Midostaurin in de behandeling van *FLT3* gemuteerde AML eligible voor intensieve chemotherapie

In AML patienten met een *FLT3* mutatie (ITD of TKD) die eligible zijn voor intensieve chemotherapie wordt de multi-kinase remmer midostaurin (Rydapt) toegevoegd aan de behandeling.

Midostaurin wordt conform de EMA registratie gegeven:

- Direct aansluitend op de twee remissie-inductiekuren, onafhankelijk van leeftijd): dag 8 t/m 21 van kuur 1 en kuur 2: Dosering 50 mg 2dd

- Direct aansluitend op de mitoxantrone/etoposide consolidatie kuur (indien gegeven): dag 8 t/m 21: Dosering 50 mg 2dd

- als onderhoudsbehandeling na consolidatie middels een derde kuur of autologe stamceltransplantatie. Midostaurin in de onderhoudsfase kan gestart worden na hematologisch herstel (ANC ≥ 1×10^9/L en thrombo ≥ 50 × 109/L en niet eerder dan 30 dagen na autologe stamceltransplantatie. Dosering 50 mg 2 dd, gedurende 1 jaar.

<u>Opmerkingen ten aanzien van bijwerkingen en aandachtspunten bij toediening:</u>

- In de RATIFY studie werden geen additionele graad ≥ 3 adverse events gezien met midostaurin in vergelijking met placebo, met uitzondering van huidafwijkingen (rash/desquamatie; 14 vs 8%)

- Andere vermeldenswaardige (zeldzame) bijwerkingen zijn QT verlenging en longtoxiciteit (interstitiele beelden). Een vollediger lijst van bijwerkingen kan gevonden worden in het ‘farmacotherapeutisch kompas’.

- Aanwijzingen voor toediening: In het centrum in Europa waar de meeste ervaring is met het geven van midostaurin in de geregistreerde setting (Ulm) worden geen standaard ECG bepalingen of spiegelbepalingen verricht.

- Er zijn evenwel een aantal aandachtspunten voor het gelijktijdig gebruik van middelen met mogelijke interactie. Aangezien er op dit moment geen ervaring is met het toedienen van midostaurin bij AML in het ErasmusMC is het voorstel de volgende aanbevelingen (ten aanzien het gelijktijdig gebruik van co-medicatie) in acht te nemen (de tekst is in het Engels omdat een dergelijke paragraaf opgenomen zal worden in het nieuw HOVON-AML-FLT3 protocol). Samengevat:

1. Midostaurin mag niet gecombineerd worden met paracetamol. Remming van de glucuronisatie van paracetamol kan in zeldzame gevallen leiden tot leverfalen.

2. Indien midostaurin gecombineerd wordt met sterke CYP3A4 remmers (zie tabel) dan dient een ECG gemaakt te worden voor start van de co-medicatie en op dag 5. Dosisreductie van midostaurin kan plaatsvinden op geleide van de QT tijd.

3. Midostaurin mag niet gecombineerd worden met sterke CYP3A4 inductoren (zie tabel) omdat dit de Midostaurin expositie verlaagd.

Appendix 1: Midostaurin. Concomitant treatment.

Prohibited Medications During Therapy with Midostaurin

Paracetamol (per oral and i.v. administration)

The **co-administration of paracetamol together with the tyrosine kinase inhibitor midostaurin is prohibited** due to rare cases of tyrosine kinase inhibitor-induced inhibition of paracetamol glucuronidation. This may lead to severe and fatal liver toxicity.

Interactions with strong inhibitors of Cytochrome P450-3A4

Coadministration of strong CYP3A4 inhibitors with midostaurin have the potential to increase exposure of midostaurin, albeit with limited clinical relevance. Treatment with strong CYP450 3A4 inhibitors should be generally avoided and alternative therapeutics which do not strongly inhibit CYP450 3A4 activity should be considered. Grapefruit juice should not be ingested during study treatment. In situations where satisfactory therapeutic alternatives do not exist (for example, if treatment with antibiotics, antifungals (azoles) or antivirals is required that are used as standard of care to prevent or treat infections), monitor patients closely for toxicity. A list of strong CYP3A4 inhibitors can be found in appendix 2.

In case of comedication with strong CYP3A4 inhibitors ECGs have to be performed before start of comedication as well as on day 5; In case of QTcF interval increase, dose of midostaurin should be adapted according to appendix 3.

Interactions with strong inducers of Cytochrome P450 3A4

Coadministration with potent CYP450 3A4 inducers may reduce exposure to midostaurin. To avoid sub-therapeutic exposure to midostaurin, **potent CYP450 3A4 inducers should not be co-administered**. A list of strong CYP3A4 inducers can be found in appendix 2.

Appendix 2. List of Cautionary Concomitant Medications with Midostaurin

The following list describes medications and foods that are common strong inhibitors of CYP3A. This list should not be considered all inclusive. Consult individual drug labels for specific information on a compound's propensity to inhibit CYP3A.

Strong CYP3A Inhibitors

Drug Type	**Generic Drug Name**
Human Immunodeficiency Virus Protease Inhibitors	Indinavir, Nelfinavir, Lopinavir, Ritonavir, Saquinavir, Tipranavir
Food/Juice	Grapefruit juice
Antifungal agents	Itraconazole, Ketoconazole, Posaconazole, Voriconazole
Others	Boceprevir, Telaprevir Clarithromycin, Telithromycin, Troleandomycin Cobicistat, Nefazodone

CYP: cytochrome P450.

Treatment with concomitant drugs that are strong inducers of CYP3A are prohibited. The following list describes medications and foods that are common strong inducers of CYP3A. This list should not be considered all inclusive. Consult individual drug labels for specific information on a compound's propensity to induce CYP3A.

Strong CYP3A Inducers

Drug Type	**Generic Drug Name**
Antiepileptic, Anticonvulsant	Carbamazepine, Phenytoin
Antibiotic	Rifampicin, Rifabutin
Food/Juice Supplement	St. John's Wort
Others	Avasimibe, Mitotane, Phenobarbital

CYP: cytochrome P450.

Appendix 3a. Dose adjustments Midostaurin during remission induction and consolidation cycles

Criteria for Midostaurin dose reduction/interruption and re-initiation of Midostaurin for adverse drug reactions during remission induction and consolidation cycles. . Non-hematological toxicity of midostaurin may include prolongation of the QTcF interval.

Hematological toxicities:	
Any hematological toxicity	No dose modifications are required for hematologic toxicity due to Midostaurin
Non-Hematological toxicities:	
Pulmonary toxicity	For ≥ grade 3 pulmonary infiltrate, interrupt midostaurin for the remainder of the cycle. Resume midostaurin at the same dose when infiltrate resolves to ≤ grade 1. Missed doses of midostaurin will not be made up.
Cardiac toxicity	For QTcF interval > 470 ms and ≤ 500 ms, check magnesium and potassium levels and correct any abnormalities. lf possible, stop any medications that may prolong the QTcF interval. Decrease Midostaurin to 50 mg once daily for the remainder of the cycle. Resume Midostaurin at the initial dose in the next cycle provided that QTcF interval improves to ≤ 470 ms at the start of that cycle. Otherwise continue Midostaurin 50mg once daily. For QTcF interval > 500 ms, check magnesium and potassium levels and correct any abnormalities. Hold or interrupt midostaurin for the remainder of the cycle, and, if possible, stop any medications that may prolong the OTcF interval. lf QTcF improves to ≤ 470 ms just prior to the next cycle, resume midostaurin at the initial dose. lf QTcF interval is not improved in time to start the next cycle, midostaurin may be held up to 28 days. lf there is no improvement after 28 days, midostaurin must be discontinued. Chemotherapy will be continued.
Other toxicities	Grade 1/2: No dose modifications for any grade 1 or 2 non-hematologic toxicity. Grade 3/4: lf a patient experiences other grade 3/4 non-hematologic toxicity considered at least possibly related to Midostaurin, Midostaurin will be interrupted until toxicity resolves to ≤ grade 1. If the toxicity resolves prior to day 21, then restart at same dose to complete current cycle. Missed doses of Midostaurin will not be made up. At recurrence of the same AE or appearance of a new AE grade 3 or greater probably or possibly due to Midostaurin, Midostaurin will be interrupted until resolution of the AE to grade ≤ 1. The patient may resume treatment at 50 mg once daily. At the third occurrence of a prior AE or appearance of a new AE grade 3 or

	greater, probably or possibly due to Midostaurin, Midostaurin must be discontinued. Chemotherapy will be continued.

Appendix 3b. Dose adjustments during Midostaurin maintenance

Criteria for Midostaurin dose reduction/interruption and re-initiation of Midostaurin for suspected adverse drug reactions.

Hematological toxicities:	
Any hematological toxicity	In the presence of CTC-grade 4 neutropenia or thrombocytopenia during post-consolidation therapy, midostaurin must be held until ANC ≥ 1.0 x 10^9/L and platelets ≥ 100 x 10^9/L. A relapse of AML needs to be considered as an alternative explanation of continuing neutropenia. Once ANC ≥ 1.0 x 10^9/L, then resume midostaurin at the previous dose. lf neutropenia and/or thrombocytopenia persists for more than 28 days, then discontinue Midostaurin therapy and patient goes off protocol.
Non-Hematological toxicities:	
Pulmonary toxicity	For ≥ grade 3 pulmonary infiltrate, interrupt midostaurin for the remainder of the cycle. Resume midostaurin at the same dose when infiltrate resolves to ≤ grade 1. Missed doses of Midostaurin will not be made up.
Cardiac toxicity	For QTcF interval > 470 ms and ≤ 500 ms, check magnesium and potassium levels and correct any abnormalities. If possible, stop any medications that may prolong the QTcF interval. Decrease midostaurin to 50mg once daily until QTcF interval improves to ≤ 470 ms, and then resume Midostaurin at previous dose. Otherwise continue Midostaurin at 50mg once daily. See section 10.2.1 for further information on QTcF assessment For QTcF interval > 500 ms, immediately stop midostaurin, check magnesium and potassium levels and correct any abnormalities. If possible, stop any medication, which may prolong the QTc interval. Once QTc interval improves to ≤ 470 ms, resume midostaurin at 50mg BID. lf QTcF interval remains > 470 ms (for more than three weeks), discontinue midostaurin until QTcF improves to < 470 ms, then resume midostaurin at 50mgBID. Missed doses of Midostaurin will not be made up. If treatment therapy interruption of midostaurin takes longer than 2 months, Midostaurin should be discontinued and patient will go off protocol treatment. The patient is followed up according the protocol. See section 10.2.1 for further information on QTcF assessment
Other toxicities	Grade 1/2: Persistent grade 1 or 2 toxicity during maintenance therapy that patients deem to be unacceptable may prompt a study drug interruption for as long as 28 days. A study drug interruption in excess of 28 days will require discontinuation of study treatment Grade 3/4: For grade 3/4 non-hematologic toxicities that are considered to be at least possibly related to midostaurin, interrupt midostaurin. Resume Midostaurin at the same dose when toxicity resolves to grade 2. lf Midostaurin is held tor more than 28 days, then discontinue Midostaurin maintenace and

	patient goes off protocol. At recurrence of the same AE or appearance of a new AE grade 3 or greater probably or possibly due to Midostaurin, Midostaurin will be interrupted until resolution of the AE to grade ≤ 2. The participant may resume treatment at 50 mg once daily. If the drug was reduced for an event that was later deemed unrelated, allow re-escalation to the original dose. At the third occurrence of a prior AE or appearance of a new AE grade 3 or greater at least possibly due to Midostaurin, Midostaurin must be discontinued and patient goes off protocol.