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Discrepancies association between FLT3 inhibitors use and prognosis of acute myeloid leukemia: systematic review and meta-analysis

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Abstract

Acute myeloid leukemia (AML) is a malignancy of proliferative, clonal, abnormally, or poorly differentiated cells of the hematopoietic system, characterized by clonal evolution and genetic heterogeneity. Mutations of the FMS-like tyrosine kinase 3 (FLT3) gene occur in approximately 30% of all AML cases, with the internal tandem duplication (ITD) representing the most common type of FLT3 mutation. FLT3-ITD is a common driver mutation that presents with a high leukemic burden and confers a poor prognosis in patients with AML. In this systematic review and meta-analysis, we present a detailed review of current clinical evidence of FLT3 inhibitors and their use in AML, and discrepancies association between FLT3 inhibitors use and prognosis of acute myeloid leukemia and maintenance setting.

Keywords: FLT3 inhibitors, Acute myeloid leukemia, Systematic review, FMS-like tyrosine kinase 3

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Introduction

Acute myeloid leukemia (AML) is a malignancy of proliferative, clonal, abnormally, or poorly differentiated cells of the hematopoietic system, characterized by clonal evolution and genetic heterogeneity [1]. Mutations of the FMS-like tyrosine kinase 3 (FLT3) gene occur in approximately 30% of all AML cases, with the internal tandem duplication (ITD) representing the most common type of FLT3 mutation (FLT3-ITD; approximately 25% of all AML cases) [2]. FLT3-ITD is a common driver mutation that presents with a high leukemic burden and confers a poor prognosis in patients with AML [4]. Patients with FLT3-ITD mutations tend to have a particularly unfavorable prognosis, with an increased risk of relapse and shorter

overall survival (OS) compared with patients without the mutation [5]. A recent meta-analysis demonstrated that the presence of FLT3-ITD is associated with a poor prognosis in terms of OS and relapse-free survival (RFS; hazard ratios of 1.86 and 1.75, respectively). Given the high frequency with which FLT3 mutations occur in AML, a number of TKIs are under development that disrupt the oncogenic signaling initiated by FLT3 [6]. In addition to a variety of improved treatment strategies in AML, the recognition that FLT3-ITD is an adverse prognostic marker, the integration of FLT3 inhibitors into the treatment algorithm, and the increased use of alloHSCT have led to improvements over the past 15 years in clinical outcomes in patients with FLT3-ITD-mutated AML [7]. Notably, this trend was observed retrospectively in a single-tertiary-center study evaluating differences in clinical outcomes in patients with newly diagnosed FLT3-ITD-mutated AML from 2000 to 2014, whereby a higher proportion of patients achieved CR in successive years and the corresponding median OS and median time to relapse increased significantly and incrementally over time with the introduction of alloHSCT and FLT3 inhibitors for the treatment of patients with FLT3-ITD mutations [8].

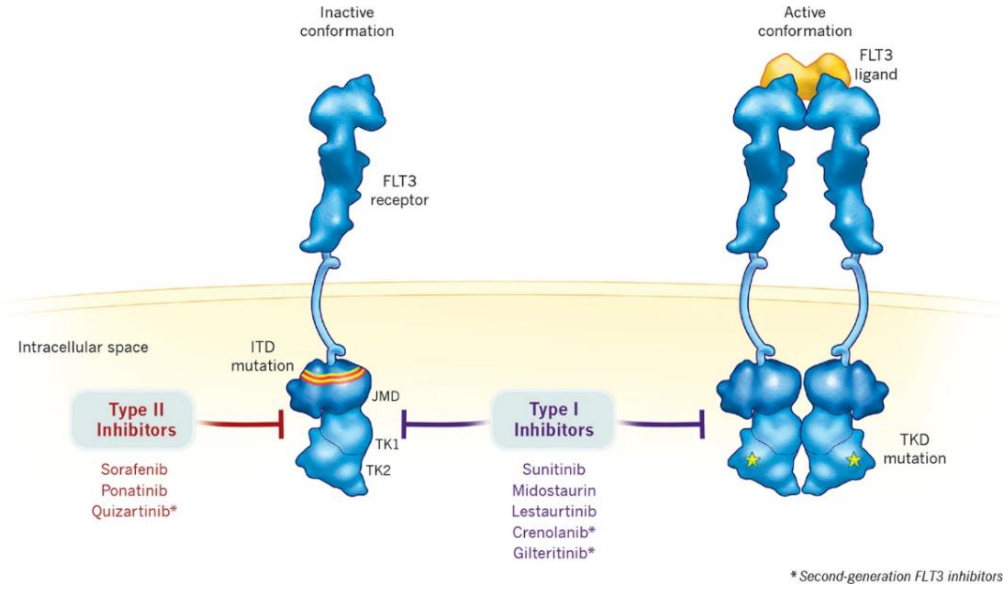

Figure 1.

Type I FLT3: inhibitors bind the FLT3 receptor in the active conformation, either near the activation loop or the ATP-binding pocket and are active against ITD and TKD mutations. Type II FLT3 inhibitors bind the FLT3 receptor in the inactive conformation in a region adjacent to the ATP-binding domain. As a result of this binding affinity, type II FLT3 inhibitors prevent activity of ITD mutations but do not target TKD mutations. FLT3, FMS-like tyrosine kinase; ITD, internal tandem duplication; JMD, juxtamembrane domain; TK, tyrosine kinase; TKD, tyrosine kinase domain [9].

Classification of FLT3 inhibitors

FLT3 inhibitors can be classified using two primary schemas: generation and type. The first-generation FLT3 inhibitors were tyrosine kinase inhibitors (TKIs) with multi-kinase target activity [10]. Existing first-generation TKIs include lestaurtinib (CEP-701), sunitinib (SU11248), midostaurin (PKC412), and sorafenib (BAY43-9006) [11]. The antileukemic effects of these multi-kinase inhibitors likely derive from the simultaneous inhibition of FLT3 and parallel pathways, but multiple off-target effects also bring about increased toxicities [12]. Subsequently, second-generation FLT3 inhibitors with higher selectivity and inhibitory activity were identified [13]. Second-generation FLT3 inhibitors can more selectively inhibit FLT3, and thus have greater clinical potential and fewer off-target effects. Second-generation FLT3 inhibitors include gilteritinib (ASP2215), quizartinib (AC220), and crenolanib (CP868596). In plasma, first-generation inhibitors have higher IC50 values and shorter half-lives than their second-generation counterparts, which explains their limited clinical potency [14].

Furthermore, these FLT3 inhibitors can be roughly classified into two types according to the binding mode to FLT3 [15]. Type I inhibitors bind to the ATP-binding site in the intracellular active pocket and enable downregulation of the phosphorylation of both ITD and TKD mutations. In contrast, because type II inhibitors are designed to favorably bind to the hydrophobic space of the inactive conformation of FLT3, they are made inaccessible by TKD mutations [16].

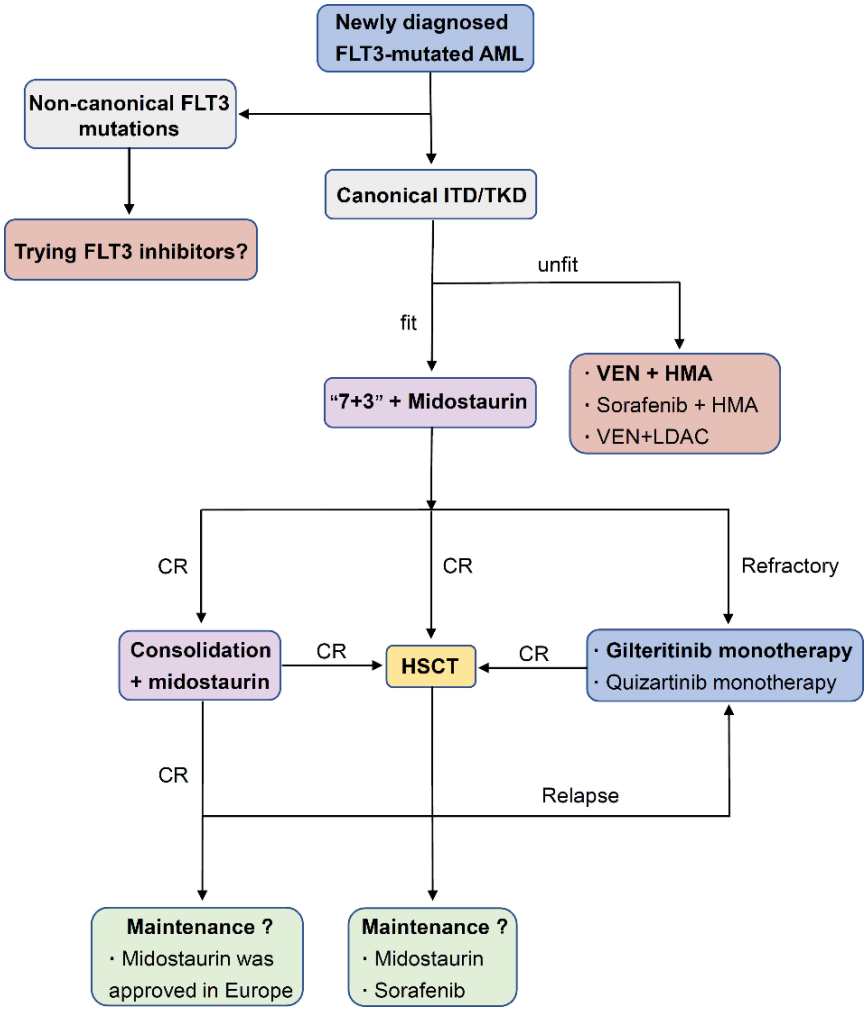

Figure 1.

Applications of FLT3 inhibitors in AML.

Resistance to FLT3 inhibition

Primary resistance to TKI treatment is not well elucidated. Secondary resistance is almost universally seen after prolonged use in various types of malignancies, usually due to emerging mutation in or near the kinase domain of the RTK [17]. Some TKI-resistant mutations have a predominant pattern, e.g, ABL1 T315I in TKI-treated chronic myeloid leukemia or EGFR T790M in EGFR TKI-treated non-small-cell lung cancer. As previously noted, FLT3 mutation is not the early event in the evolution of AML and thus not required for AML growth and proliferation; thus, loss of FLT3 mutation is common and may result in loss of response to FLT3 inhibitor (FLT3 independence) [18]. Several secondary RTK-resistant mutations have been described after quizartinib use and could be heterogeneous even within a single patient.36 Most of the mutations after quizartinib use happen at D835 residue [19].

Methods and analysis

A comprehensive search of Pubmed, Embase, Cochrane Central Register of Controlled Trials, Web of Science. The risk of bias will be assessed using the approach recommended by Cochrane Handbook for Systematic Reviews of Interventions. We will conduct the meta-analysis to synthesise the evidence for each outcome, if possible. The heterogeneity will be statistically assessed using a χ^2 test and I^2 statistic. This protocol is developed following the guideline of Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols (PRISMA-P) 2015. [20]

Results

Table 1.

Characteristics of individual studies included in the meta-analysis.

Author	Year	*FLT3*-ITD+ patients, N	Median bp (range)	Cut-off, bp	Cut-off selection	HR for death
Engen et al.	2022	77	57 (17-139)	≥50 *vs.* <50	'Minimum *P* value'	1.5
Cucchi et al.	2022	101	49 (4-158)	≥48 *vs.* <48	literature	1.03
Castaño-Bonilla et al.	2021	112	43 (2-211)	≥48 *vs.* <48	median	0.22
Cucchi et al.	2021	110	54 (4-156)	≥48 *vs.* <48	literature	1.34
Schlenk et al.	2020	94	54 (14-220)	≥48 *vs.* <48	literature	1.22
Zhang et al.	2020	88	59 (19-227)	>69 *vs.* <69	'Minimum *P* value'	1.54
Liu et al.	2019	80	40 (8-60)	≥39 *vs.* <39	median	2.41
Kim et al.	2019	70	58 (15-120)	≥70 *vs.* <70	'Minimum *P* value'	2.10
Koszarska et al.	2018	67	44 (4-190)	≥48 *vs.* <48	literature	1.72
Schlenk et al.	2017	311	49 (16-155)	≥48 *vs.* <48	literature	1.12
Blau et al.	2017	64	69 (22-193)	>61 *vs.* <61	median	0.76
Schiller et al.	2016	49	43 (2-134)	≥45 *vs.* <45	median	2.64

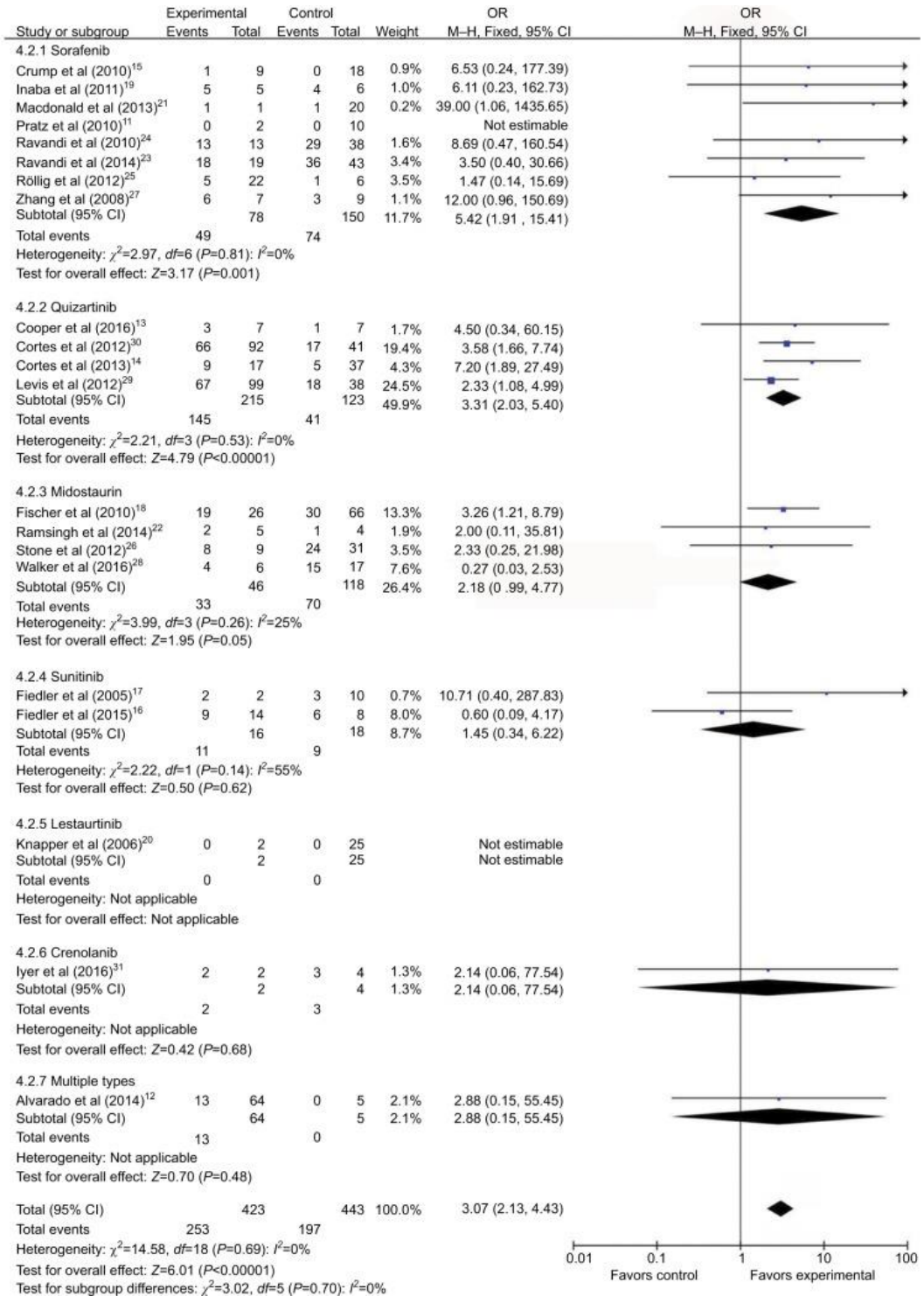

Figure 1.

Meta-analysis of studies reporting FLT3-internal tandem duplication length and overall survival in acute myeloid leukemia patients. Results are provided separately for (a) the Dutch-Belgian Cooperative Trial Group for Hematology-Oncology (HOVON)/Swiss Group for Clinical Cancer Research (SAKK) HOVON 102 AML/SAKK 30/09 trial and (b) the HOVON 132 AML/SAKK 30/13 trial. N: number of FLT3-ITD-positive acute myeloid leukemia (AML) patients in study; HR; hazard ratio for death; 95% CI: 95% confidence interval; ITD: internal tandem duplication; Cut-off: cut-off value used for group comparison of short and long FLT3-ITD lengths, reported in base pairs (bp).

Publication bias

Because only five studies were included in Part I, funnel plots had low power and were not used in test for publication bias. In Part II, we obtained symmetric funnel plots for the synthesis of CR and ORR, indicating mild publication bias

Discussion

FLT3 inhibitors undergoing clinical evaluation were divided into the first-generation agents (including sunitinib, midostaurin, and lestaurtinib) with relative nonspecificity and multiple targets and the second-generation agents (including sorafenib, quizartinib, and crenolanib) with a higher selectivity against mutant FLT3 [21]. A host of first-generation FLT3 inhibitors were limited by their suboptimal propensity for AML control in vivo or their off-target effects, frequently producing a peripheral blast cell clearance and BM blast cell persistence [22].

In our systematic review and meta-analysis, no patient was found to achieve ORR with lestaurtinib monotherapy, and 52.1% patients responded to sunitinib monotherapy with the best outcome of PR 22,10. It was documented that midostaurin as a single agent could reduce blast count in peripheral blood in 70% patients, and the peripheral blood and BM BR was shown in 53.3% patients with monotherapy in studies from our analysis 22,31 [23-32].

For second-generation FLT3 inhibitors, quizartinib monotherapy has been reported with composite CR (CRc; including CR, CRi, and CRp) in 46–57% patients with relapsed/refractory (R/R) AML 14,46,4 [33-35].

Crenolanib, as a single agent, achieved the CRc up to 44% in this patient population 41–59 [36], the median OS for quizartinib and crenolanib in initial clinical studies was reported up to 168 and 259 days, and median EFS could achieve 74 and 56 days, respectively [37-39], which is similar or better than conventional chemotherapy with median OS of 198 days and 4-month EFS ranging from 16.6% to 37.7%.50–52 [40], improvement on EFS and RFS has also been seen from the use of sorafenib [41].

Our systematic review and meta-analysis have several limitations. First, we could only systematically investigate the univariable effect of FLT3-ITD length, since multivariable analyses were provided in only seven of the 22 included reports [42]. In three of these seven reports, FLT3-ITD length remained a relevant prognostic factor in multivariable analysis with FLT3-ITD-AR, FLT3-ITD-AR, sex and cytogenetic risk [43] and FLT3-ITD-AR, NPM1, TP53 and CEBPa mutations and cytogenetic risk [44]. However, due to the limited, heterogenous, and potentially preferential reporting of association analyses, it remains unclear whether FLT3-ITD length has additional prognostic value over the FLT3-ITD-AR, and whether this also depends on the presence of other prognostic factors, such as the FLT3-ITD insertion site [45]. We therefore call for broader and homogeneous reporting of statistical tests to

reproduce and facilitate further research. Second, our results may only apply to patients treated in regimens without FLT3-TKI. Our results indicate that AML patients with a long FLT3-ITD length have a moderately but statistically significantly higher risk of death, compared with patients with a short FLT3-ITD length. Long FLT3-ITD length might be associated with a higher degree of constitutive kinase activation leading to a more aggressive phenotype [46].

Alternatively, long FLT3-ITD length may be a surrogate for ITD localization in the tyrosine kinase domain rather than in the juxta-membrane domain, which is associated with drug resistance and inferior OS [47]. Others suggest an association independent of ITD localization, since the authors observed poor OS in AML patients with long FLT3-ITD within the juxta-membrane domain [48-52].

Conclusion

FLT3 inhibitors has provided us with numerous powerful creative treatment tools, survival remains poor in FLT3-mutated AML, and new strategies need to be explored. The influence of FLT3 inhibitor tolerance has become an inevitable issue.

Competing interests

The authors declare that they have no competing interests.

Author contributions

The authors met the criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE). The authors were fully responsible for all content and editorial decisions, were involved at all stages of manuscript development, and approved the final version that reflects the authors' interpretations and conclusions.

References

1. Levis M, Ravandi F, Wang ES, et al. Results from a randomized trial of salvage chemotherapy followed by lestaurtinib for patients with FLT3 mutant AML in first relapse. Blood. 2011;117(12):3294–3301.
2. Marcucci G, Haferlach T, Döhner H. Molecular genetics of adult acute myeloid leukemia: prognostic and therapeutic implications., J Clin Oncol, 2011; 29(5): 475-486).
3. Döhner H, Weisdorf DJ, Bloomfield CD. Acute myeloid leukemia. N Engl J Med. 2015;373:1136–52.

4. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127(20):2391–2405.
5. Döhner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Buchner T, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129:424–47.
6. Papaemmanuil E, Gerstung M, Bullinger L, et al. Genomic Classification and Prognosis in Acute Myeloid Leukemia. N Engl J Med. 2016;374(23):2209–2221.
7. chetelig J, Rollig C, Kayser S, Stoelzel F, Schaefer-Eckart K, Haenel M, et al. Validation of the ELN 2017 Classification for AML with intermediate risk cytogenetics with or without NPM1-mutations and high or low Ratio FLT3-ITDs. Blood. 2017;130:2694.
8. Nakao M, Yokota S, Iwai T, et al. Internal tandem duplication of the flt3 gene found in acute myeloid leukemia. Leukemia. 1996;10(12):1911–1918.
9. Daver, N., Schlenk, R.F., Russell, N.H. et al. Targeting FLT3 mutations in AML: review of current knowledge and evidence. Leukemia 2019; 33: 299–312.
10. Grunwald MR, Tseng LH, Lin MT, Pratz KW, Eshleman JR, Levis MJ, et al. Improved FLT3 internal tandem duplication PCR assay predicts outcome after allogeneic transplant for acute myeloid leukemia. Biol Blood Marrow Transplant. 2014;20:1989–95.
11. Small D. FLT3 mutations: biology and treatment. Hematology Am Soc Hematol Educ Program. 2006:178–184.
12. George TI, Tworek JA, Thomas NE, Fatheree LA, Souers RJ, Nakhleh RE, et al. Evaluation of testing of acute leukemia samples: survey result from the College of American Pathologists. Arch Pathol Lab Med. 2017;141:1101–6.
13. Cortes JE, Kantarjian HM, Kadia TM, Borthakur G, Konopleva M, Garcia-Manero G. et al. Crenolanib besylate, a type I pan-FLT3 inhibitor, to demonstrate clinical activity in multiply relapsed FLT3-ITD and D835 AML. J Clin Oncol. 2016;34:7008
14. Cortes JE, Tallman MS, Schiller GJ, Trone D, Gammon G, Goldberg SL, et al. Phase 2b study of two dosing regimens of quizartinib monotherapy in FLT3-ITD mutated, relapsed or refractory AML. Blood. 2018;132:598–607.
15. Port M, Bottcher M, Thol F, Ganser A, Schlenk R, Wasem J, et al. Prognostic significance of FLT3 internal tandem duplication, nucleophosmin 1, and CEBPA gene mutations for acute myeloid leukemia patients with normal karyotype and younger than 60 years: a systematic review and meta-analysis. Ann Hematol. 2014;93:1279–86.

16. Whitman SP, Archer KJ, Feng L, et al. Absence of the wild-type allele predicts poor prognosis in adult de novo acute myeloid leukemia with normal cytogenetics and the internal tandem duplication of FLT3: a cancer and leukemia group B study. Cancer Res. 2001;61(19):7233–7239.
17. Wattad M, Weber D, Döhner K, Krauter J, Gaidzik VI, Paschka P, et al. Impact of salvage regimens on response and overall survival in acute myeloid leukemia with induction failure. Leukemia. 2017;31:1306–13.
18. Stone RM, Collins R, Tallman MS, et al. Effect of cytarabine/anthracycline/crenolanib induction on minimal residual disease (MRD) in newly diagnosed FLT3 mutant AML. Journal of Clinical Oncology. 2017;35:7016.
19. Branford S, Melo JV, Hughes TP. Selecting optimal second-line tyrosine kinase inhibitor therapy for chronic myeloid leukemia patients after imatinib failure: does the BCR-ABL mutation status really matter?, Blood, 2009;114 (27):5426-5435.
20. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015;349:g7647.
21. Ho AD, Schetelig J, Bochtler T, et al. Allogeneic Stem Cell Transplantation Improves Survival in Patients with Acute Myeloid Leukemia Characterized by a High Allelic Ratio of Mutant FLT3-ITD. Biol Blood Marrow Transplant. 2016;22(3):462–469.
22. Ho AD, Schetelig J, Bochtler T, Schaich M, Schafer-Eckart K, Hanel M, et al. Allogeneic stem cell transplantation improves survival in patients with acute myeloid leukemia characterized by a high allelic ratio of mutant FLT3-ITD. Biol Blood Marrow Transplant. 2016;22:462–9.
23. Böiers C, Buza-Vidas N, Jensen CT, et al. Expression and role of FLT3 in regulation of the earliest stage of normal granulocyte-monocyte progenitor development. Blood. 2010;115(24):5061–5068.
24. Levis M, Ravandi F, Wang ES, et al. Results from a randomized trial of salvage chemotherapy followed by lestaurtinib for patients with FLT3 mutant AML in first relapse. Blood. 2011;117(12):3294–3301.
25. Stone RM, Mandrekar SJ, Sanford BL, Laumann K, Geyer SM, Bloomfield CD, et al. The addition of midostaurin to standard chemotherapy decreases cumulative incidence of relapse (CIR) in the international prospective randomized, placebo-controlled, double-blind trial (CALGB 10603 / RATIFY [Alliance]) for newly diagnosed acute myeloid leukemia (AML) patients with FLT3 mutations. Blood. 2017;130:2580.

26. Li L, Piloto O, Nguyen HB, et al. Knock-in of an internal tandem duplication mutation into murine FLT3 confers myeloproliferative disease in a mouse model. Blood. 2008;111(7):3849–3858.
27. Branford S, Melo JV, Hughes TP. Selecting optimal second-line tyrosine kinase inhibitor therapy for chronic myeloid leukemia patients after imatinib failure: does the BCR-ABL mutation status really matter?, Blood, 2009; 114 (27):5426-5435.
28. Chen YB, Li S, Lane AA, et al. Phase I trial of maintenance sorafenib after allogeneic hematopoietic stem cell transplantation for fms-like tyrosine kinase 3 internal tandem duplication acute myeloid leukemia. Biol Blood Marrow Transplant. 2014;20(12):2042–2048.
29. Döhner K, Thiede C, Larson RA, Prior TW, Marcucci G, Jones D, et al. Prognostic impact of NPM1/FLT3-ITD genotypes from randomized patients with acute myeloid leukemia (AML) treated within the international RATIFY Study. Blood. 2017;130:467.
30. Abdelall W, Kantarjian HM, Borthakur G, et al. The Combination of Quizartinib with Azacitidine or Low Dose Cytarabine Is Highly Active in Patients (Pts) with FLT3-ITD Mutated Myeloid Leukemias: Interim Report of a Phase I/II Trial. Blood. 2016;128:1642.
31. Maziarz RT, Patnaik MM, Scott BL, Mohan SR, Deol A, Rowley SD, et al. RADIUS: a phase 2, randomized trial of standard of care (SOC) with or without midostaurin to prevent relapse following allogeneic hematopoietic stem cell transplant (alloHSCT) in patients (pts) with FLT3-Itd-mutated acute myeloid leukemia (AML). Blood. 2016;128:2248.
32. Pace U et al. A ribozyme which discriminates in vitro between PML/RAR alpha, the t(15;17)-associated fusion RNA of acute promyelocytic leukemia, and PML and RAR alpha, the transcripts from the nonrearranged alleles. Cancer Res. 1994;54(24):6365-9.
33. Röllig C et al. Does time from diagnosis to treatment affect the prognosis of patients with newly diagnosed acute myeloid leukemia? Blood. 2020;136(7):823-30.
34. Dohner H et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129(4):424-47.
35. Short NJ et al. Association of measurable residual disease with survival outcomes in patients with acute myeloid leukemia: a systematic review and meta-analysis. JAMA Oncol. 2020;6(12):1890-9.
36. Tamamyan G et al. Frontline treatment of acute myeloid leukemia in adults. Crit Rev Oncol Hematol. 2017;110:20-34.

37. Stone RM et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. N Engl J Med. 2017;377(5):454-64.
38. Voso MT et al. Midostaurin in patients with acute myeloid leukemia and FLT3-TKD mutations: a subanalysis from the RATIFY trial. Blood Adv. 2020;4(19):4945-54.
39. Larson RA et al. An analysis of maintenance therapy and post-midostaurin outcomes in the international prospective randomized, placebo-controlled, double-blind trial (CALGB 10603/RATIFY [Alliance]) for newly diagnosed acute myeloid leukemia (AML) patients with FLT3 mutations. Blood. 2017;130(Supplement 1):145.
40. Burchert A et al. Sorafenib maintenance after allogeneic hematopoietic stem cell transplantation for acute myeloid leukemia with FLT3-Internal tandem duplication mutation (SORMAIN). J Clin Oncol. 2020;38(26):2993-3002.
41. PrECOG, LLC. Randomized trial of gilteritinib vs midostaurin in FLT3 mutated acute myeloid leukemia. NCT03836209. https://clinicaltrials.gov/ct2/show/NCT03836209.
42. Wang ES et al. Low relapse rate in younger patients ≤ 60 years old with newly diagnosed FLT3-mutated acute myeloid leukemia (AML) treated with crenolanib and cytarabine/anthracycline chemotherapy. Blood. 2017;130(Supplement 1):566.
43. Arog Pharmaceuticals, Inc. A phase II study of crenolanib in relapsed/refractory acute myeloid leukemia patients with FLT3 activating mutations. NCT01657682. https://clinicaltrials.gov/ct2/show/NCT01657682.
44. Mathew NR et al. Sorafenib promotes graft-versus-leukemia activity in mice and humans through IL-15 production in FLT3-ITD-mutant leukemia cells. Nat Med. 2018;24(3):282-91.
45. Bohl SR et al. New targeted agents in acute myeloid leukemia: new hope on the rise. Int J Mol Sci. 2019;20(8):1983.
46. Schmalbrock LK, Cocciardi S, Dolnik A, et al. Clonal Evolution of FLT3-ITD Positive AML in Patients Treated with Midostaurin in Combination with Chemotherapy within the Ratify (CALGB 10603) and AMLSG 16-10 Trials. Blood. 2017;130:182.
47. Cortes JE, Kim DW, Pinilla-Ibarz J, et al. PACE Investigators A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias., N Engl J Med, 2013; 369 (19):1783-1796.
48. Schiller GJ, Tallman MS, Goldberg SL, et al. Final results of a randomized phase 2 study showing the clinical benefit of quizartinib (AC220) in patients with FLT3-ITD positive relapsed or refractory acute myeloid leukemia. Journal of Clinical Oncology. 2014;32:7100.
49. Sandmaier BM, Khaled S, Oran B, Gammon G, Trone D, Frankfurt O. Results of a phase 1 study of quizartinib as maintenance therapy in subjects with acute myeloid

leukemia in remission following allogeneic hematopoietic stem cell transplant. Am J Hematol. 2018;93:222–31.

50. Zhang XW, Yan XJ, Zhou ZR, et al. Arsenic trioxide controls the fate of the PML-RARalpha oncoprotein by directly binding PML., Science, 2010; 328 (5975):240-243.
51. Patnaik MM. The importance of FLT3 mutational analysis in acute myeloid leukemia. Leuk Lymphoma. 2018;59:2273–86.
52. Cooper BW, Kindwall-Keller TL, Craig MD, et al. A phase I study of midostaurin and azacitidine in relapsed and elderly AML patients. Clin Lymphoma Myeloma Leuk. 2015;15(7):428–432.