Updated Efficacy and Safety From the Phase 3 RESONATE-2™ Study: Ibrutinib As First-Line Treatment Option in Patients 65 Years and Older With Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Abstract 234

Barr P, Robak T, Owen C, Tedeschi A, Bairey O, Bartlett N, Burger J, MD, Hillmen P, Coutre S, Devereux S, Grosicki S, McCarthy H, Li J, Simpson D, Offner F, Moreno C, Zhou C, Styles L, James D, Kipps TJ, Ghia P

Background

- **CLL: older population with frequent comorbidities[1]**
  - **Fludarabine-based regimens unsuitable for frail or older patients[2]**
  - **Chlorambucil: has been a standard first-line therapy in older patients**
- **Ibrutinib: first-in-class, oral, covalent BTK inhibitor**
  - **Approved by FDA and EMEA for CLL and allows for treatment without chemotherapy in all lines of therapy**
- **Phase II PCYC-1102/1103 study: treatment-naïve (TN) CLL[3]**
  - **With extended treatment (median 46 mo), complete response (CR) rate has increased (29%), with 65% of patients continuing on therapy**
- **Phase III PCYC-1115 (RESONATE-2™): ibrutinib in TN CLL/SLL patients ≥65 years of age[4,5]**
  - **Superior PFS, OS, ORR, and hematologic improvement, and a tolerable safety profile of ibrutinib vs chlorambucil**
  - **84% reduction in the risk of death at median follow-up of 18.4 months**
- **Current analysis is with median follow-up of 29 months**

CLL, chronic lymphocytic leukemia; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SLL, small lymphocytic lymphoma

1. Thurmes P, et al. *Leuk Lymphoma*. 2008;49(1):49-56. 2. Eichhorst BF, et al. *Blood*. 2009;114(16):3382-3391. 3. O'Brien S, et al. *Blood.* 2016;128: Abstract 233. 4. Burger JA, et al. *N Engl J Med*. 2015;373(25):2425-2437. 5. Tedeschi A, et al. *Blood.* 2015;128: Abstract 495.
Barr P, et al. *Blood.* 2016;128: Abstract 234.

RESONATE-2 (PCYC-1115/1116) 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

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

RANDOMIZE 1:1

ibrutinib 420 mg once daily until progression

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

CLL progression or 1115 study closure

PCYC-1116 Extension Study*

In clb arm, n = 55 crossed over to ibrutinib following PD

Efficacy (PFS, OS, ORR) determined by investigator-assessment.

*Patients could enroll in separate extension study PCYC-1116 after independent review committee–confirmed PD or at study PCYC-1115 closure for continuing treatment and follow-up.

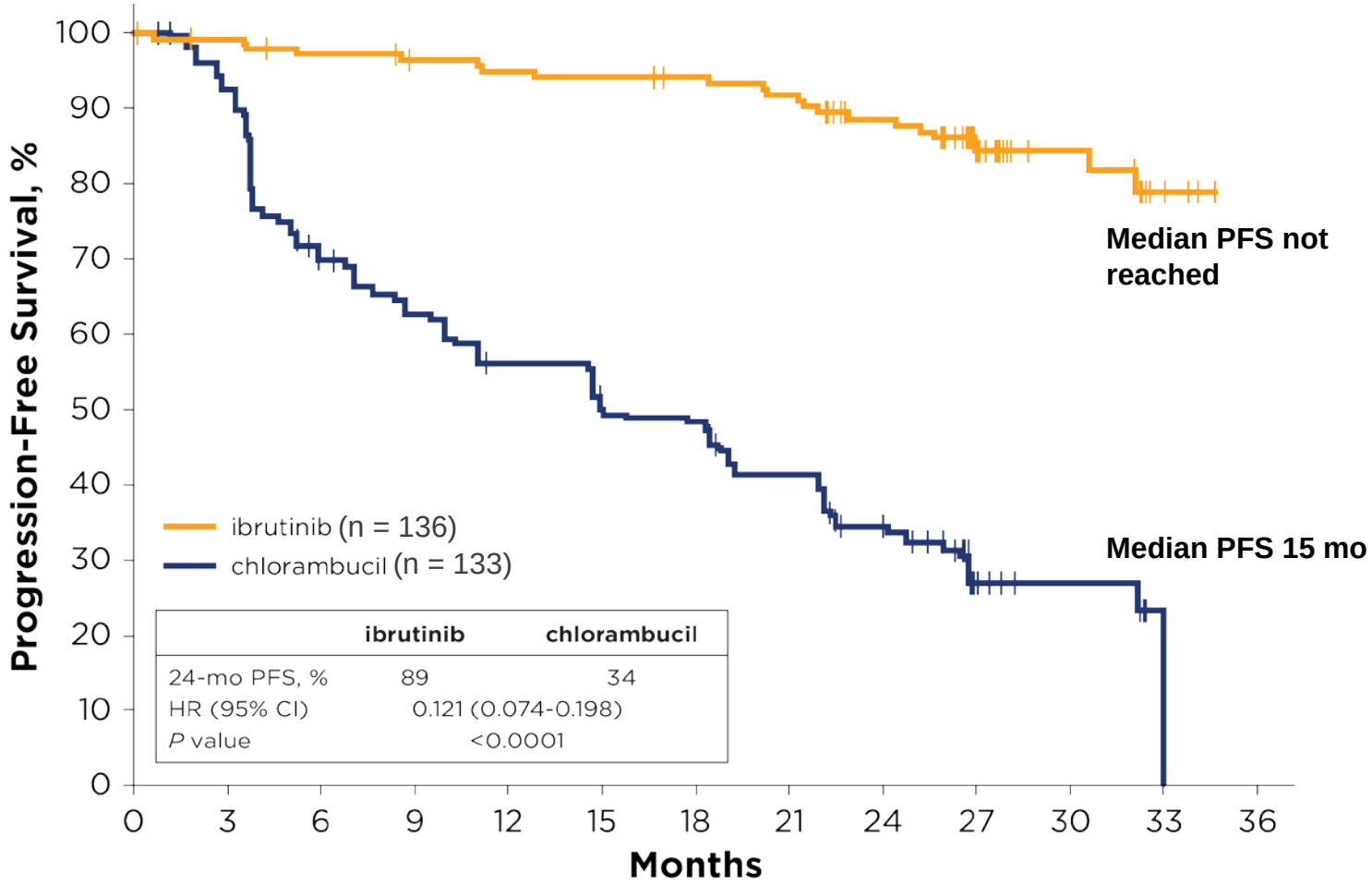
Barr P, et al. *Blood.* 2016;128: Abstract 234.

Patient Characteristics

Characteristic	Ibrutinib (n = 136)	Chlorambucil (n = 133)
Median age, years (range)	73 (65–89)	72 (65–90)
≥70 years, %	71	70
ECOG performance status, %		
1	48	50
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 x 10^9/L, %	26	21
Del11q, %	21	19
Unmutated IGHV, %	43	45

Barr P, et al. *Blood.* 2016;128: Abstract 234.

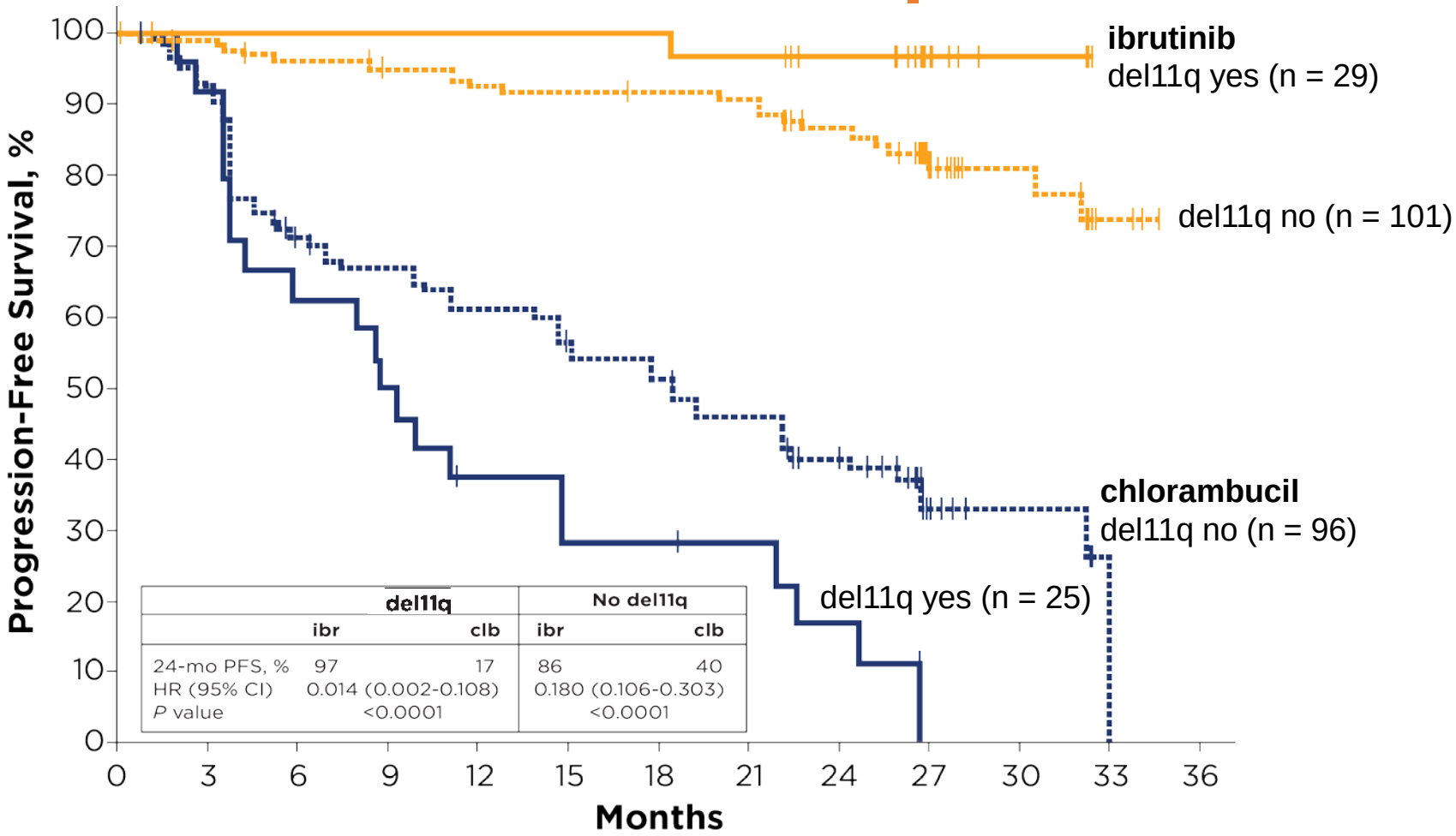
Ibrutinib Prolonged PFS Over Chlorambucil



- 88% reduction in the risk of progression or death for patients randomized to ibrutinib
- Subgroup analysis of PFS revealed that benefit was observed across all subgroups

Barr P, et al. *Blood.* 2016;128: Abstract 234.

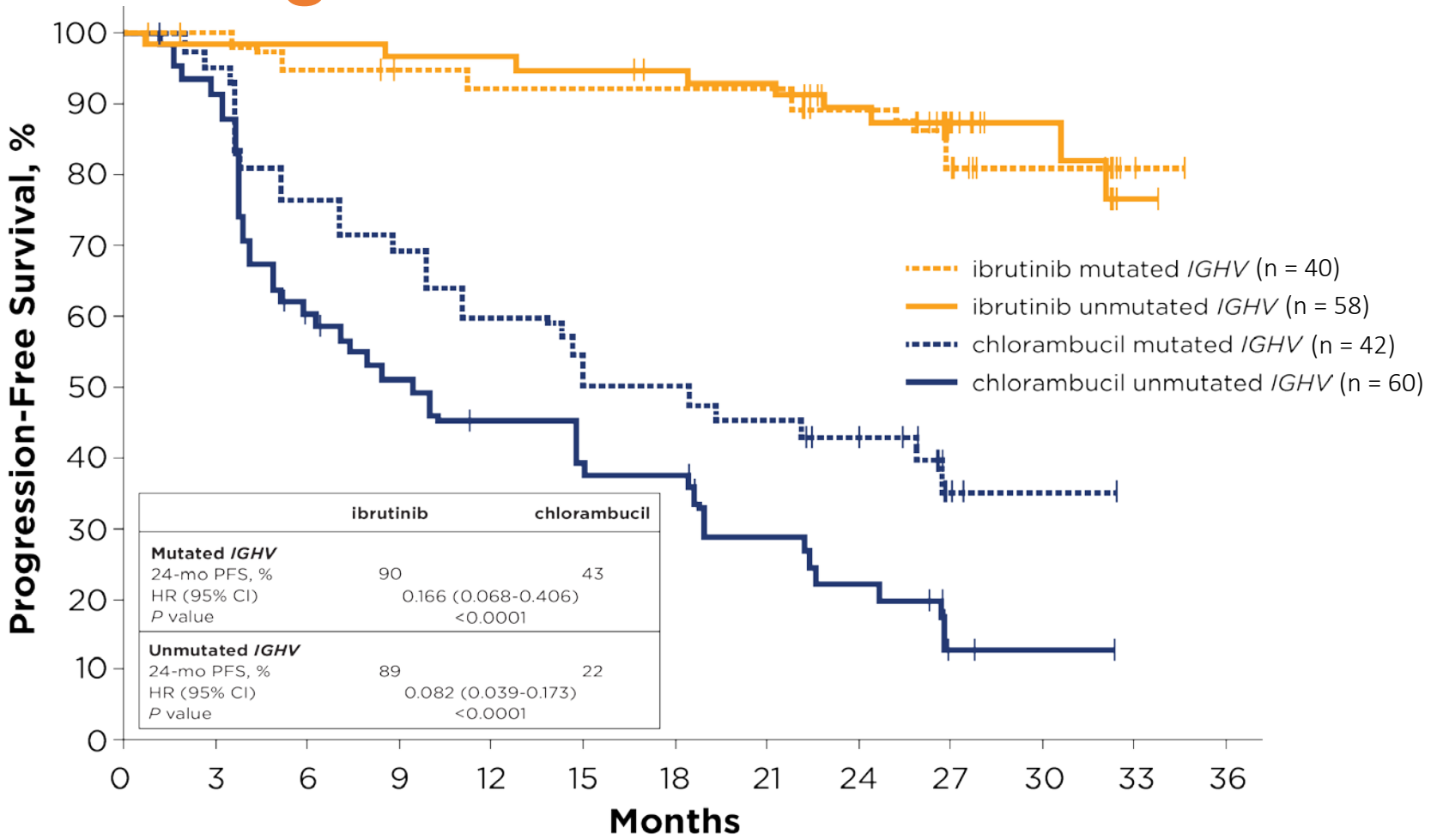
Ibrutinib Significantly Improved PFS in Patients With Del11q



- In del11q subgroup, Ibrutinib led to 99% reduction in risk of progression or death and 82% reduction in those without del11q, compared to chemotherapy

Barr P, et al. *Blood.* 2016;128: Abstract 234.

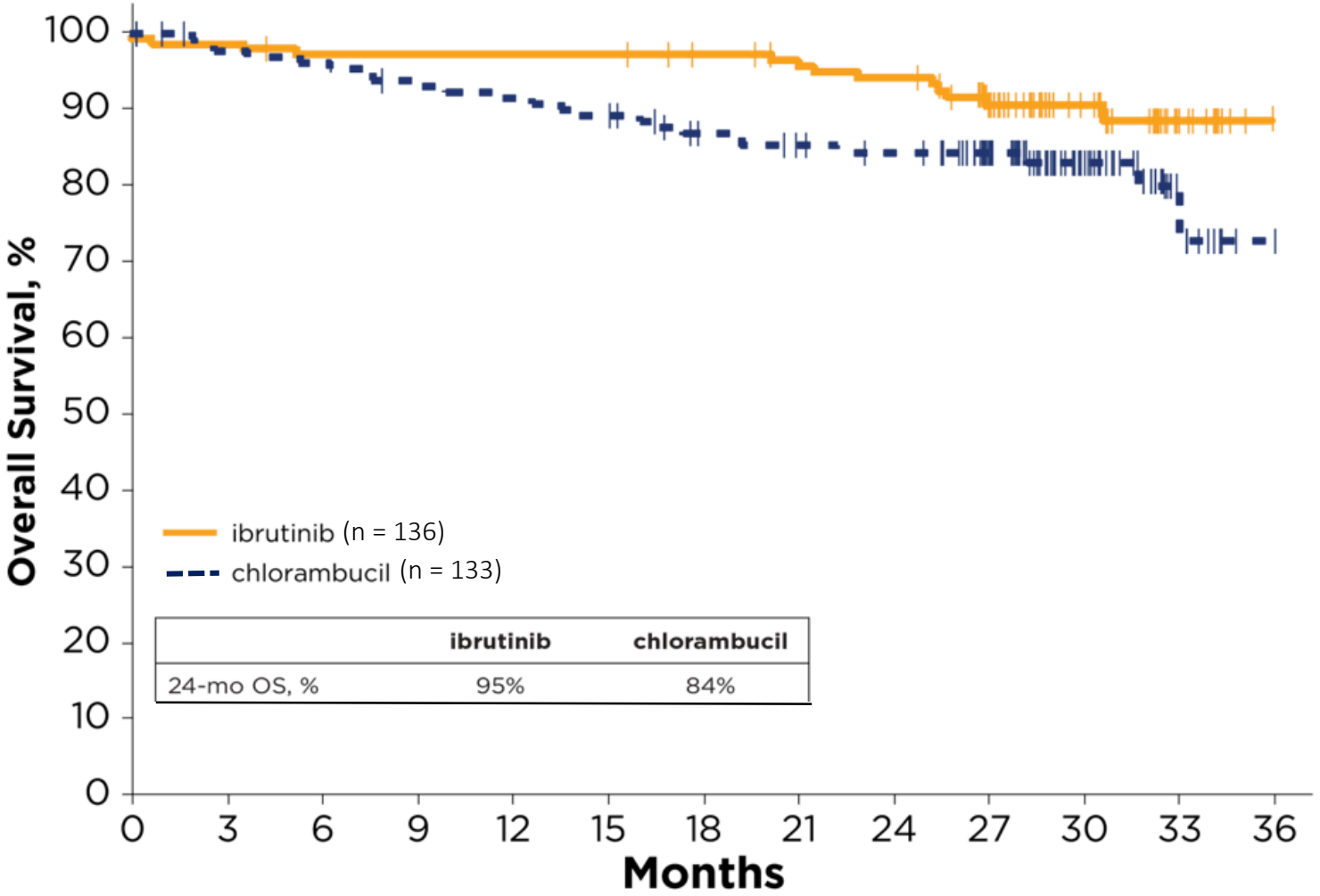
Ibrutinib Significantly Improved PFS in Patients Regardless of *IGHV* Status



- Ibrutinib led to 83% and 92% reduction in the risk of progression or death in patients with mutated and unmutated *IGHV*, respectively, compared to chemotherapy

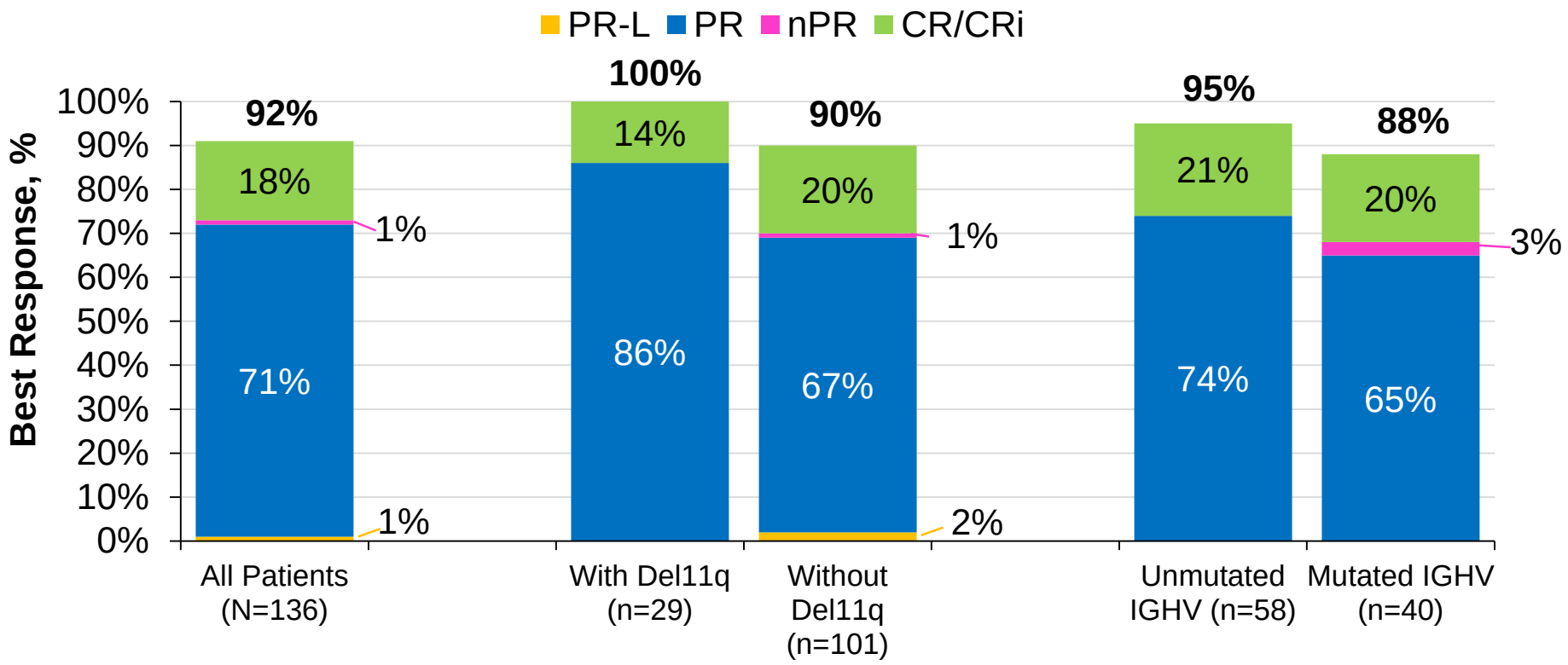
Barr P, et al. *Blood.* 2016;128: Abstract 234.

Ibrutinib Continues to Demonstrate OS Benefit Over Chlorambucil With Longer Follow-Up and Cross-Over



Barr P, et al. *Blood.* 2016;128: Abstract 234.

ORR in the Ibrutinib* Arm



- Ibrutinib CR rates continue to improve over time: increasing from 7% at 12 months to 15% at 24 months to 18% with median follow-up of 29 months.

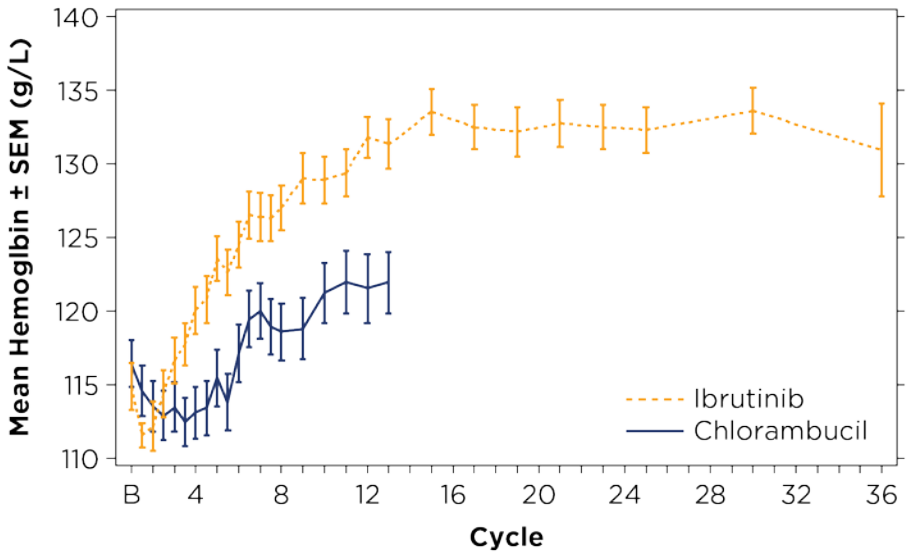
**Response rates with chlorambucil are the same as in the original report (Burger NEJM 2015)*

Barr P, et al. *Blood.* 2016;128: Abstract 234.

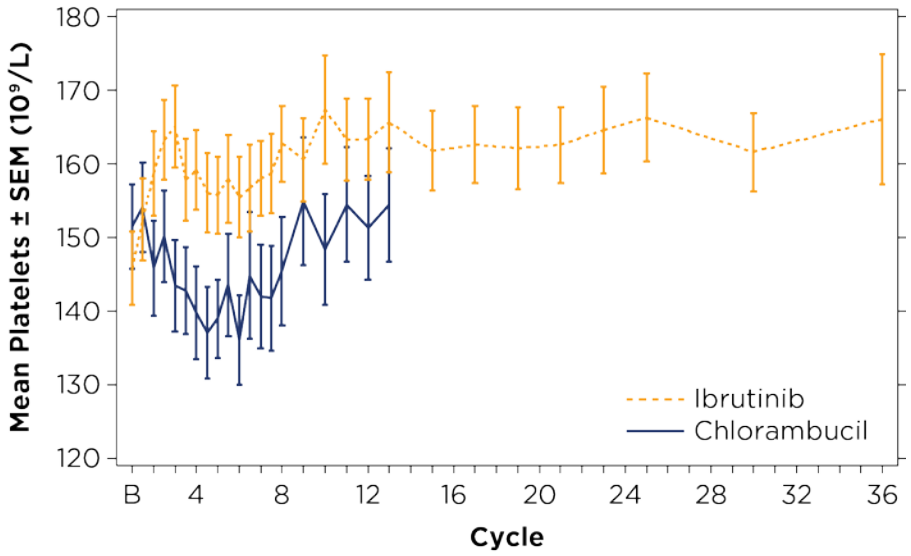
CR, complete response; CRi, CR with incomplete blood count recovery

Improvement in Hematologic Function

Hemoglobin Over Time



Platelet Count Over Time



- Sustained improvement in hemoglobin in patients with anemia: 90% with ibrutinib vs 45% with chlorambucil (*P*<.0001)
- Sustained improvement in platelet counts in patients with thrombocytopenia: 80% with ibrutinib vs 46% with chlorambucil (*P* = .0055)

Barr P, et al. *Blood.* 2016;128: Abstract 234.

Most Patients Remain on Ibrutinib Treatment

	First-Line Ibrutinib n = 135
Median duration of ibrutinib treatment, mo (range)	29 (1-36)
Treatment duration, n (%)	
≤12 months	14 (10)
>12-24 months	9 (7)
>24-36 months	112 (83)
Continuing ibrutinib on study, n (%)	107 (79)
Discontinued ibrutinib, n (%)	28 (21)
Disease Progression	4 (3)
AEs	16 (12)
Death	6 (4)
Withdrawal of consent	2 (1)
Investigator decision	0

- 79% of patients continue on ibrutinib treatment on study with 83% of patients receiving at least 2 years of treatment

Barr P, et al. *Blood.* 2016;128: Abstract 234.

Most Frequent AEs in Ibrutinib Arm

Ibrutinib Arm n = 135						
Adverse Event, %	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Any Grade**
Diarrhea	30	12	4	0	0	45
Fatigue	22	10	2	0	0	33
Cough	22	6	0	0	0	28
Anemia	6	10	6	1	0	23
Nausea	16	7	1	0	0	23
Peripheral edema	15	5	1	0	0	21
Arthralgia	11	7	2	0	0	20
Pyrexia	13	7	1	0	1	20

- Additional AEs of clinical interest
  - Major hemorrhage occurred in 7% of ibrutinib-treated patients (1 Grade 2, 7 Grade 3, 1 Grade 4; 5 in first 12 months and 4 between 1-2 years)
  - Atrial fibrillation occurred in 10% of ibrutinib-treated patients (1 Grade 1, 7 Grade 2, 6 Grade 3)
  - No PJP occurred

Barr P, et al. *Blood.* 2016;128: Abstract 234.

AE, adverse event

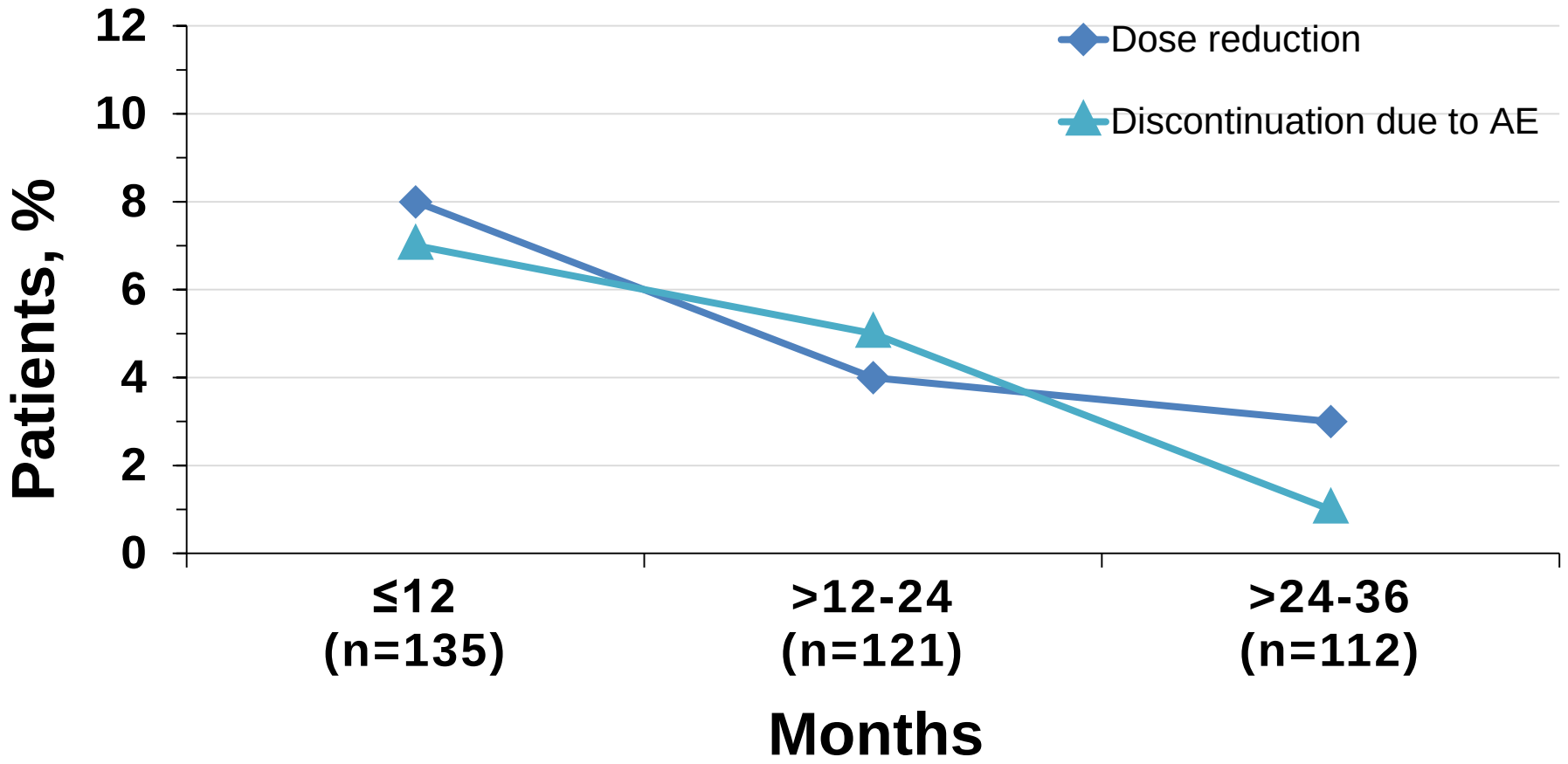
Treatment-Emergent AEs (≥Grade 3) Over Time in First-Line Ibrutinib Patients (≥4% Over 29 Months Median Follow-Up)

	Ibrutinib Arm		
	0-≤12 months (n = 135), %	>12-24 months (n = 123), %	>24-36 months (n = 112), %
Neutropenia	8	4	0
Pneumonia*	5	2	1
Anemia	6	1	1
Hypertension	4	2	0
Hyponatremia	2	2	0
Atrial fibrillation	1	0	4

- Grade ≥3 AEs in ≥4% of patients over the 29 mo follow-up: neutropenia (12%), pneumonia (7%), anemia (7%), hypertension (5%), hyponatremia (4%), and atrial fibrillation (4%)
- Most Grade ≥3 AEs in ibrutinib-treated patients decreased over time

Barr P, et al. *Blood.* 2016;128: Abstract 234.

Dose Reduction and Discontinuation Rates Decrease Over Time for First-Line Ibrutinib



- AEs in ≥2 patients leading to discontinuation of ibrutinib: hemorrhage (3), infection (3), atrial fibrillation (2), and rash (2)

Barr P, et al. *Blood.* 2016;128: Abstract 234.

Outcomes Following First-Line Ibrutinib Discontinuation

Patients Evaluated for Outcomes	Discontinued Due to AE n = 16	Discontinued Due to PD n = 4	Discontinued Due to Any Cause n = 22
Median follow-up, mo	13	10	13
Median OS, mo	NR	NR	NR
Remain alive, n (%)	13 (81)	2 (50)	16 (73)

- Of 7 patients who received subsequent therapy (FCR [n = 3], BR [n = 2], chlorambucil [n = 1], radiation [n = 1], 6 (86%) remained alive with median 21 (range: 9-25) months follow-up.
  - Current data reflect that 2 BR patients achieved a PR; 1 FCR and 1 chlorambucil achieved a PR. The other 2 FCR patients did not continue into the extension study, so their response information is not available

Barr P, et al. *Blood.* 2016;128: Abstract 234.

BR, bendamustine + rituximab; FCR, fludarabine + cyclophosphamide + rituximab.

Conclusions

- **With a median time on study of 29 months, ibrutinib continued to have substantial efficacy, with 88% reduction in risk of progression or death compared to chlorambucil**
  - **24-mo PFS: 89% vs 24%**
  - **24-mo OS: 95% vs 84%, reflects 55 patients who crossed over to ibrutinib**
- **Within the ibrutinib arm, robust outcomes were observed for those with del11q or unmutated *IGHV***
  - **In the chlorambucil arm, patients with del11q or unmutated *IGHV* experienced inferior outcomes**
- **The quality of responses has improved over time, with 18% of CLL/SLL patients achieving a CR/CRi with single-agent ibrutinib**
- **Rates of treatment-limiting AEs, including dose reductions and discontinuations, decreased over time, with 79% of this elderly patient population continuing daily ibrutinib**

Barr P, et al. *Blood.* 2016;128: Abstract 234.