Chapter 1: Defining AML: Impacting the Current Standard of Care

Welcome to *Managing AML*, I am Dr. Elias Jabbour. In today's presentation, I will review the evolving treatment landscape in AML. In this video, I provide you with background on new agents recently approved in the treatment of AML, including safety, efficacy, and side-effect profiles to consider in treatment. We will explore how new and emerging targeted agents in AML will impact the current treatment paradigm, and we will develop strategies for employing best practices to optimize selection and sequencing of treatments. Let's begin.

The Evolving Treatment Landscape in AML

2017 ELN Risk Stratification by Genetics

Risk Category	Genetic Lesion
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 gene mutations) 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* and *FLT3*-ITD^{high*}** **Mutated *RUNX1*†** **Mutated *ASXL1*†** **Mutated *TP53***

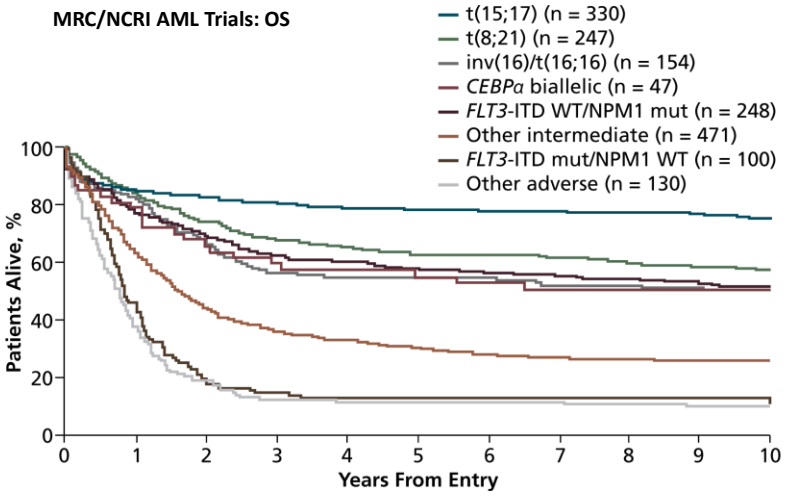
* Low, low allelic ratio (<0.5); high, high allelic ratio (≥0.5);
† These mutations should not be used as adverse prognostic markers if they co-occur with favorable-risk AML subtypes.

CBF=core-binding factor; ITD=internal tandem duplication; NPM1=nucleophosmin 1
Döher H, et al. *Blood*. 2017;129(4):424-447.

Today, AML is no longer one treatment, one disease. In fact, due to the recent advances in the knowledge of molecular profiles, karyotyping, and the physiopathology of the disease, we are able to classify AML into different categories: favorable, intermediate, and adverse; and that will have implications into the treatment and the outcome of the disease. As you can see on this slide, we are highlighting some of the chromosomal abnormalities that must be done upfront and certain molecular features, among them for example, the FLT3-ITD allele burden (low or high); other mutations encountered; among them as you can see in adverse features, TP53 and others.

The Evolving Treatment Landscape in AML

Cytogenetic and Molecular Abnormalities: Survival



MRC=Myeloma Research Consortium; NCRI=National Cancer Research Institute
Smith ML, et al. *Blood Rev*. 2011;25:39-51.

Here I am showing you a couple of my curves showing the outcome of AML patients based on their karyotypic abnormalities as well as molecular abnormalities. As you can see, the blue curve is t(15;17) – or what you call acute promyelocytic leukemia – with the best outcome cure rate, approaching 80%. That is followed by core-binding factor-positive (CBF) acute leukemia, essentially t(8;21) and inv(16). As you can see, molecular features are part of the baseline features. For example, the brown and the gray curves are those with the FLT3 ITD-mutated NPM1 wild type. This group of patients had the worst outcome; and for these patients, we should explore new agents, clinical trials, and transplantation in first remission. During my talk, I will highlight some of the advances made in this field.

The Evolving Treatment Landscape in AML

Molecular Studies in AML

Marker	%	Prognosis
FLT3 ITD/mutation	30	Worse
NPM1 mutation	50	Better
IDH1-2 mutations	20-30	Worse or neutral
C-kit mutation- CBF	15	Worse
↑ BCL2	10-20	Worse
MLL PTD	7	Worse
DNMT3A mutation	22	Worse
ASXL1; TET2	10	Worse; epigenetic modulation
P53 mutation	5-20	Very poor
↑ EVI1 expression	10	Very poor

IDH1/2=isocitrate dehydrogenase; PTD=partial tandem duplications
Kantarjian H. *Am J Hematol.* 2016;91:131-145.

Here is a summary table of some molecular abnormalities I encountered that can have implications on the treatment decisions and outcome for our patients. For example, FLT3 ITD mutation is encountered in about 30% of cases and definitely confers a bad outcome. In contrast, NPM1 mutation, encountered in about 50% of cases, definitely confers a better outcome. In addition to these classical features, we now have the IDH1 and IDH2 mutations that can have implications in treatment, and the implication outcome is still unknown. C-kit mutations in core-binding factor AML, overexpression of BCL-2, and other mutations are encountered here. For example, we know that the p53 mutation, encountered in up to 20% of patients, and confers a very poor outcome; and the list goes on and on. The important thing about this information is that we can go after certain targets to try to neutralize their impact and further improve the outcome.

The Evolving Treatment Landscape in AML

Monitoring Minimal Residual Disease in AML

- Should be standard of care—Rx decisions

Disease	FCM-MRD	Molecular MRD
Acute promyelocytic leukemia	--	**PML-RAR alpha**
CBF AML: t(8;21); inversion 16	--	**PCR for CBF**
Other AML	**4-8 color flow cytometry**	**?NPM1**

Kantarjian H. *Am J Hematol.* 2016;91:131-145.

In addition to the baseline features, today one critical element to assess is what we call minimal residual disease. In fact, patients who do respond morphologically and demonstrate evidence of minimal residual disease have a poor outcome. We know, in contrast, that patients who do respond and achieve what you call negative minimal disease status will have a better outcome. I am highlighting here acute promyelocytic leukemia as well as CBF leukemia where we can monitor MRD by PCR. For other leukemias, we are using flow cytometry. Maybe in the future using these targets of NPM1, we can track the clone and see the depth of the response and the impact that this depth can have on outcome.

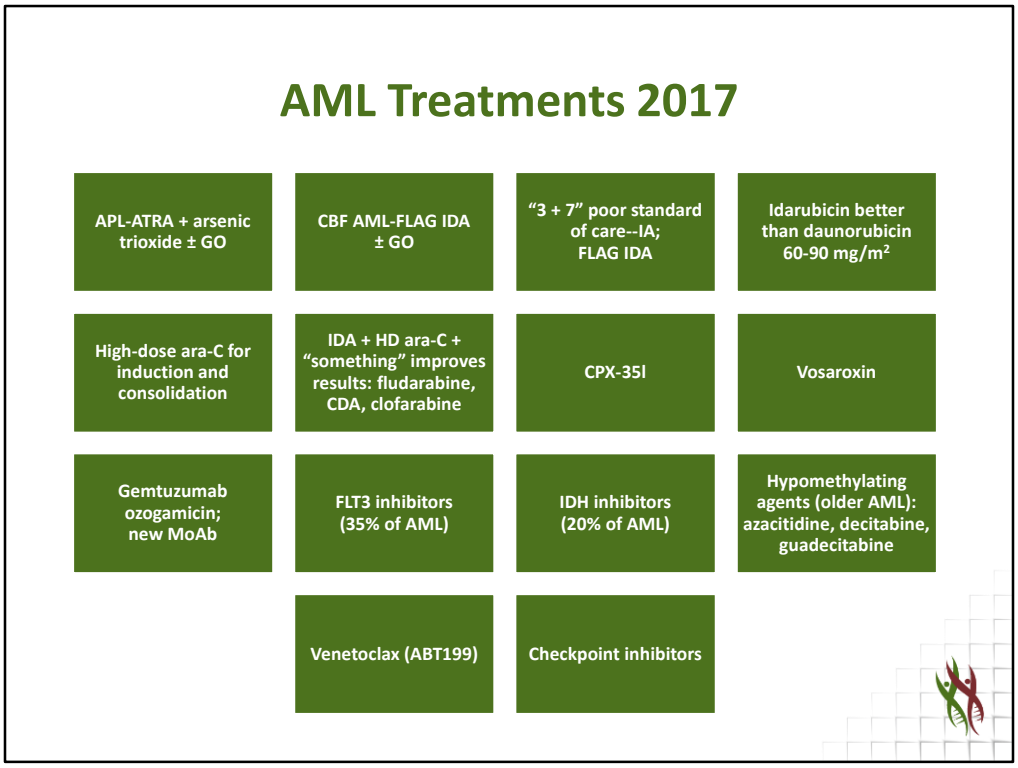
The Evolving Treatment Landscape in AML

New AML Categories

- APL
- CBF AML
- De novo younger AML
- De novo older AML
- MDS → AML; therapy-related AML
- Complex karyotype
- Diploid karyotype and FLT3-ITD
- AML and p53/EVI1

Therefore, as I said during the beginning of my talk, AML is not one disease. We are able to categorize AML in different subsets. Listed here: acute promyelocytic leukemia, core-binding factor AML, de novo younger AML, and de novo older AML (because these patients have different biology and different tolerance to chemotherapy), myelodysplastic syndrome evolving into AML (or what we call therapy-related AML), acute myeloid leukemia with complex karyotype, AML with diploid karyotype and FLT3 ITD, and those with very bad molecular features like p53 mutation and EVI mutation.

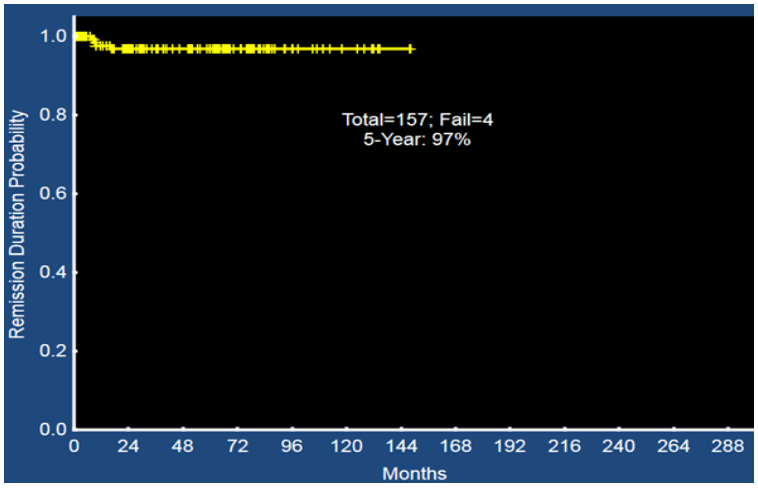
The Evolving Treatment Landscape in AML



In 2017, we have different treatments for different subsets. For example, we are moving into what we call a chemotherapy-free regimen for APL, where we are relying on ATRA/arsenic trioxide. For CBF AML, 3+7 is a standard of care, but is a poor standard of care and there is room for improvement; FLAG-IDA can be better. Idarubicin is better than daunorubicin. On the role of high-dose ARA-C: can we add something into 3+7 or combine two drugs? We will investigate some of these approaches. There are new agents like CPX-351, vosaroxin, gemtuzumab ozogamicin, and a panoply of new monoclonal antibodies. There are FLT3 inhibitors that can help a third of AML patients, and IDH inhibitors that are effective in 20% of AML patients. For the group of patients who are unfit for intensive chemotherapy, we know that the newer generation of HMAs (or hypomethylating agents) are helpful. A new era of investigations includes venetoclax (or anti BCL-2) as well as checkpoint inhibitors.

The Evolving Treatment Landscape in AML

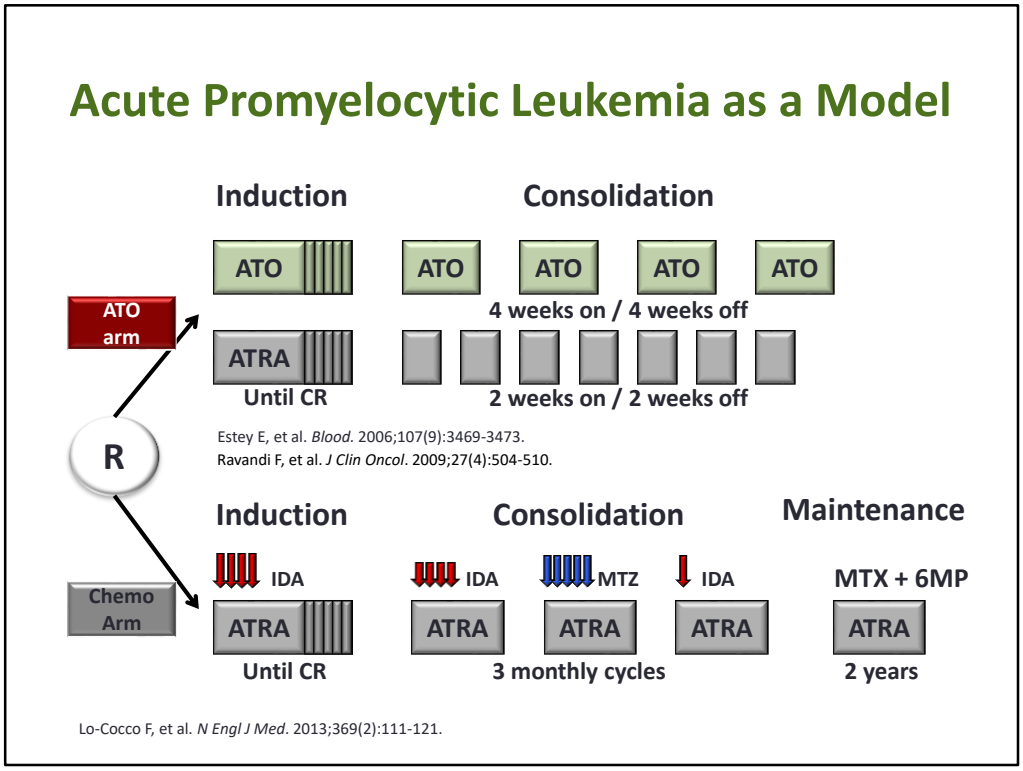
APL: Complete Response Duration with ATRA + Arsenic



Ravandi F, et al. *J Clin Oncol*. 2009;27(4):504-510.

Just to give you an idea of the progress essentially in APL where chemo-free regimen has been quite successful, here are the data from MD Anderson, where cure rates are approaching 100%. Patients' complete response (CR) duration at five years is 97%.

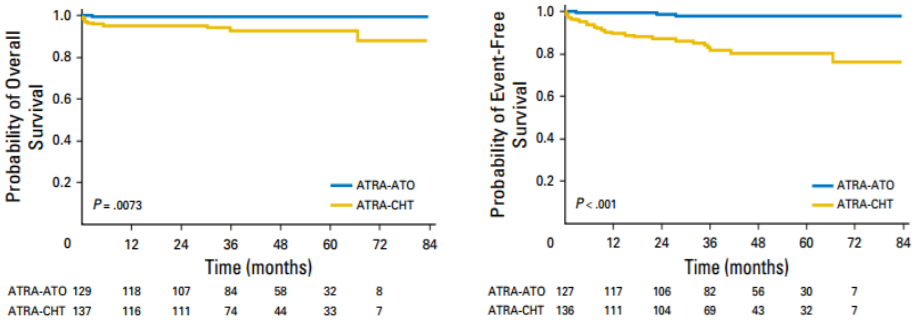
The Evolving Treatment Landscape in AML



That was later confirmed in a European randomized trial where patients with low-risk APL were randomized to either: ATRA/arsenic induction/consolidation; or standard of care involving ATRA and idarubicin induction, consolidation, and maintenance.

The Evolving Treatment Landscape in AML

APL-Outcome with ATRA + AS2O3 vs AIDA

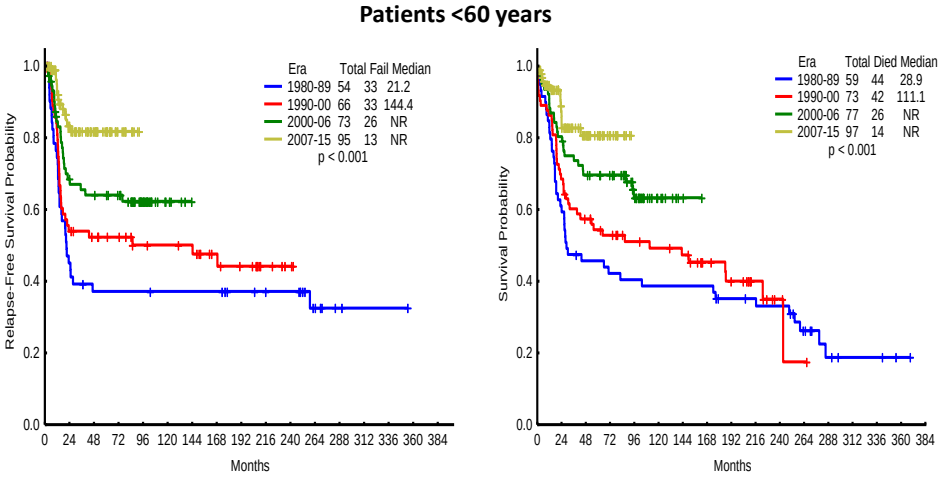


Platzbecker U, et al. *J Clin Oncol.* 2017;35(6):605-612.

The study has shown that a chemo-free regimen can induce better outcome, better progression-free survival, and overall survival compared to traditional chemotherapy, and here we prove that we can move away from chemotherapy to chemotherapy-free regimens.

The Evolving Treatment Landscape in AML

CBF AML: Overall Survival and Relapse-free Survival: Historical Data at MDACC

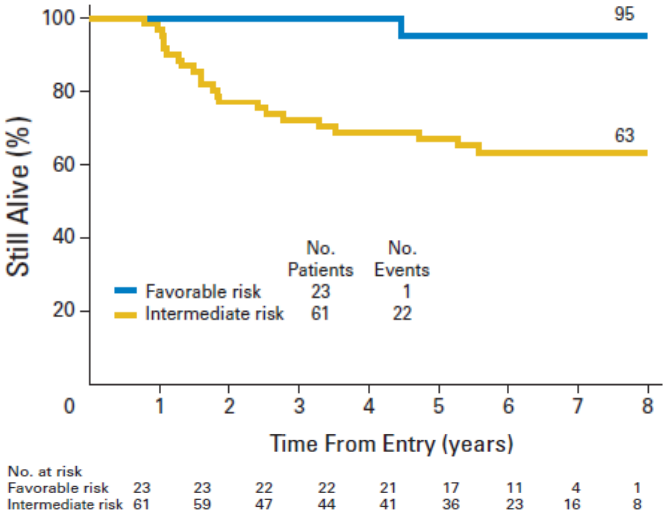


Kantarjian H. *Am J Hematol.* 2016;91:131-145.

Another area where we are making progress is in what we call CBF leukemias. These patients do benefit from high-dose chemotherapy, essentially the FLAG-IDA regimen seen in the yellow curve at the top. Clearly that translates into an improvement in outcome, and that has been shown by other investigators as well.

The Evolving Treatment Landscape in AML

FLAG-IDA x 2, HD Ara-C x 2-Survival in Favorable and Intermediate Risk



Burnett AK, et al. *J Clin Oncol*. 2013 (e-Pub), Myeloma Research Consortium.

Here I am showing you the data from the Myeloma Research Consortium (MRC) from the UK, published by Dr. Burnett in JCO, where patients with favorable-risk karyotype do benefit from FLAG-IDA and high-dose ARA-C. You can see the survival being 95% compared to 63% for patients who have intermediate-risk features at baseline.

The Evolving Treatment Landscape in AML

% Patients with AML Eligible for "3 + 7"

AML Category	%	Rx	% Cure
APL	5-10	ATRA + AS2O3 ± GO	90
CBF AML	10-15	FAI, FLAG-IDA ± GO	80+
Age >70 years; unfit	50+	HMAs; low intensity Rx; investigational	<20
Fit but secondary, Rx-related (20-30% of total)	10	CPX351	<10
Fit, 3+7	25	3+7	25-35
Fit	NA	FLAG-IDA	50-60

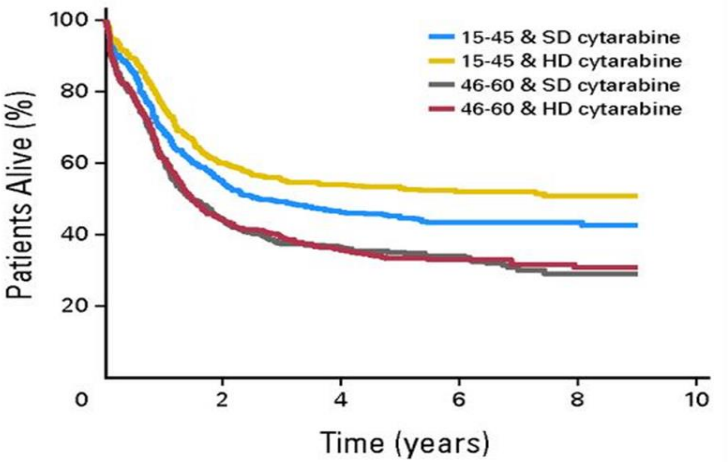
HMAs=hypomethylating agents

Kantarjian H. *Am J Hematol.* 2016;91:131-145.

3+7 is our standard of care: how many patients benefit from this regimen? Here is a table summarizing the difference subsets of AML, starting with APL where the cure rate is approaching 90%. CBF leukemia with high-dose ARA-C is good, at an 80% cure rate. For patients who are 70 years and older and unfit for chemotherapy: 3+7 is not the way to go. They are 50% of the patient population and the cure rate is below 20%. For patients who are fit but have secondary AML or have MDS evolving into AML, I will show you later CPX-351 has shown to improve survival for these patients, and therefore this is the new standard of care. Fit patients where 3+7 is an option is only 25% of the patient population, and the cure rate is about 35%. That is definitely a poor standard and we need to improve on it. Finally, in fit patients who can tolerate intensive chemotherapy, survival can be better. I want to highlight that with patients aging, with the new treatments available, MDS prevalence is increasing and half of them will progress into AML; and these patients do benefit better from newer agents like CPX-351.

The Evolving Treatment Landscape in AML

High Dose Ara-C vs Standard Dose Ara-C Induction in AML (EORTC-GIMEMA)



Willemze R, et al. *J Clin Oncol*. 2014;32(3):219-228.

Clearly there is a role for high-dose cytarabine during induction/consolidation, as shown in this graph here where patients up to the age of 45 who received high-dose cytarabine did perform much better than those who received standard dose. Therefore, at least today, patients who are younger (up to 45) should benefit from high-dose cytarabine during induction and consolidation.

The Evolving Treatment Landscape in AML

FLAG-IDA

- Fludarabine-30 mg/m^2/Dx5

  Ara-C 2 g/m^2/Dx5

  IDA 10 mg/m^2/Dx3

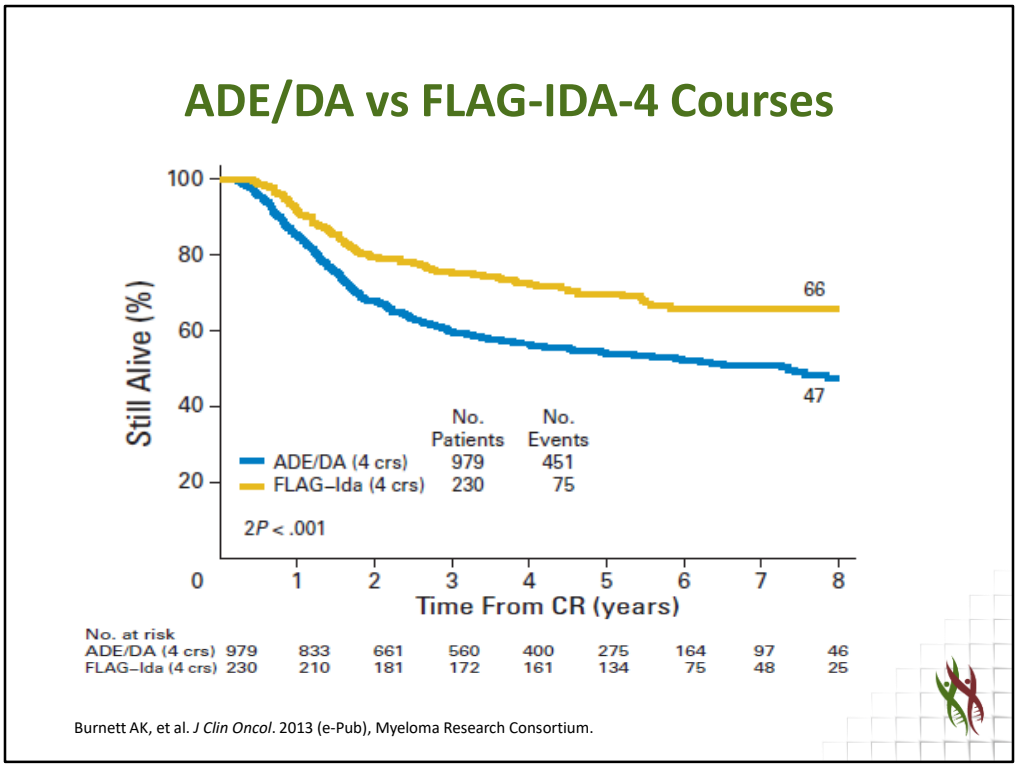
  Two inductions

- FLAG-IDAx2 → HD Ara-C 1.5-3 g/m^2 Q12h D1, 3, 5—x2

Burnett AK, et al. *J Clin Oncol*. 2013 (e-Pub), Myeloma Research Consortium.

Here, I am showing the data from the MRC where patients received a triplet upfront for two cycles, followed by two cycles of high-dose ARA-C.

The Evolving Treatment Landscape in AML



Burnett AK, et al. *J Clin Oncol*. 2013 (e-Pub), Myeloma Research Consortium.

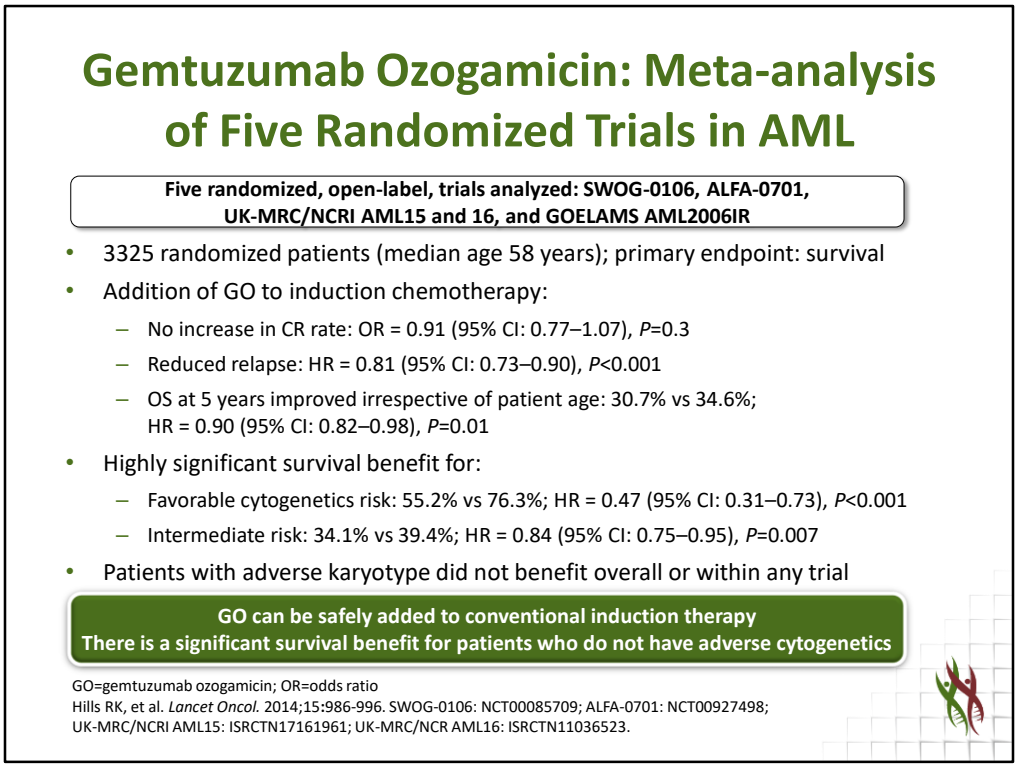
Clearly there was an improvement in outcome in patients in whom they were able to deliver four courses; survival was 66% compared to 47% for those who did not receive the FLAG-IDA regimen.

The Evolving Treatment Landscape in AML

Promising Targeted Treatments

- FLT3 inhibitors (35%)
- IDH 1-2 inhibitors (20%)
- Antibodies (monoclonal, bispecific) targeting CD33 and CD123 (100%)
- Venetoclax (100%)
- Checkpoint inhibitors (100%)
- CAR T targeting CD33 and CD123 (100%)

Where are we going from here? Well, again as I said, we are making progress, but we can further improve on it. There is promising targeted therapy available to us today, and the FDA has approved several drugs recently that I will go over. FLT3 inhibitors can be used in a third of the patient population; IDH1 and IDH2 inhibitors in 20%. We have antibodies, among them gemtuzumab ozogamicin which was recently approved. We have the BCL-2 inhibitors and checkpoint inhibitors, and CAR T-cells hold promise in the future of AML therapy.

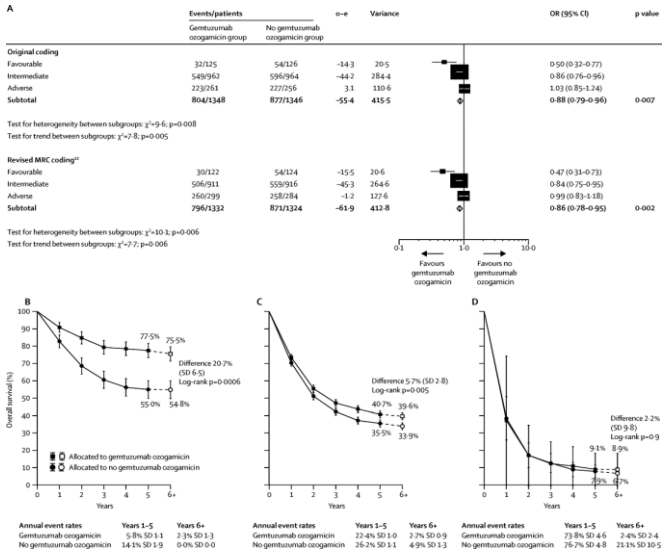


CHAPTER 2: Monoclonal Antibodies, Epigenetic Modifiers, Cytotoxic Agents, Checkpoint Inhibitors, and HMAs

Let's start with gemtuzumab ozogamicin. Here are the data from the meta-analysis showing the improvement in outcome. More than 3000 patients were randomized and, while gemtuzumab ozogamicin (brand name Mylotarg™) did not show any improvement in the CR rate, it did decrease the rate of relapse and improved survival at five years, mainly among the group of patients who had favorable and intermediate-risk karyotype. Based on these data and based on other randomized trials, the FDA has again approved the drug to be added to chemotherapy.

The Evolving Treatment Landscape in AML

Gemtuzumab Ozogamicin in Induction Therapy
Meta-analysis of Five Randomized Trials



Hills RK, et al. *Lancet Oncol.* 2014;15(9):986.

In fact, here is the forest plot showing you the advantage of gemtuzumab ozogamicin across the board, except in patients with a very bad karyotype.

The Evolving Treatment Landscape in AML

Gemtuzumab Ozogamicin

- Adults with newly diagnosed CD33 positive acute myeloid leukemia
- Adults and children 2 years and older with relapsed or refractory CD33 positive AML
- **Use GO 3 mg/m^2 x1 for induction and x1 during 1 consolidation course**
- **Refer to package insert for complete prescribing information**

Mylotarg Prescribing Information: *https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761060lbl.pdf*

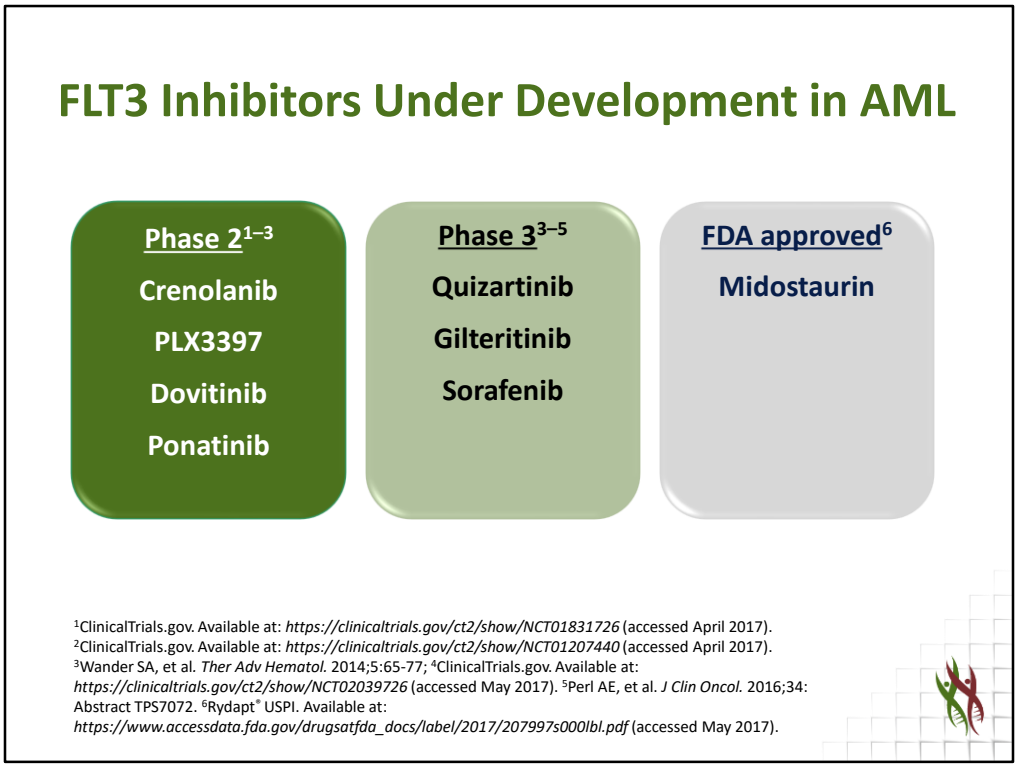
The U.S. Food and Drug Administration granted new approval to gemtuzumab ozogamicin (Mylotarg) for the first-line treatment of newly-diagnosed CD33-positive acute myeloid leukemia (AML) in adult patients. The drug was also approved for treatment of relapsed or refractory CD33-positive AML in both adults and pediatric patients ≥2 years of age. This agent may be used in combination with daunorubicin and cytarabine for adult patients, or as a monotherapy for certain adult and pediatric patients. The standard dosing according to the label for newly diagnosed, de novo AML on a combination regimen is:

- Induction: 3 mg/m^2 (up to one 4.5 mg vial) on Days 1, 4, and 7 in combination with daunorubicin and cytarabine
- Consolidation: 3 mg/m^2 on Day 1 (up to one 4.5 mg vial) in combination with daunorubicin and cytarabine.

The standard dosing according to the label for relapsed or refractory AML on a single-agent regimen is:

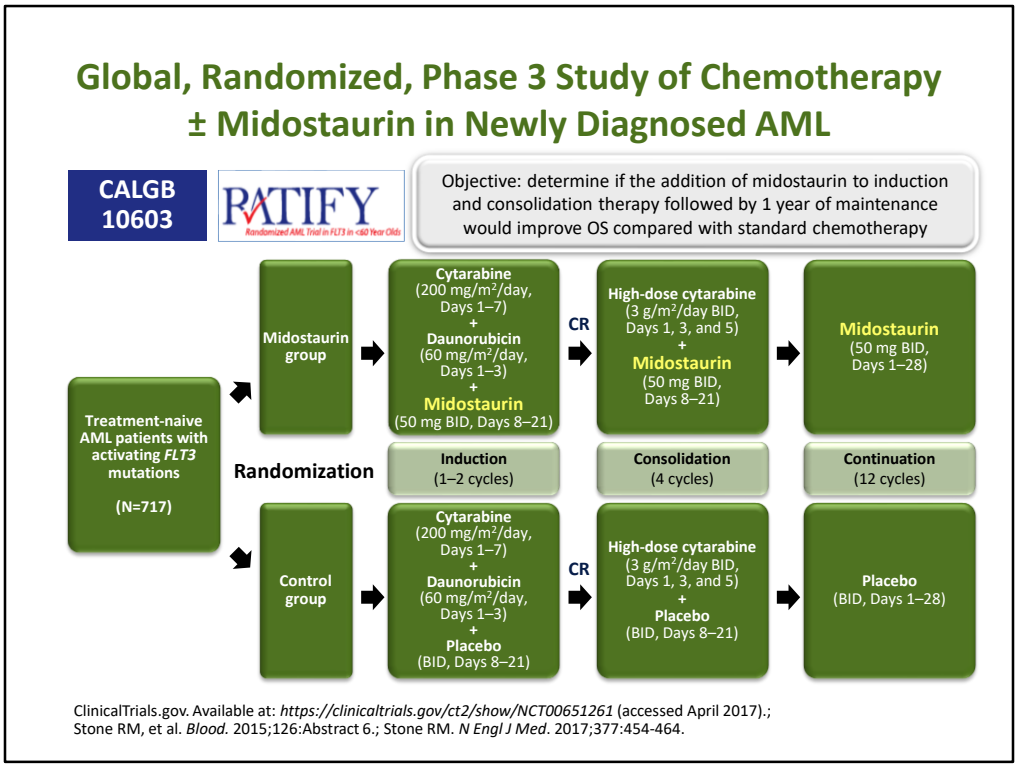
- 3 mg/m^2 on Days 1, 4, and 7

The Evolving Treatment Landscape in AML



Another chapter: the FLT3 inhibitors. We have one drug approved, and we have a panoply of medications going from early trials to randomized trials to phase III trials. Midostaurin was recently approved for AML FLT3 ITD-positive. We have drugs undergoing investigation in phase III, for example: quizartinib, gilteritinib, and sorafenib. We have other compounds in phase II studies, like crenolanib.

The Evolving Treatment Landscape in AML

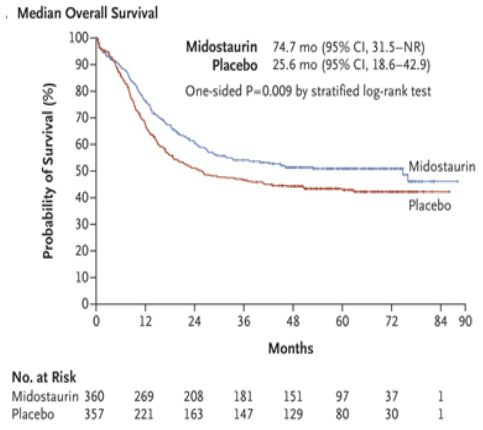


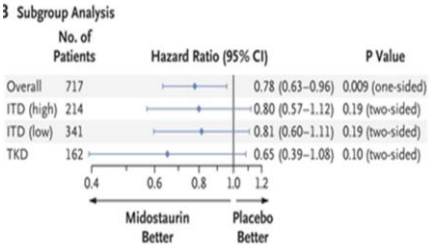
ClinicalTrials.gov. Available at: *https://clinicaltrials.gov/ct2/show/NCT00651261* (accessed April 2017).; Stone RM, et al. *Blood.* 2015;126:Abstract 6.; Stone RM. *N Engl J Med*. 2017;377:454-464.

Here, I am showing you the data from the RATIFY trial which was a randomized trial in patients with treatment-naïve AML harboring FLT3 mutation. Patients were randomized to either 3+7 with or without midostaurin given during induction, consolidation, and maintenance.

The Evolving Treatment Landscape in AML

Chemo Rx ± Midostaurin in AML (RATIFY)





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

This study had a primary endpoint of survival, and the primary endpoint was met. There was an improvement in overall survival by two months, and this difference was significant. As you can see on the slide**,** there is a forest plot where we have seen an advantage across the board overall, in patients with ITD high and low allele burden, as well as in patients with point mutations.

The Evolving Treatment Landscape in AML

Gilteritinib (ASP2215) in FLT3-mutated AML

Phase 1/2, open-label, dose-escalation or concomitant dose-expansion study (NCT02014558)[1]

- Next-generation FLT3/AXL inhibitor[1]
- Preclinical activity against *FLT3*-ITD activating and *FLT3*-D835 resistance mutations[1]

Efficacy[1]

Gilteritinib 20–450 mg QD	R/R AML (N= 252)
Treated with ≥80 mg QD, n	169
ORR, n (%)	88 (52)
CRc, n (%)	69 (41)
PR, n (%)	19 (11)
Median survival, weeks	31

Safety[1]

- Most commonly reported treatment related AEs: diarrhea (16%) and fatigue (15%)
- Seven deaths were considered possibly/probably related to treatment

Ongoing phase 3 studies of gilteritinib maintenance in *FLT3*-mutated AML[2,3]

ORR=overall response rate; CRc=composite complete response; PR=partial remission

[1]Perl AE, et al. *Blood.* 2016;128:Abstract 1069; [2]ClinicalTrials.gov. Available at: *https://clinicaltrials.gov/ct2/show/NCT02927262* (accessed May 2017).
[3]ClinicalTrials.gov. Available at: *https://clinicaltrials.gov/ct2/show/NCT02997202* (accessed May 2017).

Another compound being assessed in FLT3-mutated AML is called gilteritinib. In vitro, the drug has shown activity in FLT3 ITD (internal tandem duplication) as well as in point mutation. In a phase I/II study, the drug has shown activity with 50% objective response rate, and CR being 41%. The side effect profile was very tolerable. The drug is being assessed today in a randomized phase III study, and hopefully we can get this new drug in FLT3-mutated AML.

The Evolving Treatment Landscape in AML

Quizartinib in FLT3-ITD Positive or Negative AML

Phase 2, quizartinib monotherapy in *FLT3*-ITD-positive or -negative AML[1,2]

Cohort 1: patients aged ≥60 years with AML relapsed in <1 year or refractory to 1L chemotherapy (N=134)[1]

	FLT3-ITD+	*FLT3*-ITD–
Patients, n (%)	92 (69)	41 (31)
CRc, %	54	32
CR	0	2
CRp	3	2
CRi	51	27
CRc in pts refractory to last therapy, %	39	44

Cohort 2: adult patients with AML relapsed or refractory to 2L salvage HSC chemotherapy or relapsed after T (N=137)[2]

	FLT3-ITD+	*FLT3*-ITD–
Patients, n (%)	99 (72)	38 (28)
CRc, %	44	34
CR	4	3
CRp	0	3
CRi	40	29
CRc in pts refractory to last therapy, %	47	31

- For both cohorts, safety findings were manageable, and were primarily myelosuppression and QT prolongation that was mitigated with dose modifications[1,2]

Ongoing phase 3 study in R/R *FLT3*-ITD-positive AML[3]

HSCT=hematopoietic stem cell transplant; CRp=complete response with incomplete platelet recovery; CRi=CR with incomplete platelet/neutrophil recovery

[1]Cortes JE, et al. *Blood.* 2012;120:Abstract 48; [2]Levis MJ, *et al. Blood.* 2012;120:Abstract 673; [3]ClinicalTrials.gov. Available at: *https://clinicaltrials.gov/ct2/show/NCT02039726* (accessed May 2017).

Another compound, quizartinib, was assessed in FLT3 ITD positive and negative AML. There were two cohorts: patients who were in salvage 1 who had a first remission within 12 months, and in cohort 2 were patients who failed two salvage therapies or relapsed post transplantation. We have seen a higher response rate among the patients with FLT3 IDT-mutated in cohort 1, 69% compared to 31% for patients with wild type; it is the same story in cohort 2 in patients who failed multiple salvages. The drug is also being assessed today in a randomized phase III setting in patients with FLT3 ITD AML. I have shown you so far, the data on monoclonal antibodies, among them gemtuzumab ozogamicin and FLT3 inhibitors.

The Evolving Treatment Landscape in AML

Enasidenib (AG221) in Relapsed/Refractory AML

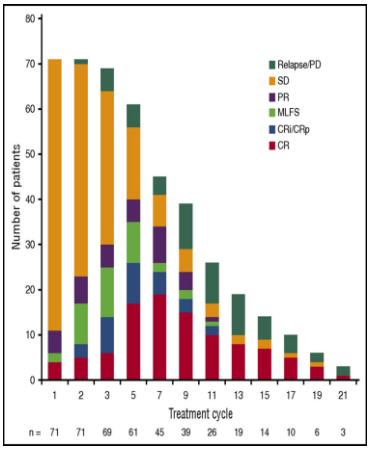
- 239 patients Rx with enasidenib 50-650 mg orally daily; 153 patients Rx with 100 mg daily in Phase 2
- **ORR 70/239 = 40%; median RD 5.8 mos; median OS 9.3 mos**
- CR 19%; median OS 19.7 mos
- Grade 3-4 AEs: ↑ bili 12%; differentiation syndrome 7%

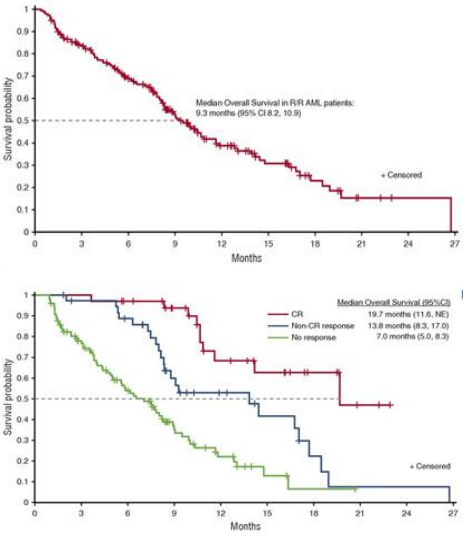
Stein E, et al. *Blood*. 2017;130(6):722-731.

Another chapter where we are very excited is a mutation of an enzyme called isocitrate dehydrogenase. We know that the enzyme is important for the normal functioning of cell metabolism. A mutation of these pathways is involved in a dysfunctioning and leukemia progression. IDH1 and IDH2 inhibitors are being assessed. Here, I am showing you the data from enasidenib which is an IDH2 inhibitor. 240 patients were treated in a phase I/phase II setting. 150 received the dose sequence for phase II which is 100 mg daily. These patients are refractory/relapsed. We have seen a 40% response rate, with a median duration of response of 6 months, and a median overall survival of 9.3 months. That is significant, knowing that historically the median survival is only 4 months; and that is intent to treat. If you look at the patients who achieved CR of 19%, the median survival was 20 months. Based on these data, the FDA granted an approval this summer for enasidenib for patients with refractory AML and patients harboring IDH2 mutation. The safety profile was very tolerable: we have seen an increase in bilirubin. One thing that physicians should be aware of is what we call differentiation syndrome where at the beginning, you can see an increase in the white count and then later on, the count stabilizes. That does not mean the patient is progressing.

The Evolving Treatment Landscape in AML

Enasidenib (AG221) in R-R AML





Stein E, et al. *Blood*. 2017;130(6):722-731.

If you look at the data more in depth, these show you the responses improving with time. What you can see in red is the CR. You can see the CR improving with the cycles. The time to respond may take some time and therefore physicians should not be discouraged if they see an increase in the white count earlier on and then they can decrease, and we can have an improvement in the response rate. Median overall survival is nine months. What you can see on this slide is that CR is much better, 20 months survival. Even among patients who show stability or non-CR responses, we have seen an improvement in outcome: 14 months survival. Clearly it is a drug to be given. It is approved today for refractory/relapsed patients, but the drug is further being developed in the frontline and in relapse, in combination with chemotherapy and hypomethylating agents.

The Evolving Treatment Landscape in AML

Venetoclax Plus DAC/AZA in Rx-naïve AML

- 57 patients, median age 75 years (65-85) Rx with VEN+DAC (n=23), VEN+AZA (n=22), VEN+DAC+Azole (n=12)
- Venetoclax 400-1200 mg/D

Outcome	VEN+DAC (n=23)	VEN+AZA (n=22)	V+D+Posa (n=12)	Total (n=57)
CR	8 (35)	6 (27)	0 (0)	14 (25)
CRi	6 (26)	7 (32)	8 (67)	21 (37)
PR	1 (4)	---	---	1 (2)
ORR	15 (65)	13 (59)	8 (67)	36 (63)

Median response duration 8.4 mos
Median survival 15.2 mos

DiNardo CD. *Lancet Oncol.* (Submitted)

Another chapter I am very excited about is the BCL-2 inhibitors. We know that venetoclax is approved today for CLL patients harboring 17p deletion. We know that BCL-2 expression does confer survival of the cancer clones in leukemia, and therefore it makes sense to investigate the drug in AML. As a single agent, it had modest activity. At MD Anderson we explored this drug in combination with HMA therapy in treatment-naïve AML. Keep in mind these patients are not fit for intensive chemotherapy. We addressed the combinations of venetoclax plus decitabine or azacitidine, or venetoclax, decitabine and posaconazole, which is a metabolizer of the drug. Overall, we have seen a 60% response rate and a median survival of 15 months, which is unheard of and is very good. This drug is being further developed in a randomized trial and hopefully will get an approval in AML.

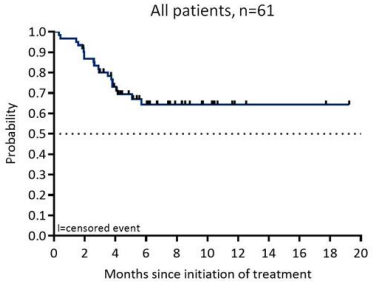
The Evolving Treatment Landscape in AML

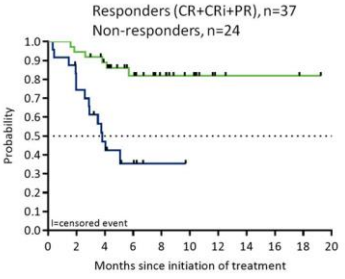
Venetoclax + Low-dose Cytarabine: Phase 1/2 Study in Older AML Patients

Overall response, n (%)	VEN 600 mg (N=61)
Complete remission (CR)	13 (21)
CR with incomplete marrow recovery (CRi)	20 (33)
Partial remission (PR)	4 (7)
Resistant/progressive disease	23 (38)
Incomplete data due to discontinuation	1 (2)
CR+CRi*	**33 (54)**
Overall response rate (CR+CRi+PR)	**37 (61)**

*23/33 (70%) of CR/CRi achieved during Cycle1 and Cycle 2

- Patients ≥65 years
- Venetoclax Phase 2 dose: 600 mg
- ORR (CR+Cri+PR) correlates highly with overall survival





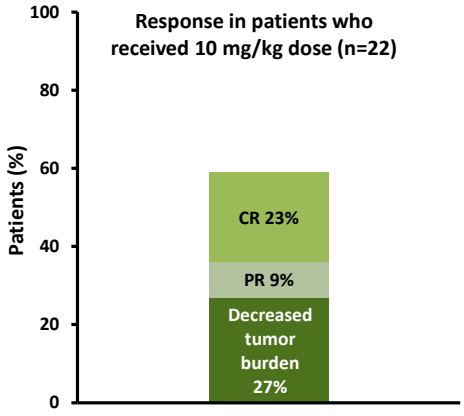
Wei AH, et al. *ASH* 2016;Abstract 102.

One may think, "Well, I cannot use decitabine or azacitidine because my patient has progressed from MDS. Can we combine it with low-dose ARA-C?" Here are data from Australia where the drug was combined with low-dose ARA-C. The dose is different than combination with HMA: where it is 400 mg per day in the HMA population, here we are giving 600 mg per day. As you can see, we have a similar response rate; objective response rate being 60%. The outcome is better for responder patients, with a shortfall that the median has not been reached. Venetoclax is a new promising compound to be further developed and assessed in AML population.

The Evolving Treatment Landscape in AML

Ipilimumab in Patients with Hematologic Malignancies Who Relapse after Allogeneic HSCT

Phase 1/1b, multicenter, investigator-initiated study to determine the safety and efficacy of ipilimumab in patients who relapse after allogeneic HSCT



Efficacy

- 28 patients enrolled (12 with AML)
- 5 of 22 patients who received 10 mg/kg ipilimumab achieved CR
  - 4 AML patients
- 1-year OS: 49% (median follow-up 15 months [range 8–27])

Safety

- Among the 22 patients who received 10 mg/kg ipilimumab, DLTs included n=2 chronic GVHD of the liver and n=1 grade 2 acute GVHD of the gut, all of which resolved with glucocorticoids

GVHD=graft-versus-host disease
Davids MS, et al. *N Engl J Med.* 2016;375:143–153.

Checkpoint inhibitors in immune-oncology are finding their place in every cancer. The idea is not anymore to go after the tumor, but to harness the immune system to go and attack the cancer cells. Here are some pivotal data from AML. Patients who failed transplantation received ipilimumab at 10 mg/kg. We're seeing a response in 60% of the patients, with the one-year survival being 49%. One should be careful when using ipilimumab because activated T-cells may lead to more GvHD; although in this small study, they were very well tolerable and most of the GvHD were grade 1 and 2 and responded well to steroids.

The Evolving Treatment Landscape in AML

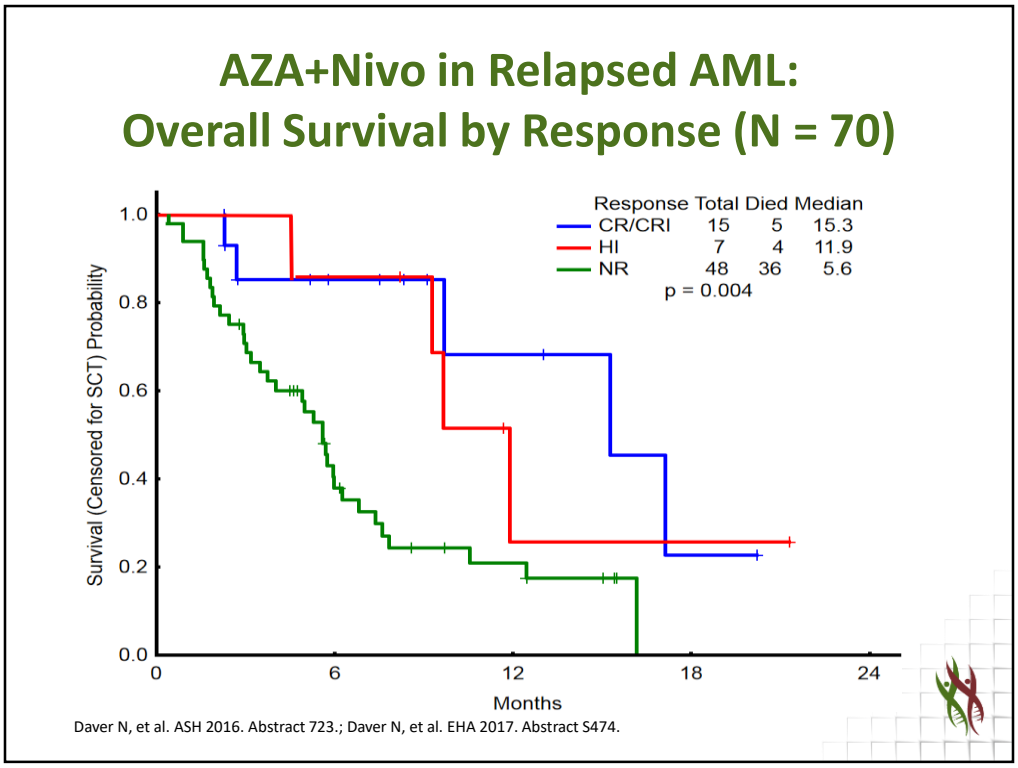
AZA+Nivo in Relapsed AML: Response (N=70)

Best response / Outcome	N (%) / Med [Range]
Evaluable	70
ORR	**22 (34)**
CR/CRi	15 (23)
HI + 50% blast reduction (6 mo+)	7 (11)
50% reduction in blast	17 (24)
Progression/**Stable disease (6 mo+)**	26 [21/**5**]
8-week mortality	5 (7)
Median cycles to response	2 [1 – 13]
Median follow-up	8.6 mo [2.8 – 21.3]

HI=hematologic improvement
Daver N, et al. ASH 2016. Abstract 723.; Daver N, et al. EHA 2017. Abstract S474.

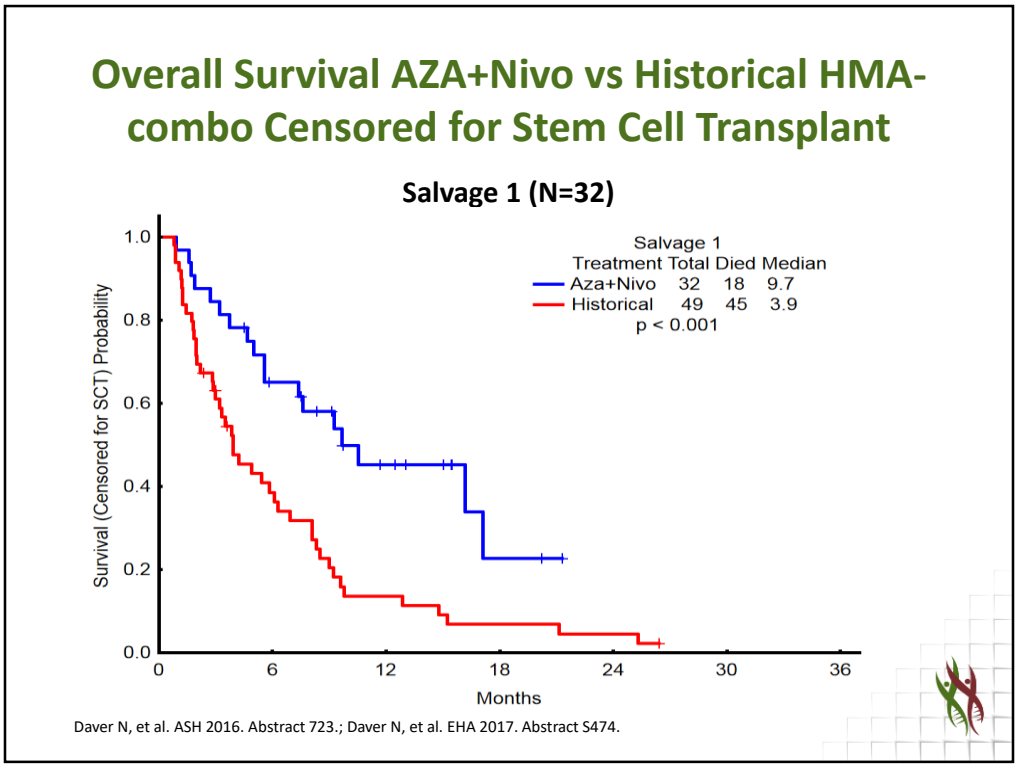
At my institution, we have moved into combining nivolumab. Nivolumab is safer than ipilimumab, and we combine azacitidine plus nivolumab in relapsed AML patients. The objective response rate was 34%, considering CR, CRi and HI. We have 24% who had 50% reduction in the blasts, and some of them had stable disease. We have a very low 8-week mortality rate of 7%, with follow-up being 8 months today.

The Evolving Treatment Landscape in AML



If you look at the outcome with 70 patients treated, we have a median survival of 15 months for those who achieved a CR or CRi; less so for patients who did not respond, and HI is 12 months.

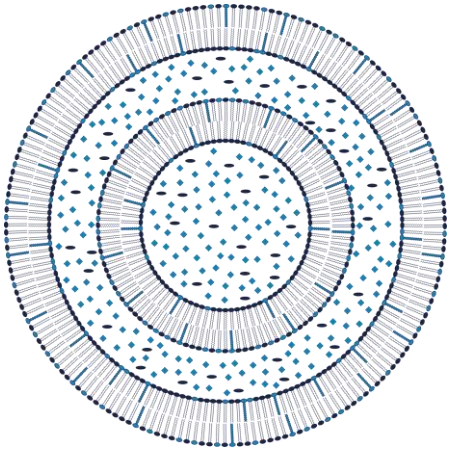
The Evolving Treatment Landscape in AML



Let us put things in perspective. If you look at the salvage 1 patients, when you compare to historical data, we double survival. We know for these patients, there is nothing we can offer them. Standard of care is very poor, and aza/nivo is a promising venue to further be explored.

The Evolving Treatment Landscape in AML

CPX-351: Using Liposomes As a Drug Delivery System



- 100 nm bilamellar liposomes
- 5:1 molar ratio of cytarabine to daunorubicin
- Maximally synergistic ratio in cell lines
- Accumulates in bone marrow with preferential uptake by leukemic cells
- MTD: 101 units/m^2 on Days 1, 3, and 5

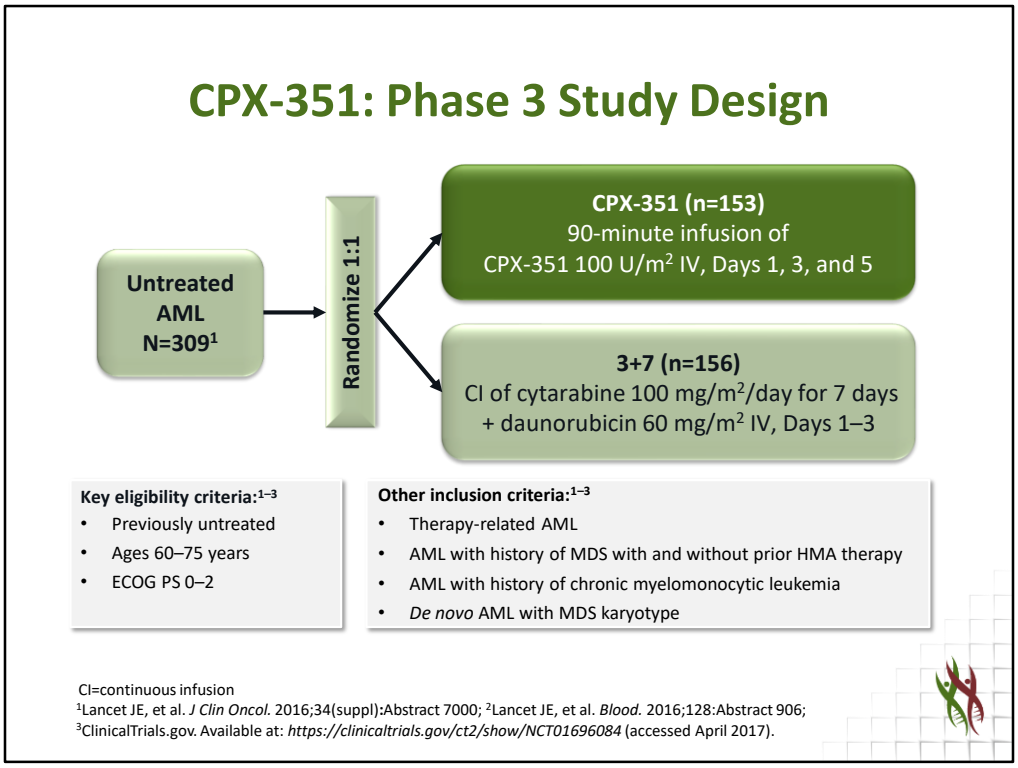
DSPC DSPG Cholesterol Cytarabine Daunorubicin

MTD=maximum tolerated dose: DSPC=desaturated phosphatidylcholine: DSPG=distearoyl phosphatidylglycerol

Feldman EJ, et al. *J Clin Oncol.* 2011;29:979-985.

On to other chapters, other novelties in AML. CPX-531 is essentially using a liposomal formulation of daunorubicin and cytarabine that can deliver the drug in a more efficient way to the cancer cells. The MTD was 101 units/m^2 and that was given on days 1, 3 and 5.

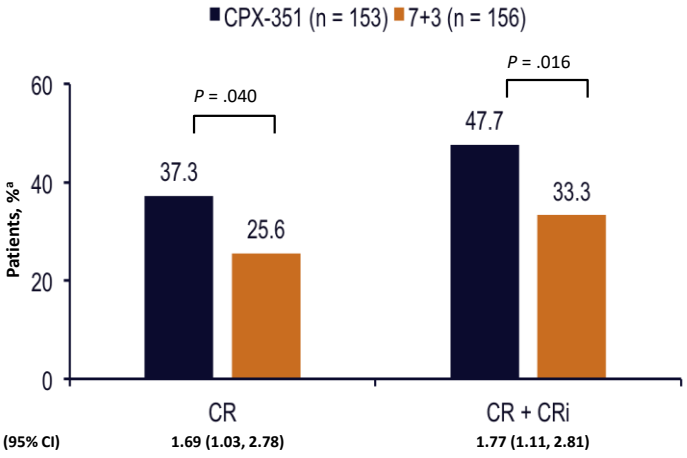
The Evolving Treatment Landscape in AML



The drug was explored in a phase III study in patients with AML with bad features. In ages 60-75, they have therapy-related AML, AML with MDS who failed on non-HMA therapy, or AML with MDS karyotype. We know these patients have a very poor outcome. They were randomized to CPX, induction/consolidation, or 3+7, the dose of daunorubicin being 60 mg/m^2.

The Evolving Treatment Landscape in AML

CPX-351 Versus 3+7 in High-Risk AML: Response Rate



Odds Ratio (95% CI)	1.69 (1.03, 2.78)	1.77 (1.11, 2.81)

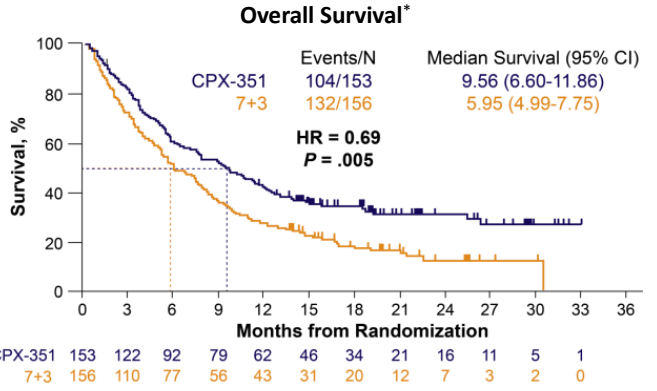
[a] Percentages reflect number with endpoint out of column total.
Odds ratios are calculated with the 3+7 arm as the reference group; *P* value is from a comparison of rates between treatment arms and is based on the Mantel-Haenszel test stratifying by age and AML type.

Lancet JE, et al. *J Clin Oncol.* 2016;34(suppl):Abstract 7000.

Response rates were in favor of CPX-351. CR only had an improvement from 25% to 37%, and CR/CRi had an improvement from 33% to 47.7%.

The Evolving Treatment Landscape in AML

CPX-351 Versus 3+7 in Newly Diagnosed Secondary AML: Clinical Outcomes



	CPX-351 (n=153)	3+7 (n=156)	Odds Ratio	*P* value
CR+CRi	47.7%	33.3%	1.77 (1.11, 2.81)	0.016
HSCT rate	34.0%	25.0%	1.54 (0.92, 2.56)	0.098
Deaths ≤60 Days*	13.8%	21.8%		

*Kaplan-Meier estimate; CI=confidence interval
Medeiros BC, et al. ASH 2016. Abstract 902.

That translates into an improvement of overall survival where standard of care had a survival of 6 months compared to 9.56 months for patients who receive CPX. Based on this data, the drug was approved by the FDA. Indeed, those who had CPX had high response rate and had high transplant rate. Again, the drug was more effective and safer with a lower early death defined at 60 days or two months.

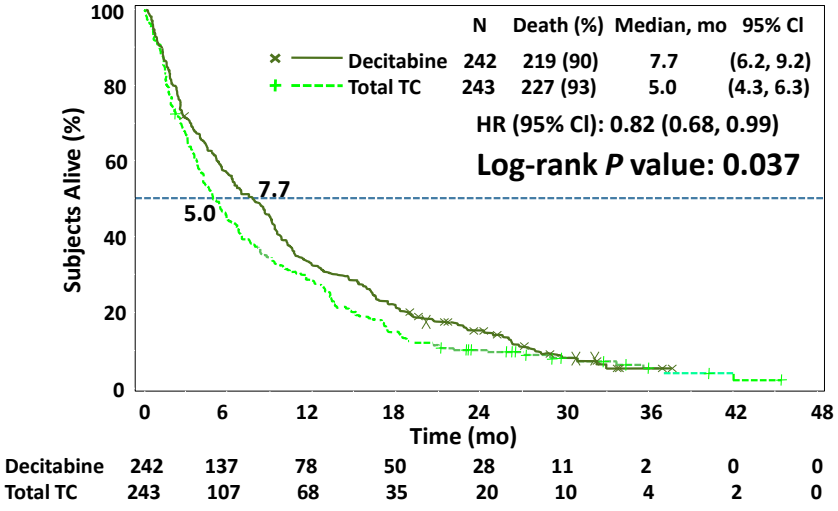
Management of Acute Leukemia in the Elderly: First a Definition

- Who is “elderly”?
- Age cut-off 60, 65, 70, older?
- **My definition: any patient in whom expected induction mortality (8-week mortality) is more than 20-30%** + short median survival/low cure rate with standard intensive chemo Rx

Beyond that, what do we have for elderly patients who are not fit for chemotherapy? Who is elderly? Because with the population aging, we cannot say 60 or 65. What is the cutoff? My definition is patients who are unfit for chemotherapy and where early mortality rate is more than 20% to 30%. We know these patients cannot tolerate intensive chemotherapy due to bad biology, and they have a low cure rate with standard chemotherapy.

The Evolving Treatment Landscape in AML

Decitabine vs SC or LD Ara-C in Elderly AML: Survival with 446 Deaths (CCO 2010)

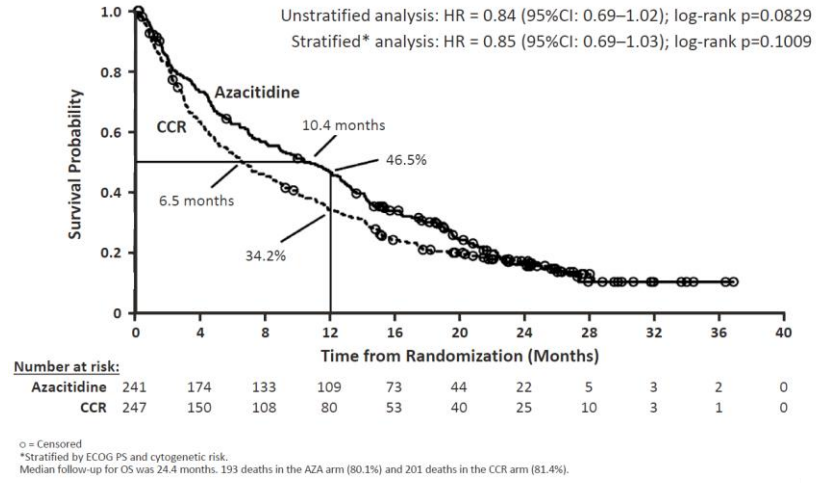


Kantarjian HM, et al. *J Clin Oncol*. 2012;30(21):2670-2677.

What do we have for these patients? HMA therapy is standard of care. Here are the data from decitabine compared to what we have, showing an improvement in survival from 5 months to 7.7 months.

The Evolving Treatment Landscape in AML

Azacitidine vs Conventional Care Regimens (CCR) in Older Patients with Newly Diagnosed AML with >30% Blasts



Dombret H, et al. *Blood*. 2015;126(3):291-299.

This was also shown with azacitidine. In the subset of patients with 30% of blasts and more, there was an improvement in survival favoring azacitidine. These drugs are approved in Europe for AML. In the USA, they are approved for MDS, but they are becoming standard of care.

The Evolving Treatment Landscape in AML

Clofarabine-LD Ara-C Alternating with Decitabine in Elderly AML Therapy

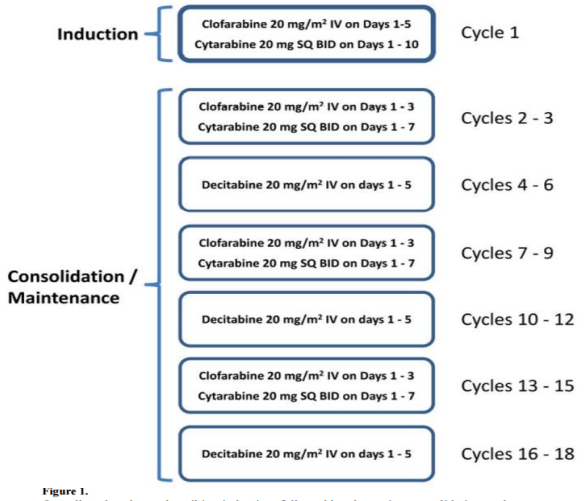


Figure 1.
Overall study schema describing induction, followed by alternating consolidation cycles.

Kadia TM, et al. *Cancer*. 2015;121(14):2375-2382.

Can we improve on that? At MD Anderson, we are. We are building into decitabine and low-dose cytarabine by adding clofarabine or cladribine, and the responses are very promising.

AML: Important Leads

- **FLT3 inhibitors; IDH1/2 inhibitors**
- **Venetoclax**
- **Antibodies:** monoclonal, bispecific constructs (CD33, CD123) [GO, SGN-33A, AMG330, others]
- CAR-T cell therapies
- CPX351; vosaroxin
- **Checkpoint inhibitors**

What are the important leads in AML? To conclude, I would like to leave you with these key takeaway points. FLT3 inhibitors are really important: they improve survival in a third of the patient population. IDH1 and IDH2 inhibitors are very promising in 20% of AML population. Venetoclax is an important lead. Antibodies (gemtuzumab ozogamicin, other bispecific constructs and other antibodies) and CAR T-cell therapy are important, CPX-351 was approved, and checkpoint inhibitors are important, and are being developed for AML patients.

Thank you for viewing this activity.