# New Chemotherapy and Antimicrobial Prophylaxis in Acute Myeloid Leukemia: Practical Tips

Alli Graner, PharmD, BCOP

Clinical Pharmacy Specialist, Hematology/Oncology

Nebraska Medicine

# Disclosures

No relevant financial disclosures

# Objectives

| | |
|---|---|
| Discuss | Discuss therapies for Acute Myeloid Leukemia and their potential interactions with antimicrobial prophylaxis medications. |
| Describe | Describe pharmacodynamic and pharmacokinetic interactions of medications. |
| Review | Review recommendations for dose adjustments and monitoring plans if a drug interaction is present. |

# Background – NCCN Infection Prevention

## Overall Infection Risk

| | | |
|---|---|---|
| High[b] | • Allogeneic HCT including cord blood<br>• Acute leukemia<br>▸ Induction<br>▸ Consolidation/maintenance[c]<br>• Alemtuzumab therapy<br>• Moderate to severe GVHD<br>• Anticipated neutropenia greater than 10 days | • Bacterial - Consider fluoroquinolone prophylaxis during neutropenia[e]<br>• Fungal - Consider prophylaxis during neutropenia (INF-2); consider PJP prophylaxis (INF-6)<br>• Viral - During neutropenia and longer depending on risk (INF-3, INF-4, INF-5) |

## NCCN Acute Myeloid Leukemia Infection Prevention

**Bacterial:** Fluoroquinolone (TMP/SMX, cephalosporins)

- During neutropenia

**Fungal:** Posaconazole (voriconazole, isavuconazole, amphotericin, echinocandins, fluconazole)

- During neutropenia

**Viral:** Acyclovir (valacyclovir, famciclovir)

- During neutropenia and longer

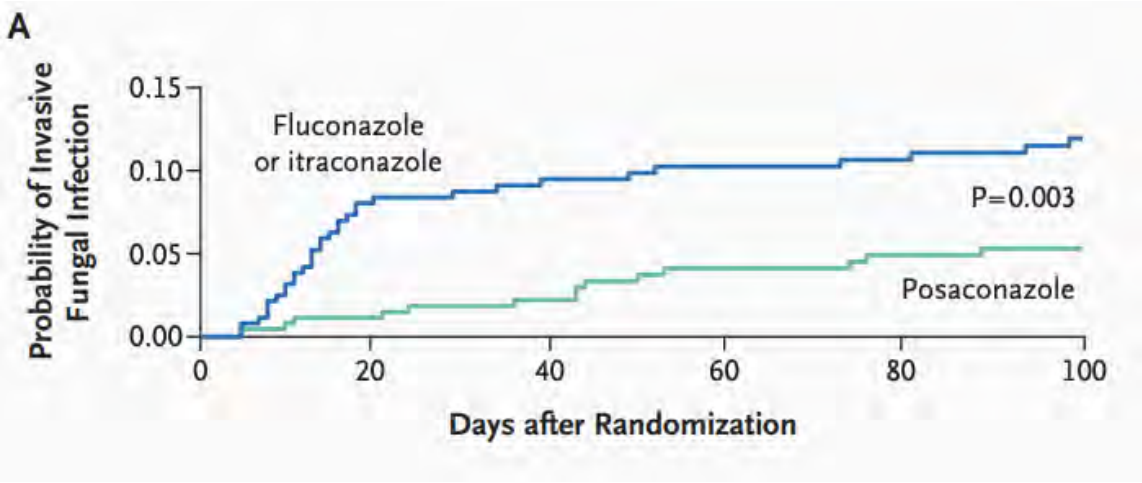
NCCN Prevention and Treatment of Cancer Related Infections: Version 2.2023.

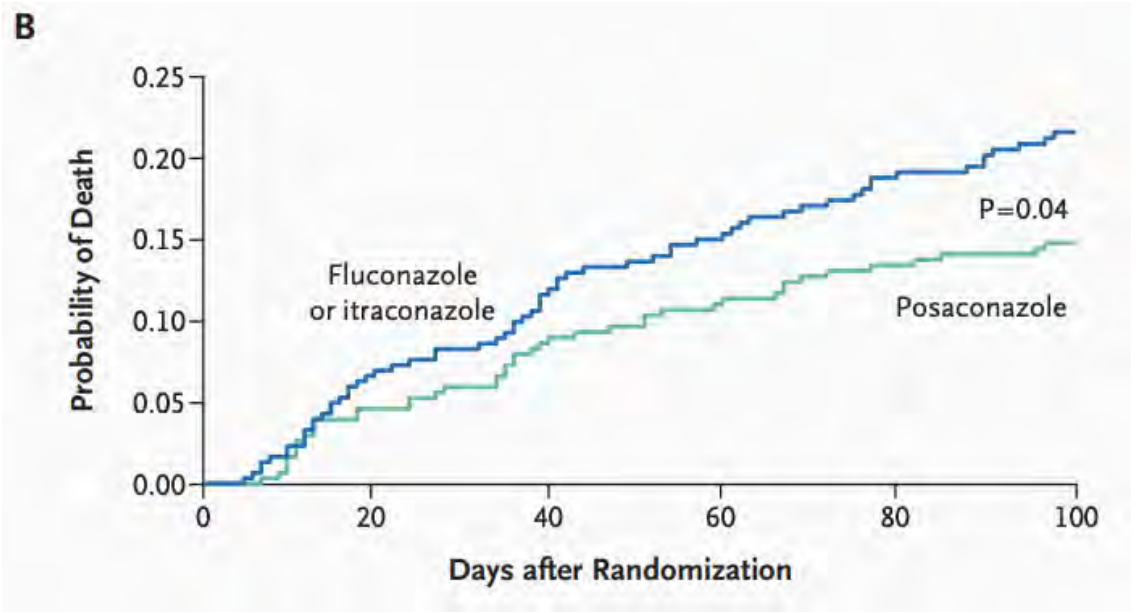
# AML Infection Prevention

## NCCN Guidelines

Category 1: Posaconazole

Category 2B:
Voriconazole, isavuconazole, echinocandins, amphotericin B, fluconazole




NCCN Prevention and Treatment of Cancer-Related Infections: Version 2.2023

Cornely, et al, N Engl J Med 2007;356:348-359.

# Triazole Antifungals for AML Prophylaxis

| | Fluconazole | Itraconazole | Voriconazole | Isavuconazole | Posaconazole |
|---|---|---|---|---|---|
| **NCCN Recommendation as AML fungal prophylaxis** | Category 2B (if mold activity is not needed) | No comment | Category 2B | Category 2B | Category 1 |
| Least coverage → Most coverage | | | | | |
| **Coverage** | Yeast:<br>Candida spp. (most)<br>C. Neoformans<br><br>Dimorphic:<br>coccidioidomycosis | Plus:<br><br>Molds:<br>Aspergillus spp.<br>Fusarium<br><br>Dimorphic:<br>Blastomyces<br>Histoplasma | Plus:<br><br>Yeast:<br>Additional Candida spp.<br><br>Molds:<br>Aspergillus spp.<br>(less resistance) | Plus:<br><br>Molds: Mucor | Similar coverage to isavuconazole |

NCCN Prevention and Treatment of Cancer-Related Infections Version 2.2023
Spencer et al, Fungal Biology Reviews 2023

# Trizole Antifungals for AML Prophylaxis

| | Fluconazole | Itraconazole | Voriconazole | Isavuconazole | Posaconazole |
|---|---|---|---|---|---|
| NCCN Recommendation | Category 2B (if mold activity is not needed) | No comment | Category 2B | Category 2B | Category 1 |
| Administration | Oral and IV | Oral | Oral and IV | Oral and IV | Oral and IV |
| Enzyme Interaction | Moderate CYP3A4 and 2C9 Inhibitor<br><br>Strong CYP2C19 Inhibitor | Strong CYP3A4 Inhibitor | Strong CYP3A4 Inhibitor<br><br>Moderate CYP2C19 Inhibitor | Moderate CYP3A4 Inhibitor | Strong CYP3A4 Inhibitor<br><br>P-gp Inhibitor |
| Class Side Effects | Liver enzyme elevations, GI disturbances, QTc prolongation | | | | |
| Additional Considerations | Renal dose adjustments | Contraindicated in systolic heart failure | Hallucinations, visual disturbances, TDM recommended | May shorten QTc interval | Tablet and solution dosing is different, TDM recommended |

**Cost/Insurance Coverage

# Interaction Types – PK/PD

## Pharmacokinetic Interactions

What the body does to the drug

Absorption, Distribution, Metabolism, and Excretion

## Pharmacodynamic Interactions

What the drug does to the body

# Pharmacokinetics - Metabolism

## Phase I

Oxidation, reduction, hydrolysis

Lipophilic ➡ hydrophilic/polar

## Phase II

Methylation, acetylation, glucuronidation

Conjugation ➡ excretable, nontoxic substances

## Phase III

Transportation of molecules across membranes

Excretion

### Cytochrome P450 Family

- CYP3A4 – oxidizes over half of common medications
  - Inhibited by triazole antifungals

# Interaction Types – PK/PD

## Pharmacokinetic Interactions

What the body does to the drug

Absorption, Distribution, Metabolism, and Excretion

## Pharmacodynamic Interactions

What the drug does to the body

Anti-infective PD Interactions:

- QTc prolongation
- Hepatotoxicity
- GI disturbances

# AML Targeted Therapies

| BCL2: | FLT-3: | IDH1/2: | CD33: | Hedgehog Pathway: |
| --- | --- | --- | --- | --- |
| • Venetoclax | • Midostaurin<br>• Quizartinib<br>• Gilteritinib<br>• Sorafenib | • Ivosidenib<br>• Enasidenib | • Gemtuzumab | • Glasdegib |

# NCCN Preferred AML Therapies

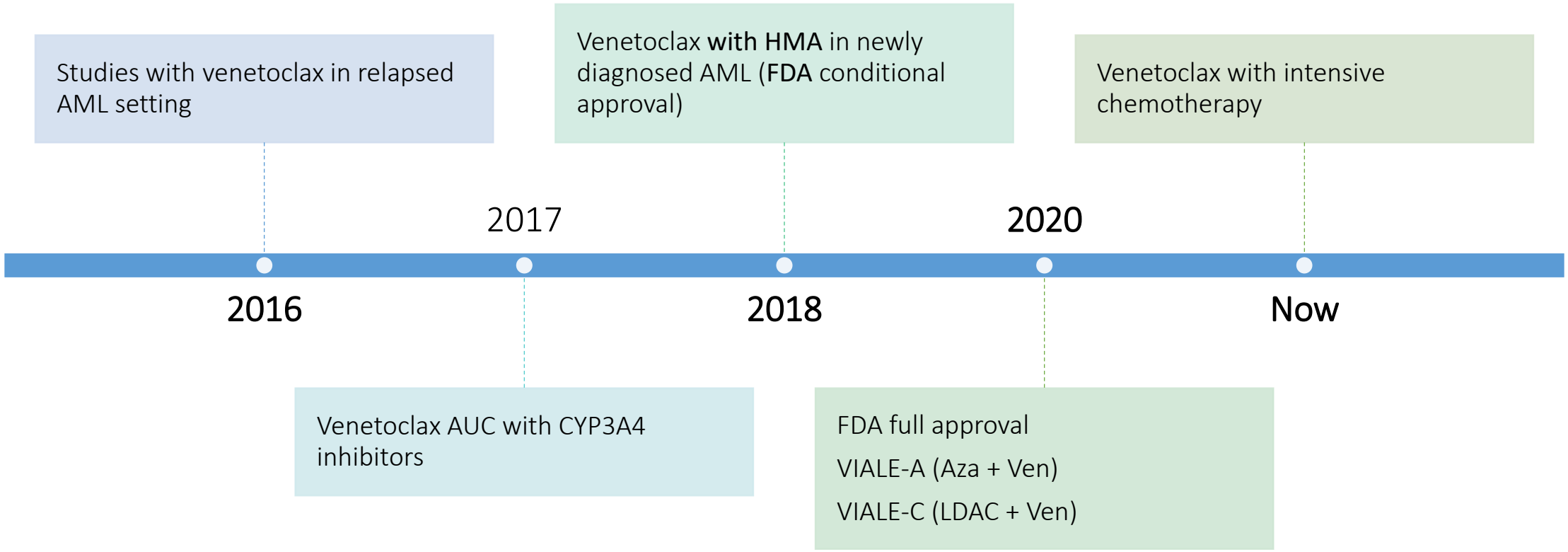
## "Intensive Induction Eligible"

- **Favorable Risk**: 7+3 + GO
- **FLT3 Mutation:** 7+3 + Midostaurin or 7+3 + Quizartinib
- **Intermediate Risk/Poor Risk:** 7+3
- **TR-AML:** 7+3 or liposomal daunorubicin and cytarabine (>60 y.o.)

## "Intensive Induction Ineligible"

- **No Actionable Mutation:** Azacitadine + venetoclax
- **FLT3 Mutation:** Azacitadine + venetoclax
- **IDH1 or IDH2 Mutation:** Azacitadine + venetoclax or Azacitadine + ivosidenib

# Venetoclax in AML



# Venetoclax in AML

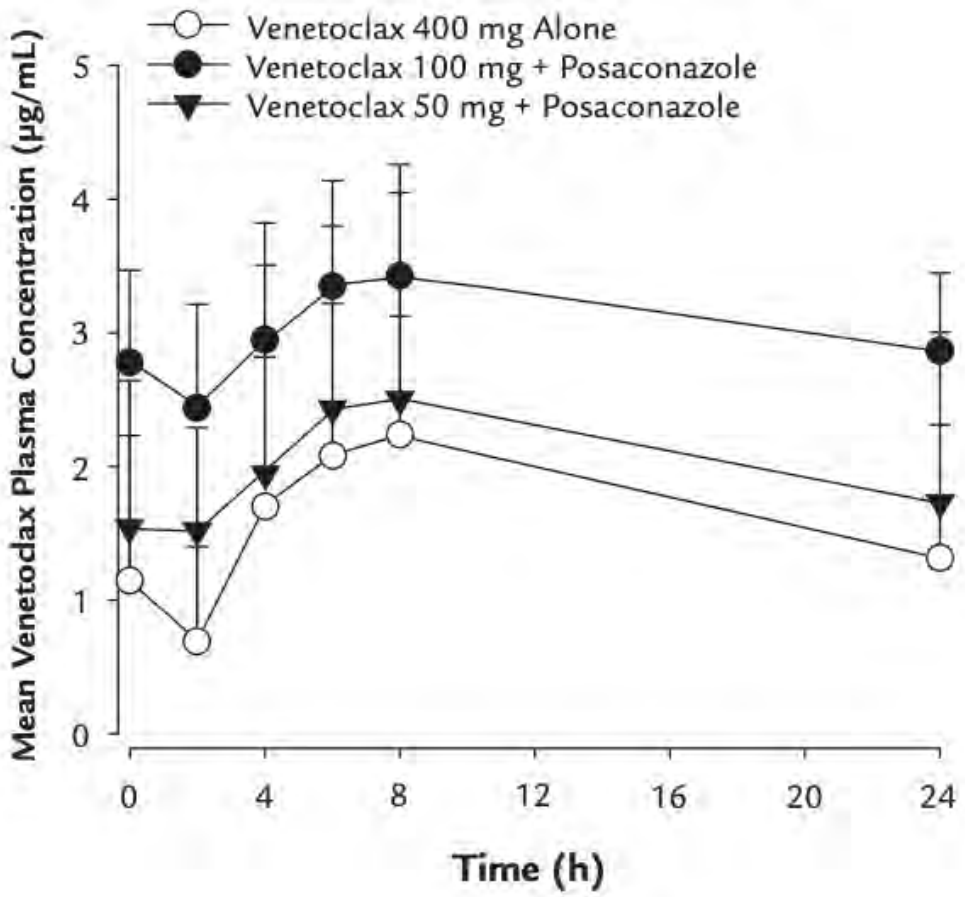
| | Konopleva 2016 – Phase II | DiNardo 2019 – Phase Ib |
|---|---|---|
| **Treatment population** | Relapsed/Refractory | Newly diagnosed, >65 y.o.<br>• with azacitidine or decitabine |
| **Goal dose** | 800 mg daily | 400 mg, 800 mg, 1200 mg |
| **Febrile neutropenia** | 31% | 35% - 50% |
| **Infections** | Total: 47%<br>UTI: 16%, PNA: 25%, Sepsis 6% | Total: 74%<br>Grade 3/4 Fungal: 8%, PNA 18%, Sepsis 10% |
| **Dose interruptions** | 25% | 47% |
| **Venetoclax dose reductions** | NA | CYP3A4 inhibitors/inducers prohibited |
| **Antifungal use in venetoclax group** | Not reported | Echinocandins (46%) |

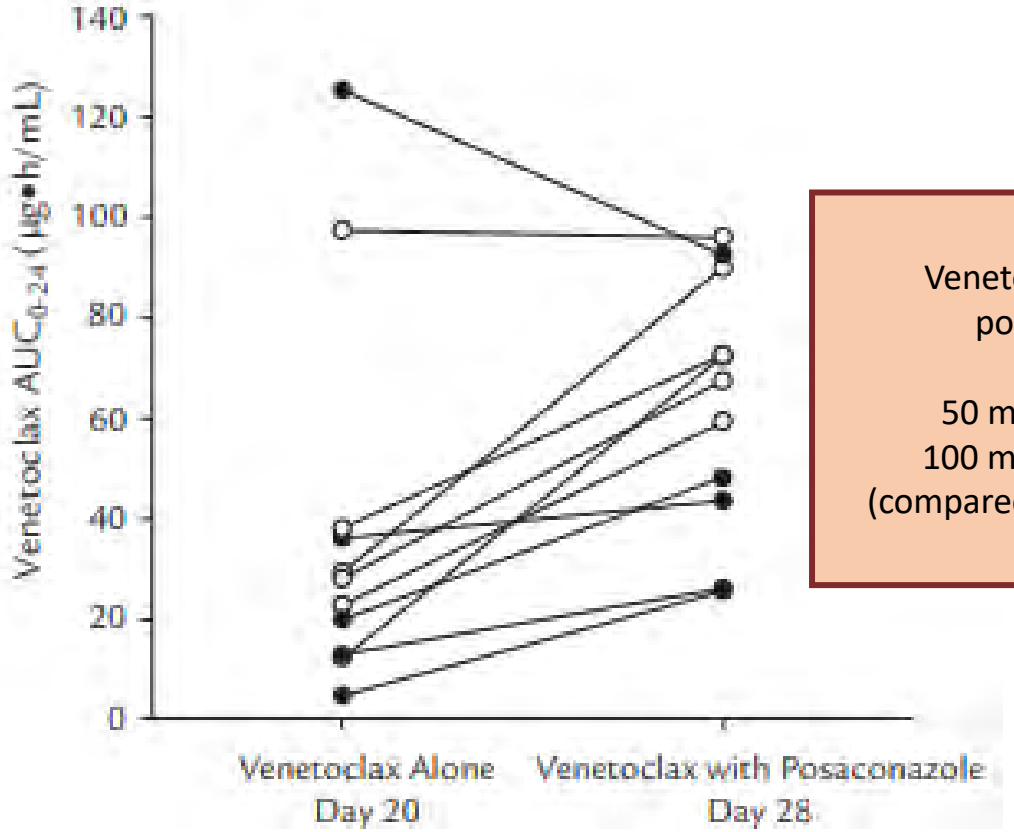
Konopleva M, et al. Cancer Discov. 2016;6(10):1106–1117.
Dinardo C, et al. Blood. 2019;133(1):7-17.10

# Venetoclax AUC

Agarwal, 2017
Venetoclax + decitabine: blood samples on days 20 and 28

- Days 1-5: ven ramp-up
- Days 6-20: ven 400 mg
- Days 21-28: ven 100 mg (n = 6) or ven 50 mg (n = 5) with posaconazole 300 mg




Venetoclax AUC with posaconazole

50 mg: 76% higher
100 mg: 155% higher
(compared to 400 mg alone)

# Venetoclax Confirmatory Trials

| | DiNardo 2020 – Phase III (VIALE-A)<br>N=427 | Wei 2020 – Phase III (VIALE-C)<br>N=210 |
|---|---|---|
| **Goal dose** | 400 mg | 600 mg |
| **Concomitant AML treatment** | Azacitidine | Low-dose cytarabine |
| **Venetoclax dose reductions** | CYP3A4 inhibitors: 200 mg (moderate), 50 mg (strong) | CYP3A4 inhibitors: 300 mg (moderate), 50 mg (strong) |
| **Concomitant antifungals** | Ampho B (5%), echinocandin (15%), fluconazole (15%), posaconazole (15%), voriconazole (6%) | Specifics not reported |

DiNardo CD, et al. N Engl J Med. 2020;383:617-29
Wei AH, et al. Blood. 2020;135(24):2137-2145

# Venetoclax Adverse Events

| | Konopleva 2016<br>Phase II<br>N=32 | DiNardo 2019<br>Phase Ib<br>N=145 | DiNardo 2020<br>Phase III (VIALE-A)<br>N=427 | Wei 2020<br>Phase III (VIALE-C)<br>N=201 |
|---|---|---|---|---|
| Goal Dose | 800 mg daily | 400 mg, 800 mg, 1200 mg | 400 mg | 600 mg |
| Venetoclax Dose Reductions | NA | CYP3A4 inhibitors/inducers prohibited | CYP3A4 inhibitors: 200 mg (moderate), 50 mg (strong) | CYP3A4 inhibitors: 300 mg (moderate), 50 mg (strong) |
| Grade 3/4 Neutropenia | NA | NA | Control: 28%<br>Venetoclax: 42% | Control: 16%<br>Venetoclax: 46% |
| Febrile Neutropenia | 31% | 400 mg: 50%<br>800 mg: 35% | Control: 19%<br>Venetoclax: 42% | Control: 29%<br>Venetoclax: 32% |
| Infections | Total: 47%<br>UTI: 16%, PNA: 25%, Sepsis 6% | Total: 74%<br>Grade 3/4 Fungal: 8%,<br>PNA: 18%, Sepsis: 10% | Control: 67%<br>Venetoclax: 84% | Control: 22%<br>Venetoclax: 26%<br>(only listed serious AEs: PNA, Sepsis) |
| Dose Interruptions | 25% | 47% | Control: 57%<br>Venetoclax: 72% | Control: 53%<br>Venetoclax: 63% |

# Full FDA Approval – Venetoclax for AML

## VIALE-A

Venetoclax dosing:

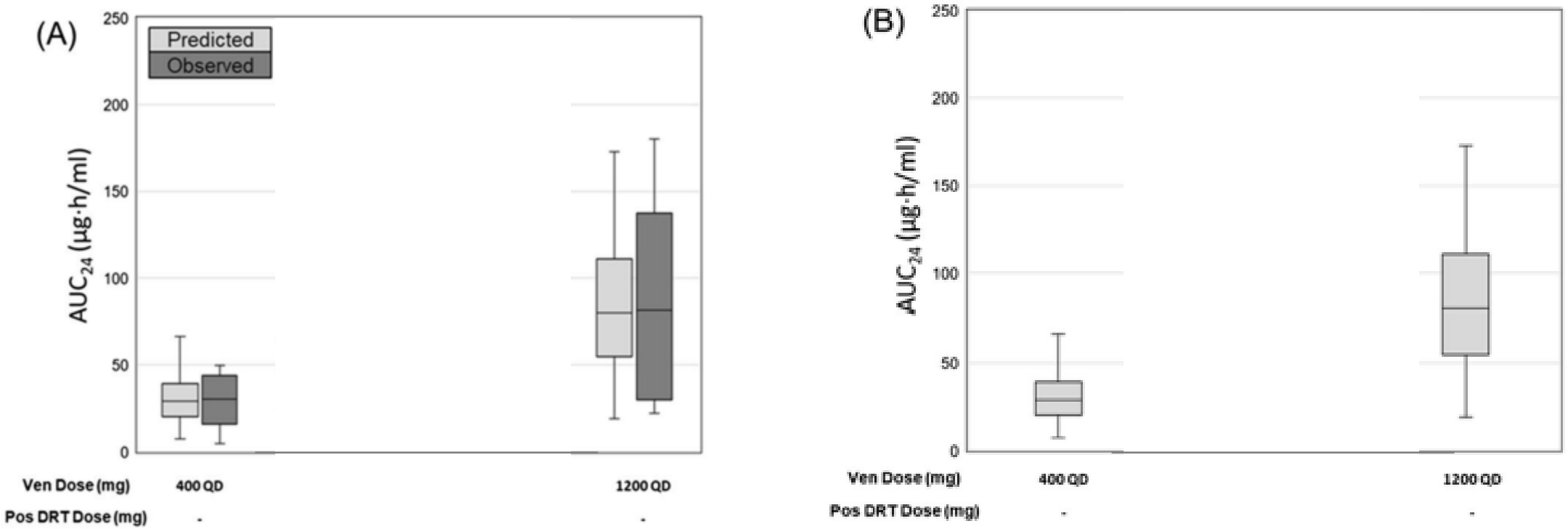
- No inhibitors: 400 mg
- Moderate CYP3A4 inhibitors:  200 mg
- Strong CYP3A4 inhibitors: 50 mg

## VIALE-C

Venetoclax dosing:

- No inhibitors: 600 mg
- Moderate CYP3A4 inhibitors:  300 mg
- Strong CYP3A4 inhibitors: 50 mg

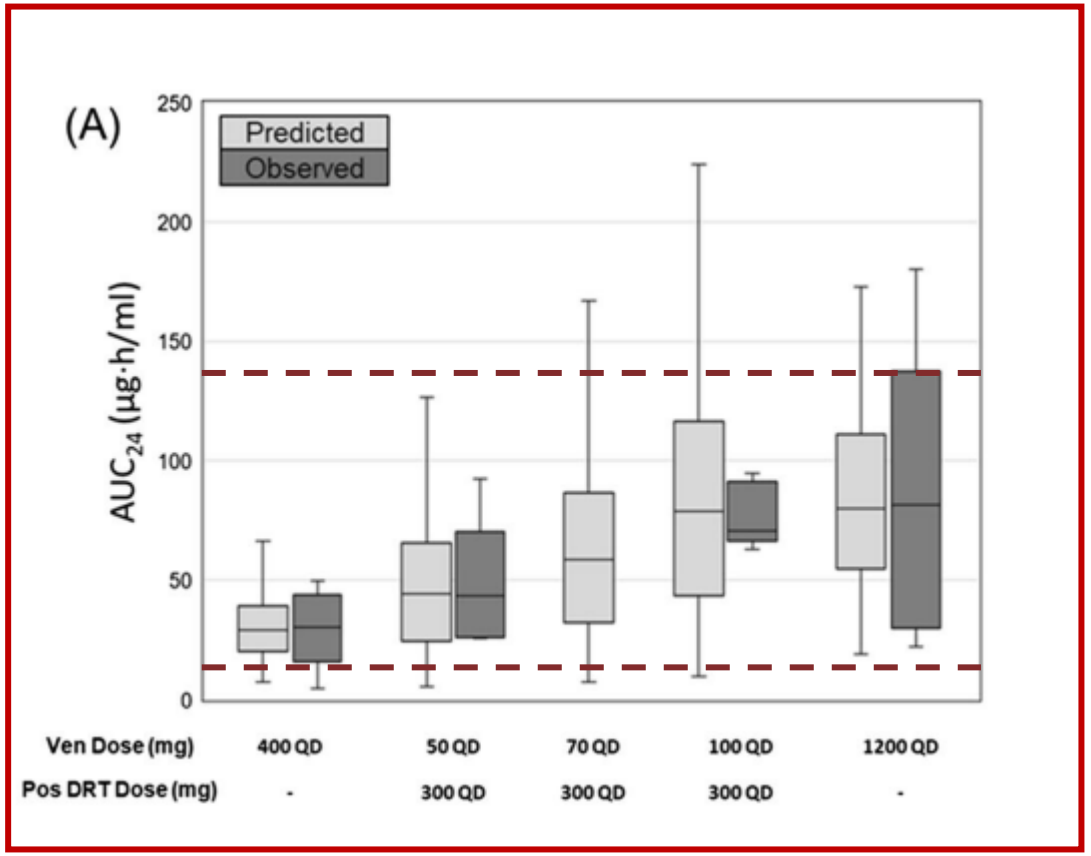
# Venetoclax AUC

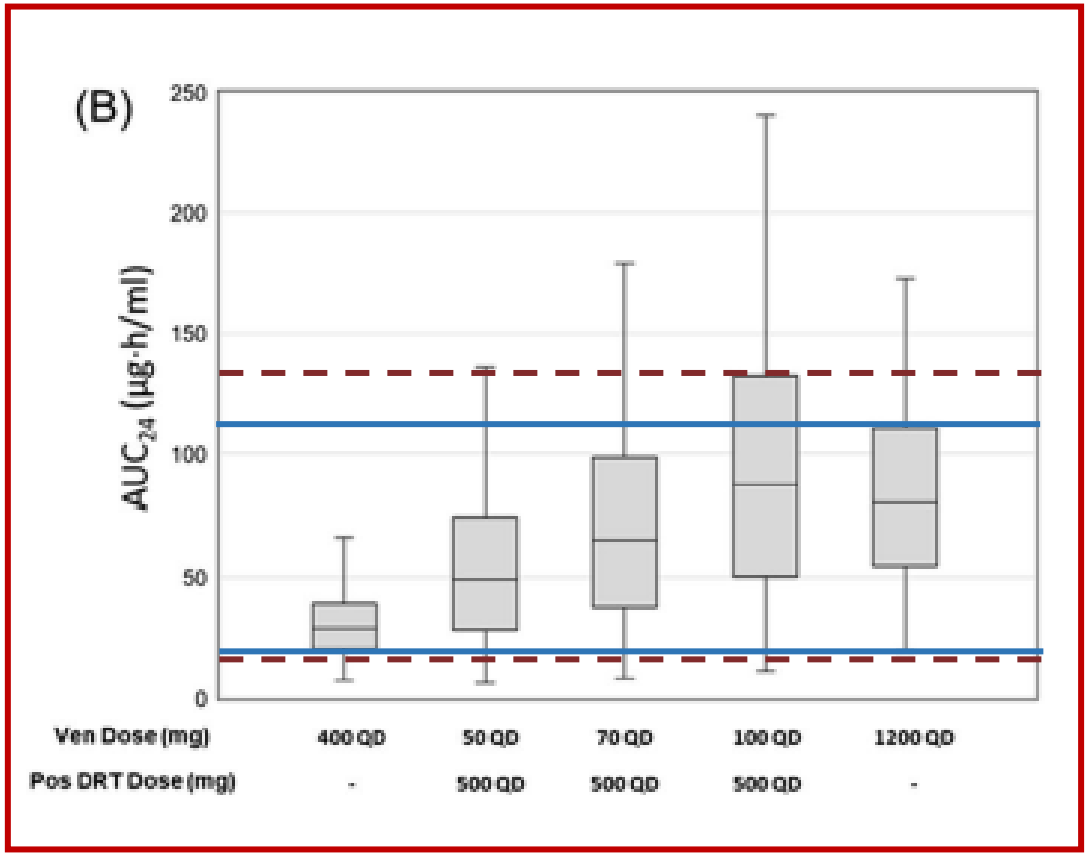



- Venetoclax 400 mg dose alone = minimum efficacy
- Venetoclax 1200 mg dose alone = maximum tolerated dose

Bhatnagar S, et al. Cancer Chemotherapy and Pharmacology. 2021; 87:465–474

# Venetoclax AUC




- Venetoclax 400 mg dose alone = minimum efficacy
- Venetoclax 1200 mg dose alone = maximum tolerated dose
- Model B concludes that 70 mg is likely a safe dose at posaconazole doses up to 500 mg

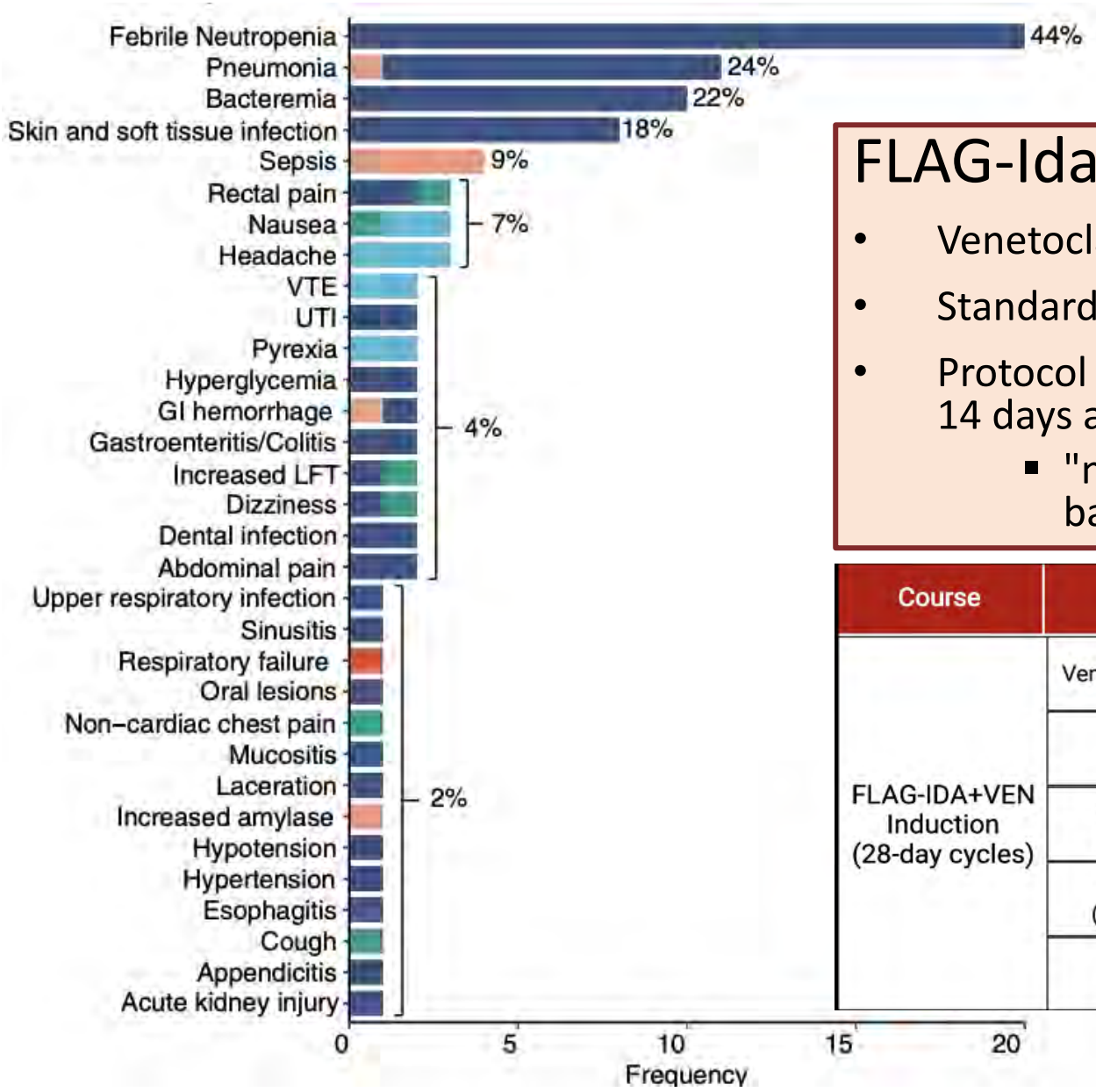
Bhatnagar S, et al. Cancer Chemotherapy and Pharmacology. 2021; 87:465–474

# Package Insert Recommendations – Venetoclax in AML

| | No CYP3A4 Inhibitor | Moderate CYP3A4 Inhibitor | Strong CYP3A4 Inhibitor or P-gp Inhibitor | Posaconazole |
|---|---|---|---|---|
| **Venetoclax ramp-up dose** | Day 1: 100 mg<br>Day 2: 200 mg<br>Day 3: 400 mg<br>Day 4: 400 mg<br>Or 600 mg | Reduce dose by at least 50% | Day 1: 10 mg<br>Day 2: 20 mg<br>Day 3: 50 mg<br>Day 4: 100 mg | Day 1: 10 mg<br>Day 2: 20 mg<br>Day 3: 50 mg<br>Day 4: 70 mg |
| **Venetoclax maintenance dose** | HMA: 400 mg<br>LDAC: 600 mg | HMA: 200 mg<br>LDAC: 300 mg | 100 mg daily | 70 mg daily |
| **Indication in AML**: In combination with azacitidine, or decitabine, or low-dose cytarabine for the treatment of newly diagnosed acute myeloid leukemia (AML) in adults 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy | | | | |

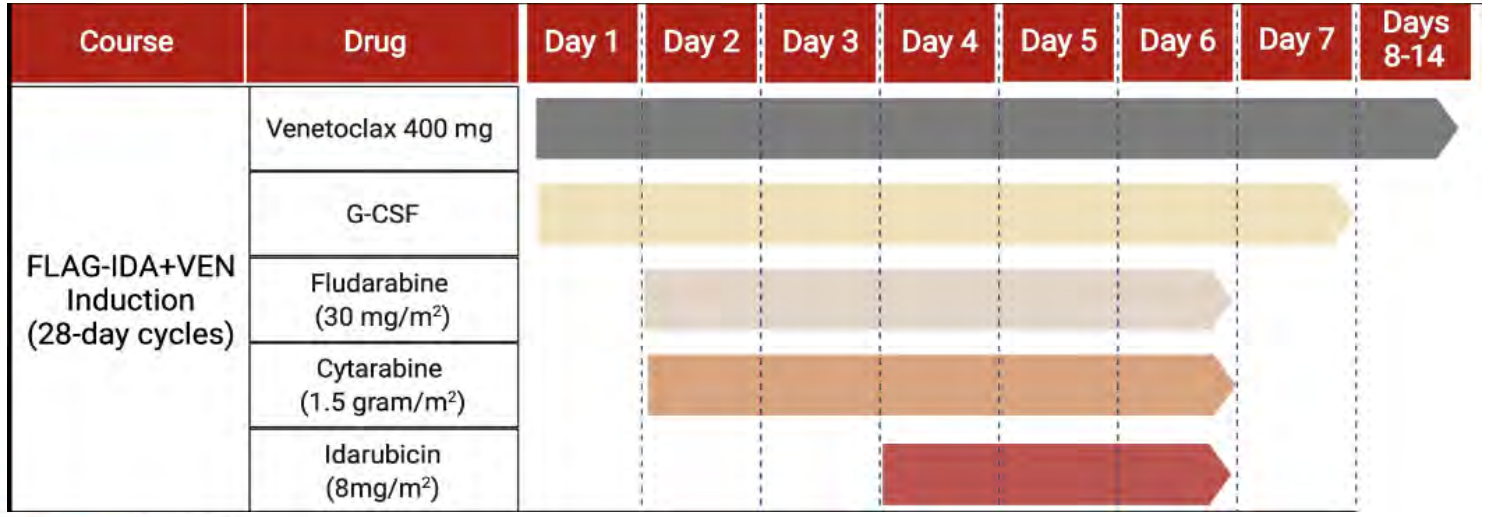
Venetoclax (Venclexta) [Package Insert] 2022

# Venetoclax and Intensive Chemotherapy




## FLAG-Ida + venetoclax

- Venetoclax dose adjustments per package insert
- Standard prophylaxis when neutropenic
- Protocol amendment to decrease venetoclax duration from 21 to 14 days and cytarabine dose from 2 g/m2 to 1.5 g/m2
  - "neutropenia and neutropenia-related infections including bacteremia/sepsis in 5/6 patients during cycle 1"




DiNardo CD, et al. J Clin Oncol 39:2768-2778. Lachowiez et al, Blood.2021;138(S1):701
Dinardo CD, et al. Am J Hematol. 2022;97:1035–1043

# Duration of Cytopenia

| Adverse Reaction | Occurrence | Dose Modification |
|---|---|---|
| Grade 4 neutropenia or thrombocytopenia | Prior to remission | No dose interruption prior to remission |
| | First occurrence after achieving remission + lasting ≥ 7 days | **Delay** subsequent cycles. Restart venetoclax at same dose/duration when resolved to Grade 1 or 2 |
| | Subsequent occurrences after achieving remission + lasting ≥ 7 days | **Delay** subsequent cycles. Restart venetoclax at **same dose and decrease duration** by 7 days next cycle when resolved to Grade 1 or 2 |

NCCN Guideline Tips

- Treatment breaks if in remission - ie extend cycles from 28 to 42 days
- Delay in count recovery - reduce venetoclax duration and/or HMA dose
- "Refer to package insert and consult a pharmacist for potential drug interactions"

Did the patient have any concurrent medication changes? Was venetoclax's dose adjusted, if needed?

Venetoclax (Venclexta) [Package Insert] 2022

# Venetoclax Dosing Considerations

Venetoclax tablet strengths: 10 mg, 50 mg, 100 mg

Administration errors with different strengths at home

Insurance coverage of tablet strength

Bone marrow reserve and duration of neutropenia

Need to assess venetoclax dose when changing other medications

1. Review patient's concomitant medications
   - Dosing in trials is inconsistent pending concurrent medication exclusions, trial start date, etc
     - Consult PI for dose recommendations
     - Consider patient's comorbidity and social situation
2. Venetoclax dose and/or duration may lead to prolonged neutropenia
   - Patients should be taking antifungal, antibiotic, and antiviral prophylaxis
   - Aggressive treatment vs. already in remission
3. Setting up patients for success
   - If concurrent interacting drug or venetoclax dose is changed (mid-cycle or with the next cycle), are the instructions clear?
   - Do patients have the correct tablets

# FLT3 Targets

# Midostaurin

## Indication: FLT3-ITD and FLT3-TKD mutations

## Dosing: 50 mg PO BID, Days 8-21

- Induction and consolidation
- Twice daily maintenance continually

## Anti-infective Interaction:

- PK: CYP3A4 substrate
  - PI recs: consider alternate therapy or monitor patients for increased risk of adverse reactions when given with strong CYP3A4 inhibitor
- PD: QT prolongation

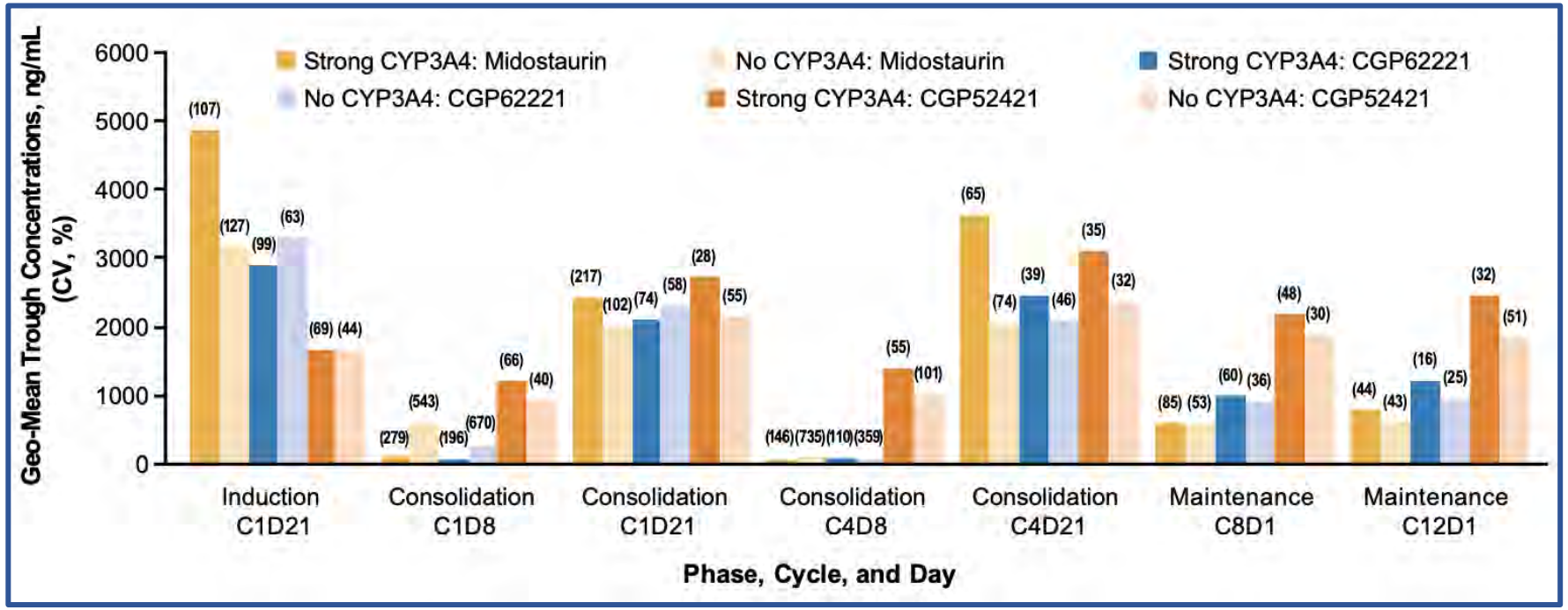
## Warning for pulmonary toxicity

## Monitoring:

- Consider interval ECG if taken concurrently with medications that can prolong the QT interval
  - AML trials used corrected QTcF with Fredericia's formula

Midostaurin (Rydapt) [package insert] 2023.

# Midostaurin Pharmacokinetics RATIFY Post-Analysis




- Midostaurin metabolized to 2 active metabolites: CGP62221 > CGP52421
- PK increases with CYP3A4 inhibitors at steady state are smaller in magnitude than after single doses

Sechaud R, et al. Cancer Chemotherapy and Pharmacology 2022;90:19–27

# Midostaurin Adverse Events

**Table 3** Frequency of grade 3/4 AEs in patients who received midostaurin with a ≥2% difference between subgroups of concomitant CYP3A4 use

| Concomitant treatment with strong CYP3A4 inhibitor | Events, % | | Absolute difference, % |
|---|---|---|---|
| | Yes ($n$=214) | No ($n$=131) | Yes vs no |
| Pneumonia | 15.4 | 9.2 | 6.2 |
| Sepsis | 9.3 | 3.1 | 6.2 |
| Febrile neutropenia[a] | 85.5 | 79.4 | 6.1 |
| C-reactive protein increased | 5.6 | 0 | 5.6 |
| γ-glutamyltransferase increased | 6.1 | 1.5 | 4.6 |
| Infection | 5.1 | 0.8 | 4.3 |
| Device-related infection | 17.8 | 13.7 | 4.1 |
| Pyrexia | 4.2 | 0.8 | 3.4 |
| Hypocalcemia | 7.0 | 3.8 | 3.2 |
| Stomatitis[a] | 4.7 | 1.5 | 3.2 |
| Blood lactate dehydrogenase increased | 2.8 | 0 | 2.8 |
| Hyperbilirubinemia | 5.1 | 2.3 | 2.8 |
| Anal infection | 3.3 | 0.8 | 2.5 |
| Syncope | 5.6 | 3.1 | 2.5 |
| Neutrophil count decreased[a] | 96.3 | 93.9 | 2.4 |
| Hemoglobin decreased[a] | 93.9 | 91.6 | 2.3 |
| Alanine aminotransferase increased | 13.6 | 11.5 | 2.1 |
| Pneumonia fungal | 2.8 | 0.8 | 2.0 |
| Urinary tract infection | 5.1 | 3.1 | 2.0 |

| Event, n (%) | Patients receiving anti-fungal agents and midostaurin (n = 227) | Patients who did not receive anti-fungal agents (n = 74) |
|---|---|---|
| **Patients with ≥1 AE** | 225 (99.1) | 70 (94.6) |
| Grade ≥3 | 198 (87.2) | 56 (75.7) |
| Treatment-related | 178 (78.4) | 53 (71.6) |
| Leading to treatment discontinuation | 24 (10.6) | 5 (6.8) |
| Leading to dose adjustment/interruption | 88(38.8) | 25 (33.8) |
| **Patients with ≥1 SAE** | 110 (48.5) | 27 (36.5) |
| Grade ≥3 | 108 (47.6) | 26 (35.1) |
| Treatment-related | 54 (23.8) | 8 (10.8) |

Schlenk, 2019
Induction death rate: Cohort 2 (2.9%) vs Cohort 1 (15.9%)
Cohort 2: 25 mg every other day (6.2% of patients with strong CYP3A4 inhibitors)

Sierra J, et al. Blood Advances 2023; 7(21):6441-6450.
Sechaud R, et al. Cancer Chemotherapy and Pharmacology 2022;90:19–27
Schlenk R, et al. Blood 2019; 133(8): 840-851.

# Midostaurin Pharmacodynamics

| | All patients | 18-60 y.o. | 60-71 y.o. |
|---|---|---|---|
| Schlenk, 2019 (n = 248) | | | |
| Cardiac, total | 13% | 6% | 22% |
| Cardiac, general | 7% | 4% | 12% |
| Cardiac, arrhythmia | 6% | 2% | 10% |
| Sierra, 2023 (n = 301) | | | |
| QTcF >30-60 ms | 23.9% | | |
| QTcF >60 ms | 10.8% | | |
| New >450-480 ms | 11.9% | | |
| New >480-500 ms | 3.5% | | |
| New >500 ms | 3.9% | | |
| Studies reporting on efficacy and safety in population >60 y.o. | | | |

| | Package Insert Dose Adjustment Recommendations |
|---|---|
| QTc >470-500 ms | Decrease to 50 mg daily. Can increase to 50 mg BID at next cycle if <470 ms |
| QTc >500 ms | Hold for rest of cycle. Can resume at 50 mg BID at next cycle if <470 ms |

| RATIFY Protocol | Package Insert |
|---|---|
| ECG rior to midostaurin dose on Days 8, 10, and 21 of each cycle | "Consider ECG with concomitant QTc prolongating medications" |
| Optimize electrolytes | Half-life: 21 hours |

Sierra J, et al. Blood Advances 2023; 7(21):6441-6450.
Schlenk R, et al. Blood 2019; 133(8): 840-851.
Midostaurin (Rydapt) [package insert] 2023.
Stone RM, et al. N Engl J Med 2017;377:454-64.

# Midostaurin and Prophylaxis

Induction and consolidation with high infection rates

Maintenance with fewer adverse events

NCCN guidelines
"No significantly increased risks for infections"

| | Induction | Consolidation | Maintenance |
|---|---|---|---|
| Overall AEs | 94.7% | 92.9% | 62.4% |
| Most Common: | | | |
| Neutropenia | 48.6% | 24.3% | 12.9% |
| Nausea | 25.2% | 31.9% | 19.4% |

Sierra J, et al. Blood Advances 2023; 7(21):6441-6450.
NCCN Acute Myeloid Leukemia: Version 6.2023

# Midostaurin Dosing Considerations

## Dosing midostaurin at 50 mg BID with a strong CYP3A4 inhibitor is likely safe

- If recurrent or severe AEs, consider holding or decreasing dose

## Increase ECG monitoring recommended with concomitant QTc prolongating drugs

- Pre-dose ECG with QTcF < 470 msec to start
- Consider monitoring within first week of midostaurin
- Refer to PI if QTcF > 470 ms
- Concomitant medications with fluoroquinolones and azoles

## Assess need for anti-infective supportive care with midostaurin

- Consider stopping azole antifungal during maintenance
- Reassess with prolonged neutropenia

# Quizartinib

## Indication: FLT3-ITD mutation

## Dosing:

- Induction 35.4 mg **(days 8-21)** and consolidation 35.4 mg daily **(days** 6-19)
- Maintenance: **26.5 mg daily** with potential for dose increase to 53 mg

## Anti-infective Interaction:

- PK: CYP3A4 substrate
  - Strong CYP3A4 inhibitors: For goal dose of 35.4 mg and 26.5 mg, reduce dose to 17.7 mg
- PD: QT prolongation

## Boxed warnings for QT prolongation, Torsades de Pointes, and Cardiac Arrest

## Monitoring

- ECG prior to initiation then weekly during treatment
  - AML trials used corrected QTcF with Fredericia's formula

Erba HP, et al. Lancet 2023;401:1571-1583

Quizartinib [Package Insert] 2023

# QuANTUM-First

- Standard infectious prophylaxis allowed
  - Unknown number of patients on therapies with drug interactions
- Quizartinib dose reduced by 50% with strong CYP3A4 inhibitors
- QTc monitoring at baseline, then weekly during induction and consolidation
  - "Increased" QTc monitoring with concurrent QTc prolongating medications
- Aggressive electrolyte replacement

| | **Quizartinib** (N=265) | **Placebo** (N=268) |
|---|---|---|
| Dose reductions due to QTc Prolongation | 4% | 1% |
| New >450 and ≤480 ms | 27.5% | 16% |
| New >480 and ≤500 ms | 5.7% | 1.5% |
| New >500 ms | 2.3% | 0.7% |
| Cardiac arrest with ventricular fibrillation | 0.8% | 0% |
| Ventricular tachycardia | 0.4% | 0.4% |
| Time to ANC > 1000/mm3 | 36 days | 29 days |

Author's conclusion: QT prolongation with quizartinib is manageable with dose modification and correction of electrolyte atypicalities."

Erba HP, et al. Lancet 2023;401:1571-1583

# Quizartinib PK/PD Considerations

## Pharmacokinetics

- Known CYP3A4 substrate
- QTc prolongation is dose and concentration dependent
- PK study for dose adjustment recommendations with strong CYP3A4 inhibitors
- QuANTUM-First trial proved safety and efficacy of lower dose with strong CYP3A4 inhibitors

## Pharmacodynamics

- QTc prolongation caused by different mechanism than most QTc prolongating medications
- Inhibiting both could lead to greater risk of arrhythmias
- QTc monitoring after starting additional drugs with PD interaction

# Quizartinib Dosing Considerations

## Increased quizartinib concentration is associated with greater AEs, especially QTc prolongation

- Follow recommendations for 17.7 mg dose when used with strong CYP3A4 inhibitor
- Starting azole prior to quizartinib?

## Increase ECG monitoring recommended with concomitant QTc prolongating drugs

- Assess concomitant medications with increased QT intervals
- Pre-dose ECG with QTcF < 450 msec to start
- Refer to PI if QTcF > 480 ms during treatment

## Assess need for anti-infective supportive care with quizartinib

- Expected neutropenia with induction and consolidation
- Consider stopping azole antifungal during maintenance
- Reassess with prolonged neutropenia

# Summary

Prolonged neutropenia puts patients undergoing treatment for Acute Myeloid Leukemia at high risk for bacterial, fungal, and viral infections

Triazole antifungals inhibit CYP3A4 which may lead to increased concentrations of AML medications, potentially causing additional side effects

Triazole antifungals and newer AML therapies may prolongate QTc intervals

Refer to study protocols and package insert for dose adjustment and monitoring recommendations when using new therapies with triazole antifungals

# New Chemotherapy and Antimicrobial Prophylaxis in Acute Myeloid Leukemia: Practical Tips

Alli Graner, PharmD, BCOP

Clinical Pharmacy Specialist, Hematology/Oncology

Nebraska Medicine

# Package Insert Recommendations

| | Dosing | Dose Adjustments | PD Monitoring |
|---|---|---|---|
| Gilteritinib | 120 mg daily | Strong CYP3A4 Inhibitors:<br>No preemptive dose adjustments<br>• Increase monitoring for AEs<br>• Interrupt and resume at 80 mg | QTc: ECG prior to initiation then on cycle 1, days 8 and 15, plus prior to the start of cycles 2 and 3 |
| Ivosidenib | 500 mg daily | Strong CYP3A4 Inhibitors:<br>Decrease ivosidenib dose to 250 mg daily | QTc: ECG prior to initiation, then weekly x3 weeks, then monthly for the duration of treatment<br>• Increase monitoring with concurrent QTc prolonging medications |