NOVEL TARGETED THERAPIES: IBRUTINIB

1st postgraduate CLL conference – Bologna

November 13, 2017

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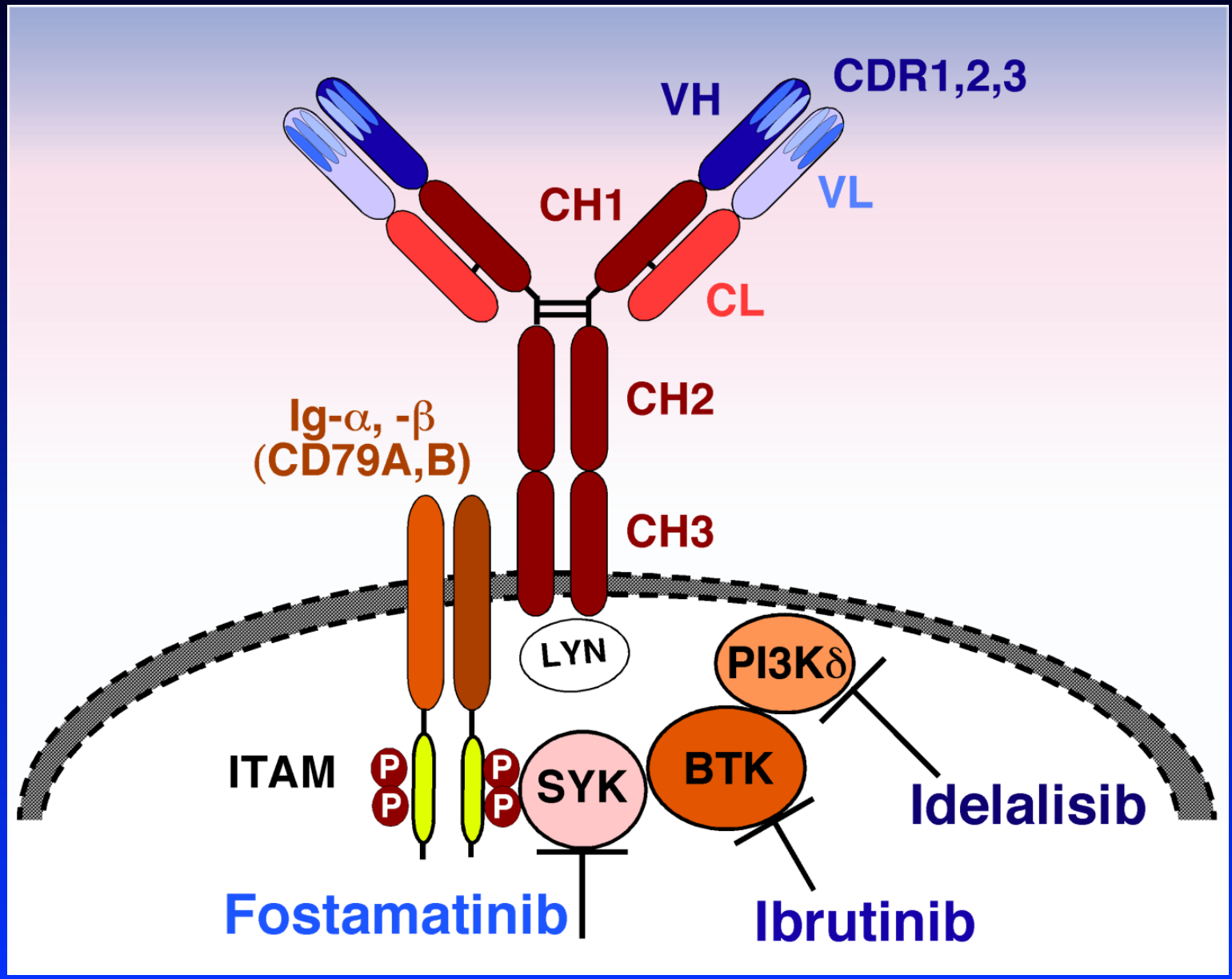
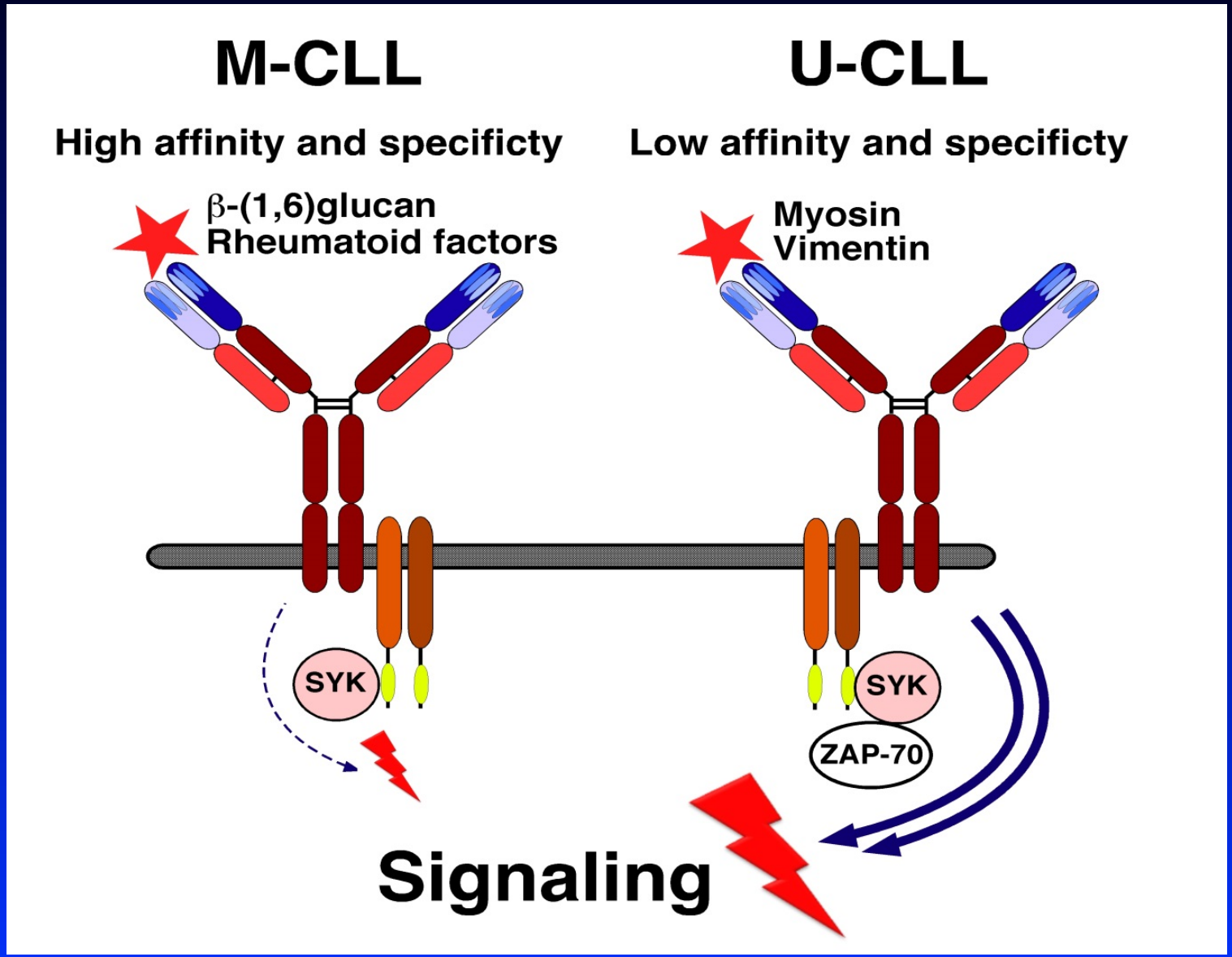
MD Anderson Cancer Center, Houston, Texas, USA

Targets in the BCR signaling pathway



From: Burger JA & Chiorazzi N: Trends Immunol. 2013

Model of BCR activation in CLL



From: Burger JA & Chiorazzi N: Trends Immunol. 2013

The discovery of agammaglobulinaemia in 1952

Colonel Ogden Bruton (*1908, †2003)
Chief of Pediatrics at
Walter Reed Army Hospital

Photo from: Ponader S & Burger JA,
J Clin Oncol. 32:1830-9

From: Bruton, OC: Agammaglobulinemia, *Pediatrics* 1952;9;722-728

AGAMMAGLOBULINEMIA

By Col. Ogden C. Bruton, M.C., U.S.A.
Washington, D.C.

THE complete absence of gamma globulin in human serum with a normal total protein as determined by electrophoretic analysis does not appear to have as yet been reported in the literature. Stern[1] mentions two cases of hypoproteinemia in children who had "almost complete absence of gamma globulin and were singularly free from infection." Schick[2] reported a similar congenital case without nephrosis with a review of the literature in which the total protein was low, the gamma globulin fraction low, and edema present. The latter findings in nephrosis are well known. Krebs[3] reported a case in which there was a "depression or gamma globulin in hypoproteinemia due to malnutrition." The present author had the opportunity of following a patient without nephrotic syndrome, with normal nutrition, with complete absence of the gamma globulin fraction and normal total serum protein through several years of many infections, including 19 episodes of clinical sepsis in which some type pneumococcus was recovered by blood culture 10 times. This entity, which, it was found, could be controlled by supplying gamma globulin as contained in concentrated immune human serum globulin, appears to be unique.

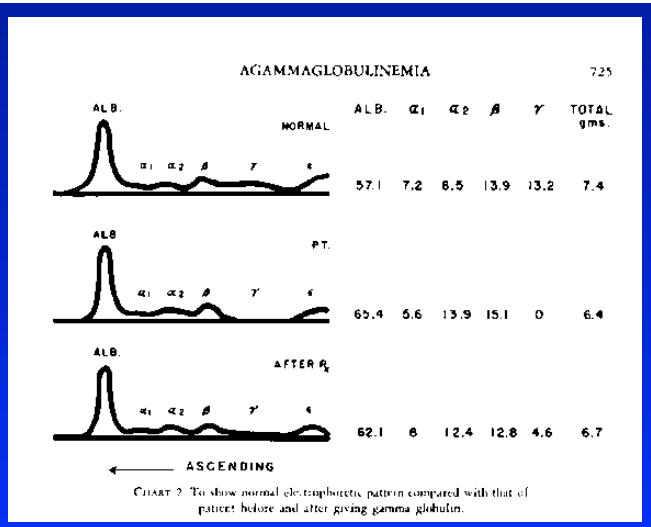
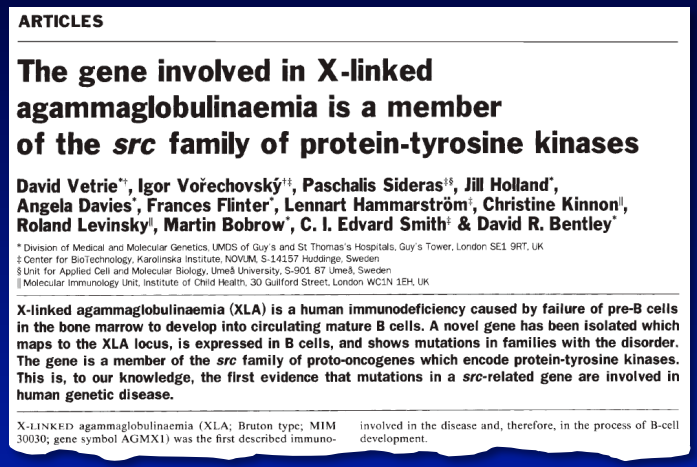


Chart 2. To show normal electrophoretic pattern compared with that of patient before and after giving gamma globulin.

Discovery of BTK as the cause for agammaglobulinemia (1993)



ARTICLES

The gene involved in X-linked agammaglobulinaemia is a member of the *src* family of protein-tyrosine kinases

David Vetrie*†, Igor Vořechovský†‡, Paschalis Sideras‡§, Jill Holland*, Angela Davies*, Frances Flinter*, Lennart Hammarström‡, Christine Kinnon‖, Roland Levinsky‖, Martin Bobrow*, C. I. Edvard Smith‡ & David R. Bentley*

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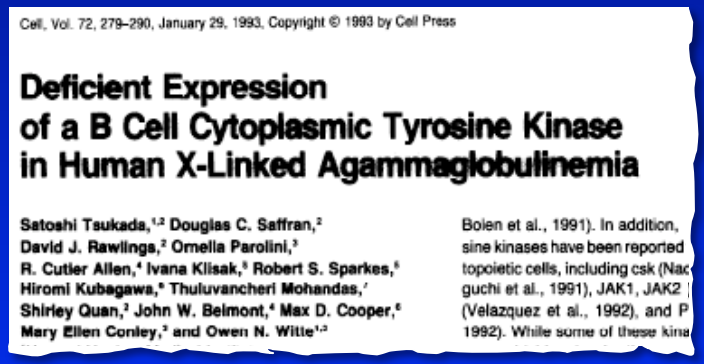
‖ Molecular Immunology Unit, Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK

X-linked agammaglobulinaemia (XLA) is a human immunodeficiency caused by failure of pre-B cells in the bone marrow to develop into circulating mature B cells. A novel gene has been isolated which maps to the XLA locus, is expressed in B cells, and shows mutations in families with the disorder. The gene is a member of the *src* family of proto-oncogenes which encode protein-tyrosine kinases. This is, to our knowledge, the first evidence that mutations in a *src*-related gene are involved in human genetic disease.

X-LINKED agammaglobulinaemia (XLA; Bruton type; MIM 30030; gene symbol AGMX1) was the first described immuno- involved in the disease and, therefore, in the process of B-cell development.

From: Vetrie, D et al. *Nature* 1993;361(6409); 226-33



Cell, Vol. 72, 279–290, January 29, 1993, Copyright © 1993 by Cell Press

Deficient Expression of a B Cell Cytoplasmic Tyrosine Kinase in Human X-Linked Agammaglobulinemia

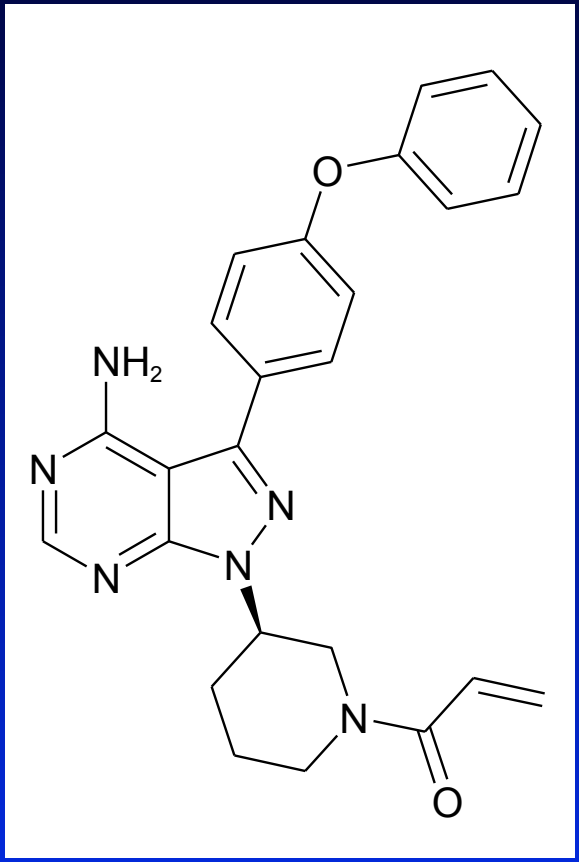
Satoshi Tsukada,[1,2] Douglas C. Saffran,[2] David J. Rawlings,[2] Ornella Parolini,[3] R. Cutler Allen,[4] Ivana Klisak,[5] Robert S. Sparkes,[5] Hiromi Kubagawa,[6] Thuluvancheri Mohandas,[7] Shirley Quan,[3] John W. Belmont,[4] Max D. Cooper,[6] Mary Ellen Conley,[3] and Owen N. Witte[1,2]

Bolen et al., 1991). In addition, sine kinases have been reported topoietic cells, including csk (Nac guchi et al., 1991), JAK1, JAK2 (Velazquez et al., 1992), and P 1992). While some of these kina

From: Tsukada, S et al. *Cell* 1993;72;279-90

- Mapped to Xq22
- Role in normal B cell function, autoimmune disorders and B cell malignancies
- Expressed in most hematopoietic cells, except T lymphocytes and plasma cells

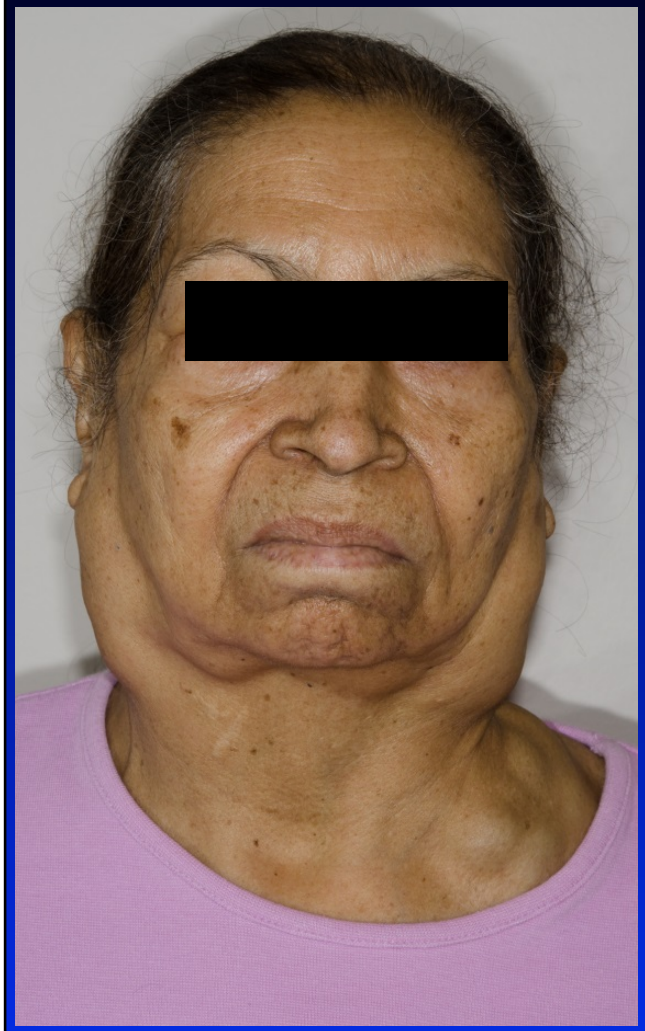
Ibrutinib (PCI-32765)



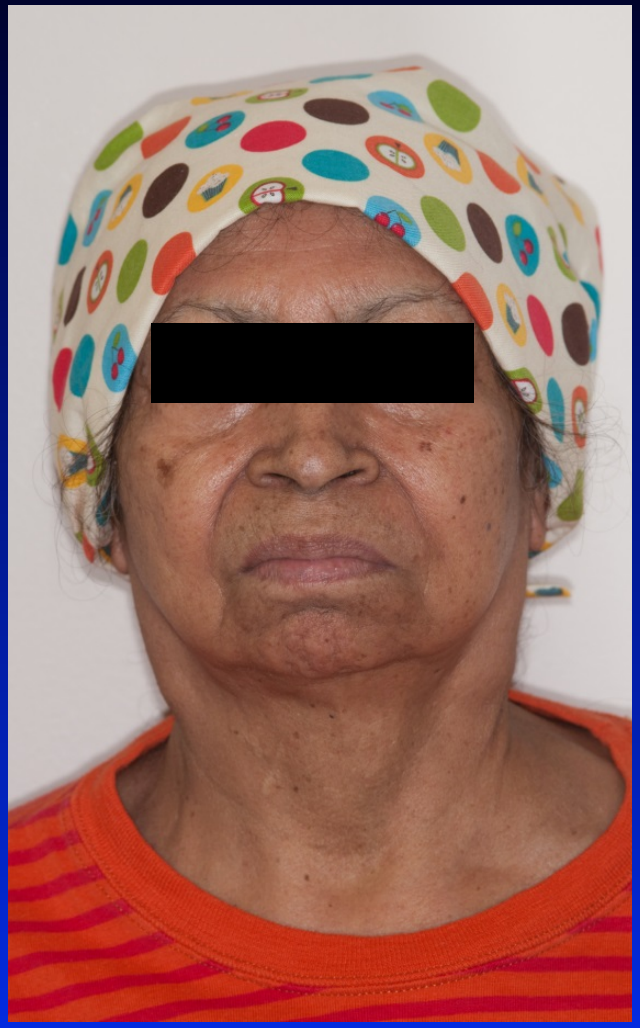
- Forms a specific bond with cysteine-481 in BTK
- Highly potent BTK inhibition at IC_{50} = 0.5 nM
- Orally administered with once daily dosing resulting in 24-hr target inhibition
- No cytotoxic effect on T-cells or natural killer (NK)-cells
- In chronic lymphocytic leukemia (CLL) cells promotes apoptosis and inhibits CLL cell proliferation, migration and adhesion

Advani, R. et al, *J Clin Oncol*. 2012;42:7906.
Honigberg LA et al, *Proc Natl Acad Sci* U S A.2010;107:13075.
Herman SEM et al, *Blood*.2011;117: 6287-6296.
Ponader, et al, ASH Meeting Abstracts. 2010; 116:45.

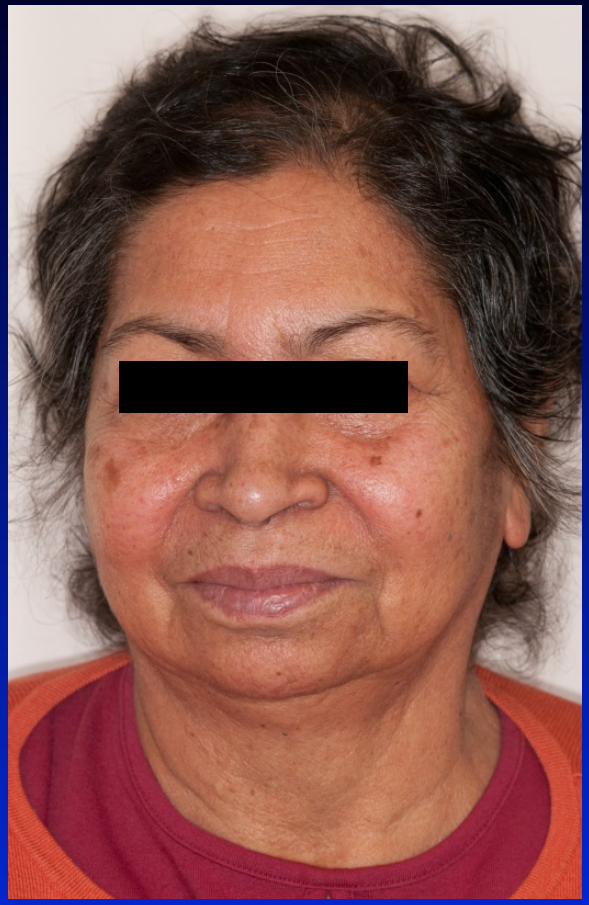
Marked Reductions in Lymphadenopathy



Before ibrutinib+R (iR)

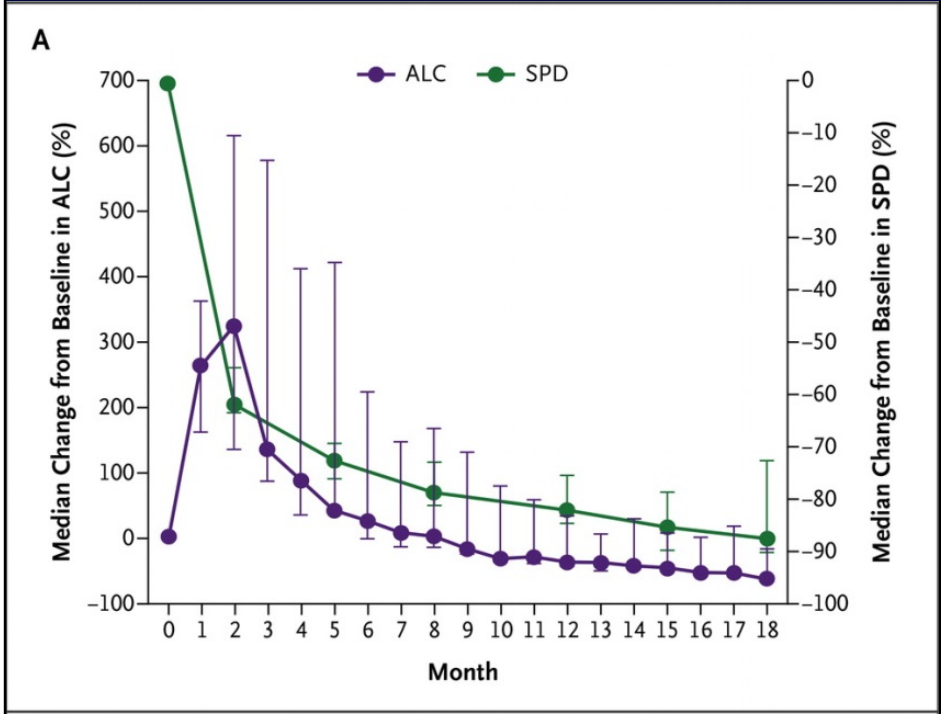


2 weeks iR

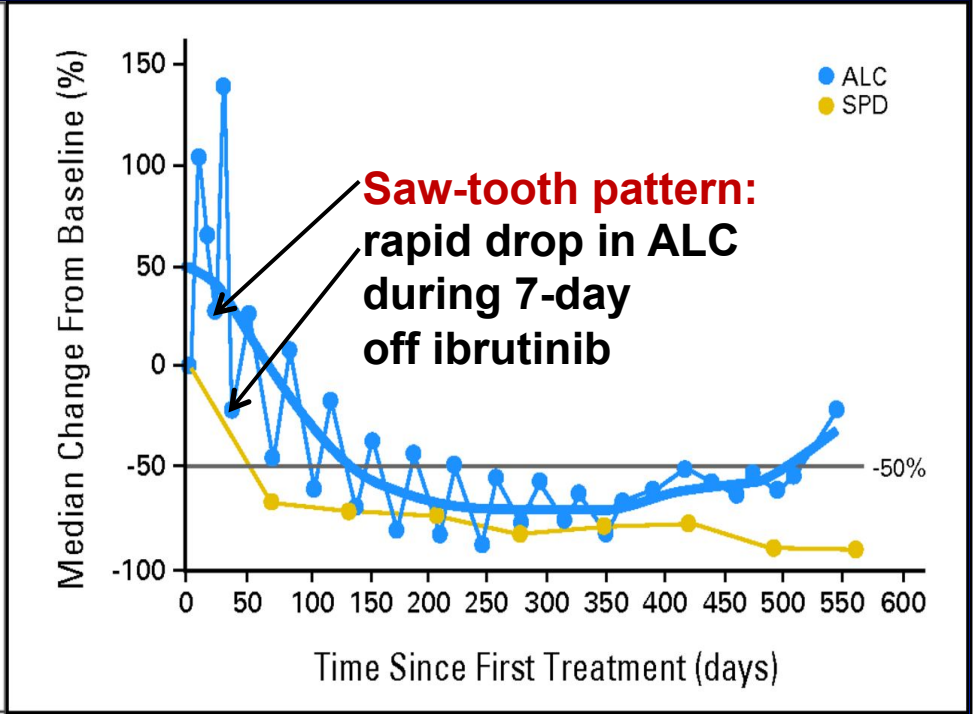


9 months iR

Ibrutinib-induced CLL cell Redistribution: Blood Lymphocytes vs Lymph Nodes



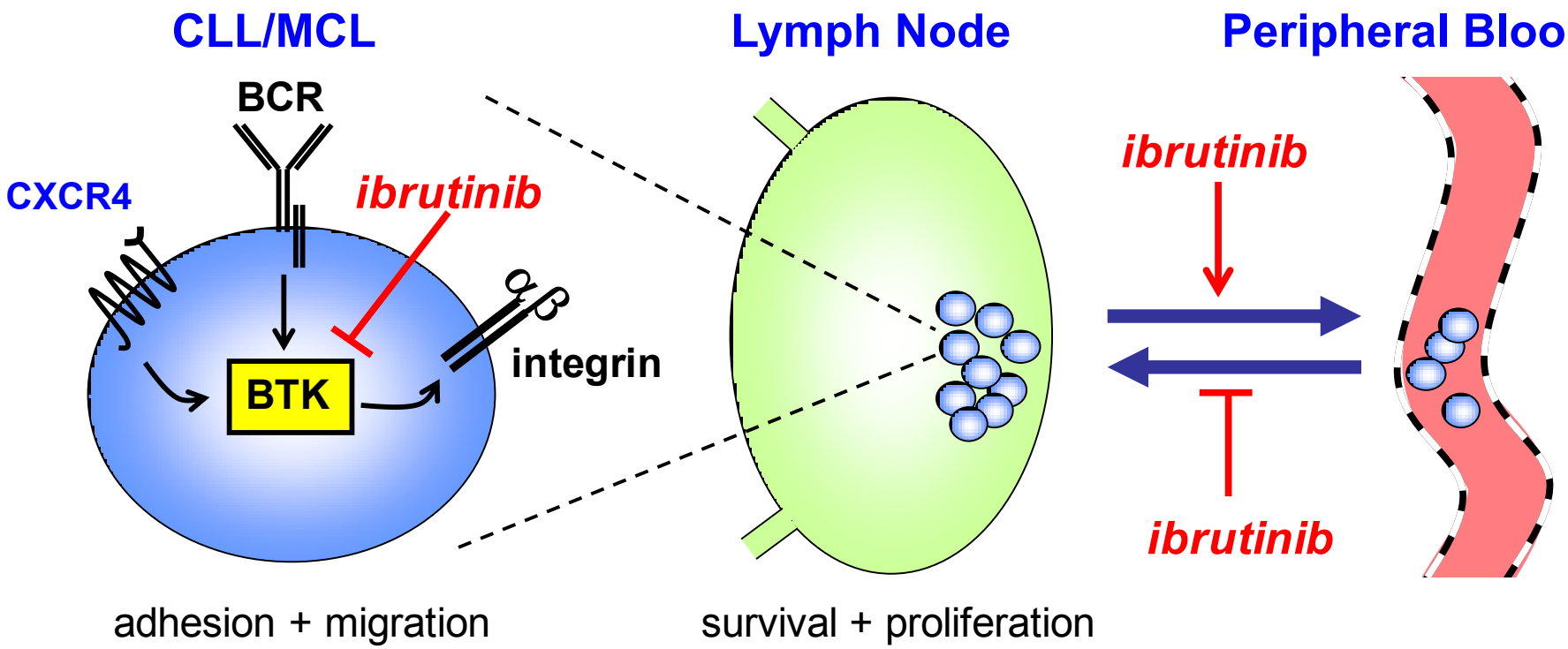
From: Byrd JC et al, NEJM 2013



From: Advani RH et al, JCO 2013

- **Redistribution** of tissue CLL cells into the PB causes early lymphocytosis (up to 3-fold increase)
- **Class effect** of kinase-inhibitors targeting BTK, PI3K, and SYK
- **Saw-tooth pattern** due to re-homing of CLL cells during "off-drug" period

Mechanism of Treatment Related Lymphocytosis in Chronic Lymphocytic Leukemia (CLL) and Mantle Cell Lymphoma (MCL)



- Ibrutinib blocks BTK inducing b-cell apoptosis and disruption of b-cell adhesion in lymph nodes
- B-cells egress into peripheral blood
- Ibrutinib blocks b-cells from migrating back to lymph nodes resulting in treatment related lymphocytosis

de Rooij MFM, et al. *Blood. 2012;* 119:2590-2594.

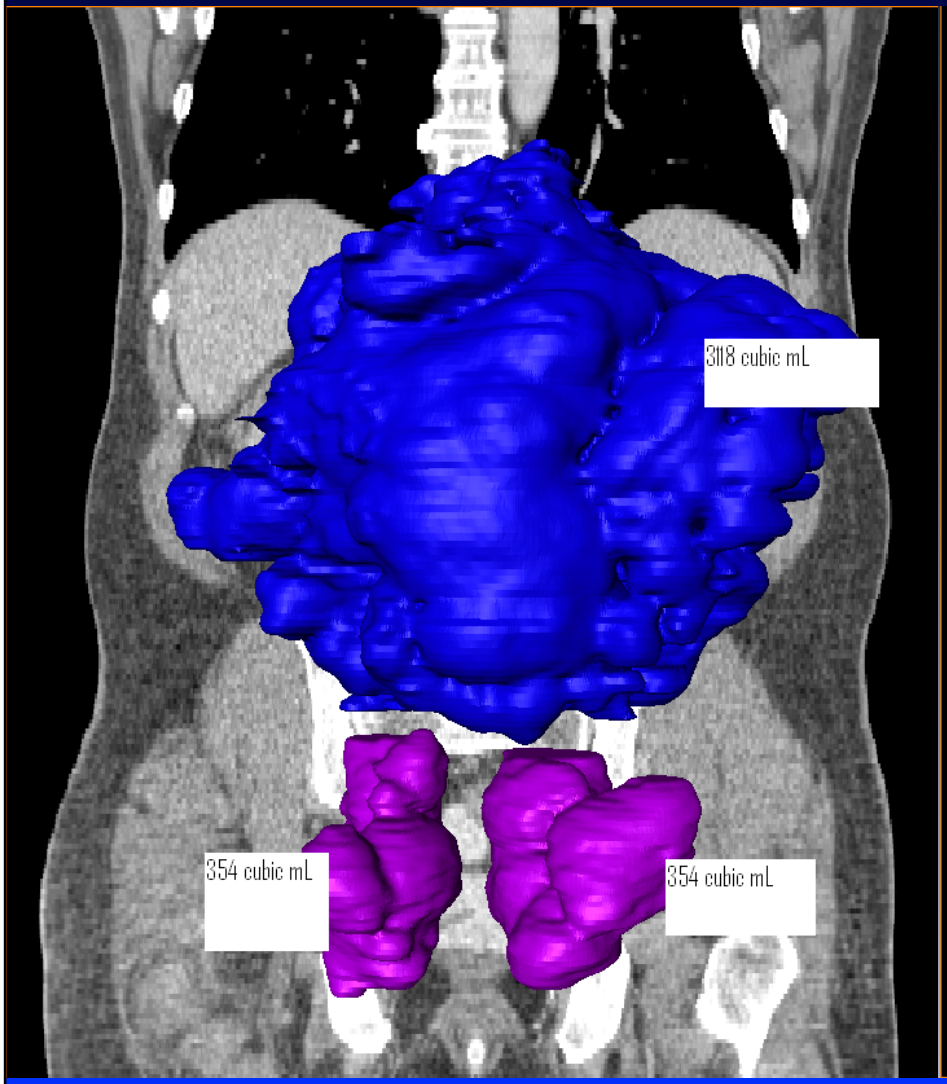
BCR kinase-inhibitors: what is the MOA?

Direct versus indirect effects:

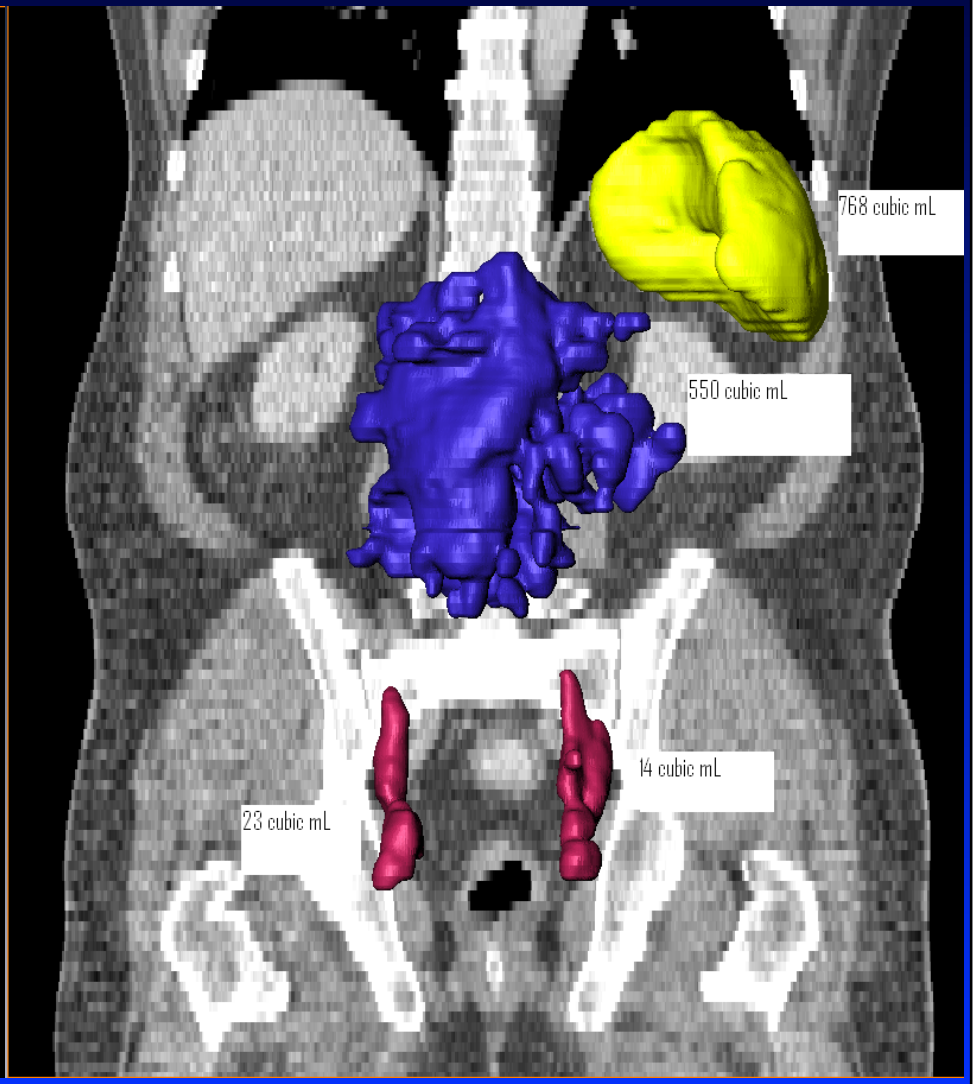
- Is the displacement from the microenvironment the principal MOA?
- Or is BCR signaling inhibition, causing growth arrest and apoptosis, the key MOA?

Volumetric changes during ibrutinib therapy

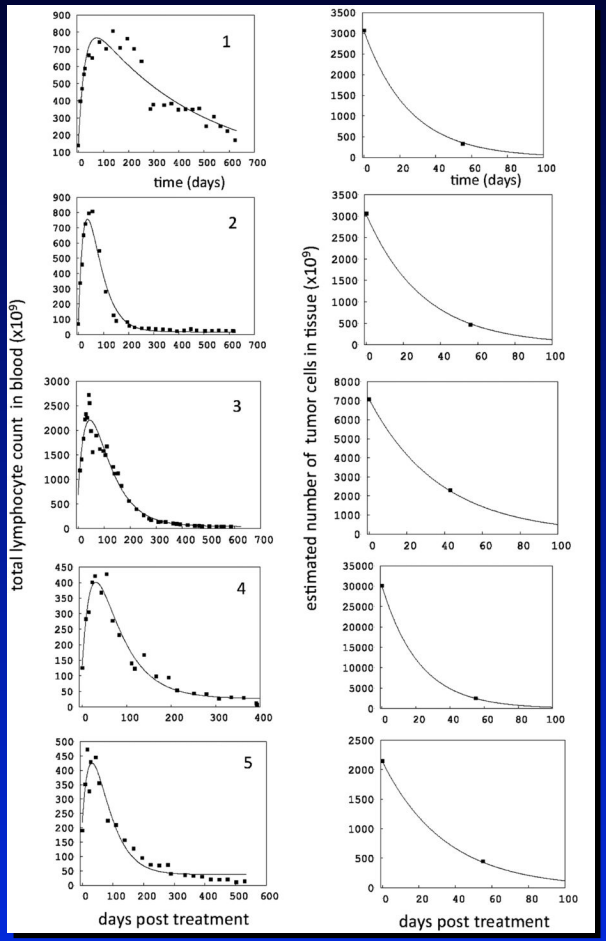
Before ibrutinib



3 months on ibrutinib



Dynamics of PB and tissue CLL cells during ibrutinib therapy

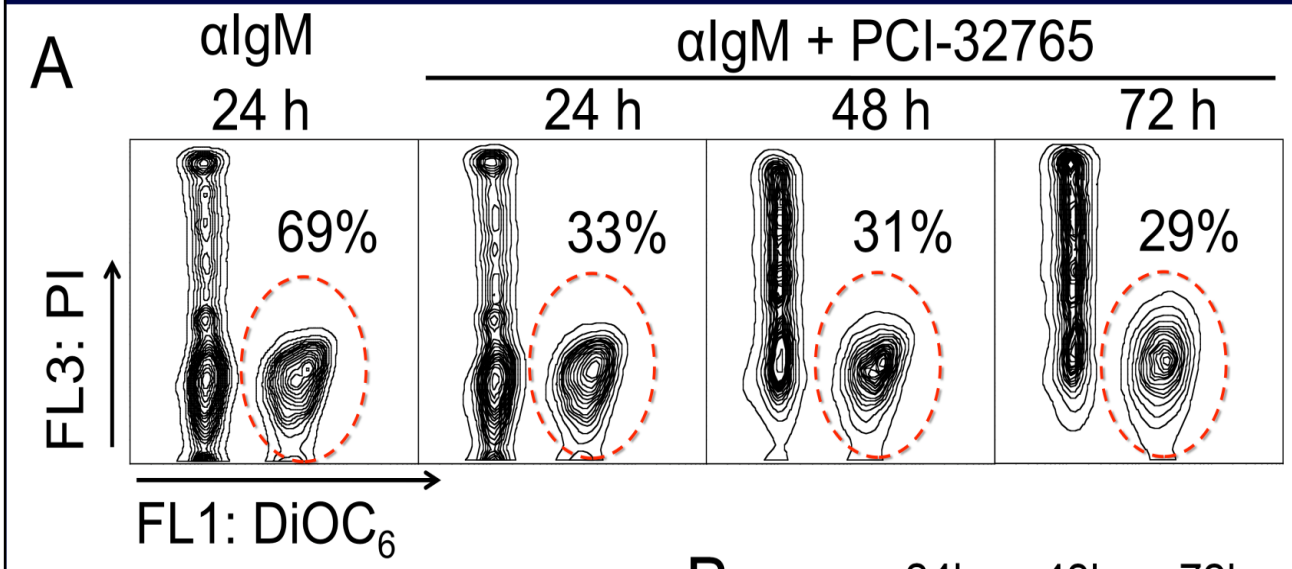


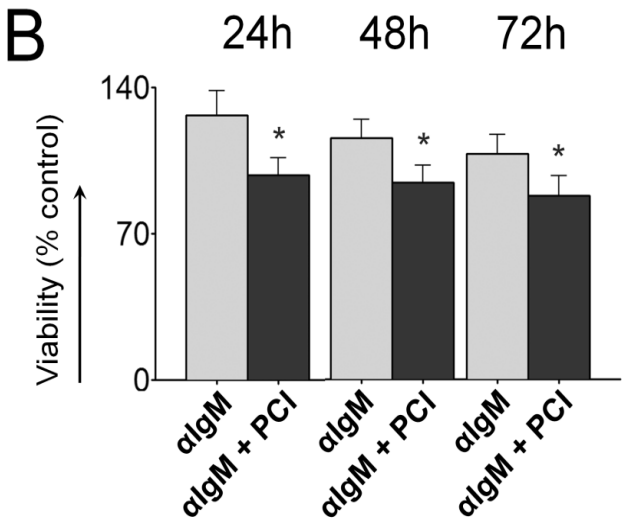
- During ibrutinib therapy, 1.7% of blood and 2.7% of tissue CLL cells die per day
- The fraction of CLL cells that redistribute into the blood during ibrutinib treatment represents 23.3% ± 17% of the tissue disease burden

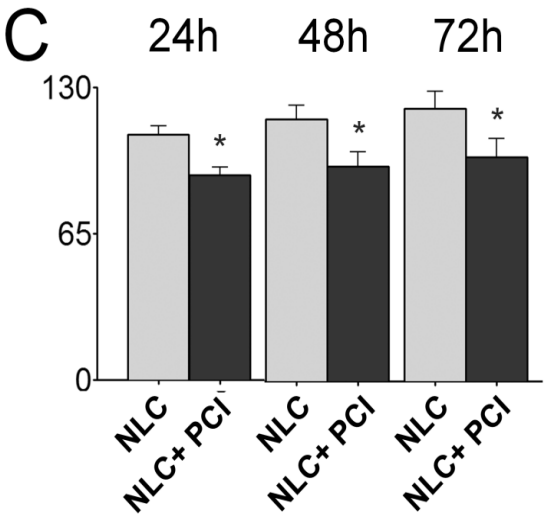
- Serial ALC (left column)
- serial volumetric analysis (right column) of CLL disease burden

From: Wodarz D et al, Blood 2014

Effects of Ibrutinib on CLL viability

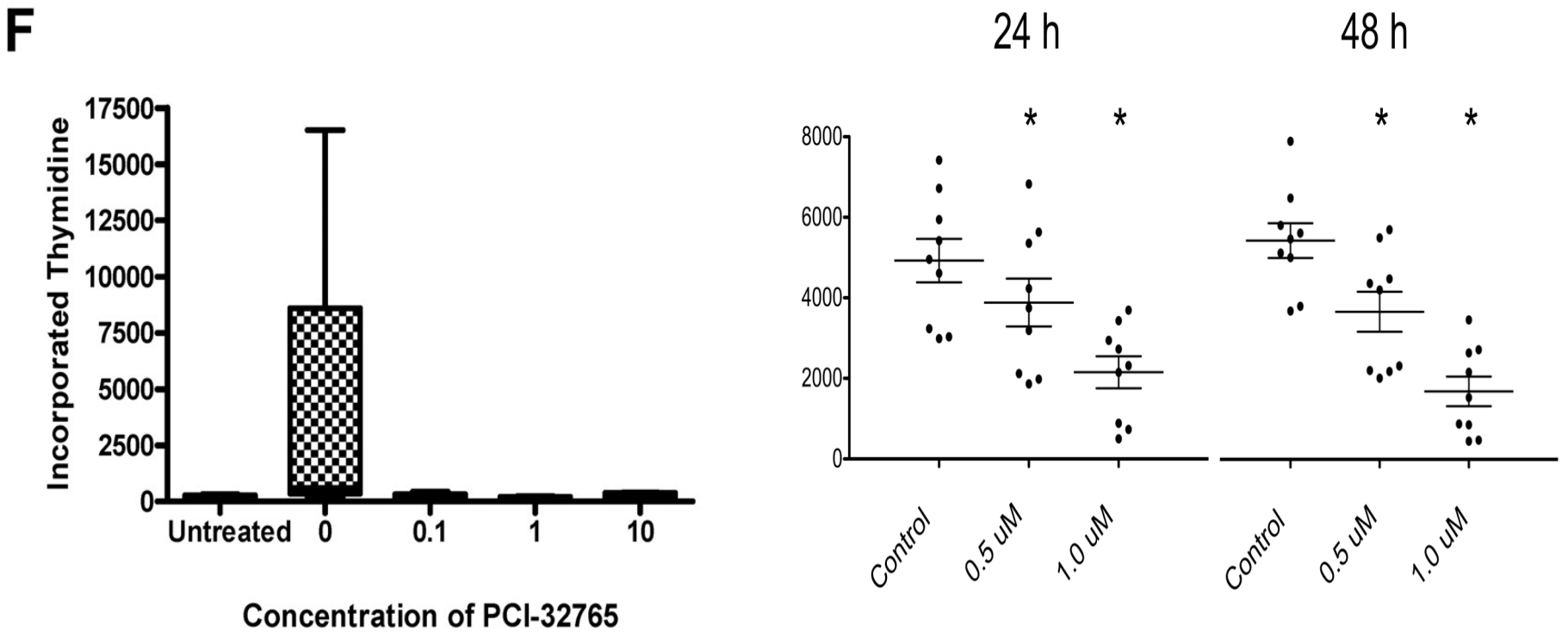






S. Ponader et al., Blood 119: 1182-9, 2012

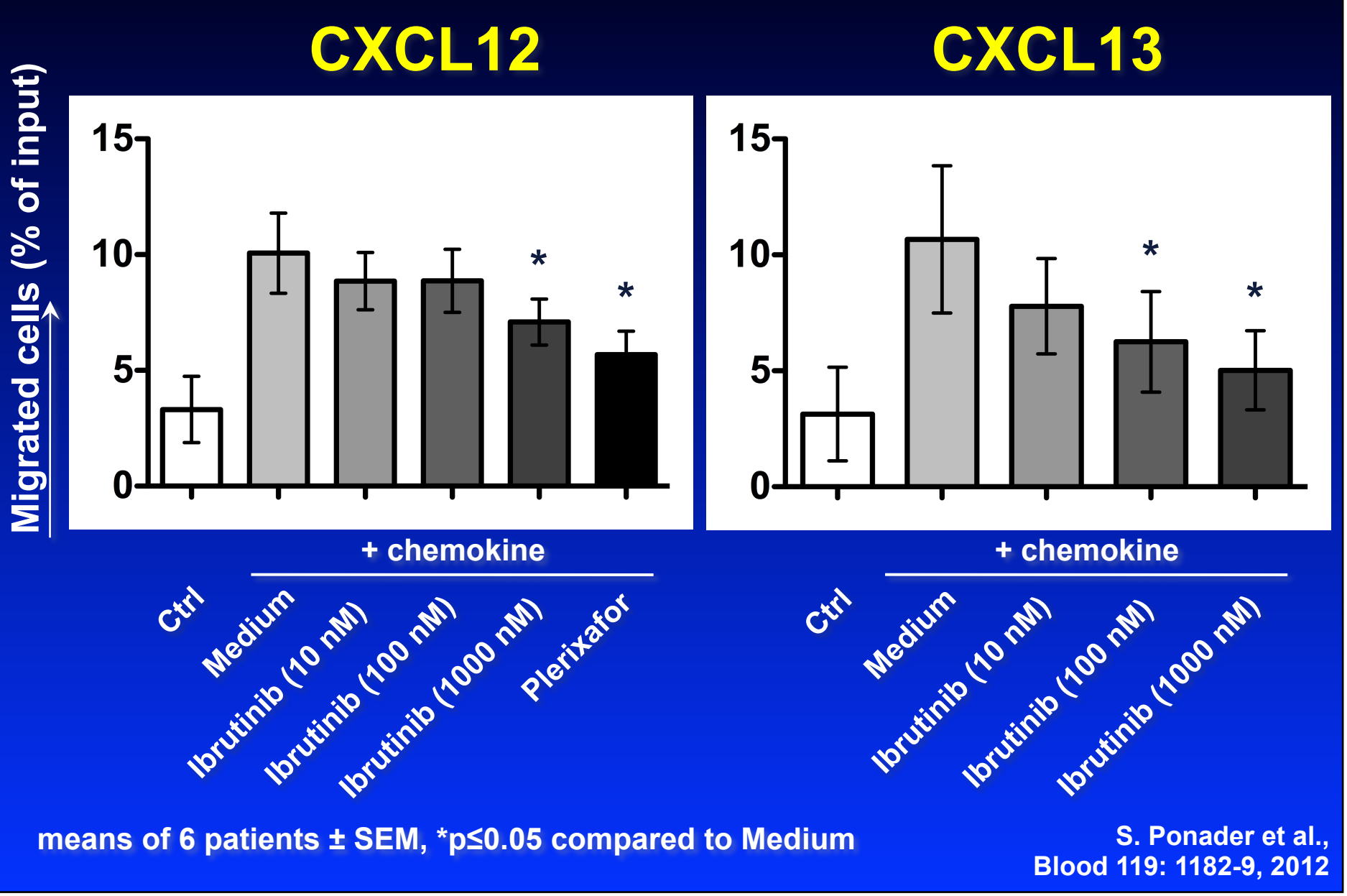
Ibrutinib inhibits proliferation of CLL cells



From: Herman SEM et al., Blood 117: 6287-6296 (2011)

S. Ponader et al., Blood 119: 1182-9, 2012

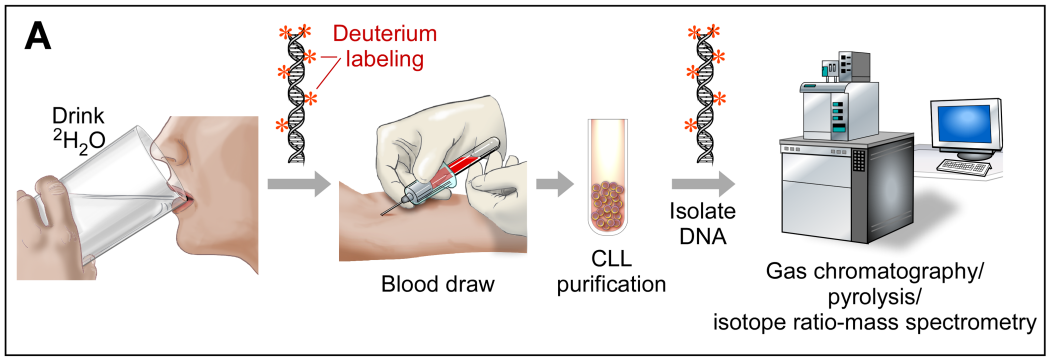
Ibrutinib inhibits CLL cell chemotaxis

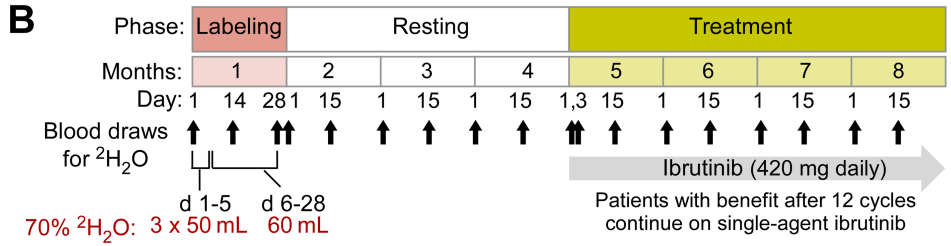


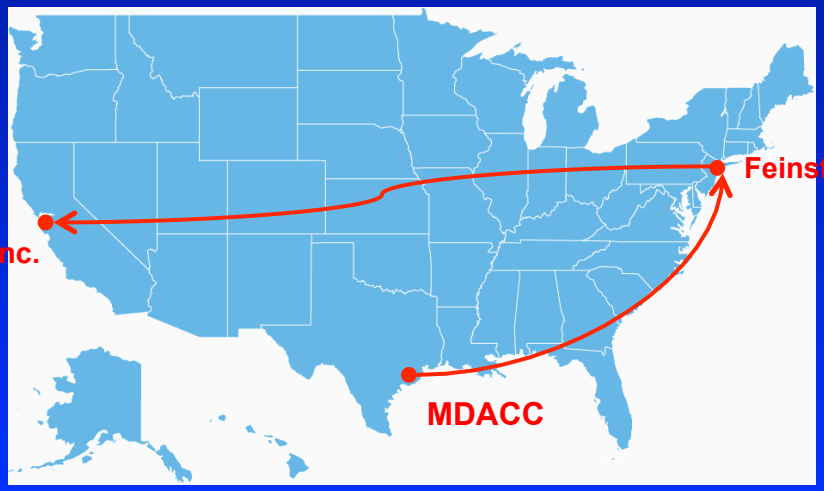
means of 6 patients ± SEM, *p≤0.05 compared to Medium

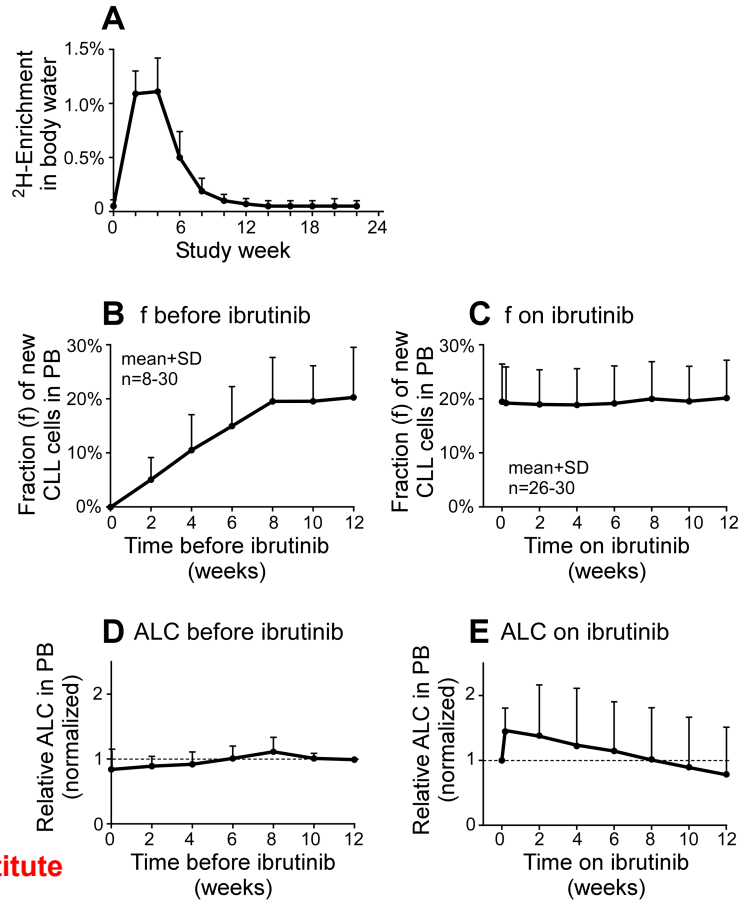
S. Ponader et al.,
Blood 119: 1182-9, 2012

Heavy water labeling of CLL cells prior to ibrutinib therapy



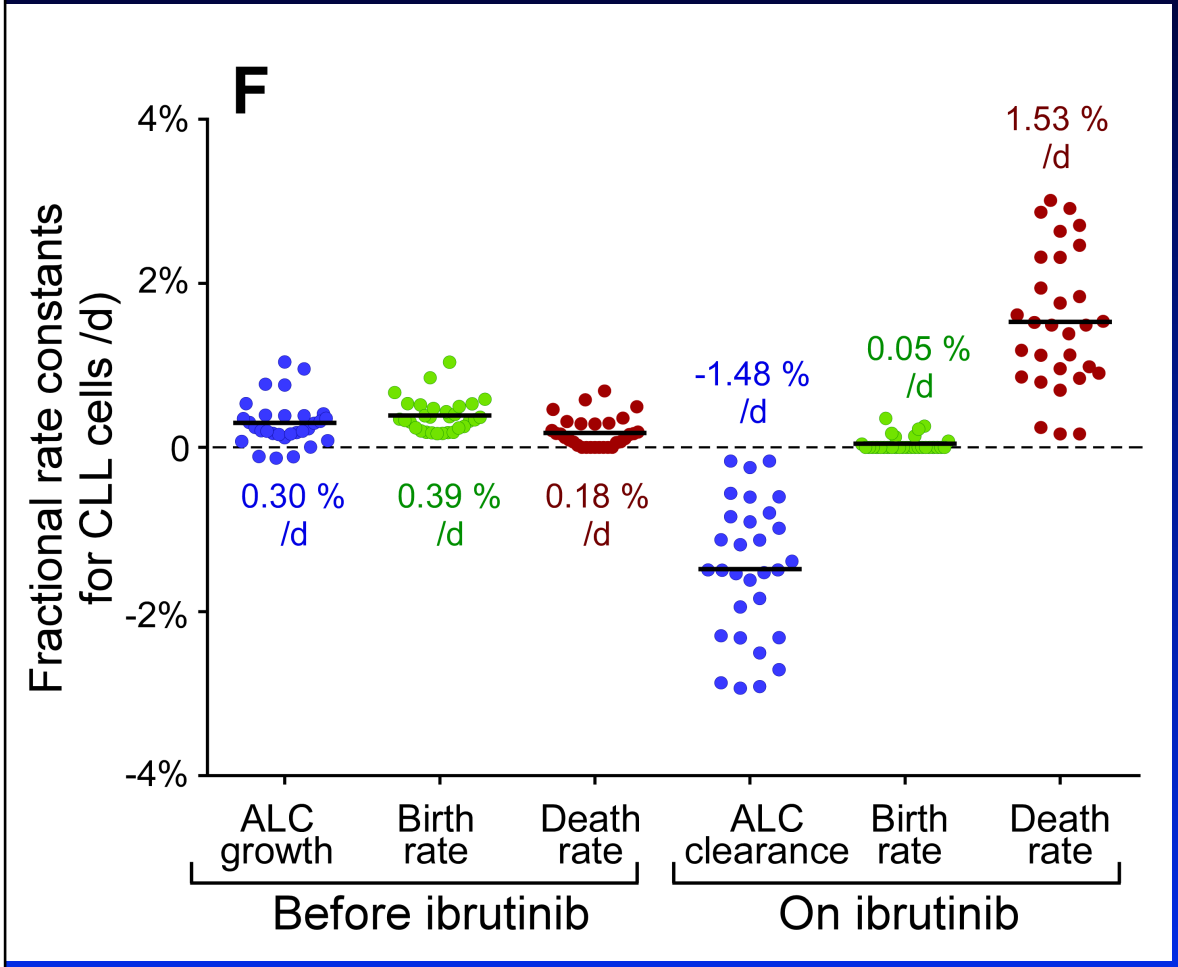






Burger J et al. JCI Insight 2017 Jan 26;2(2):e89904.

Heavy water labeling of CLL cells prior to ibrutinib therapy: Effects of ibrutinib on birth and death rates



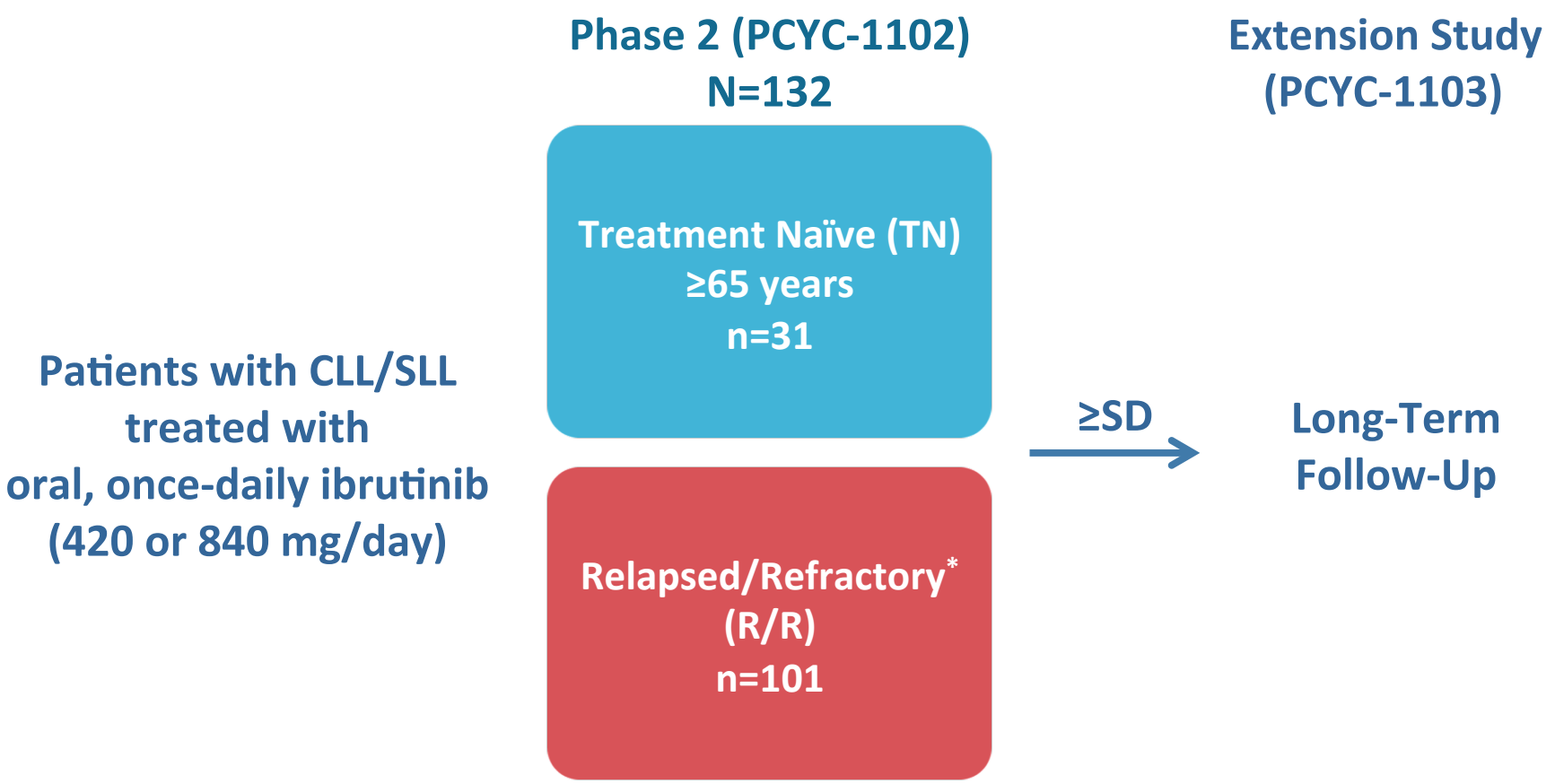
- CLL cell proliferation ("birth") rates: before ibrutinib therapy 0.39% down to 0.05% on ibrutinib
- Death rates increased from 0.18% to 1.5%
- Overall response rate of 97%.
- First direct *in vivo* measurements of ibrutinib's anti-leukemia activity
- Profound inhibition of CLL cell proliferation
- Promotion of high rates of CLL cell death.

Burger J et al. JCI Insight 2017 Jan 26;2(2):e89904.

Lessons about ibrutinib mechanism of action in CLL

- Dual action of ibrutinib:
  - inhibits proliferation
  - accelerates CLL cell death in 2 ways
    - **Acutely** causing death of BCR signaling-dependent CLL cells (mostly in tissues)
    - **Chronically** by deprivation of blood CLL cells from other tissue survival signals

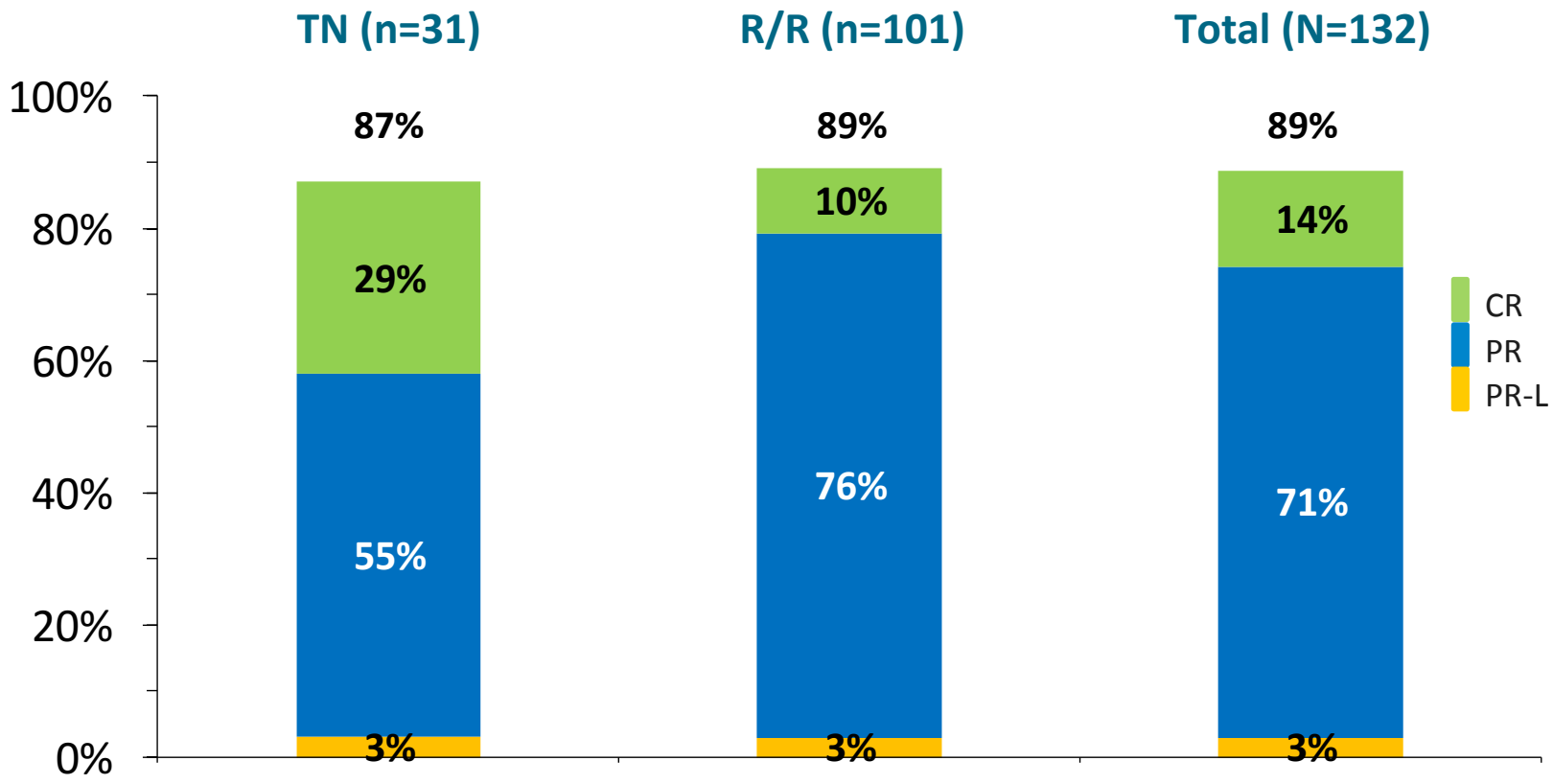
PCYC-1102/1103 Phase 2 Study Design



*R/R includes patients with high-risk CLL/SLL, defined as progression of disease <24 months after initiation of a chemoimmunotherapy regimen or failure to respond

ASH 2016, 1102-03 5-year Update; O'Brien et al.

Best Response

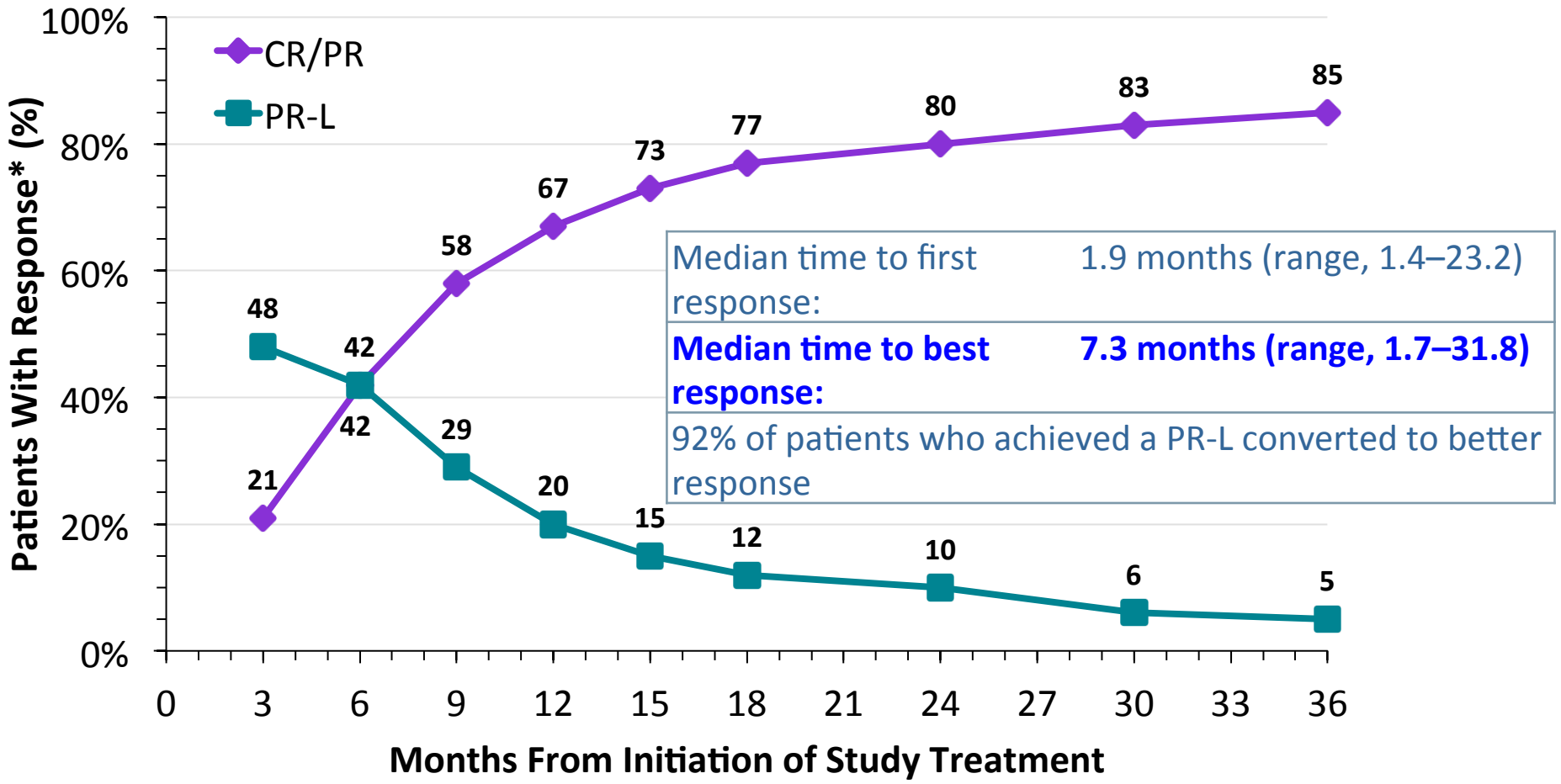


Median DOR, months (range)	NR (0.0+ to 65.5+)	56.8 (0.0+ to 65.5+)	NR (0.0+ to 65.5+)
Median follow-up, months (range)	62 (1 – 67)	49 (1+ – 67)	56 (1+ – 67)

NR, not reached.

ASH 2016, 1102-03 5-year Update; O'Brien et al.

Response Over Time



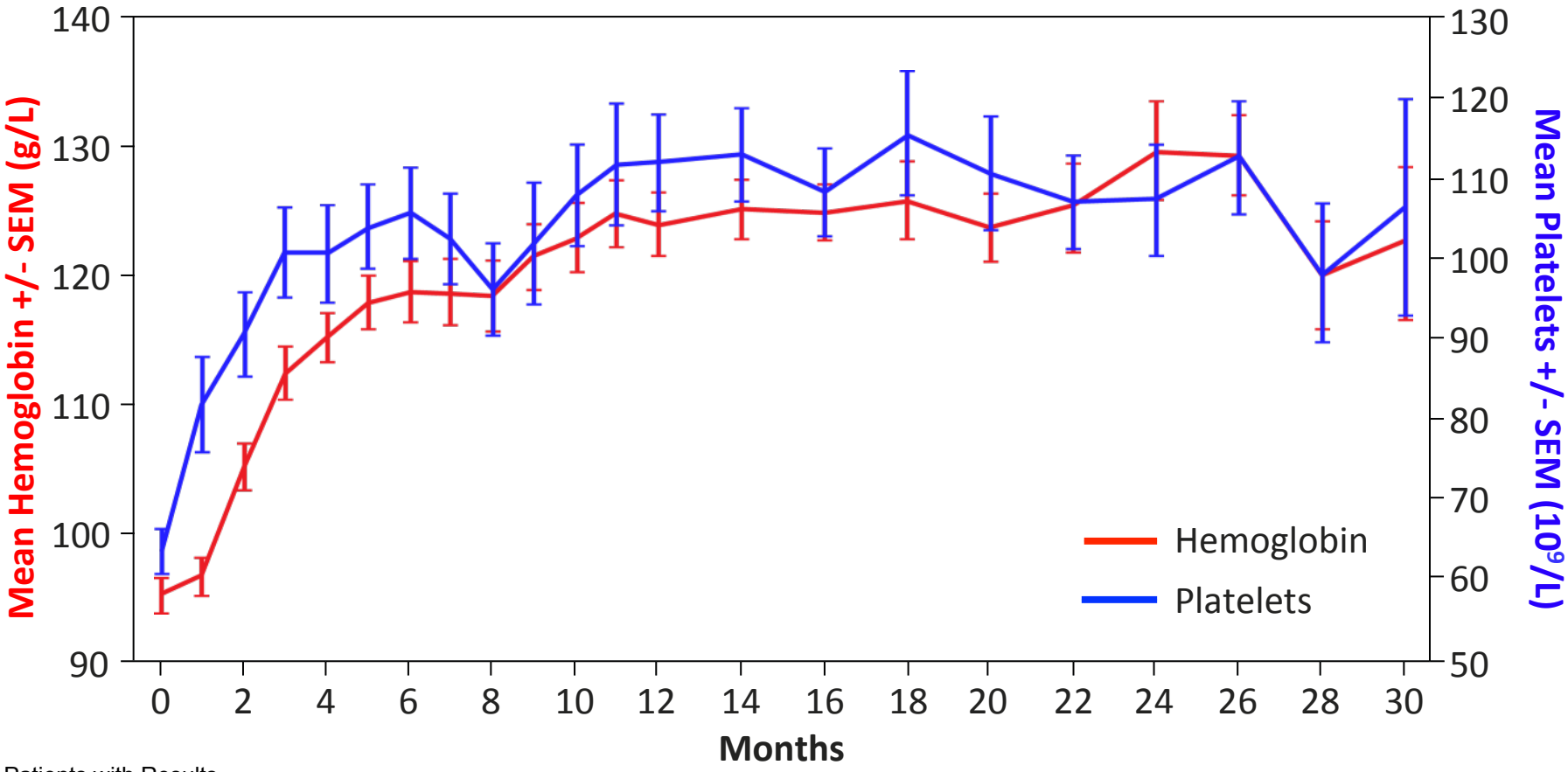
Median time to first response:	1.9 months (range, 1.4–23.2)
Median time to best response:	**7.3 months (range, 1.7–31.8)**
92% of patients who achieved a PR-L converted to better response	

Best response to ibrutinib improves over time

American Society of Clinical Oncology 2014, PCYC 1102/1103, O'Brien et al.

*Cumulative response as assessed by investigator

Platelet Counts and Hemoglobin Levels*



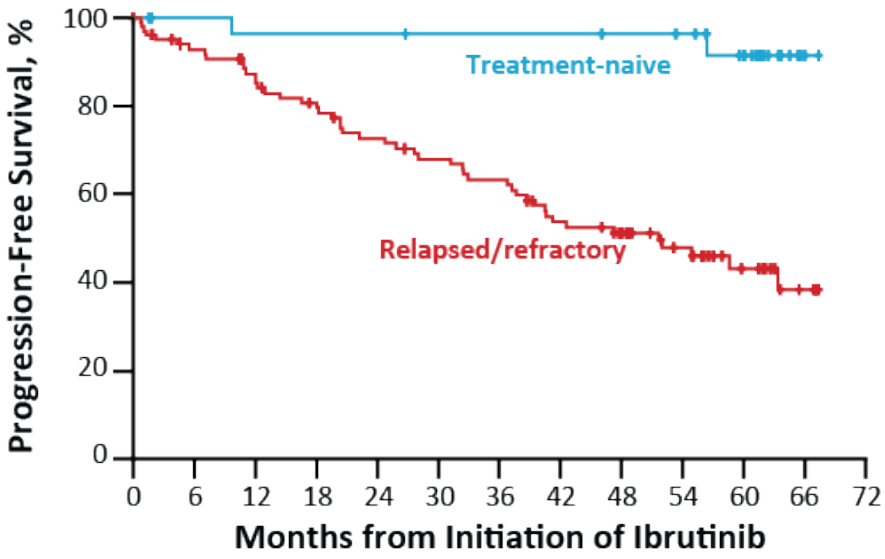
Patients with Results																					
Hemoglobin	53	52	48	46	44	40	42	41	40	38	42	40	39	38	36	35	27	31	21	24	15	13
Platelets	61	61	59	56	55	52	52	49	47	45	50	45	44	47	42	42	35	37	28	27	23	14

American Society of Clinical Oncology 2014, PCYC 1102/1103, O'Brien et al.

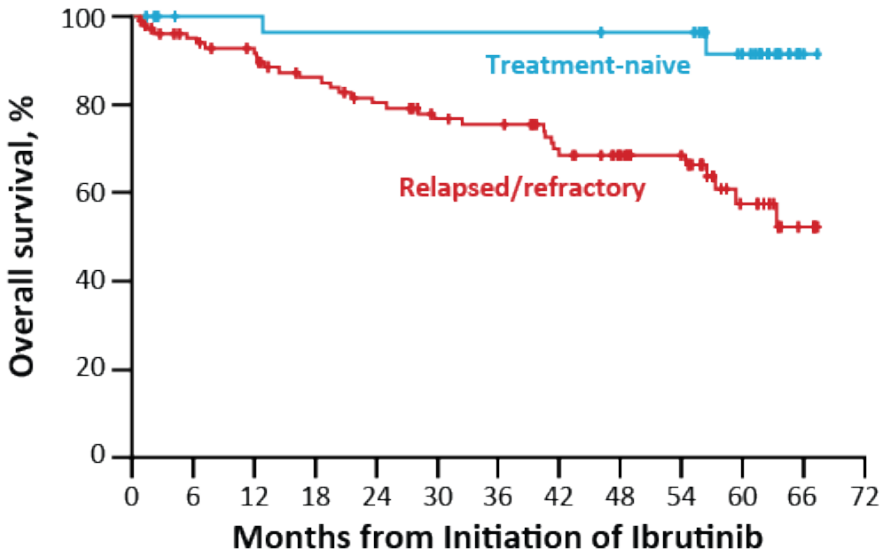
*All treated patients with baseline anemia or thrombocytopenia

Survival Outcomes: Overall Population

Progression-Free Survival



Overall Survival



	Median PFS	5-year PFS
TN (n=31)	NR	92%
R/R (n=101)	52 mo	43%

	Median OS	5-year OS
TN (n=31)	NR	92%
R/R (n=101)	NR	57%

NR, not reached.

ASH 2016, 1102-03 5-year Update; O'Brien et al.

Ibrutinib Treatment Continued in 65% of TN and 30% of R/R Patients

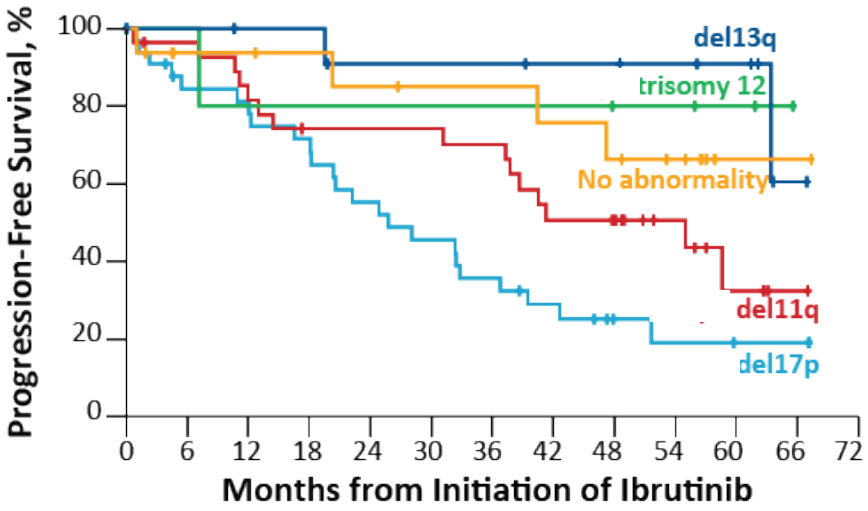
Disposition	TN (n=31)	R/R (n=101)
Median time on study, months (range)	62 (1–67)	49 (1–67)
Duration of study treatment, n (%)		
≤1 year	5 (16%)	24 (24%)
>1–2 years	0	14 (14%)
>2–3 years	1 (3%)	9 (9%)
>3–4 years	1 (3%)	19 (19%)
≥4 years	24 (77%)	35 (35%)
Patients remaining on ibrutinib therapy, n (%)	**20 (65%)**	**30 (30%)**
Primary reason for discontinuation, n (%)		
Progressive disease	1 (3%)	33 (33%)
Adverse event	6 (19%)	21 (21%)
Consent withdrawal	3 (10%)	5 (5%)
Investigator decision	0	11 (11%)
Lost to follow-up	1 (3%)	1 (1%)

- After ~5 years of follow-up, 65% of TN and 30% of R/R patients continue treatment on study.

ASH 2016, 1102-03 5-year Update; O'Brien et al.

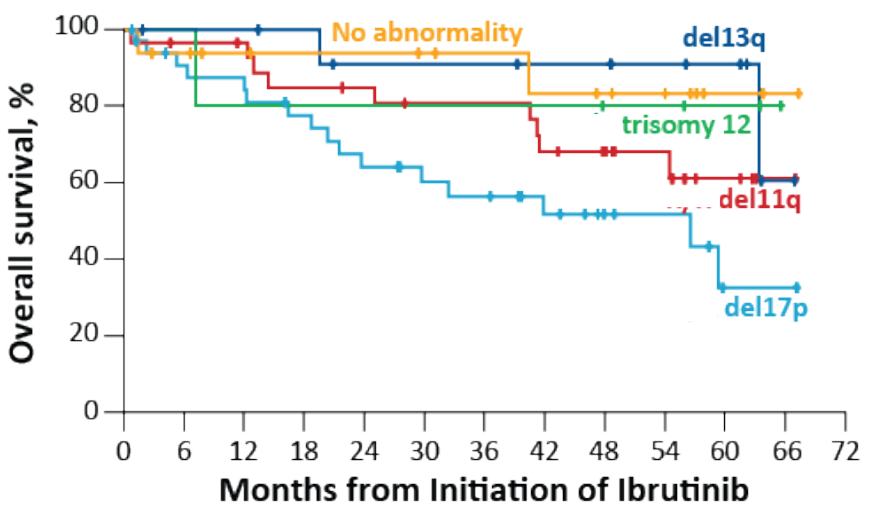
Survival Outcomes by Chromosomal Abnormalities Detected by FISH in R/R Patients*

Progression-Free Survival



	Median PFS	5-year PFS
Del17p (n=34)	26 mo	19%
Del11q (n=28)	55 mo	33%
Trisomy 12 (n=5)	NR	80%
Del13q (n=13)	NR	91%
No abnormality** (n=16)	NR	66%

Overall Survival

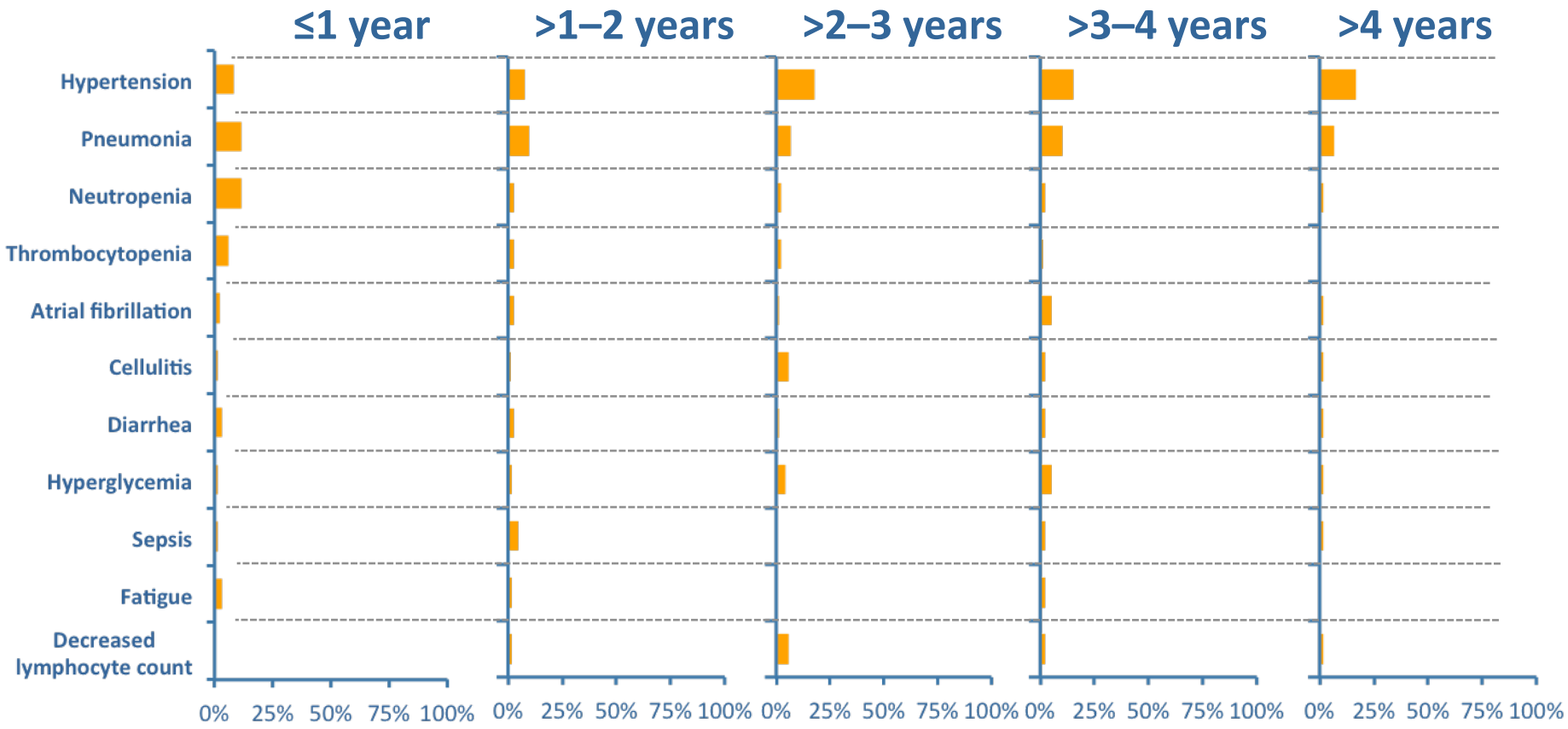


	Median OS	5-year OS
Del17p (n=34)	57 mo	32%
Del11q (n=28)	NR	61%
Trisomy 12 (n=5)	NR	80%
Del13q (n=13)	NR	91%
No abnormality** (n=16)	NR	83%

*Only 2 patients in the TN group showed PD or death. Subgroup analyses, therefore, focused on the R/R population.
**No del17p, del11q, del13q, or trisomy 12; in hierarchical order for del17p, and then del11q
NR, not reached.

ASH 2016, 1102-03 5-year Update; O'Brien et al.

Onset of Most Grade ≥3 Adverse Events Decreased Over Time

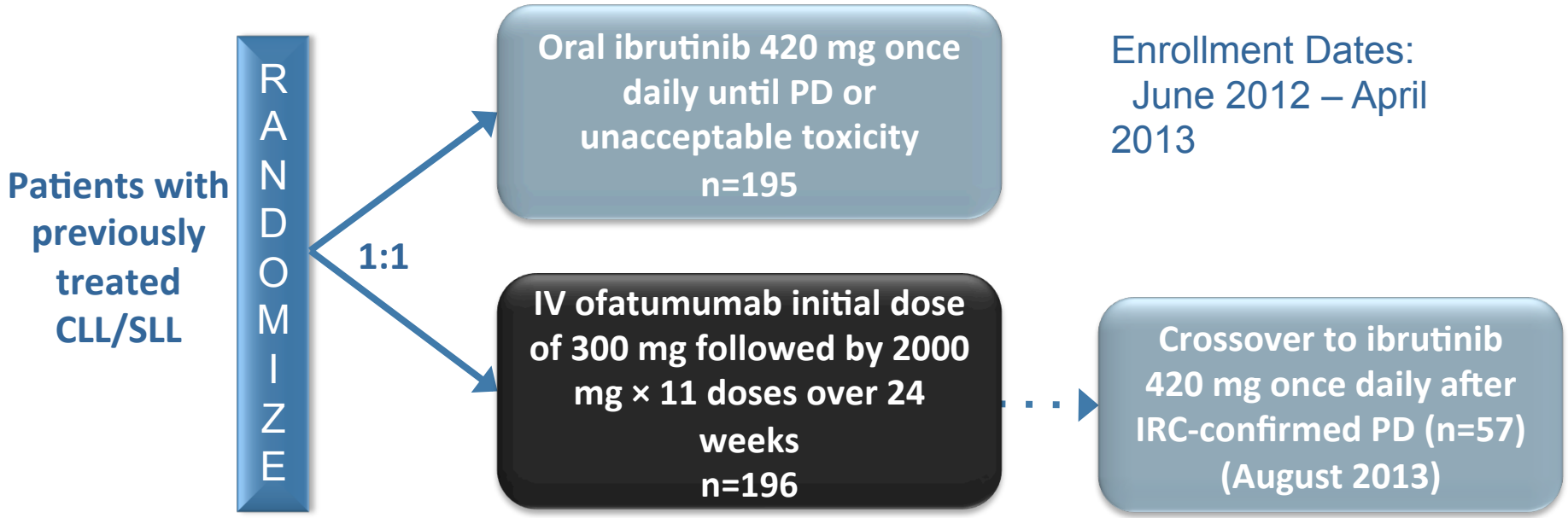


- Dose reductions and dose discontinuations due to AEs occurred more frequently in R/R patients than in TN patients, and during the first year after treatment compared with subsequent time periods.

*Listed adverse events include those that occurred in ≥5% of patients in all-treated population; denominator for each term and time period can vary based on those at risk

ASH 2016, 1102-03 5-year Update; O'Brien et al.

RESONATE™ Phase 3 Study Design



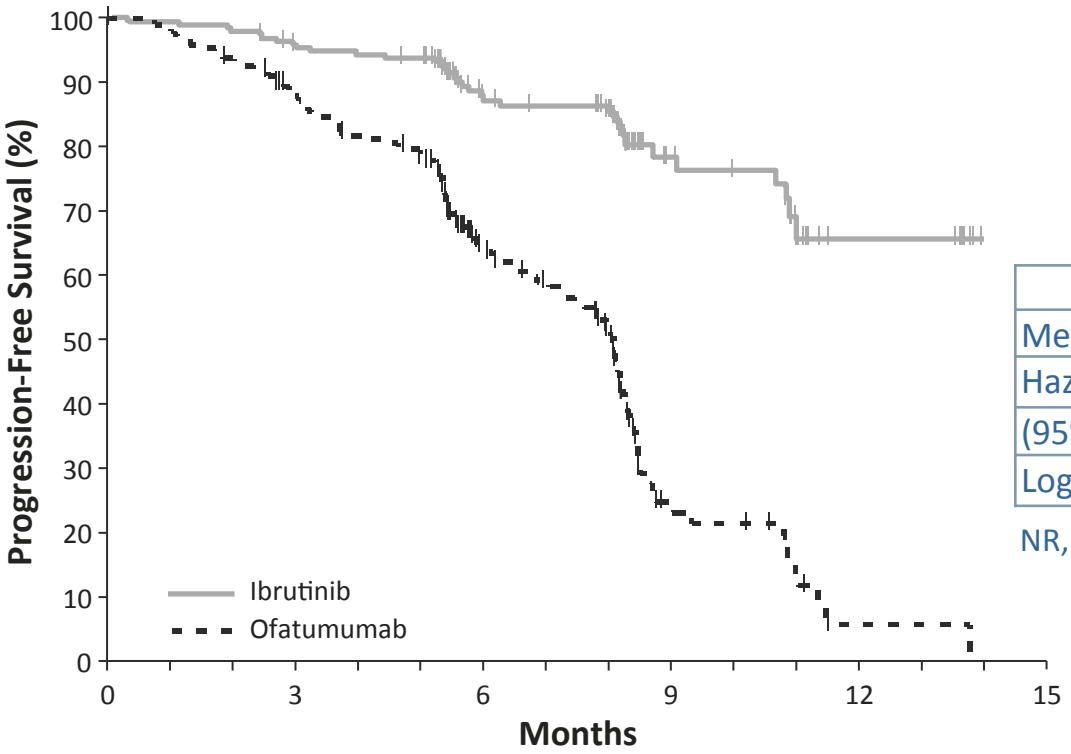
Enrollment Dates: June 2012 – April 2013

- 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 et al. ASCO 2014, Abstract LBA7008

Progression-Free Survival



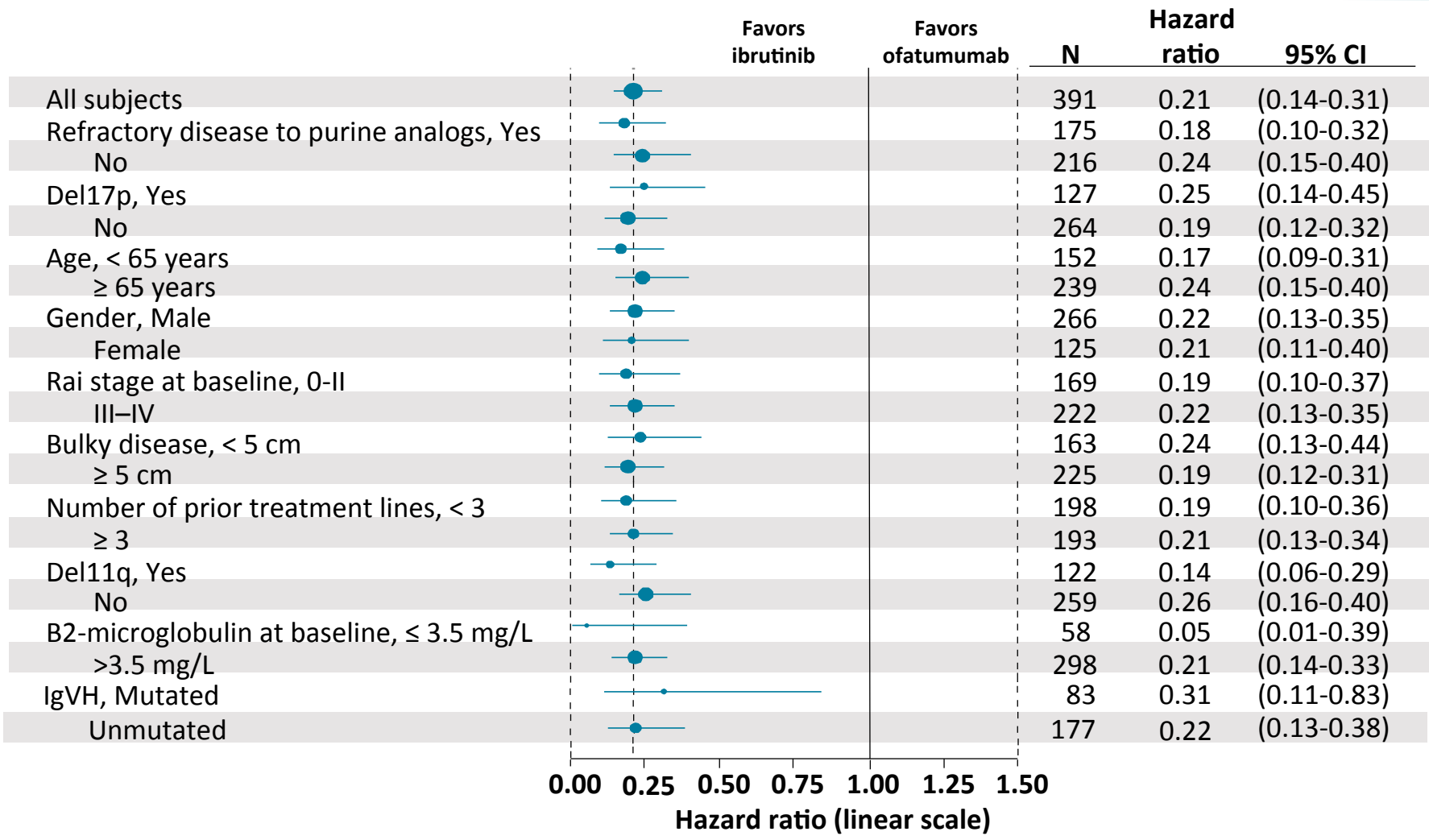
	Ofatumumab	Ibrutinib
Median time (mo)	8.08	NR
Hazard ratio	0.215	
(95% CI)	(0.146-0.317)	
Log-rank *P* value	< 0.0001	

NR, not reached.

- Ibrutinib significantly prolonged PFS; median not reached vs. 8.1 months for ofatumumab
- 78% reduction in the risk of progression or death
- Investigator assessed PFS hazard ratio 0.133 (95% CI: 0.085-0.209) p value < 0.0001
- Richter's transformation was confirmed in 2 patients on each arm. An additional patient on the ibrutinib arm experienced disease transformation to prolymphocytic leukemia

Byrd et al. ASCO 2014, Abstract LBA7008

Progression-Free Survival by Baseline Characteristics and Molecular Features



Byrd et al. ASCO 2014, Abstract LBA7008

RESONATE™-2 (PCYC-1115) Study Design

Patients (N=269)
- Treatment-naïve CLL/ SLL with active disease
- Age ≥65 years
- For patients 65-69 years, comorbidity that may preclude FCR
- del17p excluded
- Warfarin use excluded

RANDOMIZE 1:1

ibrutinib 420 mg once daily until PD or unacceptable toxicity

chlorambucil 0.5 mg/kg (to maximum 0.8 mg/kg) days 1 and 15 of 28-day cycle up to 12 cycles

IRC-confirmed progression

PCYC-1116 Extension Study*

In clb arm, n=43 crossed over to ibrutinib

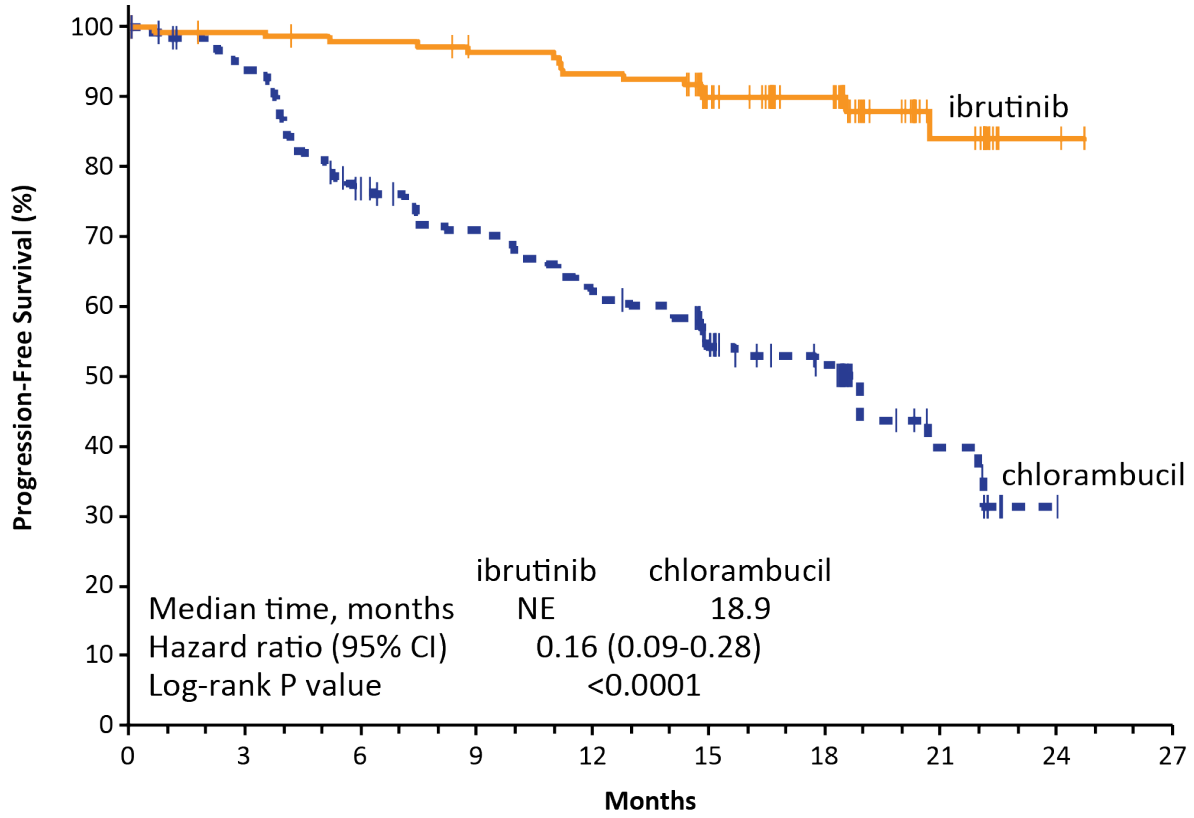
Stratification factors
- ECOG status (0-1 vs. 2)
- Rai stage (III-IV vs. ≤II)

*Patients with IRC-confirmed PD enrolled into extension Study 1116 for follow-up and second-line treatment per investigator's choice (including ibrutinib for patients progressing on chlorambucil with iwCLL indication for treatment).

- Phase 3, open-label, multicenter, international study
- **Primary endpoint**: PFS as evaluated by IRC (2008 iwCLL criteria)[1,2]
- **Secondary endpoints**: OS, ORR, hematologic improvement, safety

1. Hallek et al. *Blood*. 2008;111:5446-5456; 2. Hallek et al, *Blood.* 2012; e-letter, June 04, 2012.

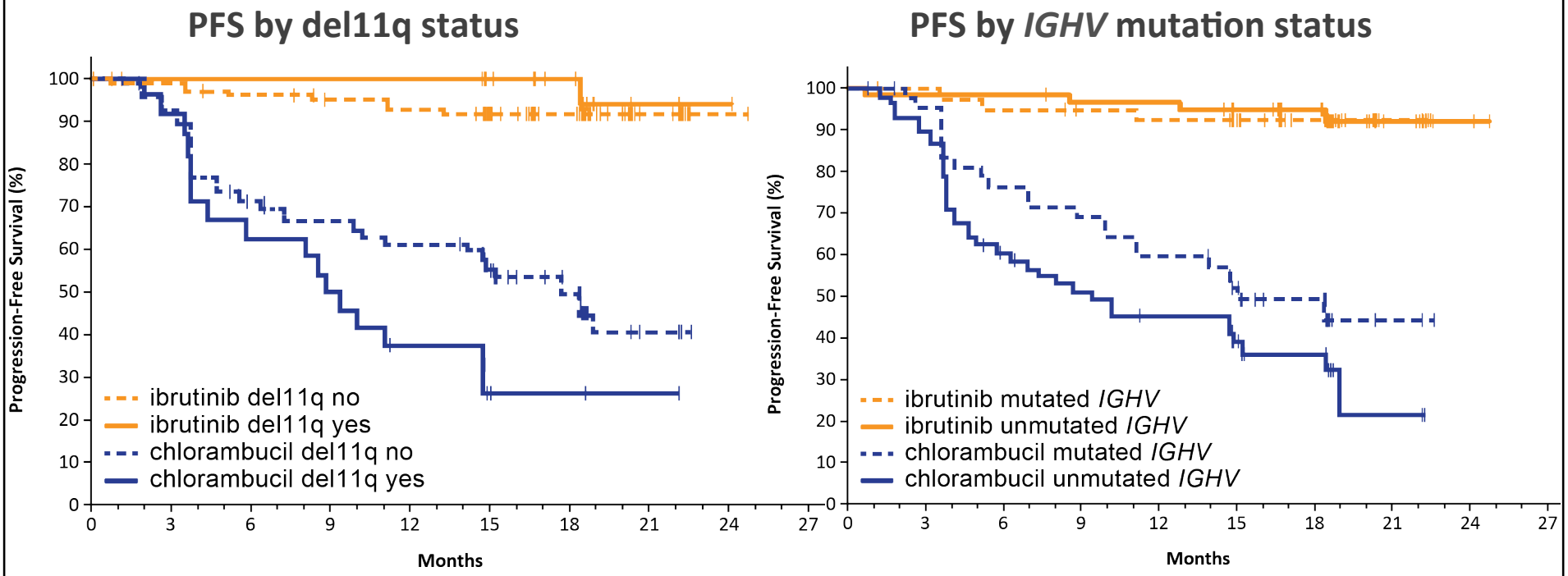
PFS by Independent Assessment



- 84% reduction in risk of progression or death with ibrutinib
- 18-month PFS rate: 90% with ibrutinib vs. 52% with chlorambucil
- Median follow-up: 18.4 months

Burger JA et al., NEJM 373(25):2425-37, 2015

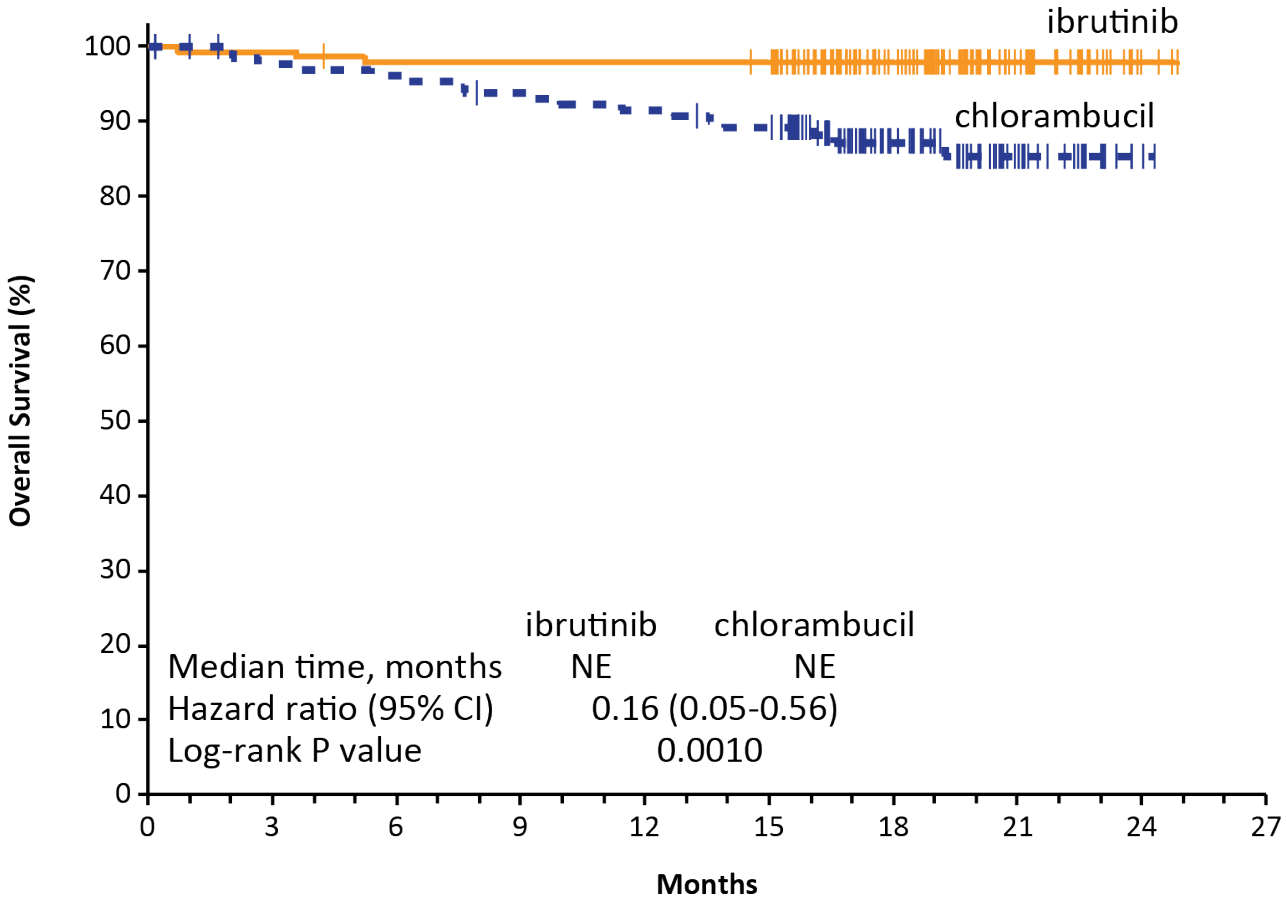
PFS by Investigator for High-Risk Subgroups



- Median PFS in del11q subgroup: NR with ibrutinib vs. 9 months with chlorambucil (HR=0.02, *P*<0.0001)
- Median PFS in unmutated *IGHV* subgroup: NR with ibrutinib vs. 9 months with chlorambucil (HR=0.06, *P*<0.0001)
- Ibrutinib: 18-month PFS 92% in *IGHV* mutated, 95% in unmutated subgroup

Burger JA et al., NEJM 373(25):2425-37, 2015

Overall Survival



- 84% reduction in risk of death with ibrutinib
- 24-month OS rate: 98% with ibrutinib and 85% with chlorambucil
- 3 deaths on ibrutinib arm vs. 17 deaths on chlorambucil arm

Burger JA et al., NEJM 373:2425-37, 2015

Additional Safety Results

	ibrutinib (n = 135)			chlorambucil (n = 132)		
Median exposure, months (range)	17.4 (0.7-24.7)			7.1 (0.5-11.7)		
Adverse event	**Any**	**G3**	**G4**	**Any**	**G3**	**G4**
Hypertension	14%	4%	0	0	0	0
Atrial fibrillation	6%	1%	0	1%	0	0
Major hemorrhage	4%	3%	1%	2%	2%	0

- On ibrutinib arm
  - The 6 patients (4%) with grade 3 hypertension were managed with anti-hypertensive medication and did not require dose modification of ibrutinib
    - 4 of 6 patients: history of hypertension
  - Among 8 patients (6%) with atrial fibrillation, 2 discontinued ibrutinib
    - 7 of 8 patients: history of hypertension, CAD, and/or myocardial ischemia
  - Among 6 patients (4%) with major bleeding, 3 discontinued ibrutinib
    - 3 of 6 patients: concomitant LMWH, aspirin, or vitamin E at time of event

Overall, 19% of patients on the ibrutinib arm received anticoagulants and 47% received antiplatelet agents

Conclusions

- Ibrutinib is highly effective therapy for relapsed CLL and previously untreated CLL
- More selective than chemotherapy but not without toxicity
- Ibrutinib FDA approved for R/R CLL- 2014
- Ibrutinib FDA approved for untreated CLL – 2016
- 2nd generation BTK inhibitors in clinical trials

Challenges and open questions

1. **Indefinite therapy = cumulative toxicity and risk for developing resistance.** Combination trials, such as venetoclax + ibrutinib or iFCG to achieve MRD-negativity, then stop therapy
2. **Mechanism of action:** contribution of BCR signaling inhibition vs. anoikis
3. **Resistance:** how to manage high-risk patients on ibrutinib, cellular therapy vs. venetoclax, timing
4. What to do with **younger low-risk patients**, CIT vs. BTKi

Collaborators:

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- UCSD: T Kipps, L Rassenti
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- DFCI, Broad I: C Wu, D Landau

My laboratory: Mariela Sivina, Julia Hoellenriegel, Stefan Koehrer, Ekaterina Kim, Elisa ten Hacken, Shubhchintan Randhawa

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Thank-you!

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