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Review Article

Prognostic Weight of FLT3-ITD Allelic Ratio in Newly Diagnosed Acute Myeloid Leukemia

Gregor F^{1*}, Ivanic A² and Ilavsky S³

¹Department of Laboratory Hematology, Iskar Institute of Clinical Coagulation Medicine, Poland

²Department of Cellular Therapy and Transplantation, Loire Center for Coagulation and Hemostasis Research, Latvia

³Department of Transfusion Medicine and Blood Banking, Osam Institute of Applied Hematology, Czech Republic

*Address for Correspondence: Ferdinand Gregor, Department of Laboratory Hematology, Iskar Institute of Clinical Coagulation Medicine, Poland; E-mail: ferdinand.gregor@iskar.edu

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Abstract

Background: FLT3 internal tandem duplication (ITD) is among the most common and prognostically consequential mutations in newly diagnosed acute myeloid leukemia (AML), but its clinical impact is not uniform across patients.

Objective: To synthesize the published evidence on how the FLT3-ITD mutant-to-wild-type allelic ratio, rather than mutation presence alone, shapes prognosis, interacts with NPM1 co-mutation status, and informs the use of FLT3 inhibitors and allogeneic transplantation.

Methods: Narrative review of landmark cohort studies, European LeukemiaNet risk-classification updates, and randomized phase 3 trials of midostaurin, gilteritinib, quizartinib, and sorafenib in FLT3-mutated AML.

Findings: High allelic ratio (≥ 0.5) confers markedly worse relapse-free and overall survival than low-ratio disease, an effect layered onto NPM1 mutation status; FLT3 inhibitors improve survival across the newly diagnosed and relapsed/refractory settings, and inhibitor-era trials have generally not shown ratio to modify drug benefit, prompting the 2022 ELN revision that removed the ratio-based split for NPM1-mutated, FLT3-ITD-positive disease.

Conclusions: Allelic ratio remains a useful marker of FLT3 dependency and relapse risk that should inform transplant referral and maintenance decisions, but its role is increasingly one input among measurable residual disease and co-mutation data rather than a standalone risk cutoff.

Keywords: FLT3-ITD; allelic ratio; acute myeloid leukemia; NPM1; FLT3 inhibitors

1. Introduction

FLT3 internal tandem duplication was first described three decades ago as an in-frame insertion within the juxtamembrane domain of the FLT3 receptor tyrosine kinase, identified in a subset of acute myeloid leukemia samples by Nakao and colleagues using a simple genomic PCR assay [1]. What began as a curiosity of exon 14/15 length polymorphism turned out to be one of the two or three most consequential single lesions in adult AML. Kiyoi and colleagues linked the duplication to leukocytosis and, in a cohort large enough to matter, to shortened survival [2], and within a few years the UK Medical Research Council group confirmed the finding at scale: among 854 patients enrolled on the AML10 and AML12 trials, FLT3-ITD was present in roughly 27% of cases and independently predicted both relapse and overall survival after adjustment for cytogenetic risk group [3]. Thiede and colleagues, working through 979 patients treated on German multicenter protocols, reported an ITD frequency close to 23% and confirmed the adverse association across FAB subtypes [4]. By the early 2000s, FLT3-ITD positivity itself was accepted as bad news, and it had already become the mutation most consistently invoked when clinicians discussed molecularly targeted approaches to AML risk assessment [5].

What took longer to appreciate was that "FLT3-ITD positive" is not a single biological state. Duplications vary in length from a few base pairs to over 100, insert at different points within the juxtamembrane and adjacent tyrosine kinase domain 1, and — critically — occupy a variable fraction of the leukemic allele pool. Whitman and colleagues showed that loss of the wild-type FLT3 allele, leaving leukemic cells effectively hemizygous for the mutant, tracked with a particularly poor outcome in cytogenetically normal AML, an observation that reframed FLT3-ITD as a dosage phenomenon rather than a binary mutation call [6]. That reframing is the subject of this review: how the allelic ratio of mutant to wild-type FLT3, now measured routinely by fragment-length PCR or

targeted next-generation sequencing at diagnosis, has become a continuous prognostic variable that reshapes European LeukemiaNet risk stratification, transplant referral, and the interpretation of trials testing FLT3 inhibitors in both the frontline and relapsed settings.

2. FLT3-ITD biology and detection methods

FLT3 is a class III receptor tyrosine kinase expressed on early myeloid and lymphoid progenitors; ligand binding drives receptor dimerization and downstream activation of RAS-MAPK, PI3K-AKT, and STAT5 signaling. The internal tandem duplication disrupts the autoinhibitory function of the juxtamembrane domain, producing constitutive, ligand-independent kinase activity. Because the duplicated sequence is an in-frame insertion of variable length rather than a substitution, it can be resolved by capillary fragment-length analysis of a PCR product spanning exons 14 and 15, a method that also yields the relative peak-area ratio of mutant to wild-type product — the basis for the allelic ratio measurement used in most published cohorts [4,7]. Schnittger and colleagues catalogued the diversity of insertion sites and lengths across a large diagnostic series and showed that both length and location within the juxtamembrane-TKD1 region correlate with mutant burden and, independently, with outcome [7]. Insertions that extend into the first beta-strand of the tyrosine kinase domain rather than remaining confined to the juxtamembrane region carry a distinctly worse prognosis, a finding first quantified by Kayser and colleagues in an analysis in which TKD1-inserted ITD conferred resistance to induction chemotherapy and inferior relapse-free survival compared with juxtamembrane-only insertions [8]. Next-generation sequencing panels have since largely supplanted fragment analysis for detecting co-mutations but are only gradually replacing it for ITD quantification, because short-read assemblers handle long, GC-rich duplications poorly; most allelic-ratio data guiding clinical decisions today still derive from the fragment-analysis platform that Kottaridis, Thiede, and Gale used to build

the original evidence base [3,9].

3. Allelic ratio as a continuous prognostic variable

The single most influential demonstration that ratio, not presence or absence, drives risk came from Gale and colleagues, who reanalyzed a large cohort of young adults with AML using quantitative measurement of ITD mutant-to-wild-type signal [9]. Patients with a high allelic ratio, conventionally defined at or above 0.5, had roughly a three-fold increase in relapse risk compared with those with a low ratio, and five-year overall survival diverged sharply — in the range of 15% for high-ratio disease versus close to half for low-ratio disease within the same cytogenetically normal, NPM1-unmutated stratum [9]. That paper also showed that ITD length and number of duplicated clones added little once ratio was accounted for, which is part of why allelic ratio, rather than length or insertion count, became the parameter written into subsequent risk-classification schemes. Kayser and colleagues' TKD1-insertion data reinforced the same conclusion from a different angle: insertion site correlated with ratio and with resistance to the first cycle of induction, and multivariable models that included ratio retained it as an independent predictor of both event-free and overall survival [8]. In pediatric AML, Meshinchi and colleagues found essentially the same gradient — high-ratio FLT3-ITD was associated with markedly worse event-free survival than low-ratio disease, with the low-ratio group behaving closer to FLT3-wild-type patients than to their high-ratio ITD-positive counterparts [10]. The practical consequence is that a diagnostic FLT3 assay reporting only "ITD detected" without a quantitative ratio now under-informs the treating physician; the ratio, not the mutation call, is what most contemporary risk algorithms actually consume.

4. Interaction with NPM1 and co-mutation context

FLT3-ITD rarely occurs alone, and its prognostic weight is not separable from the mutation landscape it sits within. Roughly a third of adult AML carries a mutation in NPM1,

first shown by Falini and colleagues to produce aberrant cytoplasmic localization of nucleophosmin and to define a molecularly distinct, generally favorable-risk subgroup within cytogenetically normal AML [11]. Schlenk and colleagues, studying patients enrolled on German AML Study Group protocols, showed that NPM1 mutation without FLT3-ITD carried a good prognosis that allogeneic transplantation in first remission did not improve, whereas the presence of FLT3-ITD — particularly at high allelic ratio — eroded that favorable effect and identified patients for whom transplant in first complete remission produced a clear survival benefit [12]. Thiede and colleagues' companion analysis of NPM1 mutation prevalence and prognostic impact across nearly 1,500 adults reinforced the same interaction: NPM1-mutated, FLT3-ITD-negative disease had the best outcomes, NPM1-wild-type, FLT3-ITD-positive disease the worst, and the NPM1-mutated/FLT3-ITD-positive group fell in between, with allelic ratio determining where within that middle group a given patient actually sat [13]. Broader genomic profiling has since placed this three-way interaction inside a larger mutational context. Patel and colleagues, analyzing patients from the ECOG E1900 trial with integrated sequencing, found that FLT3-ITD's prognostic effect was modulated by co-occurring DNMT3A and NPM1 status and, unexpectedly, by anthracycline dose during induction [14]. Papaemmanuil and colleagues, sequencing over five thousand AML cases, formalized AML genomics into class-defining subgroups and confirmed that FLT3-ITD, when it co-occurs with NPM1 mutation and no adverse-risk cytogenetic lesion, drives a genomically coherent subgroup whose outcome is disproportionately sensitive to ITD allelic burden rather than to the NPM1 mutation itself [15]. This is the mechanistic basis for the 2017 European LeukemiaNet recommendation to split NPM1-mutated, FLT3-ITD-positive AML by allelic ratio, assigning low-ratio disease to the favorable-risk category and high-ratio disease to intermediate risk [16].

Table 1: How FLT3-ITD allelic ratio modifies NPM1-based risk stratification under the 2017 European LeukemiaNet framework, reflecting the outcome gradient first described across these cohorts [11,12,13,9,16].

NPM1 status	FLT3-ITD status	2017 ELN risk group	Key source
Mutated	Negative	Favorable	[13]
Mutated	Low ratio (<0.5)	Favorable	[16]
Mutated	High ratio (>=0.5)	Intermediate	[9]
Wild-type	Negative	Intermediate	[16]
Wild-type	Any ratio	Adverse	[12]

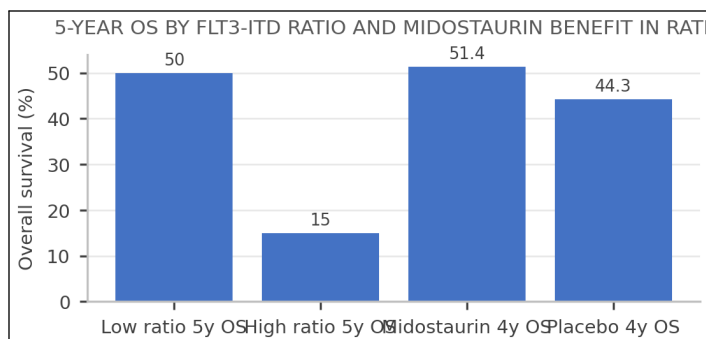


Figure 1: Five-year overall survival diverges sharply by FLT3-ITD allelic ratio, at roughly 50% for low-ratio (<0.5) versus roughly 15% for high-ratio (>=0.5) disease in young adult AML [9], while addition of midostaurin to chemotherapy narrows a comparable gap in the unselected FLT3-mutated RATIFY population, with 4-year overall survival of 51.4% versus 44.3% for placebo [17].

5. FLT3 inhibitors and how they change the calculus

The clinical relevance of allelic ratio did not stay static once small-molecule FLT3 inhibitors entered practice, because the drugs both improve outcomes across ratio strata and complicate the biological argument for why ratio mattered in the first place. The RATIFY trial, led by Stone and colleagues, randomized newly diagnosed FLT3-mutated (ITD or TKD) AML patients aged 18-60 to induction and consolidation chemotherapy with or without the multikinase inhibitor midostaurin; four-year overall survival was 51.4% with midostaurin versus 44.3% with placebo, a statistically significant improvement that held across FLT3-ITD allelic-ratio subgroups in prespecified analysis [17]. A subsequent Alliance analysis of the same cohort, focused on relapse rather than overall survival, confirmed that midostaurin's principal effect was

a reduction in relapse incidence rather than a change in complete remission rate, consistent with a drug acting on residual FLT3-driven clones after induction [18]. Pratz and colleagues had earlier shown, using an ex vivo phospho-flow assay, that the degree of FLT3 mutant allelic burden correlated with in vitro sensitivity to FLT3 inhibition, providing a mechanistic rationale for why high-ratio disease — biologically more dependent on FLT3 signaling — might derive proportionally more benefit from inhibitor therapy even though it starts from a worse baseline [19].

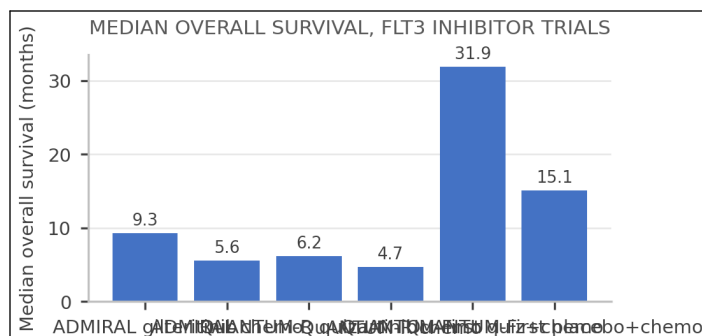


Figure 2: Median overall survival with FLT3 inhibitors versus control across three randomized phase 3 trials: gilteritinib 9.3 months versus chemotherapy 5.6 months in relapsed/refractory disease (ADMIRAL) [21]; quizartinib 6.2 months versus chemotherapy 4.7 months in relapsed/refractory FLT3-ITD disease (QuANTUM-R) [20]; and quizartinib plus chemotherapy 31.9 months versus placebo plus chemotherapy 15.1 months in newly diagnosed FLT3-ITD disease (QuANTUM-First) [24].

In the relapsed and refractory setting, allelic ratio again shaped both trial design and result. Cortes and colleagues' QuANTUM-R trial restricted enrollment to FLT3-ITD-positive relapsed or refractory AML and randomized patients to the selective inhibitor quizartinib versus salvage chemotherapy; median overall survival was 6.2 months with quizartinib against 4.7 months with chemotherapy, a modest but statistically significant gain in a population selected specifically for ITD positivity rather than for ratio [20]. Perl and colleagues' ADMIRAL trial tested the type I inhibitor gilteritinib against salvage chemotherapy in relapsed or refractory FLT3-mutated AML (ITD or TKD) and reported a median overall survival of 9.3 months versus 5.6 months, with the survival curves

separating early and persisting on longer follow-up [21,22]. Neither trial reported allelic ratio as a major effect modifier of inhibitor benefit, an observation that, taken together with the 2022 European LeukemiaNet revision removing the allelic-ratio split for NPM1-mutated, FLT3-ITD-positive disease, reflects a genuine shift in the field: once an effective FLT3-directed drug is available for essentially every ITD-positive patient, the biological argument for a ratio-based prognostic cutoff weakens, even though the underlying disease biology that produced the original cutoff has not changed [23]. Most recently, Erba and colleagues extended FLT3 inhibition to the frontline setting in QuANTUM-First, combining quizartinib with standard induction and consolidation in newly diagnosed FLT3-ITD AML; median overall survival was 31.9 months with quizartinib versus 15.1 months with placebo, again in a trial that enrolled by ITD positivity without an allelic-ratio threshold [24]. Sorafenib, an earlier and less selective FLT3 inhibitor, showed a more modest and cytogenetics-independent benefit in the SORAML trial conducted by Röllig and colleagues in an unselected younger AML population, improving event-free survival without a clear overall survival advantage [25], and its principal contemporary role is as post-transplant maintenance, where Burchert and colleagues' SORMAIN trial demonstrated a substantial reduction in relapse and improvement in relapse-free survival among FLT3-ITD-positive patients randomized to sorafenib versus placebo after allogeneic transplantation [26].

6. Transplant in first remission: who still needs it

Allogeneic hematopoietic cell transplantation in first complete remission remains the most reliable way to consolidate high-risk FLT3-ITD AML, and allelic ratio continues to inform who is referred even as inhibitor availability broadens. Schlenk and colleagues' original demonstration that transplant benefit concentrated in the FLT3-ITD-positive, particularly high-ratio, subgroup rather than in NPM1-mutated/FLT3-ITD-negative

patients established the template still used in multidisciplinary planning: transplant in first remission for high-ratio or NPM1-wild-type FLT3-ITD disease, and chemotherapy consolidation alone, reserving transplant for relapse, in low-ratio NPM1-mutated disease [12]. Measurable residual disease assessment has begun to refine that binary further. Ivey and colleagues showed, in standard-risk (which in practice means largely NPM1-mutated) AML, that persistence of NPM1 transcript by quantitative PCR after induction predicted relapse far better than mutation status alone, a principle increasingly applied alongside FLT3-ITD ratio rather than in place of it, since ITD subclones can be lost or gained between diagnosis and relapse in ways that NPM1 mutation typically is not [27]. Where post-transplant FLT3-ITD status is known, Burchert and colleagues' SORMAIN data argue for FLT3-directed maintenance regardless of the diagnostic allelic ratio, since ratio at diagnosis does not reliably predict ITD clonal burden at the time of transplant [26]. The net effect of a decade of inhibitor trials has been to narrow, but not eliminate, the group of FLT3-ITD patients for whom transplant in first remission is unambiguously indicated: very high allelic ratio, adverse co-mutations such as DNMT3A or adverse-risk cytogenetics, and persistent measurable residual disease after induction remain the strongest indications, while low-ratio, NPM1-mutated, chemosensitive disease increasingly tolerates a chemotherapy-plus-inhibitor strategy with transplant held in reserve [23,14].

Table 2: Trials shaping the decision to transplant or add a FLT3 inhibitor in first remission, with reported survival or relapse endpoints [17,26,21,24].			
Trial	Population	Intervention	Reported outcome
RATIFY [17]	Newly diagnosed FLT3-mutated	Midostaurin + chemotherapy	4y OS 51.4% vs 44.3%
SORMAIN [26]	Post-transplant FLT3-ITD	Sorafenib maintenance	Improved relapse-free survival
ADMIRAL [21]	Relapsed/refractory FLT3-mutated	Gilteritinib vs chemotherapy	Median OS 9.3 vs 5.6 mo

Trial	Population	Intervention	Reported outcome
QuANTUM-First [24]	Newly diagnosed FLT3-ITD	Quizartinib + chemotherapy	Median OS 31.9 vs 15.1 mo

7. Conclusion

Three decades after its discovery, FLT3-ITD has moved from a binary mutation call to a quantitative, continuous variable whose allelic ratio predicts relapse risk, modifies the prognostic weight of co-occurring NPM1 mutations, and — until recently — determined who was referred for transplant in first remission [1,6,9]. The arrival of midostaurin, gilteritinib, and quizartinib has changed the practical stakes of that measurement without eliminating it: inhibitor-era trials have generally not shown allelic ratio to modify drug benefit, which is one reason the European LeukemiaNet retired its ratio-based split for NPM1-mutated FLT3-ITD disease in 2022, even as ratio's original correlation with relapse biology remains intact [17,21,23]. What allelic ratio still does, reliably, is flag the patients whose disease is most FLT3-dependent and therefore most likely to relapse if that dependency is not directly targeted — by an inhibitor, by transplant, or, in the patients who need it most, by both [8,26,24]. The open question for the next decade is less whether ratio matters and more how to combine it with measurable residual disease and co-mutation data into a single, dynamic risk estimate that updates as a patient moves from diagnosis through induction to consolidation, rather than the static, diagnosis-only snapshot the field has relied on since Gale and colleagues first quantified the ratio effect [9,27].

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