Practical Considerations for Treatment of Relapsed/Refractory FLT3-ITD Acute Myeloid Leukaemia with Quizartinib: Illustrative Case Reports

David Martínez-Cuadrón1,2 · Gabriela Rodríguez-Macías3 · Rebeca Rodríguez-Veiga1 · Blanca Boluda1 · Pau Montesinos1,2

Published online: 7 January 2020 © The Author(s) 2020

Abstract
Quizartinib is a tyrosine kinase inhibitor selectively targeting the FMS-like tyrosine kinase 3 (FLT3) receptor that has been developed for the treatment of acute myeloid leukaemia (AML). The Phase 3 QuANTUM-R study investigated the efficacy of quizartinib monotherapy in patients with relapsed/refractory FLT3-ITD mutation-positive AML. The clinical course of four QuANTUM-R participants exemplifies issues specific to quizartinib treatment and is described here. Patient 1 was FLT3-ITD mutation-negative at AML diagnosis, but became FLT3-ITD mutation-positive during treatment that included several lines of chemotherapy and was therefore a suitable candidate for quizartinib. Because of the clonal shifts of AML during treatment, retesting genetic alterations at each relapse or resistance may help to identify candidates for targeted treatment options. Patient 2 developed QTc prolongation during quizartinib treatment, but the QTc interval normalised after dose reduction, allowing the patient to continue treatment and eventually resume the recommended dose. Patient 3 responded to quizartinib and was scheduled for haematopoietic stem cell transplant (HSCT), but developed febrile neutropenia and invasive aspergillosis during conditioning and subsequently died (to avoid drug-drug interactions, no azole antifungal was administered concomitantly). Care is required when selecting concomitant medications, and if there is potential for interactions (e.g. if prophylactic azole antifungals are required) the quizartinib dose should be reduced to minimise the risk of QTc prolongation. Patient 4 was able to undergo HSCT after responding to quizartinib and experienced a durable response after HSCT while on quizartinib maintenance therapy. Together, these cases illustrate the main issues to be addressed when managing patients under quizartinib, allowing for adequate scheduling and tolerability, bridging to HSCT, and durable remission on maintenance therapy in some patients.

1 Introduction
Acute myeloid leukaemia (AML) is an aggressive clonal haematological malignancy in which the haematopoietic process for myeloid cells is altered, resulting in differentiation arrest of myeloid progenitor cells and the proliferation of undifferentiated or poorly differentiated blood cells in bone marrow and blood [1, 2].

Approximately 30% of patients with AML have a mutation in the gene for FMS-like tyrosine kinase 3 (FLT3) [3], which may be an internal tandem duplication (ITD) mutation (the most common form) or a point mutation in the tyrosine kinase domain (TKD) [4]. The presence of an FLT3-ITD mutation is prognostic of a poor outcome in terms of survival and risk of relapse [5–10], and partially counteracts the normally favourable prognostic benefit of having a nucleophosmin (NPM1) gene mutation [6, 7]. For example, studies showed a significantly shorter median duration of overall survival (OS) in patients with mutant FLT3-ITD compared with wild-type FLT3 (13.8 vs 22 months, respectively) [8], and that the 3-year OS rate in these two groups was 14 and 22–23%, respectively [7, 10]. The tyrosine kinase inhibitor quizartinib (AC220; Daiichi Sankyo) is highly selective for FLT3, with up to tenfold higher affinity for FLT3 than for other receptor tyrosine

---

1 Hematology Department (Torre G, Planta 7), Hospital Universitari i Politècnic La Fe, Avinguda Fernando Abril Martorell, 106, CP 46026 Valencia, Spain
2 CIBERONC, Instituto Carlos III, Madrid, Spain
3 Hospital General Universitario Gregorio Marañón, Madrid, Spain

△ Adis
Quizartinib is a tyrosine kinase inhibitor that selectively targets FLT3-ITD mutations in patients with acute myeloid leukaemia, so it is worthwhile retesting mutation status at each relapse to identify patients who become candidates for quizartinib after converting from FLT3-ITD mutation-negative to -positive during chemotherapy.

There is a potential for QTcF prolongation during quizartinib treatment, but this is almost invariably asymptomatic and reversible, and can be easily managed by dose reduction.

Quizartinib is metabolised by cytochrome P450 3A4 enzymes, so careful attention should be paid to the choice of concomitant medications, including antifungal prophylaxis, to avoid drug–drug interactions.

2 Changes in Mutational Status

The genomic architecture of AML evolves through the course of the disease, as chemotherapy and disease progression affect blast characteristics [16–19]. Relapse is often caused by the emergence of chemo-resistant clones after treatment [20]. However, because mutations like FLT3 are now targets for novel chemotherapeutic agents, it is worthwhile retesting a patient’s molecular biology at relapse to identify the emergence of novel mutations that may be sensitive to targeted therapies. The following case description involves a patient who was FLT3-ITD-negative at diagnosis but was later found to be FLT3-ITD-positive after five regimens of unsuccessful treatment, including haematopoietic stem cell transplantation (HSCT).

2.1 Illustrative Case

A previously healthy 46-year-old male with no medical history was diagnosed with AML after presenting with skin lesions, anaemia (haemoglobin 10.3 g/dL), thrombocytopenia (platelets 35 × 10⁹ cells/L), and leucocytosis (white blood cells 19.5 × 10⁹ cells/L; 20% blasts in peripheral blood). Bone marrow assessment showed 15% blast cells and evidence of fibrosis. Cytogenetics were 46,XY[21], and the patient’s mutational analysis was positive for NPM1 and negative for FLT3-ITD.

The patient received induction therapy according to the PETHEMA LMA 2010 < 65 regimen (idarubicin 12 mg/m²/day on Days 1–3 of the cycle and cytarabine 200 mg/m²/day on Days 1–7) [21], but did not respond. The patient then underwent three regimens of salvage chemotherapy (high-dose cytarabine, FLAG-Ida [fludarabine, cytarabine, and granulocyte-colony stimulating factor with idarubicin] [21], and a clinical trial with intensive treatment) without response. The final salvage treatment attempted was sequential HSCT, which achieved a complete response.

Two months after the HSCT, the patient relapsed and met the criteria to be enrolled in the QuANTUM-R study, with an FLT3-ITD mutation (ratio 0.06), and a normal ECG (mean QTcF 407 ms). He was randomised to quizartinib with a starting dose of 30 mg/day in cycle 1. This dose was well tolerated, with no ECG changes, so the quizartinib dose was increased to 60 mg/day as planned in the study protocol.

Cycle 2 evaluations showed a continuing response, with 2% blast cells in bone marrow and haematologic recovery. On Day 1 of cycle 5, the patient had reported a submandibular growth. Unlike a computed tomography (CT) scan of the head and neck (Fig. 1), where the tumour appeared to be left submaxillitis and reactive lymphadenopathy, subsequent biopsy showed that it was a granulocytic sarcoma. As the patient had no evidence of bone marrow infiltration (no blast cells with complete donor chimerism in the subsequent assessment) and had already undergone numerous salvage treatments, continuation of quizartinib with the addition of radiotherapy to treat extramedullary disease was considered the best treatment option.

Afterwards, bone marrow evaluations showed persistent complete response, but at the end of cycle 9, the patient developed abdominal pain, hyperbilirubinaemia and renal impairment, with CT evidence of tumoural infiltration of the gall bladder and extrahepatic bile ducts, and bilateral involvement of the kidneys and ureters (Fig. 2a, b). The patient also had a thrombosis in the horizontal segment of
the left portal vein, and a partial thrombosis in the right portal branch for the anterior segments. At this time, the patient’s bone marrow contained 7% blast cells. Quizartinib treatment was stopped and the patient withdrew from the study. Despite an initial response to two cycles of non-intensive chemotherapy after trial withdrawal, new extra medullary relapse occurred and the patient died 14 months after the last study visit.

2.2 Discussion

This case illustrates that mutational status can change during the course of AML, particularly in treated patients, such that a patient who initially presents as FLT3-ITD negative may become FLT3-ITD positive.

There may be a number of reasons why a patient presents with a negative FLT3-ITD status and later becomes FLT3-ITD positive, including AML blasts gaining this mutation during the course of treatment. Such shifts in FLT3 status have been reported previously by numerous researchers [22–27] and are more common than changes in NPM1 status between diagnosis and relapse. Among the changes in FLT3 mutations reported during the course of AML treatment, the gain of ITD is more common than the loss of TKDs [24].

The possibility of an undetected FLT3 mutation at diagnosis in this case is unlikely since modern high-sensitivity PCR assays are able to detect FLT3 mutations when such mutations are present in ≤ 1% of cells [12, 28].

Fig. 1 Axial CT scan at the C1 level showing submaxillary swelling and lymphadenopathy on the left side

Fig. 2 Coronal (a) and axial (b) CT scans of the abdomen showing extramedullary disease with ureteral involvement after cycle 9 of quizartinib

3 Managing ECG Changes

Quizartinib is associated with QTcF prolongation [13], which is a marker for potentially serious cardiac arrhythmias such as torsade de pointes [29] and requires careful management. In the Phase 1 quizartinib study, 5% of patients developed grade 3 QTc prolongation [13], which affected the protocols for the subsequent Phase 2 and 3 studies, including QuANTUM-R [12, 30]. The QuANTUM-R study used a lower dose of quizartinib (60 mg/day) than had been used in the Phase 1 (maximum tolerated dose 200 mg/day) and
Phase 2 (135 mg/day for men and 90 mg/day for women in the majority of patients) studies [15]. It was hypothesised that a 60 mg/day dose of quizartinib would be as effective as the higher doses, but would be associated with a lower risk of heart rate abnormalities.

The case report below describes a patient in the QuANTUM-R study who developed grade 2 QTcF prolongation (QTcF > 480 ms) but was able to continue quizartinib treatment at a reduced dose and subsequently achieved a complete remission.

### 3.1 Illustrative Case

A previously healthy 34-year-old male with no medical history of interest was diagnosed with AML after presenting with anaemia (haemoglobin 7.9 g/dL), leukopenia (white blood cells 0.83 × 10^9 cells/L; 1% blast cells) and thrombocytopenia (64 × 10^9 cells/L). At diagnosis, his bone marrow showed 81% blast cells and his cytogenetic profile was 47,XY,+6(11)/46,XY[3]. Mutational analysis showed that he was NPM1 negative and FLT3-ITD positive (ratio 0.31).

The patient underwent 1 cycle of induction therapy with PETHEMA LMA 2010 < 65 and achieved a complete response, but with positive minimal residual disease (MRD). Consolidation therapy using the same regimen was completed without complications. HSCT was planned, but he relapsed within 1 month of completing consolidation therapy (the bone marrow contained 34% blast cells). On assessment, this patient was eligible for the QuANTUM-R trial. At study entry, there was an FLT3-ITD mutation (ratio 0.58) and there were no ECG abnormalities (mean baseline QTcF interval of 384 ms) (Fig. 3a). He was transfusion dependent and was receiving ciprofloxacin and isoniazid prophylaxis (positive QuantiFeron test for tuberculosis infection at diagnosis), fluconazole, ceftibuten and levofloxacin.

The patient was randomised to quizartinib and received cycle 1 treatment at 30 mg/day without adverse events (AEs) and with no pathological ECG changes excepting a heart rate of 58 beats/min; the dose of quizartinib was increased to 60 mg/day on Day 15. During cycle 4, a routine ECG showed an increase in the QTcF interval to 488 ms (Fig. 3b), requiring a reduction in the quizartinib dose to 30 mg/day (electrolytes were within normal range at this time). After cycle 4, the patient’s QTcF interval normalised to 403 ms, and the quizartinib dose was increased to 60 mg/day.

Bone marrow assessment showed a complete response after cycle 5 (with partial remission reached after cycle 1 and 3). Allogeneic HSCT was performed after the cycle 6. The patient received four post-HSCT cycles of quizartinib; although he remained bradycardic, he did not experience any significant complications. Twenty-three months after the HSCT, the patient was alive and in complete remission with no evidence of MRD.

### 3.2 Discussion

This case illustrates that quizartinib treatment can be successfully continued, albeit at a reduced dose, in patients who develop grade ≤ 2 QTcF prolongation (QTcF < 499 ms), a finding consistent with data from the Phase 1 and 2 studies [12, 13]. In the Phase 1 and 2 studies with quizartinib, QTcF prolongation was reversible, asymptomatic and not associated with any arrhythmias [12, 13], which was also true of the patient from QuANTUM-R reported here. Although potential drug-drug interactions could have contributed to the QTcF prolongation seen in this patient, pharmacokinetic studies indicate that quizartinib dose reductions are not required when coadministered with weak or moderate CYP3A4 inhibitors [14, 31], such as isoniazid and fluconazole, respectively. No other concomitant medications with known interactions were administered in this patient. It is encouraging to know that any QTcF prolongation that may occur with quizartinib is almost invariably asymptomatic and reversible, and can be easily managed by dose reduction.

### 4 Potential Drug–Drug Interactions

Oral quizartinib is extensively metabolised in the liver by the cytochrome P450 (CYP) 3A4 enzyme, producing a major metabolite that is also active against FLT3 in vitro [32]. Therefore, the antitumour activity of quizartinib may be affected by agents that are inhibitors or inducers of CYP3A4 (e.g. azole antifungal agents). In addition, in vitro data indicate that quizartinib inhibits the ATP-binding cassette (ABC) G2, also known as breast cancer resistance protein (BCRP), at pharmacologically relevant doses, which may also have pharmacokinetic implications [33].

To date, little is known about the potential for quizartinib to interact with other agents used clinically in the treatment of AML. This case describes a patient who developed repeated infections during the course of her AML and required prophylaxis with multiple anti-infective agents during treatment with quizartinib. When choosing prophylactic agents, we avoided strong CYP3A4 inhibitors to minimise the potential for drug-drug interactions.

### 4.1 Illustrative Case

A 34-year-old woman with no significant medical history was diagnosed with AML. Cytogenetics showed a normal (46,XX) karyotype and she was negative for NPM1, and positive for FLT3-ITD mutations (ratio unknown at diagnosis).

The patient began induction treatment with the PETHEMA LMA 2010 < 65 regimen and experienced a partial response after 2 cycles (6% blasts in bone marrow). In addition, she experienced neutropenic enterocolitis,
Fig. 3  ECG from a patient (a) at screening, showing a normal QTcF interval (385 ms), and (b) during quizartinib 60 mg, when QTcF was prolonged to 488 ms, prompting a dose reduction
mucositis (grade 2), and Enterococcus faecium bacteraemia. As salvage therapy, FLAG-Ida was administered, followed by Clostridium difficile colitis and bacteraemia (causative pathogens were coagulase-negative Staphylococcus and Escherichia coli) but no complete remission was obtained. Nevertheless, the patient underwent allogeneic HSCT from a 9/10 HLA-matched unrelated donor, achieving complete remission with complete chimerism according to the bone marrow assessment performed on Day 31. Unfortunately, by day 121, the patient relapsed and was selected for the QuANTUM-R study.

The patient was randomised to quizartinib and was treated with a 30 mg/day dose in cycle 1, increasing to 60 mg/day in subsequent cycles, as she met the corresponding criteria. She also received antimicrobial prophylaxis with levofloxacin, cotrimoxazole and acyclovir. Rather than initiating antifungal prophylaxis, monitoring the patient twice weekly for the presence of Aspergillus antigens in blood was considered the best choice. At the end of cycle 3, the patient was hospitalised for bacteraemia, which was resolved with teicoplanin. Although the causative pathogen was coagulase-negative Staphylococcus, computed tomography scan of the thorax was normal and Aspergillus antigens in blood were consistently negative, quizartinib was stopped for 1 week and the patient received posaconazole during this time.

After cycle 4, the bone marrow assessment showed complete response, so a second allogeneic HSCT was planned. Antifungal prophylaxis with micafungin was added to her previous prophylactic regimen during conditioning, but the patient developed fever despite the broad infectious coverage. On Day 3 from HSCT, a chest x-ray showed bilateral infiltrates. Throughout treatment, the patient had returned consistently negative results for Aspergillus antigenaemia but bronchoalveolar lavage fluid was positive for Aspergillus spp. Finally, she developed respiratory failure and died due to invasive fungal infection.

4.2 Discussion

This complex patient experienced multiple infective complications during the course of the AML. In addition to regularly monitoring for the presence of Aspergillus antigens (which is an accurate marker for invasive fungal infections [34]), when quizartinib was initiated, physicians considered antimicrobial agents with known little potential for drug–drug interactions [35]. In fact, only when quizartinib was stopped, the patient received a strong CYP3A4 inhibitor like posaconazole. However, regular ECG monitoring and dose reduction (which is recommended when strong CYP3A4 inhibitors are co-administered [14]) could have been considered a better option.

This case highlights the importance of introducing antifungal prophylaxis, while reducing the dose of quizartinib, which is preferable to avoid the use of some necessary drugs that could improve the prognostic of the disease [36].

5 Maintenance Therapy

There is currently limited information about the durability of response to quizartinib or whether quizartinib can be used as maintenance therapy after HSCT. The following case describes a patient who achieved an early complete remission and was subsequently able to undergo HSCT, and then went on to receive quizartinib maintenance therapy.

5.1 Illustrative Case

A 55-year-old man with an unremarkable medical history was diagnosed with AML. At diagnosis, he had a haemoglobin level of 10.7 g/dL, white blood cell count of \(1.7 \times 10^9\) cells/L, 24% blasts and a platelet count of \(151 \times 10^9\) L. Based on his bone marrow assessment, which had a blast count of 87%, the patient’s karyotype was 46,XY[21], and he was negative for NPM1 mutation but positive for FLT3-ITD mutation (ratio 0.67).

The patient received induction therapy with the PETHEMA LMA 2010 < 65 regimen, but did not respond. According to his clinical profile, the patient was a candidate for FLAG-Ida (fludarabine, cytarabine and idarubicin), but his mutation status also made quizartinib a treatment option. At this time, the patient was FLT3-ITD positive with a ratio of 0.11, had 45% bone marrow blasts, was not taking any concomitant medication, and had no pathological ECG findings (baseline QTcF interval of 374 ms).

The patient entered the QuANTUM-R study and was randomised to oral quizartinib at a starting dose of 30 mg/day, increasing the dose of quizartinib to 60 mg/day during this course. The patient did not develop fever ≥ 38 °C or any form of cytopenia.

After the first cycle of quizartinib, the patient’s bone marrow aspirate contained 3% blasts, and his blood count parameters had improved from baseline (haemoglobin 13.5 g/dL, platelets \(337 \times 10^9\)/L, and white blood cells \(2.1 \times 10^9\) cells/L, including neutrophils \(2.1 \times 10^9\) cells/L). Complete remission was maintained and quizartinib was discontinued after 7 days of cycle 4 to initiate the HSCT preparation protocol. A myeloablative haploidentical HSCT was performed without serious complications. The patient was receiving standard anti-infective prophylaxis and immunosuppressive therapy with posaconazole, sirolimus, cotrimoxazole, prednisone and acyclovir when a bone marrow assessment 80 days post-HSCT showed no blasts. At this time, quizartinib was restarted at an initial dose of 20 mg/day on...
account of the patient had also a neutrophil count $> 1 \times 10^9$ cells/L and platelets $> 50 \times 10^9$/L, and no evidence of acute or chronic GVHD. QTcF remained within normal limits on Day 15, so the dose of quizartinib was increased to 30 mg/day according to the study protocol. On Day 1 of cycle 3, posaconazole was withdrawn and the dose was increased again to 60 mg/day. The patient remains in remission while continuing quizartinib treatment; to date he has received 35 cycles (4 prior to and 31 since the HSCT) without complications or the need for concomitant treatment.

5.2 Discussion

To date, there is limited information about the long-term use of quizartinib as maintenance therapy. One small Phase 1 study evaluated quizartinib as maintenance therapy in a cohort of 13 patients who had undergone allogeneic HSCT [37]. Treatment with quizartinib was continued for 24 cycles unless the patient relapsed or had persistent grade 3 or 4 toxicity [37]. Three patients died during this study, but 10 patients were treated with quizartinib for more than 1 year, and six of these patients received treatment for almost 2 years [37]. The overall survival ranged from 13 to 142 weeks; nine patients survived for $>1$ year and four for $> 2$ years [37]. No patient showed a reduction in donor chimerism during maintenance quizartinib treatment after HSCT [37]. In this small study, the most common grade 3 or 4 AEs were haematological, with grade 3 or 4 leukopenia, anaemia, thrombocytopenia or lymphopenia each occurring in two patients (15%) and neutropenia developing in three (23%) [37]. Six patients received granulocyte colony-stimulating factor.

In our case study, the patient did not develop any cytopenias during quizartinib treatment, before or after HSCT. These promising data suggest that quizartinib can rapidly produce complete remission in some patients with relapsed/refractory AML, consistent with the response seen in the current case study, allowing them to undergo HSCT. Moreover, quizartinib can be safely continued as long-term maintenance therapy after HSCT.

6 Closing Remarks

These cases illustrate several of the key issues to be addressed when treating patients with AML, particularly when transitioning to treatment with quizartinib.

- Monitoring the genomic architecture of AML during the disease course, and retesting genetic alterations at each relapse or when resistance to treatment emerges may identify mutations that are sensitive to targeted therapies, such as quizartinib.

- There is a potential for QTcF prolongation with quizartinib or arising out of pharmacokinetic drug-drug interactions. Careful monitoring of the ECG means that risk mitigation strategies, such as dose reductions when QTcF prolongation exceeds 480 ms or switching/discontinuing coadministered drugs, should be implemented without interrupting quizartinib treatment.

- In some circumstances, managing drug interactions is preferable, so that patients can be treated concomitantly with the necessary drugs, in this case azoles and quizartinib.

- Quizartinib can be continued as long-term maintenance therapy after HSCT until relapse or unacceptable toxicity, although the optimal duration of maintenance therapy is unknown at present.

While quizartinib appears to be an effective and well-tolerated treatment option for patients with FLT3-ITD relapsed/refractory AML, adequate management of these key issues remains essential for therapeutic success.

Acknowledgements The authors thank Catherine Rees of Springer Healthcare Communications who assisted in the writing of the outline and first draft of this manuscript. This medical writing assistance was funded by Daiichi Sankyo.

Author Contributions David Martínez-Cuadrón and Pau Montesinos conceived the article; David Martínez-Cuadrón, Gabriela Rodríguez-Macías, Rebeca Rodríguez-Veiga and Blanca Boluda identified suitable cases for inclusion and provided data of patients treated in their institutions; all authors wrote the paper, reviewed the manuscript and approved the final version for submission.

Compliance with Ethical Standards

Funding Daiichi Sankyo provided financial support for medical writing services.

Ethics approval and consent to participate All patients gave written consent to take part in the study and the study was approved by the health authorities. The reference committee was the Ethical Committee of the Hospital Universitari i Politècnic La Fe, Valencia.

Conflict of interest David Martínez-Cuadrón has acted in an advisory role for JazzPharma, Novartis, Pfizer, Teva and Daiichi Sankyo; has served on the Speakers’ Bureau of Pfizer, Janssen, Amgen and Gilead; and has received travel grants from JazzPharma, Novartis, Pfizer and Amgen. Pau Montesinos has provided consultations or acted in an advisory role for JazzPharma, Novartis, AbbVie, Celgene, Shire, Takeda, Daiichi Sankyo, Pfizer, Tolero and Agios; has served on the Speakers’ Bureau of Otsuka, Novartis, AbbVie, Celgene, Incyte, Daiichi Sankyo and Pfizer; has received research funding from Novartis, Janssen, Celgene, Daiichi Sankyo, Pfizer and Teva; and has received travel grants from Teva, Novartis, Celgene, Daiichi Sankyo and Amgen. Rebeca Rodríguez-Veiga has served on the Speakers’ Bureau of Teva, Pfizer, Janssen and Novartis; and has received travel grants from Sanofi and Daiichi Sankyo. All other co-authors: nothing to disclose.

△ Adis
References

1. Dohner H, Weisdorf DJ, Bloomfield CD. Acute myeloid leukemia. N Engl J Med. 2015;373(12):1136–52.
2. Grove CS, Vassiliou GS. Acute myeloid leukaemia: a paradigm for the clonal evolution of cancer? Dis Model Mech. 2014;7(8):941–51.
3. Ley TJ, Miller C, Ding L, et al. Genomic and epigenomic landscapes of adult de novo acute myeloid leukemia. N Engl J Med. 2013;368(22):2059–74.
4. Mrozek K, Marcucci G, Paschka P, et al. Clinical relevance of mutations and gene-expression changes in adult acute myeloid leukemia with normal cytogenetics: are we ready for a prognostically prioritized molecular classification? Blood. 2007;109(2):431–48.
5. Boissel N, Cayuela JM, Preudhomme C, et al. Prognostic significance of FLT3 internal tandem repeat in patients with de novo acute myeloid leukemia treated with reinforced courses of chemotherapy. Leukemia. 2002;16(9):1699–704.
6. Gale RE, Green C, Allen C, et al. The impact of FLT3 internal tandem duplication mutant level, number, size, and interaction with NPM1 mutations in a large cohort of young adult patients with acute myeloid leukemia. Blood. 2008;111(5):2776–84.
7. Lazenby M, Gilkes AF, Marini C, et al. The prognostic relevance of flt3 and npm1 mutations on older patients treated intensively or non-intensively: a study of 1312 patients in the UK NCI AML16 trial. Leukemia. 2014;28(10):1953–9.
8. Patel JP, Gonen M, Figueroa ME, et al. Prognostic relevance of integrated genetic profiling in acute myeloid leukemia. N Engl J Med. 2012;366(12):1079–89.
9. Ravandi F, Kantarjian H, Faderl S, et al. Outcome of patients with FLT3-mutated acute myeloid leukemia in first relapse. Leuk Res. 2010;34(6):752–6.
10. Whitman SP, Maharry K, Radmacher MD, et al. FLT3 internal tandem duplication associates with adverse outcome and gene- and microRNA-expression signatures in patients 60 years of age or older with primary cytogenetically normal acute myeloid leukemia: a Cancer and Leukemia Group B study. Blood. 2010;116(18):3622–6.
11. Zarrinkar PP, Gunawardane RN, Cramer MD, et al. AC220 is a uniquely potent and selective inhibitor of FLT3 for the treatment of acute myeloid leukemia (AML). Blood. 2009;114(14):2984–92.
12. Cortes J, Perl AE, Dohner H, et al. Quizartinib, an FLT3 inhibitor, as monotherapy in patients with relapsed or refractory acute myeloid leukemia: an open-label, multicentre, single-arm, phase 2 trial. Lancet Oncol. 2018;19(7):889–903.
13. Cortes JE, Kantarjian H, Foran JM, et al. Phase I study of quizartinib administered daily to patients with relapsed or refractory acute myeloid leukemia irrespective of FMS-like tyrosine kinase 3-internal tandem duplication status. J Clin Oncol. 2013;31(29):3681–7.
14. Daiichi Sankyo. Quizartinib hydrochloride tablets: Japanese prescribing information. 2019. http://www.pmda.go.jp/PmdaSearch/yakuDetail/430574_4291060F1021_1_02#HDR_Warnings. Accessed 13 Nov 2019.
15. Cortes JE, Khaleel S, Martinelli G, et al. Quizartinib versus salvage chemotherapy in relapsed or refractory FLT3-ITD acute myeloid leukaemia (QuANTUM-R): a multicentre, randomised, controlled, open-label, phase 3 trial. Lancet Oncol. 2019;20(7):984–97.
16. Parkin B, Oullette P, Li Y, et al. Clonal evolution and devolution after chemotherapy in adult acute myelogenous leukaemia. Blood. 2013;121(2):369–77.
17. Ding L, Ley TJ, Larson DE, et al. Clonal evolution in relapsed acute myeloid leukaemia revealed by whole-genome sequencing. Nature. 2012;481(7382):506–10.
18. Zhang X, Lv D, Zhang Y, et al. Clonal evolution of acute myeloid leukemia highlighted by latest genome sequencing studies. Oncotarget. 2016;7(36):58586–94.
19. Short NJ, Kantarjian H, Ravandi F, et al. A phase I/II randomized trial of clofarabine or fludarabine added to idarubicin and cytarabine for adults with relapsed or refractory acute myeloid leukemia. Leuk Lymphoma. 2018;59(9):813–20.
20. Hassan C, Afshinnekoo E, Li S, et al. Genetic and epigenetic heterogeneity and the impact on cancer relapse. Exp Hematol. 2017;54:26–30.
21. Bergua JM, Montesinos P, Martinez-Cuadrón D, et al. A prognostic model for survival after salvage treatment with FLAG-Ida±gemtuzumab-ozogamicine in adult patients with refractory/refractory acute myeloid leukemia. Br J Haematol. 2016;174(5):700–10.
22. Cloos J, Goemans BF, Hess CJ, et al. Stability and prognostic influence of FLT3 mutations in paired initial and relapsed AML samples. Leukemia. 2006;20(7):1217–20.
23. Kottaridis PD, Gale RE, Langabeer SE, et al. Studies of FLT3 mutations in paired presentation and relapse samples from patients with acute myeloid leukemia: implications for the role of FLT3 mutations in leukemogenesis, minimal residual disease detection, and possible therapy with FLT3 inhibitors. Blood. 2002;100(7):2393–8.
24. McCormick SR, McCormick MJ, Grutkoski PS, et al. FLT3 mutations at diagnosis and relapse in acute myeloid leukemia: cytogenetic and pathologic correlations, including cuplike blast morphology. Arch Pathol Lab Med. 2010;134(8):1143–51.
25. Heist EK, Huang CF, Wu JH, et al. Internal tandem duplication of FLT3 in relapsed acute myeloid leukemia: a comparative analysis of bone marrow samples from 108 adult patients at diagnosis and relapse. Blood. 2002;100(7):2387–92.
26. Shih LY, Huang CF, Wu JH, et al. Heterogeneous patterns of FLT3 Asp(835) mutations in relapsed de novo acute myeloid leukemia: a comparative analysis of 120 paired diagnostic and relapse bone marrow samples. Clin Cancer Res. 2004;10(4):1326–32.
27. Bacher U, Haferlach T, Kern W, et al. A comparative study of molecular mutations in 381 patients with myelodysplastic syndrome and in 4130 patients with acute myeloid leukemia. Haematologica. 2007;92(6):744–52.
28. Ziai JM, Siddon AJ. Pathology consultation on gene mutations in acute myeloid leukemia. Am J Clin Pathol. 2015;144(4):539–54.
29. Heist EK, Ruskjn JN. Drug-induced arrhythmia. Circulation. 2010;122(14):1426–35.
30. A phase 3 open-label randomized study of quizartinib (AC220) monotherapy versus salvage chemotherapy in subjects with tyrosine kinase 3—internal tandem duplication (FLT3-ITD) positive acute myeloid leukemia (AML) refractory to or relapsed after first-line treatment with or without hematopoietic stem cell transplantation (HSCCT) consolidation [ClinicalTrials.gov record: NCT02039726] [database on the Internet]2018 [cited December 10 2018]. https://clinicaltrials.gov/ct2/show/NCT02039726.
31. Li J, Kankam M, Trone D, et al. Effects of CYP3A inhibitors on the pharmacokinetics of quizartinib, a potent and selective FLT3 inhibitor, and its active metabolite. Br J Clin Pharmacol. 2019;85(9):2108–17.

32. Sanga M, James J, Marini J, et al. An open-label, single-dose, phase 1 study of the absorption, metabolism and excretion of quizartinib, a highly selective and potent FLT3 tyrosine kinase inhibitor, in healthy male subjects, for the treatment of acute myeloid leukemia. Xenobiotica. 2017;47(10):856–69.

33. Bhullar J, Natarajan K, Shukla S, et al. The FLT3 inhibitor quizartinib inhibits ABCG2 at pharmacologically relevant concentrations, with implications for both chemosensitization and adverse drug interactions. PLoS One. 2013;8(8):e71266.

34. Patterson TF, Thompson GR 3rd, Deaning DW, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;63(4):e1–60.

35. Dodds-Ashley E. Management of drug and food interactions with azole antifungal agents in transplant recipients. Pharmacotherapy. 2010;30(8):842–54.

36. Rodríguez-Veiga R, Montesinos P, Boluda B, et al. Incidence and outcome of invasive fungal disease after front-line intensive chemotherapy in patients with acute myeloid leukemia: impact of antifungal prophylaxis. Ann Hematol. 2019;98(9):2081–8.

37. Sandmaier BM, Khaled S, Oran B, et al. 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(2):222–31.39. Fluconazole 50 mg Capsules. Summary of Product Characteristics. [database on the Internet] 2018 [cited 5 April 2019]. https://www.medicines.org.uk/emc/product/6077/smpc/print.