Chronic lymphocytic Leukemia
after IwCLL, ICML and EHA 2017

Ann Janssens, MD, PhD
Hematology, UZ Leuven
Brussels, 14 September 2017
Front line treatment CLL

Active or progressive disease

No 17p13-del/TP53-mut

Unfit for FCR

BR, Ob-Chl, ibrutinib

17p13-del/TP53-mut

fit for FCR

FCR > 65 j: FCR, BR

ibrutinib

Wait & see

No active or progressive disease

17p13-del/TP53-mut

R-idelalisib, allo-SCT

Janssens et al, B J Hematol 2015
**Response front line treatment CLL**

- **Chl**
  - ORR 30-50%
  - CR 0-2%
  - mPFS 11m

- **R-Chl**
  - ORR 65.7%
  - CR 7%
  - mPFS 16.3m

- **Ob-Chl**
  - ORR 77%
  - CR 22%
  - mPFS 26.7m

- **FCR**
  - ORR 90-95%
  - CR 40-44%
  - mPFS 55m

- **BR**
  - ORR 96%
  - CR 31%
  - mPFS 41m

- **Ibrutinib**
  - ORR 92%
  - CR 18%
  - mPFS NR
Treatment R/R CLL

Early relapse (< 36 m),
17p13-del/TP53-mut

Fit: ibrutinib, R-idelalisib
Unfit: Ibrutinib, R-idelalisib
allo-SCT

Late relapse (> 36 m)

Fit for CIT

Unfit for CIT

Fit: CIT

Unfit: ibrutinib, R-idelalisib

Janssens et al, BJ Hematol 2015
Updated Guidelines for the Diagnosis and Treatment of Chronic Lymphocytic Leukemia: A Report from the International Workshop on Chronic Lymphocytic Leukemia (IWCLL)

MICHAEL HALLEK, MD, PHD
CENTER OF INTEGRATED ONCOLOGY,
UNIVERSITY OF COLOGNE
COLOGNE, GERMANY
IWCLL updated guidelines for diagnosis and treatment in CLL

- **Reasons to revise:**
  - Major innovations, genomic landscape, therapeutics
- **Change as little as possible**
- **Indications for treatment:**
  - in general practice stayed UNCHANGED for first and other lines
- **Prognostic factors:**
  - Rai-Binet staging: lab, hands and brain
- **Scores:** not a single score will be proposed
- **Treatment:**
  - Non CIT for those who relapse <24 mo after the termination of previous treatment or acquired a 17p del/p53 mut
  - alloBMT for a selected group defined by ERIC/EBMT

Hallek et al, ?, to be published
IWCLL updated guidelines for diagnosis and treatment in CLL

- **Response assessment:**
  - >2 mo after completion after a treatment of defined duration
  - For continuous treatment: 2 mo after maximum response
  - In clinical trials: response has to persist for 2 months

- **MRD:**
  - in pb (at least 2 mo after a treatment of defined duration or maximum response on a continuous treatment), BM to confirm the pb MRD (-) especially if monoclonals are used, MRD 4 colour flow <1/10000

- **CT scan:**
  - Lymph nodes: use Cheson criteria 2014
  - Spleen < 13cm?
  - Big liver?, nodule(s) in liver is active disease

- **(Transient) lymphocytosis** is not progressive disease or failing treatment if on BCRi

Hallek et al, ?, to be published
Favorable outcome of patients with persistent splenomegaly but MRD- disease

Kovacs et al., JCO, 2016
Complex Karyotype in Patients Treated With Ibrutinib

Effect of Complex Karyotype on Survival in 88 Patients With Relapsed CLL Treated With Ibrutinib-based Therapy at MD Anderson Cancer Center.[a]

- No Complex Karyotype (n = 35)
- Complex Karyotype (n = 21)

Baseline Variables Associated With Disease-related Discontinuation in 31 Patients With Relapsed CLL Treated With Ibrutinib at Ohio State University.[b]

<table>
<thead>
<tr>
<th>Predictors on Univariate Analysis</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased number of prior therapies</td>
<td>HR = 1.12; P = .03</td>
</tr>
<tr>
<td>BCL6 abnormalities</td>
<td>HR = 3.77; P &lt; .001</td>
</tr>
<tr>
<td>MYC abnormalities</td>
<td>HR = 2.59; P = .01</td>
</tr>
<tr>
<td>del(17p)</td>
<td>HR = 2.28; P = .03</td>
</tr>
<tr>
<td>Complex karyotype</td>
<td>HR = 5.17; P = .003</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Independent Predictors on Multivariate Analysis</th>
<th>HR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCL6 abnormalities</td>
<td>HR = 2.70; P = .01</td>
<td></td>
</tr>
<tr>
<td>Complex karyotype</td>
<td>HR = 4.47; P = .007</td>
<td></td>
</tr>
</tbody>
</table>

Complex Karyotype in Patients Treated With Idelalisib/Rituximab

Effect of Complex Karyotype on Survival in 127 Patients With Relapsed CLL Treated in a Phase 3 Trial of Idelalisib or Placebo Plus Rituximab

Reproduced with permission of ASH, from Outcome of patients with complex karyotype in a phase 3 randomized study of idelalisib plus rituximab for relapsed chronic lymphocytic leukemia, Kreuzer KA, et al., 128, 2016; permission conveyed through Copyright Clearance Center, Inc.
Complex Karyotype in patients treated with venetoclax

Anderson et al., Blood 2017
MBL: CLL type, atypical CLL type non-CLL (CD 5-) type

Low-count MBL (<500/µl) no follow-up, no progression

High-count MBL 500-5000/µl

MBL: CLL type, atypical CLL type non-CLL (CD 5-) type

Low-count MBL (<500/µl) no follow-up, no progression

High-count MBL 500-5000/µl

Hallek et al. Blood 2008
Swerdlow et al., Blood 2016
CLL-MBL: most cells persist!

Mean: 0.40 clonal cells/μL

Mean: 50.6 clonal cells/μL

<table>
<thead>
<tr>
<th>Condition</th>
<th>Transient</th>
<th>Persistent</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLL-like</td>
<td>10%</td>
<td>90.0%</td>
</tr>
<tr>
<td>Atypical CLL</td>
<td>44.4%</td>
<td>55.6%</td>
</tr>
<tr>
<td>CD5- CLL</td>
<td>33.3%</td>
<td>66.7%</td>
</tr>
</tbody>
</table>
MBL-CLL like

- Risk of progression
  - High-count MBL: 1%/y
  - CLL: 5000-10000: 3%/y
  - CLL >10000: 5%/y
- Outcome (PFS-OS) less for >11000 monoclonal B-cells
- Prognostic factors identical to CLL
- Risk factors for MBL?
- **Do not label this patients as cancer patients!!!**

  **but**

- **Immune dysfunction identical to CLL**
  - antibodies to latent virussen increased, Ig to S. Pneumoniae decreased
  - Hospitalizations and infections: MBL and CLL identical
  - Vaccinate as early as possible, conjugated is better

- **Secondary cancer risk identical to CLL**
Outcomes of Ibrutinib-Treated Patients With CLL/SLL With High-Risk Prognostic Factors in an Integrated Analysis of 3 Randomized Phase 3 Studies

- Genomic abnormalities del(17p) and del(11q), as well as unmutated IGHV are prognostic factors for poor outcomes to chemoimmunotherapy for patients with CLL/SLL\textsuperscript{1,2}

Thomas J. Kipps, et al.


**Study Design**

**RESONATE-2 (PCYC-1115/1116)**

**Patients (N=269)**
- TN with active disease
- Age ≥65 years
- Del(17p) excluded

ibrutinib 420 mg once daily until PD or unacceptable toxicity (n=136)

chlorambucil 0.5 mg/kg (to maximum 0.8 mg/kg) days 1 and 15 of 28-day cycle up to 12 cycles (n=133)

PCYC-1116 Extension Study
In chlorambucil arm, n=64 crossed over to ibrutinib

**Extension Study**
In chlorambucil arm, n=64 crossed over to ibrutinib

**RESONATE (PCYC-1112)**

**Patients (N=391)**
- ≥1 prior therapy
- Inappropriate or refractory to purine analog therapy

ibrutinib 420 mg once daily until PD or unacceptable toxicity (n=195)

ofatumumab IV initial dose 300 mg followed by 2000 mg × 11 doses over 24 weeks (n=196)

In ofatumumab arm, n=131 crossed over to ibrutinib following PD

**HELIOS (CLL3001)**

**Patients (N=578)**
- ≥1 prior therapy del(17p) excluded

BR (maximum of 6 cycles) + ibrutinib 420 mg once daily starting on cycle 1, day 2 (n=289)

BR (maximum of 6 cycles) + placebo once daily starting on cycle 1, day 2 (n=289)

In BR + placebo arm, n=142 crossed over to ibrutinib following PD

Genomic Risk Factors are not Associated With Inferior Response Rates in Ibrutinib-Treated Patients

- **Unmutated IGHV**
  - Present: 90, Absent: 89
  - $P=0.87$, OR=1.06

- **Trisomy 12**
  - Present: 85, Absent: 91
  - $P=0.11$, OR=1.56
  - $P=0.04$, OR=1.71

- **Complex Karyotype**
  - Present: 88, Absent: 89
  - $P=0.73$, OR=0.84
  - $P=0.36$, OR=0.67

- **Del(11q)**
  - Present: 91, Absent: 90
  - $P=0.78$, OR=1.09
  - $P=0.22$, OR=0.76

---

**Present**

- **ORR**
  - 90
  - 85
  - 88
  - 91

- **CR**
  - 29
  - 33
  - 22
  - 22

**Absent**

- **ORR**
  - 89
  - 91
  - 89
  - 90

- **CR**
  - 26
  - 22
  - 24
  - 27
For Ibrutinib-Treated Patients, PFS With Unmutated IGHV not Significantly Worse Than PFS With Mutated IGHV

In ibrutinib-treated patients, PFS at 36 months:
- 70% with unmutated IGHV vs 77% with mutated IGHV

Median follow-up 36.4 months (95% CI 35.8-37.1)
Trisomy 12 was not Associated With Inferior PFS in Ibrutinib-Treated Patients

- In ibrutinib-treated patients, PFS at 36 months:
  - 73% with both presence or absence of trisomy 12

Median follow-up 36.4 months (95% CI 35.8-37.1)
Complex Karyotype was not Associated With Inferior PFS in Ibrutinib-Treated Patients

In ibrutinib-treated patients, PFS at 36 months:

- 65% with presence of complex karyotype vs 72% with absence of complex karyotype

Median follow-up 36.4 months (95% CI 35.8-37.1)

- In ibrutinib-treated patients, PFS at 36 months:
  - 65% with presence of complex karyotype vs 72% with absence of complex karyotype

- Comparator-treated, without complex karyotype (n=327)
  - Progression-Free Survival, %
  - Median follow-up 36.4 months (95% CI 35.8-37.1)
11q Deletion was not Associated With Inferior PFS in Ibrutinib-Treated Patients

Median follow-up 36.4 months (95% CI 35.8-37.1)

- In ibrutinib-treated patients, PFS at 36 months:
  - 74% with presence of del(11q) vs 68% with absence of del(11q)

Ibrutinib-treated, with del(11q) (n=168)
Ibrutinib-treated, without del(11q) (n=382)
Comparator-treated, with del(11q) (n=137)
Comparator-treated, without del(11q) (n=407)

P=0.08
HR=0.73

P<0.01
HR=1.88
Genomic Risk Factors are not Associated With Shorter OS in Ibrutinib-Treated Patients

<table>
<thead>
<tr>
<th></th>
<th>IGHV</th>
<th>Trisomy 12</th>
<th>Complex Karyotype</th>
<th>Del(11q)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unmut. (n=334)</td>
<td>Mut. (n=113)</td>
<td>With (n=90)</td>
<td>Without (n=314)</td>
</tr>
<tr>
<td>42-month OS, %</td>
<td>78</td>
<td>84</td>
<td>82</td>
<td>80</td>
</tr>
<tr>
<td>Log-rank P value (HR)</td>
<td>0.41 (1.21)</td>
<td>0.92 (1.02)</td>
<td>0.91 (0.96)</td>
<td>0.08 (0.73)</td>
</tr>
</tbody>
</table>
Conclusions

• Ibrutinib-treated patients with trisomy 12 had significantly higher rate of CR, however PFS and OS were similar vs those without trisomy 12

• Presence of unmutated *IGHV*, del(11q), or complex karyotype were adverse prognostic factors for PFS in comparator-treated patients, but not ibrutinib-treated patients

• Although results from a phase 2 study of heavily-pretreated patients suggested del(11q) may be an adverse prognostic factor for PFS in ibrutinib-treated patients, results of this integrated analysis of three phase 3 studies suggest a trend for longer PFS vs those without del(11q)

• Results suggest that genomic risk factors associated with poor outcomes with traditional therapies have less relevance with ibrutinib treatment

*Kipps T, et al., Hematol Oncol 2017;35 S2:109-111*
Complex Karyotype?

• However, it was suggested that CLL with >3 cytogenetic aberrations are not equivalent meaning that patients with co-existing trisomies have a favorable outcome and patients with >5 aberrations represent an aggressive subgroup.

• The outcome of 3580 CLL/MBL patients from 22 European centers with a karyotype available before the start of first line treatment was evaluated.

• The investigators have to conclude that complex karyotype with >5 aberrations emerges as a prognostic adverse risk group independent of stage, IGVH and p53 function and that this finding needs prospective validation.

Baliakis et al., Haematologica 2017;102,S2: S461)
5 y experience with single agent ibrutinib in R/R CLL: Responses to the BCRi are not forever and new treatment options are still necessary

<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, oral presentation and abstract
Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label, phase 2 study

Lancet Oncol, 2016

N=107
M age 67y
M Previous R/2

- Of 45 patients tested, 18 achieved MRD-negativity in peripheral blood
Stilgenbauer et al., Haematologica 2017;102,S2:S771

VENETOCLAX ASSESSMENT RESPONSE TO VENETOCLAX

**Table 1. Patient Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients</th>
<th>N=158</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), years</td>
<td>50 (18–83)</td>
<td></td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td>Male</td>
<td>89 (57)</td>
</tr>
<tr>
<td>ECOG performance status, n (%)</td>
<td>0</td>
<td>89 (44)</td>
</tr>
<tr>
<td>1</td>
<td>76 (48)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>11 (7)</td>
<td></td>
</tr>
<tr>
<td>Number of prior therapies, median (range)</td>
<td>2 (1–11)</td>
<td></td>
</tr>
<tr>
<td>Flutamide complete remission, n (%)</td>
<td>80 (50)</td>
<td></td>
</tr>
<tr>
<td>Flutamide refractory, n (%)</td>
<td>45 (29)</td>
<td></td>
</tr>
<tr>
<td>Prior BCL2 n (%)</td>
<td>18 (11)</td>
<td></td>
</tr>
<tr>
<td>CARD15 category n (%)</td>
<td>Low</td>
<td>36 (23)</td>
</tr>
<tr>
<td>Median</td>
<td>80 (50)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>52 (33)</td>
<td></td>
</tr>
<tr>
<td>ALC, median (range), x10^9/L</td>
<td>21 (3–380)</td>
<td></td>
</tr>
<tr>
<td>CD53, n (%)</td>
<td>79 (50)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2. Patient Disposition**

<table>
<thead>
<tr>
<th>All enrolled patients, n</th>
<th>158</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time on venetoclax, median (range), months</td>
<td>23.0 (0.9–30.2)</td>
</tr>
<tr>
<td>Active as of April 2017, n (%)</td>
<td>79 (50)</td>
</tr>
<tr>
<td>Disease progression, n (%)</td>
<td>79 (50)</td>
</tr>
<tr>
<td>CLL disease progression</td>
<td>38 (24)</td>
</tr>
<tr>
<td>Richter’s transformation</td>
<td>17 (11)</td>
</tr>
<tr>
<td>AIE</td>
<td>16 (10)</td>
</tr>
<tr>
<td>Stem cell transplant</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Withdrawn consent</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Deaths, n (%)</td>
<td>52 (33)</td>
</tr>
</tbody>
</table>

**Figure 3. Best Objective Response**

**N=158**

**Stilgenbauer et al., Haematologica 2017;102,S2:S771**

**Figure 4. Survival on Venetoclax Monotherapy**

**Median (95% CI): 27.2 (21.9,-) Months after First Dose**

**Overall Survival**

**Median (95% CI): 38.8 (33.8,-) Months after First Dose**
Long term follow-up confirms durable and sustained efficacy

- Median time to first response: 1 month (range: 0.5 – 4.4)
- Median time to CR/CRi: 9.8 months (range: 2.7 – 31.1)

Previously Untreated (n=5)

<table>
<thead>
<tr>
<th>CR/CRi</th>
<th>n PR/PR</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>40%</td>
<td>40%</td>
<td>20%</td>
</tr>
</tbody>
</table>

Prior BCRI (n=18)

<table>
<thead>
<tr>
<th>CR/CRi</th>
<th>n PR/PR</th>
<th>SD</th>
<th>PD</th>
<th>NE</th>
</tr>
</thead>
<tbody>
<tr>
<td>11%</td>
<td>50%</td>
<td>33%</td>
<td>0</td>
<td>6%</td>
</tr>
</tbody>
</table>

12-month PFS estimate: 50%
12-month OS estimate: 54%

*One patient discontinued after the first venetoclax dose, one patient died after 3 weeks of treatment due to liver dysfunction not related to venetoclax, and one patient had pseudo obstruction of the small bowel mesentery and retroperitoneum during dose ramp up and discontinued the study.

As of 4Apr2017
Outcomes with the alternative therapy following discontinuation of ibrutinib or idelalisib

- Multicenter, retrospective analysis of 123 pts who discontinued either ibrutinib or idelalisib-based therapy for any reason (93 ibrutinib and 30 idelalisib)
- Toxicity was most common reason for discontinuation

<table>
<thead>
<tr>
<th>Alternate KI</th>
<th>Bcl-2i</th>
<th>CIT</th>
<th>CD20 Tx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>38</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>ORR</td>
<td>50%</td>
<td>76%</td>
<td>25%</td>
</tr>
<tr>
<td>CR</td>
<td>0%</td>
<td>7%</td>
<td>17%</td>
</tr>
<tr>
<td>PR</td>
<td>50%</td>
<td>69%</td>
<td>8%</td>
</tr>
<tr>
<td>SD</td>
<td>30%</td>
<td>16%</td>
<td>33%</td>
</tr>
<tr>
<td>PD</td>
<td>20%</td>
<td>8%</td>
<td>42%</td>
</tr>
</tbody>
</table>

Idela-ibru: ORR 64%
Ibru-idela: ORR 28%

Mato et al., Ash 2015, abstract 719, Blood 2016, epub
Venetoclax showed high ORR in heavily pretreated CLL patients relapsing after a BCRi,

- For all patients, estimated 12-month PFS was 72% and 12-month OS was 90%

*Best response assessed by independent review committee (IRC); NR by IRC includes SD or PD.

Data Cut-off was June 10, 2016. BCRi=B-Cell Receptor Inhibitor. CLL=Chronic Lymphocytic Leukemia.

Jones JA, et al. Oral #637. 58th ASH Annual Meeting; December 3-6, 2016; San Diego, CA.
patients unresponsive or intolerant to venetoclax will still be responsive to BCRi

- As we know from the M14-032 trial that patients who are progressive, intolerant on or after BCRi are still responsive to bcl-2 antagonists, we can wonder if patients unresponsive or intolerant to venetoclax will still be responsive to BCRi. 10/67 with BTKi naive R/R CLL treated patients on early phase venetoclax trials at 2 Australian centers received subsequent a BTKi. Responses were seen with BTKi (ibrutinib n=9, new BTKi n=1) therapy in 9/10 patients post PD on venetoclax (5/6 at progression and 4/4 after the control of Richter syndrome (RS)). The investigators concluded that cross-resistance between Bcl-2 and BTKi is not manifest in most patients and justify the use of BTKi therapy after failure of venetoclax in BTKi-naive patients.

Anderson et al., Hematol Oncol 2017;35 S2:236-237
With the current knowledge, the new oral agents are given till progression or till intolerance.

Sequential „triple T-concept“: CLL2-BXX studies

DEBULKING

INDUCTION

MAINTENANCE (MRD tailored)

CLL2-BIG: Bendamustin, Ibrutinib, GA101 (Obinutuzumab)
CLL2-BAG: Bendamustin, ABT-199 (GDC-0199), GA101 (Obinutuzumab)
CLL2-BCG: Bendamustin, CAL-101 (Idelalisib), GA101 (Obinutuzumab)
CLL2-BIO: Bendamustin, Ibrutinib, Ofatumumab
MRD: the holy grail for cure
CLL2-BIG (bendamustine-obinutuzumab-ibrutinib followed by ibrutinib and ob maintenance)

- n=66; 27 treatment-naïve (TN) and 31 R/R with a median of 1 prior treatment line
- ORR of 100% and an MRD (-) rate of 47% in the pb at end of induction.
- Grade 3-4 adverse events (AEs) occurred in 19 patients (33%) during induction therapy (neutropenia and thrombocytopenia being the most common).
- 1 toxic death was reported.

von Tresckow et al., Blood 2016;128:640
**phase-II CLL2-BAG trial:**

**best abstract Lugano meeting**

- **B debulking:** 71% *(if lymphocyte count ≥ 25,000/µl and/or lymph nodes ≥ 5cm)*
- **induction with Ob and venetoclax** (6m) and **maintenance therapy** *(continuous venetoclax and G every 3 m until MRD (-) CR or for up to 24m in fit and unfit, TN and R/R CLL.)*
- N=66 patients (34 TN, 29 R/R), median n° of prior treatment lines: 2, median age of 59y.
- ORR 97% (TN 100%, R/R 93%)
- MRD (-) rate of 89% in pb (<10^-4 by flow cytometry) at end of induction.
- grade 3-4 SAEs: 66, 3 toxic deaths (3 fatal septicemias in R/R pts). The most common AEs were infection, hematological toxicities and infusion related events.
- 5 laboratory TLS events (1 during B debulking, 1 in induction cycle 1 with G, 2 in C 3 and 1 in C 4 with G and ven).

*Cramer et al, Haematologica 2017;102 S2: S464*
### BAG: Bendamustine, ABT199, GA101

<table>
<thead>
<tr>
<th>Response (according to IWCLL guidelines)</th>
<th>all patients (n=63)</th>
<th>treatment-naïve (n=34)</th>
<th>relapsed/refractory (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>5 (7.9%)</td>
<td>3 (8.8%)</td>
<td>2 (6.9%)</td>
</tr>
<tr>
<td>CRi</td>
<td>1 (1.6%)</td>
<td>-</td>
<td>1 (3.4%)</td>
</tr>
<tr>
<td>unconfirmed clinical CR/CRi</td>
<td>19 (30.1%)</td>
<td>14 (41.2%)</td>
<td>5 (17.2%)</td>
</tr>
<tr>
<td>PR</td>
<td>36 (57.1%)</td>
<td>17 (50.0%)</td>
<td>19 (65.5%)</td>
</tr>
<tr>
<td>SD</td>
<td>1 (1.6%)</td>
<td>-</td>
<td>1 (3.4%)</td>
</tr>
<tr>
<td>PD</td>
<td>1 (1.6%)</td>
<td>-</td>
<td>1 (3.4%)</td>
</tr>
<tr>
<td>MRD in peripheral blood</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>negative (&lt; 10⁻⁴)</td>
<td>56 (88.9%)</td>
<td>33 (97.1%)</td>
<td>23 (79.3%)</td>
</tr>
<tr>
<td>intermediate (≥ 10⁻⁴ and &lt; 10⁻²)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>positive (≥ 10⁻²)</td>
<td>4 (6.3%)</td>
<td>1 (2.9%)</td>
<td>3 (10.3%)</td>
</tr>
<tr>
<td>missing</td>
<td>3 (4.8%)</td>
<td>-</td>
<td>3 (10.3%)</td>
</tr>
<tr>
<td>MRD in bone marrow</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>negative (&lt; 10⁻⁴)</td>
<td>8 (12.7%)</td>
<td>4 (11.8%)</td>
<td>4 (13.8%)</td>
</tr>
<tr>
<td>intermediate (≥ 10⁻⁴ and &lt; 10⁻²)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>positive (≥ 10⁻²)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>missing</td>
<td>55 (87.3%)</td>
<td>30 (88.2%)</td>
<td>25 (86.2%)</td>
</tr>
</tbody>
</table>
Can we expect that ibrutinib and venetoclax works synergistic?
Can we expect that ibrutinib and venetoclax work synergistic?
investigate the safety and efficacy of ibrutinib combined with venetoclax in patients with R/R CLL.

After 8 weeks of ibrutinib monotherapy, venetoclax was added with weekly escalations from 10 to a final dose of 400mg/day.

The primary end-point of the trial is MRD eradication (defined as less than 1 CLL cell in 10,000) in the BM after 12m of ibrutinib + venetoclax.

50 patients will be treated. 35 patients are enrolled and 21 patients have completed already the dose escalation phase.

The level of CLL in the pb increased during the 8 w of ibrutinib monotherapy from a median of 50000/μl (range: 0 to 330) to 55000/μl (range: 0 to 237000) and then fell during the first 8 weeks of combined ibrutinib with venetoclax (4w dose escalation followed by 4w at 400mg/day) from a median of 55000/μl to a median of 1,7/μl (range; 0 to 3100). The rate of fall is rapid in all patients with a median of 3 log reduction in CLL level after 8w of combined therapy.

The combination of ibrutinib with venetoclax is well tolerated; only a single case of lab TLS.

*The investigators concluded that the rapid reduction in the pb CLL level even during the escalation phase of venetoclax with ibrutinib suggests a potent synergy between the drugs* 

Hillmen et al, Haematologica 2017;102 S2:S770
Cycle 1-2
Ibrutinib 420 mg, day 1-28

Cycle 3
Ibrutinib 420 mg, day 1-28
Venetoclax 20 mg, day 1-7
50 mg, day 8-14
100 mg, day 15-21
200 mg, day 22-28

Cycle 4-15
Ibrutinib 420 mg, day 1-28
Venetoclax 400 mg, day 1-28

Study design
Phase-II trial, prospective, multicenter, open-label, randomized.

Patient population
Fit (CIRS ≤ 6) and unfit (CIRS > 6) patients with a creatinine clearance ≥ 30 ml/min with previously treated CLL with or without TP53 aberrations requiring treatment.

N=230
HOVON 141
CLL13-trial/GAIA

Standard chemoimmunotherapy (SCIT)

vs. ABT-199 + R vs. ABT-199 + G vs. ABT-199 + I + G

Fit CLL patients
(CIRS ≤ 6 & normal CrCl)

Stratification according to age, Binet stage and region
Randomization

FCR/BR*

230

RVe

230

GVe

230

GIVe

230

MRD negativity at month

15

PFS

920 pts

* ≤ 65 years: FCR
> 65 years: BR
[50% FCR / 50% BR]
1: 5 week dose titration phase: 20-50-100-200-400mg

2: Hydration, anti-hyperuricemic drugs, hospitalization and laboratory control according to tumor burden (Consider upgrading risk group if CrCl <80 ml/min, huge splenomegaly, important pre-existing co-morbidities and pre-existing, not corrected, electrolyte or uric acid values)

**Low Risk**
- All nodes <5cm “and” ALC <25000/ml
- 2 à 3 d before start
- 2L oral hydration allopurinol
- Lab predose at each ramp-up dose
  - Lab at 6-8h, at 24h after 20-50 mg

**Median Risk**
- One node 5-10cm “or” ALC≥25000/ml
- 2 à 3 d before start
- 2L oral hydration
  - Allopurinol
  - Consider IV fluid
- Lab predose at each ramp-up dose
  - Lab at 6-8h, at 24h after 20-50 mg

**High Risk**
- One node≥10cm “or” One node 5-10cm with ALC≥25000/ml
- 2 à 3 d before start
- 2L oral hydration
  - Allopurinol or rasburicase if uric acid is elevated
  - Consider IV fluid
  - 150-200ml/h if tolerated
- Lab predose at each ramp-up dose
  - Lab at 4h, 8h, 12h, 24h after 20-50mg
  - Lab at 6-8h, 24h at 100-200-400mg
Tumor debulking and reduction in TLS risk: analysis from single-agent ibrutinib studies

**RESONATE-2 (PCYC-1115/1116)**

Patients (N=269)
- TN with active disease
- Age ≥65 years
- Del(17p) excluded

Ibrutinib 420 mg once daily until PD or unacceptable toxicity (n=135)

- Chlorambucil 0.5 mg/kg (to maximum 0.8 mg/kg) days 1 and 15 of 28-day cycle up to 12 cycles (n=133)

Response evaluation at d113

**RESONATE (PCYC-1112)**

Patients (N=391)
- ≥1 prior therapy
- Inappropriate or refractory to purine analog therapy

Ibrutinib 420 mg once daily until PD or unacceptable toxicity (n=195)

- Ofatumumab IV initial dose 300 mg followed by 2000 mg × 11 doses over 24 weeks (n=196)

Response evaluation at d78

**PCYC-1102**

Patients (N=94)
- R/R n= 67
- Naïve n=27

Ibrutinib 420 mg once daily until PD or unacceptable toxicity (n=94)

Response evaluation at d56

---

most patients with baseline high-risk TLS were reduced to moderate or low risk at first assessment and that debulking with ibrutinib lead-in may effectively reduce TLS risk for venetoclax and the intensity of TLS monitoring.
Patterns of Ibrutinib Discontinuation: OSU Institutional Experience

Cumulative Incidence of Discontinuation of Ibrutinib Therapy

- Other event
- Transformation
- CLL progression

No. at risk | 308 | 274 | 247 | 226 | 206 | 179 | 118 | 90 | 64 | 40 | 24 | 5 | 0

<table>
<thead>
<tr>
<th>Cumulative Incidence Estimates (95% CI)</th>
<th>At 2 Years</th>
<th>At 3 Years</th>
<th>At 4 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLL progression</td>
<td>5.0% (2.5% to 7.5%)</td>
<td>10.8% (7.1% to 14.4%)</td>
<td>19.1% (13.9% to 24.3%)</td>
</tr>
<tr>
<td>Transformation</td>
<td>7.3% (4.3% to 10.2%)</td>
<td>9.1% (5.8% to 12.4%)</td>
<td>9.6% (6.2% to 13.0%)</td>
</tr>
<tr>
<td>Other event</td>
<td>18.7% (14.3% to 23.1%)</td>
<td>23.9% (19.0% to 28.8%)</td>
<td>25.0% (20.0% to 30.1%)</td>
</tr>
</tbody>
</table>

Survival after Ibrutinib Discontinuation:
OSU Institutional Experience

Woyach et al. JCO (2017) E-pub ahead of print
Richter syndrome: then and now

20% of RS downgraded to CLL in prolymphocytoid evolution after hematopathology revision

Gaidano, IWCLL 2017
Post remission SCT is a potentially curative approach for Richter syndrome (EBMT)

A) Allo-SCT=25
B) Nonrelapse Mortality (progression) Time (months)
C) Overall Survival (progression) Time (months)

A) Auto-SCT=34
B) Nonrelapse Mortality (progression) Time (months)
C) Overall Survival (progression) Time (months)

Prognosticators: Chemosensitive disease RIC

Cwynarski et al, JCO 2012

Gaidano, IWCLL 2017
Adopt a biopsy policy
Close monitoring of CLL with
- IGHV4-39 with stereotyped HCDR3 (subset II)
- NOTCH1 mutations

Clinical suspicion of RS
- Bulky
- Extranodal
- B symptoms
- HIGH LDH

Manage as a CLL
PET
PET tailored biopsy

CLL or "accelerated" CLL
CLL relationship
CLonally related RS
Clinical trial or R-CHOP of OFAR or R-Hyper-CVAD

Denor
Allo SCT

Clonally unrelated RS
Manage as a de novo DLBCL (i.e., R-CHOP)

Auto SCT Clinical trial Follow-up

Second cancer
DLBCL
## Other investigational drugs

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>Patients</th>
<th>RS type</th>
<th>Regimen</th>
<th>ORR</th>
<th>CR</th>
<th>PFS/FFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kuruvilla 2014</td>
<td>Clinical trial</td>
<td>6</td>
<td>DLBCL</td>
<td>Selinexor</td>
<td>33%</td>
<td>0%</td>
<td>na</td>
</tr>
<tr>
<td>Hillmen, 2016</td>
<td>Clinical trial</td>
<td>29</td>
<td>DLBCL</td>
<td>Acalabrutinib</td>
<td>38%</td>
<td>14%</td>
<td>3 months</td>
</tr>
<tr>
<td>Tsang, 2016</td>
<td>Retrospective</td>
<td>4</td>
<td>DLBCL</td>
<td>Ibrutinib</td>
<td>75%</td>
<td>25%</td>
<td>na</td>
</tr>
<tr>
<td>Ding, 2016</td>
<td>Clinical trial</td>
<td>9</td>
<td>DLBCL</td>
<td>Pembrolizumab</td>
<td>44%</td>
<td>11%</td>
<td>na</td>
</tr>
<tr>
<td>Davids, 2017</td>
<td>Clinical trial</td>
<td>7</td>
<td>DLBCL</td>
<td>Venetoclax</td>
<td>43%</td>
<td>0%</td>
<td>na</td>
</tr>
</tbody>
</table>

Gaidano, IWCLL 2017
Treatment algorithm for patients with R/R CLL

BCRi → Response
- Continue BCRi → no response
  - alternative BCRi – venetoclax

<table>
<thead>
<tr>
<th>Factors favoring</th>
<th>Novel agents</th>
<th>alloBMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>age</td>
<td>&gt;70 y</td>
<td>&lt;70 y</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>yes, severe</td>
<td>No, moderate</td>
</tr>
<tr>
<td>fitness</td>
<td>poor</td>
<td>good</td>
</tr>
<tr>
<td>17pdel, P53 mut</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>PFS</td>
<td>&gt;3 y</td>
<td>&lt; 3 y</td>
</tr>
<tr>
<td>Fully matched donor</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Transplant risk</td>
<td>high</td>
<td>low</td>
</tr>
</tbody>
</table>

Montserrat, Dreger et al. 2017

Continue novel agent or alloBMT
Front line treatment CLL

Active or progressive disease

No 17p13-del/TP53-mut
- Unfit for FCR
  - BR, Ob-Chl, ibrutinib
- Fit for FCR
  - FCR
  - > 65 j: FCR, BR

17p13-del/TP53-mut
- ibrutinib
- R-idelalisib, venetoclax, allo-SCT

No active or progressive disease
- Wait & see

Janssens et al, B J Hematol 2015
Update needed!
Treatment R/R CLL

Early relapse (< 36 m),
17p13-del/TP53-mut

Fit

Unfit

ibrutinib, R-idelalisib

Ibrutinib, R-idelalisib

venetoclax, allo-SCT

venetoclax

Late relapse (> 36 m)

Fit for CIT

Unfit for CIT

ibrutinib, R-idelalisib

CIT

venetoclax

Janssens et al, B J Hematol 2015
Update needed!
Toxicities of CLL treatment

- Cytopenias
- Infections
- GI intolerance
- Drug-drug interactions
- Tumor lysis
- Bleeding
- Afib/Hypertension
- Infections
- Arthralgia
- Diarrhea
- Drug-drug interactions
- Fatigue
- Clonal selection
- Sec malignancies
- Physical, emotional
- Financial toxicity
Highlight CLL 2017?