Changing Landscape in Chronic lymphocytic leukaemia (CLL)

Peter Hillmen
peter.hillmen@nhs.net
University of Leeds
United Kingdom
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Disclosures – Peter Hillmen

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

Research/trial support
• Abbvie
• Gilead
• Janssen
• Novartis/GSK
• Pharmacyclics
• Roche

No share ownership, patents or board membership
Chronic Lymphocytic Leukaemia: A rapidly changing world!

- Different/long-term side-effects: chemo-related side-effects, secondary malignancy, infusion reactions, immuno-suppression, bleeding, arrhythmia, TLS, colitis/pneumonitis etc etc
- Practicalities: iv, oral, long-term until PD, requiring hospital admission
- Cost: only cure (or death) is cheap
- Last not least: Different biology

UK FRONT-LINE CLL TRIALS

<table>
<thead>
<tr>
<th>Year</th>
<th>Trial Name</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>1978</td>
<td>MRC CLL1</td>
<td>n=660</td>
</tr>
<tr>
<td>1988</td>
<td>MRC CLL2</td>
<td>n=640</td>
</tr>
<tr>
<td>1993</td>
<td>MRC CLL3</td>
<td>n=418</td>
</tr>
<tr>
<td>2003</td>
<td>LRF CLL4</td>
<td>n=777</td>
</tr>
<tr>
<td>2014</td>
<td>NCRI RIALTO</td>
<td>n=565</td>
</tr>
<tr>
<td>2019</td>
<td>NCRI FLAIR1</td>
<td>n=565</td>
</tr>
<tr>
<td>2019</td>
<td>NCRI FLAIR2</td>
<td>n=822</td>
</tr>
</tbody>
</table>

Morphology

- Flow
- FISH
- Sanger
- NGS
- WGS

- Chlorambucil
- Prednisolone
- Fludarabine
- Cyclophosphamid
- Campath
- Ofatumumab
- Ibrutinib
- Venetoclax
- Obinutuzumab
- Idelalisib
- Rituximab
- Chlorambucil
- Ofatumumab
- AZD6738
- TGR-1202
- CAR-T
Pathophysiology of CLL: proliferation and apoptosis

Proliferation

Apoptosis

Ibrutinib

Ki-67 expression

Venetoclax

BCL-2 expression
CLL treatment algorithm in February 2018

Earlier stage, asymptomatic

- All
  - Observe
    - No 17p-, No TP53mut
      - FCR
        - CR / PR
          - Observe
          - 2nd line ibrutinib or Ridelalisib Venetoclax Consider AlloSCT
    - 17p- and/or TP53mut
      - Ibrutinib and (?Allo-SCT?)
        - SD / PD
          - Observe

Advanced stage, symptomatic CLL (“active disease”)

- Fit (young)
  - Observe
    - No 17p-, No TP53mut
      - FCR
        - CR / PR
          - Observe
          - 2nd line ibrutinib or Ridelalisib Venetoclax Consider AlloSCT
  - Ibrutinib and (?Allo-SCT?)
    - SD / PD
      - Observe

- Unfit (old)
  - Observe
    - No 17p-, No TP53mut
      - Obi-Clb OR Ibrutinib
        - CR / PR
          - Observe
          - 2nd line BCRi or Venetoclax
    - 17p-, and/or TP53mut
      - Ibrutinib
        - CR / PR
          - Observe
          - 2nd line BCRi or Venetoclax

- Frail (very old)
  - Observe
    - No 17p-, and/or TP53mut
      - Ibrutinib
        - SD / PD
          - Observe
          - 2nd line BCRi or Venetoclax
  - BSC (?) OR ibrutinib OR chlorambucil
    - Benefit ?
      - 2nd line ?
Major advances in CLL therapy in 2018+

1. Changing front-line therapy for all patients
2. Chemoimmunotherapy disappearing for relapsed CLL
3. Explanation of the mechanism of resistance to novel therapies
4. Chemotherapy free combinations – defined duration of targeted therapy
ECOG-ACRIN E1912 Trial: Ibrutinib & Rituximab Improves Progression Free and Overall Survival Relative to FCR in Younger Patients with Previously Untreated Chronic Lymphocytic Leukemia (CLL)

Tait Shanafelt, Xin Victoria Wang, Neil E. Kay, Susan O’Brien, Jacqueline Barrientos, Curt Hanson, Harry Erba, Rich Stone, Mark Litzow, Marty Tallman

ASH, December 2018; Abst No: LBA-6
Study design

**E1912**

Eligibility:
- Previously untreated CLL
- Requires treatment (IWCLL 2008)
- Age ≤ 70
- ECOG 0-2
- CrCl > 40
- Able to tolerate FCR
- No deletion 17p by FISH

Planned Accrual: 519

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**Arm A – Ibrutinib + Rituximab**

Cycles 1:
- Ibrutinib 420 mg PO daily, days 1-28

Cycle 2:
- Ibrutinib 420 mg PO daily, days 1-28
- Rituximab 50 mg/m² IV, day 1
- Rituximab 325 mg/m² IV, day 2

Cycles 3-7:
- Ibrutinib 420 mg PO daily, days 1-28
- Rituximab 500 mg/m² IV, day 1

Cycle 8 until progression:
- Ibrutinib 420 mg PO daily, days 1-28

**Arm B - FCR**

Cycles 1-6:
- Fludarabine 25 mg/m² IV, days 1-3
- Cyclophosphamide 250 mg/m² IV, days 1-3

Cycle 1:
- Rituximab 50 mg/m² IV, day 1, cycle 1
- Rituximab 325 mg/m² IV, day 2, cycle 1

Cycle 2-6:
- Rituximab 500 mg/m² IV, day 1, cycles 2-6

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Shanafelt *et al.* ASH 2018
Patient Characteristics Were Well Balanced

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>IR n=354</th>
<th>FCR n=175</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (y)</td>
<td>58</td>
<td>57</td>
<td>58</td>
</tr>
<tr>
<td>Age &gt; 60</td>
<td>41.0%</td>
<td>40.0%</td>
<td>40.6%</td>
</tr>
<tr>
<td>Female</td>
<td>33.3%</td>
<td>31.4%</td>
<td>32.7%</td>
</tr>
<tr>
<td>ECOG = 0</td>
<td>63.8%</td>
<td>62.3%</td>
<td>63.3%</td>
</tr>
<tr>
<td>Rai stage 0</td>
<td>3.1%</td>
<td>5.1%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Rai stage I-II</td>
<td>52.8%</td>
<td>53.7%</td>
<td>53.1%</td>
</tr>
<tr>
<td>Rai stage III-IV</td>
<td>44.1%</td>
<td>41.1%</td>
<td>43.1%</td>
</tr>
<tr>
<td>FISH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11q deletion</td>
<td>22.0%</td>
<td>22.3%</td>
<td>22.2%</td>
</tr>
<tr>
<td>Trisomy 12</td>
<td>19.8%</td>
<td>15.4%</td>
<td>18.3%</td>
</tr>
<tr>
<td>13q deletion</td>
<td>34.2%</td>
<td>33.1%</td>
<td>33.8</td>
</tr>
<tr>
<td>B2M &gt;3.5 mg/L</td>
<td>51.9%</td>
<td>48.0%</td>
<td>50.6%</td>
</tr>
<tr>
<td>IGHV Unmutated*</td>
<td>75.0%</td>
<td>61.7%</td>
<td>71.1%</td>
</tr>
</tbody>
</table>

* Tested in 437 (82%) patients

Shanafelt et al. ASH 2018
Progression Free Survival

Intent to Treat

Number at risk: IR (37 events/354 cases) FCR (40 events/175 cases)

Number at risk: IR (33 events/332 cases) FCR (39 events/166 cases)

HR = 0.35 (95% CI 0.22-0.56) One sided p = 1.62 × 10^-6

HR = 0.32 (95% CI 0.20-0.51) One sided p = 3.74 × 10^-7

Shanafelt et al. ASH 2018
# PFS Sub-Group Analysis

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>E</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All randomized</td>
<td>529</td>
<td>77</td>
<td>0.35</td>
<td>(0.22, 0.56)</td>
</tr>
<tr>
<td>Eligible</td>
<td>498</td>
<td>72</td>
<td>0.32</td>
<td>(0.20, 0.51)</td>
</tr>
<tr>
<td>Female</td>
<td>173</td>
<td>19</td>
<td>0.30</td>
<td>(0.12, 0.77)</td>
</tr>
<tr>
<td>Male</td>
<td>356</td>
<td>58</td>
<td>0.40</td>
<td>(0.23, 0.67)</td>
</tr>
<tr>
<td>Age &lt; 60</td>
<td>314</td>
<td>51</td>
<td>0.32</td>
<td>(0.18, 0.56)</td>
</tr>
<tr>
<td>Age &gt;= 60</td>
<td>215</td>
<td>26</td>
<td>0.44</td>
<td>(0.20, 0.97)</td>
</tr>
<tr>
<td>ECOG PS 0</td>
<td>335</td>
<td>46</td>
<td>0.26</td>
<td>(0.14, 0.47)</td>
</tr>
<tr>
<td>ECOG PS 1 or 2</td>
<td>194</td>
<td>31</td>
<td>0.61</td>
<td>(0.29, 1.27)</td>
</tr>
<tr>
<td>Rai Stage 0–II</td>
<td>301</td>
<td>41</td>
<td>0.35</td>
<td>(0.18, 0.65)</td>
</tr>
<tr>
<td>Rai Stage III–IV</td>
<td>228</td>
<td>36</td>
<td>0.38</td>
<td>(0.19, 0.74)</td>
</tr>
<tr>
<td>Splenomegaly No</td>
<td>311</td>
<td>39</td>
<td>0.36</td>
<td>(0.19, 0.70)</td>
</tr>
<tr>
<td>Splenomegaly Yes</td>
<td>218</td>
<td>38</td>
<td>0.32</td>
<td>(0.17, 0.63)</td>
</tr>
<tr>
<td>Lymphadenopathy No</td>
<td>159</td>
<td>16</td>
<td>0.44</td>
<td>(0.14, 1.42)</td>
</tr>
<tr>
<td>Lymphadenopathy Yes</td>
<td>370</td>
<td>61</td>
<td>0.35</td>
<td>(0.21, 0.59)</td>
</tr>
<tr>
<td>Dohner Del(11q22)</td>
<td>117</td>
<td>22</td>
<td>0.24</td>
<td>(0.10, 0.62)</td>
</tr>
<tr>
<td>Dohner Trisomy 12</td>
<td>97</td>
<td>10</td>
<td>0.73</td>
<td>(0.19, 2.89)</td>
</tr>
<tr>
<td>Dohner Normal</td>
<td>106</td>
<td>18</td>
<td>0.78</td>
<td>(0.29, 2.04)</td>
</tr>
<tr>
<td>Dohner Del(13q)</td>
<td>179</td>
<td>19</td>
<td>0.22</td>
<td>(0.08, 0.60)</td>
</tr>
<tr>
<td>IGHV Mutated</td>
<td>114</td>
<td>14</td>
<td>0.44</td>
<td>(0.14, 1.35)</td>
</tr>
<tr>
<td>IGHV Unmutated</td>
<td>281</td>
<td>41</td>
<td>0.26</td>
<td>(0.14, 0.50)</td>
</tr>
</tbody>
</table>
Progression Free Survival: IGHV Status

**IGHV Unmutated**

- HR = 0.26 (95% CI 0.14-0.50)
- One-sided p < 0.00001
- IR (20 events/ 210 cases)
- FCR (21 events/ 71 cases)

**IGHV Mutated**

- HR = 0.44 (95% CI 0.14 – 1.36)
- One-sided p = 0.07
- IR (8 events/ 70 cases)
- FCR (6 events/ 44 cases)

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Overall Survival

Intent to Treat

<table>
<thead>
<tr>
<th>Probability</th>
<th>Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR = 0.17 (95% CI 0.05-0.54)</td>
<td></td>
</tr>
<tr>
<td>One sided p&lt;0.0003</td>
<td></td>
</tr>
<tr>
<td>IR (4 events/ 354 cases)</td>
<td></td>
</tr>
<tr>
<td>FCR (10 events/ 175 cases)</td>
<td></td>
</tr>
</tbody>
</table>

Eligible

<table>
<thead>
<tr>
<th>Probability</th>
<th>Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR = 0.13 (95% CI 0.03-0.46)</td>
<td></td>
</tr>
<tr>
<td>One sided p&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>IR (3 events/ 332 cases)</td>
<td></td>
</tr>
<tr>
<td>FCR (10 events/ 166 cases)</td>
<td></td>
</tr>
</tbody>
</table>

Shanafelt et al. ASH 2018
## Causes of Death

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>IR n=354</th>
<th>FCR n=175</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLL</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Unexplained/unwitnessed</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Other: acute/chronic respiratory failure; hx lung adenocarcinoma</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Acute respiratory failure</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Metastatic colon Cancer</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Drug overdose</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>4</strong></td>
<td><strong>10</strong></td>
</tr>
</tbody>
</table>

Death during active treatment +30 days: IR n=3, FCR n=1
## Grade 3-5 Treatment Related Adverse Events Throughout Observation

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>IR (%)</th>
<th>FCR (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>22.7%</td>
<td>43.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anemia</td>
<td>2.6%</td>
<td>12.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2.9%</td>
<td>13.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any Infection</td>
<td>7.1%</td>
<td>19.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Infection</td>
<td>5.4%</td>
<td>8.2%</td>
<td>0.24</td>
</tr>
<tr>
<td>Neutropenic fever</td>
<td>2.3%</td>
<td>15.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2.9%</td>
<td>0.0%</td>
<td>0.04</td>
</tr>
<tr>
<td>Bleeding</td>
<td>1.1%</td>
<td>0.0%</td>
<td>0.32</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7.4%</td>
<td>1.9%</td>
<td>0.01</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2.6%</td>
<td>0.6%</td>
<td>0.19</td>
</tr>
<tr>
<td><strong>Any Grade 3 or higher AE</strong></td>
<td><strong>58.5%</strong></td>
<td><strong>72.1%</strong></td>
<td><strong>P=0.004</strong></td>
</tr>
</tbody>
</table>
Conclusions

➢ Ibrutinib and rituximab provides superior PFS and OS compared to FCR for patients with previously untreated CLL

➢ Ibrutinib and rituximab was well tolerated in patients < age 70

➢ The need for indefinite therapy should be evaluated in future clinical trials testing novel agent combination therapy
  
  – EA9161 (NCT03701282; pts age<70) & A041702 (NCT03737981; pts age>70)

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Untreated patients age ≥ 65 who meet IWCLL criteria for CLL treatment

PRE-REGISTER

Stratify*

RANDOMIZE

Bendamustine 90mg/m2 days 1&2 of each 28 day cycle +
Rituximab 375 mg/m2 day 0 cycle 1,
then 500 mg/m2 day 1 cycles 2-6

Ibrutinib 420mg daily until disease progression

Ibrutinib 420mg daily until disease progression +
Rituximab 375 mg/m2 weekly for 4 weeks starting cycle 2 day 1,
then day 1 of cycles 3-6

Stratification
• High risk vs intermediate risk Rai Stage
• Presence vs absence of del(11q22.3) or del(17p13.1) on FISH performed locally
• < 20% vs ≥ 20% Zap-70 methylation of CpG 3 performed centrally
Patient Disposition

644 Patients Screened

547 Patients Randomized 1:1:1

Bendamustine + Rituximab N=183

- Analysis
  - Primary endpoint: n=176
    - (7 ineligible)
  - Adverse events: n=176
    - (7 did not start treatment)
  - All secondary endpoints: n=183

N=30 patients crossed over from BR to ibritinib

Ibrutinib N=182

- Analysis
  - Primary endpoint: n=178
    - (4 ineligible)
  - Adverse events: n=180
    - (2 did not start treatment)
  - All secondary endpoints: n=182

Ibrutinib + Rituximab N=182

- Analysis
  - Primary endpoint: n=170
    - (12 ineligible)
  - Adverse events: n=181
    - (1 did not start treatment)
  - All secondary endpoints: n=182

- 52 did not meet eligibility criteria
- 19 did not register per investigator decision
- 16 did not register per patient decision
- 10 did not register for other reasons
## Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total N=547</th>
<th>BR N=183</th>
<th>Ibrutinib N=182</th>
<th>IR N=182</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median (range)</td>
<td>71 (65-89)</td>
<td>70 (65-86)</td>
<td>71 (65-89)</td>
<td>71 (65-86)</td>
</tr>
<tr>
<td>Male, %</td>
<td>67</td>
<td>65</td>
<td>68</td>
<td>69</td>
</tr>
<tr>
<td>ECOG 0-1, %</td>
<td>97</td>
<td>95</td>
<td>97</td>
<td>99</td>
</tr>
<tr>
<td>White blood cell count x10^3/μL, median (range)</td>
<td>82 (4-518)</td>
<td>92 (7-518)</td>
<td>79 (6-438)</td>
<td>70 (4-481)</td>
</tr>
<tr>
<td>FISH Characteristics, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Del (17p)</td>
<td>6</td>
<td>8</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Del (11q)</td>
<td>19</td>
<td>18</td>
<td>19</td>
<td>21</td>
</tr>
<tr>
<td>TP53 mutation, %</td>
<td>10</td>
<td>9</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Complex Karyotype, %</td>
<td>29</td>
<td>27</td>
<td>24</td>
<td>36</td>
</tr>
<tr>
<td>Zap-70 Unmethylated, %</td>
<td>53</td>
<td>52</td>
<td>53</td>
<td>53</td>
</tr>
<tr>
<td>IGVH unmutated*, %</td>
<td>61</td>
<td>58</td>
<td>63</td>
<td>61</td>
</tr>
</tbody>
</table>

*N= 360 total*
Primary Endpoint: Progression Free Survival

Eligible Patient Population

Pairwise Comparisons

I vs BR:
Hazard Ratio 0.39
95% CI: 0.26-0.58
(1-sided P-value <0.001)

IR vs BR:
Hazard Ratio 0.38
95% CI: 0.25-0.59
(1-sided P-value <0.001)

IR vs I:
Hazard Ratio 1.00
95% CI: 0.62-1.62
(1-sided P-value 0.49)
Response Rates and Minimal Residual Disease
Intention-to-Treat Patient Population

- **Overall Response Rates**
  - BR: 81% (95% CI: 75 - 87%)
  - Ibrutinib: 93% (95% CI: 88 - 96%)
  - IR: 94% (95% CI: 89 - 97%)

- **Complete Response Rates**
  - BR: 26% (95% CI: 20 - 33%)
  - Ibrutinib: 7% (95% CI: 4 - 12%)
  - IR: 12% (95% CI: 8 - 18%)

- **Minimal Residual Disease negative in marrow at 9 months**
  - BR: 8% (95% CI: 5 - 13%)
  - Ibrutinib: 1% (95% CI: <1 - 3%)
  - IR: 4% (95% CI: 2 - 8%)
Overall Survival
Intention-to-Treat Patient Population

Median Follow-up: 38 months

<table>
<thead>
<tr>
<th>Arm</th>
<th>N</th>
<th>24 Month Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>BR</td>
<td>183</td>
<td>95% (95% CI: 91-98%)</td>
</tr>
<tr>
<td>I</td>
<td>183</td>
<td>90% (95% CI: 85-94%)</td>
</tr>
<tr>
<td>IR</td>
<td>182</td>
<td>94% (95% CI: 89-97%)</td>
</tr>
</tbody>
</table>

| Arm A (BR) | 183 | 166 | 163 | 160 | 153 | 143 | 98 | 53 | 23 |
| Arm B (I)  | 182 | 175 | 166 | 161 | 156 | 146 | 100 | 62 | 26 |
| Arm C (IR) | 182 | 172 | 169 | 165 | 161 | 147 | 100 | 55 | 24 |
## Grade 3, 4, or 5 Adverse Events

During treatment or follow-up (excluding crossover)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>BR N=176</th>
<th>Ibrutinib N=180</th>
<th>IR N=181</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Hematologic – no. (%)</td>
<td>107 (61)</td>
<td>74 (41)</td>
<td>70 (38)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anemia</td>
<td>22 (13)</td>
<td>21 (12)</td>
<td>11 (6)</td>
<td>0.09</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>71 (40)</td>
<td>27 (15)</td>
<td>39 (22)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>26 (15)</td>
<td>12 (7)</td>
<td>9 (5)</td>
<td>0.008</td>
</tr>
<tr>
<td>All Non-hematologic – no. (%)</td>
<td>111 (63)</td>
<td>133 (74)</td>
<td>134 (74)</td>
<td>0.04</td>
</tr>
<tr>
<td>Bleeding</td>
<td>0 (0)</td>
<td>3 (2)</td>
<td>5 (3)</td>
<td>0.46</td>
</tr>
<tr>
<td>Infections</td>
<td>26 (15)</td>
<td>37 (21)</td>
<td>37 (20)</td>
<td>0.62</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>13 (7)</td>
<td>3 (2)</td>
<td>1 (1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>5 (3)</td>
<td>17 (9)</td>
<td>10 (6)</td>
<td>0.05</td>
</tr>
<tr>
<td>Hypertension</td>
<td>25 (14)</td>
<td>53 (29)</td>
<td>61 (34)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Unexplained/unwitnessed death</td>
<td>2 (1)</td>
<td>7 (4)</td>
<td>4 (2)</td>
<td>0.24</td>
</tr>
</tbody>
</table>

- Deaths during active treatment + 30 days: 2 (1%), 13 (7%), 13 (7%)
- Deaths during active treatment + 30 days, up to 6 cycles: 2 (1%), 3 (2%), 6 (3%)
Conclusions

- Ibrutinib or ibrutinib plus rituximab significantly prolongs PFS compared with BR in the frontline setting for older CLL patients.
- Rituximab does not improve PFS over ibrutinib alone.
- BTK inhibition with ibrutinib is not without significant toxicity in older patients, so close monitoring is still warranted.
  - Strategies to discontinue therapy are of great interest.
- Clinical trials for this patient population are still of high clinical interest; the cooperative group setting remains a reasonable avenue to complete these large studies.
  - A041702 (NCT03737981) and EA9161 (NCT03701282)
Phase 3 iLLUMINATE Study of Ibrutinib-G vs Clb-G in Patients With TN CLL/SLL

Key eligibility criteria
• Age ≥65 years of age or < 65 years old with ≥1 coexisting condition (CIRS score > 6, CrCl < 70 mL/min, and/or del(17p) or TP53 mutation)

**Ibr-G (n = 113)**
Ibr 420 mg/d continuously
G 1000 mg, d1/2 (split), 8, and 15 c1, then d1 (6 cycles)

**Clb-Ga (n = 116)**
Clb 0.5 mg/kg, d1 and 15 (6 cycles)
G 1000 mg, days 1/2 (split), 8, and 15 c1, then d1 (6 cycles)

aPatients with PD on Clb-G could cross over Ibr monotherapy as next-line therapy (n=46).

Primary endpoints: PFS (IRC)
Secondary endpoints: PFS in high-risk patients, MRD, ORR, OS, safety, infusion-related reactions

Moreno et al. ASH 2018. Abstract 691.
Phase 3 iLLUMINATE Study of Ibrutinib-G vs Clb-G in Patients With TN CLL/SLL

Summary
- Ibr-G demonstrated improved PFS vs Clb-G irrespective of high-risk genomic features
- ORR, CR, and undetectable MRD were also higher with Ibr-G vs G-Clb
- Ibr-G demonstrated tolerability with no new safety signals, and represents effective chemotherapy-free regimen for firstline CLL/SLL

<table>
<thead>
<tr>
<th>Outcomes, %</th>
<th>Ibr-G (n=113)</th>
<th>Clb-G (n=116)</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median IRC-assessed PFS, mo</td>
<td>NR</td>
<td>19.0</td>
<td>0.231 (0.145-0.367)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>30 mo PFS rate, %</td>
<td>79</td>
<td>31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median INV-assessed PFS, mo</td>
<td>NR</td>
<td>21.9</td>
<td>0.260 (0.163-0.415)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median PFS in high-risk (del (17p)/TP53 mutation, del (11q), and/or unmutated IGHV), mo</td>
<td>NR</td>
<td>14.7</td>
<td>0.154 (0.087-0.27)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>30-mo OS rate, %</td>
<td>86</td>
<td>85</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Response, %
- IRC (INV)-assessed ORR | 88 (91) | 73 (81) |
- IRC (INV) CR/CRi | 19 (41) | 8 (16) |
- Undetectable MRD in BM/PB (<10⁻⁴) | 35 | 25 |

AEs Overall
- Median duration of treatment, months (range) | 29.3 (0.10–36.6) | 5.1 (0.03–6.7) |
- Most common grade ≥3 AEs
  - Any | 77 % | 72 % |
  - Neutropenia | 36 % | 46 % |
  - Thrombocytopenia | 19 % | 10 % |
  - Pneumonia | 7 % | 4 % |
  - Atrial fibrillation | 5 % | 0 % |
  - Febrile neutropenia | 4 % | 6 % |
  - Anemia | 4 % | 8 % |
  - Hypertension | 4 % | 3 % |
  - Neutrophils decreased | 4 % | 0 % |
  - Infusion-related reaction | 2 % | 8 % |

- In non-del(17p): 74% reduction in risk of PD or death with I+G
- In unmutated IGHV without del(17p): 85% improvement in PFS vs G-Clb
- 40% of Clb-G pts received single-agent Ibr as second-line therapy

Moreno et al. ASH 2018. Abstract 691.
Ibrutinib in Frontline CLL at ASH

**iLLUMINATE (Moreno #691)**
- Included high risk

- Median follow-up: 31 mo
- Age 65+ or younger unfit (physical or cytogenetics)
- I+G vs G+C
- PFS (IRC) HR: 0.231 (0.145-0.367)
- OS HR: 0.921 (0.470-1.722)
- uIGHV: Median PFS NR vs 14.6 mo

**ALLIANCE (Woyach #6)**
- Included del(17)p

- Median follow-up: 32 mo
- Age 65+
- Ibr vs IR vs BR
- PFS (INV) HR:
  - I vs BR: 0.39 (0.26-0.58)
  - IR vs BR: 0.38 (0.25-0.59)
  - I vs IR: 1.0 (0.62-1.62)
- OS HR: no difference
- mIGHV: 2-γ for I = 86%
  - 2-γ for IR = 88%

**E1912 (Shanafelt LBA-4)**
- No del(17)p

- Median follow-up: 33 mo
- Age 70 or younger
- IR vs FCR
- PFS (INV) HR: 0.35 (0.22-0.5)
- OS HR: 0.17 (0.05-0.54)
- uIGHV: 0.26 (0.14-0.5)
  - mIGHV: 0.44 (0.14-1.36)

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: Venetoclax+rituximab in relapsed CLL

R/R CLL (N=389)

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

Ven 400 mg orally once daily to PD, cessation for toxicity, or max 2 yrs from C1D1

Rituximab
375 mg/m² D1C1; 500 mg/m² D1C2–6

Bendamustine
70 mg/m² D1,2 C1–6 + Rituximab

• 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.

Patient characteristics were balanced between arms

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>VenR (n=194)</th>
<th>BR (n=195)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, yrs (range)</td>
<td>64.5 (28–83)</td>
<td>66 (22–85)</td>
</tr>
<tr>
<td>Patients with lymphocyte count ≥25 x 10^9/L, n (%)</td>
<td>129 (66.5)</td>
<td>134 (68.7)</td>
</tr>
<tr>
<td>del(17p) and/or TP53 mut, n/N (%)†‡</td>
<td>72/178 (40.4)</td>
<td>75/170 (44.1)</td>
</tr>
<tr>
<td>Unmutated IGHV, n/N (%)*</td>
<td>123/180 (68.3)</td>
<td>123/180 (68.3)</td>
</tr>
<tr>
<td>Number of prior therapies, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>111 (57.2)</td>
<td>117 (60.0)</td>
</tr>
<tr>
<td>2</td>
<td>57 (29.4)</td>
<td>43 (22.1)</td>
</tr>
<tr>
<td>3</td>
<td>22 (11.3)</td>
<td>34 (17.4)</td>
</tr>
<tr>
<td>&gt;3</td>
<td>4 (2.1)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Prior therapies, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alkylating agent</td>
<td>185 (95.4)</td>
<td>182 (93.3)</td>
</tr>
<tr>
<td>Bendamustine</td>
<td>4 (2.1)</td>
<td>5 (2.6)</td>
</tr>
<tr>
<td>Purine analog</td>
<td>158 (81.4)</td>
<td>157 (80.5)</td>
</tr>
<tr>
<td>Anti-CD20 antibody</td>
<td>148 (76.3)</td>
<td>153 (78.5)</td>
</tr>
<tr>
<td>B-cell receptor pathway inhibitors</td>
<td>3 (1.5)</td>
<td>5 (2.6)</td>
</tr>
</tbody>
</table>

*Central laboratory; †Cut-off for del(17p) positive is 7%; ‡Cut-off for TP53 is ≥5% variant allele frequency in coding region.
Data cut-off date: May 8, 2018

Patient disposition: all patients are off therapy

389 patients randomized

194 assigned to VenR

194 treated (187 received VenR)

174 completed VenR

130 completed 2-yr VenR without PD

Median follow-up: 36.1 mo
Median treatment exposure: 24.4 mo (range 0.1–27.8)

195 assigned to BR

188 treated

154 completed 6 cycles BR

30 discontinued study
• Death: 22
• Physician decision: 1
• AE: 1
• Lost to follow-up: 1
• Withdrawal by patient: 5

63 discontinued study
• Death: 39
• Physician decision: 2
• Lost to follow-up: 1
• Withdrawal by patient: 21

Data cut-off date: May 8, 2018

Investigator-assessed PFS

VenR: median PFS NR
BR: median PFS 17.0 months

- Median follow-up 23.8 mo (range 0.0–37.4)

EOCT, end of combination therapy; EOT, end of therapy; NR, not reached.

Superior PFS with VenR vs BR maintained with 1 additional year of follow-up: Update

Investigator-assessed PFS

- Median follow-up 36.0 mo (range 0.0–48.6); VenR 36.1 mo, BR 35.9 mo

Data cut-off date: May 8, 2018

Treatment effect with VenR consistent across subgroups

**Investigator-assessed PFS**

<table>
<thead>
<tr>
<th>Demographic subgroups</th>
<th>Total n</th>
<th>VenR n</th>
<th>Median*</th>
<th>BR n</th>
<th>Median</th>
<th>HR</th>
<th>95% Wald CI</th>
<th>VenR better</th>
<th>BR better</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All pts</strong></td>
<td>389</td>
<td>194</td>
<td>NR</td>
<td>195</td>
<td>17.0</td>
<td>0.19</td>
<td>(0.14–0.27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>186</td>
<td>97</td>
<td>NR</td>
<td>89</td>
<td>15.4</td>
<td>0.17</td>
<td>(0.11–0.27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥65 years</td>
<td>203</td>
<td>97</td>
<td>NR</td>
<td>106</td>
<td>22.3</td>
<td>0.21</td>
<td>(0.14–0.33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Number of prior regimens</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>228</td>
<td>111</td>
<td>44.3</td>
<td>117</td>
<td>16.6</td>
<td>0.16</td>
<td>(0.10–0.25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;1</td>
<td>161</td>
<td>83</td>
<td>NR</td>
<td>78</td>
<td>18.6</td>
<td>0.24</td>
<td>(0.15–0.38)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>del(17p)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>250</td>
<td>127</td>
<td>NR</td>
<td>123</td>
<td>21.4</td>
<td>0.19</td>
<td>(0.13–0.29)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal</td>
<td>92</td>
<td>46</td>
<td>NR</td>
<td>46</td>
<td>15.4</td>
<td>0.21</td>
<td>(0.11–0.39)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TP53</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unmutated</td>
<td>276</td>
<td>144</td>
<td>NR</td>
<td>132</td>
<td>21.2</td>
<td>0.16</td>
<td>(0.10–0.24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutated</td>
<td>99</td>
<td>48</td>
<td>36.0</td>
<td>51</td>
<td>12.9</td>
<td>0.25</td>
<td>(0.15–0.43)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TP53 mut and/or del(17p)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unmutated</td>
<td>201</td>
<td>106</td>
<td>NR</td>
<td>95</td>
<td>22.8</td>
<td>0.16</td>
<td>(0.10–0.27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutated</td>
<td>147</td>
<td>72</td>
<td>NR</td>
<td>75</td>
<td>14.6</td>
<td>0.23</td>
<td>(0.15–0.37)</td>
<td></td>
<td></td>
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<tr>
<td><strong>del(11q)</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>217</td>
<td>112</td>
<td>44.3</td>
<td>105</td>
<td>22.1</td>
<td>0.26</td>
<td>(0.17–0.39)</td>
<td></td>
<td></td>
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<tr>
<td>Abnormal</td>
<td>125</td>
<td>61</td>
<td>NR</td>
<td>64</td>
<td>15.7</td>
<td>0.11</td>
<td>(0.05–0.21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>IGHV</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutated</td>
<td>104</td>
<td>53</td>
<td>NR</td>
<td>51</td>
<td>24.2</td>
<td>0.16</td>
<td>(0.07–0.33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unmutated</td>
<td>246</td>
<td>123</td>
<td>44.3</td>
<td>123</td>
<td>15.7</td>
<td>0.16</td>
<td>(0.11–0.24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bulky disease (lymph nodes with the largest diameter)</strong></td>
<td>197</td>
<td>100</td>
<td>44.3</td>
<td>97</td>
<td>17.0</td>
<td>0.19</td>
<td>(0.12–0.29)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥5 cm</td>
<td>172</td>
<td>84</td>
<td>NR</td>
<td>88</td>
<td>15.8</td>
<td>0.20</td>
<td>(0.13–0.32)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Medians in the VenR arm could not be reliably estimated due to too few pts at risk.

Data cut-off date: May 8, 2018
Clinically meaningful improvement in OS with VenR vs BR maintained after 3 years

**Unstratified HR 0.51 (95% CI 0.30–0.86).**

Median follow-up: 36.0 months (range 0.0–48.6). Median per arm: VenR 36.1 months; BR 35.9 months.

Subsequent treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>VenR (n=194)</th>
<th>BR (n=195)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts with ≥1 treatment, n (%)</td>
<td>27 (13.9)</td>
<td>91 (46.7)</td>
</tr>
</tbody>
</table>

Most BR pts had active therapy after PD: 46/91 received ibrutinib and 7/91 had Ven

**Data cut-off date: May 8, 2018**

Grade 3–4 AEs; ≥2% difference between arms

*Note: AE reporting period longer with VenR vs BR*

<table>
<thead>
<tr>
<th>AE, n (%)</th>
<th>VenR (n=194)</th>
<th>VenR combination period (n=194)</th>
<th>Ven monotherapy period (n=171)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>114 (58.8)</td>
<td>106 (54.6)</td>
<td>20 (11.7)</td>
</tr>
<tr>
<td>Anemia</td>
<td>21 (10.8)</td>
<td>16 (8.2)</td>
<td>5 (2.9)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>11 (5.7)</td>
<td>9 (4.6)</td>
<td>3 (1.8)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>7 (3.6)</td>
<td>7 (3.6)</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>10 (5.2)</td>
<td>8 (4.1)</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td>4 (2.1)</td>
<td>4 (2.1)</td>
<td>0</td>
</tr>
<tr>
<td>TLS</td>
<td>6 (3.1)</td>
<td>6 (3.1)</td>
<td>0</td>
</tr>
<tr>
<td>Clinical TLS*</td>
<td>1 (0.5)</td>
<td>1 (0.5)</td>
<td>0</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>4 (2.1)</td>
<td>4 (2.1)</td>
<td>0</td>
</tr>
<tr>
<td>Hypotension</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypogammaglobulinemia</td>
<td>4 (2.1)</td>
<td>3 (1.5)</td>
<td>1 (0.6)</td>
</tr>
</tbody>
</table>

*TLS occurred during previous ramp-up schedule prior to current approved treatment ramp up. Treatment-emergent AEs are included. Multiple occurrences of the same AE in an individual are counted only once on individual rows and separately for total. AE reporting period: up to 90 days after end of bendamustine treatment (max 6 mo); up to 28 days after end of Ven treatment (max 2 yrs).

Data cut-off date: May 8, 2018

Modest progression in the first 12 months after completion of Ven monotherapy

At risk, n 130
Events, n 0

Pts with events, n (%) 6-mo PFS, % (95% CI) 1-yr PFS, % (95% CI)
Ven (n=130) 16 (12.3) 92.0 (87.3–96.8) 87.4 (81.1–93.8)

Median follow-up (off-treatment): • 9.9 mo (range 1.4–22.5)

End of Ven

Time after end of fixed-duration treatment (months)

At risk, n 130 120 92 56 22 8 4 1
Events, n 0 6 10 14 14 15 15 16

Data cut-off date: May 8, 2018

MRD status over time in VenR arm: high uMRD rate is sustained

- At EOCT, the majority of pts had uMRD status
- Most MRD+ pts at EOCT had low-MRD+ status

Data cut-off May 8, 2018; median follow-up: 36.0 months. Missing values also include pts who have not yet reached the time point

VenR (n=194)
- Withdraw
- PD/death
- Missing/undetermined
- High-MRD+ ($\geq 10^{-2}$)
- Low-MRD+ ($10^{-4}$ to $<10^{-2}$)
- uMRD ($<10^{-4}$)

Kater, et al. ASH 2018
MRD status over time in VenR arm: high uMRD rate is sustained

- High uMRD rates sustained
- Among pts converting from uMRD to MRD+, most change to low-MRD+ and many remain low-MRD+ over time

Data cut-off May 8, 2018; median follow-up: 36.0 months. Missing values also include pts who have not yet reached the time point

Kater, et al. ASH 2018
MRD status over time in VenR arm: high uMRD rate is sustained

- Few low-MRD+ pts progressed
- Pts who did progress had mainly converted to high-MRD+ first

Data cut-off May 8, 2018; median follow-up: 36.0 months. Missing values also include pts who have not yet reached the time point

Kater, et al. ASH 2018
uMRD status at EOCT highly predictive of prolonged PFS

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

Kater, et al. ASH 2018
MRD conversion after stopping Ven monotherapy for pts who were progression-free at EOT

At EOT (Month 24; n=130):
- 83 High-MRD+ (\(\geq 10^{-2}\))
- 14 Low-MRD+ (\(10^{-4}\) to \(<10^{-2}\))
- 23 uMRD (<\(10^{-4}\))
- 10 Missing

At 9.9 months median follow-up since EOT:
- 58 uMRD (<\(10^{-4}\))
- 21 Low-MRD+ (\(10^{-4}\) to \(<10^{-2}\))
- 4 High-MRD+ (\(\geq 10^{-2}\))
- 1 PD

Kater, et al. ASH 2018
MRD conversion after stopping Ven monotherapy for pts who were progression-free at EOT

At EOT (Month 24; n=130):

- Missing
- High-MRD+ (£10^{-2})
- Low-MRD+ (10^{-4} to <10^{-2})
- uMRD (<10^{-4})

At 9.9 months median follow-up since EOT:

- Missing

MRD conversion after stopping Ven monotherapy for pts who were progression-free at EOT

At EOT (Month 24; n=130):
- Missing: 10
- High-MRD+ ($\geq 10^{-2}$): 83
- Low-MRD+ ($10^{-4}$ to $<10^{-2}$): 14
- uMRD ($<10^{-4}$): 23

At 9.9 months median follow-up since EOT:
- Missing: 58
- High-MRD+ ($\geq 10^{-2}$): 21
- Low-MRD+ ($10^{-4}$ to $<10^{-2}$): 14
- uMRD ($<10^{-4}$): 11

Kater, et al. ASH 2018
Conclusion

• After median 36 months’ follow-up, and with all patients off therapy (median 9.9 months), PFS is significantly prolonged with VenR versus BR.

• With this longer follow-up, clinically meaningful OS benefits of VenR are observed.

• High rate of uMRD was observed with VenR and MRD status at cessation is a strong predictor of durable PFS off-drug.

• The VenR regimen is well tolerated and no new safety signals noted.

• Overall, these data establish the feasibility and support the use of fixed-duration VenR for the majority of patients with R/R CLL.
**RESONATE Trial compared to MURANO in relapsed CLL**

Major difference is median lines of therapy: (3 vs 1, respectively)

**RESONATE - ibrutinib**
- 3-year PFS rate: 59% with ibrutinib vs 3% with ofatumumab

Byrd J et al, ASCO, June 2017

**MURANO – venetoclax+rituximab**
- 3-year PFS rate: 71% with ven+ritux vs 15% with benda+fit

Seymour JF, et al. ASH 2018
Ibrutinib Plus Venetoclax in Relapsed, Refractory CLL: Results of the Bloodwise TAP CLARITY Study

Peter Hillmen, Andy Rawstron, Kristian Brock, Samuel Muñoz-Vicente, Francesca Yates, Rebecca Bishop, Donald MacDonald, Christopher Fegan, Alison McCaig, Anna Schuh, Andrew Pettitt, John G. Gribben, Piers Patten, Stephen Devereux, Adrian Bloor, Christopher P. Fox, Francesco Forconi, Talha Munir

Abstract: 182
Saturday, December 1, 2018: 2:15 PM
Treatment Schedule and Stopping Rules

- **Venetoclax (400mg/day)**
- **Ibrutinib (420mg/day)**

Stopping rules: Duration of therapy is double time to MRD4 negative

1) MRD negative (<0.01%) at M8 stop I+V at M14
2) MRD negative (<0.01%) at M14 or M26 stop I+V at M26
3) MRD positive (≥0.01%) at M26 continue ibrutinib monotherapy

Hillmen et al. ASH 2018; Abst 182
IWCLL Responses in rel/refr CLL Month 14 (12 months I+V)

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>CR</th>
<th>CRi</th>
<th>PR</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients*</td>
<td>49</td>
<td>22 (44%)</td>
<td>5 (10%)</td>
<td>20 (40%)</td>
<td>47 (94%)</td>
</tr>
<tr>
<td>FCR/BR relapsed &lt;36 months¹</td>
<td>20</td>
<td>8 (40%)</td>
<td>2 (10%)</td>
<td>9 (45%)</td>
<td>19 (95%)</td>
</tr>
<tr>
<td>Prior idelalisib²</td>
<td>9</td>
<td>3 (33%)</td>
<td>1 (11%)</td>
<td>4 (44%)</td>
<td>8 (89%)</td>
</tr>
</tbody>
</table>

¹ Percentages calculated over the total number of patients who had FCR/BR and relapsed <36 months and have been assessed for response
² Percentages calculated over the total number of patients who had Idelalisib before joining the study and have been assessed for response

Date of data lock: 05 November 2018
Peripheral Blood

Venetoclax

Ibrutinib

Bone Marrow

Venetoclax

Ibrutinib

Percentage of patients

MRD response by timepoint

NA
>10%
1-10%
0.1-1%
MRD3 (<0.1%)
MRD4 (<0.01%)
MRD5 (<0.001%)

*PB & BM MRD negative pts at Month 8 & 14 stop I+V

All 6 reaching M26 remain MRD negative to date

All remaining patients stop venetoclax at Month 26

MRD4+ patients continue ibrutinib after Month 26

Hillmen et al. ASH 2018; Abst 182
Combined Ibrutinib and Venetoclax in Patients with Treatment-Naïve High-Risk Chronic Lymphocytic Leukemia (CLL)


Department of Leukemia, MDACC
ASH 2018, Abstract 186
Responses Improve with Ongoing Ibrutinib + Venetoclax Therapy in previously untreated CLL

**Graph:***

- Y-axis: 0 to 100
- X-axis: 3 mo IBR, 3 mo VEN+IBR, 6 mo VEN+IBR, 9 mo VEN+IBR, 12 mo VEN + IBR, 18 mo VEN + IBR
- Categories: n=75, n=72, n=70, n=60, n=33, n=26

**Bar Chart Details:***

- **3 mo IBR**:
  - PR%: 96
  - CR/CRi %: 43
  - BM U-MRD4 %: 17

- **3 mo VEN+IBR**:
  - PR%: 0
  - CR/CRi %: 57
  - BM U-MRD4 %: 27

- **6 mo VEN+IBR**:
  - PR%: 61
  - CR/CRi %: 73
  - BM U-MRD4 %: 40

- **9 mo VEN+IBR**:
  - PR%: 83
  - CR/CRi %: 88
  - BM U-MRD4 %: 52

- **12 mo VEN + IBR**:
  - PR%: 88
  - CR/CRi %: 61
  - BM U-MRD4 %: 12

- **18 mo VEN + IBR**:
  - PR%: 96
  - CR/CRi %: 69
  - BM U-MRD4 %: 4

**References:**

Jain et al, ASH 2018, Abs 186
Front-line trial for patients fit for FCR: NCRI Flair (CLL10) Trial

Front Line therapy in CLL: Assessment of Ibrutinib plus Rituximab

Patients with CLL requiring therapy by IWCLL Criteria (n=754)

- FCR
  - 6 monthly pb MRD until positive x3
  - IWCLL Assess
  - BMAT
  - Max. 6 years

- Ibrutinib-R
  - 6 monthly pb MRD until negative & stop
Previously untreated fit patients with CLL (N=772)
(Considered fit for FCR; Age ≤75 years; eGFR ≥30 ml/min; <20% del(17p))

Randomise

FCR  Ibrutinib + rituximab  Ibrutinib monotherapy  Ibrutinib + venetoclax

Duration of therapy defined by MRD (or 6 years)

Primary endpoint: PFS
Comparisons: I+R vs FCR (n=772)

Hillmen et al. ASH 2018; Abst 182
Previously untreated fit patients with CLL
(N=1516)
(Considered fit for FCR; Age ≤75 years;
eGFR ≥30 ml/min; <20% del(17p))

Randomise

FCR
Ibrutinib + rituximab
Ibrutinib monotherapy
Ibrutinib + venetoclax

Duration of therapy defined by MRD (or 6 years)

Primary endpoint: PFS
Comparisons:  I+R vs FCR (n=772)
I+V vs FCR (n= 548)
I+V vs I (n=548)

Hillmen et al. ASH 2018; Abst 182
Previously untreated fit patients with CLL (N=1516)
(Considered fit for FCR; Age ≤75 years; eGFR ≥30 ml/min; <20% del(17p))

Randomise

FCR

Ibritinib + rituximab

Ibritinib monotherapy

Ibritinib + venetoclax

Duration of therapy defined by MRD (or 6 years)

Primary endpoint: PFS

Comparisons:
- I+R vs FCR (n=772)
- I+V vs FCR (n=548)
- I+V vs I (n=548)

As of 28th January 2019
Centres open: 107
1070 patients randomised in total (71% of 1516)
772 randomised to FCR vs IR
(122 patients randomised to I+V)

Hillmen et al. ASH 2018; Abst 182
Ongoing trials with obinutuzumab + ibrutinib + venetoclax (GIVe)

Most common grade ≥3 AEs: neutropenia (50%), lymphopenia (33%), hypertension (25%), and fatigue (17%)

- No cases of clinical or lab TLS were observed

PB, peripheral blood.
* 6 patients have reached response assessment after completing 8 cycles of therapy;
† <65 years of age; ‡ >65 years of age.

Ongoing trials with obinutuzumab + ibrutinib + venetoclax (GIVe)

Phase 1b/2 study of GIVe in R/R CLL (N=12 to date)\(^1\)

- ORR 100%
- CR/CRi n=1
- MRD– in PB and BM
- PR n=5
- 1 pt MRD– in PB
- 1 pt MRD– in PB + BM

GCLLSG CLL13 trial (ongoing, planned N=920)

- Previously untreated fit patients with CLL (CIRS ≤6; normal creatinine clearance; no del(17p)/TP53 mutation)
- Randomise
  - FCR\(^†\) or BR\(^‡\)
  - Venetoclax + rituximab
  - Venetoclax + obinutuzumab
  - Venetoclax, obinutuzumab ibrutinib

Follow-up for progression and survival

- 2 primary endpoints
  - Rate of MRD negativity in PB
  - PFS

PB, peripheral blood.

* 6 patients have reached response assessment after completing 8 cycles of therapy;
1 <65 years of age; \(^†\)>65 years of age.

Emergence of resistance to targeted therapies

Ibrutinib (Btk inhibitor)
- Emergence of Btk C481S mutations and PLC-\(\gamma\)2 mutations
- 8/10 CLL progressions on ibrutinib

Venetoclax (Bcl-2 inhibitor)
- Emergence of Bcl-2 Gly101Val mutations
- 7/15 CLL progressions on venetoclax

Blombery et al., Cancer Discovery, 2018, Online Dec 4
The evolutionary landscape of chronic lymphocytic leukemia treated with ibrutinib targeted therapy

Landau et al., Nature Comm, 2018; 8: 2185
Continuous therapy at maximal tolerated dose (MTD)
- Sensitive cells are rapidly eliminated and the resistant cells have a selective advantage leading to treatment failure.

Evolution of resistance to therapy → intra-tumoral Darwinian dynamics

Evolution-based (intermittent treatment) strategy → treatment is halted before sensitive cells are eliminated.
Resistant cells have a disadvantage when "off-therapy" so the tumour remains sensitive.

Darwinian dynamics
A Randomised Phase III Trial Comparing Continuous with Intermittent Treatment With Ibrutinib in front-line and relapsed CLL ("Intermittent Treatment Trial")

**Randomisation (1:1). N = 800**
Stratification factors: no of prior therapies, time on current therapy, MRD, VH status, BTK inhibitor

- Continuous treatment until disease progression
  - N = 400

- Intermittent treatment strategy until treatment strategy failure
  - N = 400
    - Stop treatment
    - Treatment re-start criteria reached
    - Treatment stopping criteria reached
    - Restart treatment

HTA (NIHR) funded
Will open end of 2019
FLAIR patients eligible but including relapsed patients
Primary end-point = treatment strategy failure

Assessments until disease progression/ treatment strategy failure
3 monthly assessments: assessment for restarting/ stopping treatment, standard investigations, QoL & health economics questionnaires, (data collected 6 monthly unless start/stop treatment)
CLL treatment algorithm in February 2019

Earlier stage, asymptomatic

- All
  - Observe
  - V_H mutated and No 17p-, No TP53mut
    - FCR or ibrutinib
      - CR / PR
        - Observe
      - SD / PD
  - V_H unmutated or 17p- and/or TP53mut
    - Ibrutinib
      - Observe
      - CR / PR
      - SD / PD
      - 2nd line Venetoclax+rituximab
        - Consider AlloSCT

Advanced stage, symptomatic CLL (“active disease”)

- Fit (young)
  - Observe
  - Ibrutinib
    - Observe
    - CR / PR

- Unfit (old)
  - No 17p-, No TP53mut
    - Ibrutinib
      - Observe
      - CR / PR
  - 17p-, and/or TP53mut
    - Ibrutinib
      - Observe
      - CR / PR
  - Frail (very old)
    - BSC (?)
      - OR ibrutinib
      - OR chlorambucil
      - Benefit ?
      - 2nd line Venetoclax+rituximab
        - *
Conclusions: getting close to curing CLL?

1. Eradication of measurable residual disease is the strongest predictor of survival in CLL
2. “Novel” targeted therapies have dramatically changed the outcome of patients with CLL but are generally given continuously
3. Combinations of key pathway inhibitors leads to the eradication of MRD promising a fixed duration of therapy
4. Emergent resistance mutations are now described and strategies to control resistance are being studied
5. Cure for the majority of patients with CLL is increasingly likely!
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NCRI CLL Trials Sub-group

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Dena Howard
Claire Hutchinson
Ben Kennedy
Scott Marshall
Alison McCaig

Helen McCarthy
Mel Oates
Piers Patten
Andy Pettitt
Chris Pocock
Guy Pratt
Anna Schuh (Chair)
Jon Strefford
Renata Walewska
Nick York

HMDS, Leeds

Andy Rawstron
Abraham Varghese
Jane Shingles

Telah Munir
Ruth de Tute
Cathy Burton

Francesca Yates
Sophie Cramp
Sonia Fox
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20-23 SEPTEMBER 2019 EDINBURGH

YOUNG INVESTIGATOR MEETING:
20 SEPTEMBER 2019

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