<table>
<thead>
<tr>
<th>Topics</th>
<th>Number of abstracts</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLL – Biology/Translational</td>
<td>10 + 38 (2 oral + 2 poster sessions)</td>
</tr>
<tr>
<td>CLL - Clinical</td>
<td>5 + 18 (1 oral + 1 poster session)</td>
</tr>
</tbody>
</table>
Genetic determinants of fludarabine-resistance in chronic lymphocytic leukemia (CLL) (Messima, Roma)

Genome-wide genetic analysis reveals global deregulation of methyltransferase genes in chronic lymphocytic leukemia (Parker, Southampton)

Association between molecular lesions and specific B-cell receptor subsets in chronic lymphocytic leukemia (Rossi, Novara)

Distinct frequency and profiles of tP53 gene mutations in CLL subgrups with distinct antigen receptors: evidence for antigen-driven selection of genomic aberrations (Malcikova, Brno)

Comprehensive genome-wide analysis of CLL samples from UK 1° line and elapsed/refractory clinical trials (Robbe, Oxford)
3 novel pathways in CLL

**NOTCH**

(NOTCH1)

**Splicing**

(SF3B1)

**NF-κB**

(BIRC3)

Stereotyped receptors in CLL

- 30.4% of all CLL cases (2308/7596)

![Diagram of antibody structure with labeled CDRs and FRs]

**IGHV**

- FR1
- CDR1
- FR2
- CDR2
- FR3
- CDR3
- IGHJ

**Frequency of stereotypy, %**

- **Cohort size, N**

**Figure:** Agathangelidis et al., 2012 Blood
Genetic defects in Subsets are not random.

NOTCH1 M

SF3B1 M

Cumulative events

Subsets

Rossi et al, Blood, 2013

Strefford et al, Leukemia, 2013
**NOTCH1:**
- wild type
- mutated

**Therapy:**
- FCR
- FC

-Stilgenbauer et al. ASH 2012, Abstract 433
**Figure B**

Percent Survival

- **TP53 mut (18)**
- **TP53 wt (54)**

**TP53 mut vs wt:**
HR 1.21 (0.54-2.74); p 0.64

Months from SCT

**Figure D**

Percent Survival

- **SF3B1 mut (16)**
- **NOTCH1 mut (10)**
- **SF3B1 + NOTCH1 wt (45)**

**SF3B1 mut vs wt:**
HR 1.24 (0.53-2.92); p .62

**NOTCH1 mut vs wt:**
HR 0.76 (0.29-1.99); p .58

Months from SCT
Scientific Working Group
European research Initiative on CLL (ERIC)

- CLL therapy: the microenvironment as a target (Burger, Houston)
- Novel immunotherapeutic approaches in CLL (Baigi, Monza)
- New humanized type II CD20-antibodies (Goede, Cologne)

Education Session

- Old and new treatments for relapsed CLL, focussing on biology of the disease (O’Brien, Houston)
Obinutuzumab (GA101) or Rituximab ® + Chlorambucil (CLB) versus CLB alone in patients with CLL and pre-existing medical conditions (comorbidities): final stage 1 results of the CLL11 phase 3 trial (Goede, Cologne)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Therapy</th>
<th>n</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chl-R (Foà)</td>
<td>A</td>
<td>54 (of 98)</td>
<td>16.7% 81.4% 7.4%</td>
</tr>
<tr>
<td>Chl-R (Hillmen)</td>
<td>B</td>
<td>100</td>
<td>12 (12%) 80 (80%) 17 (17%)</td>
</tr>
<tr>
<td>UK CLL4 (Chl only)</td>
<td>C</td>
<td>200</td>
<td>12 (6%) 132 (66%) 60 (30%)</td>
</tr>
</tbody>
</table>

A) CLB 8mg/m2 d1-7 q28d up to 8x + R 375 mg/m2 c1-2, 500 mg/m2 c3-8, followed by R-maintenance 375 mg/m2 q 2 m for 2 yrs
B) CLB 10 mg/m2 d1-7 q28d up to 6x + R 375 mg/m2 c1, 500 mg/m2 c2-6
C) CLB like B without R
CLL11: Study design

Previously untreated CLL with comorbidities
Total CIRS* score > 6 and/or creatinine clearance < 70 ml/min
Age ≥ 18 years
N = 780 (planned)

*Cumulative Illness Rating Scale

- GA101: 1,000 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
- Clb: 0.5 mg/kg day 1 and day 15 cycle 1–6, every 28 days
- Patients with progressive disease in the Clb arm were allowed to cross over to G-Clb

Stage I, n = 590
- GA101 + chlorambucil x 6 cycles
- Chlorambucil x 6 cycles
- Rituximab + chlorambucil x 6 cycles

Additional 190 patients to complete stage II
- Stage Ia
  - G-Clb vs Clb
- Stage Ib
  - R-Clb vs Clb

Stage II
- G-Clb vs R-Clb
### Significantly improved PFS with an acceptable safety profile

<table>
<thead>
<tr>
<th></th>
<th>Stage Ia Clb, n = 118</th>
<th>Stage Ia G-Clb, n = 238</th>
<th>Stage Ib Clb, n = 118</th>
<th>Stage Ib R-Clb, n = 233</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median observation time, months</td>
<td>14.2</td>
<td></td>
<td>15.2</td>
<td></td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR, %</td>
<td>30.2</td>
<td>75.5</td>
<td>30.0</td>
<td>65.9</td>
</tr>
<tr>
<td>CR, %</td>
<td>0</td>
<td>22.2</td>
<td>0</td>
<td>8.3</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>10.9</td>
<td>23.0</td>
<td>10.8</td>
<td>15.7</td>
</tr>
<tr>
<td>MRD-negative in blood, %</td>
<td>0</td>
<td>31</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>MRD-negative in bone marrow, %</td>
<td>0</td>
<td>17</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td><strong>Safety, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade ≥ 3 AEs during treatment</td>
<td>41</td>
<td>67</td>
<td>41</td>
<td>46</td>
</tr>
<tr>
<td>IRRs</td>
<td>n/a</td>
<td>21</td>
<td>n/a</td>
<td>4</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>15</td>
<td>34</td>
<td>15</td>
<td>25</td>
</tr>
<tr>
<td>Infections</td>
<td>11</td>
<td>6</td>
<td>11</td>
<td>8</td>
</tr>
</tbody>
</table>

Elaboration from text data¹

Type 1 error controlled through closed test procedure; p-value of the global test was <.0001.

* In the G-Clb arm < 10% of patients had reached the median at cutoff; therefore, in contrast to the Clb arm the G-Clb median PFS could not be reliably estimated due to the few patients at risk at time of G-Clb median.

Independent Review Committee (IRC) - assessed PFS was consistent with investigator-assessed PFS

CI = confidence interval; HR = hazard ratio.
The BCL-2 inhibitor ABT-199 (GDC-0199) is active and well tolerated in ultra high risk relapsed/refractory chronic lymphocytic leukemia (CLL) (Roberts, Melbourne)

Randomized comparison of FCR-lite and CLR (Chlorambucil plus rituximab) regimens in elderly patients with chronic lymphocytic leukemia (Nikitin, Moscow)

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Hairy cell leukemia: evaluation of long term outcomes in 487 patients (Cornet, Caen)

Update on a phase 1 study of the selective PI3K-delta inhibitor, IDEALLISIB (GS-1101) in combination with ofatumumab in patients with relapsed or refractory chronic lymphocytic leukemia (Coutre, Stanford)
<60 years \(\rightarrow\) FCR

61 – 70 years \(\rightarrow\) CIRS-G

> 71 years

<6 \(\rightarrow\) ChlR \(\rightarrow\) Randomization

7 \(\rightarrow\) FCR-Lite
### Grade III - IV Hematological Toxicity:

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>ClbR (n=47)</th>
<th>FCR-Lite (n=45)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myelotoxicity in general</td>
<td>15 (34.8%)</td>
<td>22 (45%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>15 (32%)</td>
<td>17 (38%)</td>
<td>0.7</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5 (10.6%)</td>
<td>4 (8.8%)</td>
<td>0.9</td>
</tr>
<tr>
<td>Anemia</td>
<td>2 (4%)</td>
<td>2 (4.4%)</td>
<td></td>
</tr>
<tr>
<td>AIHA</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PRCA</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Number of patients with at least one grade III or IV event
Response rate: ClbR vs. FCR-Lite

<table>
<thead>
<tr>
<th></th>
<th>ClbR (n=47)</th>
<th>FCR-Lite (n=45)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR MRD -ve</td>
<td>0</td>
<td>14 (31%)</td>
<td>0.0013</td>
</tr>
<tr>
<td>CR MRD +ve</td>
<td>5 (10.6%)</td>
<td>5 (11%)</td>
<td>-</td>
</tr>
<tr>
<td>nPR</td>
<td>1 (2.1%)</td>
<td>2 (4.4%)</td>
<td>-</td>
</tr>
<tr>
<td>PR</td>
<td>35 (74.5%)</td>
<td>22 (49%)</td>
<td>0.02</td>
</tr>
<tr>
<td>OR</td>
<td>41 (87%)</td>
<td>43 (95%)</td>
<td>0.3</td>
</tr>
<tr>
<td>No response</td>
<td>6 (14.9%)</td>
<td>2 (4.4%)</td>
<td>0.3</td>
</tr>
</tbody>
</table>
Cumulative Proportion Surviving (Kaplan-Meier)

- Complete
- Censored

M = 37.1 months

M = 26 months

P = 0.01
The BCL-2 inhibitor ABT-199 (GDC-0199) is active and well tolerated in ultra high risk relapsed/refractory chronic lymphocytic leukemia (CLL) (Roberts, Melbourne)

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Best Percent Change from Baseline in Nodal Size by CT Scan

Median Time to 50% Reduction

- All CLL: 1.4 months (range 0.7 to 13.7)
- del(17p): 1.4 months (range 1.1 to 2.7)
- Flu-Refractory: 1.4 months (range 0.7 to 2.9)

N = 51 evaluable (at minimum, 6 week assessment).
Percent Change from Baseline in Lymphocyte Count and Bone Marrow Infiltrate

**Lymphocyte Count**

- **Median Time to 50% Reduction**
  - All CLL: 0.5 months (0.1 to 1.4)
  - del(17p): 0.3 months (0.1 to 0.9)
  - Flu-Refractory: 0.4 months (0.1 to 1.4)

**Bone Marrow Infiltrate**

- Patients with lymphocyte count >5 x 10^9/L at baseline
- N = 30 evaluable (at minimum, 6 weeks assessment).

Anti-tumor activity of ABT-199 was observed in all tumor compartments.
# Best Responses in ABT-199 Treated High Risk CLL Patients

<table>
<thead>
<tr>
<th>Best Response</th>
<th>All CLL N=55$^a$</th>
<th>del(17p) N=16$^a$</th>
<th>Flu-Refractory N=18$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate</td>
<td>46 (84)</td>
<td>13 (81)</td>
<td>14 (78)</td>
</tr>
<tr>
<td>Complete response</td>
<td>6 (11)</td>
<td>1 (6)</td>
<td>-</td>
</tr>
<tr>
<td>CR with incomplete marrow recovery</td>
<td>4 (7)</td>
<td>1 (6)</td>
<td>3 (17)</td>
</tr>
<tr>
<td>Partial response</td>
<td>36 (65)</td>
<td>11 (69)</td>
<td>11 (61)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>4 (7)</td>
<td>1 (6)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Disease progression</td>
<td>1 (2)</td>
<td>1 (6)</td>
<td>-</td>
</tr>
</tbody>
</table>

Responses assessed by IWCLL 2008 Criteria

$^a$ 1 subject has not reached Week 6 for evaluation by scan.

$^b$ 18 evaluable, 3 subjects discontinued prior to Week 6 assessment.
SIMULTANEOUS SESSION
CLL: Clinical studies

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SIMULTANEOUS SESSION
CLL – MICROENVIRONMENTAL INTERACTIONS

Phase 1 study of single agent CC-292, a highly selective Bruton’s tyrosine kinase (BTK) inhibitor, in relapsed/refractory chronic lymphocytic leukemia (CLL) and non B-cell-non Hodgkin lymphoma (B-NHL) (Brown, Boston)

Silencing of Bruton’s tyrosine kinase by RNA interference induces apoptosis in primary chronic lymphocytic leukemia (Bojnik, Rome)

Endothelin-1/ETA receptor signaling mediates survival, drug-resistance and microenvironmental interactions of chronic lymphocytic leukemia cells (Maffei, Modena)

Proteomic profiling of Chronic lymphocytic leukemia (CLL) Cells: identification of thymosin beta 4 as differentially reguated protein (Morabito, Cosenza)

B cell receptor stereotypy makes a clinical difference in CLL: revelations from a multi-institutional series of 4615 cases (Baliakas, Thessaloniki)
QUESTIONS

1. Should the new genetic mutations be included in the work-up before treatment?

2. What is the new gold standard for the treatment of elderly patients?

3. Is FCR going to be challenged by the inhibitors in first line setting?
THE END