# Quizartinib and Intermediate Dose Cytarabine Consolidation Therapy[i]

## INDICATIONS FOR USE:

| INDICATION | ICD10 | Regimen Code | HSE approved reimbursement status* |
|---|---|---|---|
| Quizartinib in combination with cytarabine consolidation chemotherapy for adult patients with newly diagnosed acute myeloid leukaemia (AML) who are FLT3-ITD mutation positive. | C92 | 00887a | 1/2/2025 |

* This applies to post 2012 indications only

## TREATMENT:

*The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.*

- Consolidation treatment is administered as detailed in the treatment table below for up to 4 cycles.
- Patients should have previously received one to two cycles of induction therapy **(Ref NCCP Regimen 886 Quizartinib, DAUNOrubicin and Cytarabine Induction Therapy OR NCCP Regimen 891 Quizartinib, IDArubicin and Cytarabine Induction Therapy)** and should have achieved complete remission or complete remission with incomplete neutrophil or platelet recovery.
- For patients who proceed to haematopoietic stem cell transplantation (HSCT), quizartinib should be stopped 7 days before the start of a conditioning regimen. It may be resumed after completion of the transplant based on white blood cell count (WBC) and at the discretion of the treating physician for patients with sufficient haematologic recovery and with ≤ Grade 2 graft-versus-host disease (GVHD), not requiring the initiation of new systemic GVHD therapy within 21 days, following the dosing recommendations

Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered.

| Admin. Order | Day | Drug | Dose | Route | Diluent & Rate | Cycle |
|---|---|---|---|---|---|---|
| 1 | 1, 3 and 5 | Cytarabine[a] | 1500mg/m$^2$ **AM** | IV infusion | 500mL NaCl 0.9% over 4 hours | Every 28 days |
| 2 | 1, 3 and 5 | Cytarabine[a] | 1500mg/m$^2$ **PM** (12 hours after start of **AM** infusion) | IV infusion | 500mL NaCl 0.9% over 4 hours | Every 28 days |
| 3 | 6 to 19 inclusive | Quizartinib[b, c, d] | 35.4mg daily | PO | n/a | Every 28 days |
| [a]Patients aged ≥ 61 years should receive cytarabine 1000 mg/m$^2$ TWICE a day. | | | | | | |
| [b]Quizartinib tablets should be taken at approximately the same time each day with or without food. Quizartinib tablets are commonly available as 17.7mg and 26.5 mg tablets | | | | | | |

| |
|---|
| [c]If a dose of quizartinib is missed or not taken at the usual time, the patient should take the dose as soon as possible on the same day and return to the usual schedule the following day. The patient should not take two doses on the same day. |
| [d]If the patient vomits after taking quizartinib, the patient should not take an additional dose that day but take the next dose the following day at the usual time. |

Note: Administration volumes and fluids have been standardised to facilitate electronic prescribing system builds.

## ELIGIBILITY:

- Indication as above
- ECOG 0-2
- Newly diagnosed AML with FLT3 mutation confirmed using a validated test

## CAUTIONS:

- Patients who are at significant risk of developing QT interval prolongation including:
  - patients with uncontrolled or significant cardiovascular disease,
  - myocardial infarction within 6 months
  - uncontrolled angina pectoris
  - uncontrolled hypertension
  - congestive heart failure
  - history of clinically relevant ventricular arrhythmias or torsade de pointes,
  - patients receiving concomitant medicinal products known to prolong the QT interval.

## EXCLUSIONS:

- Hypersensitivity to quizartinib, cytarabine, or to any of the excipients
- Diagnosis of acute promyelocytic leukaemia (APL), French American-British classification M3 or WHO classification of APL with translocation, t(15;17)(q22;q12) or BCR ABL positive leukaemia
- Congenital long QT syndrome
- QTcF interval >450 ms
- Severe renal or hepatic impairment
- Pregnancy
- Breastfeeding

## PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Haematologist working in the area of haematological malignancies.

## TESTS:

**Baseline tests:**

- FBC, renal and liver profile, potassium, magnesium
- ECG
- Pregnancy test within 7 days of starting treatment
- Hepatitis B virus (HBV) serology [HBV sAg, HBV sAb, HBV cAb], hepatitis C virus (HCV) serology, human immunodeficiency virus (HIV) serology, cytomegalovirus (CMV) serology [IgG] and additional screening as clinically indicated
  *Reference Regimen Specific Complications for information on Hepatitis B reactivation

**Regular tests:**

- FBC, renal and liver profile, potassium, magnesium
- ECG
  - Once weekly during quizartinib treatment or more frequently as clinically indicated.
  - Monitoring should be performed more frequently in patients who:
    - are at significant risk of developing QT interval prolongation and torsade de pointes or
    - if quizartinib is being used concomitantly with medicinal products known to prolong the QT interval or
    - if patients experience diarrhoea or vomiting

**Disease monitoring:**

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

## DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.

**Table 1: Dose adjustments for adverse reactions and/or concomitant use with strong CYP3A inhibitors during consolidation treatment with quizartinib**

| Full dose | Dose reductions | | |
|---|---|---|---|
| | Adverse reaction | Concomitant strong CYP3A inhibitors | Adverse reaction and concomitant strong CYP3A inhibitors |
| 35.4mg | 26.5mg | 17.7mg | Interrupt |

**Table 2: Dose Modification for Adverse Events**

| Adverse reaction | Recommended dose modification |
|---|---|
| QTcF 450-480 ms (Grade 1) | Continue quizartinib dose. |
| QTcF 481-500 ms (Grade 2) | • Reduce quizartinib dose (see Table 1) without interruption.<br>• Resume quizartinib at the previous dose in the next cycle if QTcF has decreased to < 450 ms. Monitor the patient closely for QT prolongation for the first cycle at the increased dose. |
| QTcF ≥ 501 ms (Grade 3) | • Interrupt quizartinib.<br>• Resume quizartinib at a reduced dose (see Table 4) when QTcF returns to < 450 ms. |
| Recurrent QTcF ≥ 501 ms (Grade 3) | • Permanently discontinue quizartinib if QTcF > 500 ms recurs despite appropriate dose reduction and correction/elimination of other risk factors (e.g., serum electrolyte abnormalities, concomitant QT prolonging medicinal products). |
| Torsade de pointes; polymorphic ventricular tachycardia; signs/symptoms of life-threatening arrhythmia (Grade 4) | • Permanently discontinue quizartinib. |
| Grade 3 or 4 non-haematologic adverse reactions | • Interrupt quizartinib.<br>• Resume treatment at the previous dose if adverse reaction improves to ≤ Grade 1.<br>• Resume treatment at a reduced dose (see Table 1) if adverse reaction improves to < Grade 3.<br>• Permanently discontinue if Grade 3 or 4 adverse reaction persists beyond 28 days and is suspected to be associated with quizartinib. |
| Persistent Grade 4 neutropenia or thrombocytopenia without active bone marrow disease | Reduce the dose (see Table 1) |

* Grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (NCI CTCAE v4.03)

## Renal and Hepatic Impairment:

**Table 3: Dose modification in renal and hepatic impairment**

| Drug | Renal Impairment | | Hepatic Impairment | |
|---|---|---|---|---|
| **Quizartinib** | **Mild/moderate** | No dose adjustment is recommended | **Mild/moderate** | No dose adjustment is recommended |
| | **Severe** | Not recommended for use in patients with severe renal impairment (CrCl < 30 mL/min, estimated by Cockcroft-Gault), as safety and efficacy have not been established in this population. | **Severe** | Not recommended for use in patients with severe hepatic impairment (Child-Pugh Class C), as safety and efficacy have not been established in this population |
| **Cytarabine** | **CrCl (mL/min)** | **Dose** | **Mild/moderate** | No need for dose adjustment is expected |
| | >60 | 100% | | |
| | 31-59 | 50% of the original dose | | |
| | <30 | Not recommended | **Severe:** | Consider 25-50% of the original dose and increase if tolerated |
| | Haemodialysis | 50% of the original dose, start haemodialysis 4-5 hours after administration | | |
| Quizartinib: Renal and hepatic - SmPC<br>Cytarabine: Renal and hepatic – Giraud et al 2023 | | | | |

## SUPPORTIVE CARE:

## EMETOGENIC POTENTIAL:

- As outlined in NCCP Classification Document for Systemic AntiCancer Therapy (SACT) Induced Nausea and Vomiting Available on the NCCP website

**Quizartinib**: Moderate to high (**Refer to local policy).**
**Cytarabine:** Moderate **(Refer to local policy)**

**For information:**
**Within NCIS regimens, antiemetics have been standardised by the Medical Oncologists and Haemato-oncologists and information is available in the following documents:**

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - Available on the NCCP website
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - Available on the NCCP website

## PREMEDICATIONS:

**Cytarabine:**

To prevent a chemical induced conjunctivitis developing with cytarabine, prednisoLONE eye drops (e.g. Pred Mild®) 1-2 drops per eye 4 hourly during waking hours prior to cytarabine and continued 5 days post treatment should be administered.

## OTHER SUPPORTIVE CARE: State whether recommended or required

- Tumour lysis syndrome prophylaxis **(Refer to local policy).**
- Proton pump Inhibitor **(Refer to local policy).**
- Anti-viral prophylaxis **(Refer to local policy).**
- Anti-fungal prophylaxis **(Refer to local policy).** Strong CYP3A4 inhibitors (e.g. posaconazole) can increase quizartinib exposure. If concomitant use is required, the dose of quizartinib should be reduced as per table 1.

## ADVERSE EFFECTS:

- Please refer to the relevant Summary of Product Characteristics (SmPC) for details.
- Quizartinib is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.

## REGIMEN SPECIFIC COMPLICATIONS

- **Hepatitis B Reactivation:** Patients should be tested for both HBsAg and HBcoreAb as per local policy. If either test is positive, such patients should be treated with anti-viral therapy **(Refer to local infectious disease policy).** These patients should be considered for assessment by hepatology.

## DRUG INTERACTIONS:

- Current SmPC and drug interaction databases should be consulted for information.

## REFERENCES:


1. Erba HP, et al. Quizartinib plus chemotherapy in newly diagnosed patients with FLT£-internal-tandem-dubplication-positive acute myeloid leukaemia (QuANTUM-First): A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2023. 13;401(10388):1571-1583.
2. Giraud E L, Lijster B D, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Available at: https://pubmed.ncbi.nlm.nih.gov/37269847/
3. Quizartinib (Vanflyta®) Summary of Product Characteristics. Last updated 27/8/2024. Accessed December 2024. Available at https://www.ema.europa.eu/en/documents/product-information/vanflyta-epar-product-information_en.pdf
4. Cytarabine Solution for Injection Summary of Product Characteristics. Last updated: 06/12/2024. Accessed December 2024. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0822-200-002_06122024145744.pdf


| Version | Date | Amendment | Approved By |
|---|---|---|---|
| 1 | 1/2/2025 | | NCCP Myeloid SACT CAG |

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] This is an unlicensed posology for the use of cytarabine in Ireland. Patients should be informed of this and consented to treatment in line with the hospital's policy on the use of unlicensed medication and unlicensed or "off label" indications. Prescribers should be fully aware of their responsibility in communicating any relevant information to the patient and also ensuring that the unlicensed or "off label" indication has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy.