NDA 212166: QUIZARTINIB

INTRODUCTORY COMMENTS

Oncologic Drugs Advisory Committee Meeting
May 14, 2019

Donna Przepiorka, MD, PhD
Division of Hematology Products
Office of Hematology & Oncology Products

QUIZARTINIB

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

Treatments Applicable to Patients with Relapsed or Refractory (R/R) FLT3$^+$ AML

Drug or Class	Population	CR	CR/CRh	Median OS
Cytotoxics	Relapse 1 FLT3$^+$ AML	12 - 24%	-	3.3-5.8 mos
Low-dose Cytarabine*	R/R FLT3$^+$ AML	0%	-	4.0 mos
Hypomethylating Agents*	R/R FLT3$^+$ AML	10-11%	-	6.2 mos
Gilteritinib	R/R FLT3$^+$ AML	12%	21%	9.0 mos

CR, Complete remission; CRh, CR with partial hematological recovery; OS, overall survival; R/R, relapsed or refractory

*Off-label use

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

HR, Hazard ratio

ISSUE #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.

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?

ISSUE #2

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

	Quizartinib (N = 245)	Chemotherapy (N=122)
OS		
Median (95% CI) in weeks	26.9 (23.1, 31.0)	20.4 (17.0, 25.2)
Hazard ratio (95% CI)	0.77 (0.59, 0.99)	--
1-sided p*	0.019	--

*Statistically significant if $p < 0.02319$

Concern 1: Lack of Internal Consistency

	Quizartinib (N = 245)	Chemotherapy (N=122)
OS		
Median (95% CI) in weeks	26.9 (23.1, 31.0)	20.4 (17.0, 25.2)
Hazard ratio (95% CI)	0.77 (0.59, 0.99)	--
1-sided p	0.019	--
EFS		
Median (95% CI) in weeks	6.0 (0.1, 8.3)	3.7 (0.4, 6.0)
Hazard ratio (95% CI)	0.9 (0.71, 1.16)	--
1-sided p	0.1138	--
CR (95% CI)	4% (2%, 7%)	1% (0%, 4.5%)
CR/CRh (95% CI)	11% (7%, 16%)	--

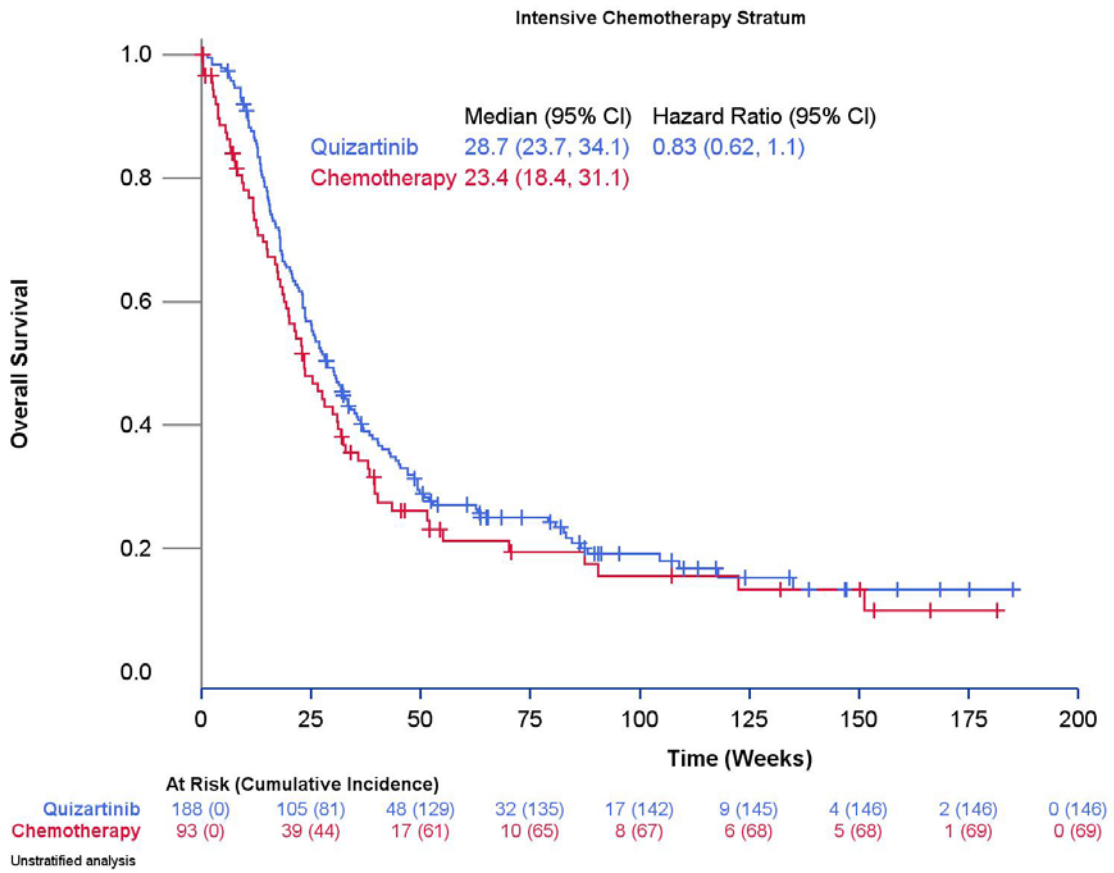
Concern 2: Impact of Subsequent Therapies

- Patients in both arms initiated subsequent therapies

	Intensive Stratum		Low-Intensity Stratum	
Subsequent Therapy	**Quizartinib (N=188)**	**Chemotherapy (N=93)**	**Quizartinib (N=57)**	**Chemotherapy (N=29)**
Allo HSCT	73 (39%)	21 (23%)	13 (23%)	0 (0%)
In CR	3 (1.5%)	0 (0%)	0 (0%)	0 (0%)
Not in CR	70 (37%)	21 (23%)	13 (23%)	0 (0%)

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

			Randomized-Not-Treated			Randomized-Treated		
Cohort	**Stratum**	**N**	**EC8**	**ED8**	**GE8**	**EC8**	**ED8**	**GE8**
Quizartinib	LDAC	57	0	1	1	0	7	48
	MEC/FLAG-IDA	188	0	2	0	1	8	177
	Total	**245**	**0**	**3**	**1**	**1**	**15**	**225**
Chemotherapy	LDAC	29	1	2	4	0	8	14
	MEC/FLAG-IDA	93	6	3	12	2	13	57
	Total	**122**	**7**	**5**	**16**	**2**	**21**	**71**

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

		Randomized-Not-Treated			Randomized-Treated		
Cohort	**Stratum**	**EC8**	**ED8**	**GE8**	**EC8**	**ED8**	**GE8**
Chemotherapy	LDAC	1	2	4	0	8	14
	MEC; FLAG-IDA	6	3	12	2	13	57

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

Impute Randomized Not Treated Patients with >= 8 Weeks of Follow-up (1 quizartinib; 16 chemotherapy)	Estimated HR (95% CI)	Proportion of Times Imputations Failed To Show Superiority of Quizartinib
Impute All (π=0)	0.87 (0.67, 1.14)	99%
Impute Half (π=0.5)	0.83 (0.64, 1.07)	94%
Impute None (π=1.0)	0.78 (0.61, 1.00)	50%

- 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

Issue #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.

Safety Analysis

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

Safety Population

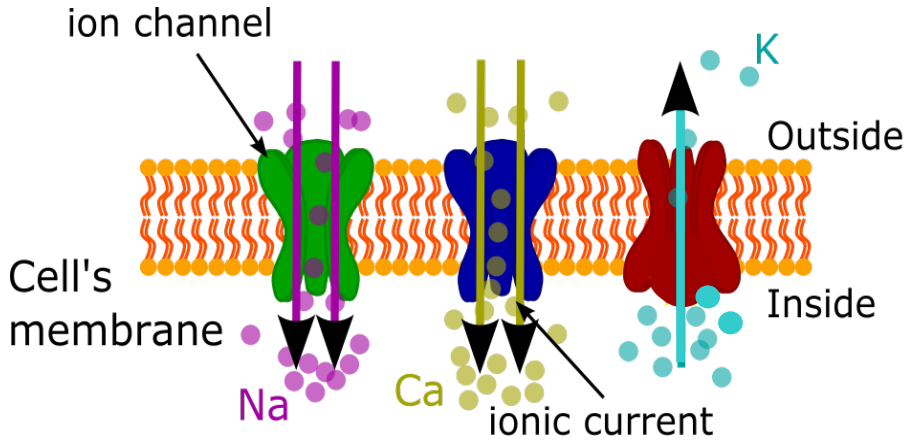
Focus		
Study AC220-007	**R/R FLT3-ITD+ AML** **Quizartinib monotherapy (N=241)**	**Median Exposure** **3 cycles** (97 days; range 1-1333)
	Control Chemotherapy (N=94)	1 cycle (5 days; range 2-84)
Supportive		
Studies 2689-CL-2004 AC220-002 CP0001	R/R AML Quizartinib monotherapy (N=483)	**2 cycles** (62 days; range 2-1044)
Ongoing Study AC220-A-U302 *(limited data)*	Newly-diagnosed, FLT3-ITD+ AML Quizartinib in combination with intensive chemotherapy (N=168)* Placebo in combination with intensive chemotherapy (N=168)*	--

**Data cut-off 8.30.2018*

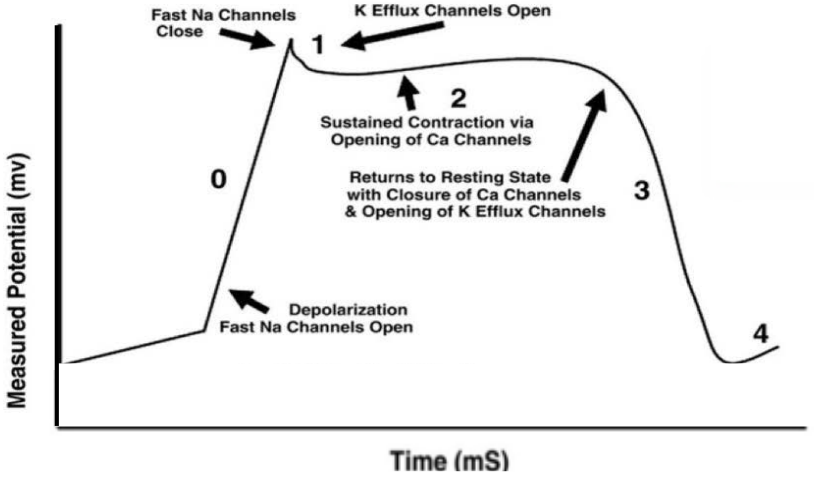
Safety Review Strategy

- 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



Vicente J et al, Clinical Pharmacology &Therapeutics 103(1), 54-66 (2018)

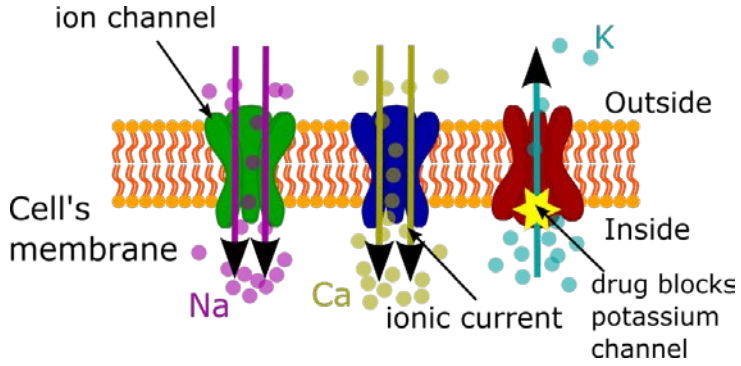


Adapted from Delk, Holstege and Brady, Am J of Emerg Med 25(6), 672-687 (2007)

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

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

Background: IKs Role in Cardiac Repolarization



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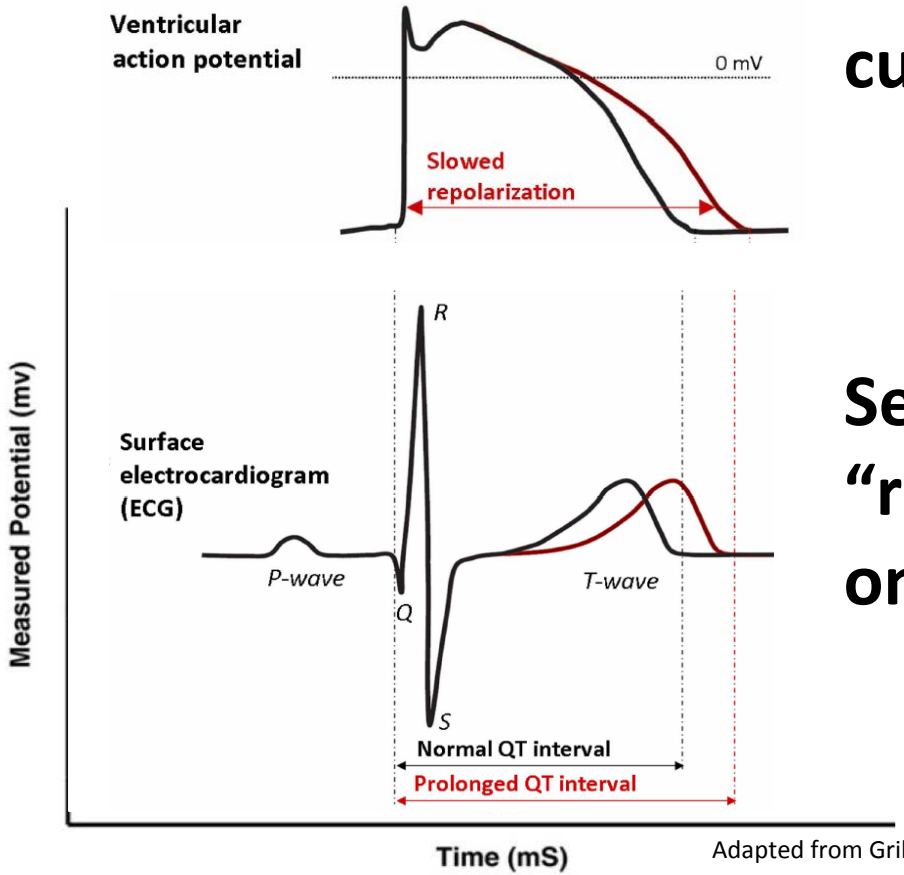


Repolarization of the action potential controlled by the outward delayed-rectifier currents

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

Second current provides "repolarization reserve" when one channel is blocked

Adapted from Grilo LS, Carrupt PA and Abriel H, Frontiers in Pharmacology 1(137), 1-11 (2010)

Clinical Consequences of IKs Blockade

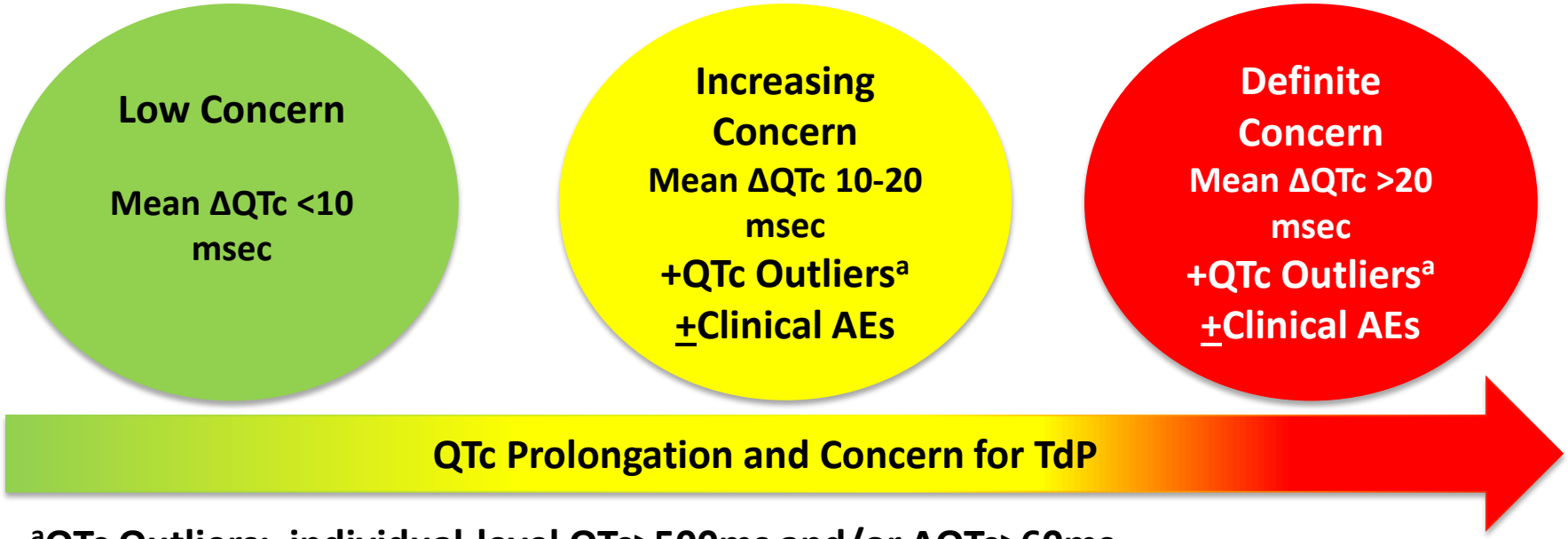
- FDA unaware of approved products with QTc prolongation at clinical exposures that predominantly block IKs
- Lessons from AR Long QT Syndrome Type 1 (LQT1):
  - Blunted response of IKs in the setting of β-adrenergic stimulation (exercise, emotional distress)
  - QT interval fails to shorten during tachycardia=highly 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 Prologation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs

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

https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E14/E14_Guideline.pdf



[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

QTc Prolongation and Concern for TdP

[a]QTc Outliers: individual-level QTc>500ms and/or ΔQTc>60ms

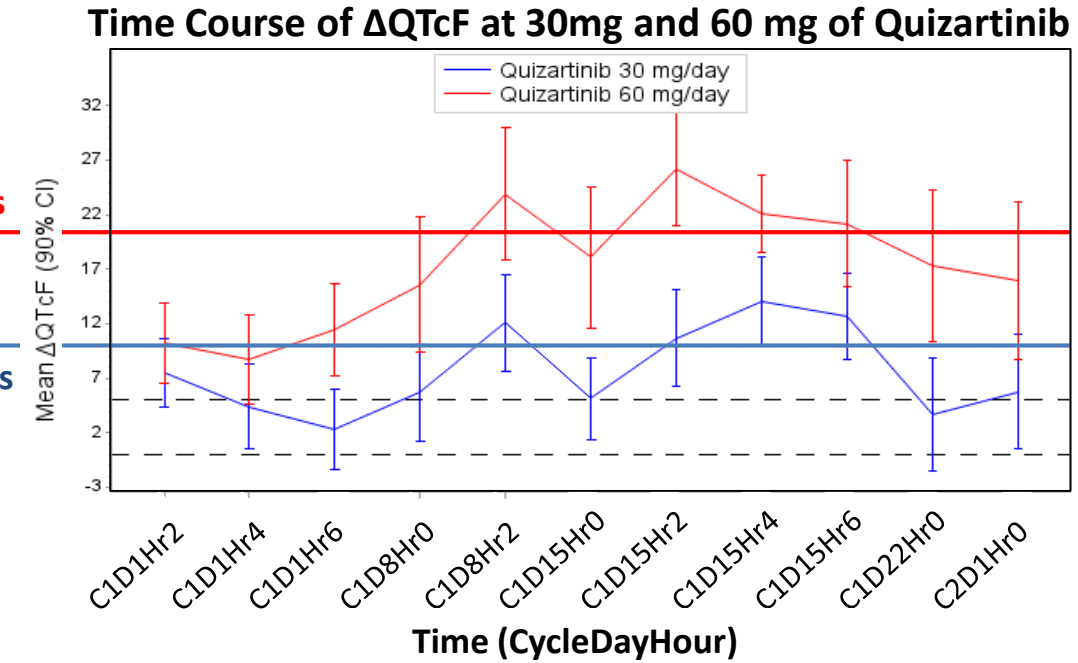
Adapted with permission from C. Garnett, PharmD

Quizartinib Block IKs and Prolongs QTc

- Quizartinib is a predominant IKs blocker
  - IC50 < 300 nM for IKs blockade in vitro
  - Quizartinib steady state C_{max} in clinical PK study (60 mg dose):
    - Cmax (total)= 870 nM
    - Cmax (free) = 8.7 nM
- Study 2689-CL-2004 (Randomized dose-finding study in R/R AML)
  - At 60 mg, the largest mean ΔQTcF was 26 ms (90% CI: 21, 31 ms)

Per ICH E14: "substantially increased likelihood of being proarrhythmic" → **> 20 ms**

< 10 ms



"Guidance for Industry. E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs" (October 2005)

FDA IRT Review. Only timepoints at which the sample size is at least 70% of total population are used for this representation

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

	Quizartinib N=241	Chemotherapy N=94
Cardiac arrest	0	1 (1.1%)
Electrocardiogram QT prolonged	64 (26.6%)	2 (2.1%)
Fall	11 (4.6%)	2 (2.1%)
Syncope	12 (5.0%)	2 (2.1%)
Ventricular tachycardia	1 (0.4%)	3 (3.1%)

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)

APL, acute promyelocytic leukemia

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

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

*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

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

*Level 1 narrow Standardized MedDRA Queries (SMQs)

Prolonged Cytopenias, Study AC220-007

- Median neutrophil count on the quizartinib arm remained <700 Gi/L through Cycle 3 D1, even in patients achieving CR/CRh

- Median platelet count on the quizartinib arm remained <75,000 Gi/L through Cycle 2 D15, even in patients achieving CR/CRh

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

Study AC220-007 Outcomes Overview

Safety Outcomes

- Adverse reactions:
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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 arrythmias

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
- Ann Farrell, MD
- Christine E Garnett, PharmD
- Gerlie Gieser, PhD
- Danuta Gromek-Woods, PhD
- Elizabeth Everhert, PhD
- Rabiya Haider, PharmD
- Dalong Huang, Phd
- Lars Johannesen, PhD
- Aviva Krauss, MD
- Shwu-Luan Lee , PhD
- John Leighton, PhD
- Michael Y Li, PhD
- Liang Li, PhD
- Yuan-Li Shen, DrPH
- Min Lu, MD, MPH
- Lian Ma, PhD
- Sherita McLamore, PhD
- Hina Mehta, PharmD
- Djelila Mezaache, PhD
- Till Olickal, PhD
- Donna Przepiorka, MD, PhD
- Mohammad A Rahman, PhD
- Nam Atiqur Rahman, PhD
- Christopher Sheth, PhD
- Rajeshwari Sridhara, PhD
- David G Strauss, PhD
- Allen Williams, PhD
- Wendy W Wu, PhD
- Yuching Yang PhD
- Ben Zhang, PhD
- Nan Zheng, PhD
- Jeanne Fourie Zirkelbach, PhD


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