Treatment of chronic lymphocytic leukemia

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Indolent lymphoma

Frequency of subtypes

- Follicular: 31%
- B-CLL: 38%
- Waldenstrom: 6%
- MALT: 8%
- B-PLL: 1%
- HCL: 3%
- MCL: 4%
- Unknown: 4%
- Other indolent: 5%
Chronic lymphocytic leukemia
Definition

- >5,000/µL clonal B-cells in peripheral blood
- immunphenotype: CD19⁺CD5⁺CD23⁺
**CLL in the elderly**

**Tip of the iceberg**

<table>
<thead>
<tr>
<th>Genetic lesion 13q14 / equivalent</th>
<th>Aging immune system</th>
<th>Specific antigen receptor</th>
<th>Escape from B-cell homeostasis</th>
<th>CLL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
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</tr>
<tr>
<td>10</td>
<td></td>
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<tr>
<td>100</td>
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</tr>
<tr>
<td>1000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10,000</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Population prevalence**

- 0.02%
- 0.05%
- 1%
- 20%

**Health Issues**

- No known effect
- Impaired B-cell function
- Treatment for progressive disease

**A. Rawstron**
Clinical Staging
Binet (1981)

**Stage A:** no anemia, no thrombocytopenia <3 LN-regions* enlarged

**Stage B:** no anemia, no thrombocytopenia >3 LN-regions* enlarged

**Stage C:** anemia (Hb <10 g/dl) and/or thrombocytopenia <100/nl

* Only physical examination, no ultrasound, no CT!
CLL8: FC +/- Rituximab
Overall survival

Hallek, Lancet 2011
Fitness status and treatment

Front-line CLL

- MRD-/OS
- Durable remission
- Symptom control/palliation

Very fit

FCR-lite?
CVP-R?
CHOP-R?
B (R)?
Clb-R?
Ofatumumab

Very unfit

Chlorambucil-R
Chlorambucil-G
German guidelines for first-line treatment of CLL (Onkopedia) *Update 2016*

**Asymptomatic**

- All
  - Without del(17p13) or TP53mut
    - ≤65 years: **FCR** → CR/PR → Watch and wait
    - >65 years: **BR** → SD/PD → Watch and wait

**Symptomatic**

- Fit (go go)
  - **FCR** → CR/PR → Second-line therapy

- Frail (no go)
  - Best supportive care
Long-term remissions after FCR chemoinmunotherapy in previously untreated patients with CLL: updated results of the CLL8 trial


**FCR:** median PFS: 56.8 months
Long term remissions after FCR chemoimmunotherapy

Overall survival (OS) in IGHV mutated/unmutated patients

Median observation time 5.9 years

Median OS
- FCR IGHV mutated: Not reached
- FC IGHV mutated: Not reached
- FCR IGHV unmutated: 86 months
- FC IGHV unmutated: 75 months

Fischer, Blood 2016
Very low-risk group even cured by chemotherapy FCR?

age/sex matched general population

- Very low-risk group even cured by chemotherapy FCR?
- Low risk: mutated IGHV, no 11q-, no 17p-

### Pairwise comparisons of the OS curves

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>5-years OS</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>90</td>
<td>91.4</td>
<td>87.1-95.7</td>
</tr>
<tr>
<td>32</td>
<td>197</td>
<td>83.2</td>
<td>80.0-86.4</td>
</tr>
<tr>
<td>14</td>
<td>30</td>
<td>57.5</td>
<td>47.6-67.4</td>
</tr>
</tbody>
</table>

### Events vs. Total

- **Events**: 5, 32, 14
- **Total**: 90, 197, 30

### Cumulative Probability of OS (%)

- Months: 0, 20, 40, 60, 80, 100
- Cumulative Probability: 0, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120

### Pairwise Comparisons

<table>
<thead>
<tr>
<th></th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.0341</td>
</tr>
<tr>
<td></td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Rossi, Blood 2015**
Bendamustine:
An ‘agent’ with a long history

- synthesis: W. Ozegowski, D. Krebs, Institute of Microbiology and Experimental Therapy, Jena (1962)
- Published in Journal für Praktische Chemie, Vol. 20, issue 3-4, 1963
- IMET 3393 was developed by H. Knöll and later named Cytostasan
CLL10 Study: FCR vs BR

Patients with untreated, active CLL without del(17p) and good physical fitness (CIRS ≤ 6, creatinine clearance ≥ 70 ml/min)

Randomization

FCR
- Fludarabine 25 mg/m² i.v., days 1-3
- Cyclophosphamide 250 mg/m², days 1-3,
- Rituximab 375 mg/m² i.v. day 0, cycle 1
- Rituximab 500 mg/m² i.v. day 1, cycle 2-6

BR
- Bendamustine 90 mg/m² day 1-2
- Rituximab 375 mg/m² day 0, cycle 1
- Rituximab 500 mg/m² day 1, cycle 2-6

Non-Inferiority of BR in comparison to FCR for PFS:
HR (λ BR/FCR) less than 1.388
**FCR vs BR for fit patients**

**Progression-free survival**

Patients ≤ 65 years:  \( P < 0.001 \)
- FCR: 53.6 months
- BR: 38.5 months

Patients > 65 years:  \( P = 0.170 \)
- FCR: not reached
- BR: 48.5 months

*Eichhorst, Lancet Oncol 2016*
### CLL10 Study: FCR VS BR
Infections CTC 3-4

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>FCR (% of pt)</th>
<th>BR (% of pt)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Infections</td>
<td>39.1</td>
<td>26.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Infections during therapy only</td>
<td>22.6</td>
<td>17.3</td>
<td>0.1</td>
</tr>
<tr>
<td>Infections during first 5 months after therapy</td>
<td>11.8</td>
<td>3.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All infections in patients ≤ 65 years</td>
<td>35.2</td>
<td>27.5</td>
<td>0.1</td>
</tr>
<tr>
<td>All infections in patients &gt; 65 years</td>
<td>47.7</td>
<td>20.6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Eichhorst, Lancet Oncol 2016
Classification of patients by a geriatric assessment
CLL11 Trial of GCLLSG

Previously untreated CLL

Total CIRS score >6 and/or creatinine clearance <70 mL/min

N=780 (planned)

2:1:2

- **GA101 + chlorambucil x 6 cycles**
- **Chlorambucil x 6 cycles (control arm)**
- **Rituximab + chlorambucil x 6 cycles**

- GA101: 1000 mg days 1, 8, and 15 cycle 1; day 1 cycles 2–6, every 28 days
- Rituximab: 375 mg/m² day 1 cycle 1, 500 mg/m² day 1 cycles 2–6, every 28 days
- Chlorambucil: 0.5 mg/kg day 1 and day 15 cycle 1–6, every 28 days
**G–Clb vs. R–Clb vs. Chlorambucil**

**Response rates**

![Bar chart showing response rates for G–Clb, Clb, and R–Clb.]

- **G–Clb (N=238)**
  - Complete response: 22.3%
  - Partial response: 55.0%

- **Clb (N=118)**
  - Complete response: 31.4%
  - Partial response: 58.4%

- **R–Clb (N=233)**
  - Complete response: 7.3%
  - Partial response: 58.4%

*P < 0.001 for all comparisons*

*Goede, NEJM 2014*
CLL11: R-Clb versus G-Clb
Progression-free survival

Clb + obinutuzumab
Clb + rituximab

Stratified HR: 0.39
95% CI, 0.31-0.49
P<0.0001

Goede, NEJM 2014
Communication to Investigators about increased risk of tumor lysis syndrome (TLS) in patients with Chronic Lymphocytic Leukemia (CLL) treated with GAZYVA/GAZYVARO plus bendamustine, and additional risk minimization measures to be implemented for patients at risk for TLS

Dear Investigator,

F. Hoffmann-La Roche Ltd. (Roche) would like to inform you about 2 fatal cases of Tumor Lysis Syndrome reported in the GREEN study (MO28543, NCT01905943), a single-arm Phase IIIb study evaluating the safety of GAZYVA/GAZYVARO as monotherapy and in combination with chemotherapy (chlorambucil: Clb, Fludarabine, Cyclophosphamide: FC, Bendamustine) in previously untreated and relapsed/refractory patients with CLL. Both cases occurred during the first line treatment with GAZYVA/GAZYVARO plus bendamustine. The patients had a high tumour load ($\geq 25 \times 10^9$/L absolute lymphocyte count and / or bulky disease) and / or renal impairment at baseline and developed TLS after the Cycle1 Day1-2 infusions of 1000 mg GAZYVA/GAZYVARO plus 90 mg/m² bendamustine. In the same study, the sponsor also observed an overall incidence of 8-10% of reported TLS (clinical or laboratory) in patients with CLL treated with GAZYVA/GAZYVARO plus bendamustine.
German guidelines for first-line CLL of CLL (Onkopedia) Update 2016

**Asymptomatic**

- **All**
  - **Fit (go go)**
    - Without del(17p13) or TP53mut
      - ≤65 years: **FCR**
      - >65 years: **BR**
    - With del(17p13) or TP53mut
    - **Watch and wait**
  - **Unfit (slow go)**
    - Without del(17p13) or TP53mut
    - With del(17p13) or TP53mut
  - **Second-line therapy**
    - Watch and wait

**Symptomatic**

- **Fit (go go)**
  - Ibrutinib or (Idelalisib+R)
    - **CR/PR**
    - SD/PD
    - **Watch and wait**
- **Unfit (slow go)**
  - Chl + Obin or Chl + Ofa or B + Ritux (Chl + Ritux) or (B + Ofa)
  - **CR/PR**
  - SD/PD
  - **Watch and wait**
- **Unfit (slow go)**
  - Ibrutinib or (Idelalisib+R)
  - **CR/PR**
  - SD/PD
  - **Second-line therapy**
- **Frail (no go)**
  - Best supportive care

**Wendtner, DGHO guidelines 2016**
German guidelines for first-line CLL (Onkopedia)
CLL: imbalance of life and death signals

**BCR**
- Ibrutinib, Idelalisib

**TLR**
- MyD88

**NFκB**

**Cell Survival**

**Chemotherapy**
- Radiation
- Oncogenic stress

**ATM**

**p53**

**NOXA, PUMA**

**ABT-199**

**Programmed Cell Death**

**Chemotherapy**
- Radiation
- Oncogenic stress
CLL: imbalance of life and death signals

**BCR**  
Ibrutinib, Idelalisib

**TLR**  
MyD88

NFκB

Cell Survival

Chemotherapy  
Radiation  
Oncogenic stress

ATM

p53

NOXA, PUMA

ABT-199

Programmed Cell Death

**CLL:** imbalance of life and death signals
Ibrutinib: RESONATE Update
*Progression free survival (PFS) – All Patients*

- Ibrutinib lengthened PFS (median not reached vs. 8.1 mo, HR=0.106, P<0.001).
- 12-month PFS rate improved (84% vs. 18%, P<0.001).

*Maintenance Ibrutinib after Rituximab-CHOP in Unselected Subjects with Early-Stage Diffuse Large B-Cell Lymphoma (ASH Abstract 2014 #3331)*
**Phase 3, International, open-label, randomized, multicenter study**

- Treatment naïve CLL or SLL requiring therapy; >65 years

**Study Design**

- **N=269**

**Randomize 1:1**

**Oral ibrutinib**

420 mg once daily*  
\[ n = 136 \]

*until PD or unacceptable toxicity

**Oral Chlorambucil**

0.5mg/kg d1 & 15 of 28d cycle for 12 cycles*  
\[ n = 133 \]

*dose increased to max of 0.8mg/kg, if tolerated. Treatment for 12 cycles, or PD, lack of efficacy or unacceptable toxicity

**Patients with IRC-confirmed PD were enrolled into a separate extension study PCYC-1116-CA for follow-up and second-line treatment per investigator’s choice (including ibrutinib for patients progressing on chlorambucil)**

**Burger, N Engl J Med 2015**
Progression-free Survival

**Burger, N Engl J Med 2015**

**A Progression-free Survival According to Independent Assessment**

- **Patients with Progression-free Survival (%)**
- **Chlorambucil** vs **Ibrutinib**
- **Median (mo)**: Chlorambucil 18.9, Ibrutinib NR
- **Hazard ratio, 0.16 (95% CI, 0.09–0.28); P<0.001**

**No. at Risk**

<table>
<thead>
<tr>
<th></th>
<th>Ibrutinib</th>
<th>Chlorambucil</th>
</tr>
</thead>
<tbody>
<tr>
<td>27</td>
<td>136</td>
<td>133</td>
</tr>
<tr>
<td>24</td>
<td>133</td>
<td>121</td>
</tr>
<tr>
<td>21</td>
<td>130</td>
<td>95</td>
</tr>
<tr>
<td>18</td>
<td>126</td>
<td>85</td>
</tr>
<tr>
<td>15</td>
<td>122</td>
<td>74</td>
</tr>
<tr>
<td>12</td>
<td>122</td>
<td>49</td>
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<tr>
<td>9</td>
<td>98</td>
<td>34</td>
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<tr>
<td>6</td>
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</tr>
<tr>
<td>3</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

**A Overall Survival**

- **Patients Who Survived (%)**
- **Chlorambucil** vs **Ibrutinib**
- **Hazard ratio, 0.16 (95% CI, 0.05–0.56); P=0.001 by log-rank test**

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Ibrutinib</th>
<th>Chlorambucil</th>
</tr>
</thead>
<tbody>
<tr>
<td>27</td>
<td>136</td>
<td>133</td>
</tr>
<tr>
<td>24</td>
<td>134</td>
<td>127</td>
</tr>
<tr>
<td>21</td>
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<td>6</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>0</td>
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</table>

**Months**
PFS, Including Extension Study

Idelalisib + R vs Placebo + R

All Patients

<table>
<thead>
<tr>
<th>Group</th>
<th>Median PFS (95% CI)</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDELA + R</td>
<td>19.4 mo (16.6, -)</td>
<td>0.25 (0.16, 0.39)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PBO + R</td>
<td>7.3 mo (5.5, 8.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sharman, ASH, 2014: #330
Pl3Ki side effects

Colitis
PI3Ki side effects
pneumonitis
German guidelines for first-line CLL (Onkopedia)
Background: Mechanism of action of Venetoclax

1. An Increase in BCL-2 Expression Allows the Cancer Cell to Survive
   - Pro-apoptotic Proteins (BAX, BAK)
   - Anti-apoptotic Proteins (BCL-2)

2. Venetoclax Binds to and Inhibits Overexpressed BCL-2
   - BH3-only
   - BAX
   - BCL-2

3. Apoptosis is Initiated
   - Apoptosome
   - APAF-1
   - Cytochrome C
   - Active Caspase
   - Procaspase

Gerecitano, ASH 2015, #254
Venetoclax in relapsed CLL (p53-)

Best Response

<table>
<thead>
<tr>
<th></th>
<th>Arm 1</th>
<th>Arm 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response</td>
<td>85 (79.4)</td>
<td>79 (73.8)</td>
</tr>
<tr>
<td>CR or CRi</td>
<td>8 (7.5)</td>
<td>17 (15.9)</td>
</tr>
<tr>
<td>nPR</td>
<td>3 (2.8)</td>
<td>4 (3.7)</td>
</tr>
<tr>
<td>PR</td>
<td>74 (69.2)</td>
<td>58 (54.2)</td>
</tr>
<tr>
<td>No response</td>
<td>22 (20.6)</td>
<td>28 (26.2)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>NA</td>
<td>24 (22.4)</td>
</tr>
<tr>
<td>Disease progression</td>
<td>NA</td>
<td>2 (1.9)</td>
</tr>
<tr>
<td>Incomplete data</td>
<td>NA</td>
<td>2 (1.9)</td>
</tr>
</tbody>
</table>

- 25 of 48 patients with no CLL in the bone marrow
- 18 of 45 patients assessed were MRD-negative in PB
Venetoclax in relapsed CLL (p53-) 
Durability of Responses

Stilgenbauer, Lancet Oncology 2016

- 12-month estimates:
  - All responders: 84.7%
  - CR/CRi/nPR: 100%
  - MRD-negative: 94.4%

- 12-month estimates (95% CI):
  - PFS: 72.0% (61.8, 79.8)
  - OS: 86.7% (78.6, 91.9)
**Venetoclax in relapsed CLL (p53-)**

**Treatment-Emergent Adverse Events**

<table>
<thead>
<tr>
<th>Event</th>
<th>Any grade n (%)</th>
<th>Grade 3/4 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any treatment-emergent adverse event</td>
<td>103 (96)</td>
<td>81 (76)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>46 (43)</td>
<td>43 (40)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>31 (29)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>31 (29)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Anemia</td>
<td>29 (27)</td>
<td>19 (18)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>23 (22)</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>21 (20)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>20 (19)</td>
<td>16 (15)</td>
</tr>
<tr>
<td>Hyperphosphatemia</td>
<td>17 (16)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>16 (15)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Upper respiratory tract infection b</td>
<td>16 (15)</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>

*Stilgenbauer, Lancet Oncology 2016*
German guidelines for relapsed CLL (Oncopedia)
Fourth Generation of GCLLSG Trials
Risk, Stage and Fitness Adapted, Using Targeted Agents

Inactive Binet A

CLL12
Comprehensive biological & genetic risk assessment

W&W W&W Ibrutinib
Low, intermediate, high, very high

W&W

Active disease

CLL13
Go go

FCR/BR AR AG AIG

Disease (MRD) eradication and longer survival

CLL14
Slow go

CLB-G AG

Long-term disease-control with minimal side effects

Delay disease onset
Strategies for the future to achieve long-term disease control in CLL

Debulking
- Mild chemotherapy with agents like bendamustine or fludarabine

Induction (combination therapy)
- Kinase inhibitor(s)
- Antibody
- Bcl2 antagonist

MRD tailored maintenance (single agents)
- Antibody
- Lenalidomide
- Kinase inhibitor
- Bd2 antagonist

1-2 months (1–2 courses)
6-12 months
1 year - ∞

Hallek, Blood. 2013;122(23)
Conclusions

• Chemoimmunotherapy: long-term remissions in CLL pts (fit, IGHV mut etc.)

• Chemoimmunotherapy: treatment-free periods!

• Chemoimmunotherapy: more cost-effective

• novel agents: long-term toxicities unknown

• Chemoimmunotherapy in combination with novel drugs reasonable
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MEDIZINISCHE KLINIK UND POLIKLINIK III
DIREKTOR PROF. DR. W. HIDDEMANNN