# Quizartinib (Vanflyta®) in combination with standard cytarabine and anthracycline induction and cytarabine consolidation chemotherapy, followed by single-agent maintenance therapy for patients with newly diagnosed acute myeloid leukaemia (AML)

## General information [1]

### Drug description

The active substance of Vanflyta® is quizartinib, a protein kinase inhibitor. Quizartinib, together with its major metabolite AC886, inhibits the receptor tyrosine kinase FLT3 by preventing autophosphorylation of the receptor, thereby inhibiting further downstream FLT3 receptor signalling and blocking FLT3-ITD-dependent cell proliferation.

### Indication

Quizartinib (Vanflyta®) is indicated in combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy, followed by Vanflyta® single-agent maintenance therapy for adult patients with newly diagnosed AML that is FLT3-ITD positive.

## Incidence [2]

The incidence of AML is approximately 3.7 cases per 100,000 population per year and increases with age with age-specific incidences exceeding 100 cases per 100,000 population in patients older than 70 years.

## Current treatment [2]

❖ For the treatment of patients with FLT3 mutation, Onkopedia recommends the following:

- Patients with FLT3-ITD or FLT3-TKD mutation should receive midostaurin from day 8-21 of induction therapy.
- According to data from a randomized placebo-controlled trial, midostaurin in combination with standard chemotherapy can significantly prolong both EFS, RFS, and OS in FLT3-mutated AML patients up to 60 years of age. Based on this study, midostaurin was approved by the EMA in 2017 for combination with standard induction chemotherapy, chemo consolidation, and as maintenance therapy for twelve 28-day cycles in patients with newly diagnosed FLT3-mutated AML.
- Deviating from the study population (age 18-59 years), approval was granted without an upper age restriction.
- Data for patients aged 60-70 years are available from a phase II study.
- In patients for whom HSCT planned, midostaurin should be discontinued 48 hours prior to conditioning therapy.
- When used concomitantly with strong inhibitors of CYP3A4 (e.g., ketoconazole, posaconazole, voriconazole, ritonavir, or clarithromycin), increased attention should be paid to toxicities, especially in patients aged >60 years, because of the risk of midostaurin level elevations.
- Strong CYP3A4 inducers (e.g., carbamazepine, rifampicin, enzalutamide, phenytoin, St. John's wort) should not be given concomitantly because of the decrease in levels of midostaurin.

## Regulatory status

### EMA

**Approval status for this indication**: On 14 September 2023, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Vanflyta®.

UPDATE: Marketing authorisation issued on 06/11/2023

<u>The full indication is:</u>

❖ Vanflyta® is indicated in combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy, followed by Vanflyta® single-agent maintenance therapy for adult patients with newly diagnosed AML that is FLT3-ITD positive.

Vanflyta is available as 17.7 mg and 26.5 mg film-coated tablets.

**Other indications**: none

✓ **Medicine is under additional monitoring**

### FDA [3, 4]

**Approval status for this indication**: On 20 July 2023, the FDA approved quizartinib (Vanflyta®) with standard cytarabine and anthracycline induction and cytarabine consolidation, and as maintenance monotherapy following consolidation chemotherapy, for the treatment of adult patients with newly diagnosed AML that is FLT3 ITD-positive, as detected by an FDA-approved test.

✓ Priority review
✓ Fast track designation
✓ Orphan drug designation

Limitations of Use: Vanflyta® is not indicated as maintenance monotherapy following allogeneic HSCT; improvement in OS with Vanflyta® in this setting has not been demonstrated.

FDA also approved LeukoStrat CDx FLT3 Mutation Assay as a companion diagnostic for Vanflyta®.

**Other indications**: none

## Manufacturer

Vanflyta® is manufactured by Daiichi Sankyo Inc.

## Costs

Currently, there is no cost information available.

## Posology [5]

- Treatment with Vanflyta® should be initiated by a physician experienced in the use of anti-cancer therapies.
- Before taking Vanflyta®, AML patients must have confirmation of FLT3-ITD positive AML using a CE-marked in vitro diagnostic (IVD) medical device with the corresponding intended purpose. If a CE-marked IVD is not available, confirmation of FLT3-ITD positive AML should be assessed by an alternate validated test.
- ECGs should be performed, and electrolyte abnormalities should be corrected prior to initiation of treatment.
- Vanflyta® should be administered in combination with standard chemotherapy at a dose of 35.4 mg (2 × 17.7 mg) once daily for two weeks in each cycle of induction. For patients who achieve CR or CRi, Vanflyta® should be administered at 35.4 mg once daily for two weeks in each cycle of consolidation chemotherapy followed by Vanflyta® single-agent maintenance therapy initiated at 26.5 mg once daily. After two weeks the maintenance dose should be increased to 53 mg (2 × 26.5 mg) once daily if the QT interval corrected by Fridericia's formula (QTcF) is ≤ 450 ms. Single-agent maintenance therapy may be continued for up to 36 cycles.

## Warnings and precautions [3, 5]

- **Vanflyta® prolongs the QT interval**
  - Prior to Vanflyta® administration and periodically, perform electrocardiograms (ECGs), monitor for hypokalaemia or hypomagnesemia, and correct deficiencies.
- **Torsades de pointes and cardiac arrest** have occurred in patients receiving Vanflyta®.
  - Do not administer Vanflyta® to patients with severe hypokalaemia, severe hypomagnesemia, or long QT syndrome.
- Do not initiate treatment with Vanflyta® or escalate the Vanflyta® dose if the QT interval corrected by Fridericia's formula (QTcF) is greater than 450 ms.
- Monitor ECGs more frequently if concomitant use of drugs known to prolong the QT interval is required.
- Reduce the Vanflyta® dose when used concomitantly with strong CYP3A inhibitors, as they may increase quizartinib exposure.
- **QT prolongation, torsades de pointes, and cardiac arrest**
  - Monitor electrocardiograms and levels of serum electrolytes.
  - Reduce, interrupt, or permanently discontinue Vanflyta® as appropriate.
- **Infections in elderly patients**
  - Fatal infections have occurred more frequently with quizartinib in elderly patients (i.e., older than 65 years), compared to younger patients especially in the early treatment period. Patients older than 65 years of age should be closely monitored for the occurrence of severe infections during induction.
- **Embryo-foetal toxicity**
  - Vanflyta® can cause foetal harm.
  - Advise females of reproductive potential and males with female partners of reproductive potential of potential risk to a foetus and to use effective contraception.
- In the U.S., Vanflyta® is available only through a restricted program called the Vanflyta® Risk Evaluation and Mitigation Strategy **(REMS)**.
- Patient card
  - The prescriber must discuss the risks of Vanflyta® therapy with the patient. The patient will be provided with the patient card with each prescription (included in the medicinal product pack).

## Study characteristics [6-8]

| Trial name | *n* | Intervention (I) | Comparator (C) | PE | Median follow-up | Characteristics | Biomarker | Funding | Publication(s) |
|---|---|---|---|---|---|---|---|---|---|
| QuANTUM-First NCT02668653 | 539 (1:1) | Induction therapy[1] + quizartinib 40 mg or placebo | Induction therapy + quizartinib 40 mg or placebo | OS in the ITT population | 39.2 months in both groups | randomised, double-blind, placebo-controlled, | FLT3-ITD | Daiichi Sankyo | QuANTUM-First trial [7] |

[1] During the first induction cycle, all patients received a standard 7 + 3 induction regimen with cytarabine 100 mg/m² per day (200 mg/m² per day allowed if institutional or local standard) by continuous intravenous infusion from day 1 to day 7 and anthracycline (daunorubicin 60 mg/m² per day or idarubicin 12 mg/m² per day) by intravenous infusion on days 1, 2, and 3. Patients were randomly assigned on day 7 to receive quizartinib or placebo. Patients with complete remission or complete remission with incomplete neutrophil or platelet recovery received standard consolidation with high-dose cytarabine plus quizartinib (40 mg per day orally) or placebo, allogeneic haematopoietic cell transplantation (allo-HCT), or both as consolidation therapy, followed by continuation of single-agent quizartinib or placebo for up to 3 years.

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| | | orally once per day for 14 days | orally once per day for 14 days | | | global phase 3 study | | | |

| Inclusion criteria[2] | Exclusion criteria | Patient characteristics at baseline (I vs. C) |
|---|---|---|
| **Inclusion Criteria – Randomization**<br>❖ ≥18 years of age or the minimum legal adult age and ≤75 years of age (at screening).<br>❖ Newly diagnosed, morphologically documented primary AML or AML secondary to myelodysplastic syndrome or a myeloproliferative neoplasm, based on the WHO 2008 classification (at screening).<br>❖ ECOG PS 0-2<br>❖ Presence of fms related receptor tyrosine kinase 3–internal tandem duplication (FLT3-ITD)–activating mutation in bone marrow (allelic frequency of ≥3% FLT3-ITD/total FLT3).<br>❖ Receipt of standard 7+3 induction chemotherapy regimen as specified in the protocol.<br>❖ Adequate renal function defined as creatinine clearance >50 mL/min, as calculated with the modified Cockcroft-Gault equation.<br>❖ Adequate hepatic function defined as:<br>• Total serum bilirubin ≤1·5 × upper limit of normal (ULN) unless the patient had documented Gilbert's syndrome or the increase was related to increased unconjugated (indirect) bilirubin due to haemolysis<br>• Serum alkaline phosphatase, aspartate transaminase, and alanine transaminase ≤2·5 × ULN.<br>❖ Serum electrolytes within the institution's normal limits: potassium, calcium (total calcium, calcium corrected for serum albumin in case of hypoalbuminemia, or ionized calcium), and magnesium. If outside of the institution's normal range, patient was eligible when electrolytes were corrected.<br>❖ If a woman of childbearing potential, must have had a negative serum pregnancy test upon entry into this study and must have been willing to use highly effective birth control upon enrolment, during the treatment period, and for 6 months following the last dose of investigational drug or cytarabine, whichever was later. If male, must have been surgically sterile or willing to use highly effective birth control upon enrolment, during the treatment period, and for 6 months following the last dose of investigational drug or cytarabine, whichever was later.<br>**Inclusion Criteria – Consolidation Phase**<br>❖ In order to enter in the consolidation phase and receive consolidation therapy, patients must have achieved complete remission (CR) or CR with incomplete neutrophil or platelet recovery (CRi), based on local | **Exclusion Criteria**<br>❖ Diagnosis of APL, French-American-British classification M3 or WHO classification of APL with translocation, t(15;17)(q22;q12), or BCR::ABL-positive leukaemia; patients who underwent diagnostic workup for APL and treatment with all-trans-retinoic acid (ATRA), but who were found not to have APL, were eligible (treatment with ATRA must have been discontinued before starting induction chemotherapy).<br>❖ Diagnosis of AML secondary to prior chemotherapy or radiotherapy for other neoplasms.<br>❖ Prior treatment for AML, except for the following allowances: Leukapheresis, treatment for hyperleukocytosis with hydroxyurea, cranial radiotherapy for central nervous system (CNS) leukostasis, prophylactic intrathecal chemotherapy, growth factor/cytokine support.<br>❖ Prior treatment with quizartinib or other FLT3-ITD inhibitors.<br>❖ Prior treatment with any investigational drug or device within 30 days before randomization (within 2 weeks for investigational or approved immunotherapy) or concurrent participation in other investigational procedures.<br>❖ History of known CNS leukaemia, including cerebrospinal fluid positive for AML blasts; lumbar puncture was recommended for patients with symptoms of CNS leukaemia to rule out extramedullary CNS involvement.<br>❖ History of other malignancies, except adequately treated nonmelanoma skin cancer, curatively treated in situ disease, or other solid tumours curatively treated with no evidence of disease for at least 2 years.<br>❖ Uncontrolled or significant cardiovascular disease, including any of the following:<br>• Bradycardia of <50 beats per minute, unless the patient had a pacemaker; QTcF interval >450 ms<br>• Diagnosis of or suspicion of long QT syndrome (including family history of long QT syndrome)<br>• Systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥110 mm Hg<br>• History of clinically relevant ventricular arrhythmias (e.g., ventricular tachycardia, ventricular fibrillation, or torsade de pointes) | ❖ Median age: 56.0 (range 23-75) vs. 56.0 years (range, 20-75)<br>❖ Age ≥60 years: 40% vs. 40%<br>❖ Male sex: 46% vs. 45%<br>❖ ECOG PS:<br>• 0: 32% vs. 36%<br>• 1: 50% vs. 50%<br>• 2: 18% vs. 13%<br>❖ AML type<br>• De novo AML: 91% vs. 94%<br>• Secondary AML: 9% vs. 6%<br>❖ Cytogenetic risks:<br>• Favourable: 5% vs. 7%<br>• Intermediate: 74% vs. 71%<br>• Unfavourable: 7% vs. 10%<br>• Unknown: 14% vs. 11%<br>• Missing: 0 vs. <1%<br>❖ Mutated NPM: 53% vs. 52%<br>❖ Mutated CEBPA: 23% vs. 24%<br>❖ VAF:<br>• ≥3% to ≤25%: 35% vs. 36%<br>• >25% to ≤50%: 53% vs. 51%<br>• >50%: 11% vs. 13%<br>❖ WBC count at diagnosis of AML:<br>• <40 × 109/L: 50% vs. 51%<br>• ≥40 × 109/L: 50% vs. 49% |

[2] For detailed in- and exclusion criteria, please see Supplementary Appendix.

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| laboratory results, at the end of the induction phase, and must have been able to begin consolidation phase within 60 days of day 1 of the last induction cycle.<br>**Inclusion Criteria – Continuation Phase**<br>❖ Patients must have satisfied all of the following criteria to start the continuation phase and receive continuation therapy:<br>• No active acute or grade ≥3 graft-versus-host disease (GVHD)<br>• No initiation of therapy for active GVHD (prophylaxis was allowed) within 21 days<br>• Confirmed <5% of blasts based on the most recent bone marrow aspirate, based on the local laboratory results, performed within 28 days before cycle 1 day 1 of continuation therapy<br>• Absolute neutrophil count (ANC) >500/mm3 and platelet count >50,000/mm3 without platelet transfusion support within 24 hours before cycle 1 day 1 of continuation therapy<br>• Able to have begun continuation phase within 60 days of day 1 of the last consolidation cycle received or within 180 days after allogeneic hematopoietic cell transplantation. | • History of second (Mobitz II) or third-degree heart block (patients with pacemakers were eligible if they had no history of fainting or clinically relevant arrhythmias while using the pacemaker)<br>• History of uncontrolled angina pectoris or myocardial infarction within 6 months before screening<br>• History of New York Heart Association class 3 or 4 heart failure<br>• Left ventricular ejection fraction ≤45% or less than the institutional lower limit of normal per multigated acquisition scan or echocardiogram done within 30 days before randomization.<br>• Complete left bundle branch block.<br>❖ Active acute or chronic systemic fungal, bacterial, or viral infection not well controlled by antifungal, antibacterial, or antiviral therapy.<br>❖ Known active clinically relevant liver disease (e.g., active hepatitis B or active hepatitis C).<br>❖ Known history of human immunodeficiency virus (HIV). Patients should have been tested for HIV before randomization if required by local regulations or EC.<br>❖ History of hypersensitivity to any excipients in the quizartinib/placebo tablets.<br>❖ Women who were pregnant or breastfeeding<br>❖ Otherwise considered inappropriate for the study by the investigator. | |

| **Efficacy** (I vs. C) | **Safety** (I vs. C) |
|---|---|
| **Data cutoff (13 August 2021); median follow-up: 39.2 months**<br>**Median OS:** 31.9 months (95% CI 21.0–NE) vs. 15.1 months (13.2–26.2); HR for death 0.78 (95% CI 0.62–0.98); p=0.032<br>**OS sensitivity analysis** that censored patients who received allo-HCT at any time: HR 0.75 (95% CI, 0.56–1.01)<br>OS in a post-hoc subgroup analysis by age: HR 0.68 (95% CI, 0.49–0.95) in patients younger than 60 years; HR 0.91 (95% CI, 0.66–1.26) in patients aged ≥60 years.<br>**Event-free survival**[3]**:** HR 0.92 (95% CI 0.75–1.11); p=0.24<br>**EFS with the original protocol definition** of lack of induction treatment success as not having composite CR by the end of induction up to day 56 (0.73, 0.59–0.90, p-nominal=0.0031; or lack of induction treatment success as not having CR by the end of induction up to day 56 (0.82, 0.67–1.00, p-nominal=0.032)<br>**CR**: 54.9 (95% CI, 48.7-60.9) vs. 55.4 % (95% CI, 49.2-61.4)<br>**CRi:** 16.8% (95% CI, 12.5-21.8) vs. 9.6% (95% CI, 6.4–13.7)<br>**CRc (CR+CRi):** 71.6% (95% CI, 65.8-77.0) vs. 64.9% (95% CI, 58.9-70.6)<br>**CR with FLT3-ITD MRD negativity**: 20.1 % (95% CI, 15.5-25.5) vs. 18.8% (95% CI, 14.3-24.0)<br>**CR with FLT3-ITD MRD negativity:** 10.8 % (95% CI, 7.4-15.2) vs. 7.0% (95% CI, 4.3-10.7)<br>**CRc with FLT3-ITD MRD negativity**: 24.6 % (95% CI, 19.6-30.2) vs. 21.4% (95% CI,16.7-26.8)<br>**CRc with FLT3-ITD MRD negativity**: 13.8% (95% CI, 9.9-18.5) vs. 7.4% (4.6-11.2)<br>**Median duration of CR**: 38.6 months (95% CI 21.9–NE) vs. 12.4 months (95% CI, 8.8–22.7); HR 0.62 (95% CI, 0.45–0.86) | **AEs:** n=264/265 (100%) vs. n=265/268 (99%)<br>**Drug-related AEs**: n=160/265 (60%) vs. n=97/268 (36%)<br>**Grade ≥3 AEs (including grade 5):** n=244/265 (92%) vs. n=240/268 (90%)<br>**Drug-related grade ≥3 AEs (including grade 5):** n=118/265 (45%) vs. n=65/268 (24%)<br>**AEs associated with fatal outcome**: n=30/265 (11%) vs. n=26/268 (10%)<br>**Grade 5 infections and infestations**: n=20/265 (8%) vs. n=12/268 (4%)<br>**Drug-related AEs associated with fatal outcome**: n=4/265 (2%) vs. n=4/268 (1%)<br>**Serious AEs**: n=143/265 (54%) vs. n=123/268 (46%)<br>**Drug-related serious AEs:** n=41/265 (15%) vs. n=29/268 (11%)<br>**AEs associated with discontinuation**: n=54/265 (20%) vs. n=23/268 (9%) |

[3] Based on the definition of lack of induction treatment success as not having complete remission within 42 days from the start of the last induction cycle.

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| **Relapse-free survival in patients with CR during induction**: HR 0.61 (95% CI, 0.44–0.85)<br>**Median relapse-free survival**: 39.3 months (22.6–NE) vs. 13.6 months (9.7–23.7)<br>**Reduced cumulative incidences of relapse in patients with CR**: 18.7% (95% CI, 12.7–25.6) vs. 34.9% (95% CI, 27.1–42.7) at 12 months and 31.2% (95% CI, 23.5–39.2) vs. 43.3% (95% CI, 34.9–51.3) at 24 months | **Deaths within 30 days of study drug initiation**: n=15/254 (6%) vs. n=9/268 (3%)<br>**Deaths within 60 days of study drug initiation**: n=20/265 (8%) vs. n=13/268 (5%) |

## Patient-reported outcomes

According to the study protocol, subject reported QoL and symptoms as assessed with the EORTC QLQ-C30 Questionnaire and general health status assessed using EuroQol (EQ-5D-5L) Questionnaire were defined as exploratory efficacy endpoints. Currently, results are not available.

## ESMO-MCBS of Haematological Malignancies version 1.0 [9]

| Scale | Int. | Form | MG ST | MG | HR (95% CI) | Score calculation | PM | Toxicity | QoL | AJ | FM |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Original | NC | 2a | ≥12 - <24 months | OS: +16.8 months | 0.78 (0.62-0.98) | HR ≤ 0.70 AND gain ≥5 months | 4 | - | - | - | 4 |

## Risk of bias (RCT) [10]

| Adequate generation of randomisation sequence | Adequate allocation concealment | Blinding | Selective outcome reporting unlikely | Other aspects which increase the risk of bias | **Risk of bias** |
|---|---|---|---|---|---|
| yes<br>low risk | yes<br>low risk | yes<br>low risk | yes<br>low risk | yes[4]<br>high risk | **High risk** |

## Ongoing trials [11]

| NCT number/trial name | Description | Estimated study completion date |
|---|---|---|
| NCT04047641 | A combination of cladribine, idarubicin, cytarabine and quizartinib for the treatment of patients with newly diagnosed or relapsed/refractory AML and high-risk MDS. | 12/2023 |
| NCT04128748 | A phase I/II study of liposomal cytarabine and daunorubicin (CPX-351) in combination with quizartinib in patients with AML and high risk MDS. | 12/2023 |
| NCT04107727 | A randomized phase II trial to compare the efficacy and safety of standard chemotherapy plus quizartinib vs. standard chemotherapy plus placebo in adult patients with newly diagnosed $FLT_3$ wild-type AML. | 09/2024 |
| NCT04687761 | A phase I-II, multicentre, open-label clinical trial to assess the safety and tolerability of the combination of low-dose cytarabine or azacitidine, plus venetoclax and quizartinib in newly diagnosed AML patients aged ≥60 years ineligible for standard induction chemotherapy. | 11/2024 |

## Available assessments

- NIHR published the Health Technology Briefing "Quizartinib with chemotherapy for $FLT_3$-ITD positive acute myeloid leukaemia" in November 2021 [12].
- According to NICE, the appraisal "Quizartinib for induction, consolidation and maintenance treatment of newly diagnosed $FLT_3$-ITD-positive acute myeloid leukaemia ID4042" is currently in progress [13].
- No assessments were identified via CADTH, ICER and G-BA.

## Other aspects and conclusions

- In September 2023, the **CHMP adopted a positive opinion**, recommending the granting of a marketing authorisation for Vanflyta®, indicated in combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy, followed by Vanflyta® single-agent maintenance therapy for adult patients with newly diagnosed AML that is $FLT_3$-ITD positive. Marketing authorisation was issued on 06 November 2023. This indication was also **approved by the FDA** in July 2023.
- **QuANTUM-First** (NCT02668653) is a randomised, double-blind, placebo-controlled, global **phase 3 study**, assessing the effect of quizartinib versus placebo on OS in patients with $FLT_3$-ITD-positive newly diagnosed AML. Patients aged 18–75 years with primary newly diagnosed AML, or AML secondary to MDS or a myeloproliferative neoplasm, with an $FLT_3$-ITD mutation and able to receive standard induction chemotherapy were eligible. Patients had to have a variant allelic frequency of 3% or more, an ECOG PS of 0–2 and adequate cardiac, renal, and hepatic function at randomisation. Patients diagnosed with APL with t(15;17), BCR-ABL1-positive leukaemia, or AML secondary to previous chemotherapy or radiotherapy were excluded.
- The **primary endpoint** of QuANTUM-First was **OS.** At a median follow-up of 39.2 months in both groups, median OS was 31.9 months (95% CI 21.0–NE) vs. 15.1 months (95% CI, 13.2–26.2); HR was 0.78 (95% CI 0.62–0.98); p=0.032
- Although defined as exploratory efficacy endpoint; **patient-reported outcomes are currently not available**.
- The **ESMO-MCBS for Hamatological Malignancies** was applied, resulting a final adjusted magnitude of clinical benefit **grade 4**.

[4] The sponsor and the study steering committee designed the study. Data were collected by the investigators and monitored by the sponsor. The sponsor and all authors were responsible for data analysis and interpretation.

- The **risk of bias was considered high**, based on the sponsor´s contribution to study design, data collection, - analysis and – interpretation.
- There was **no ongoing phase 3** trial identified; however, 4 phase 1-2 trials, evaluating the role of quizartinib for the treatment of patients with newly diagnosed AML, were identified.
- In conclusion, the efficacy and safety results of the QuANTUM-First trial need to be substantiated by positive patient-reported outcomes and further phase 3 data.

**First published:** 10/2023
**Last updated**: 01/2024

Abbreviations: AE=adverse event, AJ=adjustment, AML=acute myeloid leukaemia, ANC= absolute neutrophil count, APL=acute promyelocytic leukaemia, ATRA=all-trans-retinoic acid, C=comparator, CADTH=Canada´s Drug and Health Technology Agency, CEBPA=CCAAT/enhancer binding protein alpha, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CNS=central nervous system, CR=complete response, CRi = complete remission with incomplete blood count recovery, ECG=electrocardiogram, EFS=event-free survival, EMA=European Medicines Agency, EORTC-QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire, EQ-5D-5L= EuroQol Group 5-Dimension 5-Level questionnaire, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, G-BA=Gemeinsamer Bundesausschuss, GVHD= Graft-versus-host disease, HR=hazard ratio, HSCT= hematopoietic stem cell transplantation, I=intervention, ICER=Institute for Clinical and Economic Review, ITD=internal tandem duplication, Int.=intention, MDS=Myelodysplastic Syndrome, MG=median gain, MRD= minimal residual disease, n=number of patients, NE=not estimable, NICE=National Institute for Health Care Excellence, NPM1=nucleophosmin 1, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, RFS=recurrence-free survival, SAE=serious adverse event, ST=standard treatment, TKD=tyrosine kinase domain, ULN=upper limit of normal, VAF=variant allelic frequency, WBC=white blood cell, WHO=World Health Organization

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