

***Front-line treatment with the combination
obinutuzumab-chlorambucil for CLL in real-world clinical
practice: results of a multinational, multicenter study by
the ERIC and the Israeli CLL study group***

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Introduction

- In recent years, considerable progress has been made in frontline therapy for elderly/physically unfit patients with CLL.
- The combination of obinutuzumab and chlorambucil (O-Clb) has been shown to prolong PFS and OS compared to chlorambucil alone.
- More recently, obinutuzumab given in combination with either ibrutinib or venetoclax improved PFS but not OS when compared to O-Clb.

Study objectives

- To examine the efficacy and safety of frontline treatment with O-Clb for CLL in a “real-world” setting
- To determine its relevance in the chemo-free era, particularly in patients with low-risk disease.

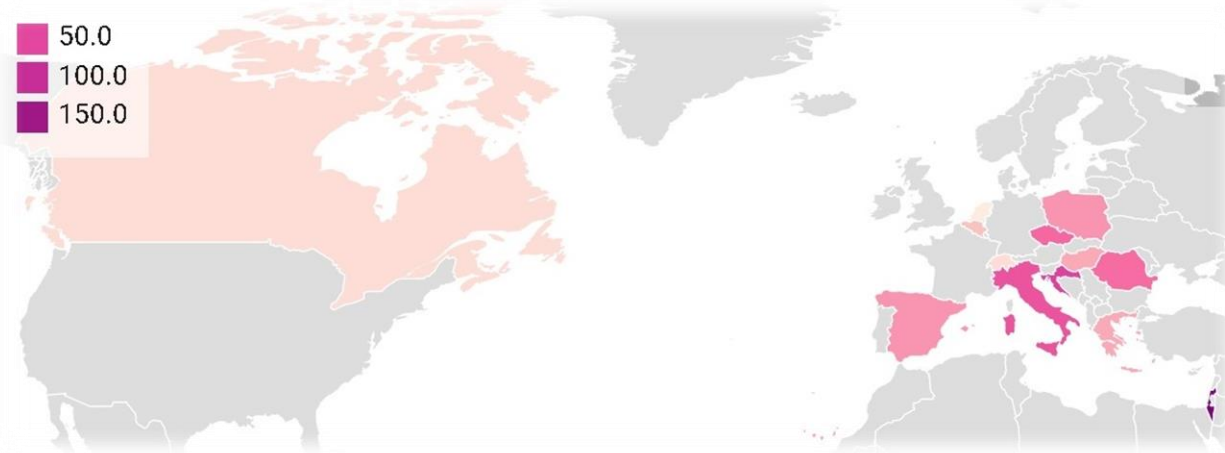
Study design

- A retrospective, multinational, multicenter co-operative study of the European Research Initiative on CLL (ERIC) and the Israeli CLL Study Group (ICLLSG)
- Included 437 patients from 51 centers in Europe, Israel, Canada and Argentina, treated during 2014-2019.
- Our analysis excluded cases with documented del(17p13.1) or *TP53* mutations, who are no longer treated with chemotherapy.

Total patients: 437

**Medical centers: 51
represent 40 cities,
located in 13 different
countries:**

- Belgium (5 patients)**
- Canada (3)**
- Croatia (56)**
- Czech Republic (33)**
- Greece (9)**
- Hungary (4)**
- Israel (187)**
- Italy (45)**
- The Netherlands (1)**
- Poland (35)**
- Romania (32)**
- Spain (19)**
- Switzerland (3)**



Patient characteristics

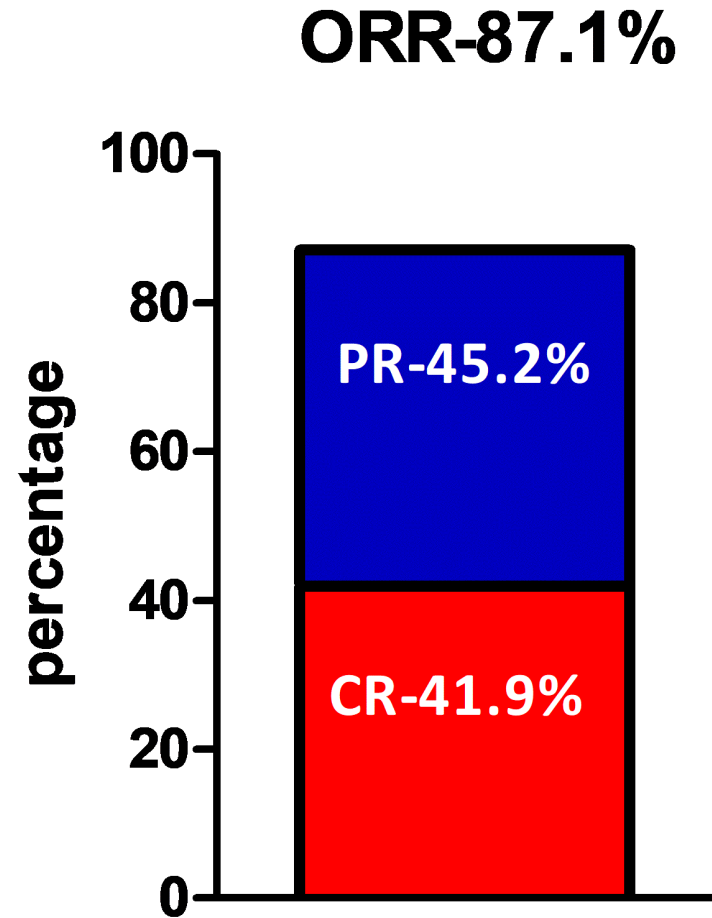
Median age (range)	75.9	(57.1-95.8)
	<u>N</u>	<u>%</u>
Male sex (N, %)	261	59.7
Binet (available = 431)		
A	74	17.2
B	167	38.8
C	190	44.1
Median CIRS Score (range)) (available = 337)	8 (0-46)	
Median calculated creatinine clearance, mL/min (available = 363)	61.1 (0.2 – 151.2)	
Median β -2-microglobulin (mg/L) (available=274)	4.3 (1.6 – 18.5)	
FISH (available = 333)		
Normal	134	40.2
del13q	92	27.6
Trisomy 12	45	13.5
del11q	62	18.6
IGVH mutational status (available = 115)		
Mutated	41	35.7
Unmutated	74	64.3
Bulky disease (available = 431)		
Lymph nodes diameter \leq 5cm	337	78.2
Lymph nodes diameter >5cm	94	21.8
Median follow-up time from initial diagnosis, months (range)	37 (<1-461)	

Dose modifications

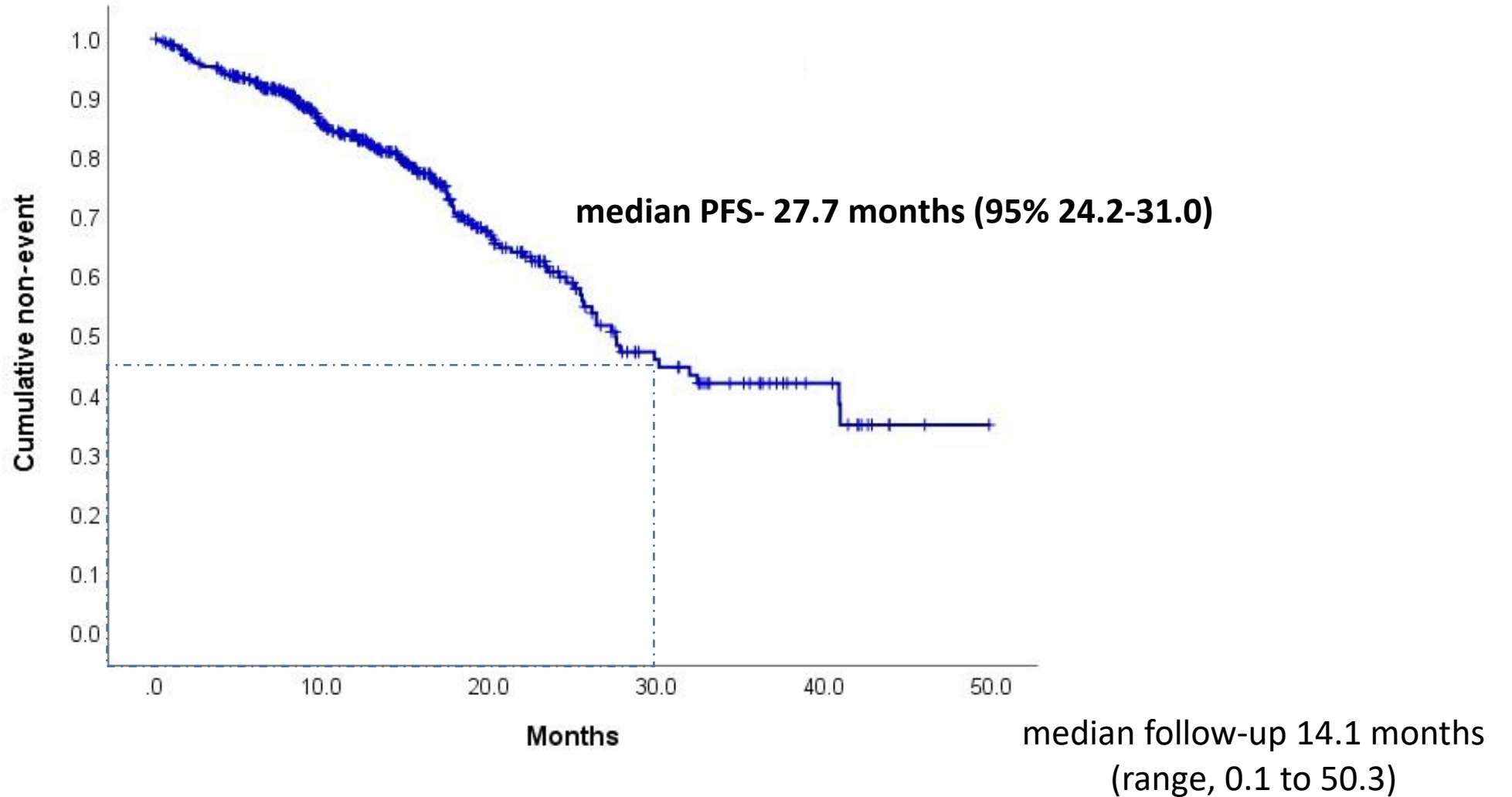
- 93.3% (n=408) of patients were treated with O-Clb.
- 6.7% (n=29) of the patients were treated with O alone.
- Median number of treatment cycles- 6 (range, 1 - 6).
- Median relative dose intensity (RDI) for O was 100% (range, 1.3 – 112.5) and 75.1% (range, 1.9 – 175.0) for chlorambucil.
- Chlorambucil dose was reduced in 27.2% (n=119) patients.

Clinical Response

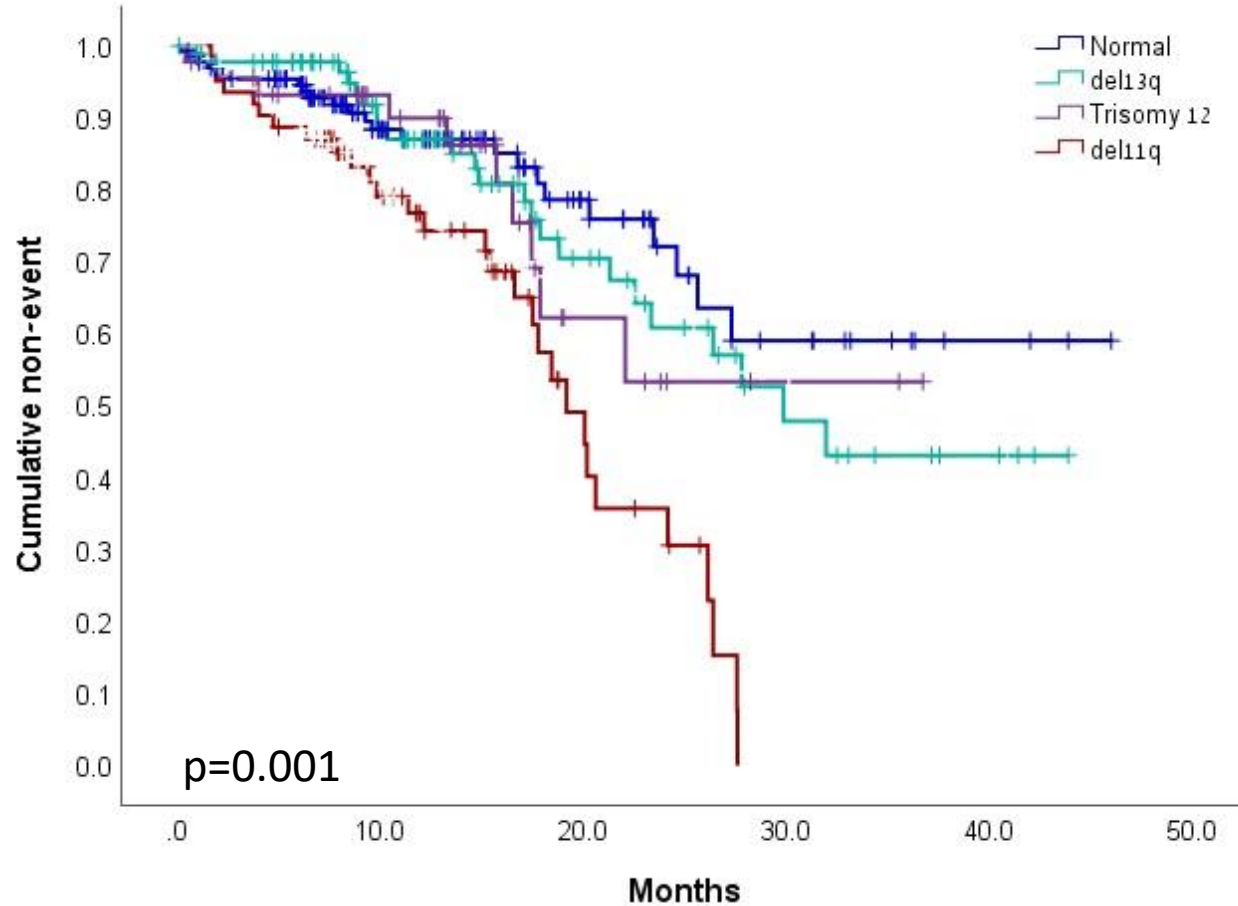
Response was evaluated according to the IWCLL 2018 criteria for general clinical practice



Progression free survival

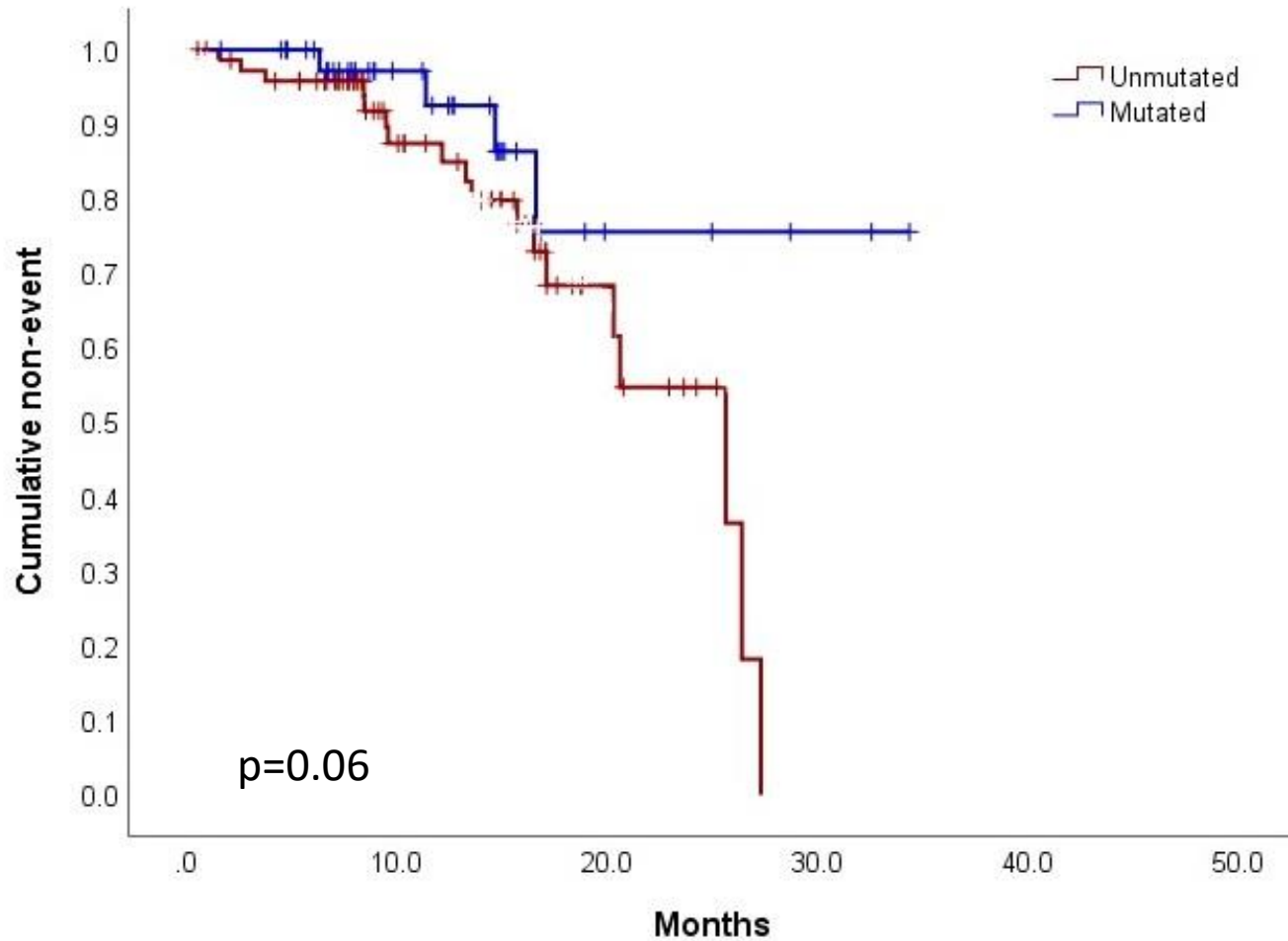


PFS by chromosomal abnormalities



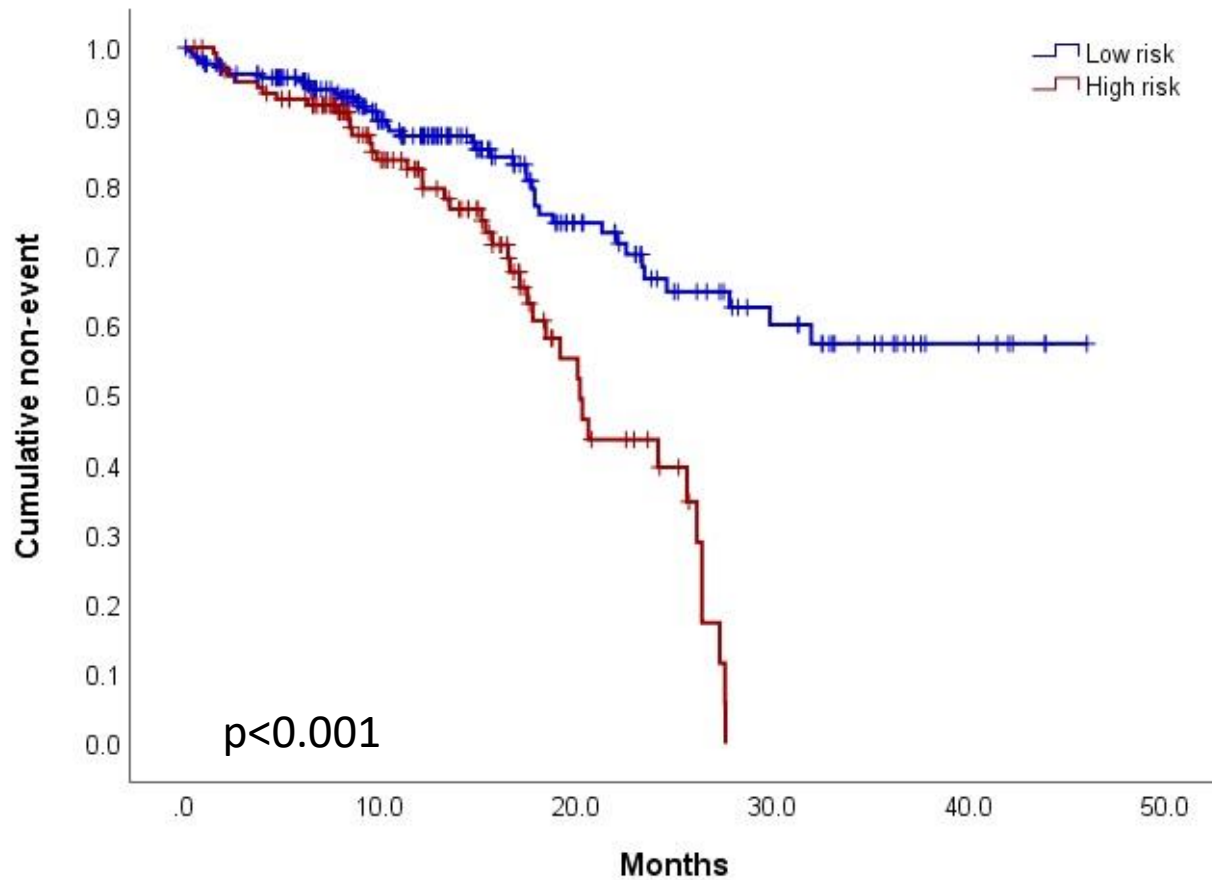
FISH	median, months (95% CI)
Del11q	19.2m (16.0-22.3)
Trisomy 12	NR
Del13q	29.9m (22.8-36.9)
No abnormality detected	NR

PFS by IGHV mutational status



IGHV mutational status	median, months (95% CI)
mutated IGHV	NR
Unmutated IGHV	25.6m (18.7-32.5)

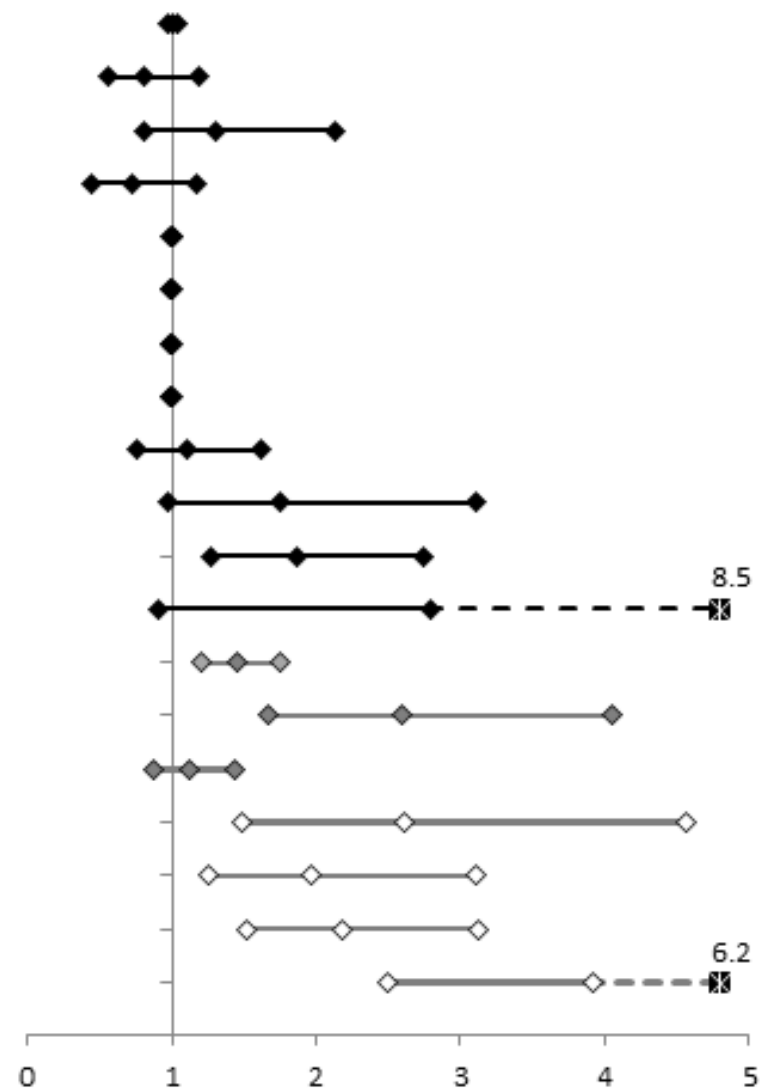
PFS by FISH and IGHV mutational status



Risk group	median, months (95% CI)
Low risk: non-del11q and m-IGHV	NR
High-risk: del11q and/or u-IGHV	20.2m (18.4-21.9)

Univariate analysis for PFS

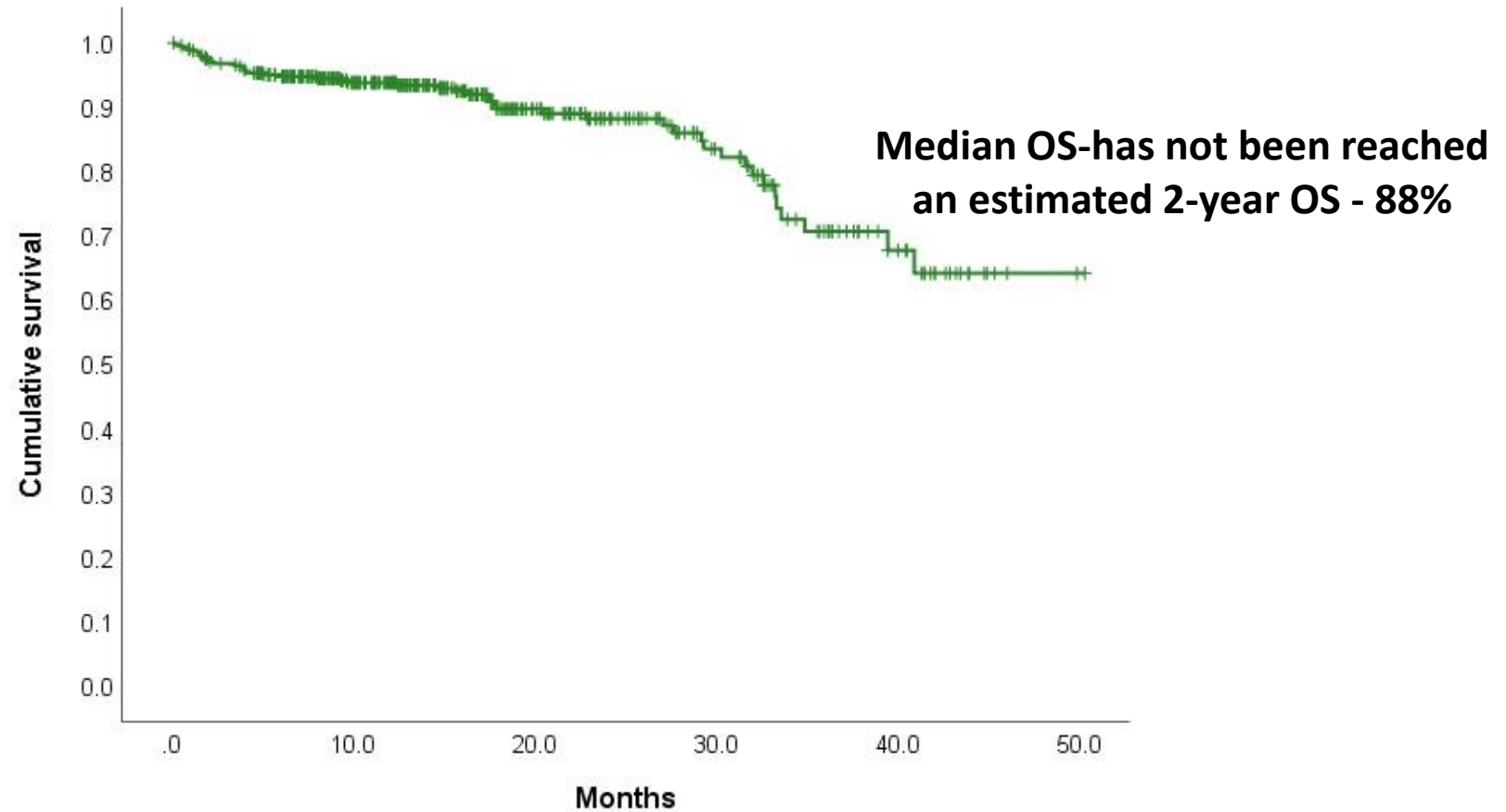
Variable	Hazard ratio	95% CI
Age at 1st treatment start	1.01	0.98 1.03
Female sex	0.82	0.56 1.18
CIRS Total Score (>6)	1.31	0.81 2.13
B symptoms	0.73	0.45 1.18
Absolute lymphocyte count	1.001	0.999 1.003
Hemoglobin	0.999	0.992 1.007
Platelets	0.998	0.996 1.001
Creatinine clearance	0.996	0.99 1.003
Elevated lactate dehydrogenase	1.11	0.76 1.62
B-2-Microglobulin (≥ 3.5 mg/L)	1.74	0.98 3.12
Lymph nodes (>5cm - as longest diameter)	1.87	1.27 2.75
Unmutated IGHV	2.79	0.92 8.49
→ FISH Dohner scale (del11q as the severest abnormality)	1.45	1.2 1.75
→ High risk level (del11q and/or unmutated IGHV)	2.60	1.67 4.05
Binet (severity: A<B<C)	1.12	0.88 1.43
→ Obinutuzumab monotherapy	2.61	1.49 4.56
→ <80% Chlorambucil RDI	1.97	1.25 3.10
→ <100% Obinutuzumab RDI	2.18	1.52 3.13
→ Less than CR	3.92	2.5 6.16



Multivariate analysis for PFS

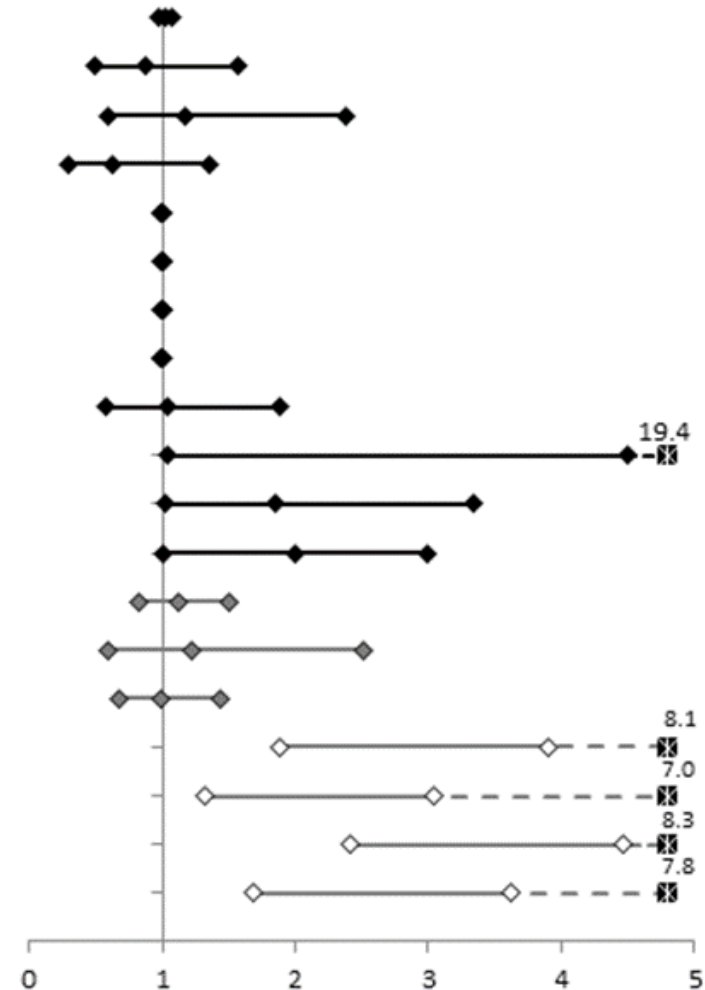
Variable	Hazard ratio	95% CI	<i>p</i> -value
High risk disease [del(11q22.3) and/or unmutated- <i>IGHV</i>]	2.41	1.53-3.79	<0.001
Lymph nodes (diameter > 5.0cm)	1.56	0.98-2.48	0.062
Obinutuzumab monotherapy	3.95	1.67-9.36	0.002
<%100 Obinutuzumab RDI	2.64	1.70-4.12	<0.001
Less than CR	3.23	1.88-5.56	<0.001

Overall survival



Univariate analysis for OS

Variable	Hazard ratio	95% CI	
Age at 1st treatment start	1.03	0.98	1.07
Female sex	0.88	0.49	1.57
CIRS Total Score (>6)	1.18	0.58	2.38
B symptoms	0.63	0.29	1.36
Absolute lymphocyte count	0.997	0.993	1.001
Hemoglobin	1.000	0.987	1.012
Platelets	1.000	0.998	1.002
Creatinine clearance	0.995	0.985	1.006
Elevated lactate dehydrogenase	1.04	0.58	1.88
B-2-Microglobulin (≥ 3.5 mg/L)	4.49	1.04	19.39
Lymph nodes (>5cm - as longest diameter)	1.85	1.02	3.34
Unmutated IGHV	1.58	0.16	15.31
FISH Dohner scale (del11q as the severest abnormality)	1.12	0.83	1.51
High risk level (del11q and/or unmutated IGHV)	1.22	0.59	2.52
Binet (severity: A<B<C)	0.99	0.68	1.44
Obinutuzumab monotherapy	3.91	1.89	8.12
<80% Chlorambucil RDI	3.04	1.33	6.97
<100% Obinutuzumab RDI	4.47	2.41	8.29
Less than CR	3.62	1.69	7.77



Multivariate analysis for OS

Variable	Hazard-ratio	95% CI	p-value
Lymph node diameter >5cm	1.63	0.87-3.07	0.130
Obinutuzumab monotherapy	2.69	1.25-5.81	0.011
<100% Obinutuzumab RDI	4.40	2.28-8.47	<0.001
Less than CR	4.01	1.79-8.95	0.001

Grade ≥3 Adverse Events

	Grade ≥3 (incl. G5)	Grade 5
	N (%)	N (%)
Adverse events of grade ≥3	153 (35.0)	7 (1.6)
Adverse events of grade ≥3 that occurred in ≥ 3% of the patients and/or grade 5:		
<u>Hematologic toxicity:</u>	89 (20.4)	
Neutropenia	63 (14.4)	
Thrombocytopenia	16 (3.7)	
Pancytopenia	5 (1.1)	
Anemia	5 (1.1)	
Infusion related reaction	38 (8.7)	
<u>Infections:</u>	34 (7.8)	6 (1.4)
Febrile neutropenia	5 (1.1)	
Sepsis	7 (1.6)	5 (1.1)
Osteomyelitis	1 (0.2)	1 (0.2)
Tumor lysis syndrome	13 (3.0)	
Gastrointestinal bleeding	1 (0.2)	1(0.2)

Conclusion

- In a “real-world” setting, frontline treatment with O-C1b achieves PFS comparable to that reported in clinical trials.
- Inferior outcomes were noted in patients with del(11q22.3) and/or unmutated IGHV and those treated with obinutuzumab-monootherapy.
- O-C1b can be still considered as legitimate frontline therapy for unfit CLL patients with low-risk disease.

**THANKS
FOR
LISTENING**

Back-up slides

Next line of treatment

- During the study follow-up period, alternative, second line therapy was administered to 69 patients (15.7%).
- Median time to next treatment was not reached.
- The most common second-line therapy used was ibrutinib (66.7%) followed by chemo±immunotherapy (18.8%).

Multivariate analysis regarding clinical CR

Variable	Odds ratio	95% CI		<i>p-value</i>
Female sex	1.66	1.08	2.54	0.020
Binet (A<B<C)	0.69	0.51	0.92	0.013
Bulky (≥ 5.0 cm)	0.37	0.21	0.65	<0.001
Platelet count (continuous)	1.003	1.000	1.006	0.047
≥ 100 obinutuzumab dosage	1.91	1.23	2.97	0.004