Administration of Quizartinib
ICD-10 Coordination and Maintenance Committee Meeting
March 7, 2023

These materials are presented pursuant to the provisions of the FDA guidance on "Drug and Device Manufacturer Communications With Payors, Formulary Committees, and Similar Entities" pertaining to communications regarding unapproved drug products and unapproved uses of approved drug products. We emphasize that the product addressed herein is investigational at this time and has not been determined to be safe and effective by the FDA. This information is current as of [08/15/2022] and is subject to change based on new data and/or FDA actions with respect to pending applications.

PP-US-QZ-0259   08/22

AML is an aggressive and rare cancer of the blood and bone marrow

Disease overview

AML is a rapidly growing type of blood cancer in which immature bone marrow cells (blasts) are overproduced and accumulate in bone marrow and other tissues[1-3]

~30%

of newly diagnosed patients with AML have a *FLT3* mutation[4-6]

Estimated incidence

(United States)

Newly diagnosed cases in 2022[7]:

20,050

Incidence rate (per 100,000) in 2019[8]:

4.1

Poor prognosis

The probability of long-term survival for patients with AML is low

AML is the leading cause of death among adult leukemias, accounting for

~48% of deaths

due to leukemia[9,a]
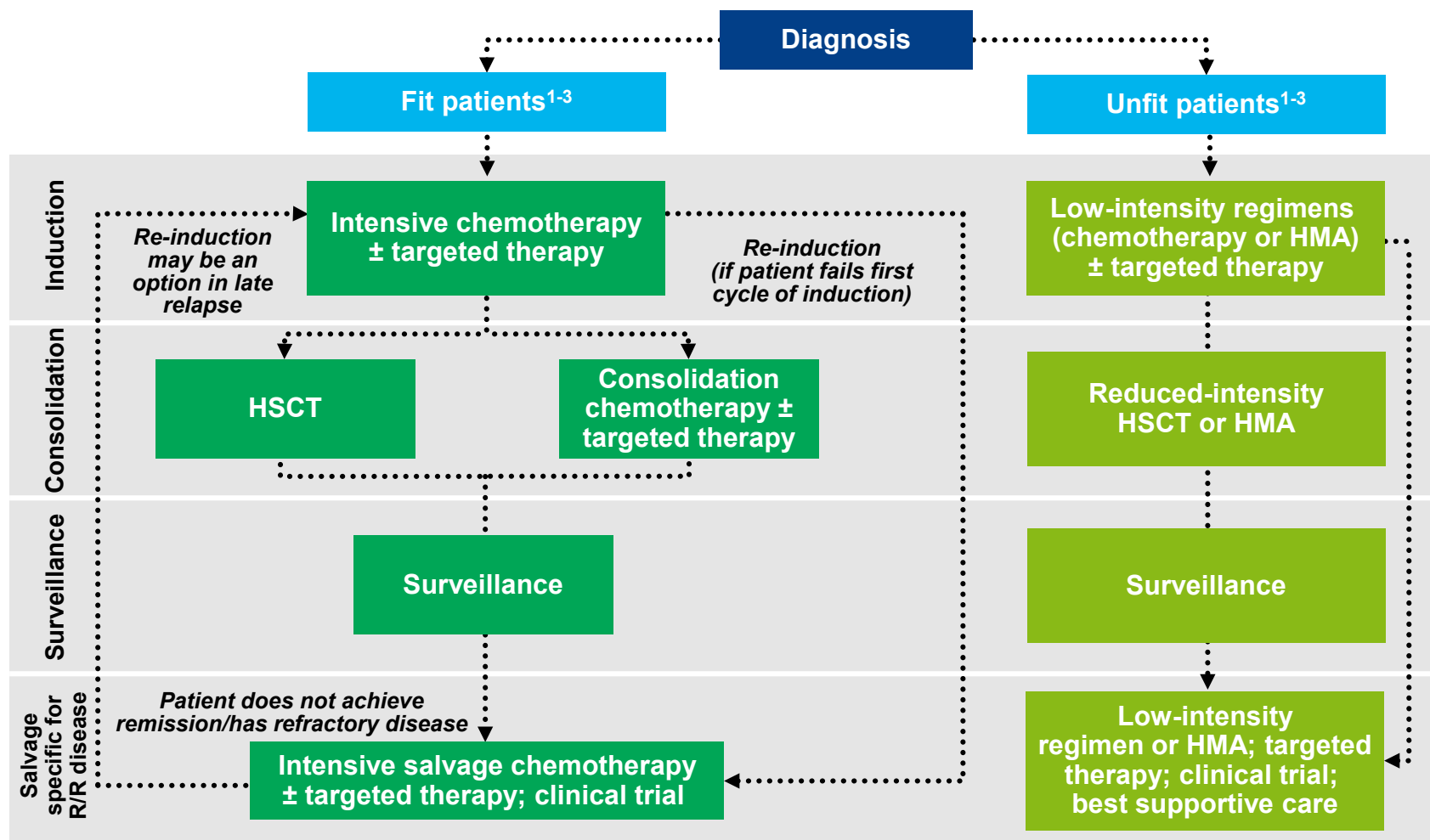
The 5-year survival rate for AML is only

30.5%[7]

[a]Based on an estimated 24,000 deaths due to leukemia in the United States in 2022. Estimated deaths are based on 2005-2019 US mortality data as reported to the National Center for Health Statistics.

Abbreviation: FLT3, fms-like tyrosine kinase 3.

References: 1. Adult acute myeloid leukemia treatment (PDQ®)—patient version. National Cancer Institute. Updated March 4, 2022. Accessed June 24, 2022. https://www.cancer.gov/types/leukemia/patient/adult-aml-treatment-pdq#section/all **2.** Ferrara F, et al. *Lancet*. 2013;381(9865):484-495. **3.** Liesveld JL, Lichtman MA. Acute myelogenous leukemia. In: Kaushansky K, Lichtman MA, Prchal JT, et al, eds. Williams Hematology. 9th ed. New York, NY: McGraw Hill Education; 2016. **4.** Kantarjian HM, et al. *Cancer*. 2021;127(8):1186-1207. **5.** Kantarjian H, et al. *Blood Cancer J.* 2021;11(2):41. **6.** Grimwade D, et al. *Blood*. 2016;127(1):29-41. **7.** Cancer stat facts: leukemia—acute myeloid leukemia (AML). Surveillance, Epidemiology, and End Results (SEER) Program. Accessed June 13, 2022. https://seer.cancer.gov/statfacts/html/amyl.html **8.** SEER*Explorer: An interactive website for SEER cancer statistics. Accessed June 22, 2022. Surveillance Research Program, National Cancer Institute https://seer.cancer.gov/statistics-network/explorer/ **9.** Siegel RL, et al. *CA Cancer J Clin*. 2022;72(1):7-33.

Treatment Differs for Fit and Unfit AML Patients

Simplified treatment flow diagram based on ELN/NCCN Guidelines. Patient fitness is assessed throughout the course of treatment.

Abbreviations: ELN, European LeukemiaNet; HMA, hypomethylating agent; NCCN, National Comprehensive Cancer Network; R/R, relapsed/refractory.

References: 1. Döhner H et al. *Blood*. 2017;129(4):424-447. **2.** NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Acute Myeloid Leukemia V.2.2022. © National Comprehensive Cancer Network, Inc. 2022. All rights reserved. Accessed August 22, 2022. **3.** Percival ME, Estey E. *Clin Adv Hematol Oncol*. 2017;15(8):632-642.

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Molecular testing identifies specific mutations that can further refine risk categories, another crucial aspect of assessing prognosis and making treatment decisions
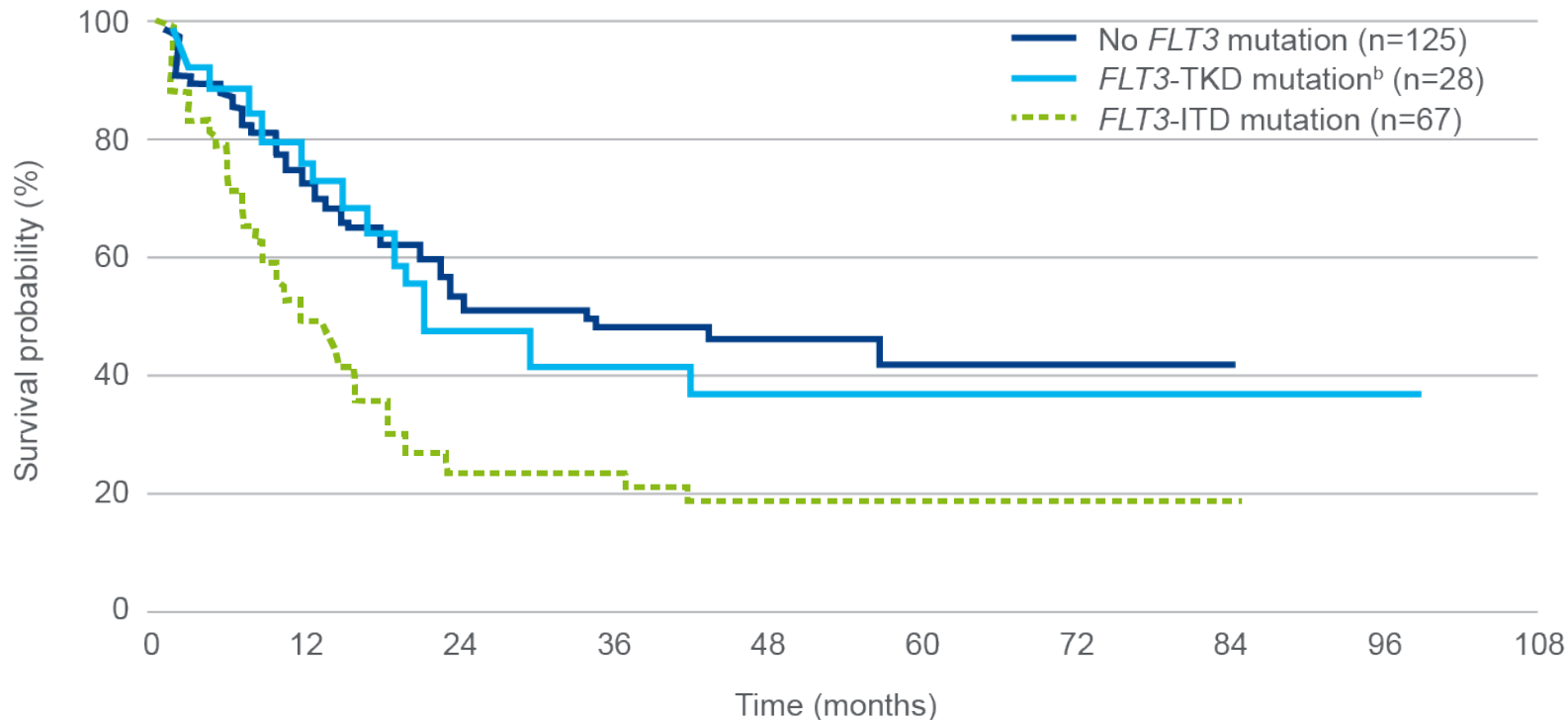
- **There are two subtypes of the *FLT3* mutation[2-4,6]**
  - **Internal tandem duplication (ITD); estimated 25% prevalence[1-5]**
  - Tyrosine kinase domain (TKD) point mutations (most commonly D835); estimated 7% prevalence[2,6]
- **Numerous studies have shown the poor prognosis associated with *FLT3*-ITD+ AML[2]**
  - Shorter remission durations and worse survival outcomes compared with *FLT3*-Wild Type (FLT3-WT)[7-8]
- ***FLT3*-TKD is less common and has undetermined prognostic significance[2]**

References: 1. Döhner H, et al. *N Engl J Med*. 2015;373(12):1136-1152. **2.** NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Acute Myeloid Leukemia V.2.2022. © National Comprehensive Cancer Network, Inc. 2022. All rights reserved. Accessed August 22, 2022. **3.** Santos FPS, et al. *Cancer*. 2011;117(10):2145-2155. **4.** Schneider F, et al. *Ann Hematol*. 2012;91(1):9-18. **5.** Dohner H, et al. *Blood*. 2017;129(4):424-447. **6.** Grimwade D, et al. *Blood*. 2016;127(1):29-41. **7.** Fröhling S, et al. *Blood*. 2002;100(13):4372-4380. 8**.** Brunet S, et al. *J Clin Oncol*. 2012;30(7):735-741.

Overall survival in AML by *FLT3* mutation status[1,a]

Legend:
— No *FLT3* mutation (n=125)
— *FLT3*-TKD mutation[b] (n=28)
---- *FLT3*-ITD mutation (n=67)

Y-axis: Survival probability (%)
X-axis: Time (months)

In a separate analysis of 206 AML patients with normal cytogenetics and *FLT3*-ITD data who underwent allogeneic HSCT during CR1, **those with *FLT3*-ITD mutations[2]:**

- **were 3.4x more likely to relapse** than those with no *FLT3*-ITD mutations
- had a **relapse rate of 30%** at 2 years (vs 16% for those without *FLT3*-ITD mutations)
- had **>2x the risk** of relapse or death

[a]German study of 523 younger adult patients (aged ≤60 years) with mostly de novo AML (from 2 trials), treated with intensive induction and consolidation regimens. Patients in this analysis had normal cytogenetics (n=224), and median follow-up was 34 months. The objective was to assess the prognostic relevance of *FLT3* mutations.

[b]*FLT3* D835 (TKD) mutation.

Abbreviations: CR1, complete remission after first induction; HSCT, hematopoietic stem cell transplant; ITD, internal tandem duplication; TKD, tyrosine kinase domain; WT, wild-type.

References: 1. Fröhling S, et al. *Blood*. 2002;100(13):4372-4380. **2.** Brunet S, et al. *J Clin Oncol.* 2012;30(7):735-741.

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In a phase 3 trial, patients up to age 59 treated with midostaurin had a **cumulative incidence of relapse of**

40% at 2 years[1]

Cumulative incidence of relapse[1,a]

Arm	Median	(95% CI)
Midostaurin	NE	(NE–31.3)
Placebo	NE	(NE–17.6)
		+ Censor

No. at Risk

Midostaurin	212	147	105	94	73	36	9	0
Placebo	191	102	76	68	56	22	6	0

aTreating death as a competing risk (protocol complete responses only).

Abbreviations: NE, not evaluable; OS, overall survival.

Reference: 1. Stone RM, et al. *N Engl J Med.* 2017;377(5):454-464.

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Quizartinib

Proposed indication statement:

Quizartinib is a kinase inhibitor indicated in combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy, and as continuation monotherapy following consolidation, for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) that is FMS-like tyrosine kinase 3 internal tandem duplication (FLT3-ITD) positive as detected by an FDA-approved test.
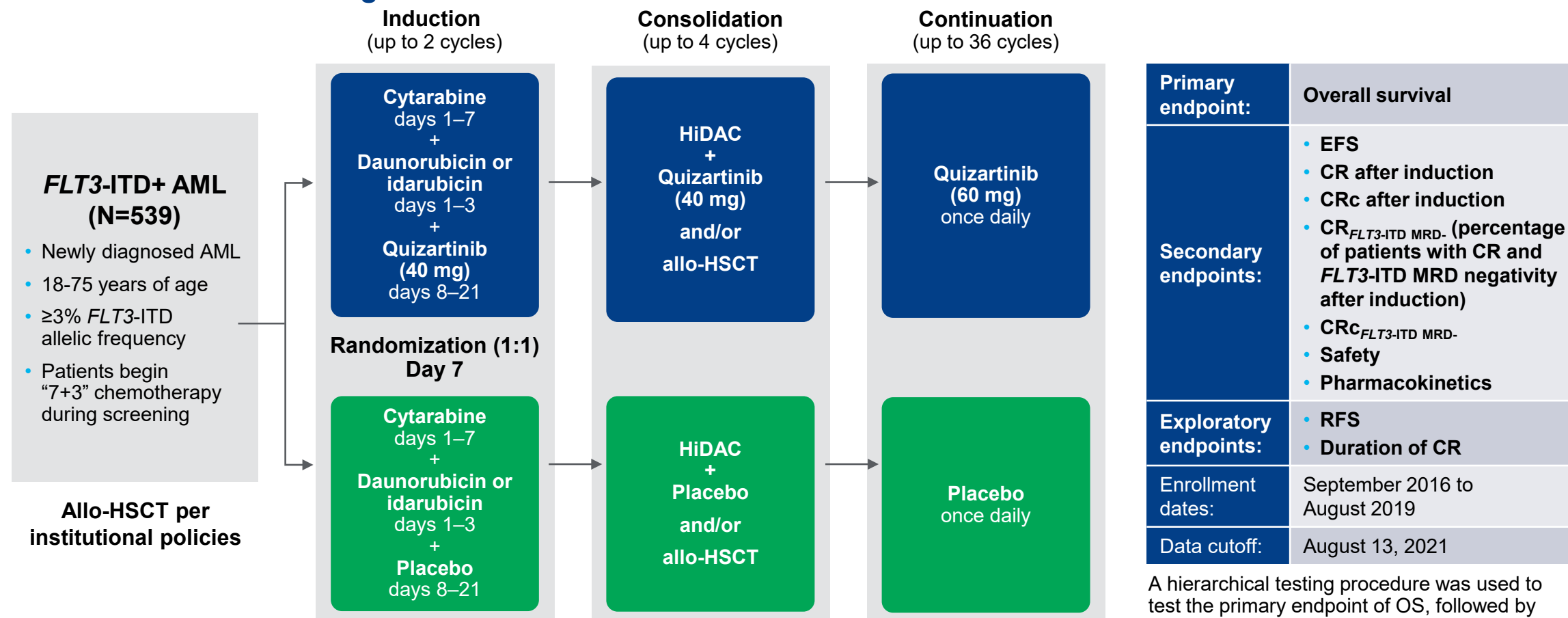
- Quizartinib is a kinase inhibitor with a proposed indication in combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy, and as continuation monotherapy following consolidation, for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) that is FLT3-ITD positive as detected by an FDA-approved test

- Quizartinib may be taken with or without food at approximately the same time every day

- Warnings and Precautions for Quizartinib Include:

  – QT interval prolongation

  – Embryo-Fetal Toxicity

  – Quizartinib is contraindicated in patients with congenital long QT syndrome

- The safety of quizartinib is based on 265 patients taking quizartinib and 268 patients taking placebo diagnosed with FLT3-ITD positive AML

- Median duration of therapy was 10.7 weeks (range: 0.1 to 184.1) for patients in the quizartinib arm versus 9.5 weeks (range: 0.4 to 181.9) for patients in the placebo arm

- Quizartinib administration would be documented in the medication administration record (MAR) in the patient's medical record (PMR)

Prescribing Information for VANFLYTA (quizartinib). Daiichi Sankyo.

A phase 3 randomized study vs placebo in patients aged 18-75 years with up to 3 years of continuation therapy[1,2]

QuANTUM-First trial design[1,2]

	Induction (up to 2 cycles)	Consolidation (up to 4 cycles)	Continuation (up to 36 cycles)

FLT3-ITD+ AML (N=539)
- Newly diagnosed AML
- 18-75 years of age
- ≥3% *FLT3*-ITD allelic frequency
- Patients begin "7+3" chemotherapy during screening

Allo-HSCT per institutional policies

Randomization (1:1) Day 7

Induction (arm 1): Cytarabine days 1–7 + Daunorubicin or idarubicin days 1–3 + Quizartinib (40 mg) days 8–21

Consolidation (arm 1): HiDAC + Quizartinib (40 mg) and/or allo-HSCT

Continuation (arm 1): Quizartinib (60 mg) once daily

Induction (arm 2): Cytarabine days 1–7 + Daunorubicin or idarubicin days 1–3 + Placebo days 8–21

Consolidation (arm 2): HiDAC + Placebo and/or allo-HSCT

Continuation (arm 2): Placebo once daily

Primary endpoint:	**Overall survival**
Secondary endpoints:	• EFS • CR after induction • CRc after induction • $CR_{FLT3\text{-ITD MRD-}}$ (percentage of patients with CR and *FLT3*-ITD MRD negativity after induction) • $CRc_{FLT3\text{-ITD MRD-}}$ • Safety • Pharmacokinetics
Exploratory endpoints:	• RFS • Duration of CR
Enrollment dates:	September 2016 to August 2019
Data cutoff:	August 13, 2021

A hierarchical testing procedure was used to test the primary endpoint of OS, followed by EFS, CR, and CRc.

Abbreviations: CRc, composite complete remission; EFS, event-free survival, MRD, minimum residual disease; RFS, relapse-free survival.

References: 1. Erba H, et al. Presented at the European Hematology Association Annual Meeting; Vienna, Austria; June 9–12, 2022. Abstract S100. **2.** ClinicalTrials.gov identifier: NCT02668653. Updated April 15, 2022. Accessed July 22, 2022. https://clinicaltrials.gov/ct2/show/NCT02668653

Quizartinib is an investigational agent and has not been approved by the United States Food and Drug Administration for any indication; therefore, its safety and efficacy have not been established.

Inclusion criteria

- Age ≥18 and ≤75 years
- Newly diagnosed AML
- Morphologically documented primary AML or AML secondary to MDS or MPN, based on the WHO 2008 classification (at screening)
- *FLT3*-ITD positive, defined as an allelic frequency of ≥3% (*FLT3*-ITD/total *FLT3*)
- Patient is receiving standard "7+3" induction chemotherapy regimen, as specified in the protocol
- ECOG performance status of 0-2 at the time participant signs first ICF
- Adequate renal, hepatic function; serum electrolytes within normal limits (potassium, calcium, and magnesium)

Exclusion criteria

- Diagnosis of APL or *BCR-ABL*+ leukemia
- AML secondary to prior chemotherapy or radiotherapy for neoplasms
- History of known CNS leukemia, including cerebrospinal fluid positive for AML blasts
- Prior treatment for AML
- Prior treatment with any investigational drug (including quizartinib or other *FLT3* inhibitors) or device within 30 days prior to randomization or current participation in other investigational procedures
- History of other malignancies, except adequately treated non-melanoma skin cancer, curatively treated in situ disease, or other solid tumors curatively treated with no evidence of disease for ≥2 years
- Uncontrolled or significant cardiovascular disease or active clinically relevant liver disease
- Uncontrolled active acute or chronic systemic fungal, bacterial, or viral infection

Abbreviations: APL, acute promyelocytic leukemia; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; ICF, informed consent form; ITD, internal tandem duplication; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; WHO, World Health Organization.

Reference: ClinicalTrials.gov identifier NCT02668653. Updated April 15, 2022. Accessed July 25, 2022. https://clinicaltrials.gov/ct2/show/NCT02668653

Baseline patient characteristics in QuANTUM-First

Patient characteristic	Quizartinib (n=268)[a]	Placebo (n=271)[a]
Age, years		
Median range	56 (23-75)	56 (20-75)
≥60 years, %	39.9	40.2
Gender, %		
Male	46.3	44.6
Female	53.7	55.4
Race, %		
White	59.3	60.1
Asian	29.9	28.8
Black or African-American	0.7	1.8
American Indian or Alaska Native	0	0.4
Other races	10.1	8.9
Region, %		
North America	6	6.6
Europe	60.8	60.1
Asia/other regions	33.2	33.2

[a]Three patients in the ITT set were randomized but not treated.

Abbreviation: ITT, intention to treat.

Reference: Erba H, et al. Presented at the European Hematology Association Annual Meeting; Vienna, Austria; June 9–12, 2022. Abstract S100.

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Baseline disease characteristics in QuANTUM-First

Disease characteristic, %	Quizartinib (n=268)[a]	Placebo (n=271)[a]
ECOG performance status[b]		
0	32.5	36.2
1	50.0	50.2
2	17.5	13.3
Cytogenic risks		
Favorable	5.2	7
Intermediate	73.5	71.2
Unfavorable	7.1	10.0
Unknown	14.2	11.4
Missing	0	0.4
Mutated NPM1	53.0	51.7
***FLT3*-ITD/total *FLT3*[c,d]**		
≥3% to ≤25%	35.1	36.2
>25% to ≤50%	53.4	50.9
>50%	11.2	12.9
WBC count at diagnosis of AML		
<40×10^9/L	50.4	50.6
≥40×10^9/L	49.6	49.4

[a]Three patients in the ITT set were randomized but not treated in each arm.
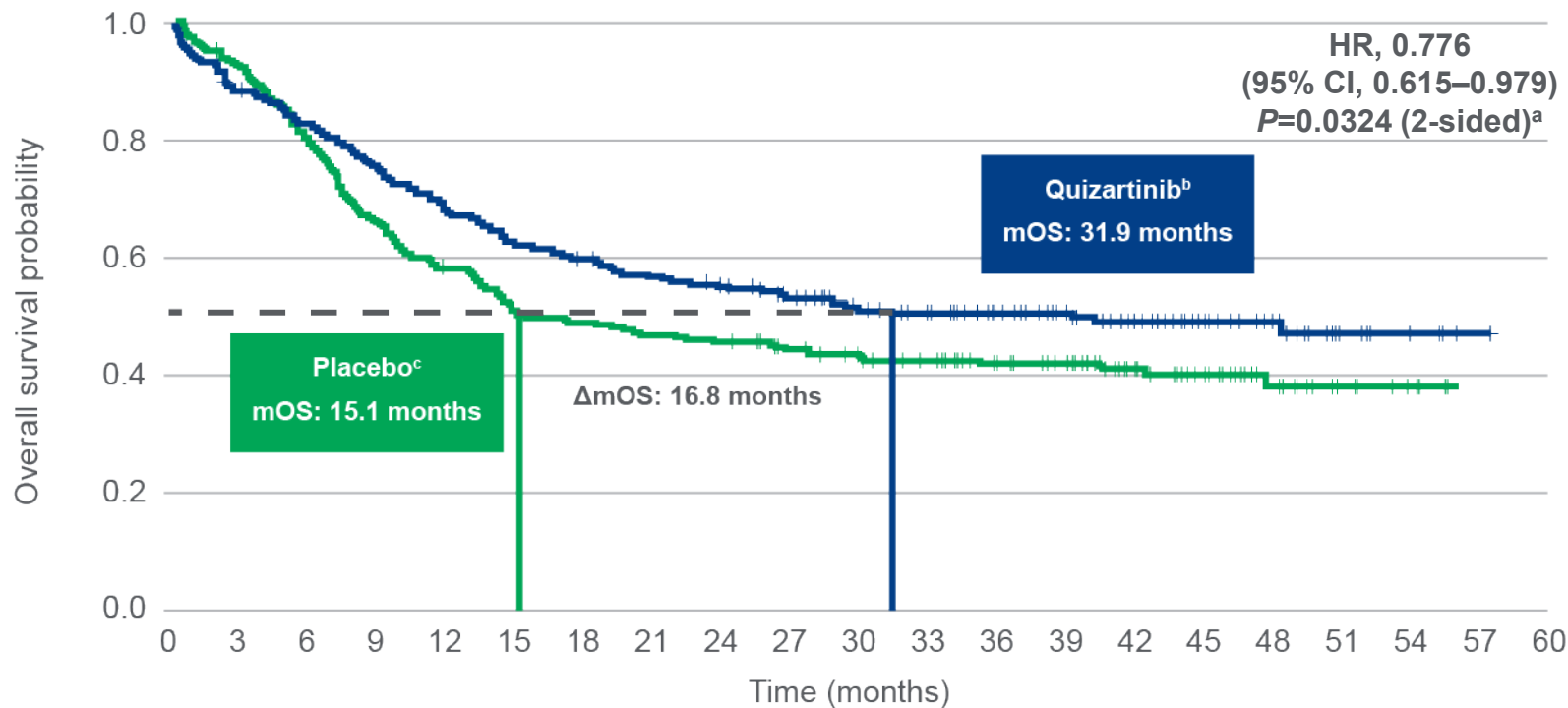[b]One patient in the placebo group was missing an ECOG status.
[c]Variant allele frequency was assessed by central lab testing.
[d]One patient with unknown *FLT3*-ITD/total *FLT3* was positive per local laboratory testing.

Abbreviation: WBC, white blood cell.

Reference: Erba H, et al. Presented at the European Hematology Association Annual Meeting; Vienna, Austria; June 9–12, 2022. Abstract S100.

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Quizartinib + chemotherapy reduced the risk of death by 22% and more than doubled the median OS compared with placebo + chemotherapy.

HR, 0.776
(95% CI, 0.615–0.979)
P=0.0324 (2-sided)[a]

Quizartinib[b]
mOS: 31.9 months

Placebo[c]
mOS: 15.1 months

ΔmOS: 16.8 months

No. at risk																				
Quizartinib	268	233	216	195	176	162	153	145	139	126	110	96	83	68	53	36	24	8	4	1	0
Placebo	271	249	211	175	151	131	126	121	117	103	97	81	70	56	39	31	17	8	5	0	0

[a]*P*-value was calculated using a stratified log-rank test.
[b]Median follow-up time for quizartinib arm, 39.2 months.
[c]Median follow-up time for placebo arm, 39.2 months.

Abbreviations: CI, confidence interval; HR, hazard ratio; mOS, median overall survival.
Reference: Erba H, et al. Presented at the European Hematology Association Annual Meeting; Vienna, Austria; June 9–12, 2022. Abstract S100.

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Response and duration of CR[a]

Parameter	Quizartinib (n=268)	Placebo (n=271)
CRc		
%	71.6	64.9
95% CI	(65.8–77.0)	(58.9–70.6)
CR		
%	54.9	55.4
95% CI	(48.7–60.9)	(49.2–61.4)
CRi		
%	16.8	9.6
95% CI	(12.5–21.8)	(6.4–13.7)
Duration of CR		
Median, months	38.6	12.4
95% CI	(21.9–NE)	(8.8–22.7)

- Numerically higher rates of CRc were observed in the quizartinib arm compared with the placebo arm, primarily driven by an increased rate of CRi
- CR rates were similar between treatment arms
- Duration of CR was approximately 38.6 months in the quizartinib arm and 12.4 months in the placebo arm

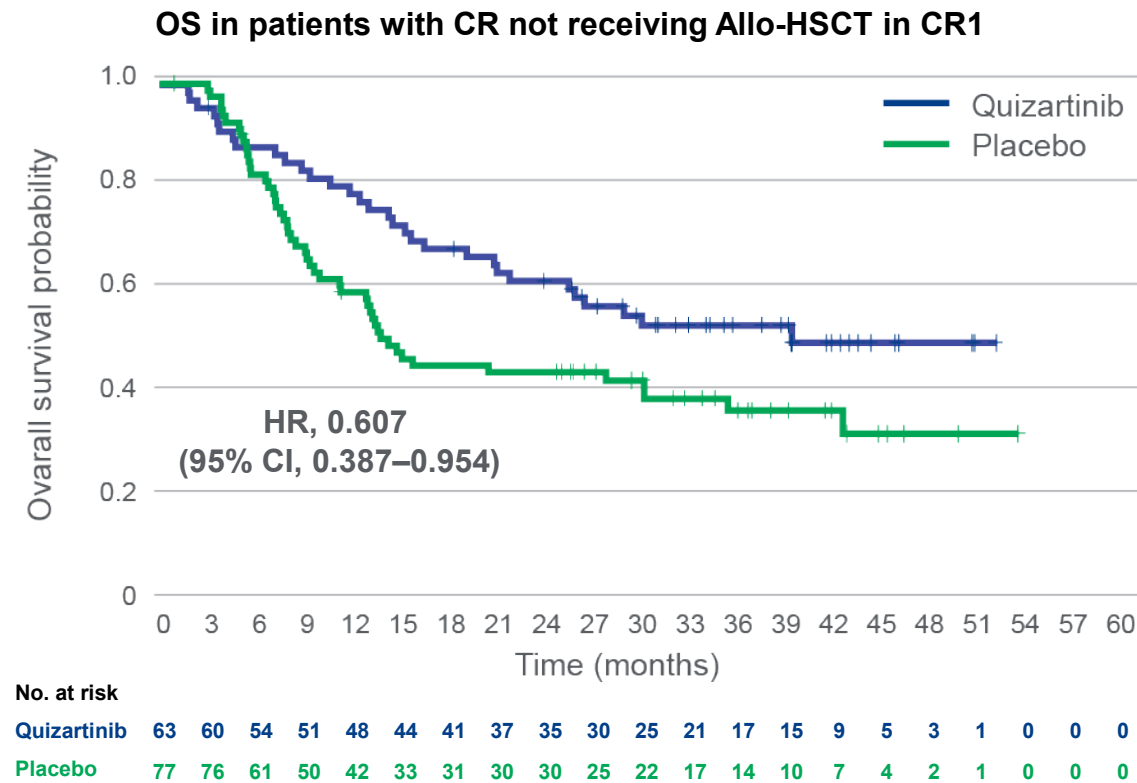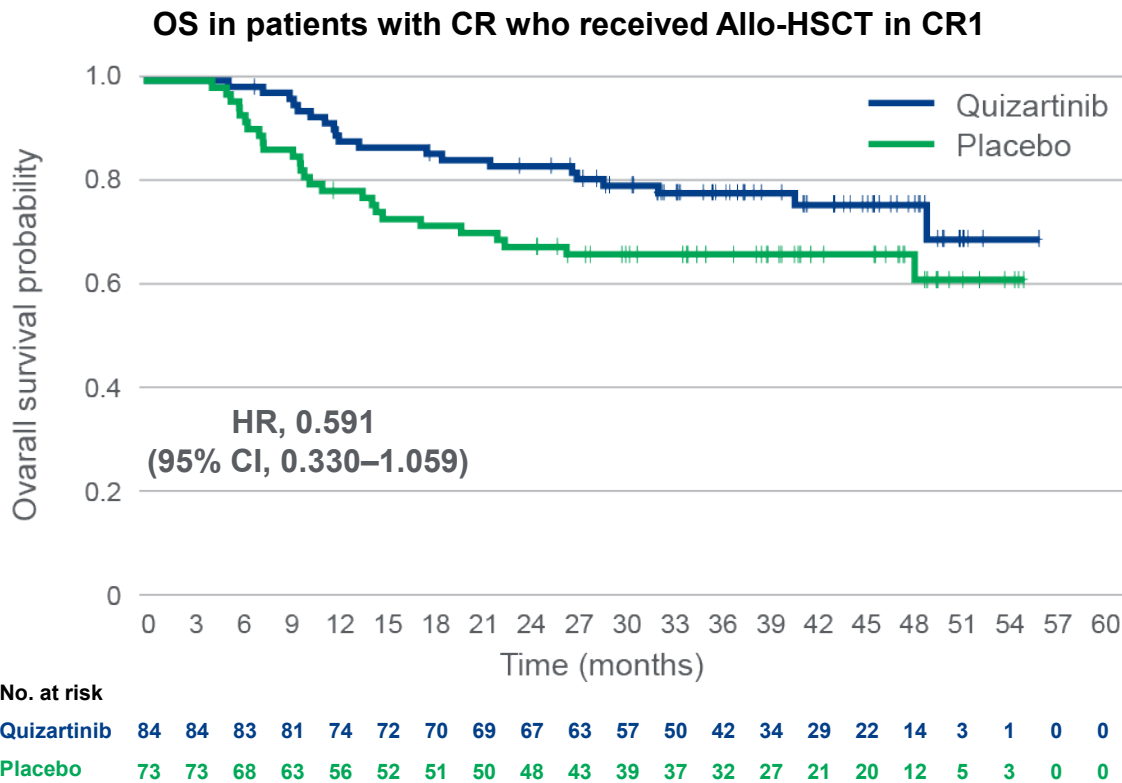[a]By end of induction by independent review committee.

Abbreviations: CR, complete response; CRc, composite complete remission; CRi, complete remission with incomplete neutrophil or platelet recovery; NE, not evaluable.

Reference: Erba H, et al. Presented at the European Hematology Association Annual Meeting; Vienna, Austria; June 9–12, 2022. Abstract S100.

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OS trended longer with quizartinib in patients who achieved CR regardless of receiving transplant in CR1.

OS in patients with CR who received Allo-HSCT in CR1

HR, 0.591
(95% CI, 0.330–1.059)

No. at risk																			
Quizartinib	84	84	83	81	74	72	70	69	67	63	57	50	42	34	29	22	14	3	1	0	0
Placebo	73	73	68	63	56	52	51	50	48	43	39	37	32	27	21	20	12	5	3	0	0

OS in patients with CR not receiving Allo-HSCT in CR1

HR, 0.607
(95% CI, 0.387–0.954)

No. at risk																				
Quizartinib	63	60	54	51	48	44	41	37	35	30	25	21	17	15	9	5	3	1	0	0	0
Placebo	77	76	61	50	42	33	31	30	30	25	22	17	14	10	7	4	2	1	0	0	0

- Subgroup analysis for descriptive purposes only

[a]By end of induction by IRC.

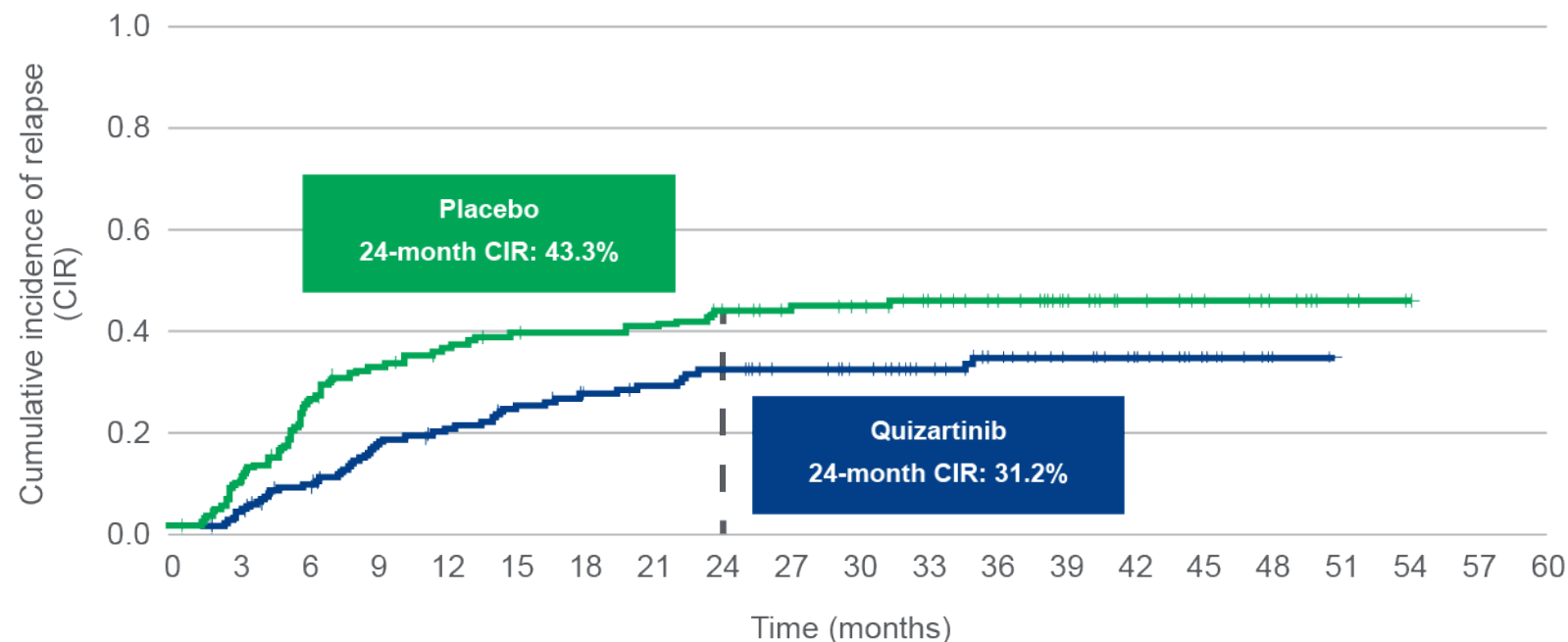Abbreviation: Allo-HSCT, allogeneic hematopoietic stem cell transplantation; CR, complete remission; OS, overall survival.

Reference: Erba H, et al. Presented at the European Hematology Association Annual Meeting; Vienna, Austria; June 9–12, 2022. Abstract S100.

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- In a prespecified exploratory analysis, RFS was longer in patients treated with quizartinib who achieved CR at the end of induction
- The hazard ratio of 0.613 strongly favored quizartinib

HR, 0.613 (95% CI, 0.444–0.845)

Quizartinib mRFS: 39.3 months

Placebo mRFS: 13.6 months

No. at risk

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60
Quizartinib	147	140	123	111	97	90	84	77	71	63	57	48	36	31	24	13	6	0	0	0	0
Placebo	150	136	103	82	70	63	60	58	52	47	44	39	31	24	18	14	10	4	2	0	0

aBy end of induction by independent review committee.

Abbreviation: mRFS, median relapse-free survival.

Reference: Erba H, et al. Presented at the European Hematology Association Annual Meeting; Vienna, Austria; June 9–12, 2022. Abstract S100.

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Quizartinib reduced rates of relapse in patients who achieved CR by the end of induction phase, indicating that quizartinib + chemotherapy may be able to prevent relapse compared with standard chemotherapy and surveillance alone.

No. at risk

Quizartinib	147	140	123	111	97	90	84	77	71	63	57	48	36	31	24	13	6	0	0	0	0
Placebo		150	136	103	82	70	63	60	58	52	47	44	39	31	24	18	14	10	4	2	0	0

[a]By end of induction by independent review committee.

Abbreviations: CIR, cumulative incidence of relapse; CR, complete remission.

Reference: Erba H, et al. Presented at the European Hematology Association Annual Meeting; Vienna, Austria; June 9–12, 2022. Abstract S100.

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Quizartinib dosage forms and strengths

Expected to be supplied as 17.7-mg and 26.5-mg tablets[1,2]:

- 17.7-mg tablets supply 20-mg of quizartinib dihydrochloride
- 26.5-mg tablets supply 30-mg of quizartinib dihydrochloride
- Both tablet strengths available in 14- and 28-tablet bottles

Illustrative Dosing

Daily dose of quizartinib dihydrochloride	Tablets per day required to achieve dose
20 mg	17.7 mg
30 mg	26.5 mg
40 mg	17.7 mg 17.7 mg
60 mg	26.5 mg 26.5 mg

Select notes on dosing

- QTcF was routinely monitored throughout QuANTUM-First[3]
- Each cycle (for induction, consolidation and maintenance) is approximately 28 days[4]
- Quizartinib dosage should be reduced in patients receiving strong CYP3A inhibitors[1]

Anticipated dosing schedule for quizartinib based on QuANTUM-First[1,2]

28-Day Cycles

Induction phase

1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28

1-2 cycles

Consolidation phase

1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28

Up to 4 cycles and/or HSCT

Continuation phase

1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28

Up to 36 cycles

Legend: 7+3 | quizartinib | cytarabine | no treatment

Induction chemotherapy: 7+3/cytarabine 100 mg/m^2/day, daunorubicin 60 mg/m^2/day or idarubicin 12 mg/m^2/day, quizartinib initiated on day 6 if 5+2 regimen is used in cycle 2.

Consolidation chemotherapy: cytarabine 3 g/m^2/day.

References: 1. ClinicalTrials.gov identifier NCT02668653. Updated April 15, 2022. Accessed July 25, 2022. https://clinicaltrials.gov/ct2/show/NCT02668653 **2.** Schlenk F, et al. Poster presented at: ESMO 2017; Madrid, Spain; September 8-12, 2017.

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