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AML Course 2025

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Overview

- Introduction
  - European Leukemia Network
    - ELN 2022 risk stratification : Patients receiving intensive chemotherapy
    - ELN 2024 risk stratification: Patients receiving less-intensive chemotherapy
    - ELN 2025: Fitness assessment recommendations
- AML Treatment Belgium (reimbursed)
  - Newly diagnosed AML
    - High-intensive chemotherapy
    - Medium-intensive chemotherapy
    - Non-intensive chemotherapy
  - R/R AML

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Patient receiving intensive chemotherapy

ELN AML 2022 CLASSIFICATION

Döhner H, Wei AH, Appelbaum FR, Craddock C, DiNardo CD, Dombret H, Ebert BL, Fenaux P, Godley LA, Hasserjian RP, Larson RA, Levine RL, Miyazaki Y, Niederwieser D, Ossenkoppele G, Röllig C, Sierra J, Stein EM, Tallman MS, Tien HF, Wang J, Wierzbowska A, Löwenberg B. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood. 2022 Sep 22;140(12):1345-1377. doi: 10.1182/blood.2022016867. PMID: 35797463.

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2022 Risk classification by genetics at initial diagnosis

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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Relevant diagnostic changes in ELN 2022: **favorable risk**

- Both monoallelic and biallelic in-frame b-ZIP mutations of CEBPA are now considered favorable-risk AML.

- NPM1-mutated AML is considered a favorable-risk disease.
  - Except in presence of cytogenetic abnormalities with an unfavorable risk!

- AML with a hyperdiploid karyotype is no longer considered a poor-risk disease.

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Relevant diagnostic changes in ELN 2022: **intermediate risk**

- FLT3-ITD Allelic Ratio (AR) is no longer relevant for risk classification; therefore, FLT3-ITD-mutated AMLs are considered intermediate-risk disease, regardless of NPM1 mutation status.

- The presence of t(9;11)(p21.3;q23.3) = intermediate risk, takes precedence over rare, concurrent adverse risk gene mutations
  - Except: KMT2A partial tandem duplication (PTD

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Relevant diagnostic changes in ELN 2022: **adverse risk**

- TP53 mutation at a variant allele fraction of at least 10% defines a new entity AML.
  - Irrespective of the TP53 allelic status (mono- or biallelic mutation)
  - TP53 mutations are significantly associated with AML with complex and monosomal karyotype

- AML with myelodysplasia-related gene mutations (ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and/or ZRSR2) should not be used as an adverse prognostic markers if they co-occur with favorable-risk AML subtype.

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Relevant diagnostic changes in ELN 2022: **adverse risk**

- Complex karyotype:
  - 3 unrelated chromosome abnormalities in the absence of other class-defining recurring genetic abnormalities.

- Monosomal karyotype:
  - Presence of two or more distinct monosomies (excluding loss of X or Y)
  - One single autosomal monosomy in combination with at least one structural chromosome abnormality (excluding core-binding factor AML).

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Relevant diagnostic changes in ELN 2022: **germline**

- Given the risk of germline predisposition for all patients with hematological malignancies, regardless of age, testing should be performed as early as possible.

- When identified, germline variants should be used as diagnostic qualifiers for the AML category!

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Patients receiving hypomethylating agents with/without venetoclax/ivosidenib

ELN AML 2024 CLASSIFICATION

Döhner H, DiNardo CD, Appelbaum FR, Craddock C, Dombret H, Ebert BL, Fenaux P, Godley LA, Hasserjian RP, Larson RA, Levine RL, Miyazaki Y, Niederwieser D, Ossenkoppele G, Röllig C, Sierra J, Stein EM, Tallman MS, Tien HF, Wang J, Wierzbowska A, Wei AH, Löwenberg B. Genetic risk classification for adults with AML receiving less-intensive therapies: the 2024 ELN recommendations. Blood. 2024 Nov 21;144(21):2169-2173. doi: 10.1182/blood.2024025409. PMID: 39133932.

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Genetic risk classification for adults with AML receiving less-intensive therapies: the 2024 ELN recommendations

Risk category	Genetic abnormality
Favorable	Mutated *NPM1* (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt}) Mutated *IDH2* (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt}) Mutated *IDH1** (*TP53*^{wt}) Mutated *DDX41*† Other cytogenetic and/or molecular abnormalities‡ (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt})
Intermediate	Other cytogenetic and molecular abnormalities‡ (*FLT3*-ITD^{pos} and/or *NRAS*^{mut} and/or *KRAS*^{mut}; *TP53*^{wt})
Adverse	Mutated *TP53*

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Median OS times by genetic marker

Genetic marker	Median OS, mo
Favorable-risk group	
Mutated *NPM1* (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt})	39
Mutated *IDH2* (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt})	37
Mutated *IDH1** (*TP53*^{wt})	29
Mutated *DDX41*	>24
AML with MR gene mutations (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt})	23
Intermediate-risk group	
AML with MR gene mutations (*FLT3*-ITD^{pos} and/or *NRAS*^{mut} and/or *KRAS*^{mut}; *TP53*^{wt})	13
Other cytogenetic and molecular abnormalities (*FLT3*-ITD^{pos} and/or *NRAS*^{mut} and/or *KRAS*^{mut}; *TP53*^{wt})	12
Adverse-risk group	
Mutated *TP53*	5-8

*Favorable risk (median OS time) applies specifically to patients treated with AZA + IVO, irrespective of the presence of activating signaling gene mutations.

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ELN 2022 MRD DIAGNOSIS, FOLLOW UP

Döhner H, DiNardo CD, Appelbaum FR, Craddock C, Dombret H, Ebert BL, Fenaux P, Godley LA, Hasserjian RP, Larson RA, Levine RL, Miyazaki Y, Niederwieser D, Ossenkoppele G, Röllig C, Sierra J, Stein EM, Tallman MS, Tien HF, Wang J, Wierzbowska A, Wei AH, Löwenberg B.

Genetic risk classification for adults with AML receiving less-intensive therapies: the 2024 ELN recommendations. Blood. 2024

Nov 21;144(21):2169-2173. doi: 10.1182/blood.2024025409. PMID: 39133932.

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MRD Management update

- Pre-allo-SCT MRD positivity is an independent adverse risk factor for post-transplant outcomes
- No evidence for interventions for pre-allo MRD eradication (e.g., extra-intensive chemotherapy)
- MAC regimen is the preferred regimen for fit, young patients with MRD positivity

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Impact of ELN risk score & MRD on decision to go transplant ?

Disease	Disease status	MSD allo	MUD allo	MMAD allo	Auto
Haematological malignancies					
AML[a]	CR1 (favourable risk and MRD−)[b]	GNR/II	GNR/II	GNR/II	CO/I
	CR1 (favourable risk and MRD+)[b]	S/II	CO/II	CO/II	GNR/II
	CR1 (intermediate risk)[b]	S/II	CO/II	CO/II	CO/I
	CR1 (adverse risk)[b]	S/II	S/II	S/II	GNR/I
	CR2	S/II	S/II	S/II	CO/II
	APL Molecular CR2	S/II	CO/II	GNR/III	S/II
	Relapse or refractory	CO/II	CO/II	CO/II	GNR/III

Snowden JA, Sánchez-Ortega I, Corbacioglu S, Basak GW, Chabannon C, de la Camara R, Dolstra H, Duarte RF, Glass B, Greco R, Lankester AC, Mohty M, Neven B, de Latour RP, Pedrazzoli P, Peric Z, Yakoub-Agha I, Sureda A, Kröger N; European Society for Blood and Marrow Transplantation (EBMT). Indications for haematopoietic cell transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe, 2022. Bone Marrow Transplant. 2022 Aug;57(8):1217-1239. doi: 10.1038/s41409-022-01691-w. Epub 2022 May 19. PMID: 35589997; PMCID: PMC9119216.

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What is fit?

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ELN 2025 fitness assessment recommendations

Venditti A, Palmieri R, Maurillo L, Röllig C, Wierzbowska A, de Leeuw D, Efficace F, Curti A, Ngai LL, Tettero J, Adès L, Almeida A, Bullinger L, Dennis M, Esteve J, Ferrara F, Heuser M, Huls G, Lübbert M, Mehta P, Montesinos P, Pabst T, Récher C, Rossi G, Russell N, Sierra J, Stauder R, Vey N, Walter RB, Wang E, Nier S, Martins CG, Ossenkoppele G.

Fitness assessment in acute myeloid leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. Blood Adv. 2025

May 13;9(9):2207-2220. doi: 10.1182/bloodadvances.2024013744. PMID: 39913928; PMCID: PMC12083920.

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TREATMENT AML

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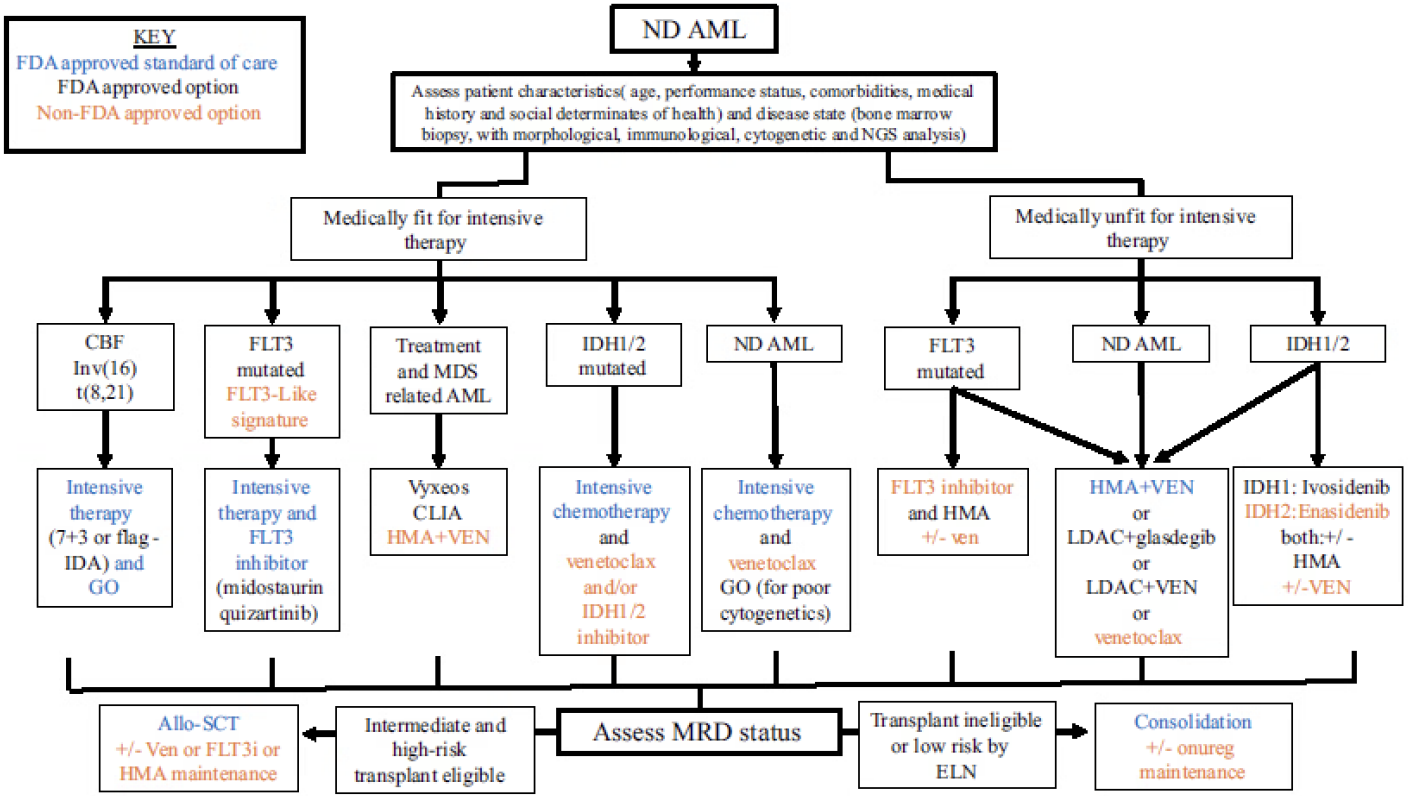
Overview of upfront therapy in AML



Forsberg M, Konopleva M. AML treatment: conventional chemotherapy and emerging novel agents. Trends Pharmacol Sci. 2024 May;45(5):430-448. doi: 10.1016/j.tips.2024.03.005. Epub 2024 Apr 20. PMID: 38643058.

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Reimbursed treatments for newly diagnosed AML in Belgium

- ***High-intensive chemo***
  - 7 + 3 (Cytarabine + Daunorubicin/Idarubicin)
    - **CD33+** : addition of **gemtuzumab ozogamicin**
    - **FIt-3 ITD/TKD positive**: addition of **midostaurin** from day 8–21
    - F**lt-3 ITD positive**: addition of **quizartinib** from day 8-21
  - (FLA-G-IDA)
- ***Medium-intensive chemo***
  - All patients: Venetoclax – Azacitidine
  - **IHD1-mutated** patients: **Ivosidenib** – Azacitidine
- *Non-intensive chemo*
  - Azacitidine
  - Low dose Cytarabine
  - Low dose alkylators

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HIGH-INTENSIVE CHEMO

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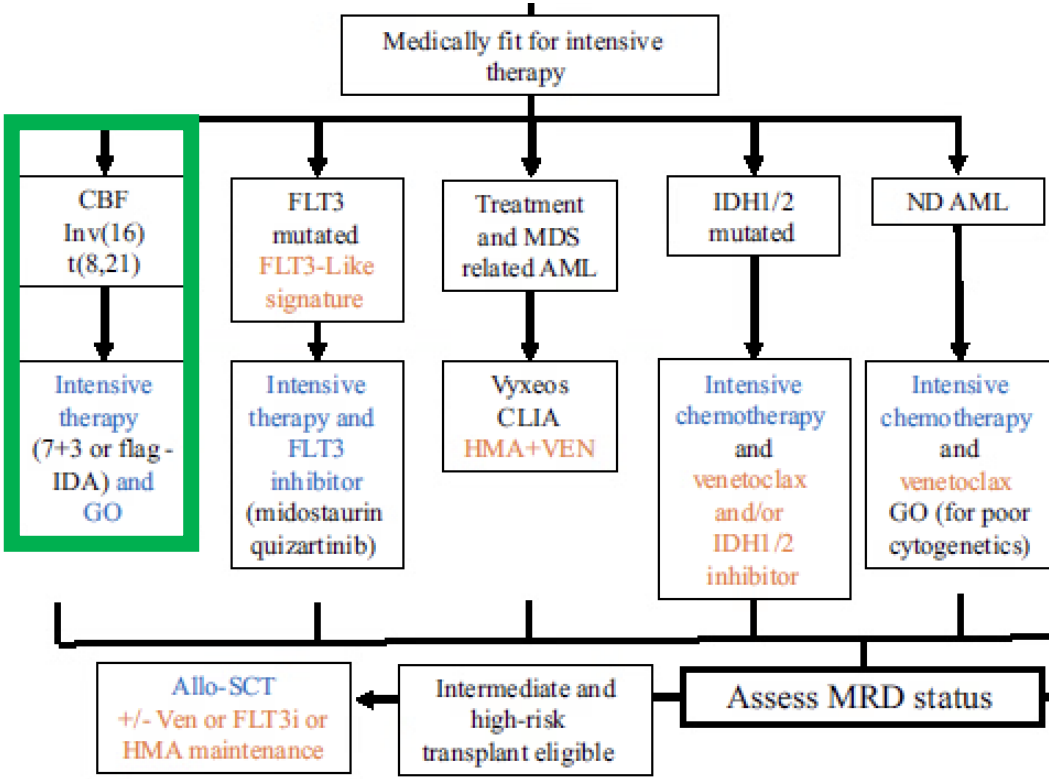
IC reimbursed in Belgium



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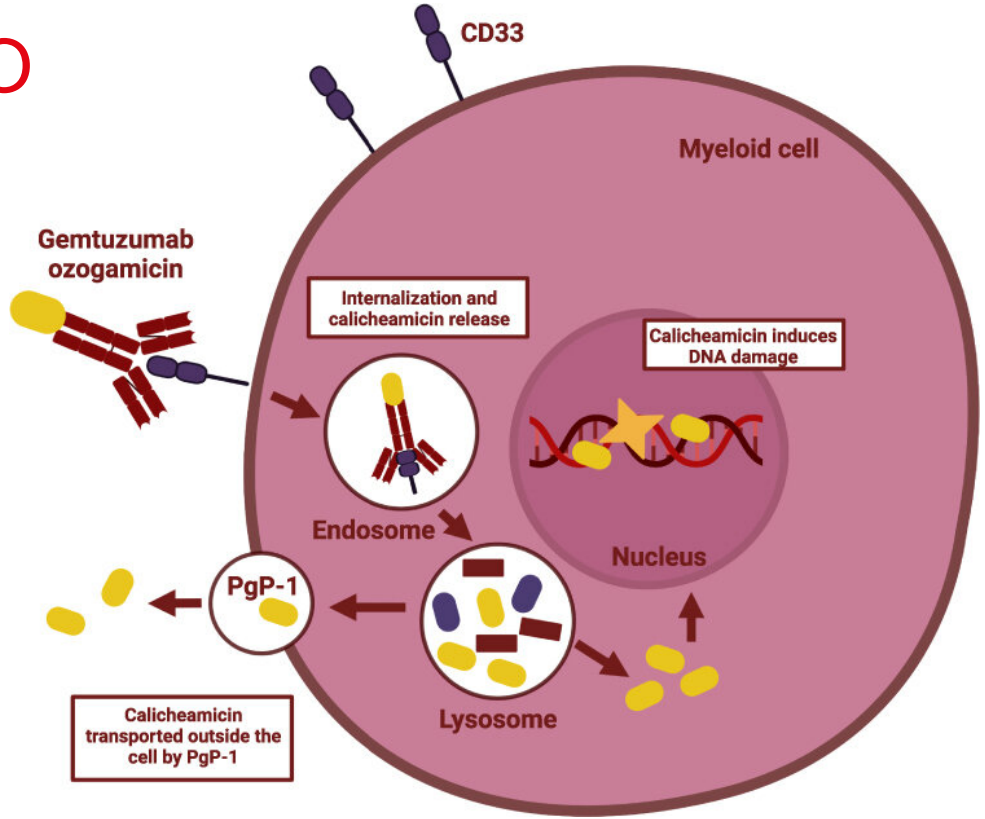
CD33+ AML: 7+3 + GO



Wijnen NE, Koedijk JB, Klein K, Luesink M, Goemans BF, Zwaan CM, Kaspers GJL. Treating CD33-Positive de novo Acute Myeloid Leukemia in Pediatric Patients: Focus on the Clinical Value of Gemtuzumab Ozogamicin. *Onco Targets Ther*. 2023;16:297-308
https://doi.org/10.2147/OTT.S263829

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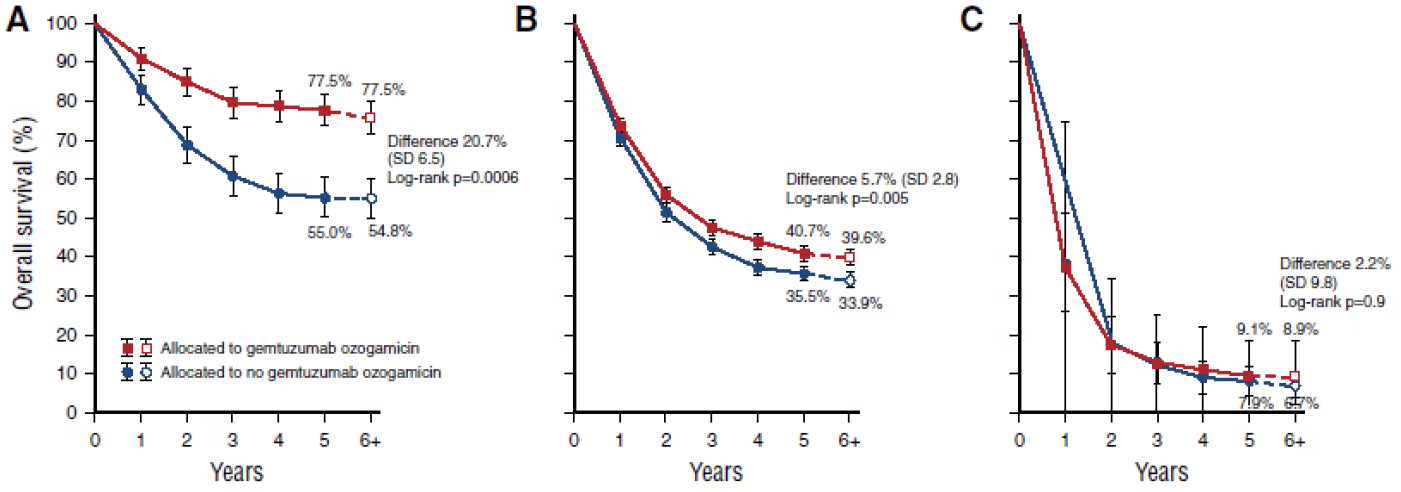
ALFA-0701 trial



Favorable risk

Intermediate risk

Adverse risk

Lambert J, Pautas C, Terré C, Raffoux E, Turlure P, Caillot D, Legrand O, Thomas X, Gardin C, Gogat-Marchant K, Rubin SD, Benner RJ, Bousset P, Preudhomme C, Chevret S, Dombret H, Castaigne S. Gemtuzumab ozogamicin for *de novo* acute myeloid leukemia: final efficacy and safety updates from the open-label, phase III ALFA-0701 trial. Haematologica. 2019 Jan;104(1):113-119. doi: 10.3324/haematol.2018.188888. Epub 2018 Aug 3. PMID: 30076173; PMCID: PMC6312010.

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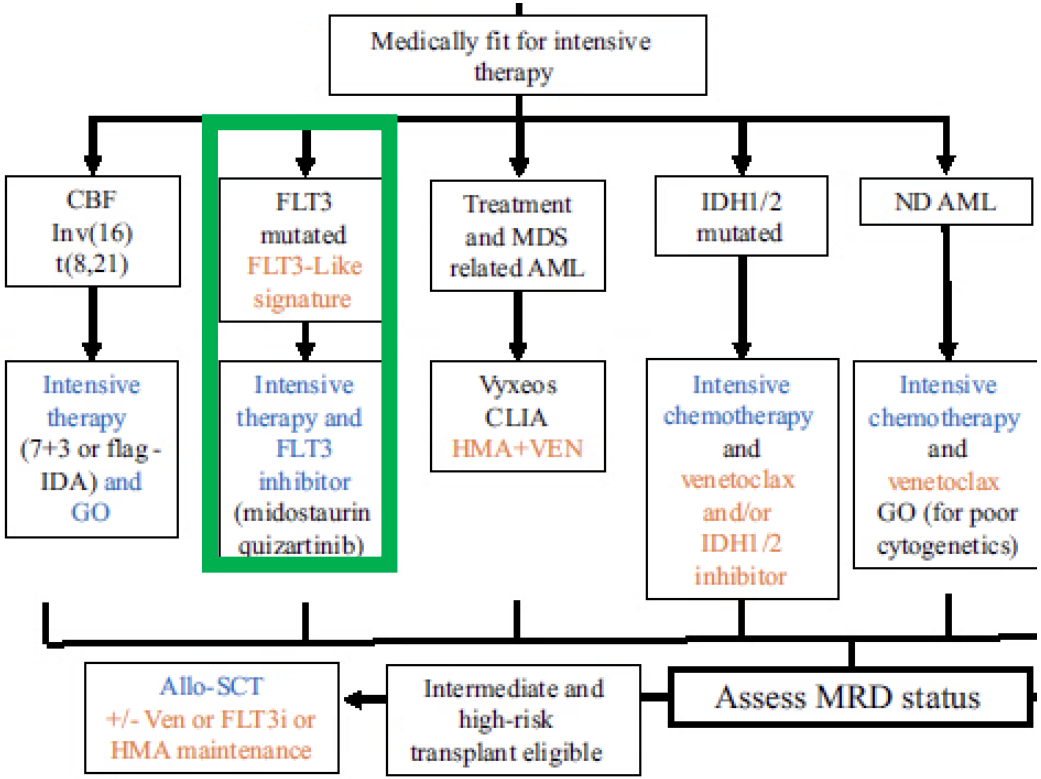
IC reimbursed in Belgium



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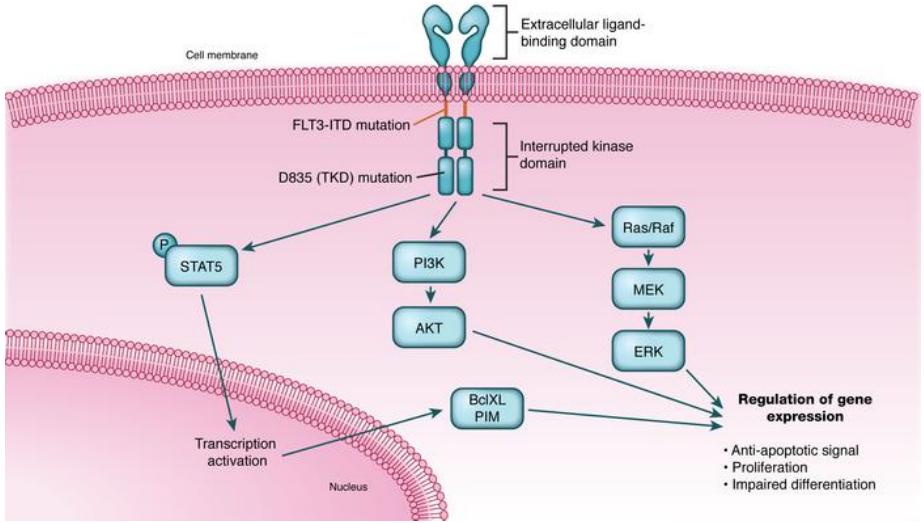
FLT3 ITD/TKD + AML

- FLT3 mutations are very frequent:
  - ITD 20-30%
  - TKD 5-10%
- FLT3 encodes a tyrosine kinase involved in:
  - Cell proliferation
  - Anti-apoptosis
  - Differentiation block
- FLT3-ITD = intermediate risk
- FLT3-ITD NGS can be used as follow-up MRD (current practice in US)



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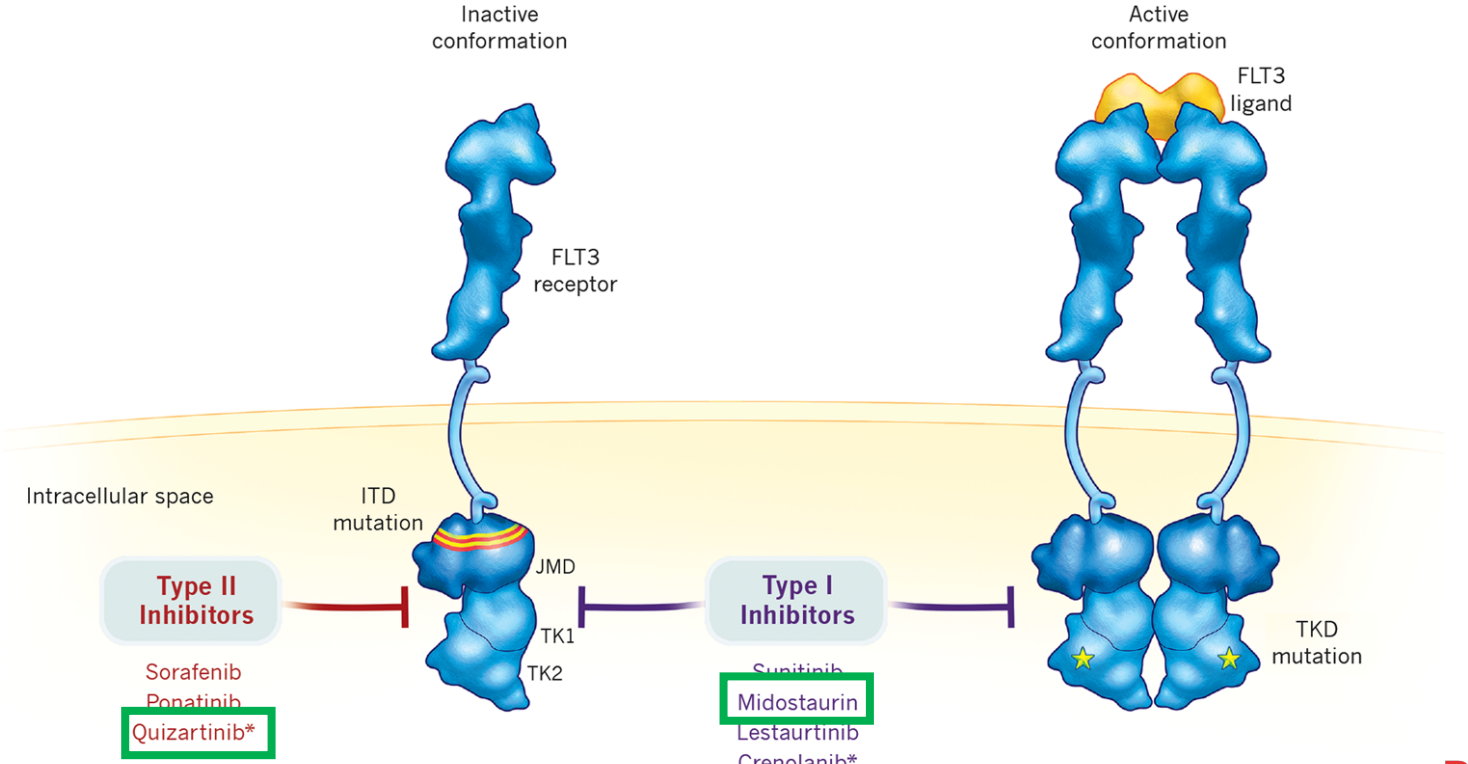
FLT3-inhibitors: type I vs II



Daver, N., Schlenk, R.F., Russell, N.H. *et al.* Targeting *FLT3* mutations in AML: review of current knowledge and evidence. *Leukemia* **33**, 299–312 (2019). https://doi.org/10.1038/s41375-018-0357-9

* *Second-generation FLT3 inhibitors*

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FLT3 ITD/TKD$_{pos}$ AML patients:

7+3 and Midostaurin

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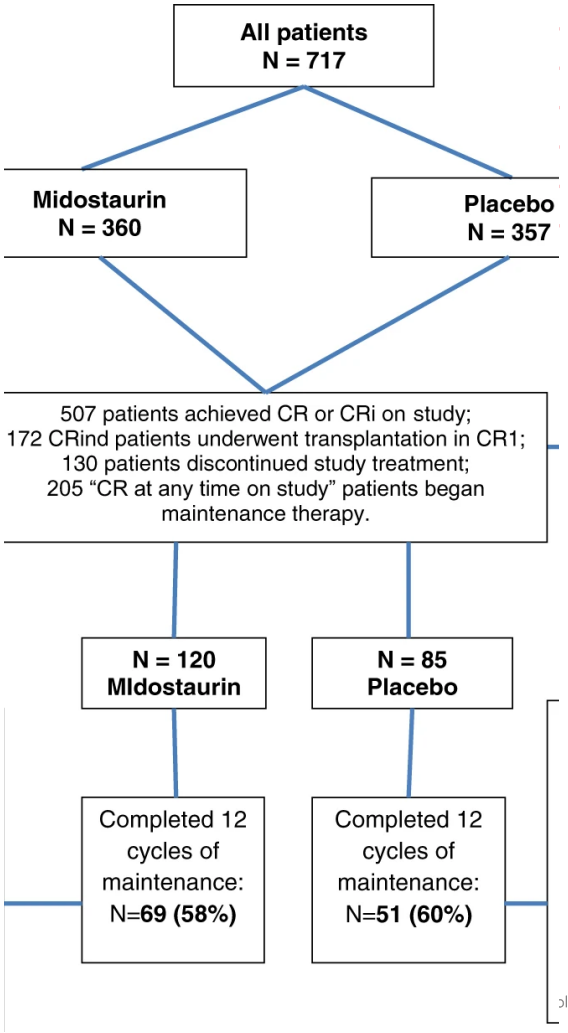
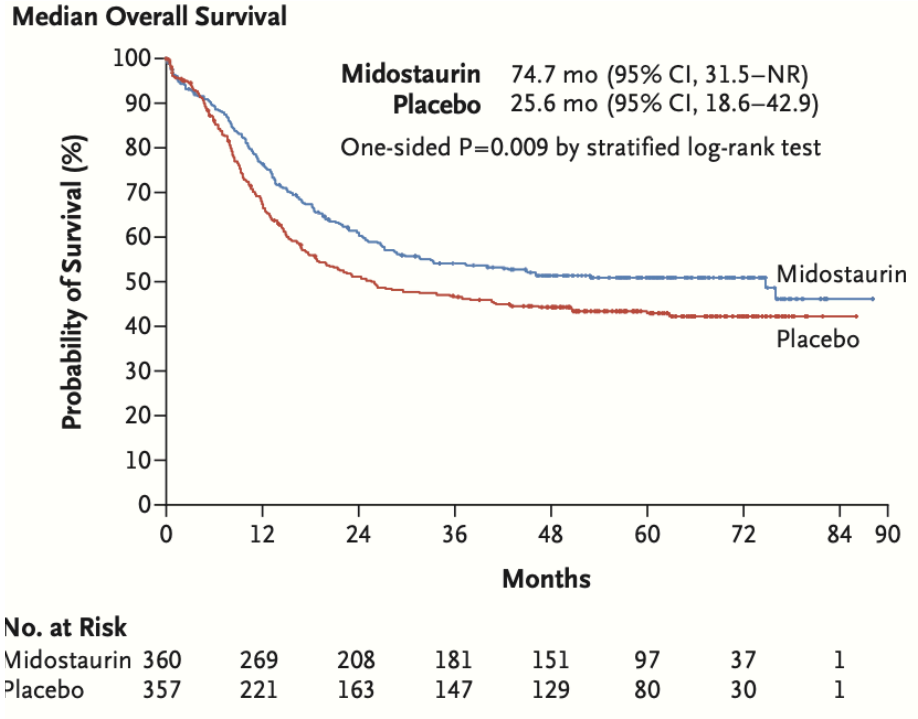
Ratify trial: 7 + 3 and midostaurin (type I inhibitor)



Stone RM, Mandrekar SJ, Sanford BL, Laumann K, Geyer S, Bloomfield CD, Thiede C, Prior TW, Döhner K, Marcucci G, Lo-Coco F, Klisovic RB, Wei A, Sierra J, Sanz MA, Brandwein JM, de Witte T, Niederwieser D, Appelbaum FR, Medeiros BC, Tallman MS, Krauter J, Schlenk RF, Ganser A, Serve H, Ehninger G, Amadori S, Larson RA, Döhner H. Midostaurin plus Chemotherapy for Acute Myeloid Leukemia with a FLT3 Mutation. N Engl J Med. 2017 Aug 3;377(5):454-464. doi: 10.1056/NEJMoa1614359. Epub 2017 Jun 23. PMID: 28644114; PMCID: PMC5754190.

Ratify results:



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FLT3 ITD_{pos} AML patients: 7+3 and Quizartinib

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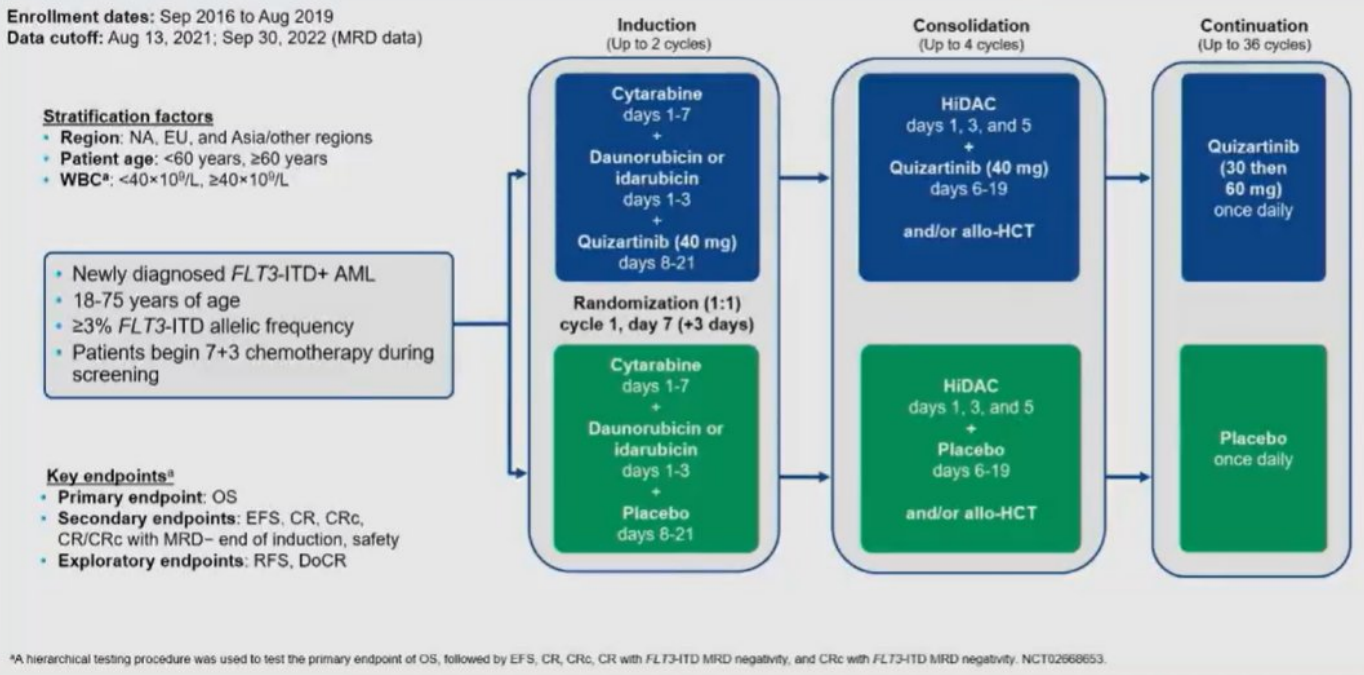
Quantum first trial: 7 + 3 and Quizartinib (type II inhibitor)



Erba HP, Montesinos P, Kim HJ, Patkowska E, Vrhovac R, Žák P, Wang PN, Mitov T, Hanyok J, Kamel YM, Rohrbach JEC, Liu L, Benzohra A, Lesegretain A, Cortes J, Perl AE, Sekeres MA, Dombret H, Amadori S, Wang J, Levis MJ, Schlenk RF; QuANTUM-First Study Group. Quizartinib plus chemotherapy in newly diagnosed patients with FLT3-internal-tandem-duplication-positive acute myeloid leukaemia (QuANTUM-First): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2023 May 13;401(10388):1571-1583. doi: 10.1016/S0140-6736(23)00464-6. Epub 2023 Apr 25. Erratum in: Lancet. 2023 Oct 14;402(10410):1328. doi: 10.1016/S0140-6736(23)02235-3. PMID: 37116523.

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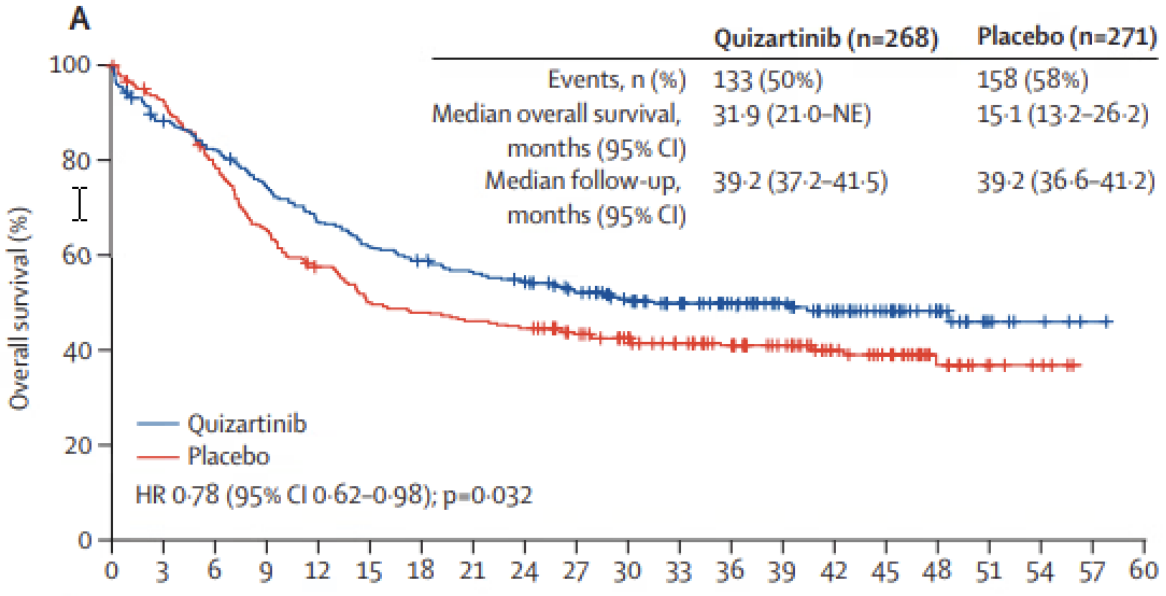
Results



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MEDIUM-INTENSIVE CHEMO

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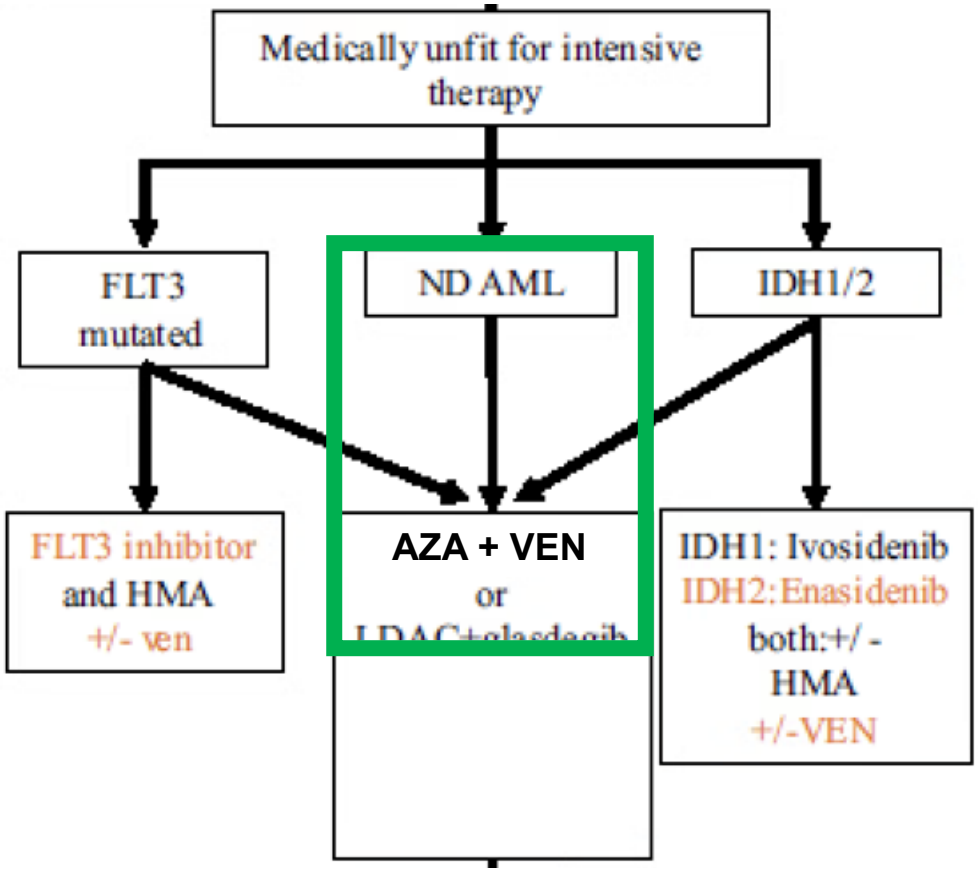

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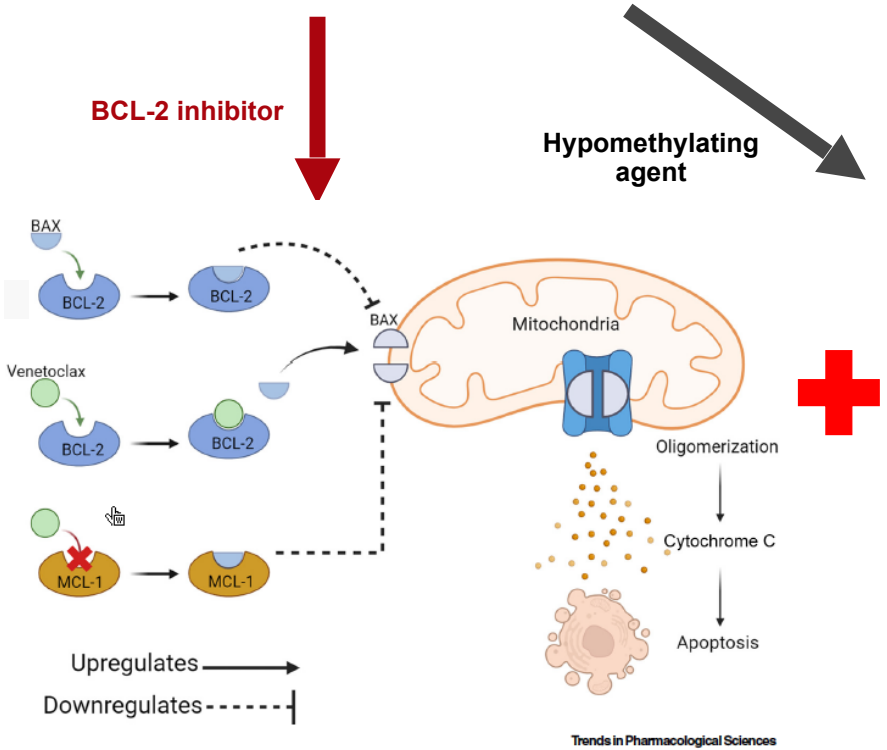
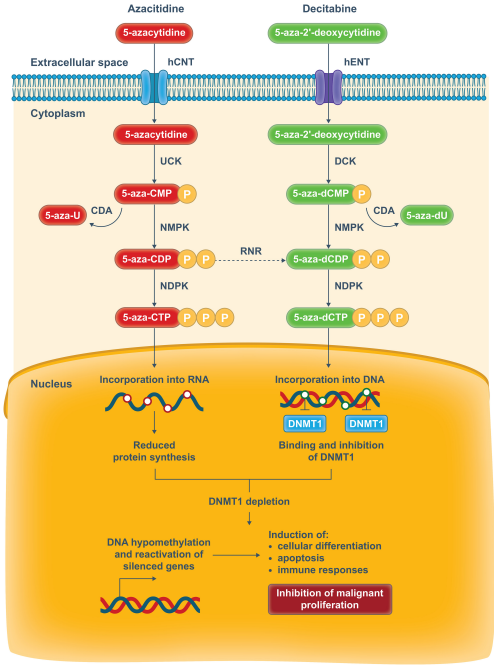
AML

Venetoclax + Azacitidine





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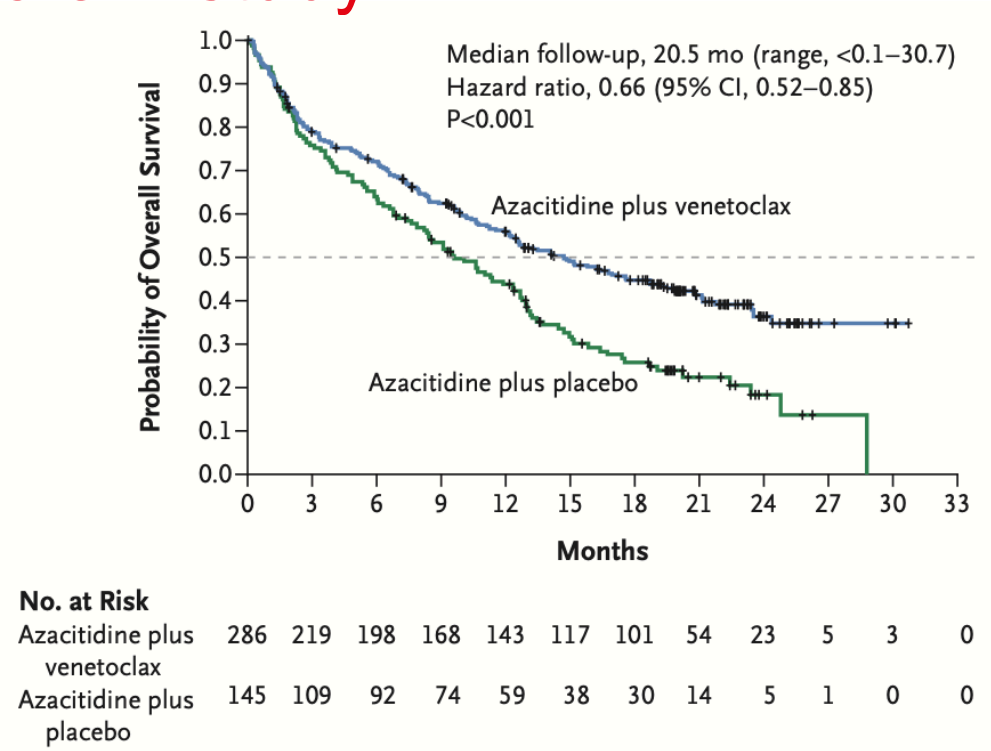
VEN- AZA Viale-A study



No. at Risk

Azacitidine plus venetoclax	286	219	198	168	143	117	101	54	23	5	3	0
Azacitidine plus placebo	145	109	92	74	59	38	30	14	5	1	0	0

Erba HP, Montesinos P, Kim HJ, Patkowska E, Vrhovac R, Žák P, Wang PN, Mitov T, Hanyok J, Kamel YM, Rohrbach JEC, Liu L, Benzohra A, Lesegretain A, Cortes J, Perl AE, Sekeres MA, Dombret H, Amadori S, Wang J, Levis MJ, Schlenk RF; QuANTUM-First Study Group. Quizartinib plus chemotherapy in newly diagnosed patients with FLT3-internal-tandem-duplication-positive acute myeloid leukaemia (QuANTUM-First): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2023 May 13;401(10388):1571-1583. doi: 10.1016/S0140-6736(23)00464-6. Epub 2023 Apr 25. Erratum in: Lancet. 2023 Oct 14;402(10410):1328. doi: 10.1016/S0140-6736(23)02235-3. PMID: 37116523.

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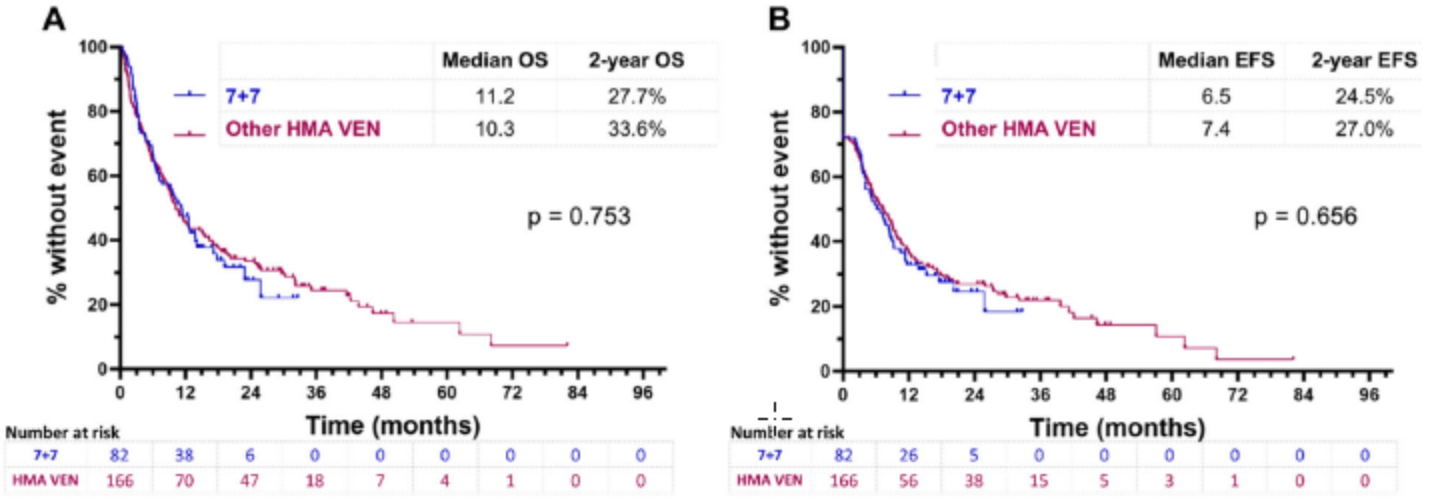
Ideal regimen: Ven + Aza 7+7?



Willekens C, et al. Reduced venetoclax exposure to 7 days vs standard exposure with hypomethylating agents in newly diagnosed AML patients. Blood Cancer J. 2025 Apr 17;15(1):68. doi: 10.1038/s41408-025-01269-x. PMID: 40246832; PMCID: PMC12006504.

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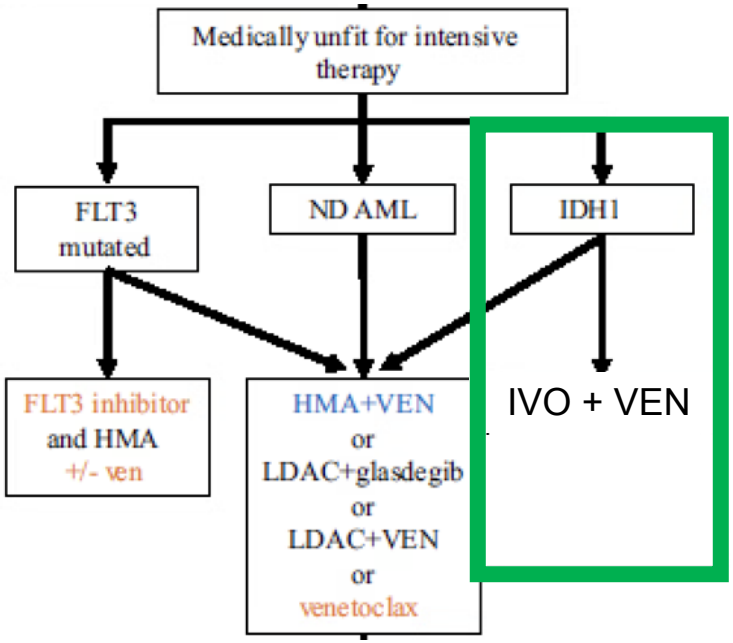

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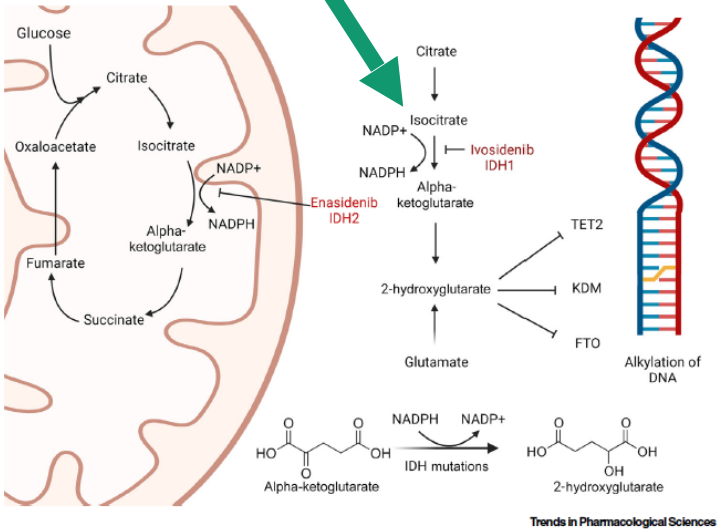
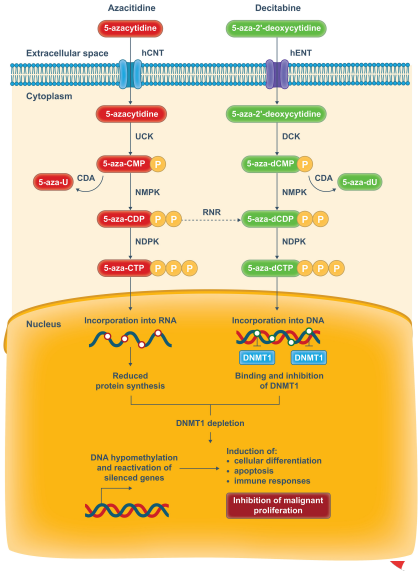
IDH1-mutated AML

Ivosidenib + Azacitidine

IDH-1 inhibitor

Hypomethylating agent





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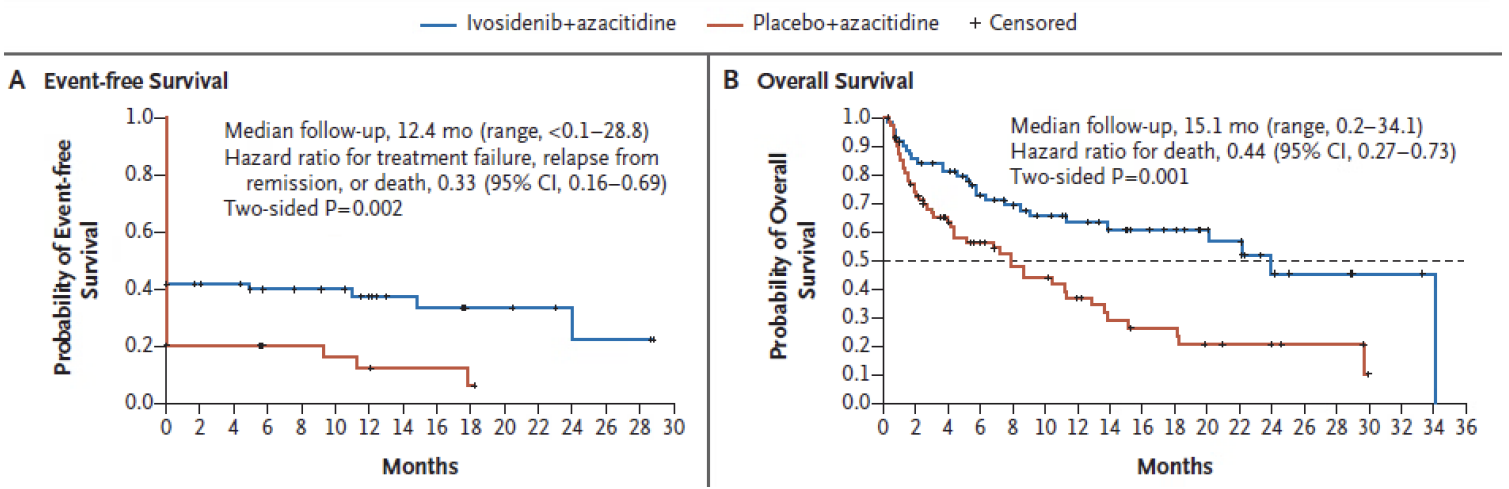
IVO- AZA : AGILE study



Montesinos P, Recher C, Vives S, Zarzycka E, Wang J, Bertani G, Heuser M, Calado RT, Schuh AC, Yeh SP, Daigle SR, Hui J, Pandya SS, Gianolio DA, de Botton S, Döhner H. Ivosidenib and Azacitidine in *IDH1*-Mutated Acute Myeloid Leukemia. N Engl J Med. 2022 Apr 21;386(16):1519-1531. doi: 10.1056/NEJMoa2117344. PMID: 35443108.

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RELAPSED AML

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Relapsed AML

Reimbursed:
Intensive chemotherapy: HOVON 7 + 3, FLAG-IDA,
FLT3-ITD/TKD+ AML: **Gilteritinib**
Oral alkylating agents (hydrea, myleran)

Not reimbursed:
Intensive chemotherapy + venetoclax
LDAC + venetoclax
Azacitidine + venetoclax

Future?
Menin inhibitors for KMT2Ar or NPM1m AML
Revuminib (FDA approved 2024 for KMT2Ar)
Ziftomenib, bleximenib, enzomenib under investigation

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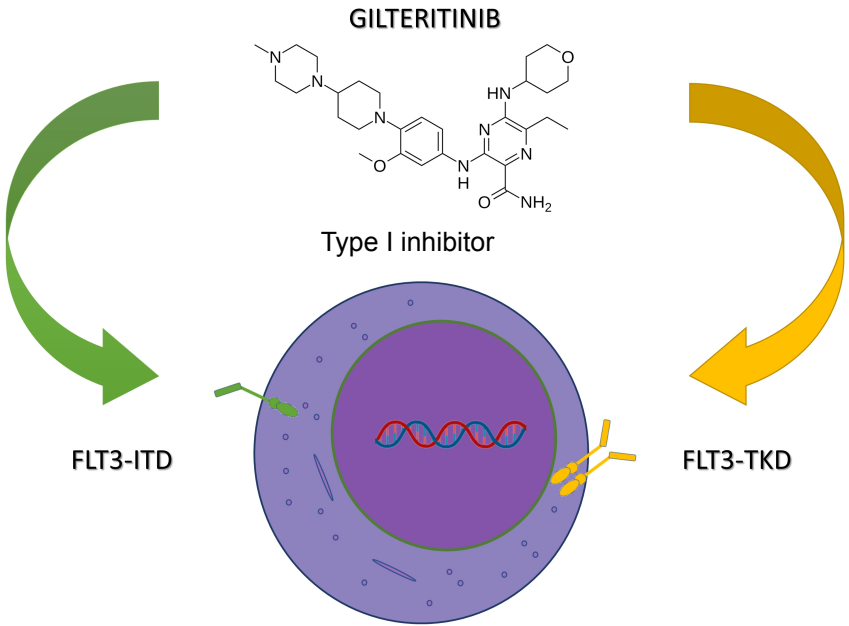
R/R AML FLT3 TKD/ITD$_{pos}$: Gilteritinib



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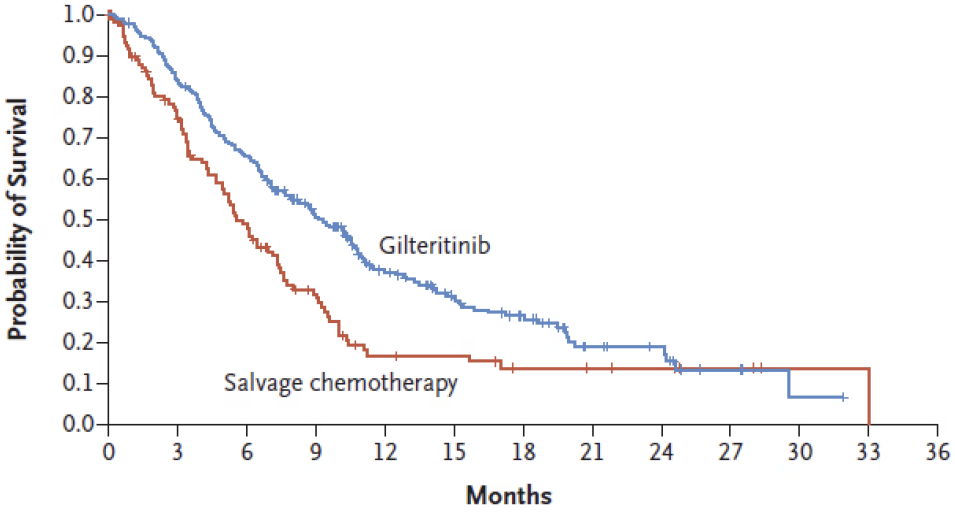
Results Admiral trial

A **Overall Survival**



	Median Overall Survival (95% CI)
	mo
Gilteritinib	9.3 (7.7–10.7)
Salvage Chemotherapy	5.6 (4.7–7.3)

Hazard ratio for death, 0.64 (95% CI, 0.49–0.83)
P<0.001

Perl AE, Martinelli G, Cortes JE, Neubauer A, Berman E, Paolini S, Montesinos P, Baer MR, Larson RA, Ustun C, Fabbiano F, Erba HP, Di Stasi A, Stuart R, Olin R, Kasner M, Ciceri F, Chou WC, Podoltsev N, Recher C, Yokoyama H, Hosono N, Yoon SS, Lee JH, Pardee T, Fathi AT, Liu C, Hasabou N, Liu X, Bahceci E, Levis MJ. Gilteritinib or Chemotherapy for Relapsed or Refractory *FLT3*-Mutated AML. N Engl J Med. 2019 Oct 31;381(18):1728-1740. doi: 10.1056/NEJMoa1902688. Erratum in: N Engl J Med. 2022 May 12;386(19):1868. doi: 10.1056/NEJMx220003. PMID: 31665578.

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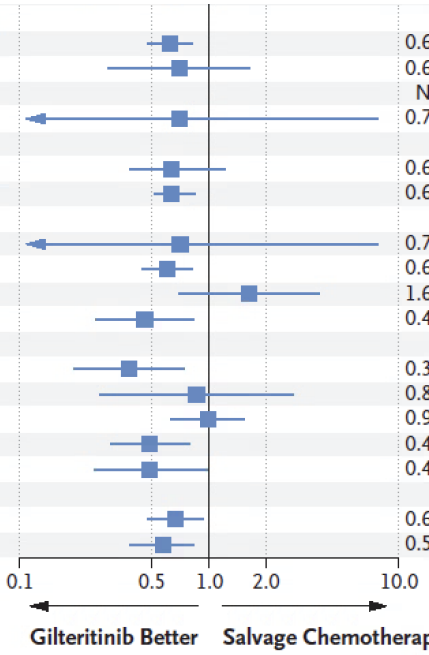
Results

FLT3 mutation type			
FLT3 ITD alone	145/215	81/113	0.62 (0.47–0.82)
FLT3 TKD alone	16/21	8/10	0.69 (0.29–1.64)
FLT3 ITD and *FLT3* TKD	6/7	0	NE (NE–NE)
Other	4/4	1/1	0.70 (0.06–7.92)
Previous use of *FLT3* inhibitor			
Yes	26/34	12/15	0.63 (0.32–1.27)
No	145/213	78/109	0.63 (0.48–0.83)
Cytogenetic risk status			
Favorable	3/4	1/1	0.70 (0.06–7.92)
Intermediate	119/182	63/89	0.60 (0.44–0.82)
Unfavorable	22/26	7/11	1.63 (0.69–3.85)
Unknown	27/35	19/23	0.46 (0.25–0.84)
Response to first-line therapy per IRT			
Relapse ≤6 mo after allogeneic HSCT	24/31	16/17	0.38 (0.20–0.75)
Relapse >6 mo after allogeneic HSCT	10/17	4/8	0.86 (0.26–2.80)
Primary refractory disease without HSCT	70/98	28/48	0.99 (0.63–1.55)
Relapse ≤6 mo after composite complete remission and no HSCT	47/67	28/34	0.49 (0.30–0.80)
Relapse >6 mo after composite complete remission and no HSCT	20/34	14/17	0.49 (0.25–0.98)
Preselected chemotherapy per IRT			
High intensity	96/149	52/75	0.66 (0.47–0.93)
Low intensity	75/98	38/49	0.56 (0.38–0.84)



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Take home message

- Despite increased use of the ICC classification, the WHO remains the basis for reimbursement in Belgium.
- Fit patients and <70-75 years: first-choice treatment is high-intensive chemotherapy +/- alloSCT.
- ≧75 years or unfit: wait for IDH1 status before starting AZA-based therapy.

  IDH1 patients are undertreated with Ven-Aza.
- FLT3-ITD/TKD must be (re)assessed at diagnosis and after each recurrence!
- MRD is essential for follow-up and has therapeutic implications.
- Venetoclax + Azacitidine 7+7: less might be more for elderly/frail patients

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