Efficacy and safety of BR outside clinical trials in previously untreated older patients with CLL: an indirect comparison with ibrutinib

1. Efficacy and safety of BR in previously untreated CLL (GIMEMA and ERIC centres)

2. Comparison with ibrutinib in patients with CLL treated in the front-line setting at 20 community and academic cancer centers in the U.S.

ERIC european research initiative on CLL

GIMEMA Gruppo Italiano Malattie EMatologiche dell'Adulto

1. Efficacy and tolerability of Bendamustine and Rituximab outside clinical trials in previously untreated CLL

A retrospective/prospective study by the ERIC-GIMEMA groups

Inclusion criteria

- Diagnosis of CLL / Small Lymphocytic Lymphoma (CLL/SLL) according to the WHO classification 2008.
- Patients who were treated with **first line with BR between 2008 and 2014** (GIMEMA group and the ERIC group).
- CLL requiring therapy according to the NCI criteria and treated with at least one cycle of BR as first-line treatment
- **Creatinine clearance <70 ml/min and/or or CIRS>6**
- Age ≥ 18 years.
- Signed written informed consent according to ICH/EU/GCP and national local law.

ERIC european research initiative on CLL

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Baseline characteristics in 157 unfit patients treated with BR first line
(creatinine clearance <70 ml/min or CIRS>6)

	level	Overall
n		157
age (median [range])		72.47 [39.05, 88.91]
clinical_stage (%)	Binet A or Rai 0	53 (41.1)
	Binet B-C or Rai I-IV	76 (58.9)
serum_beta2 (%)	Normal	19 (16.8)
	High	94 (83.2)
Crea Cl (median [range])		59.75 [0.00, 137.00]
IGHV (%)	Mutated	44 (49.4)
	Unmutated	45 (50.6)
TP53 status (%)	No Deletion 17p/TP53 mutation	108 (82.4)
	Deletion 17p and/or TP53 mutation	23 (17.6)
FISH (%)	13q-	34 (30.6)
	+12	24 (21.6)
	11q-	10 (9.0)
	17p-	7 (6.3)
	no-aberration	36 (32.4)
sex (%)	Male/female	95/64 (60.5/39,5%)
ecog (%)	0	68 (43.3)
	1	70 (44.6)
	2	14 (8.9)
	4	2 (1.3)
number_of_comorbidities (%)	0-1/2 or more	48/108 (30.8/69,2%)

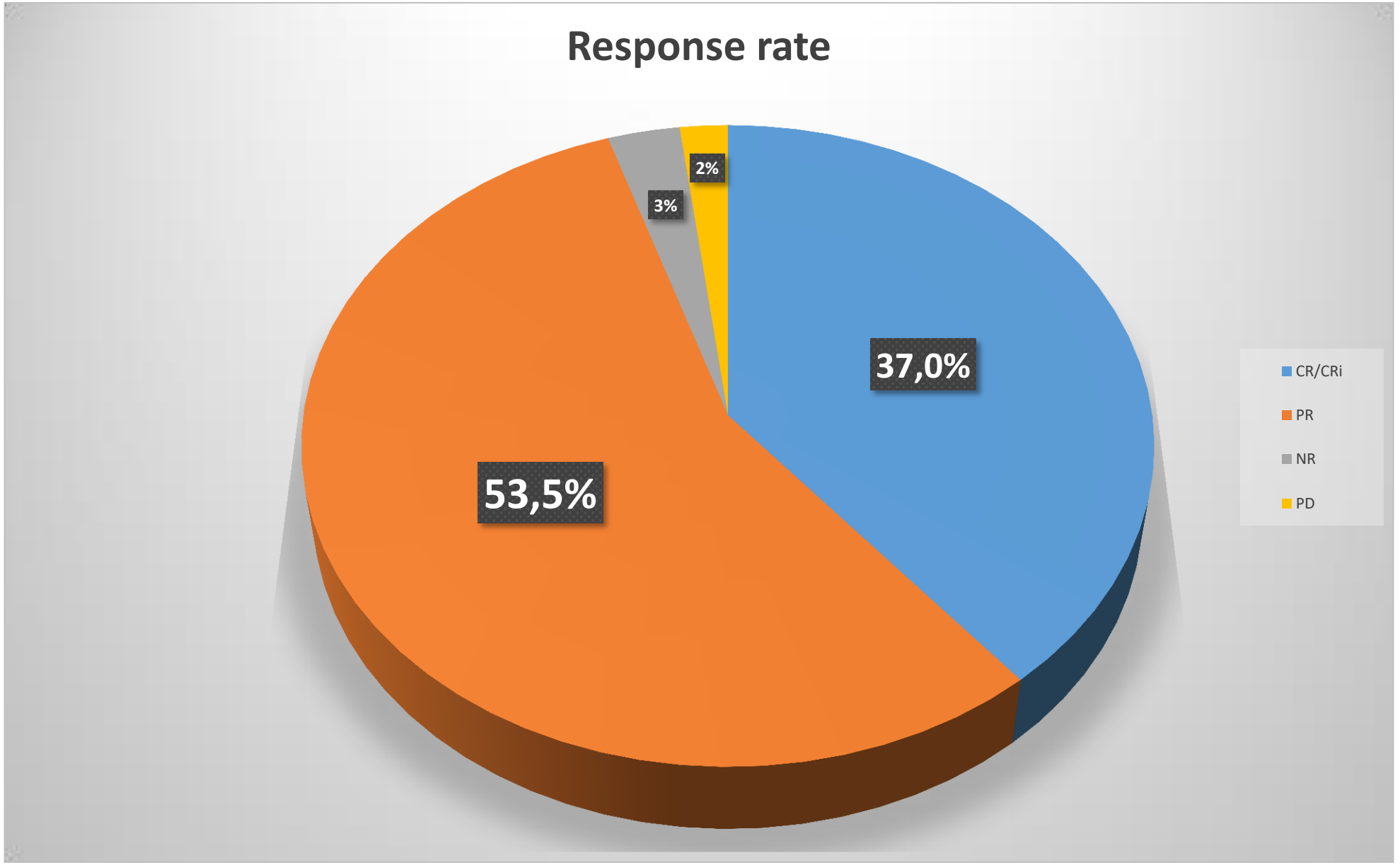
157 unfit pts (BR first line)

Reason for treatment discontinuation	Frequency	Percent
End of planned therapy	114	73.08
Patient decision	3	1.92
Toxicity	28	17.95
Other	10	6.41
Unknown	1	0.64

% patients with adverse events of interest in 157 unfit pts (BR first line)

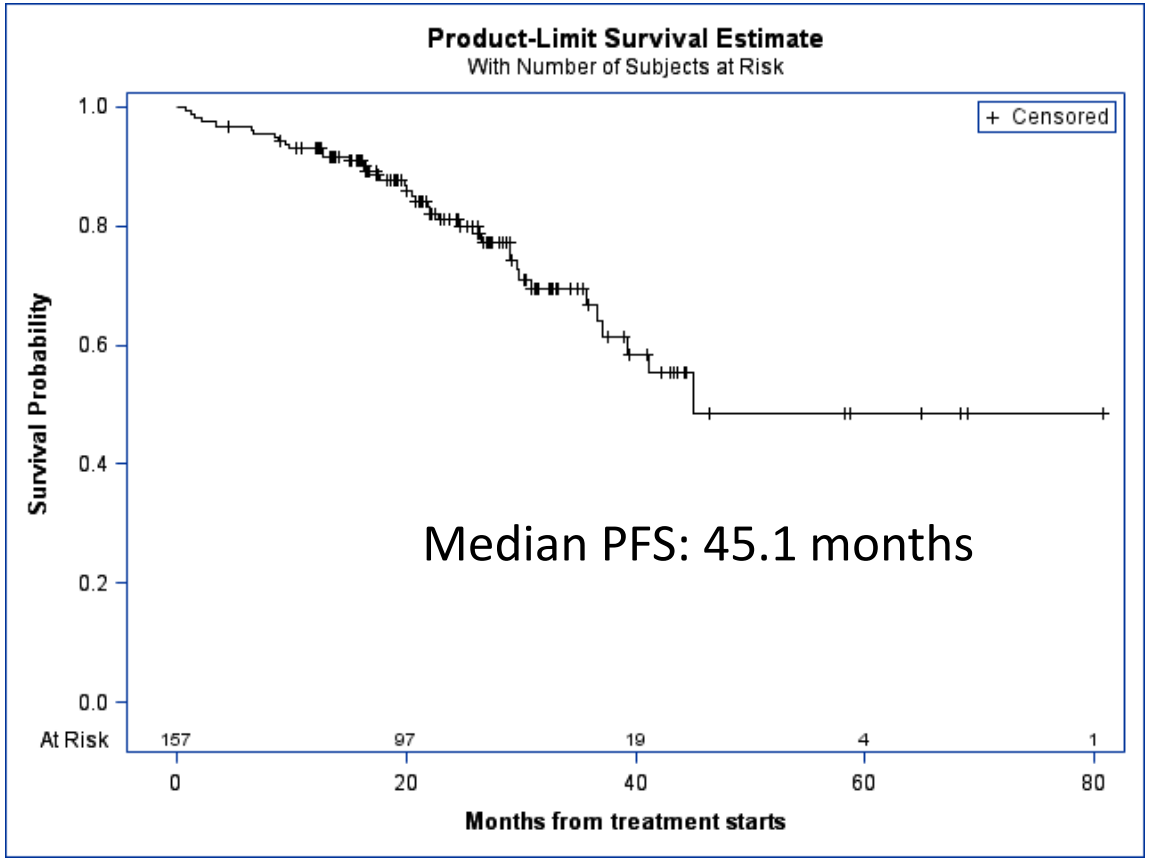
SOC (PT)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total (%)
Blood and lymphatic system disorders (total)	1	10	19	15	0	45
Febrile neutropenia	0	1	3	0	0	4
Neutropenia	0	4	9	12	0	25
Pancytopenia	0	3	7	2	0	12
Anemia				1		1
Thrombocytopenia	1	2	0	0	0	3
Gastrointestinal disorders	0	4	0	0	0	4
Infections and Infestations	1	4	4	1	1	11
Skin and subcutaneous tissue disorders	1	1	3	0	0	5

157 unfit pts (BR first line)



Primary endpoint: PFS

median follow-up 26.25 months (range: 0.79-80.76)

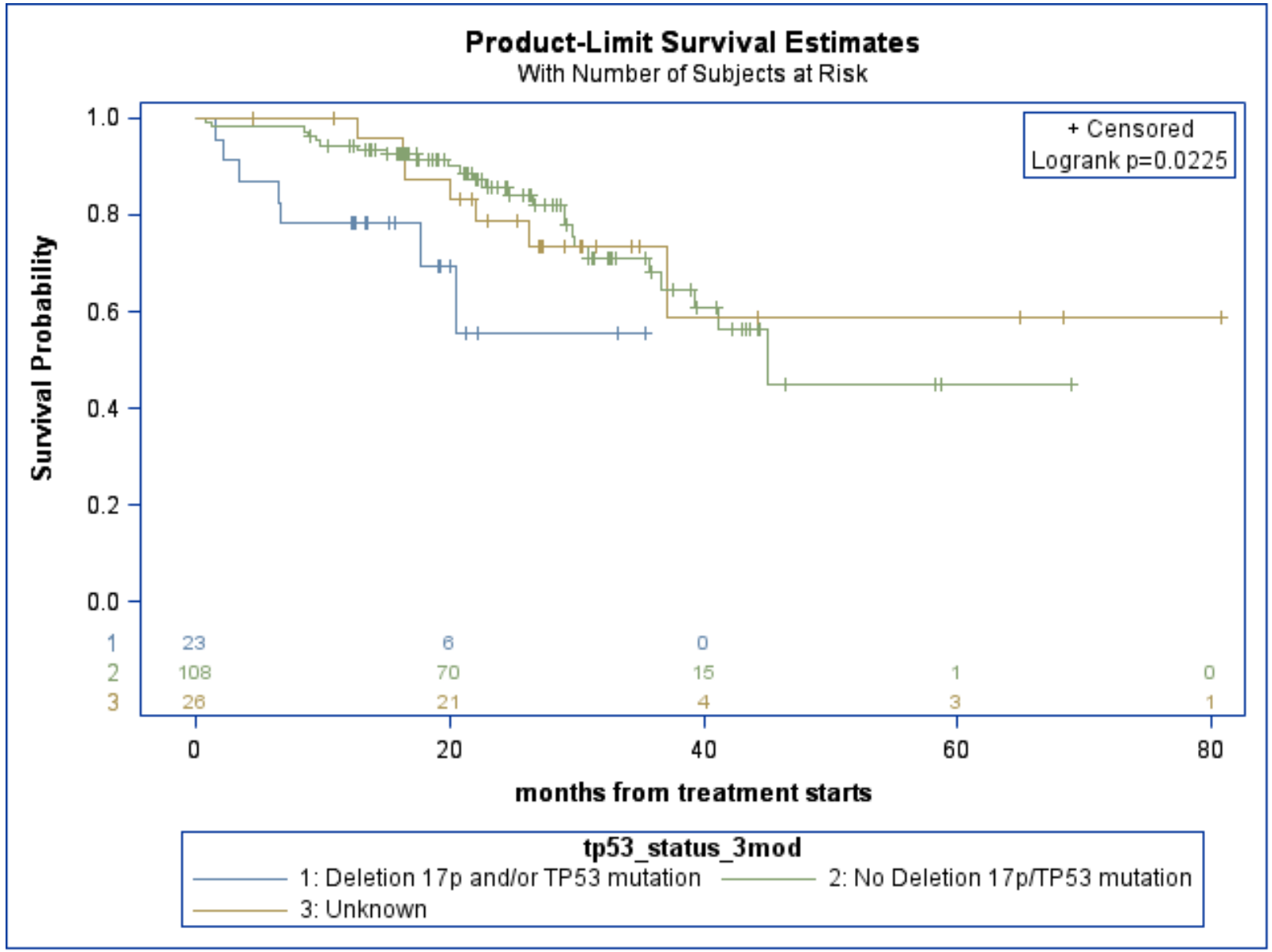


Months	Estimate	Lower 95% CI	Upper 95% CI
12	93.0	89.0	97.1
24	81.0	74.5	88.2
36	66.8	57.1	78.1

PFS univariate analyses

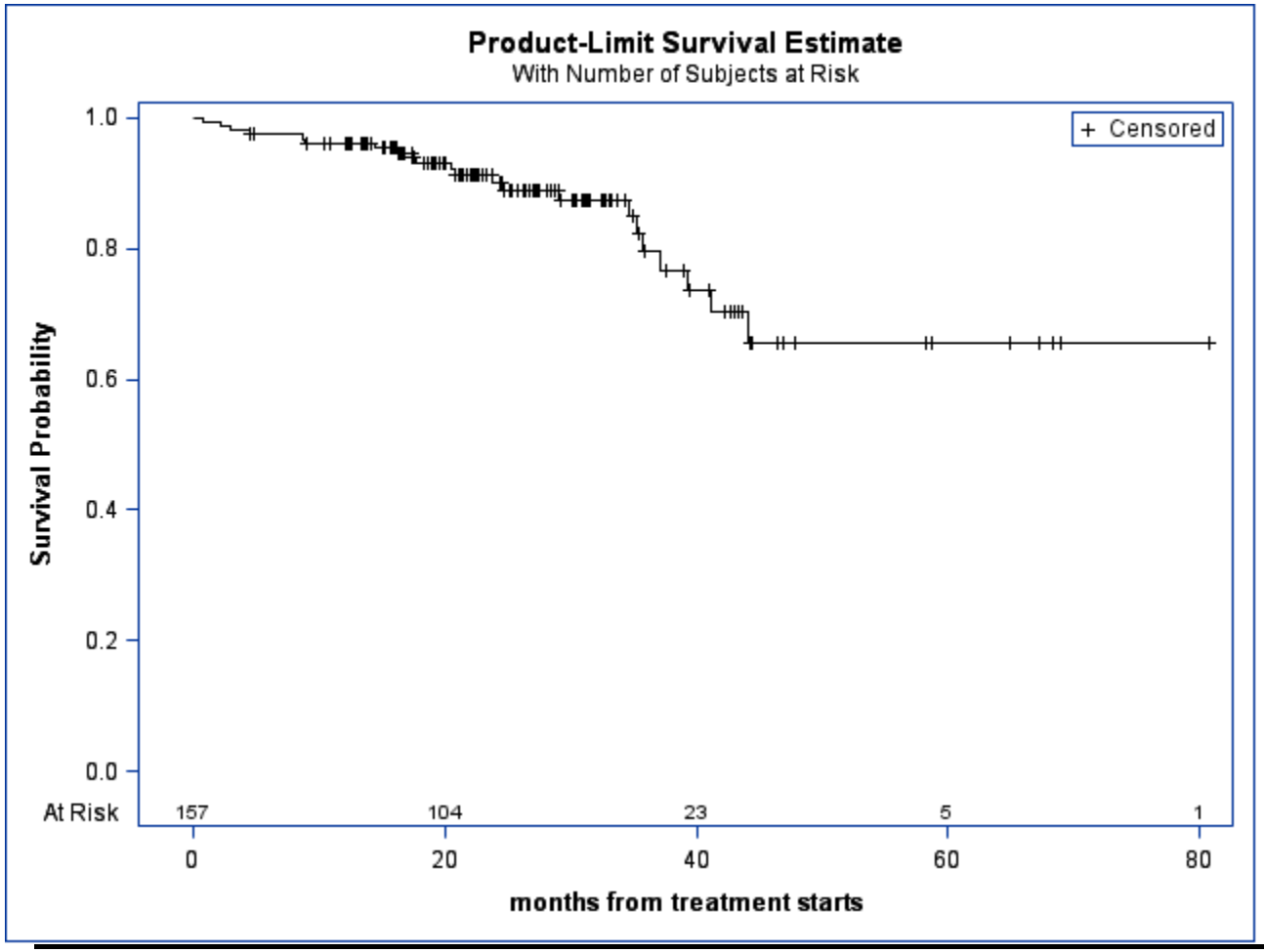
Label	Pr > ChiSq	Hazard Ratio	95% Lower Confidence Limit for Hazard Ratio	95% Upper Confidence Limit for Hazard Ratio
>65yy vs <=65yy	0.2439	1.854	0.657	5.233
Binet B-C or Rai I-IV vs Binet A or Rai 0	0.0667	2.161	0.948	4.923
Beta2 micro High vs Normal	0.3611	1.634	0.570	4.690
IGHV Unmutated vs Mutated	0.0739	2.292	0.923	5.694
Deletion 17p and/or TP53 mutation vs No Deletion 17p/TP53 mutation	0.0116	3.140	1.292	7.636
PD/SD/NR/Death/Not evaluable vs CR/CRi/PR/nPR/LPR	0.0003	4.201	1.916	9.209
PR/nPR/LPR/PD/SD/NR/Death/Not evaluable vs CR/CRi	0.0002	6.174	2.393	15.931

PFS by TP53 status in 157 unfit pts (BR first line)



OS in 157 unfit pts (BR first line)

Secondary endpoint: OS

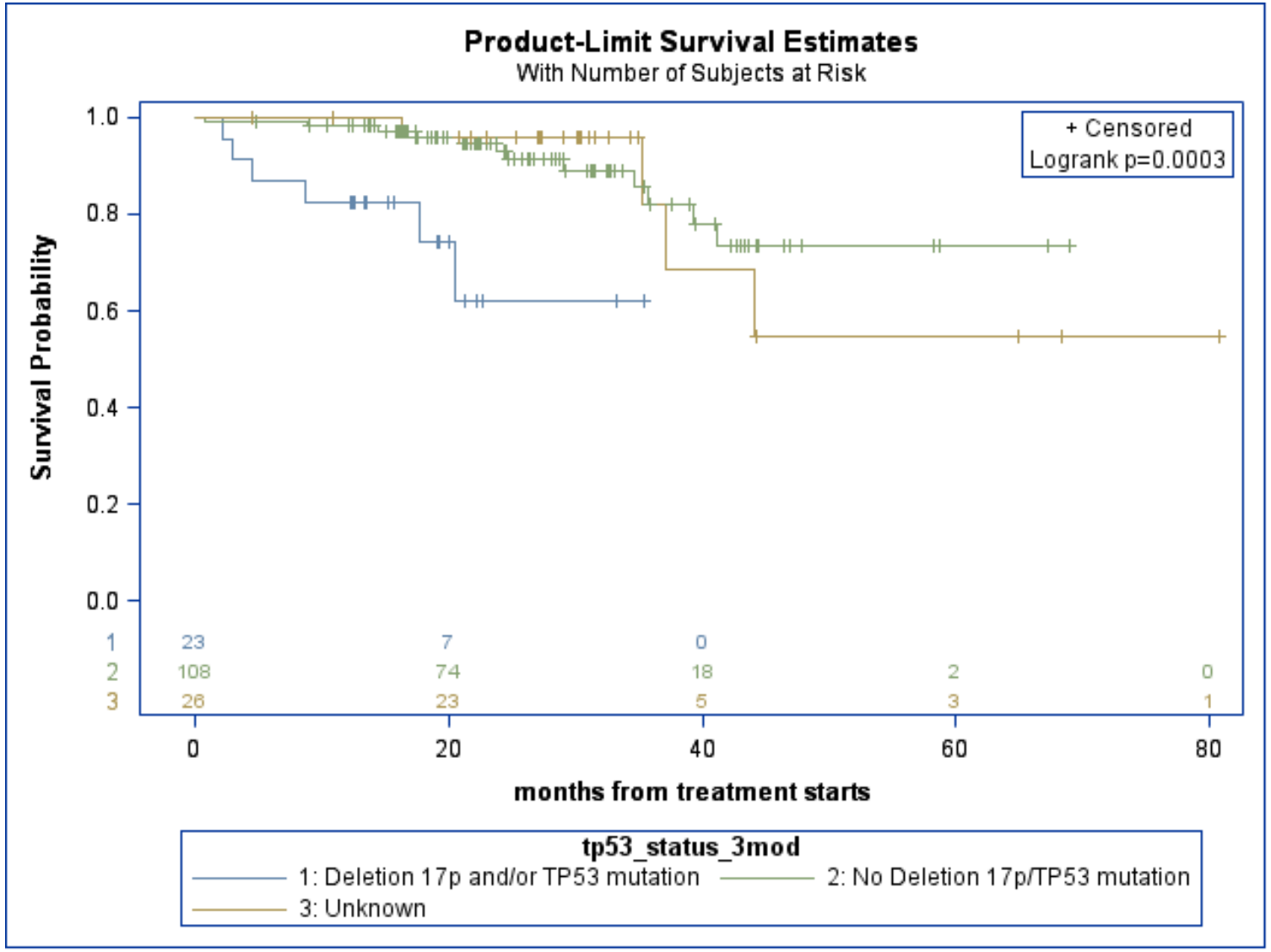


months	estimate	lower 95%CI	Upper 95%CI
12	96.2	93.2	99.2
24	90.1	85.0	95.5
36	79.5	70.0	90.5

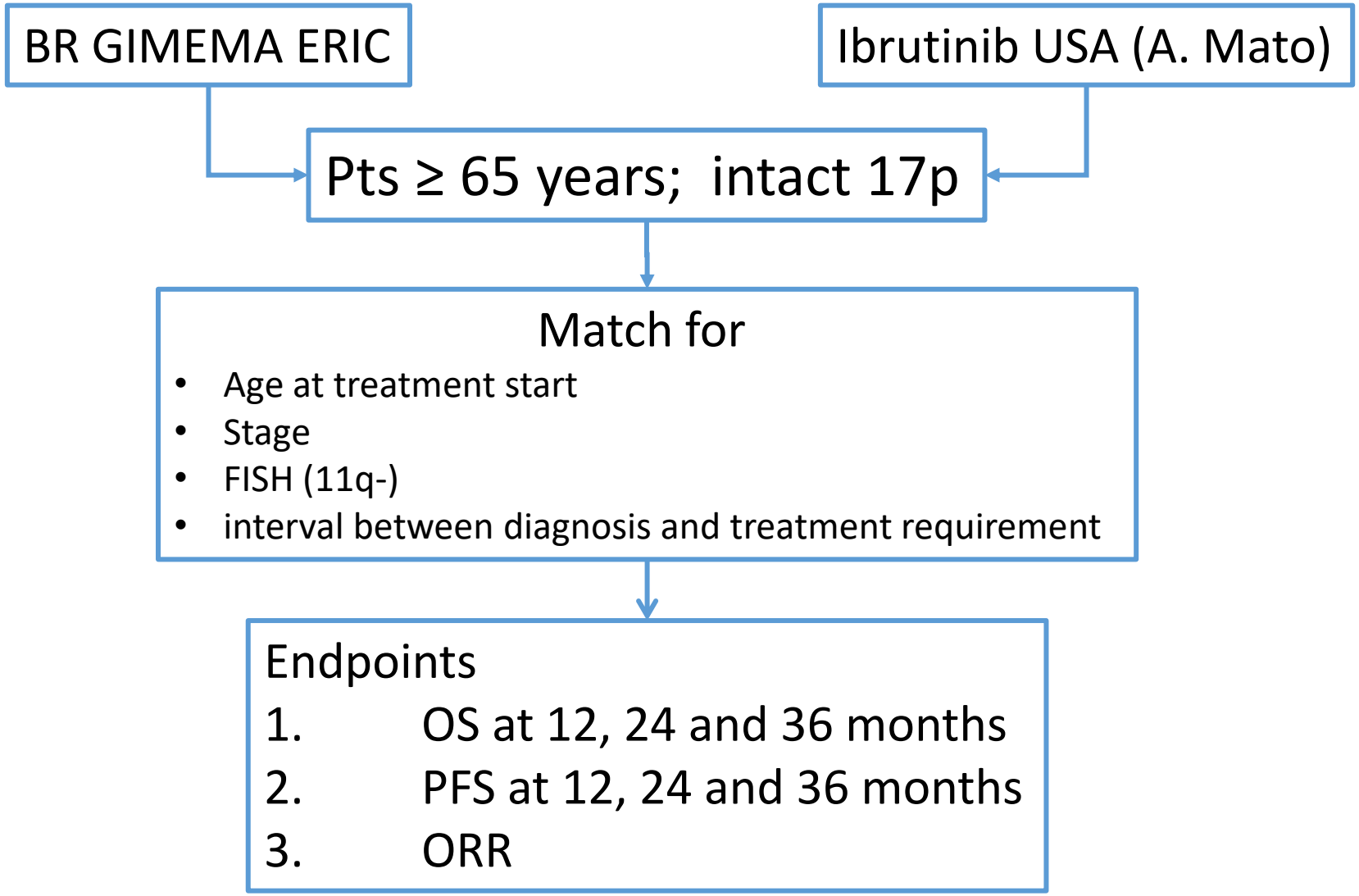
OS in 157 unfit pts (BR first line): univariate analysis

Label	Pr > ChiSq	Hazard Ratio	95% Lower CI for HR	95% Upper CI for HR
Age >65 years vs <65 years	0.1808	3.948	0.528	29.497
Binet B-C or Rai I-IV vs Binet A or Rai 0	0.1232	2.415	0.787	7.411
beta2 High vs Normal	0.1701	4.107	0.546	30.915
IGHV Unmutated vs Mutated	0.7608	1.227	0.328	4.593
Deletion 17p and/or TP53 mutation vs No Deletion 17p/TP53 mutation	0.0010	6.138	2.078	18.131
PD/SD/NR/Death/Not evaluable vs CR/CRi/PR/nPR/LPR	<.0001	8.426	3.517	20.190

OS by 17p status in 157 pts (first line BR treatment with Creatinine clearance <70 ml/min or CIRS>6)



MATCHED ADJUSTED INDIRECT COMPARISON WITH IBRUTINIB IN FIRST LINE

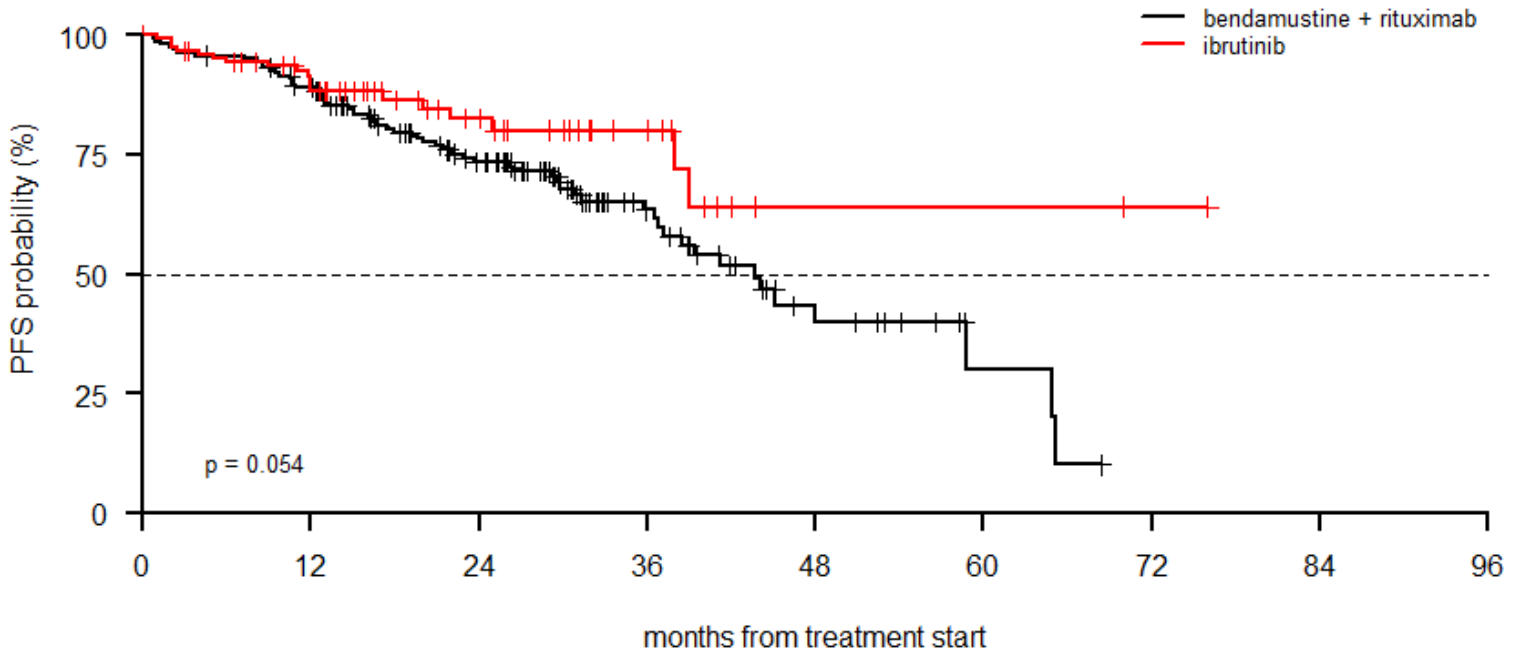


Baseline characteristics in the BR and in the ibrutinib cohorts

	Stratified by drug			
	level	bendamustine + rituximab	ibrutinib	p
n. of patients		165	162	
age (median [range])		72.30 [65.23, 88.91]	74.00 [65.00, 96.00]	0.105
Age (%)	<=70 years	53 (32.1)	53 (32.7)	1.000
	>70 years	112 (67.9)	109 (67.3)	
sex (%)	M	106 (64.2)	102 (63.0)	0.900
	F	59 (35.8)	60 (37.0)	
Time dx-trx as continuous (median [range])		26.81 [0.00, 229.84]	43.00 [0.00, 600.00]	<0.001
Time between diagnosis _trx (%)	<36 months	99 (60.0)	69 (42.6)	0.002
	>=36 months	66 (40.0)	93 (57.4)	
RAI stage (%)	0-2	79 (63.2)	59 (38.1)	<0.001
	3-4	46 (36.8)	96 (61.9)	
del11q (%)	No	101 (89.4)	125 (87.4)	0.771
	Yes	12 (10.6)	18 (12.6)	

PFS in the BR and in the ibrutinib cohorts

Median follow-up Ibrutinib cohort (CI-95%): 13 months (10.74;14) IQR (time): (8;24)
Median follow-up BR cohort (CI-95%): 29 months (26.48;31.02) IQR (time): (21.41;41.88)



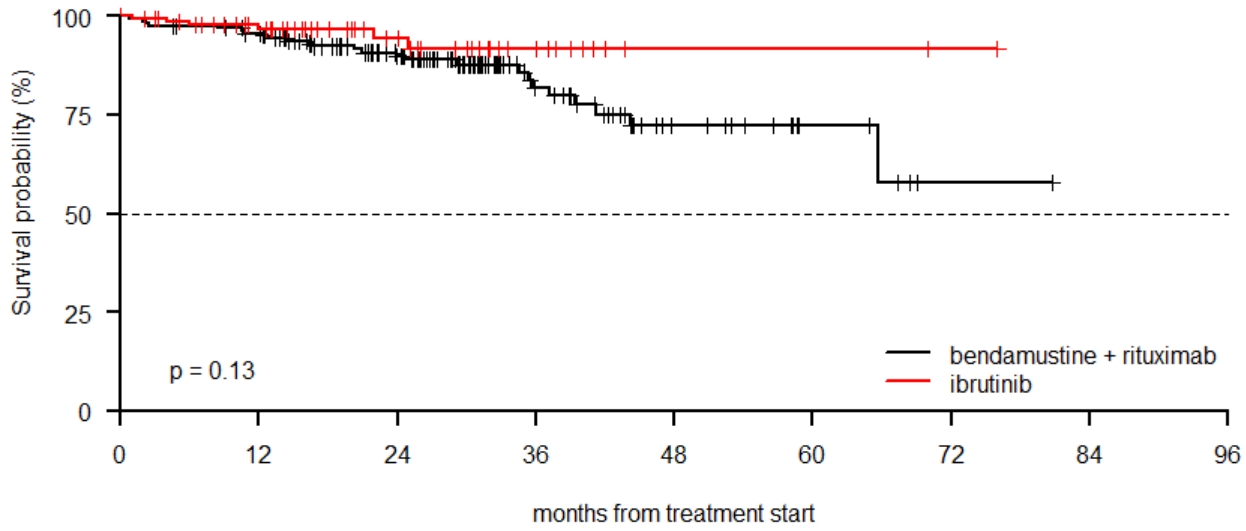
	months	estimate	lower 95%CI	Upper 95%CI
BR	12	89	84.3	93.9
BR	24	73.5	66.7	81
BR	36	63.4	54.9	73.1
BR	48	39.8	28.3	56
ibrutinib	12	88.2	82.5	94.4
ibrutinib	24	82.5	74.6	91.4
ibrutinib	36	80.1	71.3	90.1
ibrutinib	48	64.1	46	89.3

Univariate and multivariate analysis: ibrutinib treatment and age are an independent predictors of longer PFS

Univariate	HR	Lower 95%CI	Higher 95%CI	p
Age as continuous	1.05	1.02	1.09	0.0023
time dx to treatment as continuous	1	0.99	1	0.6204
del11q Yes vs. No	2.13	1.04	4.37	0.0399
Ibr vs. BR	0.6	0.36	1.01	0.0541
age >70 vs. <70 years	1.17	0.72	1.91	0.516
RAI 3-4 vs 0-2	1.09	0.66	1.79	0.7326
interval Dx-treatment >36 mos vs <36 months	0.89	0.57	1.38	0.6055

Multivariate	HR	Lower 95%CI	Higher 95%CI	p
Age	1.06	1.02	1.1	0.0011
Ibr vs. BR	0.55	0.33	0.93	0.0261

No difference in overall survival in the BR and in the ibrutinib cohorts



level	months	estimate	lower 95%CI	Upper 95%CI
BR	12	95.7	92.7	98.9
BR	24	89.9	85.2	94.9
BR	36	81.9	74	90.6
BR	48	72.2	61.5	84.8
ibrutinib	12	96.6	93.4	100
ibrutinib	24	94.4	89.1	100
ibrutinib	36	91.7	84.6	99.4
ibrutinib	48	91.7	84.6	99.4

Conclusions

- BR proved to be an effective and safe regimen in 157 «unfit» patients treated outside clinical trials in centres belonging to the GIMEMA and ERIC network

- In this analysis, the median PFS = 41.5 months; CR/Cri rate =37% and OS =79,5% patients alive at 36 months with BR is superimposable to the data from a trial enrolling fluda-ineligible patients (CR 24%; median PFS 40 months*)

- A Matched adjusted indirect comparison with 162 patients age ≥ 65 years treated with ibrutinib at 20 community and academic cancer centers in the U.S. showed that:

  - Ibrutinib was an independent predictor of a longer PFS
  - Overall survival did not show any difference in the BR cohort and in the ibrutinib cohort

* Michallet AS et al - MABLE study - Haematologica. 2018 ;103(4):698-706