ManagingAML

New Treatment Paradigms in AML: A Focus on Maintenance Therapy

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Welcome to *Managing AML.* I am Dr. Pinkal Desai and today I'm going to discuss new treatment paradigms in AML, a focus on maintenance therapy.

Case Question

- 68-year-old patient in good health presents with a WBC of 30k and is diagnosed with AML with normal cytogenetics. Rest of myeloid mutation panel shows DNMT3A mutation. Patient is treated with IDA/DNR + cytarabine and achieved an MRD negative CR. What is the next step in treatment?
  - A. Cytarabine consolidation for 4 cycles
  - B. Cytarabine consolidation followed by Oral azacitidine maintenance
  - C. Allogeneic transplant
  - D. Allogeneic transplant followed by Oral azacitidine maintenance

Before we begin the presentation, I would like to present a question, a hypothetical case, that we will take an audience poll.

A 68-year-old patient in good health presents with a white cell count of 30,000 is diagnosed with AML with normal cytogenetics. Rest of the myeloid mutation panel shows a DNMT3A mutation. The patient is treated with 7 and 3 and achieved a MRD-negative complete remission.

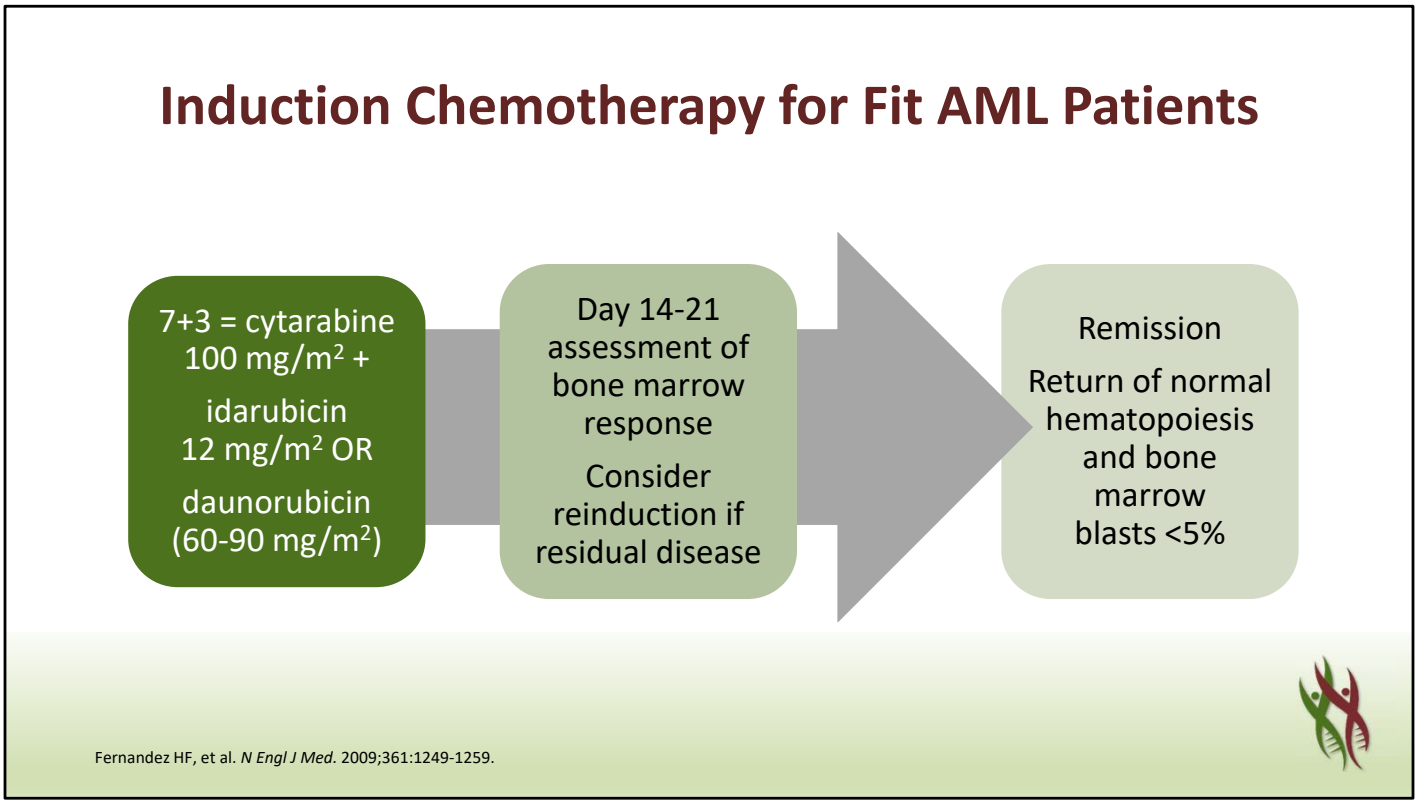
What is the next step in treatment?
a. Cytarabine consolidation for four cycles
b. Cytarabine consolidation followed by oral azacitidine maintenance
c. Allogeneic transplant
d. Allogeneic transplant followed by oral azacitidine maintenance.

European LeukemiaNet Prognostic Classification

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

*Low, low allelic ratio (<0.5); high, high allelic ratio (≥0.5); as determined by GeneScan analysis. **The presence of t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse-risk gene mutations. #Three or more unrelated chromosome abnormalities in the absence of one of the World Health Organization-designated recurring translocations or inversions, ie, t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23.3), t(6;9), inv(3) or t(3;3); AML with *BCR-ABL1*. ++Defined by the presence of one single monosomy (excluding loss of X or Y) in association with at least one additional monosomy or structural chromosome abnormality (excluding core-binding factor AML). ***These markers should not be used as an adverse prognostic marker if they co-occur with favorable-risk AML subtypes. +*TP53* mutations are significantly associated with AML with complex and monosomal karyotype.

I'm going to now review some of the data on maintenance therapy in AML. As you all are aware, we have an ELN prognostic classification of AML, which divides it into favorable, intermediate, and adverse risk based on cytogenetics and molecular markers. This helps us decide what a therapy plan is made post-induction in terms of whether these patients go to transplant or not.



In short, induction chemotherapy for fit AML therapy includes for fit AML patients include 7 and 3 based chemotherapy, and an assessment of bone marrow response on day 14 through 21 with consideration for re-induction if there is residual disease. The goal is to gain remission, which is return of normal hematopoiesis and bone marrow blast being less than 5%.

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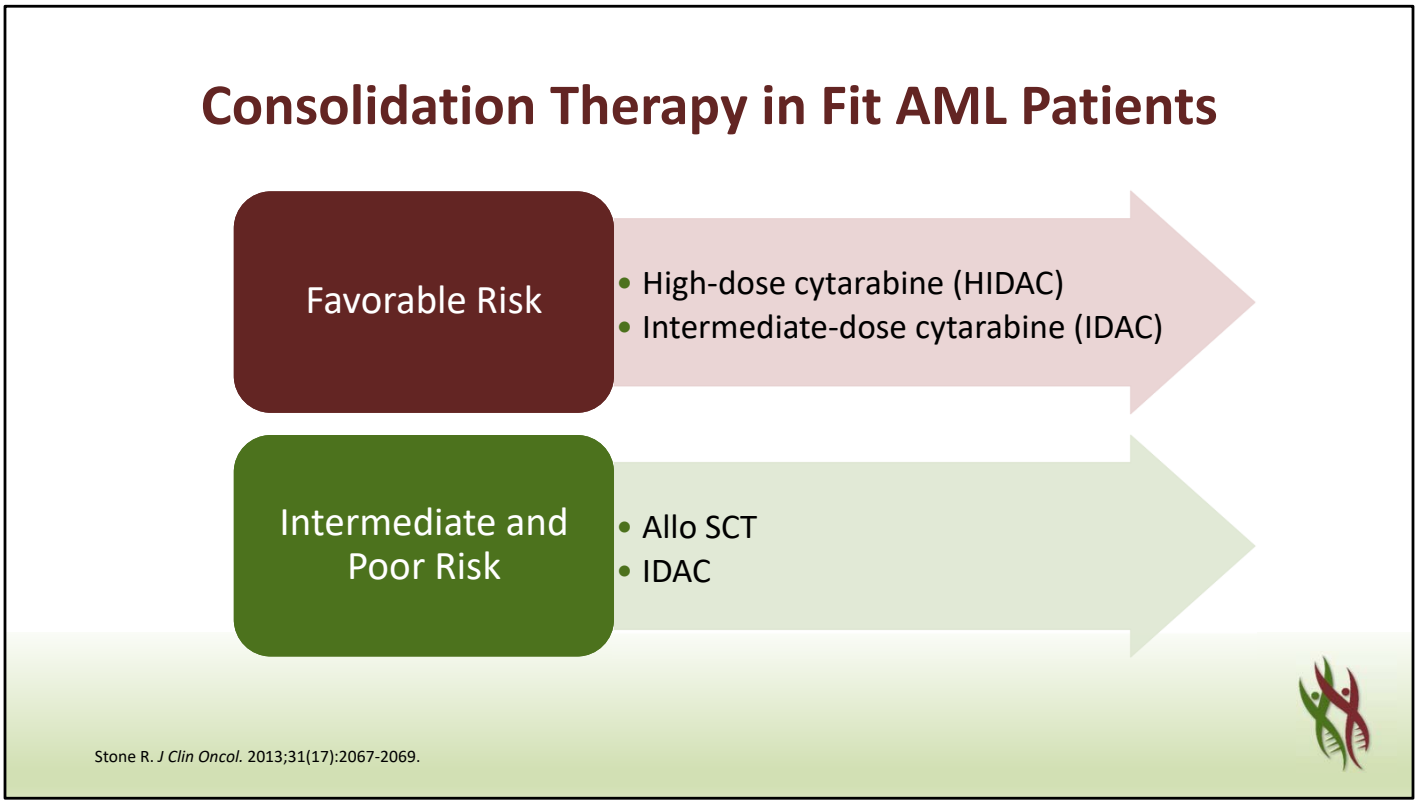


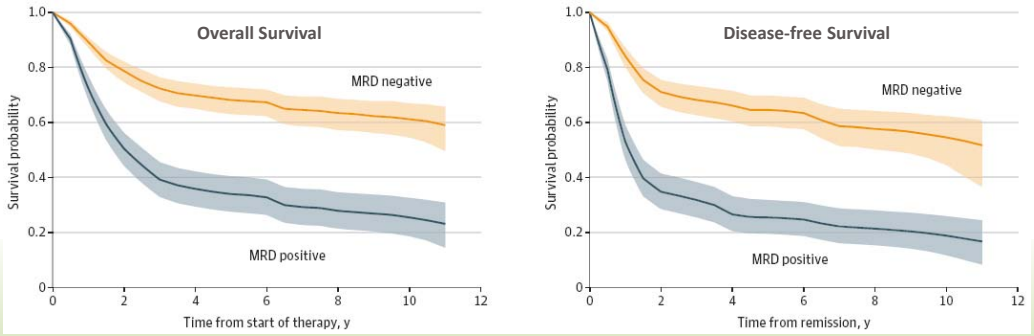
Once induction is complete and a patient achieves remission, favorable risk patients are usually treated with chemotherapy alone and do not go for stem cell transplant based on a higher or equivalent chance of survival with chemotherapy consolidation compared to transplant. While intermediate and poor-risk patients, we consider stem cell transplant, but some patients depending on personal choice or non-availability of donors can go through consolidation as well.

Post this, what do we have once we complete the consolidation? What was the standard of care in the past? It was just a follow-up. Maintenance was not our standard of care until more recent data.

Measurable Residual Disease (MRD)

- Presence of MRD in bone marrow of patients with AML in remission after intensive chemotherapy (IC) is predictive of early relapse[1]
- Identification of ≥0.1% MRD by multiparameter flow cytometry (MFC) is an important prognostic marker that can help guide treatment decisions[2]

Impact of MRD on relapse and survival for patients with AML in remission post-IC[3]:



1. Ravandi F, et al. *Blood Adv.* 2018;2:1356-1366. 2. Schuurhuis GJ, et al. *Blood.* 2018;131(12):1275-1291. 3. Short N, et al. *JAMA Oncol.* 2020;6(12):1890-1899.

Why is maintenance an important thing to consider? Because we know that patients in remission are still MRD-positive, and a lot of patients are still MRD-positive and that is it's an important predictive of early relapse. If the patient has an MRD more than 0.1% by flow, as you see in this data, both for survival and disease-free survival, MRD-negative patients have better survival and disease-free survival compared to MRD-positive. Can we do something that would actually reduce the risk of relapse by giving more maintenance therapy and perhaps helping these patients who are MRD-positive? Would it be helpful in MRD-negative patients as well? Because as we know, MRD measurement is just a test, and based on the most available testing, you can say somebody is positive or negative, but in reality, MRD-negative patients may still have minute residual populations.

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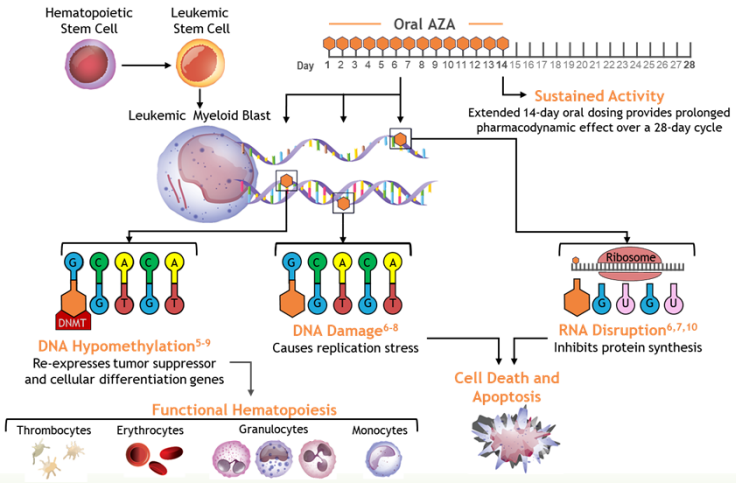
Oral Azacitidine

- Oral azacitidine (Oral AZA [CC-486]):
  - Oral HMA with a distinct PK/PD profile from injectable AZA; the two are not bioequivalent[1,2]
  - Oral AZA was recently approved in the US for continued treatment of adult patients with AML in first CR/CRi post-IC and not able to complete intensive curative therapy (eg, HSCT)[3]
- Oral dosing allows for extended drug exposure during each treatment cycle to prolong AZA activity[1,2,4]



1. Garcia-Manero G, et al. *J Clin Oncol*. 2011;29(18):2521-2527. 2. Laille E, et al. *PLoS One*. 2015;10(8):e0135520. 3. ONUREG® (azacitidine) tablets [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; Rev. 9/2020. 4. Savona R, et al. *Am J Hematol*. 2018;93(10):1199-1206. 5. Stresemann C, et al. *Mol Cancer Ther*. 2008;7:2998-3005. 6. Hollenbach P, et al. *PLoS One*. 2010;5(2):e9001. 7. Scott LJ. *Drugs*. 2016;76(8):889-900. 8. Stresemann C, Lyko F. *Int J Cancer*. 2008;123(1):8-13. 9. Aimiuwu J, et al. *Blood*. 2012;119(22):5229-5238. 10. Leone G, et al. *Curr Med Chem*. 2008;15(13):1274-1287

AZA, azacitidine; CR, complete remission; CRi, CR with incomplete blood count recovery; HMA, hypomethylating agent; HSCT, hematopoietic stem cell transplant; IC, intensive chemotherapy; PD, pharmacodynamic; PK, pharmacokinetic

Now, oral azacitidine was a drug that was designed to have a distinct pharmacokinetic and dynamic profile from injectable azacitidine. These are not two bioequivalent drugs. The idea for oral azacitidine was to give a 14-day cycle which gives a prolonged pharmacodynamic effect over a 28-day cycle. The idea was to give a slow exposure and DNA hypomethylation over time to benefit the residual disease.

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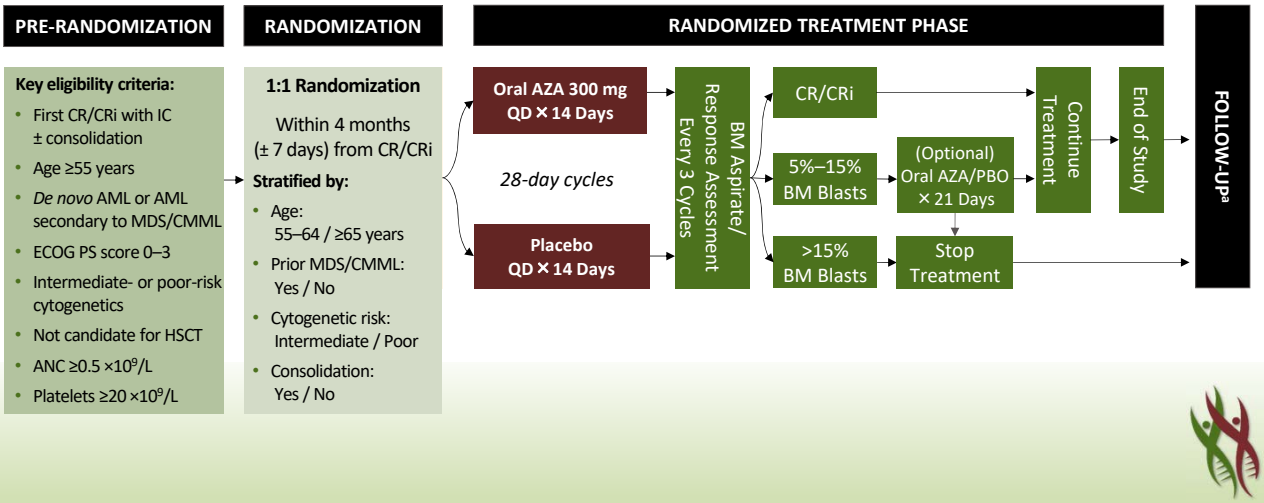
QUAZAR AML-001: Study Design and Eligibility Criteria

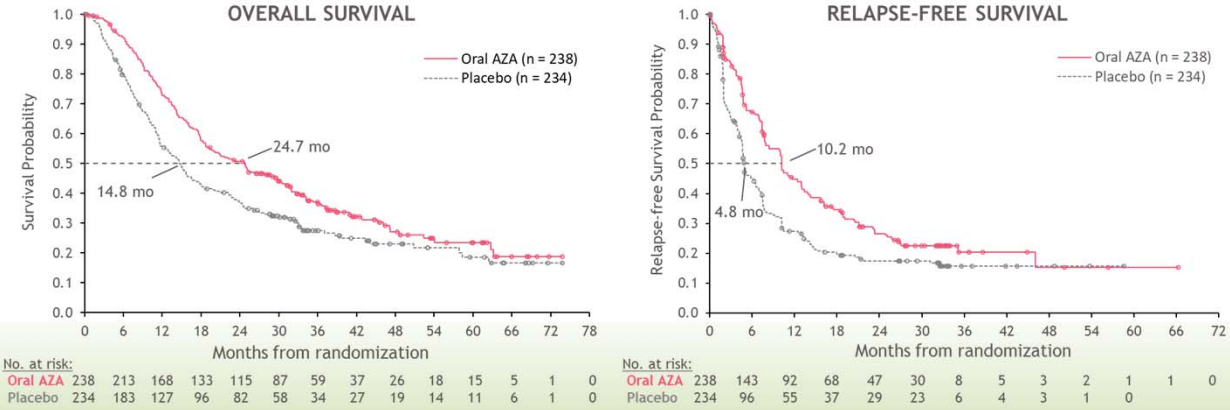
International, multicenter, placebo (PBO)-controlled, double-blind, randomized, phase III trial of Oral AZA as maintenance treatment for patients with AML in first remission (NCT01757535)



The QUAZAR AML-001 study randomized patients to do maintenance versus not. The way the study was designed that patients over 55 years old who had de novo or secondary AML, intermediate or poor-risk cytogenetics, and were not candidates for stem cell transplant were randomized one-to-one after completion of their primary therapy. Which would include seven and three and consolidation to either receiving oral azacitidine 14 days out of a 28-day cycle in continuation cycles versus placebo given at the same way. The treatments were continued, bone marrow assessment was made every three cycles to assess for MRD and remission status, and treatment continued in both arms until the end of study.

Overall Survival

- Oral AZA 300 mg QD was associated with significantly improved overall survival (OS) (*P*=.0009) and relapse-free survival (RFS) (*P*=.0001) vs PBO[1]



1. Wei A, et al. *Blood*. 2019;134(Supplement_2):LBA-3.

The primary endpoint of this was overall survival and as you look at this data, these were published in the *New England Journal of Medicine*, giving oral azacitidine had a significant overall survival advantage, 24.7 months versus 14.8 months, which is the placebo arm. Similarly, for relapse-free survival, oral azacitidine was statistically significant over placebo 10 versus 4.8 months.

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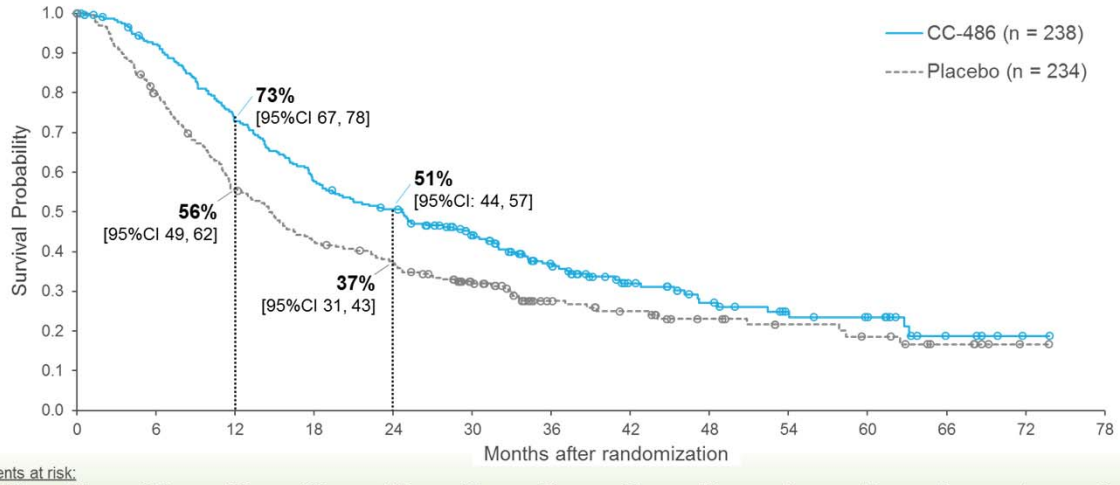
One-year and Two-year Survival Rates



Patients at risk:

CC-486	238	213	169	133	115	87	59	37	26	18	15	5	1	0
Placebo	234	183	128	96	82	58	34	27	19	15	11	6	1	0

95%CI, 95% confidence interval.

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

If you look at one- and two-year survival rates, again, patients in the oral azacitidine arm, 73% were alive at one year and 51% at two years compared to placebo, which is 56% and 37%.

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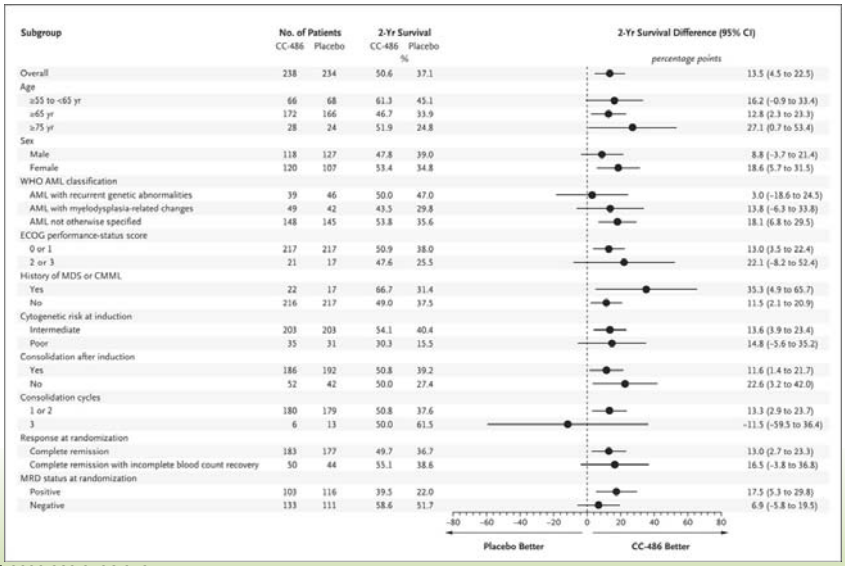
Univariate Analyses of Overall Survival at Two Years in Patient Subgroups Defined on the Basis of Clinically Relevant Baseline Characteristics



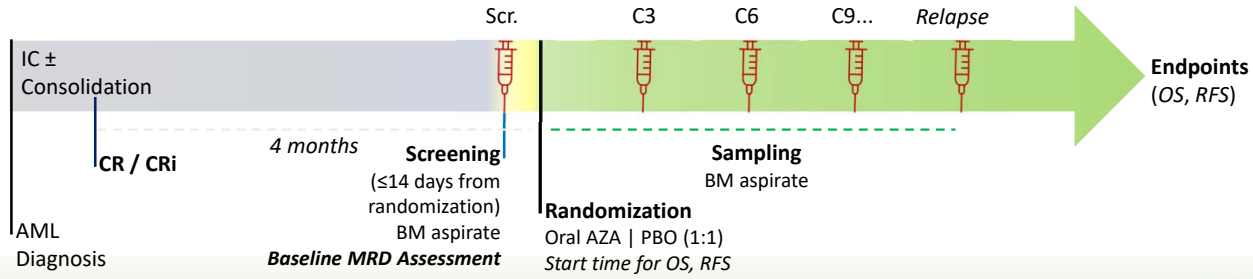
Subgroup	No. of Patients CC-486	No. of Patients Placebo	2-Yr Survival % CC-486	2-Yr Survival % Placebo	2-Yr Survival Difference (95% CI) percentage points
Overall	238	234	50.6	37.1	13.5 (4.5 to 22.5)
Age					
≥55 to <65 yr	66	68	61.3	45.1	16.2 (−0.9 to 33.4)
≥65 yr	172	166	46.7	33.9	12.8 (2.3 to 23.3)
≥75 yr	28	24	51.9	24.8	27.1 (0.7 to 53.4)
Sex					
Male	118	127	47.8	39.0	8.8 (−3.7 to 21.4)
Female	120	107	53.4	34.8	18.6 (5.7 to 31.5)
WHO AML classification					
AML with recurrent genetic abnormalities	39	46	50.0	47.0	3.0 (−18.6 to 24.5)
AML with myelodysplasia-related changes	49	42	43.5	29.8	13.8 (−6.3 to 33.8)
AML not otherwise specified	148	145	53.8	35.6	18.1 (6.8 to 29.5)
ECOG performance-status score					
0 or 1	217	217	50.9	38.0	13.0 (3.5 to 22.4)
2 or 3	21	17	47.6	25.5	22.1 (−8.2 to 52.4)
History of MDS or CMML					
Yes	22	17	66.7	31.4	35.3 (4.9 to 65.7)
No	216	217	49.0	37.5	11.5 (2.1 to 20.9)
Cytogenetic risk at induction					
Intermediate	203	203	54.1	40.4	13.6 (3.9 to 23.4)
Poor	35	31	30.3	15.5	14.8 (−5.6 to 35.2)
Consolidation after induction					
Yes	186	192	50.8	39.2	11.6 (1.4 to 21.7)
No	52	42	50.0	27.4	22.6 (3.2 to 42.0)
Consolidation cycles					
1 or 2	180	179	50.8	37.6	13.3 (2.9 to 23.7)
3	6	13	50.0	61.5	−11.5 (−59.5 to 36.4)
Response at randomization					
Complete remission	183	177	49.7	36.7	13.0 (2.7 to 23.3)
Complete remission with incomplete blood count recovery	50	44	55.1	38.6	16.5 (−3.8 to 36.8)
MRD status at randomization					
Positive	103	116	39.5	22.0	17.5 (5.3 to 29.8)
Negative	133	111	58.6	51.7	6.9 (−5.8 to 19.5)

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

Looking at various subgroups of ages, sex, WHO AML classification prior history of MDS or not, whether they got consolidation after seven and three or not, cytogenetically, all of this and MRD positivity, you could see that all of these subgroups favor the oral azacitidine arm and this led to the approval of this drug which is currently now approved for this.

MRD Assessments

- MFC assessments were performed centrally by flow cytometry using bone marrow aspirates collected at screening (ie, after CR/CRi and any consolidation), at cycles 3, 6, 9, 12, 15, 18, 21, 24, 30, and 36 (and as clinically indicated), until time of relapse
- Samples were analyzed with a panel of 22 cell surface markers using an MRD+ cutoff of ≥0.1%



Roboz G, et al. ASH 2020. Abstract 692.

The indication is anybody who has had intensive chemotherapy and has not gotten to stem cell transplant for whatever reason whether not recommended because of comorbidities or patient preference. These are for intermediate- and poor-risk cytogenetics. Now, what is interesting is the question is, does this drug help in MRD positive or MRD negative patients? As we know, MRD assessment was done every three cycles on study.

MRD Endpoints

MRD Endpoint	Criteria
MRD+ / MRD– status	European LeukemiaNet (ELN) threshold[1]: ≥0.1% vs <0.1%
MRD response	Conversion from MRD+ to MRD– for ≥2 consecutive post-BL visits
Time to MRD response	Time from MRD+ to first of ≥2 consecutive MRD– post-BL visits
Duration of MRD–	Time from first MRD– assessment (BL or on-study) to last MRD–

- OS, RFS, and duration of MRD– were estimated using Kaplan-Meier methods
- Multivariate (MV) Cox regression analyses used to evaluate associations between BL MRD status (MRD+ vs MRD–) and randomized treatment arm (Oral AZA vs PBO) on OS and RFS outcomes

1. Schuurhuis GJ, et al. *Blood.* 2018;131(12):1275-91.; Roboz G, et al. ASH 2020. Abstract 692.

MRD positivity and negativity was defined by an ELN risk more than 0.1% versus less than 0.1%. The study also looked at MRD response, how many of patients converted MRD positive to negative on the drug, time to MRD response, and duration of MRD.

Patients and Baseline Characteristics

- The MRD evaluable cohort comprised 463/472 randomized patients (98.1%; Oral AZA, n=236; PBO, n=227) who had samples available at BL and at ≥1 post-BL visit
- MRD+ at BL:
  - Oral AZA: 44% (n=103)
  - PBO: 51% (n=116)
- BL characteristics were similar between MRD+ and MRD– patients, and between Oral AZA and PBO within each MRD subgroup (MRD+/MRD–)

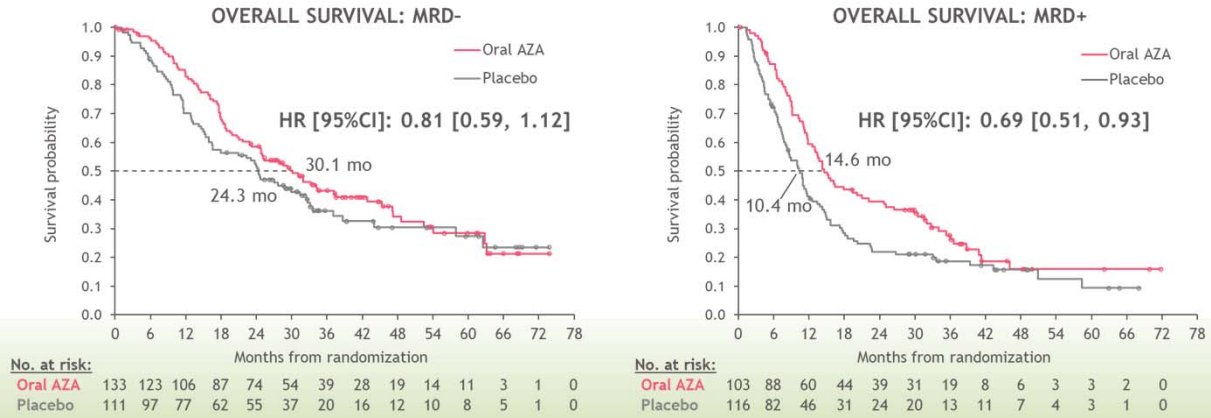
Characteristic	MRD+ (n = 219)	MRD– (n = 244)
Age, years, median (range)	69 (55, 84)	68 (55, 86)
Age ≥75 years, n (%)	23 (11)	28 (11)
de novo AML, n (%)	196 (89)	225 (92)
ECOG PS score, n (%)		
0	113 (52)	111 (45)
≥1	106 (48)	133 (55)
NCCN cytogenetic risk at diagnosis, n (%)		
Intermediate	184 (84)	214 (88)
Poor	35 (16)	30 (12)
Response following induction, n (%)		
CR	182 (83)	193 (79)
CRi	37 (17)	51 (21)
Received consolidation, n (%)		
Yes	172 (79)	182 (75)
1 cycle	39 (18)	53 (22)
2 cycles	7 (3)	9 (4)
3 cycles	1 (0.5)	0
No	47 (21)	45 (18)

Roboz G, et al. ASH 2020. Abstract 692.

Within the MRD evaluable cohort, both groups, oral azacitidine versus placebo, if you look at the characteristic of these patients, they were pretty similar across before they actually started their study drug showing that the randomization was successful.

Overall Survival by Baseline MRD Status and Treatment Arm

- Treatment with Oral AZA resulted in improved OS from time of randomization compared with PBO in patients who were MRD+ or MRD– at study entry

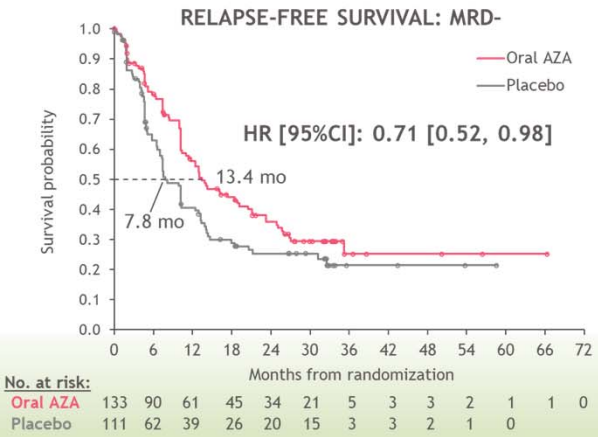


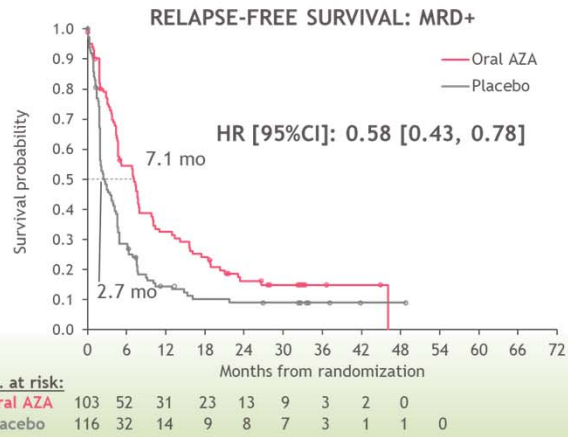
Roboz G, et al. ASH 2020. Abstract 692.

If you look at now survival in both groups, MRD negative and positive, the drug showed survival advantage in both situations, 30 versus 24 months in MRD negative and 14 versus 10 months in MRD positive response.

Relapse-free Survival by Baseline MRD Status and Treatment Arm

- Median RFS was also prolonged with Oral AZA vs PBO within each BL MRD subgroup (MRD+, MRD–)





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Relapse-free survival was also similarly prolonged in patients who had oral azacitidine versus placebo and this was true for both MRD negative and MRD positive subgroups.

Multivariate Analysis

- In MV analysis, Oral AZA showed a significant treatment benefit vs PBO on both OS (*P*=.0067) and RFS (*P*<.0001) independent of BL MRD status (MRD+/MRD–)
- Presence of MRD at study entry was highly significantly associated with shorter OS and RFS (both *P*<.0001) after controlling for randomized treatment arm (Oral AZA/PBO)

Multivariate analysis of OS (BL MRD status and randomized treatment arm)		
Parameter	**HR**	***P* value**
BL MRD: MRD+ vs MRD–	**1.85**	**<0.0001**
Tx Arm: Oral AZA vs PBO	**0.74**	**0.0067**

Multivariate analysis of RFS (BL MRD status and randomized treatment arm)		
Parameter	**HR**	***P* value**
BL MRD: MRD+ vs MRD–	**2.04**	**<0.0001**
Tx Arm: Oral AZA vs PBO	**0.63**	**<0.0001**

Roboz G, et al. ASH 2020. Abstract 692.

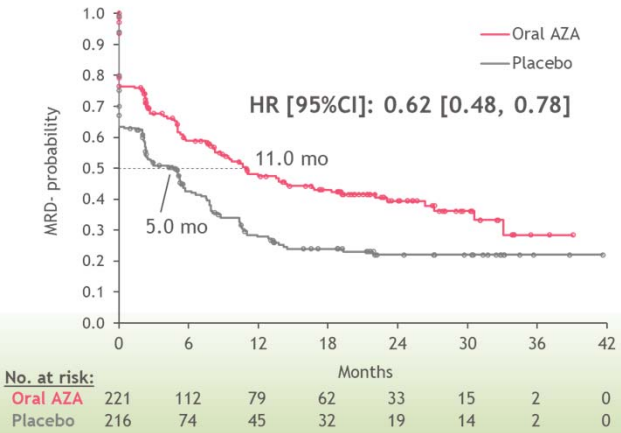
This showed that treatment with oral azacitidine had a significant benefit irrespective of the MRD status and this was based on a multivariable analysis.

MRD Response and Overall Duration of MRD Negativity

- Oral AZA was associated with a higher rate of MRD response (BL MRD+, became MRD- on-study) vs PBO: 37% vs 19%, respectively

MRD Response	Oral AZA	Placebo
MRD+ at screening, n	**103**	**116**
MRD responders, n/N (%)	**38/103 (37%)**	**22/116 (19%)**
Time to MRD response, n/N (%)		
>3 to ≤6 months	7/38 (18%)	6/22 (27%)
>6 months	9/38 (24%)	1/22 (5%)

- The median duration of MRD negativity (BL MRD– and MRD responders) was extended with Oral AZA vs PBO

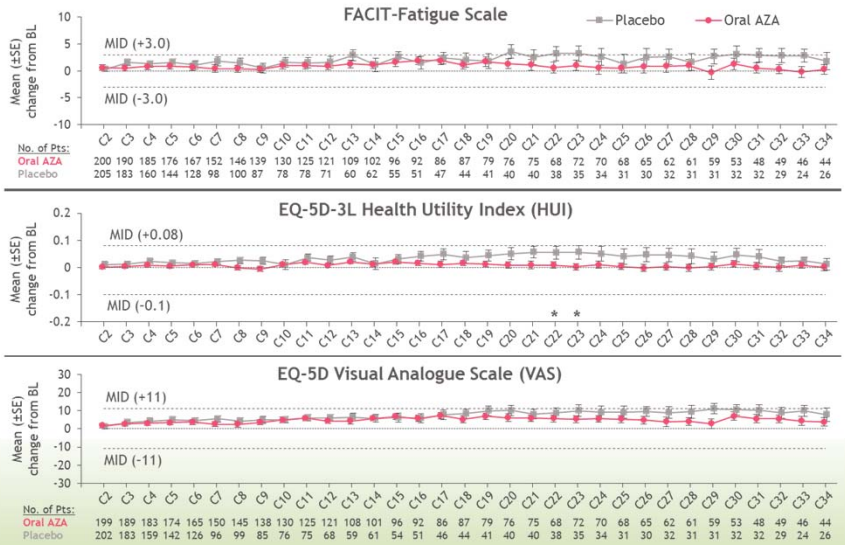


Roboz G, et al. ASH 2020. Abstract 692.

Moreover, looking at patients who had an MRD response, how many of them had MRD positive and then became negative; 37% of patients on the oral azacitidine became MRD negative on study versus 19% on placebo, which is basically residual chemotherapy negativity over time. Also, if you look at the timing, less than six months versus more than six months, people on oral azacitidine therapy continued to have these MRD negativity responses over time with prolonged use of the drug, while that dropped in the placebo arm. Most of the effect was early on from the chemotherapy. The median duration of MRD negativity was also higher in the oral azacitidine arm compared to placebo.

QOL Changes From Baseline

- No clinically meaningful differences observed between treatment arms
  - Statistically significant differences in EQ-5D-3L HUI scores at cycle 22 (*P*=.048) and cycle 23 (*P*=.033) were likely due to chance

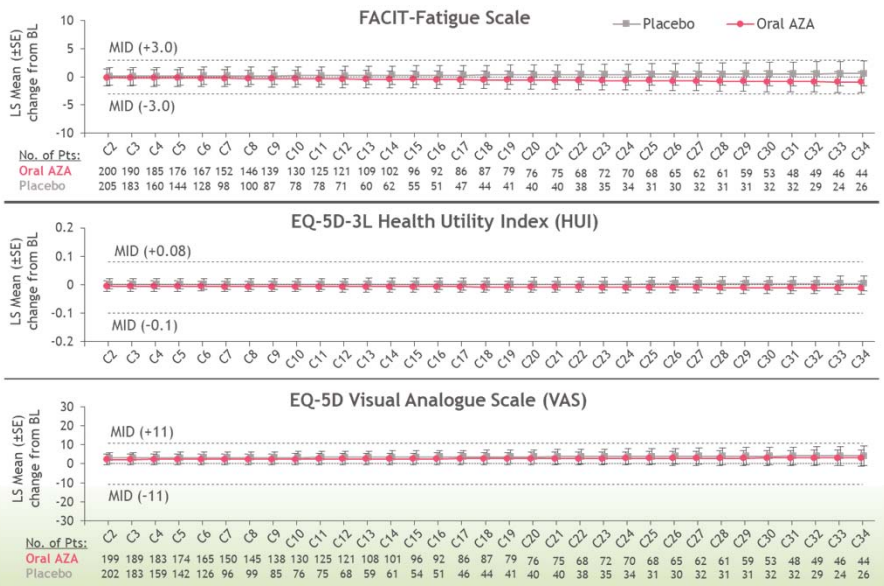


Roboz G, et al. ASH 2020. Abstract 692.

Now the big question is, sure we're improving survival, but at what cost? There was recent analysis presented in ASH 2020 where there was measurement of quality of life, measures on the drug and if you look at the fatigue scale here, both placebo which is grey and oral azacitidine which is pink looks like they are overlapping.

Longitudinal Analysis (MMRM)

- No statistically significant or clinically meaningful differences between arms
- No difference in overall change in FACIT-Fatigue or ED-5D-3L scores
  - Did not exceed prespecified minimally important difference (MID) thresholds
- Supports Oral AZA relative to placebo

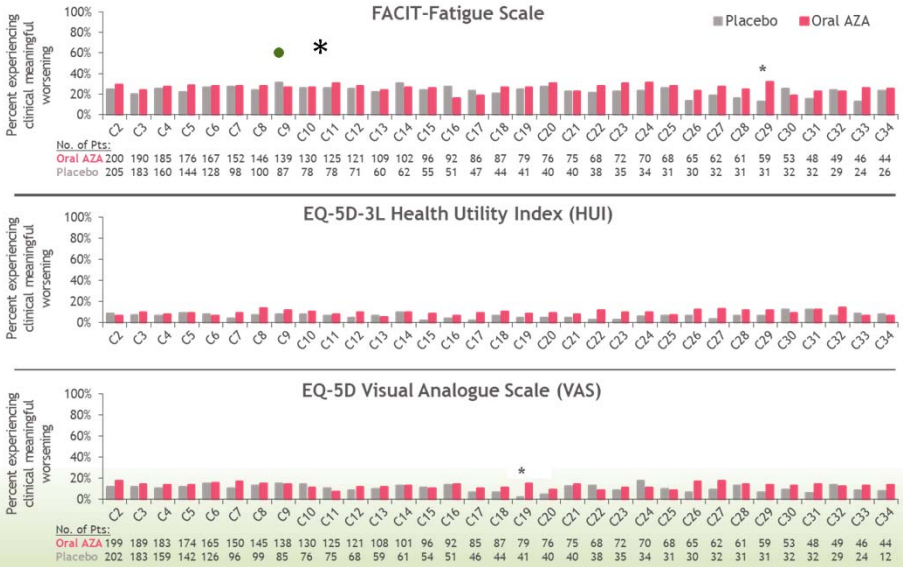


Roboz G, et al. ASH 2020. Abstract 692.

Longitudinal analysis over many cycles showed5 essentially overlapping scores. Health utility index was also equivalent. Patients were not getting hospitalized more on one arm versus the other.

Rate of Clinically Meaningful Deterioration

- Rates of clinically meaningful deterioration were low and similar between arms at almost all post-BL visits
  - Rates statistically significant in favor of placebo at cycle 19 (EQ-5D VAS; *P*=.031) and cycle 29 (FACIT-Fatigue; *P*=.034)
- No statistically significant difference in time to definitive HRQoL deterioration on any instrument

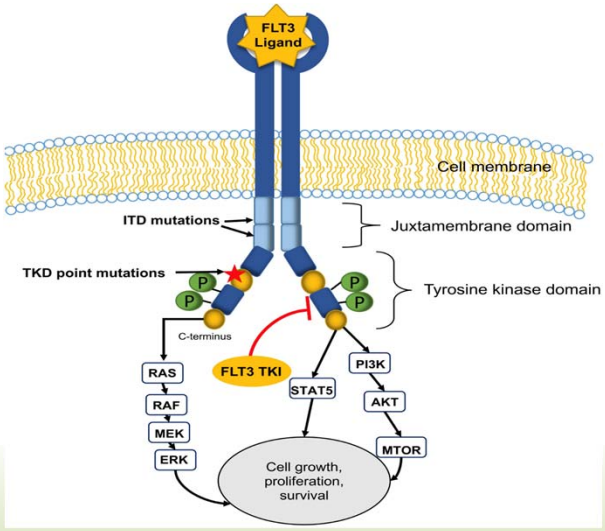


Roboz G, et al. ASH 2020. Abstract 692.

Rate of clinically meaningful deterioration from previous cycle was also pretty much not significant between the arm except for one cycle over here. Overall, you can say that this drug is well-tolerated compared to placebo

New Treatment Paradigms in AML: A Focus on Maintenance Therapy

Biology of FLT3 in AML



- FLT 3 mutations occur in 25%-30% if newly diagnosed AML
- FLT 3 ligand binding activates FLT3 receptor and increased cell proliferation
- High allele ratio ITD mutations are considered poor risk in absence of NPM1 and are currently transplanted in CR1
- TKD mutations do not confer high risk behavior in newly diagnosed leukemia

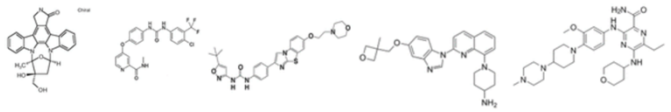
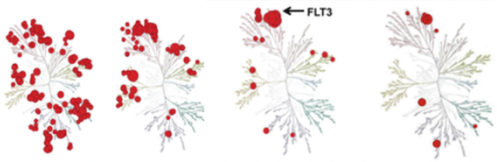
Weis T. et al. *Crit Rev Oncol Hematol*. 2019;141:125-138.

Now, we know that oral azacitidine is a maintenance strategy for patients who are older or had chemotherapy and not gone to transplant. What about other maintenance strategy? We know that FLT3 AML has targetable agents. We know FLT3 has a high risk of relapse, but some patients are not transplanted with FLT3. What could they potentially get?

New Treatment Paradigms in AML: A Focus on Maintenance Therapy

	Less potent FLT3 inhibition	Potent FLT3 inhibition
Type I	Midostaurin	Crenolanib (FLT3 ITD, TKD D835, PDGFR) Gilteritinib (FLT 3 ITD, TKD D835, AXL)
Type II	Sorafenib	Quizartinib (FLT3 ITD, PDGFR, KIT)

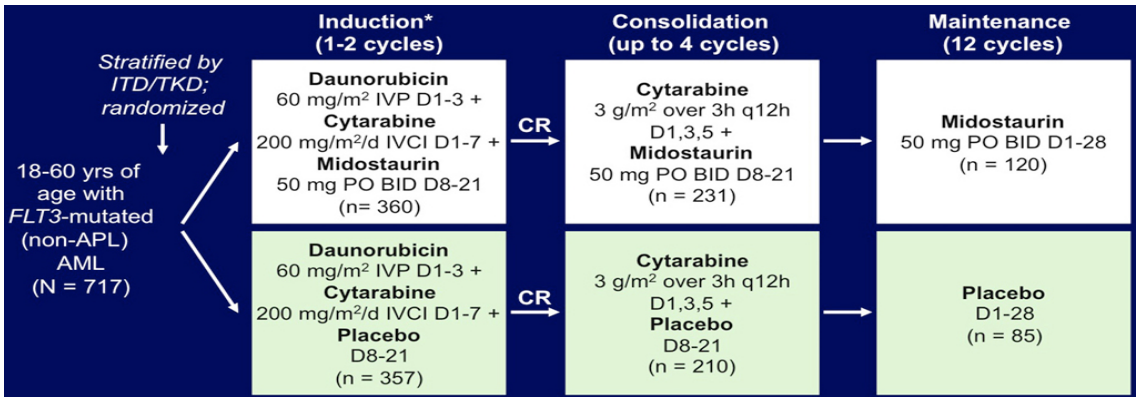
- FLT 3 inhibitors vary with regards to potency of FLT inhibition, off target effects and mechanism of binding to active and inactive conformation of FLT3

Inhibitor	Midostaurin	Sorafenib	Quizartinib	Crenolanib	Gilteritinib
IC_{50} against FLT3 (nM)	<10	58	1.1	1.3	0.29
Structure					
Kinase dendrogram					not available

Karaman MW, et al. *Nat Biotechnol*. 2008;26(1):127-132.; Karrinkar PP, et al. *Blood*. 2009;114(14):2984-2992.

Now, there are several FLT3 inhibitors that are currently undergoing clinical trials as noted on this slide. I'm not going to go into details with this.

RATIFY: Study Design



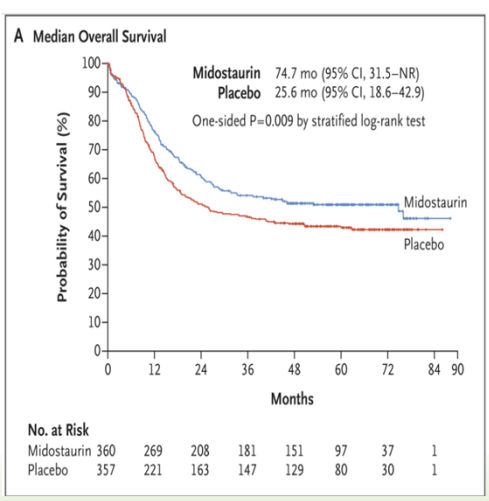
- Double-blind, placebo-controlled, randomized phase III study
  - Primary endpoint: OS (not censored for SCT)
  - Secondary endpoint: EFS

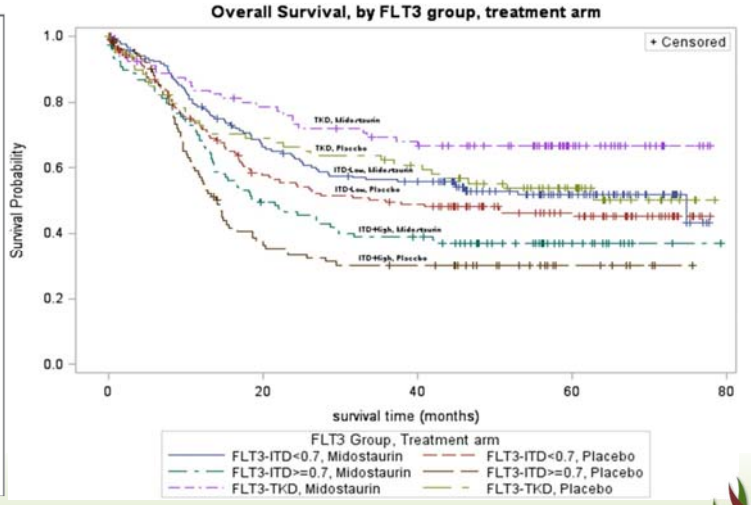
*Hydroxyurea allowed for ≤5 days prior to induction therapy
Stone RM, et al. ASH 2015. Abstract 6.

Briefly, we know that the RATIFY study design—the study led to the approval of midostaurin for FLT3 mutated AML, where midostaurin was given with induction, consolidation, and maintenance for 12-cycle posttreatment. This included both post-transplant and also patients who didn't go for transplant got maintenance as well.

New Treatment Paradigms in AML: A Focus on Maintenance Therapy

Midostaurin Improves Survival in All FLT3 Mutated AML

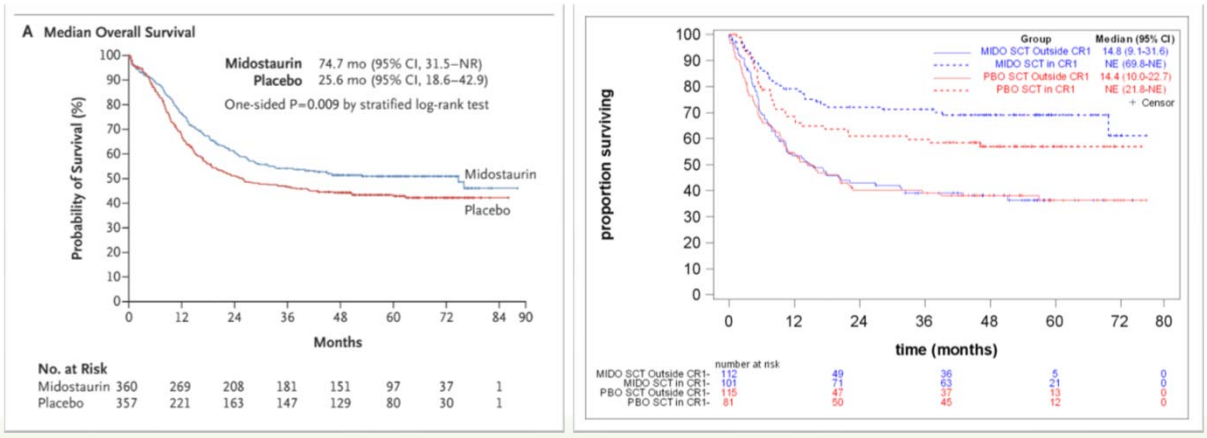




Stone R, et al. *Blood*. 2015;126:6.; Stone RM, et al. *N Engl J Med*. 2017;377(5):454-464.

Midostaurin improved overall survival in patients compared to placebo and this benefit was seen across all FLT3 subgroups TKD, ITD-high and ITD-low.

Midostaurin Plus Chemotherapy for Acute Myeloid Leukemia With a *FLT3* Mutation – the Impact of SCT

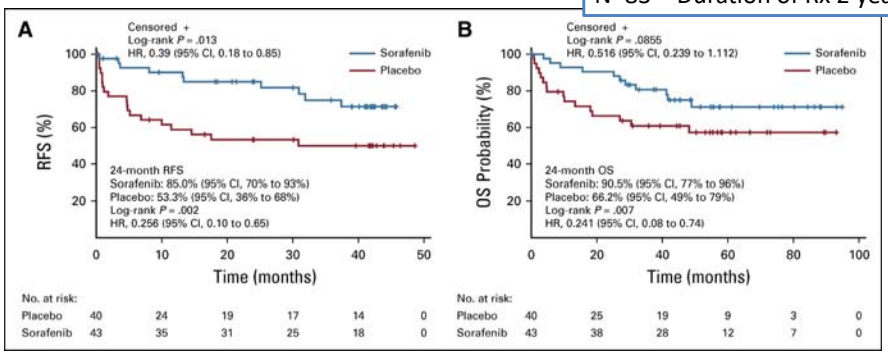


Stone RM, *N Engl J Med*. 2017;377(5):454-464.

Moreover, its impact in the post-transplant area was also seen where, if the patients did get midostaurin post-transplant, their survival was better. Which is the blue arm compared to the red arm which is placebo patients who did not get midostaurin.
If somebody does not go for a stem cell transplant, FLT3 maintenance strategy is there and available. I'll discuss a little bit down the line on which one to choose from.

Sorafenib Maintenance After Allo-SCT for AML With *FLT3*–ITD (SORMAIN)

N=83 – Duration of Rx 2 years



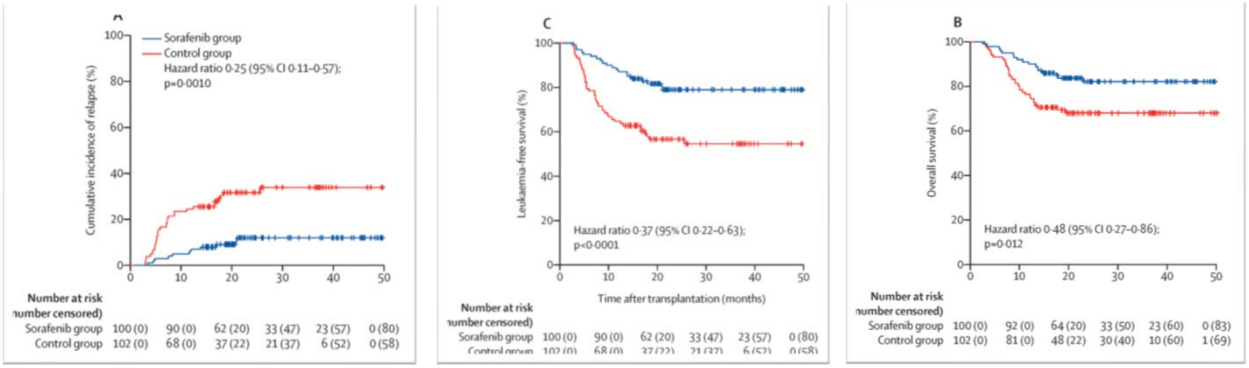
Relapse-free survival (RFS) and overall survival (OS) in patients positive for FMS-like tyrosine kinase 3–internal tandem duplication acute myeloid leukemia in complete remission after hematopoietic stem cell transplantation treated with sorafenib versus placebo (intention-to-treat population). (A) Kaplan-Meier curves for RFS in the sorafenib group and the placebo group. In total, 29 RFS events were recorded: 10 in the sorafenib group (8 relapses, 2 deaths) and 19 in the placebo group (17 relapses, 2 deaths). (B) Kaplan-Meier curves for OS in the sorafenib group and the placebo group. Tick marks indicate censoring of data. In total, 27 deaths were recorded, 11 in the sorafenib group and 16 in the placebo group. HR, hazard ratio.

Burchert A, et al. *J Clin Oncol.* 2020;382993-383002.

Switching gears a little bit on another aspect of maintenance therapy, which is post-transplant maintenance therapy. There was a trial called in the SORMAIN trial that looked at the sorafenib maintenance after allo-SCT that showed that patients who got sorafenib had superior survival as well as recurrent relapse-free survival compared to placebo. The concept of FLT3 maintenance post-transplant is pretty well established and most centers would give it now.

New Treatment Paradigms in AML: A Focus on Maintenance Therapy

Sorafenib Maintenance in Patients with *FLT3*-ITD AML Undergoing Allo-SCT: An Open-label, Multicenter, Randomized Phase 3 Trial



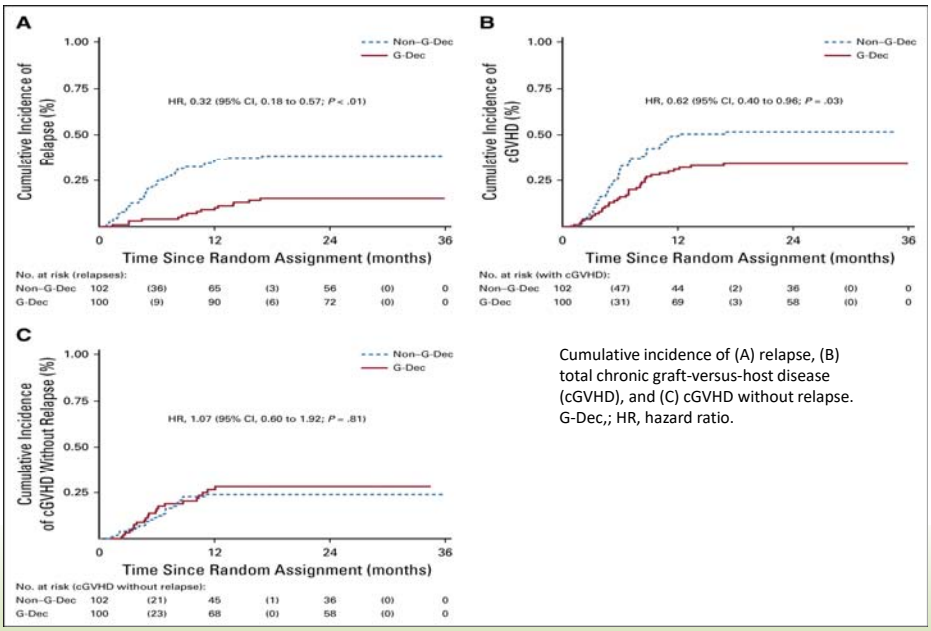
N=202 -Duration of Rx 6 mo

Li X, et al. *Lancet Oncol.* 2020;21:1201.

This was another study similarly looking at sorafenib maintenance post-allo-SCT with benefit seen to the sorafenib arm for all incidents for relapse, leukemia-free survival, and overall survival. In addition, there are other FLT3 inhibitors that are currently undergoing clinical trials for post-transplant maintenance. This includes gilteritinib and continuation of some of the frontline FLT3 agents like crenolanib.

New Treatment Paradigms in AML: A Focus on Maintenance Therapy

Recombinant Human Granulocyte Colony-stimulating Factor Plus Decitabine Maintenance Post Allo-SCT



Cumulative incidence of (A) relapse, (B) total chronic graft-versus-host disease (cGVHD), and (C) cGVHD without relapse. G-Dec,; HR, hazard ratio.

Lei Gao, et al. *J Clin Oncol.* 2020;384249-384259.

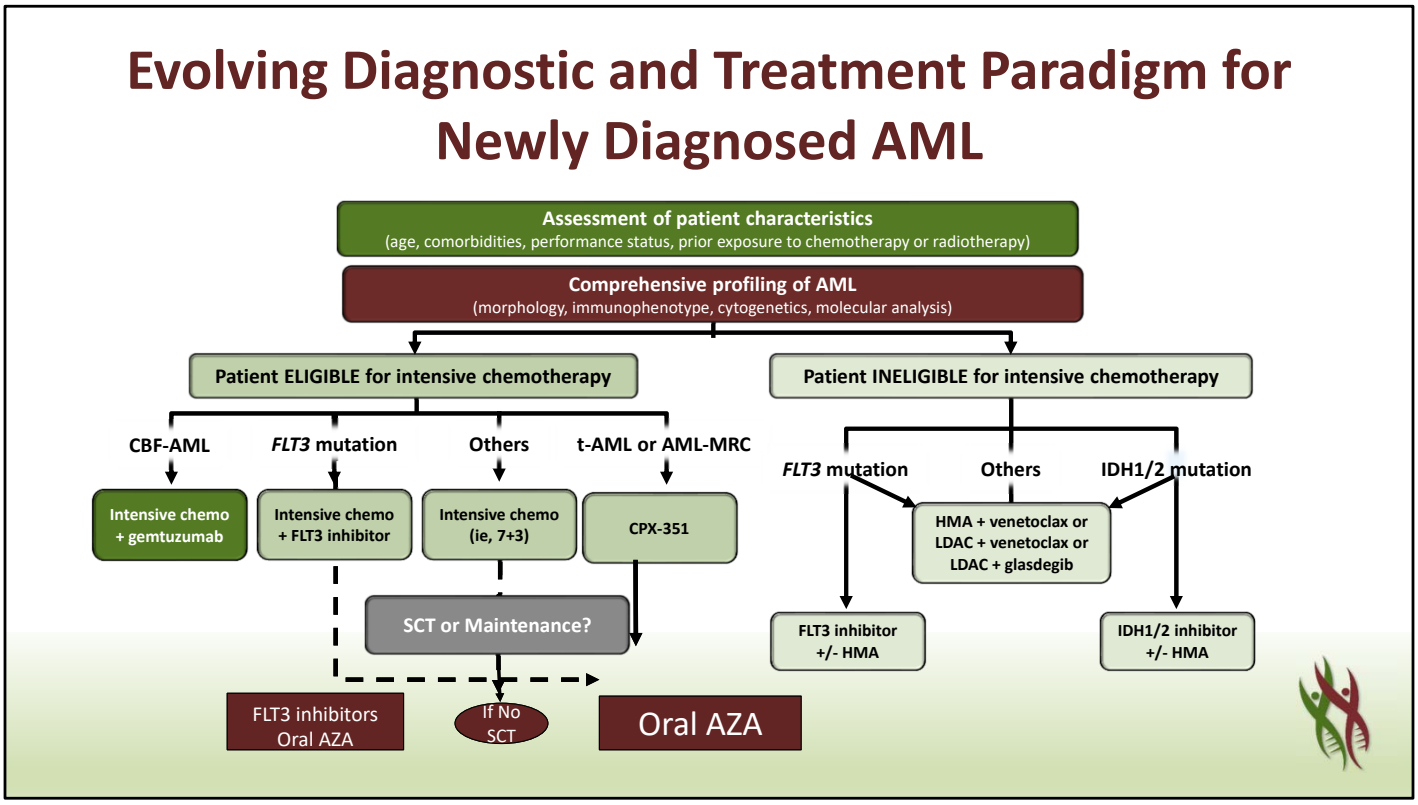
Another interesting study that was also published was the combination of decitabine plus recombinant human granulocyte colony-stimulating factor where the combination of the two compared to placebo led to decreased incidence of relapse as evidenced by the red arm compared to the blue which is the non-G decitabine arm. This is an interesting concept as well in the post-transplant setting.

Other Drugs Being Studied

- FLT3 inhibitors
- IDH inhibitors
- HMA+venetoclax

Several other maintenance strategies are being used, for example, other FLT3 inhibitors as I had mentioned, IDH inhibitors for patients who have an IDH mutation. Also, clinical trials are currently ongoing using hypomethylating agents and venetoclax both in the setting of post-chemotherapy without transplant and in the post-transplant setting. We are yet to find out whether all of these strategies are going to be incremental or more beneficial than the currently approved oral azacitidine maintenance.

New Treatment Paradigms in AML: A Focus on Maintenance Therapy



If you look at the evolving paradigm of post-transplant or patients who have not had a transplant and what do we do in their maintenance strategy. Our focus here, patients eligible for intensive chemotherapy, if you have a good risk like core-binding factor AML, chemotherapy is the standard of care. There is no maintenance after this, these patients were not included in the QUAZAR trial which led to the oral azacitidine approval, favorable risk cytogenetics were excluded. For these patients, the standard of care still is observation. For patients who have FLT3 mutation or therapy-related AML or for the intermediate, you decide whether this patient needs to go for a stem cell transplant or maintenance. If the patient decides that there is no SCT or no stem cell transplant, then if you have a FLT3 mutation, FLT3 inhibitors are available for maintenance therapy and most people would actually choose that because the biology of the disease is driven by the FLT3 mutation. In patients who have a very low FLT3 allele ratio, FLT3-TKD mutations, for example, oral azacitidine is an option. In patients who had therapy-related, again, oral azacitidine would be the maintenance option. If the patients are transplanted, then the post-transplant maintenance a complicated decision point depending on their mutations and other aspects that we discussed in the post-transplant maintenance strategy. For patients who are not eligible for intensive chemotherapy, there is no true maintenance to some extent, because all of these therapies are continuation cycles and they are maintenance in its own right because you just keep taking these cycles until the patient relapses, which most people older patients who are ineligible for intensive chemotherapy and not transplanted would. There's no true maintenance strategy and that's not where oral azacitidine has been studied or approved.

New Treatment Paradigms in AML: A Focus on Maintenance Therapy

- 68-year-old patient in good health presents with a WBC of 30k and is diagnosed with AML with normal cytogenetics. Rest of myeloid mutation panel shows DNMT3A mutation. Patient is treated with IDA/DNR + cytarabine and achieved an MRD negative CR. What is the next step in treatment?
  - A. Cytarabine consolidation for 4 cycles
  - B. Cytarabine consolidation followed by Oral azacitidine maintenance
  - C. Allogeneic transplant
  - D. Allogeneic transplant followed by Oral azacitidine maintenance

Now that we've heard all of the data that I presented, let's go back to our question and see if we can get to the correct answer. A 68-year-old patient in good health presents with a white cell count of 30k, patient has AML with normal cytogenetics, with a DNMT 3 mutation and is treated with 7 and 3 and achieved in MRD negative remission. Please check which answers might be correct.

Now let's go through the data and this question. This patient is by ELN risk intermediate cytogenetics with intermediate molecular markers. These patients should be considered for allogeneic stem cell transplants, so C, allogeneic transplant, is a correct answer. However, many patients do not go for a stem cell transplant or decide not to go for a stem cell transplant due to comorbidities and in that situation cytarabine consolidation followed by oral azacitidine maintenance would be another correct answer. Cytarabine consolidation alone would not be standard because of survival advantage, which is seen with oral azacitidine. Allogeneic transplant followed by oral azacitidine maintenance again would not be correct because this is not the setting in which oral azacitidine was used. This study only used oral azacitidine in patients who did not go for stem cell transplant and it's used in the post-transplant period. There's no data on its use, so that would be incorrect as well. Now to make this a bit complicated, what if this patient had a FLT3-TKD mutation? Now that brings into another layer of complexity because technically, FLT3 maintenance therapy is not an approved indication, but many people believe that if the biology of the disease is driven by FLT3, then FLT3 could be given as a maintenance strategy. Many clinical trials are using the strategy of post chemotherapy FLT3 maintenance.

In this setting, if you have a TKD, would the maintenance be oral azacitidine or would it be the continuation of the FLT3 inhibitor like midostaurin that was started at the beginning of the patient's induction based on the RATIFY study? I think the answer to that question is not really yet answered. We don't know which is a better strategy in that situation of FLT3 or oral azacitidine. This is why more and more data and deeper analysis of the current clinical trials is important to come to the right decision. Until then, for somebody who is in this bucket, B and C would be the correct answer.