

# Bendamustine and rituximab as first-line treatment for symptomatic splenic marginal zone lymphoma: long-term outcome and impact of early unmeasurable minimal residual disease attainment from the BRISMA/IELSG36 phase II study

## Authors

Emilio Iannitto,<sup>1,2</sup> Simone Ferrero,<sup>3</sup> Côme Bommier,<sup>4,5</sup> Daniela Drandi,<sup>3</sup> Martina Ferrante,<sup>3</sup> Krime Bouabdallah,<sup>6</sup> Sylvain Carras,<sup>7</sup> Guido Gini,<sup>8</sup> Vincent Camus,<sup>9</sup> Salvatrice Mancuso,<sup>10</sup> Luigi Marcheselli,<sup>11</sup> Angela Ferrari,<sup>12</sup> Michele Merli,<sup>13</sup> Benoit Tessoulin,<sup>14</sup> Caterina Stelitano,<sup>15</sup> Kheira Beldjord,<sup>4</sup> Giovanni Roti,<sup>16</sup> Fabrice Jardin,<sup>8</sup> Barbara Castagnari,<sup>17</sup> Francesca Palombi,<sup>18</sup> Lucile Baseggio,<sup>19</sup> Alexandra Traverse-Glehen,<sup>20</sup> Claudio Tripodo,<sup>2</sup> Anna Marina Liberati,<sup>21</sup> Margherita Parolini,<sup>22</sup> Sara Usai,<sup>23</sup> Caterina Patti,<sup>24</sup> Massimo Federico,<sup>25</sup> Maurizio Musso,<sup>1</sup> Marco Ladetto,<sup>26</sup> Emanuele Zucca<sup>27</sup> and Catherine Thieblemont<sup>4,5</sup>

<sup>1</sup>La Maddalena Department of Oncology, Oncohematology and Bone Marrow Transplantation Unit, Palermo, Italy; <sup>2</sup>Tumor Immunology Unit, Department of Health Sciences, University of Palermo School of Medicine, Istituto di Patologia Generale, Palermo, Italy; <sup>3</sup>Division of Hematology, Department of Molecular Biotechnologies and Health Sciences, University of Torino, Torino, Italy; <sup>4</sup>Université Paris Cité, Paris, France; <sup>5</sup>AP-HP, Hôpital Saint-Louis, Hemato-oncologie, Paris, France; <sup>6</sup>CHU de Bordeaux - Hôpital Haut Lévêque and Centre François Magendie, Service d'Hématologie Clinique et Thérapie Cellulaire, Pessac, France; <sup>7</sup>Université Grenoble Alpes, Institute for Advanced Biosciences, INSERM U1209, CNRS UMR 5309, University Hospital, Molecular Biology and Hematology Departments, Grenoble, France; <sup>8</sup>Ematologia AOU delle Marche, Ancona, Italy; <sup>9</sup>Department of Hematology, Centre Henri Becquerel, Rouen, France; <sup>10</sup>Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties (PROMISE), Hematology Unit, University of Palermo, Palermo, Italy; <sup>11</sup>Fondazione Italiana Linfomi ETS, Modena,

Italy; <sup>12</sup>Azienda Unità Sanitaria Locale-IRCCS Arcispedale Santa Maria Nuova, Reggio Emilia, Italy; <sup>13</sup>Hematology, Ospedale di Circolo e Fondazione Macchi - ASST Sette Laghi, Varese, Italy; <sup>14</sup>Nantes University Hospital and CRC2 NA, Nantes, France; <sup>15</sup>UO Ematologia AO Bianchi-Melacrino-Morelli, Reggio Calabria, Italy; <sup>16</sup>Dipartimento di Medicina e Chirurgia, Università di Parma, AOU di Parma, Parma, Italy; <sup>17</sup>Department of Hematology, Ravenna Hospital, Ravenna, Italy; <sup>18</sup>Hematology Unit, IRCCS Regina Elena National Cancer Institute, Roma, Italy; <sup>19</sup>Laboratoire d'Hématologie Biologique, Groupement Hospitalier Lyon-Sud/Hospices Civils de Lyon, Lyon, France; <sup>20</sup>Service d'Anatomie Pathologique, Groupement Hospitalier Lyon-Sud/Hospices Civils de Lyon, Lyon, France; <sup>21</sup>Oncohematology Unit, University of Perugia, Azienda Ospedaliera S.Maria, Terni, Italy; <sup>22</sup>Ematologia Istituto Romagnolo Per Lo studio dei Tumori Dino Amadori, Meldola, Italy; <sup>23</sup>Ospedale Oncologico A. Businco, Cagliari, Italy; <sup>24</sup>U.O.C. di Oncoematologia Ospedali Riuniti Villa Sofia - Cervello, Palermo, Italy; <sup>25</sup>CHIMOMO Department, University of Modena and Reggio Emilia, Modena, Italy; <sup>26</sup>University of Eastern Piedmont Amedeo Avogadro, S.S. Antonio and Biagio and Cesaro Arrigo Hospital, Alessandria, Italy and <sup>27</sup>IOSI, Oncology Institute of Southern Switzerland and Institute of Oncology Research (IOR), International Extranodal Lymphoma Study (IELSG), Bellinzona, Switzerland

Correspondence:

E. IANNITTO - emilio.iannitto@gmail.com

<https://doi.org/10.3324/haematol.2023.284109>

## Supplement File Legends

### Table S 1

#### SLSG response criteria for SMZL and Lugano 2014 response criteria for non-Pet avid NHL

# Matutes E. et al. Leukemia 2008; 22:487-495; \* Cheson B. et al. JCO 2014; 32, 3059-3068.  
SMZL: splenic marginal zone lymphoma; SLSG: splenic lymphoma study group; NR: no-response/progression; CR: complete remission; PR: partial remission; IHC: immunohistochemistry; PPD: cross product of the longest transverse diameter of a lesion and perpendicular diameter; SPD: sum of the product of the perpendicular diameters for multiple lesions.

### Table S 2

#### Presenting and demographic data on diagnosis.

#Montalban C. et al. Simplification of risk stratification for splenic marginal zone lymphoma: a point-based score for practical use. Leuk Lymphoma. 2014;55(4):929-31. @Arcaini L. et al. Splenic marginal zone lymphoma: a prognostic model for clinical use. Blood 2006;107(12):4643-9.  
Abbreviation. ALC: absolute lymphocyte count; Hb: Hemoglobin; LDH: lactate dehydrogenase; B2M: beta-2 microglobulin; IIL: Intergruppo Italiano Linfomi; HPLL: Hemoglobin, Platelets, LDH, extra-hilar lymphadenopathy.

### Figure S1 A

#### MRD shrinkage in bone marrow assessed at different time points.

Abbreviation. MRD levels at different time points measured by ddPCR and expressed as copies out of 250ng of genomic DNA. Black lines represent the median MRD level at each time point: DIA 1.3E-01 (range: 1.3E-03 -1.7), ER 4.7E-05 (range: BQL – 2.3E-01); EOT 1.4E-05 (range: BQL – 6.7E-05), FU1 1E04 (range: BQL – 8.1E-01). Abbreviations: MRD minimal residual disease; DIA, diagnosis; ER, early restaging; EOT end of treatment; FU1, one-year follow-up; BQL, positive below quantity limit value; NEG, negative; R, represents a patient who will relapse in the subsequent FU.

### Figure S1 B

#### MRD shrinkage in peripheral blood assessed at different time points.

Abbreviation. MRD levels at different time points measured by ddPCR and expressed as copies out of 250ng of genomic DNA. Black lines represent the median MRD levels level at each time point: DIA 2.7E-01 (range 2.8E-03 – 1.4E+00), ER BQL (range BQL – 3.9E-01), EOT BQL (range: BQL – 4E-05), FU1 5.3E-05 (range BQL -8.8E-01). Abbreviations: MRD minimal residual disease; DIA, diagnosis; ER, early restaging; EOT end of treatment; FU1, one-year follow-up; BQL, positive below quantity limit value; NEG, negative; R, represents a patient who will relapse in the subsequent FU.

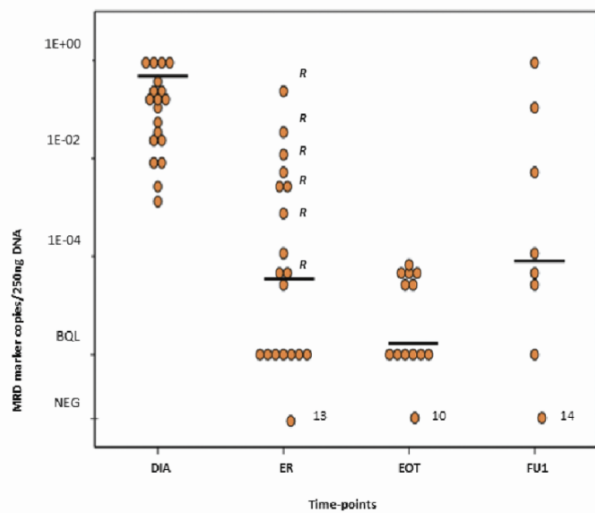
**Table S 1**

	<b>SLSG criteria. #</b>	<b>The Lugano classification * CT – based response (non avid NHL)</b>
<b>CR</b>	<ul style="list-style-type: none"> <li>➤ Resolution of organomegaly</li> <li>➤ Hb &gt; 12 g dl</li> <li>➤ Platelets &gt; 100.000/mmc</li> <li>➤ Neutrophils &gt; 1500/mmc</li> <li>➤ No evidence of circulating clonal B cells</li> <li>➤ No evidence or minor BM infiltration detected by immunohistochemistry</li> </ul>	<p>Complete radiologic response</p> <ul style="list-style-type: none"> <li>➤ Spleen &lt; 13 cm in vertical length)</li> <li>➤ Nodal masses &lt; 1.5 cm</li> <li>➤ Bone marrow normal by morphology; if indeterminate, IHC negative</li> </ul>
<b>PR</b>	<p>&gt;50% improvement; this should include:</p> <ul style="list-style-type: none"> <li>➤ Resolution or decrease of spleen size</li> <li>➤ Improvement on cytopenias</li> <li>➤ Decrease in lymphadenopathy</li> <li>➤ Decrease of BM infiltration</li> </ul>	<p>All the following:</p> <ul style="list-style-type: none"> <li>➤ Spleen must have regressed by &gt; 50% in length beyond normal</li> <li>➤ &gt;50% decrease in SPD of up to 6 target measurable nodes and extranodal sites</li> <li>➤ Bone marrow : not applicable</li> </ul>
<b>NR</b>	<p>Less than 10% improvement on the disease manifestations or deterioration of the above, respectively.</p>	<p>Spleen: increase by 50% of the extent of the prior size or if normal, &gt; 2 cm from the baseline .</p> <p>Nodes: Increase by &gt; 50% from PPD nadir.</p>

**Table S2**

<b>Parameter</b>	<b>N</b>	<b>years [2.5-97.5 Percentile]</b>	
Median age	56	66 [37-78]	
<b>Parameter</b>	<b>N</b>	<b>N</b>	<b>%</b>
Age>60	56	41	73
Gender, Male	56	33	59
Stage IV	56	56	100
LDH>ULN	55	22	40
Hb < 12 g/dL	56	26	46
Hb < 10 g/dL	56	10	18
Albumin < 3.5 g/dL	52	8	15
Platelets <150·10 <sup>3</sup> /mm <sup>3</sup>	56	42	75
Platelets < 80·10 <sup>3</sup> /mm <sup>3</sup>	56	8	14
ALC >5000/mm <sup>3</sup>	55	31	56
B2M>UNL	50	46	92
<b>HPLL SMZL score#</b>	55		
A (1)		28	52
B (2)		25	46
C (3)		1	2
<b>IIL Prognostic score@</b>	55		
Low (0)		22	40
Intermediate (1)		14	25
High (2-3)		19	35

Figure S1 (A)



(B)

