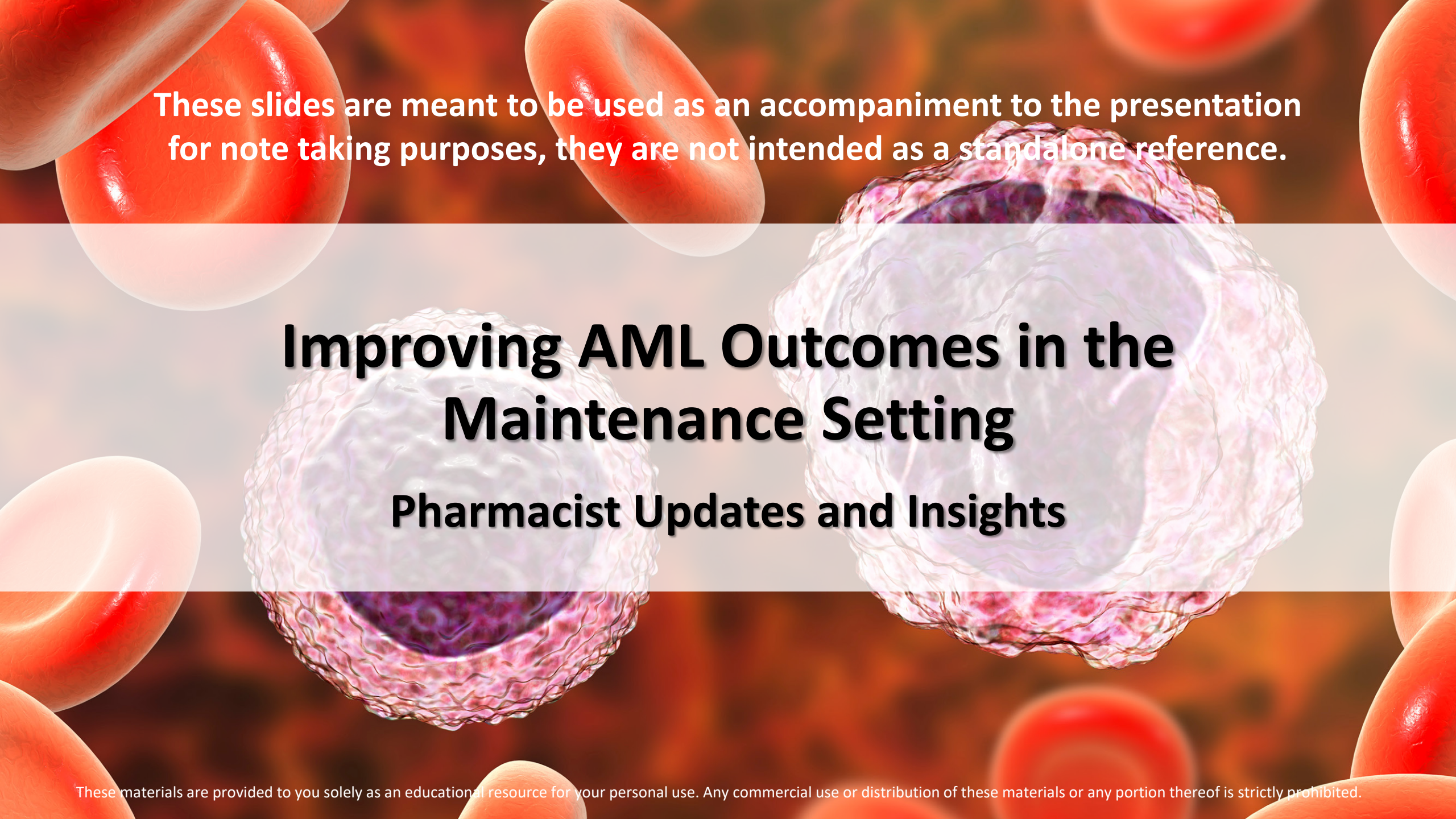
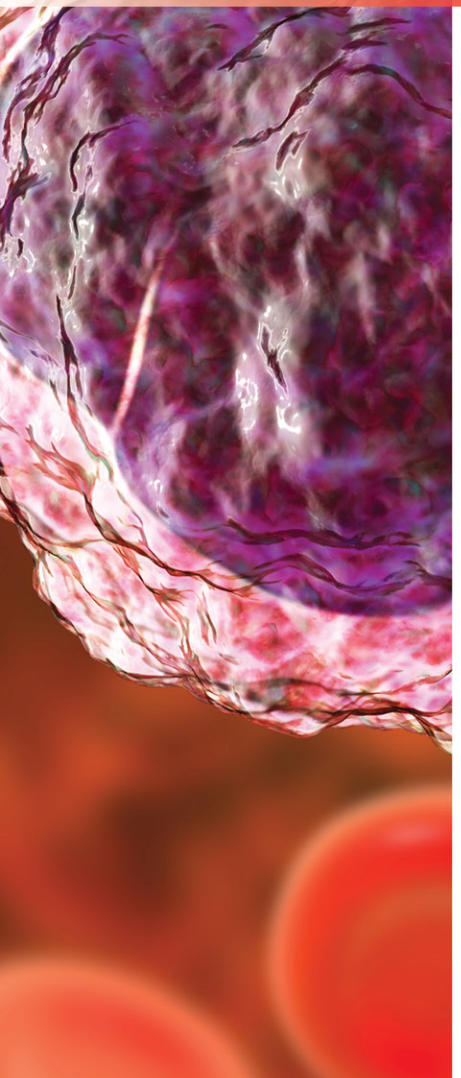


These slides are meant to be used as an accompaniment to the presentation for note taking purposes, they are not intended as a standalone reference.

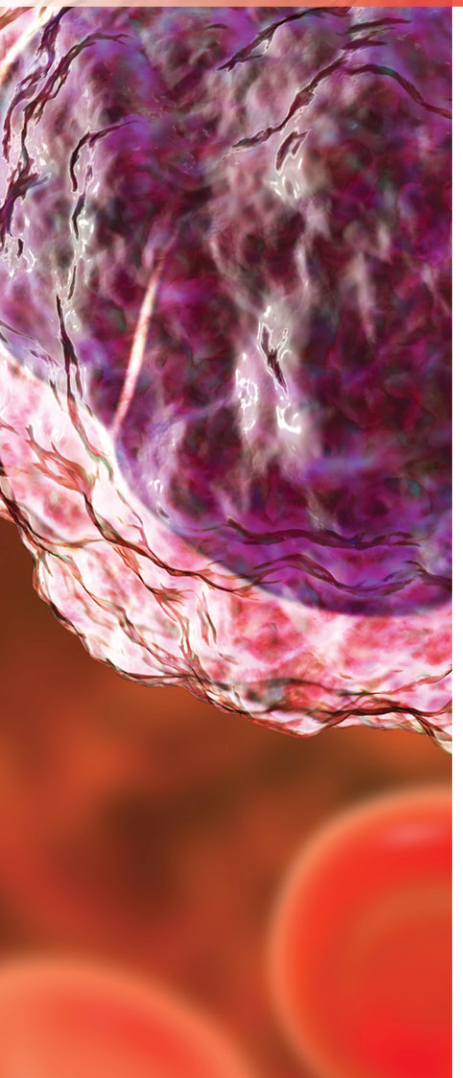
# Improving AML Outcomes in the Maintenance Setting

## Pharmacist Updates and Insights



This educational activity is sponsored by Postgraduate Healthcare Education, LLC, and is supported by an educational grant from Bristol Myers Squibb.

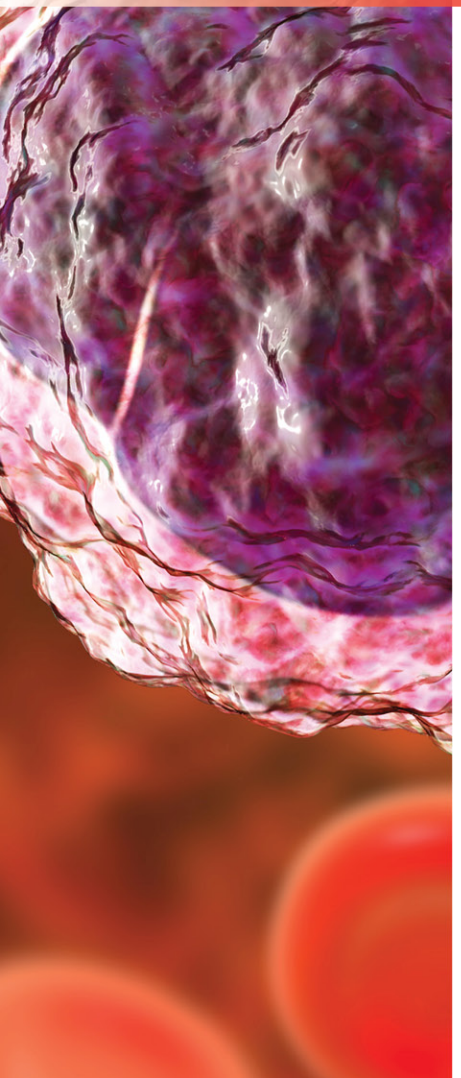
# Faculty



**Megan May, PharmD, BCOP**
Clinical Oncology Pharmacist Specialist
Baptist Health Lexington's Cancer Center
Lexington, Kentucky

Dr May is a board-certified oncology pharmacist currently serving as a Clinical Oncology Pharmacy Specialist at Baptist Health Lexington's Cancer Center in Lexington, KY. She received her Doctor of Pharmacy from Samford University's McWhorter School of Pharmacy in Birmingham, AL, and completed a Pharmacy Practice Residency at Shands Jacksonville Medical Center, and a Hematology/Oncology Pharmacy Residency at the Medical University of South Carolina. In addition to direct patient care, Dr May plays an active role in the education of pharmacy students and residents. Over the past few years, she has served on various committees and in leadership positions for several national professional organizations. Dr May has authored review articles, presented research posters, and given presentations both regionally and nationally.

# Disclosures



**Dr May** has disclosed that she has no actual or potential conflicts of interest related to this program.

The clinical reviewer, Lisa Holle, PharmD, BCOP, FHOPA, FISOPP, has disclosed that she has no actual or potential conflicts of interest related to this program.

Susanne Batesko, RN, BSN, Robin Soboti, RPh, and Susan R. Grady, MSN, RN, as well as the planners, managers, and other individuals, not previously disclosed, who are in a position to control the content of Postgraduate Healthcare Education, LLC (PHE) continuing education (CE) activities, hereby state that they have no relevant conflicts of interest and no financial relationships or relationships to products or devices during the past 12 months to disclose in relation to this activity. PHE is committed to providing participants with a quality learning experience and to improve clinical outcomes without promoting the financial interests of a proprietary business.

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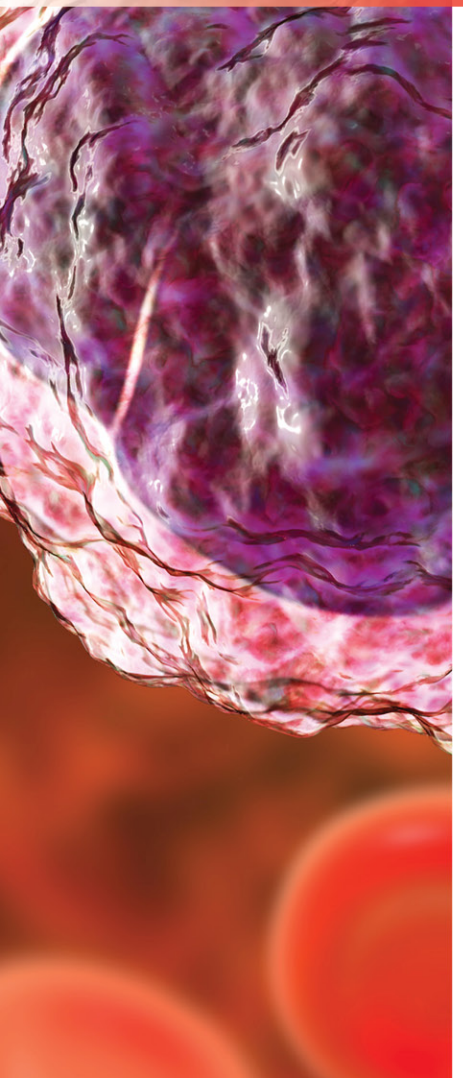

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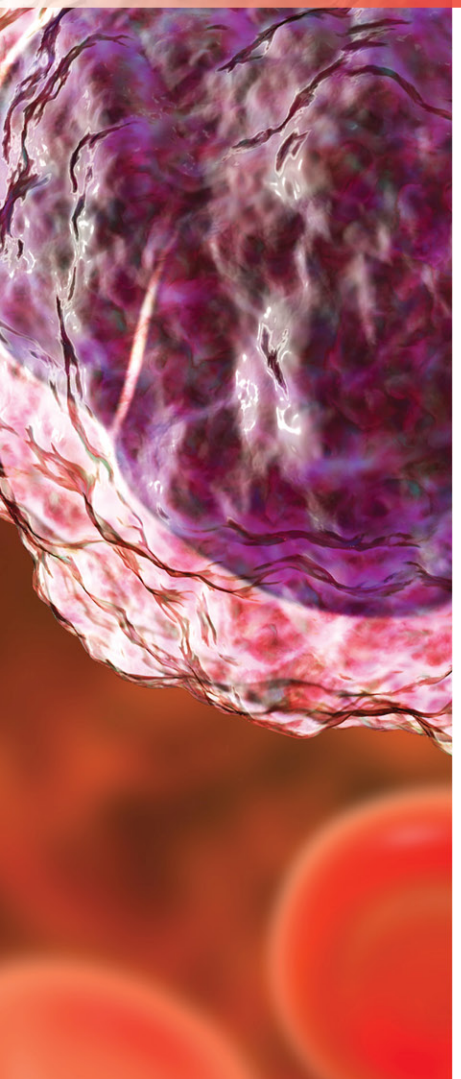
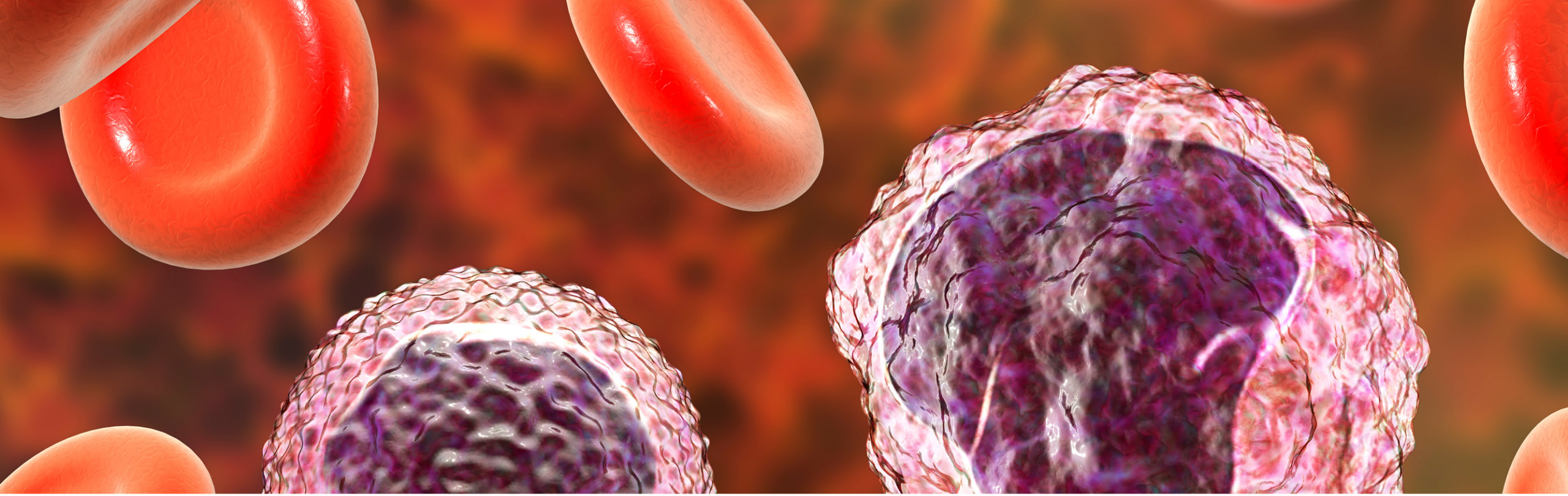


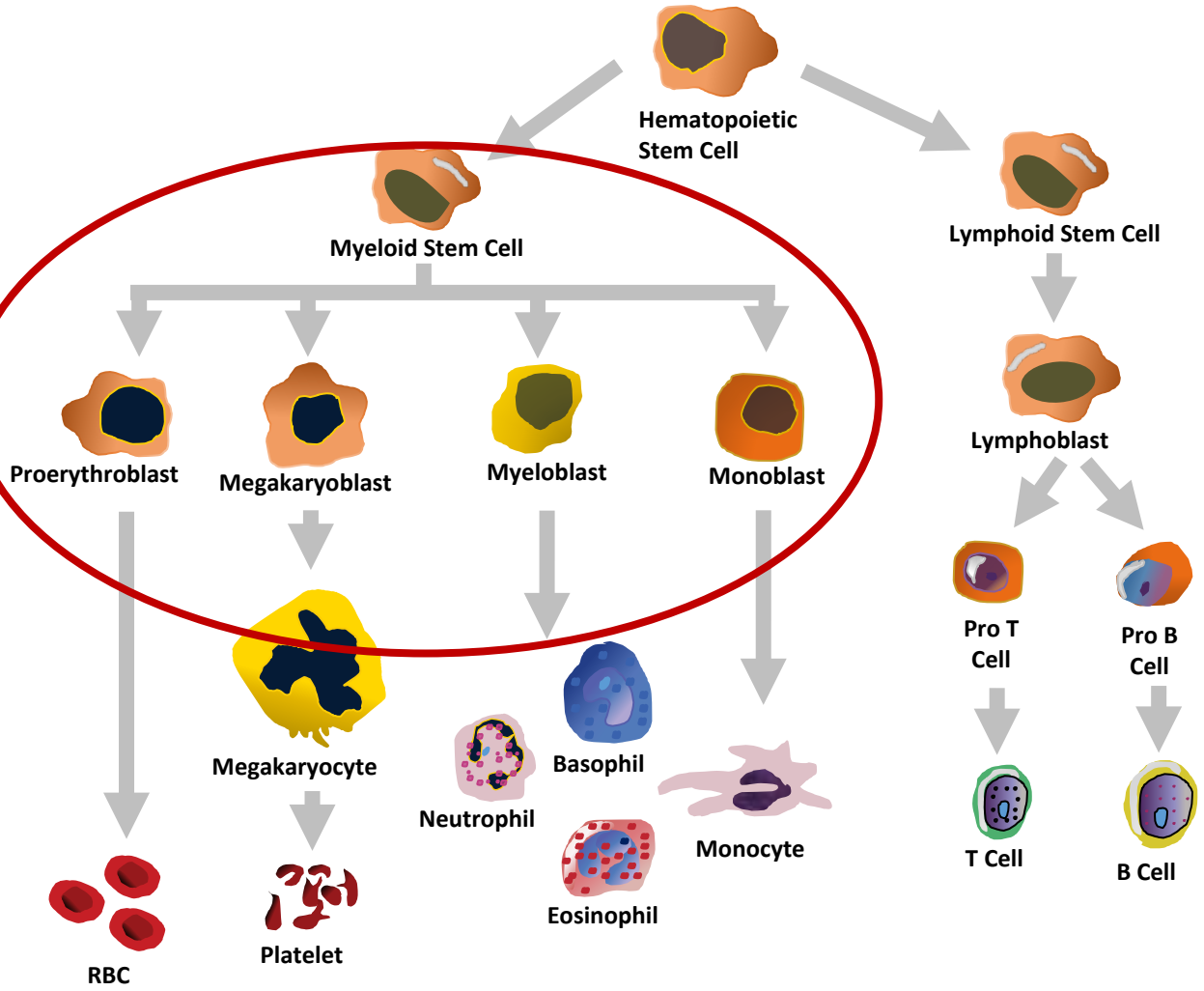
# Learning Objectives

- **Discuss** current and emerging treatment options for AML maintenance regarding efficacy, toxicities, and routes of administration
- **Formulate** effective strategies to identify and manage toxicities and promote safe and adherent use of agents used in AML maintenance treatment
- **Develop** a treatment plan based on current evidence for a patient undergoing AML maintenance therapy



# Background

# AML Fast Facts

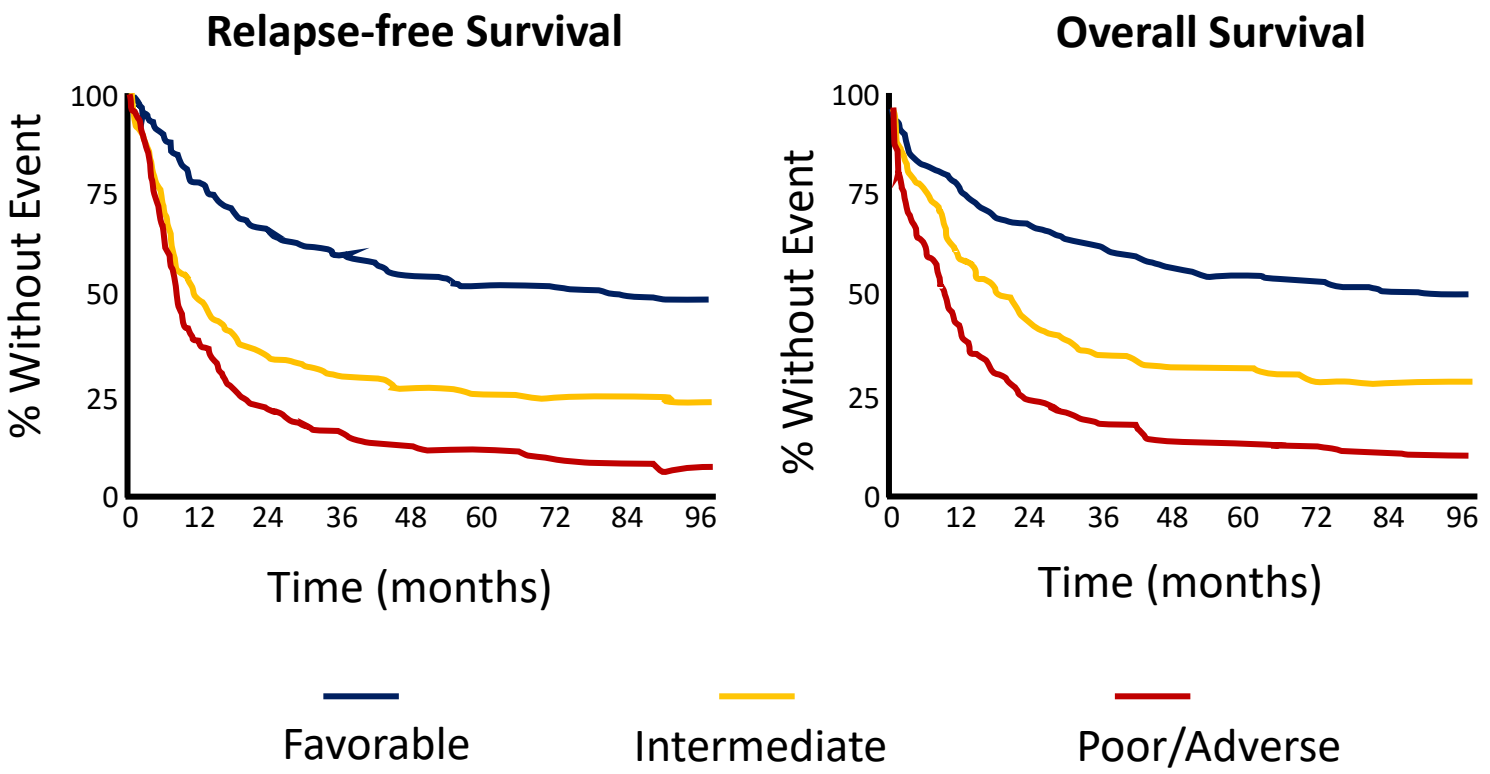



- Incidence: 20,050 estimated new cases and 11,540 estimated deaths in 2022
  - Diagnosis median age: 68 years
  - Death median age: 73 years

National Cancer Institute. Cancer stat facts: leukemia. Available at: https://seer.cancer.gov/statfacts/html/amyl.html. Accessed on April 26, 2022.

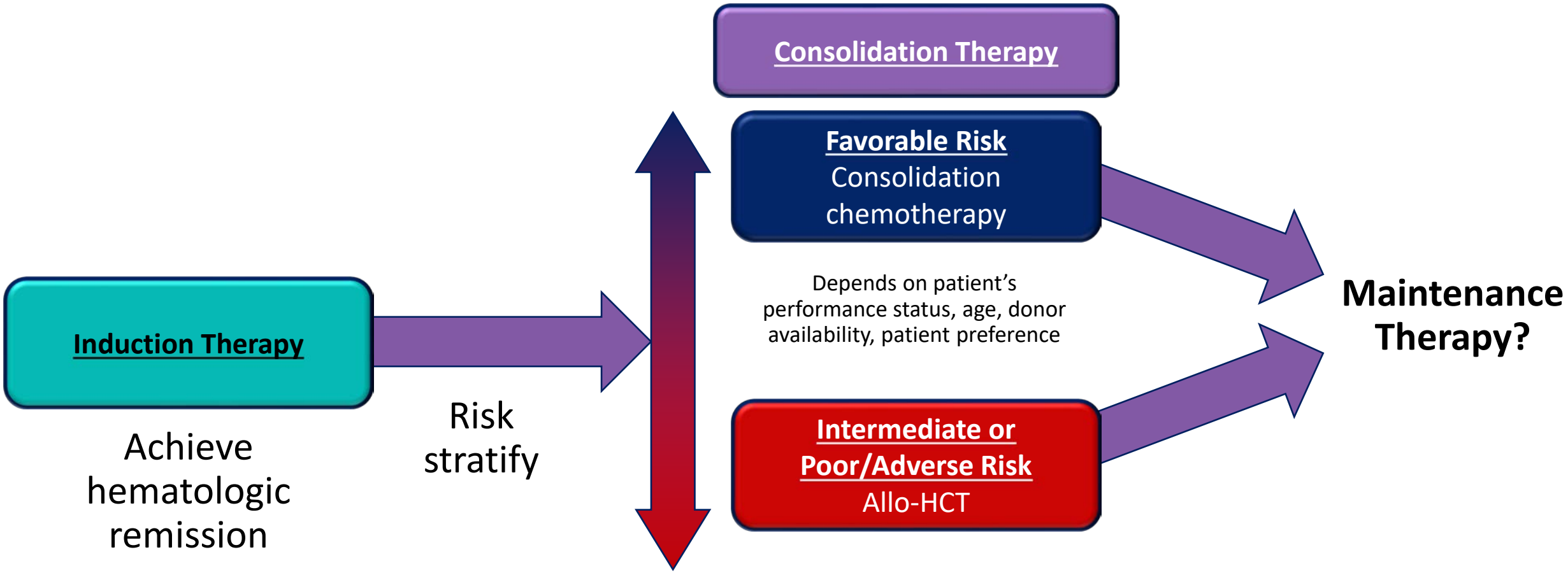
# Prognosis

| European Leukemia Net Risk Stratification for AML | | |
|---|---|---|
| **Risk** | **Cytogenetics** | **Gene Mutations** |
| Favorable | inv (16); CBFB-MYH11<br>t(16;16); CBFB-MYH11<br>t(8;21); RUNX1-RUNX1T1 | Biallelic mutated CEBPα<br>mNPM1 + w/o FLT3-ITD<br>mNPM1 + FLT3-ITD$^{low}$ |
| Intermediate | t(9;11); MLLT3-KMT2A<br>Other cytogenetic abnormalities | mNPM1 + FLT3-ITD$^{high}$<br>WT NPM1 w/o FLT3-ITD$^{low}$ |
| Poor or adverse | Complex (≥ 3 chromosomal abnormalities)*<br>Monosomal karyotype<br>–5, del(5q), –7<br>del(17p), –17<br>11q23 abnormalities other than t(9;11); KMT2A rearranged<br>inv(3) or t(3;3); GATA2, MECOM(EVI1)<br>t(6;9); DEK-NUP214 | Wild-type NPM1 and FLT3-ITD$^{high}$<br>Mutated TP53<br>Mutated RUNX1<br>Mutated ASXL1 |



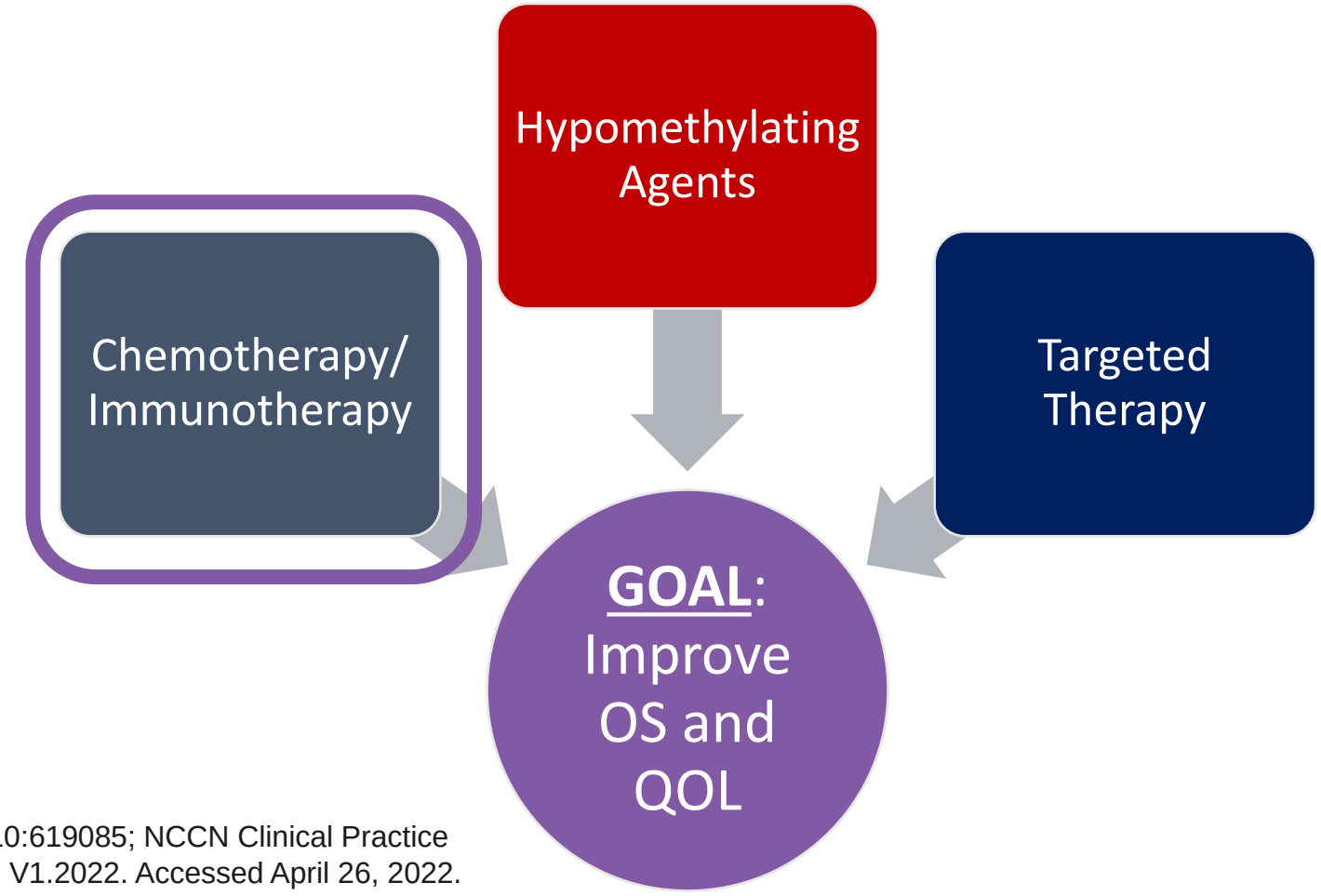

Herold T, et al. *Leukemia*. 2020;34(12):3161-3172.

# Treatment Paradigm

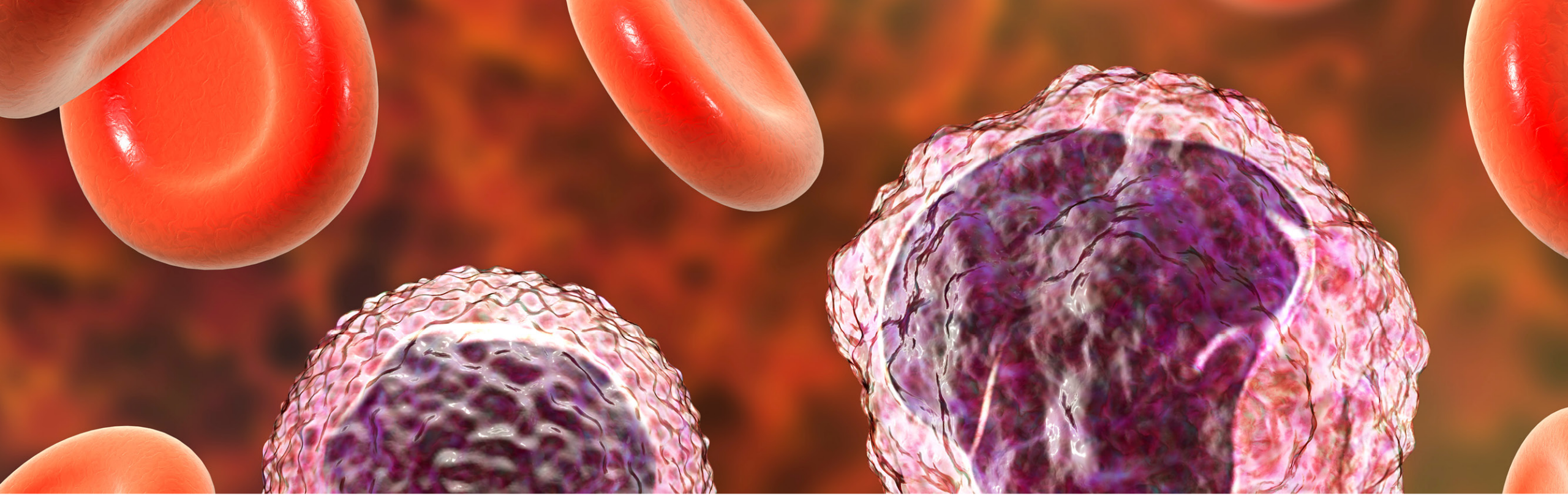



Saultz JN, et al. *J Clin Med*. 2016;5(3):33; NCCN Clinical Practice Guidelines: Acute Myeloid Leukemia. V1.2022. Accessed April 26, 2022.

# Options for Maintenance




Reville PK, et al. *Front Oncol*. 2021;10:619085; NCCN Clinical Practice Guidelines: Acute Myeloid Leukemia. V1.2022. Accessed April 26, 2022.

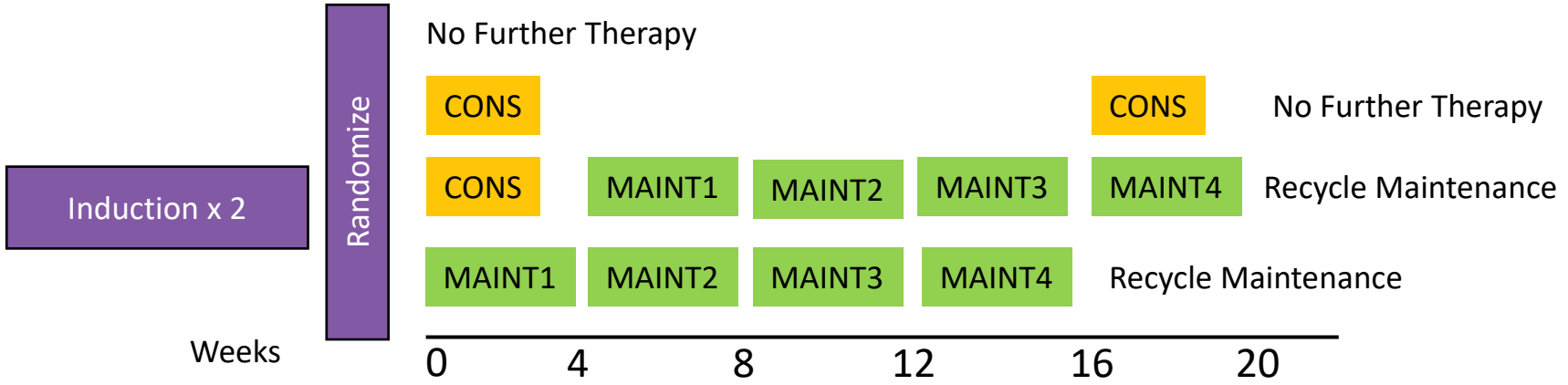


# Chemotherapy/Immunotherapy

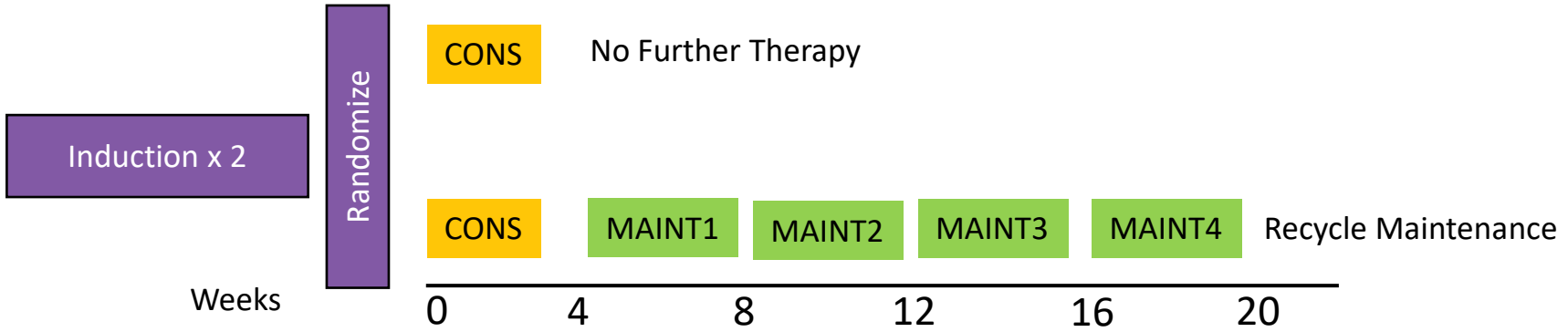
# Impact of Consolidation and/or Maintenance Chemotherapy: The German AML Cooperative Group

**Objective**: Assess impact of consolidation and/or maintenance chemotherapy on relapse risk

## 1978 Pilot Study




## 1982 Randomized Trial




**Maintenance Cycle 1:**
Ara-C 100 mg/m$^2$ q12h SQ days 1-5
DNR 45 mg/m$^2$ IV days 3 and 4

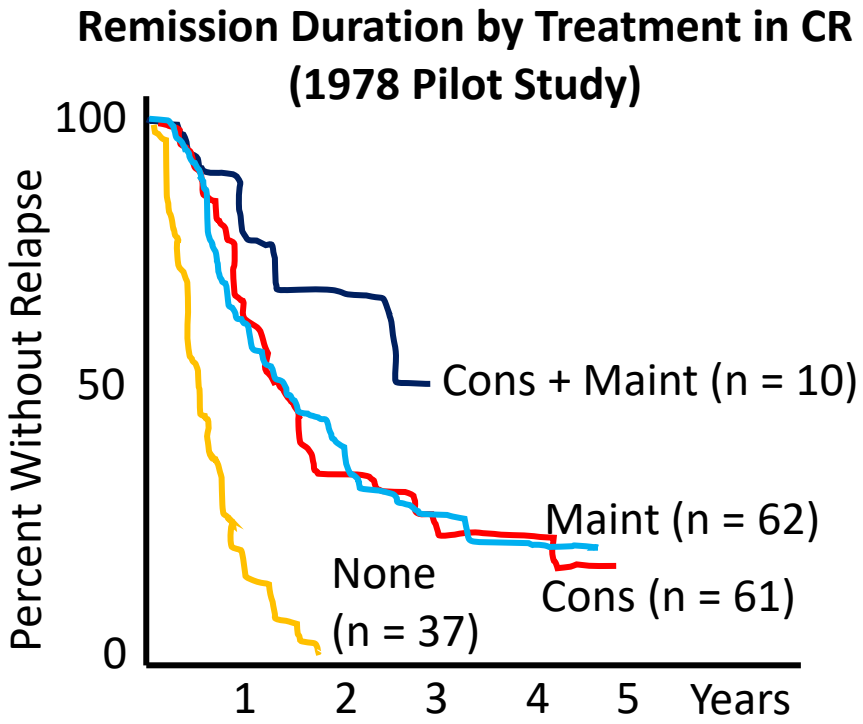
**Maintenance Cycles 2 and 4:**
Ara-C 100 mg/m$^2$ q12h SQ days 1-5
TG 200 mg/m$^2$/d PO days 1-5

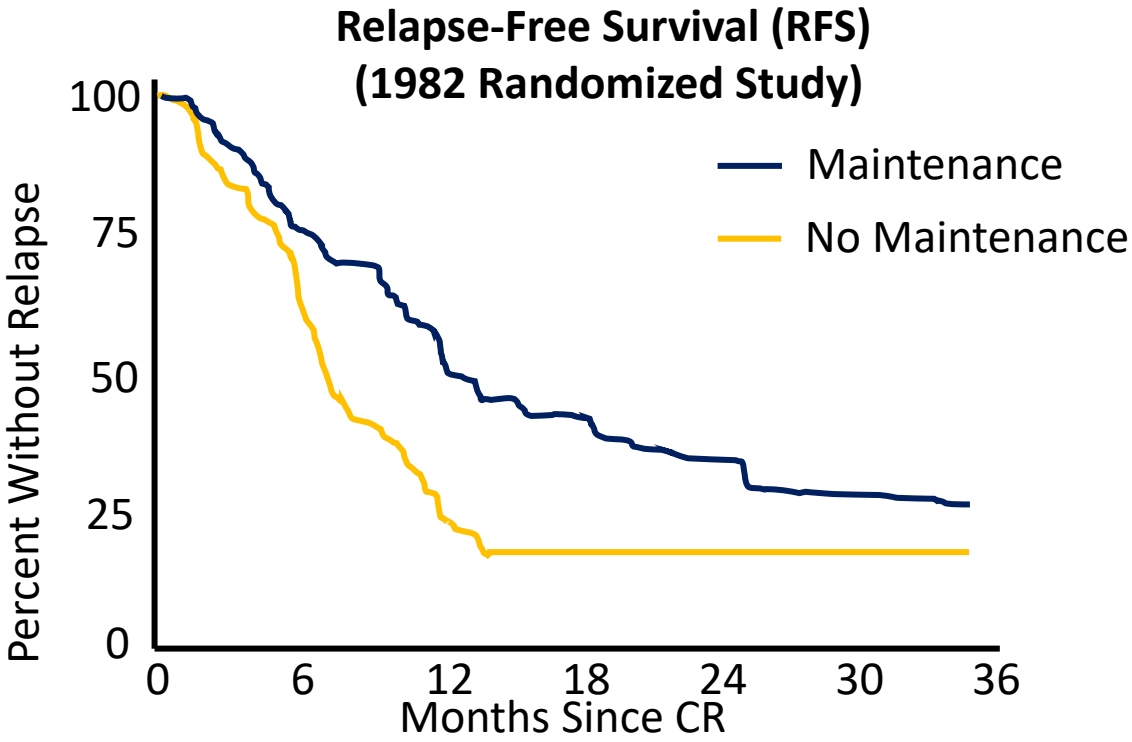
**Maintenance Cycle 3:**
Ara-C 100 mg/m$^2$ q12h SQ days 1-5
Cyclophosphamide 1 g/m$^2$ IV day 3

Abbreviations: Ara-C, cytosine arabinosodie; CONS, consolidation; DNR, anorubicin; MAINT, maintenance; TG, 6-thioguanine.

Buchner T, et al. *J Clin Oncol*. 1985;3(12):1583-1589.

# Impact of Consolidation and/or Maintenance Chemotherapy: The German AML Cooperative Group




- If you do nothing after induction therapy, all patients will relapse
- Maintenance chemotherapy improves RFS

Buchner T, et al. *J Clin Oncol*. 1985;3(12):1583-1589.

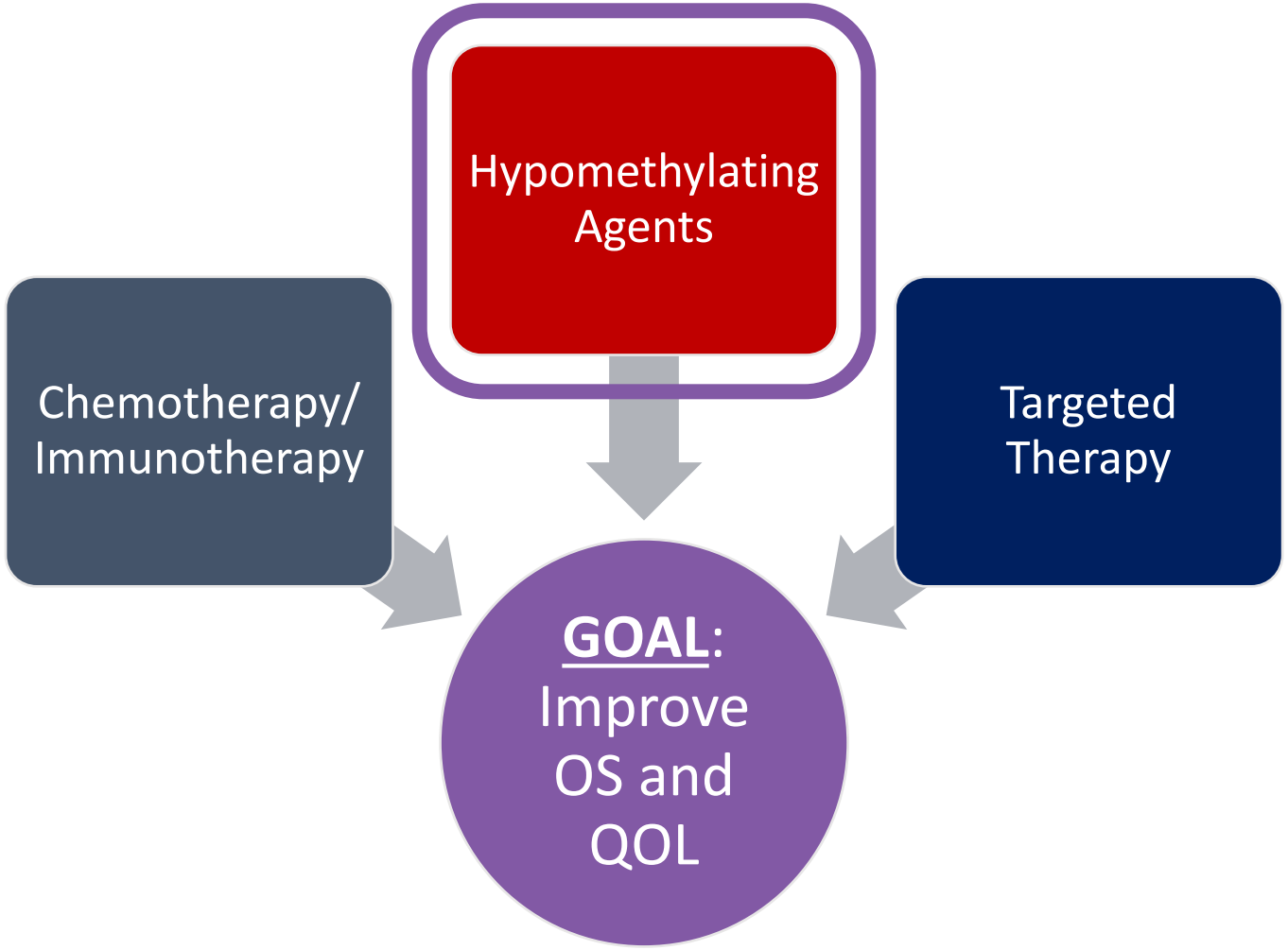
# Other Randomized Trials

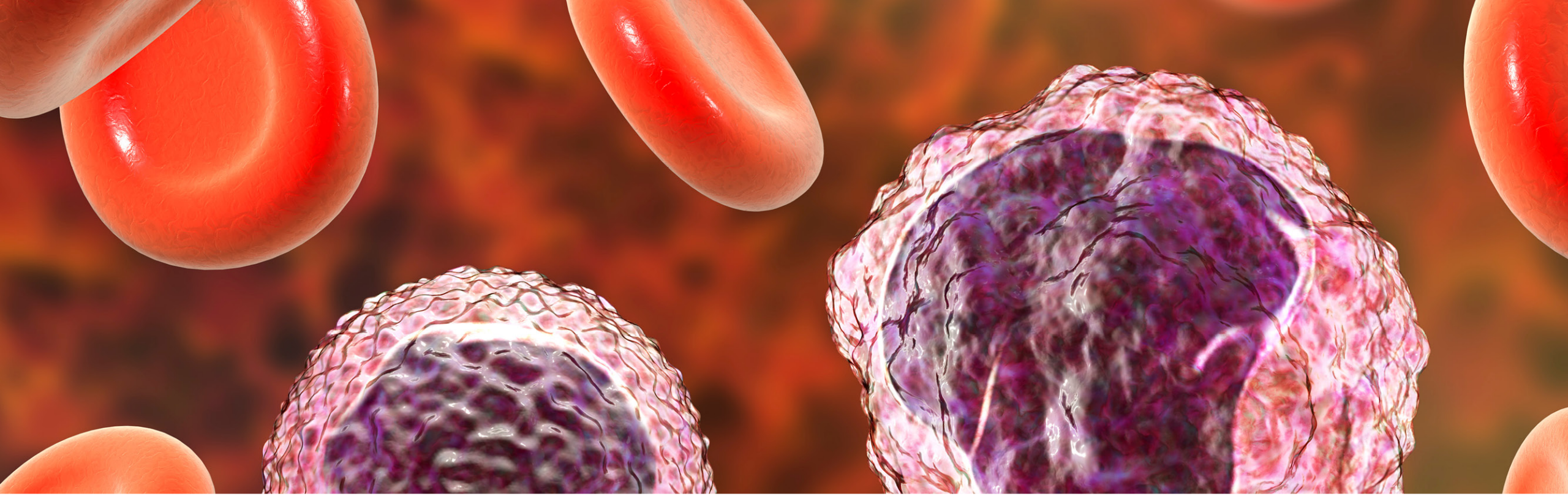
Sauter C, et al. *Lancet*. 1984;1(8373):379–382.
Johnson SA, et al. *Acta Oncol*. 1988;27(5):527–529.
Löwenberg B, et al. *J Clin Oncol*. 1998;16(3):872–881.
Palva IP, et al. *Eur J Haematol*. 1991;47(3):229–233.
Perel Y, et al. *J Clin Oncol*. 2002;20(12):2774–2781.
Reville P, et al. *Front Oncol*. 2021;10(619085):1-10.

| | N | Age | Maintenance Regimen Arms | DFS/LFS/RFS | OS |
|---|---|---|---|---|---|
| Swiss Group | 74 | 7-65 | • Ara-C + TG alternating with Ara-C + VC + prednisone<br>• Placebo | No difference in DFS | No difference in OS |
| SW Leukemia Group | 32 | 18-74 | • TG + etoposide alternating with CCNU<br>• Placebo | No difference in DFS | Not reported |
| EORTC/HOVON | 147 | 60-88 | • Low-dose Ara-C<br>• Placebo | Median DFS 51 weeks vs 29 weeks ($P$ = 0.006) | No difference in OS |
| Finnish Leukemia Group | 108 | 16-59 | • Ara-C + TG<br>• Human leukocyte interferon<br>• Placebo | No difference in DFS | No difference in OS |
| Group LAME | 70 | < 20 | • Oral 6-mercaptopurine + pulse SQ cytarabine<br>• Placebo | No difference in 5-year DFS | Inferior OS |
| AML-12 | 550 | 15-60 | • Interleukin-2<br>• Placebo | No difference in DFS | Inferior OS |
| UK MRC | 362 | 44-75 | • Interferon alpha<br>• Placebo | No difference in DFS | No difference in OS |

No improvement in OS with chemotherapy and/or immunotherapy maintenance

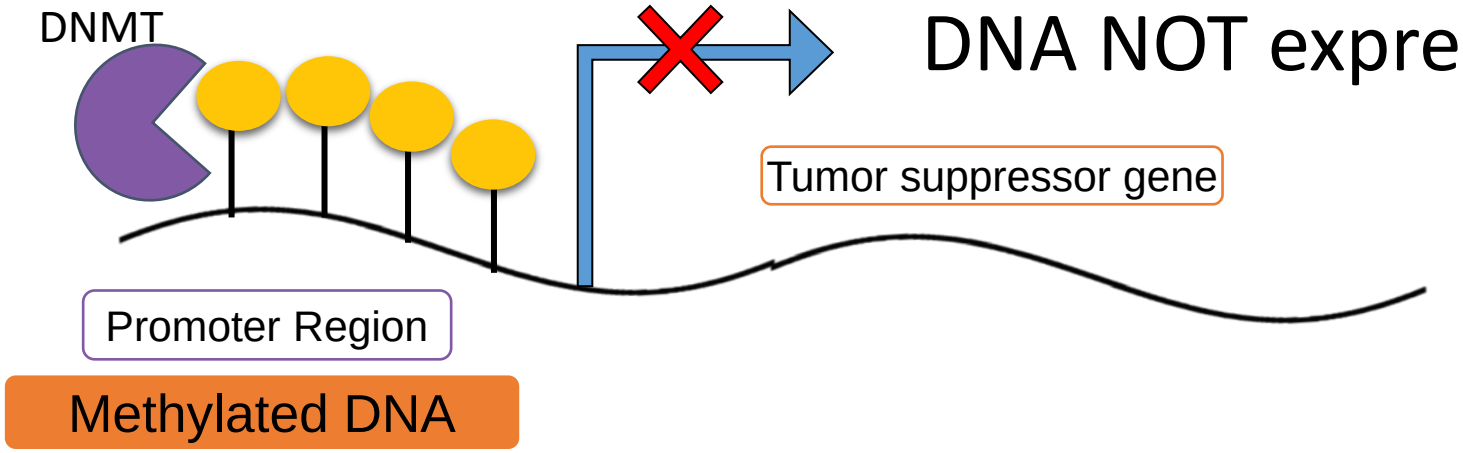
# Options for Maintenance

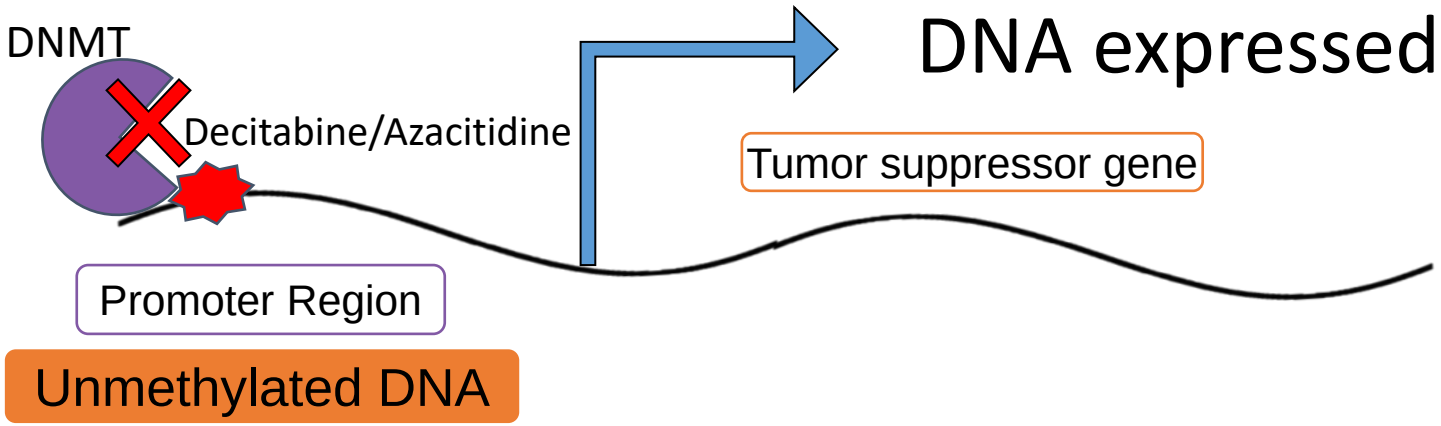




# Hypomethylating Agents

# Hypomethylating Agent Mechanism of Action



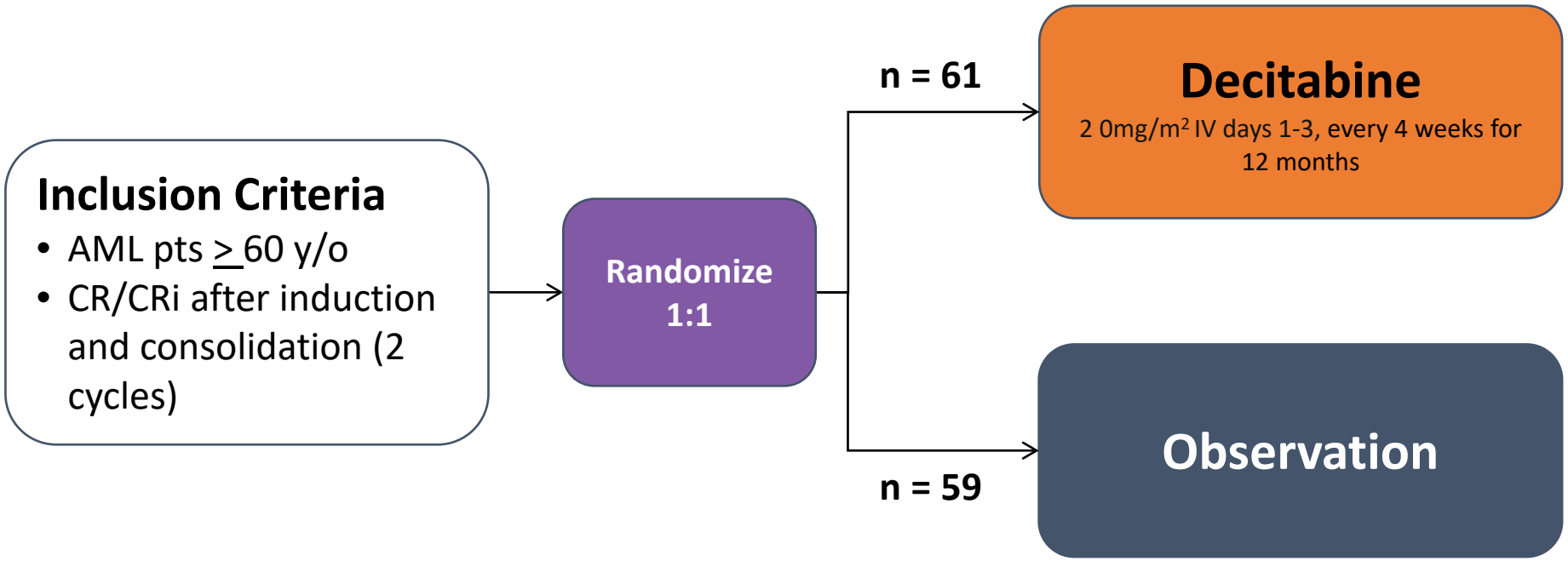




Abbreviation: DNMT, DNA methyltransferase

Christman JK. *Oncogene*. 2002;21(35):5483-5495.

Worden FP, Perissinotti AJ, Marini BL, eds. *Cancer Pharmacology & Pharmacotherapy Review*. demosMEDICAL; 2016.

# ECOG-ACRIN E2906: Decitabine Maintenance




**Key Patient Characteristics**

- Median age: 69 years
- Mostly intermediate risk (74.2%)
- 87.5% of patients were FLT3-ITD-negative
- 96% ECOG PS 0-1

## Study Design

Phase 2, open-label, randomized controlled trial (RCT)

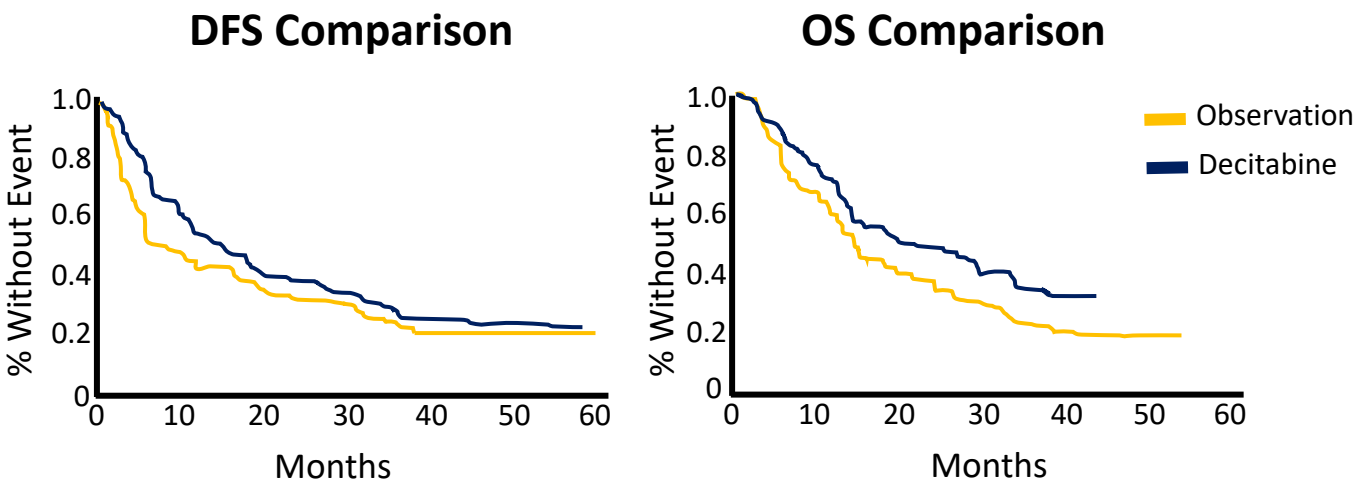
## Primary Outcome

Disease-free survival

Foran JM, et al. *Blood*. 2019;134(suppl 1):115.

# Outcomes: Decitabine Maintenance

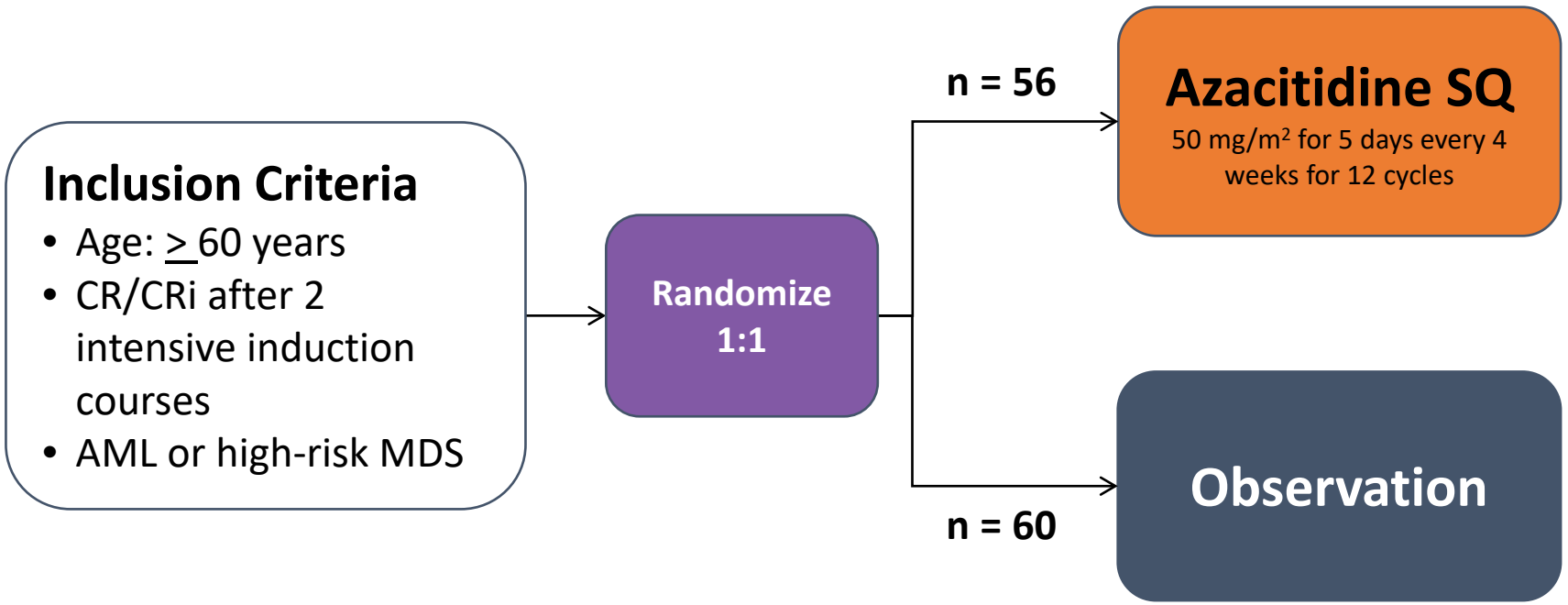
| | DFS | OS | FLT3-ITD negative OS |
|---|---|---|---|
| Decitabine | 15.3 months | 25.8 months | 38.3 months |
| Observation | 8.2 months | 19.5 months | 25.2 months |
| | HR = 0.77<br>95% CI, 0.50-1.19<br>*P* = 0.12 | HR = 0.69<br>95% CI, 0.43-1.09<br>*P* = 0.06 | P = 0.039 |




- Decitabine maintenance for 1 year was associated with improved OS and a trend for a longer DFS
- A significantly improved outcome was observed for the FLT3-ITD negative subgroup

Foran JM, et al. *Blood*. 2019;134(suppl 1):115.

# HOVON97: Azacitidine Maintenance




| | Observation | Azacitidine |
|---|---|---|
| Median age | 69 | 69 |
| WHO PS<br>0<br>1<br>2 | <br>38%<br>57%<br>- | <br>52%<br>30%<br>9% |
| AML | 90% | 89% |
| Unfavorable cytogenetics | 23% | 16% |

## Study Design

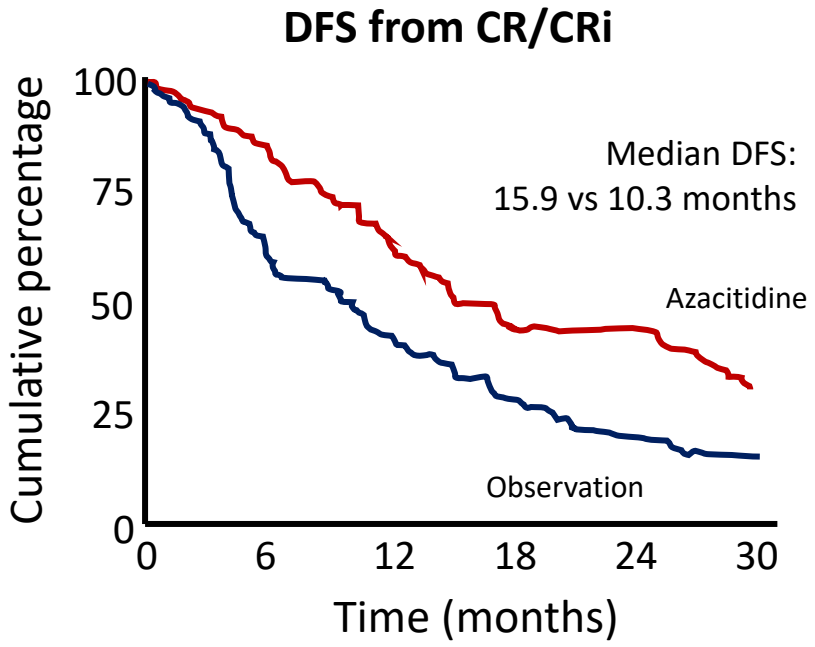
Phase 3, open-label, RCT

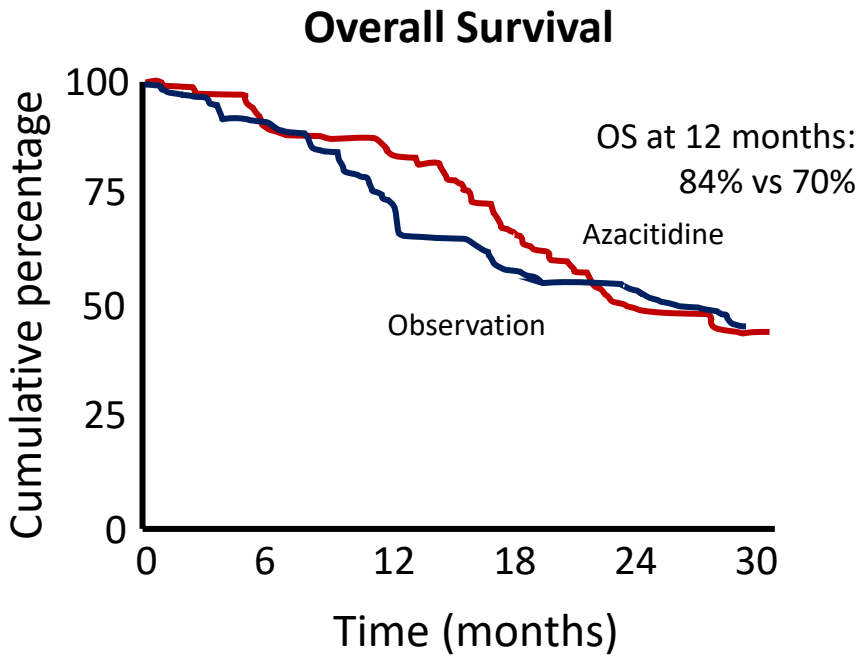
## Primary Outcome

Disease-free survival

Huls G, et al. *Blood*. 2019;133(13):1457-1464.

# Outcomes: Azacitidine Maintenance




- Improved DFS, but no improvement in OS with azacitidine SQ maintenance
- Higher frequency of severe side effects with maintenance (25% vs 7%)

Huls G, et al. *Blood*. 2019;133(13):1457-1464.

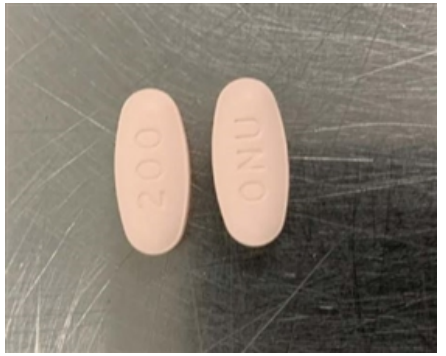
# Oral Azacitidine

**FDA approval September 2020** for continued treatment of patients with acute myeloid leukemia who achieved first complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following intensive induction chemotherapy and are not able to complete intensive curative therapy

**Dose**: 300 mg PO once daily days 1-14 of 28-day cycle until disease progression or unacceptable toxicity

- Anti-emetic premedication required for first 2 cycles

Oral azacitidine should not be used as a substitute for other formulations



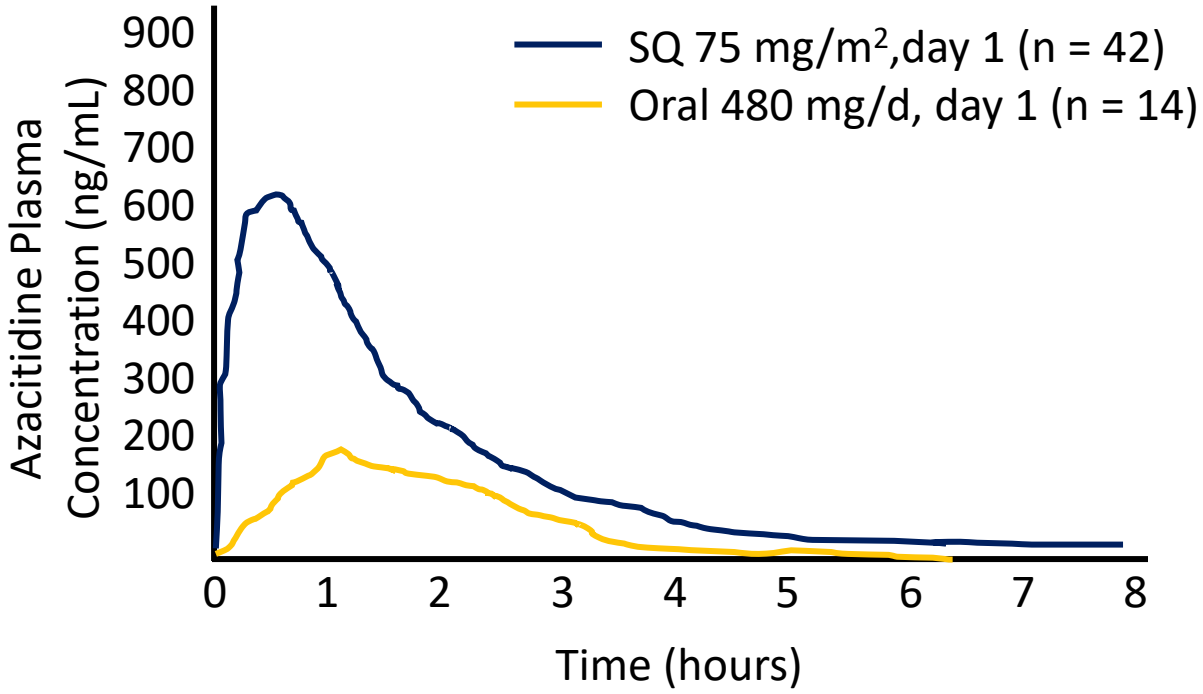

https://www.uofmhealth.org/health-library/d05293a1

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-onureg-azacitidine-tablets-acute-myeloid-leukemia

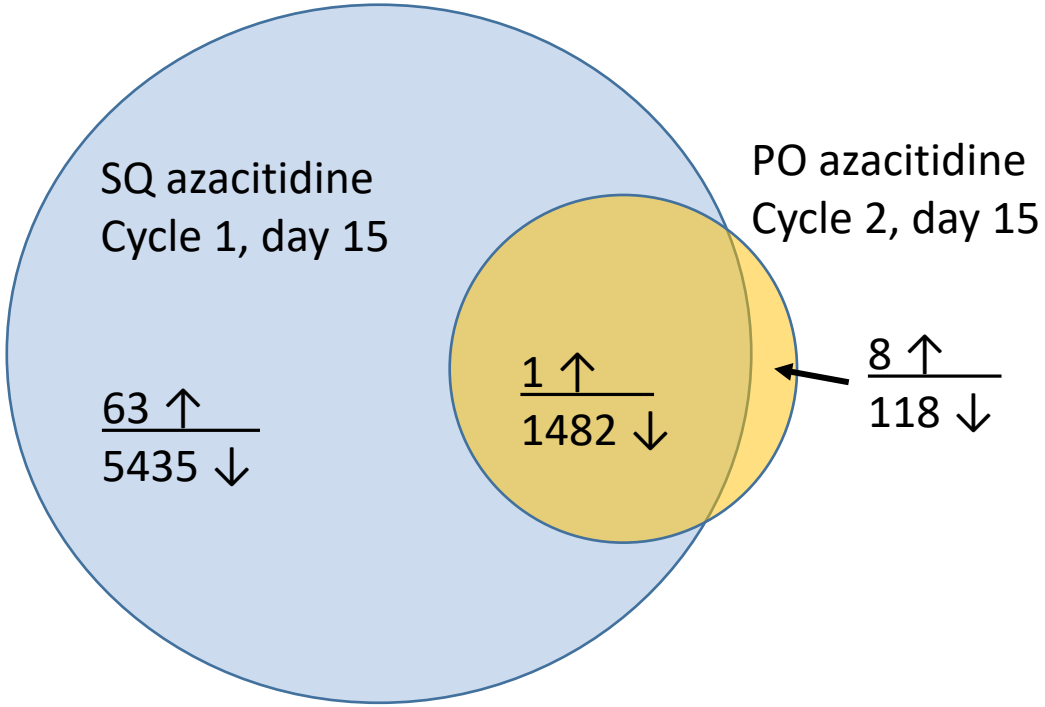
Onureg. Package insert. Celgene; 2020.

# Oral vs IV/SQ Azacitidine

## Bioavailability

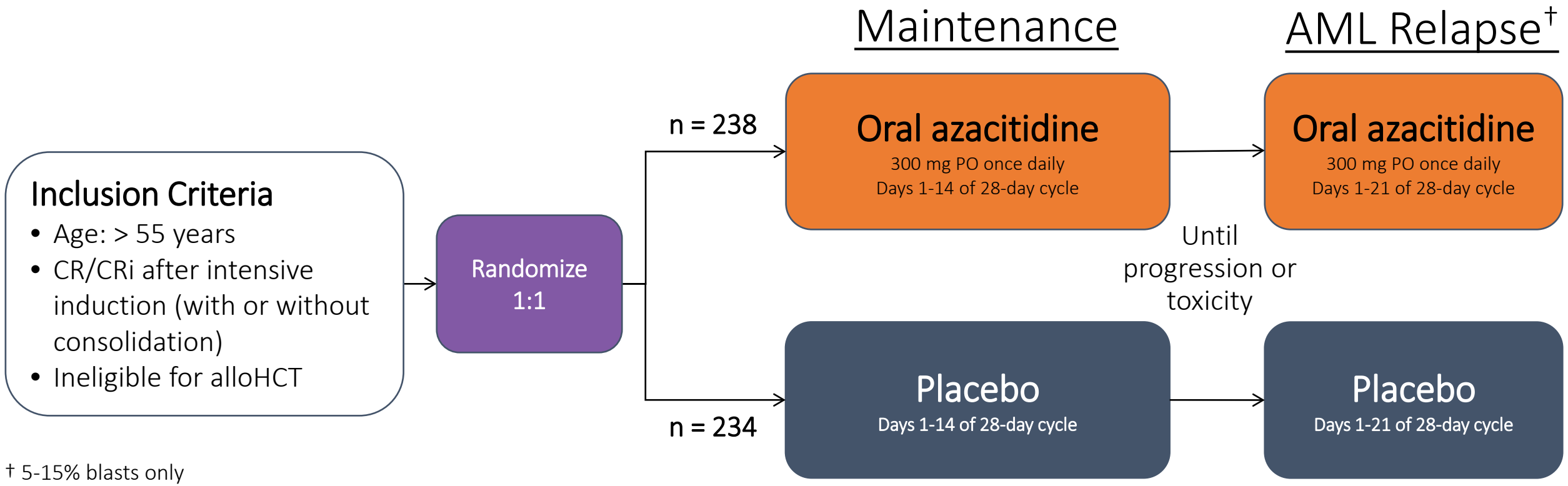



## Hypomethylation Potential




Garcia-Manero G, et al. *J Clin Oncol*. 2011;29(18):2521-2527.

# QUAZAR AML-001: Oral Azacitidine




† 5-15% blasts only

## Study Design

Phase 3, double-blind, RCT

## Primary Outcome

Overall survival

Wei AH, et al. *N Engl J Med*. 2020;383(26):2526-2537.

# QUAZAR AML-001: Baseline Characteristics

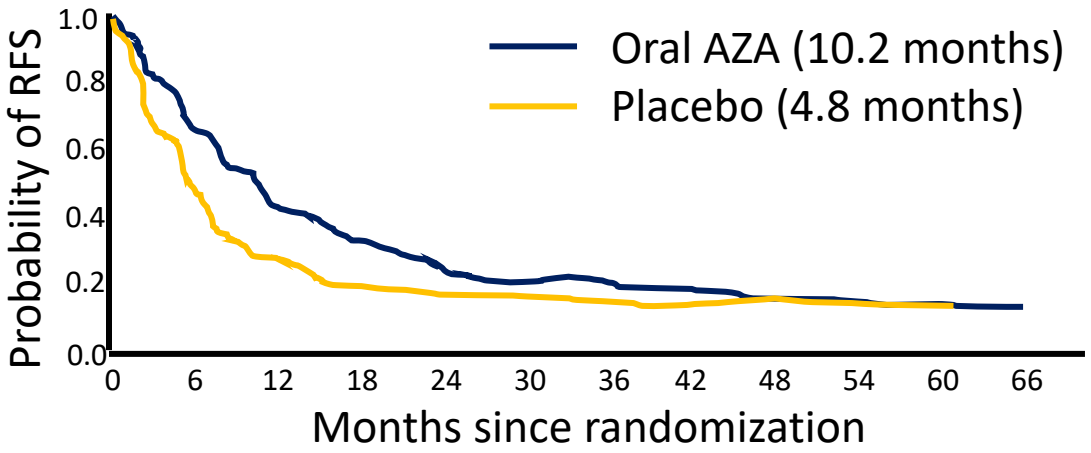
| | Oral azacitidine | Placebo |
|---|---|---|
| Median age (range) | 68 (55-86) | 68 (55-82) |
| ECOG PS | | |
| 0 | 49% | 47% |
| 1 | 42% | 45% |
| 2 or 3 | 9% | 7% |
| Cytogenetic risk | | |
| Intermediate | 85% | 87% |
| Poor | 15% | 13% |
| Median BM blasts (range) | 2 (0-5%) | 2 (0-6.5%) |
| Measurable residual disease positivity ($10^{-3}$) | 43% | 50% |
| Median time from CR/CRi to randomization (days) | 84.5 | 86 |

| | Oral azacitidine | Placebo |
|---|---|---|
| Number of consolidation cycles | | |
| 0 | 22% | 18% |
| 1 | 46% | 44% |
| 2 | 29% | 33% |
| 3 | 3% | 6% |
| 4 | 0% | 0% |
| Reason for AlloHCT ineligibility | | |
| Age | 65% | 65% |
| Comorbidities | 22% | 21% |
| No donor | 16% | 15% |
| Patient decision | 8% | 14% |
| Performance Status | 6% | 4% |
| Unfavorable Cytogenetics | 3% | 4% |
| Other | 12% | 9% |

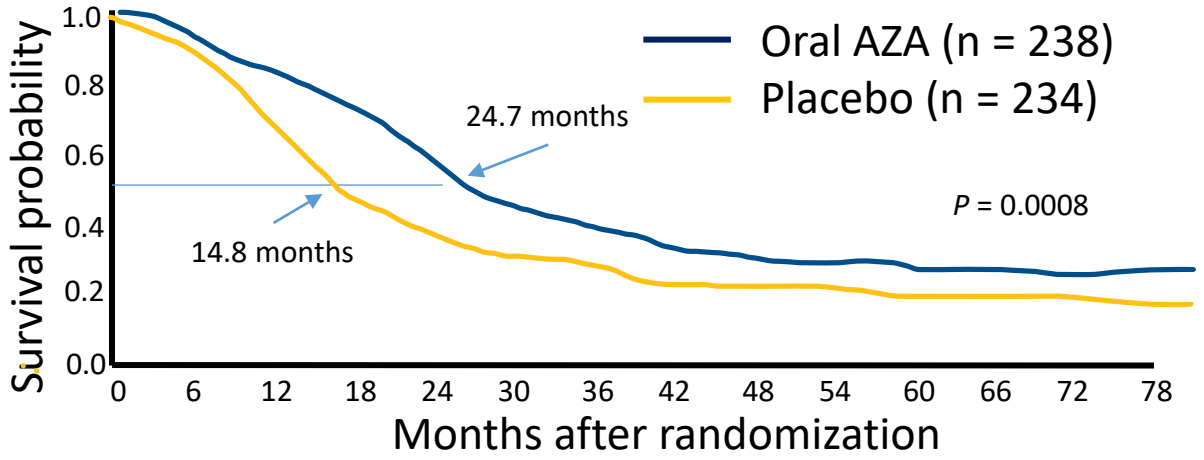
Wei AH, et al. *N Engl J Med*. 2020;383(26):2526-2537.

# QUAZAR AML-001: Efficacy

**Relapse-Free Survival**




**Overall Survival**

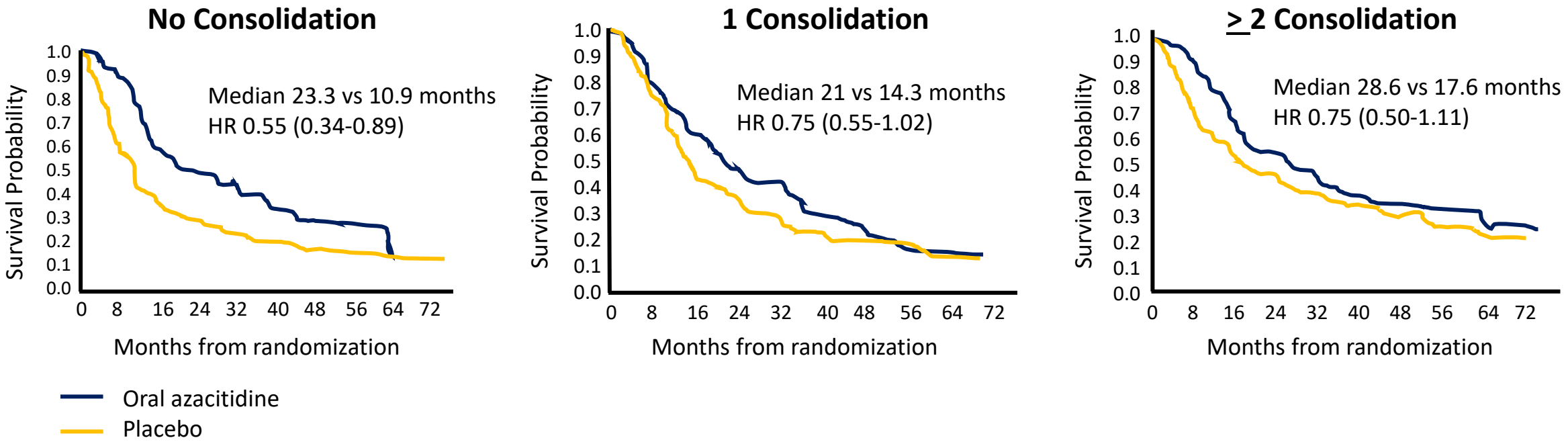



| Post-study treatment | Oral Azacitidine | Placebo |
|---|---|---|
| **Any subsequent therapy** | **58%** | **73%** |
| Intensive chemotherapy | 29% | 38% |
| Low-intensity therapy | 40% | 47% |
| Stem cell transplant | 6% | 14% |


Wei AH, et al. *N Engl J Med*. 2020;383(26):2526-2537.
Wei AH, et al. ASH Annual Meeting Oral Presentation. Section 615, abstract 871.

# Impact of Consolidation Therapy

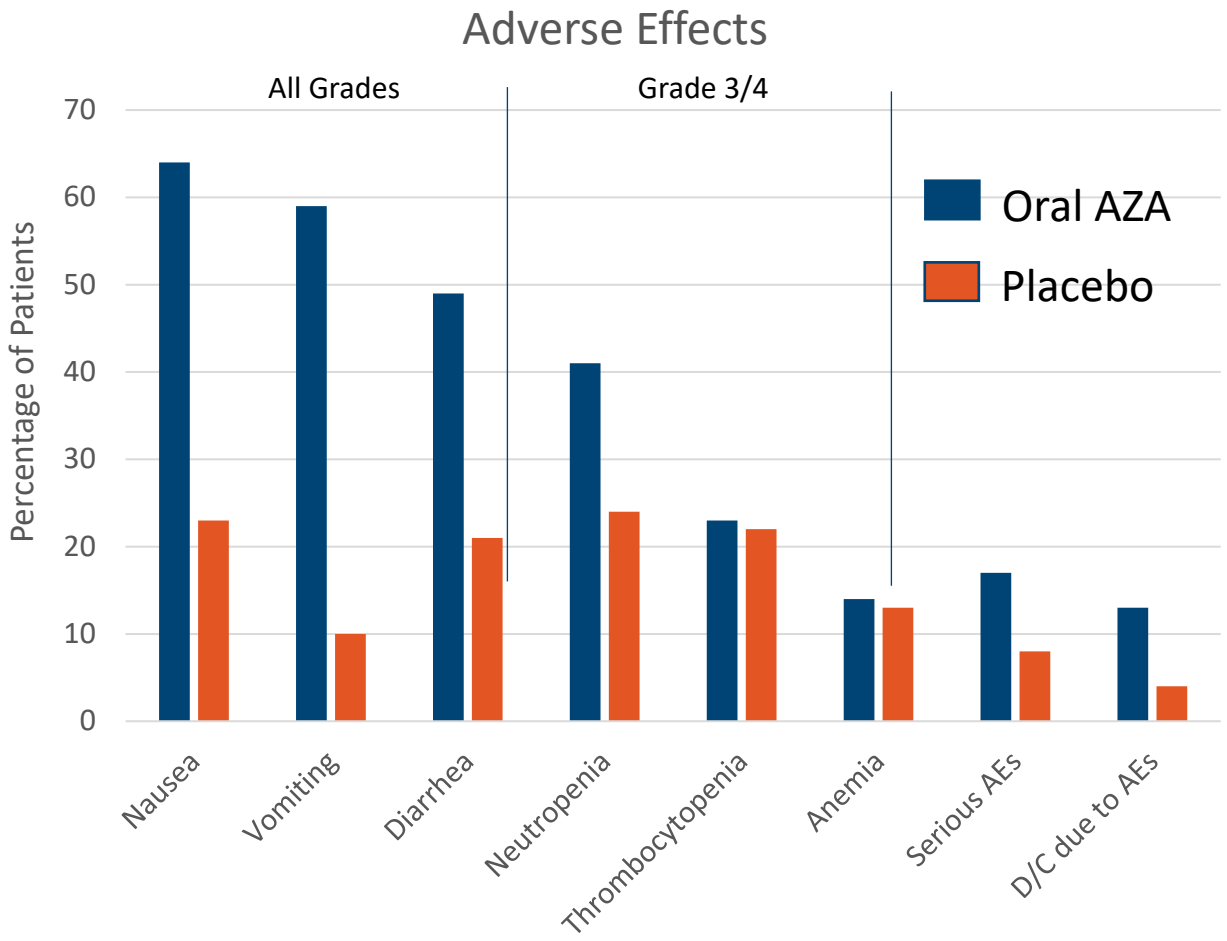
**Overall Survival**




OS benefit restricted to patients who did not receive consolidation

Wei A, et al. *Blood*. 2020;136(suppl 1):38–40.

# Toxicity and QOL Analysis




**Quality of Life**

- QOL assessed via the FACIT-Fatigue scale and EQ-5D-3L Health Utility Index
- QOL not worse for CC-486 except for cycles 22 and 23 (no adjustment for multiplicity)

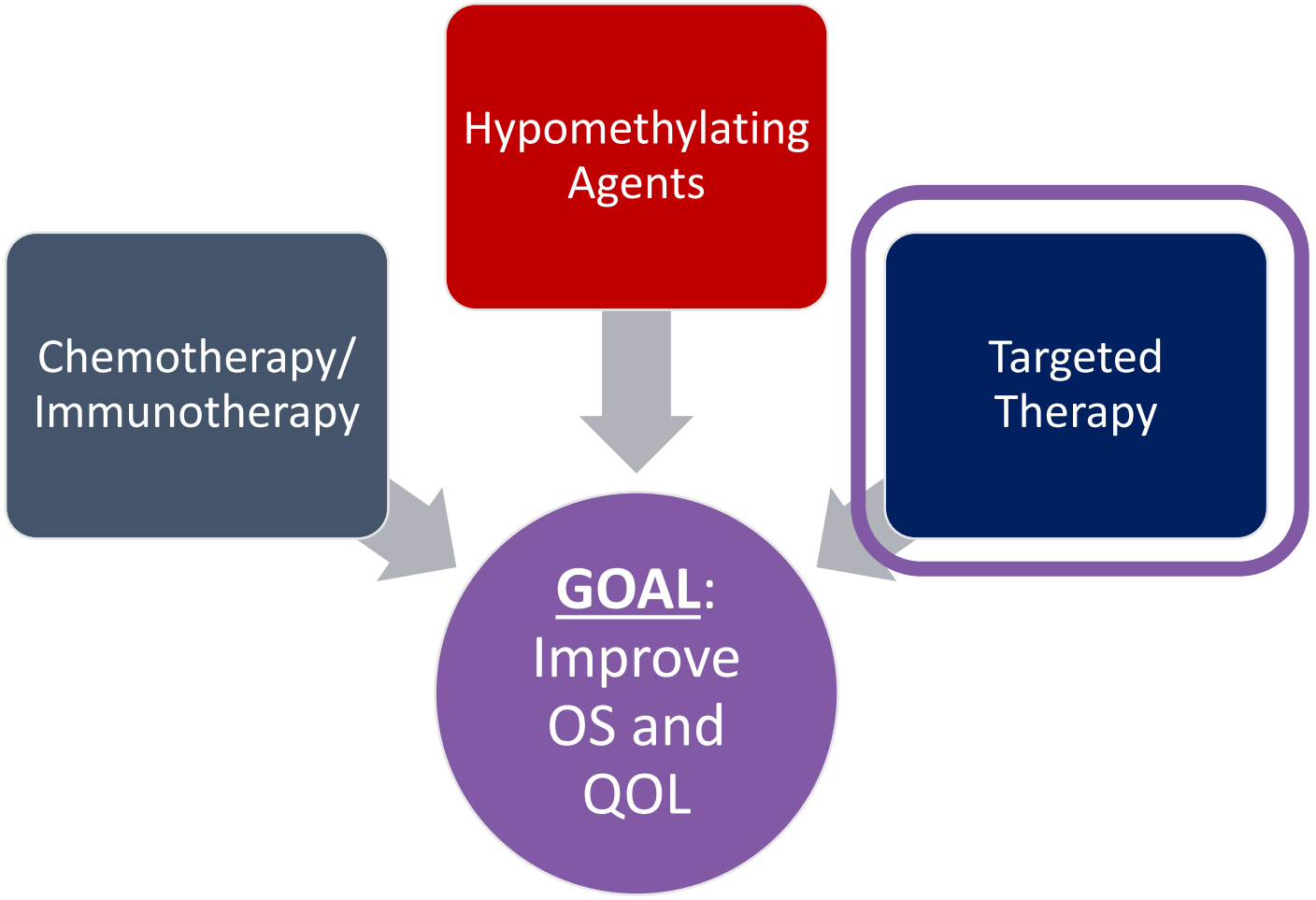
Wei AH, et al. *N Engl J Med*. 2020;383(26):2526-2537.

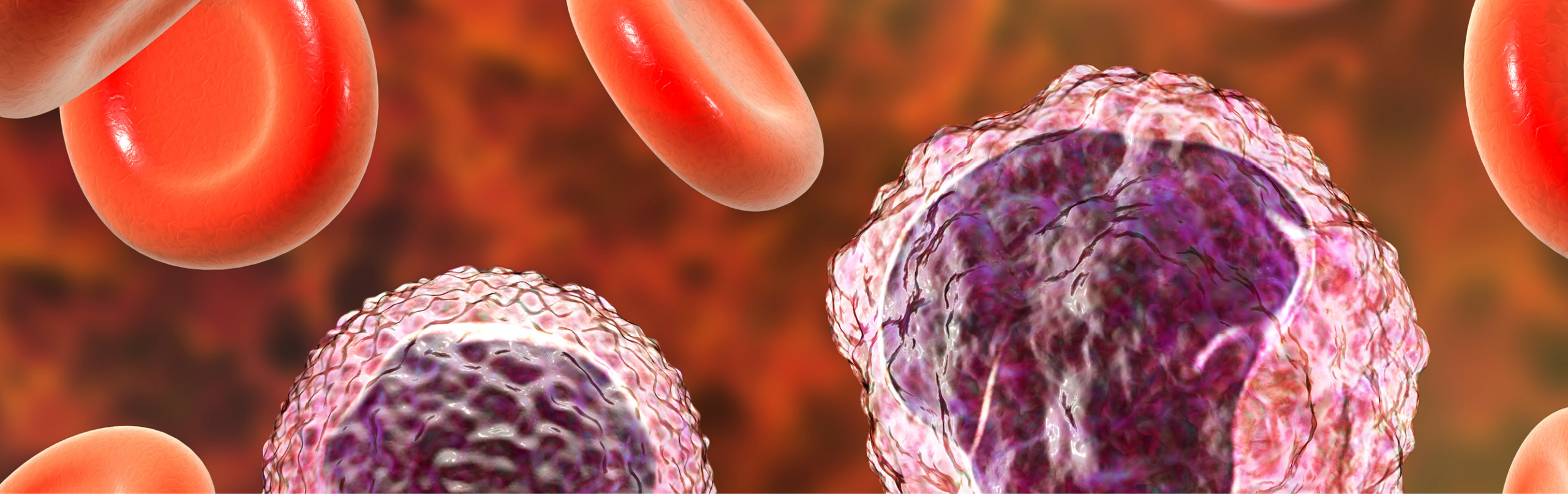
# Summary

- Maintenance parenteral hypomethylating agents do not consistently improve DFS and OS
- Oral azacitidine is the first agent to improve OS as maintenance therapy
- NCCN recommends to use this for patients with intermediate or poor risk disease
  - Who received prior intensive chemotherapy and are now in remission
  - Completed no consolidation, some consolidation, or a recommended course of consolidation AND
  - No alloHSCT is planned
- Do not substitute oral azacitidine with IV/SQ azacitidine

NCCN Clinical Practice Guidelines: Acute Myeloid Leukemia. V1.2022. Accessed April 26, 2022.

# Options for Maintenance





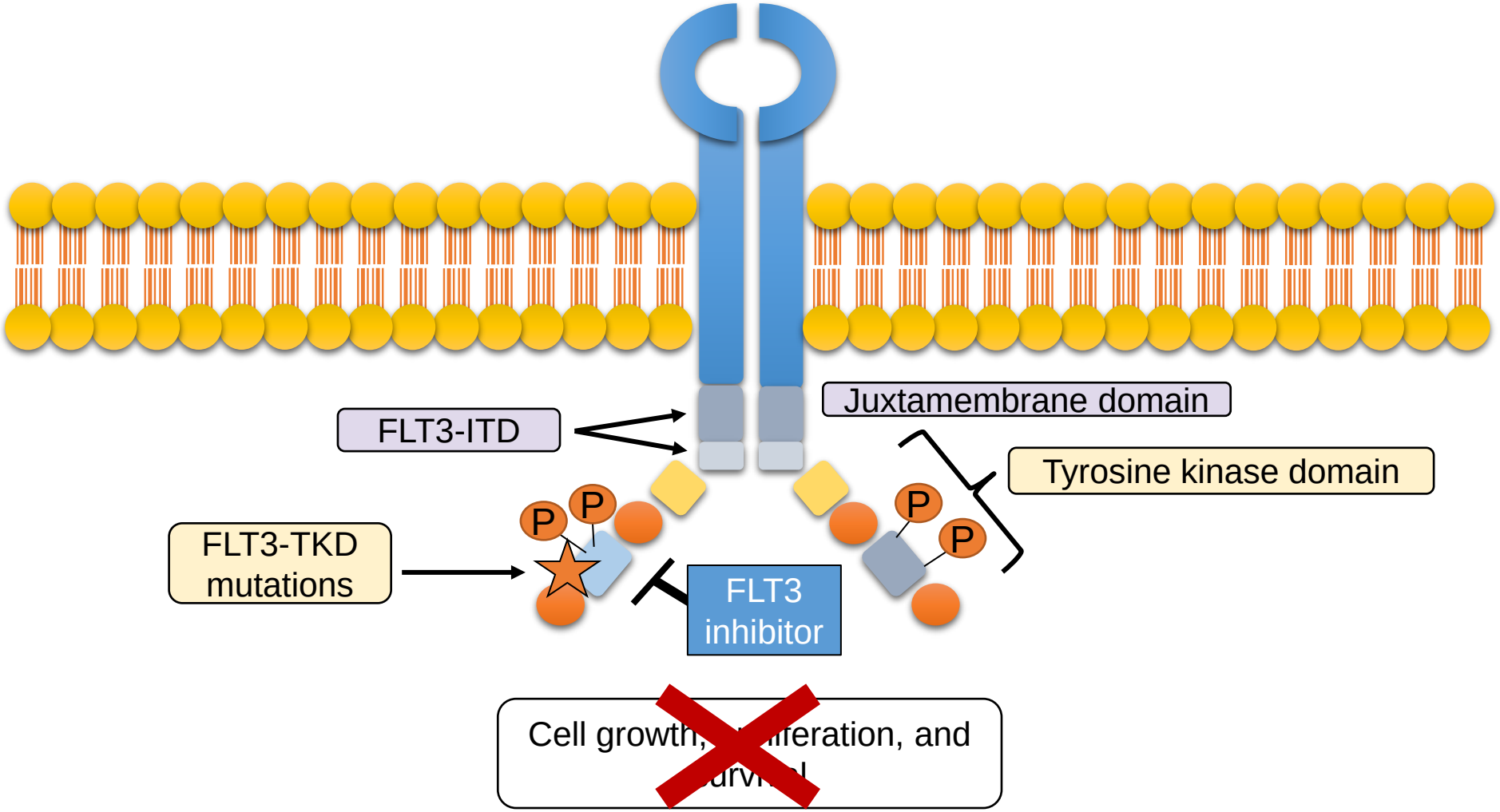
# Targeted Therapy

# FLT3-ITD Mutations

- FLT3 internal tandem duplication (FLT3-ITD) mutations occur in approximately 25% of adults with AML
  - Shorter remissions and higher relapse rates
- FLT3+ TKD AML 5-year survival is 53%
- FLT3+ ITD AML 5-year survival rate is as low as 15%
- Complete FLT3 mutation testing is important to identify appropriate patients for targeted treatment options
  - NCCN Guidelines for AML recommend molecular genetic testing for AML mutations during the initial patient workup to establish the diagnosis

Antar AI, et al. *Leukemia*. 2020;34(3):682-696.; NCCN Clinical Practice Guidelines: Acute Myeloid Leukemia. V1.2022. Accessed April 26, 2022.

# FLT3 Mutations and Maintenance Therapy



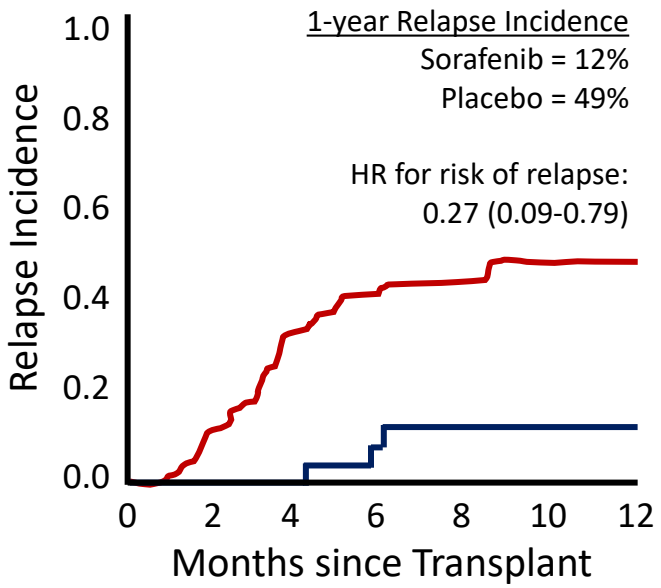

- Prognostic and predictive biomarker
- Type 1 inhibitors (midostaurin, gilteritinib)
- Type 2 inhibitors (sorafenib)

Weis TM, et al. *Crit Rev Oncol Hematol*. 2019;141:125-138.

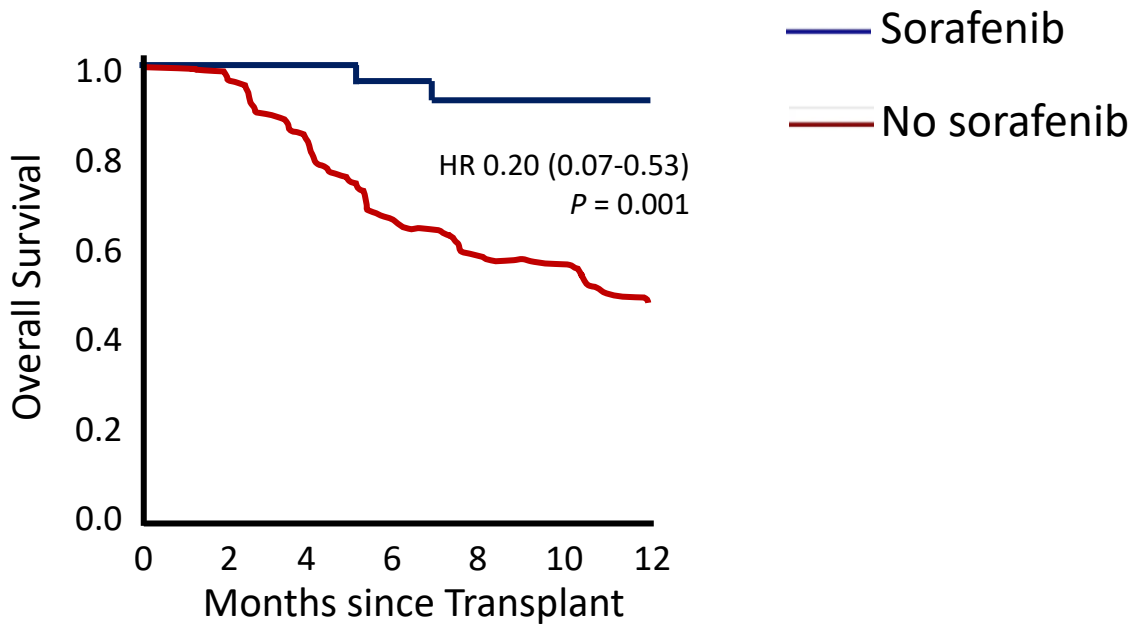
# Early Data: Retrospective Studies Suggest Benefit

- Retrospective, cohort study (n = 84)
- Patients who receive sorafenib vs no maintenance post-alloHCT
- Median 78 days post-HCT, median starting dose 400 mg/d (ending dose 200 mg/d)

**Cumulative Incidence of Relapse**

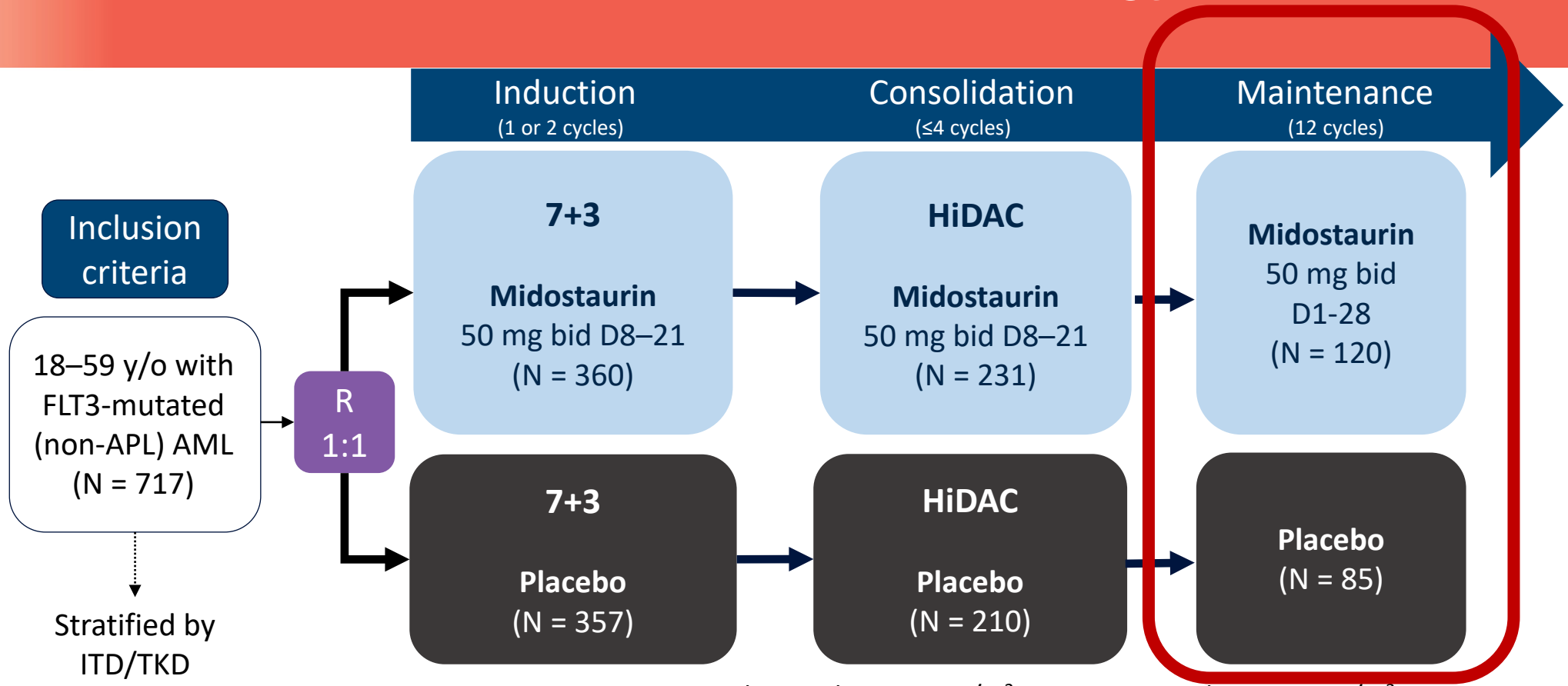



**Overall Survival**




Chappell G, et al. *Bone Marrow Transplant*. 2019;54(9):1518-1520.

# RATIFY Trial




7+3 = daunorubicin **60** mg/m$^2$ D1, 2, 3 + cytarabine 200 mg/m$^2$ D1–7
APL, acute promyelocytic leukemia; HiDAC, high-dose cytarabine

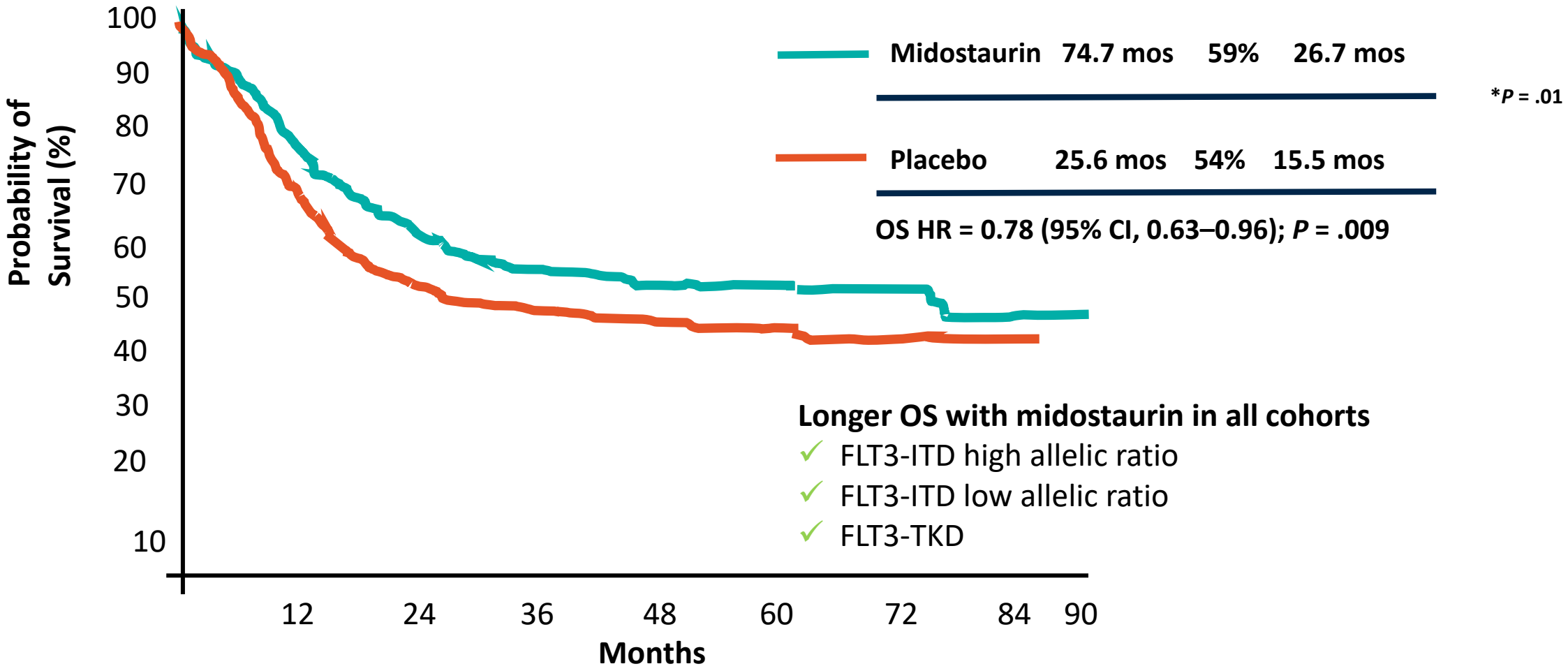
**Study Design**
Phase 3 double-blind RCT

**Primary End Point**
OS (not censored for SCT)

**Secondary End Point**
EFS

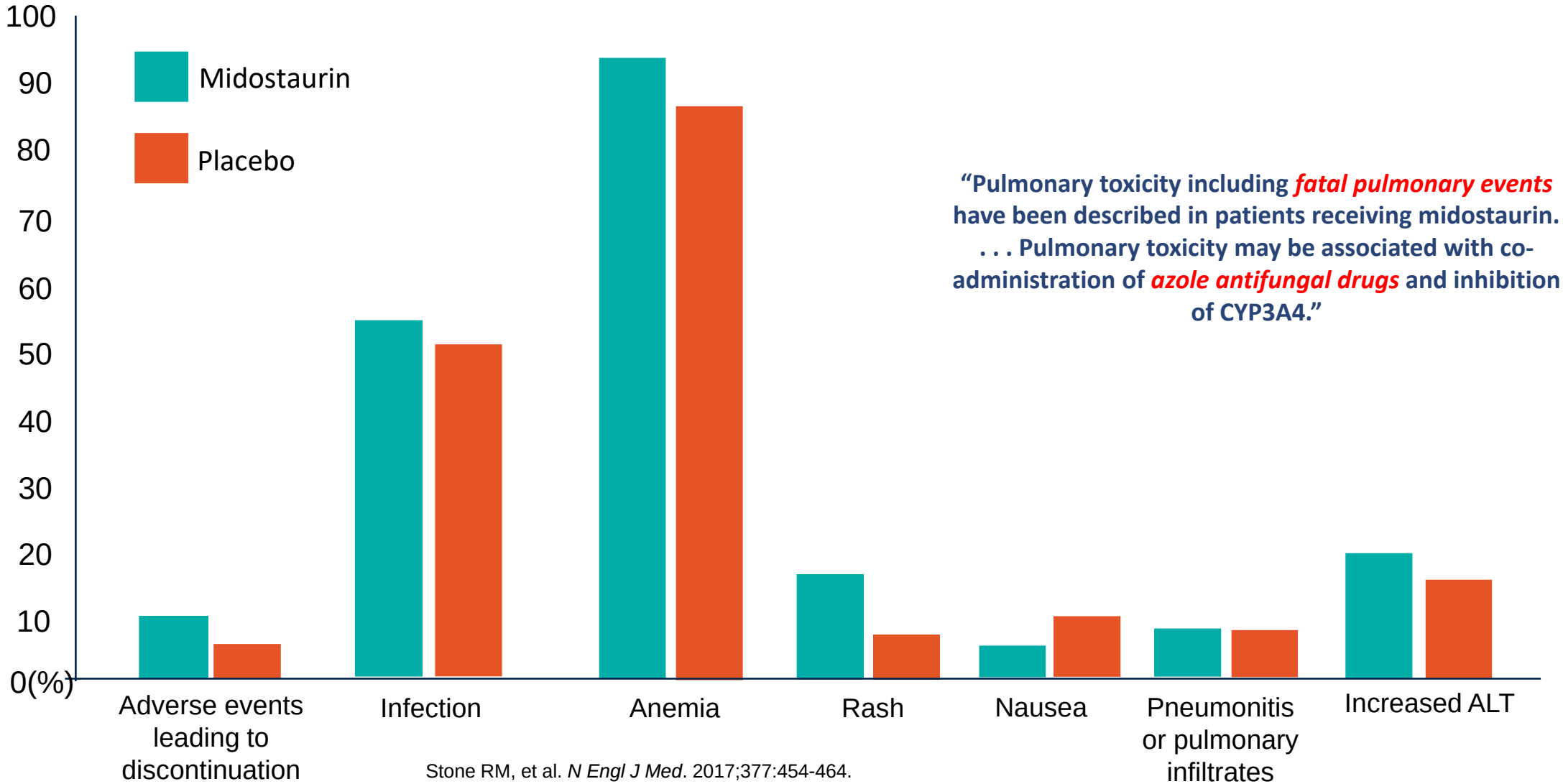
Stone RM, et al. *N Engl J Med.* 2017;377:454-464.

# Midostaurin Improves OS in FLT3+ AML




Stone RM, et al. *N Engl J Med.* 2017;377:454-464

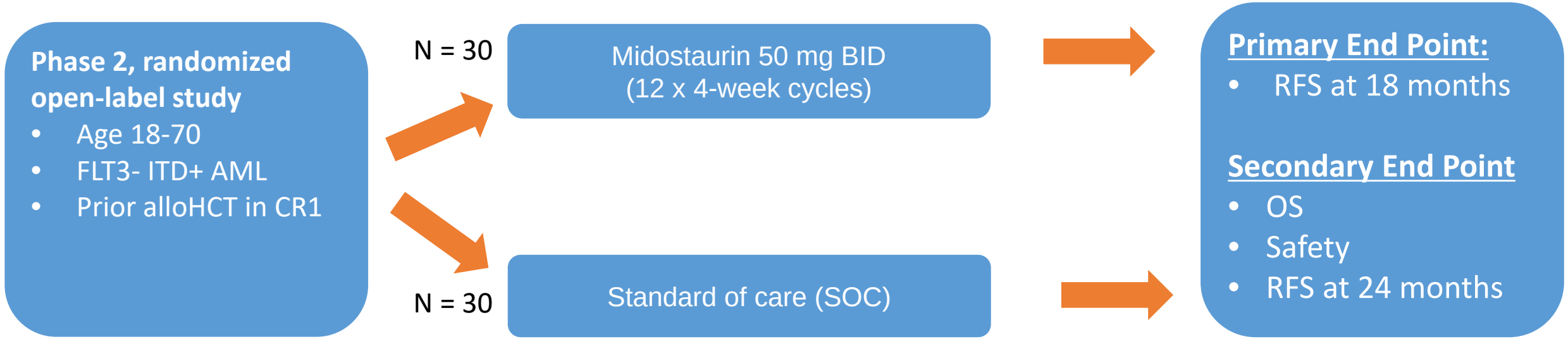
# Midostaurin: Toxicity Profile




**"Pulmonary toxicity including *fatal pulmonary events* have been described in patients receiving midostaurin. . . . Pulmonary toxicity may be associated with co-administration of *azole antifungal drugs* and inhibition of CYP3A4."**

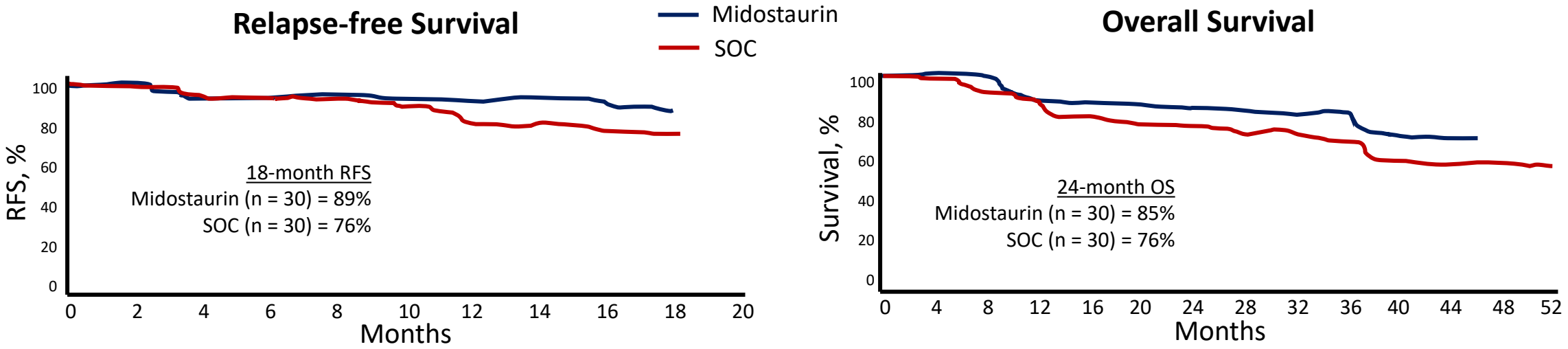

Stone RM, et al. *N Engl J Med*. 2017;377:454-464.
Stone RM, et al. *N Engl J Med*. 2017;377:454-464. Appendix [Protocol].

# RADIUS Trial: Midostaurin post-AlloHCT




Maziarz RT, et al. *Bone Marrow Transplant*. 2021;56(5):1180-1189.

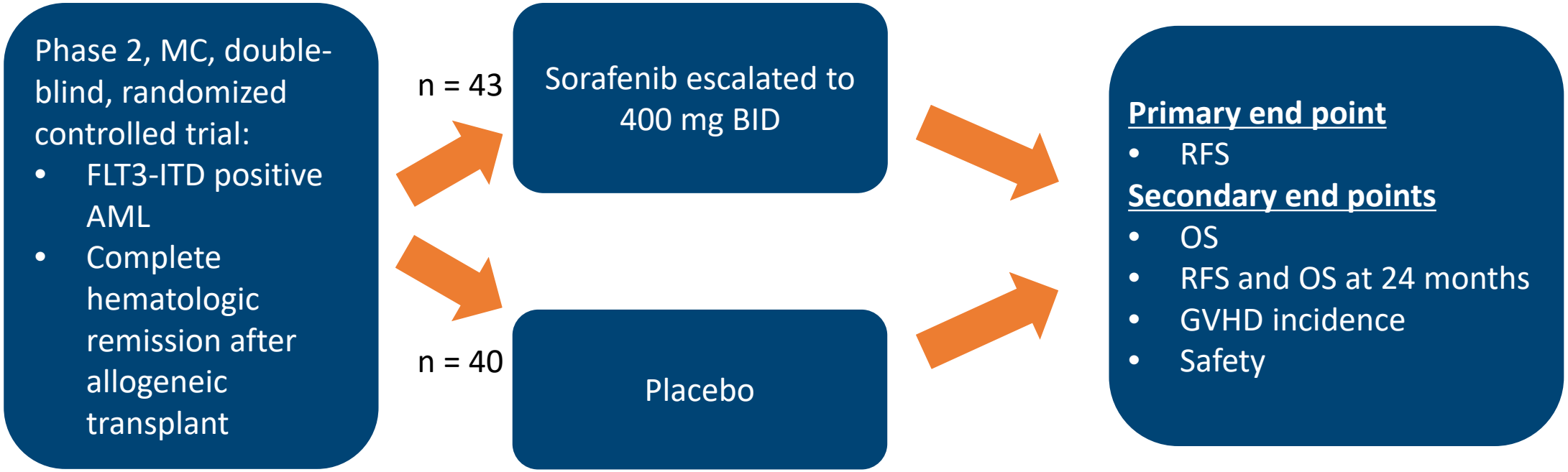
# RADIUS Trial: Midostaurin Outcomes




- No improvement in RFS or OS with midostaurin in FLT3-ITD+ AML
- AEs more common in midostaurin arm (similar AE profile to RATIFY trial)

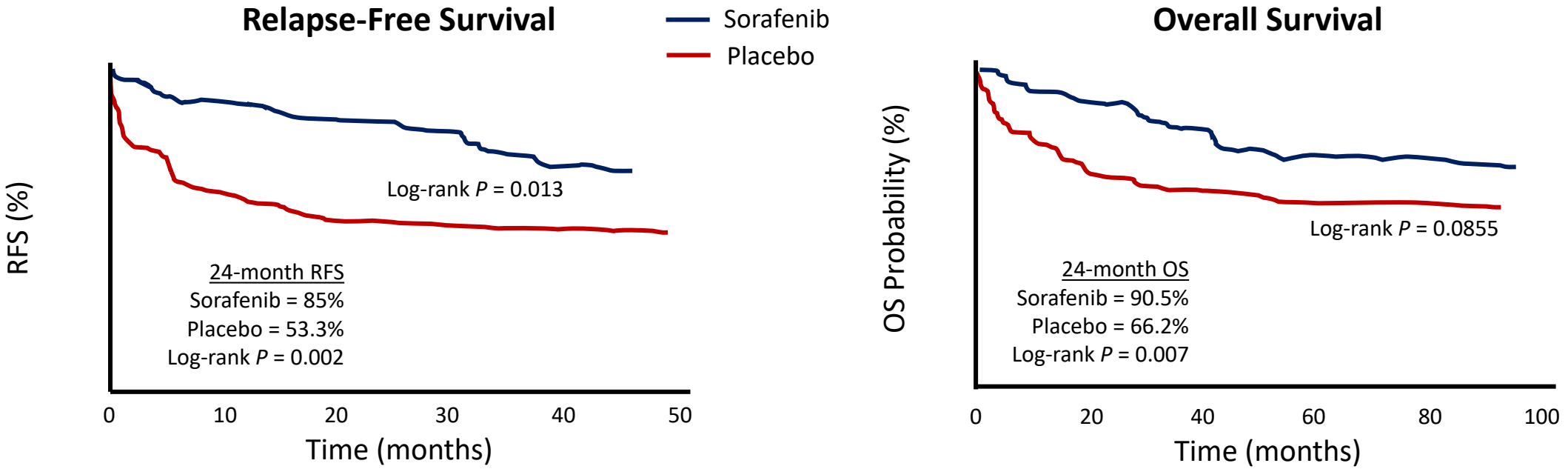
Maziarz RT, et al. *Bone Marrow Transplant*. 2021;56(5):1180-1189.

# SORMAIN Trial




Burchert A, et al. *J Clin Oncol*. 2020;38(26):2993-3002.

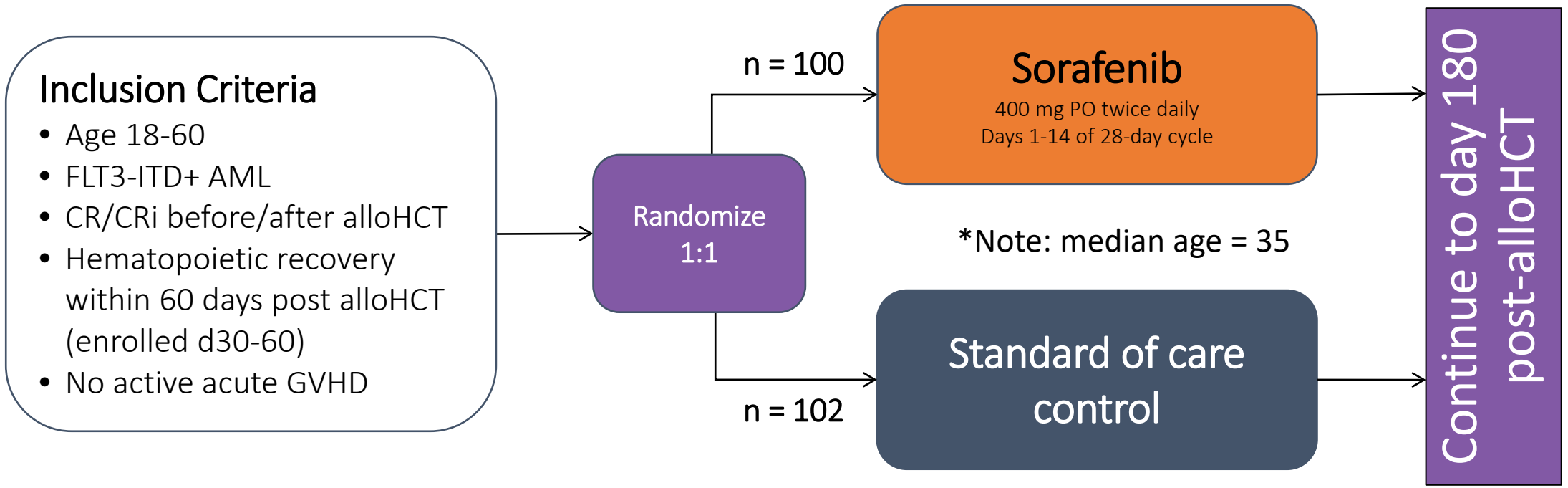
# SORMAIN Trial: Sorafenib Outcomes




- Improved median RFS with sorafenib. Median OS not reached in both arms
  - Improved 24-month OS with sorafenib
- Numerically higher acute and/or chronic GVHD with sorafenib (76.8 vs 59.8%)
- No difference in other AEs between the two groups

Burchert A, et al. *J Clin Oncol*. 2020;38(26):2993-3002.

# Sorafenib Phase 3 Maintenance Trial




## Study Design

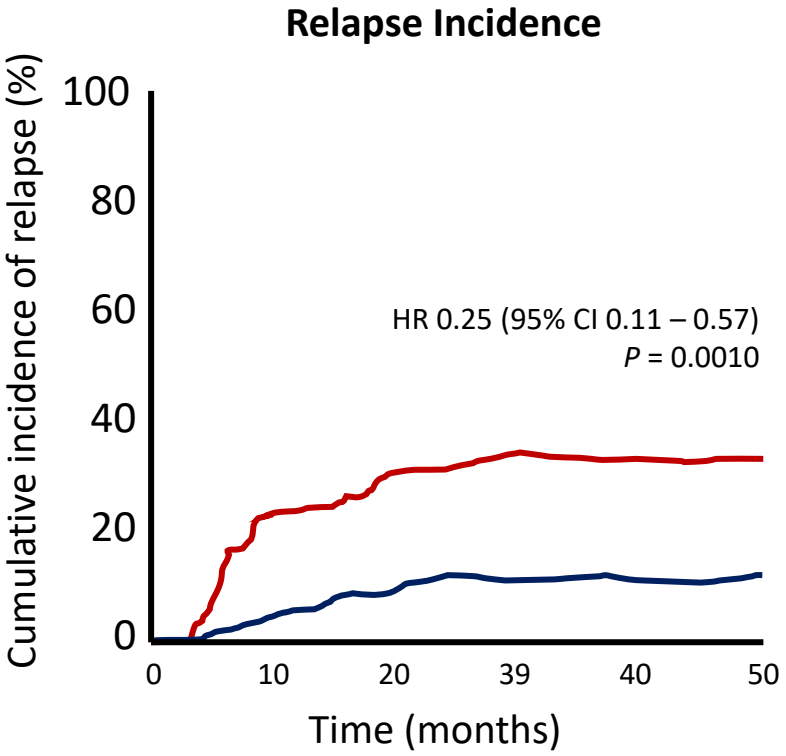
Phase 3, open-label, RCT

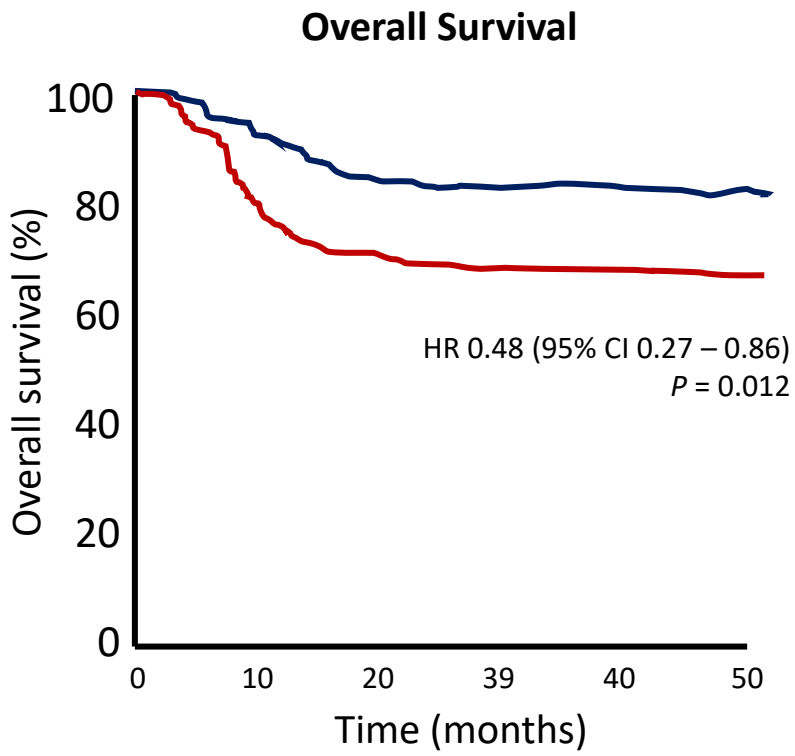
## Primary Outcome

Cumulative incidence of relapse

Xuan L, et al. *Lancet Oncol*. 2020;21(9):1201-1212.

# Sorafenib: Phase 3 Maintenance Results




| **Key Outcomes (Sorafenib vs Placebo)** | 2-year CIR | 2-year OS |
|---|---|---|
| | 11.9% vs 31.6% | 82.1% vs 68.0% |

Xuan L, et al. *Lancet Oncol*. 2020;21(9):1201-1212.

# Sorafenib Maintenance: Toxicity

| | Sorafenib (n = 100) | | Control (n = 102) | |
|---|---|---|---|---|
| | **Grade 1-2** | **Grade 3-4** | **Grade 1-2** | **Grade 3-4** |
| **Thrombocytopenia** | - | 13% | - | 6% |
| **Neutropenia** | - | 9% | - | 4% |
| **Skin toxicity** | 20% | 7% | 9% | 1% |
| **GI toxicity** | 25% | 11% | 20% | 8% |
| **Hepatobiliary/pancreatic** | 16% | 5% | 17% | 6% |
| **Infections** | 8% | 25% | 9% | 24% |
| **Acute GVHD** | 8% | 23% | 6% | 21% |
| **Chronic GVHD** | 5% | 18% | 5% | 17% |

**~ 60% required dose modification (interruption/reduction) due to AEs (median dose intensity 400 mg/d)**

Xuan L, et al. *Lancet Oncol*. 2020;21(9):1201-1212.

# Future Directions: Newer FLT3i

## Gilteritinib — FLT3-ITD and FLT3 TKD inhibitor

- FDA approved for relapsed/refractory FLT3+ AML
- BMT CTN 1506 – phase 3 of gilteritinib as post-HCT maintenance in FLT3-ITD+ AML (NCT02997202)
- Phase 2 MORPHO trial (gilteritinib vs placebo) ongoing for FLT3-ITD+ AML post-HCT (NCT02997202)

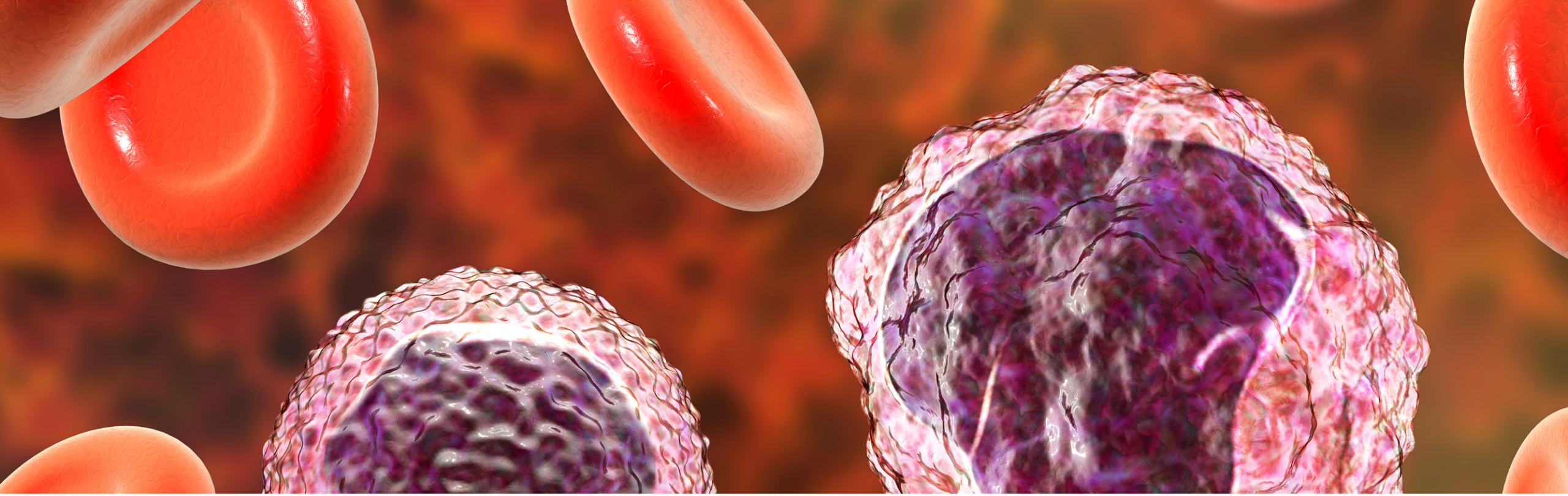
## Quizartinib — FLT3-ITD inhibitor

- Not yet FDA approved
- QUANTUM-FIRST design similar to midostaurin RATIFY trial (NCT02668653)

## Crenolanib — FLT3-ITD and FLT3 TKD inhibitor

- Not yet FDA approved
- Uncontrolled, phase 2 study in FLT3-ITD or TKD+ AML post-HCT (NCT02400255)

https://clinicaltrials.gov/ct2/home.



# Management of Adverse Events and Considerations for the Pharmacist

# FLT3i: Toxicity and Key Considerations

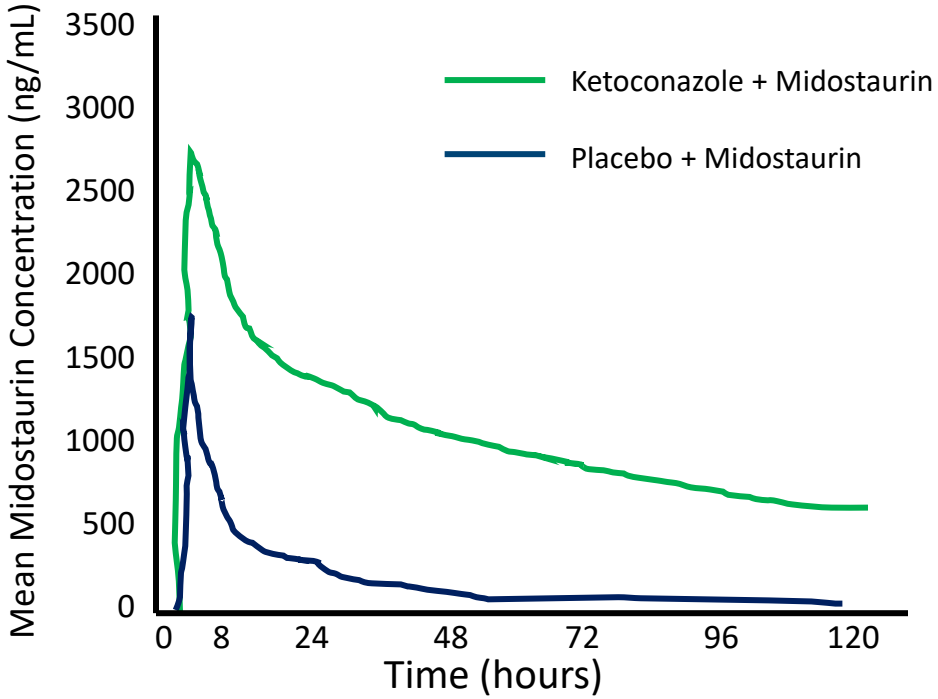
| Sorafenib | |
|---|---|
| **First Generation, Class 2, FLT3-ITD** | |
| **Off-Target Kinase Inhibition** | C-CRAF, BRAF, *m*BRAF, KIT, RET, RET/PTC, VEGF(1,2,3), PDGFR-β |
| **FDA Approval** | • Unresectable hepatocellular carcinoma<br>• Advanced renal cell carcinoma<br>• Locally recurrent or metastatic progressive, differentiated thyroid carcinoma refractory to iodine treatment |
| **Dose in AML** | 400 mg (2 tabs) PO BID **without food** |
| **Metabolism** | Hepatic via CYP3A4 and UGT1A9 |
| **DDI** | Sorafenib inhibits UGT1A1, UGT1A9, and P-glycoprotein *in vitro*<br>AUC parent ≈ with ketoconazole<br>AUC N-oxide metabolite below level of detection |
| **Dosing Modifications** | Temporary interruption required for major surgical procedures<br><br>No dose adjustments required for hepatic or renal dysfunction<br><br>Specific adjustments required for adverse reaction management |
| **Major Toxicity/ Unique Outlier** | ≥ 20%: diarrhea, fatigue, infection, alopecia, hand-foot skin reaction, rash, weight loss, decreased appetite, nausea, gastrointestinal and abdominal pains, hypertension, hemorrhage |

| Midostaurin | |
|---|---|
| **First Generation, Class 1, FLT3-ITD, FLT3-TKD** | |
| **Off-Target Kinase Inhibition** | KIT, PDGFR-α/β, PKC |
| **FDA Approval** | • Newly diagnosed AML with FLT3+ in combination with cytarabine and daunorubicin<br>• Systemic mastocytosis with associated hematological neoplasm<br>• Mast cell leukemia |
| **Dose in AML** | 50 mg (2 caps) PO BID **with food** |
| **Metabolism** | Hepatic via CYP3A4 (major) |
| **DDI** | **CYP3A4**<br>AUC parent 10.4-fold with ketoconazole<br>AUC parent 96% with rifampicin |
| **Dosing Modifications** | Consider alternative therapies or monitor for increased risk of ADR when used with strong CYP3A4 inhibitors<br>Avoid use with strong CYP3A4 inducers<br>No dose adjustments required for hepatic or renal dysfunction |
| **Major Toxicity/ Unique Outlier** | ≥ 20%: febrile neutropenia, nausea, mucositis, vomiting, headache, petechiae, musculoskeletal pain, epistaxis, device-related infection, hyperglycemia, electrocardiogram (ECG) QT prolonged, upper respiratory tract infection |

Nexavar. Package insert. Bayer; 2018.
Rydapt. Package insert. Novartis; 2021.

# Post-HCT FLT3i and Azole Antifungals

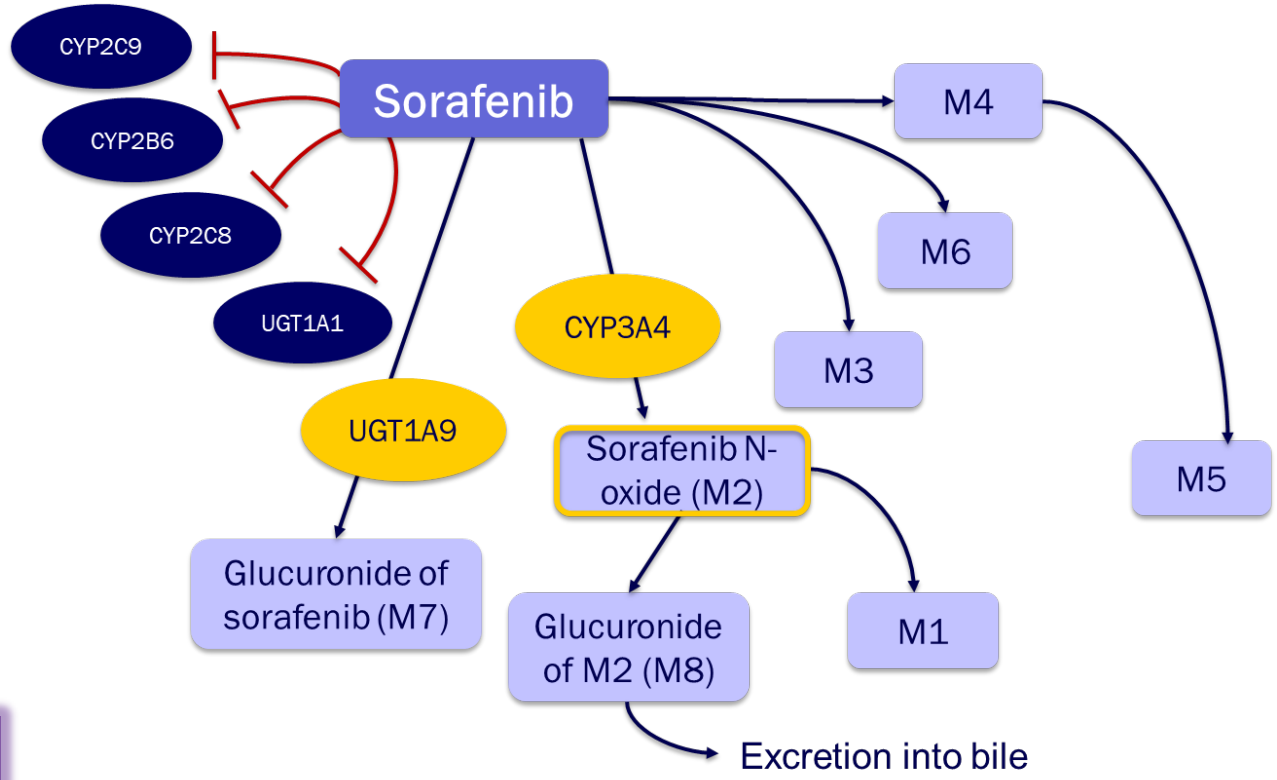
## MIDOSTAURIN




**"Pulmonary toxicity including *fatal pulmonary events* have been described in patients receiving midostaurin…pulmonary toxicity may be associated with co-administration of *azole antifungal drugs* and inhibition of CYP3A4."**

Dutreix C, et al. *Cancer Chemother Pharmacol*. 2013;72(6):1223-1234.

## SORAFENIB




Inaba H, et al. *J Clin Oncol*. 2011;29(24):3293-3300.

Li L, et al. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2010;878(29):3033-3038.

# Dermatologic Toxicities Associated with Sorafenib

| Dermatologic Toxicity Grade | Occurrence | Sorafenib Dose Modification |
|---|---|---|
| Grade 2: Painful erythema and swelling of the hands or feet and/or discomfort affecting normal activities | First occurrence | Continue sorafenib treatment and consider topical therapy for symptomatic relief. If no improvement within 7 days, see below. |
| | No improvement within 7 days or second or third occurrence | Interrupt sorafenib treatment until resolved or improved to grade 0 to 1. When resuming treatment, decrease dose by 1 dose level. |
| | Fourth occurrence | Discontinue sorafenib treatment. |
| Grade 3: Moist desquamation, ulceration, blistering, or severe pain of the hands or feet, resulting in inability to work or perform activities of daily living | First occurrence | Interrupt sorafenib treatment until resolved or improved to grade 0 to 1. When resuming treatment, decrease dose by 1 dose level |
| | Second occurrence | Interrupt sorafenib treatment until resolved or improved to grade 0 to 1. When resuming treatment, decrease dose by 1 dose level. |
| | Third occurrence | Discontinue sorafenib treatment. |

Nexavar. Package insert. Bayer; 2018.

# Nausea Associated with Oral Azacitidine

| Adverse Event | Oral Azacitidine (n = 236) | | Placebo (n = 233) | |
|---|---|---|---|---|
| | All Grades (%) | Grade 3 or 4 (%) | All Grades (%) | Grade 3 or 4 (%) |
| Nausea | 65 | 3 | 24 | < 1 |
| Vomiting | 60 | 3 | 10 | 0 |

- Patients should take an antiemetic 30 minutes prior to each dose of oral azacitidine for the first 2 cycles
  - Anti-emetic prophylaxis may be omitted after 2 cycles if there has been no nausea and vomiting

| Dose Modifications for Grade 3/4 Nausea or Vomiting | |
|---|---|
| First occurrence | Interrupt until grade 1 then resume at 300 mg dosage |
| Second occurrence | Interrupt until grade 1 then reduce to 200 mg dosage |
| Third occurrence | Reduce treatment by 7 days |
| Fourth occurrence | Discontinue treatment |

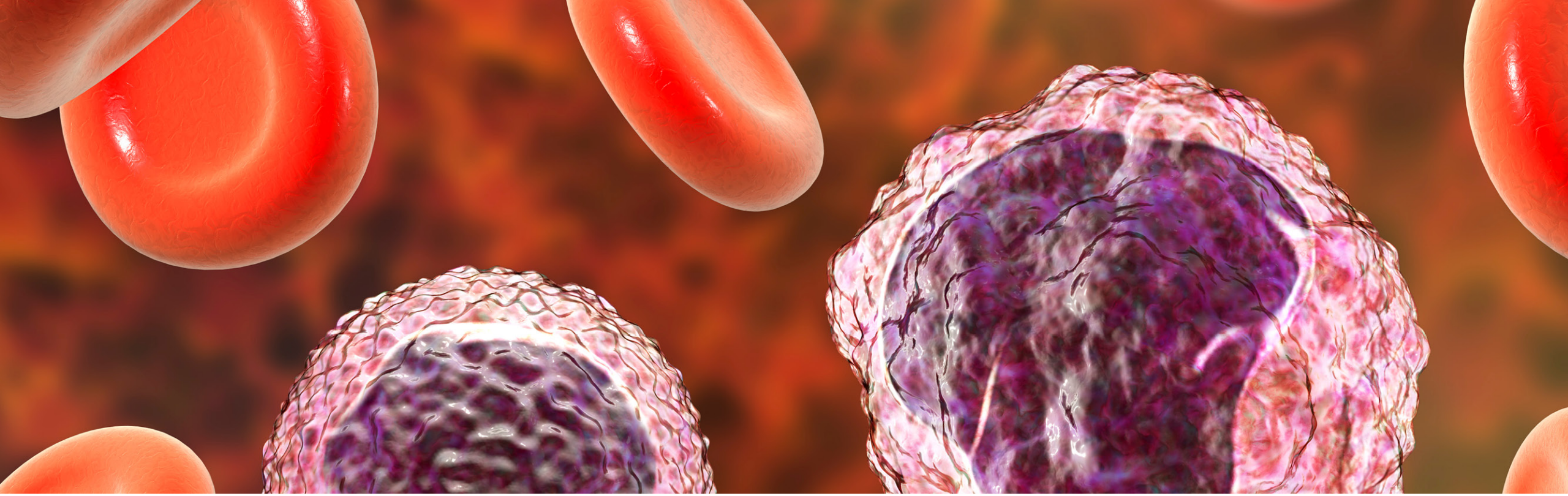
Wei AH, et al. *N Engl J Med*. 2020;383(26):2526-2537.
Onureg. Package insert. Celgene Corp; 2021.

# Nausea Associated with Midostaurin

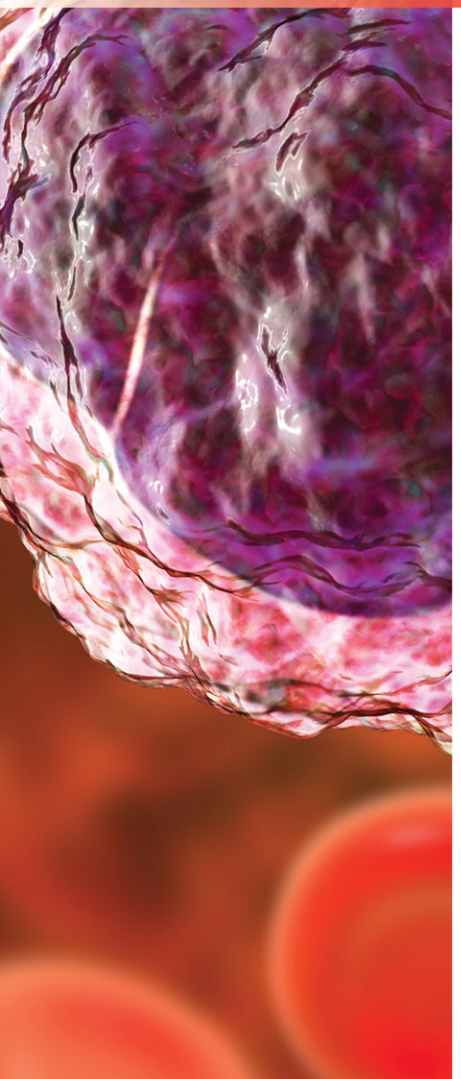
| Adverse Event | Midostaurin + Chemotherapy (n = 229) | | Chemotherapy + Placebo (n = 226) | |
|---|---|---|---|---|
| | All Grades (%) | Grade 3 or 4 (%) | All Grades (%) | Grade 3 or 4 (%) |
| Nausea | 83 | 6 | 70 | 10 |
| Vomiting | 61 | 3 | 53 | 5 |

- Midostaurin is associated with a moderate or high emetic potential
  - Patients should take an anti-emetic 30 minutes prior to each dose of midostaurin

Rydapt. Package insert. Novartis; 2021.



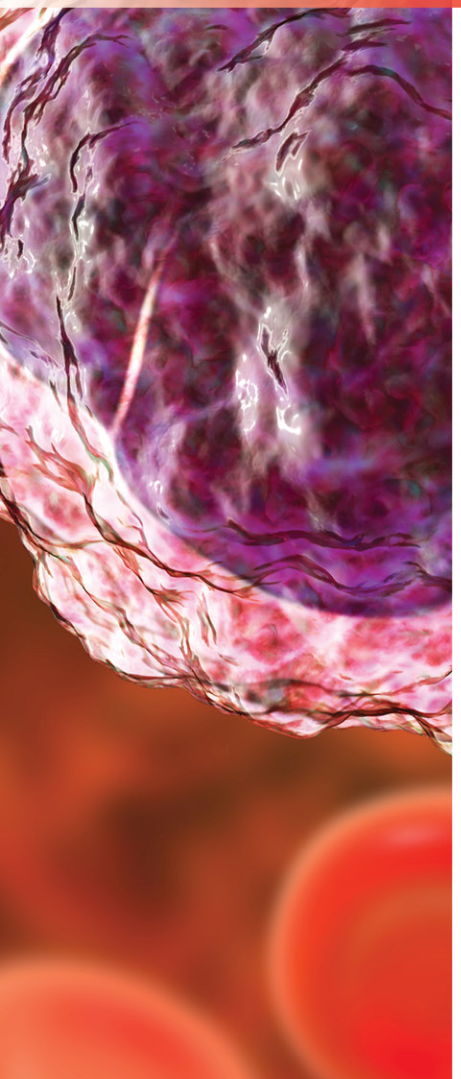
# Adherence Considerations



# Patient Preference and Adherence

- As more oral therapies are becoming available, patient preference is shifting
  - Factors in favor of oral regimens include convenience, at-home treatment, therapy schedule, and side effect profile
- Patient preference does not always equate to increased adherence
  - Studies have reported oral chemotherapy adherence rates ranging from 15% to 97%
  - Multiple factors probably contribute to this wide range, including medication adverse effects and cost concerns

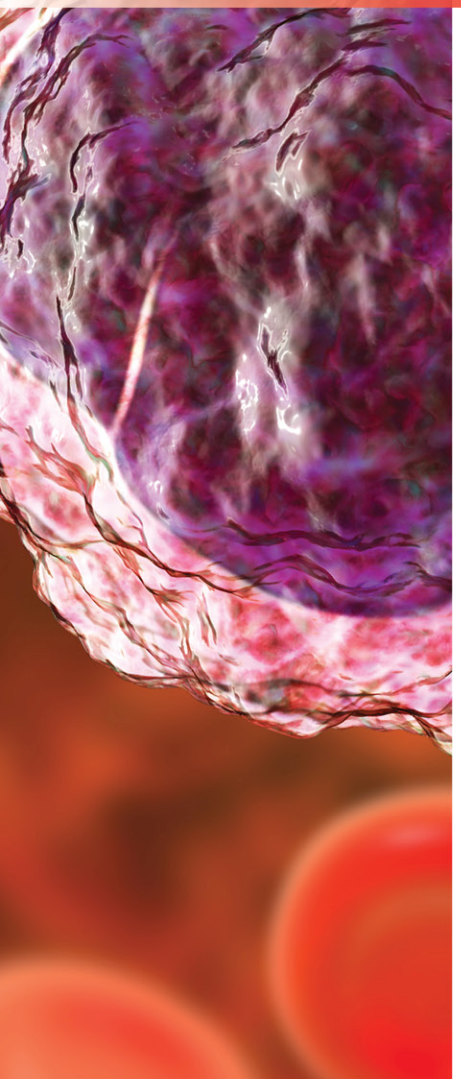
Eek D, et al. *Patient Prefer Adherence*. 2016;10:1609-1621; Hansen LA. *Hematol Oncol Pharm*. 2012.



# Ensuring Patient Access

- The cost of cancer care continues to be a barrier of effective care
  - Reports of patients reducing doses or skipping treatments to save money
- Whereas the median monthly household income has stayed relatively flat, the cost of cancer care has continued to climb
- The estimated annualized cost of oral medications is $4200
- Pharmacists must use every resources to lower the cost of care for patients
  - Patient assistance programs
  - Drug-discount coupons
  - Charitable organizations and foundations

Prasad V, et al. *Nat Rev Clin Oncol*. 2017;14(6):381-390; Mariotto AB, et al. *Cancer Epidemio Biomarkers Prev*. 2020;29(7):1304-1312.

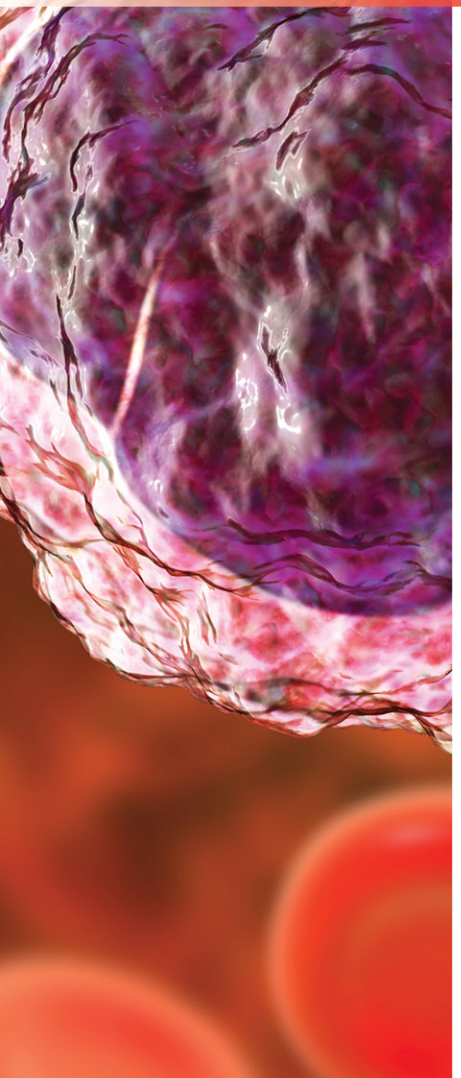


# Pharmacists Considerations

- Treatment decision-making/provider consultation

- Patient/family consulting, education, and support
  - Medication adherence
  - Adverse event recognition and management
  - Drug-drug and drug food interactions
  - Financial toxicity

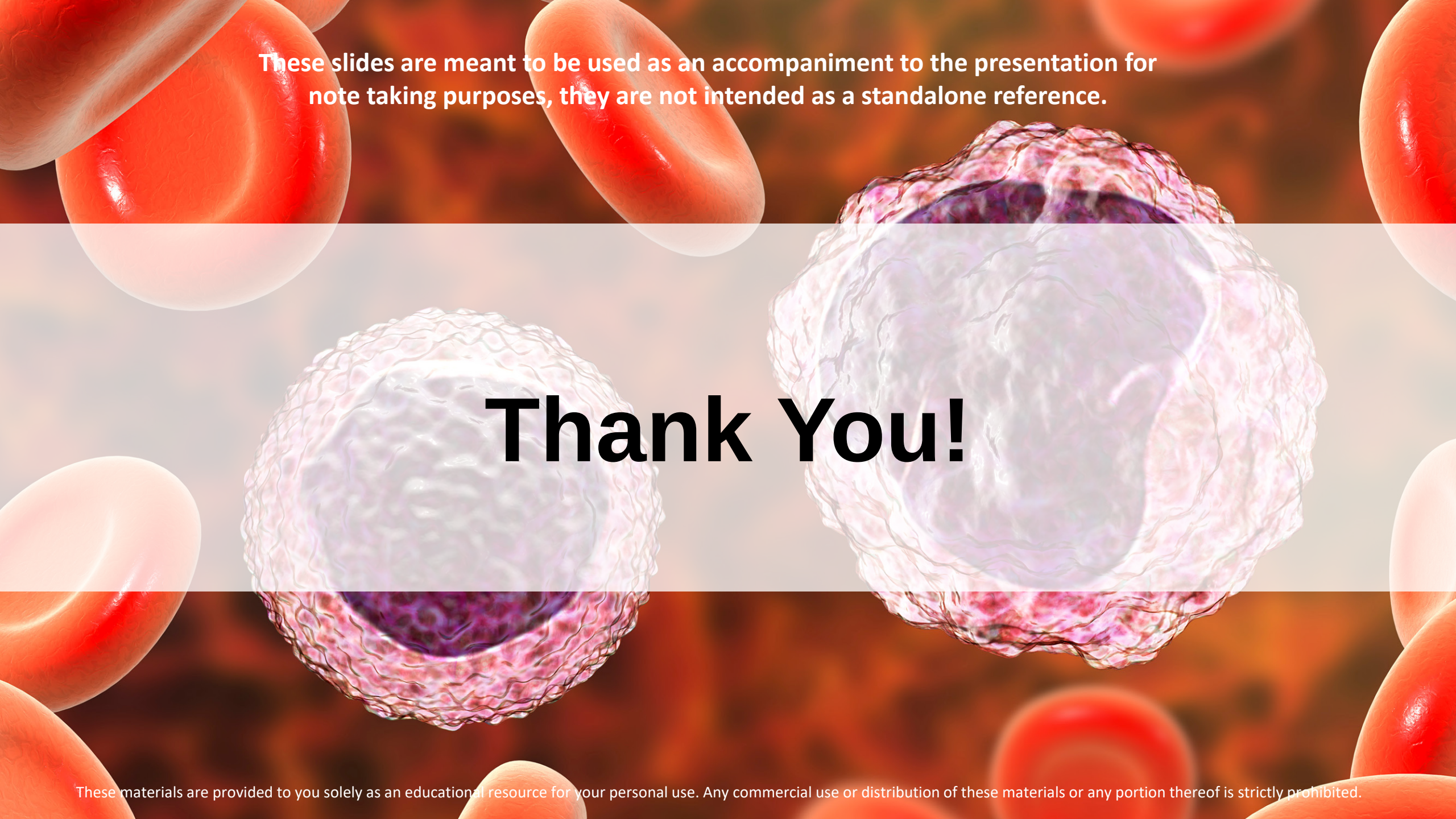
- Formulary and clinical pathway development



# Summary

- Improvements in OS and quality of life remain the goals for maintenance therapy approaches
- Several options available for AML maintenance
  - Chemotherapy/immunotherapy
  - Hypomethylating agents
  - Targeted therapy
- Pharmacist play an important role in assisting patients receiving AML maintenance therapy
  - Educate, prevent and manage toxicities related to maintenance therapy agents
  - Awareness of drug-drug interactions

# Questions and Answers



These slides are meant to be used as an accompaniment to the presentation for note taking purposes, they are not intended as a standalone reference.

# Thank You!