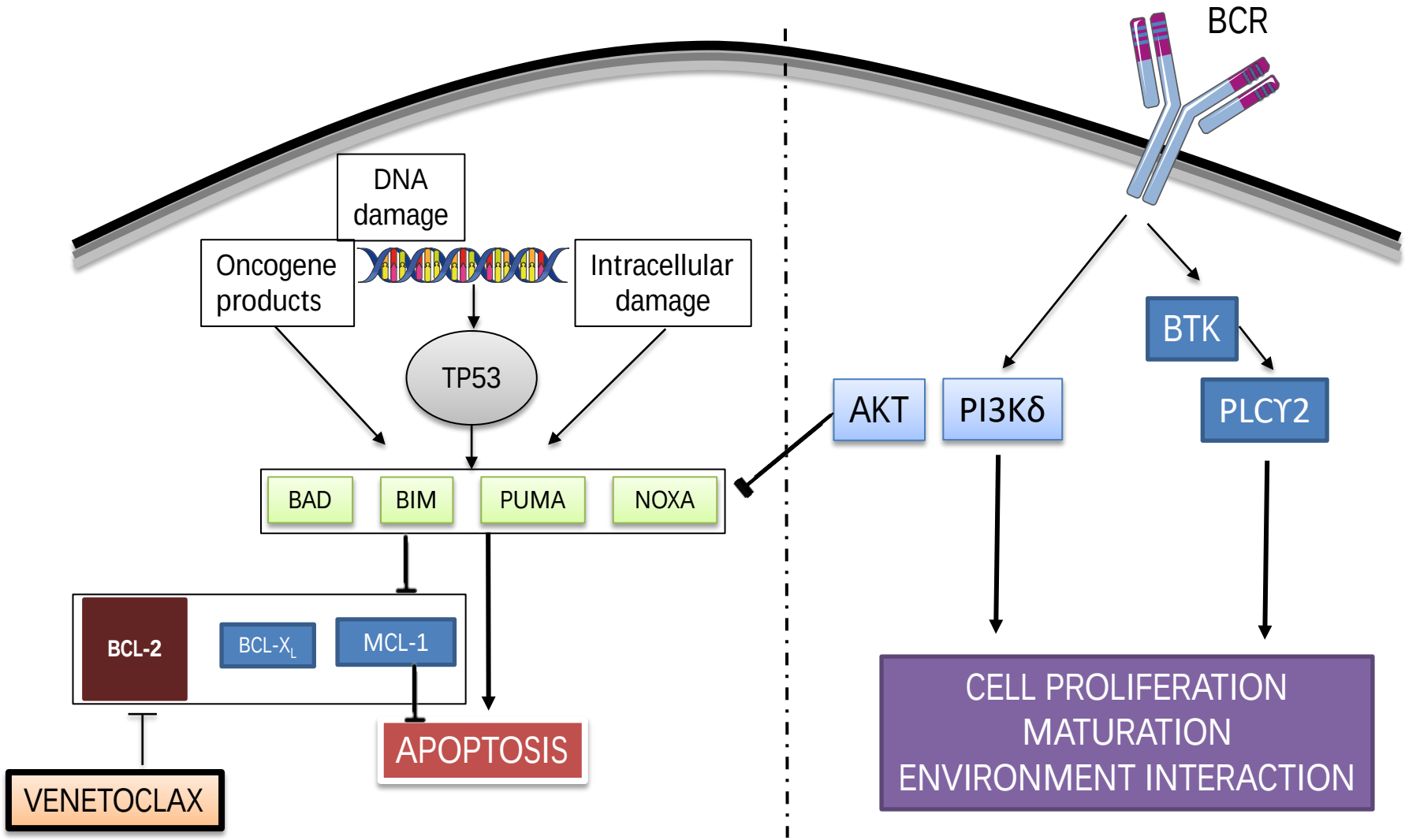
LLC: Nuevas opciones terapéuticas

Francesc Bosch
Department of Hematology
Hospital Universitari Vall d'Hebron, Barcelona, Spain
fbosch@vhebron.net

Workshop Leucemia Linfática Crónica
Sociedad Chilena de Hematología
Santiago de Chile
Viernes 11 de Noviembre de 2016

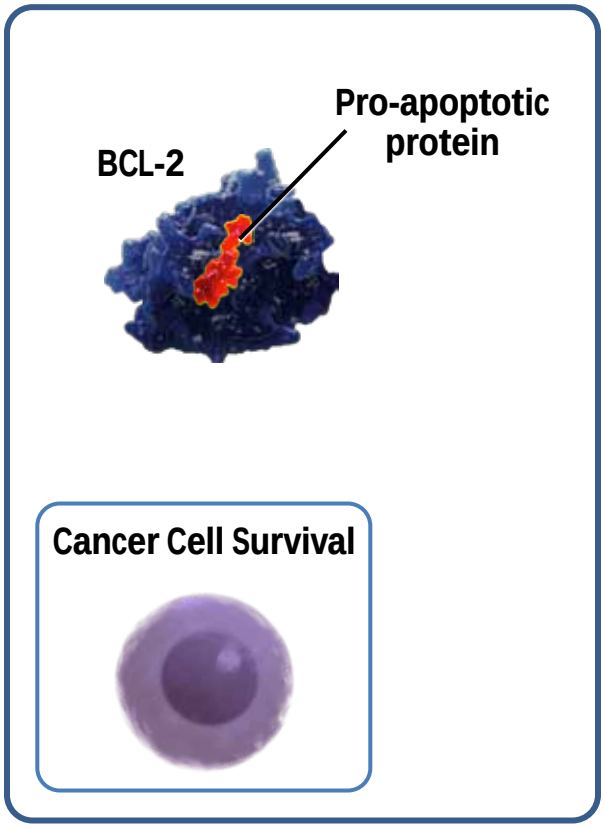
Important signaling pathways in CLL



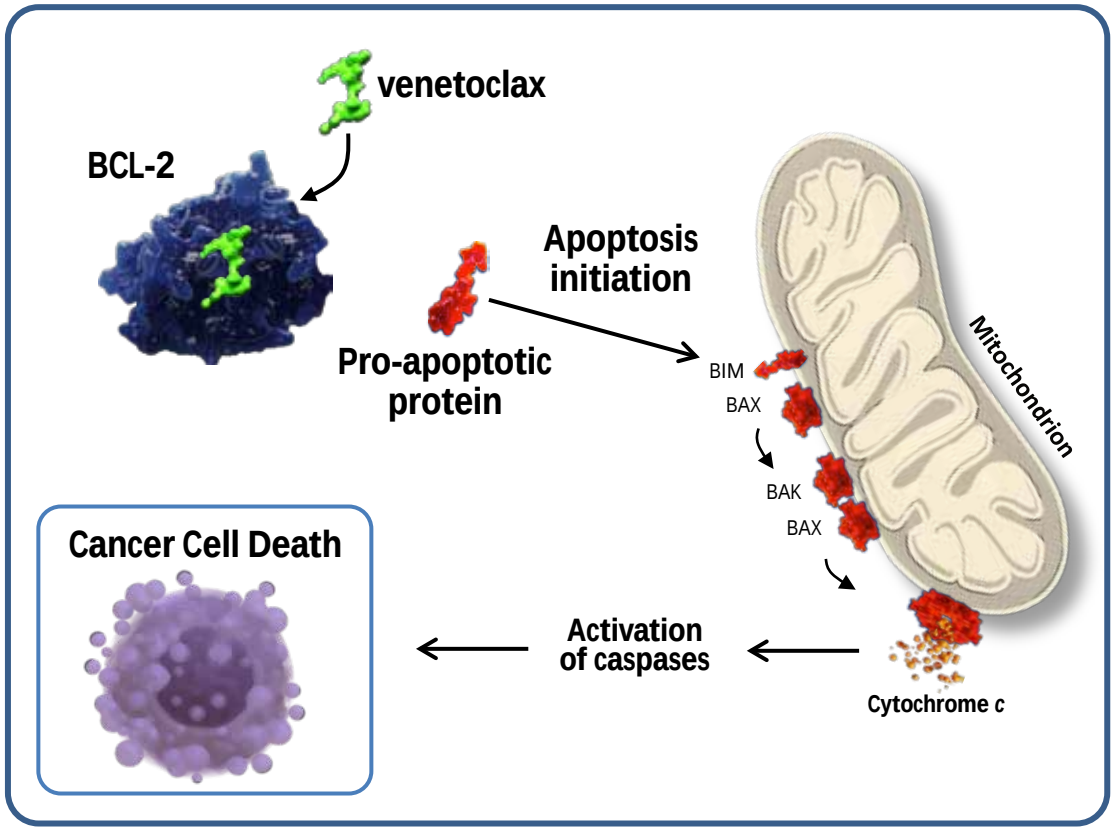
Adapted from Czabotar PE et al. *Nat Rev Mol Cell Biol*. 2014;15(1):49-63, Ashkenazi A. *Nat Rev Drug Discov*. 2008;7(12):1001-12, and Elmore S. *Toxicol Pathol*. 2007;35(4):495-516.

Venetoclax is a BCL-2 Selective Inhibitor

Restoration of apoptosis through BCL-2 inhibition



BCL-2 overexpression allows cancer cells to evade apoptosis by sequestering pro-apoptotic proteins.



Venetoclax binds selectively to BCL-2, freeing pro-apoptotic proteins that initiate programmed cell death (apoptosis).

Final approved version – 20May2016

Venetoclax Clinical Trial Program: CLL Studies

Phase 1

M12-175

Relapsed/refractory CLL or NHL monotherapy[1]

M13-365

Relapsed/refractory CLL combination therapy (venetoclax + rituximab)[2]

Phase 2

M13-982

Relapsed/refractory CLL 17p deletion monotherapy[3]

M14-032

Relapsed/refractory CLL BCRi failures monotherapy[4]

Phase 3

MURANO

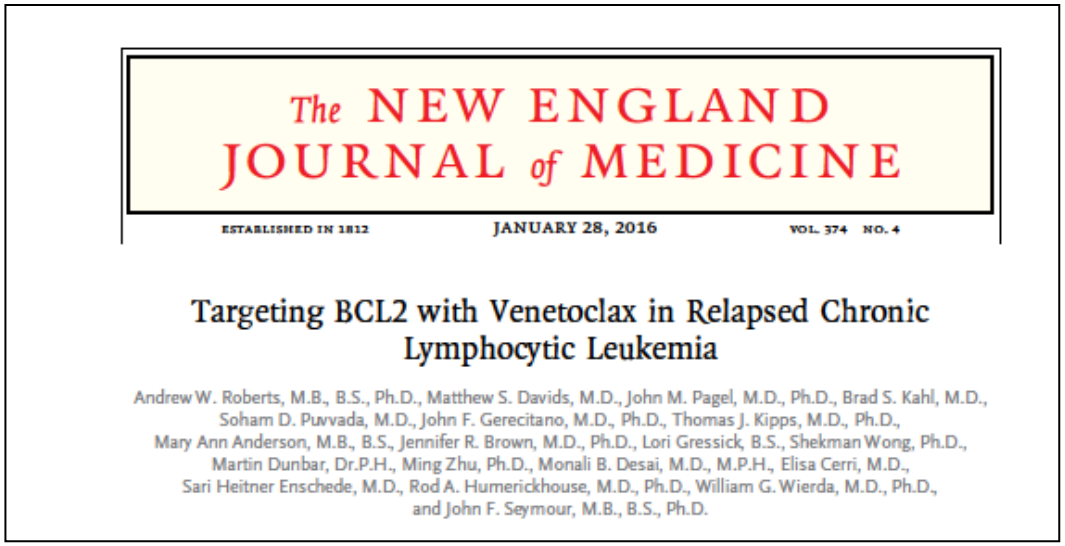
Relapsed/refractory CLL combination therapy (+ rituximab) versus bendamustine + rituximab

CLL14

First line CLL combination therapy (+ obinutuzumab) versus Obinutuzumab +chlorambucil

1. Roberts el al. N Engl J Med 2016; 374:311-322
2. Ma S et al. ASH 2015, abstract #80273;
3. Stilgenbauer S, et al. Lancet Oncology, 2016;
4. Ma S et al. ASH 2015, abstract #80273

M12-175. Phase 1 venetoclax monotherapy in CLL/SLL



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 28, 2016 VOL. 374 NO. 4

Targeting BCL2 with Venetoclax in Relapsed Chronic Lymphocytic Leukemia

Andrew W. Roberts, M.B., B.S., Ph.D., Matthew S. Davids, M.D., John M. Pagel, M.D., Ph.D., Brad S. Kahl, M.D., Soham D. Puvvada, M.D., John F. Gerecitano, M.D., Ph.D., Thomas J. Kipps, M.D., Ph.D., Mary Ann Anderson, M.B., B.S., Jennifer R. Brown, M.D., Ph.D., Lori Gressick, B.S., Shekman Wong, Ph.D., Martin Dunbar, Dr.P.H., Ming Zhu, Ph.D., Monali B. Desai, M.D., M.P.H., Elisa Cerri, M.D., Sari Heitner Enschede, M.D., Rod A. Humerickhouse, M.D., Ph.D., William G. Wierda, M.D., Ph.D., and John F. Seymour, M.B., B.S., Ph.D.

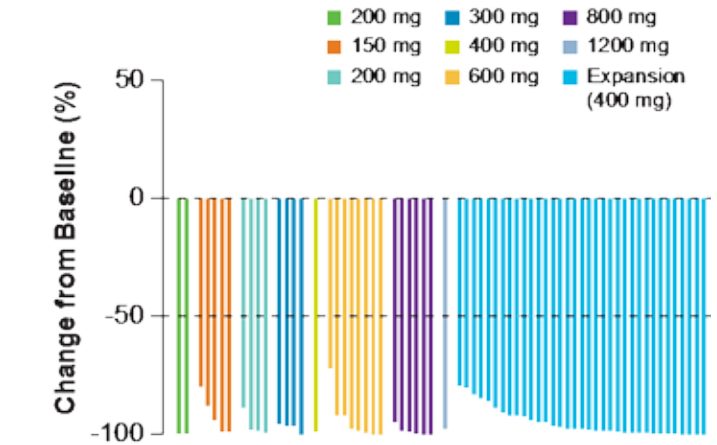
This study was a Phase 1, open-label multicenter dose escalation trial

- Patients in the dose escalation cohort were divided into 8 dosing groups (150 mg – 1200 mg)

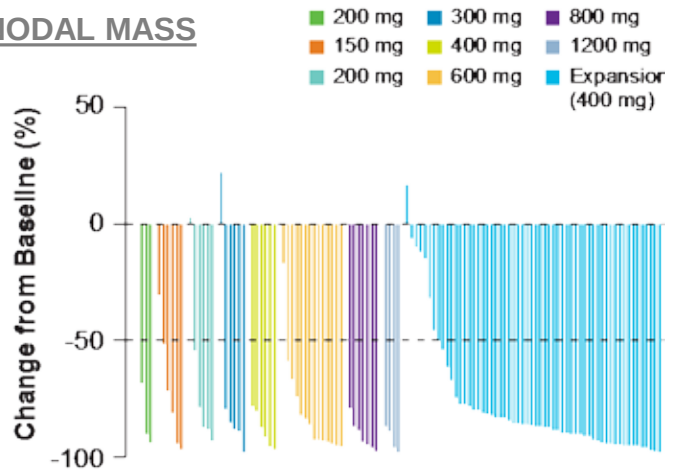
Roberts el al. N Engl J Med 2016; 374:311-322

Reductions in CLL Burden With Venetoclax

ABSOLUTE LYMPHOCYTE COUNT

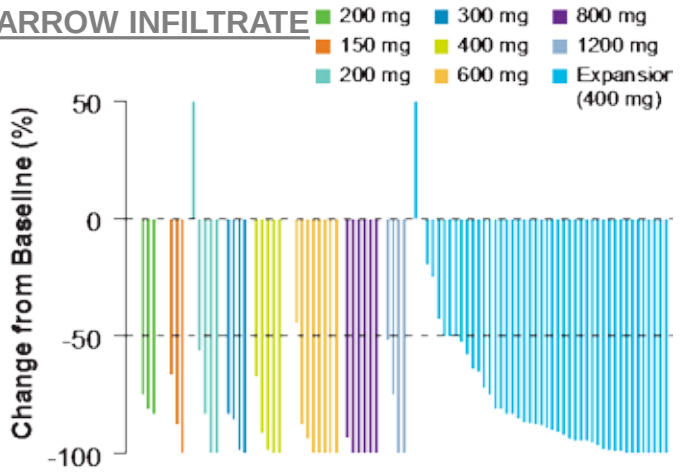


NODAL MASS



Median time to:	N	Median (range)
Lymphocytes <4000/mm^3	65	22 (1-451) days
50% reduction in nodal size	99	42 (20-417) days
Nodes <1.5 cm	34	8 (1-27) months
Complete clearance of bone marrow infiltrate	26	6 (2-22) months

BONE MARROW INFILTRATE

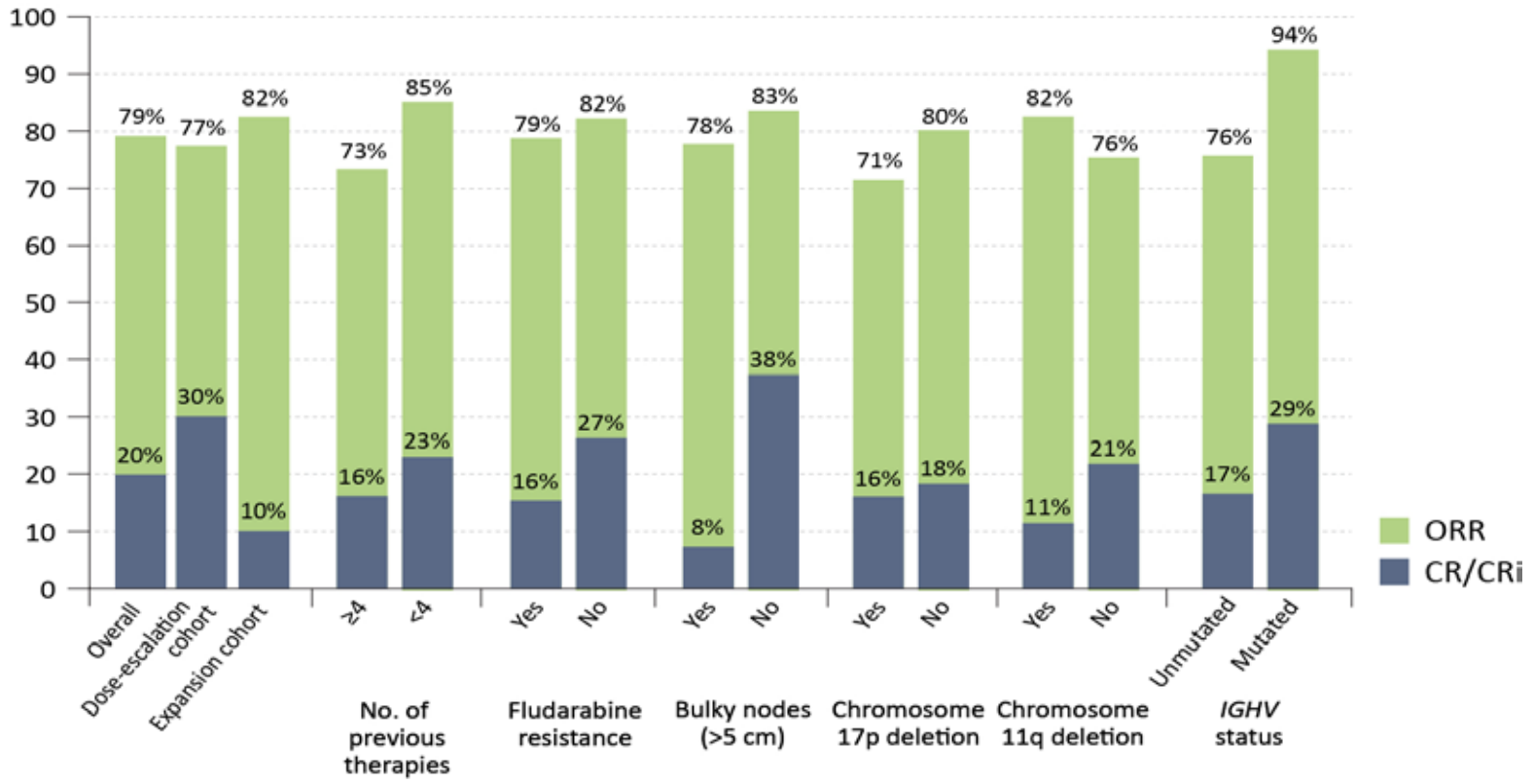


Venetoclax was active at all doses studied and induced rapid and deep reductions in CLL burden as measured by all three important compartments (peripheral blood, lymph nodes, and bone marrow) in R/R CLL

Note: Lymphocyte count in peripheral blood is reported only for the 66 patients who had lymphocytosis immediately before administration of venetoclax

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

M12-175 Efficacy: Overall Response Rate



- Median time to first objective response: 6 (range 5 to 24) weeks
- Median time to CR/CRi: 6 (3 to 19) months (3 CR achieved after 1 year of treatment)
- 17/23 patients who achieved CR/CRi had multicolor flow cytometric testing for MRD and 6 (35%) of those tested were negative by standard criteria (5% of all patients).

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

Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label, phase 2 study

Stephan Stilgenbauer, Barbara Eichhorst, Johannes Schetelig, Steven Coutre, John F Seymour, Talha Munir, Soham D Puvvada, Clemens-Martin Wendtner, Andrew W Roberts, Wojciech Jurczak, Stephen P Mulligan, Sebastian Böttcher, Mehrdad Mobasher, Ming Zhu, Monali Desai, Brenda Chyla, Maria Verdugo, Sari Heitner Enschede, Elisa Cerri, Rod Humerickhouse, Gary Gordon, Michael Hallek, William G Wierda

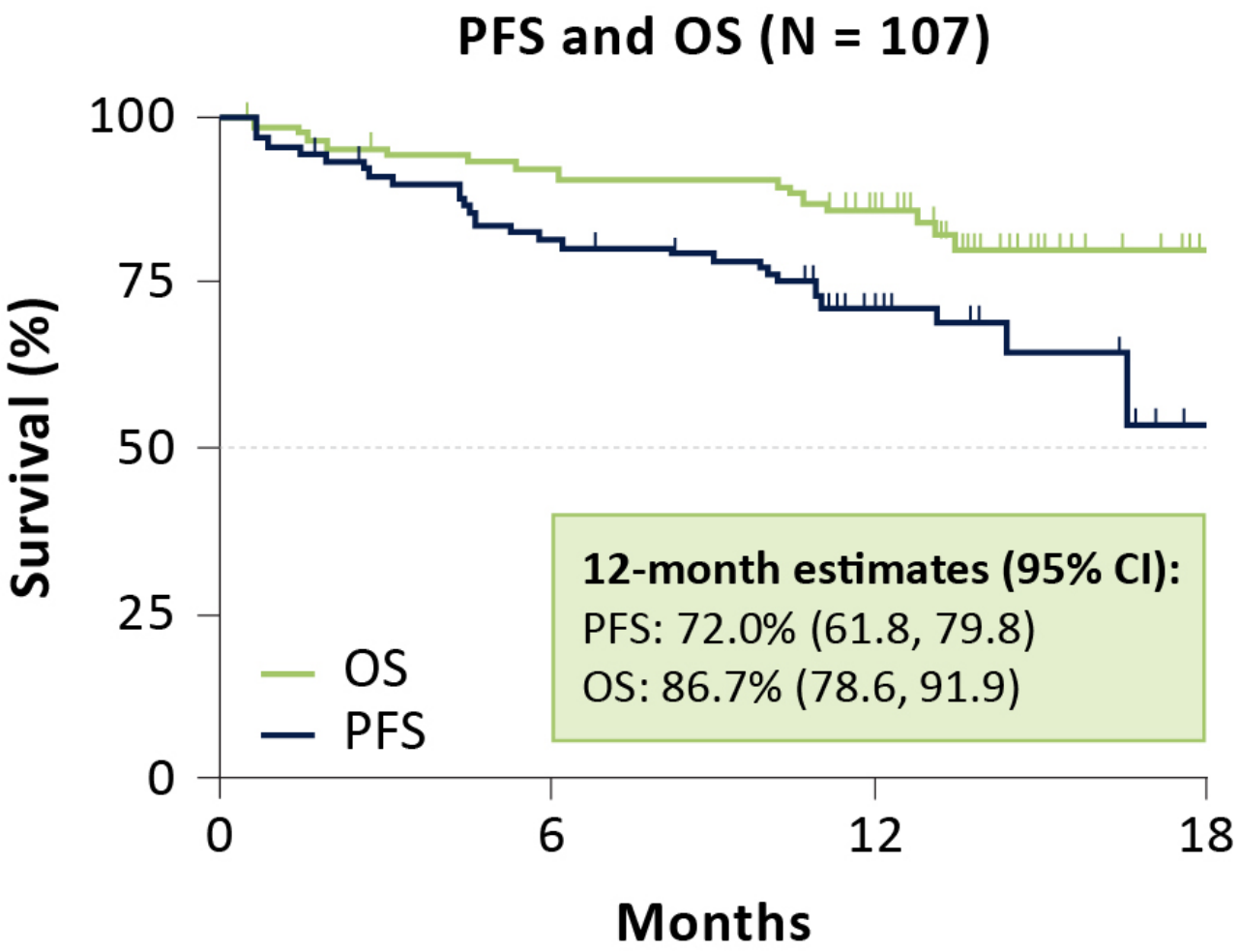
Stilgenbauer S, et al. Lancet Oncology, 2016
Published Online May 10, 2016
http://dx.doi.org/10.1016/S1470-2045(16)30019-5

Baseline Characteristics

Characteristic n, %	R/R CLL n = 107
Median time on study	12.1 months
Median (range) age	67 (37–85) years
Male sex	70 (65%)
Median prior regimens (range)	2 (1–4)
Prior bendamustine / refractory	54 (50%) / 38 (70%)
Prior fludarabine / refractory	78 (73%) / 34 (44%)
ECOG grade 1/2	56 (52%) / 9 (8%)
One or more nodes ≥ 5 cm	57 (53%)
ALC ≥25 x 10^9/L	54 (51%)
TLS risk category: Low / Medium / High	19 (18%) / 43 (40%) / 45 (42%)
Rai stage III or IV	51 (48%)
TP53 Mutation: Yes	60 (72%)
IGHV unmutated	30 (81%)

Stilgenbauer S, et al. Lancet Oncology, 2016

PFS and OS by IRC



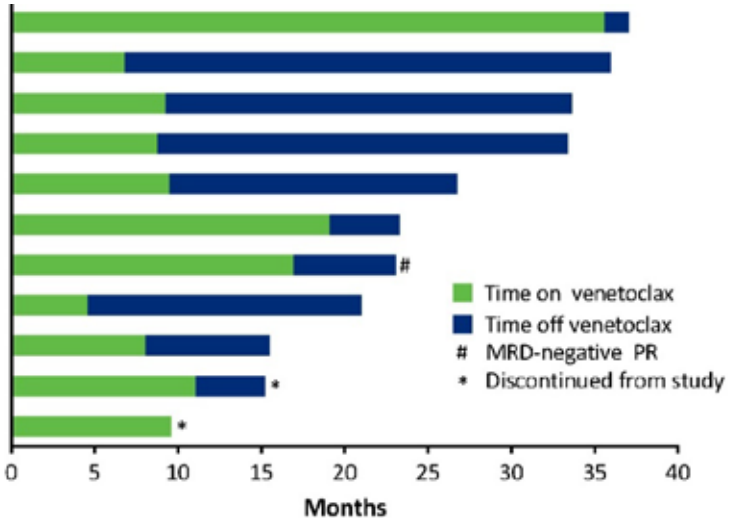
Overall median PFS and OS were not yet reached

Stilgenbauer S, et al. Lancet Oncology, 2016

M13-165. Phase 1b trial Venetoclax in combination with Rituximab in R/R CLL

Venetoclax plus rituximab is highly active in patients with relapsed/refractory CLL

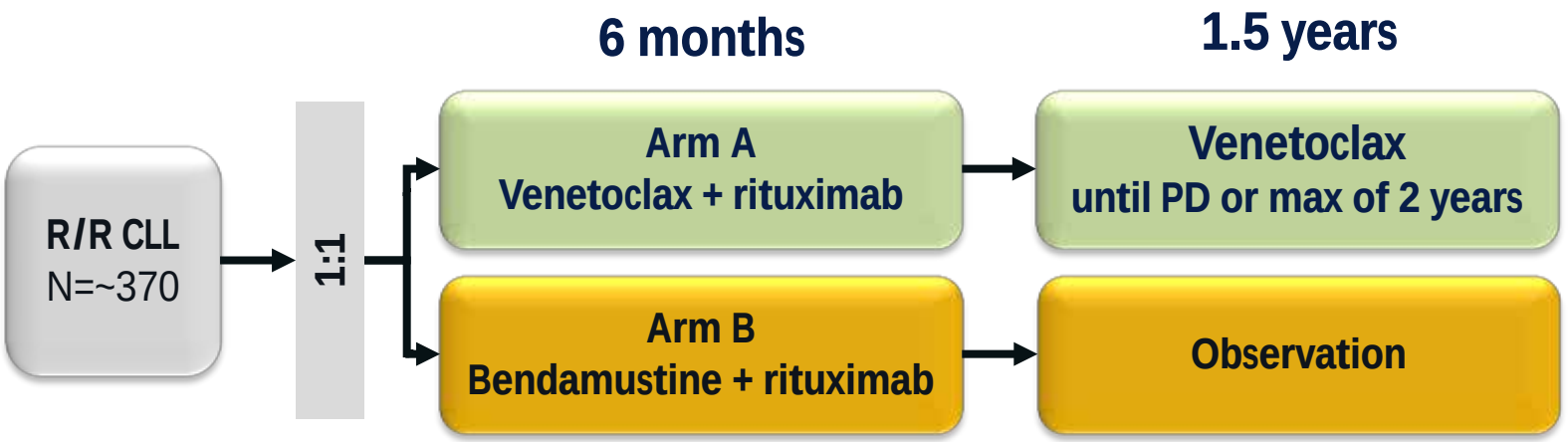
- The **overall response rate is 86%** to date, including **47% CR/CRi**
- **MRD-negativity** in the bone marrow is observed in **55%** (27/49) patients
- All MRD-negative patients have maintained their response



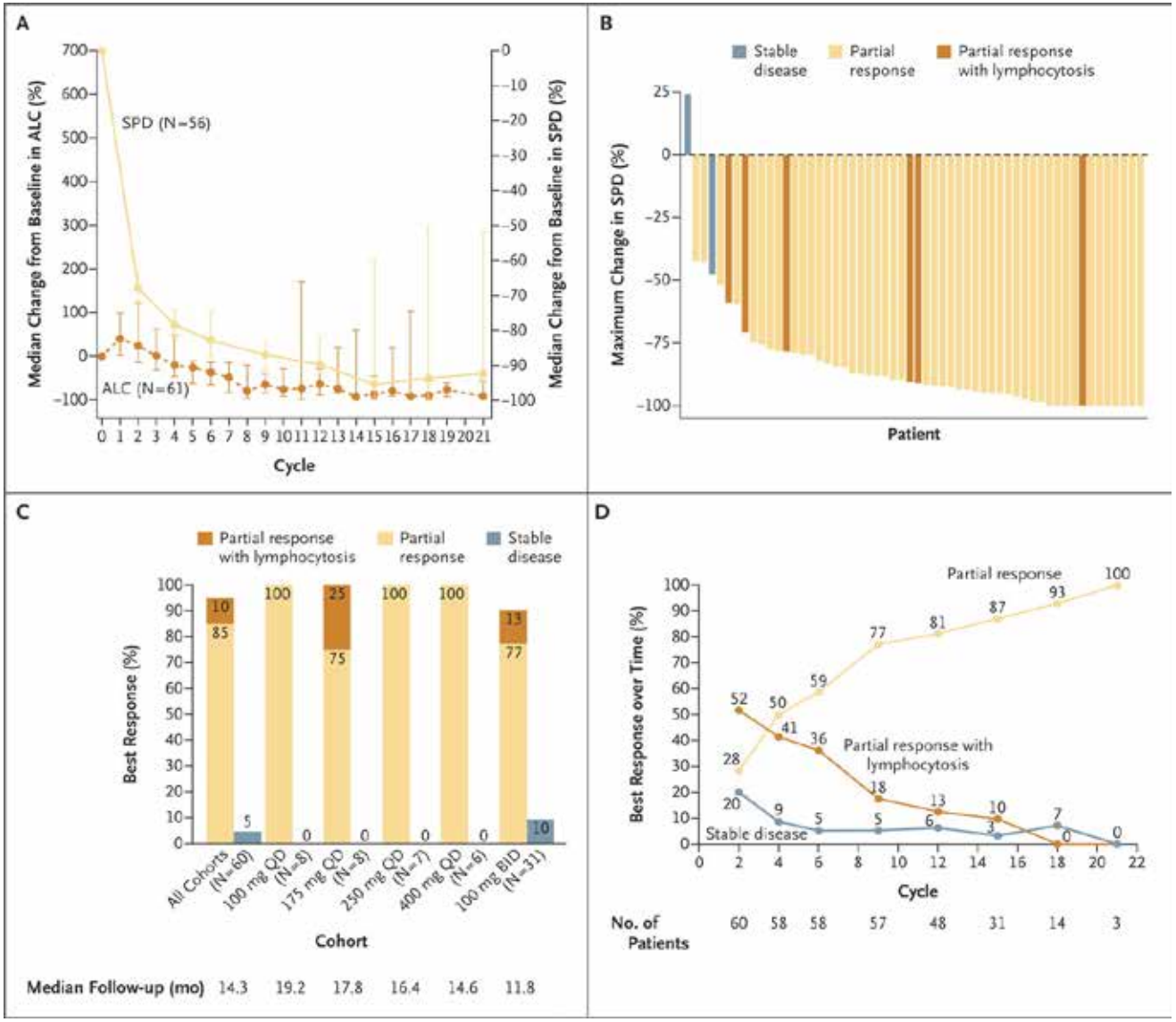
- Eleven patients have stopped venetoclax after achieving CR or MRD-negativity
- Two patients who were MRD-positive have progressed; venetoclax re-treatment in one patient resulted in PR at 3 months
- None of the MRD-negative patients have progressed off therapy

Ma S et al. ASH 2015, abstract #80273

Venetoclax in combination with Rituximab in R/R CLL
Phase 3 MURANO trial



Second generation BTK inhibitor Acalabrutinib



Byrd JC et al. N Engl J Med 2016;374:323-332.

RELAPSED AFTER KINASE INHIBITORS

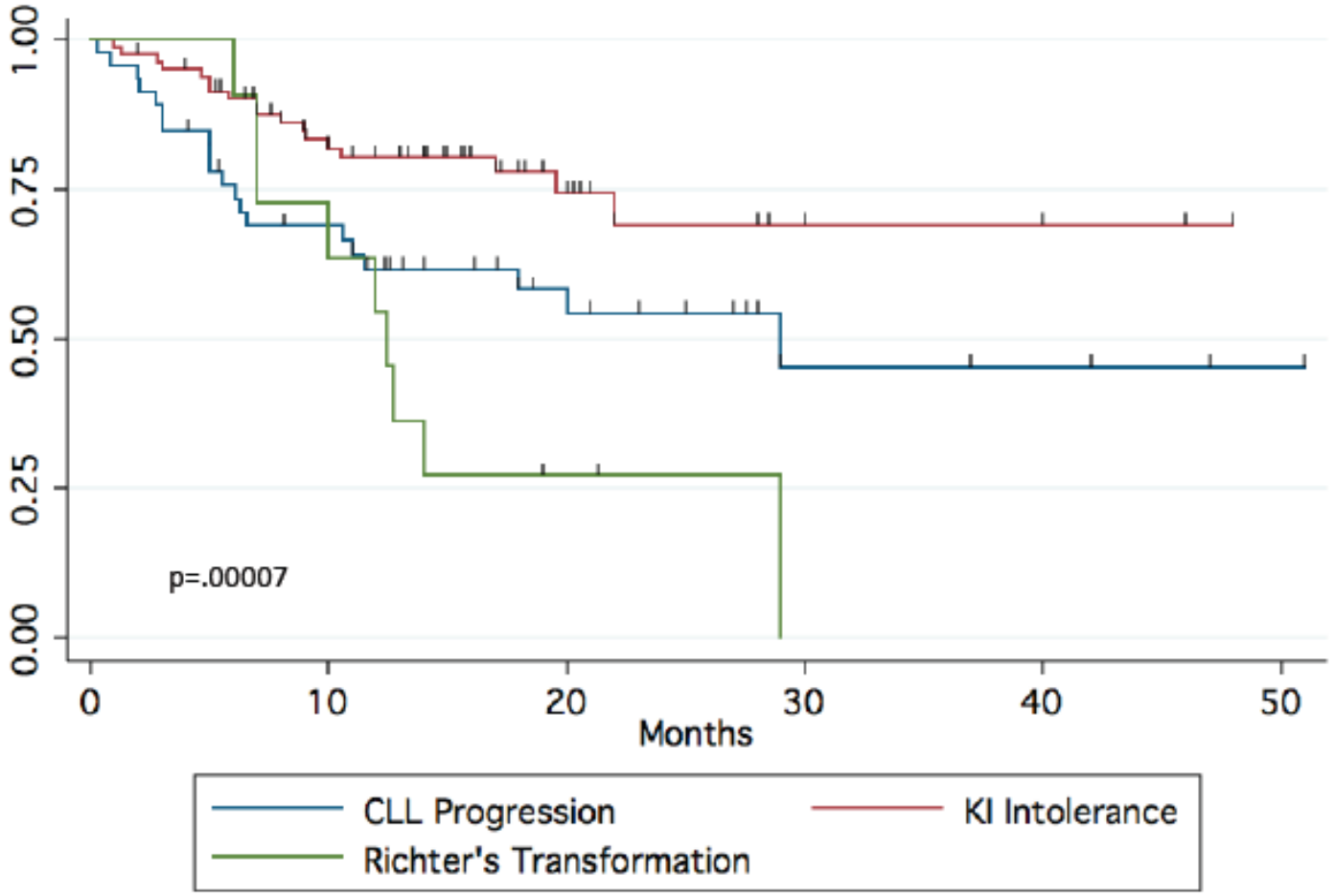
Case 3

- 64 yo female
- 2009 à CLL, stage B, del13q
- 2011 à FCR x 6 à CR
- 2013 à Progression à BR à PR
- 2015 à Ibrutinib à progression after 12 months

Ibrutinib: reasons for discontinuation

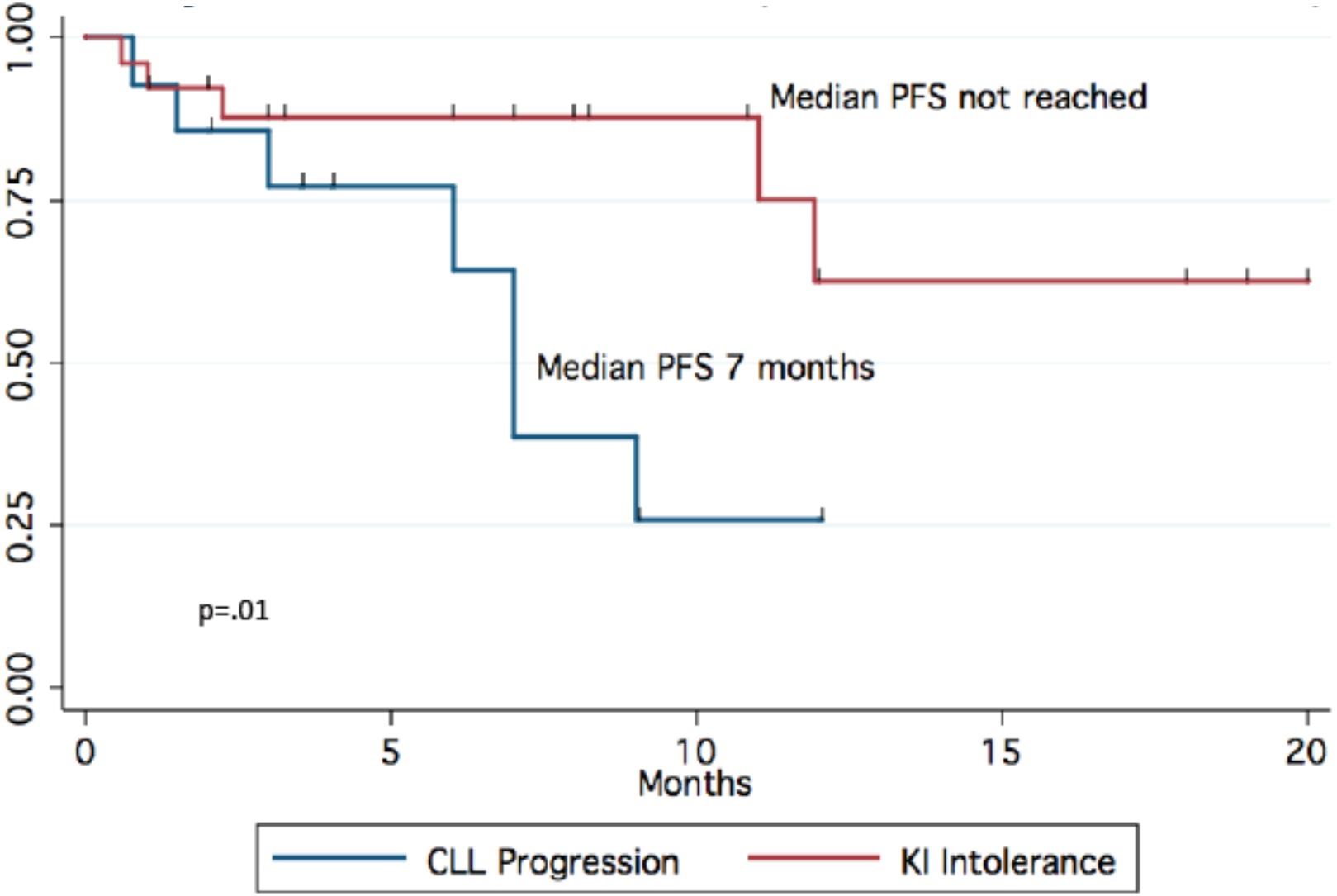
- 30% (at 4 years) of patients receiving ibrutinib will discontinue therapy
  - Intolerance / toxicity: 20%
  - Disease progression: 10%
    - Adcquisition of mutations
    - Richter's transformation
- Therapeutic approach (?)
  - Change KI / Venetoclax
  - Consider allogeneic stem-cell transplantation

KI discontinuation: OS by reason



Mato et al, Blood 2016 (ePub)

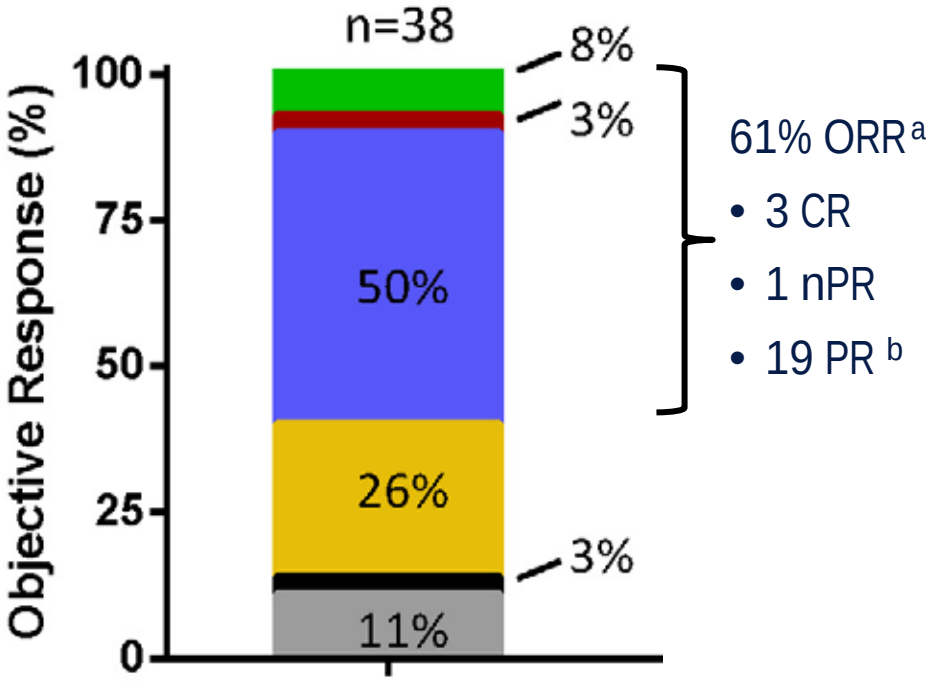
PFS by discontinuation Treated with alternate KI



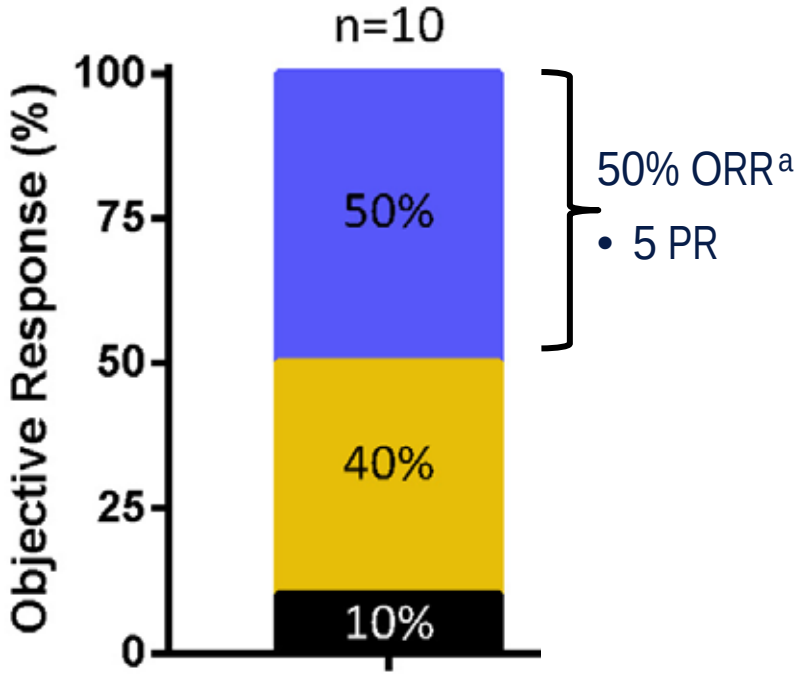
Mato AR et al, Blood 2016 (ePub)

M14-032: Phase 2 Study of Venetoclax Monotherapy CLL Relapsed After or Refractory to Ibrutinib or Idelalisib Therapy

Ibrutinib Arm



Idelalisib Arm



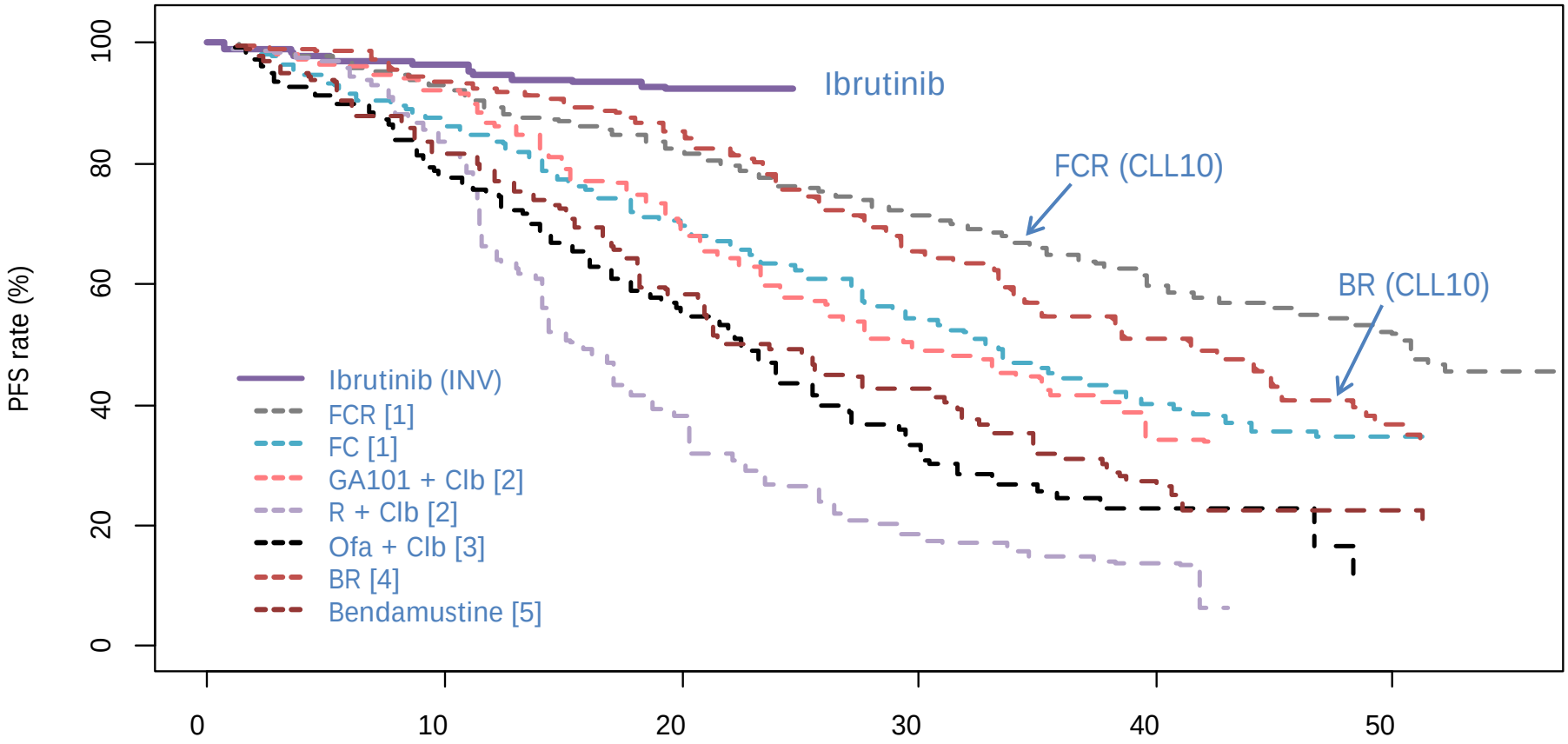
CR SD
nPR PD
PR D/C without assessment

Jones et al, ASH 2015

CLL in 2016: Unanswered questions

1. Long-term activity
   - Median survival of CLL is long
   - Follow-up of patients receiving newer treatments is short
   - QoL

Indirect Naïve Comparison of PFS: RESONATE 2™ v. "young fit + elderly" treatment regimens

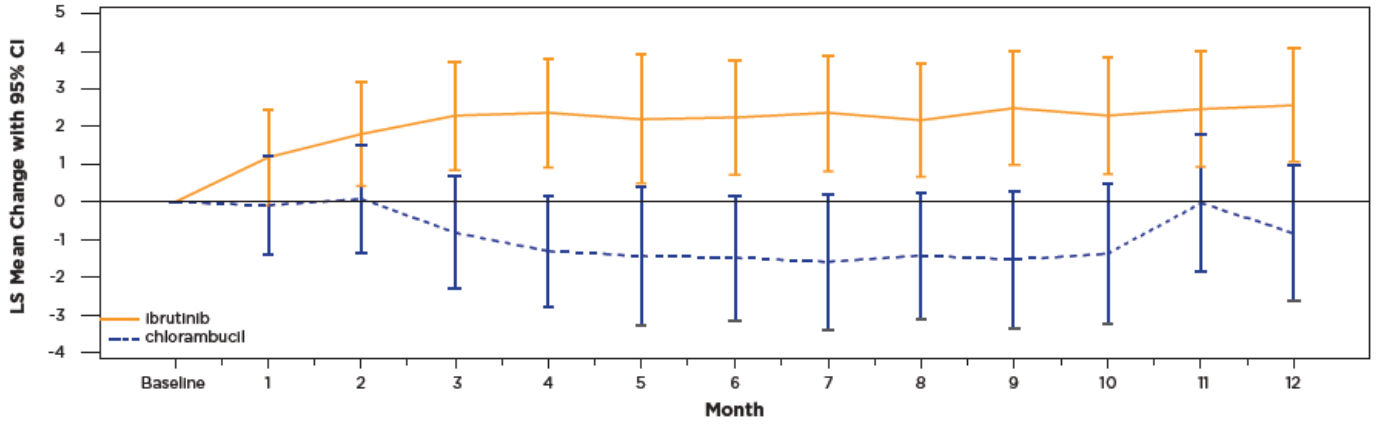


BR=bendamustine+rituximab; Clb=chlorambucil; FC=fludarabine+cyclophosphamide; FCR=fludarabine+ cyclophosphamide+rituximab; GA101=obinutuzumab; INV=investigator; Ofa=ofatumumab; R=rituximab

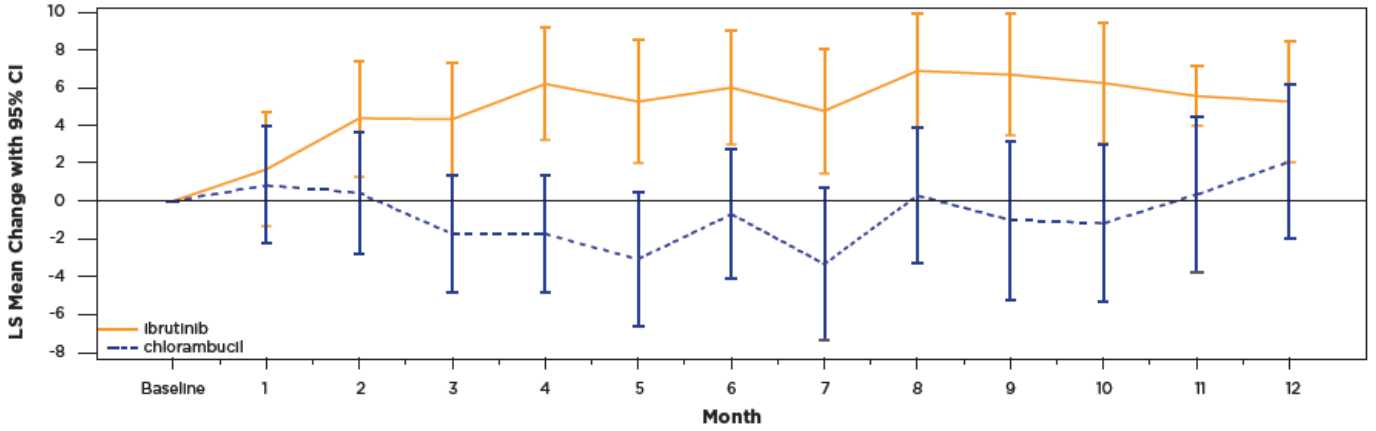
[1] Hallek, et al. 2010; [2] Goede et al, 2015; [3] Hillmen et al. 2015; [4] Eichhorst et al. ASH 2014; [5] Knauf et al. 2009

Change in Patient-Reported QOL Measures Over Time

FACIT-Fatigue Score* Over Time



EORTC QLQ-C30 Global Health Status Score* Over Time



Least square mean change from baseline.

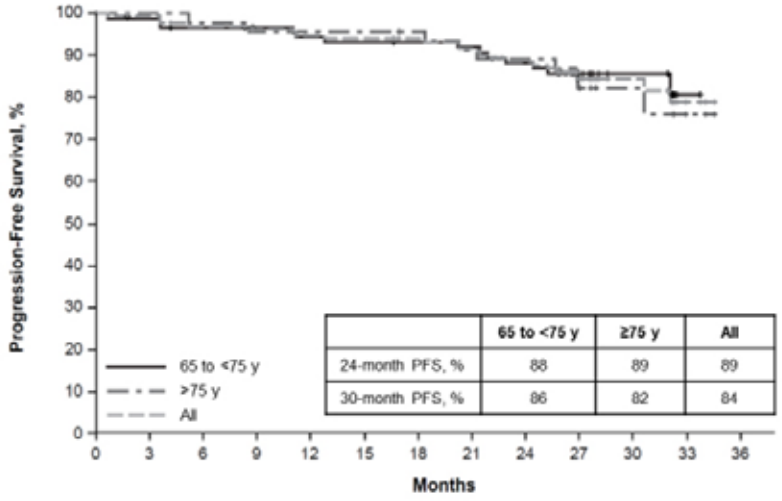
Ghia P et al. EHA 2016; Abstract P217 (Poster Presentation)

Update on the Resonate & Resonate-2: PFS

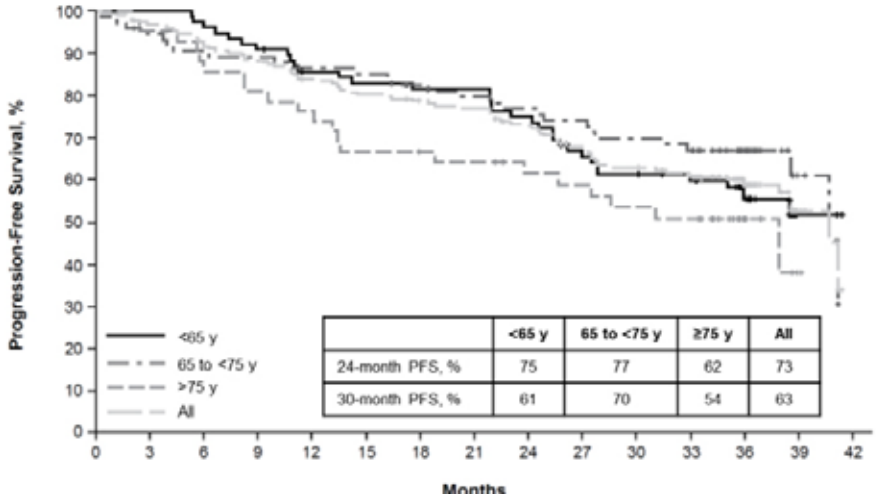
ASH | 58th Annual Meeting & Exposition
San Diego, CA · December 3-6, 2016

2041 Outcomes of Ibrutinib Therapy By Age in Patients with CLL/SLL: Analyses from Phase 3 Trial Data (RESONATE and RESONATE-2)

Jennifer A. Woyach, MD[1], Peter Hillmen[2], Jennifer R. Brown, MD, PhD[3], Steven E. Coutre, MD[4], Paul Barr, MD[5], Susan M. O'Brien, MD[6], Jacqueline C. Barrientos, MD[7], Stephen Devereux, PhD, FRCP, FRCPath[8], Neil E. Kay, MD[9], Nishitha Reddy, MD, MSCI, MBBS[10], Stephen Mulligan, MBBS, MD, FRACP, FRCPA[11], Alessandra Tedeschi[12], Cathy Zhou, MS[13*], Joi Ninomoto, PharmD[13*], Danelle F. James, MD[13*], John C. Byrd, MD[14] and Jan Burger, MD, PhD[15]*



	65 to <75 y	≥75 y	All
24-month PFS, %	88	89	89
30-month PFS, %	86	82	84



	<65 y	65 to <75 y	≥75 y	All
24-month PFS, %	75	77	62	73
30-month PFS, %	61	70	54	63

CLL in 2016: Unanswered questions

1. Long-term activity?
2. Short and long-term toxicities of the new drugs? Chemo free ≠ toxicity free!!

Main toxicities of the new therapies

		Frequency	Mechanism
Ibrutinib	Diarrhea	30% grade 1-2 First three months	EGFR inhibition
	Bleeding	30-40% Grade 1-3 2% severe	Platelet aggregation
	Cardiovascular	FA: Up to 15%, grade 1-2 HTA: 15% long-term	Tec inhibition? ?
Idelalisib	Infections	CMV and P jirovecii Unkonwn	Drug-class effect
	Pneumonitis	10%, grade 3-4	
	Late onset diarrhea	30-40% grade 3-4	
	Autoimmune Hepatitits	15% grade 1-3 (higher in front line)	
Venetoclax	Tumor-lysis syndrome	10% severe	Rapid cell death
	Neutropenia	30%	BCL2 in neutrophils

CLL in 2016: Unanswered questions

1. Long-term activity?
2. Short and long-term toxicities of the new drugs? Chemo free ≠ toxicity free!!
3. Goal of therapy?

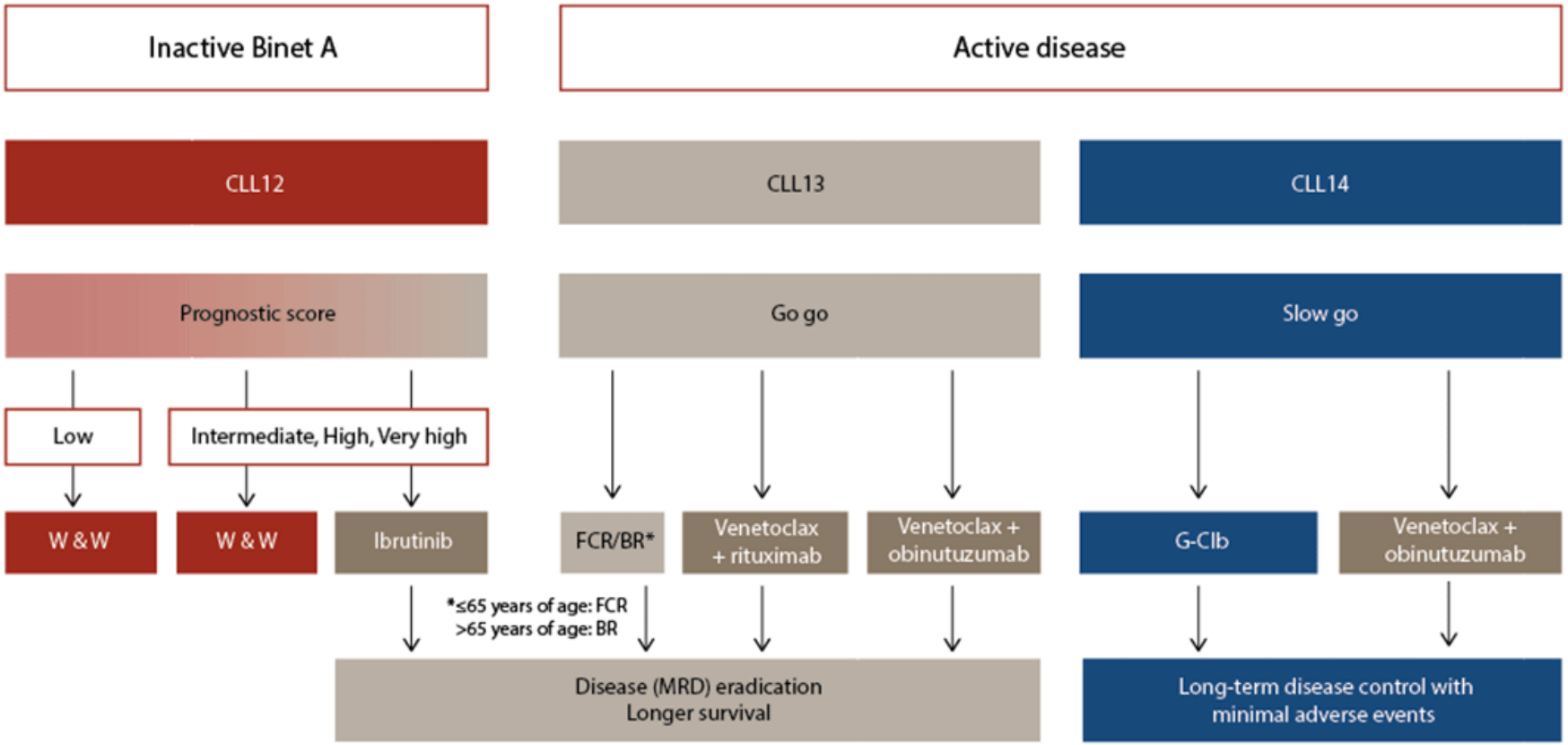
   MRD negativity?

   Continous therapy?

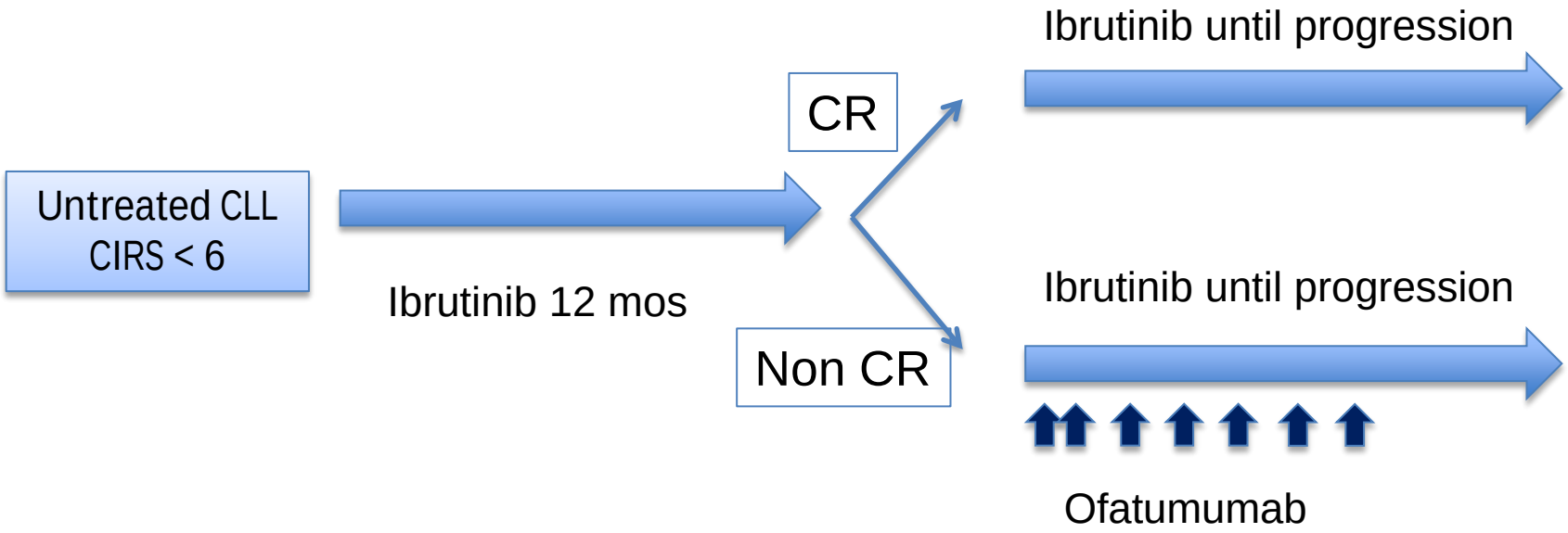
   FUTURE à MRD negativity without chemotherapy

   - Venetoclax + obinutizimab + ibrutinib
   - Ibrutinib + sequential ofatumumab

New combinations: The German CLL trials



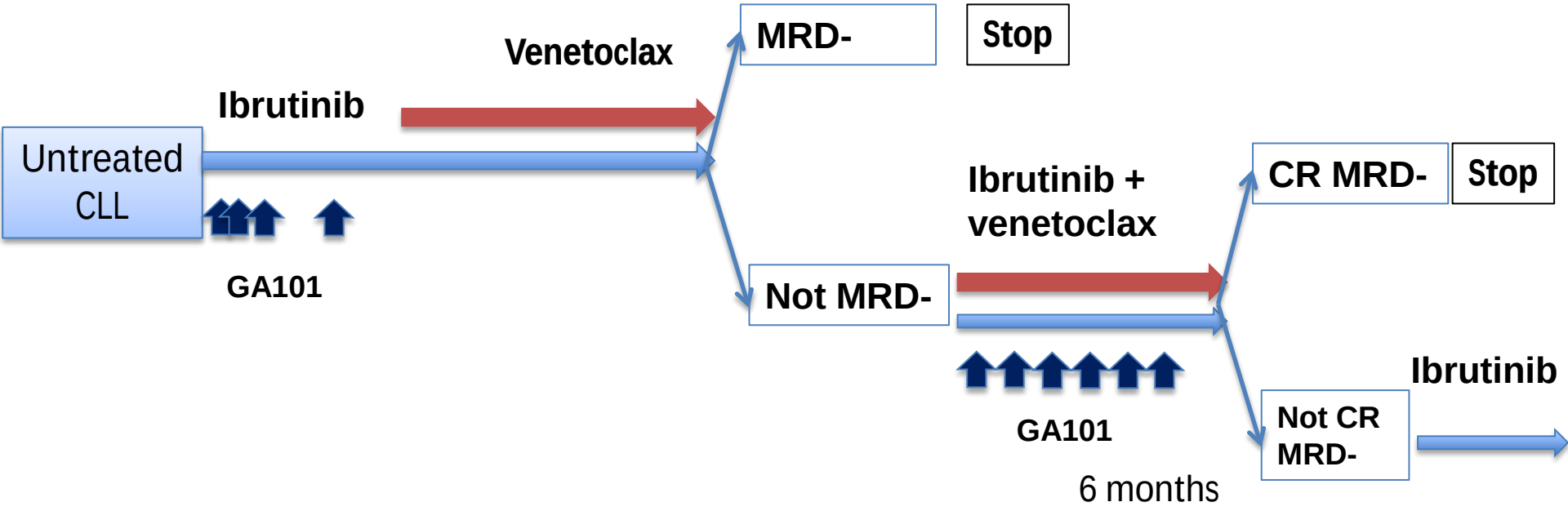
GELLC-7: Study design



- **Ibrutinib** 420 mg will be administered orally once daily on a continuous schedule until disease progression, unacceptable toxicity
- **Ofatumumab:** 300 mg C1D1 / 1000 mg C1D8 / 1000 mg C2 – C6
- **Duration of the study**: 72 months
  - Recruitment 18 months
  - Treatment period 18 months
  - Follow-up period: 36 months
- n=86; number of centers: 20-25

GELLC-8: Study design

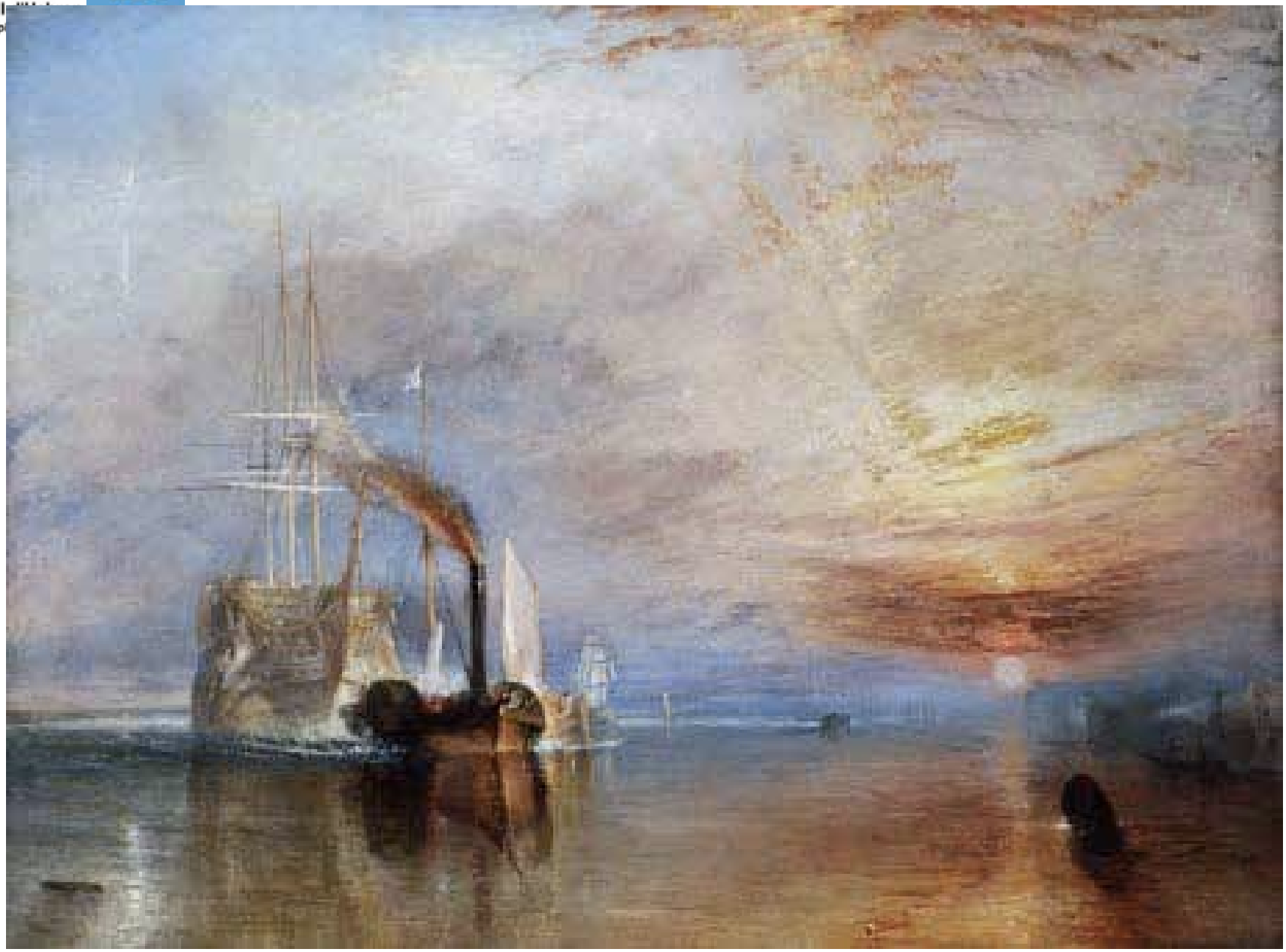
Non-randomized phase II multi-center study



Debulking: - Ibrutinib x 2 cycles (28 days cycle)
- Obinutuzumab 1000mg days 1,8,15 cycle 1
day 1 cycle 2

Treatment phase: Ibrutinib + venetoclax x 10 cycles (28 days cycle)

Consolidation phase MRD guided: Ibrutinib + venetoclax + Obinutuzumab 1000 mg day 1 x 6 cycles



MJ Terol
Pau Abrisqueta
Sabela Bobillo
Marta Crespo
Neus Villamor
María J Terol
Eva González-Barca
Marcos González
Christelle Ferrà
Eugenia Abella
Julio Delgado
Yolanda González
Isidro Jarque
Ana Muntañola
Mireia Constants
Lourdes Escoda
Bruno Montoro
Javier Loscertales
JA Hernández-Rivas
Jose A García-Marco

Peter Hillmen, Leeds, UK
Susan O'Brien, Houston, USA
Jennifer Brown, Boston, USA
Torsten Zenz, Heidelberg, Germnay
Stephan Stilgenbauer, Ulm, Germany
John Seymour, Melbourne, Australia