Combining novel agents in chronic lymphocytic leukemia:

greater than the sum of its parts?

Arnon Kater
CLL/SLL: Background

- More than 20,000 estimated new cases in 2019 in the United States alone\textsuperscript{[1]}
  - Most common type of leukemia in adults (37%)
- Median age at diagnosis: 70 yrs\textsuperscript{[2]}
- SLL and CLL considered the same B-cell malignancy\textsuperscript{[3]}
  - CLL: > 5000 clonal lymphocytes in peripheral blood
  - SLL: presence of lymphadenopathy and/or splenomegaly and < 5000 clonal lymphocytes in peripheral blood
- Historical 5-yr survival: 66% (range: few mos to normal life span)\textsuperscript{[4]}
  - Current (2009-2015) 5-yr survival: 85%\textsuperscript{[2]}

CLL: Prognostic Value of FISH

Probability of OS From Diagnosis, by Genetic Aberration

- 17p deletion
- 11q deletion
- 12q trisomy
- 13q deletion as sole abnormality

Patients Surviving (%) vs. Mos
CLL: Impact of TP53 Mutations and TP53 Deletion on OS (N = 1148)

- OS effect of TP53 wild type:
  - vs TP53 mut only: \( P = .013 \)
  - vs TP53 del only: \( P = .006 \)
  - vs TP53 mut + del: \( P < .001 \)

Analysis based on cases referred to the Munich Leukemia Laboratory between August 2005 and May 2013.
Survival in CLL According to *IGHV* Mutational Status

---

**All Patients (n = 84)**

- Mutated
- Unmutated

- *P* = .001

**Binet Stage A Patients (n = 62)**

- Mutated
- Unmutated

- *P* = .0008

---


**Until this year: no clinical consequence!**
Debulking

Combining targeted agents

Aiming for MRD negativity

Clone eradication

Chemotherapy

CIT

Monotherapy targeted agents

T-cell based therapy

CAR Bispecific antibodies
1. How do novel agents actually work?
   - BTK inhibition
   - Bcl2 inhibition

2. Can we expect synergy between novel agents?
   - BTK inhibition + anti-CD20
   - Bcl2 inhibition + anti-CD20
   - BTK inhibition + Bcl2 inhibition

3. Future: clone eradication?
   - Autologous T cell therapy finally at reach?
Ibrutinib treatment: proof-of-concept role in microenvironment

RESONATE study Extended follow-up

Brown, Leukemia 2018

4 weeks on / 1 week off

ALC: Absolute Lymphocyte Count
SPD: Sum of Product Diameter, Lymph Node Reduction

Byrd, JCO 2011
Phase III RESONATE-2 Trial of Ibrutinib vs Chlorambucil in Patients 65 Yrs of Age or Older With Untreated CLL/SLL

- An international, randomized phase III trial

- Primary endpoint: PFS

- Secondary endpoints: OS, ORR, EFS, rate of hematologic improvement, and safety

Burger. NEJM. 2015;373:2425.
**RESONATE-2: 5-Yr Follow-up Results**

- Ibrutinib was generally well tolerated with no new safety signals reported with long-term follow-up (many adverse events decreased over time)
- More than one half (58%) of patients remained on ibrutinib at the 5-yr follow-up

---

Phase III E1912 Trial of Ibrutinib + Rituximab vs FCR in Patients ≤ 70 Yrs of Age With Previously Untreated CLL

- Primary analysis of randomized, open-label phase III trial (data cutoff: October 24, 2018)
  - Stratified by age (< vs ≥ 60 yrs), ECOG PS (0/1 vs 2), stage (III-IV vs I-II), del(11q22.3) vs other
  - Patients with previously untreated CLL requiring treatment per iwCLL 2008, ≤ 70 yrs of age, ECOG PS 0-2, CrCl > 40 mL/min, ability to tolerate FCR, no del(17p) by FISH (N = 529)

- Primary endpoint: PFS
  - Study has 80% power to detect PFS HR for IR vs FCR of 0.67 using stratified log-rank test, with prespecified boundary of 2.87 for first PFS interim analysis corresponding to 1-sided $P = .0025$

- Secondary endpoints: OS, safety

E1912: PFS (Primary Endpoint) and OS in ITT Population

PFS

HR: 0.35 (95% CI: 0.22-0.56; 1-sided P < .001)
IR (37 events/354 cases)
FCR (40 events/175 cases)

Patients at Risk, n
- 354
- 339
- 298
- 148
- 16
- 175
- 147
- 112
- 90
- 0

OS

HR: 0.17 (95% CI: 0.05-0.54; 1-sided P < .001)
IR (4 events/354 cases)
FCR (10 events/175 cases)

Patients at Risk, n
- 354
- 347
- 318
- 166
- 18
- 175
- 155
- 130
- 58
- 1

E1912: PFS by *IGHV* Status

**IGHV Unmutated**

HR: 0.26 (95% CI: 0.14-0.50; 1-sided *P* < 0.00001)

IR (20 events/210 cases)

FCR (21 events/71 cases)

**Probability**

Yrs

Patients at Risk, *n*

0 1 2 3 4

210 203 177 90 12

71 64 43 14 0

**IGHV Mutated**

HR: 0.44 (95% CI: 0.14-1.36; 1-sided *P* = .07)

IR (8 events/70 cases)

FCR (6 events/44 cases)

**Probability**

Yrs

Patients at Risk, *n*

0 1 2 3 4

70 67 59 25 2

44 38 31 18 0

Lymph node: CLL’s pits stop

Adapted from Facteau, Front Biosci 2012
BTK-inhibition targets BCR- and chemokine-controlled integrin-mediated adhesion (retention) and migration (homing) to the lymph node microenvironment.
Venetoclax selectively inhibits Bcl2

CLL cells express Bcl2, inhibiting apoptosis

Venetoclax inhibits Bcl2

Inducing apoptosis

BH3-only proteins

Mitochondria

Bcl2

Bax and Bak

Cytochrome c

Caspase cascade

Cell death

Kindly provided by Matthew Davids
Venetoclax

- **BCL-2**
- **BCL-X<sub>L</sub>**
- **BCL-W**
- **BCL-B**
- **BFL-1**
- **MCL-1**

- **BAK**
- **BAX**

**Expressed in blood CLL**

**Expressed in LN CLL**
‘LNN CLL’: Resistance to venetoclax

Smit, Blood 2007
Hallaert, Blood 2008
Pascutti, Blood 2013

Thijssen, Haematologica 2015
Venetoclax single agent data: sensitivity differs between compartments

Data pooled from 4 trials:
Blood uMRD 27%
Marrow uMRD 16%

Roberts. NEJM 2015
Roberts, Blood 2019
## Efficacy

<table>
<thead>
<tr>
<th></th>
<th>Blood (MRD)</th>
<th>Marrow (MRD)</th>
<th>Lymph node (CR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BTKi</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Bcl2i</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Hematologist’s reflex: add anti-CD20
Ibrutinib and anti-CD20; different kinetics

Clinical meaningful?

*In vitro* inhibition of ADCC by αCD20

Faster normalization lymph counts

![Graph showing ADCC inhibition](image1)

Da Roit, Haematologica 2015

![Graph showing lymph count normalization](image2)

Burger, Blood 2019

No improved PFS / OS

Ibr+Obi: increased uMRD

![Graph showing PFS and uMRD](image3)

Burger, Blood 2019

Moreno, Lancet Oncol. 2019
Venetoclax + rituximab

Lessons from Murano study

R/R CLL pts: Ven 400 mg for 2 yrs vs Benda 70mg/M2 6 cycles; both arms 6 cycles rituximab

HR 0.16 (95% CI: 0.12, 0.23); p<0.0001 (stratified)

IRC-assessed ORR

Difference in uMRD rates: **49.0%**

Seymour, NEJM 2018
Kater, JCO 2019
Venetoclax + Obinutuzumab
Lessons from the CLL14 study

TN CLL pts: Ven 400 mg for 1 yr vs CLB for 1 yr; both arms 6 cycles obinutuzumab

Hazard ratio 0.35 (95% CI 0.23 – 0.53), P < 0.0001
28 months median follow-up

<table>
<thead>
<tr>
<th></th>
<th>Venetoclax–Obinutuzumab</th>
<th>Chlorambucil–Obinutuzumab</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients, N</td>
<td>216</td>
<td>216</td>
<td></td>
</tr>
<tr>
<td><strong>Peripheral blood</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative (&lt;10⁻⁴)</td>
<td>76 %</td>
<td>35 %</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Bone marrow</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative (&lt;10⁻⁴)</td>
<td>57 %</td>
<td>17 %</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Fischer, NEJM 2019
## Efficacy

<table>
<thead>
<tr>
<th></th>
<th>Blood (MRD)</th>
<th>Marrow (MRD)</th>
<th>Lymph node (CR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BTKi</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Bcl2i</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Blood (MRD)</th>
<th>Marrow (MRD)</th>
<th>Lymph node (CR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BTKi+αCD20</td>
<td>+/-</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>Bcl2i+αCD20</td>
<td>++</td>
<td>++</td>
<td>+/-</td>
</tr>
</tbody>
</table>
Theoretical synergy BTK-i and Bcl2-i
**Ibrutinib + Venetoclax Relapsed setting**

*UK experience*

FLAIR trial: R/R CLL pts: 2 cycles ibr monotherapy followed by combination with Ven 400mg

![Diagram showing treatment schedule](image)

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

<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><strong>All patients</strong></td>
<td>49</td>
<td>22 (44%)</td>
<td>5 (10%)</td>
<td>20 (40%)</td>
<td>47 (94%)</td>
</tr>
</tbody>
</table>

**Marrow MRD**

*Hillmen, ASH 2018*
Ibrutinib + Venetoclax Relapsed setting

Hovon/Nordic experience

Hovon141 trial: R/R CLL pts: 2 cycles ibr monotherapy followed by combination with Ven 400mg

<table>
<thead>
<tr>
<th>No.</th>
<th>CR</th>
<th>CRi</th>
<th>PR</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>51</td>
<td>61%</td>
<td>6%</td>
<td>29%</td>
</tr>
</tbody>
</table>

Kater, EHA 2019
Ibrutinib + Venetoclax 1st-line setting

MDACC

MDACC trial: TN CLL pts: 3 cycles ibr monotherapy followed by combination with Ven 400mg 24 cycles

Venetoclax, with dose escalated weekly to 400 mg once daily

Ibrutinib, 420 mg daily

Cycle

Patients with a Response (%)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>96</td>
<td>43</td>
<td>27</td>
<td>83</td>
<td>88</td>
<td>96</td>
</tr>
<tr>
<td>0</td>
<td>17</td>
<td>40</td>
<td>52</td>
<td>61</td>
<td>69</td>
</tr>
<tr>
<td>17</td>
<td>27</td>
<td>17</td>
<td>12</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Complete remission, with or without normal blood count recovery</td>
<td>Partial remission</td>
<td>Undetectable MRD in bone marrow</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Efficacy

<table>
<thead>
<tr>
<th></th>
<th>Blood (MRD)</th>
<th>Marrow (MRD)</th>
<th>Lymh node (CR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BTKi</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Bcl2i</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>BTKi+αCD20</td>
<td>+/-</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>Bcl2i+αCD20</td>
<td>++</td>
<td>++</td>
<td>+/-</td>
</tr>
<tr>
<td>BTKi+Bcl2i</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
</tbody>
</table>
Does order and sequence matter?
Ibrutinib-obi for R/R CLL

Primary endpoint: MRD negativity (< 0.01% in PB and BM) at 9 mo

The largest impact on MRD when Obi was added after > 1 y of Ibr treatment

Rawstron, ASH 2018
Modulation of surface antigens expression under ibrutinib treatment

**Antigen**
- CD29
- CD49d
- CD49e
- CD54
- CD184
- CD19
- CD79b
- IgM

**CD29**
- CD20
- CD200
- CD38
- CD22
- CD305

**Pathway**
- Adhesion homing
- Adhesion homing
- Adhesion homing
- Adhesion homing
- Adhesion homing
- BCR molecules
- BCR molecules
- BCR molecules

**CD20**
- CLL markers
- CLL markers
- CLL markers
- BCR inhibitors
- BCR inhibitors

**CD23**
- CLL markers
- CLL markers
- BCR inhibitors
- BCR inhibitors

**FCµR**
- CLL markers
- CLL markers
- BCR inhibitors
- BCR inhibitors

**p**
- <0.001
- 0.004
- 0.012

**Weeks under ibrutinib**
- week0
- week2
- week24
- week48
- week72
- week96

Rossi, ASH 2018
• **Intensification in patients with suboptimal response to V+I:**
  – No CR and/or
  – No uMRD

• **Intensification with Obinutuzumab for 6 cycles**
Concept richtlijn CLL 2019: 1ste lijn

CLL met behandelindicatie

IGHV gemuteerd
geen 17p-deletie en TP53-mutatie

IGHV ongemuteerd
geen 17p-deletie en TP53-mutatie

17p-deletie / TP53-mutatie

HOVON-(associated) studie

fit

niet fit

chemo-immunotherapie

1. Chl-O
2. Chl-R
3. Ibrutinib of Ven-O

als chemo-immunotherapie:
≥ 65-70 jr: FCR
> 65-70 jr: BR

HOVON-(associated) studie

fit

niet fit

chemo-immunotherapie

of ibrutinib

1. Chl-O of ibrutinib of Ven-O
2. Chl-R

H158 studie

1. Ibrutinib
2. Venetoclax-(obinutuzumab)
3. Idelalisib-rituximab
Concept richtlijn CLL 2019: R/R

Recidief/progressie CLL met behandelindicatie

- **fit en laat recidief na CIT***
  1. Ven-R
  2. FCR, BR of Chl-R
  3. Ibrutinib

- **niet fit en laat recidief na CIT***
  1. Ibrutinib of Ven-R
  2. BR of Chl-R

- **vroeg recidief na CIT***
  17p-deletie / TP53-mutatie
  recidief na ibrutinib, venetoclax of idelalisib
  1. Ibrutinib of Ven-R
  2. Idelalisib-rituximab
Acknowledgements

**Own lab**
Hanneke ter Burg
Ingrid Derks
Renate de Boer
Denise Nieuwenhuize
Antoinet Schoonderwoerd
Tom Hofland
Iris de Weerdt
Armando van Bruggen
Alexander Leeksma
Marco Haselager

Jenkau Chen
Raquel Delgado
Chiara Montironi
Gaspard Cretenet
Sanne Tonino
Julie Dubois
Fleur Peters
**Eric Eldering**
**Arnon Kater**

- **Hovon clinical trial group** (Mark-David Levin, Sabina Kersting)
- GCLL study group (M. Hallek, B. Eichhorst, S. Stilgenbauer, K. Fischer)
- Nordic CLL study group (C. Niemann)

Collaborators: Jos Melenhorst and Carl June, UPenn