

## Efficacy of bendamustine and rituximab as first salvage treatment in chronic lymphocytic leukemia and indirect comparison with ibrutinib: a GIMEMA, ERIC and UK CLL FORUM study

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Received: February 6, 2018.

Accepted: April 18, 2018.

Pre-published: April 19, 2018.

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Supplementary Table 1. Enrollment by Center in the BR cohort

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096 Hematology and Clinical Immunology, Department of Medicine, University of Padua, Italy	16
012 Hematology, Niguarda Cancer Center, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy	16
602 Hospital Costa del Sol, Marbella, Málaga, Spain	15
033 Hematology Unit, Città della Salute e della Scienza, University of Turin, Italy	15
027 Hematology, Università Cattolica del Sacro Cuore, Policlinico A. Gemelli, Rome, Italy	13
138 Hematology Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy	12
108 Hematology Department, Fondazione IRCCS Istituto Nazionale Tumori, Milano, Italy	11
601 Hematology Hospital Clinic, Barcelona, Spain.	11
042 Hematology Unit, Fondazione IRCCS Policlinico San Matteo Pavia	10
113 Hematology and Cellular Therapy, Ospedale C. e G. Mazzoni, Ascoli Piceno, Italy	9
065 Hematology, Department of Medical Sciences, St. Anna University Hospital, Ferrara, Italy	8
600 Hematology Unit, Hospital Universitario 12 de Octubre, Madrid, Spain	8
028 Hematology, Department of Biomedical Sciences and Hematology, "Sapienza" University, Rome, Italy	7
035 Hematology, San Bortolo Hospital, Vicenza, Italy	7
025 Hematology, San Carlo Hospital, Potenza, Italy	6
041 Hematology and Transplant Unit, San Maurizio Hospital, Azienda Sanitaria dell'Alto Adige, Bolzano, Italy	6
085 Hematology Unit, University Hospital, Modena, Italy	6
008 Hematology Unit, Azienda Universitaria Ospedaliera Policlinico Vittorio Emanuele, Catania, Italy	6
043 Hematology, Department of Cell Therapy and Hematology, University Hospital, Verona, Italy	5
062 Hematology Unit, Arcispedale S. Maria Nuova, Reggio Emilia, Italy	5
147 Oncology Unit, Cardinal Massaia Hospital, Asti, Italy	4
009 Hematology Unit, A. Pugliese Hospital, Azienda Ospedaliera Pugliese Ciaccio, Catanzaro, Italy	4
038 Hematology, University Hospital, Parma, Italy	4
115 Hematology, DIMECS e Dipartimento Oncologico, Università del Piemonte Orientale Amedeo Avogadro, Novara, Italy	4
605 Hematology, University Hospital-IBSAL and CIBERONC, Salamanca, Spain	4
604 Hospital de la Santa Creu i Sant Pau, Barcellona, Spain	4
067 Hematology and Transplant Unit - A.O. Senese - Policlinico Le Scotte, Siena, Italy	3
001 Azienda Ospedaliero Universitaria Ospedali Riuniti Umberto I G.M. Lancisi, G. Salesi Ancona, Italy	3
Hematology Unit, Careggi Hospital, Florence, Italy	3
051 Division of Experimental Oncology, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy	2
125 Ospedale Infermi, Rimini, Italy	2
607 Fundaleu, Buenos Aires, Argentina	2
603 1st Department of Medicine General University Hospital, Praga, Czech Republic	2
301 Policlinico di Tor Vergata Università of Rome, Italy	1
142 Hematology and Transplant Unit - Dipartimento di Oncologia ed Ematologia - AUSL Ospedale G. da Saliceto Piacenza, Italy	1
608 Hematology, University Hospital, Hradec Kralove, Czech Republic	1
606 Hematology and Oncology, Department of Internal Medicine, University Hospital, Brno Czech Republic	1

## Methods

Study data were collected and managed using REDCap<sup>1</sup> electronic data capture tools hosted at GIMEMA Foundation.

- 1) Paul A. Harris, Robert Taylor, Robert Thielke, Jonathon Payne, Nathaniel Gonzalez, Jose G. Conde, Research electronic data capture (REDCap) – A metadata-driven methodology and workflow process for providing translational research informatics support, *J Biomed Inform.* 2009 Apr;42(2):377-81.

Supplementary Table 2. ORR univariate analysis in the BR cohort.

Variable	ORR		p
	PD/SD/NR/Death/Not evaluable	CR/PR	
	N (%)	N (%)	
Age (years) ≤65/66-75/>75	10/18/14 (14.5/17.6/21.2)	59/84/52 (85.5/82.4/78.8)	0.59
Gender M/F	28/14 (16.7/20.3)	140/55 (83.3/79.7)	0.51
Stage Others/Rai III/IV or Binet C	27/11 (16.4/24.4)	138/34 (83.6/75.6)	0.21
Bulky lymph nodes (>5cm) no/yes	34/6 (16.7/30.0)	170/14 (83.3/70.0)	0.14
Comorbidities 0-1/≥2	14/28 (14.3/20.4)	84/109 (85.7/79.6)	0.22
Creatinine clearance (ml/min) ≤70/>70	21/19 (21.0/16.8)	79/94 (79.0/83.2)	0.44
CD38 (>20%) negative/positive	12/11 (23.1/19.0)	40/47 (76.9/81.0)	0.60
FISH 13q-/12/11q-/17p-/no-aberrations	6/1/10/7/8 (13.3/3.1/26.3/30.4/17.8)	39/31/28/16/37 (86.7/96.9/73.7/69.6/82.2)	0.04
IGVH mutated/unmutated	8/24 (20.0/22.6)	32/82 (80.0/77.4)	0.73

Supplementary Table 3. Causes of death in single patients in the BR cohort (total n=9)

AHIA and DVT
Toxicity due to bone marrow transplantation
Primary multifocal encephalitis
Autoimmune hepatitis
Heart failure
Ictus cerebri
Intracranial hemorrhage
Kidney failure
Treatment-related toxicity

Supplementary Table 4. Adverse events grade ≥3 in the BR cohort

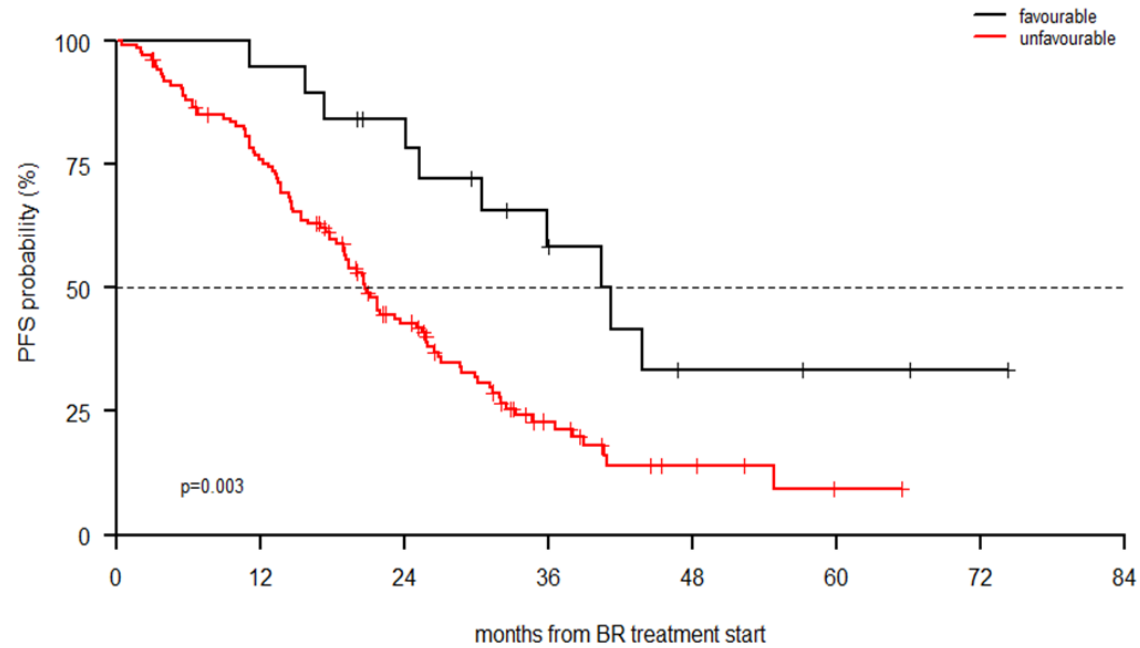
	<b>Grade 3</b>	<b>Grade 4</b>	<b>Grade 5</b>	<b>Total</b>
<b>Cytopenia</b>	<b>37</b>	<b>22</b>		<b>59</b>
Neutropenia (febrile)	3	1		4
Neutropenia	27	18		45
Anaemia	1			1
Haemolysis		2		2
Thrombocytopenia	5	1		6
Pancytopenia	1			1
<b>Cardiac disorders</b>	<b>1</b>			<b>1</b>
Tachycardia	1			1
<b>Infections and Infestations</b>	<b>10</b>	<b>2</b>		<b>12</b>
Pneumonia or lung infection	7			7
Pneumocystis jiroveci pneumonia		1		1
Cutaneous, including herpes zoster	1	1		2
Oropharyngeal candidiasis	1			1
Sepsis	1			1
<b>Injury poisoning and procedural complications</b>	<b>1</b>			<b>1</b>
Infusion-related reaction	1			1
<b>Nervous system disorders</b>	<b>1</b>		<b>1</b>	<b>2</b>
Neuropathy, peripheral	1			1
Varicella post-encephalitis			1	1
<b>Renal and urinary disorders</b>	<b>1</b>			<b>1</b>
Renal failure, acute	1			1
<b>Respiratory toracic and mediastinal disorders</b>		<b>1</b>		<b>1</b>
Respiratory distress syndrome, acute		1		1
<b>Skin and subcutaneous tissue disorders</b>	<b>2</b>			<b>2</b>
Dermatitis, exfoliative	1			1
Rash	1			1
<b>Total</b>	<b>53</b>	<b>25</b>	<b>1</b>	<b>79</b>

Supplementary Table 5. OS in 95 patients in the ibrutinib cohort (UK + GIMEMA NPP)

<b>Variable</b>	<b>Estimate at 24 months (95% CI)</b>	<b>p</b>
Age years (%) ≤65/>65	65.3/66.9 (47.5-89.9)/(55.7-80.3)	0.75
Gender (%) M/F	63.4/70.1 (51.3-78.2)/(55.3-88.9)	0.63
ECOG PS (%) 0-1/≥2	73.1/34.7 (63.1-84.8)/(15.8-76.0)	0.05
Months between 1 <sup>st</sup> line and 2 <sup>nd</sup> line (%) < 36/≥36	65.7/66.7 (54.0-79.9)/(48.1-92.4)	0.98
<b>1st line therapy chemotherapy only/CIT (%)</b>	75/63.5 (58.1-96.7)/(52.2-77.2)	0.62
<b>ORR rate to 1<sup>st</sup> line treatment (%) no/yes</b>	62.2/66.1 (40.8-94.9)/(54.8-79.7)	0.61
<i>IGHV</i> (%) mutated/unmutated	57.7/57.4 (34.7-96.0)/(35.1-93.9)	0.54
17p- (%) no/yes	69.3/68.1 (53.5-89.8)/(55.8-83.0)	0.98

CIT: chemoimmunotherapy

Supplementary Figure 1. PFS in the BR cohort according to the model based on 17p deletion, IGHV status and stage. The favorable group includes patients with mutated IGHV, early/intermediate stage, intact 17p.



	n	events	median	0.95 LCL	0.95 UCL
risk=favourable	19	10	40.4	30.5	NA
risk=unfavourable	136	98	20.7	18.9	25.7



Supplementary Figure 2. TTNT in 237 patients treated with BR (a) by FISH (b) and type of front-line treatment (c).

