CLL - ibrutinib

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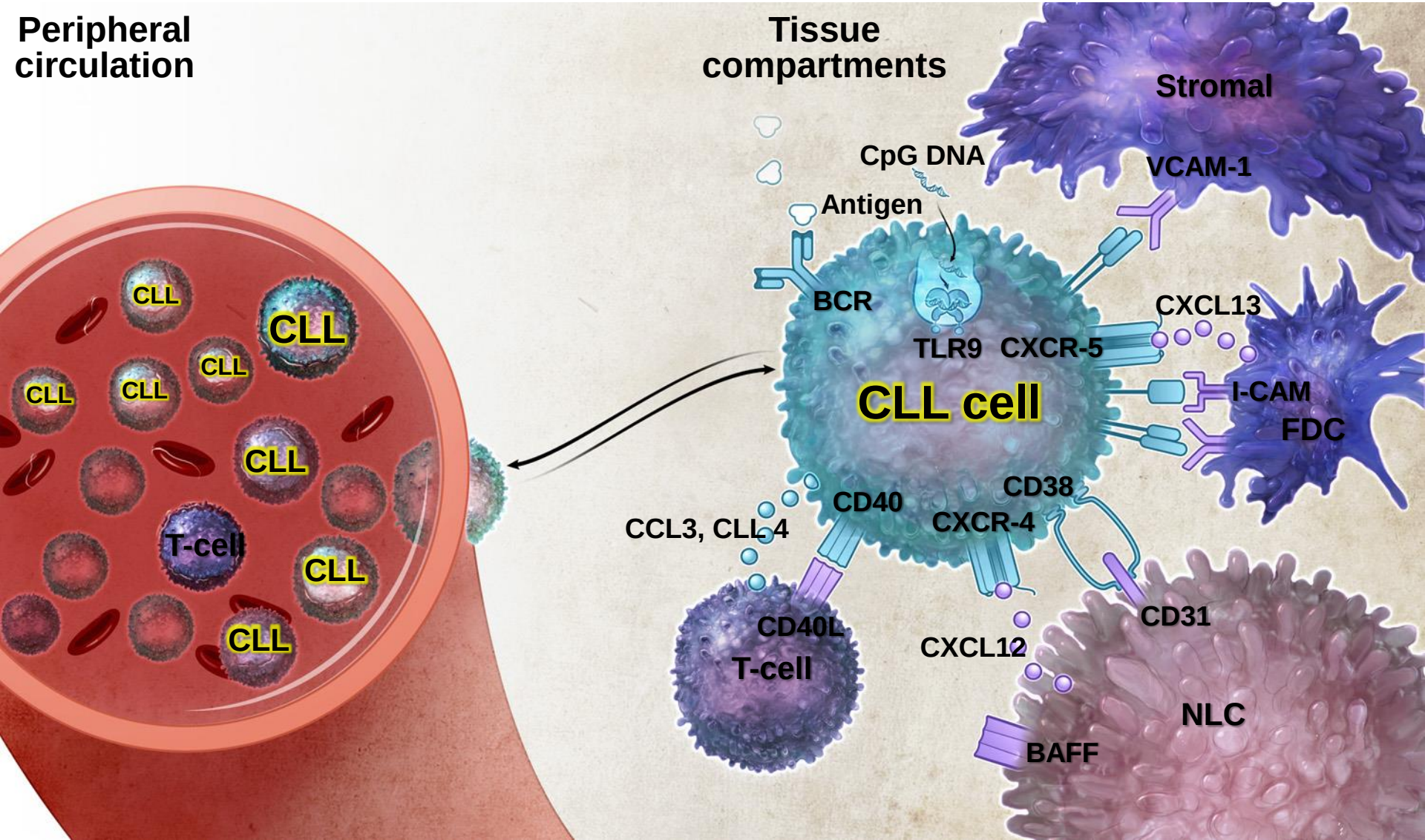
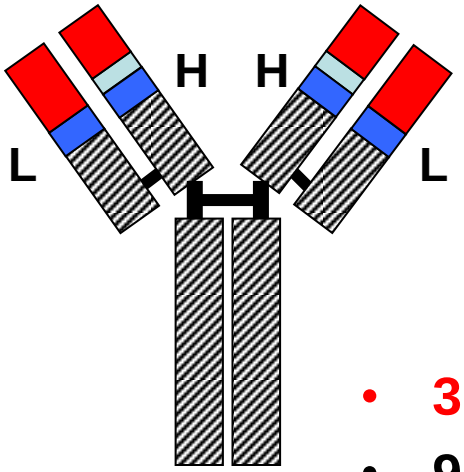
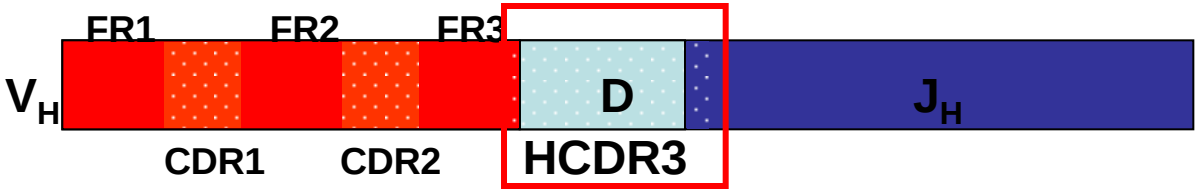
10th May 2016

“Life Cycle”of the CLL Cell



Is the proliferation in CLL antigen-driven? - the significance of stereotyped receptors





- **30.4% of all CLL cases (2308/7596)**
- **952 stereotyped antigen receptors (subsets)**
- **943 cases (41% of stereotyped) fall into 19 subsets**

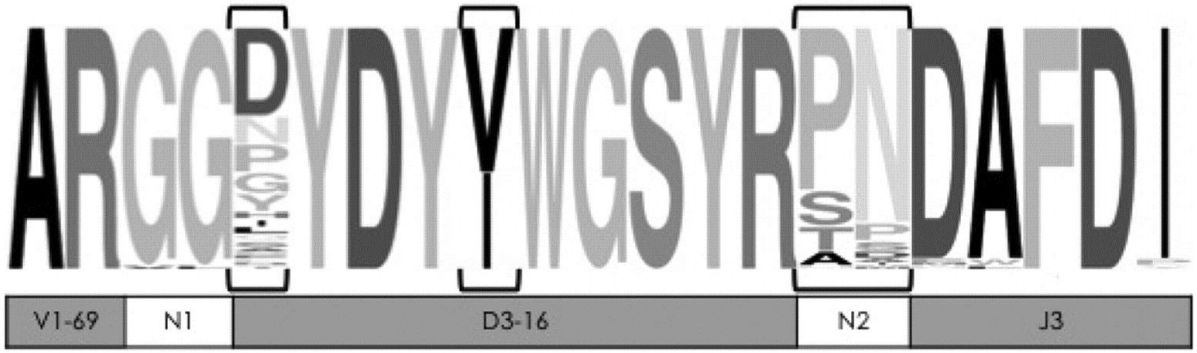
Subset 6 (VH 1-69)

No. cases 68

Phylogenetic clan: I

SHM = unmutated

VH CDR3: 21AA



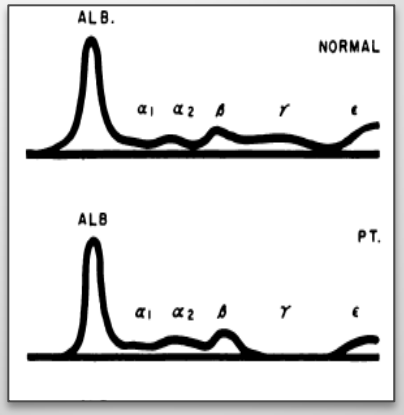
Agathangelidis et al, Blood 2012, 119: 4467-75.

Development of ibrutinib

Person

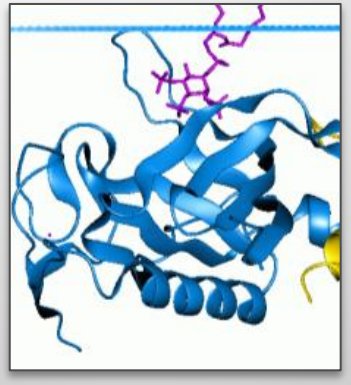
Ogden *Bruton*
(1908-2003)

Disease



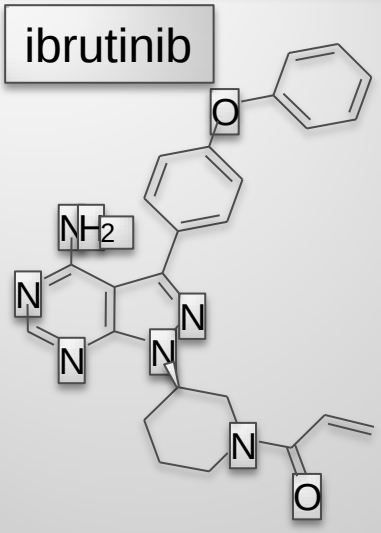
Bruton's
Agammaglobulinemia,
1952

Enzyme



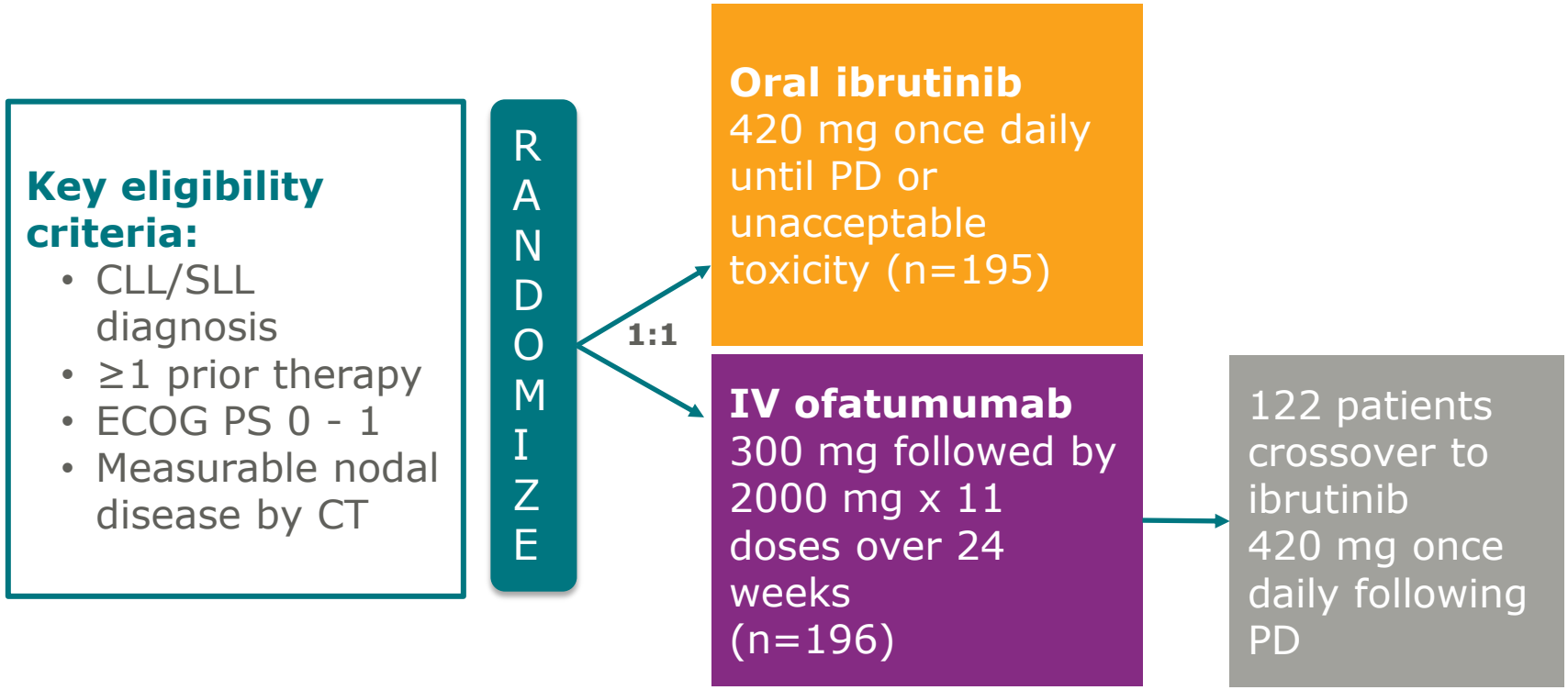
Bruton
Tyrosine
Kinase, 1993

Drug



Synthesized 2005
First in human 2009
1st approval 2013

RESONATE: study design



Endpoints: PFS, OS, ORR, safety

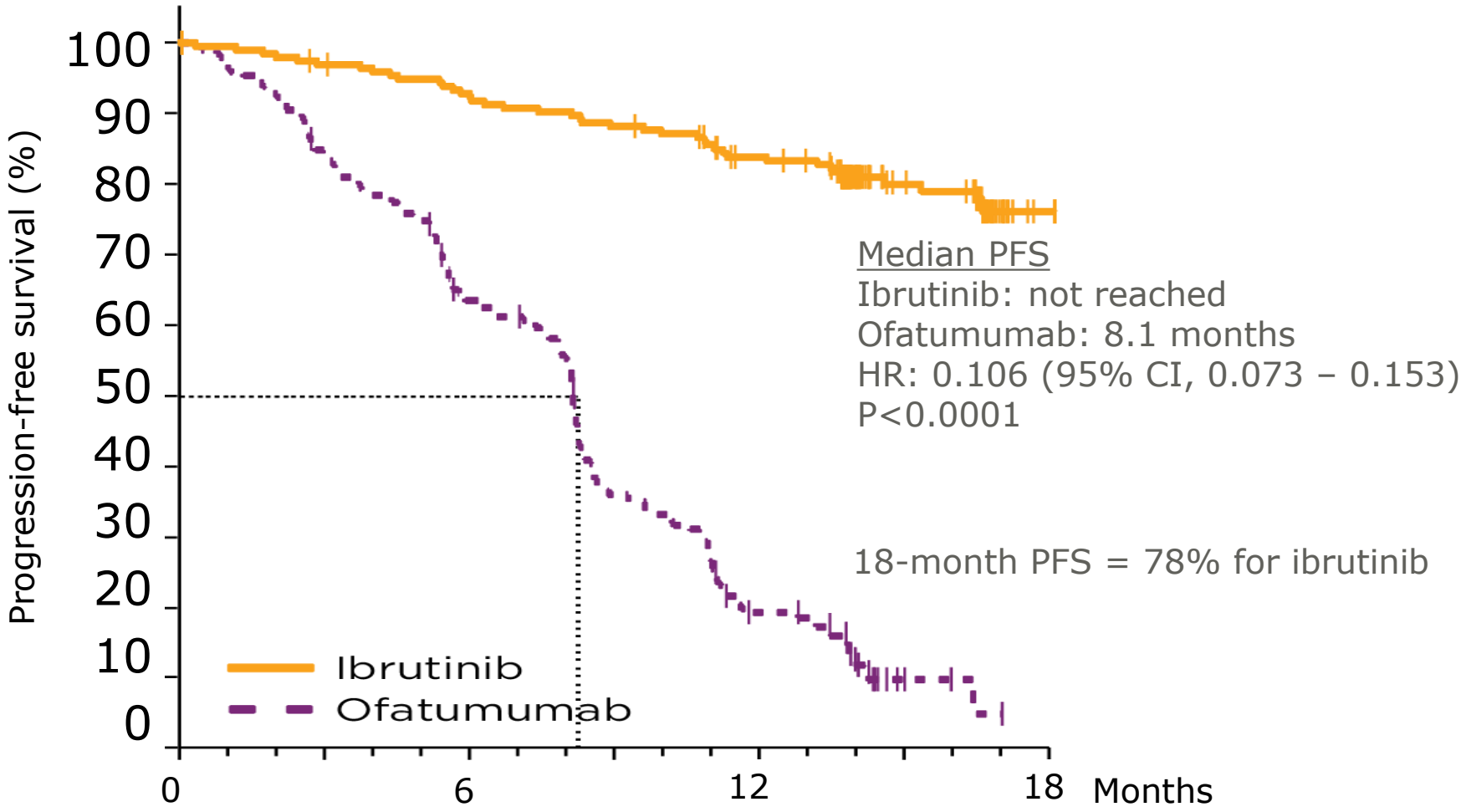
Byrd *et al*. **N Engl J Med**. 2014 Jul 17;371(3):213-23.

Resonate: Baseline Characteristics

Characteristic	ibrutinib (N=195)	ofatumumab (N=196)
Median age, years (range) ≥70 years	67 (30-86) 40%	67 (37-88) 41%
Male	66%	70%
Rai stage III/IV	56%	58%
Median number of prior therapies (range) 1 2 ≥3	3 (1-12) 18% 29% 53%	2 (1-13) 28% 27% 46%
Del17p	32%	33%
Del11q	63/190 (33%)	59/191 (31%)
Trisomy 12	22/138 (16%)	27/145 (19%)
Complex karyotype	39/153 (25%)	32/145 (22%)
CD38 (≥30%)	69/160 (43%)	69/155 (45%)
IGHV Unmutated Mutated	 98/134 (73%) 36/134 (27%)	 83/132 (63%) 49/132 (37%)

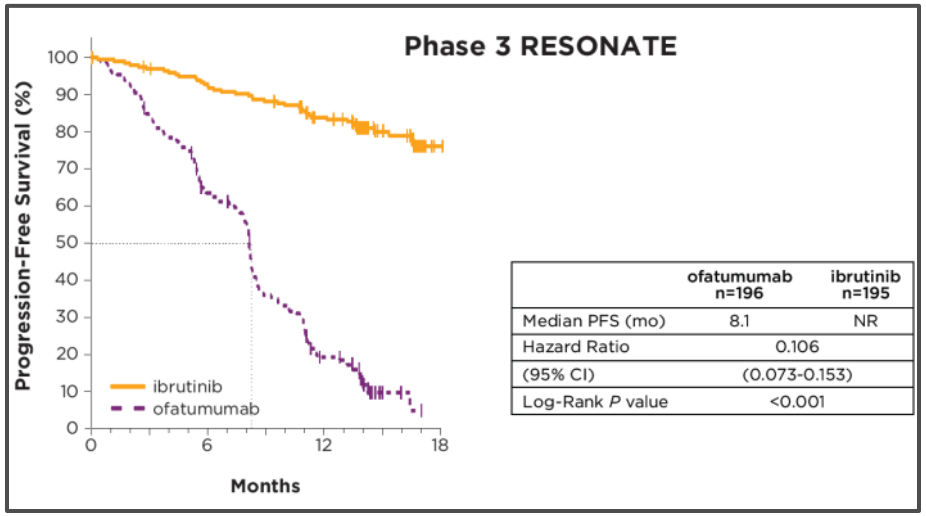
BSH 2015, PCYC-1112, Dearden C, et al.

RESONATE: superior PFS

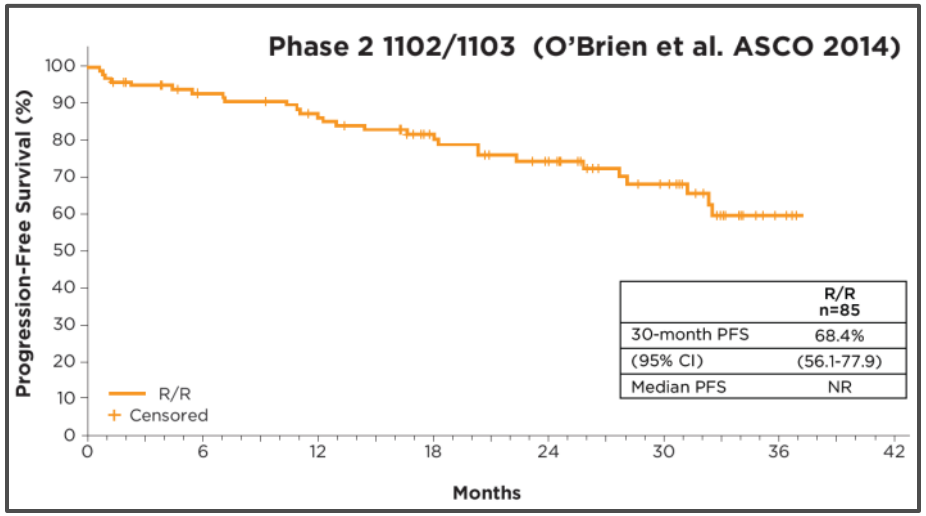


Byrd *et al*. **N Engl J Med**. 2014 Jul 17;371(3):213-23.

Progression-Free Survival with ibrutinib in relapsed, refractory CLL (PCYC-1112 & 1102)



	ofatumumab n=196	ibrutinib n=195
Median PFS (mo)	8.1	NR
Hazard Ratio	0.106	
(95% CI)	(0.073-0.153)	
Log-Rank *P* value	<0.001	

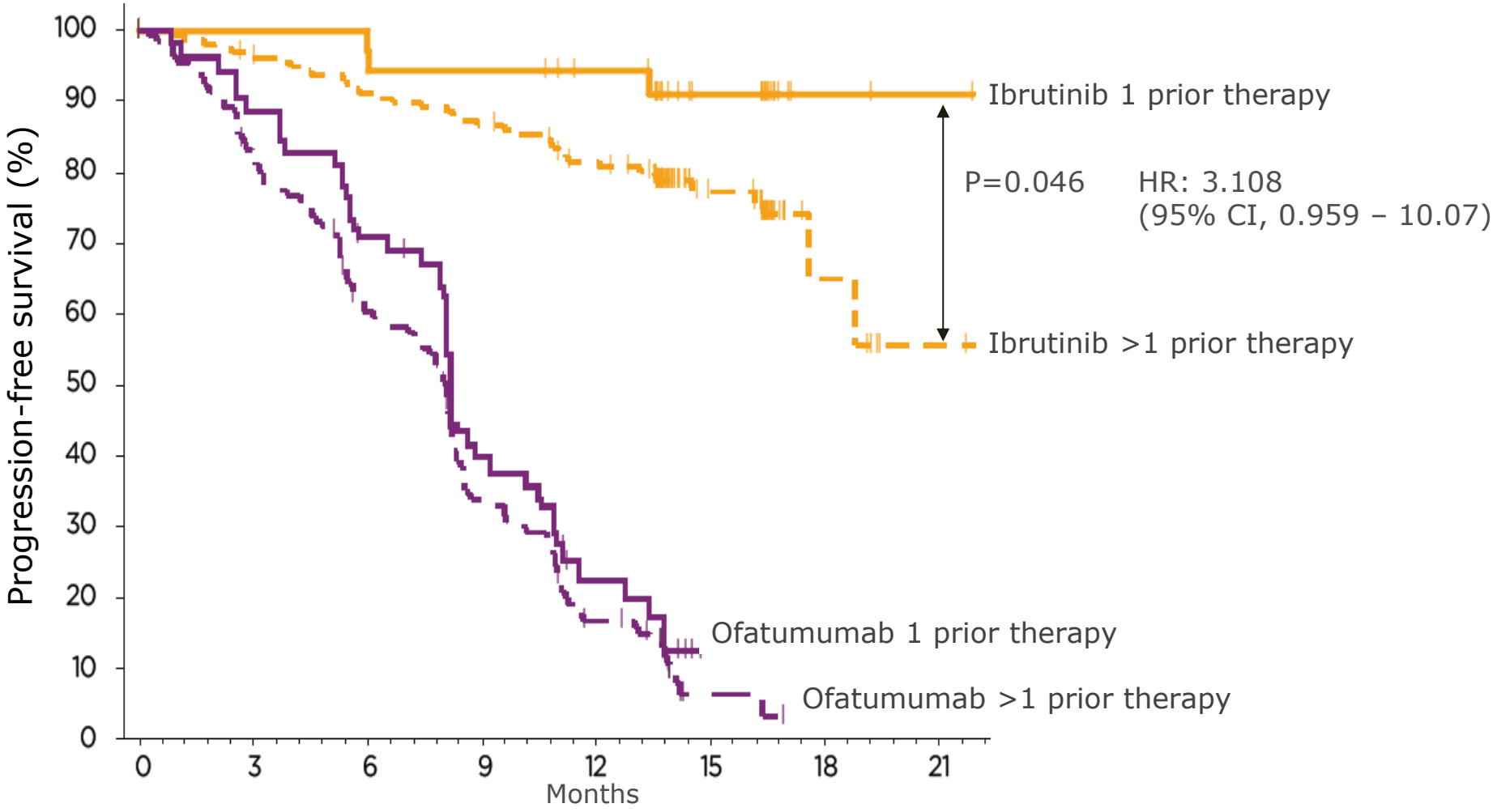


	R/R n=85
30-month PFS	68.4%
(95% CI)	(56.1-77.9)
Median PFS	NR

- Median follow-up was 16 months vs. 12 months for ibrutinib vs. ofatumumab
- Ibrutinib treatment significantly lengthened PFS (median not reached vs. 8.1 mo, HR=0.106, 95% CI 0.073-0.153, *P*<0.001)
- 12-month PFS rate was significantly improved for ibrutinib vs. ofatumumab (84% vs.18%, *P*<0.001)

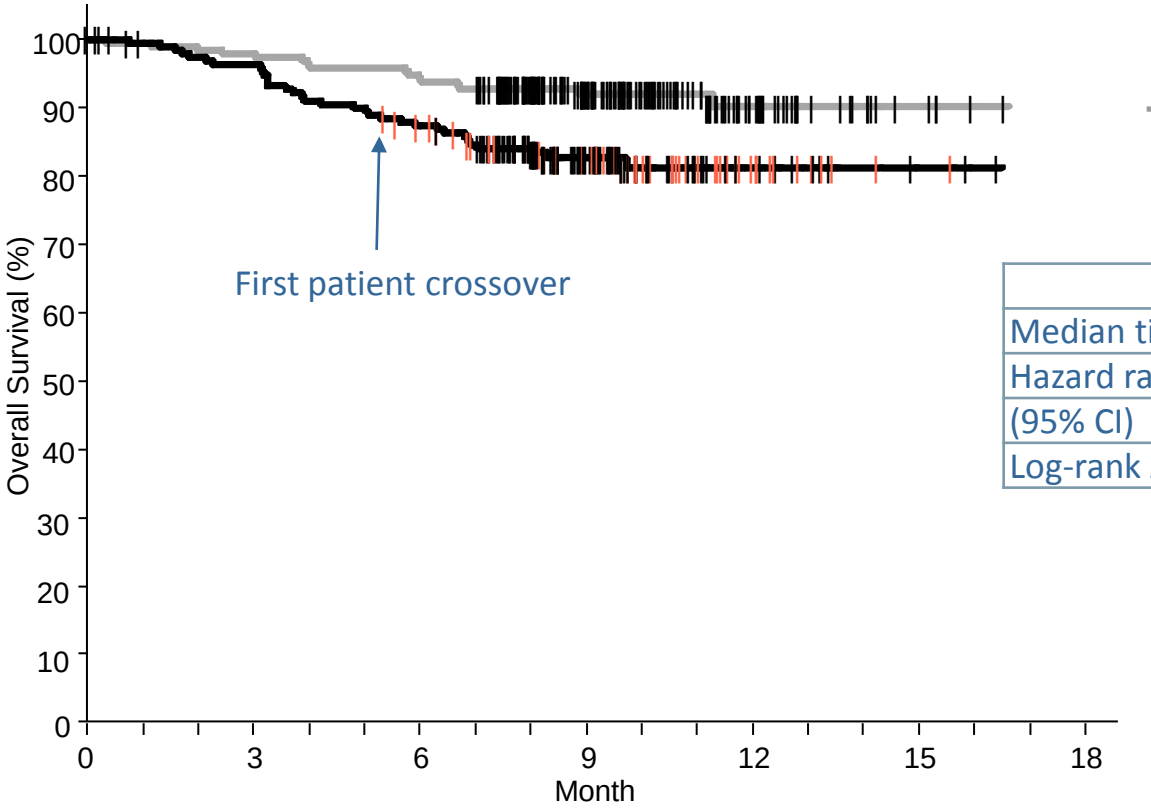
Byrd *et al*. **N Engl J Med**. 2014 Jul 17;371(3):213-23.

RESONATE: significantly better PFS with earlier treatment



Byrd *et al*. **N Engl J Med**. 2014 Jul 17;371(3):213-23.

Overall Survival in the Resonate (PCYC-1112) Trial (Censored at cross-over)



	Ofatumumab	Ibrutinib
Median time (mo)	NR	NR
Hazard ratio	0.434	
(95% CI)	(0.238-0.789)	
Log-rank *P* value	0.0049	

- Ibrutinib significantly prolonged OS compared with ofatumumab
- This represents a 57% reduction in the risk of death for the ibrutinib arm
- At the time of this analysis, 57 patients initially randomized to ofatumumab were crossed over to receive ibrutinib following IRC-confirmed PD

Byrd *et al*. **N Engl J Med**. 2014 Jul 17;371(3):213-23.

Summary of Safety for Ibrutinib Over 16-Month Follow-Up in RESONATE Trial

- The most frequently reported preferred terms were diarrhea, fatigue, cytopenia, constipation, and pneumonia (most grade 1)
- The most frequent grade 3/4 AEs for ibrutinib were neutropenia (18%), pneumonia (9%), thrombocytopenia (6%), anemia (6%), hypertension (6%)

Atrial fibrillation of any grade occurred in 13 (7%) ibrutinib-treated patients, which includes 3 additional patients reported since interim analysis

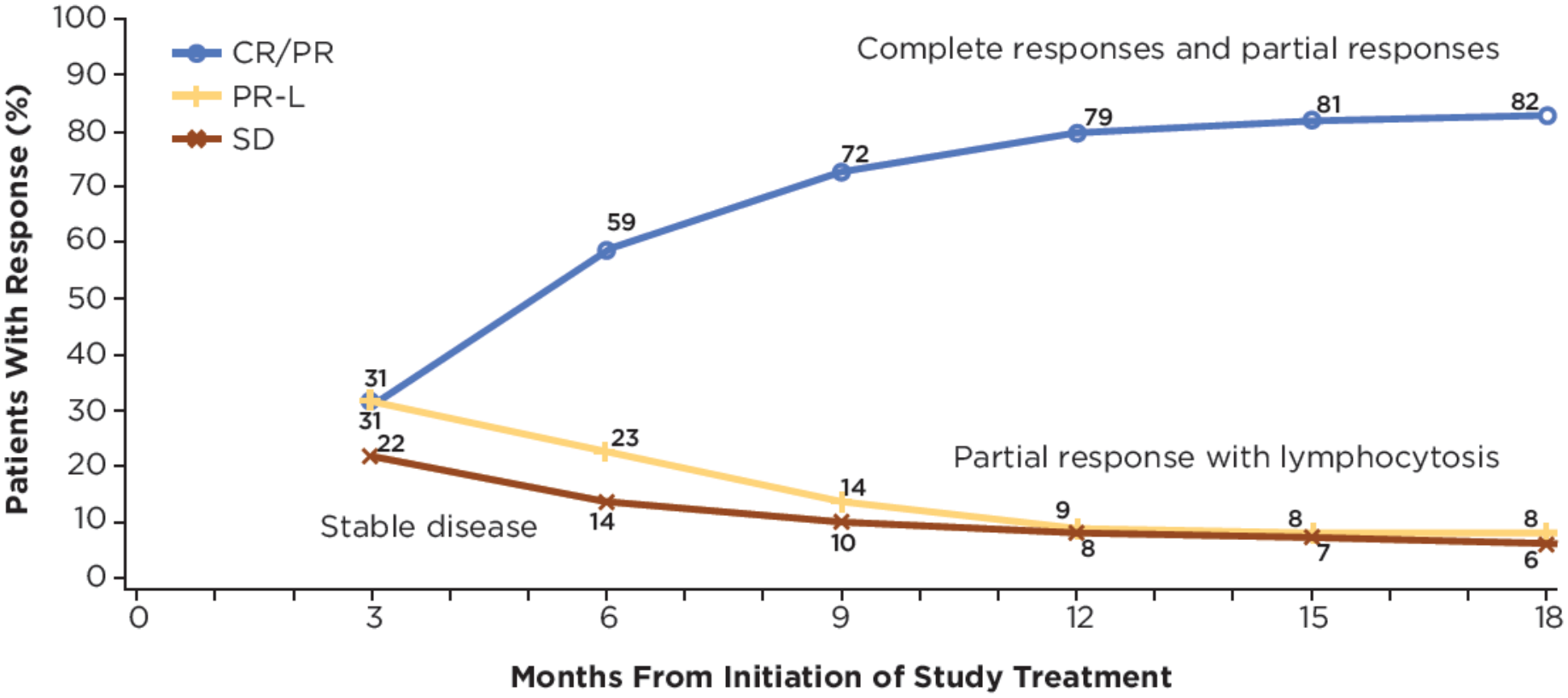
- 1 patient discontinued due to atrial fibrillation
- Of note, prior medical history of atrial fibrillation was reported more frequently for ibrutinib (5.6%) vs. ofatumumab (2.6%)

Bleeding AEs occurred in 48% of patients, the majority were grade 1 (40%), with grade 2 events reported in 6%, grade 3 (2%), and grade 4 (1%).

- Grade ≥3 bleeding events included grade 3 epistaxis (n=1), grade 3 spontaneous hematoma (n=1), and grade 4 subdural hematoma (n=1)
- There were no grade 5 events

Jennifer Brown, et al. Poster #3331, ASH2014

Cumulative Best Response To Ibrutinib Over Time - changing to continuous maintenance therapy



- Most patients experienced a transient increase in blood lymphocyte counts that frequently resolved with continued ibrutinib treatment and patients achieved deeper responses

Byrd *et al*. **N Engl J Med**. 2014 Jul 17;371(3):213-23.

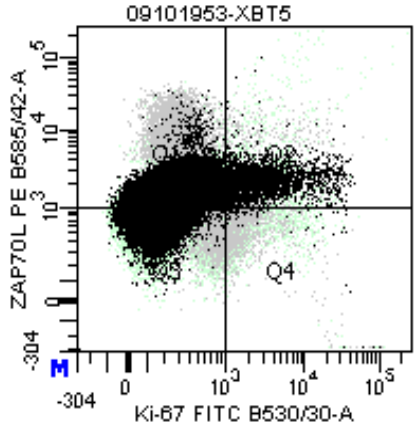
Bloodwise TAP

Beating blood cancer since 1960

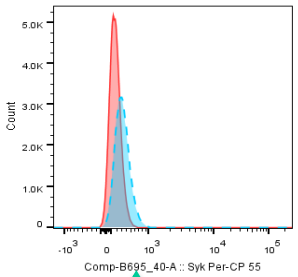
IcICLLe

Translational Research

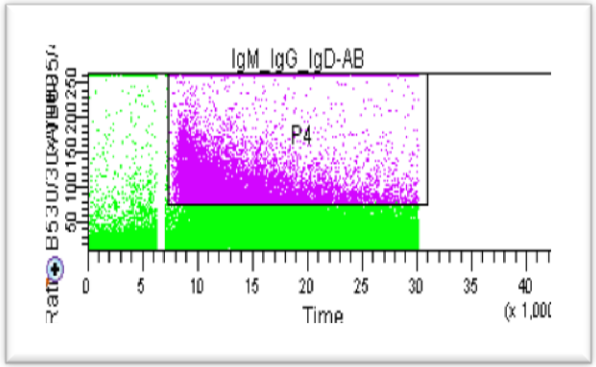
Immunophenotyping



PhosPho Flow (signaling)



Calcium flux (functional)



Ibrutinib
420mg/day

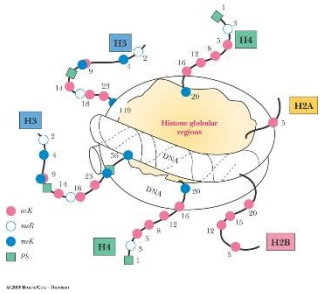
N=40 → Extension study

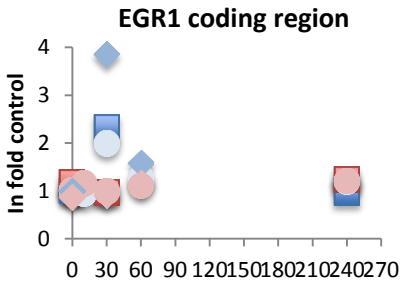
Frequent Samples:

PB: -14d, 0, 4, 24, 7d, 14d, 28d, 56d, 6mo

BM: -14d, 28d, 6mo

Epigenetics

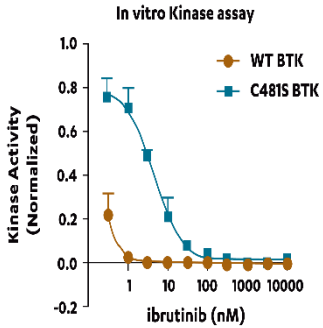




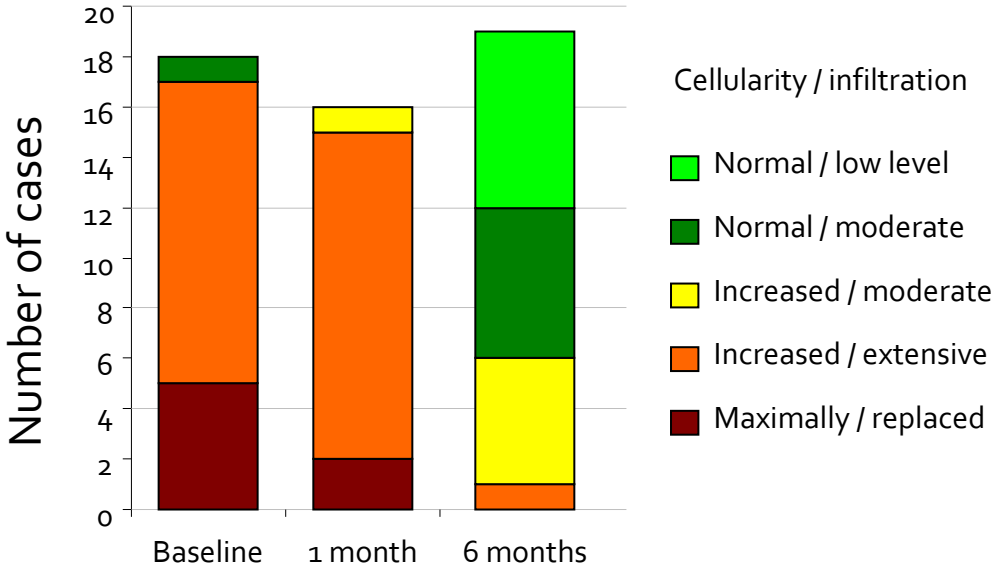
Genetics

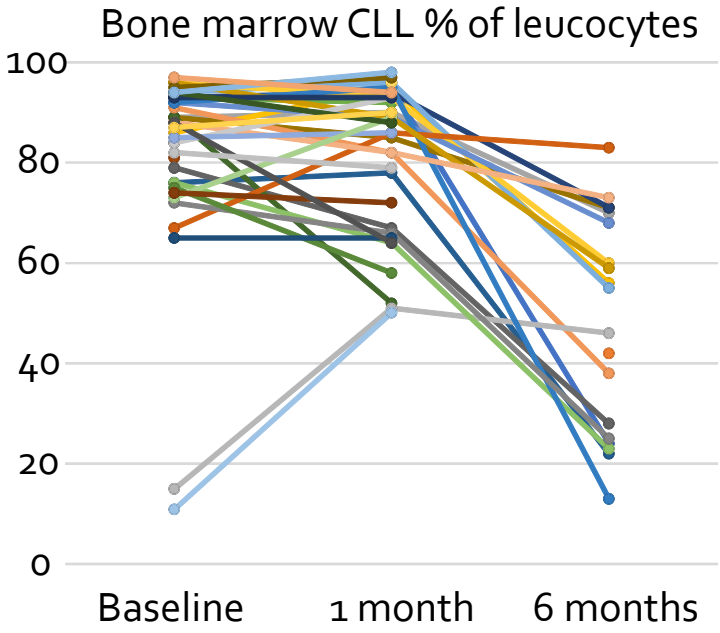
Genomics england

Resistance mechanisms



Kinetics of response in bone marrow: no change at 1 M, reduction at 6M





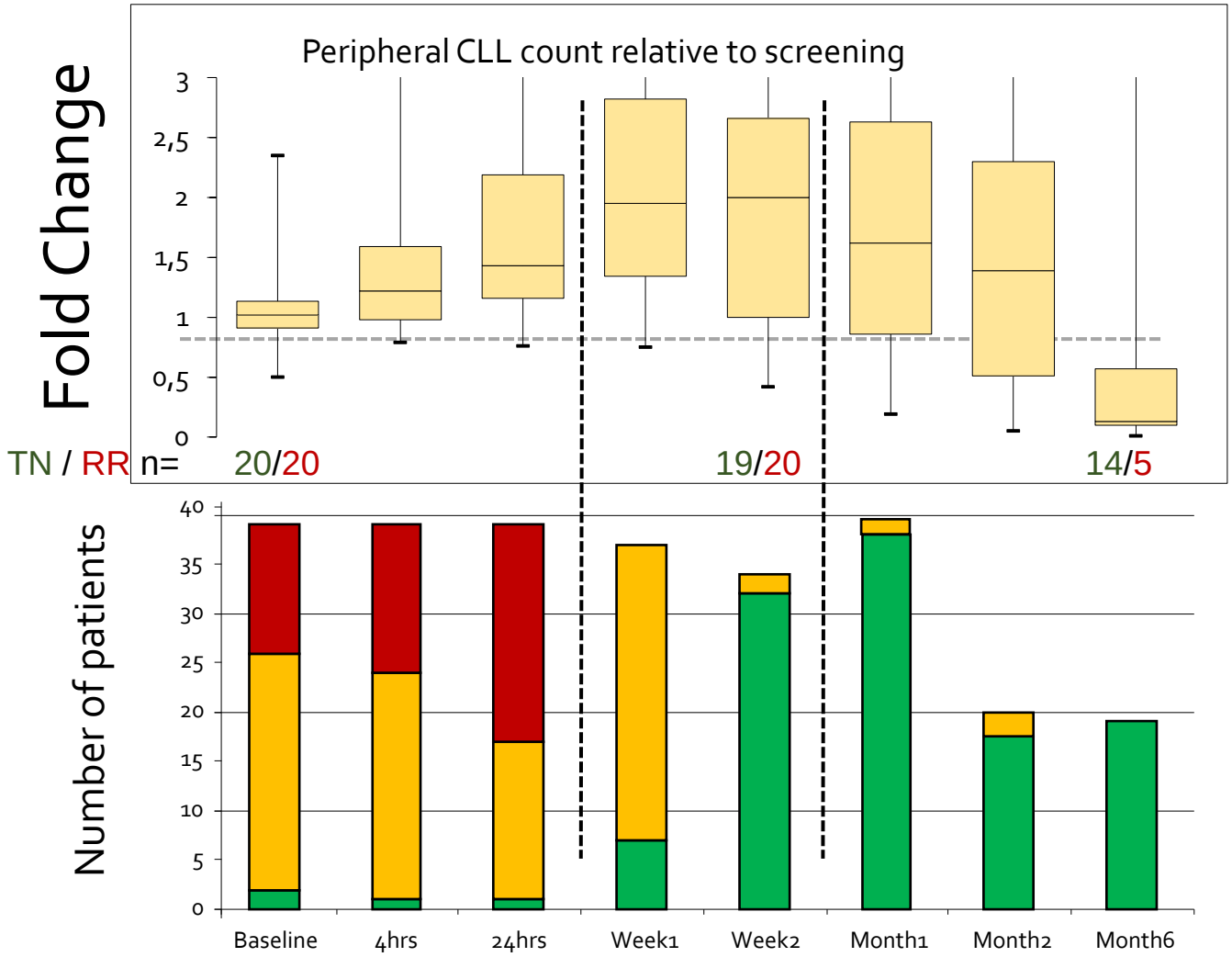
Quantifiable (>20%) reduction of BM CLL in 13/19 evaluable
6/19 achieved <30% BM CLL

The Leeds Teaching Hospitals NHS
NHS Trust

Bloodwise TAP
Beating blood cancer since 1960

UNIVERSITY OF LEEDS

Rapid (4-24hrs) entry of proliferating cells into blood. Peripheral counts peak at week 1 as proliferation starts to decline



The Leeds Teaching Hospitals NHS
NHS Trust

Bloodwise
Beating blood cancer since 1960

TAP

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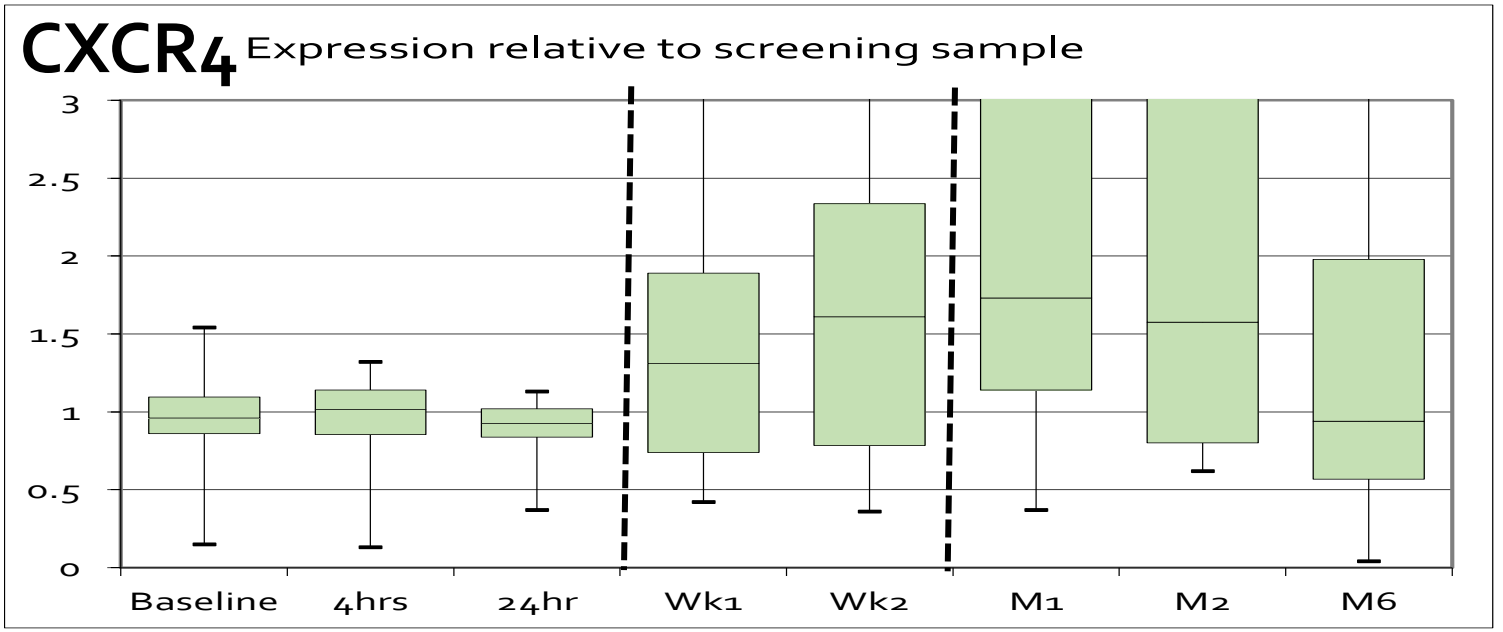
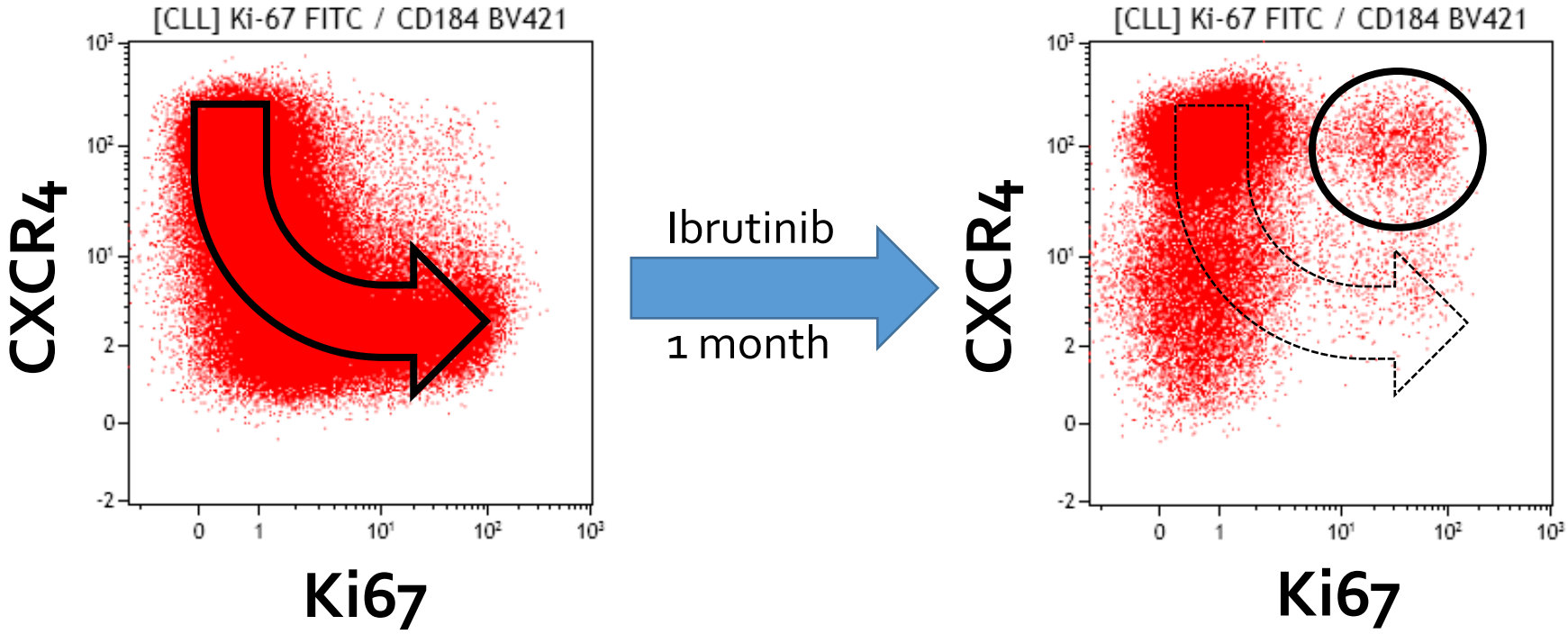
Changes in markers associated with cell trafficking and adhesion begin to occur as the peripheral counts are peaking



Increases CXCR4 and CD24 expression and decreases in CCR7, CD31 and CD11a followed the same pattern, i.e. changes emerge after 1-2 weeks of treatment and then stabilise subsequently

? Return to baseline for CXCR4 expression at 6 months ?

Loss of normal proliferating CLL cell expression profile during ibrutinib therapy



The plots show CXCR4 vs. Ki67 in the same patient at baseline and then after 1 month of ibrutinib therapy

Conclusions of IcICLLe Trial

- Redistribution of CLL cells during ibrutinib occurs very rapidly – faster than changes in proteins associated with proliferation, cell trafficking or adhesion.
- Bone marrow responses become apparent after 6 months of ibrutinib treatment
- CD20 expression decreases while BCL2 expression remains strong throughout 6 months of treatment
- Changes in CLL cells correlate with the loss of the proliferative fraction, mostly stabilising after one month

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ibrutinib as Initial Therapy for Patients with Chronic Lymphocytic Leukemia

J.A. Burger, A. Tedeschi, P.M. Barr, T. Robak, C. Owen, P. Ghia, O. Bairey, P. Hillmen, N.L. Bartlett, J. Li, D. Simpson, S. Grosicki, S. Devereux, H. McCarthy, S. Coutre, H. Quach, G. Gaidano, Z. Maslyak, D.A. Stevens, A. Janssens, F. Offner, J. Mayer, M. O'Dwyer, A. Hellmann, A. Schuh, T. Siddiqi, A. Polliack, C.S. Tam, D. Suri, M. Cheng, F. Clow, L. Styles, D.F. James, and T.J. Kipps, for the RESONATE-2 Investigators*

N Engl J Med 2015; 373:2425-2437

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

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

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

*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

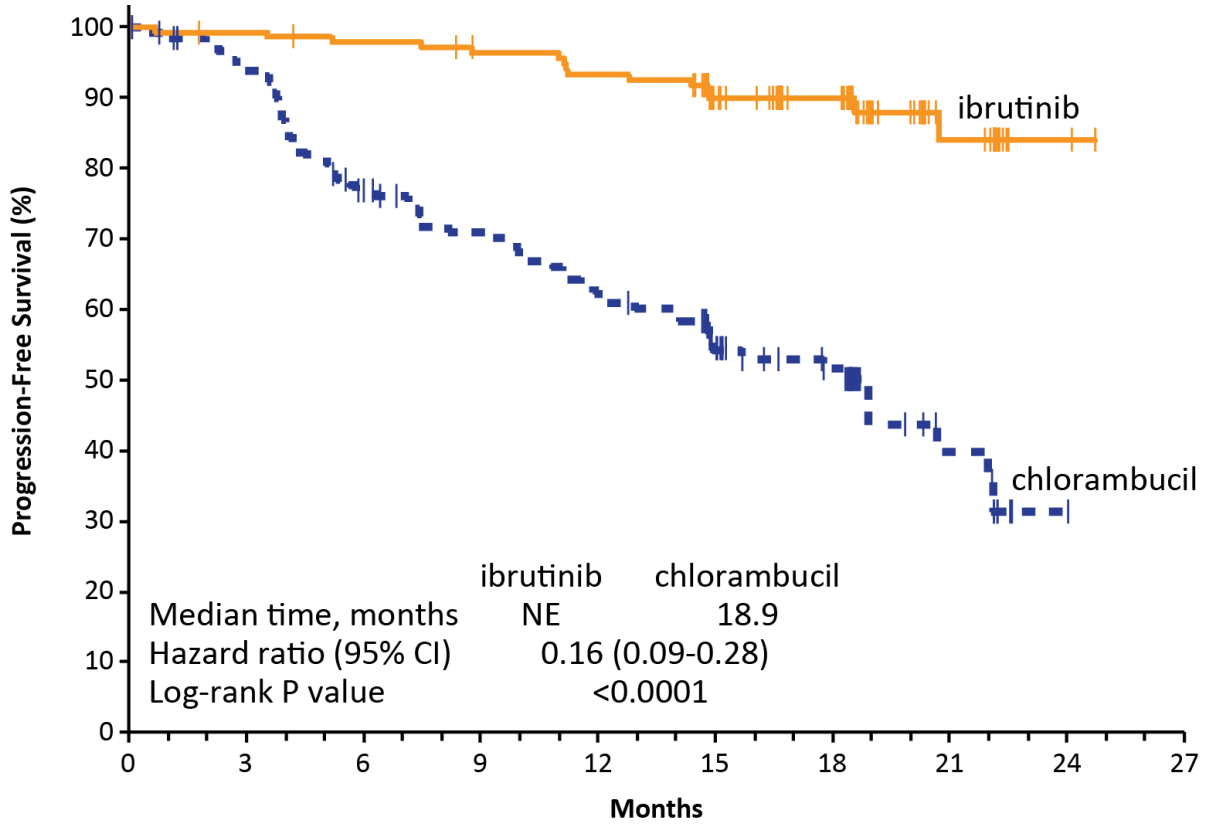
1. Hallek et al. *Blood*. 2008;111:5446-5456; 2. Hallek et al, *Blood.* 2012; e-letter, June 04, 2012.

Resonate-2: Patient Characteristics

Characteristic	ibrutinib (n = 136)	chlorambucil (n = 133)
Median age, years (range) ≥70 years, %	73 (65–89) 71	72 (65–90) 70
ECOG status 2, %	8	9
Rai stage III or IV, %	44	47
CIRS score >6, %	31	33
Creatinine clearance <60 ml/min, %	44	50
Bulky disease ≥5 cm, %	40	30
β2-microglobulin >3.5 mg/L, %	63	67
Hemoglobin ≤11 g/dL, %	38	41
Platelet count ≤100,000 per mm^3, %	26	21
Del11q, %	21	19
Unmutated *IGHV,* %	43	45

Burger *et al.,* N Engl J Med 2015; 373:2425-2437

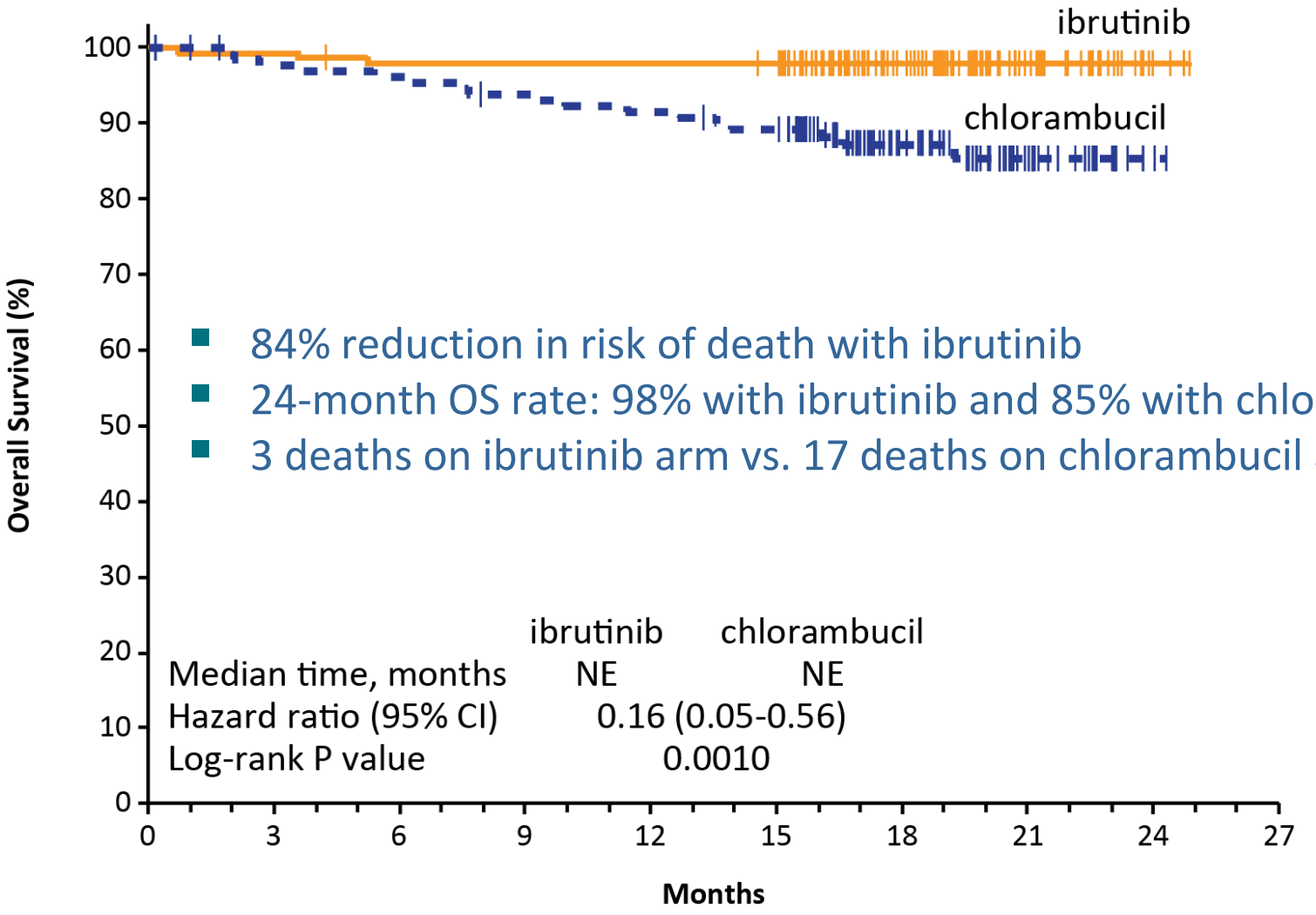
Resonate 2: PFS by Independent Assessment



- 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 *et al.,* N Engl J Med 2015; 373:2425-2437

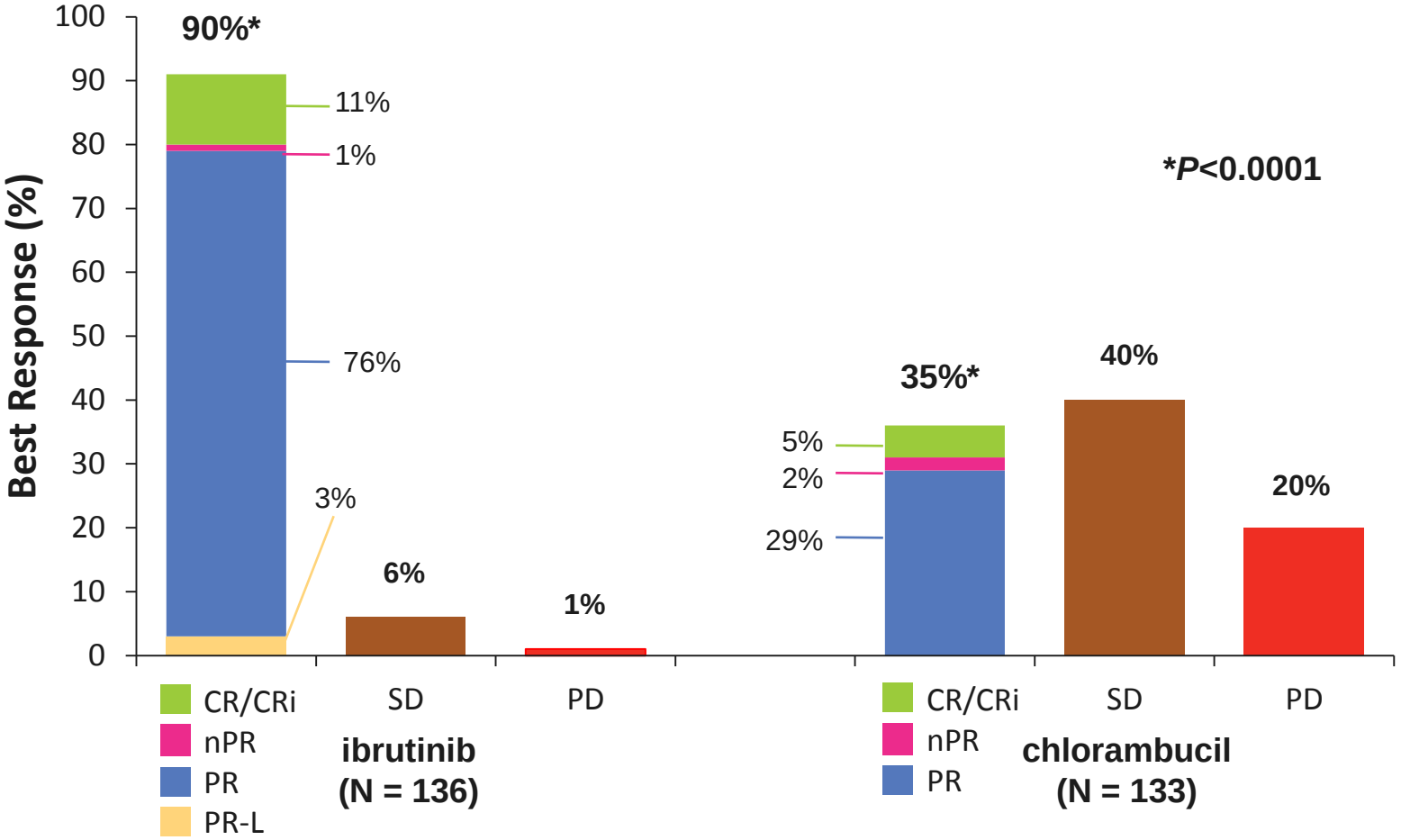
Resonate-2: Overall Survival



- 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 *et al.,* N Engl J Med 2015; 373:2425-2437

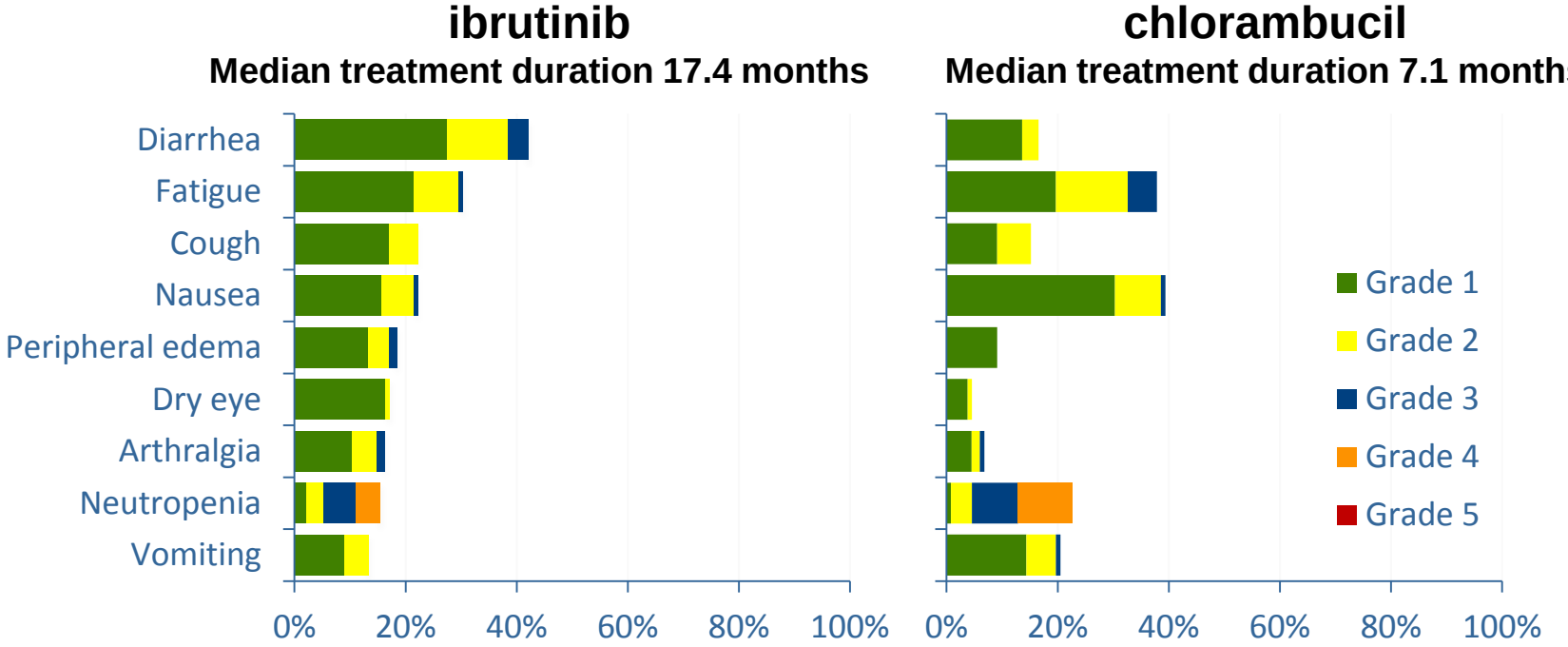
Resonate-2: Response by Investigator Assessment



- ORR at 8 months: 82% with ibrutinib vs. 30% with chlorambucil
- ORR with ibrutinib higher than with chlorambucil at all time points

Burger *et al.,* N Engl J Med 2015; 373:2425-2437

Resonate-2: Most Common Adverse Events*



*Adverse event that occurred in ≥15% of patients in either treatment arm, and that were imbalanced between treatment arms by a difference in frequency of ≥5%.

- Majority of the common AEs on ibrutinib arm were grade 1 and did not result in treatment discontinuation
- On the chlorambucil arm, fatigue, nausea, vomiting, and cytopenias occurred more frequently vs. ibrutinib
- Grade 3 maculopapular rash (no grade 4) in 3% for ibrutinib vs. 2% for chlorambucil

Burger *et al.,* N Engl J Med 2015; 373:2425-2437

Resonate-2: 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 haemorrhage	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

Burger *et al.,* N Engl J Med 2015; 373:2425-2437

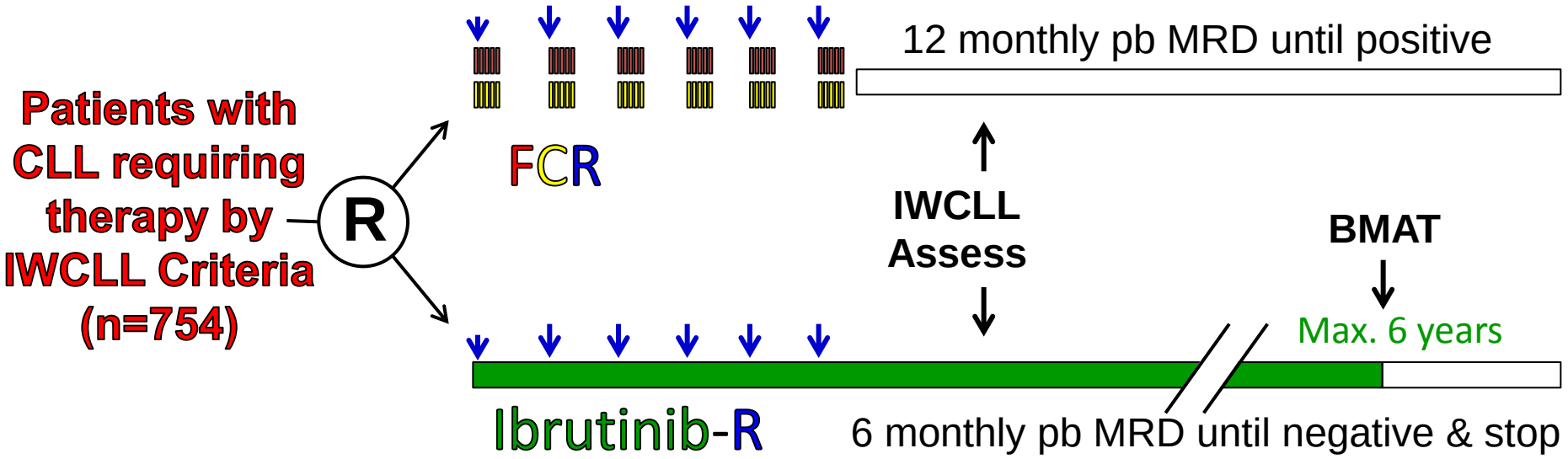
Resonate-2: Conclusions

- Efficacy of ibrutinib in treatment-naïve CLL confirmed in this phase 3 RESONATE-2 study
  - 91% reduction in risk of progression (by investigator) and 84% reduction in risk of death with ibrutinib compared with chlorambucil
  - Ibrutinib significantly improved bone marrow function as reflected by sustained increase in hemoglobin and platelets
- In this older population with frequent comorbidities, oral once-daily ibrutinib was administered with the majority (87%) of patients continuing on ibrutinib treatment with a median of 1.5 years follow-up
- Ibrutinib showed favorable benefit-risk profile as first-line treatment of patients with CLL/SLL versus traditional chemotherapy

Burger *et al.,* N Engl J Med 2015; 373:2425-2437

Front-line trial for patients fit for FCR: NCRI *Flair* (CLL10) Trial

Front Line therapy in CLL: Assessment of Ibrutinib plus Rituximab



End-points: Primary – PFS; Secondary – Overall Survival, MRD, IWCLL response, safety, QoL, cost effectiveness

Ibrutinib – 6 monthly PB MRD → stop if MRD negative or 6 years

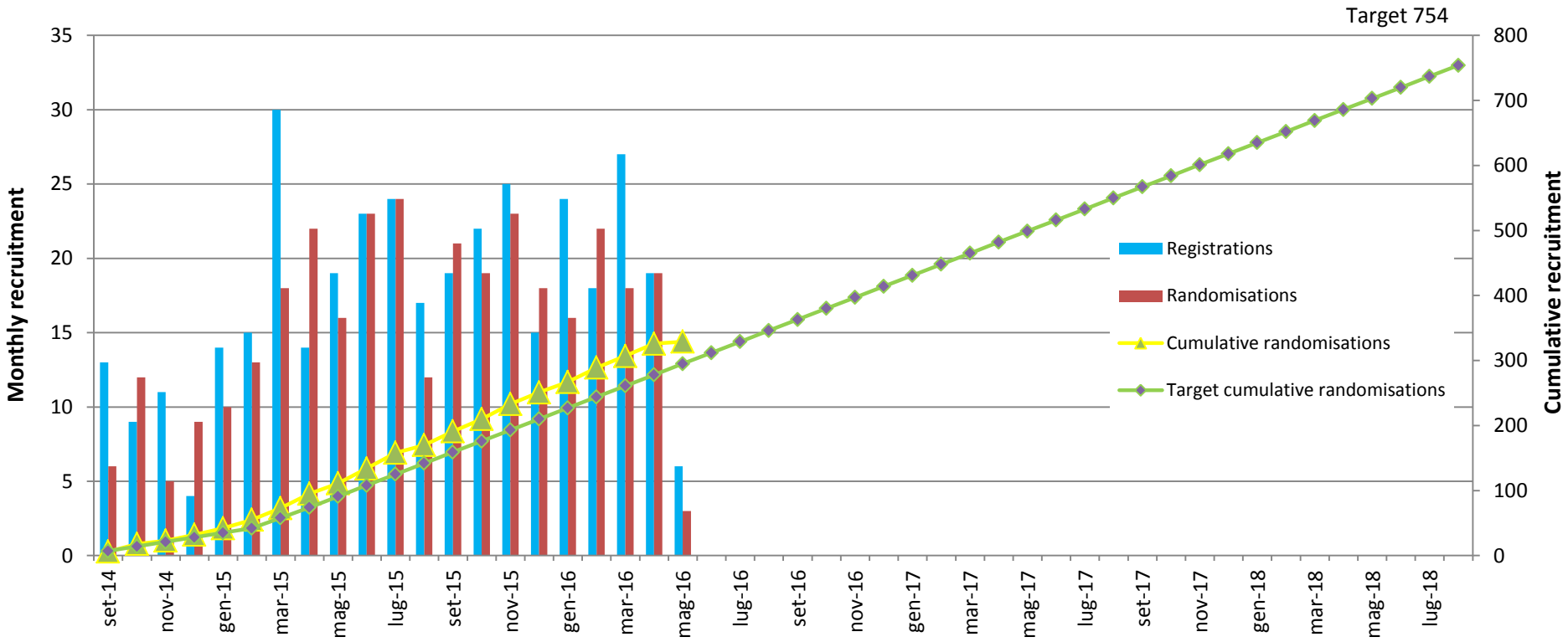
Assumptions: Med PFS – FCR 4.5 yrs; IR 6 yrs (HR 0.75)

Statistics: 80% power at the 5% significance level

Centres – 70+ UK Centres; FPFV – Sept 2014

Front-line trial for patients fit for FCR: NCRI *Flair* (CLL10) Trial

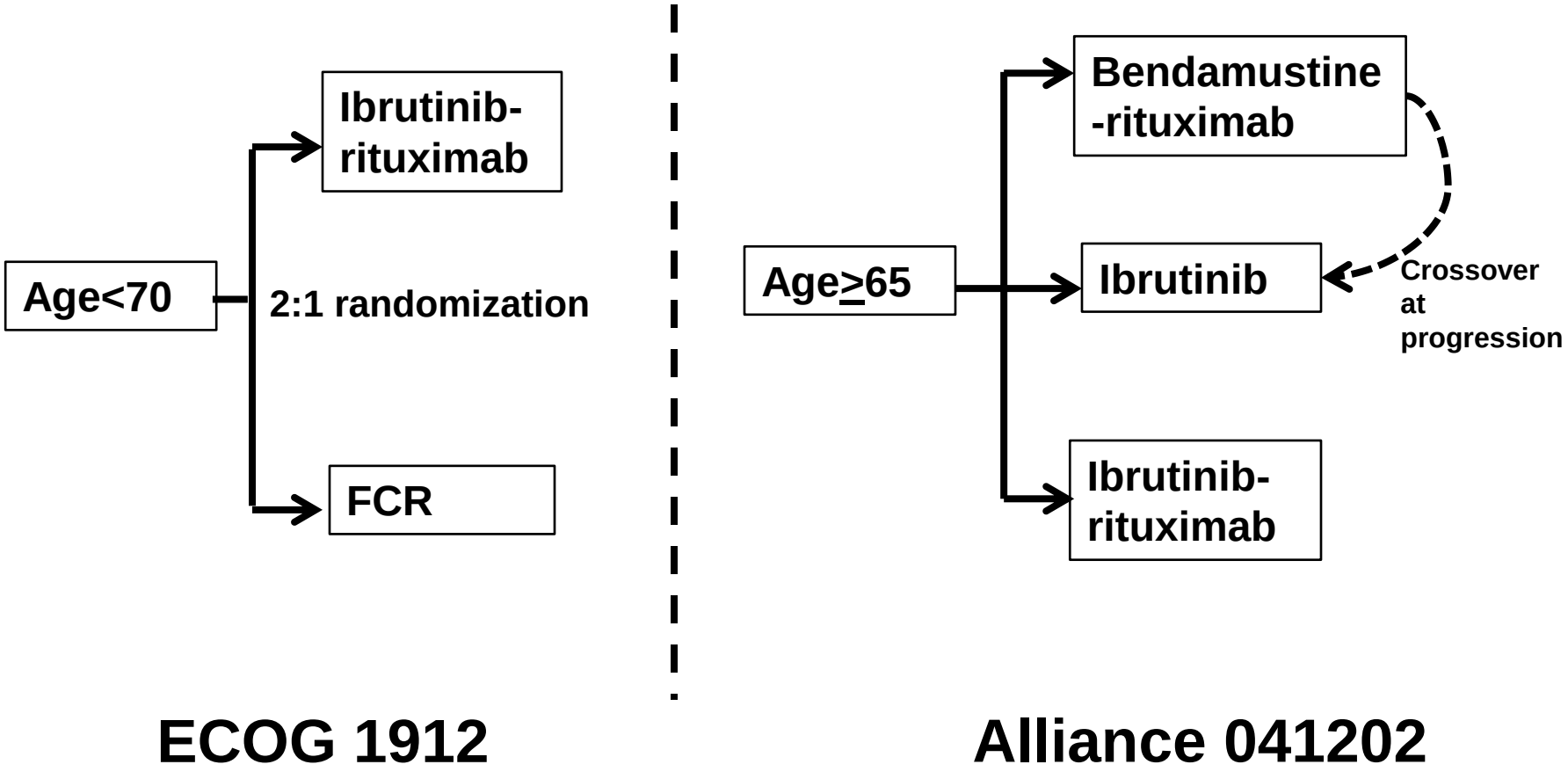
Front Line therapy in CLL: Assessment of Ibrutinib plus Rituximab



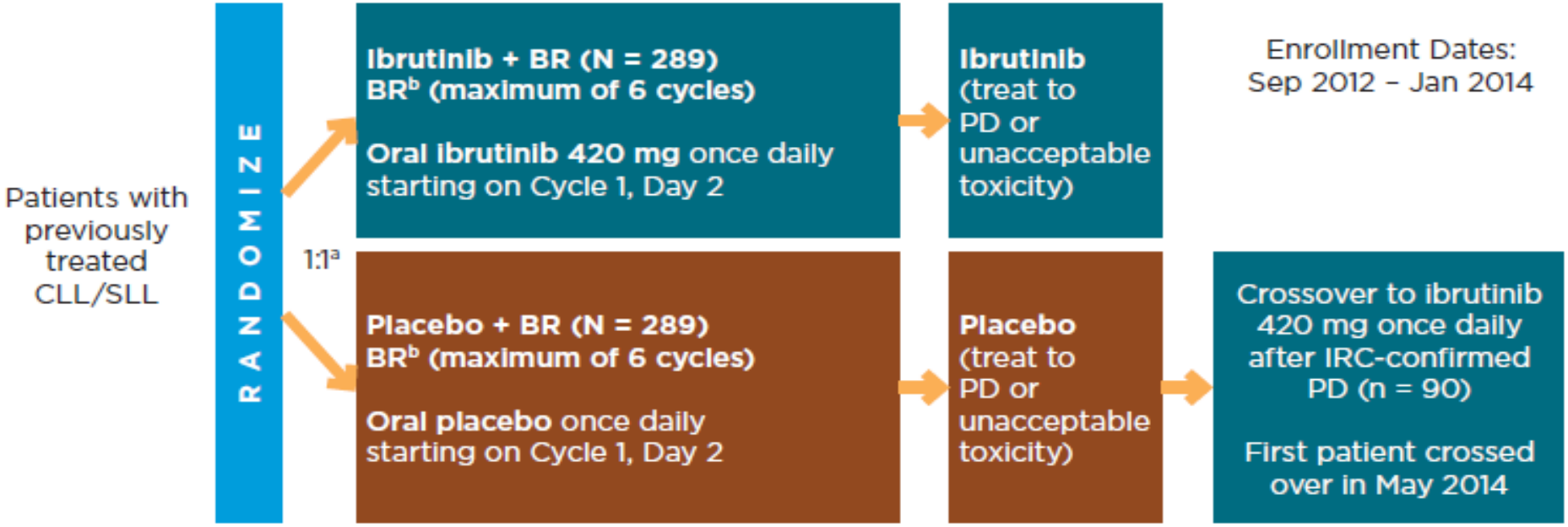
As of 10th May 2016
Number of patients registered: 370
Number of patients randomised: 329
Target (end May) 295; Centres open: 88

<u>Monthly recruitment targets (70 centres)</u>
7 per month Sept '14 – Feb '15 (6 months)
17 per month Mar '15 – Aug '18 (3.5 years)

US Intergroup: Moving Ibrutinib to Front Line Therapy



HELIOS: Phase 3 Study Design



[a]*Stratified by refractoriness to purine analog chemoimmunotherapy (failure to respond or relapse within 12 months) and the number of prior lines of therapy (1 line vs > 1 line).* [b]*BR (similar to Fischer K, et al.* J Clin Oncol. *2011;29:3559-3566).*

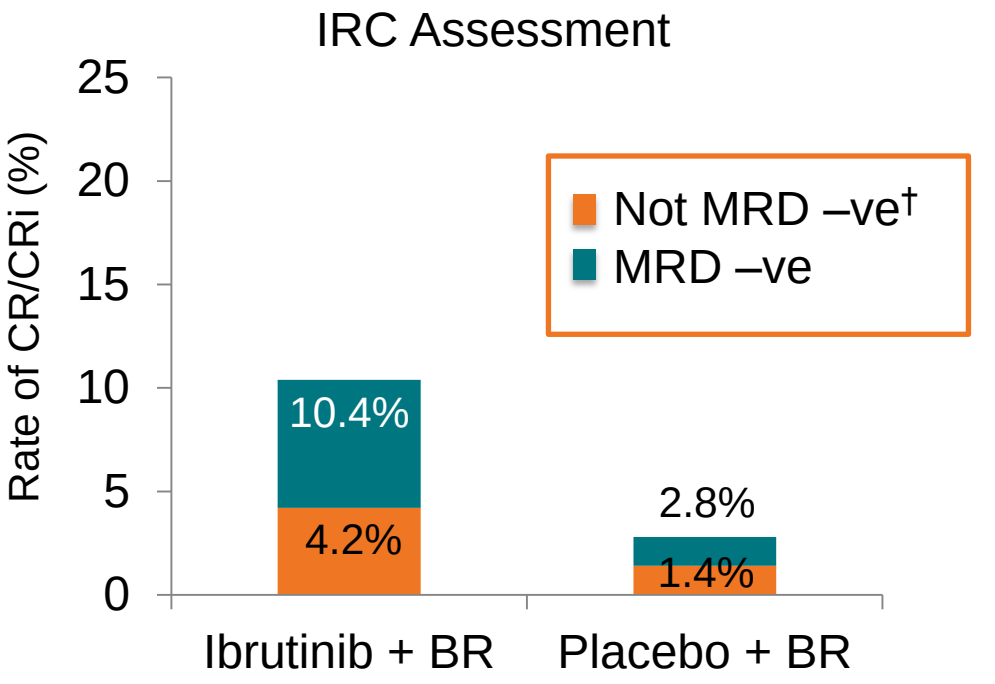
As of 1st Sept, 2015, 131 patients on the placebo arm have crossed over to receive ibrutinib

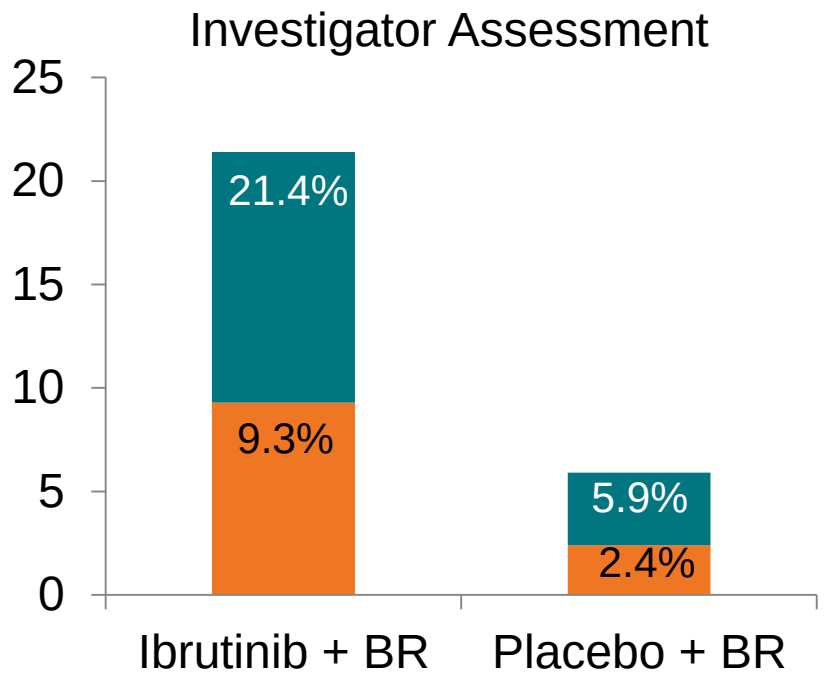
- Primary end point: PFS (by IRC)
- Secondary end points: ORR (by IRC), OS, rate of MRD-negative response, safety

Chanan-Khan et al. J Clin Oncol 2015; 33(suppl): abstract LBA7005 (oral presentation)

MRD negativity in CR/CRi Responders

ITT Population	Ibrutinib + BR (N = 289)	Placebo + BR (N = 289)	P-value
MRD –ve response*, n (%)	37 (12.8)	14 (4.8)	0.0011



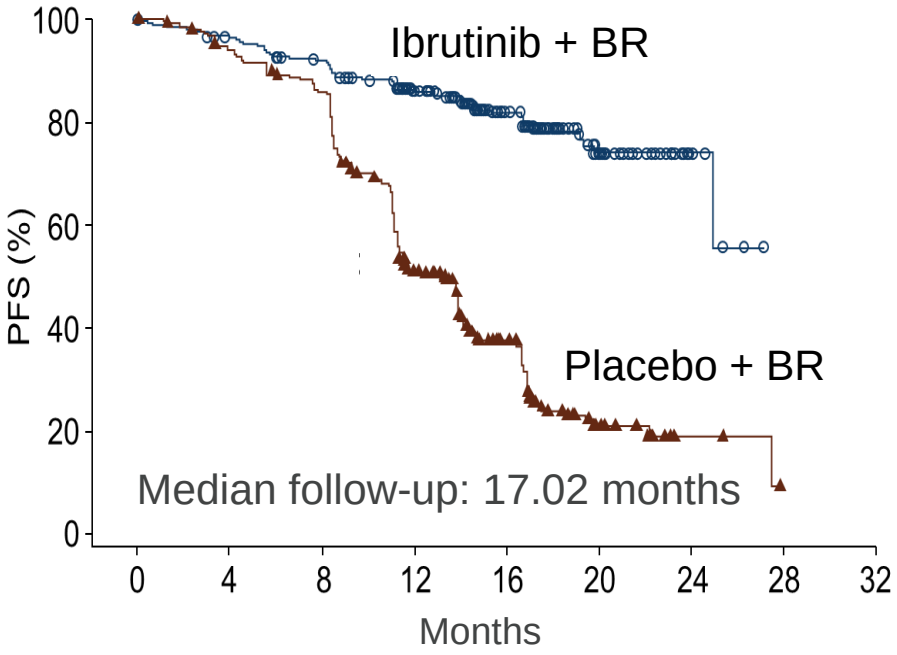


†Includes patients with missing MRD data.

Chanan-Khan et al. J Clin Oncol 2015; 33(suppl): abstract LBA7005 (oral presentation)

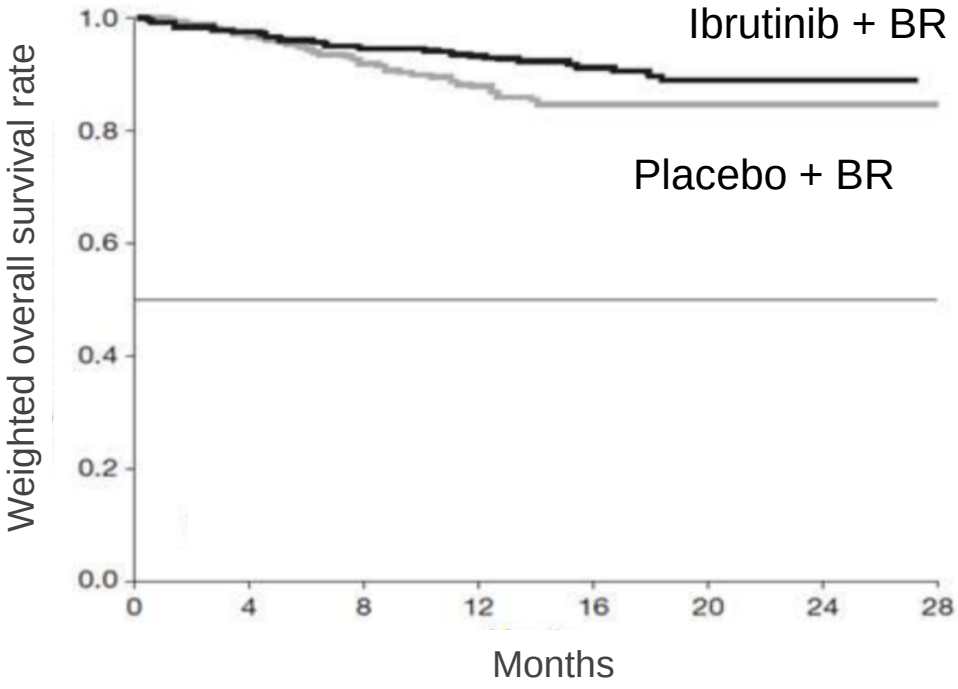
HELIOS: Superior PFS and OS

Progression Free Survival[1]



HR: 0.203 (95% CI, 0.15 – 0.28), **P<0.0001**

Overall Survival*[2]



HR: 0.58 (95% CI, 0.35 – 0.96), **P<0.05**

*adjusted for crossover

1. Chanan-Khan et al. J Clin Oncol 2015; 33(suppl): abstract LBA7005 (oral presentation)
2. Frasser et al. iwCLL 2015 (oral presentation)

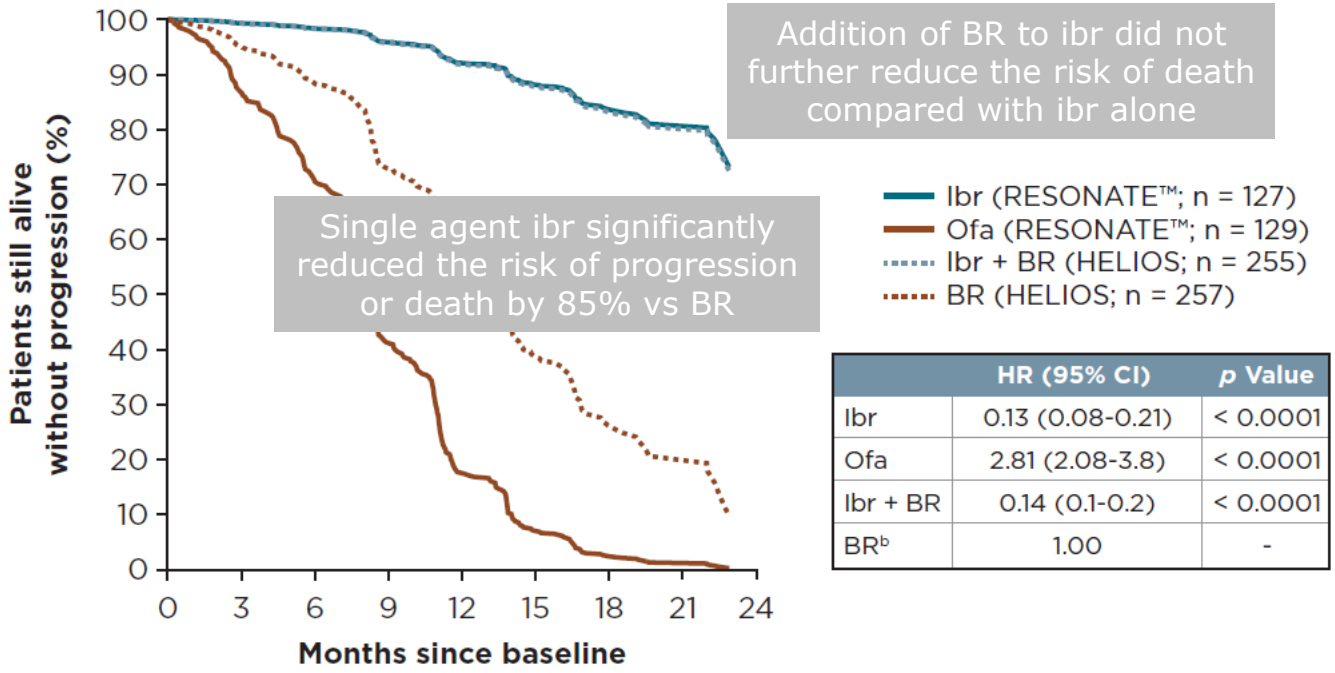
Indirect Comparison of RESONATE and HELIOS Phase 3 Trials of Ibrutinib in CLL/SLL: Efficacy

	PFS, HR (95% CI [P-value])	OS, HR (95% CI [P-value])
IBR (n=132)	0.15 (0.09, 0.23) [P<0.0001]	0.51 (0.27, 0.96) [P=0.0371]
OFA (n=132)	2.96 (2.2, 3.98) [P<0.0001]	1.24 (0.71, 2.16) [P=0.4419]
IBR + BR (n=287)	0.16 (0.11, 0.22) [P<0.0001]	0.60 (0.36, 0.99) [P=0.0439]
BR (n=289)†	1.00	1.00

*del17p patients are excluded, †BR used as a reference treatment

Hillmen P et al., ASH 2015 (abstract 2944, poster presentation)

RESONATE vs HELIOS: Predicted PFS by treatment in patients with CLL



	HR (95% CI)	*p* Value
Ibr	0.13 (0.08-0.21)	< 0.0001
Ofa	2.81 (2.08-3.8)	< 0.0001
Ibr + BR	0.14 (0.1-0.2)	< 0.0001
BR[b]	1.00	-

- Ibrutinib more effective than BR: PFS (HR 0.15) and OS (HR 0.51)
- Ibrutinib and ibrutinib + BR have similar PFS and OS; longer-term follow-up needed to understand whether the deeper responses with ibrutinib + BR will translate to improved PFS and OS
- These results support ibrutinib as appropriate choice for R/R CLL

What has changed in CLL with ibrutinib?

1. Ibrutinib is the treatments of choice for:
   a. Refractory CLL
   b. 17p deleted CLL – frontline or relapsed
   c. Relapsed CLL (?all patients or depending on length of previous remission)
2. Ibrutinib is the treatment of choice for patients in frontline CLL who are unfit for FCR (1 trial compared to single agent chlorambucil)
3. FCR remains the treatment of choice for frontline fit patients pending ongoing trials

What are the challenges and opportunities?

1. Change from short duration therapy to “maintenance”
   a. Compliance
   b. Resistance
   c. Affordability
   d. Patient selection – who are we curing with FCR?
2. Challenges/opportunities:
   a. Combination approaches ?limited duration of therapy, MRD eradication and cure
   b. Novel treatment modalities including Bcl2i (venetoclax), check-point inhibitors, novel MoAb, CAR-T-cells, etc.
   c. Role of allogeneic SCT

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National Cancer Research Institute

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Bloodwise
Beating blood cancer since 1960