Efficacy and Safety of Ibrutinib in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma With 17p Deletion: Results From the Phase II RESONATE™-17 Trial

Abstract 327

**O'Brien S, Jones JA, Coutre SE,
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Furman RR, Ilhan O, Keating M, Call TG, Brown JR, Stevens-Brogan M,
Li Y, Fardis M, Clow F, James DF, Chu AD, Hallek M, Stilgenbauer S**

Introduction

- **CLL with del17p associated with aggressive clinical course**
  - **Median survival <2 years in relapsed/refractory (R/R) CLL**
  - **Median PFS 11 months in front-line CLL with fludarabine, cyclophosphamide, and rituximab (FCR) or alemtuzumab[1,2]**
- **Ibrutinib: first-in-class, once-daily, oral, covalent BTK inhibitor indicated for**
  - **Patients with CLL who received at least 1 therapy**
  - **Patients with previously untreated del17p CLL**
- **Phase III RESONATE™ study: significant PFS and OS benefit, compared with ofatumumab, in previously-treated CLL with single-agent ibrutinib[3]**

1. Hallek M, et al. *Lancet*. 2010;376(9747):1164-1174; 2. Hillmen P, et al. *J Clin Oncol*. 2007;10(35):5616-5623; 3. Byrd JC, et al. *N Engl J Med*. 2014; 371(3):213-223.

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PCYC-1117 (RESONATE™-17) Study Design

Key eligibility criteria
- CLL/SLL
- Documentation of del17p13.1 in peripheral blood by FISH analysis*
- R/R disease after ≥1 prior therapy
- ECOG PS 0-1
- Measurable nodal disease

Single-agent ibrutinib in del17p CLL/SLL

Ibrutinib 420 mg PO daily until unacceptable toxicity or disease progression (N = 144)

Primary analysis 12 months after last patient enrolled

*Cut-off for del17p was >7% positive cells.

- **Phase II, open-label, single-arm, multicenter, international study**
- **Primary endpoint: ORR as evaluated by IRC (2008 IWCLL criteria)[1,2]**
- **Secondary endpoints: DOR, safety, tolerability**
- **Exploratory endpoints: PFS, OS**

1. Hallek M, et al. *Blood*. 2008;111(12):5446-5456; 2. Hallek M, et al. *Blood.* 2012; 210 June 04 (e-letter).

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Baseline Characteristics

Characteristics	Ibrutinib (N = 144)
CLL / SLL	95% / 5%
Median age (range), years	64 (36-89)
Rai stage III-IV	63%
Bulky disease ≥5 cm / ≥10 cm	49% / 10%
Median % del17p cells (range)	65.5% (7.5-96.5)
Del11q	16%
Median β2 microglobulin (range), mg/L	5 (2-20)
β2 microglobulin ≥3.5 mg/L	78%
Median lactate dehydrogenase (range), U/L	258 (127-1979)
Lactate dehydrogenase ≥250 U/L	53%
Median ALC x 10^9/L (range)	33 (0.4-385)
ALC ≥25.0 x 10^9/L	57%
Median hemoglobin (range), g/dL	11 (6-16)
Median platelet count x 10^9/L (range)	112 (26-637)

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Baseline Characteristics (cont'd)

Characteristics	Ibrutinib (N = 144)
Median number of prior therapies (range)	2 (1-7)
≥3 prior therapies	39%
Prior types of therapies	
Alkylating agent	81%
Purine analog	60%
Regimens with anti-CD20 antibody	74%
Alemtuzumab	22%
Lenalidomide or thalidomide	5%
PI3K inhibitor	2%

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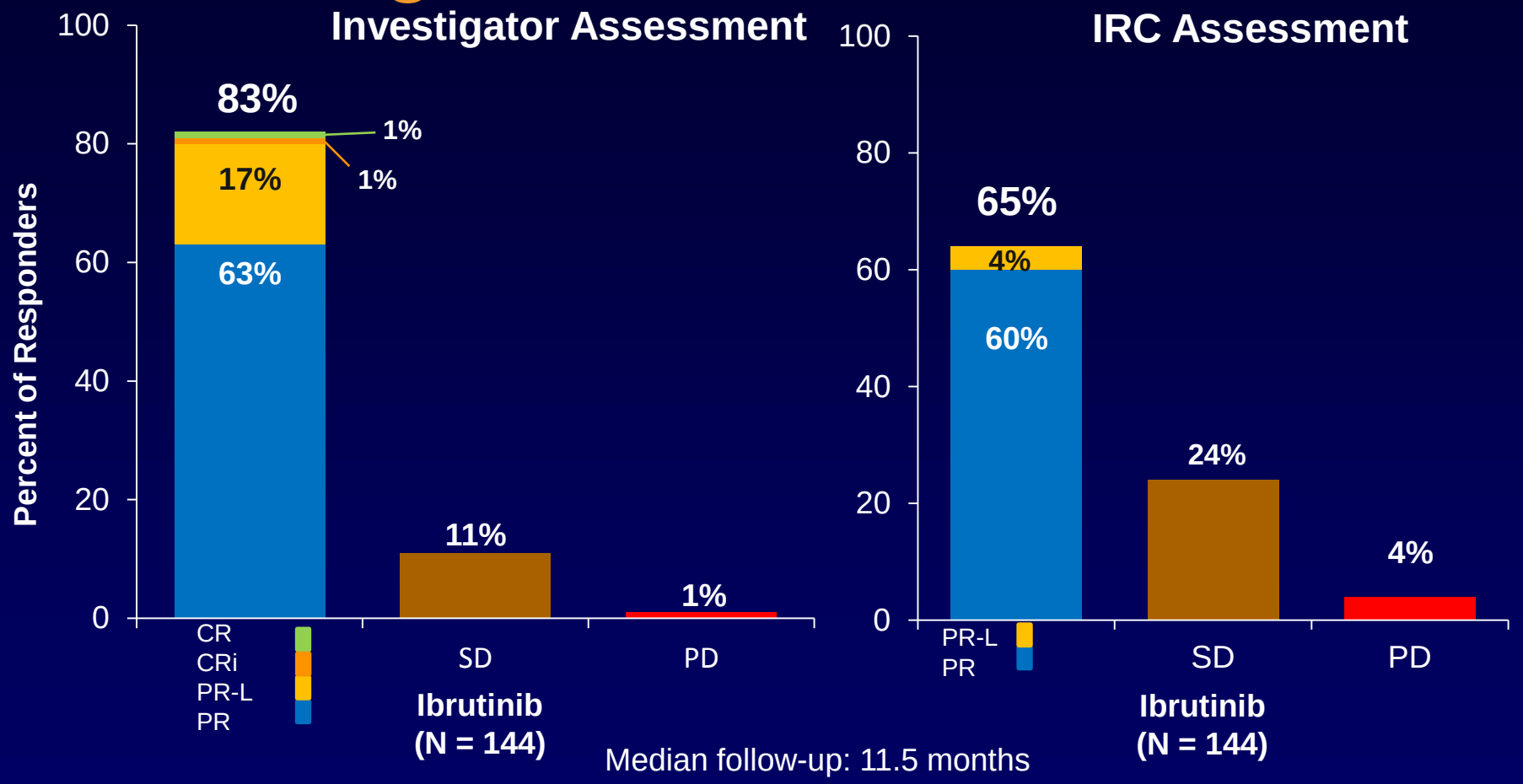
Overall Response: Investigator and IRC Assessment



Median follow-up: 11.5 months

- **Best response (ORR+PR-L) by IRC without second confirmatory CT scan: 74% (95% CI: 66-80)**
- **Median DOR was not reached; 12-month DOR rate: 88.3%**

Unknown/missing/not applicable/not evaluable: 6% (8/144); PR-L, partial response with lymphocytosis.
Confirmed responses by IRC required second confirmatory CT scan performed at least 2 months after the first scan.

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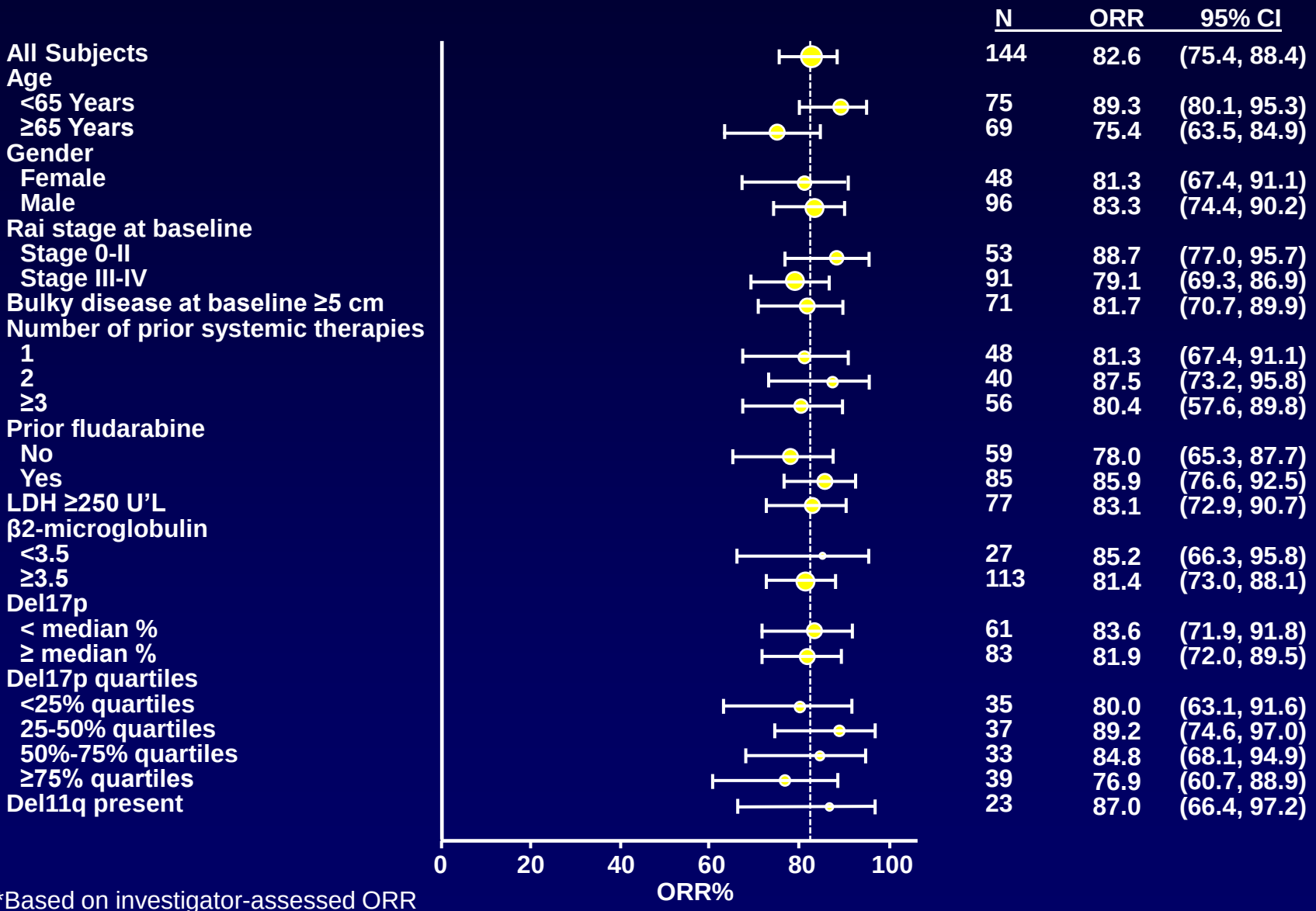
Overall Response Rate* by Subgroup



*Based on investigator-assessed ORR

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Sustained Hematologic Improvement*

Improvement in Hematologic Parameters	n (%)
Patients with any baseline cytopenia, n = 91	70 (77)
Baseline neutropenia (ANC ≤1.5 x 10^9/L), n = 26	22 (85)
Baseline anemia (Hgb ≤11 g/dL), n = 63	33 (52)
Baseline thrombocytopenia (PLT ≤100 x 10^9/L), n = 58	42 (72)

*Sustained hematologic improvement defined as increase of ≥50% over baseline (or above normal) in a hematologic parameter that was sustained continuously for ≥56 days without blood transfusion or growth factors.

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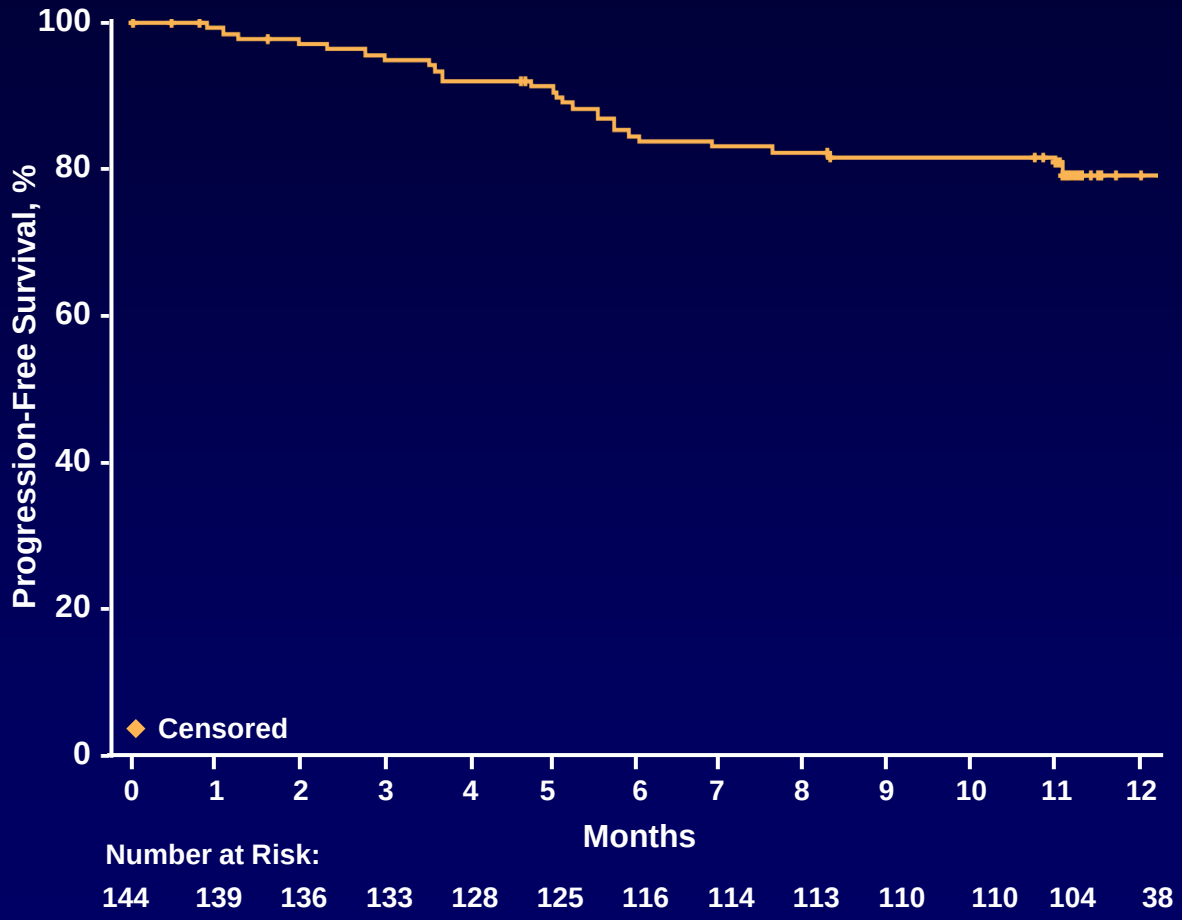
Progression-Free Survival



- **Median PFS not reached**
- **Median follow-up 11.5 months**

	N	12-month PFS rate
Overall	144	79.3%
Del17p quartiles		
<25%	35	85%
25%-50%	37	81%
50%-75%	33	83%
≥75%	39	69%

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Characteristics of Patients With PD (n = 20)

Baseline Characteristic	Richter's* (n = 11)	Non-Richter's PD (n = 9)	Non-PD (n = 124)
Median % del17p cells (range)	65% (13-92)	86% (9-95)	65% (8-97)
Del11q present, %	0	11%	18%
Median β2 microglobulin (range), mg/L	7 (3.6-9.3)	6 (2.6-16)	5 (1.8-19.8)
Median LDH (range), U/L**	471 (229-916)	327 (162-495)	249 (127-1979)
Median number of prior therapies (range)	2 (1-4)	2 (1-5)	2 (1-7)
Bulky disease			
>5 cm	64%	100%	44%
>10 cm	18%	22%	9%
Median time to PD (range), days	158 (31-337)	232 (86-421)	NA

*10 of 11 Richter's cases occurred within first 6 months (183 days); **ULN at central lab: 250 U/L

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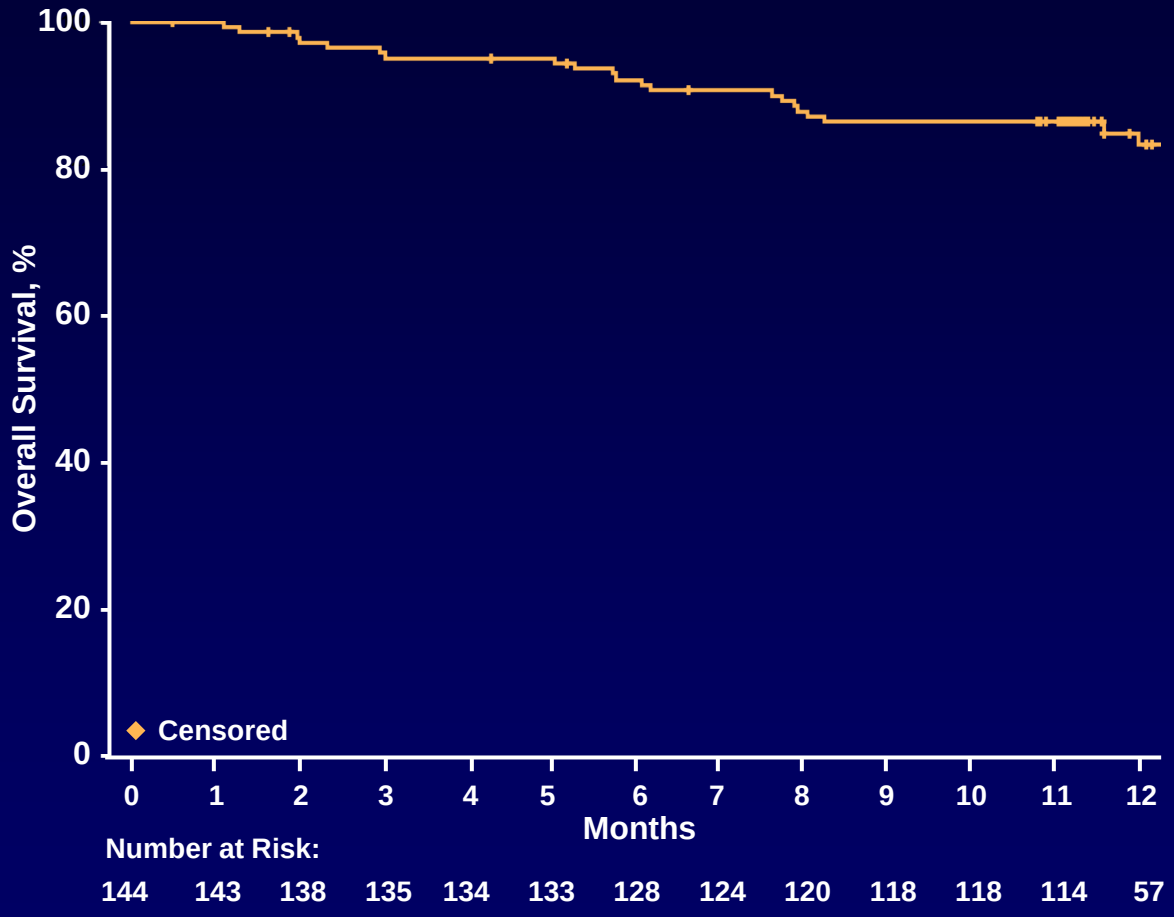
Overall Survival



- **Median OS not reached**
- **Median follow-up 11.5 months**

	N	12-month OS rate
Overall	144	83.5 %
Del17p quartiles		
<25%	35	85%
25%-50%	37	89%
50%-75%	33	86%
≥75%	39	76%

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Patient Disposition in All-Treated Population

Disposition	Ibrutinib (N = 144)
Discontinued study treatment	43 (30%)
Ongoing in treatment phase	101 (70%)
Median time on study at time of analysis, months (range)	11.5 (0.5-16.6+)
Primary reason for discontinuation	
Progressive disease	18 (13%)
AE/unacceptable toxicity*	16 (11%)
Patient withdrawal	3 (2%)
Deaths	2 (1%)
Investigator decision	
Withdrawal due to SCT	3 (2%)
Other**	1 (1%)

***Among these patients, 10 (7%) eventually had fatal events (pneumonia, sepsis, myocardial, or renal infarction, health deterioration); **Patient insurance expired**

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Treatment-Emergent Adverse Events (≥15% of Patients) Regardless of Attribution

Adverse event	Ibrutinib (N = 144)	
	Any grade, %	Grade 3-4, %
Diarrhea	36	2
Fatigue	31	1
Cough	24	<1
Arthralgia	22	1
Nausea	19	0
Hypertension	19	8
Anemia	19	8
Pyrexia	17	1
Decreased appetite	17	1
Muscle spasms	17	0
Neutropenia	17	14
Peripheral edema	15	<1

TEAE, treatment-emergent AEs were reported in all patients receiving study drug

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Safety Overview
Infections and Malignancies

Adverse Event	Ibrutinib (N = 144), %
Any grade ≥3 infection AE (in >1 patient)	24
Pneumonia	10
Urinary tract infection	3
Bronchitis	1
Cellulitis	1
Herpes zoster	1
Bacteremia	1
Sepsis	1
Septic shock	1
Skin cancers (squamous cell carcinoma or BCC)	5
Non-skin cancer	1

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Safety Overview
Atrial Fibrillation, Bleeding-Related Events and TLS

- **Atrial fibrillation of any grade (n=11; 8%)**
  - **Including grade 3-4 in 3.5% of patients**
  - **No treatment discontinuations; no grade 5 events**
  - **5 patients had history of atrial fibrillation**
- **Major bleeding, all grade 2 or 3 (n=7; 5%)**
  - **Intracranial hemorrhage, spontaneous hematoma*, traumatic hematoma, gastric ulcer hemorrhage, hematuria, hemoptysis, intercostal artery hemorrhage: 1 patient each**
    - Concomitant meds: anticoagulation (2 patients), aspirin (1 patient)
    - Factor XI deficiency in 1 patient*
- **Tumor lysis syndrome (n=1; <1%)**
  - **Non-serious event in the setting of PD on day 157, 1 day after discontinuation**

*Spontaneous hematoma; platelet count <100 x 10^9/L at time of bleeding event.

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Conclusions

- **Ibrutinib is efficacious with a favorable risk-benefit profile in largest prospective study in del17p CLL/SLL**
  - **Best response (ORR including PR-L): 83%***
  - **Median PFS and DOR: not reached at median follow up 11.5 months**
  - **12-month PFS: 79%, consistent with previously-observed efficacy[1]**
- **PFS outcomes favorable compared to that of front-line del17p CLL treated with FCR or alemtuzumab (median PFS: 11 months)[2,3]**
- **Safety profile consistent with previous reports for ibrutinib[1]**
- **Ibrutinib effective in patients with del17p CLL/SLL**

*Based on investigator-assessed ORR

1. Byrd et al. NEJM. 2013;369:32-42; 2. Hallek et al. Lancet. 2010;376:1164-74; 3. Hillmen et al. J Clin Oncol. 2007;10:5616-23;

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