Advances in the treatment of Chronic Lymphocytic Leukemia

Lab of B Cell Neoplasia - Division of Experimental Oncology
Strategic Research Program on CLL – Department of Onco-Hematology

Università Vita-Salute San Raffaele - Milano
Istituto Scientifico San Raffaele - Milano

Paolo Ghia
Disclaimer:

• The event is supported by Janssen, Pharmaceutical Companies of Johnson & Johnson in EMEA

• The views expressed in these slides are those of the individual speaker(s) and do not necessarily reflect the views of Janssen, Pharmaceutical Companies of Johnson & Johnson in EMEA

• The presentations may include discussions on off-label use of drugs
CLL treatment has evolved over multiple decades

1960s
Single-agent alkylating agents (e.g. chlorambucil)

1970s
Purine analogs (e.g. fludarabine)

1980s
Combination chemotherapy (e.g. FC)

1990s
Chemoimmunotherapy (e.g. FCR)

2000s
BR for patients not suitable for FCR²

2010s

2014-16

Novel targeted agents: idelalisib, ibrutinib and Venetoclax

Representative PFS/TFS (months)¹,a

12
20
34
58
43

¹ PFS representative only; cannot be used to compare regimens directly because results are drawn from across trials with different patient characteristics
² BR for patients not suitable for FCR


B: bendamustine; C: cyclophosphamide; CIT: chemoimmunotherapy;
CLL: chronic lymphocytic leukemia; F: fludarabine; PFS: progression-free survival; R: rituximab
ESMO 2016 guidelines update for first line CLL

Confirmed diagnosis of CLL

Early-stage (Binet A/B) with active disease or advanced stage (Binet C)

- del(17p) or TP53 mutation
  - Less fit: Ibrutinib or Idealisib + R*; Consider alloSCT in remission
  - Fit: Ibrutinib or Idealisib + R*; Consider alloSCT in remission

- No del(17p) or TP53 mutation
  - Less fit: Clb + CD20 antibody or Ibrutinib
  - Fit: FCR (BR considered in fit elderly patients with history of infections)

Early-stage (Binet A/B) without active disease

Watch and wait until symptomatic

*only if not suitable for alternative treatment*
Confirmed diagnosis of CLL

Early-stage (Binet A/B) with active disease or advanced stage (Binet C)

- del(17p) or TP53 mutation
  - Less fit
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  - Fit
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    - Idealisib + R*; Consider alloSCT in remission

- No del(17p) or TP53 mutation
  - Less fit
    - Clb + CD20 antibody
    - Or Ibrutinib
  - Fit
    - FCR (BR considered in fit elderly patients with history of infections)

Early-stage (Binet A/B) without active disease

Watch and wait until symptomatic

* only if not suitable for alternative treatment

Updated BHS guidelines for first line CLL

- **CLL Front-line**
  - Advanced or active disease
    - No 17p del/p53 mut
      - Unfit for FCR
        - BR or Chi-Ob
        - Chi-R
        - Chi
    - 17p del/p53 mut
      - Fit for FCR
        - FCR <55y: FCR or BR
      - Ibrutinib or Idena-R
        - allo SCT
  - No advanced or active disease
    - Wait & See
**Long term remissions with FCR**

### CLL8

<table>
<thead>
<tr>
<th></th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>FCR IGHV M patients</td>
<td>113</td>
</tr>
<tr>
<td>FC IGHV M patients</td>
<td>117</td>
</tr>
<tr>
<td>FCR IGHV UM patients</td>
<td>197</td>
</tr>
<tr>
<td>FC IGHV UM patients</td>
<td>195</td>
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</table>

### MDACC

<table>
<thead>
<tr>
<th></th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGHV-M, MRD neg</td>
<td>35</td>
</tr>
<tr>
<td>IGHV-M, MRD pos</td>
<td>34</td>
</tr>
<tr>
<td>IGHV-UM, MRD neg</td>
<td>35</td>
</tr>
<tr>
<td>IGHV-UM, MRD pos</td>
<td>66</td>
</tr>
</tbody>
</table>
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Early-stage (Binet A/B) without active disease

Watch and wait until symptomatic

* only if not suitable for alternative treatment


PHBE/IBR/0217/0003
**RESPONSE-2 (PCYC-1115) Study Design**

**Patients (N=269)**
- Treatment-naïve CLL/SLL with active disease
- Age ≥65 years
- For patients 65-69 years, comorbidity that may preclude FCR
- del17p excluded
- Warfarin use excluded

**Stratification factors**
- ECOG status (0-1 vs. 2)
- Rai stage (III-IV vs. ≤II)

**Randomize 1:1**

- **Ibrutinib 420 mg once daily until PD or unacceptable toxicity**
- **Chlorambucil 0.5 mg/kg (to maximum 0.8 mg/kg) days 1 and 15 of 28-day cycle up to 12 cycles**

**PCYC-1116 Extension Study**
- In clb arm, n=43 crossed over to ibrutinib

*Patients with IRC-confirmed PD enrolled into extension Study 1116 for follow-up and second-line treatment per investigator’s choice (including ibrutinib for patients progressing on chlorambucil with iwCLL indication for treatment).

**Phase 3, open-label, multicenter, international study**

**Primary endpoint:** PFS as evaluated by IRC (2008 iwCLL criteria)\(^1,2\)

**Secondary endpoints:** OS, ORR, hematologic improvement, safety

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PHBE/IBR/0217/0003

*Burger J et al, NEJM 2015*
Ibrutinib CR rates continue to improve over time: increasing from 7% at 12 months to 15% at 24 months to 18% with median follow-up of 29 months
Are We Harming Our Patients without MRD?

**RESONATE-2:** Ibrutinib vs chlorambucil

- No MRD-negative cases were reported

**GCLLSG CLL11:** Obinutuzumab + chlorambucil

- Stratified HR: 0.39
- 95% CI: 0.31–0.49
- *p* < 0.0001

- 88% reduction in the risk of progression or death for patients randomized to ibrutinib

- 41% of patients receiving chlorambucil have crossed over to receive ibrutinib

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- Less fit
  - Ibrutinib
  - Or
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- Fit
  - FCR (BR considered in fit elderly patients with history of infections)

**Early-stage (Binet A/B) without active disease**
- Watch and wait until symptomatic

* only if not suitable for alternative treatment
TP53 disruption is associated with poor prognosis

<table>
<thead>
<tr>
<th>Aberration</th>
<th>Incidence (%)</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17p del</td>
<td>7</td>
<td>32</td>
</tr>
<tr>
<td>11q del</td>
<td>18</td>
<td>79</td>
</tr>
<tr>
<td>+12</td>
<td>16</td>
<td>114</td>
</tr>
<tr>
<td>Normal</td>
<td>18</td>
<td>111</td>
</tr>
<tr>
<td>13q del</td>
<td>55</td>
<td>133</td>
</tr>
</tbody>
</table>

DNA BINDING

EX4

EX9

393

TP53

Translation of TP53

Missense

Nonsense

Frameshift

<table>
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</tr>
<tr>
<td>13q del</td>
<td>55</td>
<td>133</td>
</tr>
</tbody>
</table>

OS1

% Surviving

Months

FCR not effective in del17p/TP53 disrupted patients

CLL8: FCR

Overall survival

Time since randomisation (months)

CLL8: FCR and FC in patients with TP53 mut

Overall survival

Time (months)

No Difference in PFS With or Without Del17p

<table>
<thead>
<tr>
<th></th>
<th>No del</th>
<th>Del</th>
</tr>
</thead>
<tbody>
<tr>
<td>ibrutinib del17p, no</td>
<td>64</td>
<td>46</td>
</tr>
<tr>
<td>ibrutinib del17p, yes</td>
<td>61</td>
<td>41</td>
</tr>
<tr>
<td>ofatumumab del17p, no</td>
<td>59</td>
<td>36</td>
</tr>
<tr>
<td>ofatumumab del17p, yes</td>
<td>59</td>
<td>36</td>
</tr>
<tr>
<td>Median PFS (mo)</td>
<td>NR</td>
<td>8.2</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>NR</td>
<td>5.9</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>1.314</td>
<td>1.413</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(0.698-2.473)</td>
<td>(1.017-1.963)</td>
</tr>
<tr>
<td>P value</td>
<td>0.396</td>
<td>0.039</td>
</tr>
</tbody>
</table>

Hazard ratio (95% CI): 1.314 (0.698-2.473) vs 1.413 (1.017-1.963)

P value: 0.396 vs 0.039

Thornton et al, EHA 2015 Vienna
Sharman, ASH, 2014, Abstract 330
TP53 Network

- ERIC aims to advance assessment of TP53 aberrations through education about:
  - Importance of testing all cases needing therapy, before first and later lines of treatment
  - Quality of appropriate techniques in diagnostic laboratories to ensure reliable and comparable results between institutions → Certification of laboratories

<table>
<thead>
<tr>
<th>Disease stage</th>
<th>Clinical trial</th>
<th>General practice</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>Recommended</td>
<td>Not indicated</td>
<td></td>
</tr>
<tr>
<td>1L treatment</td>
<td>Recommended</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;2L treatment</td>
<td>Recommended</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Patients should be treated with BCR pathway inhibitor

1L: first-line; 2L: second-line
Confirmed diagnosis of CLL

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  - Fit: FCR (BR considered in fit elderly patients with history of infections)

- Watch and wait until symptomatic

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ESMO 2016 guidelines update for first line CLL

Idelalisib in first line: changes in 2016

2016

March  April  May  June  July  August  September

8 July
• PRAC concluded its review of idelalisib and recommended idelalisib-treated patients:
  • receive PJP prophylaxis during treatment and for up to 6 months after treatment end
  • are regularly monitored for CMV infection if CMV serology is positive at start of treatment or if there is a history of CMV infection
    • Patients with evidence of CMV viraemia and clinical signs of infection should have their treatment interrupted until the infection is resolved
  • are monitored for infection and have regular blood tests for white cell counts
  • PRAC also concluded that idelalisib can again be initiated in first-line CLL treatment, in patients with del(17p)/TP53 mutation who are ineligible for other therapies

22 July
• The CHMP confirmed the PRAC recommendations

15 September. Final EC decision

EC: European Commission; EMA: European Medicines Agency; CHMP: Committee for Medicinal Products for Human Use; PJP: Pneumocystis jirovecii pneumonia; PRAC: Pharmacovigilance Risk Assessment Committee

Zydelig SmPC (Date TBC 2016; available at www.ema.europa.eu).
A cross-study analysis: ORR, del(17p)

- **Median duration of response not reached at 30 months**
  - Of patients with CR/CRi (n=23), 81% maintained response at 30 months

**Median time on study, mo (range)**
- PCYC-1102/3 (n=36): 42 (0.9-61)
- PCYC-1112 (n=63): 31 (0.3-37)
- PCYC-1117 (n=144): 28 (0.5-31)
- Total (N=243): 28 (0.3-61)

*CR = CR + CRi"
Results: PFS and OS, del(17p)

- With a median (range) study duration of 28 (0.3-61+) months, median PFS and OS were not reached

<table>
<thead>
<tr>
<th>12-mo PFS, % (95% CI)</th>
<th>24-mo PFS, % (95% CI)</th>
<th>30-mo PFS, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>80% (74, 84)</td>
<td>63% (57, 69)</td>
<td>55% (48, 62)</td>
</tr>
</tbody>
</table>

Median PFS not reached

<table>
<thead>
<tr>
<th>12-mo OS, % (95% CI)</th>
<th>24-mo OS, % (95% CI)</th>
<th>30-mo OS, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>85% (80, 89)</td>
<td>75% (68, 80)</td>
<td>67% (59, 74)</td>
</tr>
</tbody>
</table>

Median OS not reached

CLL, chronic lymphocytic leukemia; IBR, ibrutinib; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma
EMA approval for Venclyxto on 08DEC16

- Venclyxto monotherapy is conditionally approved for the treatment of chronic lymphocytic leukaemia (CLL) in the presence of **17p deletion or TP53 mutation** in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor

- Venclyxto monotherapy is conditionally approved for the treatment of CLL **in without 17p deletion or TP53 mutation** in adult patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor
# Ultra-high Risk R/R CLL patients with del17p

**Best Response with Venetoclax**

<table>
<thead>
<tr>
<th>Response</th>
<th>IRC, n (%)</th>
<th>Investigator, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall Response</strong></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
Of 45 patients tested, 18 achieved MRD-negativity in peripheral blood.

- 12-month estimates (95% CI):
  - PFS: 72.0% (61.8, 79.8)
  - OS: 86.7% (78.6, 91.9)
ESMO 2015 clinical practice guidelines for R/R CLL

Relapsed CLL requiring treatment or refractory CLL

Early relapse (within 24–36 months after chemoimmunotherapy)
- **Less fit**
  - Clinical study
  - BCR inhibitor (± R)
  - (BR or FCR-Lite may be considered if no del(17p) or TP53 mutation)
- **Fit**
  - Clinical study
  - BCR inhibitor (± R)
  - Consider allo-SCT in remission

Late relapse (≥24–36 months after chemoimmunotherapy)
- **del(17p) or TP53 mutation**
  - **Less fit**
    - Clinical study
    - Repeat frontline or change to BR or BCR inhibitor (± R)
  - **Fit**
    - Clinical study
    - Repeat frontline or change to BR/FCR or BCR inhibitor (± R)
- **No del(17p) or TP53 mutation**
  - Treat as per early relapse
Updated BHS guidelines for Relapsed/Refractory CLL

- R/R CLL
  - Early relapse
    - 17p del/p53 mut
    - F/A refract
      - Unfit
        - Ibrutinib or Idela-R
      - Fit
        - Ibrutinib or Idela-R allo SCT
  - Late relapse
    - Unfit for CIT
      - Ibrutinib or Idela-R
    - Fit for CIT
      - CIT
5-year experience with ibrutinib in TN and R/R CLL

<table>
<thead>
<tr>
<th></th>
<th>Median PFS</th>
<th>5-year PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>TN (n=31)</td>
<td>NR</td>
<td>92%</td>
</tr>
<tr>
<td>R/R (n=101)</td>
<td>52 mo</td>
<td>43%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Median OS</th>
<th>5-year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>TN (n=31)</td>
<td>NR</td>
<td>92%</td>
</tr>
<tr>
<td>R/R (n=101)</td>
<td>NR</td>
<td>57%</td>
</tr>
</tbody>
</table>

O’Brien et al., ASH 2016 (abstract 233, oral presentation)
5-year experience with ibrutinib in TN and R/R

- Dose reductions and dose discontinuations due to AEs occurred more frequently in R/R patients than in TN patients, and during the first year after treatment compared with subsequent time periods.

O'Brien et al., ASH 2016 (abstract 233, oral presentation)
Searching for MRD
HELIOS (BRI versus BR)

ORR (investigator assessment)

OR = 87.2% versus 66.1% (p<0.0001)

CR/CRi
PR

As of March 2016, 60/289 (20.7%) on IBR+BR demonstrated MRD-negativity

BR, bendamustine + rituximab;
CRi, CR with incomplete marrow recovery; OR, overall response.

FRASER G, ET AL. EHA 2016

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Complete responses with BCL2 inhibitors: ABT-199

MRD-neg (% of CR) 80% 35%

M13-365: Venetoclax Combined with Rituximab in Patients with R/R CLL/SLL

- 55% of patients MRD-negative (27/49)
- 11 patients stopped venetoclax after achieving an objective response (9 MRD-negative); 9 remain in follow-up*
- None of the MRD-negative patients have progressed; 2 patients with MRD-positive CR/CRi had asymptomatic progression

* Two discontinued with no evidence of progression.
ORR to ABT-199 in CLL after Ibrutinib or Idelalisib
10 June 2016

<table>
<thead>
<tr>
<th>Best response, n (%)</th>
<th>Assessed by</th>
<th>Assessed by</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IRC</td>
<td>Investigator</td>
</tr>
<tr>
<td></td>
<td>IRC</td>
<td>Investigator</td>
</tr>
<tr>
<td>ORR</td>
<td>30 (70)</td>
<td>29 (67)</td>
</tr>
<tr>
<td>CR/CRi</td>
<td>0/1 (2)</td>
<td>2 (5)/1 (2)</td>
</tr>
<tr>
<td>nPR</td>
<td>0</td>
<td>2 (5)</td>
</tr>
<tr>
<td>PR</td>
<td>29 (67)</td>
<td>24 (56)</td>
</tr>
<tr>
<td>Non-responder*</td>
<td>13 (30)</td>
<td>14 (23)</td>
</tr>
<tr>
<td>SD</td>
<td>–</td>
<td>9 (21)</td>
</tr>
<tr>
<td>PD</td>
<td>–</td>
<td>1† (2)</td>
</tr>
<tr>
<td>D/C‡</td>
<td>–</td>
<td>4 (9)</td>
</tr>
</tbody>
</table>

*Non-responder category for IRC includes both SD or PD, which were not identified as separate categories per IRC.
†CLL progression and discontinued due to progression.
‡D/C, patient discontinued the study prior to assessment.
**ORR to ABT-199 in CLL after Ibrutinib or Idelalisib**

10 June 2016

- Median time on study (range): Arm A, 13 months (0.1–18); Arm B, 9 months (1.3–16)

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PD, progressive disease. PD-RT, progressive disease due to Richter's transformation.
Early discontinuations were due to AEs (n=3) and withdrawn consent (n=1).
Anthony Mato. Optimal Sequencing of Ibrutinib, Idelalisib, and Venetoclax in CLL: Results from a Large Multi-Center Study of 683 US-Patients

- 683 patients treated with KI therapy (IBR=621; IDELA=62) were included
- Significantly better PFS for IBR vs IDELA in all settings; front-line, R/R, clinical trials, commercial use, del17p, or CKT

Response to first kinase inhibitor

![Graph showing PFS by first KI in front-line and relapse-refractory settings](image)

- ORR 81%
- ORR 69%

![Bar chart showing ORR for IDELA and IBR](image)
ESMO 2015 clinical practice guidelines for R/R CLL

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- **Fit**
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Late relapse (≥24–36 months after chemoimmunotherapy)

- **del(17p) or TP53 mutation**
  - Less fit
    - Clinical study
    - Repeat frontline or change to BR or BCR inhibitor (± R)

  - **No del(17p) or TP53 mutation**
    - Less fit
    - Clinical study
    - Repeat frontline or change to BR/FCR or BCR inhibitor (± R)

  - **Fit**
    - Clinical study
    - Repeat frontline or change to BR/FCR or BCR inhibitor (± R)

Patients not responding nor progressing upon therapy with kinase inhibitors might be switched to a different kinase inhibitor or to BCL2 antagonists when available (according to clinical trials)


IS THIS THE END OF CHEMOTHERAPY?

CLL13-TRIAL OF THE GCLLSG in cooperation with HOVON, Nordic CLL Study Group and SAKK (GAIA)

Previously untreated Fit CLL patients (N=920) (CIRS ≤6 and normal creatinine clearance)

Randomise

- **FCR** or **BR**^<sup>^</sup>
- ABT-199 + Rituximab
- ABT-199 + Obinutuzumab
- ABT-199 + Obinutuzumab + Ibrutinib

Follow-up for progression and survival

- 2 primary endpoints
  - Rate of MRD negativity
  - PFS

Obinutuzumab: 6 cycles
Venetoclax: 12 cycles
Ibrutinib: 36 cycles or MRD<sup>neg</sup>
Laboratory of B Cell Neoplasia
Lydia Scarfò, Andreas Agathangelidis, Maria Gounari, Alessandra Rovida, Tania Veliz-Rodriguez, Engin Bojnik, Pamela Ranghetti, Federica Barbaglio, Cristina Scielzo

Laboratory of Lymphocyte Activation
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