Bendamustine + Rituximab (BR) Project
Efficacy and tolerability of Bendamustine and Rituximab in first line and second line treatment in CLL

An observational study proposed by the ERIC-GIMEMA groups

Rationale for the study (first line)

Bendamustine + Rituximab is the most widely employed regimen in first line in the young and in the elderly patient¹

In the published guidelines for the appropriate use of bendamustine in first-line therapy of CLL prepared on behalf of SIE, SIES, GITMO Group² the following unmet need were recognized:

- efficacy and safety of BR in elderly patients
- efficacy and safety of BR in unfit patients
- efficacy of BR in different risk categories.

¹ Green MR, ASH, 2014 abs # 4676
- Age ≤65 years; 66-75 years and >75 years
- 0-1 comorbidity – 2 or more comorbidities
- CIRS score ≤ 6 vs > 6
- Calculated creatinine clearance ≤ 70 vs > 70 ml/min (Cockcroft-Gault formula)
- Bulky (≥ 5cm) lymphadenopathy vs patients without bulky lymph nodes
- Advanced clinical stages (Rai III/IV, Binet C) vs other
- FISH categories (17p-, 11q-, +12, 13q-)
- IGHV mutational status (mutated vs unmutated)
- CD38 (positive vs negative)
- Analysis of the impact of TP53 mutation possible (amendment)
- Other biologic markers can studied provided that their detection (e.g. CD49d, ZAP70) can be considered “clinical practice”
Efficacy and tolerability of Bendamustine and Rituximab in first line and second line treatment in CLL

An observational study proposed by the ERIC-GIMEMA groups

Rationale for the study (second line)

Data gap
- efficacy of chemoimmunotherapy in second line
- efficacy of second line treatment in low-risk and high-risk patients

Pharmacoeconomic considerations
- Availability of new drugs is limited in a number of countries
- Biosimilar rituximab soon available
TITLE: An observational study to assess the efficacy and safety of bendamustine plus rituximab in patients affected by chronic lymphocytic leukemia

Type of study: prospective, observational study.

Population:
This cohort study will recruit chronic lymphocytic leukemia (CLL) patients who were treated with first and second-line Bendamustine plus Rituximab (BR) from January 2008 to December 2014 from European centres adhering to

- the ERIC group

- the GIMEMA group
Inclusion criteria

- Diagnosis of CLL / Small Lymphocytic Lymphoma (CLL/SLL) according to the World Health Organisation (WHO) classification 2008.
- Previously untreated CLL requiring therapy according to the NCI criteria and treated with at least one cycle of BR as first-line treatment.
- CLL that received one previous line of treatment using alkylating agents and/or purine analogues with or without monoclonal antibodies, requiring second-line therapy according to the NCI criteria and treated with at least one cycle of BR.
- Age ≥ 18 years.
- Signed written informed consent according to ICH/EU/GCP and national local law.
Exclusion criteria

- Patients who have received 2 or more lines of prior therapy

- Patients with:
  - Transformation of CLL to aggressive lymphomas (Richter’s Syndrome).
  - HIV infection.
  - Active and uncontrolled HCV and/or HBV infections or liver cirrhosis.
The primary objective of the study is to observe the progression-free survival in CLL patients treated with first and second-line BR regimen.

The secondary objectives are to assess in CLL patients treated by the BR regimen in first line and as second line treatment:
- Time to next treatment (TTNT).
- Complete response (CR) rate.
- Overall response rate (ORR).
- Overall survival (OS).
- Safety of the combination BR.
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**Methods**
- «Homogeneous» collection of data based on review of clinical records
  - Caveats
    ^ selection bias
    ^ assessment of progression
    ^ recording of AE

**Expected results on «real-world patients»**
- Efficacy
- Doses planned / administered
- Tolerability in patients with coexisting medical conditions
- AIHA
## Potential number of patients and referent investigators*

<table>
<thead>
<tr>
<th>Patients</th>
<th>Czech R</th>
<th>Sweden</th>
<th>Croatia</th>
<th>Spain</th>
<th>France</th>
<th>Denmark</th>
<th>Greece</th>
<th>Turkiye</th>
<th>Ukraine</th>
<th>Poland</th>
<th>Armenia</th>
<th>Russia</th>
<th>Italy</th>
<th>Germany</th>
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<tbody>
<tr>
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<td>20</td>
<td>91</td>
<td>10</td>
<td>80</td>
<td>50</td>
<td>7</td>
<td>10</td>
<td>5</td>
<td>7</td>
<td>3</td>
<td>14</td>
<td>356</td>
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<td></td>
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</tbody>
</table>

| Proposed Referent Investigator | Martin Spacek | Lotta Hansson <lotta.hansson@karolinska.se> | Javier De La Serna | L. Fornecker | Krysztof Giannopoulos | Robak | Antonio Cuneo | Kreutzer karl-anton.kreutzer@uni-koeln.de |

* Contact with GIMEMA data centre for special regulations before submission of the dossier to national E.C.s

- Contact with single national centres to ensure homogeneity and accuracy of data collection
Activated centres in Italy as of May 31st 2016

GIMEMA ERIC LLC1315 BR study
### Activated centres in Spain as of May 31st 2016

<table>
<thead>
<tr>
<th>Site</th>
<th>PI</th>
<th>EC opinion</th>
<th>Regulatory status</th>
</tr>
</thead>
<tbody>
<tr>
<td>600 Madrid - Hematology Hospital Universitario 12 De Octubre</td>
<td>Javier De La Serna</td>
<td>Favourable</td>
<td>Open to enrollment</td>
</tr>
<tr>
<td>601 Barcellona Hematology Hospital Clinic</td>
<td>Julio Delgado</td>
<td>Favourable</td>
<td>Open to enrollment</td>
</tr>
<tr>
<td>602 Marbella (Malaga) Hospital Costa del Sol</td>
<td>Angeles Medina Perez</td>
<td>Favourable</td>
<td>Open to enrollment</td>
</tr>
<tr>
<td>603 Salamanca</td>
<td>Marcos González</td>
<td>Under consideration</td>
<td></td>
</tr>
<tr>
<td>604 Hospital Santa Creu I Sant Pau, Barcelona</td>
<td>Carol Moreno</td>
<td>Under consideration</td>
<td></td>
</tr>
</tbody>
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### Number of patients enrolled by centre

<table>
<thead>
<tr>
<th>Center</th>
<th>Enrolled Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrara Azienda Ospedaliero Universitaria Dipartimento di Scienze Mediche Sezione di Ematologia e Fisiopatologia dell'Emostasi</td>
<td>14</td>
</tr>
<tr>
<td>Madrid - Hematology Hospital Universitario 12 De Octubre</td>
<td>12</td>
</tr>
<tr>
<td>Verona Università degli Studi di Verona - A. O. - Istituti Ospitalieri di Verona- Div. di Ematologia - Policlinico G.B.</td>
<td>8</td>
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<tr>
<td>Milano Unità Trapianto di Midollo Ist. Nazionale Tumori</td>
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<tr>
<td>Latina UOC di Ematologia con trapianto Ospedale S. Maria Goretti</td>
<td>6</td>
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<tr>
<td>Catanzaro Azienda Ospedaliera Pugliese Ciaccio - Presidio Ospedaliero A.Pugliese - Unità Operativa di Ematologia</td>
<td>5</td>
</tr>
<tr>
<td>Ascoli U.O.C. Ematologia e Terapia Cellulare - Ospedale &quot;C. e G. Mazzoni&quot; di Ascoli Piceno</td>
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<tr>
<td>Piacenza Unità Operativa Ematologia e Centro Trapianti - Dipartimento di Oncologia ed Ematologia - AUSL Ospedale G. da Saliceto</td>
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</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>59</strong></td>
</tr>
</tbody>
</table>

As of 31 May 2016
N. of cases enrolled (February-May 2016)

As of 31 May 2016
Timeline

- **November 2015**: submission of the protocol to the E.C. of the coordinating centre, Institute of Hematology, University of Ferrara

- **January 2016**: Submission of the protocol to GIMEMA and ERIC centres

- **February 2016**: eCRF database open

- **May-July 2016**: speeding up the procedures, contact with reference investigators in each country, contact with each single centre in Italy

- **December 2016**: database lock
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For any question please contact

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