Is there a role for imaging in Chronic lymphocytic leukaemia (CLL)

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Disclosures – Peter Hillmen

Advisor/consultant
• Abbvie
• Acerta
• Gilead
• Janssen
• Novartis/GSK
• Pharmacyclics
• Roche

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• Abbvie
• Gilead
• Janssen
• Novartis/GSK
• Pharmacyclics
• Roche

No share ownership, patents or board membership
Guidelines for diagnosis, indications for treatment, response assessment, and supportive management of chronic lymphocytic leukemia: an update of the NCI-sponsored guidelines from the International Workshop on Chronic Lymphocytic Leukemia

Michael Hallek,1,4 Bruce D. Cheson,7 Daniel Catovsky,6 Federico Caligaris-Cappio,6 Guillermo Dighiero,6 Hartmut Döhner,7 Peter Hillmen,8 Michael Keating,9 Emili Montserrat,10 Nicholas Chiorazzi,11 Stephan Stilgenbauer,7 Kanti R. Rai,12 John C. Byrd,13 Barbara Eichhorst,2 Susan O'Brien,14 Tadeusz Robak,15 John F. Seymour,16,17 and Thomas J. Kipps18

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Table 1. Baseline evaluation of patients with CLL

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>General practice</th>
<th>Clinical trial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tests to establish the diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBC and differential count</td>
<td>Always</td>
<td>Always</td>
</tr>
<tr>
<td>Immunophenotyping of peripheral blood lymphocytes</td>
<td>Always</td>
<td>Always</td>
</tr>
<tr>
<td><strong>Assessment before treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History and physical, performance status</td>
<td>Always</td>
<td>Always</td>
</tr>
<tr>
<td>CBC and differential count</td>
<td>Always</td>
<td>Always</td>
</tr>
<tr>
<td>Marrow aspirate and biopsy</td>
<td>When clinically indicated (unclear cytopenia)</td>
<td>Desirable</td>
</tr>
<tr>
<td>Serum chemistry, serum immunoglobulin, and direct antiglobulin test</td>
<td>Always</td>
<td>Always</td>
</tr>
<tr>
<td>Chest radiograph</td>
<td>Always</td>
<td>Always</td>
</tr>
<tr>
<td>Infectious disease status</td>
<td>Always</td>
<td>Always</td>
</tr>
<tr>
<td><strong>Additional tests before treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molecular cytogenetics (FISH) for del(13q), del(11q), del(17p), add(12) in peripheral blood lymphocytes</td>
<td>Always</td>
<td>Always</td>
</tr>
<tr>
<td>Conventional karyotyping in peripheral blood lymphocytes (with specific stimulation)</td>
<td>NGI*</td>
<td>Desirable</td>
</tr>
<tr>
<td>TP53 mutation</td>
<td>Always</td>
<td>Always</td>
</tr>
<tr>
<td>IGHV mutational status</td>
<td>Always</td>
<td>Always</td>
</tr>
<tr>
<td>Serum β₂-microglobulin</td>
<td>Desirable</td>
<td>Always</td>
</tr>
<tr>
<td><strong>CT scan of chest, abdomen, and pelvis</strong></td>
<td>NGI</td>
<td>Desirable</td>
</tr>
<tr>
<td>MRI, PET scans</td>
<td>NGI</td>
<td>NGI</td>
</tr>
<tr>
<td>Abdominal ultrasound†</td>
<td>Possible</td>
<td>NGI</td>
</tr>
</tbody>
</table>
Table 3. Recommendations regarding the response assessment in CLL patients

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>General practice</th>
<th>Clinical trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>History, physical examination</td>
<td>Always</td>
<td>Always</td>
</tr>
<tr>
<td>CBC and differential count</td>
<td>Always</td>
<td>Always</td>
</tr>
<tr>
<td>Marrow aspirate and biopsy</td>
<td>At cytopenia of uncertain cause</td>
<td>At CR or cytopenia of uncertain cause</td>
</tr>
<tr>
<td>Assessment for minimal residual disease</td>
<td>NGI</td>
<td>Desirable</td>
</tr>
<tr>
<td>Ultrasound of the abdomen†</td>
<td>Possible, if previously abnormal</td>
<td>NGI</td>
</tr>
<tr>
<td>CT scans of chest, abdomen, and pelvis</td>
<td>NGI</td>
<td>Recommended if previously abnormal and otherwise with a CR and PR</td>
</tr>
</tbody>
</table>
5. Definition of response, relapse, and refractory disease

Basic assessment of response unchanged from 2008

Table 4. Response definition after treatment of CLL patients

<table>
<thead>
<tr>
<th>Group</th>
<th>Parameter</th>
<th>CR</th>
<th>PR</th>
<th>PD</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Lymph nodes</td>
<td>None ≥1.5 cm</td>
<td>Decrease ≥50% (from baseline)*</td>
<td>Increase ≥50% from baseline or from response</td>
<td>Change of -49% to +49%</td>
</tr>
<tr>
<td></td>
<td>Liver and/or spleen size†</td>
<td>Spleen size &lt;13 cm; liver size normal</td>
<td>Decrease ≥50% (from baseline)</td>
<td>Increase ≥50% from baseline or from response</td>
<td>Change of -49% to +49%</td>
</tr>
<tr>
<td></td>
<td>Constitutional symptoms</td>
<td>None</td>
<td>Any</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>Circulating lymphocyte count</td>
<td>Normal</td>
<td>Decrease ≥50% from baseline</td>
<td>Increase ≥50% over baseline</td>
<td>Change of -49% to +49%</td>
</tr>
<tr>
<td>B</td>
<td>Platelet count</td>
<td>≥100,000/μL</td>
<td>≥100,000/μL or increase ≥50% over baseline</td>
<td>Decrease of ≥50% from baseline secondary to CLL</td>
<td>Change of -49 to +49%</td>
</tr>
<tr>
<td></td>
<td>Hemoglobin</td>
<td>≥11.0 g/dL (untransfused and without erythropoietin)</td>
<td>≥11 g/dL or increase ≥50% over baseline</td>
<td>Decrease of ≥2 g/dL from baseline secondary to CLL</td>
<td>Increase &lt;11.0 g/dL or &lt;50% over baseline, or decrease &lt;2 g/dL</td>
</tr>
<tr>
<td></td>
<td>Marrow</td>
<td>Normocellular, no CLL cells, no B-lymphoid nodules</td>
<td>Presence of CLL cells, or of B-lymphoid nodules, or not done</td>
<td>Increase of CLL cells by ≥50% on successive biopsies</td>
<td>No change in marrow infiltrate</td>
</tr>
</tbody>
</table>
NCRI trials of FCR-like therapy for fit patients with CLL

**NCRI ADMIRE** (randomised Phase II) Trial
Does the **Add**ition of Mitoxantrone **Improve** **Re**sponse to FCR chemotherapy in patients with CLL\(^1\)

Patients with CLL requiring therapy by NCI Criteria
Randomize

- FCR (n=215)
- FCM-R

**NCRI ARCTIC** (randomised Phase II) Trial
**At**tenuated dose **R**ituximab with **Chemo**Therapy **In** **CLL**\(^2\)

Patients with CLL requiring therapy by NCI Criteria
Randomize

- FCR (n=200)
- FCM-miniR

### Combined ADMIRE/ARCTIC data

(Munir et al., EHA 2014)

<table>
<thead>
<tr>
<th></th>
<th>Total FCR (n=207)</th>
<th>Total ALL (n=415)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Treatment cycles received</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 3 cycles</td>
<td>26 (12.6%)</td>
<td>55 (13.3%)</td>
</tr>
<tr>
<td>&gt; 3 cycles</td>
<td>181 (87.4%)</td>
<td>360 (86.7%)</td>
</tr>
<tr>
<td>G-CSF during treatment (cycles 1-6)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>102 (49.3%)</td>
<td>223 (53.7%)</td>
</tr>
<tr>
<td>No</td>
<td>96 (46.4%)</td>
<td>173 (41.7%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>9 (4.4%)</td>
<td>19 (4.6%)</td>
</tr>
<tr>
<td>Dose Modification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>132 (63.8%)</td>
<td>274 (66.0%)</td>
</tr>
<tr>
<td>Responses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Achieved a CR/CRi</td>
<td>137 (73.3%)</td>
<td>265 (69.7%)</td>
</tr>
<tr>
<td>Achieved an overall response</td>
<td>187 (96.9%)</td>
<td>375 (96.2%)</td>
</tr>
<tr>
<td>MRD negative</td>
<td>108 (58.1%)</td>
<td>199 (53.6%)</td>
</tr>
</tbody>
</table>

**Conclusion:** extremely high CR and MRD negative rates with oral FCR

Methods

• ARCTIC and ADMIRE were two phase IIB RCT's of fludarabine-based therapies previously untreated patients with CLL, in which 415 patients received FCR
• Local reports of CT scans performed before and three months after treatment were independently assessed by two clinicians.
• IWCLL criteria was applied to assess CT response.
• Physical examination assessments had been collected during the course of trial.
Discrepant results in physical examination and CT scan are common

- 88/248 participants (35.5%) with CR assessed by physical examination were classed as PR by CT scan.
- 39/87 participants (44.8%) with PR by physical examination were classed as CR by CT.
- Results in 144/342 participants (42.1%) in total were discrepant.
- Nodes were more frequently assessed to be larger by CT compared to physical examination (46.8%).
Patients assessed as CR by physical examination and CT had similar PFS.
Patients assessed as PR on CT appear to do better than PR on physical examination (p=0.005).
Clear PFS difference in patients achieving CR compared to PR on physical examination (p<0.0001).
PFS by CT scan response (CR/PR/PR spleen only/SD) at 3 months post-treatment

Progression-free survival by CT scan assessment of response

Log-Rank
χ² = 55.1310
P < 0.0001

n=19
n=202
n=62
n=70

No difference in PFS between those who are PR (spleen only) and those PR otherwise
OS by physical examination response and CT scan response at 3 months post-treatment

Overall survival by CT scan and Physical assessment of response

Log-Rank
$\chi^2 = 76.7868$
P $< 0.0001$

Proportion Alive

Months from Randomisation

- 1: CR CT scan
- 2: CR Physical exam
- 3: PR CT scan
- 4: PR Physical exam
- 5: SD CT scan
- 6: SD Physical exam

n=126
n=197
n=248
n=86
n=15
n=4
MRD negative CR/PR on CT assessment had a superior PFS compared to MRD positive CR/PR (p<0.0001)

PFS by CT scan response and peripheral blood MRD (MRD+CR/MRD+PR/MRD-CR/MRD-PR)

PFS by CT scan response and bone marrow MRD (MRD+CR/MRD+PR/MRD-CR/MRD-PR)
OS by CT scan response and bone marrow MRD (MRD+CR/MRD+PR/MRD-CR/MRD-PR)

MRD negative CR/PR on CT assessment had no OS difference (p=0.3779) upto date
CONCLUSIONS

• Retrospective analysis of ADMIRE and ARCTIC trials data was used to establish the additive value of CT scans as response assessment compared to physical examination.

• There were discrepancies in response assessment in 42.1% of patients between techniques.

• Importantly, patients assessed as CR or PR on CT criteria had no difference in PFS.

• There was a significant PFS difference between CR and PR classified by physical examination.
CONCLUSIONS

• CT scans gave a better assessment of total tumour bulk but did not appear to help in predicting progression.
• MRD negativity in bone marrow or peripheral blood appears to be a better predictor of PFS and OS than CT scan.
• We postulate that physical examination along with blood counts combined with MRD assessment is adequate to assess response in CLL.

What about imaging with targeted therapies?
Mr DF, Born 1955 with R/R CLL: venetoclax started April 2014 (2nd line: FCR → 17p del)

CT scan

Bone marrow MRD

Pre-venetoclax

6 months of venetoclax

Orange events = CLL cells

Purple events = T-cells

No detectable CLL <0.01%!!

Remains in remission and MRD negative February 2019
Mr G, Born 1958 with R/R CLL: venetoclax started March 2105 (6th line)

Peripheral blood MRD

Increasing lymphadenopathy October 2017
Eventually developed Richter’s transformation and died July 2018
MURANO trial establishes feasibility of time-limited venetoclax-rituximab combination therapy in relapsed/refractory chronic lymphocytic leukemia

John F Seymour,1 Thomas J Kipps,2 Barbara Eichhorst,3 Peter Hillmen,4 James D’Rozario,5 Sarit Assouline,6 Carolyn Owen,7 Tadeusz Robak,8 Javier de la Serna,9 Ulrich Jaeger,10 Guillaume Cartron,11 Marco Montillo,12 Nicole Lamanna,13 Maria Verdugo,14 Elizabeth A Punnoose,15 Yanwen Jiang,15 Jue Wang,15 Michelle Boyer,16 Kathryn Humphrey,16 Mehrdad Mobasher,15 Arnon P Kater17

1Peter MacCallum Cancer Centre, Royal Melbourne Hospital, and University of Melbourne, Melbourne, Australia; 2University of California School of Medicine, San Diego, CA, USA; 3University of Cologne, Cologne, Germany; 4St. James’ University Hospital, Leeds, United Kingdom; 5The John Curtin School of Medical Research, Australian National University, Canberra, Australia; 6Segal Cancer Center, Lady Davis Institute, Jewish General Hospital, Montreal, Canada; 7University of Calgary, Calgary, Canada; 8Medical University of Lodz, Copernicus Memorial Hospital, Lodz, Poland; 9Hospital Universitario 12 de Octubre, Madrid, Spain; 10Medical University of Vienna, Vienna, Austria; 11University Hospital Montpellier, Montpellier, France; 12Niguarda Cancer Center, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; 13Columbia University Medical Center, New York, NY, USA; 14AbbVie, North Chicago, IL, USA; 15Genentech Inc, South San Francisco, CA, USA; 16Roche Products Limited, Welwyn Garden City, United Kingdom; 17Amsterdam UMC, University of Amsterdam, Hovon CLL working group, The Netherlands
MURANO study design

R/R CLL (N=389)

Stratified by:
• Del(17p) by local labs
• Responsiveness to prior therapy
• Geographic region

Primary endpoint: investigator-assessed PFS; secondary endpoints include rate of undetectable MRD (uMRD)

Clinical response and MRD in PB/BM during Ven single-agent and at follow-up visits were assessed every 3 mo for 3 yrs, then every 6 mo thereafter or until PD

Primary analysis was pre-planned at 140 PFS events; this follow-up analysis was conducted 1 yr later

BM, bone marrow; C, cycle; D, day; PB, peripheral blood; R, randomized.

MURANO: Investigator-assessed and IRC Best Response Rates

<table>
<thead>
<tr>
<th></th>
<th>Venetoclax + rituximab (n=194)</th>
<th>Bendamustine + rituximab (n=195)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (CR, CRi, PR, nPR)</td>
<td>93.3%</td>
<td>67.7%</td>
</tr>
<tr>
<td>Complete response (CR/CRI)</td>
<td>8.2%</td>
<td>26.8%</td>
</tr>
<tr>
<td>Partial response (PR/nPR)</td>
<td>59.5%</td>
<td>66.5%</td>
</tr>
<tr>
<td>Stable disease</td>
<td>22.6%</td>
<td>2.1%</td>
</tr>
</tbody>
</table>

*p-values descriptive because the first hierarchically tested secondary endpoint was not statistically significant

MURANO: Investigator-assessed and IRC Best Response Rates

INV-Assessed

- Venetoclax + rituximab (n=194)
  - Overall (CR, CRi, PR, nPR): 93.3%
  - Complete response (CR/CRi): 8.2%
  - Partial response (PR/nPR): 26.8%
  - Stable disease: 22.6%

- Bendamustine + rituximab (n=195)
  - Overall (CR, CRi, PR, nPR): 67.7%
  - Complete response (CR/CRi): 59.5%
  - Partial response (PR/nPR): 66.5%
  - Stable disease: 2.1%

IRC-Assessed

- Venetoclax + rituximab (n=194)
  - Overall (CR, CRi, PR, nPR): 72.3%
  - Complete response (CR/CRi): 92.3%
  - Partial response (PR/nPR): 8.2%
  - Stable disease: 7.2%

- Bendamustine + rituximab (n=195)
  - Overall (CR, CRi, PR, nPR): 84.0%
  - Complete response (CR/CRi): 3.6%
  - Partial response (PR/nPR): 8.2%
  - Stable disease: 23.6%

* p-values descriptive because the first hierarchically tested secondary endpoint was not statistically significant

MURANO: CT Scan Findings and Relationship With IRC CR Rates

- 23 CR/CRi per IRC vs 68 CR/CRi per investigator assessment
  - 51 downgrades by IRC:
    - 42 VR arm, 9 BR arm
  - 6 upgrades by IRC: 6 VR arm
- ~77% of IRC CR downgrades were due to radiographic findings or issues
  - Major reason for downgrades in the VR arm were due to lesions 16–20 mm (residual nodes)
  - Major reason for downgrades in the BR arm were due to larger lesions >21 mm
- All downgraded CRs by IRC were clear in the BM per investigator assessment
- 37/42 downgraded CRs in VR arm were MRD-negative in PB; 9/9 in the BR arm were MRD-positive

<table>
<thead>
<tr>
<th>Reason for downgrade</th>
<th>B + R (n=9)</th>
<th>V + R (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT scan (all reasons)</td>
<td>7</td>
<td>33</td>
</tr>
<tr>
<td>CT scan, lesions 16–20 mm</td>
<td>2</td>
<td>18</td>
</tr>
<tr>
<td>CT scan, lesions 21–30 mm</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>CT scan, lesions &gt;30 mm</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>CT scan, anatomy missing</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>CT scan, spleen enlarged</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Bone marrow, elements missing</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Growth factor use</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Spleen/ALC</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>AE – secondary malignancy</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Unvalidated data from spreadsheets and spotfire.

PB uMRD rates higher with VenR than BR at EOCT

Consistently high uMRD rates observed in all VenR subgroups, including pts with high-risk cytogenetics and molecular factors.

<table>
<thead>
<tr>
<th>n (%)</th>
<th>n</th>
<th>uMRD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Del(11q)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>61</td>
<td>40 (65.6)</td>
<td>0.813</td>
</tr>
<tr>
<td>No</td>
<td>112</td>
<td>70 (62.5)</td>
<td></td>
</tr>
<tr>
<td>Del(17p) and/or TP53 mut</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>72</td>
<td>41 (56.9)</td>
<td>0.284</td>
</tr>
<tr>
<td>No</td>
<td>106</td>
<td>70 (66.0)</td>
<td></td>
</tr>
<tr>
<td>IGHV mutation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>123</td>
<td>75 (61.0)</td>
<td>0.819</td>
</tr>
<tr>
<td>Present</td>
<td>53</td>
<td>34 (64.2)</td>
<td></td>
</tr>
<tr>
<td>Bulky disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10 cm</td>
<td>161</td>
<td>99 (61.5)</td>
<td>0.909</td>
</tr>
<tr>
<td>≥10 cm</td>
<td>23</td>
<td>15 (65.2)</td>
<td></td>
</tr>
<tr>
<td>Lines of prior therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>111</td>
<td>71 (64.0)</td>
<td>0.704</td>
</tr>
<tr>
<td>&gt;1</td>
<td>83</td>
<td>50 (60.2)</td>
<td></td>
</tr>
</tbody>
</table>

Patients (%)

- High-MRD+ (≥10^{-2})
- Low-MRD+ (10^{-4} to <10^{-2})
- uMRD (<10^{-4})
- Withdrew
- PD/death
- Missing/undetermined

VenR (n=194); BR (n=195)
uMRD status at EOCT highly predictive of prolonged PFS

**(HR (95% CI))**

VenR uMRD vs MRD+ 0.38 (0.20, 0.72)

**Landmark PFS**

**VenR uMRD (n=120)**
**VenR MRD+ (n=42)**
+ Censored

**No. of pts at risk**
VenR uMRD 120 120 119 116 114 109 102 93 66 41 15 1
VenR MRD+ 42 41 40 39 39 38 33 29 21 10 5 4 2 1

Data cut-off May 8, 2018; median follow-up: 36.0 months
Including pts who have not progressed, died, or withdrawn from study before EOCT who are all censored
Response visit MRD PB status derived from combining ASO-PCR and flow cytometry results

uMRD status at EOCT highly predictive of prolonged PFS in both treatment arms

<table>
<thead>
<tr>
<th>BR uMRD (n=26)</th>
<th>BR MRD+ (n=88)</th>
<th>VenR uMRD (n=120)</th>
<th>VenR MRD+ (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of pts at risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>26</td>
<td>25</td>
<td>24</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>VenR uMRD</th>
<th>VenR MRD+</th>
</tr>
</thead>
<tbody>
<tr>
<td>120</td>
<td>120</td>
</tr>
</tbody>
</table>

Data cut-off May 8, 2018; median follow-up: 36.0 months
Including pts who have not progressed, died, or withdrawn from study before EOCT who are all censored
Response visit MRD PB status derived from combining ASO-PCR and flow cytometry results

PFS similar for VenR pts with CR or PR and uMRD

Findings were similar in the BR arm

Response rates
VenR: CR/CRi 27.8%, PR/nPR 65.5%
BR: CR/CRi 8.7%, PR/nPR 59.0%

Data cut-off May 8, 2018; median follow-up: 36.0 months. MRD+ does not include “missing” samples. The analysis subset includes pts who have not progressed, died or withdrawn from study before EOCT response visit. MRD PB status derived from combining ASO-PCR and flow cytometry results
Safety, Efficacy and MRD Negativity of a Combination of Venetoclax and Obinutuzumab in Patients With Previously Untreated Chronic Lymphocytic Leukemia: Results from a Phase Ib Study (GP28331)

Ian W. Flinn¹, John Gribben², Martin J.S. Dyer³, William Wierda⁴, Michael B. Maris⁵, Richard R. Furman⁶, Peter Hillmen⁷, Kerry Rogers⁸, Swaminathan Padmanabhan Iyer⁹, Surai Jones¹⁰, Yanwen Jiang¹⁰, Daniela Soriano Pignataro¹¹, Kathryn Humphrey¹¹, Mehrdad Mobasher¹⁰, Thomas J. Kipps¹²

¹. Sarah Cannon Research Institute, Nashville, TN, USA; 2. Barts Cancer Center, The London School of Medicine, London, UK; 3. Ernest and Helen Scott Haematological Research Institute, University of Leicester, Leicester, UK; 4. The University of Texas, MD Anderson Cancer Center, Houston, TX; 5. Colorado Blood Cancer Institute, Denver, CO; 6. Weill Cornell Medicine, CLL Research Center, New York, NY; 7. St. James University Hospital, Leeds, UK; 8. Division of Hematology, The Ohio State University, Columbus, OH, USA; 9. Houston Methodist Hospital, Houston, TX; 10. Genentech, Inc. South San Francisco, CA, USA; 11. F-Hoffmann-La Roche Ltd., Welwyn Garden City, UK; 12. University of California School of Medicine, San Diego, CA, USA.
MTD not reached. Safety monitoring team recommended Schedule B (G followed by VEN) and the 400 mg dose for expansion cohorts after reviewing the study and program-wide data.

G dosing schedule: C1D1: 100 mg, C1D2: 900 mg, C1D8 and 15:1000 mg, C2–6D1: 1000 mg.
Cohort 4 was not commenced. Cohort 3 final cohort.

Flinn et al., Blood, 2019, in press
Phase 1b study of venetoclax in combination with obinutuzumab in R/R and 1L CLL

### Efficacy summary (efficacy population): Responses

<table>
<thead>
<tr>
<th>Response, n (%)</th>
<th>Entire efficacy population</th>
</tr>
</thead>
<tbody>
<tr>
<td>R/R population, n</td>
<td>43</td>
</tr>
<tr>
<td>ORR</td>
<td>41 (95)</td>
</tr>
<tr>
<td>CR/CRI</td>
<td>16 (37)</td>
</tr>
<tr>
<td>PR</td>
<td>25 (58)</td>
</tr>
<tr>
<td>SD</td>
<td>2 (5)</td>
</tr>
<tr>
<td>1L population, n</td>
<td>32</td>
</tr>
<tr>
<td>ORR</td>
<td>32 (100)</td>
</tr>
<tr>
<td>CR/CRI</td>
<td>25 (78)</td>
</tr>
<tr>
<td>PR</td>
<td>7 (22)</td>
</tr>
</tbody>
</table>

### Safety summary (safety population)

<table>
<thead>
<tr>
<th></th>
<th>R/R patients (n = 45)</th>
<th>1L patients (n = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with ≥1 AE, n (%)</td>
<td>45 (100)</td>
<td>32 (100)</td>
</tr>
<tr>
<td>SAEs, n (%)</td>
<td>27 (60)</td>
<td>11 (34)</td>
</tr>
<tr>
<td>Grade 3-4 AE (at greatest intensity)</td>
<td>36 (80)</td>
<td>25 (78)</td>
</tr>
</tbody>
</table>

**Most common grade 3-4 AEs, n (%)**

<table>
<thead>
<tr>
<th></th>
<th>R/R patients</th>
<th>1L patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>26 (58)</td>
<td>17 (53)</td>
</tr>
<tr>
<td>Infections and infestations*</td>
<td>13 (29)</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>10 (22)</td>
<td>7 (22)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>7 (16)</td>
<td>4 (13)</td>
</tr>
</tbody>
</table>

*System organ class

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Flinn et al., Blood, 2019, in press
Phase 1b study of venetoclax in combination with obinutuzumab in R/R and 1L CLL

Flinn et al., Blood, 2019, in press
Progression-free Survival: All 1L Patients

- Median time on study: 18.5 months (range: 15–30)
- Median PFS = not reached
  - 12-month estimate: 100%
  - 15-month estimate: 93.8% (95% CI: 85.4, 100.0)
  - 18-month estimate: 90.5% (95% CI: 80.3, 100.0)

- Disease progression: 3 patients; no deaths
  - 2 patients had Richter transformation
    - Pt 1 (DLBCL): Day 437 (on VEN); del(17p) at baseline; BM MRD+ all assessments
    - Pt 2 (HL): Day 474 (off VEN); trisomy 12, unmutated IGHV at baseline; BM MRD– all assessments (before PD)
  - 1 patient with PD
    - Day 399 (on VEN); del(11q), del(17p), unmutated IGHV at baseline; BM MRD+ all assessments
Conclusions: the role of imaging in CLL?

1. The assessment of PR by physical examination is better at predicting outcome compared to CT-scanning
2. Significance of small volume lymph nodes and slight splenomegaly on CT as disease assessment of doubtful significance
3. MRD negative PR similar outcome to MRD negative CR
4. Regular CT-scanning to assess progression in follow-up adds potential risk with no evidence of clinical benefit
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