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Identifying a Clear Path Through the

Changing Maze of AML Management

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Supported by an independent educational grant from Daiichi Sankyo.

Agenda

- Molecular Testing
- Newly Diagnosed AML
- Relapsed/ Refractory AML
- Managing Adverse Events

Updated ELN Guidelines

Diagnosing AML

1

Immunophenotyping

- Required
- Flow cytometry is used to identify cell surface and intracellular markers

2

Cytogenetics and Molecular Testing

- Required
- Screens for genetic abnormalities defining disease/risk categories or for which there is targeted therapy

3

Biobanking

- Recommended
- Bone marrow and blood samples to be obtained at diagnosis, remission, and relapse and stored

Updated Blast Threshold

All recurrent genetic abnormalities defining specific AML subtypes, (excluding t(9;22)(q34.1;q11.2)/*BCR*::*ABL1**) are now considered to establish a diagnosis of AML **if there are ≥10% blasts in the bone marrow or blood.**

*AML with *BCR*::*ABL1 still requires* ≥20%

Döhner H, et al. *Blood.* 2022;140(12):1345-1377.

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Updated Risk Classification

Favorable

t(8;21)(q22;q22.1)/RUNX1::RUNX1T1

inv(16)(p13.1q22) *or*
t(16;16)(p13.1;q22)/CBFB::MYH11

Mutated NPM1 *without* FLT3-ITD

★ **bZIP in-frame mutated CEBPA**

Intermediate

★ **Mutated NPM1 *with* FLT3-ITD**

★ **Wild-type NPM1 *with* FLT3-ITD**

t(9;11)(p21.3;q23.3)/MLLT3::KMT2A

Cytogenetic and/or molecular abnormalities not classified as favorable or adverse

Adverse

t(6;9)(p23;q34.1)/DEK::NUP214

t(v;11q23.3)/KMT2A-rearranged

t(9;22)(q34.1;q11.2)/BCR::ABL1

t(8;16)(p11;p13)/KAT6A::CREBBP

inv(3)(q21.3q26.2) *or*
t(3;3)(q21.3;q26.2)/GATA2, MECOM(EVI1)

t(3q26.2;v)/MECOM(EVI1)-rearranged

−5 or del(5q); −7; −17/abn(17p)

Complex karyotype, monosomal karyotype

★ Mutated ASXL1, **BCOR**, **EZH2**, RUNX1, **SF3B1**, **SRSF2**, **STAG2**, **U2AF1**, *or* **ZRSR2**

Mutated TP53

★ Denotes updated categorization

Döhner H, et al. *Blood.* 2022;140(12):1345-1377.

Validating the Updated ELN Risk Categories

Sample

1457 adults with AML were risk stratified according to ELN22 categories

2022 vs 2017 Category Comparison

21.7% of patients required a revised risk allocation compared to the 2017 classification

45.6% of reallocations were to "*intermediate risk*" due to changes in the FLT3-ITD categorization

ELN22 Risk Stratification Resulted In:

Significantly distinct EFS, RFS, and OS

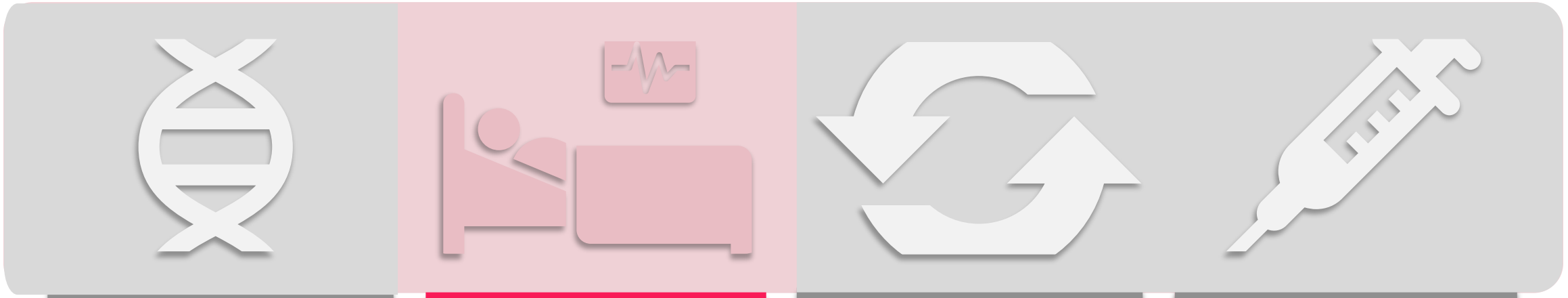
More accurate determination of "*favorable*" and "*adverse*" risk profiles

CONCLUSION

- The updated ELN22 risk stratification improves prognostication in intensively treated patients with AML
- A subset of patients (those with MR gene mutations) had heterogenous outcomes, suggesting the classification criteria may need to be re-evaluated in certain patient subgroups

Bill M, et al. Abstract S138. EHA 2023.

Agenda



- Molecular Testing
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Determining “Fitness” for Intensive Therapy

Presence of any of the following usually deems a patient “unfit” for intensive chemotherapy*

Age

≥75 years (not an absolute criterion)

ECOG Status

ECOG performance status >2

Age-related Comorbidities

Examples: Severe cardiac disorder, severe pulmonary disorder, severe kidney/liver dysfunction

Other

Any other comorbidity assessed to be incompatible with intensive chemotherapy

*While there is no accepted or validated criteria to consider a patient ineligible for intensive chemotherapy, these are used in clinical trials and have guiding utility in routine practice.

Döhner H, et al. *Blood.* 2022;140(12):1345-1377.

Treating AML in "Fit" Adults

TREATMENT PATHWAY

Induction Therapy
Goal: CR

Intensive Chemotherapy
- Anthracycline/ cytarabine backbone
- Add midostaurin for FLT3^{mut} AML
- Add gemtuzumab ozogamicin for CD-33+ AML, favorable or intermediate risk

Re-Induction Therapy
Goal: CR

Considered in patients not achieving CR/CRh/CRi

Consolidation Therapy
Goal: Deepen Remission, Maximize DOR

After CR/CRh/CRi, consolidation is administered

MRD is assessed in CR/CRh/CRi to determine treatment choice

If relapse risk exceeds 35% to 40%, consolidate with allo-HCT

± Maintenance Therapy
Goal: Reduce Relapse Risk

Minimally toxic, extended, but time-limited, course of therapy given after CR to reduce relapse risk

The role of maintenance therapy is an area of active research.

Döhner H, et al. *Blood.* 2022;140(12):1345-1377.

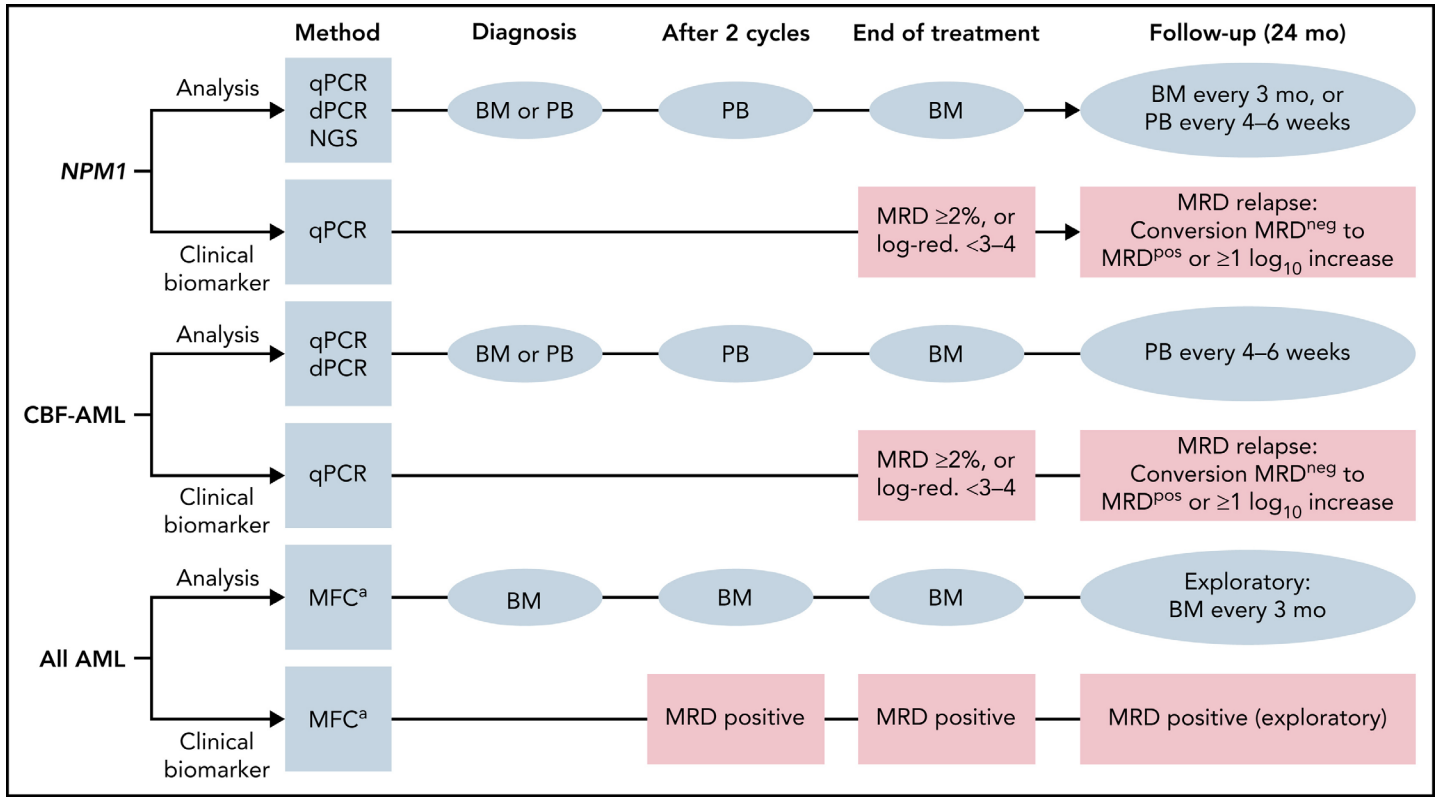
Monitoring Measurable Residual Disease (MRD)

Monitoring MRD allows clinicians to:[1]

- Quantify remission status
- Improve relapse risk assessment once a patient is in remission
- Predict an approaching relapse and start early intervention
- Utilize MRD as a surrogate endpoint in clinical trials

Recently developed next-generation sequence testing for FLT3-ITD MRD monitoring has been shown to identify patients at high risk of relapse and death[2]

Algorithm of MRD assessment and time points at which MRD is considered a clinically relevant biomarker[1]



1. Döhner H, et al. *Blood.* 2022;140(12):1345-1377.
2. Rücker FG, et al. Abstract S135. EHA 2023.

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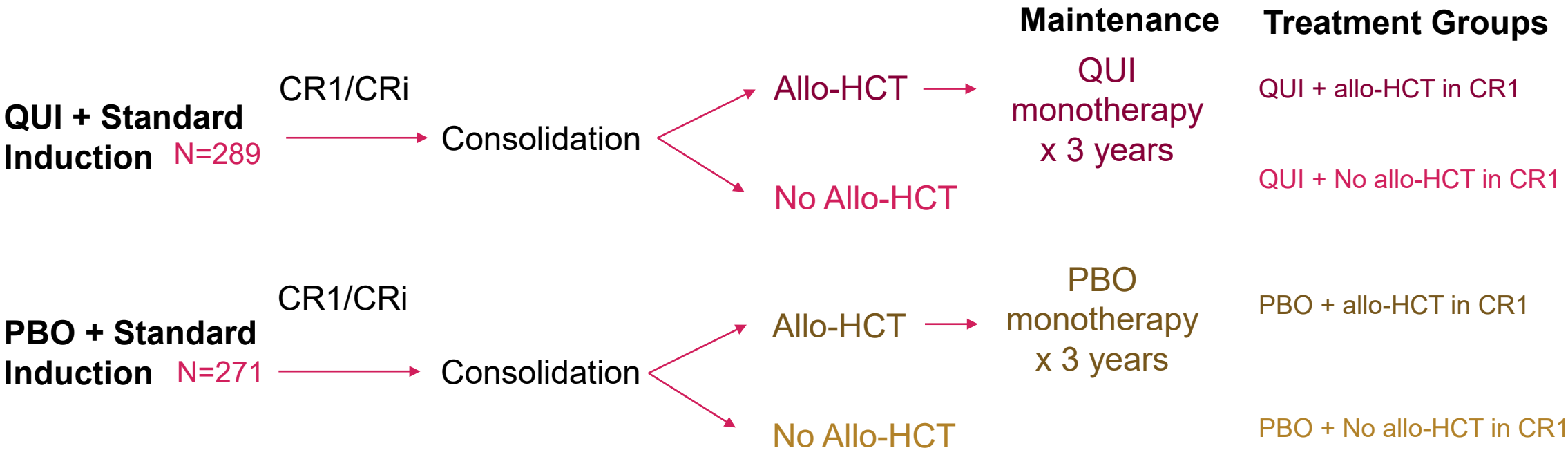
QUANTUM-First: FLT3+ AML

Updates in Treating Newly Diagnosed AML

QUESTIONS

1. What is the effect of an allo-HCT in CR1 on OS and how does treatment with quizartinib impact it?
2. Is OS after transplant affected by FLT3 minimal residual disease (MRD) status before transplant?



Schlenk R, et al. Abstract S137. EHA 2023.
Erba HP, et al. *Lancet.*2023;401(10388):1571-1583.

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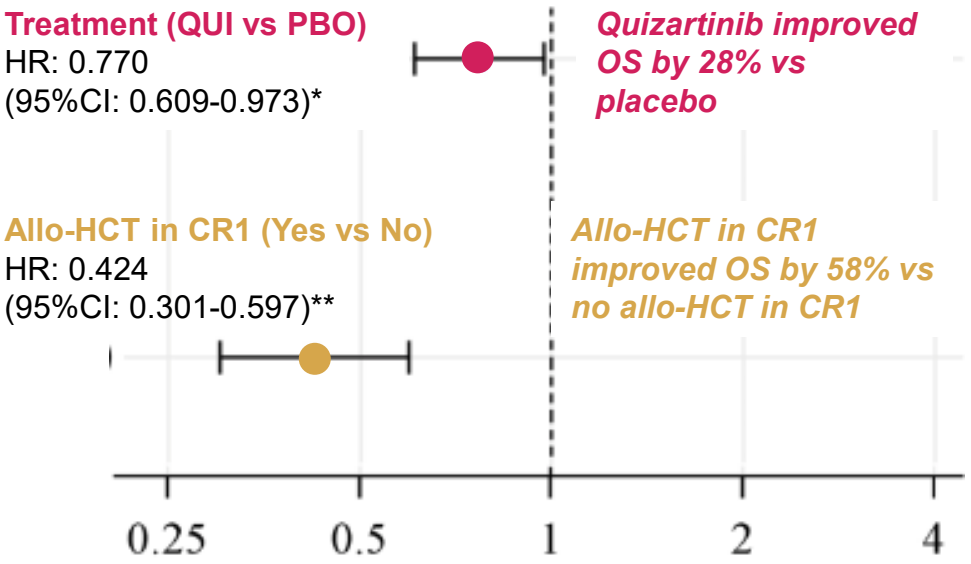

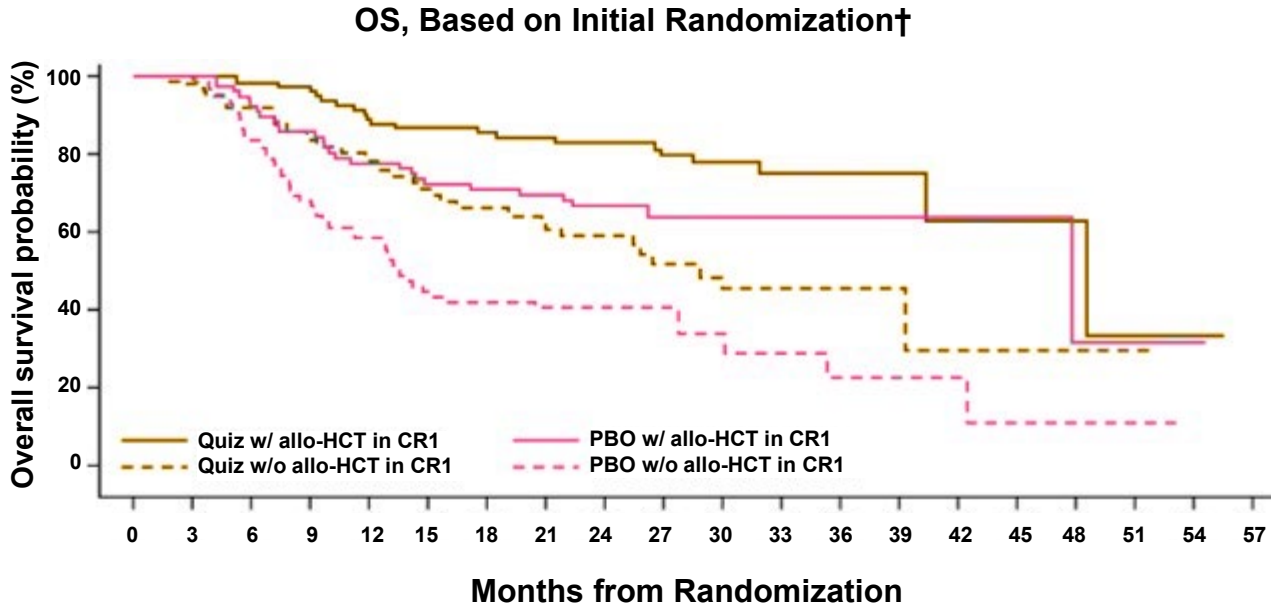

*P=.0284, **P<.0001, †Post-hoc analysis illustrating the time-dependent effect on OS of all-HCT in CR1 according to initial randomization, in patients with CR.

Schlenk R, et al. Abstract S137. EHA 2023.
Erba HP, et al. *Lancet.* 2023;401(10388):1571-1583.

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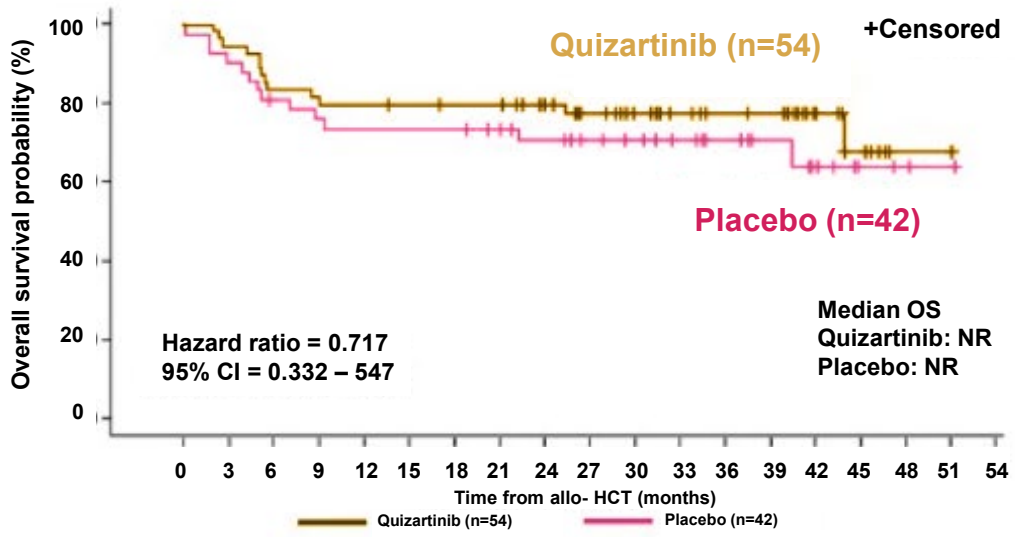
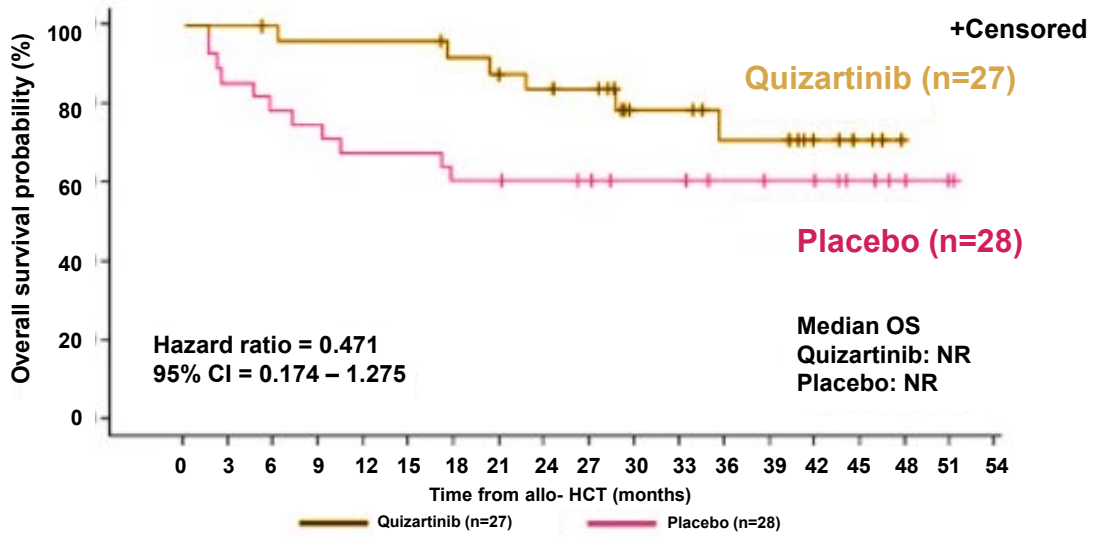
1. What is the effect of an allo-HCT in CR1 on OS and how does treatment with quizartinib impact it?
2. Is OS after transplant affected by FLT3 minimal residual disease (MRD) status before transplant?

MRD Negative (n=96)



Quizartinib improved OS by **28%** in MRD(-) patients vs placebo

MRD Positive (n=55)



Quizartinib improved OS by **53%** in MRD(+) patients vs placebo

Schlenk R, et al. Abstract S137. EHA 2023.
Erba HP, et al. *Lancet.* 2023;401(10388):1571-1583.

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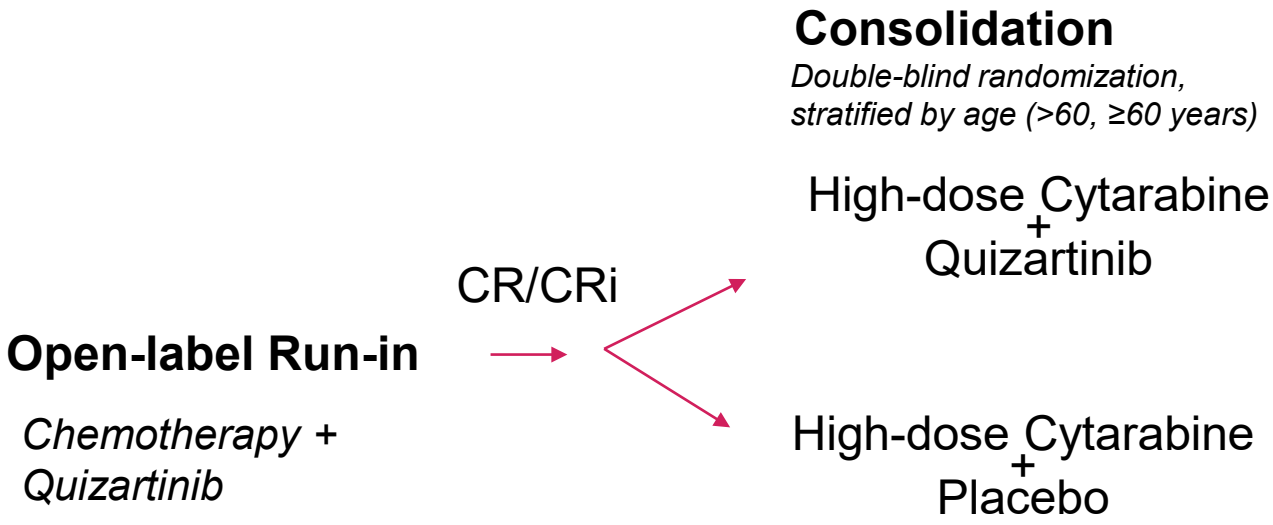
Updates in Treating Newly Diagnosed AML

QUESTION

What is the impact of adding quizartinib to standard chemotherapy on OS in fit patients newly diagnosed with FLT3-ITD *wild-type* AML?



Allo-HCT was recommended in patients with high genetic risk or intermediate risk with MRD positivity

Montesinos P, et al. Abstract S130. EHA 2023.

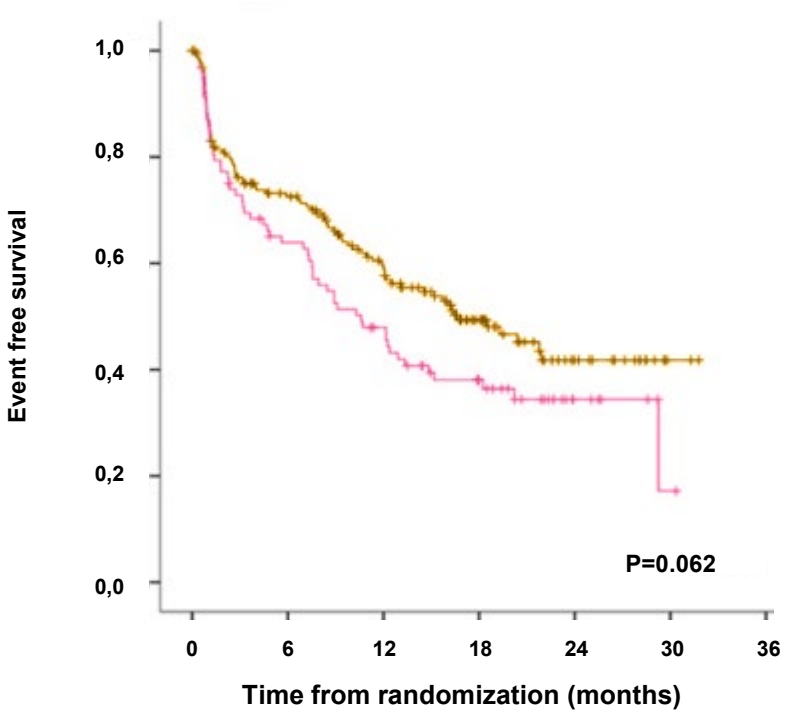
QUIWI: FLT3 Wild-Type AML

Updates in Treating Newly Diagnosed AML

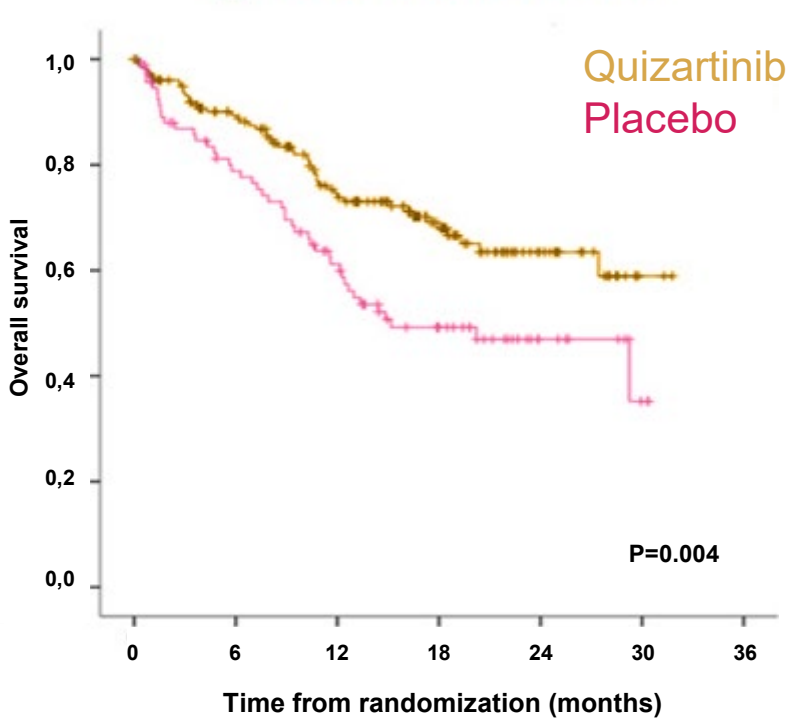
QUESTION

What is the impact of adding quizartinib to standard chemotherapy on OS in fit patients newly diagnosed with FLT3-ITD *wild-type* AML?

Event-free Survival



Overall Survival



The addition of quizartinib to standard 3+7 chemotherapy may prolong OS in newly diagnosed FLT3-ITD wild-type AML

Montesinos P, et al. Abstract S130. EHA 2023.

What About Post-transplant Maintenance Therapy?

Primary Objective

To determine if post-HCT gilteritinib maintenance improved RFS vs placebo in FLT3-ITD(+) AML transplanted in CR1

Key Secondary Objectives

Overall Survival
Effect of MRD status pre- and post-HCT on RFS and OS

Summary/Conclusion

Gilteritinib demonstrated benefit for patients with detectable MRD pre- or post-HCT versus those without detectable MRD.

Results

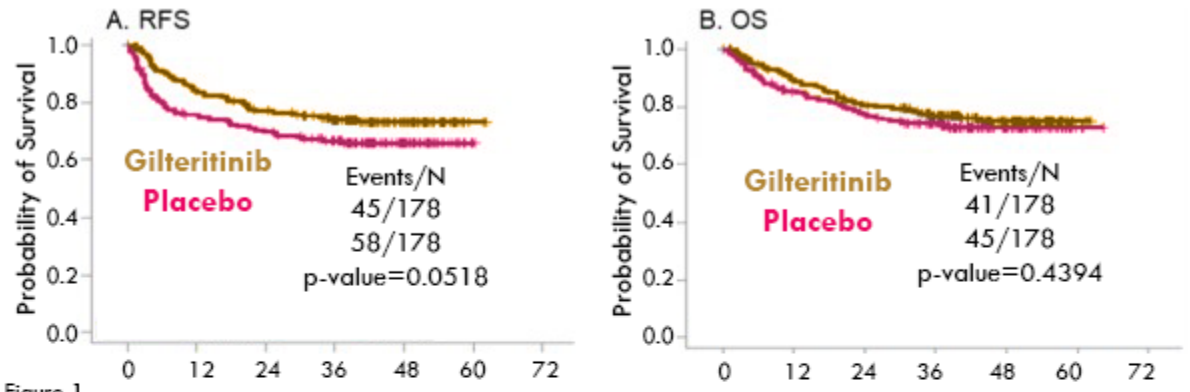


Figure 1

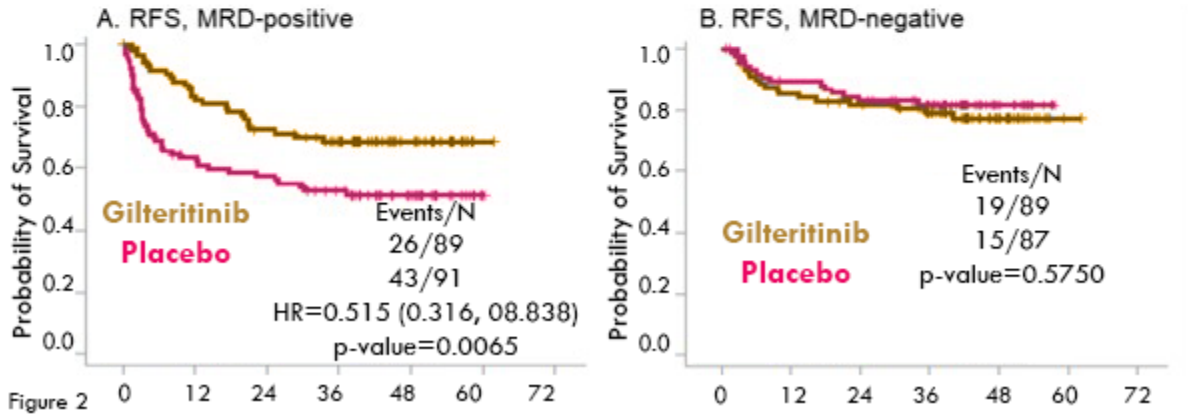


Figure 2

Levis MJ, et al. Abstract LB2711. EHA 2023.

Treating AML in “Unfit” Adults

Less Intense Regimens are Utilized for Unfit Patients

Regimens

- Azacitidine or decitabine + venetoclax
- Low-dose cytarabine + venetoclax

For Patients with IDH1^{mut} AML

- Azacitidine + ivosidenib

For Patients Intolerant to Anti-leukemic Therapy or Declining Therapy

- Best supportive care

For Very Frail Patients with IDH1^{mut} AML

- Ivosidenib monotherapy

Döhner H, et al. *Blood.* 2022;140(12):1345-1377.

Updates in Treating an Elderly Population

Patients ≥60 Years[1]

Study compared outcomes after allo-HCT for 2 regimens:[1]

1. Cladrabine + Low Dose Cytarabine + Venetoclax — N=35
2. Hypomethylating agent/ Venetoclax-based* — N=40
3. Intensive therapy* — N=42

Older patients proceeding to allo-HCT after induction with CLAD/LDAC/VEN had significantly improved mRFS, mOS, and 3-year cumulative incidence of relapse and NRM

*Retrospective comparative cohort (years: 2013 to 2022).

1. Senapati J, et al. Abstract 7047. ASCO 2023.

Newly Diagnosed Patients with AML

Updates in Treating an Unfit Elderly Population

VEN-A-QUI

A Phase 1 (N=16) and Phase 2 (N=61) study assessed the safety/efficacy of 2 triplet regimens in elderly patients unfit for intensive induction therapy.

Regimen 1 "AZA Group"	Regimen 2 "LDAC Group"
Venetoclax	Venetoclax
Azacitidine	Low-dose Cytarabine
Quizartinib	Quizartinib

Findings

40% to 45%

Similar CR/CRi/CRh range between both treatment groups and study phases.

20% vs 13%

Induction death was more frequent in the LDAC group than the AZA group

Venetoclax dose required a reduction due to substantial myelotoxicity

Both triplet regimens were feasible in this population. In FLT3-ITD+ and HMA naïve patients, mOS was not reached

HMA, hypomethylating agent

Bergua Burgues J, et al. Abstract S132. EHA 2023.

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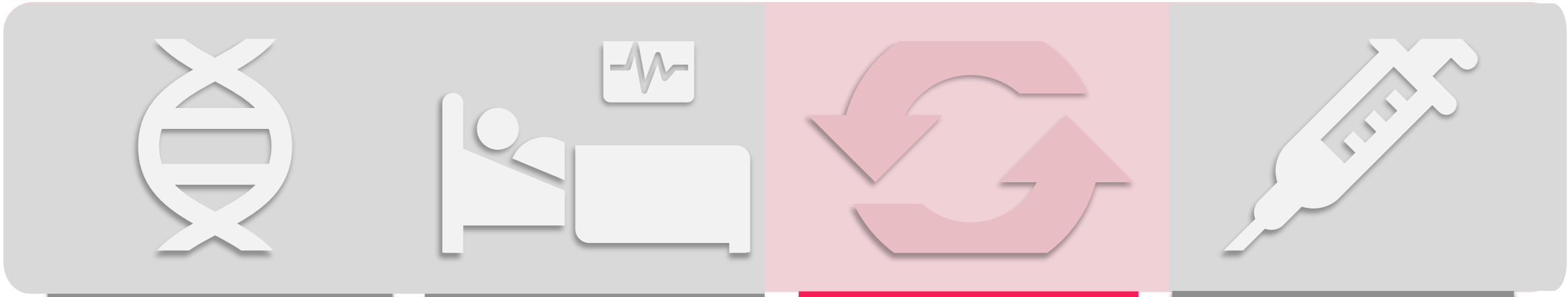
Agenda



- Molecular Testing
- Newly Diagnosed AML
- **Relapsed/ Refractory AML**
- Managing Adverse Events

Defining “Relapsed” and “Refractory” AML

Refractory Disease

No CR, CRh, or CRi at the response landmark (ie, after 2 courses of intensive induction treatment or a defined landmark, eg, 180 days after starting less-intensive therapy)

Relapsed Disease

After CR, CRh, or CRi

Bone marrow blasts ≥5%; or reappearance of blasts in the blood in at least 2 peripheral blood samples at least 1 week apart; or development of extramedullary disease

MRD Relapse

After CR, CRh, or CRi without MRD

1. Conversion from MRD(-) to MRD(+), independent of method, *or*
2. Increase of MRD copy numbers ≥1 log_{10} between any 2 positive samples in patients with $CR_{MRD\text{-}LL}$, $CRh_{MRD\text{-}LL}$, or $CRi_{MRD\text{-}LL}$ by qPCR

Döhner H, et al. *Blood.* 2022;140(12):1345-1377.

Molecular Testing at Clinical Progression

Importance

At clinical progression, there is potential for clonal evolution and the development of actionable targets not previously detected at diagnosis. Molecular re-evaluation at progression is important for determining treatment course.

Actionable Mutations for Targeted Salvage Therapy

IDH1/IDH2

Current Treatment Options
- Ivosidenib
- Enasidenib
- Olutasidenib

New or Expanded FLT3-ITD or TKD Mutations

Current Treatment Options
- Gilteritinib

Treatment Pathway for R/R AML (Fit Adults)

Molecular re-evaluation.
Clinical trial consideration

Salvage Therapy.
Goal: Cytoreduction, second remission to get to allo-HCT

Allo-HCT

Döhner H, et al. *Blood.* 2022;140(12):1345-1377.
Olutasidenib [Package Insert]. https://tinyurl.com/mr2pa6j7

Current Salvage Therapies for R/R AML

Intensive Regimens for "Fit" Patients[1]

Intermediate Dose Cytarabine	FLAG-IDA	MEC	CLAG-M	Allo-HCT
Cytarabine ± an anthracycline	Fludarabine Cytarabine G-CSF Idarubicin	Mitoxantrone Etoposide Cytarabine	Cladribine Cytarabine G-CSF Mitoxantrone	***Consider for patients:*** • With primary refractory disease, *or* • In second CR/CRh/CRi, *or* • With major cytoreduction but still have active disease after salvage therapy

Salvage Options for "Unfit" Patients[1]

FLT3^{mut} AML: FLT3 Inhibitor (Gilteritinib)
IDH1^{mut} AML: IDH1 inhibitor (Ivosidenib or Olutasidenib[2])
IDH2^{mut} AML: IDH2 Inhibitor (Enasidenib)

1. Döhner H, et al. *Blood.* 2022;140(12):1345-1377.
2. Olutasidenib [Prescribing Information]. https://tinyurl.com/mr2pa6j7

Updates in the Treatment of R/R AML

Sequencing Therapies
in R/R IDH1/2^{mut} AML

A recent retrospective study found the use of an IDH inhibitor ± a hypomethylating agent in the second-line setting following failure of intensive chemotherapy was associated with **superior OS** vs FLAG or venetoclax-based lower-intensity therapy in patients with R/R IDH1/2^{mut} AML.[1]

Gilteritinib or Venetoclax + HMA
in FLT3^{mut} (ITD/TKD) R/R AML

A retrospective analysis compared salvage treatment with gilteritinib (N=6) or venetoclax + HMA (N=10)[3]

Overcoming Resistance
with Selinexor

A small (N=12) retrospective analysis demonstrated the use of selinexor + an HMA as a **safe and viable option for unfit patients** with R/R AML, especially in patients not previously exposed to an HMA.[2]

Gilteritinib + Venetoclax + Azacitidine
in FLT3^{mut} R/R AML

This retrospective study (N=14) demonstrated a **promising response with triple therapy** for FLT3^{mut} R/R AML, with the regimen presenting as a potential bridge to allo-HCT.[4]

1. Murray G, et al. Abstract e19043. ASCO 2023; 2. Zhang J, et al. Abstract P577. EHA 2023;
3. Murray G, et al. Abstract e19046. ASCO 2023; 4. Chen N, et al. Abstract e19024. ASCO 2023.

Updates in the Treatment of R/R AML

Aim

To explore the efficacy and safety of olutasidenib in **IDH1^{mut} AML in unfit patients failing a venetoclax-based regimen**

Regimen

Olutasidenib ± Azacitadine

1 Primary Endpoint

Achievement of a CR/CRh

2 Secondary Endpoints

Time to CR+CRh
Duration of CR+CRh
Rate of transfusion independence

Results

Olutasidenib induced durable remission in IDH1^{mut} R/R AML, including those failing prior venetoclax regimens

Endpoints	Patients (%)
Achievement of CR/CRh	5/17 (29.4%, of which 23.5% were CR)
Time to CR+CRh Duration of CR+CRh	2.1 months 18.5+ months

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Cortes JE, et al. Abstract e19041. ASCO 2023.

Emerging Therapies for R/R AML

Vibecotamab[1]

- CD3-CD123 bispecific antibody engager
- Phase I trials showed activity in low-blast R/R AML
- Currently being evaluated in an open-label Phase 2 study

^{225}Ac-Lintuzumab[2]

- Targeted radiation delivery via humanized CD33 antibody conjugated to an alpha emitting isotope
- Phase 1 trial: ^{225}Ac-Lintuzumab + CLAG-M yielded improved clinical outcomes (ORR, mOS, flow MRD negativity) in high-risk populations, particularly those previously treated with venetoclax-based therapies

1. Short N, et al. Abstract TPS7076. ASCO 2023.
2. Abedin SM, et al. Abstract e19030. ASCO 2023.

KOMET-001: Ziftomenib[1]

Emerging Therapies for R/R AML

Design

Phase 1/2
Global
Open-label

Population

Adults
R/R NPM1^{mut} AML
N=20 (600 mg RP2D)

Treatment

Regimen
Ziftomenib 600 mg QD in 28-day cycles until relapse, progression, or toxicity

Mechanism:
Menin-KMT2A (MLL) inhibitor

Results

35% CR Rate
95% CI (15.4, 59.2)

35% CR/CRh Rate
95% CI (15.4, 59.2)

40% CRc Rate§
95% CI (19.1,63.9)

50% MRD Negativity Rate†
95% CI (15.7, 84.3)

45% ORR Rate‡
95% CI (23.1, 68.5)

Additional Studies

Ziftomenib is also being evaluated in the newly diagnosed and R/R settings in combination with standard of care therapies in patients with NPM1^{mut} and KMTA^{r} AML[2]

RP2D, recommended Phase 2 dose
§CR+CRh+CRi
†6 of 8 patients achieving CRc were evaluated for MRD; of those evaluated 66.7%% were MRD(-).
‡CR+CRh+Cri+MLFS

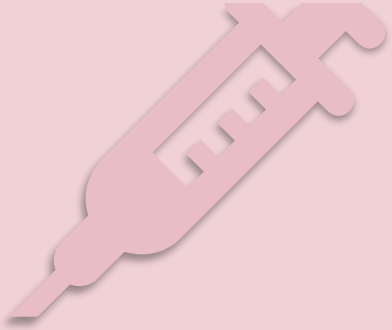
1. Abstract LB2713. EHA 2023; 2. Zeidan AM, et al. Abstract TPS7079. ASCO 2023.

Agenda

Molecular Testing

Newly Diagnosed AML

Relapsed/ Refractory AML



Managing Adverse Events

Adverse Events Requiring Special Attention

Midostaurin

QT Prolongation

Gilteritinib

QT Prolongation
Transaminase Elevation
PRES

Enasidenib

QT Prolongation
Differentiation Syndrome

Gemtauzumab Ozogamicin

Transaminase Elevation
Bilirubin Elevation
Veno-occlusive Disease (VOD)
Sinusoidal Obstructive Syndrome (SOS)

Venetoclax

Neutropenia
Thrombocytopenia
Tumor Lysis Syndrome
CYP3A Interactions

PRES, posterior reversible encephalopathy syndrome

Döhner H, et al. *Blood.* 2022;140(12):1345-1377.

Adverse Events Requiring Special Attention

Management Strategies

QT Prolongation

- Dose interruption/reduction
- Substitute QT-prolonging co-medication (if possible)
- ECG controls (midostaurin)

Transaminase/Bilirubin Elevation

Dose interruption/reduction

PRES

Discontinuation

Differentiation Syndrome

- Dexamethasone, hydroxyurea for co-occurring leukocytosis
- Dose interruption/reduction

VOD/SOS

- Dose interruption/reduction
- Supportive care
- Fluid management
- Possibly defibrotide

Döhner H, et al. *Blood.* 2022;140(12):1345-1377.

Venetoclax

Adverse Event Management: Myelosuppression

Neutropenia/Thrombocytopenia

Early response assessment

Example:

- On days 14 to 21 of cycle 1, if bone marrow blasts are <5%, stop venetoclax for up to 14 days to allow count recovery to ≥CRh
- If neutropenia does not recover with 7 days of venetoclax discontinuation, the addition of G-CSF may augment recovery

Subsequent cycles

- Azacitidine 75 mg/m^2 SC/IV on days 1 to 7 (or days 1 to 5 + days 8 to 9) or
- Decitabine 20 mg/m^2 IV on days 1 to 5 + venetoclax 400 mg daily, or
- Low-dose cytarabine 20 mg/m^2 SC on days 1 to 10 + venetoclax 600 mg QD every 4 weeks until progression.

Delayed count recovery or recurrent Grade 4 treatment-emergent neutropenia/thrombocytopenia lasting ≥7 days

Requires reductions in duration of administered venetoclax (from 28 to 21 or 14 days, or even less) and/or reductions in the dose of azacitidine, decitabine, or low-dose cytarabine if severe bone marrow hypoplasia.

CRh, complete remission with partial hematologic recovery

Döhner H, et al. *Blood.* 2022;140(12):1345-1377.

Thank You

Please take a moment and fill out the post-test and evaluation to receive CME credit.