Quizartinib (VANFLYTA) in Acute Myeloid Leukemia
National Drug Monograph
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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA APPROVAL INFORMATION

Description / MOA	Synthetic type 2 inhibitor of receptor tyrosine kinase (RTK) FLT3 that blocks downstream cell proliferation dependent on the FLT3 internal tandem duplication (ITD) of the juxtamembrane kinase domain (JKD). Quizartinib is the first FLT3 inhibitor evaluated in a newly diagnosed FLT3-ITD–positive AML population including patients age ≥ 60 years and approved for all three phases of AML chemotherapy. As a second-generation inhibitor, quizartinib was developed as a more selective FLT3 inhibitor to reduce off-target toxicities due to inhibition of other RTKs.
Indication Under Review[1]	Treatment of adults with newly diagnosed acute myeloid leukemia (AML) that is FLT3-ITD–positive as detected by an FDA-approved test, in combination with standard cytarabine and anthracycline induction and cytarabine consolidation and as maintenance monotherapy following consolidation chemotherapy. *Limitation of Use:* Not indicated as maintenance monotherapy following allogeneic hematopoietic stem cell transplantation (alloHCT). Improvement in overall survival (OS) in this setting has not been shown.
Dosage Regimen	*Induction with Cytarabine + Anthracycline 7 + 3 Regimen.* 35.4 mg PO once daily on Days 8–21 of 28-day cycle (Days 6–19 for 5 + 2 regimen). *Consolidation with High-dose Cytarabine.* 35.4 mg PO once daily on Days 6–19 for up to 4 cycles *Maintenance.* 26.5 mg PO once daily on Days 1–14 of first cycle if QTcF is ≤ 450 ms. Increase dose to 53 mg once daily on Day 15 of first cycle if QTcF is ≤ 450 ms. Maintain 26.5 mg once daily if QTcF was > 500 ms during induction or consolidation. Continue maintenance regimen without breaks between cycles for up to 36 cycles.
Dosage Forms Under Review	Tablets: 17.7 mg and 26.5 mg
REMS	Available only through a restricted distribution program, the VANFLYTA REMS, because of the serious risks of QT prolongation, torsade de pointes, and cardiac arrest. For further information, refer to PBM Formulary Management - Specialty Distribution Meds - All Documents (sharepoint.com) .

EFFICACY CONSIDERATIONS

Trial	**QuANTUM-First (NCT 02668653)**[2]
Design	Phase 3 MN DB PC RCT. Randomization was stratified by region, age (< 60 or ≥ 60 yo), and WBC (< 40 × 10^9/L or ≥ 40 × 10^9/L). Primary Efficacy Measure: Overall survival (OS) based on Kaplan-Meier estimates
Population	Newly diagnosed, primary FLT3-ITD–positive AML or AML secondary to myelodysplastic syndrome or myeloproliferative neoplasm, eligible to receive standard induction chemotherapy (N = 539) Included 18–75 yo, Variant Allelic Frequency (VAF; FLT3-ITD of total FLT3 in bone marrow or peripheral blood) of ≥ 3%, Eastern Cooperative Oncology Group performance status (ECOG PS) 0–2. Excluded AML secondary to prior chemotherapy or radiotherapy for other neoplasms, h/o CNS leukemia, QTcF > 450 ms or diagnosis or suspicion of long QT syndrome (LQTS), family h/o LQTS, uncontrolled or significant cardiovascular disease. Mean age 54 y, 40% ≥ 60 y; 25% ≥ 65 yo; 45.5% male; 3.9% from US; ECOG PS mostly 0 (34.3%) or 1 (50.1%); cytogenetic risk status was mostly intermediate (72.4%); FLT3-ITD VAF mostly ≥ 3% to ≤ 25% (35.6%) and > 25% to ≤ 50% (52.1%).
Interventions	Quizartinib vs Placebo (in combination with standard chemotherapy)

Induction Phase: Cytarabine (Ara-C) on Days 1–8 + daunorubicin or idarubicin on Days 1–3 ("7 + 3" regimen) then quizartinib 40 mg/d or placebo on Days 8–21 for up to 2 cycles. For Cycle 2, an optional, less intensive "5 + 2" regimen could be used with quizartinib starting on Day 6.

Consolidation Phase (3 options, for patients achieving complete remission [CR] or complete remission with incomplete neutrophil or platelet count recovery [CRi]):

1. High-dose Ara-C (HiDAC, adjusted for age > 60 y) on Days 1, 3, and 5 then quizartinib 40 mg/d or placebo on Days 6–19 for up to 4 cycles
2. AlloHCT
3. HiDAC on Days 1, 3, and 5 then quizartinib 40 mg/d or placebo on Days 6–19 for up to 4 cycles then alloHCT

Continuation / Maintenance Phase: Quizartinib 30 mg/d or placebo for 15 d, then (if QTcF ≤ 450 msec) 60 mg/d starting on Day 16 of Cycle 1 for up to 36 cycles (28 d/cycle) or relapse.

For Concomitant Strong CYP3A4 Inhibitor: Quizartinib 20 mg QD for induction and consolidation, and (if QTcF ≤ 450 msec) increased to 30 mg QD for continuation phase.

Results

Of 3468 patients screened, 864 (25%) were FLT3-ITD–positive and 539 (16%) were eligible for inclusion.

For quizartinib (N = 268) vs placebo (N = 271) patients, respectively:

- 192 (72%) vs 176 (65%) had composite complete remission (CR + CRi) after 1 or 2 induction cycles; 54 (20%) vs 56 (21%) received a second induction cycle.
- 173 (65%) vs 175 (65%) underwent post-remission consolidation.
- 116 (44%) of 265 vs 92 (34%) of 268 patients received continuation therapy.
- 103 (38%) vs 91 (34%) received protocol-specified alloHCT in the consolidation or continuation phase.
- 10.7 vs 9.5 wks, median duration of treatment exposure

Median follow-up: 39.2 mos in both treatment groups

Outcome	Quizartinib	Placebo	HR or Diff (95% CI)	Q
Deaths, n/N (%)	133/268 (49.6)	158/271 (58.3)	HR 0.78 (0.62, 0.98)	H
mOS time (95% CI), mo	31.9 (21.0, NE)	15.1 (13.2, 26.2)	Diff 16.8 (NR)	H
OS-6 rate (95% CI), %	82.3 (77.1, 86.4)	79.1 (73.7, 83.5)	—	ID
OS-48 rate (95% CI), %	48.4 (41.9, 54.5)	37.0 (29.8, 44.2)	—	ID

Source: 3. ID, Insufficient data; mOS, Median overall survival; OS-6 or-48, Overall survival at 6 or 48 months; NE, Not estimable; NR, Not reported; Q, GRADE quality of evidence (H, High; ID, Insufficient data)

Overall Risk of Death

- Anticipated absolute effect, 86 (3, 171) per 1000; NNT 12 (6, 344).
- HR 0.91 (0.66, 1.26) in age group ≥ 60 y (n = 107) and 0.68 (0.49, 0.95) in age group < 60 y (n = 109), post hoc subgroup analyses.

Continuation / Maintenance Phase[3]

- Median overall survival (mOS) was not reached in either the quizartinib or placebo arm.
- Deaths occurred in 25/116 (22%) vs 26/92 (28%), respectively; HR 0.68 (0.4, 1.18).
- Subgroup analyses of risk of death by alloHCT status suggested a lack of benefit in patients with alloHCT (HR 1.4 [0.60, 3.54]; n = 119) vs a benefit without alloHCT (HR 0.43 [0.19, 0.94]; n = 89).
- Relapse after achieving initial CR: 22/94 (23%) vs 8/72 (33%), respectively. Deaths after relapse: 8 (9%) vs 5 (7%), respectively.
- Median relapse-free survival (mRFS): 39.3 mos vs 13.6 mos; HR 0.61 (0.44, 0.85).
- Treatment effects seemed to plateau at 12 months for OS and RFS.
- Measurable Residual Disease (MRD) status analyses were insufficient to determine whether quizartinib maintenance therapy would benefit patients based on MRD (cutoff of 0.01%).

Notable Nonsignificant, Similar or Weak Treatment Differences

- Both the rates of CR with no MRD and rates of composite CR with no MRD were similar between treatment groups.

		• Event-free survival, CR, and OS on quizartinib maintenance post-alloHCT showed nonsignificant treatment differences. There is no evidence of benefit with post-alloHCT quizartinib maintenance therapy. There was weak evidence of benefit for post-consolidation chemotherapy (placebo group) without alloHCT.[3] • Post hoc subgroup analyses of mOS by age showed benefit in patients < 60 y and did not support efficacy of quizartinib in patients ≥ 60 yo; however, these results are inconclusive.
	Comments	*Midostaurin Considerations* • During the QuANTUM-First trial, midostaurin (the first FLT3 inhibitor approved for AML) became available in the US but was not available at the start of study enrollment and had limited access in the non-US study regions, from which most (93.7%) of the study patients enrolled. In consultation with experts, the manufacturer decided not to modify the protocol to change placebo to midostaurin since doing so would have delayed results for a life-threatening condition in urgent need of treatment options.[3] • The QuANTUM-First population was older and potentially higher-risk than the study population of the midostaurin RATIFY trial, although the methods used for risk categorization differed. RATIFY showed a mOS of 74.7 months (31.5, NR) with midostaurin vs 25.6 months (18.6, 42.9) with placebo (difference, 49.1 months) in patients with FLT3-TDK or -ITD AML with age 18–60 y and modified European LeukemiaNet (ELN) risk of mostly normal (68.6%) or intermediate II (19%). In RATIFY, the HR for risk of death analyzed by FLT3-ITD subgroup was 0.80 (0.57, 1.12) or 0.81 (0.60, 1.11) with high (> 0.7; n = 214) or low (0.05–0.7; n = 341) ratio of mutant to wild-type alleles, respectively. For a subgroup in QuANTUM-First with mutation and age characteristics similar to those of the subgroup in RATIFY (i.e., FLT3-ITD, < 60 yo), the HR was 0.68 (0.49, 0.95). *Limitations:* Lack of re-randomization at the start of the QuANTUM-First maintenance phase (not designed to assess effects of maintenance therapy).
	Other Trials of Interest	*QuANTUM-R.* Quizartinib (30-mg QD lead-in then 60 mg QD) showed an overall survival benefit over salvage chemotherapy in 367 patients with relapsed or refractory FLT3-ITD AML after a median follow-up of 23.5 months: mOS 6.2 mo (5.3, 7.2) vs 4.7 (4.0, 5.5), respectively; HR 0.76 (0.58, 0.98).[4] Three percent of patients had received midostaurin or sorafenib. Quizartinib was approved in Japan in 2019 for relapsed or refractory FLT3-ITD AML. *Q-SOC.* A phase 3 RCT comparing chemotherapy plus quizartinib vs physician's choice in newly diagnosed FLT3-ITD AML was withdrawn because the study was no longer feasible.[5]
	Evidence Gaps	Comparative efficacy and resistance development of quizartinib vs midostaurin in combination with chemotherapy

SAFETY CONSIDERATIONS	**Boxed Warnings**	QT prolongation, torsades de pointes, and cardiac arrest. Monitor for and correct hypokalemia and hypomagnesemia. Perform ECGs at baseline, weekly during induction and consolidation therapy, weekly for at least the first month of maintenance, and periodically thereafter.
	Contraindications	Severe hypokalemia, severe hypomagnesemia, LQTS, history of ventricular arrhythmias or torsade de pointes *PBM Note: The FDA defined "severe" hypokalemia as < 3 mmol/L.[3] This cutoff is categorized as a grade 3 AE according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. The FDA did not define "severe" hypomagnesemia; however, grade 3 hypomagnesemia is defined as < 0.4 mmol/L.*
	Other Warnings	VANFLYTA REMS, embryofetal toxicity
	Grade ≥ 3 AEs	92% vs 90% for quizartinib vs placebo, respectively.
	Top 5 SAEs	Febrile neutropenia (11% vs 8%, respectively), pneumonia, septic shock, sepsis, pyrexia Fatal AEs (10%) included sepsis, fungal infections, brain edema
	Top DAE	Sepsis (5%). Discontinuations due to AEs occurred in 20% vs 9%, respectively.
	Top 5 AEs	Febrile neutropenia, diarrhea, mucositis, nausea, sepsis
	QTc Prolongation	*Experience in Clinical Trials.* QTc prolongation occurred in 14% of quizartinib patients (3% Grade 3–4). Cardiac arrest occurred in 2 (0.8%) of 265 quizartinib patients in the first phase of treatment in QuANTUM-First. Of

	1,081 AML clinical trial patients in the drug development program, 0.2% developed torsade de pointes, 0.6% suffered cardiac arrest (0.4% fatal), and 0.1% developed ventricular fibrillation.[3] In the two cases of cardiac arrest that occurred during induction, the events occurred in the context of personal history of LQTS (1 case), severe hypokalemia (serum potassium 2.4 and 2.6 mmol/L) and concomitant QTc prolonging drugs. A third cardiac arrest occurred in the context of higher dose (135 mg) and concomitant strong CYP3A inhibitor. *Unique Mechanism of QT Prolongation May Increase Risk of Cardiac Arrest.* Quizartinib-associated QT/QTc prolongation occurs in a dose- and concentration-dependent manner and occurs mainly by a unique mechanism — inhibition of the slowly activating delayed rectifier potassium current (I_{Ks} inhibition). The FDA concluded that the unique mechanism of QT prolongation increases the risk of cardiac arrest relative to drugs that prolong QT by the most common mechanism, inhibition of the rapidly activating delayed rectifier potassium current (I_{Kr} inhibition).
Drug Interactions	*Strong CYP3A InHIBitors.* Reduce dosage of quizartinib. *Strong or Moderate CYP3A InDUCers.* Avoid co-use. *QT Interval Prolonging Drugs.* Monitor patients more frequently with ECG.
Pregnancy	Can cause embryofetal harm. Advise patients who can become pregnant of the potential risk to a fetus.
Lactation	Avoid breastfeeding during treatment and for one month after the last dose.
Evidence Gaps	Comparative safety of quizartinib vs midostaurin in combination with standard chemotherapy

	DRUG	VANF	CFU	FDA	NCCN AML GUIDELINES (v6.2023)[6]
PLACE IN THERAPY	**Quizartinib** *(Type 2 FLT3 selective inhibitor)*	TBD	TBD	1st-line in combination with standard cytarabine and anthracycline **induction** and cytarabine **consolidation** and as **maintenance** monotherapy after chemotherapy consolidation for newly diagnosed FLT3-ITD–positive AML. *Not indicated for post-alloHCT maintenance monotherapy*.	*AML with FLT3-ITD mutation*. Quizartinib is recommended in combination regimens used for **intensive induction** (category 1), reinduction after standard-dose cytarabine, and **consolidation** (age < 60 or ≥ 60 years). *Post alloHCT, in remission, and history of FLT3-ITD.* **Maintenance** monotherapy (category 2B). *Previously received quizartinib, no alloHCT is planned, and history of FLT3-ITD.* **Maintenance** monotherapy (category 2A).
	Midostaurin *(Type 1 FLT3 multikinase inhibitor)*	PA-F	1st-line in newly diagnosed FLT3 mutation-positive AML and eligible for standard induction and consolidation chemotherapy	1st-line in combination with standard cytarabine and daunorubicin **induction** and cytarabine **consolidation** chemotherapy for newly diagnosed FLT3 mutation-positive AML. *PBM Note: Unlike quizartinib, midostaurin is not approved for maintenance therapy.*	*AML with FLT3-ITD or FLT3-TKD mutation*. Midostaurin is recommended in combination regimens used for **intensive induction** (category 1), reinduction after standard-dose cytarabine, and **consolidation** (age < 60 or ≥ 60 years). *Post alloHCT, in remission, and history of FLT3-ITD or -TKD AML*. **Maintenance** monotherapy (category 2B; off-label).
	Gilteritinib *(Type 1 FLT3 selective inhibitor)*	PA-F	1st-line for relapsed or refractory AML with FLT3 mutation (ITD or TKD)	Relapsed or refractory AML with FLT3 mutation	*AML with FLT3 mutation, intensive induction ineligible.* Gilteritinib + azacitidine (category 2B) is Useful in Certain Circumstances for **lower intensity induction** therapy. *Post alloHCT with history of FLT3-ITD AML*. **Maintenance** monotherapy (category 2B).
	Sorafenib *(Type 2 FLT3 multikinase inhibitor)*	PA-F	No CFU for AML	Off-label for AML	*AML with FLT3 mutation, intensive induction ineligible:* Sorafenib is an Other Recommended Option ± azacitidine or decitabine for **lower intensity induction** therapy. *Post alloHCT, in remission, and history of FLT3-ITD AML*. **Maintenance** monotherapy.

VHA PLACE IN THERAPY	**Potential Use in VHA**	1. Treatment of patients with newly diagnosed FLT3-ITD–positive AML who have an absolute contraindication to midostaurin, in combination with standard chemotherapy for induction and consolidation and as maintenance monotherapy following chemotherapy consolidation without alloHCT.

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