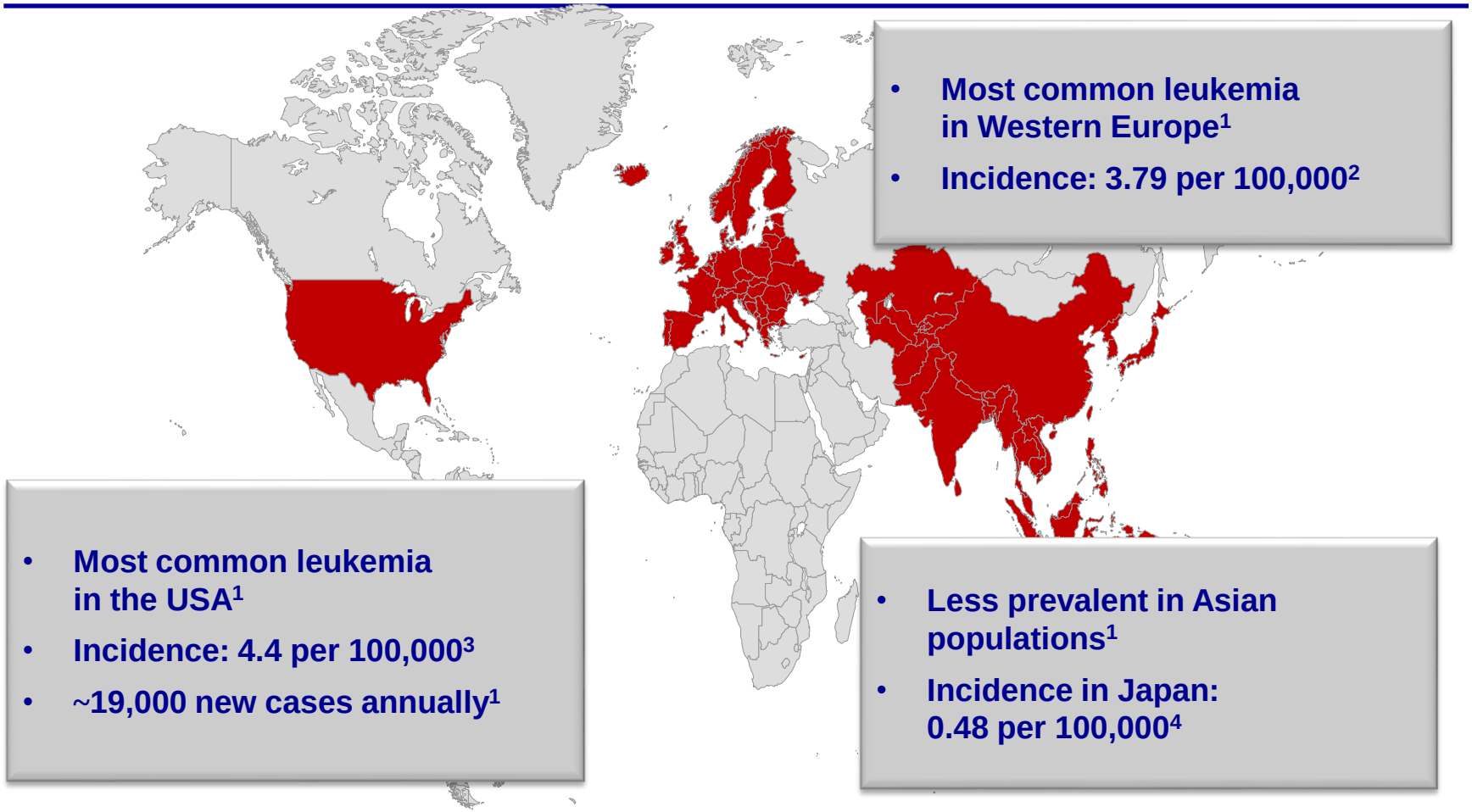
Disclosures

- **I have provided consultation, attended advisory boards and/or provided lectures for:**
- **Celgene, Mundipharma, Roche Pharma, and Janssen**

Global CLL incidence



- **Most common leukemia in Western Europe[1]**
- **Incidence: 3.79 per 100,000[2]**

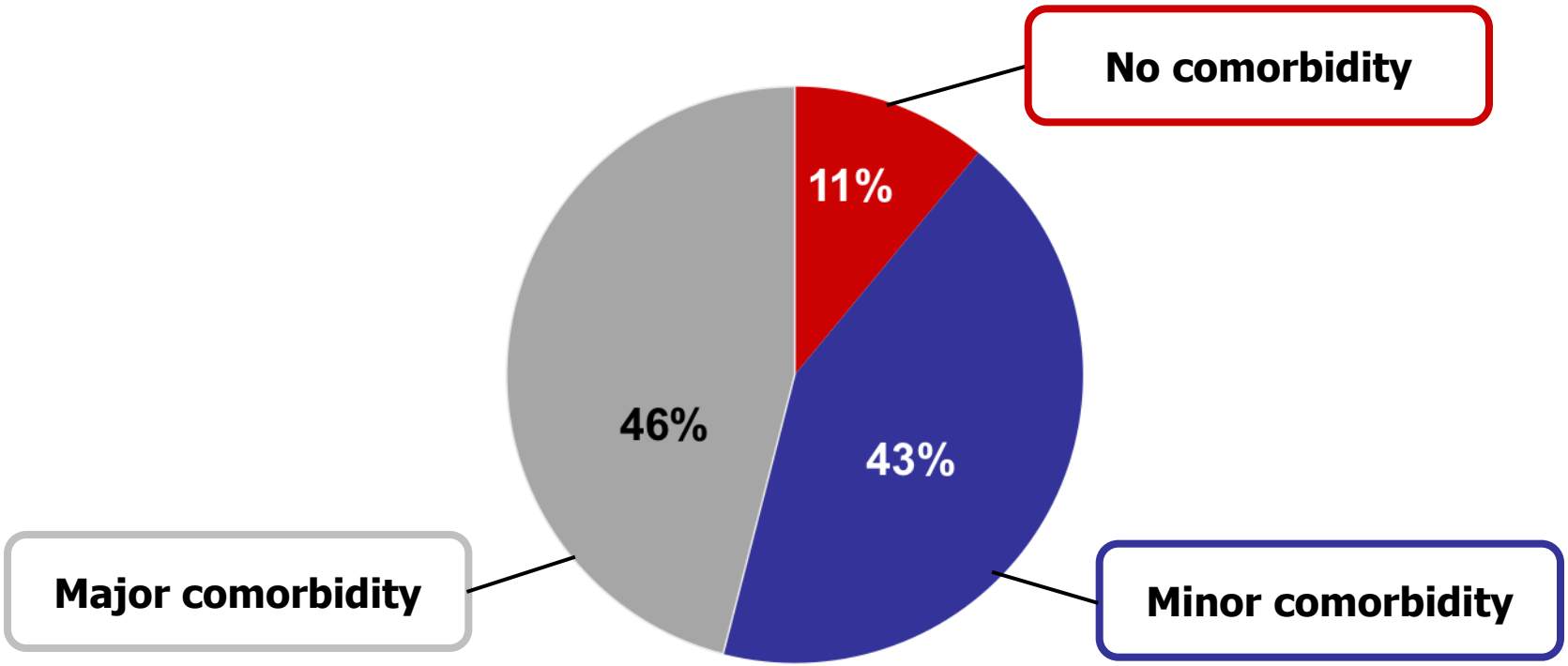
- **Most common leukemia in the USA[1]**
- **Incidence: 4.4 per 100,000[3]**
- **~19,000 new cases annually[1]**

- **Less prevalent in Asian populations[1]**
- **Incidence in Japan: 0.48 per 100,000[4]**

1. Zent CS, *et al. Cancer* 2001; 92:1325–1330; 2. Sant M, *et al. Blood* 2010; 116:3724–3734; 3. Howlader N, *et al.* SEER Cancer Statistics Review, 1975-2011. Available at: http://seer.cancer.gov/csr/1975_2011/. Accessed February 2015; 4. Isobe Y, *et al. Intern Med* 2012; 51:1977–1981.

Most patients with CLL have some form of comorbidity

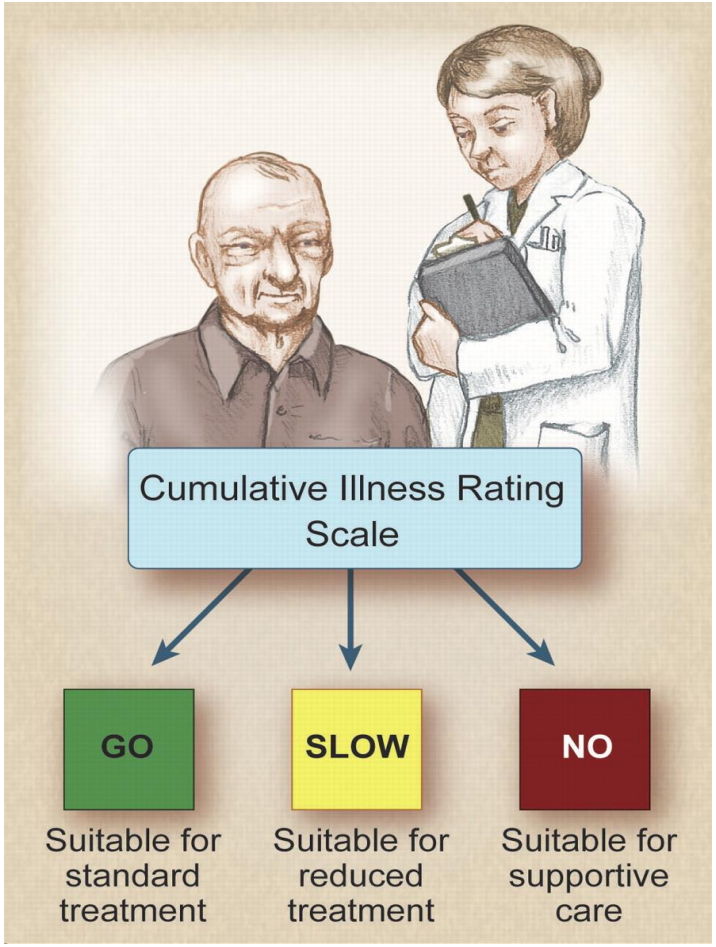
Median age at diagnosis: 71 years



CLL Mayo Clinic 1995–2006

Thurmes P, *et al. Leuk Lymphoma* 2008; 49:49–56.

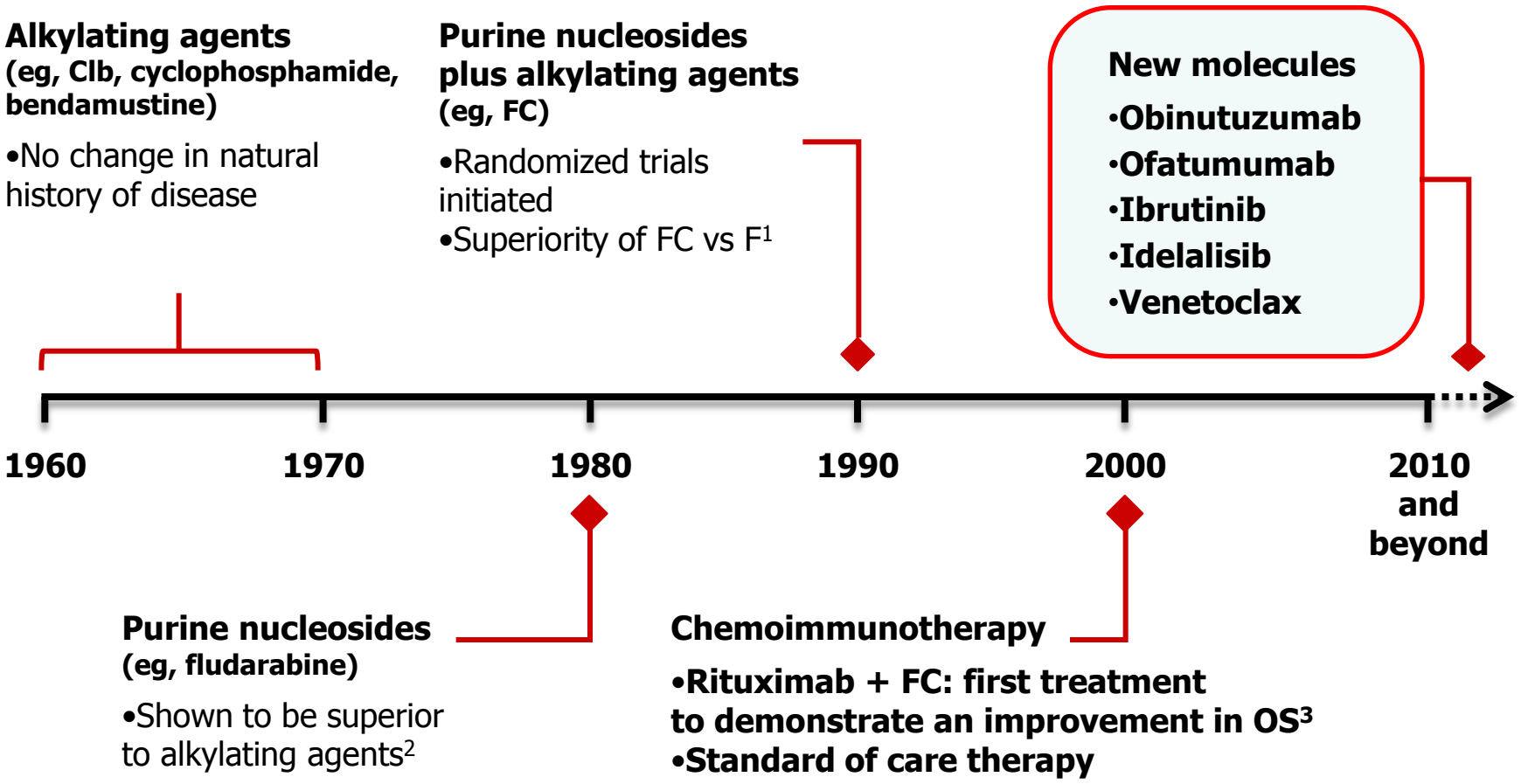
Classification of patients by a geriatric assessment (e.g. CIRS)



blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

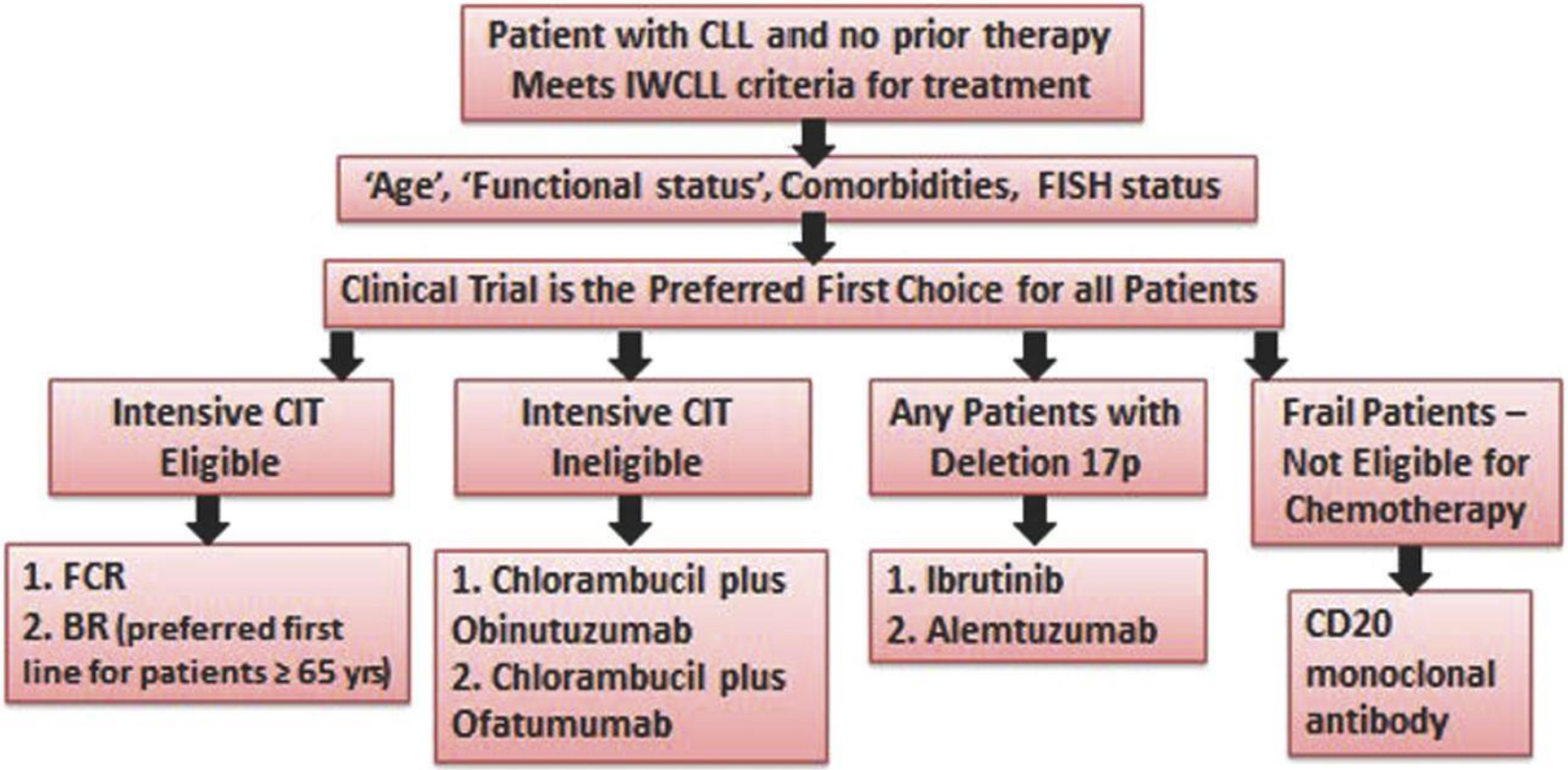
Gribben JG. Blood 2009; 114:3359–3360.
Balducci L & Extermann M., Oncologist 2000; 5:224–237

Treatment evolution in CLL



1. Eichhorst BF, *et al. Blood* 2006; 107:885–891; 2. Eichhorst BF, *et al. Blood* 2009; 114:3382–3391; 3. Hallek M, *et al. Lancet* 2010; 376:1164–1174.

Treatment algorithm for first-line therapy of CLL



CIT = Chemoimmunotherapy

Nitin Jain & Susan O'Brien Blood 2015;126:463-470

FCR chemoimmunotherapy as initial therapy for fit CLL patients

blood

2008 112: 975-980
Prepublished online Apr 14, 2008;
doi:10.1182/blood-2008-02-140582

Long-term results of the fludarabine, cyclophosphamide, and rituximab regimen as initial therapy of chronic lymphocytic leukemia

Constantine S. Tam, Susan O'Brien, William Wierda, Hagop Kantarjian, Sijin Wen, Kim-Anh Do, Deborah A. Thomas, Jorge Cortes, Susan Lerner and Michael J. Keating

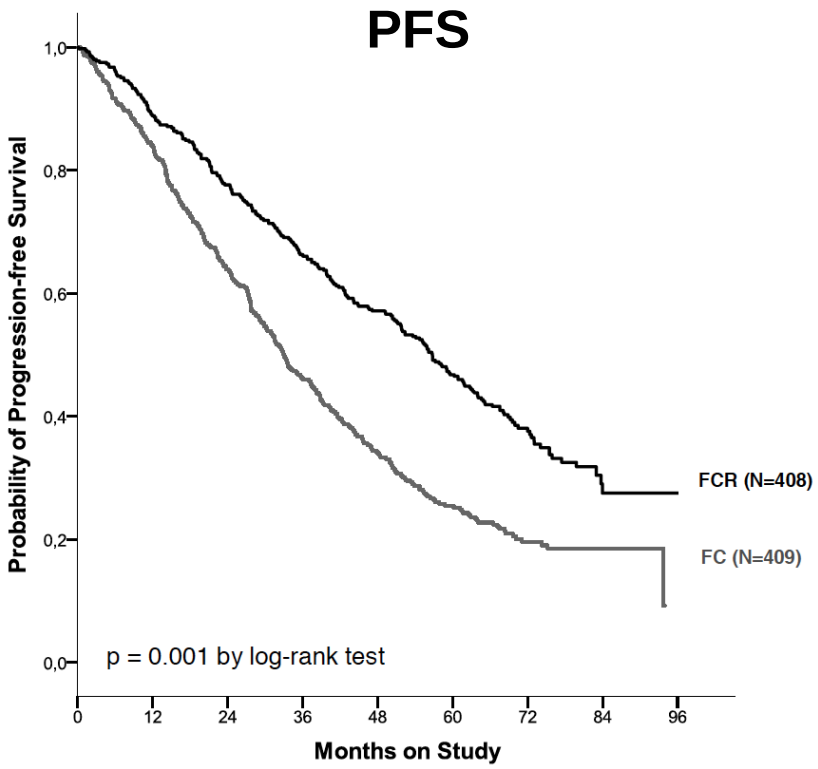
- Most active regimen in CLL.
- Toxicity manageable.
- Prolongs survival in historical comparison.

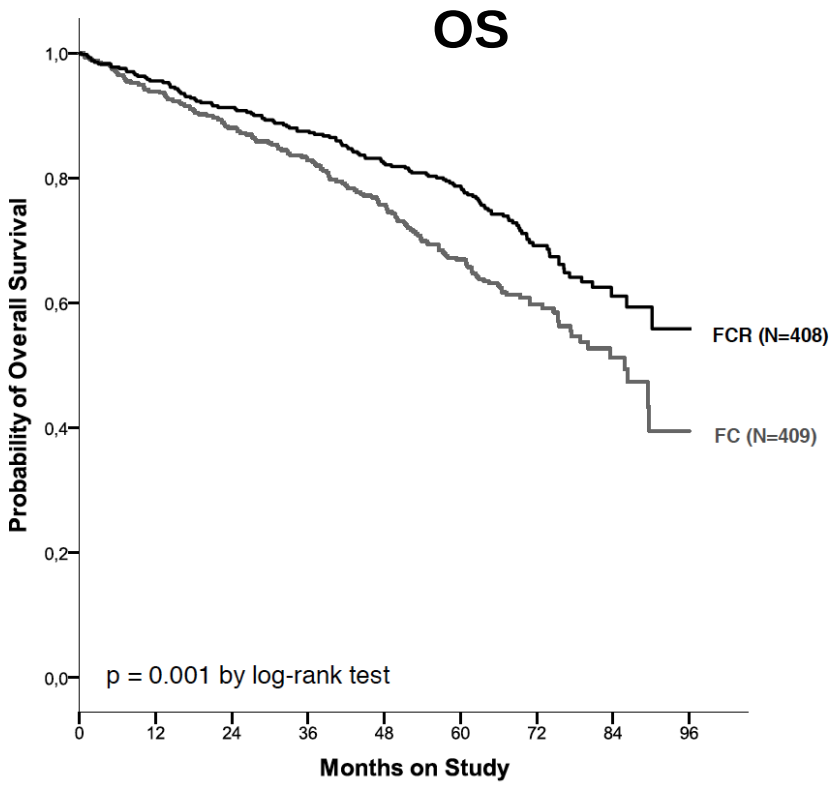
First-line chemo-immunotherapy trials for CLL

Regimen and trial	No. of patients	Median age (y)	Older patents (%)	Creatinine clearance <70 mL/min (%)	CR %	ORR %	PFS (mo)	Comments
FCR								
MDACC[12,13]	300	57	14% (≥70 y)	NR (creatinine ≥2 excluded)	72	95	80	Lower CR rate in older patients
CLL8 trial (FCR arm)[14]	408	61	11% (≥70 y) 31% (≥65 y)	Excluded	44	90	52	Patients (≥65 y) had similar CR and PFS as younger patients; however, there was more hematologic toxicity and bacterial infections in older patients
CLL10 trial (FCR arm)[16]	282	61	31% (≥65 y)	Excluded	40	95	55	
FCR-lite[25,26]	63	58	15% (≥70 y)	NR (creatinine ≥1.8 excluded)	73	94	70	
BR								
GCLLSG phase 2[15]	117	64	26% (>70 y)	35%	23	88	34	ORR inferior for older patients but similar PFS; patients with lower GFR had a response and PFS similar to those with GFR ≥70 mL/min
CLL10 trial (BR arm)[16]	279	62	39% (≥65 y)	Excluded	31	96	42	
FR								
CALGB 9712[23,24]	104	63	NR	NR (creatinine >1.5 × ULN excluded)	47	84	42	

Nitin Jain, and Susan O'Brien Blood 2015;126:463-470

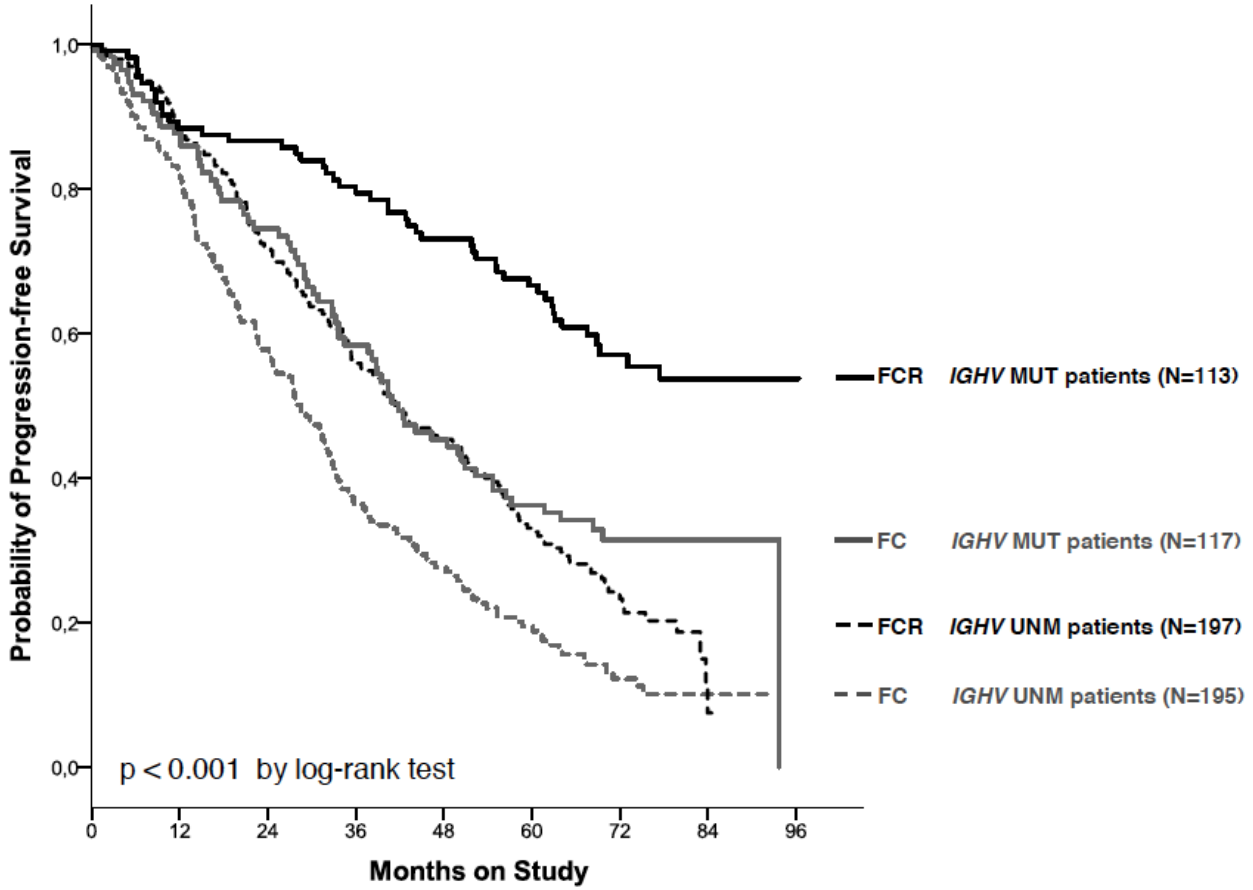
CLL-8 trial: Long-term follow-up (n=817) FCR verus FC, fit patients





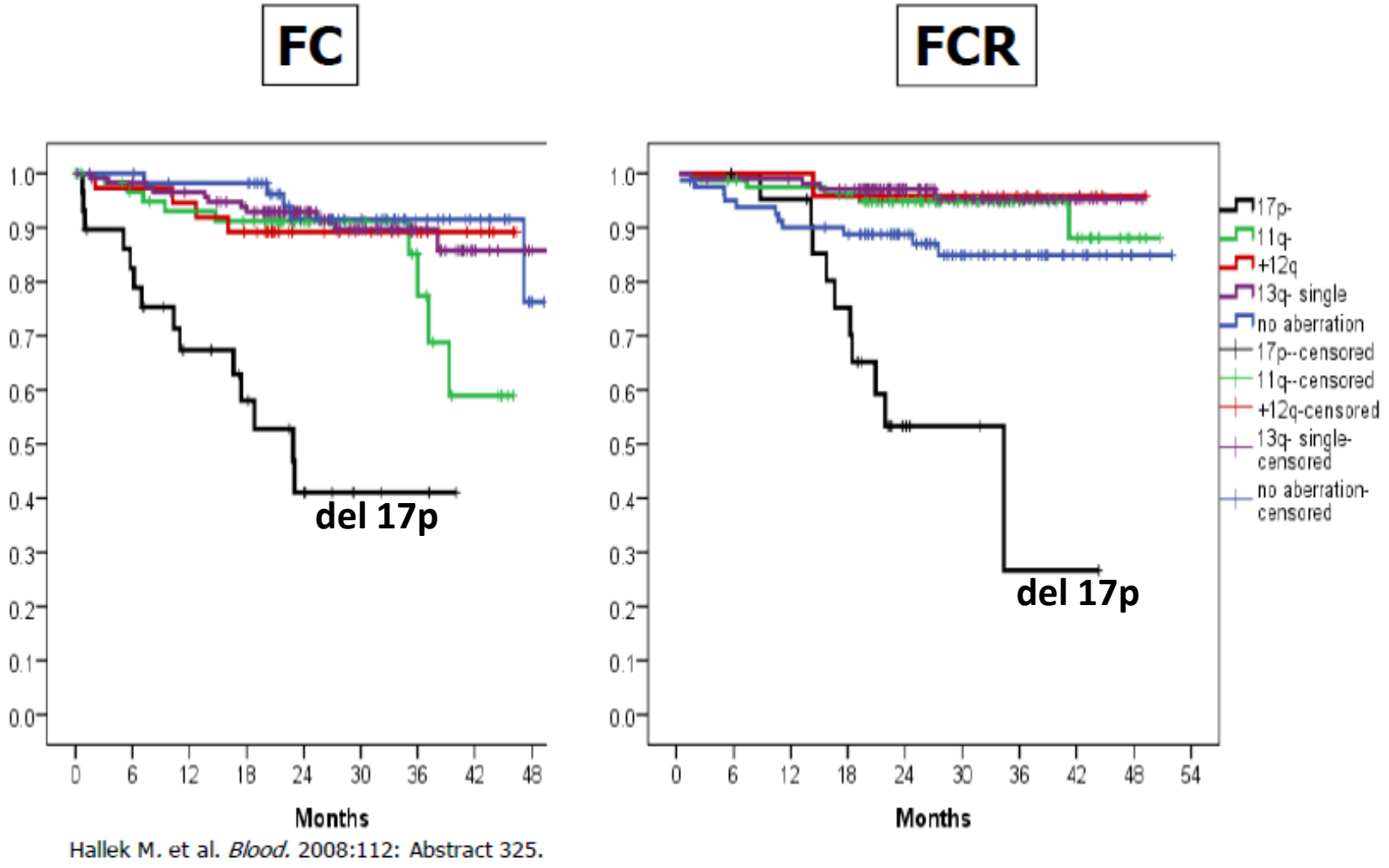
Fischer K et al., Blood Oct 2015, prepublished online

CLL-8 trial: PFS and IGHV mutated vs. unmutated (n=622)



Fischer K et al., Blood Oct 2015, prepublished online

Influence on cytogenetics del17p still unfavourable



Hallek M. et al. *Blood.* 2008:112: Abstract 325.

Toxicity FC versus FCR

	FC	FCR	p
Infections, total	**14.9%**	**18.8%**	**0.14**
Infections, if specified	**9.3%**	**13.6%**	**0.06**
Bacterial	**1.3%**	**2.2%**	**0.30**
Viral	**4.0%**	**4.2%**	**0.90**
Fungal	**0.3%**	**0.7%**	**0.33**
Parasitic	**0.0%**	**0.2%**	**0.32**

TRM: 2.0% (FCR) vs. 1.5% (FC)

Hallek M et al., ASH 2008

Bendamustine for iNHL and CLL

VOLUME 27 · NUMBER 9 · MARCH 20 2009

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

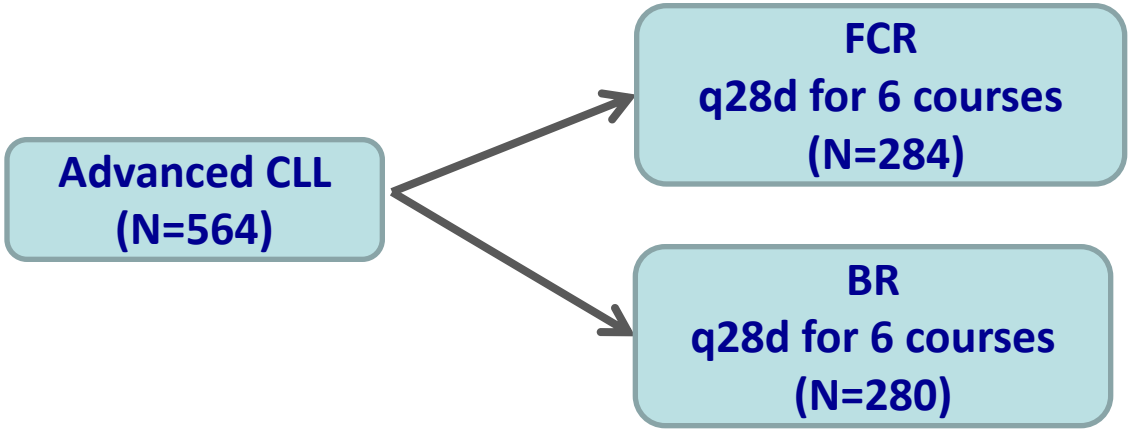
Bendamustine: Rebirth of an Old Drug

Bruce D. Cheson and Mathias J. Rummel

65-93% ORR in Phase II with moderate toxicity

CLL-10: FCR vs. BR (interim analysis) First-line, fit patients

Inclusion criteria:
- CIRS score ≤6
- CrCL ≥70 mL/min
- No del(17p)
- Fit patients



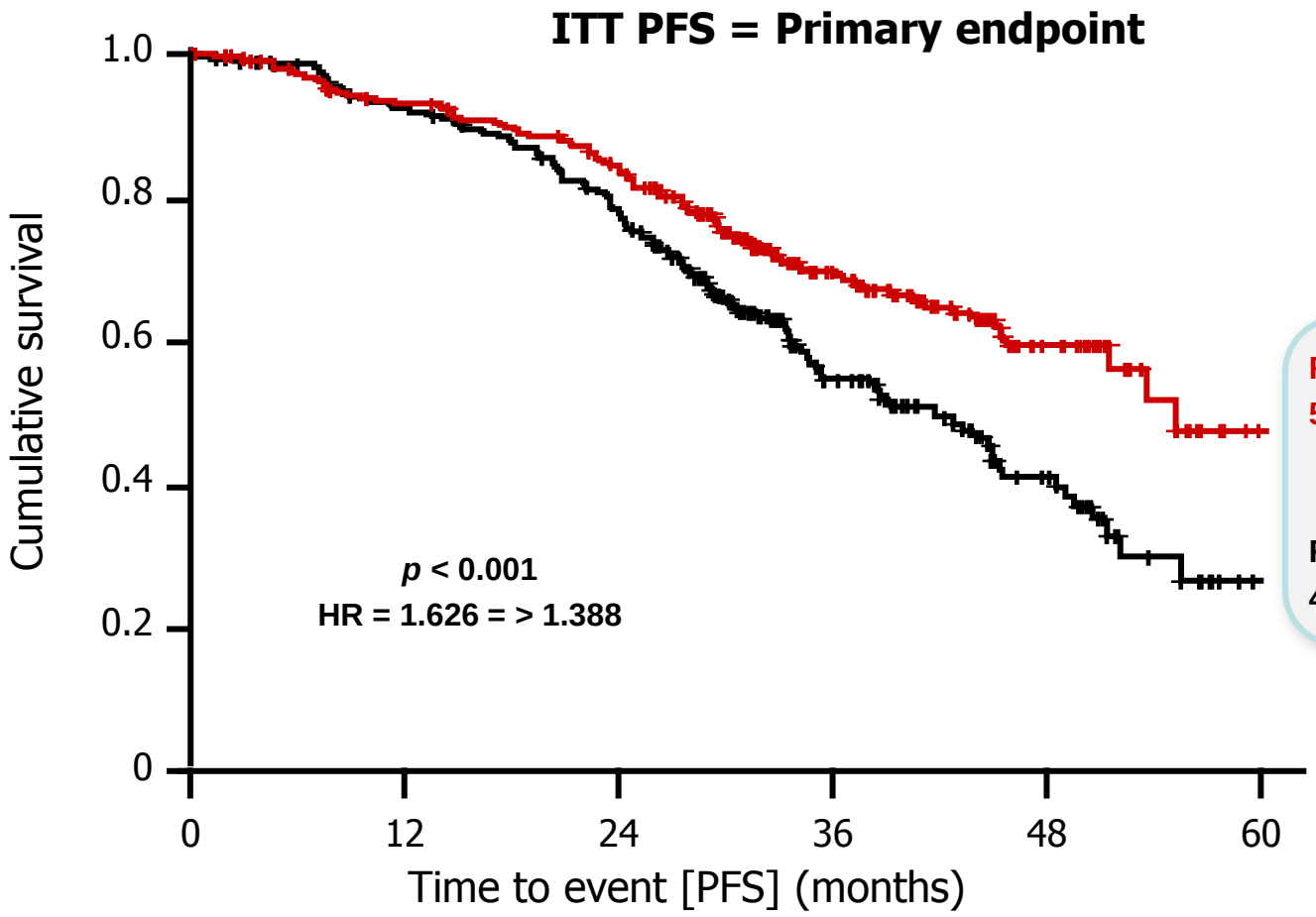
Median observation time: 28 months

Regimens:

FCR:	**Fludarabine 25 mg/m² i.v. d1–3**
	Cyclophosphamide 250 mg/m² i.v. d1–3
	Rituximab 375 mg/m² i.v. d0 (C1) then 500 mg/m² d1 (C2-6)
BR:	**Bendamustine 90 mg/m² i.v. d1-2**
	Rituximab 375 mg/m² i.v. d0 (C1) then 500 mg/m² d1 (C2-6)

Eichhorst B et al., ASH 2013, # 526

CLL10: Rituximab + FC vs Rituximab + bendamustine in first-line therapy



Rituximab + FC:
55.2 months

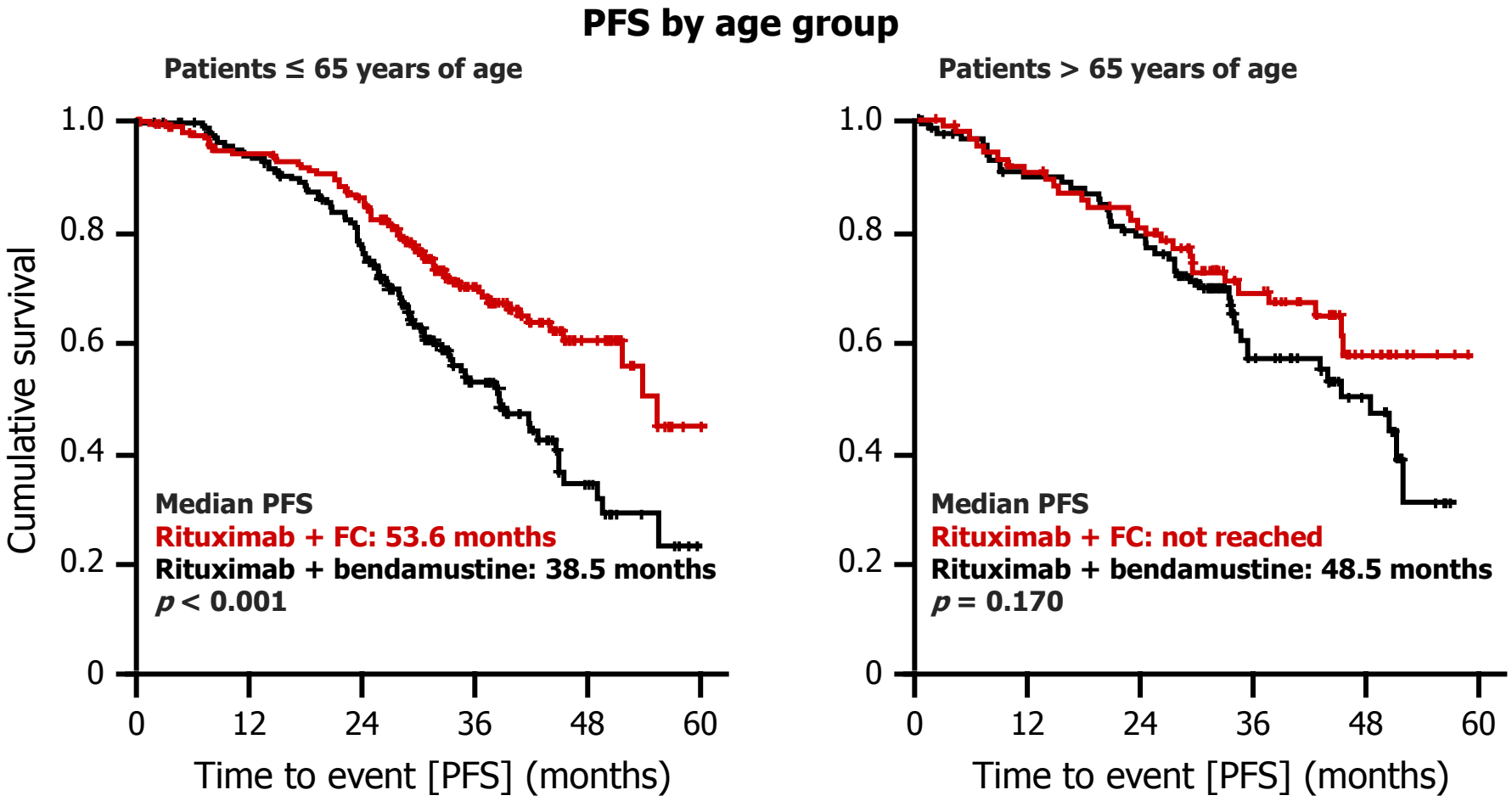
Rituximab + bendamustine:
41.7 months

So far, no benefit in OS

ITT = intent-to-treat; PFS = progression-free survival.

Eichhorst B, *et al. Blood* 2013; 122:Abstract 526

CLL10: Rituximab + FC vs Rituximab + bendamustine in first-line therapy



Eichhorst B, *et al. Blood* 2013; 122:Abstract 526 (Oral presentation).

CLL10 Study: FCR vs. BR in FrontLine

DEUTSCHE STUDIENGRUPPE

Adverse Events CTC ° 3-5 (Interval 1st cycle until 3 months after Final staging)

Adverse event	FCR (% of pt)	BR (% of pt)	p value
All	90.8	78.5	<0.001
Hematological AEs	90.0	66.9	<0.001
Neutropenia	81.7	56.8	<0.001
Anemia	12.9	9.7	0.28
Thrombocytopenia	21.5	14.4	0.036
Infection	39.0	25.4	0.001
TRM	3.9	2.1	0.23

Eichhorst B et al., ASH 2013, # 526

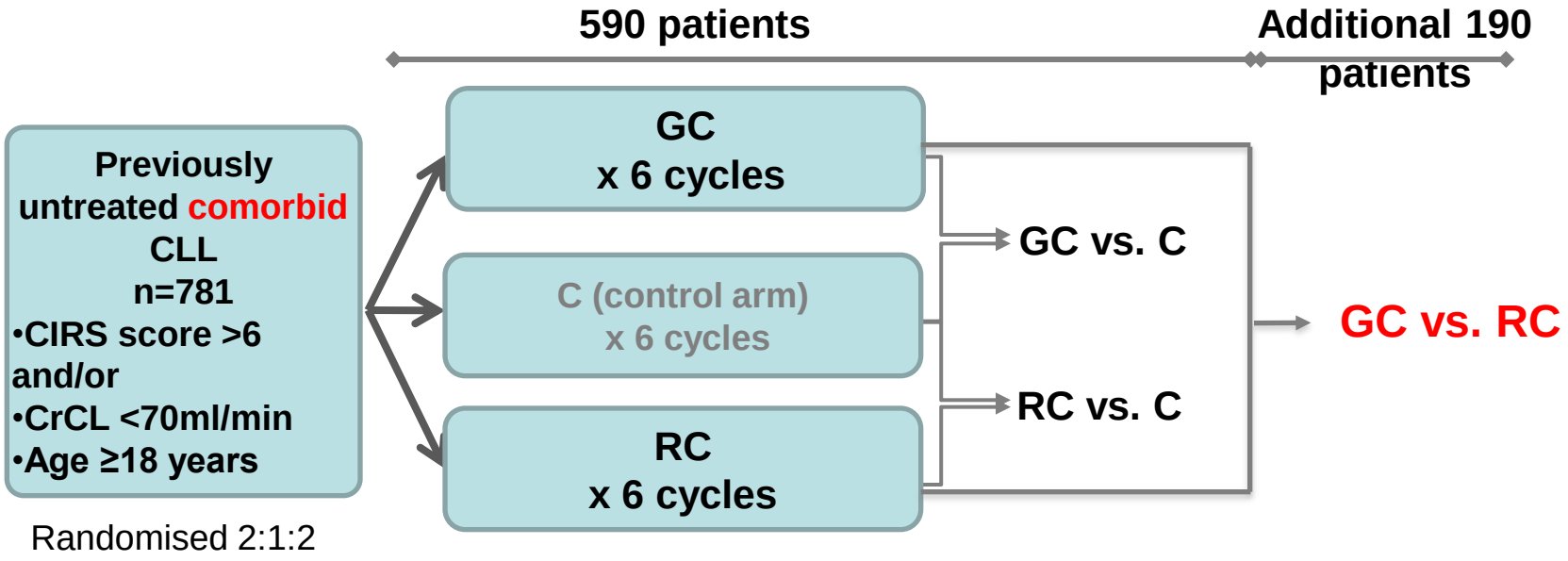
CLL-10 study - Interpretation

- **The investigators conclude that no firm recommendation supporting one regimen over the other can be given at present**
- **Probably no switch in practice**
  - **FCR for fit younger patients**
  - **BR for older fit patients**

Eichhorst B et al., ASH 2013, # 526 and
Fricker J, News. Lancet Oncology, Jan 2014

Elderly or unfit patients

Obinutuzumab + CLB (GC) vs. Rituximab + CLB (RC) Randomised phase III trial (CLL-11)



Regimens:

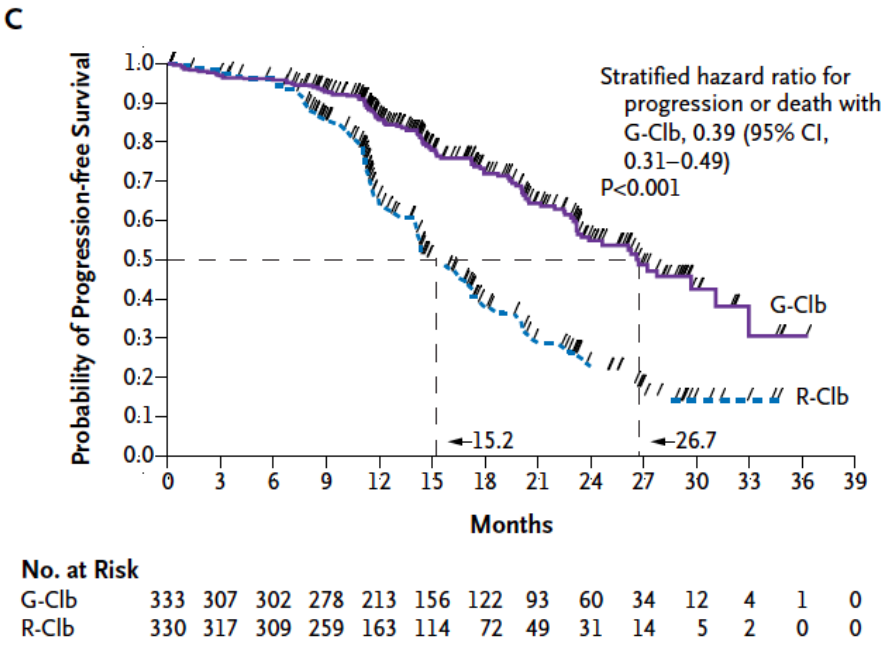
GC:	Chlorambucil 0.5 mg/kg orally d1, d15 (C1–6)
q28d	**Obinutuzumab** 100 mg i.v. d1, 900 mg d2, 1000 mg d8, d15 (C1), 1000 mg d1 (C2–6)
RC:	Chlorambucil 0.5 mg/kg orally d1, d15 (C1–6)
q28d	**Rituximab** 375 mg/m^2 i.v. d1 (C1), 500 mg/m^2 d1 (C2–6)

Obinutuzumab = GA101

Goede *et al.* ASH 2013, # 6

GC vs. RC (Stage 2 results) Randomised phase III trial (CLL-11)

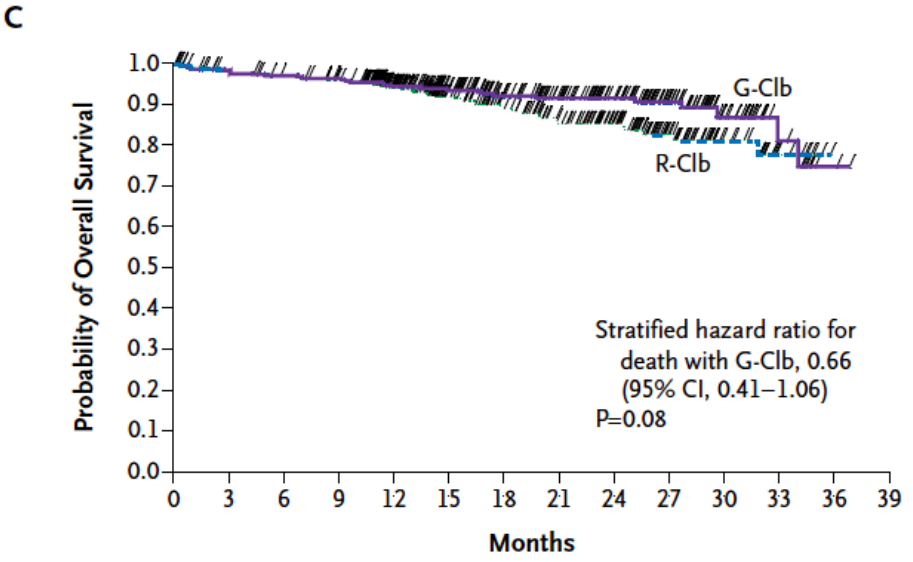
PFS



No. at Risk

G-Clb	333	307	302	278	213	156	122	93	60	34	12	4	1	0
R-Clb	330	317	309	259	163	114	72	49	31	14	5	2	0	0

OS



No. at Risk

G-Clb	333	316	310	303	261	214	170	144	115	71	34	14	2	0
R-Clb	330	320	314	305	255	203	169	138	105	61	27	8	0	0

The NEW ENGLAND JOURNAL of MEDICINE

Goede V et al., N Engl J Med 2014

CLL first-line treatment 2015

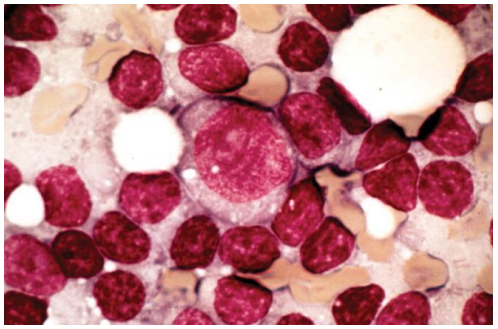
Stage	Fitness	del(17p) p53mut	Therapy
Binet A–B, Rai 0–II, inactive	Irrelevant	Irrelevant	None
Active disease or Binet C or Rai III–IV	Go go	No	FCR (BR above 65 years)
		Yes	Ibrutinib → (Allogeneic SCT)
	Slow go	No	Chlorambucil + obinutuzumab or rituximab or ofatumumab
		Yes	Ibrutinib, alemtuzumab, HD rituximab or ofatumumab

Hallek M. *Blood* 2013; 122:3723–3734.

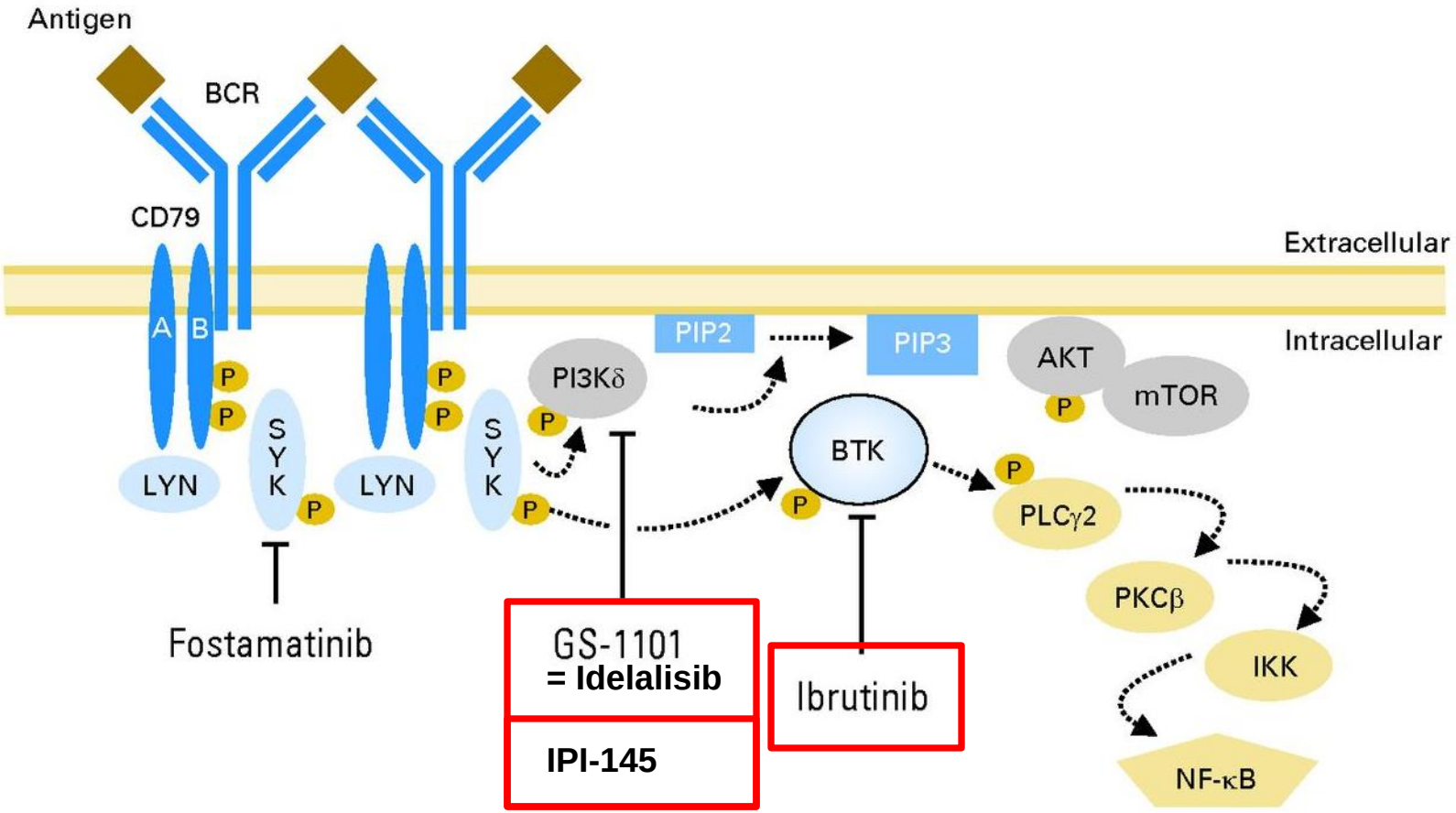
CLL
relapsed/refractory patients

New drugs

(Ibrutinib, Idelalisib, Venetoclax)

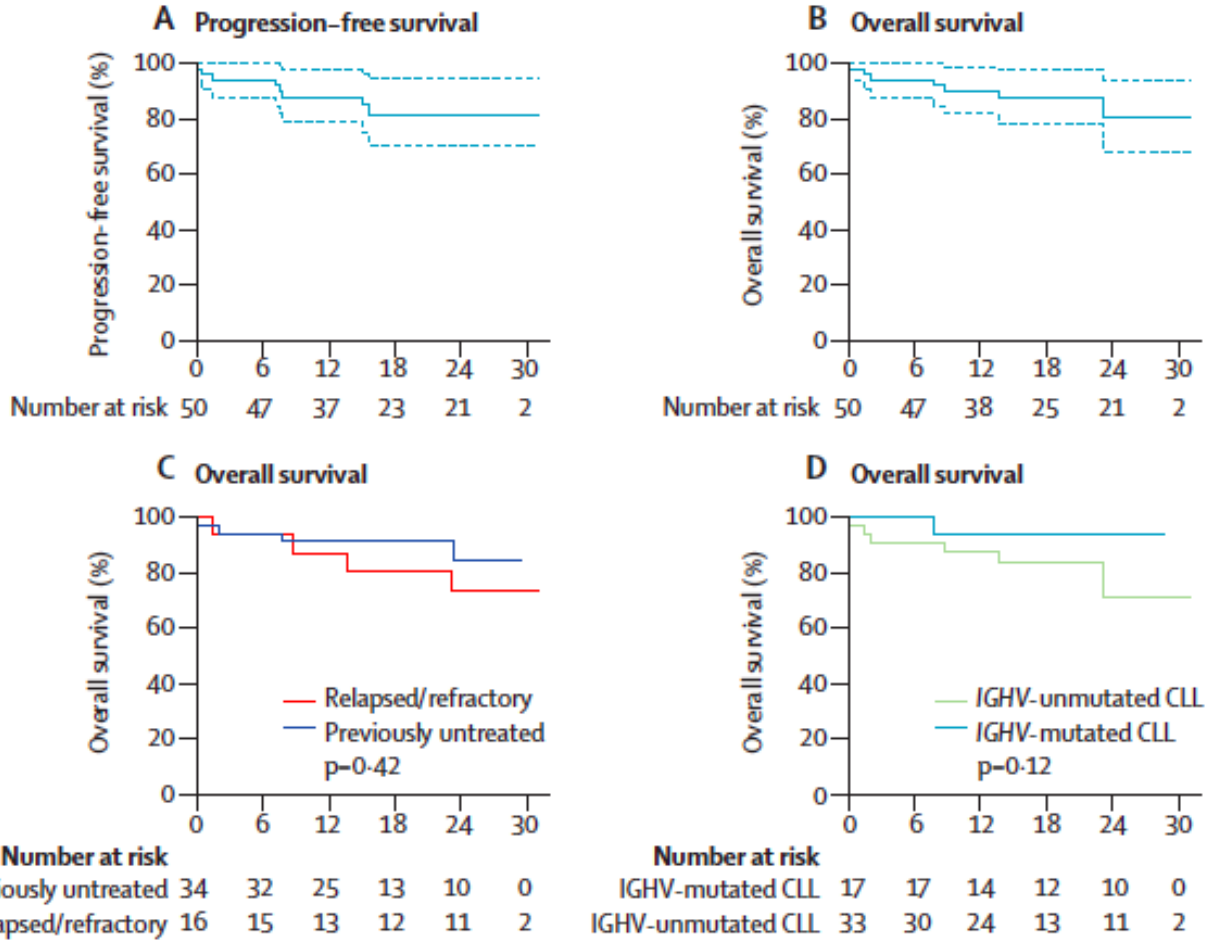


BCR signaling and its targeting (investigational) agents



Adapted from Wiestner A. JCO 2013; 31:128-130

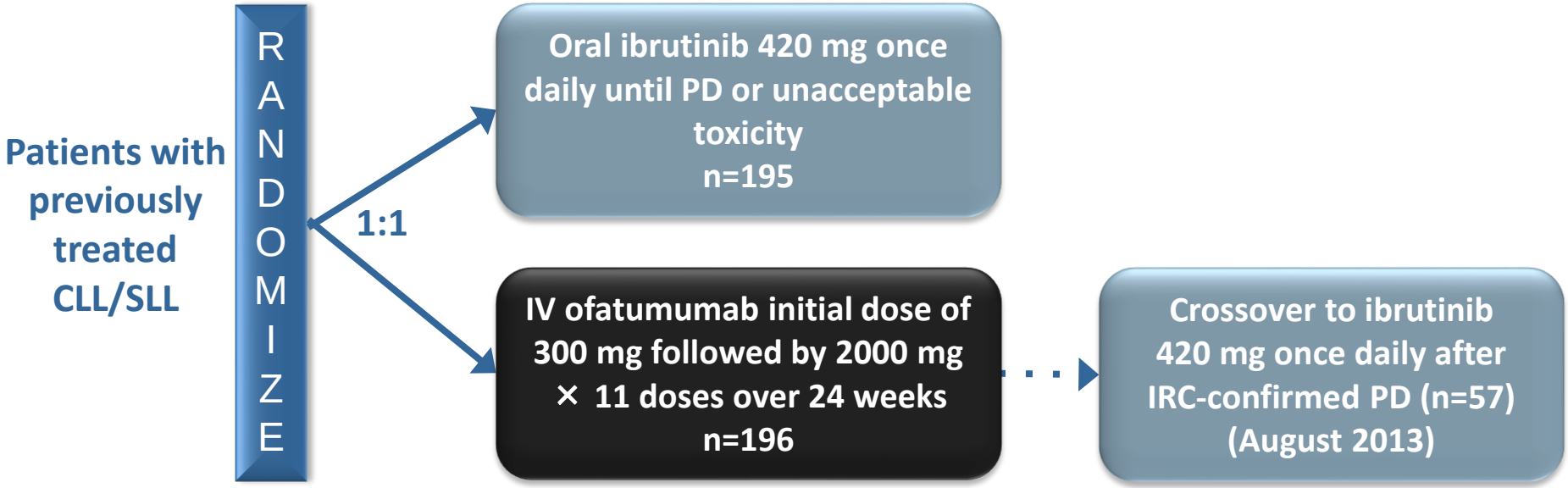
Ibrutinib for CLL with TP53 aberrations - Phase II trial



Farooqui *et al.* ASH 2013, # 673

Lancet Oncol 2015; 16: 169–76

RESONATE Phase 3 Study Design

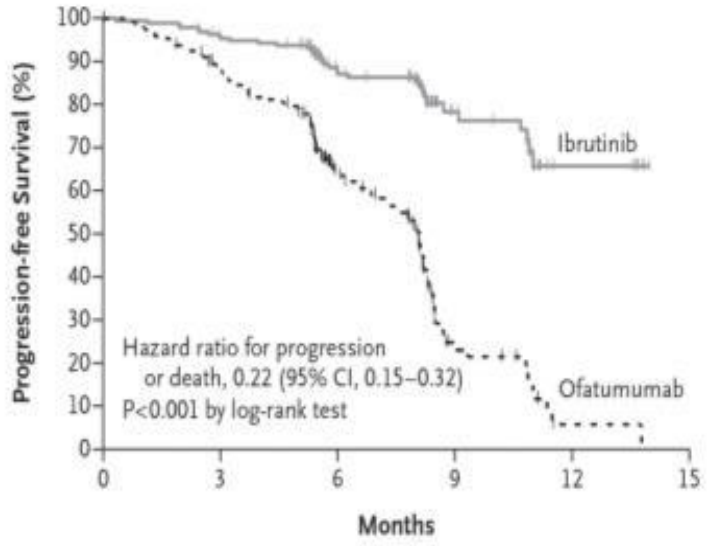


- **Stratification according to:**
  - **Disease refractory to purine analog chemoimmunotherapy (no response or relapsed within 12 months)**
  - **Presence or absence of 17p13.1 (17p del)**
- **At time of interim analysis, median time on study was 9.4 months**

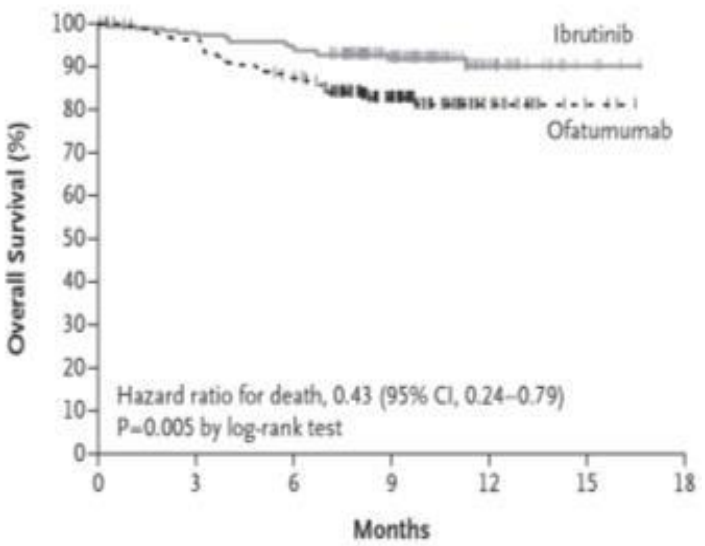
Protocol amended for crossover with support of Data Monitoring Committee and discussion with health authorities.
PD, progressive disease.

Byrd JC, et al. N Engl J Med. 2014;371:213-223.

RESONATE: Responses and Outcomes



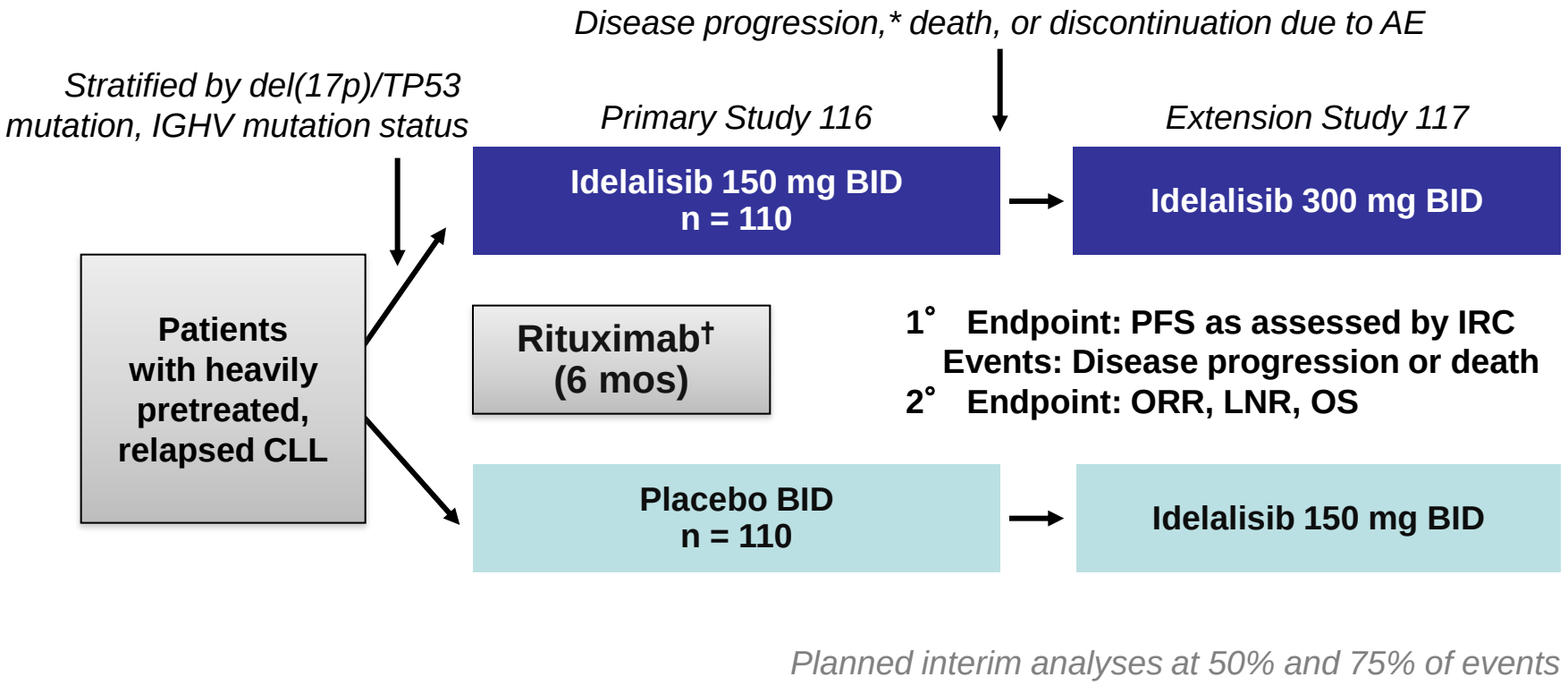
No. at Risk						
Ibrutinib	195	183	116	38	7	
Ofatumumab	196	161	83	15	1	0



No. at Risk						
Ibrutinib	195	191	184	115	32	5
Ofatumumab	196	183	164	88	21	3

Byrd JC, et al. N Engl J Med. 2014;371:213-223.

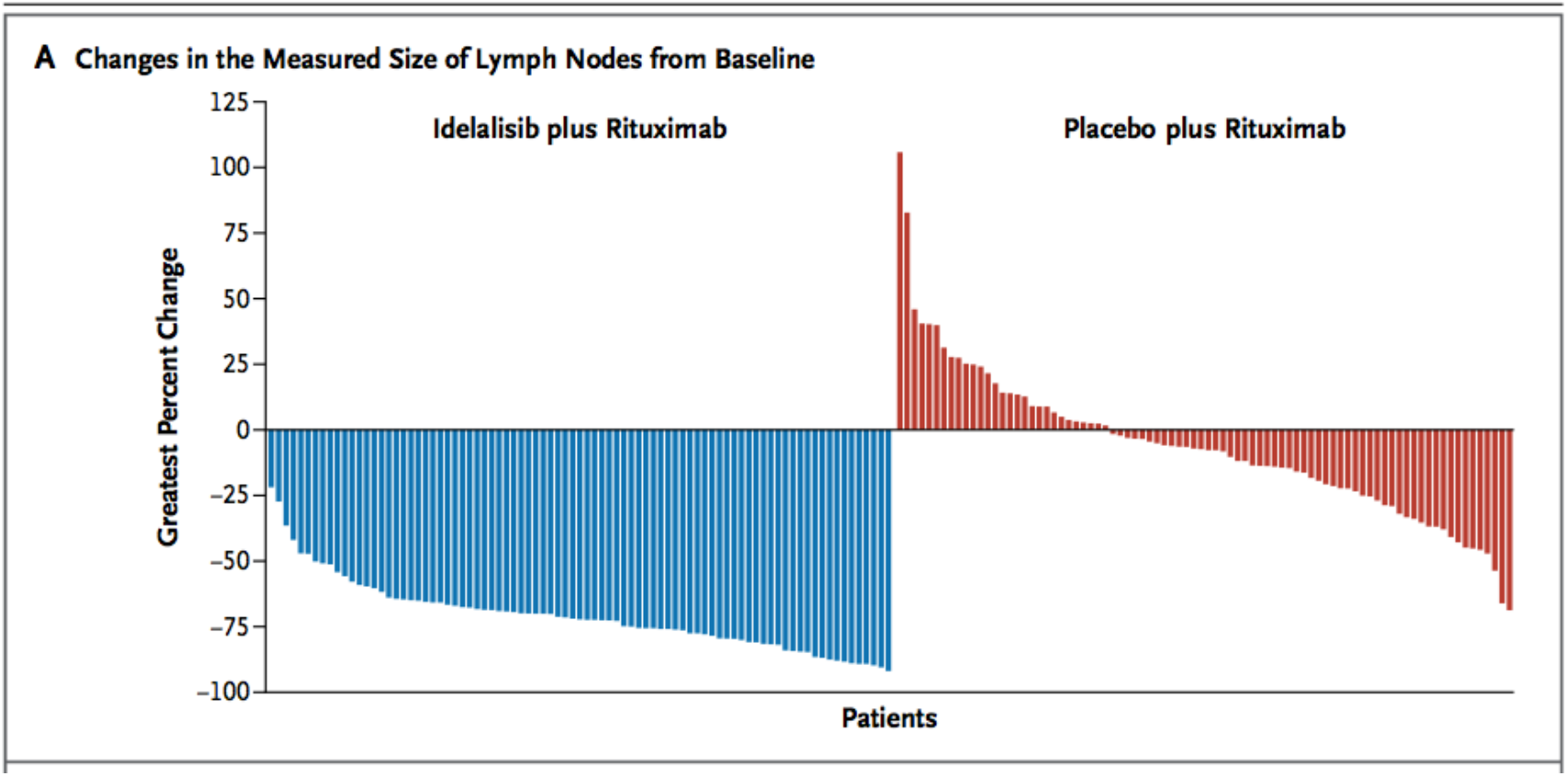
Phase III Idelalisib + Rituximab for previously treated patients with CLL



*Patients with disease progression continued on idelalisib Extension Study 117.
†Rituximab schedule: 375 mg/m^2, then 500 mg/m^2 every 2 wks x 4, then 500 mg/m^2 every 4 wks x 3.

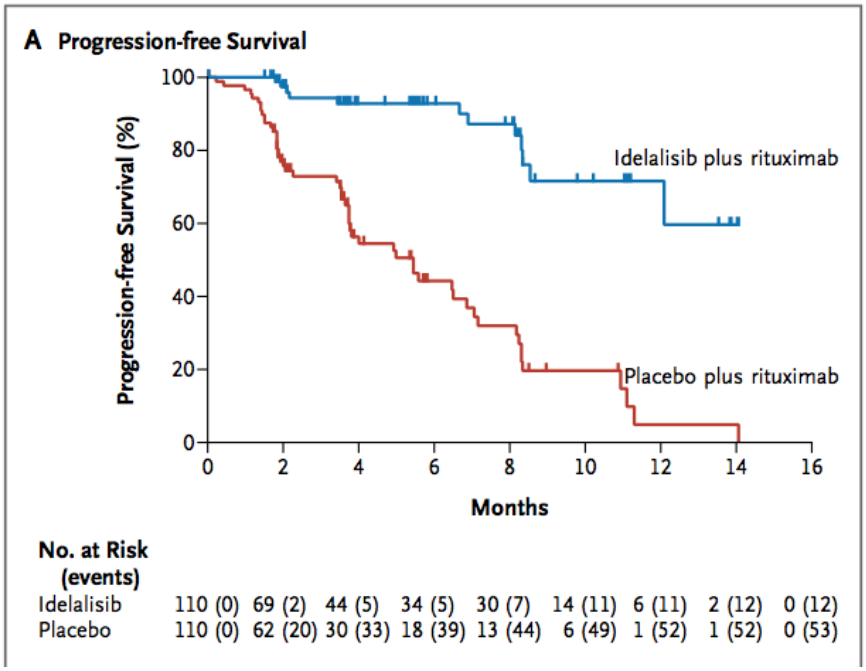
Furman R, et al. ASH 2013. Abstract LBA-6.

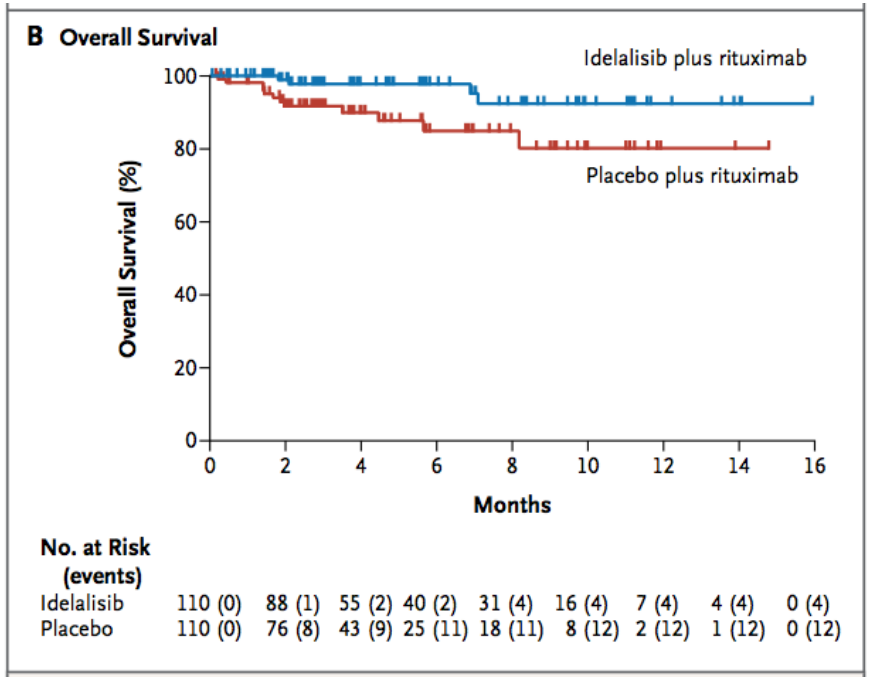
Idelalisib and Rituximab for previously treated patients with CLL: Waterfall plot



Furman R, et al. NEJM online first, Jan 22, 2014

Idelalisib and Rituximab for previously treated patients with CLL: PFS and OS

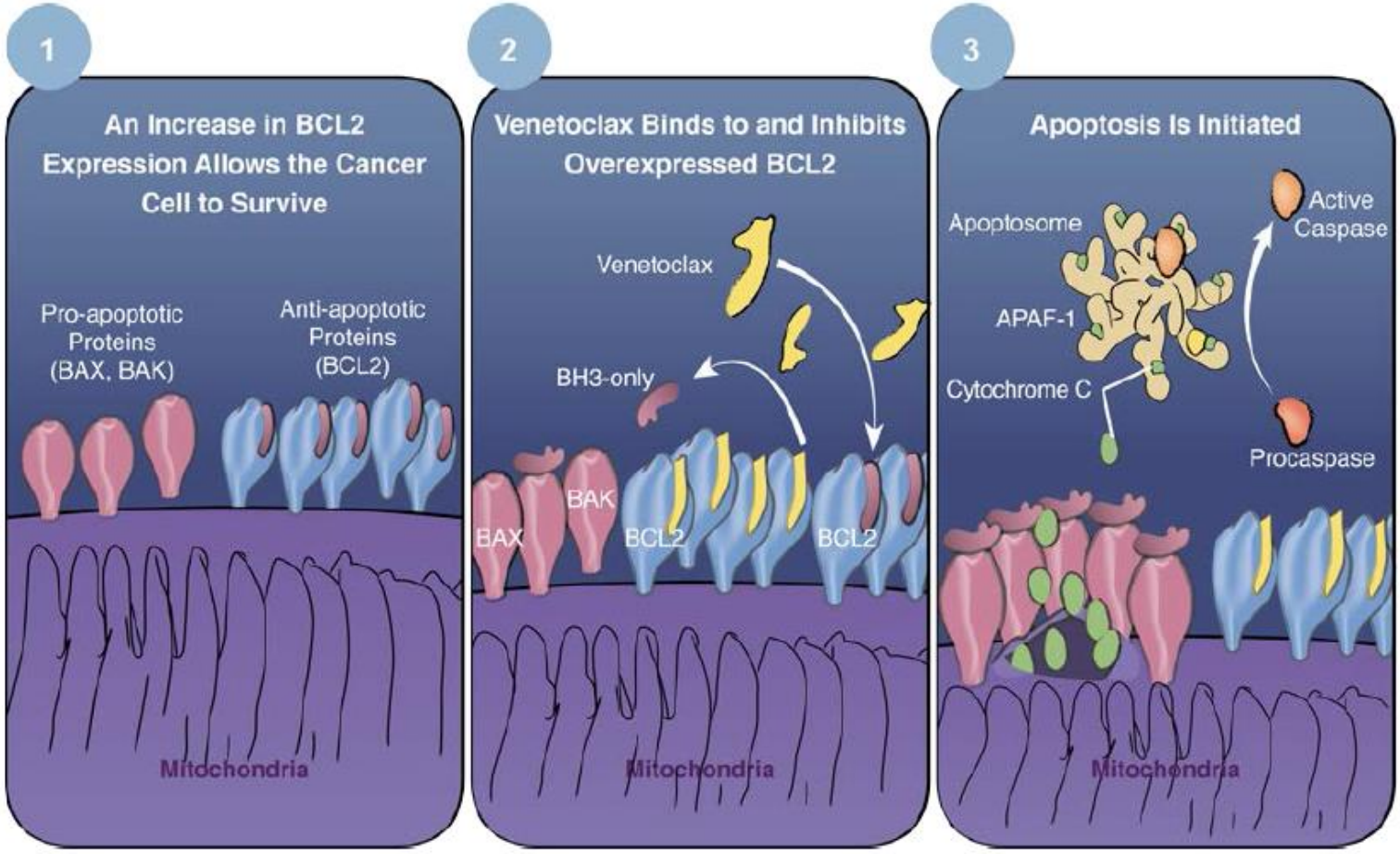




- **Excellent results**
- **in the presence or absence of high-risk genomic alterations**
- **acceptable safety profile**

Furman R, et al. NEJM online first, Jan 22, 2014

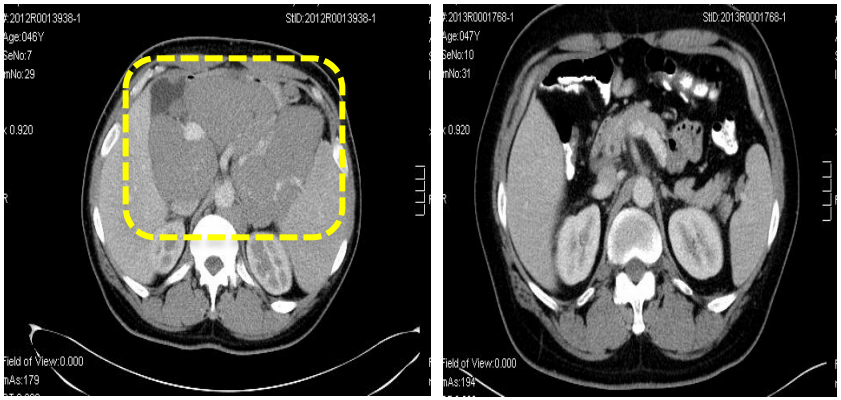
Venetoclax (ABT-199) Mechanism of Action



Venetoclax in relapsed/refractory CLL

Phase I dose escalation study (N = 78)

May 2012 Jan 2013

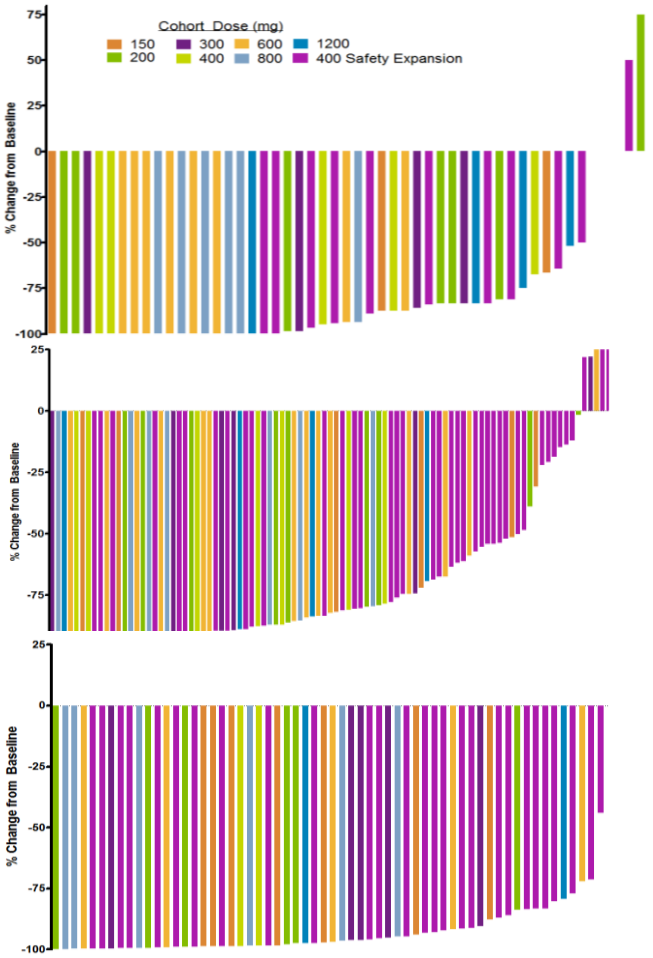


- **All patients: ORR 77%, CR/CRi rate 18%**
  - **High-risk del(17p): ORR 79%, CR/CRi rate 26%**
- **11/18 patients with CR/CRi were assessed for MRD**
  - **6 with no detectable MRD in BM**
  - **1 MRD in blood**
- **Dose-limiting toxicity: tumor lysis syndrome**
  - **Due to rapid response: careful management**

% change in bone marrow

% change in node size

% change in peripheral lymphocytes



Seymour JF, et al. EHA 2014. Abstract S702.

Venetoclax

- Oral Bcl-2 inhibitor with potent therapeutic activity
- Complete remissions in rel/ref CLL
  - MRD-negative CRs reported
- Active in very high-risk CLL: rel/ref del(17p) CLL and fludarabine-refractory CLL
- Additional combinations under study
- FDA-approval pending, breakthrough designation for del(17p)

Thank you for your kind attention

I am happy to take any questions