“Chronic Lymphocytic Leukemia and Obinutuzumab Treatment”

Laura Fogliatto

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Disclosures

- Investigator in Clinical Trials: Roche, Pfizer, MSD, Novartis, Libbs, Celgene, Abbvie e Janssen
- Advisory Board: Roche, Abbvie and Novartis
Chronic Lymphocytic Leukemia

Best first line treatment for 95 years old patients
CIRS > 6
CrCl CG ≤ 70mL/min
Age (≥65 yo)

Is the Drug Available?

Who?

Disease?

Which?

NCCN CLL Treatment Landscape

**Preferred Regimen**

- **Young/Fit**
  - Del17p Ibrutinib
  - HDMP + Rituximab
  - Obinutuzumab
  - Alemtuzumab ± Rituximab

- **Elderly**
  - Obinutuzumab + Chlorambucil*
  - Ibrutinib*
  - Rituximab + Chlorambucil
  - Bendamustine ± CD20 mAb

- **Frail**
  - Obinutuzumab + Chlorambucil*
  - Ibrutinib*
  - Ofatumumab + Chlorambucil

**Other Recommended Regimen**

- **Young/Fit**
  - FCR* Ibrutinib
  - Bendamustine ± CD20 mAb
  - FR HDMP + Rituximab
  - PCR

- **Elderly**
  - Ibrutinib*
  - Rituximab + Chlorambucil
  - Reduced-dose FCR

- **Frail**
  - Ibrutinib*
  - Reduced-dose PCR

* = Category 1

Adapted from NCCN v3.2018
Clinical Trials for Unfit Patients
Immuno-chemotherapy
COMPLEMENT 1

Unfit, TN CLL

Chlorambucil 10 mg/m²

Chlorambucil 10 mg/m² + Ofatumumab

12 months

447 patients
Endpoint: PFS
EA≥3 most common: neutropenia (26%) – O-Chlb

Hillmen P et al. The Lancet Vol 385 May 9, 2015
(CLL11) Chlorambucil + Obinutuzumab: 781 patients

Update CLL11: 40 months FUP
Progression Free Survival: G-Clb > R-Clb

Goede et al., Blood 2015, 126:1733 (ASH Annual Meeting Abstract)
CLL11: MRD AT THE END OF TREATMENT

MOLECULAR REMISSION RATE

<table>
<thead>
<tr>
<th></th>
<th>Bone Marrow</th>
<th>Peripheral Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>G-Clb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R-Clb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>26/133</td>
<td>87/231</td>
</tr>
<tr>
<td>% of MRD neg</td>
<td>19.5%</td>
<td>37.7%</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>


*DRM = Doença Residual Mínima
CLL11:
PROGRESSION FREE SURVIVAL AND NEGATIVE MRD

SLP mediana: 19.4
Median SLP not reached

Adverse Events

CLL11
Five patients who were randomised to R-Clb received one infusion of GAZYVA in error and are included in the safety population for G-Clb and not R-Clb.

Patients who received no treatment are excluded from the safety population (G-Clb = 2; R-Clb = 4).


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### CLL11 stage II: Grade ≥3 AEs

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>R-Clb (n=321)</th>
<th>G-Clb (n=336)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any grade ≥3 AE</td>
<td>186 (58)</td>
<td>239 (71)</td>
</tr>
<tr>
<td>IRRs</td>
<td>13 (4)</td>
<td>67 (20)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>91 (28)</td>
<td>111 (33)</td>
</tr>
<tr>
<td>Infections</td>
<td>46 (14)</td>
<td>41 (12)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>10 (3)</td>
<td>35 (10)</td>
</tr>
</tbody>
</table>

- All grade ≥3 AEs occurring until the **May 2013 clinical cut-off** in ≥5% of patients are shown.
- There were no deaths attributed to IRRs, neutropenia or thrombocytopenia. There were two deaths from infection in the R-Clb arm (both pneumonia) and two in the G-Clb arm (septic shock, pulmonary sepsis).

AE, adverse event; Clb, chlorambucil; CLL, chronic lymphocytic leukaemia; G-Clb, GAZYVA + Clb; IRR, infusion-related reaction; R-Clb, MabThera + Clb.
Cytokine release and IRR: CLL pts treated with Obinutuzumab

Freeman et al. Blood. 2015 Dec 10; 126(24): 2646–2649
CLL11: MOST COMUM ADVERSE EVENT IS INFUSIONAL REACTION

Atention to the first cycle: IRR grades 3 and 4 → Day 1

To reduce the IRR: pre-medication, debulking

R-Bendamustine
R- Benda, Untreated CLL, Phase II Trial, German Chronic Lymphocytic Leukemia Study Group

Rituximab 375 mg/m² C1  Rituximab 500 mg/m² C2-C6
Benda 90 mg/m² D1-2, C1-C6

117 patients fit and unfit

Primary endpoint: Overall response

R- Benda, Untreated CLL, Phase II Trial, German Chronic Lymphocytic Leukemia Study Group

- Median age 64 years (max 78 yrs)
- 1/4 population: 70 years or older
- 1/3 had a creatinine clearance $\leq$ 70 mL/min

R-Benda, efficacy

- ORR: 80%, CR 21%
- MRD in PB: 57.8%
- MRD in BM: 29.2%

• The most common adverse events were hematologic toxicities
• 1/4 was not able to complete the full six cycles
• 62.4% treatment was delayed between 1 and 28 days
• 1/2 decreased the dose due to hematologic toxicity
• 72.6% used infectious prophylaxis
• 21.4% were treated with G-CSF
Oral Target Therapy
Ibrutinib
Pts aged ≥65 yo with treatment-naïve CLL/SLL 17p deletion excluded

Primary endpoint: PFS

IBRUTINIB 420 MG/DIA continuous

CLB 0,5 mg/kg, D1 and D15 Up 12 cycles

Tedeschhi et al. Blood 2017; 126:495;
Resonate-2™

- 269 pts enrolled
- Median age: 73 years (70% ≥70 years)
- Baseline characteristics were balanced between arms:
  - 69% had comorbidities at baseline including CIRS score >6, reduced creatinine clearance, or ECOG status of 2.

Tedeschhi et al. Blood 2017; 126:495;
Resonate-2™: 3-year Follow up

PFS

- Chlorambucil: Median time (months) 15.0, Hazard ratio, 0.09 (95% CI, 0.04-0.17), P<0.0001 by log-rank test
- Ibrutinib: Median time (months) NE

SG

- Chlorambucil: Median time (months) NE
- Ibrutinib: Median time (months) NE

Tedeschhi et al. Blood 2017; 126:495;
## Adverse Events: 3-year Follow up

### Prevalence of Most Common* G≥3 AEs Over Time on Ibrutinib Arm

<table>
<thead>
<tr>
<th>Adverse Event, n(%)</th>
<th>0-1Year (N=135)</th>
<th>1-2 Years (N=123)</th>
<th>2-3 Years (N=111)</th>
<th>3-4 Years (N=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>11 (8)</td>
<td>4 (3)</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>7 (5)</td>
<td>3 (2)</td>
<td>4 (4)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td><strong>23 (17)</strong></td>
<td><strong>9 (7)</strong></td>
<td><strong>10 (9)</strong></td>
<td>0</td>
</tr>
<tr>
<td>Bleeding</td>
<td>4 (3)</td>
<td>4 (3)</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Atrial Fibrillation</strong></td>
<td><strong>2 (1)</strong></td>
<td><strong>0</strong></td>
<td><strong>4 (4)</strong></td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6 (4)</td>
<td>2 (2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>3 (2)</td>
<td>2 (2)</td>
<td>0</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (4)</td>
<td>0</td>
<td>1 (1)</td>
<td>0</td>
</tr>
</tbody>
</table>

* > 5 % of patients

Tedeschhi et al. Blood 2015 126:495
Long Term AE with Ibrutinib (Warning and Precautions)

- **Hemorrhage:**
  - **Major bleeding** in up to 6% of patients, **minor up to 50%**
  - **At risk:** use of antiplatelet or anticoagulant therapies
    - Consider the benefit-risk of withholding Ibrutinib for at least 3 to 7 days pre- and postsurgery depending upon the type of surgery and the risk of bleeding.

- **Infections** - 14% to 29% of patients.

- **Cytopenias** (Grades 3 or 4)
  - neutropenia (range, 13% to 29%),
  - thrombocytopenia (range, 5% to 17%),

https://www.imbruvica.com/prescribing-information
Long Term AE with Ibrutinib (Warning and Precautions)

- **Hypertension**
  - Hypertension (range, 6% to 17%), median time to onset of 4.6 months (range, 0.03 to 22 months).

- **Atrial Fibrillation**
  - Atrial fibrillation and atrial flutter (range, 6% to 9%)
  - **Pts at risk: hypertension, acute infections, and a previous history of atrial fibrillation.**
Cross-Trial

Ibrutinib vs Chemotherapy

Robak et al. Blood 2017 130:1750
Cross-Trial

**IBRUTINIB**

**IMMUNO-CHEMOTHERAPY**

Phase III Trials (Fit and Unfit)

- FCR – CLL8
- FCR – CLL10
- BR- CLL10
- G-Clb – CLL11
- R-Cbl – CLL11
- Ofa-Clb – COMPLEMENT1

Robak et al. Blood 2017 130:1750
## Cross-Trial: Population

### Median age

<table>
<thead>
<tr>
<th>Population</th>
<th>RESONATE-2 1brutinib N=136</th>
<th>CLL10 BR N=279</th>
<th>CLL10 FCR N=282</th>
<th>CLL8 FCR N=408</th>
<th>CLL11 G-CLB N=333</th>
<th>CLL11 R-Clb N=330</th>
<th>COMPLEMENT-1 Ofa-Clb N= 221</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>73 (65-89)</td>
<td>61 (54-69)</td>
<td>62 (55-67)</td>
<td>61 (30-80)</td>
<td>74 (39-89)</td>
<td>73 (40-90)</td>
<td>69 (35-92)</td>
</tr>
</tbody>
</table>

### Median CIRS

<table>
<thead>
<tr>
<th></th>
<th>RESONATE-2 1brutinib N=136</th>
<th>CLL10 BR N=279</th>
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<th>COMPLEMENT-1 Ofa-Clb N= 221</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median CIRS</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>8</td>
<td>8</td>
<td>9</td>
</tr>
</tbody>
</table>

### Unmutated IGHV

<table>
<thead>
<tr>
<th></th>
<th>RESONATE-2 1brutinib N=136</th>
<th>CLL10 BR N=279</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Unmutated IGHV</td>
<td>43%</td>
<td>68%</td>
<td>55%</td>
<td>63%</td>
<td>62%</td>
<td>61%</td>
<td>57%</td>
</tr>
</tbody>
</table>

### Del(17p)

<table>
<thead>
<tr>
<th></th>
<th>RESONATE-2 1brutinib N=136</th>
<th>CLL10 BR N=279</th>
<th>CLL10 FCR N=282</th>
<th>CLL8 FCR N=408</th>
<th>CLL11 G-CLB N=333</th>
<th>CLL11 R-Clb N=330</th>
<th>COMPLEMENT-1 Ofa-Clb N= 221</th>
</tr>
</thead>
<tbody>
<tr>
<td>Del(17p)</td>
<td>Excluded</td>
<td>Excluded</td>
<td>Excluded</td>
<td>7%</td>
<td>7%</td>
<td>7%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Robak et al. Blood 2017 130:1750
## Cross-Trial: Safety

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Overall Grade≥3 AE</td>
<td>73%</td>
<td>76%</td>
<td>84%</td>
<td>94%</td>
<td>70%</td>
<td>55%</td>
<td>50%</td>
</tr>
<tr>
<td>Infection Grade≥3</td>
<td>25% ≥ 65 yrs</td>
<td>25% ≥ 65 yrs</td>
<td>27% ≥ 65 yrs</td>
<td>40% ≥ 65 yrs</td>
<td>12% ≥ 65 yrs</td>
<td>14% ≥ 65 yrs</td>
<td>9% ≥ 65 yrs</td>
</tr>
<tr>
<td></td>
<td>25% ≤ 65 yrs</td>
<td>25% ≤ 65 yrs</td>
<td>27% ≤ 65 yrs</td>
<td>36% ≤ 65 yrs</td>
<td>12% ≤ 65 yrs</td>
<td>14% ≤ 65 yrs</td>
<td>9% ≤ 65 yrs</td>
</tr>
<tr>
<td>Anemia Grade≥3</td>
<td>9%</td>
<td>5%</td>
<td>10%</td>
<td>14%</td>
<td>4%</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>Neutropenia Grade≥3</td>
<td>12%</td>
<td>34%</td>
<td>59%</td>
<td>84%</td>
<td>33%</td>
<td>28%</td>
<td>26%</td>
</tr>
<tr>
<td>Thrombocytopenia Grade≥3</td>
<td>4%</td>
<td>7%</td>
<td>14%</td>
<td>22%</td>
<td>10%</td>
<td>3%</td>
<td>5%</td>
</tr>
</tbody>
</table>

*Median treatment duration was approximated using the median number and length of cycles; mean number of cycles reported for CLL8 FCR. **Grade 3-4 AEs reported for CLL8 FCR. †Data collected only for CLL10. ‡FCR N=193, BR N=171. §FCR N=86, BR N=107.*

Robak et al. Blood 2017 130:1750
Cross-Trial: PFS

Robak et al. Blood 2017 130:1750
Cross-Trial: OS

*Shaded area represents 95% confidence interval for ibritinib

Robak et al. Blood 2017 130:1750
How to treat a 95 years old patient?

Unfit /Frail Patient

With 17p deletion
- Ibrutinib
- Alternative: Venetoclax, Idelalisib

No 17p deletion
- G-CLB
- Anti-CD20+Clb
- Ibrutinib
- Rituximab + Benda

Frail: Clb, Anti-CD20

Adaptado de ESMO (http://www.esmo.org, acessed in Feb 2018; NCCN (www.nccn.org, acessed in Feb 2018; Rev Bras Hematol Hemoter 2016;38:346-57)
MRD based therapy

BIG

BAG

BIO

Bendamustine X 2

G-Ibrutinib X 6

G-Venetoclax X 6

O+Ibrutinib X 6

G 3/3 meses+ Ibrutinib cont

G 3/3 meses+ Venetoclax cont

O 3/3 meses+ Ibrutinib cont

Up to 24 months

MRD

STOP

Tresckow at al. Blood 2015 126:4151
Cramer et al. Blood 2016 128:2044
Cramer et al. Blood 2017 130:494

G: Obinutuzumab, O: Ofatumumab
Conclusions

- Single continuous oral agents are effective and have low toxicity.
  - Problems: long term adverse events, high cost
- Chlb-obinutuzumab treatment: effective, many patients achieve MRD neg and stop treatment.
  - Problems: acute toxicity (IRR) and cytopenias
- Bendamustine is effective but associated with high rates of hematologic toxicity
- Phase III trials and long term follow up are necessary
- **Recognizing patient’s fitness and disease status is mandatory before choosing the treatment**

Jain et al. Blood 2017 130:495
Stilgenbauer et al. Blood 2017 130:4309
Flinn et al. Blood 2017 130:430