Mr. B- A VA classic

- 65 yo M with multiple low-level comorbidities presents to VA for care of CLL
- PMH:
  - DJD
  - Hypothyroidism
  - Chronic sinusitis
  - HTN
  - Hyperlipidemia
  - Multiple non-melanoma skin cancers (SCC, BCC) s/p Moh’s
- Social history: no tobacco, +agent orange exposure when serving in army during Vietnam war
- No family history
CLL History

- Dx 2007 with wbc 20,000, normal HCT/plts, LAD and splenomegaly
  - CD38+, ZAP70-, FISH: del(11q) and del(13q)
- 2008: FCR x 6 cycles for LAD and wbc 80K → CR
- 2012: rapid rise in wbc and recurrent LAD and fatigue so received FCR x 6 cycles → PR
- 2013: wbc rises rapidly to 150K with doubling time of 3 weeks → BR x 3 which improved wbc to 20K but CT with worsening disease, bulky disease in retroperitoneum
- 12/9/13 Marrow: 50% small lymphocytes with CD5, CD19 and CD38 but no CD10 or CD20; no evidence of transformation
  - Flow: CLL immunophenotype 81% wbc
  - FISH: del(11q) and del(13q); negative for del(17p)
  - Cyto: multiple abnormalities including 11q and 13q with evidence of 2 subclones
CT CAP
What Next?

- Ibrutinib approved by FDA 2/12/14
- Ibrutinib started 2/27/14 (1st pt at the VA!)
  - Starting WBC 33K, 90% lymphs, ANC 660, plts 101, HCT 41
  - Wbc $\rightarrow$ 87K by March, 120K in April then normalized
- 7/24/14: CT with decrease of nodes throughout
- Remains on therapy with normal blood counts
- Now needs knee replacement . . . .
CLL: Epidemiology

- CLL is a clonal lymphoproliferative disorder of B-lymphocytes in blood, bone marrow, lymph nodes and spleen
- Most common type of leukemia in U.S.
- Median age dx 70, male>females 1.7:1

<table>
<thead>
<tr>
<th>Estimated New Cases in 2015</th>
<th>14,620</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of All New Cancer Cases</td>
<td>0.9%</td>
</tr>
<tr>
<td>Estimated Deaths in 2015</td>
<td>4,650</td>
</tr>
<tr>
<td>% of All Cancer Deaths</td>
<td>0.8%</td>
</tr>
</tbody>
</table>

(SEER)
Diagnosis CBC

Smudge cells: Ruptured CLL B cells, more fragile, not just an artifact

Amount of “smudge” related to amount of vimentin in cells which is important element of cytoskeleton for rigidity and integrity, also may participate in cell activation and signal transduction

High levels of vimentin associated with low rate of smudge cells
Smudge Cells

Nowakowski JCO 2009

10-year OS for those with smudge cells >30% was 80% vs. 50% for smudge cells <30%

%Smudge cells was an independent predictor of OS on multivariate analysis taking other prognostic factors into account

Cytoskeleton may play a distinct role in CLL biology
Diagnosis

- DX requires presence of $>5 \times 10^9/L$ B-lymphocytes in peripheral blood for $>3$ months
- Confirm clonality by flow cytometry: co-express T-cell antigen CD5 and B-cell antigens CD19,20,23. CD20, 79b and sIg are present but low compared to normal B-cells. Restricted to either kappa or lambda light chains
- Risk stratification and staging:
  - Labs, cytogenetics/FISH, imaging if clinically indicated
Wait- what about MBL

- MBL= Monoclonal B cell lymphocytosis
- The newer and cooler MGUS?
- Defined as the presence of $<5 \times 10^9/L$ clonal B-cells in peripheral blood without cytopenias, lymphadenopathy or organomegaly
- Risk factors for developing MBL: FH of CLL, genetic polymorphisms, age, certain infections like Hep C, HSV
- Risk factors for MBL progression to CLL: CD38+, unmutated IGHV, del(17p), high B-cell count
MBL: Clinical Implications

- Low-count” = <0.5x10^9/L detected in 5% adults >40 using standard sensitivity flow cytometry
  - Rarely progress to CLL
  - Life expectancy same as general population, requires no specific clinical follow up
- “High-count” = 0.5-5x10^9/L
  - High count progresses to CLL at rate of 1-2% yearly
  - Yearly CBC and lymph node exam
  - Compared to low-count MBL, higher risk of hospitalizations due to serious infections and higher risk of hematologic and non-hematologic cancers
Workup, Staging and Prognosis

Per NCCN:

- **Essential**
  - Exam: nodes and spleen
  - B symptoms, PS
  - CBC, metabolic panel
  - Flow cytometry, FISH/cytogenetics
  - Consider hepatitis B, MUGA

- **Non-essential (prior to starting treatment)**
  - CT chest/abdomen/pelvis
  - Unilateral bone marrow biopsy
  - Labs: Quant IGs, LDH, uric acid, B2-microglobulin
Staging

Dr. Rai vs. Dr. Binet
## Staging

<table>
<thead>
<tr>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>I</td>
</tr>
<tr>
<td>II</td>
</tr>
<tr>
<td>III</td>
</tr>
<tr>
<td>IV</td>
</tr>
</tbody>
</table>

### Rai System

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Risk Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Lymphocytosis, lymphocytes in blood &gt;15,000/mcL and &gt;40% lymphocytes in the bone marrow</td>
<td>Low</td>
</tr>
<tr>
<td>I</td>
<td>Stage 0 with enlarged node(s)</td>
<td>Intermediate</td>
</tr>
<tr>
<td>II</td>
<td>Stage 0–I with splenomegaly, hepatomegaly, or both</td>
<td>Intermediate</td>
</tr>
<tr>
<td>III</td>
<td>Stage 0–II with hemoglobin &lt;11.0 g/dL or hematocrit &lt;33%</td>
<td>High</td>
</tr>
<tr>
<td>IV</td>
<td>Stage 0–III with platelets &lt;100,000/mcL</td>
<td>High</td>
</tr>
</tbody>
</table>

### Binet System

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Hemoglobin ≥10 g/dL and Platelets ≥100,000/mm³ and &lt;3 enlarged areas</td>
</tr>
<tr>
<td>B</td>
<td>Hemoglobin ≥10 g/dL and Platelets ≥100,000/mm³ and ≥3 enlarged areas</td>
</tr>
<tr>
<td>C</td>
<td>Hemoglobin &lt;10 g/dL and/or Platelets &lt;100,000/mm³ and any number of enlarged areas</td>
</tr>
</tbody>
</table>
# Prognostic Factors

<table>
<thead>
<tr>
<th>Outcome Association</th>
<th>Favorable</th>
<th>Unfavorable</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA sequencing&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&gt;2% mutation</td>
<td>≤2% mutation</td>
</tr>
<tr>
<td>IGHV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flow Cytometry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD38</td>
<td>&lt;30%</td>
<td>≥30%</td>
</tr>
<tr>
<td>Zap 70</td>
<td>&lt;20%</td>
<td>≥20%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interphase Cytogenetics (FISH)&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Complex karyotype&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unfavorable</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>del(11q)</td>
<td>≥3 unrelated chromosome abnormalities in more than one cell on karyotype</td>
</tr>
<tr>
<td>del(17p)</td>
<td></td>
</tr>
<tr>
<td>+12</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>del(13q) (as a sole abnormality)</td>
</tr>
</tbody>
</table>
Prognostic Factors: Biology and Treatment Response

FCR vs FR

Figure 3: Overall survival in all patients (A), and in genetic subgroups of chemotherapy (B) and chemoinmunotherapy groups (C).

Hallek et al. 2010
## When To Treat?

<table>
<thead>
<tr>
<th>General practice</th>
<th>Clinical trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treat with Rai stage 0</td>
<td>NGI*</td>
</tr>
<tr>
<td>Treat with Binet stage A</td>
<td>NGI*</td>
</tr>
<tr>
<td>Treat with Binet stage B or Rai stage I or Rai stage II</td>
<td>Possible*</td>
</tr>
<tr>
<td>Treat with Binet stage C or Rai stage III or Rai stage IV</td>
<td>Yes</td>
</tr>
<tr>
<td>Treatment of active/progressive disease</td>
<td>Yes</td>
</tr>
<tr>
<td>Treat without active/progressive disease</td>
<td>NGI</td>
</tr>
<tr>
<td></td>
<td>RQ</td>
</tr>
</tbody>
</table>

General practice is defined as the use of accepted treatment options for a patient with CLL who is not enrolled in a clinical trial. NGI indicates not generally indicated; and RQ, research question. *Treatment is indicated if the disease is active as defined in section 4.

CLL IWG: Hallek et al., Blood 2008
When To Treat: “Active Disease”

- Evidence of progressive marrow failure (anemia/thrombocytopenia)
- Massive (>6cm below costal margin) or progressive/symptomatic splenomegaly
- Massive nodes (>10cm) or progressive symptomatic lymphadenopathy
- Progressive lymphocytosis with increase >50% in 2 months
- Lymphocyte doubling time <6 months
- Autoimmune anemia/thrombocytopenia poorly responsive to steroids
- Disease related B-symptoms: weight loss >10% in 6 months, fevers x 2 weeks, night sweats x 1 month, significant fatigue
Principles of Treatment

- Treat only when necessary*
  - Potential benefit of early-intervention therapy remains to be proven and may have risks
- Integrate biology with functional status
- Chemoimmunotherapy (CIT) remains the standard first-line treatment
- New treatments here and on the horizon directed at the biology of CLL

*Consider clinical at any stage if available
Building Blocks CIT

- **Alkylating agents and Purine analogs**
  - Fludarabine
  - Cyclophosphamide
  - Bendamustine
  - Chlorambucil
  - Pentostatin
  - Cladribine

- **Anti-CD20 Monoclonal antibodies**
  - Rituximab
  - Ofatumumab and Obinutuzumab - fully humanized with increased binding affinity to CD20 and increased cytotoxicity

- **Other Monoclonal antibodies**
  - Alemtuzumab - anti-CD52, now only compassionate use, available in Europe so on many of their guidelines
Novel Therapies

- Bruton’s tyrosine kinase inhibitor (BTK) : Ibrutinib
- PI3K inhibitor: Idelalisib
- Others
  - Bcl-2 inhibitors: ABT-199 (ventoclax)
  - IMID: Lenalidomide
  - Dasatanib, Everolimus have been tested with less promising results
  - CAR T-cells
Treatment Algorithm

Patient with CLL and no prior therapy meets IWCLL criteria for treatment

‘Age’, ‘Functional status’, Comorbidities, FISH status

Clinical Trial is the Preferred First Choice for all Patients

Intensive CIT Eligible

1. FCR
2. BR (preferred first line for patients ≥ 65 yrs)

Intensive CIT Ineligible

1. Chlorambucil plus Obinutuzumab
2. Chlorambucil plus Ofatumumab

Any Patients with Deletion 17p

1. Ibrutinib
2. Alemtuzumab

Frail Patients – Not Eligible for Chemotherapy

CD20 monoclonal antibody

Jain et al, Blood 2015
Another Treatment Algorithm

**Go-go** defined as low CIRS and good Cr
**Slow-go** impaired physical condition

### CLL first line treatment

<table>
<thead>
<tr>
<th>Stage</th>
<th>Fitness</th>
<th>del(17p)</th>
<th>p53mut</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binet A-B, Rai D-II, inactive</td>
<td>Irrelevant</td>
<td>Irrelevant</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Active disease or Binet C or Rai III-IV</td>
<td>Go go</td>
<td>No</td>
<td></td>
<td>FCR (BR above 65 years?)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td></td>
<td>ibritinib, idealisib + Rituximab (Allogeneic SCT)</td>
</tr>
<tr>
<td></td>
<td>Slow go</td>
<td>No</td>
<td></td>
<td>Chlorambucil + Obinutuzumab (GA-101) or + Rituximab or + Ofatumumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td></td>
<td>ibritinib, alemtuzumab, HD Rituximab or Ofatumumab</td>
</tr>
</tbody>
</table>

### CLL second line treatment

<table>
<thead>
<tr>
<th>Response to First-Line Therapy</th>
<th>Fitness</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td></td>
<td>Lenalidomide, BR, (other kinase inhibitors, ABT-199)</td>
</tr>
<tr>
<td>Refractory or progress within 2 years</td>
<td>Go go</td>
<td>Ibrutinib, A-Dex, FA, FCR, Allogeneic SCT (?)</td>
</tr>
<tr>
<td>Slow go</td>
<td>Change therapy (include in trial)</td>
<td>Ibrutinib, idealisib + Rituximab, Alemtuzumab for del(17p), ABT-199, FCR-lite, BR, lenalidomide, ofatumumab, HD rituximab</td>
</tr>
<tr>
<td>Progress after 2 years</td>
<td>All</td>
<td>Repeat first-line therapy</td>
</tr>
</tbody>
</table>

**Figure 3.** (a,b) Treatment algorithm for CLL patients, in first and second line indications. A, alemtuzumab; R, rituximab; O, ofatumumab; F, fludara- bine; C, cyclophosphamide; CLB, chlorambucil; HD, high-dose.

M Hallek, Am J Hematology 2015
Functional Status

- German CLL Study Group/IWG uses a comorbidity index called Cumulative Illness Rating Scale (CIRS) and kidney function to assess if patients are suitable for myelosuppressive CIT (CIRS<6, Cr clearance >70)
- In US we often use age (<65-70) and PS 0-1
Like other leukemias, presence or absence of MRD increasingly recognized as correlated with PFS and OS and it an important part of response assessment.
Young <65, Fit, no del(17p): FCR

- Hallek et al: 408 fit pts. aged 30-81 (30% > age 65) randomized to FCR vs. FC

<table>
<thead>
<tr>
<th></th>
<th>CR</th>
<th>ORR</th>
<th>PFS</th>
<th>OS-3 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>FCR</td>
<td>44%</td>
<td>90%</td>
<td>51.8mo</td>
<td>87%</td>
</tr>
<tr>
<td>FR</td>
<td>22%</td>
<td>80%</td>
<td>32.8mo</td>
<td>83%</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
<td>.012</td>
</tr>
</tbody>
</table>
Fischer et al. (JC O 2012) reported outcome of 117 pts with untreated CLL, median age 64, tx with BR
- Included 35% patients with Cr clearance <70, 26% patients >70 years
- ORR 88%, CR 23%, median PFS 34 months, similar in older pts
BR EFS Stratified by MRD, Cytogenetics

Fig 3. Event-free survival in (A) minimal residual disease (MRD) subgroups (peripheral blood) and in (B) cytogenetic subgroups. CLL, chronic lymphocytic leukemia; PD, progressive disease.
Obinutuzumab (also known as GA101) is a humanized, glyco-engineered type 2 antibody targeted against CD20.

In vitro, obinutuzumab showed superior efficacy to rituximab in inducing direct cell death and enhanced antibody-dependent cellular toxicity.

Led to a phase III randomized, open label trial of chlorambucil vs CO vs CR:

- 781 patients with untreated CLL and CIRS >6 or Cr Clearance 30-69
- Median age = 73, CR clearance 62, CIRS 8
**Chlorambucil + Obinutuzumab**

**Panel A: Response Rates**
- G-Clb (N=333)
  - Complete response: 57.7%
  - Partial response: 20.7%
- R-Clb (N=329)
  - Complete response: 58.1%
  - Partial response: 7.0%

**Panel B: MRD rates**
- Bone Marrow: 19.5% G-Clb, 2.6% R-Clb, P<0.001
- Blood: 37.7% G-Clb, 3.3% R-Clb, P<0.001

**Panel C: PFS for OC vs RC**
- 26.7mo vs 15.2 months, p<.0001
- NS for del17p
- OS not significant: death rate 8 vs 12% p.08
WHAT ABOUT PATIENT WITH DELETION 17P?
Alemtuzumab is a recombinant, fully humanized monoclonal antibody against CD52. Monotherapy with alemtuzumab has produced response rates of 33-53% with a median duration of response ranging from 8.7-15.4 months in fludarabine-refractory patients, including those with high-risk genetic markers. Hillmen et al. (JCO 2007) randomized patients to alemtuzumab vs. chlorambucil: higher rates of response, CR, PFS, and time to progression in alemtuzumab arm. Significant long term immunologic repurcussions. In the US we don’t use this—only used in Europe.
Targeting the B-Cell Receptor

B-Cell receptor signaling plays a key role in pathogenesis of CLL
Ibrutinib

- Unlike CML, there is no common genetic target for CLL
- B-cell receptor signaling has emerged as a driving factor for CLL tumor-cell survival
  - Downstream of the B-cell receptor (and critical to its function) is Bruton’s tyrosine kinase (BTK)
  - BTK mutations in humans cause X-linked agammaglobulinemia, which leads to the absence of peripheral-blood B cells, decreased levels of serum immunoglobulin, and increased infections
- Ibrutinib is an irreversible inhibitor that binds covalently to C481 of BTK
- Does not have toxic effects on normal T cells
  - Distinguishes it from most regimens used for CLL
Ibrutinib: Phase I/II

85 pts
70% R/R

Byrd et al., NEJM 2013
Ibrutinib: Phase I/II

A. Progression-free survival
   - All patients
   - No 17p or 11q deletions (n=29)
   - 11q deletion (n=23)
   - 17p deletion (n=28)
   - P=0.04 by log-rank test

B. Overall Survival
   - All patients
   - No 17p or 11q deletions (n=29)
   - 11q deletion (n=23)
   - 17p deletion (n=28)
   - P=0.15 by log-rank test

A. Progression-free survival
   - Mutated IGHV (n=12)
   - Unmutated IGHV (n=69)
   - P=0.67 by log-rank test

B. Overall Survival
   - Mutated IGHV (n=12)
   - Unmutated IGHV (n=69)
   - P=0.86 by log-rank test
Ibrutinib- Phase III Relapsed/Refractory

- 391 pts with relapsed/refractory CLL randomized to Ibrutinib vs Ofatumumab
- About 1/3 patients in each group had 17p del and another 1/3 11q del
- PFS not reached with Ibrutinib vs 8.1 months with Ofatumumab
- 12 mo OS 90% vs 81% despite crossover
- Results consistent in 17p del group

Byrd et al., NEJM 2014
Ibrutinib: Upfront

- O’Brien recently published 3 year FU of a study with 31 treatment-naïve pts and 132 R/R patients
  - Frequency of del(17p) and del(11q) was 6% and 3% in TN
- TN: ORR 84%, CR 23%, 55% PR and 6% PR-L
- TN: 96% PFS at 30 months
- Results consistent in 17p del group:
  - R/R del(17p) had 28 mo PFS
- Median time to best response was 7.4 mo
- Toxicity diminished over time
- Remissions were durable and when progression did occur was in poor risk cytogenetics
- Treatment-related lymphocytosis remained asymptomatic and did not alter longer term PFS
Ibrutinib: Upfront

- Phase II trial included 35 previously untreated patients with CLL, 16 with R/R disease (total n=51)
- 47/51 had del 17p and rest had TP53 mutation
- 92% ORR: 50% PR and 42% PR with lymphocytosis
- Of newly diagnosed numbers were similar

Farooqui et al, 2015
Mechanisms Ibrutinib Resistance

- Woyach et al (NEJM 2014): whole-exome sequencing at baseline and the time of relapse on samples from 6 patients with acquired resistance to Ibrutinib therapy
- Identified a cysteine-to-serine mutation in BTK at the binding site of Ibrutinib in 5 patients and 3 distinct mutations in PLCγ2 in 2 patients.
- Functional analysis showed that the C481S mutation of BTK resulted in a protein that no longer binds covalently and therefore is only reversibly inhibited by Ibrutinib
- The mutations found in PLCγ2 are both potentially gain-of-function mutations that lead to autonomous B-cell–receptor activity
- None of mutations were detected before drug exposure
Ibrutinib Resistance

- Patients with increased genomic instability, including those with del(17p) and del(11q), or a complex karyotype, may be at risk for relapse
- These patients may be the most rational choice for combination therapies designed to avoid the development of resistance

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yr)</th>
<th>Prior Therapies (no.)</th>
<th>Baseline Cytogenetic Features</th>
<th>Study Treatment and Daily Dose</th>
<th>Duration of Ibrutinib Treatment (days)</th>
<th>Best Response</th>
<th>Time to First Response (days)</th>
<th>Identified Mutations of Interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>59</td>
<td>5</td>
<td>del(17p13.1), trisomy 12</td>
<td>Ibrutinib, 560 mg</td>
<td>621</td>
<td>Partial</td>
<td>70</td>
<td>C481S mutation in BTK</td>
</tr>
<tr>
<td>2</td>
<td>59</td>
<td>3</td>
<td>del(11q22.3)</td>
<td>Bendamustine–rituximab for 6 cycles; ibrutinib, 420 mg</td>
<td>388</td>
<td>Complete</td>
<td>70</td>
<td>C481S mutation in BTK</td>
</tr>
<tr>
<td>3</td>
<td>51</td>
<td>2</td>
<td>complex karyotype</td>
<td>Ofatumumab for 24 wk; ibrutinib, 420 mg</td>
<td>674</td>
<td>Complete</td>
<td>85</td>
<td>C481S mutation in BTK</td>
</tr>
<tr>
<td>4</td>
<td>69</td>
<td>9</td>
<td>del(17p13.1), complex karyotype</td>
<td>Ibrutinib, 840 mg</td>
<td>868</td>
<td>Partial</td>
<td>133</td>
<td>C481S mutation in BTK</td>
</tr>
<tr>
<td>5</td>
<td>61</td>
<td>4</td>
<td>del(17p13.1), complex karyotype</td>
<td>Ofatumumab for 24 wk; ibrutinib, 420 mg</td>
<td>505</td>
<td>Partial</td>
<td>85</td>
<td>L845F, R665W, and S707Y mutations in PLCy2 and C481S mutation in BTK</td>
</tr>
<tr>
<td>6</td>
<td>75</td>
<td>2</td>
<td>del(17p13.1), complex karyotype</td>
<td>Ibrutinib, 420 mg</td>
<td>673</td>
<td>Partial</td>
<td>159</td>
<td>R665W mutation in PLCy2</td>
</tr>
</tbody>
</table>
Outcomes after development of Ibrutinib resistance are poor

Jain et al looked at 127 pts on Ibrutinib in various clinical trials- 33 or 26% had discontinued the drug after a median duration of 13 month about half from disease progression/ transformation, half from toxicity

- 58% del(17p), 54% complex karyotype, 94% unmutated IGHV
- 76% had died by follow-up with a median OS survival for all pts after discontinuation 3.1 mo
- 3 went on to HCT, 2 of those died

Need a backup plan: CAR T-cells, transplant, Idelalisib
Unique Side Effects- Bleeding?

• Our VA patients really wants a knee replacement, has been in a CR on Ibrutinib . . .

• Clinical trials have reported grade $\geq 3$ bleeding events including subdural hematomas, hematuria and GI bleeding in 5-<10% of patients

• CLL in itself causes a bleeding diathesis
Ibrutinib and Bleeding

- Lipsky et al incorporated measures of bleeding into an early phase II trial:
  - 55% patients had Gr1-2 bleeding over 24 month FU
  - Bleeding was similar to that seen in patients with mild qualitative platelet defects: bruising, epistaxis, gingival
  - Cumulative incidence of bleeding plateaued by 6 months, and then risk seemed to decrease
  - Compared to similar populations in other trials, found that Ibrutinib increased bleeding risk by 2-fold
  - Tracked many lab measures of bleeding (VWF, coagulation factors, plt aggregation studies) and confirmed earlier finding that bleeding may be mediated through inhibition of collagen-dependent platelet aggregation by Ibrutinib via affects on BTK, which affects collage-mediated plt activation through the GpVI receptor
Idelalisib

- Signaling through BCR is mediated in part by activation of the delta isoform of phosphatidylinositol 3-kinase (PI3Kδ)
- Idelalisib is a potent, oral, selective small molecule inhibitor of PI3Kδ
Idelalisib in Relapsed CLL: Phase 3 Data

- Randomized, double-blinded, placebo-controlled trial 220 pts with relapsed CLL, median age 71, CIRS score 8
- ORR 81% vs. 13%
- PFS in IR group not yet reached, 5.5 mo in R group (p<.001)
- OS: 92% vs 80% at 12 months (p=.02)
- Treatment affect similarly favorable in 17p del

Furman et al, NEJM 2014
Role of Transplant?

- Non-relapse mortality associated with conventional myeloablative allotransplant is high for patients with CLL, partly due to age/fitness/comorbidities.
- Graft vs. leukemia effect appears to play a more important role than conditioning intensity in control of MRD in CLL.
- Now most of focus is on reduced-intensity or nonmyeloablative conditioning regimens.
  - But can these be used for long term disease control?
- Sorror et al reported 5 yr FU up 82 patients with fludarabine-refractory CLL conditioned with 2Gy TBI alone or with fludarabine followed by related (52) or unrelated (30) donor transplant.
  - Median age 56, at time of HCT: 37% in a PR, 45% refractory, 11% untreated relapsed, 5% CR.
Nonmyeloablative 5-year Follow up

Outcomes:
CR and PR: 55% and 15% of patients, respectively. Higher CR rates were noted after unrelated HCT (67% v 48%)
5-year incidences of NRM 23%
Progression/relapse 38%, OS 50%, PFS 39%
Among 25 patients initially reported in CR: 8% relapsed and 8% died as a result of NRM, 84% have remained alive and in CR

GVHD:
5-year cumulative incidences of chronic GVHD were 49% for related and 53% for unrelated
5-year prevalence of patients were alive after discontinuation of all immunosuppressive medications was 38%
The median duration of treatment for chronic GVHD was 25 months

Sorror et al, JCO 2008
Impact of Prognostic Factors

Multiple factors analyzed for impact on NRM, OS and PFS
- Not associated: age, cytogenetic risk, disease status
- Lymphadenopathy >5cm at time of HCT strongly predicted increased risk of relapse and predicted PFS, OS
- HCT-CI score independently predicted risk of relapse, OS, and PFS
- Risk of relapse and PFS similar in those with refractory disease CR/PR
Current Role of Transplant?

- Used for those with relapsed CLL with poor risk features
  - Primary refractory disease
  - Relapse within 12 months following purine analog therapy
  - Patients with a TPp53 mutation/17pdeletion requiring treatment

(Dreger P et al, EBMT Guidelines)
Adoptive T-Cell Therapy

- Treatment with autologous T-cells expressing anti-CD19 chimeric antigen receptor (CART19)
- Porter et al.: initial case report demonstrating feasibility in 2011 (NEJM)
  - Took autologous T cell from the patient (17p del) and transduced with lentivirus to express the CD19-specific CAR linked to a 4-1BB (CD137) intracellular signaling domain
  - Treated pt. with pentostatin and cyclophosphamide and reinfused → obtained MRDneg CR at 10 month FU
  - CART19 cells persisted for 6 months, T1/2 = 34 days
CAR T-Cells in CLL: Early but Promising

- Porter et al. (2015): treated 14 pts with R/R CLL
  - Median FU 19 months
- ORR = 8/14 or 57% with 4 CR and 4 PR
- CAR T-cells persisted and remained functional >4 years in first two CRs
- No patient in CR has relapsed, all MRD negative
  - Response durations range from 21-53 months
  - 1 has died of infection
- All patients with CR experience cytokine-release syndrome and B-cell aplasia
- Could not identify any pretreatment demographic or disease-specific factors that predicted response
# Ongoing/Upcoming trials for Frontline

### Ongoing or planned phase 3 trials in the first-line setting for CLL

<table>
<thead>
<tr>
<th>Trial name</th>
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<th>Patient population</th>
<th>Trial design</th>
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<tbody>
<tr>
<td>RESONATE-2</td>
<td>NCT01722487</td>
<td>≥65 y; no del(17p)</td>
<td>Ibrutinib vs chlorambucil</td>
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<td>PCYC-1130-CA</td>
<td>NCT02264574</td>
<td>≥18 y</td>
<td>Ibrutinib/obinutuzumab vs chlorambucil/obinutuzumab</td>
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<td>18-70 y; no del(17p)</td>
<td>IR vs FCR</td>
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<td>UK NCRI CLL10</td>
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<td>IR vs FCR</td>
</tr>
<tr>
<td>ALLIANCE A041202</td>
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<td>≥65 y</td>
<td>Ibrutinib vs IR vs BR</td>
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<tr>
<td>GS-US-312-0118</td>
<td>NCT01980875</td>
<td>≥18 y</td>
<td>Idelalisib/obinutuzumab vs chlorambucil/obinutuzumab</td>
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<tr>
<td>GS-US-312-0123</td>
<td>NCT01980888</td>
<td>≥18 y</td>
<td>BR ± idelalisib</td>
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</tbody>
</table>

IR, ibrutinib and rituximab; NCRI, National Cancer Research Institute.

Jain et al, Blood 2015
Open Questions

- How to combine B-cell receptor targeted therapies with chemotherapy or immunotherapy
- Should BCR-targeted therapies move to frontline in younger patients without del(17p)?
- Role of transplant?
  - Are newer agents active enough to in poor-risk patients that the need for transplant is negated or pushed down treatment algorithm?
  - If transplant is reserved for those that fail newer agents, will outcomes be compromised?
- Role of CAR T-cell therapy?
<table>
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<th>References</th>
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Thank you!

- Thanks to Dr. Maloney for joining as the discussant