Results Of a Phase 1 Study Of Quizartinib (AC220, ASP2689) In Combination With Induction and Consolidation Chemotherapy In Younger Adults With Newly Diagnosed Acute Myeloid Leukemia

Jessica K. Altman MD[1], James M. Foran MD[2], Keith W. Pratz MD[3], Denise Trone[4], Guy Gammon MD[4], Jorge E. Cortes MD[5] and Martin S Tallman MD[6]

[1]Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL; [2]Division of Hematology and Medical Oncology, Mayo Clinic Florida, Jacksonville, FL;[3]Oncology, Johns Hopkins University School of Medicine, Baltimore, MD; [4]Ambit Biosciences Corporation, San Diego, CA; [5]Department of Leukemia, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX; [6]Leukemia Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center and Weill Cornell Medical College , New York, NY

Background

- FLT3 internal tandem duplication (FLT3-ITD) in AML is associated with early relapse and poor survival
- Quizartinib, an oral FLT3 inhibitor, has shown promising activity in subjects with FLT3-ITD(+) AML in Phase 1 and Phase 2 Studies of quizartinib monotherapy
- This Phase 1 dose escalation study is the first study with quizartinib in combination with standard chemotherapy in patients aged 18-60 years with newly diagnosed FLT3-ITD positive and negative AML

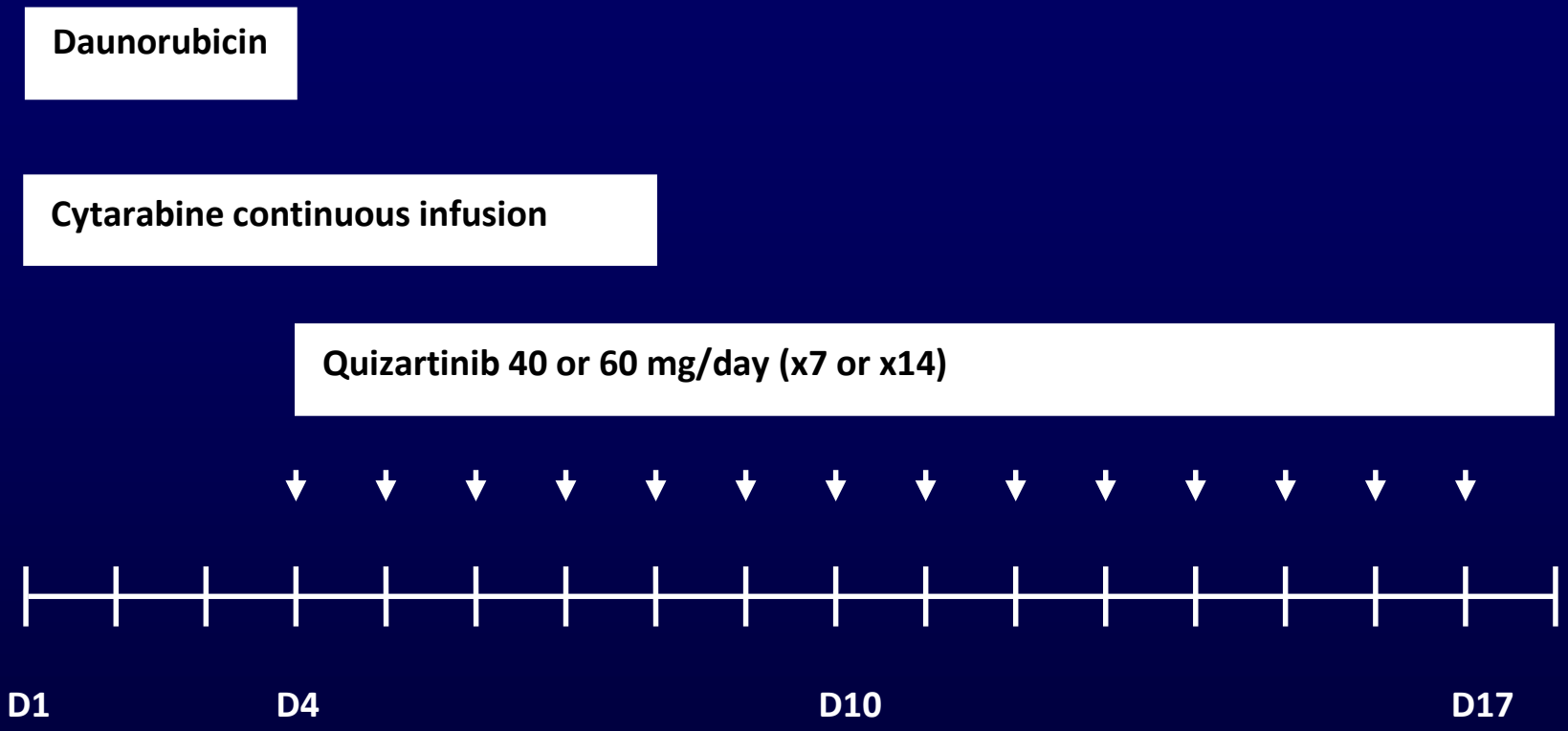
Study Design

- Phase 1 dose escalation study with modified 3 + 3 design
  - 5 or 6 subjects per cohort with minimum of 3 females
  - ≥ 2 DLT in 6 patients shows dose not tolerated and next lower dose is MTD

- Quizartinib dose levels tested:
  - Dose Level 1 (DL1) = 60 mg for 7 days
  - Dose Level 2 (DL2) = 60 mg for 14 days
  - Dose Level -1 (DL-1) = 40 mg for 14 days

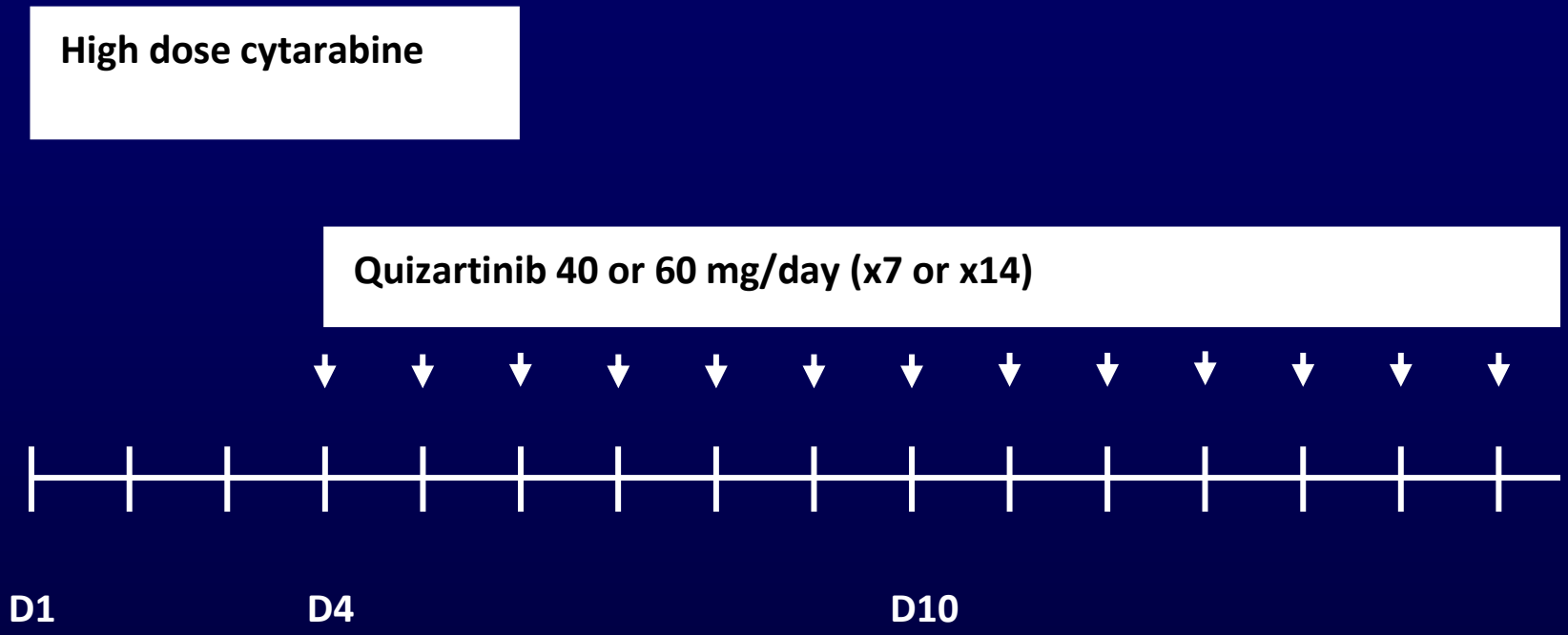
- Patients could proceed directly to a stem cell transplant after achieving a response or receive further quizartinib as maintenance therapy after consolidation

Study Design: Induction



- Cytarabine 200 mg/m^2 x 7 days and daunorubicin 60 mg/m^2 x 3 days (7+3)
- Quizartinib daily for either 7 or 14 days, starting on Day 4 of chemotherapy

Study Design: Consolidation



- High dose cytarabine 3 g/m^2 (HiDAC) q12 hours on days 1, 3, and 5
- Quizartinib daily for either 7 or 14 days, starting on Day 4 of chemotherapy

- Maintenance quizartinib daily for up to 12 x 28 day cycles

DLT Definition

Must be at least possibly related to quizartinib

- **Non-hematologic:**
  - **Any Grade ≥ 3 non-hematologic toxicity between 1st quizartinib dose and before Day 42 after last induction cycle**

- **Hematologic (after 1st quizartinib dose and if not resolved by Day 42 after last induction cycle):**
  - **Peripheral ANC <500/mm^3**
  - **Non-transfusion dependent platelet count < 20,000/mm3 due to documented bone marrow aplasia / hypoplasia**
  - **Platelet count < 50,000/mm^3 (Grade ≥ 3) that is associated with bleeding**

- **Toxicity after the 1st dose of quizartinib which causes cessation of study drug during induction**

Study Endpoints

- **Primary Objectives:**
  - **Define the DLT and MTD for quizartinib in combination with 7 + 3 induction therapy, high dose cytarabine consolidation, and as maintenance**
  - **Identify dose for future combination studies**
- **Secondary Objectives include:**
  - **Determine PK of quizartinib and chemotherapy**
  - **Evaluate efficacy of the combination**

Baseline Characteristics

	No. (%), or Median [range]		
	DL1 60mg x 7d (N = 6)	DL2 60mg x 14d (N = 6)	DL-1 40mg x 14d (N = 6)
Males	3 (50)	2 (33)	2 (33)
Age (years)	49 [23-59]	43 [24-58]	36 [22-60]
ECOG PS 0 or 1	5 (83)	5 (83)	5 (83)
ECOG PS 2	1 (17)	1 (17)	1 (17)
FLT3-ITD (+)	3 (50)	3 (50)	2 (33)
Favorable Cytogenetic Risk	0/6 (0)	0/6(0)	1/6 (17)
Intermediate/Poor Cytogenetic Risk	6/6 (100)	6/6 (100)	5/6 (83)

All subjects were enrolled in the United States.

Patient Treatment Summary

	No. (%)		
	DL1 60mg x 7d (N = 6)	DL2 60mg x 14d (N = 6)	DL-1 40mg x 14d (N = 6)
Received any study tx	6 (100)	6 (100)	6 (100)
Received quizartinib	6 (100)	6 (100)	6 (100)
Received Induction Cycle 1	6 (100)	6 (100)	6 (100)
Received Induction Cycle 2	2 (33)	3 (50)	1 (17)
Received consolidation	3 (50)	2 (33)	4 (67)
Received maintenance	1 (17)	0	0
Went to HSCT	2 (33)	3 (50)	3 (50)

Patient Disposition

	No. (%)		
	DL1 60mg x 7d (N = 6)	DL2 60mg x 14d (N = 6)	DL-1 40mg x 14d (N = 6)
Received Treatment	6 (100)	6 (100)	6 (100)
Off Treatment	6 (100)	6 (100)	6 (100)
Reasons for going off treatment			
Completed tx per protocol	1 (17)	1 (17)	1 (17)
HSCT	2 (33)	3 (50)	2 (33)
Adverse Event	0	1 (17)	0
Death	0	1 (17)	0
PD/ Lack of Response	1 (17)	0	1 (17)
Withdrawal by Subject	0	0	1 (17)
Physician Decision	1 (17)	0	1 (17)
Not fit for consolidation	1 (17)	0	0

1 additional subject in DL-1 went to HSCT but “Physician Decision” was reason for going off treatment

Adverse Event Overview

	No. (%)		
	DL1 60mg x 7d (N = 6)	DL2 60mg x 14d (N = 6)	DL-1 40mg x 14d (N = 6)
Any treatment-emergent adverse event	6 (100)	6 (100)	6 (100)
Treatment-related adverse events	6 (100)	4 (67)	5 (83)
Grade 3 or 4 adverse event	6 (100)	4 (67)	4 (67)
Serious adverse event	4 (67)	3 (50)	3 (50)
Dose-limiting toxicities	1 (17)	2 (33)	1 (17)
Adverse event leading to withdrawal	0	1 (17)	1 (17)
Adverse event leading to death	0	1 (17)	0

Grade 3 or 4 Non-Hematologic Treatment-Emergent AEs: Total Incidence ≥10%

Adverse event	No. (%) DL1 60mg x 7d (N = 6)	DL2 60mg x 14d (N = 6)	DL-1 40mg x 14d (N = 6)
Hypophosphatemia	3 (50)	1 (17)	0
Decreased appetite	2 (33)	1 (17)	2 (33)
Drug eruption	1 (17)	1 (17)	1 (17)
Hypotension	1 (17)	0	1 (17)
Nausea	1 (17)	0	1(17)
Esophagitis	1 (17)	1 (17)	0
Pulmonary Edema	1 (17)	1 (17)	0

Hematologic Recovery After Last Induction Cycle

	Median [Min, Max] (days)[a]		
	DL1 60mg x 7d (N = 6)	DL2 60mg x 14d (N = 6)	DL-1 40mg x 14d (N = 6)
ANC > 1×10^9	43 [27, 55]	30 [24, 80]	48 [34, 50]
Platelets > 100×10^9	49 [27, 92]	31 [29, 52]	36 [25, 61]

[a]18 subjects received at least 1 induction cycle and 6 received 2 cycles

Dose-Limiting Toxicities

Dose Group	Dose Limiting Toxicity	Toxicity Grade	Comments
DL1 60mg x 7d	Hyponatremia	3	Started on Day 12
DL2 60mg x 14d	Pericardial effusion[a]	3	Started on Day 41
DL2 60mg x 14d	QTc prolongation	3	Started on Day 16
DL -1 40mg x 14d	Pericarditis	3	Started on Day 7

[a] Pericardial effusion associated with invasive fungal esophageal candidiasis.

Best Response by FLT3-ITD

Best Response	No. (%)					
	DL1 60mg x 7d (N = 6)		DL2 60mg x 14d (N = 6)		DL-1 40mg x 14d (N = 6)	
	FLT3+ (N=3)	FLT3- (N=3)	FLT3+ (N=3)	FLT3- (N=3)	FLT3+ (N=2)	FLT3- (N=4)
CRc (CR+CRp+CRi)	2 (67)	3 (100)	3 (100)	3 (100)	2 (100)	2 (50)
CR	2 (67)	2 (67)	2 (67)	1 (33)	2 (100)	2 (50)
CRp	0	1 (33)	0	0	0	0
CRi	0	0	1 (33)	2 (67)	0	0
No Response	1 (33)	0	0	0	0	2 (50)

Conclusions

- The data from this Phase 1 study demonstrate that quizartinib can be safely administered with induction and/or consolidation chemotherapy in newly diagnosed younger adults with AML.
- MTD was identified as 40 mg for 14 days or 60 mg for 7 days.
- Based on these findings, Phase 3 studies in newly diagnosed AML patients are planned.

Acknowledgments

- We would like to thank all participating patients and their families, and the network of investigators, research nurses, study coordinators, and operations staff.
- Study 2689-CL-0005 (ClinicalTrials.gov identifier NCT01390337) was supported by Ambit Biosciences Corporation.

Study Investigators:

UNITED STATES J.K. Altman, J.M. Foran, K. W. Pratz, J. E. Cortes, and M.S. Tallman