Efficacy and Safety of Quizartinib (AC220) in Patients Age ≥60 Years with *FLT3*-ITD Positive Relapsed/Refractory Acute Myeloid Leukemia (AML)

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Disclosures

- **Advisory Board**

  Ambit, Arog Pharmaceuticals, Astellas, Bristol-Myers Squibb, Celgene, Clavis, Epizyme, Novartis

Background

- FMS-like tyrosine kinase 3 internal tandem duplication (*FLT3*-ITD) occur in about 20% of adult patients with acute myeloid leukemia (AML) and are associated with early relapse after standard chemotherapy and poor survival
- Quizartinib (AC220), an oral FLT3 inhibitor active against ITD mutant and wild-type FLT3, has shown promising activity in Phase 1 and 2 studies[1-3]

1. Cortes JE, et al. *J Clin Oncol*, in press.
2. Cortes JE, et al. *Blood.* 2012;12:abstr 48.
3. Levis MJ, et al. *Blood.* 2012;120:abstr 673.

Study Design and Patients

- AC220-002: Phase 2, open-label monotherapy study
- Patients with AML and documented *FLT3*-ITD status obtained by a central laboratory
- Patients enrolled into 2 cohorts
  - Cohort 1 (n=154): patients ≥60 years and relapsed/refractory to first-line chemotherapy
  - Cohort 2 (n=176): patients ≥18 years and relapsed/refractory to second-line chemotherapy or hematopoietic stem cell transplantation (HSCT)
- This analysis included all *FLT3*-ITD(+) patients from Cohort 1 (n=110) who had relapsed within <1 year or were refractory to first-line therapy

Study Conduct

Quizartinib oral solution once daily in continuous 28-day cycles until relapse, drug intolerance, or elective hematopoietic stem cell transplantation (HSCT)

- 200 mg/day for the first 17 patients enrolled, this dose was reduced due to **35% grade 3 QTcF prolongation**
- Dose in all subsequent patients
  - Male patients: 135 mg/day
  - Female patients: 90 mg/day

Endpoints

Primary: Response by modified Int'l Working Group criteria*

- Complete remission (CR) rate
- Composite CR rate (CRc): CR + CRp + CRi
  - CR
  - CRp: CR with incomplete platelet recovery: $<100\times10^9$/L
  - CRi : CR with incomplete hematologic recovery: neutrophil count $\leq10^9$/L with or without platelet count $<100\times10^9$/L; not required to be transfusion-independent
- Partial remission (PR): same criteria as for CRi, except that the bone marrow blast count was between 5%–25% and represented a >50% decrease from baseline

Secondary

- Duration of response
- Overall survival

* Cheson BD, et al. *J Clin Oncol*. 2003;21(24):4642–4649.

Baseline Characteristics by Age Group

	FLT3-ITD(+) 60–69 yrs (n=56)	*FLT3*-ITD(+) ≥70 yrs (n=54)	*FLT3*-ITD(+) Total (n=110)
Median (range) age, years	66.0 (60– 69)	73.5 (70–86)	69 (60–86)
Male sex, n (%)	29 (52)	26 (48)	55 (50)
Prior treatment and response			
Prior anthracycline/mitoxantrone, n (%)	48 (86)	39 (72)	87 (79)
Relapsed, n (%)	33 (59)	33 (61)	66 (60)
Median duration CR1, weeks	20.8	28.1	24.4
Refractory n (%)	23 (41)	21 (39)	44 (40)
Prior MDS, n (%)	10 (18)	7 (13)	17 (15)
Cytogenetics,* n (%)	32	30	62
Favorable	0	1 (3)	1 (2)
Intermediate	28 (88)	25 (83)	53 (85)
Poor	4 (13)	4 (13)	8 (13)

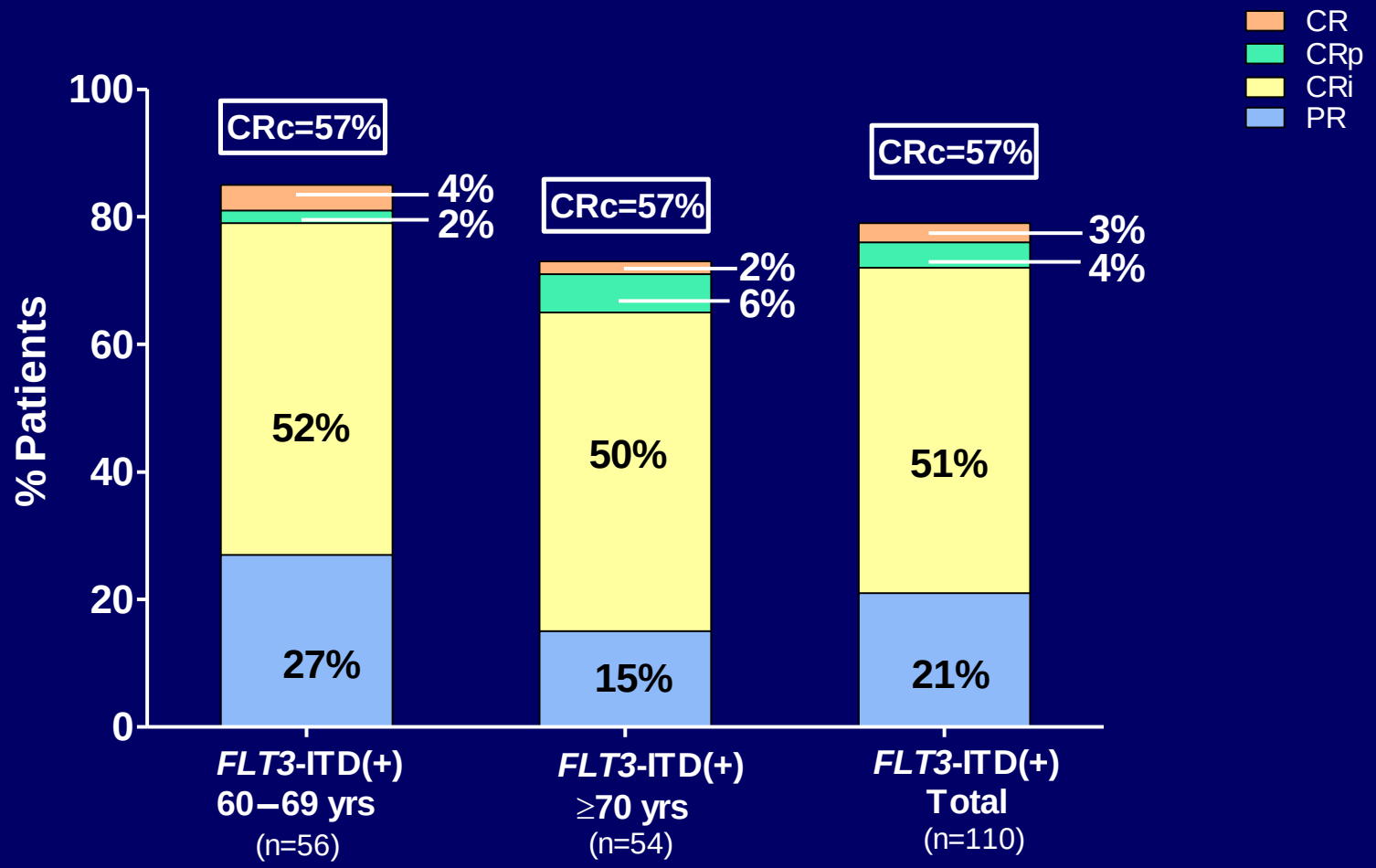
*Cytogenetic data were only collected for 56% of *FLT3*-ITD(+) patients; risk classification per Grimwade D, et al. *Blood*. 2001;98(5):1312-1320.

Patient Disposition by Age Group

	FLT3-ITD(+) 60–69 yrs (n=56)	*FLT3*-ITD(+) ≥70 yrs (n=54)	*FLT3*-ITD(+) Total (n=110)
Study treatment discontinued, n (%)	55 (98)	53 (98)	108 (98)
Lack of response/progressive disease	30 (54)	35 (65)	65 (59)
Adverse events	12 (21)	12 (22)	24 (22)
Elective stem cell transplantation	9 (16)	1 (2)	10 (9)
Death	2 (4)	4 (7)	6 (5)
Other*	2 (4)	1 (2)	3 (3)
Median duration of follow-up (range), weeks	29.7 (0.4–96.0+)	22.7 (1.0–93.0+)	25.4 (0.4–96.0+)
Median duration of quizartinib treatment (range), weeks	13.7 (0.1–63.9)	14.9 (0.9–70.6+)	14.1 (0.1–70.6+)

FLT3-ITD=FMS-like tyrosine kinase 3 internal tandem duplication.
*Other reasons for study treatment discontinuation include patient decision (n=2) and patient non-compliance (n=1).

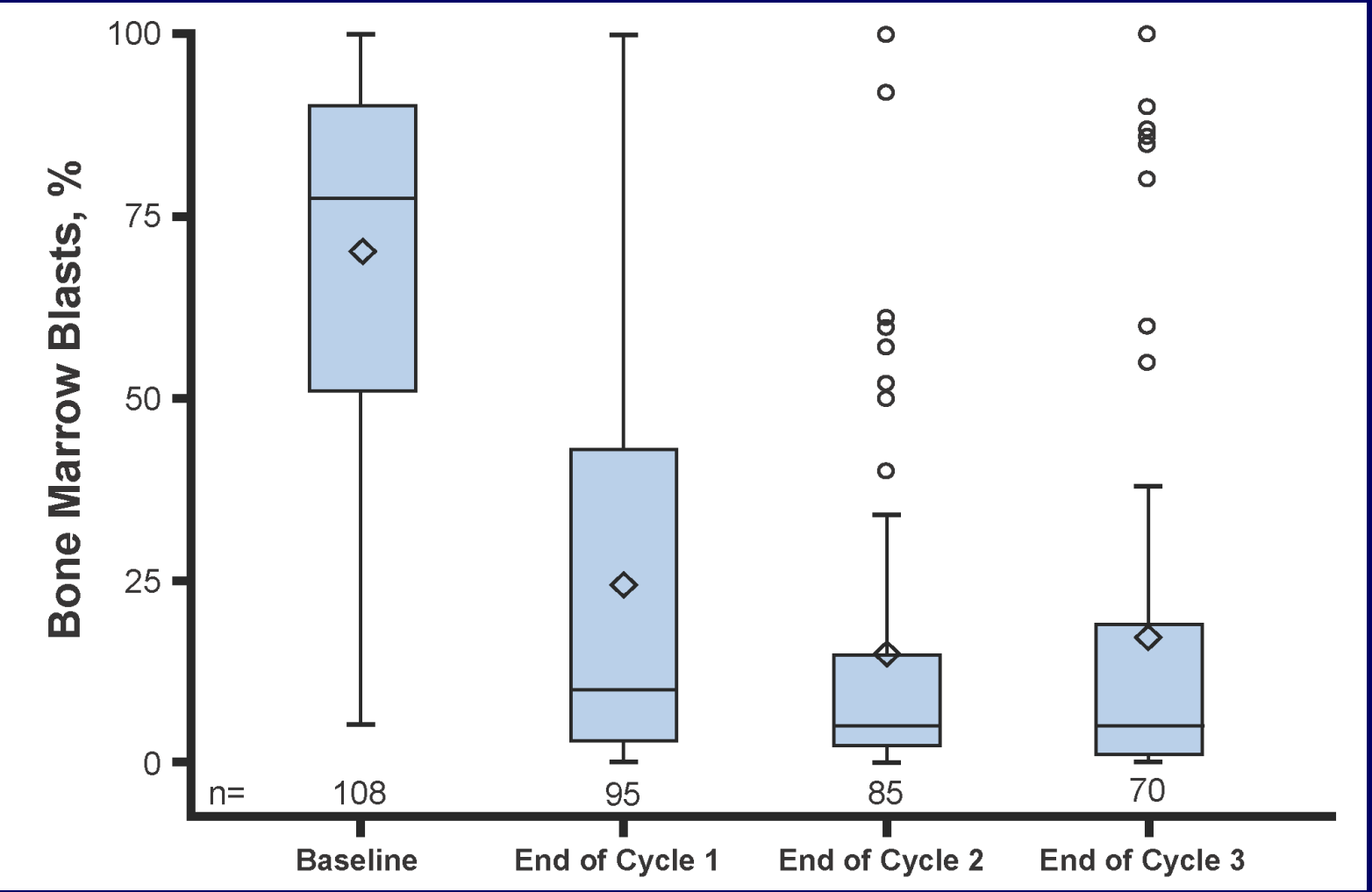
Response to Therapy



	FLT3-ITD(+) 60–69 yrs	*FLT3*-ITD(+) >70 yrs	*FLT3*-ITD(+) Total
Median (range) duration CRc, weeks	8.0 (0.1–57.9)	13.9 (0.1+–58.9)	12.1 (0.1–58.9)
Median (range) time to CRc, weeks	4.3 (2.1–20.9)	5.9 (2.1–12.3)	4.3 (2.1–20.9)

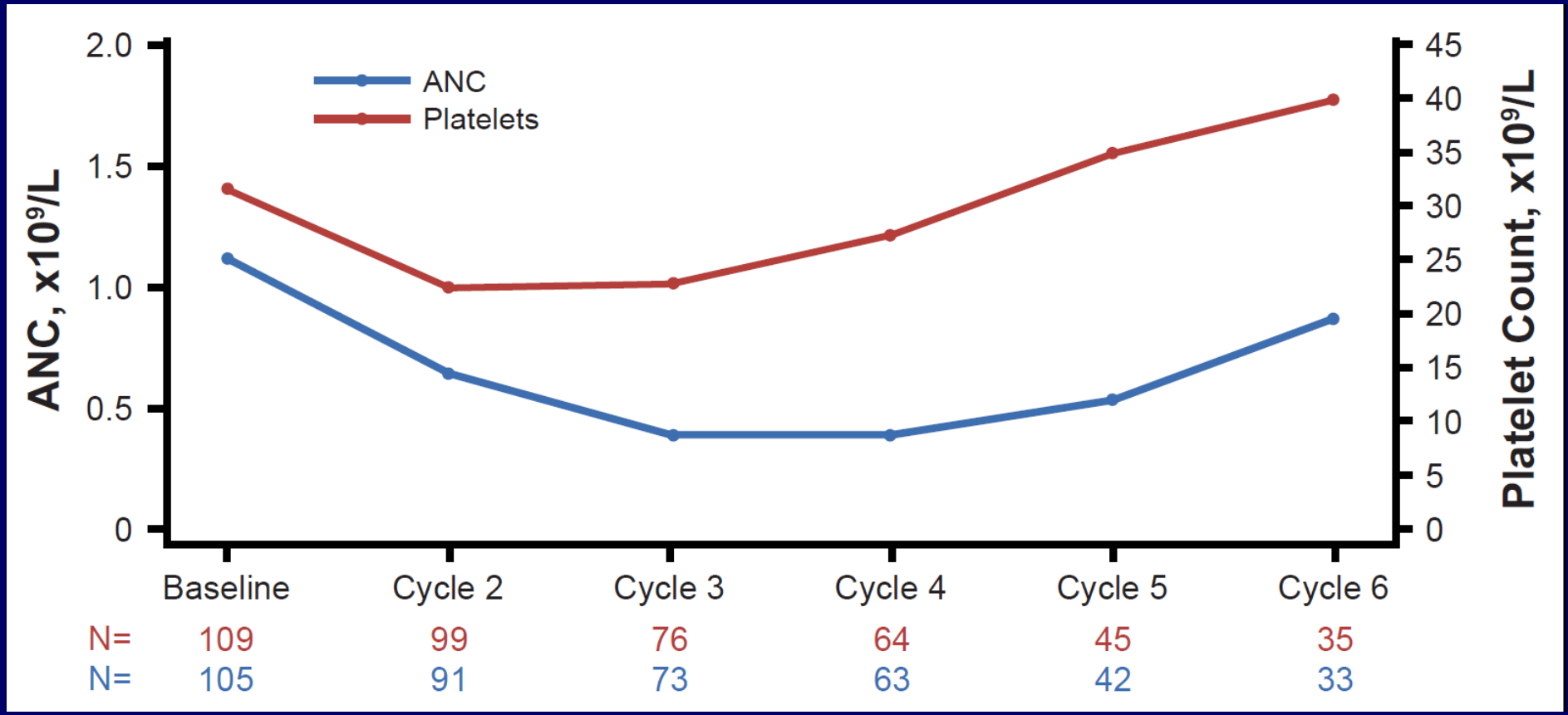
CR=complete remission; CRc=composite complete remission; CRi=complete remission with incomplete hematologic recovery; CRp=complete remission with incomplete platelet recovery; PR=partial remission.

Rapid Decrease in Bone Marrow Blasts



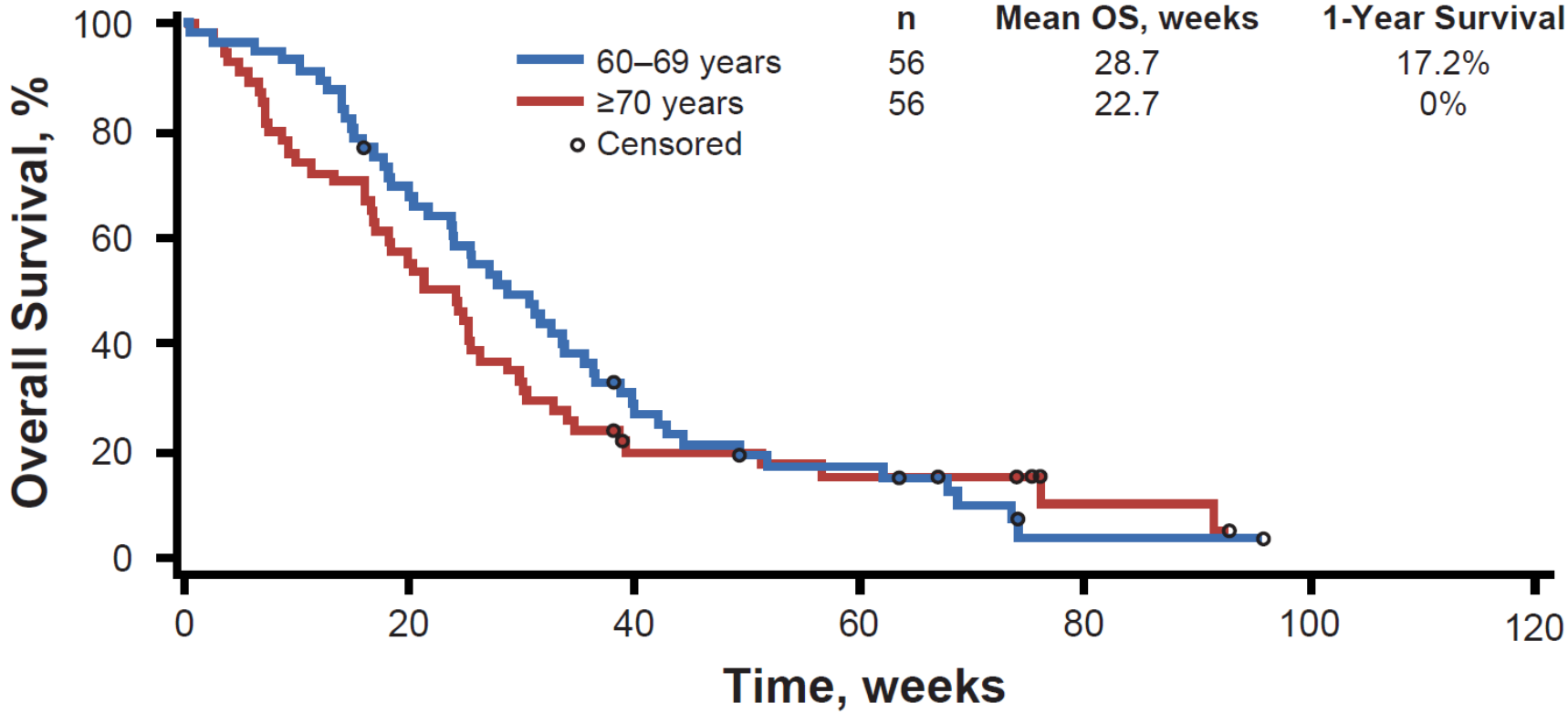
Box plots show medians (horizontal line in each box), 25th and 75th percentiles (upper and lower ends of each box), means (diamond in each box), 10th and 90th percentiles (bars), and individual outliers (circles); median BM Blast % = 77.5% (baseline), 10% (cycle 1), 4.9% (cycle 2 & cycle 3)

Median ANC and Platelets Over Time



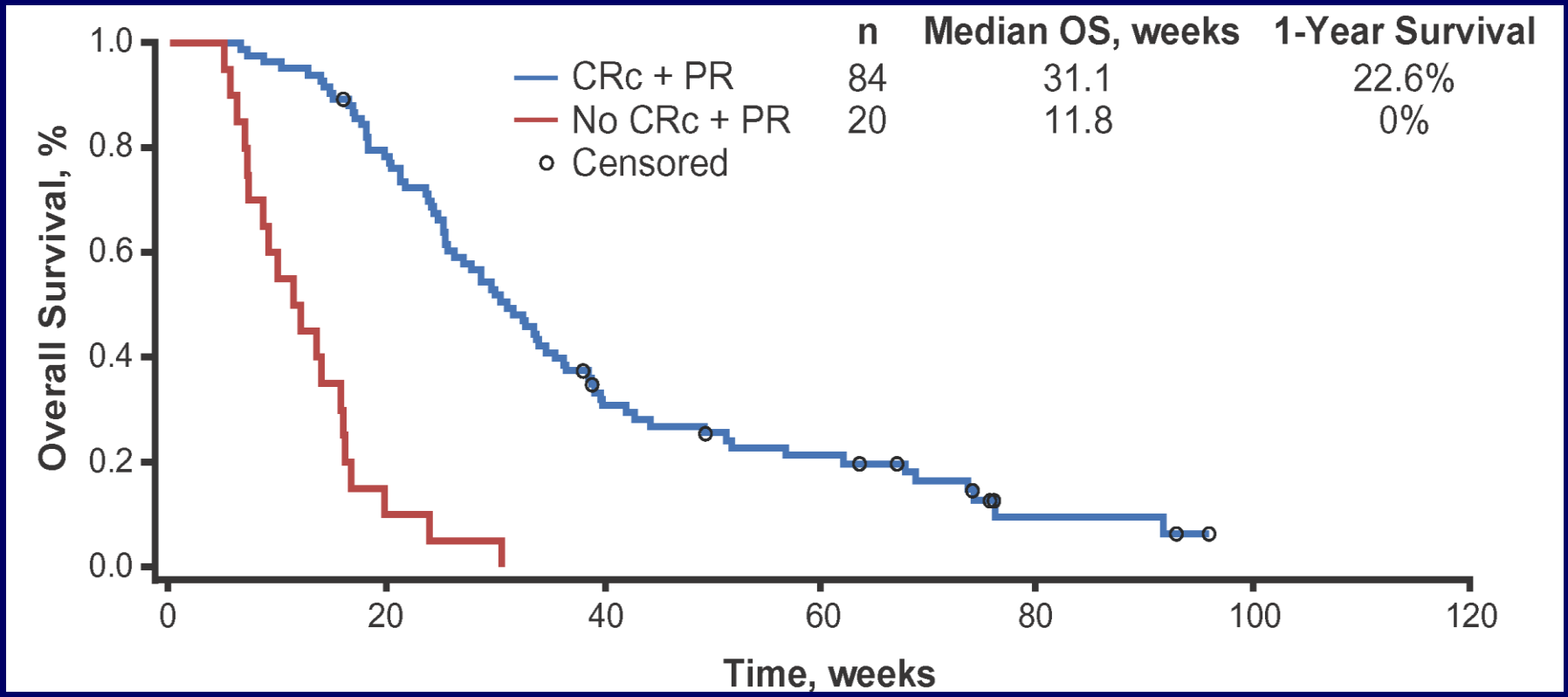
ANC=absolute neutrophil count; CRc=composite complete remission.

Overall Survival by Age Group



Median OS in all subjects ≥60 years is 25.3 weeks.

Survival by Response*



*Analysis of 104 *FLT3*-ITD(+) patients surviving ≥28 days

Long-Term Survivors

- 16 of 110 (15%) *FLT3*-ITD(+) patients remained alive for >12 months after taking quizartinib
- Of these16 long-term survivors:
  - 50% were 70 years of age or older
  - 56% were refractory to prior therapy
  - 44% were relapsed with a median CR1 of 34.0 weeks
  - All achieved at least a PR (2 CR, 2 CRp, 8 CRi, and 4 PR) to quizartinib and remained on treatment for a median of 52.1 weeks, with survival from 56–96+ weeks
- 2 Patients remain on quizartinib

Grade 3/4 Adverse Events in ≥5% Pts

Term, n (%)	*FLT3*-ITD(+) 60–69 yrs (n=56)	*FLT3*-ITD(+) ≥70 yrs (n=54)	*FLT3*-ITD(+) Total (n=110)
Anemia	18 (32)	10 (19)	28 (25)
Febrile neutropenia	15 (27)	9 (17)	24 (22)
Thrombocytopenia	12 (21)	9 (17)	21 (19)
Neutropenia	10 (18)	4 (7)	14 (13)
Electrocardiogram QTcF prolonged*	3 (5)	8 (15)	11 (10)
Leukopenia	7 (13)	4 (7)	11 (10)
Fatigue	2 (4)	5 (9)	7 (6)
Pyrexia	1 (2)	4 (7)	5 (5)

Number of patients with any grade 3 or 4 treatment-related adverse events (AE): total group: 83 (75%); 60-69 years: 40 (71%); ≥70 years: 43 (80%).

*To date, there has been 1 grade 4 QTcF prolongation (torsade de pointes), which resolved after drug discontinuation.

QTcF Prolongation

	200 mg (n=5)	135 mg (n=53)	90 mg (n=52)
Maximum post-baseline QTcF, n (%)			
>450 to ≤480 ms (grade 1)	1 (20)	16 (30)	21 (40)
>480 to ≤500 ms (grade 2)	2 (40)	15 (28)	18 (35)
>500 ms* (grade 3/4)	1 (20)	8 (15)	8 (15)
Maximum change in post-baseline QTcF, n (%)			
≤30 ms	0	3 (6)	5 (10)
>30 to ≤60 ms	2 (40)	26 (49)	26 (50)
>60 ms	3 (60)	22 (42)	20 (38)

*To date, there has been 1 grade 4 QTcF prolongation (torsade de pointes), which resolved after drug discontinuation.

Summary

- In this analysis of *FLT3*-ITD(+) patients aged ≥60 years with a poor prognosis, nearly 50% were refractory to their last therapy, and the remainder had a short median duration of CR1; 54/110 (49%) were aged ≥70 years. Despite this:
  - CRc rate: 57% for all pts and those aged ≥70 years
  - Median OS: 25.3 wks for all pts and 22.7 wks for pts aged ≥70 yrs
- 16/110 (15%) patients were alive for >12 months
  - All long-term survivors achieved at least a PR to quizartinib; median duration of treatment was 52.1 weeks
  - 8/16 (50%) long-term survivors were aged ≥70 years
- Quizartinib was generally well tolerated, with a 30-day mortality rate of 5%

Conclusions

- These data for quizartinib show encouraging survival in a subset of elderly patients with relapsed/refractory *FLT3*-ITD(+) AML
- For patients who remained alive >1 year, the majority of whom were refractory or had a short CR1 duration, the long-term survival rate supports the clinical benefit of quizartinib
- A Phase 3 study in adult relapsed or refractory *FLT3*-ITD(+) patients comparing quizartinib to salvage chemotherapy is planned to start in early 2014

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