Definition of CLL
IWCLL - 2008

- Small, clones of mature B-cells
- Atleast 5,000/ul B-cells
- Co-express CD5 and CD23
Prognostic Markers

- Interphase cytogenetics and FISH
- IGHV Mutational Status
- CD38
- ZAP-70 methylation
Interphase FISH correlates with Survival

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

# Outcome by Interphase FISH Abnormalities

<table>
<thead>
<tr>
<th>Abnormality detected by FISH</th>
<th>Median Time to Treatment (months)</th>
<th>Median Overall Survival (months)</th>
<th>Percentage of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Del 17p</td>
<td>9</td>
<td>32</td>
<td>7</td>
</tr>
<tr>
<td>Del 11q</td>
<td>13</td>
<td>79</td>
<td>18</td>
</tr>
<tr>
<td>Trisomy 12</td>
<td>33</td>
<td>114</td>
<td>16</td>
</tr>
<tr>
<td>Del 13q</td>
<td>49</td>
<td>133</td>
<td>55</td>
</tr>
<tr>
<td>Normal</td>
<td>92</td>
<td>111</td>
<td>18</td>
</tr>
</tbody>
</table>

IGHV Mutational Status predicts Survival

Hamblin et al. Blood. 1999

Median Survival
293 months (Mutated)
117 months (Unmutated)

All patients (N=84)

(P=0.001)
CD38 expression correlates with IGHV mutational status

Damle, et al, Blood, 1999
• loss of methylation at a specific single CpG dinucleotide in the ZAP-70 5’ regulatory sequence is a highly predictive and reproducible biomarker of poor prognosis in this disease

Claus et al. J Clin Oncol 2012
## Other Prognostic Markers

<table>
<thead>
<tr>
<th></th>
<th>Favorable Outcome</th>
<th>Un-Favorable Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LDH</strong></td>
<td>Low or Normal</td>
<td>Elevated</td>
</tr>
<tr>
<td><strong>Lymphocyte Doubling Time</strong></td>
<td>&gt; 12 months</td>
<td>&lt; 12 months</td>
</tr>
<tr>
<td><strong>Thymidine Kinase Activity</strong></td>
<td>Low or Normal</td>
<td>Elevated</td>
</tr>
<tr>
<td><strong>Beta-2 Microglobulin</strong></td>
<td>Low or Normal</td>
<td>Elevated</td>
</tr>
</tbody>
</table>
Prognostic factors in CLL: Summary

- Interphase-FISH cytogenetic analysis is standard of care
- Chromosomal abnormalities may change with time
- IGHV status does not change with time
- CD38 and ZAP-70 methylation correlates with IGHV
So is stage of the cancer important in CLL

- Rai/Binet Staging system has been used for a long time

- Newer molecular methods are much more useful
What do we do at Initial Presentation?

- All patients undergo
  - History and Physical
  - CBC with diff
  - CMP
  - Direct Anti-Globulin Test*
  - Quantitative Immunoglobulins
  - Infectious Serology*
  - Peripheral Blood Flow cytometry
  - +/- CT scan CAP*
  - +/- Bone Marrow Biopsy*
What do we do at Initial Presentation?

- Prognostic Markers
  - Interphase FISH
  - Conventional karyotyping
  - IGHV mutational analysis
  - ZAP-70 Methylation
  - Beta-2 microglobulin
  - LDH
  - Lymphocyte doubling time
Timing of Therapy

- Constitutional symptoms – How you feel
  - Unintentional weight loss of >10% within the previous 6 mos
  - Significant fatigue (ECOG PS 2 or worse)
  - Fevers >100.5°F for >2 wks without other evidence of infection
  - Night sweats for >1 month without evidence of infection

NCI-IWCLL recommendations, Blood, 2008
Timing of Therapy

- Worsening or steroid resistant anemia and/or thrombocytopenia
- Spleen >6cm below the left costal margin
- Lymph Nodes >10cm
- Lymphocyte doubling time (LDT) of <6 months

NCI-IWCLL recommendations, Blood, 2008
Don’t Treat

- Hypogammaglobulinemia
- Monoclonal or oligoclonal paraproteinemia
- Elevated leukocyte count

NCI-IWCLL recommendations, Blood, 2008
# Early Treatment Does not improve Survival

<table>
<thead>
<tr>
<th>Start year</th>
<th>Study name</th>
<th>Treatment</th>
<th>Deaths/Patients</th>
<th>Immediate deaths</th>
<th>Ratio of annual death rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Allocated</td>
<td>Immediate</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Immediate</td>
<td>Deferred</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1976</td>
<td>CALGB</td>
<td>Chl</td>
<td>7/22</td>
<td>9/25</td>
<td>-0.5</td>
</tr>
<tr>
<td>1978</td>
<td>MRC–CLL–1</td>
<td>Chl</td>
<td>31/37</td>
<td>32/41</td>
<td>3.7</td>
</tr>
<tr>
<td>1980</td>
<td>FRE–CLL–80</td>
<td>Chl</td>
<td>175/300</td>
<td>169/307</td>
<td>10.1</td>
</tr>
<tr>
<td>1984</td>
<td>MRC–CLL–2</td>
<td>Chl</td>
<td>76/121</td>
<td>73/118</td>
<td>5.2</td>
</tr>
<tr>
<td>1985</td>
<td>FRE–CLL–85</td>
<td>Chl+P</td>
<td>122/457</td>
<td>126/462</td>
<td>-2.0</td>
</tr>
<tr>
<td>1988</td>
<td>PETHEMA</td>
<td>Chl+P</td>
<td>21/77</td>
<td>21/81</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>432/1014</td>
<td>430/1034</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(42.6%)</td>
<td>(41.6%)</td>
<td>16.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>212.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.08 (sd = 0.07)</td>
</tr>
</tbody>
</table>

- 99% or ←→ 95% confidence intervals

Heterogeneity between 6 trials: $\chi^2_5 = 1.7; P > .1; \text{NS}$

Immediate better | Deferred better

Treatment effect $P > .1; \text{NS, adverse}$
But treatments have changed ……

- Early treatment can be considered if
  - treatment is well tolerated
  - doesn’t have too many side effects
  - and works well

- Early intervention trial of ibrutinib available at OSU soon for patients who don’t need treatment per conventional criteria
Infectious Complications

- Infections are the leading cause of death in CLL
- Most common infections are sinus, throat and chest
- It generally results from low immunoglobulin levels and defective immune system

- Intravenous immunoglobulins (IVIg) can help in some patients
How to prevent infections?

- Pneumococcal vaccine every 2-5 years (PCV13)
- Flu vaccine every year

- Avoid live virus vaccines including
  - Shingles
  - Nasal flu
  - Oral polio
  - Yellow fever
Secondary Cancers

- Patients with CLL are at a high risk of getting secondary cancers
  - Colonoscopy every 5 years
  - Skin exam by dermatologist every year
  - Mammogram every year
  - Pap smear every year
  - PSA every year
Issues with Supplements

- Metabolism uncertain
- Side effects not well characterized
- Efficacy not proven in clinical trials
- Interaction with other drugs not known

- Please tell your doctor about the type of supplement that you take
Obinutuzumab plus Chlorambucil

Stratified HR: 0.39
(95% CI: 0.31-0.49; P < .0001)

Ofatumumab + chlorambucil

mPFS: 22.4
(95% CI: 19.0-25.2)

HR 0.57; P < .001

Median follow-up: 28.9 mos

Targeting kinases in CLL

Awan F, et al, CCR 2014
Ibrutinib

- Forms a specific bond with cysteine-481 in BTK
- Highly potent BTK inhibition at $IC_{50} = 0.5\ \text{nM}$
- Orally administered with once-daily dosing resulting in 24-hr target inhibition
- No cytotoxic effect on T cells or NK cells
- Promotes apoptosis and inhibits migration and adhesion in CLL cells
PCYC-1102-CA: Phase IB/II in CLL/SLL

Total enrollment 117 patients
Dates enrolled 20th May 10 – 27th Jul 11

Co-leaders: J Byrd and S O’Brien

- **Relapsed/Refractory**
  - 420 mg/d (n=27)
  - Median follow-up 17.5 months

- **Treatment Naïve ≥ 65 yrs**
  - 420 mg/d (n=26)
  - Median follow-up 14.4 months

- **Relapsed/Refractory**
  - 840 mg/d (n=34)
  - Median follow-up 13.8 months

- **High-risk Relapsed/Refractory**
  - 420 mg/d (n=25)
  - Median follow-up 7.4 months

- **Treatment Naïve ≥ 65 yrs**
  - 840 mg/d (n=5)
  - Median follow-up 7.4 months
# Phase II CLL Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>TN ≥65 yrs (N=31)</th>
<th>R/R + HR (N=85)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 70 years, (%)</td>
<td>74%</td>
<td>35%</td>
</tr>
<tr>
<td><strong>ECOG Status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0, 1, 2</td>
<td>74%, 26%, 0%</td>
<td>41%, 56%, 2%</td>
</tr>
<tr>
<td><strong>Median Prior Therapies</strong></td>
<td>N</td>
<td>4 (1-12)</td>
</tr>
<tr>
<td><strong>Rai Stage III/IV at Baseline</strong></td>
<td>48%</td>
<td>65%</td>
</tr>
<tr>
<td><strong>Prognostic Markers, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGHV unmutated</td>
<td>55%</td>
<td>85%</td>
</tr>
<tr>
<td>del(17p13.1)</td>
<td>7%</td>
<td>35%</td>
</tr>
<tr>
<td>del(11q22.3)</td>
<td>3%</td>
<td>39%</td>
</tr>
</tbody>
</table>

Modest toxicity in phase II study similar to phase I study

NEJM 2013
Lancet Oncology
Pattern of Response: Blood Lymphocytes vs Lymph Nodes

Phase II Response and Progression-free Survival

- **R/R + High-Risk R/R (n=85)**
  - Est. PFS at 26 mo is 75%

- **Treatment Naïve (n=31)**
  - Est. PFS at 26 mo is 96%

71% ORR (2% CR)

71% ORR (10% CR)

NEJM 2013
PFS by FISH: Relapse Cohort

- del17p (n=28) Est. PFS at 26 mo is 57%
- del11q (n=23) Est. PFS at 26 mo is 73%
- No del17p or del11q (n=29) Est. PFS at 26 mo is 93%

$p=0.0437$
Early Results Of Impact: Outcome of Treatment of del(17p13.1) CLL at OSU

- Ibrutinib (n = 27)
- CDKi (n = 58)
- Other (n = 88)

P < 0.0001 by log-rank test
IB vs O: P < 0.0001
CDKi vs O: P < 0.0001
IB vs CDKi: P = 0.002
PR-L is not associated with inferior PFS compared with PR/CR at 12 months

Ibrutinib and Rituximab

Burger J et al: Lan Onc 2014
Idelalisib

- Selective PI3-K delta inhibitor
- Single agent response rate of 72%
- 39% PR and 33% PR+L
- Penumonitis, colitis, transaminitis
Idelalisib in relapsed/refractory CLL


Median PFS: 17.1 mos
Median OS: not reached

PFS (%)

OS (%)

Mos From Start of Idelalisib
Mos From Start of Idelalisib
Phase III Idelalisib and Rituximab for Previously Treated Patients With CLL

Idelalisib + rituximab
Median PFS: not reached

Placebo + rituximab
Median PFS: 5.5 mos

HR: 0.15
(95% CI: 0.08-0.28; P < .0001)

Summary

- CLL is a disease with varied presentation
- Comprehensive diagnostic and prognostic workup is important for optimal management at the time of diagnosis
- Multiple treatment options exist including chemotherapy and non-chemotherapy approaches
- Prognosis is generally excellent and improving every day