How I Treat CLL in 2019

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The James

THE OHIO STATE UNIVERSITY
COMPREHENSIVE CANCER CENTER
Objectives

• To briefly discuss risk stratification in CLL and criteria to initiate therapy

• To discuss frontline therapy for CLL
  - Where we have come from
  - Where are we now
  - Where are we going
Treatment Indications

- Marrow failure (progressive, hgb <10, plt <100k)
- Massive (≥6 cm below costal margin), symptomatic, or progressive splenomegaly
- Massive (≥10 cm), symptomatic, or progressive lymphadenopathy
- Progressive lymphocytosis (doubling time <6 months)
- Autoimmune cytopenias NOT responding to other treatment
- Organ threatening disease
- Constitutional Symptoms

Hallek at al, Blood 2018
Pre-Therapy Testing

- Disease evaluation
  - CT scans can be considered
  - Bone marrow biopsy—especially if cytopenias present

- Molecular/genomic testing
  - IGVH mutational status
  - FISH-del13q, del17p, del11q, trisomy 12
    - Stimulated karyotype can be considered
  - TP53 mutation
Where have we come from?
FCR is the Gold Standard—CLL8 Study

At 5.9 years
- Median PFS 56.8 mo vs 32.9 mo
- Median OS NR vs 86 mo

Fischer et al, Blood 2016
BR is inferior to FCR (except in older patients) CLL10 Trial

- Randomized untreated fit patients without del17p to FCR or BR
- PFS was shorter for BR vs FCR (41.7 vs 55.2, p=0.0003), except for those age 65 and older

Eichhorst et al., Lancet Hematology 2016
Long-Term FCR Data

- Two studies showing a plateau in relapse in IGHV mutated patients
- FISH panel data not available

What Do These Data Tell Us?

- Chemoimmunotherapy is superior to chemotherapy, establishing rituximab as an integral component of CLL treatment
- FCR might cure some patients, but not without cost

Thompson et al, Blood 2016
Where are we now?
Ibrutinib in Treatment-Naïve Patients (n=31)

- ORR 89% (95% CI: 81.3-94.4)
- CR rate 29% (R/R =10%)
- Median PFS not reached
- Estimated 5-year PFS is 92%
- 55% remain on treatment

O'Brien et al., Blood 2018
Ibrutinib in Treatment-Naïve CLL: RESONATE 2

- Randomized untreated patients ≥65 to ibrutinib or chlorambucil (0.5 mg/kg D1 and D15 x12 cycles)
- Median follow-up 18.4 months
- 84% lower risk of progression or death with ibrutinib
- 89% of patients progression-free at 2 years

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ECOG 1912 Study Design

Arm A – Ibrutinib + Rituximab
Cycles 1:
Ibrutinib 420 mg PO daily, days 1-28
Cycle 2:
Ibrutinib 420 mg PO daily, days 1-28
Rituximab 50 mg/m² IV, day 1
Rituximab 325 mg/m² IV, day 2
Cycles 3-7:
Ibrutinib 420 mg PO daily, days 1-28
Rituximab 500 mg/m² IV, day 1

Cycle 8 until progression:
Ibrutinib 420 mg PO daily, days 1-28

Arm B - FCR
Cycles 1-6:
Fludarabine 25 mg/m² IV, days 1-3
Cyclophosphamide 250 mg/m² IV, days 1-3
Cycle 1:
Rituximab 50 mg/m² IV, day 1, cycle 1
Rituximab 325 mg/m² IV, day 2, cycle 1
Cycle 2-6:
Rituximab 500 mg/m² IV, day 1, cycles 2-6

E1912
Eligibility:
- Previously untreated CLL
- Requires treatment (IWCLL 2008)
- Age < 70
- ECOG 0-2
- CrCl>40
- Able to tolerate FCR
- No deletion 17p by FISH

Planned Accrual: 519
529 total accrual

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Shanafelt, et al. LBA 4 ASH 2018
## E1912 Patient Characteristics

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>IR n=354</th>
<th>FCR n=175</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (y)</td>
<td>58</td>
<td>57</td>
<td>58</td>
</tr>
<tr>
<td>Age &gt; 60</td>
<td>41.0%</td>
<td>40.0%</td>
<td>40.6%</td>
</tr>
<tr>
<td>Female</td>
<td>33.3%</td>
<td>31.4%</td>
<td>32.7%</td>
</tr>
<tr>
<td>ECOG = 0</td>
<td>63.8%</td>
<td>62.3%</td>
<td>63.3%</td>
</tr>
<tr>
<td>Rai stage 0</td>
<td>3.1%</td>
<td>5.1%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Rai stage I-II</td>
<td>52.8%</td>
<td>53.7%</td>
<td>53.1%</td>
</tr>
<tr>
<td>Rai stage III-IV</td>
<td>44.1%</td>
<td>41.1%</td>
<td>43.1%</td>
</tr>
<tr>
<td>FISH 11q deletion</td>
<td>22.0%</td>
<td>22.3%</td>
<td>22.2%</td>
</tr>
<tr>
<td>Trisomy 12</td>
<td>19.8%</td>
<td>15.4%</td>
<td>18.3%</td>
</tr>
<tr>
<td>13q deletion</td>
<td>34.2%</td>
<td>33.1%</td>
<td>33.8</td>
</tr>
<tr>
<td>B2M &gt;3.5 mg/L</td>
<td>51.9%</td>
<td>48.0%</td>
<td>50.6%</td>
</tr>
<tr>
<td>IGHV Unmutated*</td>
<td>75.0%</td>
<td>61.7%</td>
<td>71.1%</td>
</tr>
</tbody>
</table>

*Tested in 437 (82%) patients

Shanafelt, et al. LBA 4 ASH 2018
E1912 Progression Free Survival

Intent to Treat

HR = 0.35 (95% CI 0.22-0.5)
One sided p<0.00001

Eligible

HR = 0.32 (95% CI 0.20-0.51)
One sided p<0.00001

Shanafelt, et al. LBA 4 ASH 2018
E1912 Overall Survival

Intent to Treat

HR = 0.17 (95% CI 0.05-0.54)
One sided p<0.0003

Eligible

HR = 0.13 (95% CI 0.03-0.46)
One sided p<0.0001

Shanafelt, et al. LBA 4 ASH 2018
E1912 Grade 3-5 Treatment Related Adverse Events Throughout Observation

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>IR (%)</th>
<th>FCR (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>22.7%</td>
<td>43.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anemia</td>
<td>2.6%</td>
<td>12.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2.9%</td>
<td>13.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any Infection</td>
<td>7.1%</td>
<td>19.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Infection</td>
<td>5.4%</td>
<td>8.2%</td>
<td>0.24</td>
</tr>
<tr>
<td>Neutropenic fever</td>
<td>2.3%</td>
<td>15.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2.9%</td>
<td>0.0%</td>
<td>0.04</td>
</tr>
<tr>
<td>Bleeding</td>
<td>1.1%</td>
<td>0.0%</td>
<td>0.32</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7.4%</td>
<td>1.9%</td>
<td>0.01</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2.6%</td>
<td>0.6%</td>
<td>0.19</td>
</tr>
<tr>
<td>Any Grade 3 or higher AE</td>
<td>58.5%</td>
<td>72.1%</td>
<td>P=0.004</td>
</tr>
</tbody>
</table>
Untreated patients age ≥ 65 who meet IWCLL criteria for CLL treatment

Stratify:
- High risk vs intermediate risk Rai Stage
- Presence vs absence of del(11q22.3) or del(17p13.1) on FISH performed locally
- < 20% vs ≥ 20% Zap-70 methylation of CpG 3 performed centrally

Bendamustine 90mg/m2 days 1&2 of each 28 day cycle + Rituximab 375 mg/m2 day 0 cycle 1, then 500 mg/m2 day 1 cycles 2-6

Ibrutinib 420mg daily until disease progression

Ibrutinib 420mg daily until disease progression + Rituximab 375 mg/m2 weekly for 4 weeks starting cycle 2 day 1, then day 1 of cycles 3-6

Documented Progression

Planned accrual: 498
Total accrual 547
## Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total N=547</th>
<th>BR N=183</th>
<th>Ibrutinib N=182</th>
<th>IR N=182</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years), median (range)</strong></td>
<td>71 (65-89)</td>
<td>70 (65-86)</td>
<td>71 (65-89)</td>
<td>71 (65-86)</td>
</tr>
<tr>
<td><strong>Male, %</strong></td>
<td>67</td>
<td>65</td>
<td>68</td>
<td>69</td>
</tr>
<tr>
<td><strong>ECOG 0-1, %</strong></td>
<td>97</td>
<td>95</td>
<td>97</td>
<td>99</td>
</tr>
<tr>
<td><strong>White blood cell count x10^3/µL, median (range)</strong></td>
<td>82 (4-518)</td>
<td>92 (7-518)</td>
<td>79 (6-438)</td>
<td>70 (4-481)</td>
</tr>
<tr>
<td><strong>FISH Characteristics, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Del (17p)</td>
<td>6</td>
<td>8</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Del (11q)</td>
<td>19</td>
<td>18</td>
<td>19</td>
<td>21</td>
</tr>
<tr>
<td>TP53 mutation, %</td>
<td>10</td>
<td>9</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Complex Karyotype, %</td>
<td>29</td>
<td>27</td>
<td>24</td>
<td>36</td>
</tr>
<tr>
<td>Zap-70 Unmethylated, %</td>
<td>53</td>
<td>52</td>
<td>53</td>
<td>53</td>
</tr>
<tr>
<td>IGVH unmutated*, %</td>
<td>61</td>
<td>58</td>
<td>63</td>
<td>61</td>
</tr>
</tbody>
</table>

* N= 360 total

Woyach et al, NEJM 2019
Primary Endpoint: Progression Free Survival
Eligible Patient Population

Pairwise Comparisons

I vs BR:
Hazard Ratio 0.39
95% CI: 0.26-0.58
(1-sided P-value <0.001)

IR vs BR:
Hazard Ratio 0.38
95% CI: 0.25-0.59
(1-sided P-value <0.001)

IR vs I:
Hazard Ratio 1.00
95% CI: 0.62-1.62
(1-sided P-value 0.49)

<table>
<thead>
<tr>
<th>Arm</th>
<th>N</th>
<th>24 Month Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>BR</td>
<td>176</td>
<td>74% (95% CI: 66-80%)</td>
</tr>
<tr>
<td>I</td>
<td>178</td>
<td>87% (95% CI: 81-92%)</td>
</tr>
<tr>
<td>IR</td>
<td>170</td>
<td>88% (95% CI: 81-92%)</td>
</tr>
</tbody>
</table>

Patients-at-Risk

<table>
<thead>
<tr>
<th>Patients-at-Risk</th>
<th>176</th>
<th>140</th>
<th>129</th>
<th>122</th>
<th>103</th>
<th>88</th>
<th>57</th>
<th>26</th>
<th>11</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>176</td>
<td>178</td>
<td>165</td>
<td>154</td>
<td>147</td>
<td>136</td>
<td>120</td>
<td>78</td>
<td>45</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>170</td>
<td>159</td>
<td>145</td>
<td>138</td>
<td>132</td>
<td>115</td>
<td>74</td>
<td>40</td>
<td>20</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Woyach et al, NEJM 2019
Overall Survival
Intention-to-Treat Patient Population

<table>
<thead>
<tr>
<th>Arm</th>
<th>N</th>
<th>24 Month Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>BR</td>
<td>183</td>
<td>95% (95% CI: 91-98%)</td>
</tr>
<tr>
<td>I</td>
<td>183</td>
<td>90% (95% CI: 85-94%)</td>
</tr>
<tr>
<td>IR</td>
<td>182</td>
<td>94% (95% CI: 89-97%)</td>
</tr>
</tbody>
</table>

Median Follow-up: 38 months

Woyach et al, NEJM 2019
Grade 3, 4, or 5 Adverse Events During treatment or follow-up (excluding crossover)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Ibrutinib</th>
<th>IR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Hematologic</td>
<td>107 (61)</td>
<td>74 (41)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anemia</td>
<td>22 (13)</td>
<td>21 (12)</td>
<td>0.09</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>71 (40)</td>
<td>27 (15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>26 (15)</td>
<td>12 (7)</td>
<td>0.008</td>
</tr>
<tr>
<td>All Non-hematologic</td>
<td>111 (63)</td>
<td>133 (74)</td>
<td>0.04</td>
</tr>
<tr>
<td>Bleeding</td>
<td>0 (0)</td>
<td>3 (2)</td>
<td>0.46</td>
</tr>
<tr>
<td>Infections</td>
<td>26 (15)</td>
<td>37 (21)</td>
<td>0.62</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>13 (7)</td>
<td>3 (2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>5 (3)</td>
<td>17 (9)</td>
<td>0.05</td>
</tr>
<tr>
<td>Hypertension</td>
<td>25 (14)</td>
<td>53 (29)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Unexplained/unwitnessed death</td>
<td>2 (1)</td>
<td>7 (4)</td>
<td>0.24</td>
</tr>
</tbody>
</table>

What Do These Data Tell Us?

- Ibrutinib is more effective than chemoimmunotherapy in the treatment of CLL
- Ibrutinib may be more toxic in older patients than in younger
- The addition of rituximab to ibrutinib does not improve PFS

Deaths:
- Deaths during active treatment + 30 days: 2 (1%), 13 (7%), 13 (7%)
- Deaths during active treatment + 30 days, up to 6 cycles: 2 (1%), 3 (2%), 6 (3%)

Woyach et al, NEJM 2019
Where are we going?
What are the ongoing questions in frontline CLL?

- Should anyone still be treated with chemoimmunotherapy?

- Can we improve on the efficacy and safety of ibrutinib by combination, time-limited therapy?

- Can we improve the safety of ibrutinib by using a different BTKi?
Should anyone still be treated with chemoimmunotherapy?

- Young, fit, IGHV mutated patients may be cured with FCR
  - Long-term follow up from ECOG study will help
  - Current trials of abbreviated FCR with targeted therapy might have a role

- Unfit patients with good risk disease may benefit from chlorambucil/obinutuzumab
Can we improve on the efficacy and safety of ibrutinib through combination, time-limited therapy?

Study Diagram

- **Obinutuzumab 1000 mg IV**
- **Ibrutinib 420 mg daily PO**
- **Venetoclax 400 mg daily PO**

*Ibrutinib continued past C14 at the discretion of the investigator

*Dose ramp-up over 5 weeks: 20mg, 50mg, 100mg, 200mg, 400mg

**Mid-Therapy**

- **Response assessed**
  - CT Scans
  - Bone Marrow Biopsy
  - Minimal Residual Disease

**End of Treatment**

Cycle length = 28 days

Rogers et al, ASH 2018
Obinutuzumab plus Venetoclax plus Ibrutinib

- 50 total patients
- Mid-Therapy Responses:
  - TN: 8 CR/CRi, 16 PR
  - RR: 6 CR/CRi, 17 PR
- End of Treatment Responses:
  - TN: 8 CR/CRi, 13 PR
  - RR: 11 CR/CRi, 11 PR
- Rate of MRD (-) CR:
  - TN: 28% (95% CI: 12-49%)
  - RR: 28% (95% CI: 12-49%)

Rogers et al, ASH 2018
A041702: Randomized phase 3 study of first-line ibrutinib/obinutuzumab vs ibrutinib/venetoclax/obinutuzumab in patients ≥70

- Primary objective is to compare the PFS
- Eligibility:
  - CLL/SLL with no prior treatments
  - Indication for treatment
  - Age ≥70
EA9161: Randomized phase 3 study of venetoclax + ibrutinib/obinutuzumab vs ibrutinib/obinutuzumab in untreated younger patients with CLL

- **Primary objective** is to compare the PFS
- **Eligibility:**
  - CLL/SLL with no prior treatments
  - Indication for treatment
  - Age ≥18 and <70
  - No deletion 17p13

Accrual = 720
Cycle length = 28 days

1. For patients on Arm B who complete 19 cycles of study treatment, ibrutinib should be continued at a rate of 420mg PO once daily under observation until disease progression
Can we Improve Safety by Using a Different BTK inhibitor?

- Acalabrutinib is more selective for BTK with less off-target kinase inhibition compared with ibrutinib in vitro

### Kinase Inhibition Average IC$_{50}$ (nM)

<table>
<thead>
<tr>
<th>Kinase</th>
<th>Acalabrutinib</th>
<th>Ibrutinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>BTK</td>
<td>5.1</td>
<td>1.5</td>
</tr>
<tr>
<td>TEC</td>
<td>126.0</td>
<td>10</td>
</tr>
<tr>
<td>ITK</td>
<td>&gt;1000</td>
<td>4.9</td>
</tr>
<tr>
<td>BMX</td>
<td>46</td>
<td>0.8</td>
</tr>
<tr>
<td>TXK</td>
<td>368</td>
<td>2.0</td>
</tr>
<tr>
<td>EGFR</td>
<td>&gt;1000</td>
<td>5.3</td>
</tr>
<tr>
<td>ERBB2</td>
<td>~1000</td>
<td>6.4</td>
</tr>
<tr>
<td>ERBB4</td>
<td>16</td>
<td>3.4</td>
</tr>
<tr>
<td>BLK</td>
<td>&gt;1000</td>
<td>0.1</td>
</tr>
<tr>
<td>JAK3</td>
<td>&gt;1000</td>
<td>32</td>
</tr>
</tbody>
</table>

Larger red circles represent stronger inhibition
Phase 1b/2 study Acalabrutinib in TN CLL

- At the median time on study of 42 months, 89% of patients remain on study treatment

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N=99</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time on study, median (range), mo</td>
<td>42 (1-48)</td>
</tr>
<tr>
<td>Remain on acalabrutinib, n (%)</td>
<td>88 (89)</td>
</tr>
<tr>
<td>Discontinued acalabrutinib, n (%)</td>
<td>11 (11)</td>
</tr>
<tr>
<td>Disease progressiona</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Adverse eventb</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Withdrawal of consent</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Otherc</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

- a Richter transformation occurred in 1 patient.
- b Adverse events leading to discontinuation were secondary malignancies (angiosarcoma, glioblastoma multiforme, small cell lung cancer; 1 patient each), sepsis (Grade 4; 1 patient) and urinary tract infection (Grade 3; 1 patient)
- c Initiation of subsequent cancer therapy (venetoclax).
Acalabrutinib Most Common Adverse Events

- Nasal congestion
- Fall
- Constipation
- Rash
- Hypertension
- Ecchymosis
- Back pain
- URTI
- Headache
- Cough
- Weight increased
- Arthralgia
- Petechiae
- Sinusitis
- Vomiting
- Fatigue
- Syncope and sepsis
- Neutropenia
- Pneumonia

Additional Grade 3/4 AEs observed in >2% of patients include neutropenia (n=8), pneumonia (n=4), and syncope and sepsis (n=3 each)

Byrd et al, ASH 2018
Adverse Events of Special Interest

What Do These Data Tell Us?

- Atrial Fibrillation in 6%
- Bruising was common, but significant bleeding was not
  - Contusion 39%, Petechiae 18%, Ecchymosis 16%
  - Grade 3 bleeding in 3%
- Hypertension in 17%, 7% grade 3
- Infections in 83%, 14% grade 3/4

Long-term follow-up of E1912 will be critical to determine how best to manage young IGHV mutated patients.

Combinations of targeted therapies appear promising, and new intergroup studies will allow the opportunity to determine whether they are better than ibrutinib.

Acalabrutinib may be more tolerable than ibrutinib, but head to head comparison will be helpful.
Conclusions

- Ibrutinib has changed the paradigm of CLL therapy, and many patients with CLL will never receive chemotherapy.

- Although our current treatments are effective, there remain areas in need of improvement.

- Prospective clinical trials remain extremely important to help determine the optimal frontline treatments for our patients with CLL.