Chronic lymphocytic leukemia

How the Experts Treat Hematologic Malignancies
Las Vegas, NV
3/2018

Tanya Siddiqi, MD
Assistant Professor
City of Hope National Medical Center
Duarte, CA
I am on the steering committee for JCAR017 (Juno Therapeutics) and on the Speaker’s Bureau for ibrutinib (Pharmacyclics) and brentuximab vedotin (Seattle Genetics). I am also on the DSMB for BeiGene’s follicular lymphoma study.
Objectives

• Epidemiology
• Diagnosis and workup
• Monoclonal B-lymphocytosis
• Prognostic markers
• Staging
• Treatment initiation guidelines
• Frontline therapeutic options
• Relapsed/refractory therapeutic options
Epidemiology

- Chronic lymphocytic leukemia (CLL) is a low grade leukemic lymphocytic lymphoma; small lymphocytic lymphoma (SLL) is a nodal form of the same disease.

- CLL/SLL is the most common hematological malignancy in the Western world; incidence is ~5/100,000 persons per year in the US.

- Median age at diagnosis ~72 years.

Epidemiology (cont.)

• Male predominance

• Higher in Caucasians

• ~10% patients with a family history of some lymphoma

• Exact etiology is unknown
Diagnosis and workup

- Rule out masquerading other lymphoma

- History and physical examination; trend of CBCs; B symptoms

- Review CBC/differential, peripheral blood smear, flow cytometry/immunophenotyping: peripheral blood lymphocytosis with the presence of ≥5000 monoclonal B-cells/uL is required

- Bone marrow biopsy not needed for diagnosis typically
Monoclonal B-lymphocytosis (MBL)

- Presence of monoclonal lymphocytosis but with <5000 B-cells/uL in the peripheral blood and no accompanying lymphadenopathy or organomegaly by physical examination or radiographical imaging, cytopenias or disease-related symptoms is defined as MBL

- Incidence in the US is 3%

- Progression to CLL/SLL can occur @ 1-2% per year
Prognostic markers in CLL/SLL

- Cytogenetics:
  - Del13q
  - Trisomy 12
  - Normal
  - Del11q
  - Del17p
  - Del6q
  - TP53 mutations
  - Notch1 mutations
  - SF3B1 mutations

- IGHV mutation status
- ZAP70
- CD38
- Lymphocyte doubling time (LDT)
- β2 microglobulin
- Stage of disease by Rai or Binet staging
### CLL Staging

**Rai stage**

<table>
<thead>
<tr>
<th>Rai stage</th>
<th>Risk category</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Low</td>
<td>Lymphocytosis alone</td>
</tr>
<tr>
<td>1</td>
<td>Intermediate</td>
<td>Lymphadenopathy</td>
</tr>
<tr>
<td>2</td>
<td>Intermediate</td>
<td>Hepato/splenomegaly</td>
</tr>
<tr>
<td>3</td>
<td>High</td>
<td>Anemia (&lt;11g/dl)</td>
</tr>
<tr>
<td>4</td>
<td>High</td>
<td>Thrombocytopenia (&lt;100,000/L)</td>
</tr>
</tbody>
</table>

**Binet stage**

<table>
<thead>
<tr>
<th>Binet stage</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>HGB≥10 g/dl, platelets ≥100/L, &lt;3 areas of lymphadenopathy/organomegaly*</td>
</tr>
<tr>
<td>B</td>
<td>HGB≥10 g/dl, platelets ≥100/L, ≥3 areas of lymphadenopathy/organomegaly*</td>
</tr>
<tr>
<td>C</td>
<td>Anemia (&lt;10g/dl), thrombocytopenia (&lt;100,000/L), or both</td>
</tr>
</tbody>
</table>

*nodal areas: cervical [head and neck], axillary, inguinal (including femoral lymph nodes), spleen, liver*
Prognostic factors

Cramer P and Hallek M. Nat Rev Clin Oncol 2011; 8: 38-47
Who needs treatment?

- International workshop on CLL (iwCLL) guidelines for treatment initiation

iwCLL guidelines for treatment initiation

- progressive marrow failure as manifested by the development of, or worsening of, anemia and/or thrombocytopenia
- massive (≥6cm below left subcostal margin), progressive, or symptomatic splenomegaly
- massive (≥10cm in longest diameter), progressive, or symptomatic lymphadenopathy
- progressive lymphocytosis with an increase of >50% over a 2 month period or LDT of <6 months
- autoimmune hemolytic anemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy
- constitutional symptoms defined as ≥1 of the following:
  (i) unintentional weight loss of ≥10% within the previous 6 months
  (ii) significant fatigue (ECOG PS ≥2; inability to work or perform usual activities)
  (iii) fevers >100.5F or 38C for ≥2 weeks without other evidence of infection
  (iv) night sweats for >1 month without evidence of infection
How to pick the right treatment?

• iwCLL guidelines for treatment initiation

• Stage of disease

• Lymphocyte doubling time and symptoms

• Cytogenetic risk

• Fitness of patient

• Response to prior therapy
**Therapeutic options for CLL**

- **Watch and wait**
  - CLL12: Placebo-Controlled, Double-Blind, Randomized, Multicenter, Three Arm Phase III Trial to Compare the Efficacy and Safety of Ibrutinib vs. Placebo in Previously Untreated Binet Stage A CLL Patients with Risk of Early Disease Progression [N=327 screened (ASH 2015 abs)]

- **Radiation**
- **Immunotherapy**
- **Chemotherapy**
- **Combination chemoimmunotherapy**
- **Novel targeted therapies**
- **Cellular therapy**
- **Clinical trials**
Common approved treatment modalities

- **Immunotherapy (monoclonal antibodies):**
  - Rituximab (against CD20)
  - Ofatumumab (against CD20)
  - Alemtuzumab (against CD52)
  - Obinutuzumab (against CD20)

- **Common chemoimmunotherapy regimens:**
  - Fludarabine + cyclophosphamide + rituximab (FCR)
  - Pentostatin + cyclophosphamide + rituximab (PCR)
  - Bendamustine + rituximab (BR)
  - Alemtuzumab ± rituximab
  - Chlorambucil + obinutuzumab
  - Chlorambucil + ofatumumab
  - High dose methylprednisolone + rituximab

- **Targeted oral therapies:**
  - Ibrutinib
  - Venetoclax
Frontline therapeutic options
German CLL study group (GCLLSG): frontline treatment

- **CLL4 study:** FC vs. fludarabine alone

- **CLL8 study:** FCR vs. FC
  - Subgroup with exceptionally good outcome has right age/fitness, mutated IGHV genes and no del17p/del11q (plateau after 4 yrs; MRD neg ≥6 yrs later)

CLL8 study: FCR vs. FC

Probability of Progression-free Survival

- FCR  IGHV MUT patients (N=113)
- FC  IGHV MUT patients (N=117)
- FCR  IGHV UNM patients (N=197)
- FC  IGHV UNM patients (N=195)

p < 0.001 by log-rank test

Months on Study
ASH2016 MDACC experience with FCR

- N=289 [median age 59 yrs]
- Prospective analysis of pts getting frontline FCR
- Bone marrow biopsy after cycle 3 (n=239) and at end of treatment (n=231)
- ORR=96%
- 19% had MRD neg after cycle 3 and 51% at end of treatment
- patients with *IGHV-M* who achieved MRD-negativity after 3 courses had a particularly favorable outcome
- The best pre-treatment predictor of achieving MRD-negativity and subsequent longer PFS was *IGHV-M*
- Despite achieving MRD-negativity, many patients subsequently relapse; serial MRD monitoring in peripheral blood can herald relapse with a lead-time of approximately 2 years and potentially direct monitoring and/or early intervention strategies.

Thompson et al. ASH abs 2016
ASH2016 MDACC experience with FCR

Thompson et al., Blood, 2016
German CLL study group (GCLLSG): frontline treatment

- CLL4 study: FC vs. fludarabine alone

- CLL8 study: FCR vs. FC
  - Subgroup with exceptionally good outcome has right age/fitness, mutated IGHV genes and no del17p/del11q (plateau after 4 yrs; MRD neg ≥6 yrs later)

- CLL10 study: FCR vs. BR

FCR vs. BR

- Phase 3 randomized trial, fit CLL patients (ages 33-81 yrs) with advanced stage disease, previously untreated, no 17p deletion
- N = 564; 6 cycles of either regimen; median followup 37.1 months

<table>
<thead>
<tr>
<th></th>
<th>FCR</th>
<th>BR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR</strong></td>
<td>95%</td>
<td>96%</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>CR</strong></td>
<td>40%</td>
<td>31%</td>
<td>0.034 [higher MRD negative CRs in FCR arm]</td>
</tr>
<tr>
<td><strong>Median PFS</strong></td>
<td>55.2 months</td>
<td>41.7 months</td>
<td>0.001 [better in &lt;65 years old]</td>
</tr>
<tr>
<td><strong>OS at 3 years</strong></td>
<td>91%</td>
<td>92%</td>
<td>0.897</td>
</tr>
<tr>
<td><strong>Severe neutropenia</strong></td>
<td>84%</td>
<td>59%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Severe infections</strong></td>
<td>39%</td>
<td>25%</td>
<td>0.001 [especially in older pts]</td>
</tr>
</tbody>
</table>

MRD in CLL

- Retrospective study
- N = 255
- CR after 1st line chemoimmunotherapy
- Median followup = 73 months from disease evaluation
- Median treatment free durations:
  - MRD neg CR – 76 months
  - MRD pos CR – 40 months
  - PR – 11 months
  - No response – 11 months
- MRD negativity also affected OS significantly

- Pts from CLL8 and CLL10 trials
- N = 542
- CR after 1st line chemoimmunotherapy
- Median followup = 45.9 months
- PFS difference \(p<0.001\):
  - MRD neg CR – 69.2 months
  - MRD pos CR – 40.4 months
- Also, PFS difference \(p<0.008\):
  - MRD neg PR – 61.7 months
  - MRD pos CR – 40.4 months
- No PFS difference between MRD neg CR and MRD neg PR

CLL Disease Progression Curve

Adapted from: www.vaccinogeninc.com/sites/default/files/images/Figure_4.jpg
Targeted therapies
Monoclonal antibodies: update

- **Anti-CD20** (dim expression on CLL/SLL cells typically)
  - Ofatumumab (+chlorambucil) – FDA approved
  - Obinutuzumab (+chlorambucil) – FDA approved
  - Ublituximab

- **Anti-CD37** (expressed strongly on the surface of B-cells and transformed mature B-cell leukemia and lymphoma cells)
GCLLSG: frontline treatment (cont.)

- **CLL11 study:** **Chlorambucil + obinutuzumab** vs. Chlorambucil + Rituximab vs. chlorambucil alone
  - Randomized, previously untreated, CLL patients with comorbidities
  - N = 781
  - Median age = 73 years
  - 3 arms of the study = G+Clb vs. R+Clb vs. Clb alone for 6 cycles

Goede V, et al. NEJM 2014; 370: 1101-10
• 3 months after treatment, CRs were seen exclusively after antibody combinations compared with Clb alone
• Median PFS was 26.7 months (G-Clb) vs 11.1 months (Clb) \([p<0.001]\) and 16.3 months (R-Clb) vs 11.1 months (Clb) \([p<0.001]\)
• G-Clb improved OS compared to Clb \((p=0.002)\)
• G-Clb improved PFS \((p<0.001)\), CRs \((20.7\% \text{ vs } 7\%)\) and molecular responses compared to R-Clb
Ibrutinib – FDA approved

- Ph1b/2 study of 85 CLL pts, mostly high risk
- ORR of 71% (2 CR, 34 PR) + 15-20% PR-L
- At 26 months, estimated PFS was 75% and OS 83%
- Well tolerated

Ibrutinib: RESONATE trial

- Phase 3 trial of ibrutinib (420mg po daily) vs. ofatumumab in r/r CLL
- N = 391
- ORR 42.6% (+20% PR-L) vs. 4.1% (p<0.001)
- Median PFS not reached (88% PFS at 6 months) vs. 8.1 months (p<0.001)
- At 12 months, OS 90% (ibru) vs. 81% (ofa) (p=0.005)

Patients with CLL/SLL treated with oral, once-daily ibrutinib (420 or 840 mg/day)

Phase 2 (PCYC-1102)
N=132

- Treatment Naïve (TN) ≥65 years n=31
- Relapsed/Refractory* (R/R) n=101

Extension Study (PCYC-1103)

≥SD

Long-Term Follow-Up

*R/R includes patients with high-risk CLL/SLL, defined as progression of disease <24 months after initiation of a chemoimmunotherapy regimen or failure to respond

5-year update, O'Brien et al. ASH 2016
<table>
<thead>
<tr>
<th>Disposition</th>
<th>TN (n=31)</th>
<th>R/R (n=101)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median time on study, months (range)</strong></td>
<td>62 (1–67)</td>
<td>49 (1–67)</td>
</tr>
<tr>
<td><strong>Duration of study treatment, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1 year</td>
<td>5 (16%)</td>
<td>24 (24%)</td>
</tr>
<tr>
<td>&gt;1–2 years</td>
<td>0</td>
<td>14 (14%)</td>
</tr>
<tr>
<td>&gt;2–3 years</td>
<td>1 (3%)</td>
<td>9 (9%)</td>
</tr>
<tr>
<td>&gt;3–4 years</td>
<td>1 (3%)</td>
<td>19 (19%)</td>
</tr>
<tr>
<td>≥4 years</td>
<td>24 (77%)</td>
<td>35 (35%)</td>
</tr>
<tr>
<td><strong>Patients remaining on ibrutinib therapy, n (%)</strong></td>
<td>20 (65%)</td>
<td>30 (30%)</td>
</tr>
<tr>
<td><strong>Primary reason for discontinuation, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>1 (3%)</td>
<td>33 (33%)</td>
</tr>
<tr>
<td>Adverse event</td>
<td>6 (19%)</td>
<td>21 (21%)</td>
</tr>
<tr>
<td>Consent withdrawal</td>
<td>3 (10%)</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Investigator decision</td>
<td>0</td>
<td>11 (11%)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>1 (3%)</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

- After ~5 years of follow-up, 65% of TN and 30% of R/R patients continue treatment on study

5-year update, O’Brien et al. ASH 2016
Cumulative Frequency of Grade ≥3 Adverse Events Over 5-Year Follow-Up

Non-hematologic ≥5%
- R/R
- TN

Hematologic
- R/R
- TN

Infectious
- R/R
- TN

5-year update, O'Brien et al. ASH 2016
## Best Response

<table>
<thead>
<tr>
<th></th>
<th>TN (n=31)</th>
<th>R/R (n=101)</th>
<th>Total (N=132)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Best Response</strong></td>
<td>87%</td>
<td>89%</td>
<td>89%</td>
</tr>
<tr>
<td><strong>Complete Remission</strong></td>
<td>29%</td>
<td>10%</td>
<td>14%</td>
</tr>
<tr>
<td><strong>Partial Remission</strong></td>
<td>55%</td>
<td>76%</td>
<td>71%</td>
</tr>
<tr>
<td><strong>PR-L</strong></td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Median DOR, months (range)</strong></th>
<th>NR (0.0+ to 65.5+)</th>
<th>56.8 (0.0+ to 65.5+)</th>
<th>NR (0.0+ to 65.5+)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median follow-up, months (range)</strong></td>
<td>62 (1 – 67)</td>
<td>49 (1+ – 67)</td>
<td>56 (1+ – 67)</td>
</tr>
</tbody>
</table>

NR, not reached.

5-year update, O’Brien et al. ASH 2016
Best Response in Patients With High-Risk Abnormalities

<table>
<thead>
<tr>
<th></th>
<th>R/R del11q (n=35)</th>
<th>R/R Unmutated IGHV (n=79)</th>
<th>R/R Complex Karyotype (n=41)</th>
<th>R/R del17p (n=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-year update, O'Brien et al. ASH 2016</td>
<td>97% 9% 86%</td>
<td>90% 9% 77%</td>
<td>90% 7% 76%</td>
<td>79% 6% 65%</td>
</tr>
</tbody>
</table>

- **CR**
- **PR**
- **PR-L**

<table>
<thead>
<tr>
<th>Median DOR, months (range)</th>
<th>38.7 (0.0+ to 65.3+)</th>
<th>53.2 (0.0+ to 65.5+)</th>
<th>38.7 (0.0+ to 65.5+)</th>
<th>30.6 (0.0+ to 65.3+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up, months (range)</td>
<td>55 (1+ – 67)</td>
<td>49 (1+ – 67)</td>
<td>55 (1 – 67)</td>
<td>47 (1 – 67)</td>
</tr>
</tbody>
</table>

NR, not reached.
Survival Outcomes: Overall Population

## Progression-Free Survival

- **Treatment-naive (TN) (n=31):** Median PFS NR, 5-year PFS 92%
- **Relapsed/refractory (R/R) (n=101):** Median PFS 52 mo, 5-year PFS 43%

## Overall Survival

- **Treatment-naive (TN) (n=31):** Median OS NR, 5-year OS 92%
- **Relapsed/refractory (R/R) (n=101):** Median OS NR, 5-year OS 57%

NR, not reached.

5-year update, O'Brien et al. ASH 2016
Ibrutinib: RESONATE-2 trial

- Ph3, international, open label, randomized trial of ibrutinib vs. chlorambucil in previously untreated older CLL/SLL patients
- N = 269
- Median age = 73 years
- ORR 86% vs. 35% (p<0.001)
- Significant improvement in EFS, PFS and OS with single agent ibrutinib compared to Clb

RESONATE-2 update

- PFS was significantly improved for ibrutinib across high-risk subgroups, including del11q and unmutated *IGHV* gene
- OS analysis resulted in 2-yr survival rate estimates of 95% (ibr) vs. 84% (clb)
- ORR was 92% with ibr vs 36% with clb (*P*<0.0001); CR/CRi within the ibr arm improved from 11% at 18.4 mo to 18% with longer follow-up of 28.6-mo

RESONATE-2 update, Barr et al.ASH2016
1 patient on each arm developed Richter’s transformation
4 patients had disease progression and discontinued ibr
41% switched from clb→ibr
Major hemorrhage in 7% (ibr) within the first 2 yrs
Atrial fibrillation in 10% (ibr)
79% pts remain on ibr with median treatment duration of 28.5 months

Table. Most frequent adverse events (≥20%)

<table>
<thead>
<tr>
<th>Adverse Event, n (%)</th>
<th>Grades 1-2</th>
<th>Grades ≥3</th>
<th>Any Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea 56 (41)</td>
<td>5 (4)</td>
<td>61 (45)</td>
<td></td>
</tr>
<tr>
<td>Fatigue 42 (31)</td>
<td>2 (1)</td>
<td>44 (33)</td>
<td></td>
</tr>
<tr>
<td>Cough 38 (28)</td>
<td>0 (0)</td>
<td>38 (28)</td>
<td></td>
</tr>
<tr>
<td>Anemia 22 (16)</td>
<td>9 (7)</td>
<td>31 (23)</td>
<td></td>
</tr>
<tr>
<td>Nausea 30 (22)</td>
<td>1 (1)</td>
<td>31 (23)</td>
<td></td>
</tr>
<tr>
<td>Peripheral edema 27 (20)</td>
<td>2 (1)</td>
<td>29 (21)</td>
<td></td>
</tr>
<tr>
<td>Arthralgia 24 (18)</td>
<td>3 (2)</td>
<td>27 (20)</td>
<td></td>
</tr>
<tr>
<td>Pyrexia 26 (19)</td>
<td>1 (1)</td>
<td>27 (20)</td>
<td></td>
</tr>
</tbody>
</table>

RESONATE-2 update, Barr et al.ASH2016
Ibrutinib vs. CIT in TN CLL

• Cross trial comparison between ibrutinib therapy in RESONATE 2 trial and CIT from published phase 3 trials (CLL8, CLL10, CLL11, and COMPLEMENT1)
• Age range 61-74 yrs
• Ibrutinib led to longer PFS compared to CIT, including in high risk populations (del17p, del11q, unmutated IGHV), probably negating the need for chemo

Robak T, et al. ASH 2017 abs.
Other targeted therapies

- **Idelalisib** - FDA approved but further trials halted due to toxicities

- **Umbralisib** – Phase 3 trials ongoing in CLL; much better safety profile than idelalisib

- **Venetoclax** – FDA approved in del17p CLL

- **Acalabrutinib** – in phase 3 trials ongoing in CLL; FDA approved for mantle cell lymphoma

- **Zanabrutinib** – in phase 3 trials for WM and CLL
ASH 2017 update (frontline therapies)

- Ibrutinib+FCR in young fit patients (DFCI) – Dr. M. Davids
  - Phase II investigator-initiated study in younger, TN patients
  - Ibrutinib for 1 week → i+FCR for upto 6 cycles → continue ibrutinib
  - Median age 55 yrs
  - 100% ORR by cycle 4 (74% PR → best response of 63% CR overall)
  - 83% best bone marrow MRD neg rate in first 35 patients
  - 50 patient expansion cohort and expanded the number of sites to 8
  - Responses deepens over time in both IGHV mutated and unmutated patients, suggesting that ibrutinib maintenance is beneficial
  - iFCR toxicities are comparable to ibrutinib and FCR individually
ASH 2017 update (frontline therapies)

- **Ibrutinib+FCG (MDACC) – Dr. Nitin Jain**
  - Investigator-initiated study in younger, TN patients, IGHV-M
  - N=36, med age 60 yrs
  - iFCG x 3 cycles → 100% ORR (44% CR, all MRD neg); marrow MRD neg rate overall 87%
  - After 6 cycles, 78% CR and 93% marrow MRD neg rate
  - Responses improve over time
  - At 1 yr all 19 patients were MRD neg (16 CR, 3 PR) and stopped ibrutinib
  - Toxicities: 11% atrial fib, 14% neutropenic fever
  - 50% FC dose reductions and 39% ibrutinib dose reductions needed
ASH 2017 update (frontline therapies)

- **Ibrutinib + G (ICLL07 FILO study) – Dr. P. Feugier**
  - N= 135, TN patients
  - Med. age 62 yrs
  - 97 evaluable pts at month 9
  - ORR 100%, CR 38%, marrow MRD neg rate of 13%
  - Acceptable toxicities

- **Venetoclax + G – Dr. I. Flinn**
  - Phase 1b, n = 32
  - Tested starting with either drug first (G first recommended for phase 2), frontline and rel/ref setting
  - 100% ORR, 72% CR (high in all subgroups)
  - 100% MRD neg at some point; 70% persisted more than 3 months
ASCH 2017 update (frontline therapies)

- **Acalabrutinib + G (Ohio State) – Dr. J. Woyach**
  - Phase 1b/2 study, no prior ibrutinib
  - Median followup 24.7 months

<table>
<thead>
<tr>
<th></th>
<th>TN</th>
<th>R/R</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>19</td>
<td>26</td>
</tr>
<tr>
<td>ORR</td>
<td>95%</td>
<td>92%</td>
</tr>
<tr>
<td>CR</td>
<td>16%</td>
<td>8%</td>
</tr>
<tr>
<td>PFS</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>
ASH 2017 update (frontline therapies)

- **Ibrutinib + venetoclax (MDACC) – Dr. Nitin Jain**
  - Phase 2
  - N = 37 rel/ref, 40 TN
  - Ibrutinib x3 cycles then venetoclax ramp up started
  - Ibrutinib continues indefinitely but venetoclax stops at 2 yrs
  - TN cohort: after 3 months of ibrutinib ORR was 97% (CR 3%); after 3 months of iV ORR was 99% (CR 61%) and ~ 30% MRD neg rate in marrow
  - R/R cohort: after 3 months of ibrutinib ORR was 91% (3% CR); after 3 months of iV ORR was 99% (42%CR) with 8% MRD neg marrows
ASH 2017 update (frontline therapies)

- Ibrutinib + venetoclax + G [Ohio State] – Dr. K. Rogers
  - Phase 1b/2 study of r/r or TN pts
  - Ph2 TN portion n = 25
  - G x8 cycles, ibrutinib cycles 2-14, venetoclax cycles 3-14
  - Median followup 14.7 months
  - Mid point response assessment (cycle 8): 96% ORR, 52% CR/CRi, 58% MRD neg in PB/marrow
GCLLSG: ongoing frontline treatment trials

- CLL14 study: Prospective, open-label, multicenter randomized phase III trial to compare the efficacy and safety of a combined regimen of obinutuzumab and venetoclax vs. obinutuzumab and chlorambucil in previously untreated patients with CLL and coexisting medical conditions
  - Accrual completed summer 2016
Frontline CLL trials at City of Hope

• Phase 2 ibrutinib+venetoclax (PCYC 1142 trial)

• Phase 3 umbralisib+ublituximab vs. Gazyva+chlorambucil [crossover allowed] – accrual completed recently

• Ph1 ibrutinib+CD37 monoclonal antibody [closing soon]
Standard of care algorithm (frontline): clinical trials if possible

Initial diagnosis of CLL

Indication for treatment?

Yes

Stage of disease?

No

Observation (“watch and wait”)

Binet A/B, no B symptoms

Physically fit?

Continue observation (“watch and wait”)

“Go go”

Del 17p/TP53 mutation?

No

Del 17p/TP53 mutation?

Yes

Clinical trial; FCR; BR (if >65 years old and/or high risk of infections)

Clinical trial; ibrutinib; discuss allogeneic HCT

Clinical trial; best supportive care

“Slow go”

Clinical trial; chlorambucil + obinutuzumab

“No go”

Clinical trial; ibrutinib
Relapsed/refractory therapeutic options
Murano trial: ASH 2017, LBA, Dr. J. Seymour

- Venetoclax + rituximab (VR) vs. BR x6 cycles [V continued for 2 yrs]
- Randomized ph3, rel/ref CLL
- Venetoclax ramp up first then R added at week 6
- Med followup 23.8 months

<table>
<thead>
<tr>
<th></th>
<th>VR</th>
<th>BR</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 389</td>
<td>194</td>
<td>195</td>
</tr>
<tr>
<td>Med. Age (yrs)</td>
<td>64.5</td>
<td>66</td>
</tr>
<tr>
<td>Med. PFS</td>
<td>Not reached</td>
<td>17 months</td>
</tr>
<tr>
<td>24 month PFS estimates</td>
<td>84.9%</td>
<td>36.3%</td>
</tr>
<tr>
<td>ORR</td>
<td>93.3%</td>
<td>67.7%</td>
</tr>
<tr>
<td>CR</td>
<td>26.8%</td>
<td>8.2%</td>
</tr>
<tr>
<td>MRD negative rate</td>
<td>83.5%</td>
<td>23.1%</td>
</tr>
<tr>
<td>Grade 3-4 neutropenia</td>
<td>57.7%</td>
<td>38.8%</td>
</tr>
<tr>
<td>Severe infections</td>
<td>15%</td>
<td>15%</td>
</tr>
</tbody>
</table>
**ASH 2017 update (rel/ref therapies)**

- **Ibrutinib + venetoclax (CLARITY trial) – Dr. Peter Hillmen**
  - N = 54
  - Ibrutinib for 8 weeks then venetoclax ramp up
  - Stopping options built in if MRD neg
  - 38 pts have reached month 8
  - 100% ORR, 39% CR, 32% marrow MRD neg, 37% PB MRD neg

- **Duvelisib vs. ofatumumab (DUO trial) – Dr. I. Flinn**
  - Ph. 3; similar benefit in del 17p pts; manageable toxicities

<table>
<thead>
<tr>
<th></th>
<th>DUV</th>
<th>OFA</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>160</td>
<td>159</td>
</tr>
<tr>
<td>Med. PFS (IRC)</td>
<td>13.3 mo</td>
<td>9.9 mo</td>
</tr>
<tr>
<td>ORR</td>
<td>73.8%</td>
<td>45.3%</td>
</tr>
</tbody>
</table>
ASH 2017 update (rel/ref therapies)

- Acalabrutinib update (ACE-CL-001 trial) – Dr. J. Byrd
  - N =134
  - Median age = 66 yrs
  - 78% pts still on treatment after median followup of 24.5 months
  - ORR 87%, ORR + PR-L 93%
  - Best response: 3% CR, 84% PR, 7% PR-L
  - Median PFS not reached, also for all high risk subgroups except complex karyotype (27.9 months)
  - Most common toxicities: diarrhea and headaches
  - Ongoing studies, also in TN patients
Cellular therapy

- Allogeneic hematopoietic cell transplantation
  - N=694 (retrospective)
  - High risk disease
  - 2 yr-NRM 28%
  - 5 yr EFS 37%

- CAR-T cells
CD19 specific CAR-T cells in CLL

- $N = 14$; median cell dose = $7.5 \times 10^8$ cells
- 4 CRs (29%), 4 (29%) PRs, ORR 57%
- CAR-T cells detectable 3 yrs later in some
- Ph2 randomized study ongoing to determine best cell dose ($n=18$, ORR39%, CR 17%)
- Expected toxicities: B cell aplasia, delayed TLS and cytokine release syndrome

CD19 specific CAR-T cells (cont.)

- **Table 2. Anti-CD19 CAR therapy for CLL**

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>ORR</th>
<th>CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of Pennsylvania 2010†</td>
<td>3</td>
<td>3/3</td>
<td>2/3</td>
</tr>
<tr>
<td>University of Pennsylvania 2014‡</td>
<td>24</td>
<td>10/24</td>
<td>5/24</td>
</tr>
<tr>
<td>National Cancer Institute§</td>
<td>4</td>
<td>3/4</td>
<td>1/4</td>
</tr>
<tr>
<td>National Cancer Institute II</td>
<td>4</td>
<td>4/4</td>
<td>3/4</td>
</tr>
<tr>
<td>Memorial Sloan-Kettering¶</td>
<td>8</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

- CAR-T cell therapy may potentially be a good alternative to RIC alloHCT for very high risk patients
- Other targets being evaluated include CD20, CD23, ROR1

Mato A and Porter D. Blood 2015; 126: 478
CD19 CAR-T cells in ibrutinib refractory CLL: ASH 2016, Dr. C. Turtle, Fred Hutchinson (Seattle)

- N = 18
- CD8+:CD4+ CAR-T cells 1:1
- Median age 60 yrs
- 11 were ibrutinib refractory, 3 were ibrutinib intolerant, 4 were refractory to venetoclax
- 12 had complex karyotype and 11 had del17p
- Flu/Cy lymphodepletion followed by CAR-T cells (MTD 2x10^6 CAR-T cells/kg)
- 4 pts had CRS gr 3-4; 4 pts had gr4 neurotoxicity
- ORR 76% (8 PR, 5 CR)
- No relapses in CR pts at median followup of 8.4 mo.
Standard of care algorithm (rel/ref): clinical trials if possible
Relapsed/refractory CLL trials at COH

- ibrutinib+venetoclax [with Stanford, coming very soon]
- Juno CAR-T cell trial (now open)
- CAR-T cell trial in B-cell lymphomas [COH, coming very soon]
- Ritonavir+metformin trial [COH]
- MRG106 in various lymphomas and leukemia
- Ph1 pembrolizumab+dinaciclib [closing soon]
- Ph1 ibrutinib+CD37 monoclonal antibody [closing soon]
Conclusions

• Explosion of novel therapies for CLL in recent years, including monoclonal antibodies (like obinutuzumab), small molecule inhibitors of various kinases (like BTK and PI3K) and the antiapoptotic pathway (especially Bcl2), and CD19-specific CAR-T cells

• These novel, non-chemotherapeutic agents may do away with the need for standard chemoimmunotherapy in CLL, especially in older/unfit patients

• Combination studies are underway to improve upon the outcomes further
Acknowledgements

- Dr. Stephen Rosen
- Dr. Stephen Forman
- Patients and their families/friends, nurses, colleagues at City of Hope National Medical Center