Ibrutinib in the Treatment of CLL

10th Canadian CLL Research Meeting

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Outline

- Single Agent Efficacy
- Single Agent Tumor Reduction
- Comparisons and Combination Treatment
- Resistance
- Safety and Tolerability
B Cell Receptor (BCR) Signaling

Ibrutinib (PCI-32765)

Wiestner, JCO 2013
Ibrutinib

- Discovered by Dr. Zhengying Pan
  - Celera Genomics

- Compound acquired by Pharmacyclics® in 2007

- Covalently binds to Cys481 on BTK

- Half life of ~ 3 hours, rapidly absorbed
  - Orally available

- Activity in multiple lymphomas

Advani et al, JCO 2013
Single Agent Ibrutinib

Class Effect: Lymphocytosis
Improved Response Over Time

ORR: 71%

2 Complete Responses

Byrd et al, NEJM 2013
Progression Free Survival

26 Month PFS: 75%

Byrd et al, NEJM 2013
NIH Experience

NHLBI Protocol 12-H-0035: NCT01500733 (Closed to Accrual)
Treatment Naïve (TN) and Relapsed/Refractory (RR) patients were eligible

Ibrutinib 420 mg daily (28 day cycles)

Cohort 1: NO 17p DEL (> 65 yo)
Cohort 2: 17p DEL

Farooqui et al, ASH 2013
Limitations of Chemoimmunotherapy

Overall Survival (%)

Del 17p

Less tolerable in elderly patients

Hallek, et al, Lancet 2010
Demographics

<table>
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<tr>
<th></th>
<th>NO 17p DEL</th>
<th>17p DEL</th>
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<tbody>
<tr>
<td>Total Patients (TN)</td>
<td>24 (8)</td>
<td>29 (15)</td>
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<tr>
<td>Median Age</td>
<td>69</td>
<td>62</td>
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<tr>
<td>Rai Stage III/IV</td>
<td>75%</td>
<td>66%</td>
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<tr>
<td>Bulky Disease</td>
<td>46%</td>
<td>41%</td>
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<td>Splenomegaly</td>
<td>71%</td>
<td>82%</td>
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- Evaluable at 6 Mo: 48 patients
  - 2 Unrelated Deaths (Infection)
  - 3 Unrelated Secondary Malignancies
    - 1 Lung Cancer, 2 Hodgkin’s Disease
Response at 6 Months

NO 17p DEL

- 82%
- 9%
- 9%

17p DEL

- 43%
- 53%
- 4%

Median F/U: 13.7 Mo

Median F/U: 14.4 Mo

PRL: Partial Response with Lymphocytosis

Farooqui et al, ASH 2013
Progression Free Survival

- 100%
- 85%

NO 17p DEL
17p DEL

Farooqui et al, ASH 2013
FDA Approval

FDA NEWS RELEASE
For Immediate Release: Feb. 12, 2014
Media Inquiries: Tara Goodin, 240-402-3167, tara.goodin@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA

FDA approves Imbruvica to treat chronic lymphocytic leukemia

FDA expands approved use of Imbruvica for chronic lymphocytic leukemia

Relapsed/Refractory: February 12, 2014

Treatment Naïve 17p: July 28, 2014
SUGGESTED TREATMENT REGIMENS
(in order of preference)

CLL without del (11q) or del (17p)
- Relapsed/Refractory therapy
  - Ibrutinib
- Chemotherapy
  - Reduced-dose FCR
e
  - Reduced-dose PCR
  - Bendamustine ± rituximab
  - High-dose methylprednisolone (HDM) + rituximab
  - Rituximab + chlorambucil
  - Ofatumumab
  - Lenalidomide ± rituximab
  - Alemtuzumab ± rituximab
  - Dose-dense rituximab (category 2B)

- Short response for age <70 y or older patients without significant comorbidities (repeating therapy used in immediate prior line not recommended)
  - Ibrutinib
  - Chemotherapy
    - FCR
e
    - PCR
    - Bendamustine ± rituximab
    - Fludarabine ± alemtuzumab
    - RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)
    - OFAR (oxaliplatin, fludarabine, cytarabine, rituximab)
    - Ofatumumab
    - Lenalidomide ± rituximab
    - Alemtuzumab ± rituximab
    - HDMP + rituximab

- Long response
  - Retreat as in first-line therapy until short response

See Supportive Care for Patients with CLL (CLL-C)
Consider prophylaxis for tumor lysis syndrome (See NHODG-B)
See monoclonal antibody and viral reactivation (NHODG-B)
Single Agent Tumor Reduction
Redistribution Lymphocytosis

Blood

Lymph node

chemokines

Kinase Inhibitor

CLL

Kinase

Kinase

integrins

BCR
Lymphocytosis

NO 17p DEL

17p DEL

Median with interquartile range

Farooqui, ASH 2013
Variability in Lymphocytosis

> 40% have a peak ALC on Day 2

Cluster 1: Highest ALC
   - Rai Stage III/IV

Cluster 3: Lowest ALC
   - IGHV Mutated
   - Bulky LAD

Herman, Niemann, Farooqui et al, *Leukemia* 2014
Persistent lymphocytosis does not worsen outcome.

Woyach et al, Blood 2014
Lymph Node Response (SPD)

**NO 17p DEL**

- Median Reduction: 75%

**17p DEL**

- Median Reduction: 70%

Farooqui et al, ASH 2013
Lymph Node Volume
Change in Splenic Volume

NO 17p DEL
Median Reduction: 40%

17p DEL
Median Reduction: 46%

Farooqui et al, ASH 2013
Spleen Volume
Bone Marrow Response

NO 17p DEL

-100
-80
-60
-40
-20
0
% Reduction

Median: 76%

17p DEL

0
-20
-40
-60
-80
-100
% Reduction

Median: 84%

CD79a

Pre

Post

Farooqui et al, ASH 2013
Bone Marrow Responses Seen at 2 Months
Total Tumor Burden

Herman, Niemann, Farooqui et al, *Leukemia* 2014
Cytogenetic Response of DEL 17p in CLL

Resolved (All patients *IGHV* Mutated) 22%

Increase 11%

Decrease 67%

All patients demonstrated a response at 6 months.

Farooqui et al, ASH Abstract 2013
Single Agent PFS at 3 years

<table>
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<tr>
<th>Del17p</th>
<th>Del11q</th>
<th>No del17p/11q</th>
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<tr>
<td>30-month PFS</td>
<td>45.9%</td>
<td>74.2%</td>
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<tr>
<td>(95% CI)</td>
<td>(25.0-64.6)</td>
<td>(53.3-86.8)</td>
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<tr>
<td>Median PFS</td>
<td>28.1 months</td>
<td>Not reached</td>
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O’Brien et al, ASCO 2014
Ibrutinib in Comparison and Combination
Ibrutinib + Rituximab

- High Risk R/R CLL (17p or 11q)

- N= 40 (39 Eval for Response)

- Responses
  - 95% Overall Response
  - 87% Partial Response
  - 8% Complete Response
  - 5% Did not respond (2 – Mucositis, Infection)

Burger et al, Lancet Oncology 2014
Ibrutinib + Rituximab

A

Weeks

Lymphocyte count (10^9/L)

B

Months

Change in sum of largest diameter of each target lesion from baseline (%)

Burger et al, Lancet Oncology 2014
Ibrutinib + Rituximab

Ibrutinib + Rituximab

18 Mo PFS: 78%

18 Mo PFS No del(17p): 83.8%
18 Mo PFS Del(17p): 78.4%

Ibrutinib vs Ofatumumab

Byrd et al, NEJM 2014
Ibrutinib vs Ofatumumab

Improvement noted along all subgroups.

Byrd et al, *NEJM* 2014
Safety and Tolerability
Viscosity

Herman, Niemann, Farooqui et al, *Leukemia* 2014
Bleeding

- Platelet dysfunction on ibrutinib. Noted bleeding and bruising events.

- Initial studies with SDH. Warfarin shoult not be used.
  - Other anticoagulants?

- No correlation with vWF and PFA (EPI and ADP) (Farooqui et al, ASH 2012)

- Reductions in collagen mediated platelet aggregation noted (Kamel et al, Leukemia 2014)
  - Associated with of clinical bleeding or bruising
Atrial Fibrillation

- Ibrutinib Package Insert
  - Incidence of 6-9%

- Atrial Fibrillation Incidence
  - 5-15% (Heeringa et al, *EHJ* 2006)

- Death on Study
NIH: Non-Hematologic Toxicity

Toxicities reported in > 5% of patients

Farooqui et al, ASH Abstract 2013
NIH: Hematologic Toxicity

- Anemia
- Low PLT
- Low ANC

Farooqui et al, ASH Abstract 2013
Ibrutinib + Rituximab Safety

- Expected Ibrutinib and Rituximab Events

  - Common: respiratory infections (11 grade 2 or 3), diarrhea, fatigue, N/V, arthralgia
  - Bleeding events: Grade 1 or 2
  - Grade ≥3 cytopenias infrequent
  - Other: Mucositis, Peripheral neuropathy, Subdural hematoma, Afib (3%)
Ibrutinib vs Ofatumumab Safety

- Expected Ibrutinib and Ofatumumab events

- Atrial fibrillation (any grade)
  - Ibrutinib: 3%
  - Ofatumumab: 0%

- Bleeding (any grade): Petichiae, Ecchymosis
  - Ibrutinib: 44% (Grade 3 – 3 pts, 1 subdural hematoma)
  - Ofatumumab: 12% (Grade 3 – 2 pts)

- Infections Grade ≥3:
  - Ibrutinib: 24%
  - Ofatumumab: 22%
Immunoglobulins

- IgG: n.s.
- IgA: <0.01
- IgM: <0.01

Infections on ibrutinib:
Decreases > 6 months on therapy

Aue et al, ASH Abstract 2013; Byrd et al, NEJM 2013
Light Chains

Aue et al, ASH 2013

Clonal light chain

Kappa+
CLL
(by flow)

mg/dl

Cycles

Pre 6 12

10

5

Kappa

Lambda+
CLL
(by flow)

mg/dl

Cycles

Pre 6 12

15

10

11

Lambda

Non-Clonal light chain

mg/dl

Cycles

Pre 6 12

2

1

lambda

mg/dl

kappa

mg/dl

kappa

Pre 6 12
Resistance
Mutations

- Progression
  - 24/267 pts (9%)
  - Richter’s: 16 pts (early < 12 mo)
  - PD: 8 pts

- Acquired mutations
  - (3 pts) C481S mutation
  - (2 pts) PLCγ2 mutation
  - (1 pt) C481S and PLCγ2

Woyach et al, ASCO 2014; Woyach et al, NEJM 2014
Disruption in Covalent Bonds

Furman et al, NEJM To the Editor 2014
Ibrutinib as single agent or in combination is effective in treatment of CLL/SLL.

Reduction in disease burden seen in all anatomic compartments.

17p DEL subclone improves during the course of treatment in the majority of patients.

Safety profile is tolerable.

Resistance patterns and immune function remains to be understood.
Future Directions / Questions to be Answered

- Combination to maximize curative intent?
- Chronic suppression of leukemic clone?
- Early intervention in patients?
- What is the role of MRD?
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Our Patients

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