Targeted Therapies in Acute Myeloid Leukemia

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Objectives:

1. Review ELN 2022 risk stratification and the importance of molecular testing in AML

2. Summarize evidence supporting the appropriate use of novel therapies in AML

3. Apply recommended strategies to identify and manage toxicities of novel therapies in AML

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Disclosures:

Sangeetha Venugopal, MD, MS

-None

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-None

ELN 2022 Risk Stratification in Acute Myeloid Leukemia

Risk category†	Genetic abnormality
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 (without adverse-risk genetic lesions) ▪ t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A*†,¶ ▪ Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	▪ t(6;9)(p23.3;q34.1)/*DEK*::*NUP214* ▪ t(v;11q23.3)/*KMT2A*-rearranged# ▪ t(9;22)(q34.1;q11.2)/*BCR*::*ABL1* ▪ t(8;16)(p11.2;p13.3)/*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, and/or ZRSR2*‡‡ ▪ Mutated *TP53*[a]

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Döhner et al *Blood* 2022; 140 (12): 1345–1377

Importance of Molecular Testing in AML

- Screening for gene mutations is required for establishing the diagnosis and to identify actionable therapeutic targets

- *FLT3,IDH1, IDH2* –preferably within 3-5 days

- PML::RARA, CBFB::MYH11, RUNX1::RUNX1T1, KMT2A rearrangements, BCR::ABL1, other fusion genes (if available) - 3-5 days

- *CEBPA,DDX41,TP53; ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2* – within the first cycle

Summary of Drug Approvals in AML

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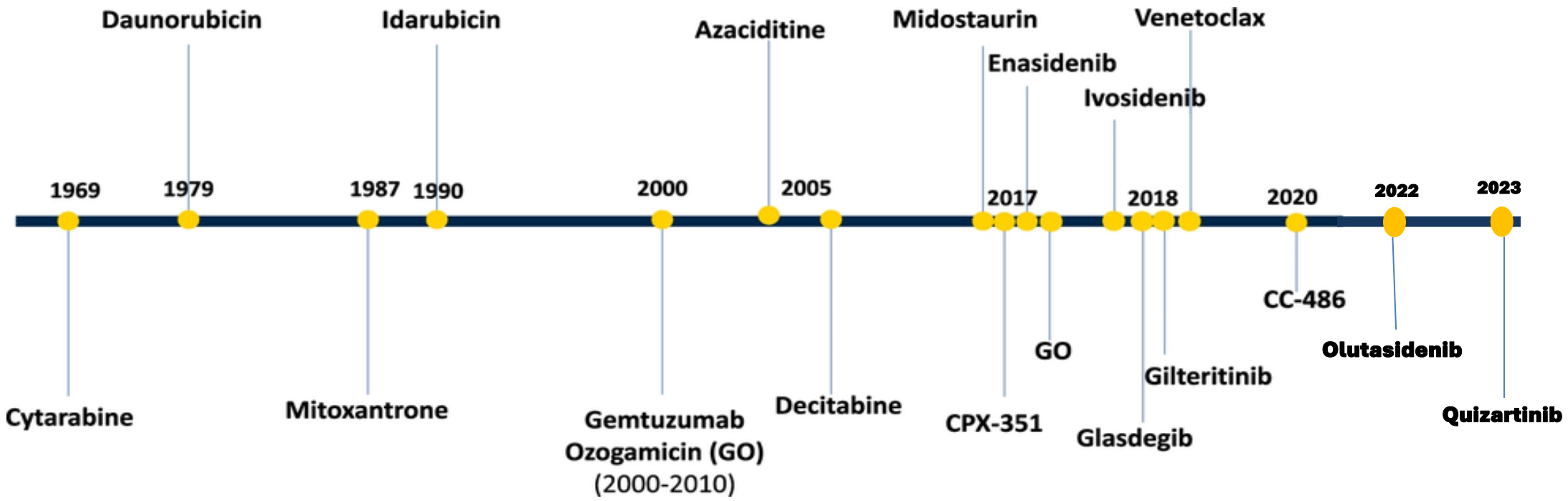

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Ochs MA, Marini BL, Perissinotti AJ, et al. Oncology stewardship in acute myeloid leukemia. *Ann Hematol*. 2022;101(8):1627-1644. doi:10.1007/s00277-022-04872-1

Approach to a patient with *FLT3* ^{mut} AML

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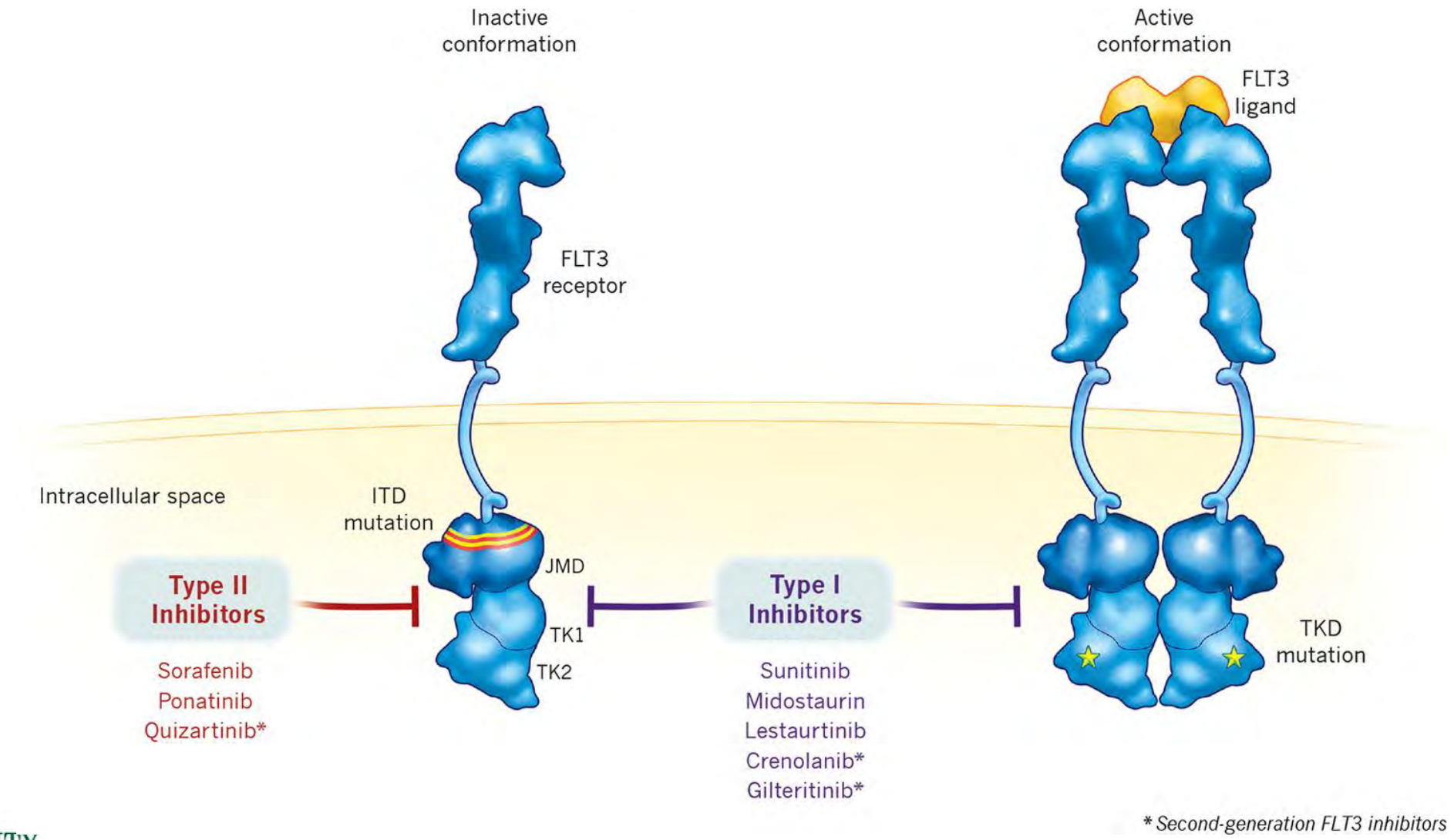

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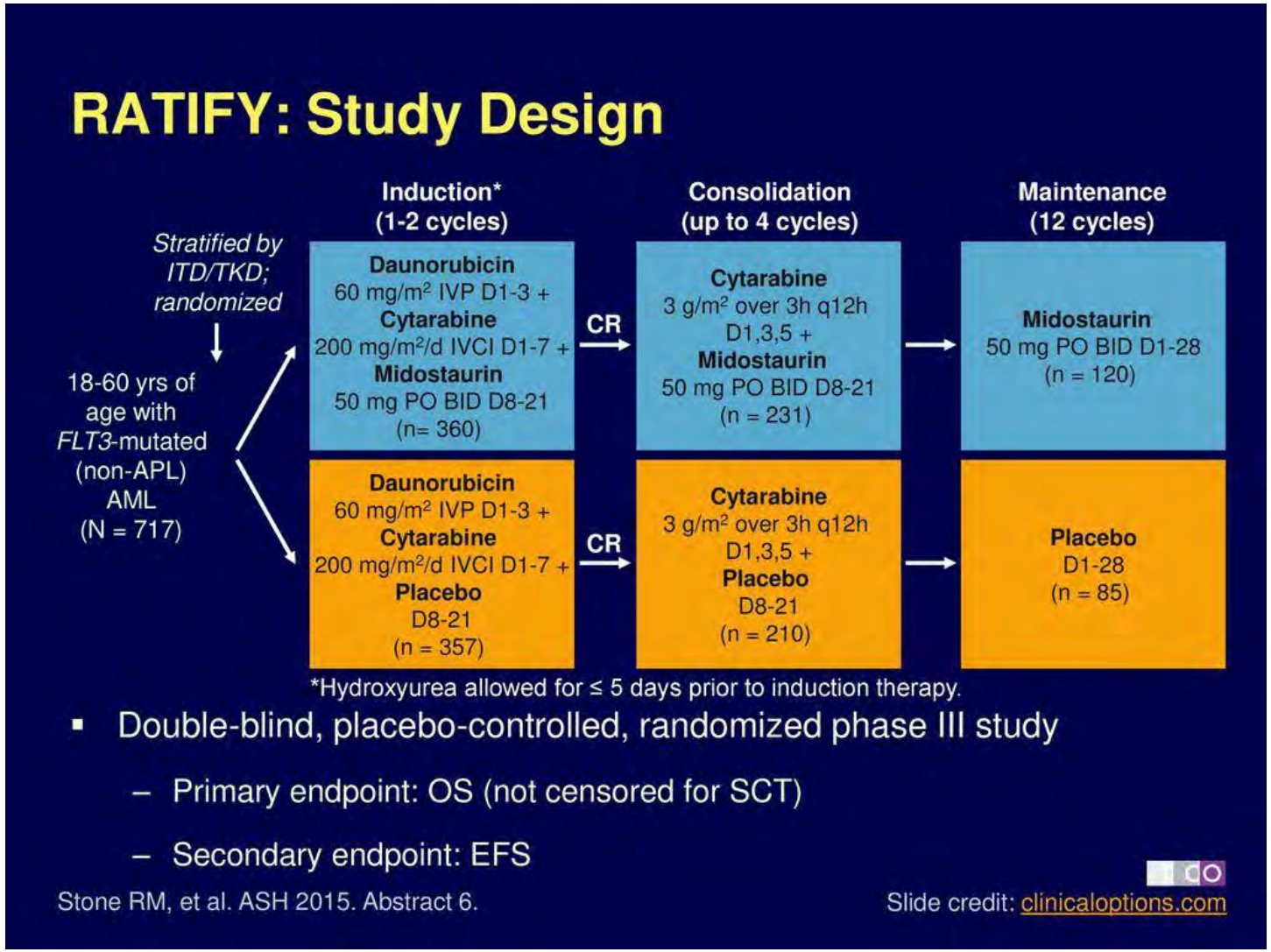
Daver N, Schlenk RF, Russell NH, Levis MJ: Targeting *FLT3* mutations in AML: review of current knowledge and evidence. Leukemia 2019; 33: pp. 299-312

Midostaurin plus Chemotherapy for Acute Myeloid Leukemia with a *FLT3* Mutation



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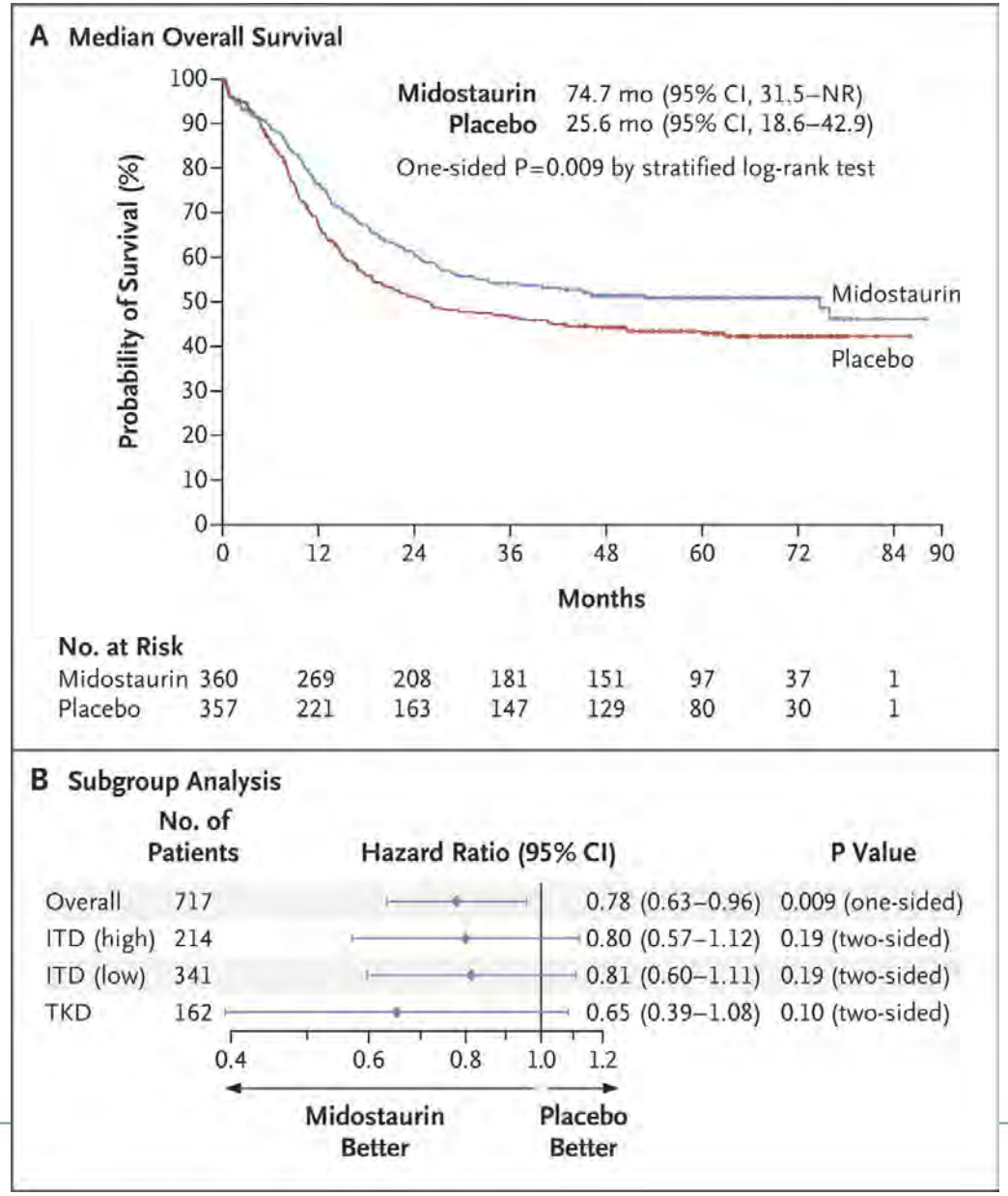
Midostaurin plus Chemotherapy for Acute Myeloid Leukemia with a *FLT3* Mutation



Stone et al, NEJM 2017

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QuANTUM-First -Quizartinib plus chemotherapy in ND *FLT3* ^{mut} AML

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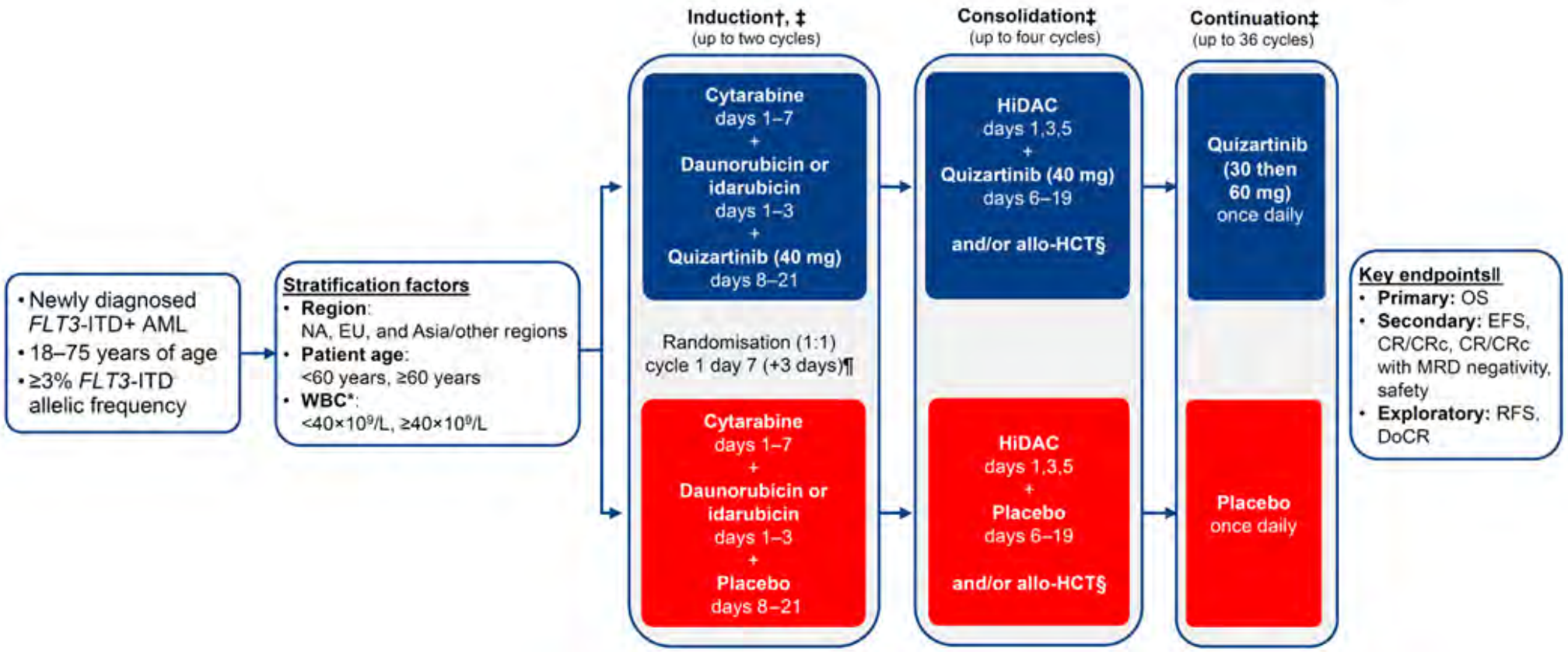

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Erba HP, Montesinos P, Kim HJ, et al. Quizartinib plus chemotherapy in newly diagnosed patients with FLT3-internal-tandem-duplication-positive acute myeloid leukaemia (QuANTUM-First) *Lancet*. 2023;401(10388):1571-1583.

QuANTUM-First -Quizartinib plus chemotherapy in ND *FLT3* ^{mut} AML

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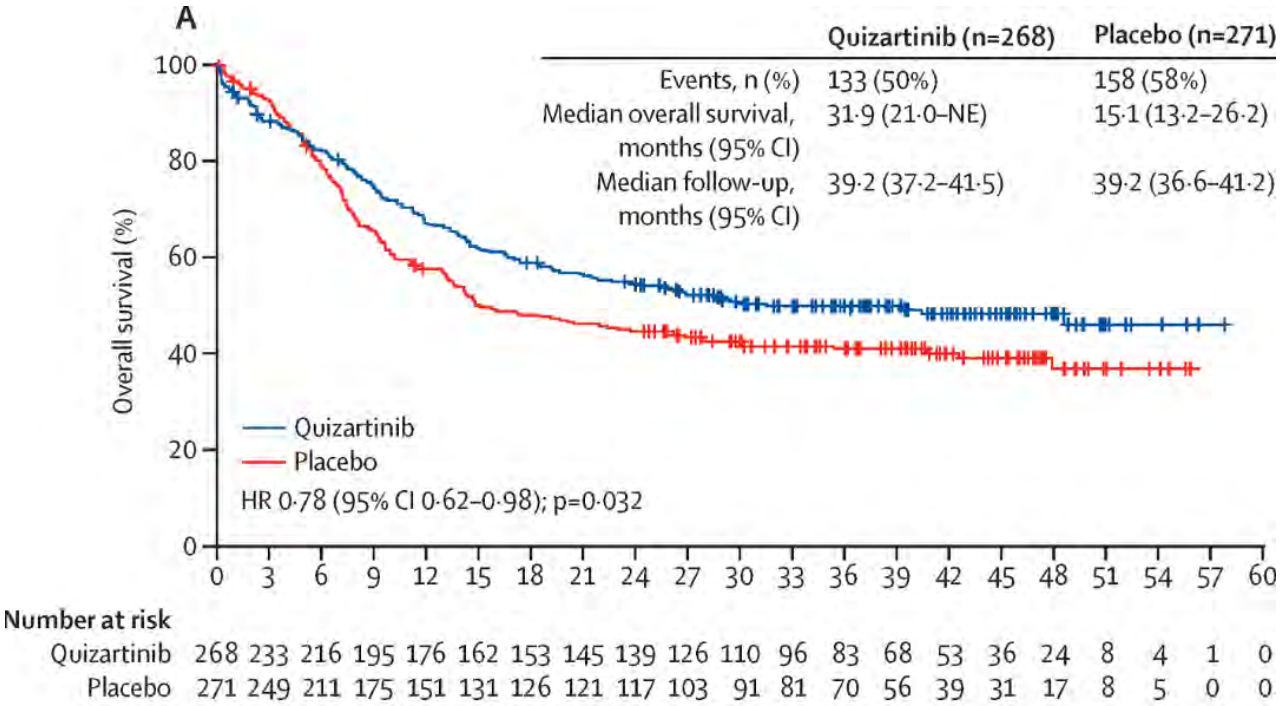

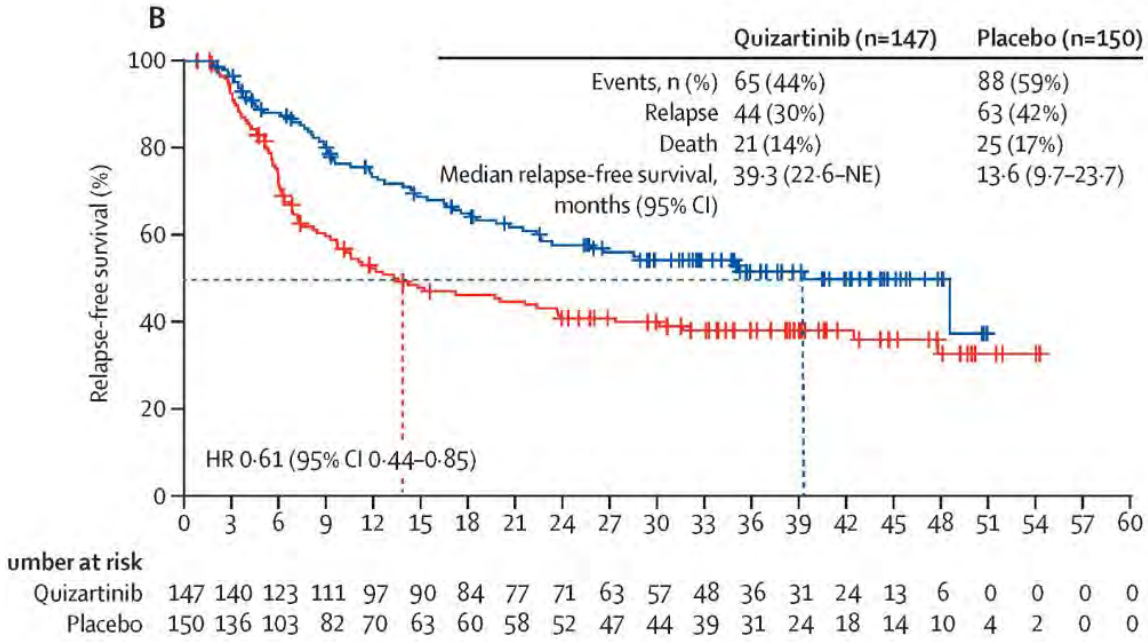

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ADMIRAL - Gilteritinib for Relapsed/ Refractory *FLT3* ^{mut} AML

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The NEW ENGLAND JOURNAL of MEDICINE

Gilteritinib vs. Salvage Chemotherapy for AML

PHASE 3, OPEN-LABEL, MULTICENTER, RANDOMIZED TRIAL

371 Patients with refractory or relapsed *FLT3*-mutated AML	Gilteritinib (120 mg per day) (N = 247)	Salvage Chemotherapy (N = 124)
Median overall survival	9.3 mo	5.6 mo
	HR for death, 0.64; 95% CI, 0.49 to 0.83; P<0.001	
Complete remission with full or partial hematologic recovery	34.0%	15.3%
	Risk difference, 18.6 percentage points; 95% CI, 9.8 to 27.4	

Lower incidence of exposure-adjusted grade ≥3 adverse events with gilteritinib

A.E. Perl et al. 10.1056/NEJMoa1902688

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FLT3 Inhibitors: Adverse Effects and Management Considerations

Name	Midostaurin	Gilteritinib	Quizartinib
Target	FLT3-ITD, FLT3-TKD	FLT3-ITD, FLT3-TKD, and FLT3-ITD-TKD	FLT3-ITD
Dose	50mg po BID with food D8-21 with induction chemotherapy or consolidation	120 mg daily for a minimum of 6 months	35.4 mg PO daily D8-21with induction chemotherapy or D6-D19 with consolidation; 26.5 mg to 53 mg orally once daily as maintenance
Adverse Effects	Febrile neutropenia, nausea, mucositis, hyperglycemia, respiratory infection, pulmonary toxicity, QTc prolongation, increased amylase/lipase	Edema, skin rash, hyponatremia, hypophosphatemia, febrile neutropenia, LFT elevations, arthralgias, differentiation syndrome, diarrhea, pancreatitis, QTc prolongation, PRES	QTc Prolongation, torsade de pointes, cardiac arrest, febrile neutropenia, myelosuppression, diarrhea, mucositis, nausea, vomiting, sepsis, upper respiratory infections, headaches,
Management Considerations	• Monitor for symptoms of Pulmonary Toxicity including interstitial lung disease and pneumonitis. • Monitor ECGs frequently	• Monitor for Differentiation Syndrome • Monitor for Posterior Reversible Encephalopathy Syndrome (PRES) which can manifest with altered mental status and seizures. Discontinue. • Obtain ECG weekly for 3 weeks first cycle, and day 1 of the next 2 cycles	• Obtain baseline potassium and magnesium and monitor and correct deficiencies. • Obtain baseline ECG, weekly for first month and periodically after • Vanflyta REMS

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Rydapt (midostaurin) [prescribing information]. East Hanover, NJ : Novartis 2017
Xospata (gilteritinib) [prescribing information]. Northbrook, IL : Astellas Pharma 2021
Vanflyta (quizartinib) [prescribing information]. Basking Ridge, NJ : Daiichi Sankyo 2023

Supportive Care: Backbone of all AML Therapy

- **Monitor for TLS at the start of any AML therapy**
  - The higher the blast burden, the higher the risk of TLS.
  - Need baseline labs, allopurinol, increased fluids, frequent lab monitoring
  - Older adults: consider initial admission for safe monitoring and aggressive fluids
- **Monitor and manage cytopenias**
  - Labs 2-3x week when starting new regimens
  - Determine acceptable transfusion parameters (ex. HGB<8, PLT <10)
  - Establish a protocol for transfusion support (infusion centers vs. ED)
  - Teach patients how to monitor for signs of worsening blood counts
- **Provide antibiotic prophylaxis for ANC < 500**
  - Cover viral, bacterial and fungal
  - May need to dose reduce for CYP considerations
- **Symptom Management: Manage common side effects**
  - Nausea
  - Diarrhea
  - Constipation
  - Mucositis

Oral Chemo is still Chemo!

R/R *IDH1*mut AML : Ivosidenib

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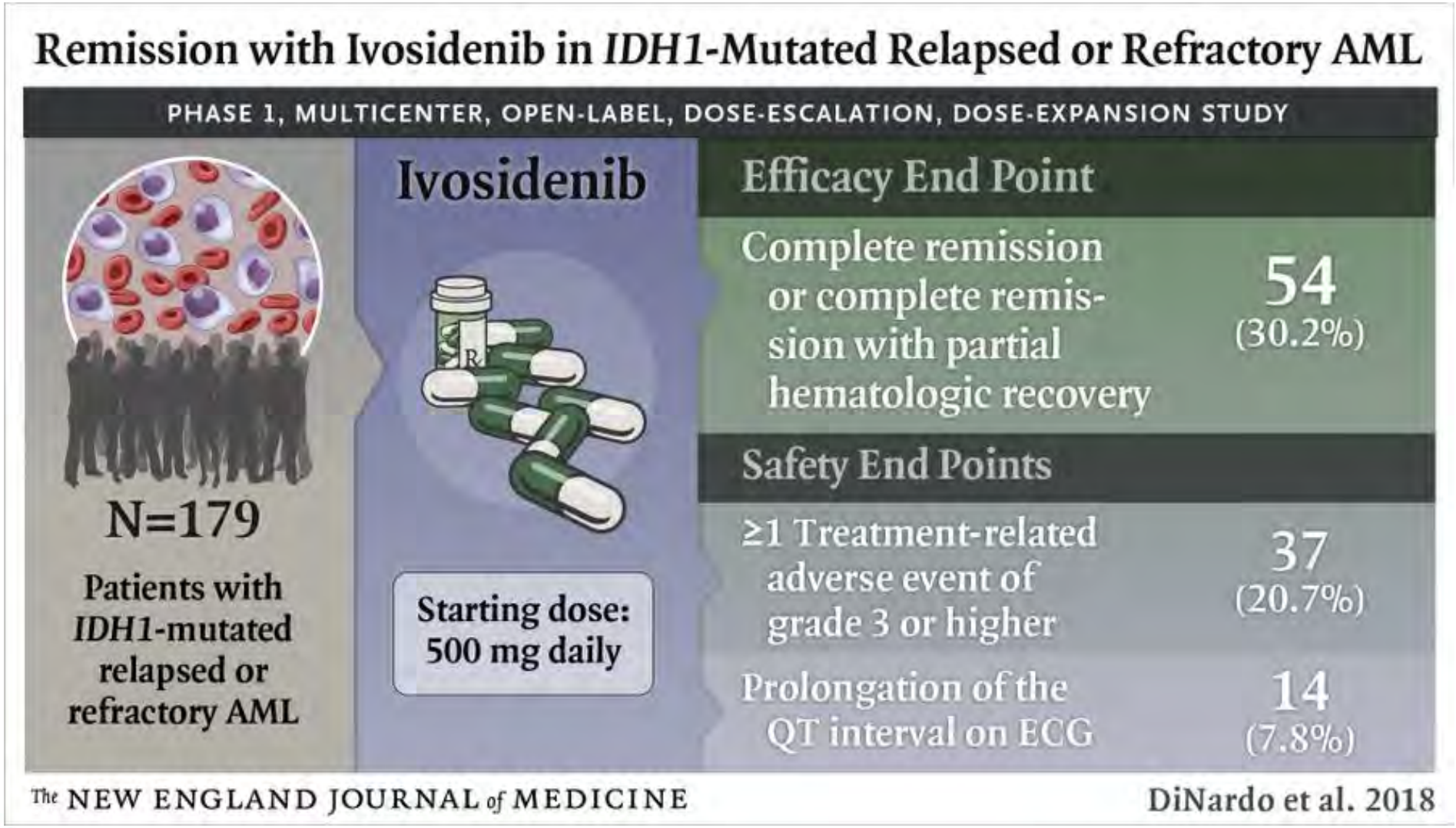

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1. de Botton S, Fenaux P, Yee K, Olutasidenib (FT-2102) induces durable complete remissions in patients with relapsed or refractory *IDH1*-mutated AML. *Blood Adv* 2023; 7 (13): 3117–3127

R/R *IDH1*mut AML : Olutasidenib

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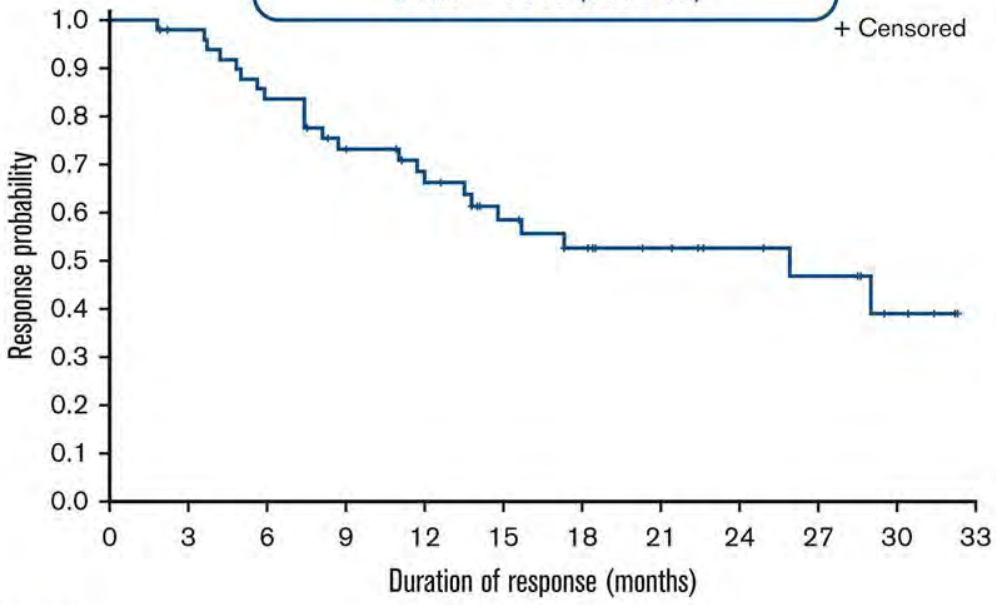
Olutasidenib induced durable remissions and transfusion independence with a well-characterized and manageable side-effect profile.

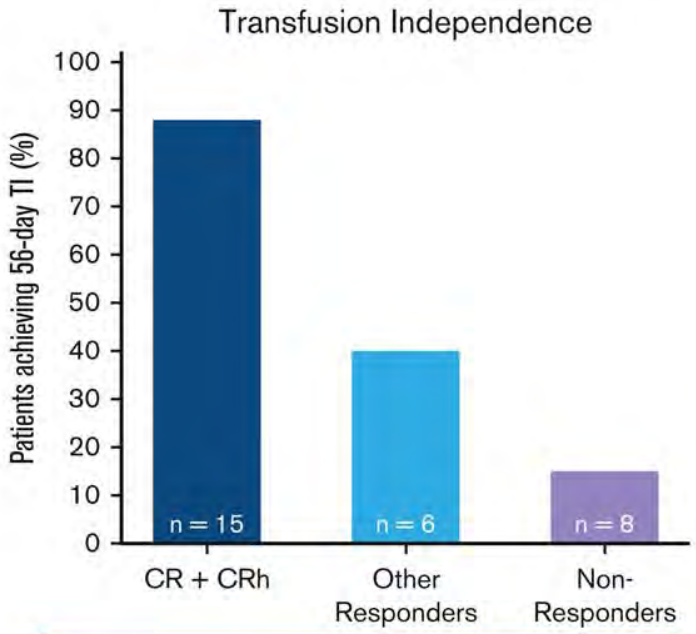
153 patients with mutant IDH1 Relapsed/Refractory AML received olutasidenib monotherapy (150 mg BID):

- Median age 71 years with median 2 prior regimens
- 70% patients had remission duration ≤12 months

CR + CRh rate = 35% (51/147)
CR rate = 32% (47/147)
ORR = 48% (71/147)



CR/CRh Responders: 51 48 41 34 29 21 17 13 10 8 4 0



16 (11%) patients proceeded to HSCT

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1. de Botton S, Fenaux P, Yee K, Olutasidenib (FT-2102) induces durable complete remissions in patients with relapsed or refractory *IDH1*-mutated AML. *Blood Adv* 2023; 7 (13): 3117–3127
2. **Venugopal S**, Watts J; Olutasidenib: from bench to bedside. *Blood Adv* 2023; 7 (16): 4358–4365

R/R *IDH2* mut AML : Enasidenib

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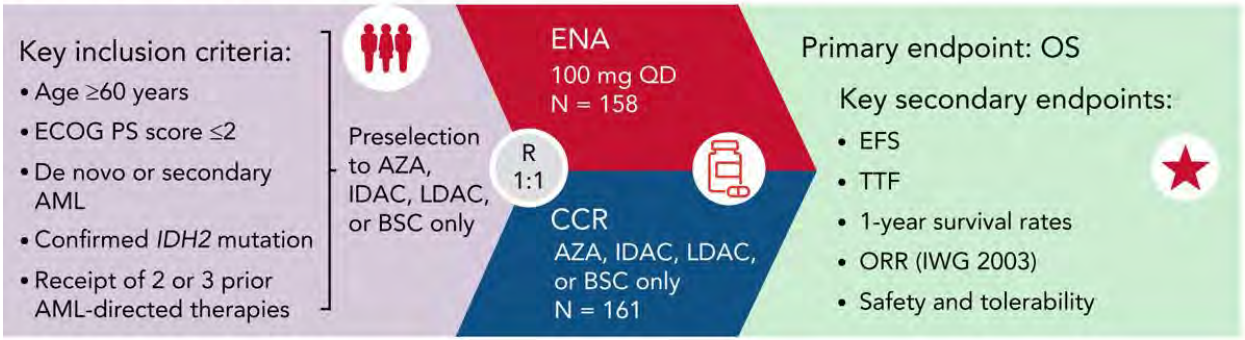
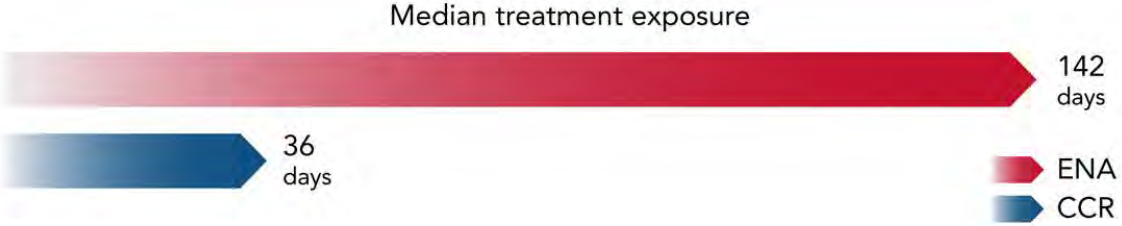
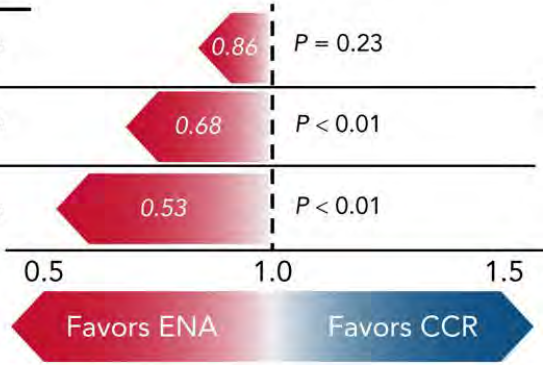
IDHentify: a randomized, open-label, phase 3 trial to evaluate the efficacy and safety of enasidenib vs. conventional care regimens in older patients with late-stage, heavily pretreated mutant-*IDH2* R/R AML

IDHentify: study design and key endpoints





	ENA	CCR	Hazard ratios	
Median OS	6.5 mo	6.2 mo	0.86	$P = 0.23$
Median EFS	4.9 mo	2.6 mo	0.68	$P < 0.01$
Median TTF	4.9 mo	1.9 mo	0.53	$P < 0.01$



AML, acute myeloid leukemia; AZA, azacitidine; BSC, best supportive care; CCR, conventional care regimens; ECOG PS, Eastern Cooperative Oncology Group performance status; ENA, enasidenib; EFS, event-free survival; IDAC, intermediate-dose cytarabine; IDH2, isocitrate dehydrogenase-2; IWG, International Working Group; LDAC, low-dose cytarabine; mo, months; ORR, overall response rate; OS, overall survival; R, randomization; R/R, relapsed/refractory; TTF, time to treatment failure.

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de Botton S, Montesinos P, Schuh AC, et al. Enasidenib vs conventional care in older patients with late-stage mutant-IDH2 relapsed/refractory AML: a randomized phase 3 trial. *Blood*. 2023;141(2):156-167

IDH Inhibitors: Adverse Effects and Management Considerations

Name	Ivosidenib	Olutasidenib	Enasidenib
Target	IDH1	IDH1	IDH2
Dose	500mg po daily, avoiding high-fat meals	150 mg po BID on empty stomach	100mg po daily
Adverse Effects	Differentiation syndrome, QTc prolongation, Guillain-Barre Syndrome, fatigue, noninfectious leukocytosis, arthralgia, edema, mucositis, rash, pyrexia, constipation	Differentiation syndrome, noninfectious leukocytosis, hepatotoxicity, fatigue, arthralgia, nausea, constipation, dyspnea, rash, mucositis, diarrhea, headache, hypertension	Differentiation syndrome, nausea/vomiting, elevated bilirubin, diarrhea, noninfectious leukocytosis, tumor lysis syndrome
Management Considerations	• Weekly ECGs for 3 weeks then monthly • Discontinue completely for Guillain-Barre Syndrome	• Monitor for frequently for hepatotoxicity with LFTs weekly for 2 months, then slowly space out if stable	• Takes up to 6 months to show a clinical response. • May increase the effect of caffeine for people who are sensitive

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Tibsovo (ivosidenib) [prescribing information]. Boston, MA : Servier Pharmaceuticals; 2023
Rezlidhia (olutasidenib) [prescribing information]. South San Francisco, CA : Rigel Pharmaceuticals; December 2022 Rev 02
Idhifa (enasidenib) [prescribing information]. Summit, NJ: Celgene Corporation; September 2019.

IDH Inhibitors: Differentiation Syndrome

Definition	Symptoms	Management
Differentiation Syndrome is associated with rapid proliferation and differentiation of myeloid cells, causing an inflammatory cytokine process. **May be life-threatening or fatal if not treated.**	• Acute Respiratory Distress • Pleural effusions • Renal impairment • Fevers • Lymphadenopathy • Bone Pain • Peripheral Edema • Rapid Weight Gain • Pericardial Effusion • Multi Organ Dysfunction • Timing: 10 days to 5 months after initiation	• Initiate oral or IV Dexamethasone 10mg q12h • If symptoms severe, or persist 48 hours after initiation of steroids, may consider holding therapy until resolution. Consider IDH inhibitors have a long half life. • Taper steroids after symptoms resolve. Symptoms may reoccur if steroids are prematurely discontinued • If proliferative with leukocytosis, consider Hydrea or other cytoreduction therapies • Monitor for TLS and DIC in more severe cases

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Differentiation syndrome. Important Safety Information. Celgene Corporation. Summit, New Jersey. 2024

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Summary:

ELN 2022 risk stratification and molecular testing in AML is useful in establishing the diagnosis and to identify actionable therapeutic targets

Novel targeted therapies in AML provide more options for FLT3 and IDH positive patients

Special considerations apply for both FLT3 and IDH inhibitors and providers should be able to identify and manage toxicities

Interdisciplinary coordination and collaboration is vital for the AML patient.

Thank you.