FLT3 inhibitors in AML

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Disclosures- Richard M. Stone, MD

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Brigham and Women’s Hospital

Yawkey Center (Clinic)
FLT3 inhibitors in AML: Outline

- FLT3 inhibitors: background
- FLT3 inhibitors - single agent
- FLT3 inhibitors + chemo
- The Future
Key Points from de novo AML genome atlas

• AML genomes have fewer mutations than most other adult cancers (n=13, 5 of which are among the 23 recurrently mutated genes)

• 9 Key categories:
  – transcription-factor fusions (18%)
  – nucleophosmin (NPM1) (27%)
  – tumor-suppressor genes (16%)
  – DNA-methylation–related genes (44%)
  – signaling genes (59%)
  – chromatin-modifying genes (30%)
  – myeloid transcription-factor genes (22%)
  – cohesin-complex genes (13%)
  – spliceosome-complex genes (14%).

The Cancer Genome Atlas Research Network
Reasons why single agent targeted tx in AML may not be ideal

- Clonal Heterogeneity
  - Need to use chemo to simplify clonal architecture
- Must hit a founder mutation to have a chance
  - We don’t have good drugs yet for founder mutations such as DNMT3, TP53, TET2, ASXL1, EZH2
    - IDH inhibitors a possible emerging exception
- Resistance mechanisms (secondary mutations in target, off target effects, up regulation of ligand- with chemo)
Overexpression is common

25-30%

5-10%

Both mutations cause spontaneous dimerization, ligand independent growth, and MPD in murine model.
Flt3 ITD and relapse

### FLT 3 inhibitors in prior studies

<table>
<thead>
<tr>
<th></th>
<th>IC$_{50}$ (medium)$^a$</th>
<th>IC$_{50}$ (plasma)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lestaurninib</td>
<td>2 nM</td>
<td>700 nM</td>
</tr>
<tr>
<td>Midostaurin</td>
<td>6 nM</td>
<td>~1000 nM</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>3 nM</td>
<td>~265 nM</td>
</tr>
<tr>
<td>Quizartinib</td>
<td>1 nM</td>
<td>18 nM</td>
</tr>
</tbody>
</table>

$a$ - **Molm-14 cells incubated in RPMI/10% FBS**  
Human kinome image generated using TREEmap software tool and reprinted with permission from KINOMEScan™, a division of DiscoveRx Co.

$b$ - **Molm-14 cells incubated in plasma**
Background

- Midostaurin (PKC412; N-benzoylstaurosporine) is a potent FLT3 (both ITD and TKD) inhibitor (IC$_{50}$ <10 nM) (also inhibits VEGFR, PKC, KIT, and PDGFR)$^{1,2}$

- Midostaurin specifically inhibits growth of leukemic cell lines made factor independent by transfection of activating FLT3 mutation (ITD or D835Y)$^2$

- Midostaurin increased survival in a murine BMT model of FLT3 ITD myeloproliferative disorder $^3$

Phase II Trial of PKC412: Clinical Activity (75 mg po TID)

- >50% reduction in BM blasts: 5/20 (25%)
  - 2 patients with <5% blasts; 1 on D 28, 1 on D 60*
- >50% reduction in PB blasts: 14/20 (70%)
- 7 (35%) with clinical benefit:

<table>
<thead>
<tr>
<th>Baseline PB blasts</th>
<th>110K</th>
<th>65K</th>
<th>21K</th>
<th>5K</th>
<th>16K</th>
<th>71K</th>
<th>46K</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best response</td>
<td>0, D 29</td>
<td>.06K, D 42</td>
<td>0, D 50</td>
<td>0.1K, D 22</td>
<td>0, D 15</td>
<td>0, D 57</td>
<td>0, D 51</td>
</tr>
</tbody>
</table>

- Comparable results with imatinib with CML-blast crisis
  - 31% HEME RESPONSE (8% CR, 18% RTC, 4% NEL

Stone et al, Blood, 2005
Study 2104: Single Agent Midostaurin Induces Blast Reduction But Not CR

<table>
<thead>
<tr>
<th>Response</th>
<th>75 mg TID FLT3mut n=20</th>
<th>50 or 100 mg BID FLT3mut n=35</th>
<th>50 or 100 mg BID FLT3wt n=57</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>0/20</td>
<td>0/35</td>
<td>0/57</td>
</tr>
<tr>
<td>Partial response</td>
<td>1/20</td>
<td>1/35</td>
<td>0/57</td>
</tr>
<tr>
<td>50% PB blast or BM reduction</td>
<td>14/20 (70%)</td>
<td>25/35 (71%)</td>
<td>24/57 (42%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[67% for 50 mg BID &amp; 76% for 100 mg BID]</td>
<td>[50% for 50 mg BID &amp; 33% for 100 mg BID]</td>
</tr>
</tbody>
</table>

Generally well tolerated

- Nausea/vomiting, diarrhea, and fatigue
- < 10% of patients experienced grade 2 or grade 3 events at doses ≤ 100 mg/day
- Hematologic toxicity was uncommon

Fischer et al, *JCO*, 2010
Phase 2 of Quizartinib in AML: Response to Quizartinib; Cohort 1

- 70% of FLT3-ITD(+) and 55% of FLT3-ITD(-) patients refractory to last prior therapy achieved at least a PR
- Median CRc duration: 10.4 wks for FLT3-ITD(+), 9.3 wks for FLT3-ITD(-)

Cortes et al (Abst 48), ASH 2012
Clinical Response to Gilteritinib Treatment by *FLT3* Mutation or TKI Status

<table>
<thead>
<tr>
<th>Clinical Response</th>
<th>Mutation Type</th>
<th>TKI Status</th>
<th>≥80 mg Gilteritinib</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>FLT3</em>-ITD</td>
<td><em>FLT3</em>-D835</td>
<td>ITD and D835</td>
</tr>
<tr>
<td>N = 142</td>
<td>only</td>
<td>only</td>
<td>only</td>
</tr>
<tr>
<td>CR</td>
<td>16 (11)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>11 (8)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CRi</td>
<td>38 (27)</td>
<td>1 (9)</td>
<td>4 (44)</td>
</tr>
<tr>
<td>PR</td>
<td>15 (11)</td>
<td>2 (18)</td>
<td>0</td>
</tr>
<tr>
<td>CRc (CR+CRp+CRi)</td>
<td>65 (46)</td>
<td>1 (9)</td>
<td>4 (44)</td>
</tr>
<tr>
<td>ORR (CRc+PR)</td>
<td>80 (56)</td>
<td>3 (27)</td>
<td>4 (44)</td>
</tr>
<tr>
<td>Prior TKI</td>
<td>N = 40</td>
<td></td>
<td>14 (35)</td>
</tr>
<tr>
<td>TKI Naïve</td>
<td>N = 127</td>
<td></td>
<td>57 (45)</td>
</tr>
</tbody>
</table>

Data presented as n (%).

CR, complete remission; CRc, composite complete remission; CRi, complete remission with incomplete hematologic recovery; CRp, complete remission with incomplete platelet recovery; ITD, internal tandem duplication; ORR, overall response rate; PR, partial response.

midostaurin, crenolanib also 'hit' ITD and tyrosine kinase domain (TKD); quizartinib potent ITD inhibitor


**TKI Naïve - No MDS**
- Total evaluable patients: 18
- CR/CRi: 7 (39%)
- PR: 2 (11%)
- ORR (CR+PR): 9 (50%)
- Blast Response: 7 (39%)
- Clinical Benefit (CR +PR+HI): 16 (89%)
- RD: 2 (11%)

**TKI Treated - No MDS**
- Total evaluable patients: 36
- CRi: 6 (17%)
- PR: 5 (14%)
- ORR (CR+PR): 11 (31%)
- Blast Response: 14 (39%)
- Clinical Benefit (CR +PR+HI): 25 (69%)
- RD: 11 (31%)
Ongoing single agent phase III trials

- Quizartinib v dealer’s choice chemo (including ‘low’ and high dose) in FLT3ITD relapsed AML, less than 6 month disease-free interval
- Gilteritinib v dealer’s choice chemo (including ‘low’ and high dose) in FLT3ITD and or TKD relapsed AML
A Cautionary Tale – CEP701 (Lestaurtinib)

- Originally developed as inhibitor of neurotrophic tyrosine kinase receptor 1
- Potent Flt3 ITD autophosphorylation inhibitor – IC50 (nM) 1.5
- Well-tolerated with modest responses as single agent in phase II trials (Smith, Blood 2004)
- Phase III trial with 224 Flt3 mutant AML patients in first relapse randomized to chemo alone or chemo + lestaurtinib, primary endpoint ➔ CR
Cephalon 204: Trial Design

- AML in first relapse with FLT3 mutation

**Randomization**
- Control: MEC or HiDAC
- Lestaurtinib: MEC or HiDAC

- Lestaurtinib 80 mg po BID

**Primary Outcome:** CR
**Secondary outcome:** Survival

Control patients eligible for crossover
Levis et al Blood 2012

**CEP 204: Results**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Chemotherapy only</th>
<th>Chemotherapy + Lestaurnitinib</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total CRp (%)</td>
<td>10 (9%)</td>
<td>10 (9%)</td>
<td>1.00</td>
</tr>
<tr>
<td>CR (%)</td>
<td>13 (12%)</td>
<td>19 (17%)</td>
<td>0.25</td>
</tr>
<tr>
<td>Total CRp (%)</td>
<td>23 (21%)</td>
<td>29 (26%)</td>
<td>0.35</td>
</tr>
<tr>
<td>1st remission 1-6 months, CRp (%)</td>
<td>6 (11%)</td>
<td>10 (19%)</td>
<td>0.42</td>
</tr>
<tr>
<td>1st remission &gt; 6 months, CRp (%)</td>
<td>17 (29%)</td>
<td>19 (32%)</td>
<td>0.84</td>
</tr>
<tr>
<td>&lt; 50 years of age, CRp (%)</td>
<td>4 (12%)</td>
<td>9 (27%)</td>
<td>0.21</td>
</tr>
<tr>
<td>≥ 50 years of age, CRp (%)</td>
<td>19 (24%)</td>
<td>20 (25%)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Safety Parameter</th>
<th>Chemotherapy only</th>
<th>Chemotherapy + Lestaurnitinib</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death Within 30 Days of Start of Treatment</td>
<td>7/109 (6%)</td>
<td>13/111 (12%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Grade 3 or 4 AE</td>
<td>101/109 (93%)</td>
<td>104/111 (94%)</td>
<td>0.8</td>
</tr>
<tr>
<td>Serious AE</td>
<td>49/109 (45%)</td>
<td>61/111 (55%)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

But plasma levels of drug too low in most pts
Cephalon 204 trial: Overall Survival

\[ p = 0.921 \]
Double-blind, placebo controlled, randomized Study of Chemotherapy + Crenolanib in Relapsed or Refractory FLT3 mutant AML

Primary Endpoint: Overall survival

- Optional second cycle
- First priority for consolidation is allogeneic HSCT

Induction
- MC + Placebo
- MC + Crenolanib

Consolidation
- MC + Placebo
- MC + Crenolanib
- 3x HiDAC + Placebo
- Allo HSCT*

Maintenance
- 1-yr Placebo
- 1-yr Crenolanib

Relapsed/refractory AML with FLT3 ITD or D835 N=325
Sorafenib in AML

- MD Anderson phase I/II sorafenib + IA (Ravandi)
  - 17/18 pts morph CR/CRp (94%, 95% CI 73-99)
- Compassionate use sorafenib, use post-alloSCT
- SAL trial >60 yrs (Serve)
  - Randomized phase II of 201 pts
  - No improvement in EFS or OS with early TRM for sorafenib
- SORAML trial <60 yrs (Röllig)
  - Randomized phase II of 276 pts
  - Median EFS of 21 mo (95% CI, 9-32) vs 9 months (4-15) for sorafenib without difference in OS
  - Trend for improved RFS and OS in FLT3-ITD

Central FLT3 Screening

**Induction**

\[ 7+3 + \text{Sorafenib} \]
Ara-C 100 mg/d CIVI D1-7
DNR 60 mg/m²/d D1-3
Sorafenib 400 mg BID d1-7

**Consolidation**

\[ \text{IntDAC + Sorafenib} \]
Ara-C 2 g/m²/d d1-5
Sorafenib 400 mg BID d1-28

**Maintenance**

12 cycles (1 year)

\[ 5+2 + \text{Sorafenib} \]

CR

No CR

Overall Survival by Age

PKC412 plus chemo in newly diagnosed, previously untreated AML: Treatment Plan

– Induction Chemotherapy
  • DNR 60 mg/m² d1, 2, 3 plus ara-C 100 mg/m² IVCI d1-7
– Post-remission chemotherapy
  • ara-C 3 gm/m² over 3h q 12h d1, 3, and 5 x 3 cycles
– PKC412
  • 100 mg po bid begin d1 (simultaneous) OR d8 (sequential) of each cycle
  • give continuously during induction and post-CR
Study Induction Scheme by Cohort

PKC412 dosed bid

- Dauno 60mg/sqm i.v.
- DDD ara-C 100mg/sqm c.i.v.

Continuous 100mg*
- 7 pts

14-day treatment 100mg*
- 7 pts
- 8 pts

14-day treatment 50mg+
- 20 pts
- 20 pts

*AE rate, dt GI tox too high

28-day cycle
Efficacy

- 80% Complete Response (CR) rate (32/40)
- 92% of FLT3mut patients had a CR
- Trend toward higher CR in FLT3mut patients
- No significant difference in response rates or duration of remission between the sequential and concomitant schedules

90% CR rate also w/ soraf+IA; Ravandi et al, JCO, 2010

Response Rate in Patients with FLT3wt and FLT3mut

- Complete Response Rate in Patients with FLT3wt and FLT3mut
  - FLT3wt (n=27): 74%
  - FLT3mut (n=13): 92%
Similar Survival Seen in Previously Untreated Patients With FLT3mut and FLT3wt Blasts

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Med OS, mo (range)</th>
<th>Alive</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITD (n=9)</td>
<td>20 (4-56)</td>
<td>3</td>
</tr>
<tr>
<td>TKD (n=4)</td>
<td>50 (39-54)</td>
<td>4</td>
</tr>
</tbody>
</table>

Stone, Leukemia, 2012
The Multi-Kinase Inhibitor Midostaurin (M) Prolongs Survival Compared with Placebo (P) in Combination with Daunorubicin (D)/Cytarabine (C) Induction (ind), High-Dose C Consolidation (consol), and As Maintenance (maint) Therapy in Newly Diagnosed Acute Myeloid Leukemia (AML) Patients (pts) Age 18-60 With FLT3 Mutations (muts): An International Prospective Randomized (rand) P-Controlled Double-Blind Trial (CALGB 10603/RATIFY [Alliance])

Abstract 6

CALGB 10603: Prospective Phase III, double-blinded randomized study of induction and consolidation +/- Midostaurin (PKC412) in newly diagnosed patients < 60 years old with FLT3 mutated AML

Not on STUDY: FLT3 WILD TYPE

Study drug is given on Days 8-21 after each course of chemotherapy, and Days 1-28 (note change) of each 28 day Maintenance cycle.
Key Eligibility Criteria

• Age 18-60, normal end-organ function
• Documented AML (non-APL)
• FLT3 mutation centrally determined prior to enrollment
  – Assessed at one of 9 academic labs around the world
  – Results within 48h
• Up to 5 days of hydroxyurea allowed prior to start of treatment while awaiting results of mutation analysis
## Protocol Therapy

<table>
<thead>
<tr>
<th>Phase</th>
<th>Drug(s)</th>
<th>Dose/Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Induction</strong></td>
<td>daunorubicin</td>
<td>60 mg/m² IVP days 1-3</td>
</tr>
<tr>
<td><em>(2nd cycle given based on d21 marrow)</em></td>
<td>cytarabine</td>
<td>200 mg/m²/d d 1-7 via IVCI</td>
</tr>
<tr>
<td></td>
<td>midostaurin</td>
<td>50 mg po bid days 8-21</td>
</tr>
<tr>
<td></td>
<td>midostaurin or placebo</td>
<td></td>
</tr>
<tr>
<td><strong>Consolidation</strong></td>
<td>cytarabine</td>
<td>3 gm/m² over 3h q 12h</td>
</tr>
<tr>
<td><em>(up to 4 cycles)</em></td>
<td>midostaurin</td>
<td>days 1, 3, and 5</td>
</tr>
<tr>
<td></td>
<td>midostaurin or placebo</td>
<td>50 mg po bid days 8-21</td>
</tr>
<tr>
<td><strong>Maintenance</strong></td>
<td>midostaurin or placebo</td>
<td>50 mg po bid days 1-28 x 12 cycles</td>
</tr>
</tbody>
</table>

- Transplant not specifically mandated

Activated May 2008; completed accrual: Oct 2011 Screened 3279 patients

Total FLT3(+): N = 887 (27% of screened)

Total randomized: N = 717 (81% of FLT3(+))

Midostaurin (MIDO), N = 360
  - Induction 1, N = 355
  - Induction 2, N = 81
  - Consolidation, N = 231
  - Maintenance, N = 120

Placebo (PBO), N = 357
  - Induction 1, N = 354
  - Induction 2, N = 101
  - Consolidation, N = 210
  - Maintenance, N = 85

## Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>MIDO</th>
<th>PBO</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median (range)</td>
<td>47.1 (19.0-59.8)</td>
<td>48.6 (18.0-60.9)</td>
<td>.27</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>.045</td>
</tr>
<tr>
<td>Female</td>
<td>187 (51.9%)</td>
<td>212 (59.4%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>173 (48.1%)</td>
<td>145 (40.6%)</td>
<td></td>
</tr>
<tr>
<td>FLT3 stratification Groups</td>
<td></td>
<td></td>
<td>.995</td>
</tr>
<tr>
<td>FLT3 TKD (No ITD)</td>
<td>81 (22.5%)</td>
<td>81 (22.7%)</td>
<td></td>
</tr>
<tr>
<td>ITD allelic ratio &lt;0.7 (+/- FLT3 TKD)</td>
<td>171 (47.5%)</td>
<td>170 (47.6%)</td>
<td></td>
</tr>
<tr>
<td>ITD allelic ratio ≥0.7 (+/- FLT3 TKD)</td>
<td>108 (30.0%)</td>
<td>106 (29.7%)</td>
<td></td>
</tr>
</tbody>
</table>

MIDO, midostaurin
## Complete Response Rates

<table>
<thead>
<tr>
<th></th>
<th>MIDO (N = 360)</th>
<th>PBO (N = 357)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR by day 60</td>
<td>212</td>
<td>191</td>
<td>.15</td>
</tr>
<tr>
<td>Rate</td>
<td>59%</td>
<td>53%</td>
<td></td>
</tr>
<tr>
<td>Time to CR, median (range)</td>
<td>35 days (20-60)</td>
<td>35 days (20-60)</td>
<td></td>
</tr>
<tr>
<td>CR in induction/consolidation**</td>
<td>239</td>
<td>211</td>
<td>.045</td>
</tr>
<tr>
<td>Rate</td>
<td>66%</td>
<td>59%</td>
<td></td>
</tr>
<tr>
<td>Time to CR, median (range)</td>
<td>37 days (20-99)</td>
<td>36 days (20-112)</td>
<td></td>
</tr>
</tbody>
</table>

**Includes all CRs reported within 30 days of ending protocol therapy

Overall Survival (Primary Endpoint)

23% Reduced Risk of Death in the MIDO Arm

Median OS: MIDO 74.7 (31.7-NE); PBO 25.6 (18.6-42.9) months

Controlled for FLT3 subtype (TKD, ITD-Low, ITD-High)

Overall Survival: Post-Transplant Treatment With MIDO Increases OS After SCT in CR1

- SCT in CR1: HR 0.61
- SCT outside CR1: HR 0.98

Conclusions

• Midostaurin, a mult-itargeted kinase inhibitor, improves OS when added to standard chemo with one year maintenance in newly diagnosed pts aged 18-60 with ITD and TKD FLT3 mutant AML, and represents a new standard of care

• OS and EFS benefit was consistent in uncensored as well as censored analyses, despite high SCT rate

• Safety profile similar in each arm

• An international academic-industry collaborative AML study based on genotype at dx is feasible

Study Design

**AMLSG 16-10** (Clinicaltrials.gov identifier, NCT01477606; EudraCT Number, 2011-003168-63)

- *FLT3 Mutation Screening Within 48 Hours*
  - Daunorubicin Cytarabine**
  - High-Dose Cytarabine***

1st priority
- Allogeneic HSCT
- 1-yr Maintenance
  - Start: Day 30 after allo HSCT

2nd priority
- PKC412
- 3x High-Dose Cytarabine
- PKC412
- 1-yr Maintenance

- *Patients may receive hydroxyurea during screening phase*
- **Optional 2nd cycle in patients achieving PR after cycle I*
- ***Cytarabine: 18-65 years, 3g/m², q12hr, day 1,3,5; >65 years, 1g/m², q12hr, day 1,3,5; optional for patients before allogeneic HSCT*

---

AML With \text{FLT3-ITD} 
AMLSG 16-10 Compared to Historical Controls

**Age 18-<60 yrs**

\begin{align*}
\text{AMLSG 16-10} & \quad n = 79 \\
\text{Historical-control AMLSG} & \quad N = 481 \\
\end{align*}

\textit{P} = .014

**Age 60-70 yrs**

\begin{align*}
\text{AMLSG 16-10} & \quad n = 37 \\
\text{Historical-control AMLSG} & \quad N = 97 \\
\end{align*}

\textit{P} = .036

FLT3 inhibitors in AML: conclusions

- Midostaurin plus chemo f/b alloSCT emerging as a new standard of care in ages 18-60
- Role of specific and nonspecific \textit{FLT3} inhibitors being explored as single agents +/- chemo, in different settings (older e.g. with HMA], relapse, post-SCT, \textit{FLT3} WT status)
- Is this really about FLT3 inhibition (Would a potent FLT3 inhibitor v multi-targeted agent be better)?
  - Off target primary resistance mechanisms described (CCND3, encodes cyclin 3) (Smith et al, ASH abst 677, 2015)
Acknowledgements

• DFCI Adult Leukemia Team
  – MDs: DeAngelo, Garcia, Steensma, Wadleigh
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  – Research RN Toomey-Matthews, CRCs, administrative support

• Other Key Local Colleagues
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  – DFHCC (MGH): Amrein, Ballen, Fathi, Graubert, Hobbs
  – DFHCC (BIDMC): Avigan, Rosenblatt

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