FCR and BR: When to use, how to use?

Mitchell R. Smith, M.D., Ph.D.
Director of Lymphoid Malignancy Program
Taussig Cancer Institute
Cleveland Clinic, Cleveland, OH
DEBATE ISSUE 2013: Which is the optimal approach: BR or FCR?

Mitchell R. Smith, M.D., Ph.D.
Director of Lymphoid Malignancy Program
Taussig Cancer Institute
Cleveland Clinic, Cleveland, OH
DEBATE ISSUE 2015:
Is There Still a Role for Immuno-Chemotherapy in Treatment of CLL?

Mitchell R. Smith, M.D., Ph.D.
Director of Lymphoid Malignancy Program
Taussig Cancer Institute
Cleveland Clinic, Cleveland, OH
DISCLOSURES

Research Funding:
Abbvie, Celgene, Jannsen, KITE,
Millennium/Takeda, Seattle Genetics

Consultant/Advisory Boards
Celgene, KITE, Spectrum
Is There Still a Role for Immuno-Chemotherapy in Treatment of CLL?

Underlying Assumptions:

• Chemotherapy is “BAD”

• Non-chemo “novel” agents are “GOOD”

• Avoiding chemo will maintain at least equivalent outcomes

• Avoiding chemo will be less toxic
Selection of Initial Therapy of CLL: Key Questions

• What patient population? Age, co-morbidities

• What regimen?

• What do we expect for outcomes?
  – Response rate
  – PFS/Duration of response
  – Overall survival
  – QoL

• What do we expect for toxicity?

• What are our options for 2nd line treatment?
The Evolution of Treatment Options in CLL

**1960-70s**
- **Alkylators**
  - RR: 50%
  - CR: 5%
  - PFS: <1 yr

**1980s**
- **Purine Analogs**
  - RR: 80%
  - CR: 10-20%
  - PFS: 1-2 yr

**1990s**
- **Purine Analog + alkylator**
  - RR: 85%
  - CR: 25%
  - PFS: 2-3 yr

**2000s**
- **Chemo-immuno therapy**
  - RR: 90%
  - CR: 40-50%
  - PFS: 3-5 yr

**2010s**
- **Novel Agents**

**DESIGNED ENDPOINTS:**
- Increase CR rate
- Achieve MRD status?
- More durable remissions
Survival of CLL Patients by Decade

<table>
<thead>
<tr>
<th>Year Rx</th>
<th>Pts.</th>
<th>Died</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1980</td>
<td>45</td>
<td>44</td>
</tr>
<tr>
<td>1980-1989</td>
<td>88</td>
<td>83</td>
</tr>
<tr>
<td>1990-1999</td>
<td>319</td>
<td>225</td>
</tr>
<tr>
<td>2000-2010</td>
<td>933</td>
<td>195</td>
</tr>
</tbody>
</table>

Courtesy of Michael J. Keating, MDACC
FCR 300: PFS and OS

Proportion Progression-free

months

PFS
OS

10 years

Courtesy of Michael J. Keating, MDACC
CLL is “TWO” Diseases: Mutated IgV$_H$ vs germline IgV$_H$

FCR 300: PFS by IgHV Mutational Status

74% of long term Survivors are mutated

10 years

Courtesy of Michael J. Keating, MDACC
## Integrated Mutational And Cytogenetic Model For CLL

<table>
<thead>
<tr>
<th>GENE</th>
<th>% @ DX</th>
<th>FUNCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP53</td>
<td>5-10</td>
<td>G1-S CHECKPOINT</td>
</tr>
<tr>
<td>NOTCH1</td>
<td>~10</td>
<td>γ-SECRETASE CLEAVAGE → TRANSCRIPTION</td>
</tr>
<tr>
<td>SF3B1</td>
<td>~ 5</td>
<td>RNA SPLICING</td>
</tr>
<tr>
<td>BIRC3</td>
<td>~ 5</td>
<td>NF-κB ACTIVATION (NON-CANONICAL PATHWAY)</td>
</tr>
<tr>
<td>MYD88</td>
<td>3</td>
<td>BCR-INDEPENDENT Ag RESPONSE VIA TLR → NF-κB</td>
</tr>
</tbody>
</table>

### Overall Survival

**TP53** and/or **BIRC3** disruption

**NOTCH1** Mut and/or **SF3B1** Mut and/or del11q22-q23 +12 and no gene mutations

Del13q14 alone

---

## INITIAL THERAPY OF CLL: 2013

<table>
<thead>
<tr>
<th>Stage</th>
<th>Fitness</th>
<th>del(17p) p53mut</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binet A-B, Rai 0-II, inactive</td>
<td>Irrelevant</td>
<td>Irrelevant</td>
<td>None</td>
</tr>
<tr>
<td>Active disease or Binet C or Rai III-IV</td>
<td>Go go</td>
<td>No</td>
<td>FCR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>Allo-SCT</td>
</tr>
<tr>
<td>Slow go</td>
<td>No</td>
<td>CLB + anti-CD20-Mab</td>
<td>Al, HD R or O</td>
</tr>
</tbody>
</table>
## INITIAL THERAPY OF CLL: Age and PS

<table>
<thead>
<tr>
<th>Stage</th>
<th>Fitness</th>
<th>del(17p) p53mut</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binet A-B, Rai 0-II, inactive</td>
<td>Irrelevant</td>
<td>Irrelevant</td>
<td>None</td>
</tr>
<tr>
<td>Active disease or Binet C or Rai III-IV</td>
<td>Go go</td>
<td>No</td>
<td>FCR</td>
</tr>
<tr>
<td></td>
<td>Slow go</td>
<td>Yes</td>
<td>Allo-SCT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>CLB + anti-CD20-Mab</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>Al, HD R or O</td>
</tr>
</tbody>
</table>

Hallek, ASH Educational Book, 2013
## INITIAL THERAPY OF CLL: del17p 2013

<table>
<thead>
<tr>
<th>Stage</th>
<th>Fitness</th>
<th>del(17p) p53mut</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binet A-B, Rai 0-II, inactive</td>
<td>Irrelevant</td>
<td>Irrelevant</td>
<td>None</td>
</tr>
<tr>
<td>Active disease or Binet C or Rai III-IV</td>
<td>Go go</td>
<td>No</td>
<td>FCR</td>
</tr>
<tr>
<td></td>
<td>Slow go</td>
<td>Yes</td>
<td>Allo-SCT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>CLB + anti-CD20-Mab</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>Al, HD R or O</td>
</tr>
</tbody>
</table>

Hallek, ASH Educational Book, 2013
# INITIAL THERAPY OF CLL: del17p 2015

<table>
<thead>
<tr>
<th>Stage</th>
<th>Fitness</th>
<th>del(17p) p53mut</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binet A-B, Rai 0-II, inactive</td>
<td>Irrelevant</td>
<td>Irrelevant</td>
<td>None</td>
</tr>
<tr>
<td>Active disease or Binet C or Rai III-IV</td>
<td>Go go</td>
<td>No</td>
<td>FCR</td>
</tr>
<tr>
<td></td>
<td>Slow go</td>
<td>Yes</td>
<td>IBRUTINIB</td>
</tr>
<tr>
<td></td>
<td>Slow go</td>
<td>No</td>
<td>CLB + anti-CD20-Mab</td>
</tr>
<tr>
<td></td>
<td>Slow go</td>
<td>Yes</td>
<td>IBRUTINIB</td>
</tr>
</tbody>
</table>

Hallek, ASH Educational Book, 2013
IMMUNO-CHEMOTHERAPY: STILL TREATMENT OF CHOICE (non-del17p)

• High response rates
• Well-known, manageable toxicities
  – Long experience
  – Comfort level with management
• Durable responses (± rituximab maintenance)
  – Limited treatment duration ⇒ prolonged treatment free-interval
• Full range of later-line treatment options
• Cost
CLL8 trial: FCR versus FC
Overall survival, updated 2012

With median observation time 5.9 years:

FCR 69.4% alive (Median not reached)
FC  62.3% alive (Median 86 months)

HR 0.68 (95% CI 0.54 - 0.86)  
\(p=0.001\)

CLL8: Overall survival by IGHV mutational status

**FCR IGHV$^{mutated}$**

**FCR IGHV$^{unmutated}$**

FC vs. FCR HR 1.63, (95% CI 0.9 - 2.9)
FCR Does not overcome del17p: German CLL8 Data

Figure: Overall survival by treatment arm and TP53 mutations

Surviving fraction

(months)

No TP53 mutation

TP53 mutation

~11%

5 years

Boettcher S et al ASH 2009
Optimal Frontline Treatment: FCR vs BR

Final Analysis of German CLL Study Group CLL10

Patients with untreated, active CLL without del(17p) and good physical fitness (CIRS ≤6, creatinine clearance ≥70 mL/min)

Randomization

FCR
- Fludarabine 25 mg/m² iv, days 1–3
- Cyclophosphamide 250 mg/m², days 1–3
- Rituximab 375 mg/m² iv day 0, cycle 1
- Rituximab 500 mg/m² iv day 1, cycle 2–6

BR
- Bendamustine 90 mg/m² day 1–2
- Rituximab 375 mg/m² iv day 0, cycle 1
- Rituximab 500 mg/m² iv day 1, cycle 2–6
BR vs FCR  
GCLLSG CLL 10 Trial

Untreated CLL without del17p in patients with CIRS score < 6, CrCl > 70

<table>
<thead>
<tr>
<th></th>
<th>FCR (284)</th>
<th>BR (280)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS (months)</td>
<td>54</td>
<td>43</td>
</tr>
<tr>
<td>Age &gt; 65</td>
<td>54</td>
<td>39</td>
</tr>
<tr>
<td>Age &lt; 65</td>
<td>NR</td>
<td>49 (p = NS)</td>
</tr>
<tr>
<td>CR</td>
<td>41%</td>
<td>32%</td>
</tr>
<tr>
<td>Blood MRD neg</td>
<td>74%</td>
<td>63%</td>
</tr>
<tr>
<td>Marrow MRD neg</td>
<td>58%</td>
<td>32%</td>
</tr>
<tr>
<td>OS 3 yr</td>
<td>91%</td>
<td>92%</td>
</tr>
</tbody>
</table>
## BR vs FCR
### GCLLSG CLL 10 Trial

Untreated CLL without del17p in patients with CIRS score < 6, CrCl > 70

<table>
<thead>
<tr>
<th></th>
<th>FCR (284)</th>
<th>BR (280)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS (months)</td>
<td>54</td>
<td>43</td>
</tr>
<tr>
<td>Age &gt; 65</td>
<td>54</td>
<td>39</td>
</tr>
<tr>
<td>Age &lt; 65</td>
<td>NR</td>
<td>49 (p = NS)</td>
</tr>
<tr>
<td>CR</td>
<td>41%</td>
<td>32%</td>
</tr>
<tr>
<td>Blood MRD neg</td>
<td>74%</td>
<td>63%</td>
</tr>
<tr>
<td>Marrow MRD neg</td>
<td>58%</td>
<td>32%</td>
</tr>
<tr>
<td>OS 3 yr</td>
<td>91%</td>
<td>92%</td>
</tr>
<tr>
<td>TRM</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>82%</td>
<td>57%</td>
</tr>
<tr>
<td>Infection for age &gt;70</td>
<td>39%</td>
<td>25%</td>
</tr>
<tr>
<td></td>
<td>48%</td>
<td>27%</td>
</tr>
</tbody>
</table>

Eichhurst ASH 2014
Optimal Frontline Treatment:
Final Analysis of an International Randomized Study of the German CLL Study Group (CLL10)

PFS benefit was **NOT** statistically significant in:
- Patients ≥ 65 years
- CIRS 4-6 (or > 1 CIRS item)
- Mutated (favorable) IGHV

Conversely, FCR better only for younger, very healthy patient with “bad” germline IgVH disease
How does BR stack up against FCR?

- Applicable to more CLL patients
  - wider age and PS
  - less concern about renal function
  - less concern about AIHA
- Less toxic
- Fewer doctor visits
- Requires less supportive care
- Less myelosuppressive, so maybe less t-MN
- Less immunosuppressive, fewer late infections
- Easier to administer later lines of therapy
- Easier to combine with novel agents
## INITIAL THERAPY OF CLL: 2015

<table>
<thead>
<tr>
<th>Stage</th>
<th>Fitness</th>
<th>del(17p) p53mut</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binet A-B, Rai 0-II, inactive</td>
<td>Irrelevant</td>
<td>Irrelevant</td>
<td>None</td>
</tr>
<tr>
<td>Active disease or Binet C or Rai III-IV</td>
<td>Go go</td>
<td>No</td>
<td>FCR vs BR</td>
</tr>
<tr>
<td></td>
<td>Slow go</td>
<td>Yes</td>
<td>IBRUTINIB</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>CLB + anti-CD20-Mab</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>IBRUTINIB</td>
</tr>
</tbody>
</table>
## INITIAL THERAPY OF CLL: 2015

<table>
<thead>
<tr>
<th>Stage</th>
<th>Fitness</th>
<th>del(17p) p53mut</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binet A-B, Rai 0-II, inactive</td>
<td>Irrelevant</td>
<td>Irrelevant</td>
<td>None</td>
</tr>
<tr>
<td>Active disease or Binet C or Rai III-IV</td>
<td>Go go</td>
<td>Yes</td>
<td>Allo-SCT</td>
</tr>
<tr>
<td></td>
<td>Slow go</td>
<td>No</td>
<td>BR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>Allo, HD R or O</td>
</tr>
<tr>
<td>Stage</td>
<td>Fitness</td>
<td>del(17p) p53mut</td>
<td>Therapy</td>
</tr>
<tr>
<td>--------------------------------------------</td>
<td>----------</td>
<td>-----------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Binet A-B, Rai 0-II, inactive</td>
<td>Irrelevant</td>
<td>Irrelevant</td>
<td>None</td>
</tr>
<tr>
<td>Active disease or Binet C or Rai III-IV</td>
<td>Go go</td>
<td>No</td>
<td>FCR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>Allo-SCT</td>
</tr>
<tr>
<td></td>
<td>Slow go</td>
<td>No</td>
<td>New anti-CD20’s</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>Al, HD R or O</td>
</tr>
</tbody>
</table>
German CLL Study Group: CLL11
chlorambucil ± rituximab or obinotuzumab

Previously untreated CLL with comorbidities
- Total CIRS score >6 and/or CrCl <70 mL/min
- Age ≥18 years

CIRS = Cumulative Illness Rating Scale; Clb = chlorambucil; CLL = chronic lymphocytic leukemia; CrCl = creatinine clearance; GA101 = obinotuzumab; G-Clb = GA101, chlorambucil; iv = intravenous; po = oral; q28d = every 28 days; R-Clb = rituximab, chlorambucil

*Chlorambucil administered at 0.5 mg/kg po on days 1 and 15 of cycles 1–6 q28d.

†GA101 administered at 1,000 mg iv on days 1, 8, and 15 of cycle 1, and then 1,000 mg iv on day 1 of cycles 2–6 q28d.

‡Rituximab administered at 375 mg/m² iv on day 1 of cycle 1, followed by 500 mg/m² iv on day 1 of cycles 2–6 q28d.
German CLL Study Group: CLL11

Untreated CLL with comorbidities (CIRS >6) → Randomize

- Obinutuzumab + Clb
- Rituximab + Clb

Response Rates

<table>
<thead>
<tr>
<th></th>
<th>Ob + Clb (N=333)</th>
<th>R + Clb (N=329)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>20.7</td>
<td>58.1</td>
</tr>
<tr>
<td>Partial response</td>
<td>57.7</td>
<td>58.1</td>
</tr>
</tbody>
</table>

Stratified hazard ratio for progression or death with G-Clb, 0.39 (95% CI, 0.31–0.49) P<0.001

Probability of progression-free survival:
- Ob + Clb
- R-Clb

Marrow MRD
- Bone Marrow: 19.5, 2.6, P<0.001
- Blood: 37.7, 3.3, P<0.001
## INITIAL THERAPY OF CLL: 2015

<table>
<thead>
<tr>
<th>Stage</th>
<th>Fitness</th>
<th>del(17p) p53mut</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binet A-B, Rai 0-II, inactive</td>
<td>Irrelevant</td>
<td>Irrelevant</td>
<td>None</td>
</tr>
<tr>
<td>Active disease or Binet C or Rai III-IV</td>
<td>Go go</td>
<td>No</td>
<td>FCR</td>
</tr>
<tr>
<td></td>
<td>Slow go</td>
<td>Yes</td>
<td>Allo-SCT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>Al, HD R or O</td>
</tr>
<tr>
<td>Stage</td>
<td>Fitness</td>
<td>del(17p) p53mut</td>
<td>Therapy</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>----------</td>
<td>-----------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>Binet A-B, Rai 0-II, inactive</td>
<td>Irrelevant</td>
<td>Irrelevant</td>
<td>None</td>
</tr>
<tr>
<td>Active disease or Binet C or Rai III-IV</td>
<td>Go go</td>
<td>No</td>
<td>FCR vs BR ?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>IBRUTINIB</td>
</tr>
<tr>
<td></td>
<td>Slow go</td>
<td>No</td>
<td>Chl + anti-CD20 Ab or BR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>IBRUTINIB</td>
</tr>
</tbody>
</table>
Selection of Initial Therapy of CLL: Key Questions

• What patient population? Age, co-morbidities, del17p

• What regimen? FCR vs BR vs αCD20 ± Chlorambucil

• What do we expect for outcomes?
  – Response rate
  – PFS/Duration of response
  – Overall survival

• What do we expect for toxicity? QoL?

• What are our options for 2nd line treatment?
How do I select 1st-line CLL Therapy?

Ibrutinib
   del17p (if anticoagulation, Afib idelalisib)

FCR
   young, healthy patient with “bad” disease
   e.g. unmutated IgVH, del11q, rapid pace

BR
   most patients

αCD20 ± Chlorambucil
   frail, elderly
TOXICITY ISSUES: Benda vs Fludarabine

COMMON CONCERNS FOR BOTH:
• Who can get safely treated with the regimen?
• Prolonged myelo-suppression
• Therapy related myeloid neoplasia (t-MN)

FLUDARABINE:
• FCR difficult in older patients
• Immuno-suppression
• Fludarabine renal excretion
• Exacerbation of AIHA

BENDAMUSTINE:
• Rash/Hypersensitivity
  – ? Possible interaction with allopurinol
Ofatumumab monotherapy: Efficacy in fludarabine-refractory patients

Ofatumumab has demonstrated activity in the treatment of fludarabine-refractory patients who are refractory to, or unsuitable for [bulky nodes], alemtuzumab.

Ofatumumab is indicated for the treatment of CLL patients double-refractory to fludarabine and alemtuzumab.

FA-ref = fludarabine- + alemtuzumab-refractory CLL; BF-ref = bulky fludarabine-refractory CLL + unsuitable for alemtuzumab therapy.

**Ibrutinib Pivotal Study: RESONATE**

Relapsed CLL after at least 1 prior therapy

- **Randomize 1:1**
  - Oral ibrutinib 420 mg once daily until PD or unacceptable toxicity  
    - n=195
  - IV ofatumumab initial dose of 300 mg followed by 2000 mg x 11 doses over 24 weeks  
    - n=196
  - Crossover to ibrutinib 420 mg once daily after IRC-confirmed PD (n=57)

Median follow up 9.4 months

Not appropriate for purine analog therapy:
- Disease progression < 3 years from prior purine analog
- Age > 70 (or > 65 with comorbidities) [MEDIAN 67 YRS]
- Purine analog associated AIHA / ITP
- Deletion 17p [~1/3 of patients on this trial]

Primary Objective: PFS by IRC per 2008 IWCLL criteria;
(2012 clarification for treatment-related lymphocytosis)

Brown, et al ASH 2014 Abstract #3331
Ibrutinib vs Ofatumumab in Previously Treated CLL: Outcomes

Progression Free Survival

Ibrutinib significantly prolonged PFS
Median not reached vs 8 mos for Ofat
78% reduction in risk of progression or death
PFS HR 0.13; p < 0.0001
HR Benefit regardless of prognostic factors

Overall Survival

Ibrutinib significantly prolonged OS
57% reduction in risk of death
Despite 57 patients on ofatumumab arm crossing over to ibrutinib after IRC-confirmed PD
CAVEATS

• R2 (Lenalidomide-rituximab)
  – High early death rate in elderly CLL lenalidomide trial

• Ibrutinib
  – Poor outcomes after ibrutinib failure
    – Richter’s in CLL?
    – Blastoid transformation in MCL?
  – Unexpected toxicities/Long term toxicities?
  – Interference with ADCC may block rituximab action

• Idelalisib
  – Autoimmune toxicities
  – Long term toxicities

• Venetoclax (ABT-199)
  – Tumor Lysis Syndrome
  – Long term toxicities
ORIGIN: Lenalidomide vs Chlorambucil initial therapy for CLL patients ≥65 yrs

- Patients: Lenalidomide 210, Chlorambucil 211
- Deaths: Lenalidomide 34, Chlorambucil 18
- HR (Len vs. Chl) (95% CI) 1.92 (1.08, 3.41)
Do we select “bad actors” after Targeted Therapy?

Poor Survival of CLL patients after discontinuation of ibrutinib.

Poor Survival of MCL patients after discontinuation of ibrutinib

Deaths/Total
25/33
Median OS - 3.1 months

Percent survival

Time in Months

0
10
20
30
40
50

0
20
40
60
80
100

D

Overall survival by response to salvage therapy

Proportion surviving

Number at risk
no response
response

Time (months)

0
6
12
18
24


Preetesh Jain et al. Blood 2015;125:2062-2067
COST

• Rituximab: $5,065/dose AWP
• Bendamustine: $52,704/6 cycles
  Generic soon: available internationally online $5,000/ 24 x 100 mg vials
  Shanafelt TD et al. The Oncologist 2010
  6 cycles = $85,000
• Ibrutinib: $12,000 per month (~ $150,000/yr)
  PharmExec.com Dec 2013

• If we treat 5,000 new CLL cases/yr in US:
  Ibrutinib = $750 million per year
  x 3.5 yr median PFS BR CLL8 = $2.6 BILLION
  BR = $425 million

Don’t even think of cost of BR + ibrutinib continuing until PD
CLL Clinical Trials in 2015

Untreated CLL
Age < 65

RANDOMIZE

FCR
Ibrutinib + Rituximab

Untreated CLL
Age ≥ 65

RANDOMIZE

BR
Ibrutinib
Ibrutinib + Rituximab
Minimal Residual Disease in CLL

Number of CLL cells (log scale)

Time from therapy

~10^{12}
~10^{10}
~10^{8}

CHLORAMBUCIL
FLUDARABINE

BR?
FCR/FR

NCI-CR
MRD negativity
Optimal Time to Start Novel Agents in CLL

- NCI-CR
- MRD negativity
- FCR/BR

Number of CLL cells (log scale)

Time from therapy
Optimal Time to Start Novel Agents in CLL?

- Maximum response
- Molecular detection of relapse
- NCI-CR
- FCR/BR
- MRD negativity
- Clinical Relapse
- Start

Number of CLL cells (log scale)

Time from therapy

~10^{12}

~10^{10}

~10^{8}
Optimal Time to Start Novel Agents in CLL?

Number of CLL cells (log scale)

-10^{12}
-10^{10}
-10^{8}

Time from therapy

- start
- Maximum response
- Molecular detection of relapse
- Clinical Relapse
- FCR/BR

Optimal Time to Start Novel Agents in CLL?
FCR 300: PFS and OS

- Proportion Progression-free
- Treat 100% of patients from the start
- 50% still not started 6 years
- 35% still not started 10 years

Adapted from Michael J. Keating, MDACC
Potential future strategies to achieve long-term control of CLL

Debulking
- Mild chemotherapy with agents like bendamustine or fludarabine
- 1-2 months (1–2 courses)

Induction (combination therapy)
- Kinase inhibitor(s)
- Antibody
- Bcl2 antagonist
- 6-12 months

MRD tailored maintenance (single agents)
- Antibody
- Lenalidomide
- Kinase inhibitor
- Bd2 antagonist
- 1 year - ∞

CAR T cell Therapy?
Conclusions

• For many, CLL is a “non-disease”, for others “real cancer”

• CLL is not curable with any current therapy, but options exist for durable, high-quality remissions

• Treatment individualized by patient “fitness”

• Molecular genetics starting to impact choice of therapy

• Anti-CD20 Ab + chemotherapy still reasonable 1st treatment for many

• Targeted therapy (alone, + MoAb, combinations) being studied, may avoid standard chemotherapy toxicity

• Many other new agents in development

CAN WE FURTHER IMPROVE SURVIVAL?