# De Novo AML

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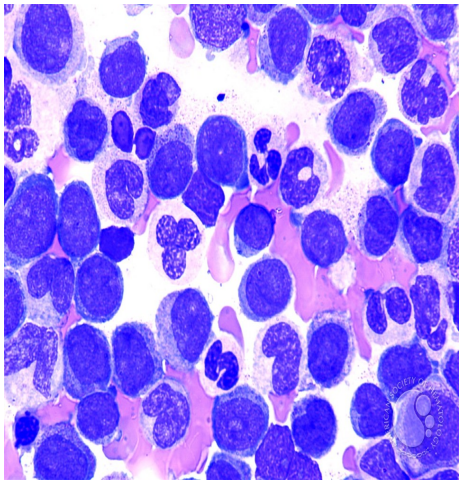
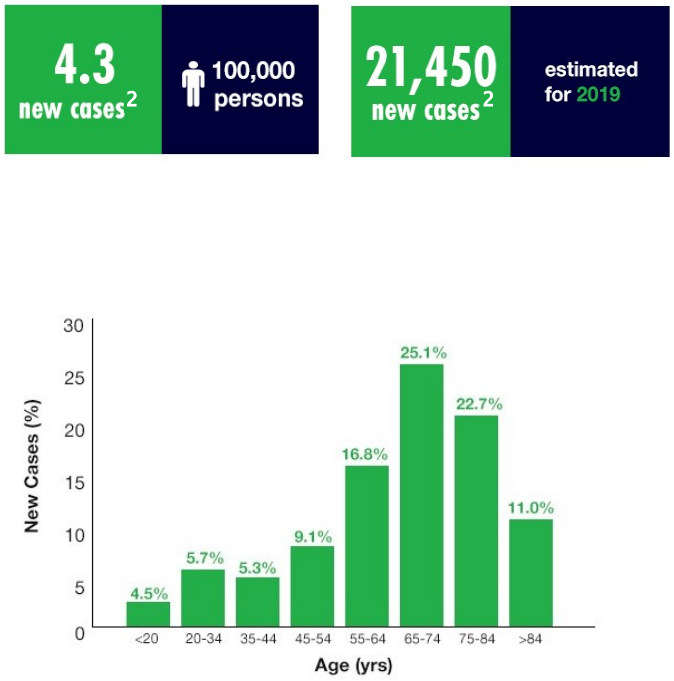
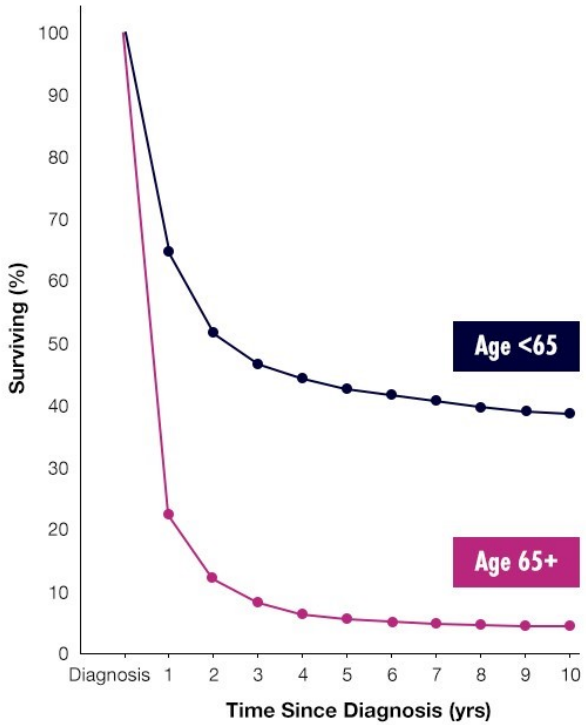
Moffitt Cancer Center

# Acute Myeloid Leukemia



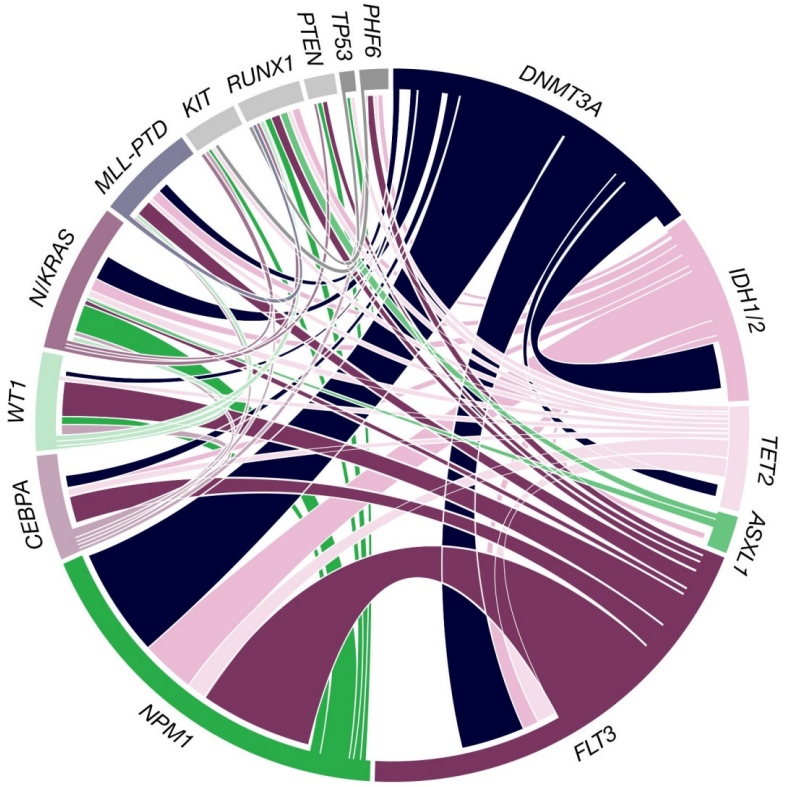



. American Society of Clinical Oncology. http://www.cancer.net/cancer-types/leukemia-acute-myeloid-aml/statistics. Accessed July 23, 2019

# AML is characterized by genetic heterogeneity

- **The complexity of each case is illustrated by the presence of multiple leukemic blast clones harboring varying genetic and epigenetic aberrations[1-3]**
- **A study of 1540 patients found[2]:**
  - 5234 driver mutations across 76 genes or genomic regions
  - 86% of patients have ***at least*** 2 mutations
- **Clonal evolution involves the acquisition and loss of specific mutations over the course of disease[4,5]**




Adapted from Patel et al, 2012.

**References: 1.** Riether C, et al. *Cell Death Differ*. 2015;22:187-198. **2.** Papaemmanuil E, et al. *N Engl J Med*. 2016;374(23):2209-2221. **3.** Watts J, et al. *F1000Research*. 2018;7:(F1000 Faculty Rev):1196. **4.** Ding L, et al. *Nature*. 2012;481(7382):506-510. **5.** Paguirigan AL, et al. *Sci Transl Med*. 2015;7(281):1-18. **6.** Patel JP, et al. *N Engl J Med*. 2012;366(12):1079-1089.

# AML classification

## 2016 WHO AML Subcategories[1]

**AML with recurrent genetic abnormalities**
- 11 different subcategories listed

**AML with myelodysplasia-related changes (AML-MRC)**

**Therapy-related myeloid neoplasms (e.g., t-AML)**

**AML, not otherwise specified**
- 9 different subcategories listed

**Myeloid sarcoma**

**Myeloid proliferations related to Down syndrome**
- 2 different subcategories listed

- Primary " de novo AML"
- Secondary AML
  - AML with MDS related changes
  - Therapy related AML

**The WHO defines AML-MRC as[1]:**

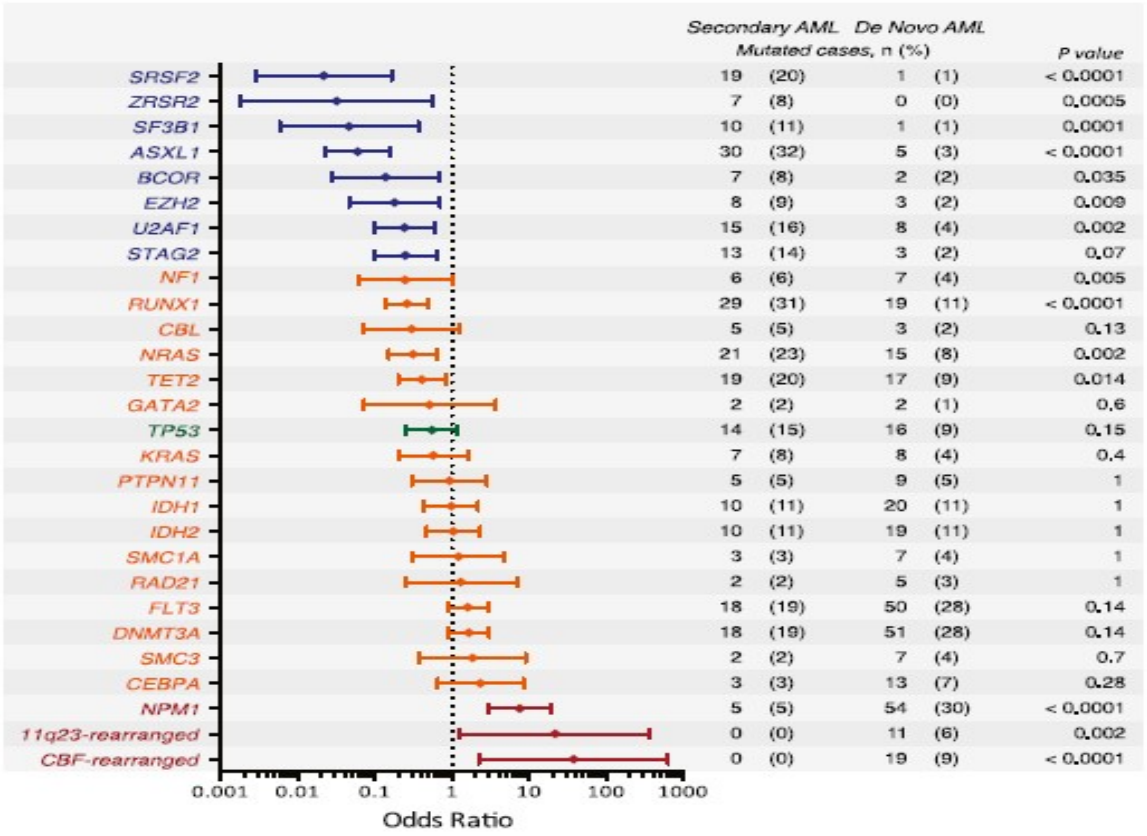
- 20% or more blasts in the peripheral blood or bone marrow and any of the following:
  - Previously documented MDS or MDS/MPN
  - Morphologic detection of multilineage dysplasia (≥50% dysplastic cells in ≥ 2 cell lines, excluding cases when a mutation of *NPM1* or biallelic mutation of *CEBPA* is present)
  - Myelodysplasia-related cytogenetic abnormalities

| Complex karyotype (3 or more unbalanced or balanced abnormalities): | |
|---|---|
| Unbalanced abnormalities | -7/del(7q), del(5q)/t(5q), i(17q)/t(17p), -13/del(13q), del(11q), del(12p)/t(12p), idic(X)(q13) |
| Balanced abnormalities | t(11;16)(q23.3;p13.3), t(3:21)(q26.2;q22.1), t(1;3)(p36.3;q21.2), t(2;11)(p21;q23.3), t(5;12)(q32;p13.2), t(5;7)(q32;q11.2), t(5;17)(q32;p13.2), t(5;10)(q32;q21.2), t(3;5)(q25.3;q35.1) |

MPN=myeloproliferative neoplasm.

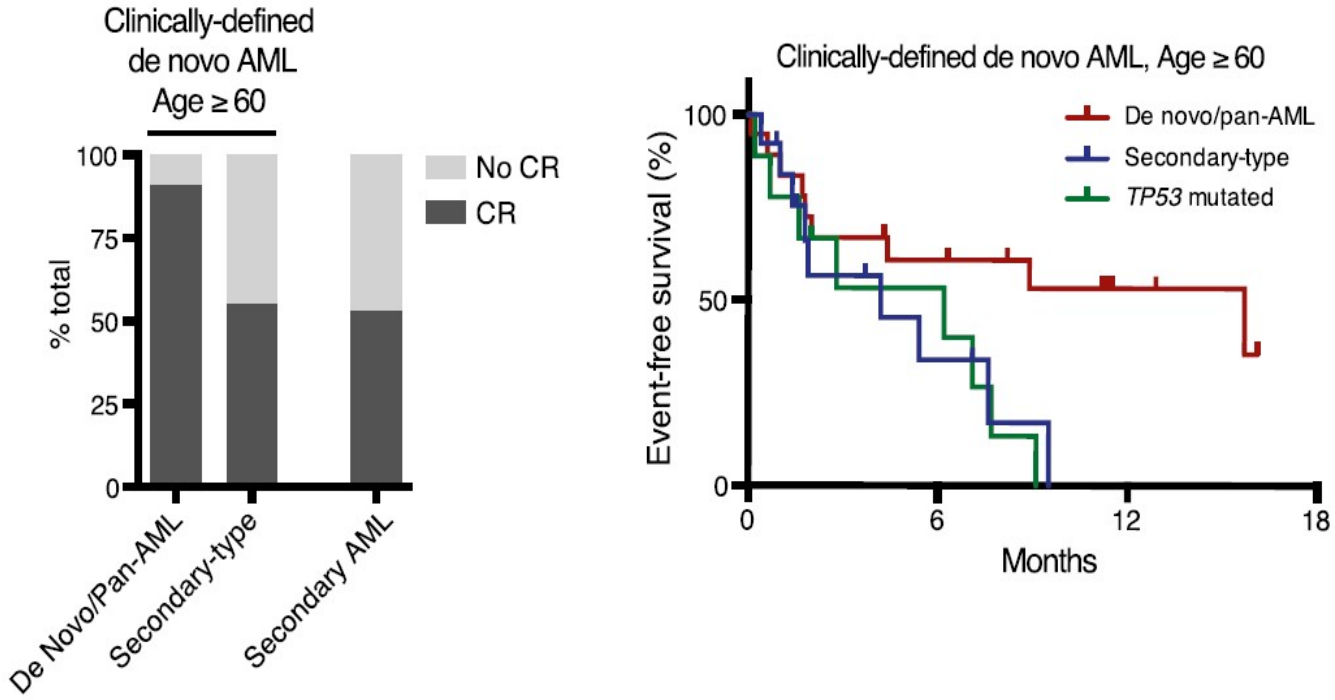
Reference: 1. Arber DA, et al. *Blood*. 2016;127(20):2391-2405.

# AML ontogeny can be mutationally defined




Lindsley, et al. Blood 2015

# Differential outcomes based on mutational profile




Lindsley, et al. Blood 2015

# AML Risk Stratification by Cytogenetics and Molecular Abnormalities (ELN Recommendations)

| Risk Status | Cytogenetics | Molecular Abnormalities |
|---|---|---|
| Favorable | t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*<br>inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* | Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD$^{low}$ or<br>Biallelic mutated *CEBPA* |
| Intermediate | t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*<br>Cytogenetic abnormalities not classified as favorable or adverse | Mutated *NPM1* and *FLT3*-ITD$^{high}$<br>Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD$^{low}$ (without adverse-risk genetic lesions) |
| Adverse | t(6;9)(p23;q34.1); *DEK-NUP214*<br>t(v;11q23.3); *KMT2A* rearranged<br>t(9;22)(q34.1;q11.2); *BCR-ABL1*<br>inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)*<br>−5 or del(5q); −7; −17/abn(17p)<br>Complex karyotype, monosomal karyotype | Wild-type *NPM1* and *FLT3*-ITD$^{high}$<br>Mutated *RUNX1*<br>Mutated *ASXL1*<br>Mutated *TP53* |

Döhner H, et al. Blood. 2017;129:424-447.

# Upfront Treatment of De Novo AML in patients eligible for Intensive chemotherapy

Who is eligible?

1. Non P53 MT AML
2. Absence of comorbidities
3. Not frail

**Good risk AML**

Induction: 3+7+GO

Consolidation: HiDAC/IDAC+/-GO

**FLt-3 MT AML**

Induction: 3+7 + Midostaurin

Consolidation : Allo-SCT

Maintenance post allo SCT: Sorafenib

**Intermediate/poor risk**

Induction: 3+7

Consolidation: allo SCT

Maintenance: oral azacitidine if no transplant

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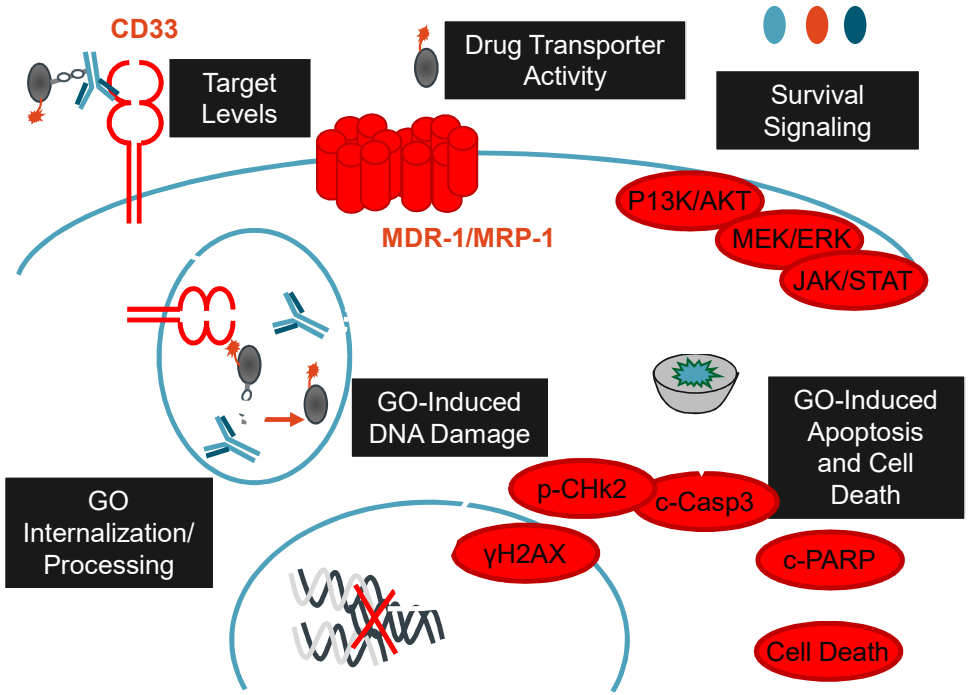
# Gemtuzumab Ozogamicin: MOA

- Monoclonal anti-CD33 antibody linked to calicheamicin-γ1[1]
- Internalized and cleaved in lysosomes to release free calicheamicin moiety[2]
- Calicheamicin moiety enters nucleus and interacts with DNA causing double-strand breaks initiating apoptosis[1-3]




1. Zein N, et al. *Science.* 1988;240:1198-1201; 2. Naito K, et al. *Leukemia.* 2000; 14:1436-1443;
3. Elmroth K, et al. *DNA Repair (Amst).* 2003;2:363-374.

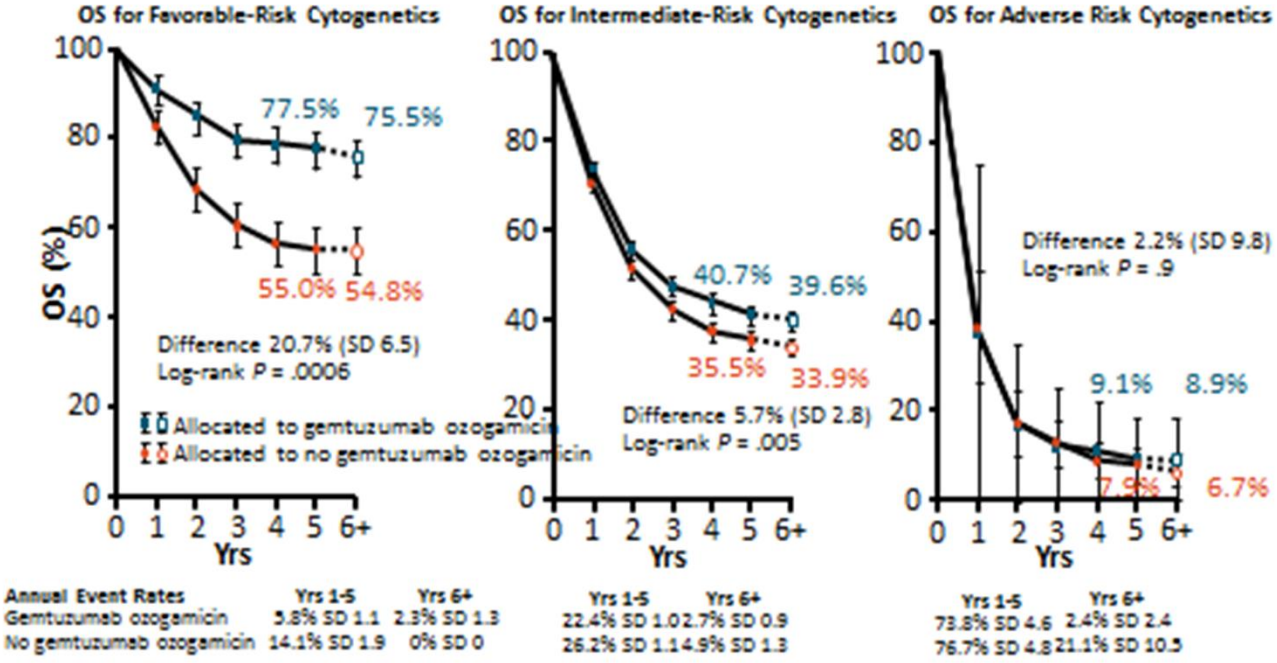
## Gemtuzumab Ozogamicin in AML:

# Phase III Results

| Study[1] | N | Treatment | Results of GO vs Comparator |
|---|---|---|---|
| MRC/NCRI AML15[2] | 1113 | GO (3 mg/m$^2$) + either ADE, DA, or FLAG-IDA | ▪ Improved 5-yr OS for favorable-risk group<br>▪ No difference in ORR, TRM, relapse, survival |
| ALFA 0701[3] | 280 | GO (3 mg/m$^2$) + DA | ▪ Improved 2-yr EFS, RFS, OS<br>▪ No difference in ORR or mortality |
| GOELAMS AML 2006 IR[4] | 238 | GO (6 mg/m$^2$) + DA induction and MA consolidation | ▪ Improved EFS in pts who did not have allogeneic HCT<br>▪ No difference in OS, ORR, TRM, 3-yr EFS |
| MRC/NCRI AML 16[5] | 1115 | GO (3 mg/m$^2$) + either DA or DCLo | ▪ Reduced 3-yr relapse risk, and superior DFS and OS<br>▪ No difference in TRM |
| SWOG S0106[6] | 595 | GO (6 mg/m$^2$) + DA | ▪ Increased TRM<br>▪ No difference in ORR, DFS, or OS |

1. Cowan AJ, et al. *Front Biosci* (Landmark Ed.) 2013;18:1311-1334; 2. Burnett AK, et al. *J Clin Oncol*. 2011;29:369-377; 3. Castaigne S, et al. *Lancet*. 2012;379:1508-1516; 4. Delaunay J, et al. ASH 2011. Abstract 79; 5. Burnett AK, et al. *J Clin Oncol*. 2012;30:3924-3931; 6. Petersdorf S, et al. *Blood*. 2013;121:4854-4860.

# Addition of Gemtuzumab Ozogamicin to Induction Therapy: Meta-analysis of 5 Randomized Trials




| Annual Event Rates | Yrs 1-5 | Yrs 6+ |
|---|---|---|
| Gemtuzumab ozogamicin | 5.8% SD 1.1 | 2.3% SD 1.3 |
| No gemtuzumab ozogamicin | 14.1% SD 1.9 | 0% SD 0 |

| | Yrs 1-5 | Yrs 6+ |
|---|---|---|
| | 22.4% SD 1.0 | 2.7% SD 0.9 |
| | 26.2% SD 1.1 | 14.9% SD 1.3 |

| | Yrs 1-5 | Yrs 6+ |
|---|---|---|
| | 73.8% SD 4.6 | 2.4% SD 2.4 |
| | 76.7% SD 4.8 | 21.1% SD 10.5 |

Hills RK, et al. Lancet Oncol. 2014;15:986-996.

**Fludarabine, Cytarabine, G-CSF and Gemtuzumab Ozogamicin (FLAG-GO) Regimen Results in Better Molecular Response and Relapse-Free Survival in Core Binding Factor Acute Myeloid Leukemia Than FLAG and Idarubicin (FLAG-Ida)**

**Figure 1** Relapse free survival (RFS) by treatment regimen

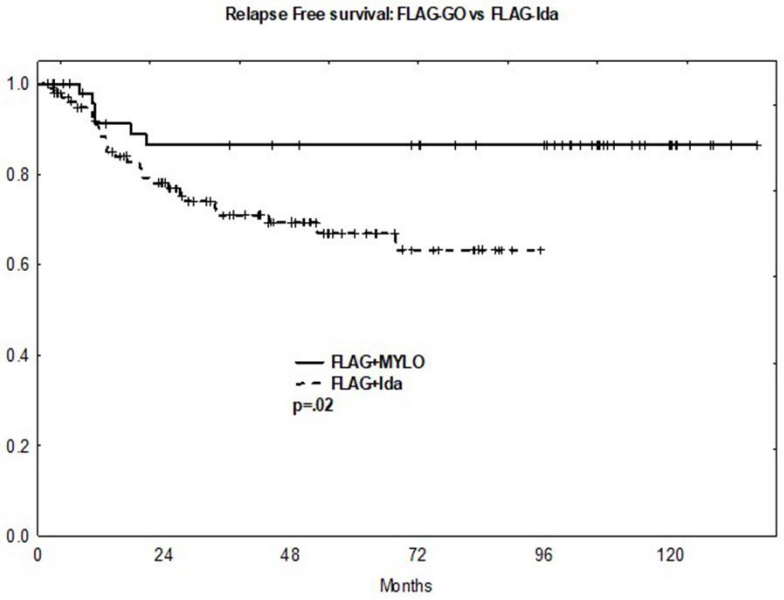
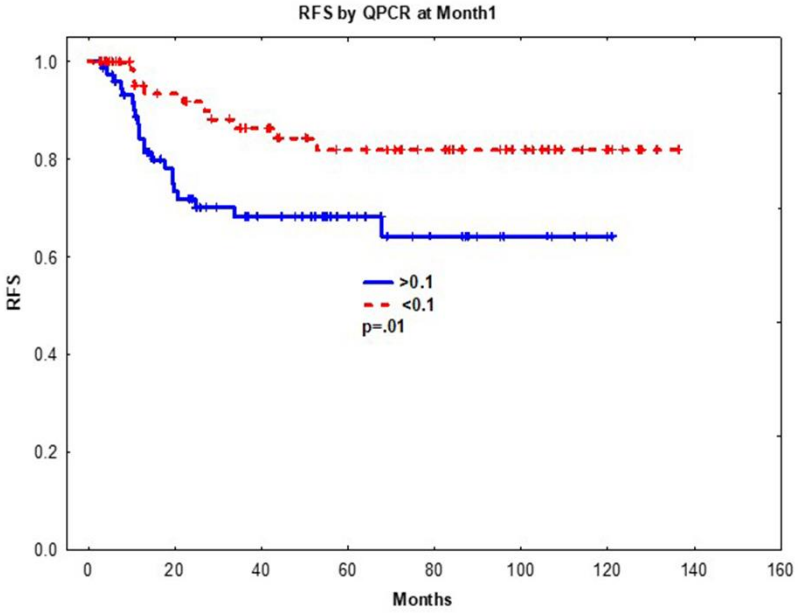



**Figure 2** RFS by QPCR response at end of induction




**Gautam M. Borthakur, Blood, 2019,**

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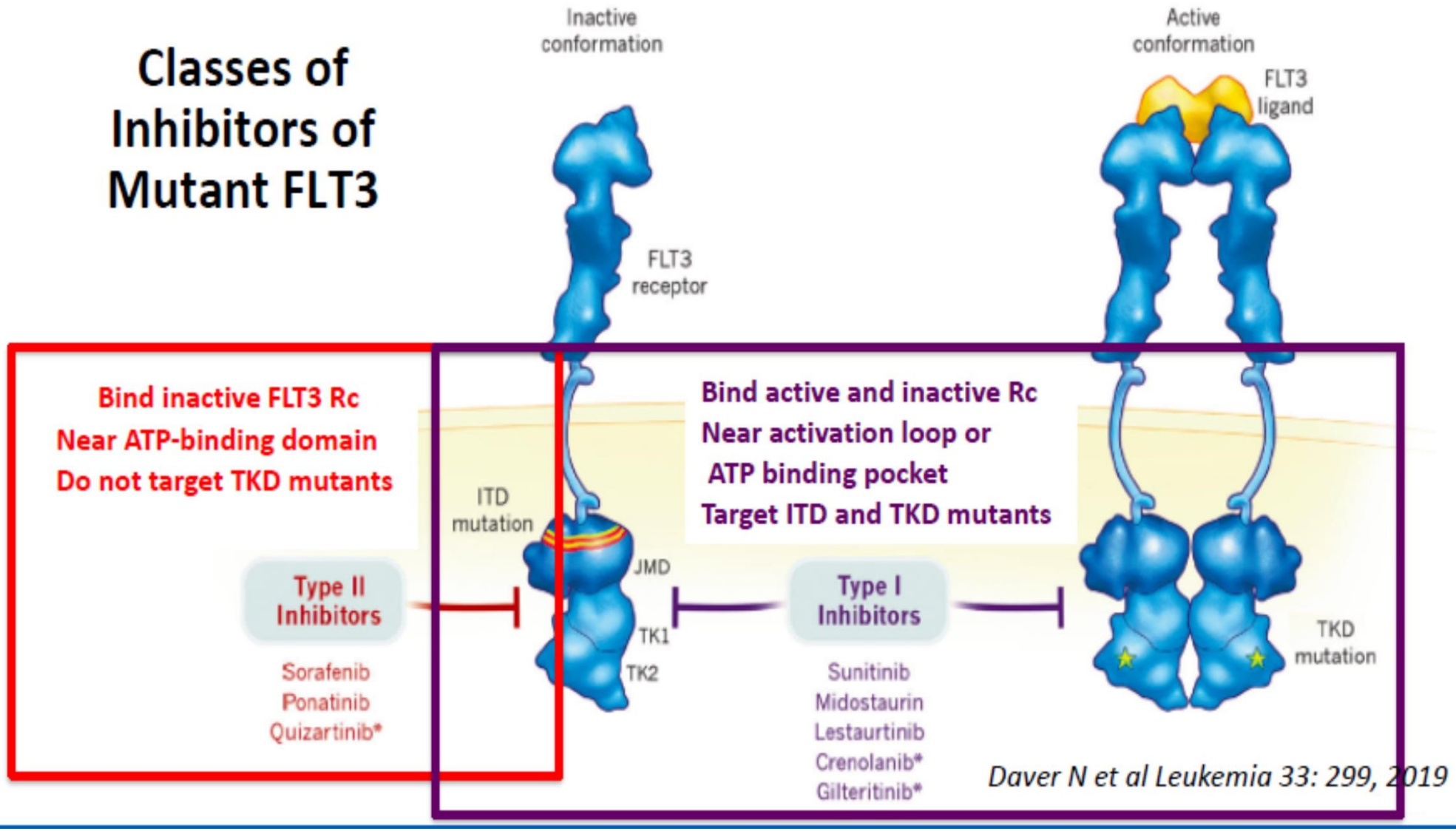
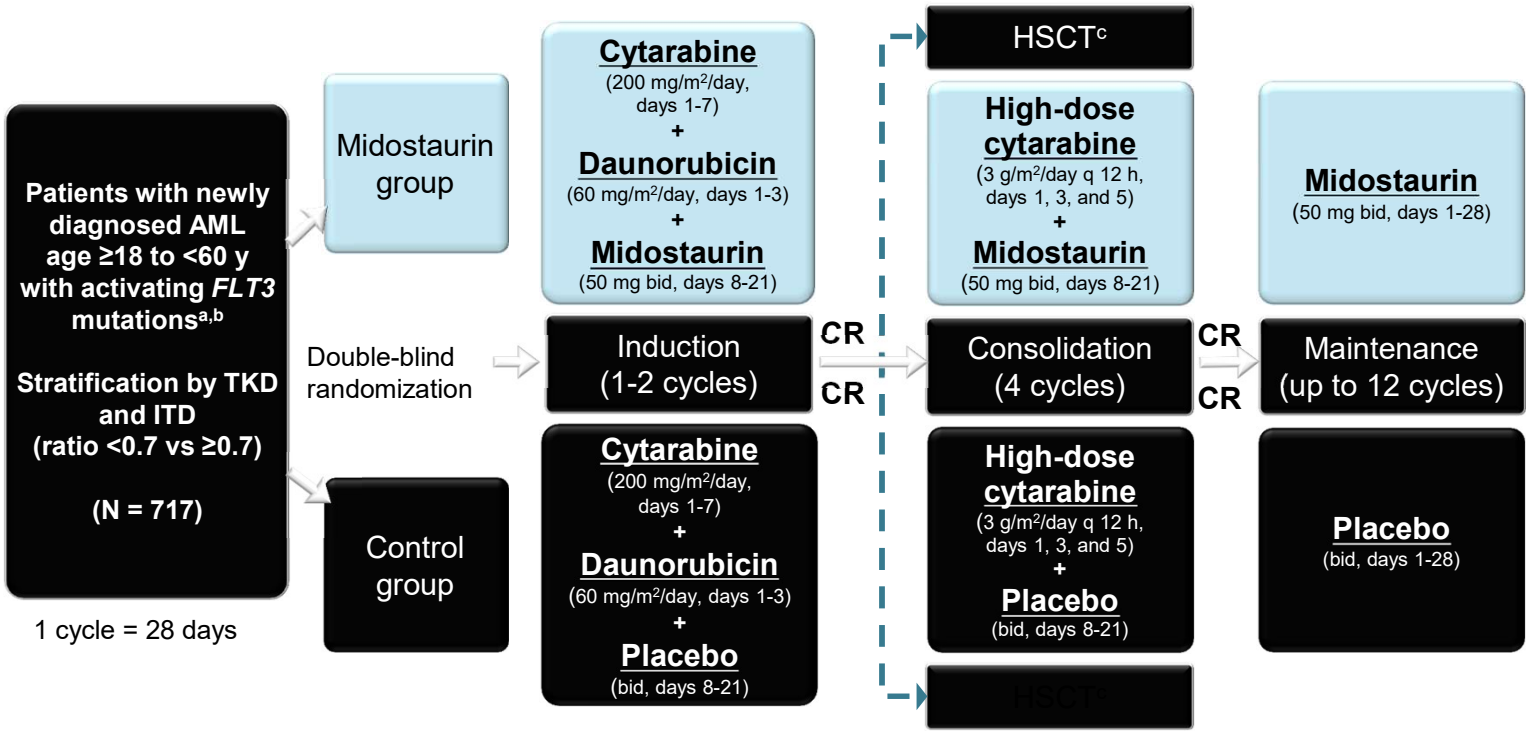
# Classes of Inhibitors of Mutant FLT3




*Daver N et al Leukemia 33: 299, 2019*

# The RATIFY Trial




**Primary Endpoint: Overall Survival**
not censored for transplantation

[a] Documented AML (no APL).

[b] Hydroxyurea therapy allowed ≤5 days prior to start of study treatment.

[c] Patients eligible for HSCT therapy no longer receive the study drug following the HSCT.

Stone R. N Engl J Med. 2017 Aug 3;377(5):454-464.

# RATIFY: Patient Characteristics

**Table 1. Baseline Characteristics of the Patients.**

| Characteristic | All Patients (N=717) | Midostaurin Group (N=360) | Placebo Group (N=357) | P Value* |
|---|---|---|---|---|
| Age at trial entry — yr | | | | 0.22 |
| Median | 47.9 | 47.1 | 48.6 | |
| Range | 18.0–60.9 | 19.0–59.8 | 18.0–60.9 | |
| Female sex — no. (%) | 398 (55.5) | 186 (51.7) | 212 (59.4) | 0.04 |
| Race — no./total no. (%)† | | | | 0.74 |
| White | 275/309 (89.0) | 147/165 (89.1) | 128/144 (88.9) | |
| Other | 34/309 (11.0) | 18/165 (10.9) | 16/144 (11.1) | |
| Subtype of *FLT3* mutation — no. (%)‡ | | | | 1.00 |
| TKD | 162 (22.6) | 81 (22.5) | 81 (22.7) | |
| ITD with low allelic ratio | 341 (47.6) | 171 (47.5) | 170 (47.6) | |
| ITD with high allelic ratio | 214 (29.8) | 108 (30.0) | 106 (29.7) | |
| Modified European LeukemiaNet classification — no./total no. (%)§ | | | | 0.15 |
| Favorable | 29/547 (5.3) | 16/269 (5.9) | 13/278 (4.7) | |
| Normal | 375/547 (68.6) | 172/269 (63.9) | 203/278 (73.0) | |
| Intermediate II | 104/547 (19.0) | 59/269 (21.9) | 45/278 (16.2) | |
| Adverse | 39/547 (7.1) | 22/269 (8.2) | 17/278 (6.1) | |

Stone R. N Engl J Med. 2017 Aug 3;377(5):454-464.

# RATIFY: Complete Response Rates

**Table 3. Summary of Complete Remission.***

| Variable | Midostaurin Group (N=360) | Placebo Group (N=357) | P Value† |
|---|---|---|---|
| Protocol-specified complete remission — no. (%) | 212 (59) | 191 (54) | 0.15 |
| Kaplan–Meier estimate of time to complete remission — days | | | |
| Median | 35 | 35 | |
| Range | 20–60 | 20–60 | |

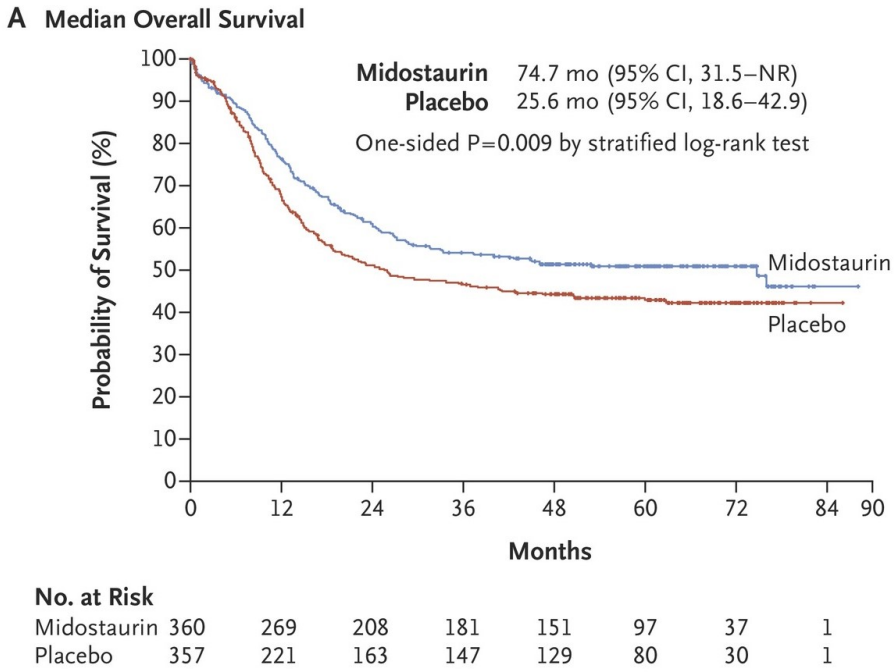
* Complete remission was defined as the presence of less than 5% blasts in the marrow or extramedullary leukemia, an absolute neutrophil count of more than 1000 per microliter, a platelet count of more than 100,000 per microliter, and the absence of blasts in the peripheral blood; in addition, per protocol, complete remission had to occur by day 60.
† P value is two-sided and was calculated with the use of Fisher's exact test.

Stone R. N Engl J Med. 2017 Aug 3;377(5):454-464.

## RATIFY: Overall Survival

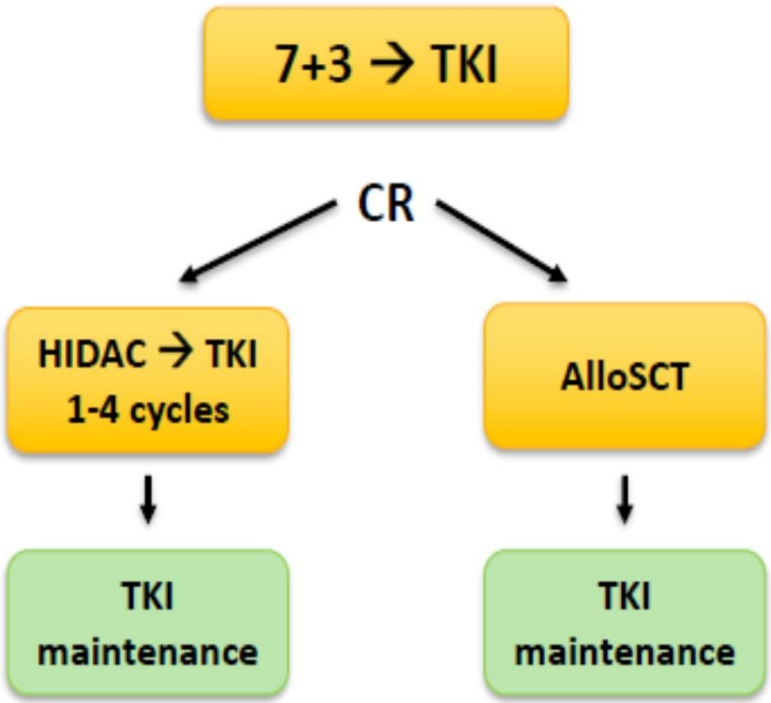
# 23% reduced risk of death in the midostaurin arm

| Arm | 4-Year Survival |
|---|---|
| MIDO | 51.4% (95% CI, 46, 57) |
| PBO | 44.2% (95% CI, 39, 50) |




Stone R. N Engl J Med. 2017 Aug 3;377(5):454-464.

# Upfront intensive therapy + TKI for newly diagnosed AML

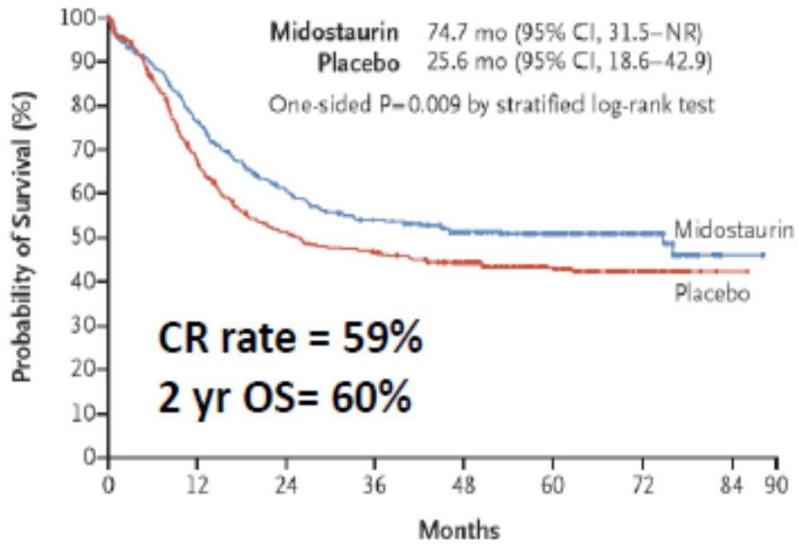



| FLT3 TKI | No. pts | CRCR/CRi/CRh |
|---|---|---|
| **Midostaurin** plus 7+3 | N=717 (ph 3) | **59%** |
| **Quizartinib** plus 7+3 | N=16 (ph 1) | **84%** |
| **Crenolanib** plus 7+3 | N=38 (ph 2) | **88%** |
| **Gilteritinib** plus 7+3 | N=33 (ph 1) | **94%** |

*Stone R et al NEJM 377(5): 454, 2017; Wang E et al ASH 2017;*
*Altman J et al AJH 93(2): 213, 2018;*
*Pratz K et al ASH 2018*

# Phase II trial of crenolanib in newly diagnosed FLT3$^{mut}$ AML

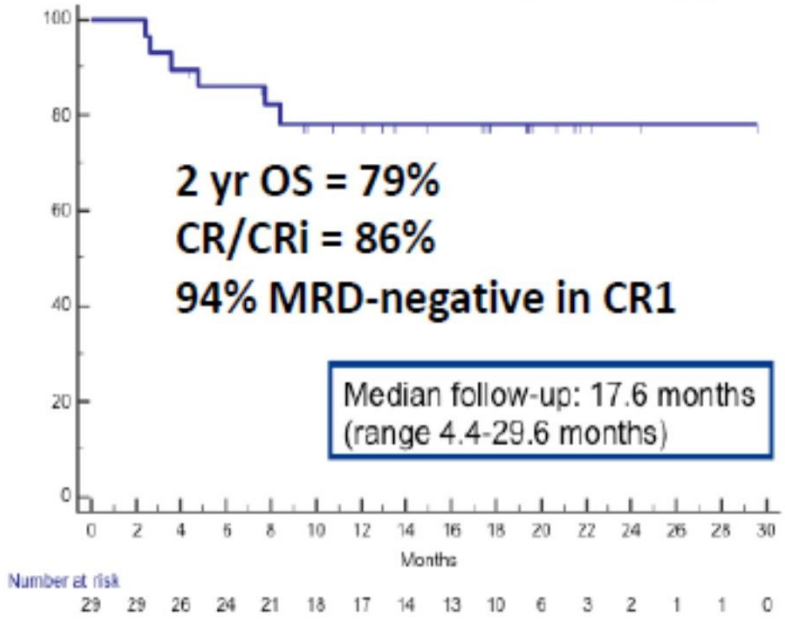
## Midostaurin/ 7+3 (RATIFY)




No. at Risk

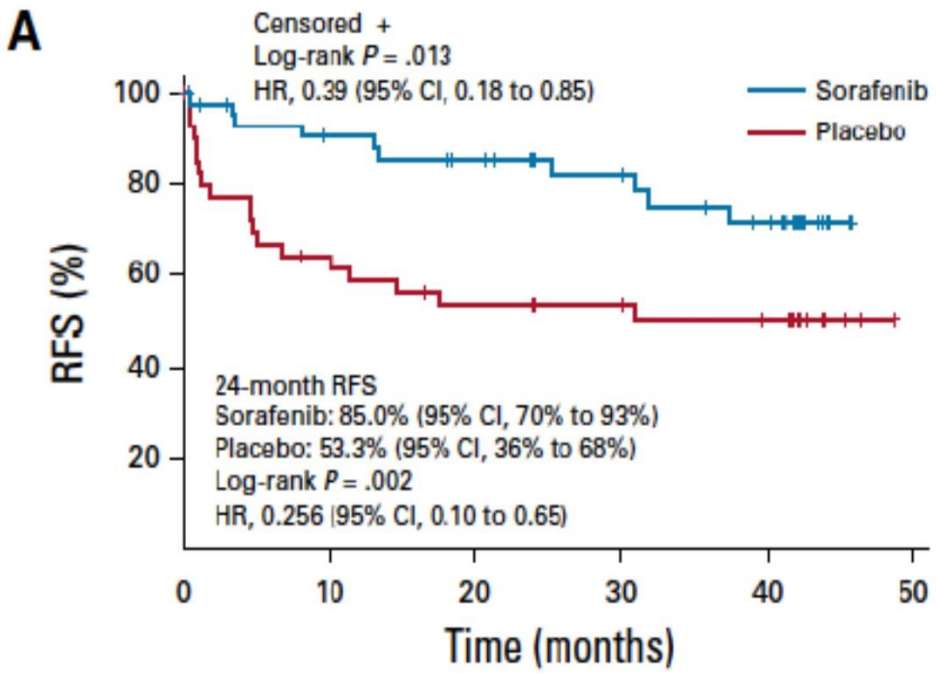
| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Midostaurin | 360 | 269 | 208 | 181 | 151 | 97 | 37 | 1 |
| Placebo | 357 | 221 | 163 | 147 | 129 | 80 | 30 | 1 |

## Crenolanib/ 7+3 (phase 2)(n=28)



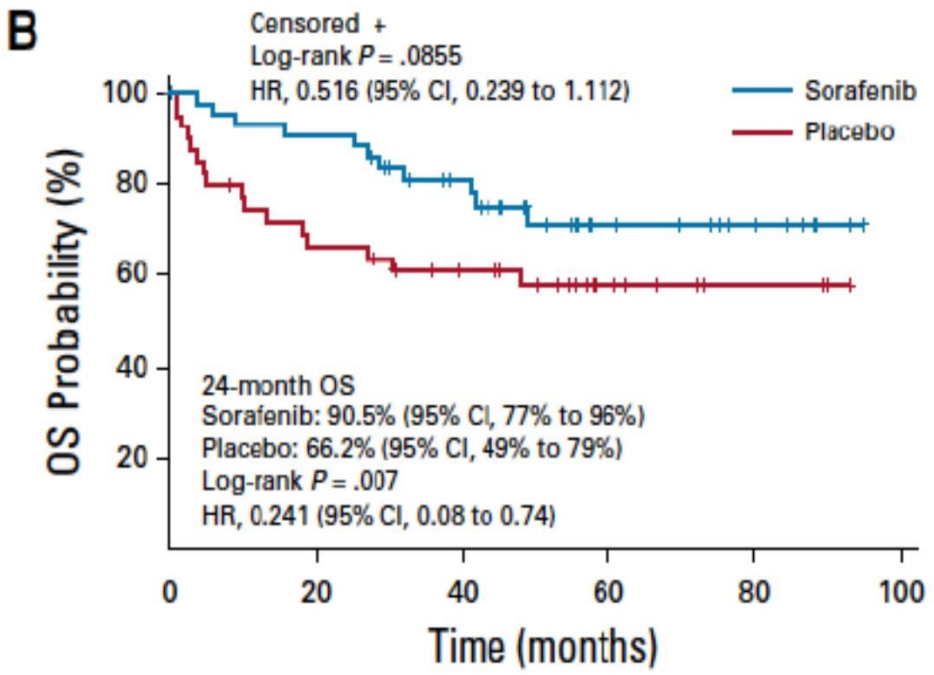

*Stone R et al NEJM 2017; Wang E et al ASH abstract 2017*

# SORMAIN: TKI maintenance following alloSCT




No. at risk:

| | | | | | | |
|---|---|---|---|---|---|---|
| Placebo | 40 | 24 | 19 | 17 | 14 | 0 |
| Sorafenib | 43 | 35 | 31 | 25 | 18 | 0 |




No. at risk:

| | | | | | | |
|---|---|---|---|---|---|---|
| Placebo | 40 | 25 | 19 | 9 | 3 | 0 |
| Sorafenib | 43 | 38 | 28 | 12 | 7 | 0 |

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

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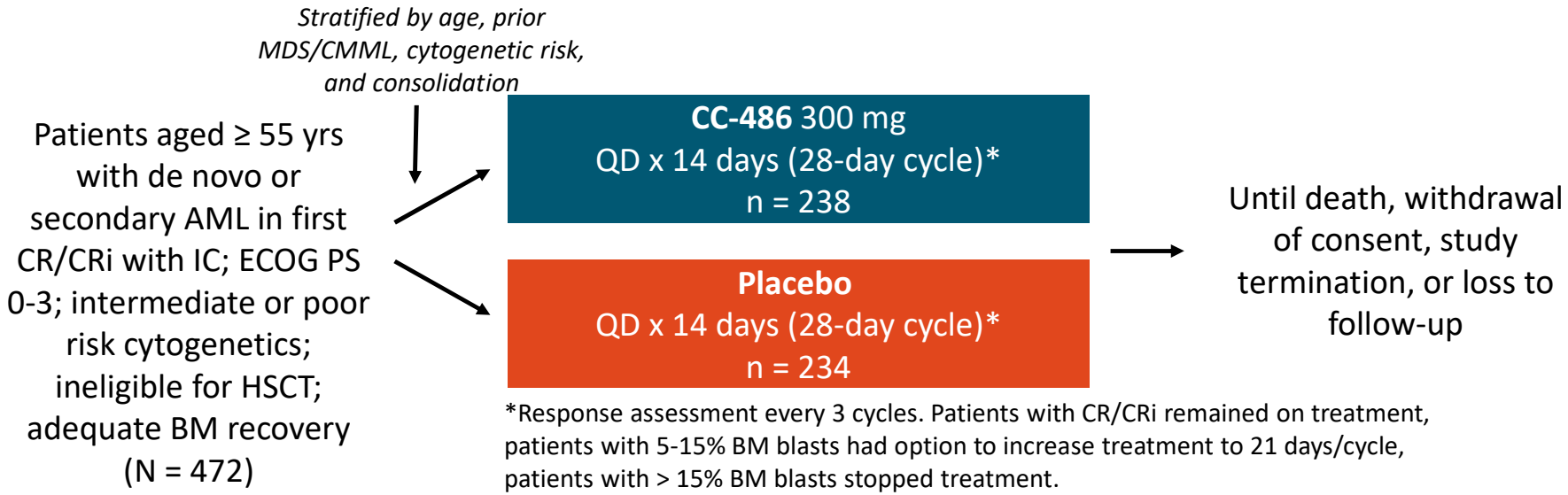
# Phase III QUAZAR AML-001: CC-486 as Maintenance Therapy in First-Remission AML—Study Design

- Multicenter, randomized, placebo-controlled, double-blind, phase III study




*Response assessment every 3 cycles. Patients with CR/CRi remained on treatment, patients with 5-15% BM blasts had option to increase treatment to 21 days/cycle, patients with > 15% BM blasts stopped treatment.

- Primary endpoint: overall survival
- Key secondary endpoints: relapse-free survival, health-related QoL, and safety

Wei. ASH 2019. Abstr LBA_3.

# QUAZAR AML-001: Baseline Characteristics

| Characteristic | CC-486 n = 238 | Placebo n = 234 |
|---|---|---|
| Median age, yrs (range) | 68 (55-86) | 68 (55-82) |
| ▪ ≥ 65 yrs, n (%) | 172 (72) | 166 (71) |
| Male, n (%) | 118 (50) | 127 (54) |
| ECOG PS score, n (%) | | |
| ▪ 0 | 116 (49) | 111 (47) |
| ▪ 1 | 101 (42) | 106 (45) |
| ▪ 2 | 21 (9) | 15 (6) |
| ▪ 3 | 0 | 2 (1) |
| De novo AML, n (%) | 213 (89) | 216 (92) |
| WHO classification, n (%) | | |
| ▪ Not otherwise specified | 148 (62) | 145 (62) |
| ▪ Myelodysplasia-related changes | 49 (21) | 42 (18) |
| ▪ Recurrent genetic abnormalities | 39 (16) | 46 (20) |

| Characteristic, n (%) | CC-486 n = 238 | Placebo n = 234 |
|---|---|---|
| NCCN cytogenetic risk | | |
| ▪ Intermediate | 203 (85) | 203 (87) |
| ▪ Poor | 35 (15) | 31 (13) |
| Response after induction | | |
| ▪ CR | 187 (79) | 197 (84) |
| ▪ CRi | 51 (21) | 37 (16) |
| Received consolidation therapy | 186 (78) | 192 (82) |
| ▪ 1 cycle | 110 (46) | 102 (44) |
| ▪ 2 cycles | 70 (29) | 77 (33) |
| ▪ 3 cycles | 6 (3) | 13 (6) |
| MRD status at randomization* | | |
| ▪ Positive | 103 (43) | 116 (50) |
| ▪ Negative | 133 (56) | 111 (47) |

*Central assessment by flow cytometry with a positive threshold of ≥ 0.1% using “different-from-normal” method.

Wei. ASH 2019. Abstr LBA_3.

# QUAZAR AML-001: Survival

| Outcome | CC-486 n = 238 | Placebo n = 234 |
|---|---|---|
| Median OS, mos (95% CI) | 24.7 (18.7-30.5) | 14.8 (11.7-17.6) |
| ▪ Stratified *P* value | .0009 | |
| ▪ Stratified HR (95% CI) | 0.69 (0.55-0.86) | |
| 1-yr survival rate, % (95% CI) | 73 (67-78) | 56 (49-62) |
| 2-yr survival rate, % (95% CI) | 51 (44-57) | 37 (31-43) |
| Relapse-free survival, mos (95% CI) | 10.2 (7.9-12.9) | 4.8 (4.6-6.4) |
| ▪ Stratified *P* value | .0001 | |
| ▪ Stratified HR (95% CI) | 0.65 (0.52-0.81) | |

- Median follow up: 41.2 months
- 1-yr relapse rate was 53% (95% CI: 46-59) in CC-486 arm vs 71% (95% CI: 65-77) in placebo arm

Wei. ASH 2019. Abstr LBA_3.

# Upfront Treatment of De Novo AML in patients not eligible for Intensive chemotherapy

Who is ineligible?

1. P53 MT AML
2. Age > 75
3. Major comorbidities
4. frail

**Intermediate/poor risk**

Azacitidine + Venetoclax

**FLt-3 MT AML**

Azacitidine + Venetoclax

Or

Azactidine+Flt-3 inhibitor

**P53 MT AML**
Clinical trials
APR-246
Magrolimab

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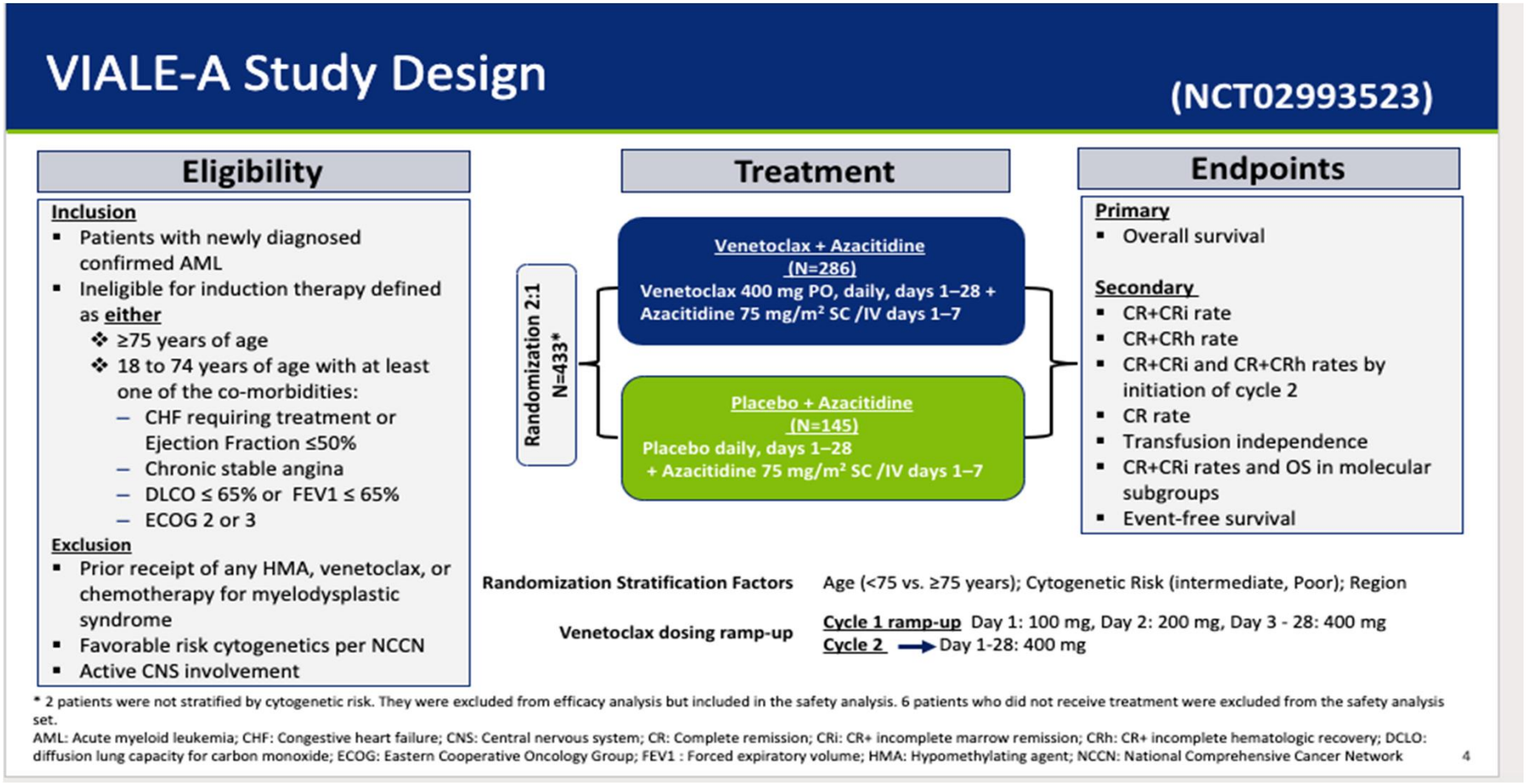
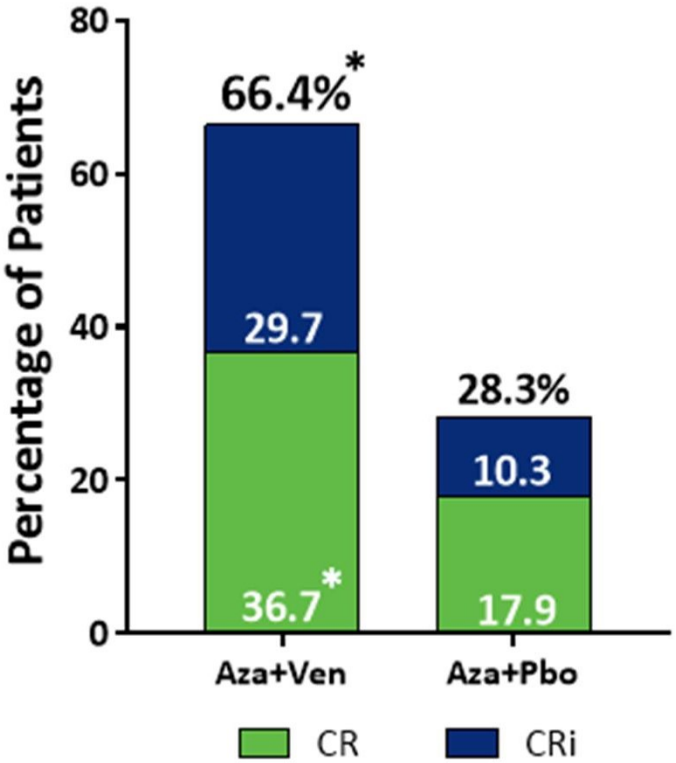
Magrolimab

# Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia




CD DiNardo et al. N Engl J Med 2020;383:617-629.

# Composite Response Rate (CR+CRi)




| | No. of treatment cycles, median (range) | Median time to CR/CRi, Months (range) | *CR+CRi by initiation of Cycle 2, n (%) |
|---|---|---|---|
| Aza+Ven (n=286) | 7.0 (1.0 – 30.0) | 1.3 (0.6 – 9.9) | 124 (43.4) |
| Aza+Pbo (n=145) | 4.5 (1.0 –26.0) | 2.8 (0.8 – 13.2) | 11 (7.6) |

*CR+CRi rate, CR rate, and CR+CRi by initiation of cycle 2 are statistically significant with p<0.001 by CMH test

Aza: Azacitidine; Pbo: Placebo; Ven: Venetoclax; CR: Complete remission; CRi: CR with incomplete-count recovery; CR was defined as absolute neutrophil count >$10^3$/μL, platelets >$10^5$/μL, red cell transfusion independence (TI), and bone marrow with <5% blasts; CRi was defined as all criteria for CR, except for neutropenia ≤$10^3$/μL or thrombocytopenia ≤$10^5$/μL.
CR + CRi rate was compared using Cochran-Mantel-Haenszel (CMH) test stratified by age (18 – < 75, ≥ 75) and cytogenetic risk (intermediate, poor).

CD DiNardo et al. N Engl J Med 2020;383:617-629.

# Summary of Adverse Events (cont.)

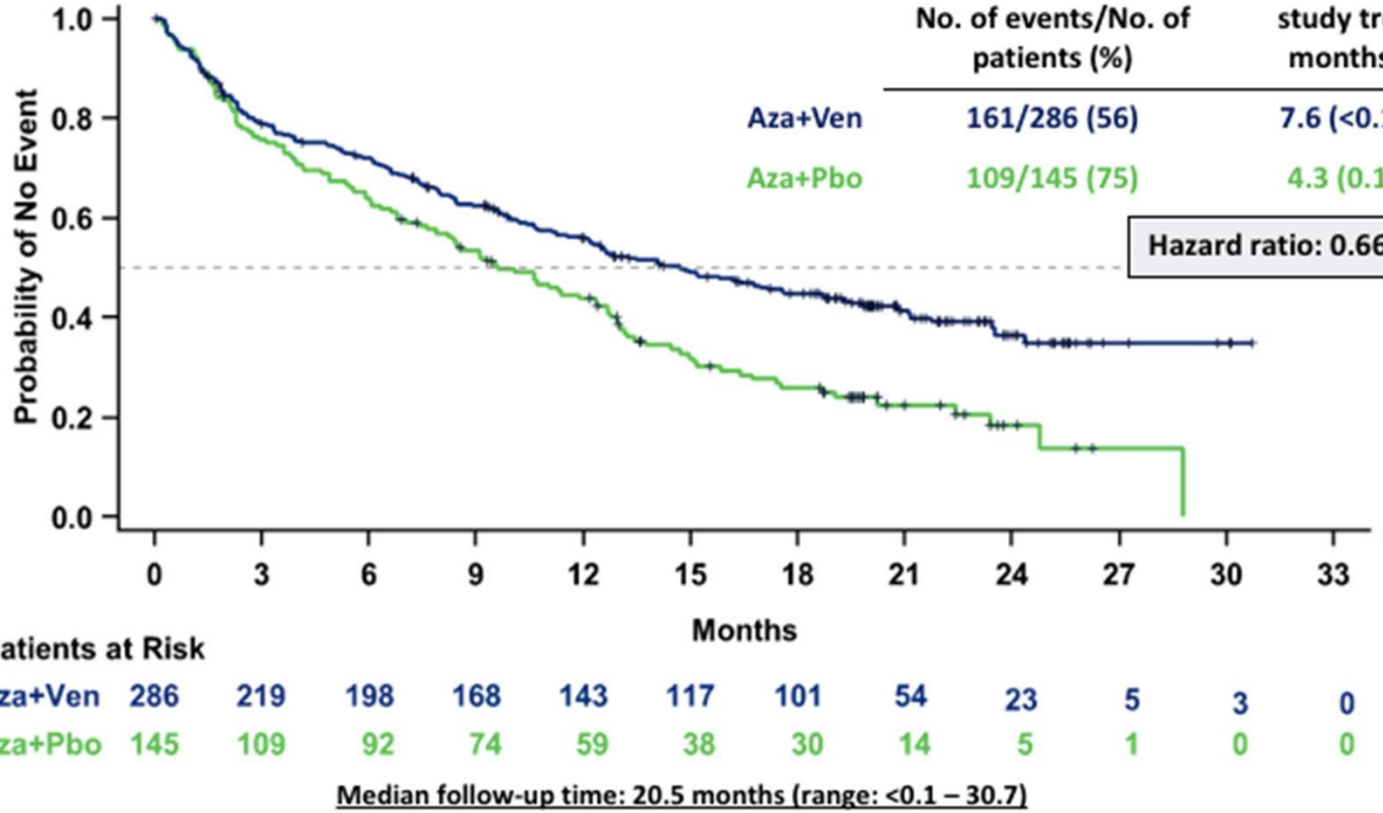
| Serious AEs in ≥5% of patients, n (%) | Aza+Ven N = 283 | Aza+Pbo N = 144 |
|---|---|---|
| **All serious AEs** | **235 (83)** | **105 (73)** |
| Febrile neutropenia | 84 (30) | 15 (10) |
| Anemia | 14 (5) | 6 (4) |
| Neutropenia | 13 (5) | 3 (2) |
| Atrial fibrillation | 13 (5) | 2 (1) |
| Pneumonia | 47 (17) | 32 (22) |
| Sepsis | 16 (6) | 12 (8) |
| **Any AE leading to:** | | |
| Dose discontinuation | 69 (24) | 29 (20) |
| Dose interruption* | 204 (72) | 82 (57) |
| Dose reduction† | 7 (3) | 6 (4) |
| **Deaths, n (%)** | | |
| ≤30 days after first dose of study drug | 21 (7) | 9 (6) |
| ≤60 days after first dose of study drug | 43 (15) | 24 (17) |
| **Other, n (%)** | | |
| Tumor lysis syndrome†† | 3 (1) | 0 |

*Dose interruptions commonly due to neutropenia (19%/10%), febrile neutropenia (20%/4%), and thrombocytopenia (10%/4%); interruptions include delays between cycles and reduced duration from 28 to 21 days per cycle for count recovery after marrow leukemia clearance; †Dose reduction for AEs or other medications; †† 3 cases of TLS during ramp up.



CD DiNardo et al. N Engl J Med 2020;383:617-629.

# Overall Survival



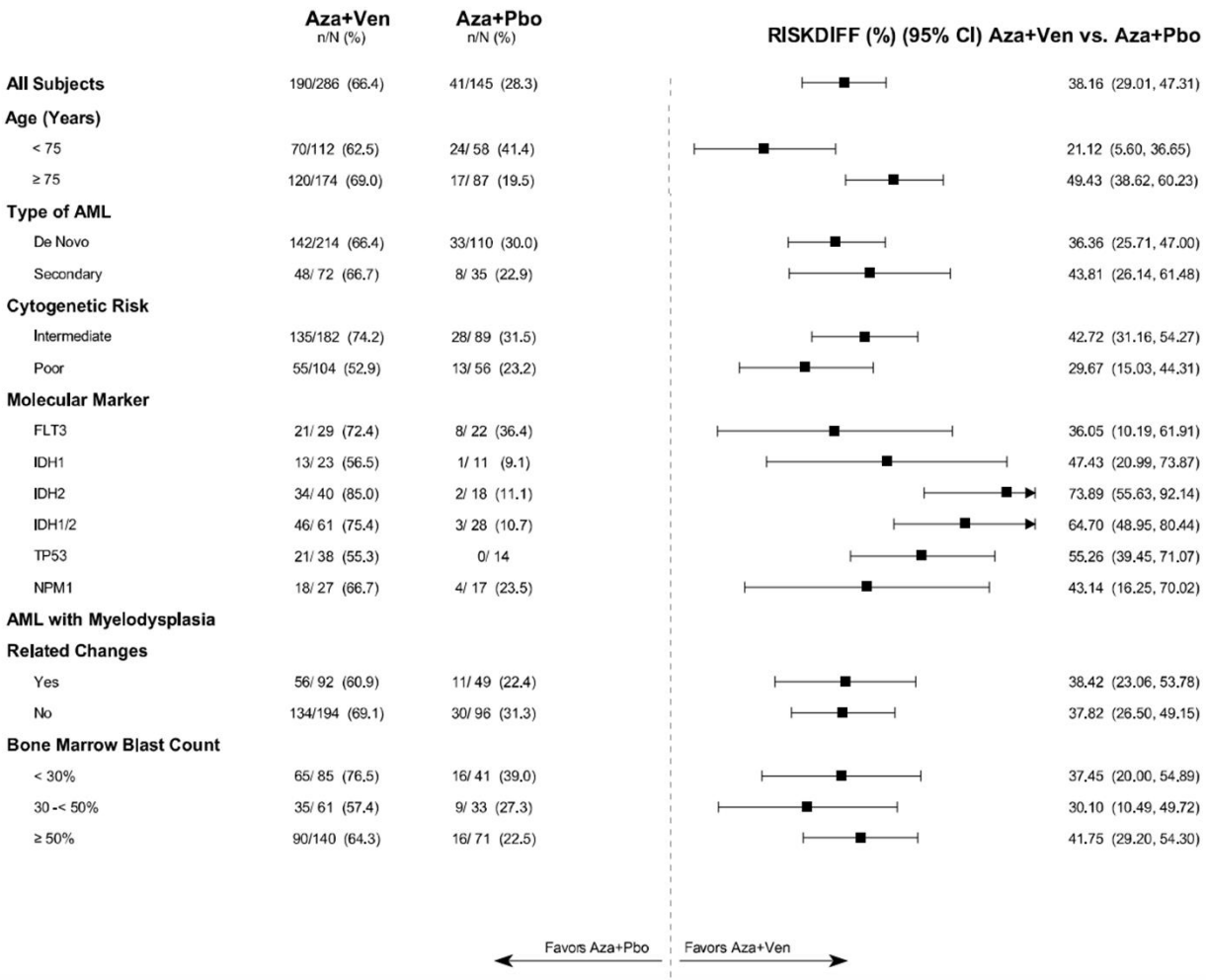

| | No. of events/No. of patients (%) | Median duration of study treatment, months (range) | Median overall survival, months (95% CI) |
|---|---|---|---|
| Aza+Ven | 161/286 (56) | 7.6 (<0.1 – 30.7) | 14.7 (11.9 – 18.7) |
| Aza+Pbo | 109/145 (75) | 4.3 (0.1 – 24.0) | 9.6 (7.4 – 12.7) |

**Hazard ratio: 0.66 (95% CI: 0.52 – 0.85), p<0.001**

**Median follow-up time: 20.5 months (range: <0.1 – 30.7)**

Aza: Azacitidine; Pbo: Placebo; Ven: Venetoclax; The distributions were estimated for each treatment arm using Kaplan-Meier methodology and compared using the log-rank test stratified by age (18-<75, ≥75 years) and cytogenetic risk (intermediate risk, poor risk). The hazard ratio between treatment arms were estimated using the Cox proportional hazards model with the same stratification factors used in the log-rank test.

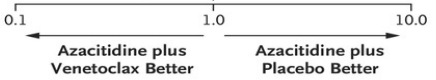
# Response to Azacitidine + Venetoclax




DiNardo et al, NEJM 2020

# Subgroup Analysis of Overall Survival.

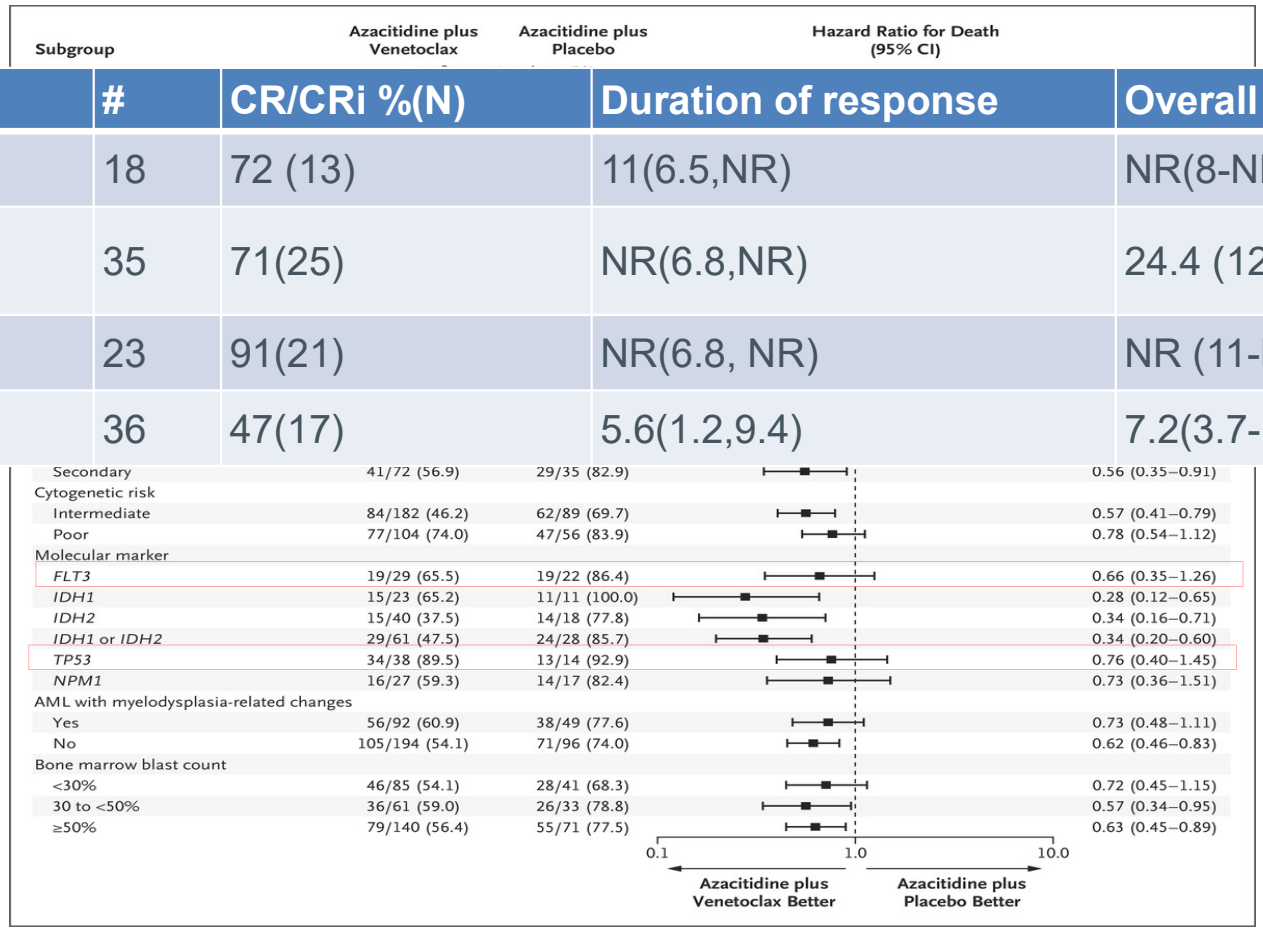
| Subgroup | Azacitidine plus Venetoclax | Azacitidine plus Placebo | Hazard Ratio for Death (95% CI) |
|---|---|---|---|
| | *no. of events/total no. (%)* | | |
| All patients | 161/286 (56.3) | 109/145 (75.2) | 0.64 (0.50–0.82) |
| Sex | | | |
| Female | 61/114 (53.5) | 41/58 (70.7) | 0.68 (0.46–1.02) |
| Male | 100/172 (58.1) | 68/87 (78.2) | 0.62 (0.46–0.85) |
| Age | | | |
| <75 yr | 66/112 (58.9) | 36/58 (62.1) | 0.89 (0.59–1.33) |
| ≥75 yr | 95/174 (54.6) | 73/87 (83.9) | 0.54 (0.39–0.73) |
| Geographic region | | | |
| United States | 27/50 (54.0) | 21/24 (87.5) | 0.47 (0.26–0.83) |
| Europe | 70/116 (60.3) | 46/59 (78.0) | 0.67 (0.46–0.97) |
| China | 9/24 (37.5) | 5/13 (38.5) | 1.05 (0.35–3.13) |
| Japan | 10/24 (41.7) | 9/13 (69.2) | 0.52 (0.20–1.33) |
| Rest of world | 45/72 (62.5) | 28/36 (77.8) | 0.73 (0.45–1.17) |
| Baseline ECOG score | | | |
| Grade <2 | 89/157 (56.7) | 65/81 (80.2) | 0.61 (0.44–0.84) |
| Grade ≥2 | 72/129 (55.8) | 44/64 (68.8) | 0.70 (0.48–1.03) |
| Type of AML | | | |
| De novo | 120/214 (56.1) | 80/110 (72.7) | 0.67 (0.51–0.90) |
| Secondary | 41/72 (56.9) | 29/35 (82.9) | 0.56 (0.35–0.91) |
| Cytogenetic risk | | | |
| Intermediate | 84/182 (46.2) | 62/89 (69.7) | 0.57 (0.41–0.79) |
| Poor | 77/104 (74.0) | 47/56 (83.9) | 0.78 (0.54–1.12) |
| Molecular marker | | | |
| *FLT3* | 19/29 (65.5) | 19/22 (86.4) | 0.66 (0.35–1.26) |
| *IDH1* | 15/23 (65.2) | 11/11 (100.0) | 0.28 (0.12–0.65) |
| *IDH2* | 15/40 (37.5) | 14/18 (77.8) | 0.34 (0.16–0.71) |
| *IDH1* or *IDH2* | 29/61 (47.5) | 24/28 (85.7) | 0.34 (0.20–0.60) |
| *TP53* | 34/38 (89.5) | 13/14 (92.9) | 0.76 (0.40–1.45) |
| *NPM1* | 16/27 (59.3) | 14/17 (82.4) | 0.73 (0.36–1.51) |
| AML with myelodysplasia-related changes | | | |
| Yes | 56/92 (60.9) | 38/49 (77.6) | 0.73 (0.48–1.11) |
| No | 105/194 (54.1) | 71/96 (74.0) | 0.62 (0.46–0.83) |
| Bone marrow blast count | | | |
| <30% | 46/85 (54.1) | 28/41 (68.3) | 0.72 (0.45–1.15) |
| 30 to <50% | 36/61 (59.0) | 26/33 (78.8) | 0.57 (0.34–0.95) |
| ≥50% | 79/140 (56.4) | 55/71 (77.5) | 0.63 (0.45–0.89) |




CD DiNardo et al. N Engl J Med 2020;383:617-629.

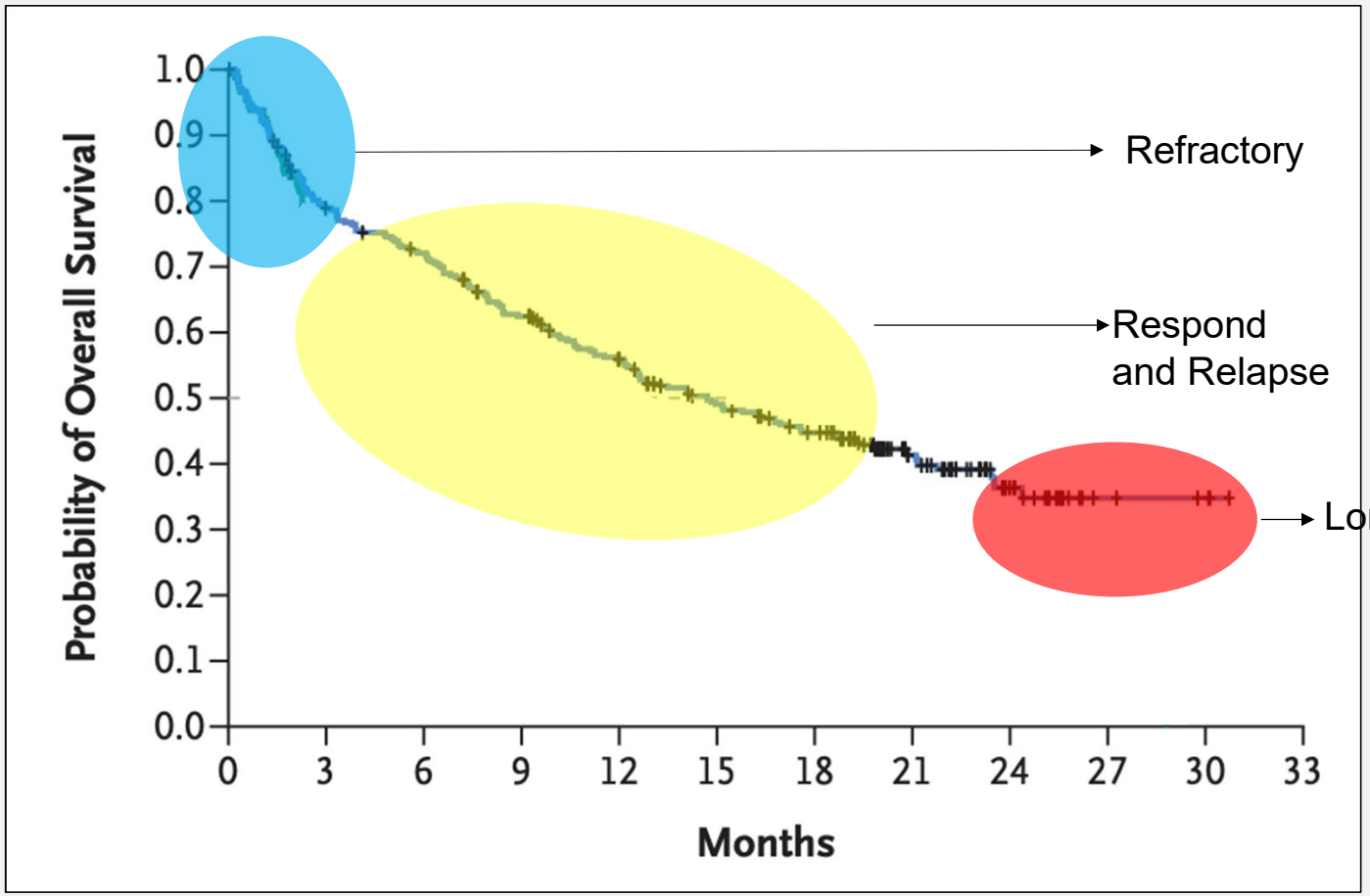
# Subgroup Analysis of Overall Survival.

| Mutation | # | CR/CRi %(N) | Duration of response | Overall Survival (mo) |
|---|---|---|---|---|
| FLT3 | 18 | 72 (13) | 11(6.5,NR) | NR(8-NR) |
| IDH ½ | 35 | 71(25) | NR(6.8,NR) | 24.4 (12.3-NR) |
| NPM1 | 23 | 91(21) | NR(6.8, NR) | NR (11-NR) |
| TP53 | 36 | 47(17) | 5.6(1.2,9.4) | 7.2(3.7-NR) |



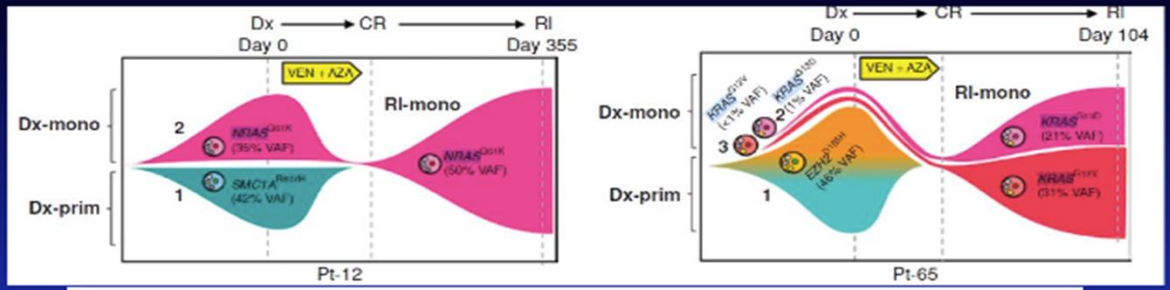

CD DiNardo et al. N Engl J Med 2020;383:617-629.

# Breaking Down the Azacitidine + Venetoclax Outcomes




DiNardo et al, NEJM 2020

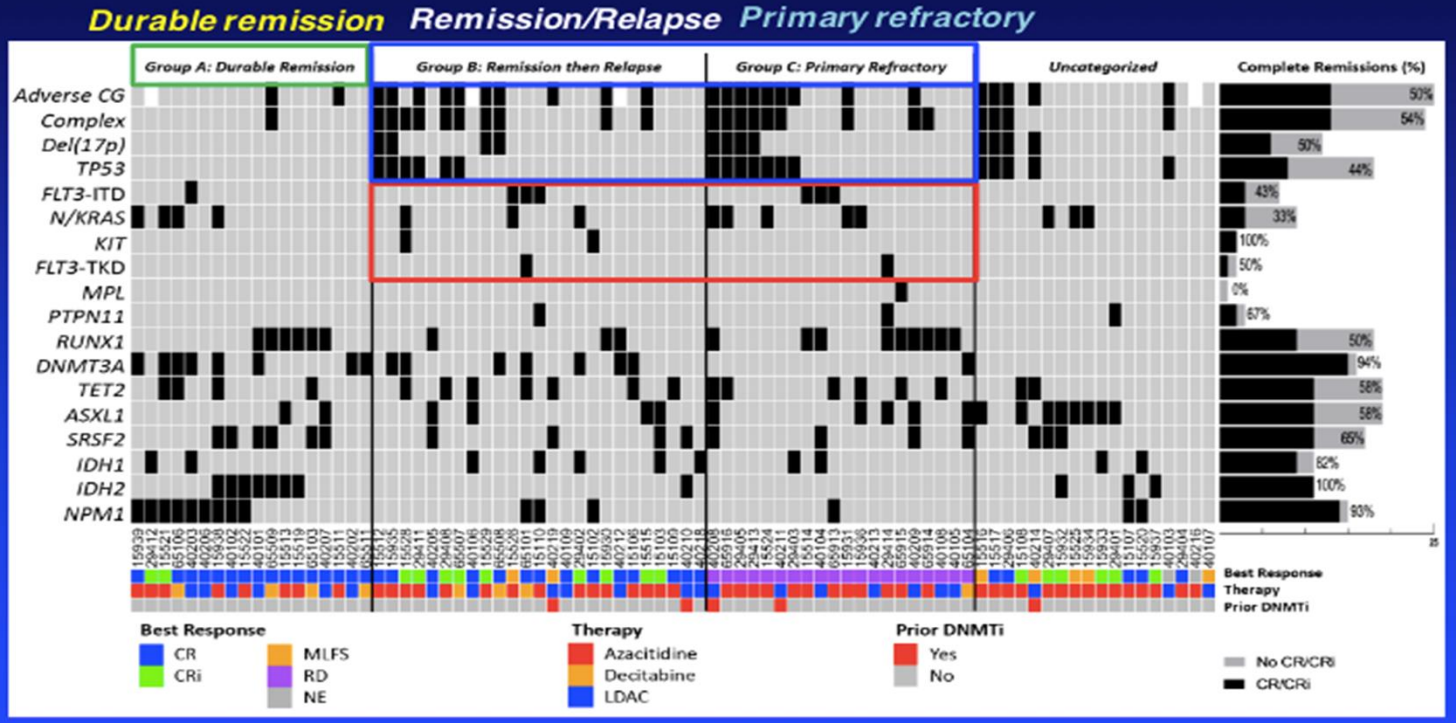
# Monocytic (M5) and RAS Mutations in VEN + AZA




| | | Univariate analysis as a predictor for refractory disease | | Multivariate analysis as a predictor for refractory disease | |
|---|---|---|---|---|---|
| Baseline variables | Value | OR (95% CI) | *P* value | OR (95% CI) | *P* value |
| Age (median) | 71.5 (22-89) | 0.984 (0.947-1.022) | 0.4028 | | |
| Sex (female) | 51 (51%) | 3.401 (1.002-11.539) | 0.0495 | 2.096 (0.417-10.544) | 0.3694 |
| Antecedent hematologic disorder | 20 (20%) | 0.573 (0.118-2.772) | 0.4884 | | |
| Complex cytogenetics | 28 (28%) | 2.667 (0.863-8.237) | 0.0883 | | |
| ELN Prognostic Group | | | | | |
| Favorable | 18 (18%) | | | | |
| Intermediate | 17 (17%) | 4.078 (0.494-33.642) | 0.0697 | | |
| Adverse | 64 (64%) | | | | |
| NA | 1 (1%) | | | | |
| RAS pathway mutations | 14 (14%) | 6.417 (1.813-22.708) | 0.0039 | 2.266 (0.201-25.522) | 0.5080 |
| *TP53* | 10 (10%) | 1.481 (0.282-7.766) | 0.6424 | | |
| *IDH1/IDH2* | 27 (27%) | NE | 0.9521 | | |
| *NPM1* | 27 (27%) | 0.162 (0.020-1.298) | 0.0865 | 0.488 (0.034-6.966) | 0.5967 |
| *FLT3-ITD* | 18 (18%) | 0.663 (0.136-3.273) | 0.6119 | | |
| *ASXL1* | 24 (24%) | 1.182 (0.339-4.122) | 0.7932 | | |
| FAB classification | | | | | |
| M0/M1 | 77 (77%) | 0.131 (0.040-0.428) | 0.0008 | | |
| M2 | 1 (1%) | | | | |
| M4 | 8 (8%) | NE | 0.9745 | | |
| M5 | 13 (13%) | 18.285 (4.701-71.129) | <0.0001 | 33.481 (2.657-421.90) | 0.0066 |
| M6a | 1 (1%) | | | | |

*Pei, ..., Jordan, Cancer Discovery 2020*

# Mechanisms of Treatment Failure After Ven + HMA/LDAC: Mutant p53




*C. DiNardo, M. Konopleva, A. Wei*
*BLOOD 2020*

# Upfront Treatment of De Novo AML in patients not eligible for Intensive chemotherapy

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**FLt-3 MT AML**

Azacitidine + Venetoclax

Or

Azactidine+Flt-3 inhibitor

**P53 MT AML**
Clinical trials
APR-246
Magrolimab

# Upfront therapy of older/unfit patient with FLT3 mutant AML

| FLT3 TKI | No pts | ORR | Duration of response |
|---|---|---|---|
| **Midostaurin + Aza** | 27 | 33% | 31 wks (no prior TKI)<br>vs. 16 wks (prior TKI) |
| **Sorafenib + Aza** | 27 | 78% | 14.5 mos (1.1 to 28.7 mos) |
| **Sorafenib + Dec** | 6 | 83%<br>(CR16%, CRi 66%) | Not determined |
| **Gilteritinib + Aza** | 15 | 60%<br>(2CR, 8CRi) | Not determined |

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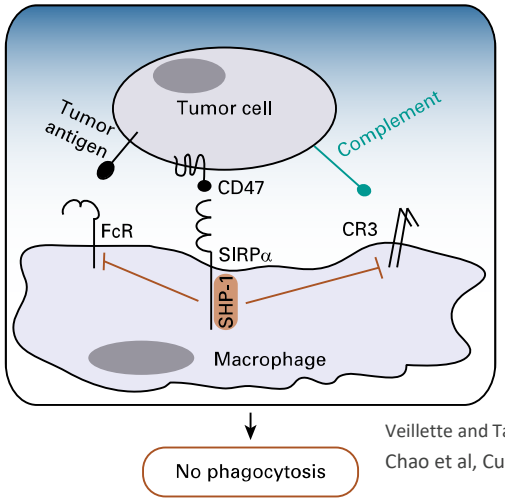
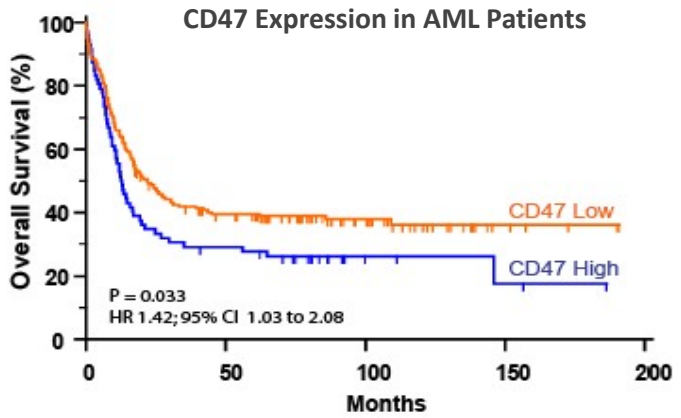
**P53 MT AML**
Clinical trials
APR-246
Magrolimab

# CD47 is a Major Macrophage Immune Checkpoint and "Do Not Eat Me" Signal in Myeloid Malignancies including MDS and AML




Veillette and Tang, JCO 2019

Chao et al, Current Opin Immunol 2012



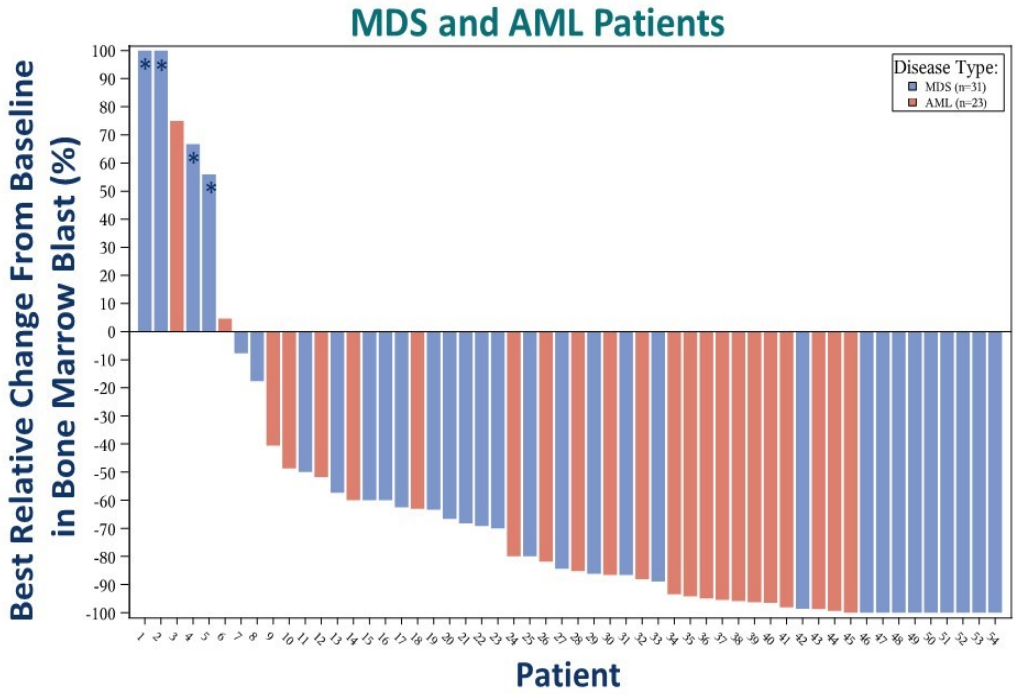

Majeti, Chao et al., Cell 2009

- CD47 is a "do not eat me" signal on cancers that enables macrophage immune evasion
- Increased CD47 expression predicts worse prognosis in AML patients

# Magrolimab + AZA Induces High Response Rates in MDS and AML

| Best Overall Response | 1L MDS N=33 | 1L AML N=25 |
|---|---|---|
| ORR | 30 (91%) | 16 (64%) |
| CR | 14 (42%) | 10 (40%) |
| CRi | NA | 4 (16%) |
| PR | 1 (3%) | 1 (4%) |
| MLFS/marrow CR | 8 (24%)<br>4 with marrow CR + HI | 1 (4%) |
| Hematologic improvement (HI) | 7 (21%) | NA |
| SD | 3 (9%) | 8 (32%) |
| PD | 0 | 1 (4%) |

Response assessments per 2006 IWG MDS criteria and 2017 AML ELN criteria. Patients with at least 1 post-treatment response assessment are shown; all other patients are on therapy and are too early for first response assessment, except for 2 MDS patients not evaluable (withdrawal of consent) and 3 AML patients (1 AE, 2 early withdrawal).




Four patients not shown due to missing values; <5% blasts imputed as 2.5%. *Baseline bone marrow blasts ≤5%.

- Magrolimab + AZA induces a 91% ORR (42% CR) in MDS and 64% ORR (56% CR/CRi) in AML
- Responses deepened over time with a 56% 6-month CR rate in MDS patients (assessed in all patients 6 months after initial treatment)
- Median time to response is 1.9 months, more rapid than AZA alone
- Magrolimab + AZA efficacy compares favorably to AZA monotherapy (CR rate 6-17%[1,2])

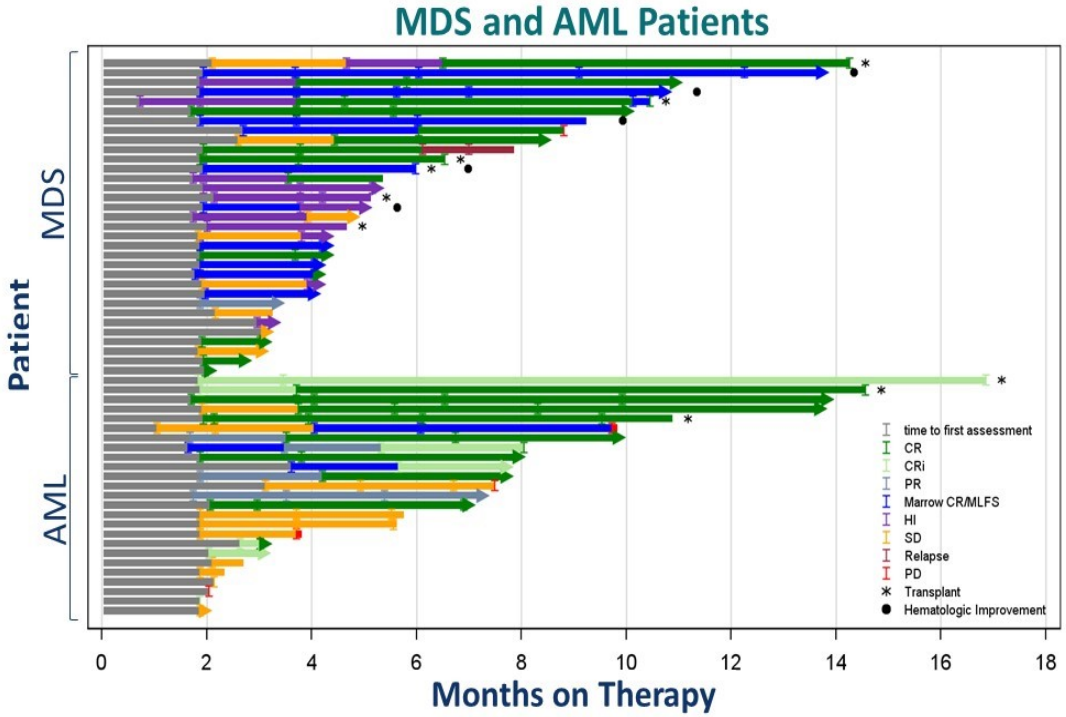
1. Azacitidine USPI. 2. Fenaux P, et al. *Lancet Oncol.* 2009 ;10(3):223-232.

Sallman et al et al, ASCO 2020 Abstract 7507

# Deep and Durable Responses Are Seen in Magrolimab + AZA Treated Patients

| Parameter | 1L MDS N=33 | 1L AML N=25 |
|---|---|---|
| RBC transfusion independence* | 11/19 (58%) | 9/14 (64%) |
| Complete cytogenetic response† | 9/26 (35%) | 6/12 (50%) |
| MRD negativity in responders | 6/30 (20%) | 8/16 (50%) |
| Median duration of response (months) | Not reached (0.03+ – 10.4+) | Not reached (0.03+ – 15.1+) |
| Median follow-up (range) (months) | 5.8 (2.0–15.0) | 9.4 (1.9–16.9) |

MRD was evaluated by multiparameter flow cytometry; cytogenetic response defined per 2003 and 2006 IWG criteria.
*Patients shown for those who were RBC transfusion dependent at baseline and achieved RBC transfusion independence at any time on study.
†Responses shown for all responding patients with abnormal cytogenetics at baseline.




- Complete cytogenetic responses and MRD negativity is observed in MDS and AML patients
- No median duration of response has been reached for MDS or AML
- 16% of patients (9/58) received an allogeneic stem cell transplant
- Median OS has not been reached in either MDS or AML patients

Sallman et al et al, ASCO 2020 Abstract 7507

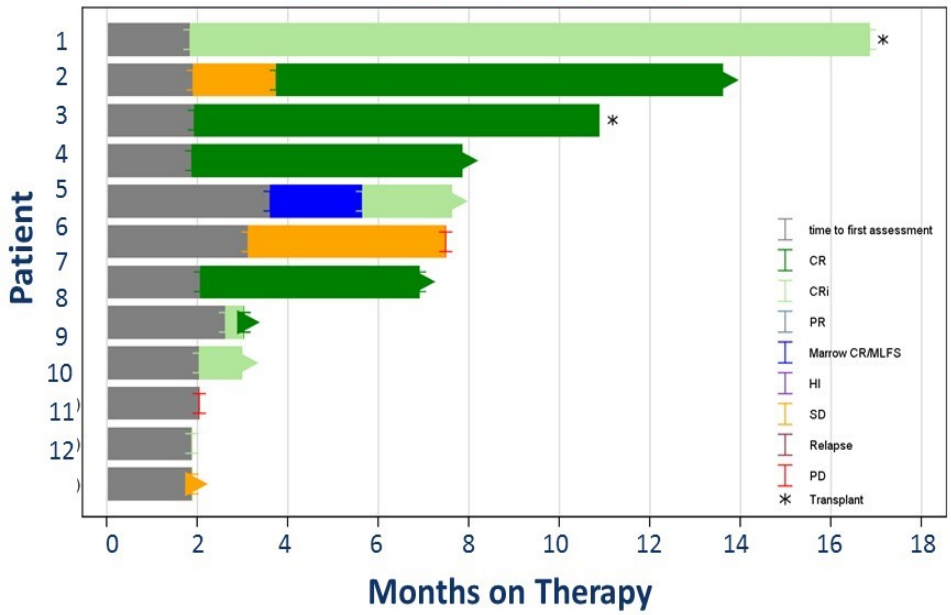
# Magrolimab + AZA Eliminates Disease in AML and MDS Patients With *TP53* Mutation

**Efficacy in *TP53*-Mutant Patients**

| Best Overall Response | AML *TP53* Mutant (N=12) | MDS *TP53* Mutant (N=4) |
|---|---|---|
| ORR | 9 (75%) | 3 (75%) |
| CR | 5 (42%) | 2 (50%) |
| CRi/marrow CR | 4 (33%) | 1 (25%) |
| Complete cytogenetic response * | 4/8 (50%) | 3/3 (100%) |
| MRD negative of responders | 4/9 (44%) | 0 |
| Median duration of response (months) | Not reached (0.03+ – 15.1+) | Not reached (0.03+ – 5.2+) |
| Survival probability at 6 months | 91% | 100% |
| Median follow-up (range) (months) | 8.8 (1.9 – 16.9) | 7 (4.2 – 12.2) |

*Responding patients with abnormal cytogenetics at baseline.

***TP53*-Mutant AML Patients**



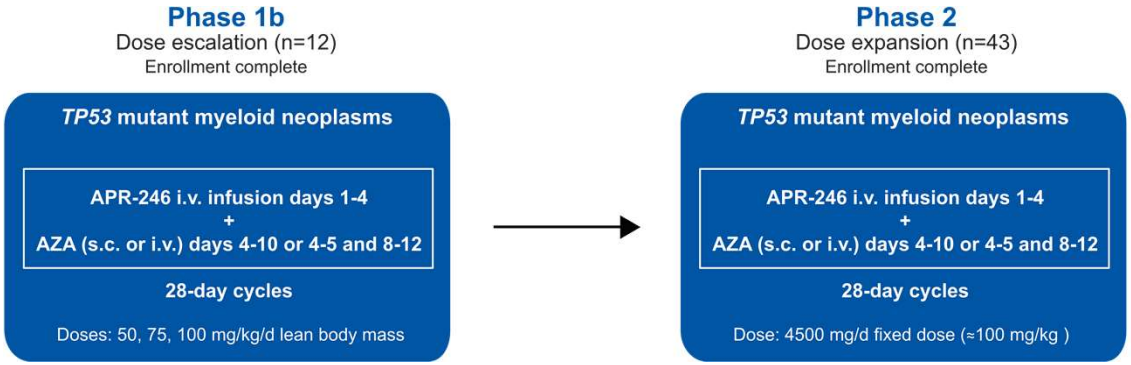

- Magrolimab + AZA has a high response rate with deep responses in *TP53*-mutant AML and MDS patients
- The estimated 6-month survival is 91% and 100% in AML and MDS patients, respectively
- Median duration and survival has not been reached, which compares favorably to current therapies
  - Venetoclax + AZA in AML: ORR 47%, DOR 5.6 mo, OS 7.2 mo[1]

Sallman et al et al, ASCO 2020 Abstract 7507

1. DiNardo CD, et al. *Blood*. 2019;133(1):7-17.

# Frontline Combination Therapy with APR-246 + Azacitidine: Study Design and Objectives

- IIT evaluating frontline APR-246 + azacitidine in *TP53* MT HMA-naïve MDS, oligoblastic AML (≤ 30% blasts) and MDS-MPN
- Phase 1b Results (Sallman D et al., ASH 2018)
  - RP2D of 4500mg/day days 1-4 (~100mg/kg LBM) + azacitidine (75mg/m$^2$)
  - Manageable G1/G2 nausea and transient neurological AEs (dizziness/altered sensation) to APR-246; No DLTs
  - Activation of p53-dependent pathways following monotherapy treatment (1 mCR+partial cytogenetic remission in lead-in phase)
- Phase 2
  - Primary: CR rate
  - Secondary: Safety, ORR, DoR, OS, p53 IHC, and Serial NGS (0.1% VAF sensitivity)



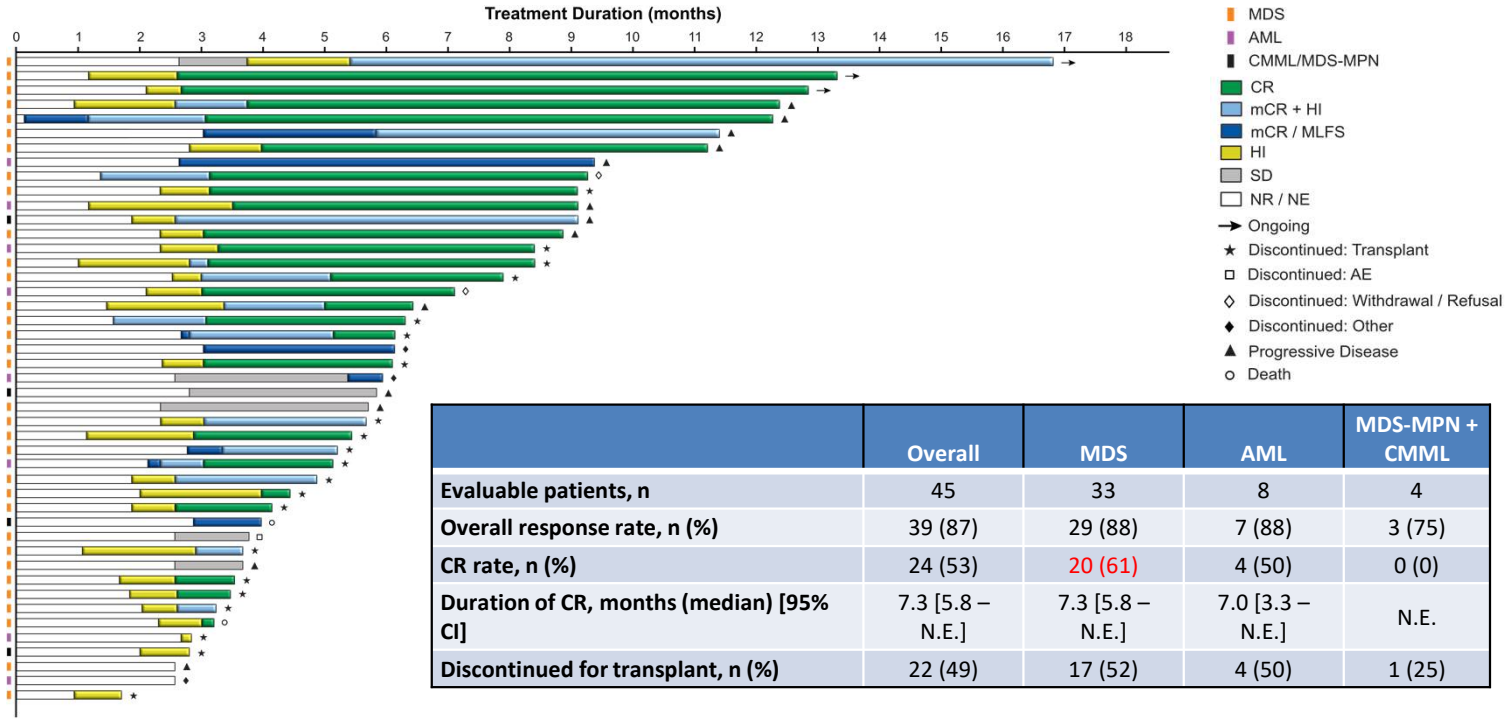

ClinicalTrials.gov NCT03072043; i.v., intravenous; s.c., subcutaneous; RP2D, recommended Phase 2 dose; CR, complete remission; DoR, duration of response; LBM, lean body mass

Sallman. ASH 2019. Abstr 676.

MOFFITT CANCER CENTER

# Response to Treatment in Evaluable Patients (n=45)

## Cutoff: November 15, 2019




| | Overall | MDS | AML | MDS-MPN + CMML |
|---|---|---|---|---|
| **Evaluable patients, n** | 45 | 33 | 8 | 4 |
| **Overall response rate, n (%)** | 39 (87) | 29 (88) | 7 (88) | 3 (75) |
| **CR rate, n (%)** | 24 (53) | 20 (61) | 4 (50) | 0 (0) |
| **Duration of CR, months (median) [95% CI]** | 7.3 [5.8 – N.E.] | 7.3 [5.8 – N.E.] | 7.0 [3.3 – N.E.] | N.E. |
| **Discontinued for transplant, n (%)** | 22 (49) | 17 (52) | 4 (50) | 1 (25) |

Median duration of follow-up = 10.8 months

Sallman. ASH 2019. Abstr 676.

# WHY? Not all CRs are the same--MRD

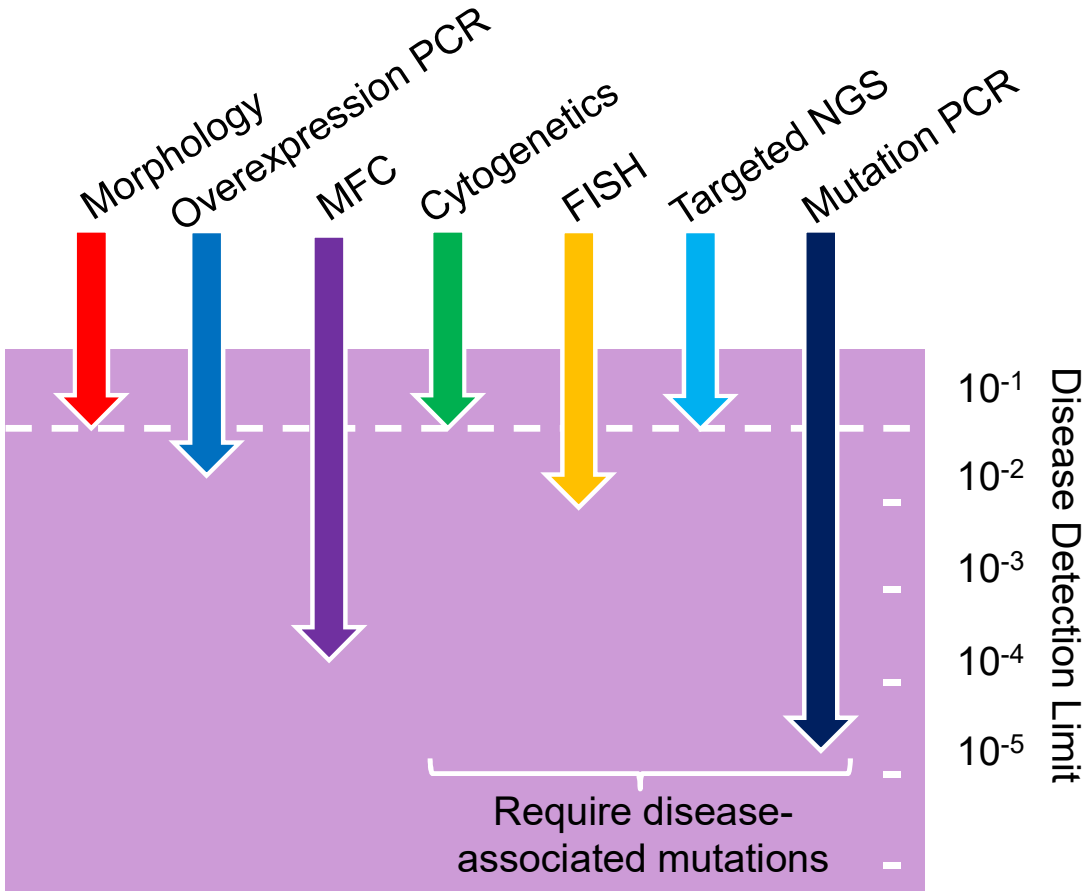
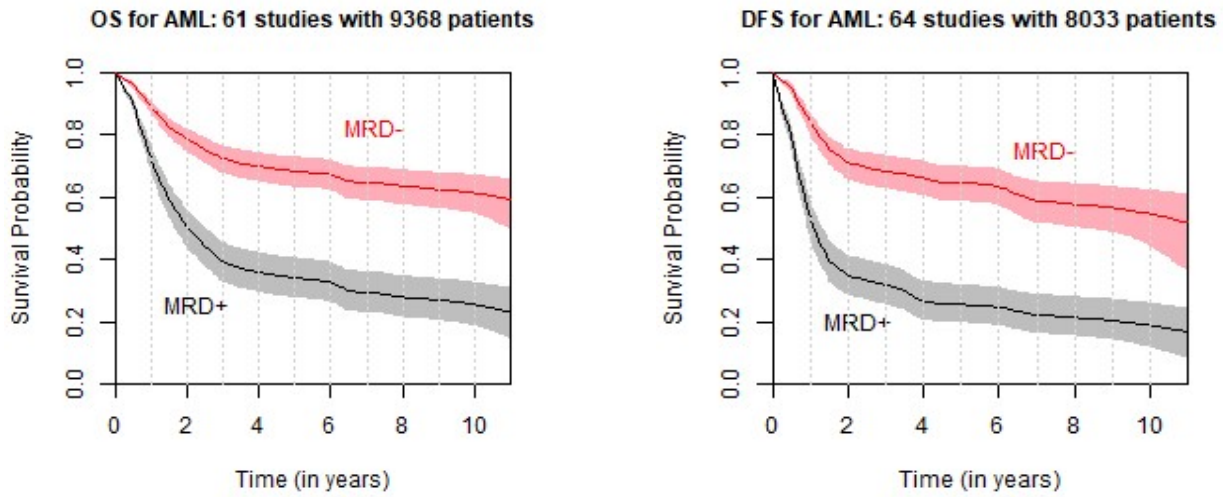



**Figure 1. Comparison of detection limits for methods of MRD assessment.** Standard morphological assessment defines CR as <5% blasts. Cytogenetics and targeted NGS have similar detection limits to morphology though can detect if the residual blasts harbor clonal abnormalities. Overexpression PCR (*e.g.*WT1) requires at least a 2-log difference in expression to discriminate from healthy BM. FISH has the sensitivity to detect 0.5% residual disease. MFC and mutation PCR have vastly improved the sensitivity of detection of MRD with detection limits ranging from 0.01% to 0.001%.

# MRD and survival

- Meta-analysis of 81 Publications




**Short N, et al JAMA Oncology October 2020**

# Conclusions

- GO addition to intensive chemotherapy (IC) improves overall survival in Good risk AML and future directions to eliminate anthracycline use.
- Flt-3 inhibitors combinations with IC is standard of care for FLT-3 MT AML.
- Maintenance therapy in AML is standard care now in FLT-3 AML after allo-SCT and for intermediate and poor risk AML after IC if no allo-SCT.
- Azacitidine and venetoclax combination is the new standard of upfront treatment in AML patients not eligible for IC.
  - Exceptions?: TP53, M5, FLT-3?
- Patients with TP53 MT AML should be enrolled on clinical trials.
- MRD assessment and disease status will guide our future tailoring of treatment.