Quizartinib, IDArubicin and Cytarabine Induction Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Quizartinib in combination with standard IDArubicin and cytarabine induction chemotherapy for adult patients with newly diagnosed acute myeloid leukaemia (AML) who are *FLT3*-ITD mutation positive	C92	00891a	1/2/2025

* This applies to post 2012 indications

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.

- Induction treatment is administered as detailed in the treatment table below for up to 2 cycles.
- Patients with persistent leukaemia after the first cycle can receive a second cycle of induction chemotherapy
- Patients with complete remission or complete remission with incomplete neutrophil or platelet recovery during induction should proceed to Consolidation Therapy **(Ref NCCP Regimen 00887 Quizartinib and Intermediate Dose Cytarabine Consolidation Therapy)**
- 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
1	1 to 3 inclusive	IDArubicin[a]	12mg/m^2 daily	IV bolus	Slow IV push via side arm NaCl 0.9% infusion (a central line is preferred)
2	1 to 7 inclusive	Cytarabine	100mg/m^2 **AM**	IV infusion	100mL NaCl 0.9% over 30 minutes
3	1 to 7 inclusive	Cytarabine	100mg/m^2 **PM (12 hours after start of AM infusion)**	IV infusion	100mL NaCl 0.9% over 30 minutes
4	8 to 21 inclusive	Quizartinib[b, c, d]	35.4mg daily	PO	n/a
[a]There is no established maximum cumulative lifetime dose for IDArubicin. **Due consideration should be given to the risk factors[i] and to the age of the patient**					
[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*-ITD 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, IDArubicin, 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 induction 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

Management of adverse events:

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. • 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. • 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. • Resume treatment at the previous dose if adverse reaction improves to ≤ Grade 1. • Resume treatment at a reduced dose (see Table 1) if adverse reaction

	improves to < Grade 3. • 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.
IDArubicin	**CrCl (mL/min)**	**Dose**	**Bilirubin (micromol/L)**	**Dose**
	≥30	No need for dose adjustment is expected	45-86	50% of original dose
	<30	Consider 67% of the original dose	>86	Not recommended
	Haemodialysis	Consider 67% of the original dose		
Cytarabine	No dose reduction necessary		No dose adjustments needed	
Quizartinib: Renal and hepatic - SmPC IDArubicin: Renal and hepatic – Giraud et al 2023 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)**
IDArubicin: Moderate **(Refer to local policy)**
Cytarabine: Low **(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: No specific recommendations

OTHER SUPPORTIVE CARE:

- 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-duplication-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. IDArubicin (Zavedos®) Summary of Product Characteristics. Last updated 6/12/2024. Accessed December 2024. Available at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0822-142-005_06122024145750.pdf
5. 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	01/02/2025		NCCP Myeloid SACT CAG

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

---

[i] Cardiotoxicity is a risk associated with anthracycline therapy that may be manifested by early (acute) or late (delayed) effects.

Risk factors for developing anthracycline-induced cardiotoxicity include:

• high cumulative dose, previous therapy with other anthracyclines or anthracenediones
• prior or concomitant radiotherapy to the mediastinal/pericardial area
• pre-existing heart disease
• concomitant use of other potentially cardiotoxic drugs

In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors above and to the age of the patient.