NDA 212166: QUIZARTINIB

INTRODUCTORY COMMENTS

Oncologic Drugs Advisory Committee Meeting
May 14, 2019

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Division of Hematology Products
Office of Hematology & Oncology Products
Quizartinib is a small molecule drug that inhibits multiple receptor tyrosine kinases, including FMS-like tyrosine kinase 3 (FLT3).

Proposed Indication
"For treatment of adults with relapsed or refractory acute myeloid leukemia (AML) which is FLT3-ITD positive, as detected by an FDA-approved test"

FLT3-ITD: FLT3 internal tandem duplication
Safe and effective treatments are needed for patients with relapsed or refractory FLT3+ AML.
**STUDY AC220-007**

- **Study Design**
  - Randomized controlled trial
  - Patients with R/R AML with FLT3-ITD
  - Comparing quizartinib to standard treatment (SOC)
  - Stratified by SOC being intensive chemotherapy or low-dose cytarabine (LDAC)

- **Outcome (FDA Analysis)**
  - OS HR: 0.77; 95% CI 0.59, 0.99
    - (1-sided p = 0.019)
  - Median OS: 6.2 months vs 4.7 months
CONCERNS ABOUT STUDY AC220-007

• Borderline treatment effect (HR 0.77; 95% CI 0.59, 0.99)
• Imbalance between arms in patients not treated
• Imbalance between arms in early censoring
• Difference in OS driven by the LDAC stratum
  LDAC Stratum HR 0.59 (95% CI 0.36, 0.97)
  Intensive Stratum HR 0.83 (95% CI 0.62, 1.11)
• The LDAC stratum had an imbalance in use of allogeneic hematopoietic stem cell transplantation (HSCT) (23% on quizartinib vs none of LDAC)
• Single trial to support the indication
Please discuss whether the results of the OS analysis of Study AC220-007 are persuasive evidence of effectiveness of quizartinib and the reasons for your opinion.
QUIZARTINIB: QTc PROLONGATION

• Prolonged QTc is associated with higher risk of potentially fatal ventricular arrhythmias

• Cardiac repolarization depends largely on IKr and IKs, the two outward potassium currents

• Quizartinib inhibits IKs and prolongs QTc
  – QTc prolongation higher with quizartinib than chemotherapy (27% vs 2%)
  – At 60 mg dose, largest mean ΔQTcF was 26 ms (90% CI: 21, 31 ms)
  – Fatal cardiac events identified by FDA

• To date, noncardiac drugs that prolong QTc inhibit IKr
  – What happens when both IKr and IKs are blocked?
Please discuss the need for and feasibility of the measures proposed to reduce the risk of life-threatening and fatal cardiac events resulting from IKs blockade if quizartinib is marketed.
STUDY AC220-007 OUTCOMES OVERVIEW

Safety Outcomes
• Adverse reactions:
  - Nausea, vomiting
  - Diarrhea
  - Elevated liver enzymes
  - Cytopenias
• Early mortality 7% vs 24%
• QTc prolonged in 27%
• 1-2% fatal cardiac events
• 7% risk of DS/AFND

Efficacy Outcomes
• OS HR 0.77 (0.59, 0.99)
  mOS 6.2 vs 4.7 months
  - not robust
• Event-Free Survival
  EFS HR 0.9 (0.71, 1.16)
  mEFS 1.4 vs 0.9 months
• CR rate 4%
• CR/CRh rate 11%
• Transfusion independence rate 26%
ISSUE #3

Do the results of Study AC220-007 demonstrate that treatment with quizartinib provides for a benefit that outweighs the safety risks for patients with relapsed or refractory AML with a FLT3-ITD?
NDA 212166

Quizartinib

FDA Presentation
Oncologic Drugs Advisory Committee Meeting
May 14, 2019
FDA Presentation Agenda

• Kunthel By, PhD (Statistical Reviewer)
  – Introduction
  – Efficacy Review

• Aviva Krauss, MD (Clinical Reviewer)
  – Safety Review
  – Summary
Efficacy Review

Kunthel By, PhD
Statistical Reviewer
Office of Biostatistics
Division of Biometrics 5
Outline Of Efficacy Presentation

• Requirements for Marketing Approval

• Efficacy (Study AC220-007)
  – Uncertainty in estimated treatment effect
    • Lack of clear, consistent treatment effect
    • Effects of subsequent therapies
    • Imbalance in patients randomized not treated & early censoring
Requirements for Marketing Approval

• Substantial evidence of safety and effectiveness
  – From adequate and well-controlled clinical investigations
    Food, Drug and Cosmetic (FD&C) Act, and its 1962 Amendments

• Outcomes in AML
  – Overall survival (OS)
  – Event-free survival (EFS)
  – durable complete remission (CR)
  – CR/CRh with associated transfusion independence (TI)
Issue 1

• Uncertainty in estimated treatment effect
  – Lack of clear, consistent treatment effect
  – Effects of subsequent therapies
  – Imbalance in patients randomized not treated & early censoring
Design of Study AC220-007 Pivotal Trial

• Open-label, randomized (2:1), active-control study of quizartinib vs chemotherapy
• ≥ 18 years old, FLT3-ITD+ AML, refractory or relapsed within 6 months of first remission
• Investigator-selected chemotherapy for stratification:
  – Intensive (MEC, FLAG-IDA) vs low-intensity (LDAC)
• Primary endpoint: overall survival (OS)
• Key secondary endpoint: event-free survival (EFS)
• 367 patients randomized (245 vs 122)
Concerns

1. Lack of internal consistency
2. Impact of subsequent therapies
3. Differential number of patients randomized but not treated (RNT)
4. Differential number of patients early censored
## Primary Efficacy Endpoint: OS

<table>
<thead>
<tr>
<th></th>
<th>Quizartinib (N = 245)</th>
<th>Chemotherapy (N=122)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (95% CI) in weeks</td>
<td>26.9 (23.1, 31.0)</td>
<td>20.4 (17.0, 25.2)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.77 (0.59, 0.99)</td>
<td>--</td>
</tr>
<tr>
<td>1-sided p*</td>
<td>0.019</td>
<td>--</td>
</tr>
</tbody>
</table>

*Statistically significant if p < 0.02319
## Concern 1: Lack of Internal Consistency

<table>
<thead>
<tr>
<th></th>
<th>Quizartinib (N = 245)</th>
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</tr>
</thead>
<tbody>
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<td>0.77 (0.59, 0.99)</td>
<td>--</td>
</tr>
<tr>
<td>1-sided p</td>
<td>0.019</td>
<td>--</td>
</tr>
<tr>
<td><strong>EFS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (95% CI in weeks)</td>
<td>6.0 (0.1, 8.3)</td>
<td>3.7 (0.4, 6.0)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.9 (0.71, 1.16)</td>
<td>--</td>
</tr>
<tr>
<td>1-sided p</td>
<td>0.1138</td>
<td>--</td>
</tr>
<tr>
<td><strong>CR (95% CI)</strong></td>
<td>4% (2%, 7%)</td>
<td>1% (0%, 4.5%)</td>
</tr>
<tr>
<td><strong>CR/CRh (95% CI)</strong></td>
<td>11% (7%, 16%)</td>
<td>--</td>
</tr>
</tbody>
</table>
Concern 2: Impact of Subsequent Therapies

- Patients in both arms initiated subsequent therapies

<table>
<thead>
<tr>
<th>Subsequent Therapy</th>
<th>Intensive Stratum</th>
<th>Low-Intensity Stratum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Quizartinib (N=188)</td>
<td>Chemotherapy (N=93)</td>
</tr>
<tr>
<td>Allo HSCT</td>
<td>73 (39%)</td>
<td>21 (23%)</td>
</tr>
<tr>
<td>In CR</td>
<td>3 (1.5%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Not in CR</td>
<td>70 (37%)</td>
<td>21 (23%)</td>
</tr>
</tbody>
</table>

Allo HSCT = allogeneic hematopoietic stem cell transplantation
Concern 2: Exploring Impact of HSCT

- Intensive Stratum
- HSCT not in CR
  - Quizartinib: 70 (37%)
  - Chemotherapy: 21 (23%)

- Possibly no quizartinib survival advantage when HSCT rates are similar.
Concern 3: Imbalance Randomized Not Treated

- 28 (23%) chemotherapy patients
- 4 (1.6%) quizartinib patients
- Possibly due to open-label nature of the study
- Impact on estimated treatment effect unknown if randomized and treated.
Concern 4: Differential Early Censoring

Terminology

• **Early censoring**: censor < 8 weeks after randomization (EC8)

• **Early death**: death < 8 weeks after randomization (ED8)

• Followed for at least 8 weeks after randomization (GE8)
  – Died on or after week 8
  – Censored on or after week 8
Concern 4: Differential Early Censoring

• Early-censored patients provide little information about treatment effect.

• Censored < 8 weeks after randomization
  – 9 (7.4%) chemotherapy
  – 1 (0.4%) quizartinib

• Impact on treatment effect unknown if longer follow-up
# Early Censoring and Randomized Not Treated

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Stratum</th>
<th>N</th>
<th>EC8</th>
<th>ED8</th>
<th>GE8</th>
<th>EC8</th>
<th>ED8</th>
<th>GE8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quizartinib</td>
<td>LDAC</td>
<td>57</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>7</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>MEC/FLAG-IDA</td>
<td>188</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>8</td>
<td>177</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>245</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>15</td>
<td>225</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>LDAC</td>
<td>29</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>0</td>
<td>8</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>MEC/FLAG-IDA</td>
<td>93</td>
<td>6</td>
<td>3</td>
<td>12</td>
<td>2</td>
<td>13</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>122</td>
<td>7</td>
<td>5</td>
<td>16</td>
<td>2</td>
<td>21</td>
<td>71</td>
</tr>
</tbody>
</table>

EC8 = Censored before 8 weeks; ED8 = Death before 8 weeks; GE8 = Followed at least 8 weeks
Stress Test

- Assess robustness of quizartinib’s OS advantage under differential RNT and EC8
- Impute survival times/statuses of RNT and EC8 patients
- Similar to Applicant; different assumptions

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>LDAC</th>
<th>Randomized-Not-Treated</th>
<th>Randomized-Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stratum</td>
<td>MEC; FLAG-IDA</td>
<td>EC8</td>
<td>ED8</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

1. Impute All
2. Impute Half
3. Impute None

RNT = Randomized not treated; EC8 = Censored before 8 weeks; ED8 = Death before 8 weeks; GE8 = Followed at least 8 weeks
### Stress Test: Estimated Treatment Effect

<table>
<thead>
<tr>
<th>Impute Randomized Not Treated Patients with &gt;= 8 Weeks of Follow-up (1 quizartinib; 16 chemotherapy)</th>
<th>Estimated HR (95% CI)</th>
<th>Proportion of Times Imputations Failed To Show Superiority of Quizartinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impute All ($\pi=0$)</td>
<td>0.87 (0.67, 1.14)</td>
<td>99%</td>
</tr>
<tr>
<td>Impute Half ($\pi=0.5$)</td>
<td>0.83 (0.64, 1.07)</td>
<td>94%</td>
</tr>
<tr>
<td>Impute None ($\pi=1.0$)</td>
<td>0.78 (0.61, 1.00)</td>
<td>50%</td>
</tr>
</tbody>
</table>

• Under reasonable assumptions about early-censored and randomized not treated patients, *observed quizartinib OS advantage is not robust*. 
Summary

• OS Results: HR 0.77 (0.59, 0.99); Difference medOS = 6.5 weeks

• Uncertainty in Estimated Treatment Effect
  – Lack of Internal Consistency: Lack of efficacy on EFS and CR
  – Impact of Subsequent Therapy
    • Imbalance in HSCT between arms
    • More quizartinib than chemotherapy patients initiated HSCT among non-responders
  – Differential randomized not treated and early censoring
    • Stress test indicates lack of robustness in estimated treatment effect
Please discuss whether the results of the OS analysis of Study AC220-007 are persuasive evidence of effectiveness of quizartinib and the reasons for your opinion.
Safety Analysis

Aviva Krauss, MD
Clinical Reviewer
Division of Hematology Products
Office of Hematology & Oncology Products
# Safety Population

## Focus

<table>
<thead>
<tr>
<th>Study AC220-007</th>
<th>R/R FLT3-ITD+ AML</th>
<th>Median Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quizartinib monotherapy (N=241)</td>
<td>3 cycles (97 days; range 1-1333)</td>
<td></td>
</tr>
<tr>
<td>Control Chemotherapy (N=94)</td>
<td>1 cycle (5 days; range 2-84)</td>
<td></td>
</tr>
</tbody>
</table>

## Supportive

<table>
<thead>
<tr>
<th>Studies</th>
<th>R/R AML</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>2689-CL-2004</td>
<td>Quizartinib monotherapy (N=483)</td>
<td>2 cycles (62 days; range 2-1044)</td>
</tr>
<tr>
<td>AC220-002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CP0001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ongoing Study</th>
<th>Newly-diagnosed, FLT3-ITD+ AML</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC220-A-U302 (limited data)</td>
<td>Quizartinib in combination with intensive chemotherapy (N=168)*</td>
</tr>
<tr>
<td></td>
<td>Placebo in combination with intensive chemotherapy (N=168)*</td>
</tr>
</tbody>
</table>

*Data cut-off 8.30.2018
Safety Review Strategy

• Slow potassium channel (IKs) blockade and cardiac toxicity
• Other safety issues:
  – Differentiation syndrome (DS) and acute febrile neutrophilic dermatosis (AFND)
  – Common treatment-emergent adverse events
  – Cytopenias
Background: IKs Role in Cardiac Repolarization

Repolarization of the action potential controlled by the outward delayed-rectifier currents

- IKr (rapid component)
- IKs (slow component)

Adapted from Delk, Holstege and Brady, Am J of Emerg Med 25(6), 672-687 (2007)

Repolarization of the action potential controlled by the outward delayed-rectifier currents

- IKr (rapid component)
- IKs (slow component)

Second current provides “repolarization reserve” when one channel is blocked
Clinical Consequences of IKs Blockade

• FDA unaware of approved products with QTc prolongation at clinical exposures that predominantly block IKs

• Lessons from AR Long QT Syndrome Type 1 (LQT1):
  – Blunted response of IKs in the setting of β-adrenergic stimulation (exercise, emotional distress)
  – QT interval fails to shorten during tachycardia=highly arrhythmogenic
  – Even patients without prolonged QT/QTc at rest are at risk
  – Use of beta blockers recommended

• Concomitant use of IKr and IKs blockade may result in reduced repolarization reserve
Guidance on Evaluation of QTc Prolongation

E14: The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs

(International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use)


- Low Concern
  - Mean ΔQTc <10 msec

- Increasing Concern
  - Mean ΔQTc 10-20 msec
  - +QTc Outliers\(^a\)
  - +Clinical AEs

- Definite Concern
  - Mean ΔQTc >20 msec
  - +QTc Outliers\(^a\)
  - +Clinical AEs

\(^a\)QTc Outliers: individual-level QTc>500ms and/or ΔQTc>60ms

Adapted with permission from C. Garnett, PharmD
Guidance on Evaluation of QTc Prolongation

- Low Concern
  - Mean ΔQTc <10 msec

- Increasing Concern
  - Mean ΔQTc 10-20 msec
  - +QTc Outliers$^a$
  - +Clinical AEs

- Definite Concern
  - Mean ΔQTc >20 msec
  - +QTc Outliers$^a$
  - +Clinical AEs

$^a$QTc Outliers: individual-level QTc>500ms and/or ΔQTc>60ms

Adapted with permission from C. Garnett, PharmD
Quizartinib Block IKs and Prolongs QTc

- Quizartinib is a predominant IKs blocker
  - IC50 < 300 nM for IKs blockade in vitro
  - Quizartinib steady state $C_{\text{max}}$ in clinical PK study (60 mg dose):
    - $C_{\text{max}}$ (total) = 870 nM
    - $C_{\text{max}}$ (free) = 8.7 nM

- Study 2689-CL-2004 (Randomized dose-finding study in R/R AML)
  - At 60 mg, the largest mean $\Delta QTcF$ was 26 ms (90% CI: 21, 31 ms)

Per ICH E14: “substantially increased likelihood of being proarrhythmic”

> 20 ms

< 10 ms

Cardiac Arrest and Sudden Death

- AC220-007: 4 deaths (1.7%)
  - Sudden death on Day 97 with prior observed QT prolongation
  - Fatal "MI" on Day 75 with prior observed QT prolongation, palpitations
  - Fatal SDH on Day 62 precipitated by a fall
  - Death on Day 31 with prior observed QT prolongation and hypokalemia

- ISS (monotherapy): additional 3 deaths (total 1%)
  - Death on Day 18 with prior atrial fibrillation and hypocalcemia
  - Fatal atrial fibrillation on Day 82
  - Fatal septic shock on Day 60 with prior observed syncope x 2

- AC220-A-U302: 5 (3%) cardiac-related deaths on the quizartinib arm (vs none on the placebo arm)
  - 2 fatal cardiac arrests
  - 1 sudden death
  - 1 fatal ventricular fibrillation
  - 1 fatal ventricular dysfunction

MI: myocardia infarction; SDH: subdural hematoma
Study AC220-007: Cardiac Events

Customized Query for QT Prolongation/Arrhythmia Events: All Cycles

<table>
<thead>
<tr>
<th>Event</th>
<th>Quizartinib</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=241</td>
<td>N=94</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>0</td>
<td>1 (1.1%)</td>
</tr>
<tr>
<td>Electrocardiogram QT prolonged</td>
<td>64 (26.6%)</td>
<td>2 (2.1%)</td>
</tr>
<tr>
<td>Fall</td>
<td>11 (4.6%)</td>
<td>2 (2.1%)</td>
</tr>
<tr>
<td>Syncope</td>
<td>12 (5.0%)</td>
<td>2 (2.1%)</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>1 (0.4%)</td>
<td>3 (3.1%)</td>
</tr>
</tbody>
</table>

FDA IRT review

- Median exposure: 3 cycles on quizartinib vs 1 cycle on the control arm
  - Cardiac-related events occurred at a higher rate on the quizartinib arm even just during Cycle 1

- Due to short exposure, safety data with continued treatment is limited
Quizartinib IKs Summary and Potential Risk Management

• Summary:
  – QTcF prolongation via IKs blockade
    • IKr+IKs blockade → no reserve for cardiac repolarization
  – Increased incidence of cardiac AEs on the quizartinib arm
  – 1-2% estimated cardiac death risk
    • Cannot rely on prior QTc prolongation to predict

• Labeling:
  • Contraindication for use with other QT-prolonging agents
  • Recommendation for prophylactic beta blockade
Issue #2

Please discuss the need for and feasibility of
a) a contraindication for use with drugs that prolong QT via the complementary IKr channel and
b) a recommendation for administration of beta blockers to prevent arrythmias
as means to reduce the risk of life-threatening and fatal cardiac events resulting from IKs blockade if quizartinib is marketed.
Safety Review Strategy

• IKs blockade and cardiac toxicity

• Other Safety issues:
  – Differentiation syndrome (DS) and acute febrile neutrophilic dermatosis (AFND)
  – Common treatment-emergent adverse events
  – Cytopenias
Differentiation Syndrome (DS) and Acute Febrile Neutrophilic Dermatosis (AFND)

- DS first described in the APL context
  - Montesinos criteria for objective diagnosis (Montesinos, Blood 2009)
  - Later with non-APL AML therapies
    - Including FLT3-targeting therapies
- AFND ("Sweet’s syndrome")
  - Reports associated with FLT3-targeted therapies
    - Biopsy proven differentiated myeloid cells (not blasts)
      (Cohen and Kurzrock, Int J of Derm 2003; Sexauer, Blood 2012; Varadarajan, JAMA, 2016)
DS and AFND Across the Quizartinib Clinical Development Program

- **DS on AC220-007**
  - 11 (5%) cases adjudicated to be DS

- **AFND**
  - ISS: 20 cases (3%)
  - 007: 8 cases (3%)

- **AFND may be a manifestation of DS**
  - 15 (7%) of patients on AC220-007 with DS/AFND

- **AC220-007: 3 fatal cases of DS (with or without AFND)**
  - 2 without treatment interruption or steroid administration
### Common Adverse Reactions, Study AC220-007: Cycle 1, LDAC Stratum

#### Adverse Reactions* with a Risk Difference (RD) > 15% Between Arms

<table>
<thead>
<tr>
<th>SMQ (Narrow)</th>
<th>Quizartinib N=55</th>
<th>LDAC N=22</th>
<th>%RD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematopoietic cytopenias</td>
<td>32 58</td>
<td>7 32</td>
<td>+26</td>
</tr>
<tr>
<td>Cardiac arrhythmias</td>
<td>13 24</td>
<td>0 0</td>
<td>+24</td>
</tr>
<tr>
<td>Torsades de pointes/QT prolongation</td>
<td>11 20</td>
<td>0 0</td>
<td>+20</td>
</tr>
<tr>
<td>Shock</td>
<td>12 22</td>
<td>1 5</td>
<td>+17</td>
</tr>
<tr>
<td>Gastrointestinal nonspecific inflammation and dysfunctional conditions</td>
<td>32 58</td>
<td>9 41</td>
<td>+17</td>
</tr>
<tr>
<td>Hemodynamic edema, effusions and fluid overload</td>
<td>12 22</td>
<td>1 5</td>
<td>+17</td>
</tr>
</tbody>
</table>

*Level 1 narrow Standardized MedDRA Queries (SMQs)
Common Adverse Reactions, Study AC220-007: Cycle 1, Intensive Chemotherapy Stratum

Adverse Reactions* with a Risk Difference (RD) > 15% Between Arms

<table>
<thead>
<tr>
<th>SMQ (Narrow)</th>
<th>Quizartinib N=186</th>
<th>Intensive Chemotherapy N=72</th>
<th>%RD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac arrhythmias</td>
<td>n=45 (24%)</td>
<td>n=4 (6%)</td>
<td>+19</td>
</tr>
<tr>
<td>Torsades de pointes/QT prolongation</td>
<td>n=42 (23%)</td>
<td>n=4 (6%)</td>
<td>+17</td>
</tr>
<tr>
<td>Shock</td>
<td>n=44 (24%)</td>
<td>n=6 (8%)</td>
<td>+15</td>
</tr>
<tr>
<td>Hemodynamic edema, effusions and fluid overload</td>
<td>n=30 (16%)</td>
<td>n=26 (36%)</td>
<td>-20</td>
</tr>
<tr>
<td>Noninfectious diarrhea</td>
<td>n=33 (18%)</td>
<td>n=30 (42%)</td>
<td>-24</td>
</tr>
<tr>
<td>Oropharyngeal disorders</td>
<td>n=42 (23%)</td>
<td>n=35 (49%)</td>
<td>-26</td>
</tr>
<tr>
<td>Gastrointestinal nonspecific inflammation and</td>
<td>n=93 (50%)</td>
<td>n=59 (82%)</td>
<td>-32</td>
</tr>
<tr>
<td>dysfunctional conditions</td>
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</tbody>
</table>

*Level 1 narrow Standardized MedDRA Queries (SMQs)
Prolonged Cytopenias, Study AC220-007

• Median neutrophil count on the quizartinib arm remained $<700 \text{ Gi/L}$ through Cycle 3 D1, even in patients achieving CR/CRh

• Median platelet count on the quizartinib arm remained $<75,000 \text{ Gi/L}$ through Cycle 2 D15, even in patients achieving CR/CRh
Safety Outcomes

• Adverse reactions:
  - Nausea, vomiting
  - Diarrhea,
  - Elevated liver enzymes
  - Cytopenias

• Early mortality 7% vs 24%
• QTc prolonged in 27%
• 1-2% fatal cardiac events
• 7% risk of DS/AFND
Study AC220-007 Outcomes Overview

Safety Outcomes
• Adverse reactions:
  - Nausea, vomiting
  - Diarrhea,
  - Elevated liver enzymes
  - Cytopenias
• Early mortality 7% vs 24%
• QTc prolonged in 27%
• 1-2% fatal cardiac events
• 7% risk of DS/AFND

Efficacy Outcomes
• OS HR 0.77 (0.59, 0.99)
  mOS 6.2 vs 4.7 months
  – Not robust
• EFS HR 0.9 (0.71, 1.16)
  mEFS 1.4 vs 0.9 months
• CR rate 4%
• CR/CRh rate 11%
• TI rate 26%
Discussion Question 1

Please discuss whether the results of the OS analysis of Study AC220-007 are persuasive evidence of effectiveness of quizartinib and the reasons for your opinion.
Discussion Question 2

Please discuss the need for and feasibility of
a) a contraindication for use with drugs that prolong QT via the complementary IKr channel and
b) a recommendation for administration of beta blockers to prevent arrhythmias
as means to reduce the risk of life-threatening and fatal cardiac events resulting from IKs blockade if quizartinib is marketed.
Voting Question:

Do the results of Study AC220-007 demonstrate that treatment with quizartinib provides for a benefit that outweighs the safety risks for patients with relapsed or refractory FLT3-ITD+ AML?
FDA Review Team

- Anamitro Banerjee, PhD
- Ferdouse Begum, PhD
- Brian Booth, PhD
- Kunthel By, PhD
- Edwin Chiu Yuen Chow, PhD
- Stephanie DeGraw, PharmD
- Albert Deisseroth, MD, PhD
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- Danuta Gromek-Woods, PhD
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- Yuching Yang PhD
- Ben Zhang, PhD
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