Ibrutinib Plus Venetoclax in Relapsed, Refractory CLL: Updated results of the Bloodwise TAP CLARITY Study

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Study End-Points

Primary end-point:
- Minimal Residual Disease (MRD) eradication (<0.01% CLL cells) in the marrow after 12 months of IBR+VEN.

Secondary end-points:
- MRD eradication (<0.01% CLL cells) in the marrow after 6 & 24 months of IBR+VEN
- Response rate, Progression-free survival (PFS) and Overall survival (OS)
- Toxicity of combination therapy (AE’s and SAE’s)

Key Exploratory end-points:
- Phosphoprotein and Bcl-2 protein expression.
- Investigation of the apoptotic pathway
- Depletion of MRD below $10^{-5}$ and $10^{-6}$ using high sensitivity flow cytometry and HTS

Key Entry Criteria

Key Inclusion Criteria:
- CLL requiring therapy according to IWCLL criteria
- Refractory/relapsed CLL defined as any of the following:
  - Patients with CLL with 17p del after at least one previous therapy.
- ECOG performance status (PS) of 0, 1, or 2
- Adequate bone marrow function (Plt >75; Neut >1.0) unless due to marrow involvement

Key Exclusion Criteria:
- Richter’s transformation or CNS involvement by CLL
- Previous treatment with ibrutinib, venetoclax or an alternative Btk or Bcl-2 inhibitor
- Active autoimmune haemolysis or immune mediated thrombocytopenia
Treatment Schedule and Stopping Rules

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
## Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients (n = 54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (Male/Female)</td>
<td>37 (69%) / 17 (31%)</td>
</tr>
<tr>
<td>Age (Median [Range])</td>
<td>64 (31 – 83)</td>
</tr>
<tr>
<td>Current Binet Stage (A / B / C / NK)</td>
<td>12 (22%) / 18 (33%) / 22 (41%) / 2 (4%)</td>
</tr>
<tr>
<td>Lymph nodes (“bulky” ≥ 5cm)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>ECOG (0/1/2/NK)</td>
<td>32 (59%) / 18 (33%) / 3 (6%) / 1 (2%)</td>
</tr>
<tr>
<td>VH (mutated/unmutated/VH3-21/failed)</td>
<td>10 (19%) / 40 (74%) / 3 (6%) / 1 (2%)</td>
</tr>
<tr>
<td>17p del</td>
<td>10/50 (20%)</td>
</tr>
<tr>
<td>11q del (not 17p del)</td>
<td>13/51 (25%)</td>
</tr>
<tr>
<td>Prior therapies (median [range])</td>
<td>1 (1 to 6)</td>
</tr>
<tr>
<td>• previous FCR or BR</td>
<td>44/54 (82%)</td>
</tr>
<tr>
<td>• relapse within 3 years of BR or FCR</td>
<td>22/44 (50%)</td>
</tr>
<tr>
<td>• previous idelalisib</td>
<td>11/54 (20%)</td>
</tr>
</tbody>
</table>

- 4 patients stopped ibrutinib before adding venetoclax due to toxicity
- 50 patients recruited to combination part of trial
- 50 patients successfully passed through venetoclax escalation phase

### Toxicity category/event

<table>
<thead>
<tr>
<th>Study Patient number</th>
<th>Toxicity category/event</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>Infections and infestations</td>
</tr>
<tr>
<td>25</td>
<td>Brain abscess</td>
</tr>
<tr>
<td>34</td>
<td>Vascular disorder</td>
</tr>
<tr>
<td>50</td>
<td>Gastrointestinal disorder, renal disorder, general disorder, injury</td>
</tr>
</tbody>
</table>

Date of data lock: 05 September 2019
Primary end-point: undetectable MRD\(_4\) (<0.01%) in BM after 12 months I+V

<table>
<thead>
<tr>
<th>All at Month 14</th>
<th>PB MRD negative</th>
<th>BM MRD negative</th>
<th>Trephine normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>29/50 (58%)</td>
<td>20/50 (40%)</td>
<td>39/48 (81%)</td>
</tr>
<tr>
<td>FCR/BR rel &lt;36 months</td>
<td>14/20 (70%)</td>
<td>9/20 (45%)</td>
<td>18/19 (95%)</td>
</tr>
<tr>
<td>Prior idelalisib</td>
<td>6/9 (67%)</td>
<td>5/9 (56%)</td>
<td>7/9 (78%)</td>
</tr>
</tbody>
</table>

50/50 patients have reached at least Month 14 and have had a bone marrow MRD PB or BM <0.01% CLL cells (10\(^{-4}\)) by flow cytometry.

Using statistical significance (alpha) of 2.5% and statistical power of 95.5%, the A’Hern design requires at least 10 of 50 patients to achieve MRD-eradication in the marrow to reach the pre-defined efficacy threshold for the combined treatment.

Assumptions: Ibr+Ven 30% MRD eradication; Ibr monotherapy <10% MRD eradication.
Treatment Schedule and Stopping Rules

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
4) MRD positive (≥0.01%) at M26 can continue venetoclax for 12 months (Amendment)
MRD level by time-point (up to Month 26)

Peripheral Blood

Venetoclax

Ibrutinib

Bone Marrow

Venetoclax

Ibrutinib

Date of data lock: 2nd August 2019

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

All 16/17 reaching M26 remain MRD negative to date

MRD4+ patients continue ibrutinib after Month 26

MRD4+ patients to continue venetoclax for 12 months
Undetectable MRD4 (<0.01% and (<0.001%) in PB and BM after 24 months I+V

<table>
<thead>
<tr>
<th>All at Month 26</th>
<th>PB MRD negative</th>
<th>BM MRD negative</th>
<th>PB MRD negative</th>
<th>BM MRD Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>All evaluable patients</td>
<td>32/46 (70%)</td>
<td>23/46 (50%)</td>
<td>21/46 (46%)</td>
<td>13/46 (28%)</td>
</tr>
</tbody>
</table>

50/50 patients have reached at least Month 14 and have had a bone marrow MRD PB or BM <0.01% CLL cells (10^-4) by flow cytometry.
Patients receiving I + V currently at Month 26 (n=28)

Note: This graph represents the data available in the database on 05-Sep-2019. Information on venetoclax pauses is still being collected and so some additional patients may have discontinued/paused venetoclax earlier than has been presented here.
Drug discontinuations at Month 26

Ibrutinib + Venetoclax discontinuations
n = 15

Venetoclax discontinuation
n = 7

Note: This graph represents the data available in the database on 05-Sep-2019. Information on venetoclax pauses is still being collected and so some additional patients may have discontinued/paused venetoclax earlier than has been presented here.
IWCLL Responses
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>50</td>
<td>23</td>
<td>5</td>
<td>20</td>
<td>48</td>
</tr>
<tr>
<td>FCR/BR relapsed &lt;36 months¹</td>
<td>20</td>
<td>8</td>
<td>2</td>
<td>9</td>
<td>19</td>
</tr>
<tr>
<td>Prior idelalisib²</td>
<td>9</td>
<td>3</td>
<td>1</td>
<td>4</td>
<td>8</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 September 2019
## Toxicity – AEs of interest

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 1&amp;2, events (patients)</th>
<th>Grade 3, events (patients)</th>
<th>Grade 4, events (patients)</th>
<th>Any Grade, events (patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation / flutter</td>
<td>3 (3)</td>
<td>3 (2)</td>
<td>0 (0)</td>
<td>6 (5)</td>
</tr>
<tr>
<td>Blood Blister(s) / Bleeding</td>
<td>12 (8)</td>
<td>2 (2)</td>
<td>0 (0)</td>
<td>14 (10)</td>
</tr>
<tr>
<td>Bruising</td>
<td>37 (20)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>37 (20)</td>
</tr>
<tr>
<td>Esophageal Hemorrhage</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Eye Haemorrhage</td>
<td>5 (4)</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>6 (5)</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Haematoma (Retroperitoneal)</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Neutrophil Count Decreased</td>
<td>3 (3)</td>
<td>24 (11)</td>
<td>10 (5)</td>
<td>37 (13)</td>
</tr>
<tr>
<td>Pleural Hemorrhage</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Retroperitoneal Haematoma*</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Tumor Lysis Syndrome</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

* The two events are thought to be the same event & are being queried

Single case of tumour lysis syndrome (at 200mg dose) – increasing phosphate and creatinine. Managed by delaying venetoclax. Rapidly re-escalated with no further TLS

Recommendation in protocol to give G-CSF to keep the neutrophil count above $1 \times 10^9$/L.

Date of data lock: 05 September 2019
Case of disease progression

- Single case of Richter’s transformation (Not biopsy proven)
- Diagnosed 2011. Treated with FCR x 6 to PR in 2013
- Progressive disease 2016. FISH del(13q14), IGHV 97.6% homology to germline VH3-21
- Achieved MRD +ve CR on CLARITY study

Combination of ibrutinib (IBR) with venetoclax (VEN) is well tolerated in relapsed, refractory CLL

- with one case of laboratory TLS
- Adverse event reported mostly grade 1 or 2 - with GI or neutropenia most common AE.

48/50 (96%) patients have an objective response and 28/50 (56%) are in CR or CRi after 12 months combined IBR+VEN

- 20/50 (40%) are MRD negative (<0.01%) in marrow after 12 months IBR+VEN
- 23/46 (50%) and 32/46 (70%) achieve MRD4 (<0.01%) in marrow and peripheral blood respectively after 24 months IBR+VEN.

The Phase III NCRI FLAIR Trial has been modified to include IBR+VEN in front-line CLL

Only one case of disease progression with Richter’s transformation
Nurses and Trial teams at the TAP Centres:

- Chris Fox, Richard Stanley – Nottingham City
- John Gribben, Samir Agrawal - St Barts, London
- Adrian Bloor, Samuel Evans – The Christie, Manchester
- Talha Munir, Morag Griffen, Peter Hillmen- St James’s University Hospital, Leeds
- Francesco Forconi, Andrew Duncombe, Liza Shiner-Clarke-Southampton General Hospital
- Anna Schuh, Stavroura Chante- Churchill Hospital, Oxford
- Piers Patten, Steve Devereux, Maria Liskova-King’s College Hospital, London
- Andrew Pettitt, Jane Tinsley- Royal Liverpool Infirmary
- Donald MacDonald, Esa Saguyan- Hammersmith Hospital, London
- Chris Fegan, Jayne Sumers- University Hospital of Wales, Cardiff
- Alison McCaig, Louise Dinnett- Beatson WOSCC, Glasgow

CRCTU (TAP):
Francesca Yates, Rebecca Bishop, Kristian Brock, Samuel Muñoz-Vicente, Rebecca Boucher Shamyla Siddique, Sonia Fox

HMDS:
Andrew Rawstron, Ruth de Tute, Surita Dalal, Katie Holmes, Nicola McWhirter, Jane Shingles, Cathy Burton

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