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ORIGINAL ARTICLE

Gilteritinib in FLT3-mutated acute myeloid leukemia: A real-world Italian experience

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Abstract

Background and Methods: This real-world study evaluated the clinical effectiveness of gilteritinib in 205 patients with relapsed or refractory (R/R) FLT3-mutated acute myeloid leukemia (AML) enrolled in the Italian expanded access since January 2018. **Results:** Of the 205 patients, 124 (60.5%) received gilteritinib as a bridging therapy to allogeneic stem cell transplantation (allo-SCT), achieving complete remission in 52.4% (n = 65). The median overall survival (OS) for the entire cohort was 11.0 months, with estimated OS rates of 46.8% at 1 year and 28.5% at 3 years. Sixty patients (48% of those bridged) underwent allo-SCT after a median of 3.7 months on gilteritinib, achieving posttransplant OS rates of 65.2% at 1 year and 56.1% at 3 years. The acquisition of FLT3 mutations at relapse and the presence of TP53 co-mutations were significantly associated with inferior outcomes. Among 46 patients (22.4%) who relapsed after allo-SCT, gilteritinib treatment yielded an overall response rate (ORR) of 54.3%, a median OS of 11.1 months, and 1- and 3-year OS rates of 49.5% and 15.5%, respectively. Additionally, 35 patients (17.1%) previously treated with nonintensive chemotherapy received gilteritinib until disease

progression or intolerance, achieving an ORR of 11.4%, a median OS of 5.9 months, and a 1-year OS rate of 29.0%.

Conclusions: These real-world data confirm that clinical outcomes achieved with gilteritinib in patients with R/R FLT3-mutated AML are consistent with those observed in pivotal clinical trials. Notably, approximately half of the transplant-eligible patients were successfully bridged to allo-SCT and demonstrated encouraging long-term survival.

KEYWORDS
acute myeloid leukemia, FLT3, gilteritinib, tyrosine kinase inhibitor, real-world

INTRODUCTION

Acute myeloid leukemia (AML) is a major contributor to cancer-related mortality, ranking as the eleventh leading cause of cancer death worldwide, with a 15% increase in incidence over the past 3 decades.[1]

Leukemogenesis is driven by the accumulation of genetic abnormalities—including somatic mutations, epigenetic alterations in immature myeloid cells, and chromosomal aberrations—that drive clonal proliferation.[2]

Molecular characterization has become central to AML diagnosis, classification, and treatment. Current guidelines emphasize genetic profiling over traditional morphology,[1] with recurrent mutations such as *FLT3*, *NPM1*, and *TP53* guiding prognostic stratification and therapeutic decisions.[3] These molecular insights have led to the development of targeted agents, among which *FLT3* inhibitors represent a key therapeutic advance.[4]

FLT3 mutations—particularly internal tandem duplications (ITD) and tyrosine kinase domain (TKD) point mutations like D835—lead to constitutive receptor activation and leukemic transformation.[5]

Gilteritinib, a type I *FLT3* inhibitor, targets both ITD and TKD mutations by binding the ATP-binding site and interacting with the F691 gatekeeper residue, as confirmed by computational modeling. In vitro assays show potent inhibition of *FLT3*, *ALK*, and *AXL*, including all tested D835 variants.[6]

Gilteritinib was first evaluated in the phase 1 Chrysalis trial, where patients with relapsed/refractory (R/R) *FLT3*-mutated AML—primarily with ITD mutations—achieved a composite complete response (CRc) rate of 41% at doses ≥80 mg. Responses occurred even in patients with dual mutations or prior resistance to sorafenib or quizartinib, and 19% proceeded to allogeneic hematopoietic stem cell transplantation (HSCT)[7]

The phase 3 Admiral trial subsequently enrolled 371 patients with FLT3-mutated AML in first relapse or refractory to initial induction therapy. Participants were randomized 2:1 or to single-agent gilteritinib or investigator-selected salvage chemotherapy (SC), including intensive and low-intensity regimens. Gilteritinib demonstrated superior efficacy, with higher CRc rates (54% vs. 22%), longer median overall survival (9.3 vs. 5.6 months; hazard ratio [HR], 0.64; $p = .001$), and a greater proportion undergoing HSCT (26% vs. 15%).[8] Common adverse events included cytopenias, infections, and elevated liver enzymes. Common adverse events included cytopenias, infections, and elevated liver transaminases.[8]

Following a 21% complete remission (CR)/complete remission with partial hematological recovery (CRh) rate in interim analysis, gilteritinib received initial approval in September 2018 from the Japanese Ministry of Health, Labour, and Welfare for the treatment of *FLT3*-mutated R/R AML,[9] followed by regulatory approvals from the US Food and Drug Administration[10] and the European Medicines Agency in October 2019.[11] In compliance with regulatory guidelines, post-marketing studies and expanded access programs (EAPs) were initiated globally to evaluate gilteritinib's safety, tolerability, and effectiveness in real-world settings.[9,12–17] In Italy, gilteritinib has been available through an EAP since January 2018. This retrospective and prospective observational study reports clinical outcomes from Italian centers participating in the national EAP.

The primary aim is to assess the real-world clinical effectiveness of gilteritinib in patients with relapsed or refractory *FLT3*-mutated AML under routine clinical practice.

MATERIALS AND METHODS

Study design

This multicenter, retro-prospective, observational study (REL-AML 002/2021) was conducted across 27 Italian hospitals involved in the gilteritinib EAP beginning in January 2018. Data acquisition was finalized, and the last follow-up was completed in October 2024, marking the formal conclusion of the study. The study was conducted under the auspices of the Rete Ematologica Lombarda (REL) network. Gilteritinib was administered as monotherapy in accordance with the approved therapeutic indication. Each enrolled patient was followed from the initiation of gilteritinib treatment until death or last contact. For the prospective component, follow-up continued for 12 months after the enrollment of the last patient.

Study population

Patients eligible for inclusion in the study were required to be over 18 years of age, have a diagnosis of relapsed or refractory acute myeloid leukemia (AML R/R) with an *FLT3* mutation confirmed on retesting, and have received gilteritinib monotherapy within the EAP. Before any data collection, all patients provided written informed consent. Ethical approval for the study was granted by CET3 Lombardia. The study was conducted in accordance with all relevant local regulations and the ethical principles outlined in the Declaration of Helsinki.

Within the relapsed and refractory cohort, patients were further categorized into two groups: patients eligible for allogeneic transplantation and patients ineligible for transplantation. Additionally, we separately analyzed the subgroup of patients who experienced relapse following transplantation and, for patients with refractory disease, we investigated the potential impact of refractoriness after one versus multiple courses of intensive chemotherapy.

Statistical analysis

End points and response criteria

The primary end point of the study was overall survival (OS), defined as the time from the initiation of gilteritinib to death from any cause. In the subgroup of patients eligible for allogeneic stem cell transplantation (allo-SCT), we analyzed the time from gilteritinib initiation to either transplantation or death, considering these as first events and treating them as competing risks.

Secondary end points included response to gilteritinib assessed as the proportion of patients who achieved CR, CR with incomplete hematologic recovery (CRi), partial response (PR), or no response (NR) according to the 2022 European LeukemiaNet (ELN) recommendations.[18]

Time-to-response was defined as the interval from gilteritinib initiation to the achievement of CR, CRh, or CRi. In responders, the duration of response was defined as the time from the achievement of CR or CRi to the loss of response (relapse or toxicity, considering transplant as a competing risk). For the SCT-eligible group, we also analyzed posttransplant survival, defined as the time from allogeneic SCT to death from any cause.

Statistical methods

The distribution of continuous variables was described by median, first and third quartiles, minimum, and maximum; categorical variables were reported as absolute and relative frequencies.

The overall survival was analyzed using the Kaplan–Meier estimator. The curves were estimated on the overall sample and within each group (post-SCT, SCT-eligible, and SCT-not-eligible). Comparison of survival curves were performed using the log-rank test and were made by *FLT3* mutation already present at diagnosis versus not present, presence versus absence of other mutations (*NPM1*, *IDH1-2*, *DNMT3A*, and *TP53*), gilteritinib initiation after a single line of chemotherapy versus multiple lines of chemotherapy, and previous tyrosine kinase inhibitor (TKI) treatment versus no treatment.

Posttransplant survival was also estimated using the Kaplan–Meier estimator on patients who received SCT.

Only for the SCT-eligible group, the crude cumulative incidences of death as first event or transplant (competing risks) were analyzed using the Aalen–Johansen estimator. To analyze the duration of response, a competing risk analysis was performed also on patients who reached CR or complete remission with partial hematologic recovery considering (progression)/relapse/toxicity and transplant as competing events.

RESULTS

A total of 205 patients were enrolled in the EAP of gilteritinib and included in this analysis.

Previous treatments

Of the 205 patients included in the study, 163 (79.5%) received intensive chemotherapy as induction before initiating gilteritinib. The remaining 42 patients (20.5%) were initially treated with less-intensive chemotherapy; among these, 35 were deemed ineligible for allo-SCT.

Within the cohort of 163 patients treated with intensive induction, 39 relapsed after allo-SCT, whereas the remaining 124 were transplant-eligible patients who either relapsed following intensive chemotherapy ($n = 82$) or were primary refractory to it ($n = 42$).

Among these 124 transplant-eligible patients, 99 (79.8%) had received standard "7 + 3" induction chemotherapy, with midostaurin administered in 64.5% ($n = 80$) of cases. The remaining 25 patients (20.2%) were treated with alternative induction regimens, including FLAI (fludarabine, cytarabine, and idarubicin), ICE (idarubicin, cytarabine, and etoposide), or liposomal daunorubicin–cytarabine (CPX-351).

Patients classified as primary refractory subsequently received second-line intensive chemotherapy, most commonly FLAG-Ida (fludarabine, cytarabine, and idarubicin) or MEC (mitoxantrone, etoposide, and cytarabine). Additional salvage treatments included venetoclax combined with a hypomethylating agent (azacitidine or decitabine).

Among the 39 patients who relapsed after allo-SCT, 30 had received the standard "7 + 3" induction chemotherapy combined with midostaurin. Overall, of the 163 patients treated with intensive regimens, 110 (67.5%) had prior exposure to a TKI before starting gilteritinib, whereas 53 (32.5%) had not.

Indication for receiving gilteritinib

A total of 148 patients (72.2%) received gilteritinib at the time of relapse, whereas 57 patients (27.8%) were treated for primary refractory disease. Based on relapse after allo-SCT or transplant eligibility, patients were categorized into three groups.

The posttransplant relapse group included 46 patients who received gilteritinib following relapse after transplantation.

The non–transplant-eligible group included 35 patients, with a median age of 75 years, who received less-intensive chemotherapy and were deemed ineligible for HSCT. Before gilteritinib initiation, 17 patients had been treated with azacitidine and venetoclax (median 3 cycles; range, 2–11), 11 with decitabine alone (median 7 cycles; range, 1–28), and seven with azacitidine alone (median 10 cycles; range, 2–16). Among the 17 patients treated with azacitidine and venetoclax (VEN-AZA), 14 of 17 (82%) were classified as ELN 2017 adverse risk, and 12 of 17 (70.5%) presented with hyperleukocytosis at the time of gilteritinib initiation and received hidroxyurea for citoreduction. Based on their response to prior therapy, 15 patients were categorized as having primary refractory disease, and 20 patients were categorized as having relapsed disease.

Gilteritinib was administered as monotherapy until disease progression or the development of unacceptable toxicity. Notably, one patient in this cohort—initially considered ineligible for transplant—ultimately proceeded to transplantation.

The transplant-eligible group comprised 124 patients, including 82 with relapsed disease and 42 with primary refractory disease, who received gilteritinib as a bridging therapy before transplantation.

Among those with primary refractory disease, 32 were refractory to a single course of intensive chemotherapy, whereas 10 were refractory to two or more courses.

The median age at diagnosis was 60 years and differed significantly among the three subgroups, as determined by the Kruskal–Wallis test (p value <.01). Patients in the transplant-not-eligible group were the oldest, with a median age of 75 years. Table 1.

A detailed breakdown of treatment regimens for each group is provided in Table 2.

Genetic landscape at diagnosis and at relapse

Most patients had de novo AML (73%), with an intermediate (38%) or adverse (40%) risk profile according to the ELN 2017 classification.[19]

FLT3 mutations were present in 175 of 205 patients (85.4%) at diagnosis, whereas 30 patients (14.6%) acquired the mutation at relapse.

At diagnosis, *FLT3*-ITD was identified in 147 of 175 patients (84.0%), whereas 23 of 175 patients (13.1%) exhibited the *FLT3*-TKD mutation; five patients (2.9%) had both FLT3-ITD and FLT3-TKD mutations.

Among the 175 patients who presented with an *FLT3*-ITD/TKD mutation, 116 (66.3%) had co-occurring mutations, either alone or in combination, including *NPM1* (83 of 175 = 47.4%), *DNMT3A* (17 of 175 = 9.7%), *IDH1/IDH2* (12 of 175 = 6.9%), and *TP53* (four of 175 = 2.3%).

Among the 30 patients who acquired *FLT3* mutations at relapse, *NPM1* was the most frequently co-mutated gene, occurring either alone or in combination with other mutations in 12 of 30 patients (40.0%). Other co-mutations included *IDH1/IDH2* in five of 30 (16.7%) and *TP53* in two of 30 (6.7%) patients.

The most prevalent co-mutations at diagnosis and relapse are summarized in Figure 1, with a detailed overview of the genomic landscape at both time points available in Table S1.

Treatment outcome and prognostic factors

Among the total cohort of 205 patients who received gilteritinib, a CR rate of 43.4% (89/205) was observed, whereas the CR with CRi rate was 8.8% (18 of 205). Overall, 52.2% (107 of 205) of patients achieved a substantial response (CR or CRi). The median OS was 10.3 months, with a 1-year OS probability of 44.4% (95% confidence interval [CI], 37.8–52.2) and a 3-year OS probability of 21.3% (95% CI, 15.8–28.7) (Figure 2A; Table 3)

Outcomes of gilteritinib treatment after allo-SCT

Among the 46 patients who experienced relapse following allogeneic transplantation, treatment with gilteritinib resulted in an overall response rate (ORR) of 54.3% (25 of 46). A total of 45.7% (21 of 46) of patients achieved CR, whereas an additional 8.7% (four of 46) attained CR with CRi. The median time to response was 66 days (Table 4). The median OS was 11.1 months, with an OS probability of 49.5% (95% CI, 36.6–67.0) at 1 year and 15.5% (95% CI, 7.15–33.6) at 3 years. The Kaplan–Meier survival curve in patients who received gilteritinib as salvage therapy following allogeneic stem cell transplantation (post-SCT group) is presented in Figure 2B.

Outcome in patients initially treated with less-intensive chemotherapy and not eligible for allo-SCT

This cohort included 35 patients. Among them, 8.6% (three of 35) achieved CR, and an additional 2.9% (one of 35) attained CR with CRi, resulting in an ORR of 11.4% (4/35). The median OS was 5.9 months, with a 1-year OS probability of 29.0% (95% CI, 16.6–50.8). The Kaplan–Meier survival curve for OS in the SCT-not-eligible group is shown in Figure 2C.

Furthermore, we observed a median survival of 7.5 months in the 17 patients who relapsed after or were refractory to venetoclax and azacitidine, compared with 5.3 months in the remaining 18 patients treated with other low-intensity chemotherapy (p = .042) (Figure S1).

TABLE 1 Patient demographics and clinical characteristics.

	Overall	Relapsed posttransplant	Transplant ineligible	Transplant eligible
Total population	205	46	35	124
Age (years) at diagnosis				
Median	60	55	75	57
Range	(18–87)	(18–72)	(53–87)	(22–82)
IQR range	(49–70)	(47.25–62)	(73–79)	(48–66)
Gender, No. (%)				
Female	111 (54.1)	28 (60.9)	15 (42.9)	68 (54.8)
Male	94 (45.9)	18 (39.1)	20 (57.1)	56 (45.2)
WBC at diagnosis ($\times 10^9$/L)				
IQR range	37	25	13.5	60
Median	1–398	2.45–327	1–263	1.59–398
Range	11–97.5	9–65	3.6–32.1	18–121
AML status: No. (%)				
De novo AML	150 (73.2)	30 (65.2)	17 (48.6)	103 (83.1)
Secondary AML	55 (26.8)	16 (34.8)	18 (51.4)	21 (16.9)
ELN 2017, No. (%)				
Favorable	42 (20.5)	8 (17.4)	4 (11.4)	30 (24.2)
Intermediate	79 (38.5)	18 (39.1)	12 (34.3)	49 (39.5)
Adverse	82 (40.0)	20 (43.5)	19 (54.3)	43 (34.7)
Unknown	2 (1.0)	0 (0.0)	0 (0.0)	2 (1.6)
Extramedullary disease, No. (%)	14 (6.8)	3 (6.5)	2 (5.7)	9 (7.3)
FLT3 mutation at diagnosis, No. (%)	175/205 (85.4)	42/46 (91.3)	25/35 (71.4)	108/124 (87.1)
FLT3-ITD	147/175 (84.0)	34/42 (81.0)	19/25 (76.0)	94/108 (87.0)
FLT3-TKD	23/175 (13.1)	7/42 (16.7)	6/25 (24.0)	10/108 (9.3)
Both	5/175 (2.9)	1/42 (2.4)	0 (0.0)	4/108 (3.7)
FLT3 mutation at relapse, No. (%)	27/205 (13.2)	4/42 (8.7)	10/35 (28.6)	16/124 (12.9)
NA, No. (%)	3/205 (1.4)	0 (0.0)	2 (5.7)	1 (0.8)

Abbreviations: AML, acute myeloid leukemia; ELN, European LeukemiaNet; ITD, internal tandem duplications; IQR, interquartile range; NA, not available; TKD, tyrosine kinase domain; WBC, white blood cell.

Outcome in patients eligible for allo-SCT

A total of 124 patients, deemed eligible for intensive treatment according to the GITMO (Gruppo Italiano Trapianto Midollo Osseo) criteria,[20] received gilteritinib as a bridge to allogeneic transplantation. The ORR in this cohort was 78 of 124 (62.9%), with a median time to response of 63 days (Table 3). CR was achieved in 65 of 124 patients (52.4%), whereas an additional 13 patients attained CR with CRi (10.5%).

The Kaplan–Meier survival curve for OS in this cohort is depicted in Figure 2D. The median OS was 11.0 months, with an estimated OS probability of 46.8% (95% CI, 38.4–57.0) at 1 year and 28.5% (95% CI, 21.0–38.7) at 3 years.

Sixty patients (48%) proceeded to transplantation after a median of 112 days (3.7 months), with a crude incidence of transplantation at 1 year of 47.1% (95% CI, 38.2–56.0) (Figure S2). Posttransplant survival was 65.2% (95% CI, 53.0–80.3) at 1 year and 56.1% (95% CI, 43.5–72.4) at 3 years (Figure S3).

Outcomes in patients refractory to single versus multiple lines of intensive chemotherapy

The median OS for the 42 patients refractory to intensive chemotherapy was 11.0 months. The OS probability was 44.2% (95% CI, 31.1–63.0) at 1 year and 27.9% (95% CI, 16.7–46.6) at 3 years

TABLE 2 Clinical and treatment features of FLT3-positive R/R AML patients by transplant status.

Characteristics	Overall (n = 205)	Relapsed posttransplant (n = 46)	Transplant ineligible (n = 35)	Transplant eligible (n = 124)
Disease status, No. (%)				
Relapsed	148 (72.2)	46 (100.0)	20 (57.1)	82 (66.1)
Primary refractory	57 (27.8)	0 (0.0)	15 (42.9)	42 (33.3)
Allogeneic transplant status, No. (%)				
Did not receive transplant	99 (48.3)	0 (0.0)	34 (97.1)	65 (52.3)
Patients receiving gilteritinib posttransplant	46 (22.4)	46 (100.0)	0 (0.0)	0 (0.0)
Patients receiving gilteritinib as bridge to transplant	60 (29.3)	0 (0.0)	1 (2.9)	59 (47.6)
Prior chemotherapy, No. (%)				
Intensive chemotherapy	163 (79.5)	39 (84.8)	0 (0.0)	124 (100.0)
TKI	113 (55.1)	32 (69.6)	1 (2.9)	80 (64.5)
Less-Intensive chemotherapy	42 (20.5)	7 (15.2)	35 (100.0)	0 (0.0)

Abbreviations: AML, acute myeloid leukemia; TKI, tyrosine kinase inhibitor; R/R, relapsed or refractory.

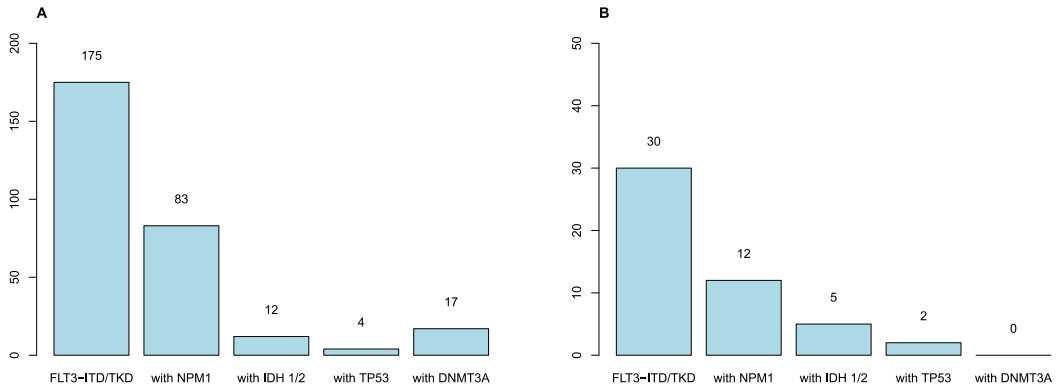

FIGURE 1 Bar charts depicting the most frequent co-mutated genes among patients who had *FLT3* mutations at diagnosis (A) and those who acquired *FLT3* mutations after diagnosis (B). FLT3-ITD/TKD: Internal tandem duplication or tyrosine kinase domain mutations in the *FLT3* gene. *DNMT3A* indicates DNA methyltransferase 3 α gene mutation; *IDH1/2*, isocitrate dehydrogenase 1 or 2 gene mutations; *NPM1*, nucleophosmin 1 gene mutation; *TP53*, tumor protein p53 gene mutation.

(Figure 2E). The overall response rate was 61.9% (Table 3). No significant difference was observed between the 10 single-refractory patients and the 32 multi-refractory patients (two or more lines of chemotherapy) in terms of either survival (p = .32) or response (p = .142) to gilteritinib (Figure 2F).

Outcome of patients achieving CR or CRi

Among the subgroup of 107 patients who achieved CR or CR with CRi, the probabilities of undergoing a transplant from the time of response were 46.1% (95% CI, 36.5–55.6) at 1 year and 47.1% (95% CI, 37.5–56.7) at 3 years. In contrast, the probability of relapse or death within 1 year was 29.8% (95% CI, 21.0–38.6), increasing to 40.7% (95% CI, 30.7–50.6) at 3 years following the achievement of response (Figure 3).

Notably, patients with CR experienced a significantly better OS compared to those who achieved CR with CRi (Figure S4). The 1- and 3-year survival probabilities in the CR group were 65.3% (95% CI, 55.6–76.6) and 39.6% (95% CI, 29.6–53.0), respectively, compared to 36.1% (95% CI, 19.2–68.1) and 12.0% (95% CI, 3.3–44.0) in the CRi group.

Prognostic impact of genetic features on survival in patients receiving gilteritinib

In the cohort of patients who received gilteritinib as a bridge to transplantation, the acquisition of a *FLT3* mutation or the presence of a *TP53* co-mutation was associated with significantly reduced survival probability (p = .0066 and p = .022, respectively), as well as a poorer response rate. In contrast, co-mutations in *NPM1*, *IDH1/2*, or

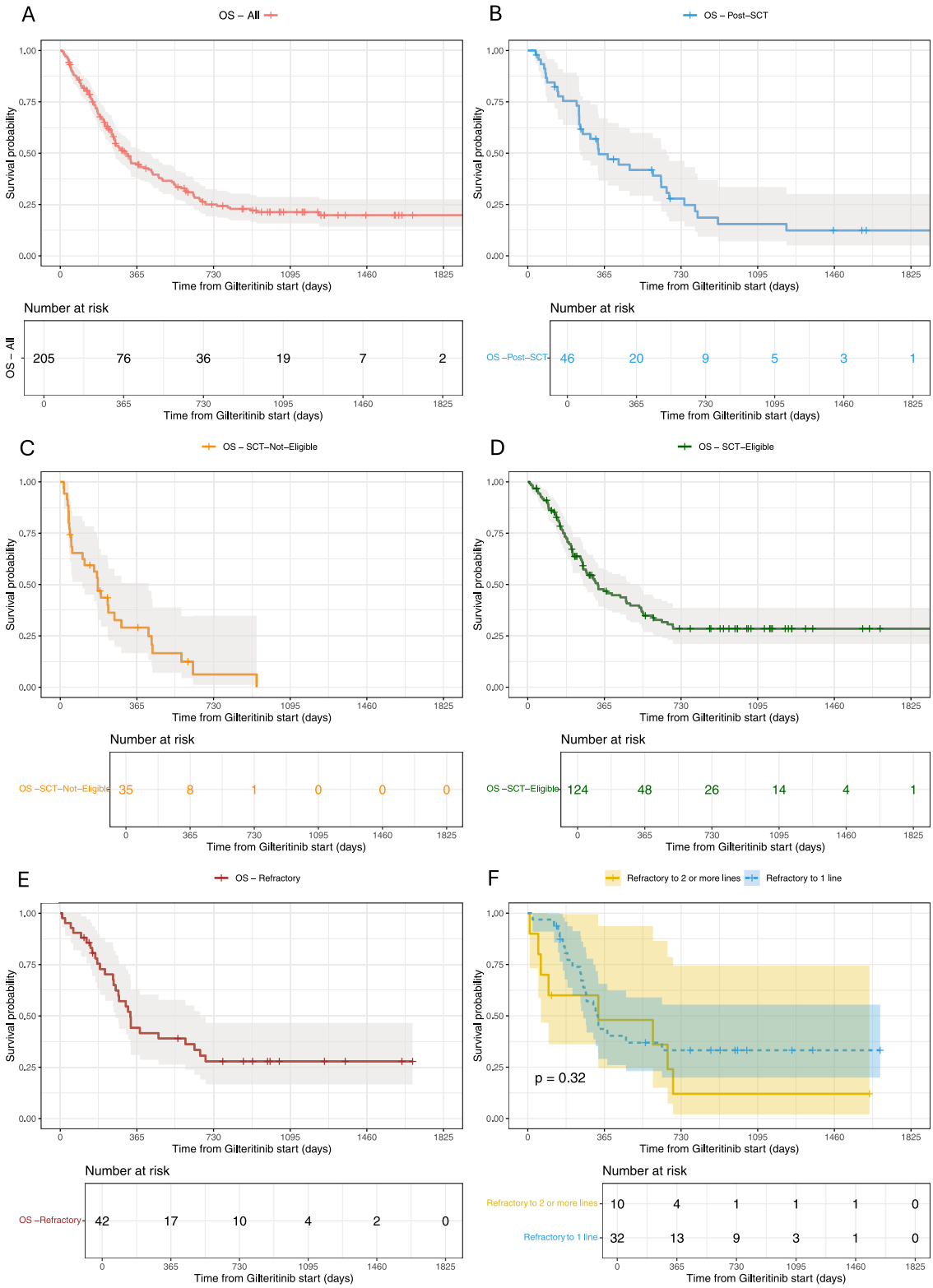

FIGURE 2 OS based on transplant eligibility and refractoriness to intensive chemotherapy. Kaplan–Meier curves showing OS in the full patient cohort (A) and stratified by transplant status: relapse posttransplant (B), transplant-ineligible (C), and transplant-eligible (D). (E and F) OS in patients refractory to intensive chemotherapy, with (F) further stratifying by number of prior chemotherapy lines (one line vs. two or more lines). OS indicates overall survival.

TABLE 3 Treatment responses in R/R patients post-intensive chemotherapy: Outcomes by transplant eligibility and prior treatment.

	All patients (R/R)				Refractory to intensive chemotherapy		
Response	Overall	Relapsed posttransplant	Transplant ineligible[b]	Transplant elegible[c]	Overall	Refractory to one line[a]	Refractory to two or more lines[a,d]
CR, No. (%)	89 (43.4)	21 (45.7)	3 (8.6)	65 (52.4)	22 (52.4)	19 (59.4)	3 (30.0)
CRi, No. (%)	18 (8.8)	4 (8.7)	1 (2.9)	13 (10.5)	4 (9.5)	3 (9.3)	1 (10.0)
PR, No. (%)	25 (12.2)	2 (4.3)	8 (22.9)	15 (12.1)	4 (9.5)	2 (6.2)	2 (20.0)
NR, No. (%)	72 (35.1)	19 (41.3)	23 (65.8)	30 (24.2)	12 (28.6)	8 (25.0)	4 (40.0)
NA, No. (%)	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Patient, No. (%)	205 (100.0)	46 (100.0)	35 (100.0)	124 (100.0)	42 (100.0)	32 (100.0)	10 (100.0)

Abbreviations: CR, complete remission; CRi, CR with incomplete hematologic recovery; NA, not available—data not available or missing; NR, no response—failure to meet criteria for CR, CRi, or PR; PR, partial response; R/R, relapsed or refractory.

[a]No significant differences were found between patients refractory to one line and to two or more lines of intensive chemotherapy in terms of response (Fisher test, p value = .142).

[b]Patients not considered candidates for transplant due to age, comorbidities, or other factors.

[c]Patients who were deemed fit for potential stem cell transplantation.

[d]Patients who failed at least two prior lines of intensive chemotherapy.

TABLE 4 Clinical outcomes with gilteritinib: Insights from Admiral trial and real-world evidence by country.

Study	Patients (n)	Median OS (months)	CR (%)	CRi (%)	CRp	PR (%)	NR (%)	NA (%)	Ref.
Italy	205	10.3	43.4	8.8	—	12.2	35.1	0.5	—
Admiral	247	9.3	21.1	25.5	13.4	13.4	26.6	—	8
France	140	6.4	25.4[a]		—	5.2	52.4	10	12
Germany	156	6.2	43.6[a]		—	23.7	25	—	19
Japan	67	—	34.3	23.9	4.5	20.9	11.9	4.5	9
United Kingdom	152	9.5	20.5	8.5	—	27.6	31.5	4	14
Israel	25	8	48	12	—	—	40	—	15
Turkey	17	11.8	64.7	5.9	17.6	11.8	—	—	20
United States	113	7	22.1	26.5[b]		—	—	—	13

Abbreviations: CR, complete remission; CRi, complete remission with incomplete hematologic recovery; CRp, complete remission with incomplete platelet recovery; PR, partial response; NR, no response; NA, not available; OS, overall survival.

[a]CR and CRi reported as combined rate.

[b]CRi includes CRp where applicable.

DNMT3A did not significantly affect survival outcomes (Figure S5; Table S2).

In the cohort of 46 patients who received gilteritinib for relapse after transplantation, those who acquired the FLT3 mutation had a trend toward worse prognosis, although this did not reach statistical significance (p = .064). The presence of co-mutations in *TP53*, *NPM1*, *IDH1/2*, or *DNMT3A* did not significantly impact survival probability (Figure S6).

In the group of patients not eligible to transplantation, no significant differences were found based on the presence or absence of the different co-mutations in terms of overall survival (Figure S7).

Impact of previous treatment with *FLT3* inhibitors

A total of 113 patients had prior exposure to *FLT3* inhibitors before initiating gilteritinib. Of these, 110 patients received midostaurin during "3 + 7" induction (including two who also received post-transplant sorafenib), and three patients received sorafenib post-transplant only. Among the 163 patients who underwent intensive chemotherapy, those with prior *FLT3* inhibitor exposure (110 patients) demonstrated significantly improved OS compared to those without such exposure (53 patients) (log-rank test, p = .0025). The Kaplan–Meier survival curves for the two groups are presented in Figure S8. In the TKI-exposed group, the median OS was 13.2

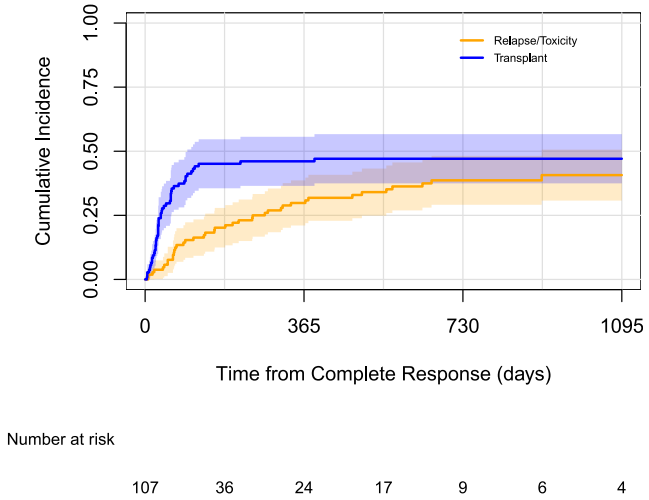

FIGURE 3 Outcomes following CR or CR with CRi. Crude cumulative incidences of hematopoietic stem cell transplant (blue line) and relapse or toxicity (orange line) in patients who achieved CR or CR with CRi. Events were analyzed using a competing risks framework from the time of best response. Shaded areas represent 95% CIs. Number at risk: patients remaining in follow-up without either event at each time point. CI indicates confidence interval; CR, complete remission; CRi, incomplete hematologic recovery.

months, with 1-year and 3-year survival rates of 51.3% (95% CI, 42.4–62.2) and 33.9% (95% CI, 25.4–45.1), respectively. In contrast, patients without prior TKI exposure had a median OS of 8.0 months, with 1-year and 3-year survival rates of 38.4% (95% CI, 26.9–54.9) and 11.1% (95% CI, 4.6–27.8), respectively. The two subgroups differed in baseline characteristics, including age distribution, ELN risk classification, and AML type (secondary vs. de novo). Patients with prior TKI exposure were younger, with a median age of 55 years compared to 58 years in the No-TKI group. Additionally, the TKI group had a lower proportion of patients with adverse ELN risk (32.7% vs. 45.3%) and secondary AML (13.6% vs. 47.2%).

DISCUSSION

The analysis of clinical data from patients enrolled in the gilteritinib EAP across Italian hospitals confirms the treatment's efficacy in improving overall survival and response rates. To the best of our knowledge, this represents the largest cohort of R/R AML patients treated with gilteritinib outside the setting of a clinical trial to date.

At diagnosis (175), *FLT3* mutation was present in 175 patients (85.4% of the total). Among these, the majority harbored the *FLT3*-ITD mutation (84%), whereas 13.1% exhibited *FLT3*-TKD and 2.9% had both ITD and TKD mutations. The most frequently observed co-mutations were *NPM1* (47.4%) and *DNMT3A* (40%), consistent with previous reports.[8] Notably, 14.6% of patients (30 patients) acquired an *FLT3* mutation at relapse, underscoring the importance of *FLT3* retesting in this setting. At relapse, *NPM1* remained the most commonly mutated gene (40%), whereas *DNMT3A* mutations were not detected. Considering the entire cohort of 205 patients who received gilteritinib, we observed an ORR of 52.2%, with a CR rate of 43.4% and a CR with CRi rate of 8.8%.

To better understand the therapeutic potency of gilteritinib in different clinical contexts, we analyzed outcomes in three distinct groups: 1) patients fit for intensive chemotherapy and candidates for allogeneic transplantation; 2) patients who relapsed after an allogeneic transplant; and 3) patients who experienced relapse or progression after less-intensive chemotherapy and received gilteritinib until progression or unacceptable toxicity. As expected, the three groups were not matched for age and performance status, with a significantly older median age (75 years) among patients unfit for intensive chemotherapy. The best outcomes were observed in the 124 patients treated with gilteritinib as a bridge to transplantation. The ORR in this cohort was 62.9%, with a CR rate of 52.2%. Nearly half of the patients in this cohort (47.6%) successfully proceeded to transplantation after a median of 3.7 months. Posttransplant survival was 65.2% (95% CI, 53.0–80.3) at 1 year and 56.1% (95% CI, 43.5–72.4) at 3 years (Figure S3). Among this group, patients who acquired the *FLT3* mutation at relapse and those with a *TP53* mutation had significantly worse outcomes, with higher mortality, a reduced response rate, and a lower number of patients proceeding to transplantation (Figure S5). Additionally, we did not observe a statistically significant difference in response to gilteritinib between patients refractory to one course versus multiple courses of intensive chemotherapy.

Gilteritinib has also shown activity in patients who relapsed following allogeneic HSCT. In this subset, the ORR was 54%, with a CR rate of 45.7% and a median time to response of 66 days. Kaplan–Meier analysis revealed an OS probability of 49.5% at 1 year, which declined to 15.6% at 3 years. The presence of co-mutations—including *NPM1*, *IDH1/2*, *TP53*, and *DNMT3A*—did not significantly impact survival outcomes. However, patients with *FLT3* mutations detected at diagnosis showed a trend toward inferior outcomes, although the difference was not statistically significant ($p = .064$). These findings underscore the need for additional strategies to sustain responses to gilteritinib in the posttransplant setting. One potential approach is prophylactic unmanipulated donor lymphocyte infusion as maintenance therapy, which has been recommended in recent expert guidelines.[21]

An unexpected finding in our study was that prior treatment with an *FLT3* inhibitor was associated with significantly improved survival compared with patients without such exposure. However, this observation should be interpreted with caution, as the two subgroups differed substantially in baseline characteristics. Patients who had received a prior *FLT3* inhibitor were younger (median age, 55 vs. 58 years), had a lower proportion of adverse ELN risk classification (32.7% vs. 45.3%), and were less likely to have secondary AML (13.6% vs. 47.2%). These imbalances suggest that the observed survival advantage may, at least in part, reflect more favorable baseline prognostic factors rather than a direct effect of prior *FLT3* inhibitor therapy. Multivariate analyses adjusting for these potential confounders would be necessary to clarify the independent impact of

prior *FLT3* inhibitor exposure; however, such analyses were not performed in the present study.

Notably, our findings are consistent with reports from the Spanish CETLAM and PETHEMA groups, which also demonstrated improved overall survival among patients previously treated with *FLT3* inhibitors compared with unexposed individuals.[22] In the Spanish cohort, unexposed patients were likewise significantly older, reinforcing the importance of adjusting for baseline imbalances when interpreting these associations.

By contrast, Yilmaz et al.[23] reported a retrospective experience from The MD Anderson Cancer Center on sequential *FLT3* inhibitor use, which highlighted a progressive decline in response rates with successive *FLT3* inhibitor treatments. This observation raises the possibility of resistance mechanisms or clonal evolution that may limit the efficacy of subsequent *FLT3* inhibitor therapies. Interestingly, CR with CRc rates were higher when *FLT3* inhibitors were combined with other agents compared to monotherapy, suggesting a potential benefit of combination strategies. It is noteworthy, however, that during the period analyzed, gilteritinib was administered as monotherapy in the relapsed/refractory setting (12 patients). The small number of patients treated with gilteritinib in this cohort underscores the need for caution when extrapolating these findings

The poorest outcomes with gilteritinib were observed in patients previously treated with less-intensive chemotherapy. In this subgroup, 65.8% of patients did not respond, the CR rate was below 10%, and the ORR was 11.4%, resulting in a 1-year OS probability of just 29%. When compared with the study by Othman et al.,[14] recently published in *Blood Advances*, our findings appear broadly consistent. In their cohort of 37 patients previously treated with VEN-AZA, a median OS of 4.5 months was reported, whereas in our cohort of 35 patients treated with less-intensive chemotherapy, the median OS was 5.9 months. At 12 months, survival rates were 15% and 29% in their and our cohorts, respectively. In both studies, no patients survived beyond 18 months, underscoring the poor prognosis in this population.

Among the 17 patients in our cohort who received VEN-AZA, we observed a median OS of 7.5 months. Although this appears slightly longer than the median OS reported by Othman et al.,[14] differences in patient characteristics and treatment patterns may account for this variability.

Overall, these findings highlight the limited efficacy of gilteritinib in patients previously exposed to hypomethylating agents (HMA)-based frontline therapy. However, it is important to recognize that this subgroup represented a particularly high-risk population compared with the other subgroups in our study. Patients in this cohort had a significantly higher median age (75 vs. 45 years), which is known to correlate with unfavorable disease biology, including a higher prevalence of adverse genetic features and a greater incidence of therapy-related or secondary AML. These factors, individually and collectively, are well established contributors to reduced treatment responsiveness and likely account for the poorer outcomes observed. Moreover, recent studies have identified molecular alterations such as *FLT3*-ITD, *NRAS/KRAS*, *TP53*, and *BAX* mutations as major drivers of resistance to venetoclax and azacitidine, as recently reviewed by Chatzilygeroudi et al.[24] in *Cancers*. Notably, mutations activating the RAS/MAPK pathway have also emerged as a common and clinically significant mechanism of secondary resistance to gilteritinib.[25]

Despite these challenges, the use of gilteritinib in relapsed/refractory AML after HMA or HMA plus venetoclax remains appropriate. The drug is approved for this indication, can be administered safely in the outpatient setting, and currently no alternative therapies are available outside of clinical trials.

The patient population included in the present study is not directly comparable to that enrolled in the Admiral trial, and several important differences should be noted. In our cohort, the proportion of patients with primary refractory disease was 27.9%, including 10 individuals who were refractory to two or more courses of intensive chemotherapy, compared with 39.4% in the Admiral study. Moreover, in our analysis, 40% of patients were classified as having an adverse risk according to the ELN classification, whereas only 10% of patients in the Admiral trial had an adverse cytogenetic risk. With regard to prior treatments, the Admiral trial population largely received anthracycline-based chemotherapy, with only 12.4% previously exposed to a TKI. In contrast, 67.5% of patients in our cohort had received a TKI before gilteritinib. Notably, 35 patients (17%), were refractory to or had relapsed after a less-intensive regimen consisting of venetoclax and azacitidine and were considered ineligible for transplant. This subgroup experienced the poorest outcomes, with a 1-year OS of 29%, likely due to a combination of older age (median age, 75 years), a high prevalence of adverse-risk ELN features (54.3%), and secondary AML (51.4%). Despite differences in baseline characteristics and prior treatment histories, our study demonstrated an ORR (CR + CRi + CRp) of 52.2%, which is comparable to the 60% observed in the Admiral trial, with a similar median OS (10.3 months vs. 9.3 months, respectively).

We acknowledge several limitations of our study. As with any retrospective analysis, there is a potential for selection bias and incomplete data capture. However, the inclusion of consecutive patients from multiple centers helps reduce this risk and enhances the generalizability of our findings. Measurable residual disease (MRD) data were not systematically collected, which limits our ability to evaluate the depth and durability of responses to gilteritinib. Nevertheless, this reflects the reality of clinical practice during the study period, when MRD assessment was not yet widely implemented outside of clinical trials. Additionally, response assessments were determined by treating clinicians rather than through standardized bone marrow evaluations at predefined intervals. Although this may have introduced some variability, it also mirrors real-world practice, where rigid response monitoring is often not feasible. Despite these constraints, our results provide valuable insights into the use of gilteritinib in routine clinical settings.

To date, seven other real-world studies on gilteritinib have been published. Notably, patients enrolled in real-world settings often differ significantly from those in clinical trials, because they are commonly excluded from such trials due to poor performance status

or extensive prior treatments. For example, in the observational study by the French AML Intergroup ALFA/FILO,[12] a substantial proportion of patients received gilteritinib in later lines of therapy, with 37.1% treated beyond the second line. Additionally, baseline performance status was considerably poorer, with 83.6% of patients having an Eastern Cooperative Oncology Group (ECOG) score ≥2, compared to only 16.6% in the Admiral trial. Similarly, the Japanese post-marketing surveillance study reported 23.4% of patients with ECOG ≥2 and 75% with multiple comorbidities, further illustrating that many patients treated in real-world practice would not meet clinical trial eligibility criteria.[9] In the UK cohort, 36% of patients received at least two prior lines of therapy before starting gilteritinib. Prior treatments included intensive chemotherapy (79%), venetoclax (24%), allogeneic HSCT (19%), and *FLT3* inhibitors—most commonly midostaurin (41%).[14] Despite these differences in patient populations, clinical outcomes in real-world studies were broadly consistent with those observed in the Admiral trial, as summarized in Table 4. Composite CR rates ranged from 43.4% in our cohort to 20.5% in the UK study, whereas median overall survival ranged from 11.8 to 6.2 months. Taken together, these real-world data support the clinical utility of gilteritinib in a broader patient population, including individuals with poor performance status or those who are heavily pretreated—groups typically underrepresented in clinical trials. In conclusion, this real-world analysis from the Italian EAP demonstrates that patients with relapsed/refractory AML treated with gilteritinib achieved clinical outcomes comparable to those observed in the pivotal Admiral trial. These findings further support the effectiveness of gilteritinib in a more heterogeneous patient population. Further studies are warranted to optimize patient selection, enhance response rates, and improve long-term outcomes.

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Roberto Cairoli: Conceptualization, funding acquisition, writing–review and editing, writing–original draft, supervision, investigation, validation, project administration, and data curation. **Lorenzo Del Castello:** Methodology, software, formal analysis, data curation, validation, writing–review and editing, writing–original draft, and investigation. **Silvia Imbergamo:** Investigation and data curation. **Elisabetta Pierdomenico:** Investigation and data curation. **Cristina Papayannidis:** Investigation and data curation. **Erika Borlenghi:** Investigation and data curation. **Calogero Vetro:** Investigation and data curation. **Patrizia Chiusolo:** Investigation and data curation. **Monica Fumagalli:** Investigation and data curation. **Clara Minotti:** Investigation and data curation. **Francesco Marchesi:** Investigation and data curation. **Massimo Bernardi:** Investigation and data curation. **Pellegrino Musto:** Investigation and data curation. **Nicola Fracchiolla:** Investigation and data curation. **Anna Candoni:** Investigation and data curation. **Monia Lunghi:** Investigation and data curation. **Maurizio Musso:** Investigation and data curation. **Fabio Guolo:** Investigation and data curation. **Donato Mannina:** Investigation and data curation. **Albana Lico:** Investigation and data curation. **Anna Maria Scattolin:** Investigation and data curation. **Monica Crugnola:** Investigation and data curation. **Sara Galimberti:** Investigation and data curation. **Gianpaolo Nadali:** Investigation and data curation. **Mauro Turrini:** Investigation and data

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CONFLICT OF INTEREST STATEMENT

Roberto Cairoli reports consulting fees from AbbVie, Janssen Global Services, LLC, and Novartis; and fees for professional activities from Astellas Pharma, Jazz Pharmaceuticals, and Kite Pharma, Inc. Anna Candoni reports consulting fees from Amgen, Jazz Pharmaceuticals, Pfizer, and Servier Pharmaceuticals LLC; and fees for professional activities from AbbVie, Astellas Pharma, and Incyte. Nicola Fracchiolla reports fees for professional activities from AbbVie. Sara Galimberti reports grant and/or contract funding from AbbVie; and fees for travel from Jazz Pharmaceuticals and Novartis. Pellegrino Musto reports fees for professional activities from Novartis. Cristina Papayannidis reports fees for professional activities from AbbVie, Amgen, Astellas Pharma, Blueprint Medicine, Bristol-Myers Squibb, Daiichi Sankyo, Janssen Pharmaceuticals, Menarini International, Otsuka Pharmaceutical, Pfizer, Servier Pharmaceuticals LLC, and Syndax. Mauro Turrini reports honoraria from Johnson & Johnson, Astellas, and ItalFarmaco; fees for travel from Jazz Ph, AstraZeneca, and Johnson & Johnson; fees for professional activities from AstraZeneca and Astellas; and an unpaid role with the Regional Committee on Acute Leukemias. Calogero Vetro reports consulting fees from AbbVie and Jazz Pharmaceuticals. The other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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