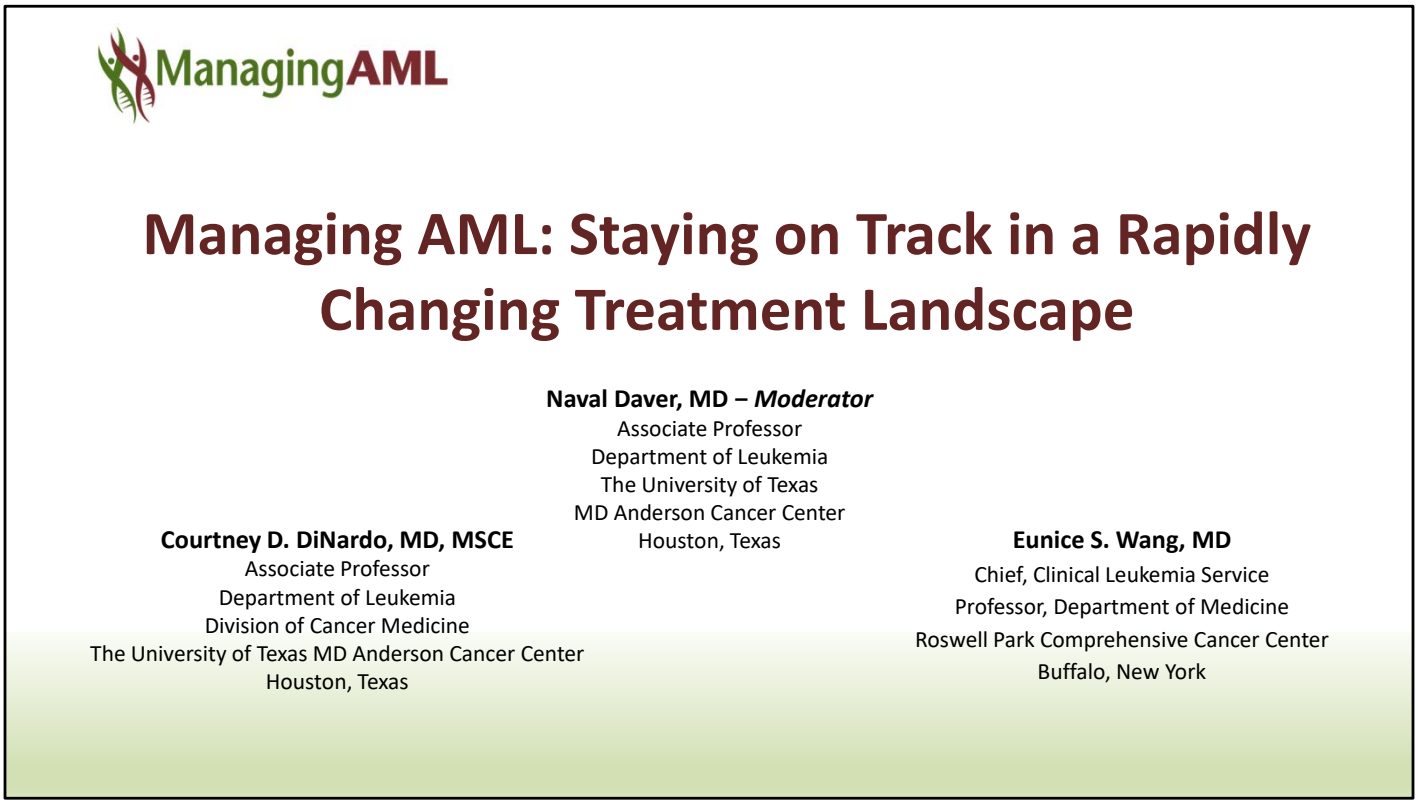


Hello and thank you for joining us. I am Naval Daver, Associate Professor at the MD Anderson Cancer Center. Joining me today are Dr. Courtney DiNardo, Associate Professor at the Department of Leukemia, University of Texas MD Anderson Cancer Center, and Dr. Eunice Wang, Chief of the Leukemia Service at Roswell Park Comprehensive Cancer Center. Welcome.

Faculty Disclosures

- **Dr. Naval Daver** has received honoraria related to formal advisory activities and as a consultant from AbbVie Inc., Agios, Astellas Pharma US, Inc., Bristol-Myers Squibb Company, Celgene Corporation – A Bristol-Myers Squibb Company, Daiichi Sankyo, Inc., ImmunoGen, Inc., Incyte Corporation, Jazz Pharmaceuticals plc, Karyopharm Therapeutics, Novartis AG, Otsuka Pharmaceutical Co., Ltd., Pfizer Inc., and Sunesis. He has received grant support related to research activities from AbbVie, Bristol-Myers Squibb, Daiichi Sankyo, Genentech, Inc., GlycoMimetics, Inc., ImmunoGen, Incyte, Karyopharm, Nohla Therapeutics, Novartis, Pfizer, SERVIER, and Sunesis.
- **Dr. Courtney DiNardo** has received honoraria as a consultant from AbbVie Inc., Agios, Celgene Corporation – A Bristol-Myers Squibb Company, Daiichi Sankyo, Inc., Immune-Onc Therapeutics, Inc., Novartis AG, and Takeda Oncology. She has received grant support related to research activities from AbbVie, Agios, Celgene Corporation – A Bristol-Myers Squibb Company, Calithera BioSciences, Inc., Daiichi Sankyo, and Immune-Onc. She has also disclosed a financial relationship with Notable.
- **Dr. Eunice Wang** has received honoraria related to formal advisory activities from AbbVie Inc., Astellas Pharma US, Inc., Bristol-Myers Squibb Company, Genentech, Inc., Jazz Pharmaceuticals plc, Kite Pharma, MacroGenics, Inc., Pfizer Inc., and PTC Therapeutics, as well as speakers' bureau activities from DAVA Oncology, Pfizer, and Stemline Therapeutics, Inc.

Here are our disclosures.

Planning Committee Disclosures

- The individuals listed below from MediCom Worldwide, Inc. reported the following for this activity: Joan Meyer, RN, MHA, Executive Director, Isabelle Vacher, Vice President of Educational Strategy, Wilma Guerra, Program Director, and Andrea Mathis, Project Manager, have no relevant financial relationships.

Learning Objectives

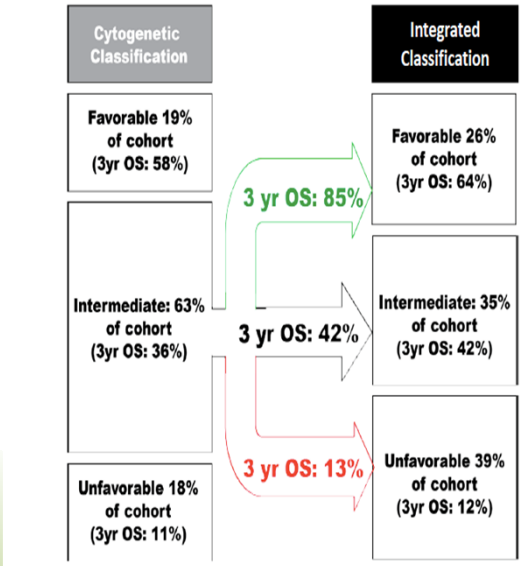
- Summarize best practice strategies in molecular and mutational analysis in AML which assist in developing a patient-centered treatment approach
- Improve knowledge of new and emerging evidence in maintenance therapy as a new standard of care in AML
- Outline guidelines and clinical trial evidence to identify appropriate treatment approaches for patients with AML
- Describe strategies for identifying and managing treatment including dosing, and management of toxicities associated with novel and emerging therapies in AML

AML Genomic Profiling: *FLT3* Mutations Are Common

How Does Mutational Profiling in AML Impact Clinical Practice?

Gene	Overall Frequency, %
FLT3 (ITD, TKD)	37 (30, 7)
NPM1	29
DNMT3A	23
NRAS	10
CEBPα	9
TET2	8
WT1	8
IDH2	8
IDH1	7
KIT	6
RUNX1	5
MLL-PTD	5
ASXL1	3
PHF6	3
KRAS	2
PTEN	2
TP53	2
HRAS	0
EZH2	0

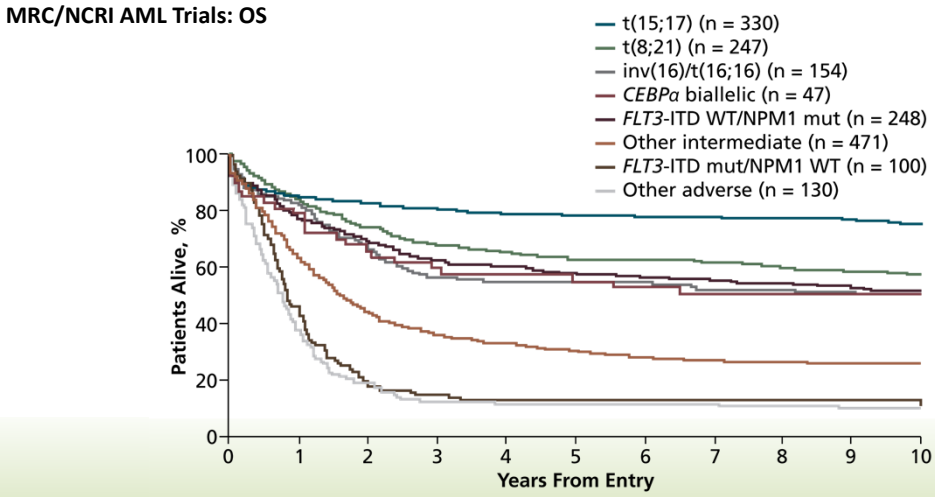
Patel JP, et al. *N Engl J Med*. 2012;366:1079-1089.



Okay, so I'm going to give a very brief introduction before I hand it over to Dr. DiNardo and then Dr. Wang to speak about the specifics of the updates and breakthroughs in newly diagnosed and relapsed AML. I think one important thing to note is that you're going to see discussed extensively throughout the talk is that molecular profiling and mutation analysis is really now critical to all treatment decisions in acute myeloid leukemia. This is true for younger AML absolutely, but also now I think percolating into older AML population.

We knew for a few years now that they had prognostic impact, as you can see here, when you add the molecular data to the cytogenetics that we've used for many decades, we can see that there is further stratification of the outcomes, and we often use this information now for deciding transplant and nontransplant decisions. But also there are a number of targeted therapies, so it's no longer just prognostic, but also has predictive value.

Cytogenetic and Molecular Abnormalities: Survival



Smith ML, et al. *Blood Rev.* 2011;25:39-51.

This is showing you that when you use cytogenetics, and at least the common molecular mutations for analysis, we're able to really understand the prognostic impact and expected outcomes for given patients with acute myeloid leukemia.

Major Targets of Past and Future Therapeutic Development

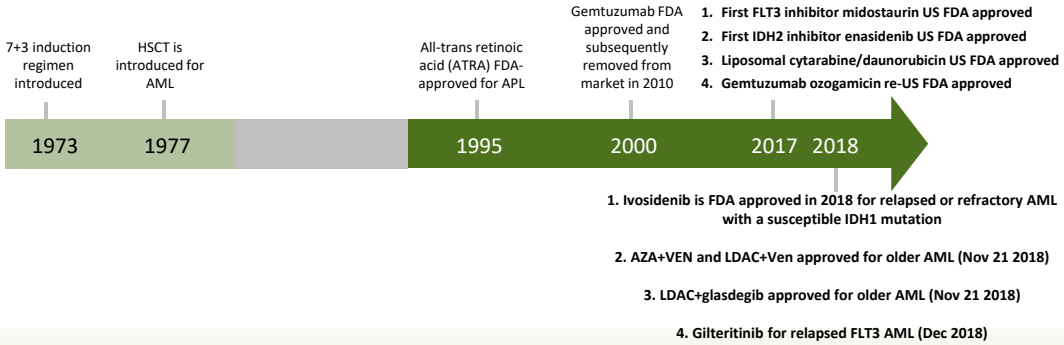
AML with *FLT3* internal tandem duplication	• Impact on both therapy and prognosis • Many *FLT3* kinase inhibitors explored in recent years…now several next-generation agents in development
***KIT* mutations in CBF AML**	• *KIT* mutations found in 30%-35% of CBF AML cases, but rare in other AML subgroups • In CBF AML, mutations cluster mainly in exons 8 and 17
IDH mutations in AML	• *IDH1/2* mutations confer a gain-of-function, including increased histone and DNA methylation and impaired cellular differentiation
***Bcl*-2 as a therapeutic target in AML**	• *Bcl*-2 binds and sequesters pro-apoptotic molecules; inhibition of *Bcl*-2 primes cancer cells for death
Epigenetic targets (EZH2, LSD1, BRD, PRMT5, others)	• Novel agents on the horizon that target specific epigenetic pathways • These are in early clinical trial development
TP53, C-CBL, MLL-Menin	• Phase 1 clinical trials

What are the important targets that are currently in development or already developed or have drugs in the pipeline that we're excited about? I think the three big ones are FLT3, ITD, as well as D835 for which they are approved agents that Dr. DiNardo and Dr. Wang will talk about. KIT mutations which there was some interest that never caught traction, but we sometimes do use KIT inhibitors in certain subsets of acute myeloid leukemia, but the big ones then are IDH as well as FLT3, and emerging I think of a lot of interest to many of us here are MLL for which there are menin inhibitors now in early trials showing some very exciting data and hopefully updates coming later in 2020 and 2021, and then TP53-directed therapies such as APR-246 and CD47 antibodies, magrolimab. So, we really do have a lot of personalization of therapies. Of course, a lot of these are being developed as single agents, but the hope is that they will move forward in combinations that will lead to not just improvement in median survival, but hopefully, long-term cure rates.

Treatment of AML (Accelerated Progress 2017-2020): History

Since its introduction in the early 1970s, 7+3 therapy (cytarabine for 7 days + anthracycline for 3 days) has been the standard of care for AML

US FDA approvals

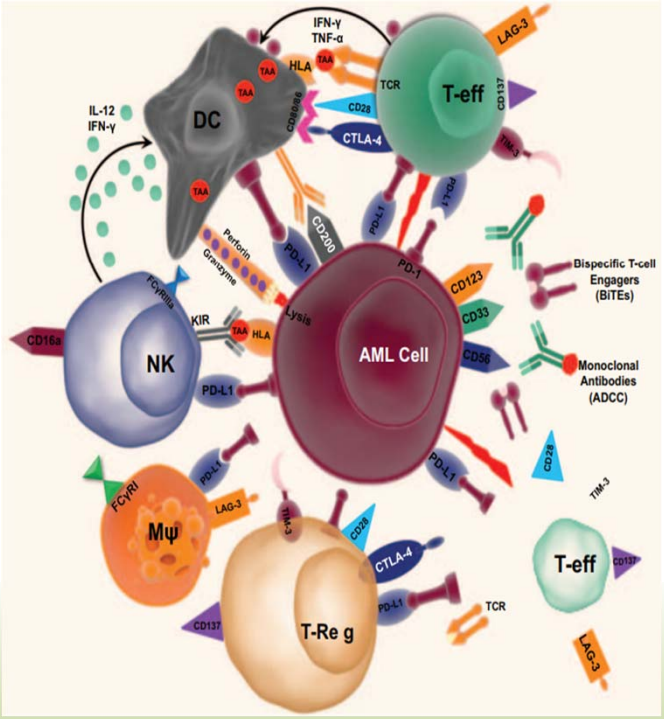


1. Ivosidenib is FDA approved in 2018 for relapsed or refractory AML with a susceptible IDH1 mutation
2. AZA+VEN and LDAC+Ven approved for older AML (Nov 21 2018)
3. LDAC+glasdegib approved for older AML (Nov 21 2018)
4. Gilteritinib for relapsed FLT3 AML (Dec 2018)

Year	1975	1980	1990	1995	2000	2005	2009	2013	2022
5-year survival	6.3%	6.8%	11.4%	17.3%	16.8%	25.7%	28.1%	27%	??

Just to highlight the progress that has happened, just looking at this even from a 10,000-foot view, you can clearly see that there is a dramatic rate of progress happening in the last two to three years. As you know, eight drugs have already been US FDA-approved for the treatment of acute myeloid leukemia, including four targeted therapies, two FLT3, and two IDH inhibitors, as well as immune drugs such as gemtuzumab, very important major breakthrough venetoclax, and other novel drugs like glasdegib and CPX and, in fact, there are also additional drugs that have shown phase III positive data such as CC-486, an oral agent, that is the first drug to show improvement in a randomized phase III study in maintenance in acute myeloid leukemia and hopefully will be a ninth drug to be approved very soon.

Managing AML: Staying on Track in a Rapidly Changing Treatment Landscape



Major Approaches to Immune Therapies in AML

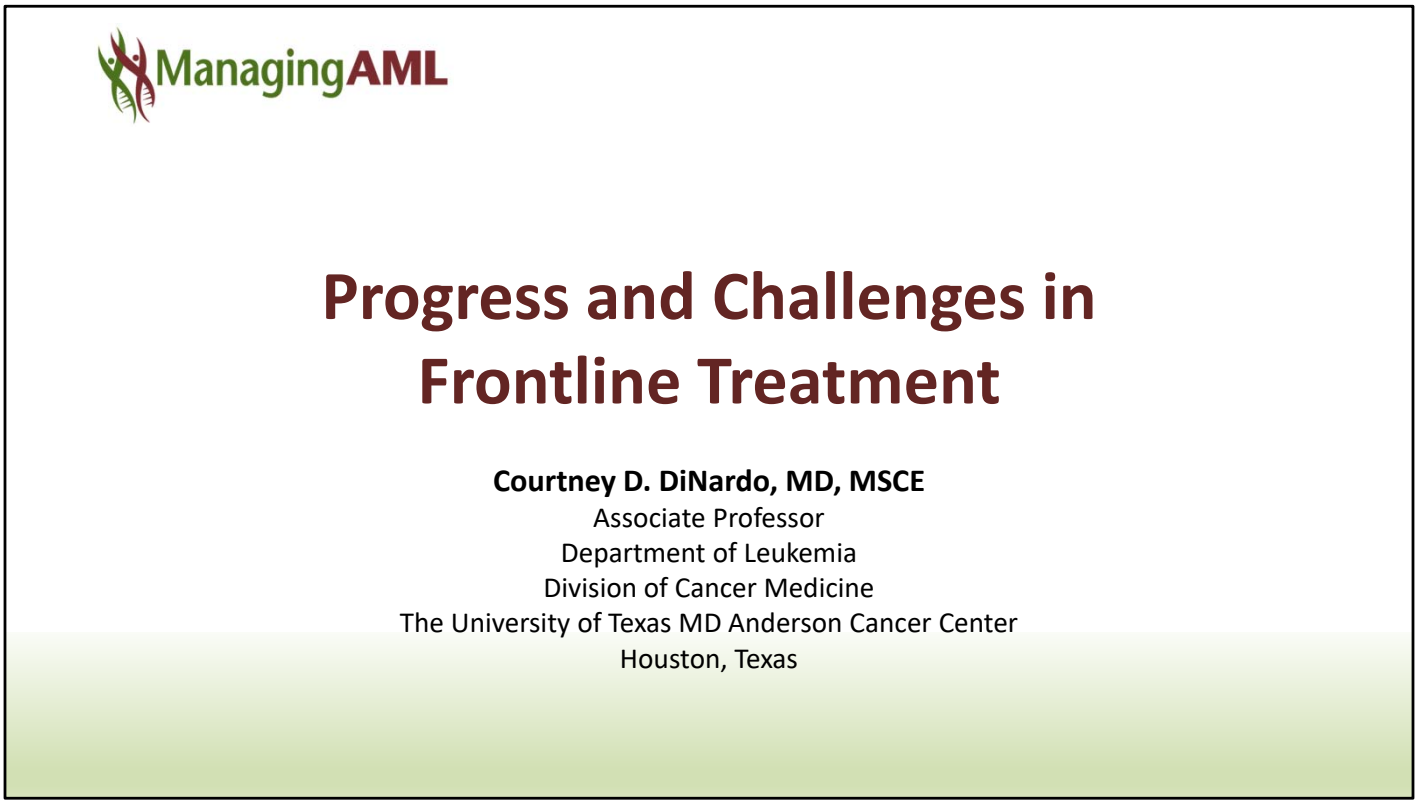
Two major approaches:

1. Antibody drug conjugates
2. T-cell based therapies
   a. Bi-specific antibodies (CD3 x AML antigen)
   b. Immune checkpoint-based approaches
   c. CAR T (CAR NK)

Assi R, et al. *Curr Opin Hematol*. 2018;25:136-145.

And then another major area of development is occurring in the immunotherapy world. There are a number of new antibody-drug conjugates looking at other targets beyond CD33 for which gemtuzumab is approved, and also T-cell-based strategies, which includes agents such as bispecific antibodies as well as macrophage and T-cell activating drugs, which I think over the next few years we're going to see more and more data, and hopefully we'll find important roles in different combinations and subsets of AML.

So with that, I am going to turn it over to my colleague, Dr. Courtney DiNardo to take over the frontline therapy. Courtney, please.

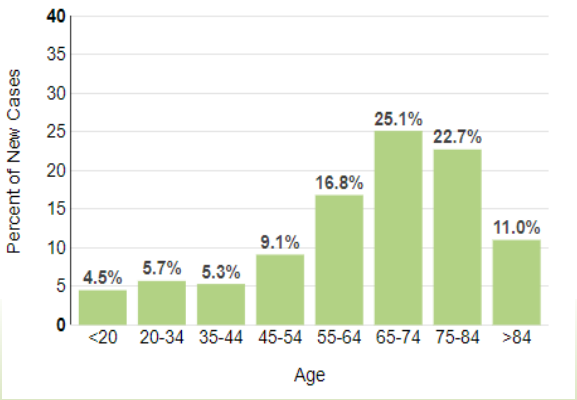


Perfect, thank you so much. So just a 10-minute brief overview of some of the progress and challenges in our frontline therapy for AML, and two slides just to kind of remind everyone what we know.

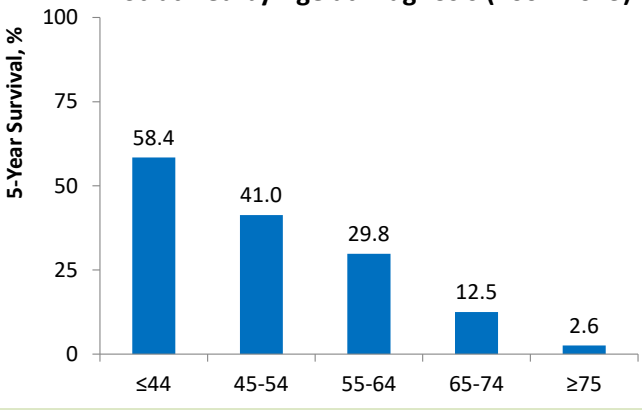
Managing AML: Staying on Track in a Rapidly Changing Treatment Landscape

Median age at diagnosis:
68 years
5-year survival is 28.3%

Incidence of AML by Age Group



5-Year Survival of Newly Diagnosed AML Stratified by Age at Diagnosis (2007-2013)



SEER 2018 data: https://seer.cancer.gov/statfacts/html

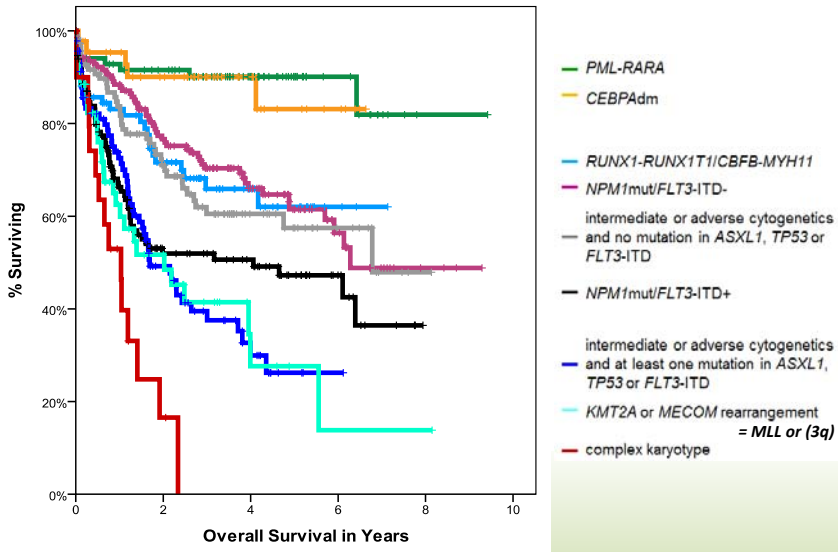
We know that the average age at AML is in general older. Most patients are going to be in their 60s and older. In the blue bars along the right, you can see that really by age, the expected survival, unfortunately, decreases pretty significantly by ongoing decades.

Using Genomic Classification to Improve AML Prognostication

APL:
PML-RARA = t(15;17)

Core-binding factor (CBF) leukemias:
RUNX1-RUNX1T1 = t(8;21)

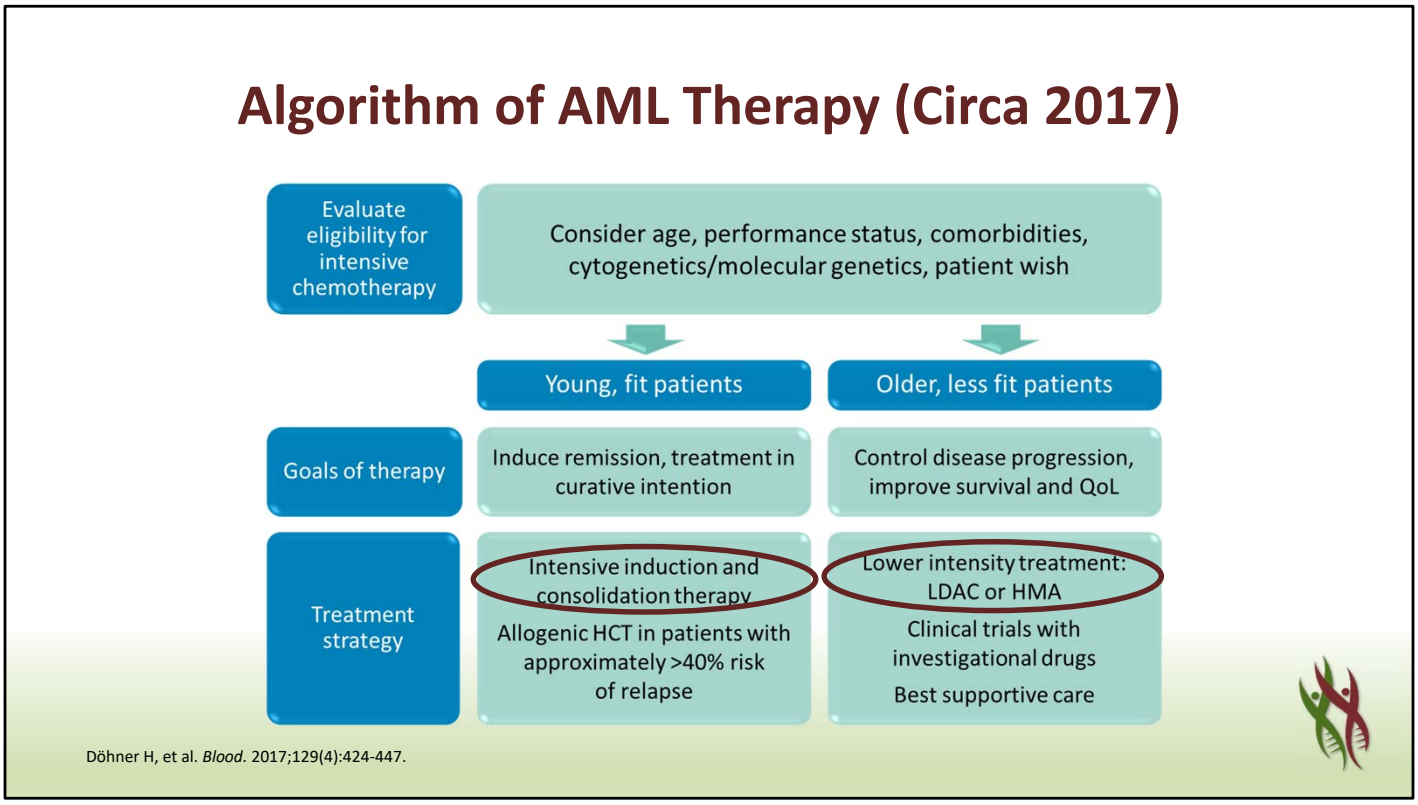
CBFB-MYH11 = inv(16) or t(16;16)



Haferlach C, et al. *Blood.* 2016;128(22):286.

We also know that genomics is really important. You already saw the slide from Dr. Daver, this is another one from Dr. Haferlach showing that with standard intensive chemotherapy or APL-based therapy, there are certain subgroups who do really well. Those with double mutant C/EBPα, core-binding factor leukemias, NPM1 mutations, and then there are those patients along the bottom, those with complex cytogenetics or MLL rearrangements, MECOM rearrangements that do, unfortunately, really poorly.

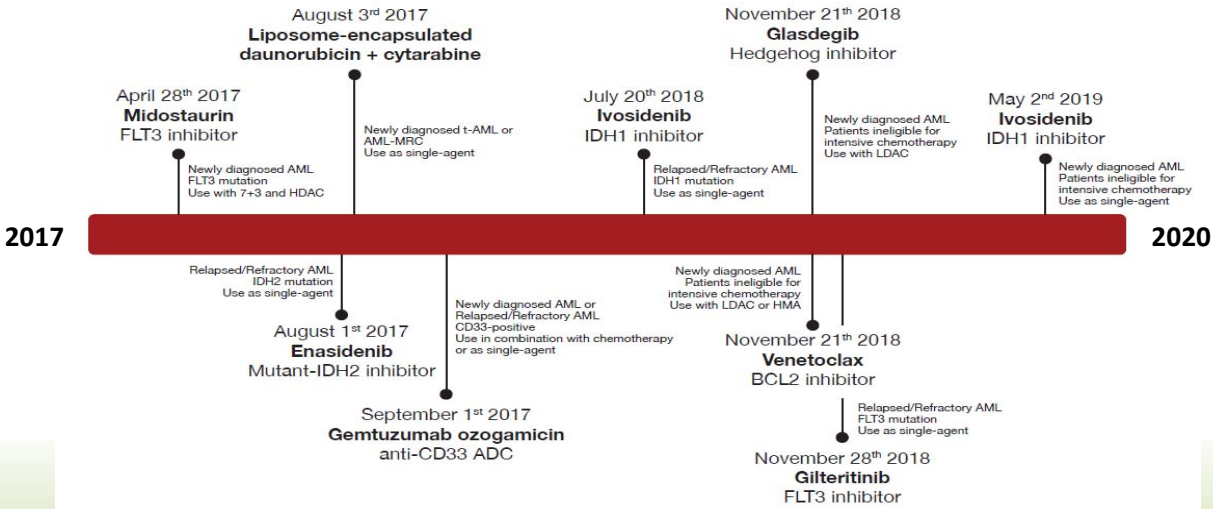
Managing AML: Staying on Track in a Rapidly Changing Treatment Landscape



So we've used that knowledge, as well as an assessment of fitness, which I'm sure we'll spend a lot of time talking about in the case presentations to really decide on our younger patients who are getting standard intensive curative therapy and then our older patients who we are trying to improve quality of life and responses, although without oftentimes a very durable response in this population. This has kind of been our ongoing algorithm that we've used for decades now.

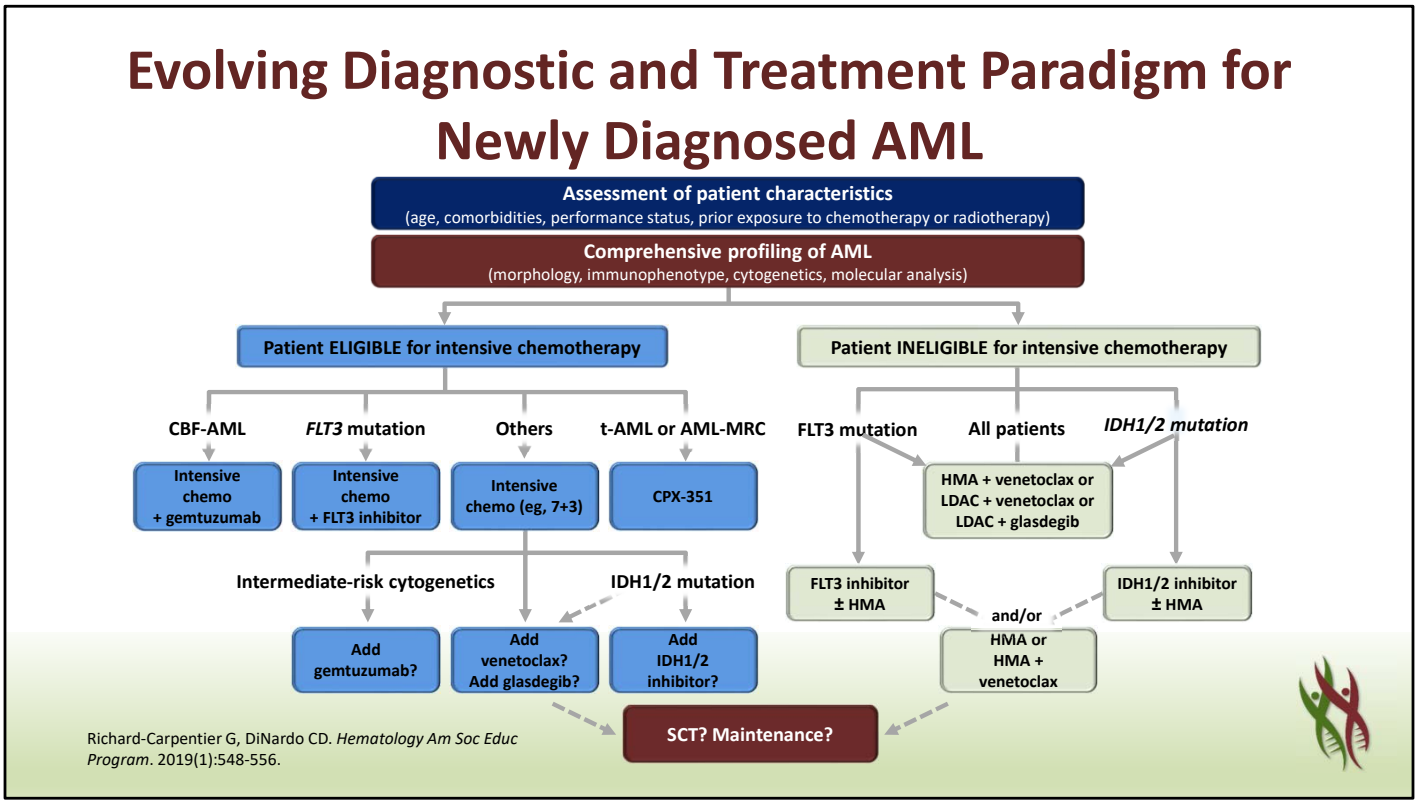
Managing AML: Staying on Track in a Rapidly Changing Treatment Landscape

The Rapidly Evolving Treatment Landscape of AML



Richard-Carpentier G, DiNardo CD. *Hematology Am Soc Educ Program*. 2019(1):548-556.

As was mentioned, there are now several new therapies for our patients. And so, we're not really deciding one of two different bins, but we're trying to now incorporate all these treatments into the best outcome for any specific patient walking in our door. We have new targeted therapies, the FLT3 inhibitors (midostaurin, gilteritinib), the IDH inhibitors, small-molecule therapies like venetoclax and glasdegib, as well as monoclonal antibody (gemtuzumab), and the liposomal-encapsulated dauno and cytarabine.

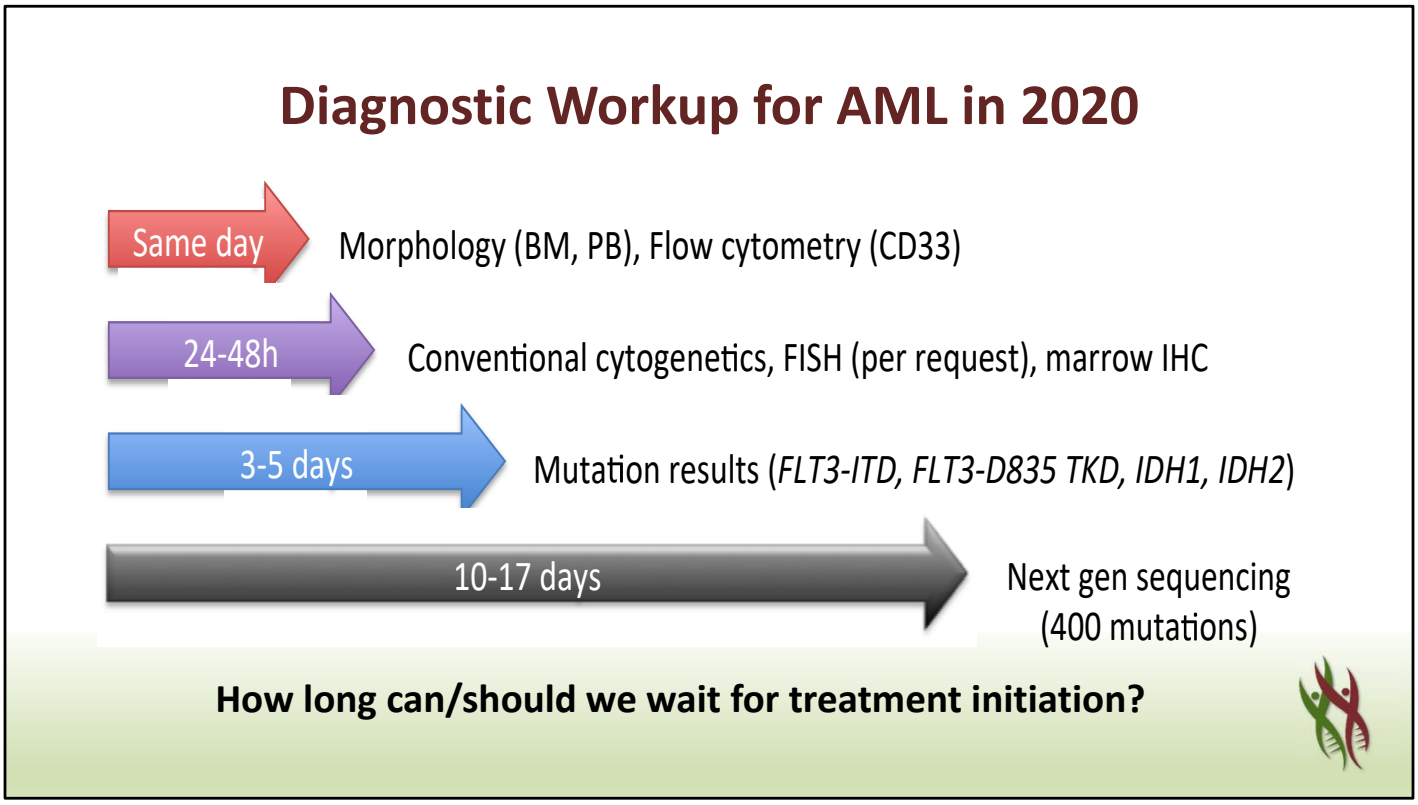


And so what I thought I would do, instead of going through all the data in each and every clinical trial, I will spend a few minutes on a few key trials that were recently presented. But here, spend a bit of time taking you through what is turning into a potential diagnostic and treatment paradigm for our newly diagnosed AML patients. In blue are patients who are eligible for intensive chemotherapy and it shows really how important genomic assessment is. So patients who are core-binding factor, in addition to intensive chemotherapy, we add gemtuzumab. In a patient with a FLT3 mutation, in addition to intensive chemotherapy, the incorporation of a FLT3 inhibitor, right now midostaurin is approved in that indication. Several other second-generation FLT3 inhibitors are under evaluation for incorporation into this area

The fourth one in blue, those with therapy-related AML or AML with MDS-related changes, that's where Vyxeos or CPX-351 is indicated specifically for that group. And then everyone else, standard intensive chemotherapy, whether that's 7+3 or a FLAG-IDA or CLIA-based approach, is currently recommended, and many different clinical trials and that second level looking at whether the incorporation of venetoclax or IDH inhibitors or gemtuzumab is going to assist in patients in that category.

On the right, are those patients ineligible for intensive chemotherapy — those that we have frequently often use azacitidine, decitabine, low-dose cytarabine alone. And here is where I'll show some data on the next slides where the hypomethylating agent with venetoclax has really shown a significant survival advantage in the VIALE-A data, that I think is now becoming, at least in the United States, a very updated standard of care regimen. But the incorporation of FLT3 inhibitors and IDH inhibitors is also appropriate and leads to many of the decisions. When you have a patient, for instance, with an IDH mutation, do you give them an IDH inhibitor or hypomethylating agents with venetoclax? Because both are approved, and both are very appropriate. And then, in patients who are eligible and appropriate to move forward with a transplant, absolutely that's the indication, but more data now coming out about the importance, finally, of maintenance therapy, CC-486. And I'll spend one slide going through that study population.

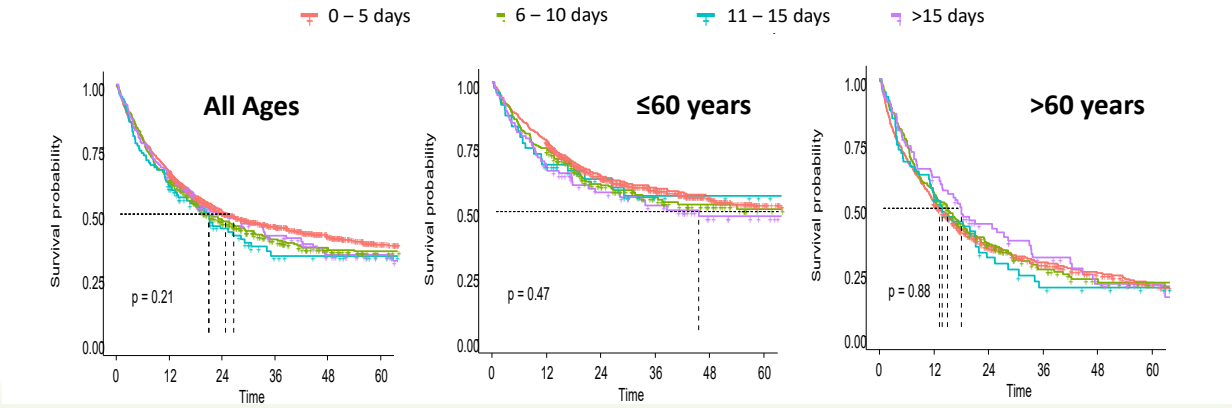
Managing AML: Staying on Track in a Rapidly Changing Treatment Landscape



We know all this information is important, but how do we actually do it? So in general, this is kind of expectations for our workup of AML in 2019-2020 where we often get the flow cytometry and morphology results within the same day. It takes about two days or so to have conventional cytogenetics rushed or FISH if we're lucky for certain of the fusion translocations, several days for mutational results, and many people will look at this slide and say, "Gosh, it takes me two weeks or three weeks to get my FLT3 or my IDH result," and so this is definitely something that's different in different institutions, in different places throughout the world. But it is possible to get mutational testing within three to five days and so I think that's definitely something we need to be pushing and working with our hematopathology colleagues to make sure this is something that is available because it is important for our patients.

Is it Safe to Wait for Genomic Information Prior to Starting Treatment?

Over 2200 patients receiving 7+3 based therapy through German SAL Registry



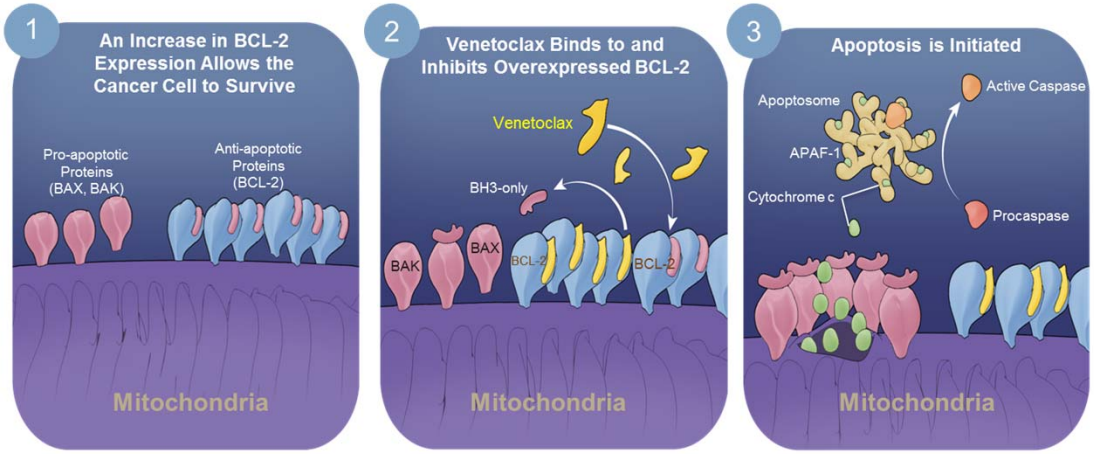
Time from diagnosis to treatment did NOT affect outcome in intensively treated patients with newly diagnosed AML (CR, early mortality, or OS)

Röllig C, et al. *Blood.* 2019;134(supplement_1):Abstract 13.

One important abstract that was presented at ASH just this past year asked that question that everyone is wondering, we know this genomic information is important, can we wait for this information now before we start our therapy? And so this is a study which looked at over 2000 patients who were receiving that standard intensive chemotherapy, 7+3, through the German Registry, and they looked at all ages and they found that the time from diagnosis to treatment didn't affect outcome in those patients who are intensively treated looking at in terms of patient response or early mortality or survival, so I think this is reassuring. But you also have to take it with the knowledge that this is a retrospective review, which is as good as the data that existed and many patients with proliferative disease probably did not wait to start treatment and treatment was started early. So it's just something to keep in mind that if you have a stable patient, absolutely, this gives us some kind of reassurance that waiting for this information is a safe thing to do.

Managing AML: Staying on Track in a Rapidly Changing Treatment Landscape

BCL2 Inhibitor Venetoclax in AML



- Cancer cells increase the expression of anti-apoptotic proteins to offset the increase in pro-apoptotic proteins, tipping the balance towards cell survival
- The large number of pro-apoptotic proteins bound and sequestered by BCL2 make cancer cells "primed" for death

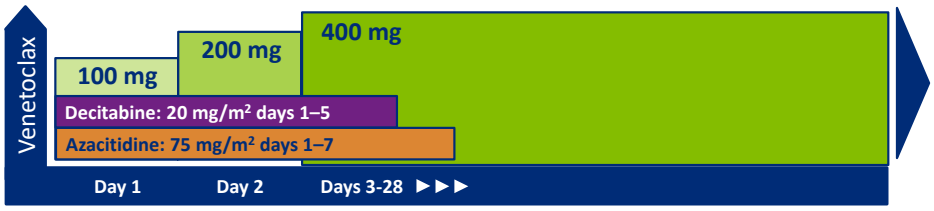
Pan R, et al. *Cancer Discov.* 2014;4(3):362-372.; Leverson JD, et al. *Sci Transl Med.* 2015;7(279):279ra40.; Souers AJ, et al. *Nat Med.* 2013;19(2):202-208.; Certo M, et al. *Cancer Cell*. 2006;9(5):351-356.

A slide or two on venetoclax and AML because I think this is one of those key new therapies that is going to be more and more relevant in AML, which is a BCL-2 inhibitor, so it allows the binding and the initiation of apoptosis through inhibition of BCL-2.

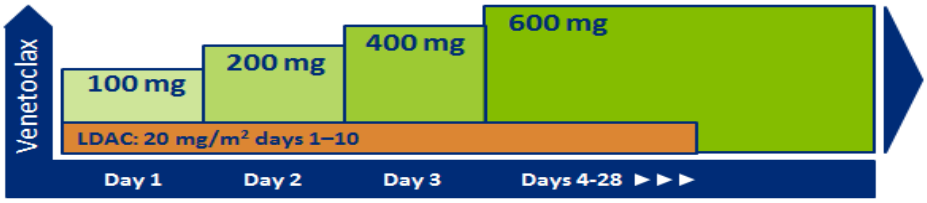
Managing AML: Staying on Track in a Rapidly Changing Treatment Landscape

Lower-Intensity Venetoclax Combinations for Newly Diagnosed "Unfit" AML

HMA + Venetoclax



LDAC + Venetoclax



Criteria:
- Newly diagnosed
- Age ≥75 years
  OR
- ECOG 2-3
- Cardiac, lung, liver or renal disease

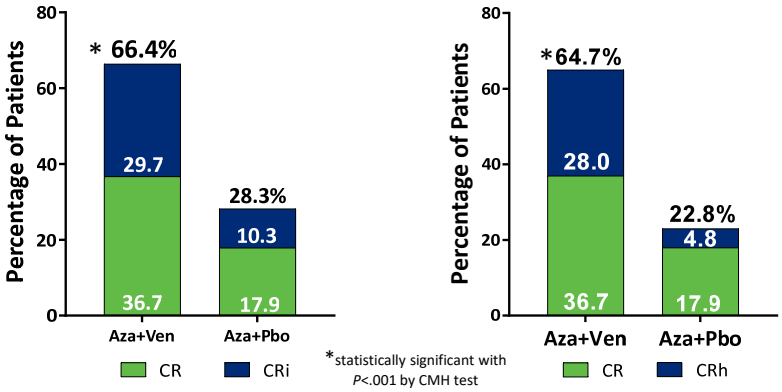
DiNardo CD, et al. *Lancet Oncol.* 2018;19(2):216-228.; Wei AH, et al. *J Clin Oncol.* 2019;37(15):1277-1284.

These are the two regimens that are approved now for our newly diagnosed older AML, just in a kind of a picture type form showing that there is a daily ramp-up of the venetoclax along with ongoing therapy of either the hypomethylating agent or the low-dose cytarabine with the population that was eligible for the trial along the right, which is an age over 75 or poor performance status or underlying comorbidities.

Managing AML: Staying on Track in a Rapidly Changing Treatment Landscape

Results of VIALE-A

- CR defined as absolute neutrophil count >10^3/µL, platelets >10^5/µL, red cell transfusion independence (TI), and bone marrow with <5% blasts
- CRi defined as all criteria for CR, except for neutropenia ≤10^3/µL *or* thrombocytopenia ≤10^5/µL
- CRh defined as all criteria for CR, except for neutropenia >0.5 x 10^3/µL, *and* platelets >0.5 x 10^5/µL



*statistically significant with *P*<.001 by CMH test

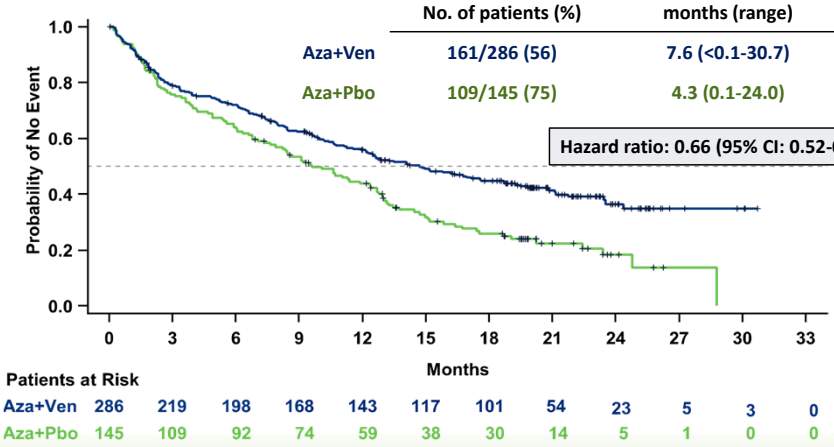
	Median Time to CR/CRi, Months (range)	*CR+CRi by Initiation of Cycle 2, n (%)	Median Time to CR/CRh Months (range)	*CR+CRh by Initiation of Cycle-2, n (%)	Median Duration of CR/CRi, Months (95% CI)	Median Duration of CR, Months (95% CI)
Aza+Ven (n=286)	1.3 (0.6-9.9)	124 (43.4)	1.0 (0.6-14.3)	114 (39.9)	17.5 (13.6-NE)	17.5 (15.3-NE)
Aza+Pbo (n=145)	2.8 (0.8-13.2)	11 (7.6)	2.6 (0.8-13.2)	8 (5.5)	13.4 (5.8-15.5)	13.3 (8.5-17.6)

DiNardo CD, et al. EHA 2020. Abstract LBA 2601.

These are two slides just going through the VIALE-A results. This is the CR/CRi and CR/CRh results with AZA and venetoclax, the large bar on the left, and the azacitidine alone on the right showing a significant improvement in the CR rate and in the composite CR/CRi and then CR/CRh rate as well as an impressive early median time to early remissions in patients with the combination.

Managing AML: Staying on Track in a Rapidly Changing Treatment Landscape

Results of VIALE-A: 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*<.001

Patients at Risk												
Aza+Ven	286	219	198	168	143	117	101	54	23	5	3	0
Aza+Pbo	145	109	92	74	59	38	30	14	5	1	0	0

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

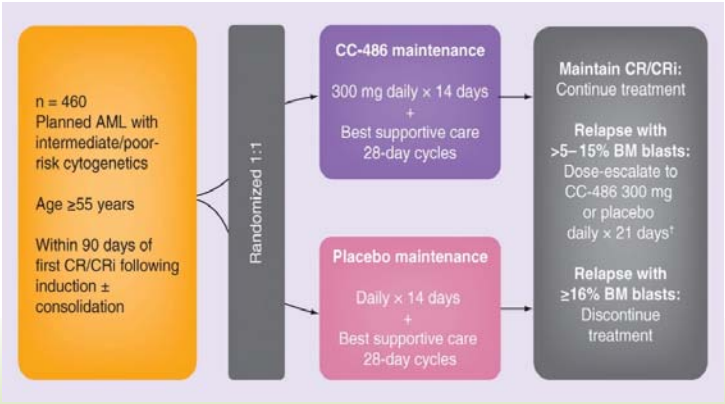
Distributions were estimated for each treatment arm using Kaplan-Meier methodology and compared using the log-rank test stratified by age (18-<75, ≥75 years) and cytogenetic risk (intermediate risk, poor risk).
The hazard ratio between treatment arms were estimated using the Cox proportional hazards model with the same stratification factors used in the log-rank test.
DiNardo CD, et al. EHA 2020. Abstract LBA 2601.

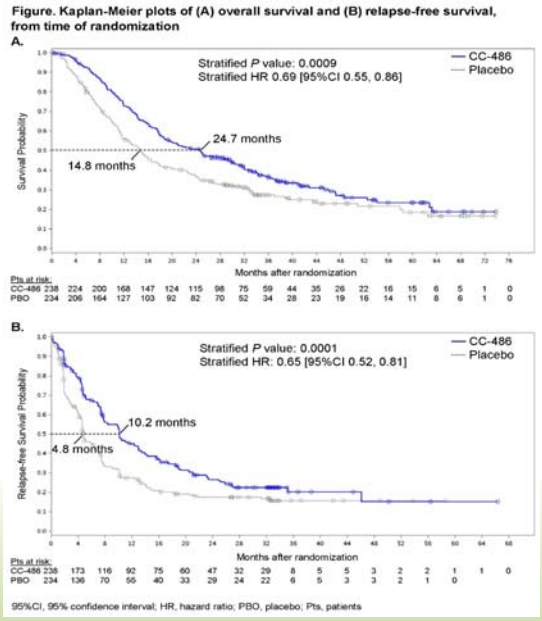
The overall survival, shown here, improving from about 10 months with azacitidine alone to 15 months with the combination, so representing one of these key trials showing a survival advantage in this older patient population.

CC-486 "Oral Azacitidine" Maintenance

QUAZAR AML-001: Randomized Placebo-Controlled Phase III Study of CC-486 (oral AZA):

Clinically meaningful improvement in both OS and RFS in older patients with AML in remission following intensive chemotherapy





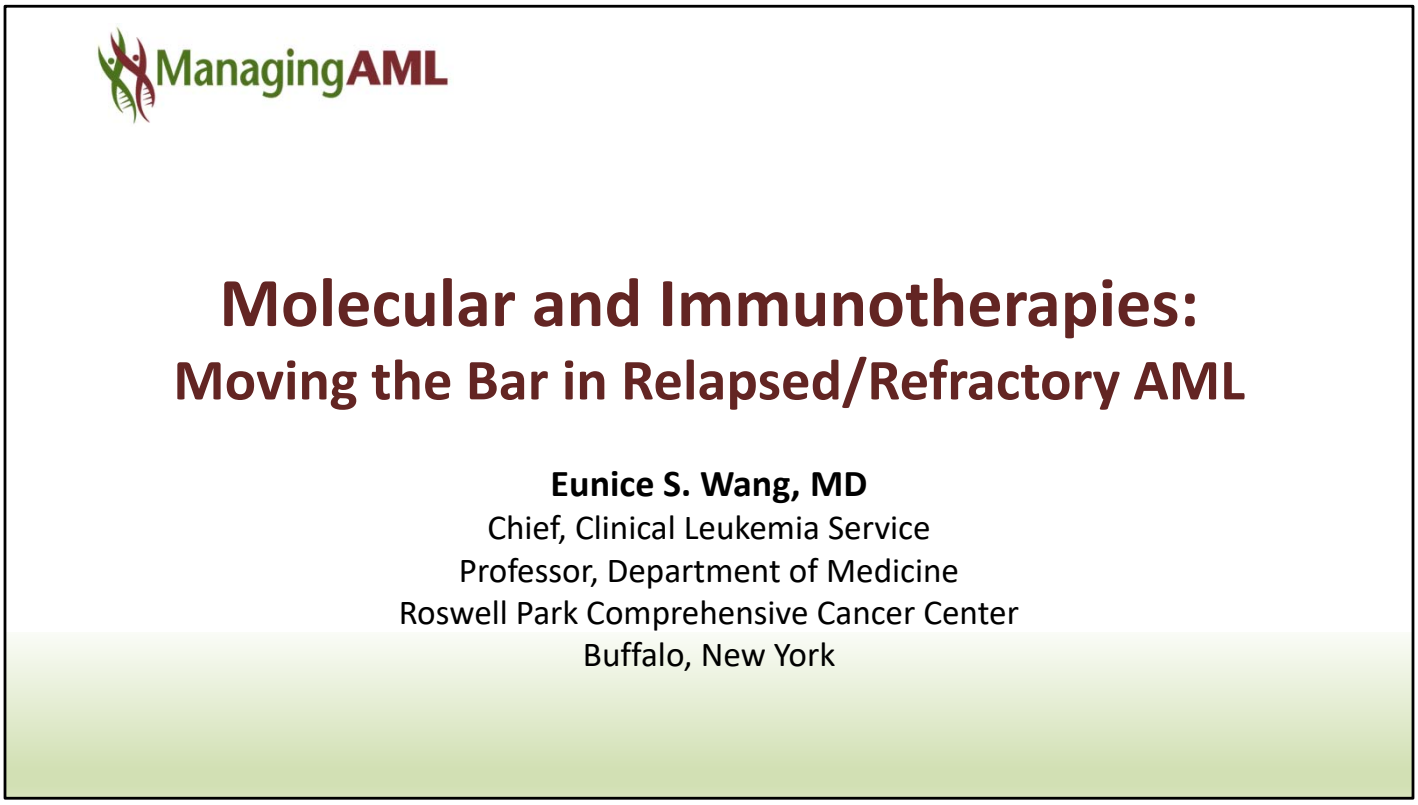
Roboz GJ, et al. *Future Oncol*. 2016;12(3):293-302.;
Wei AH, et al. *Blood*. 2019;134(Supplement_2):Abstract LBA-3.

CC-486 (oral azacitidine) was approved on September 1, 2020, by the US FDA as continued therapy for patients with AML who achieved a first CR or with CRi following intensive induction chemotherapy and who are unable to complete intensive curative therapy

The last study I want to spend just one slide going over as some baseline information because it's a newer study that has been resulted at a recent meeting is the QUAZAR AML-001 study, which is the CC-486 maintenance therapy, often called oral azacitidine. Although I think we need to be a little bit careful when we call it oral azacitidine, and I say that because the PK properties are different, so this is not something that is equivalent to the oral to the IV azacitidine dosage. It is a longer kind of more tonic, if you will, administration so that the characteristics are different. And this oral azacitidine or CC-486 maintenance was used in patients who were 55 years of age or older who had completed intensive chemotherapy, who were not going to transplant, and were enrolled within 90 days of their first CR or CRi, and they were randomized to either CC-486 or placebo. And in these slides, you can see there was essentially doubling of both the overall survival and the relapse-free survival. So expectations around this would suggest to us that this will be a new approval coming soon that will have the ability to use in patients who are in this population. Patients who were not eligible or not appropriate or have declined proceeding with the transplant after their initial remission. And so that is a whirlwind tour of the newly diagnosed landscape and two of the important recent trial studies. Thank you.

Naval Daver: Okay, well, thank you very much, Dr. DiNardo. That was really focused and

high-level overview, and I'm sure we're going to discuss a lot of the other new advances with IDH, FLT3, and how we select in the cases. And with that, I'll turn it over to Dr. Eunice Wang, my colleague from Roswell Park, to cover some of the new molecular immune therapies, especially in the relapsed setting. Eunice.

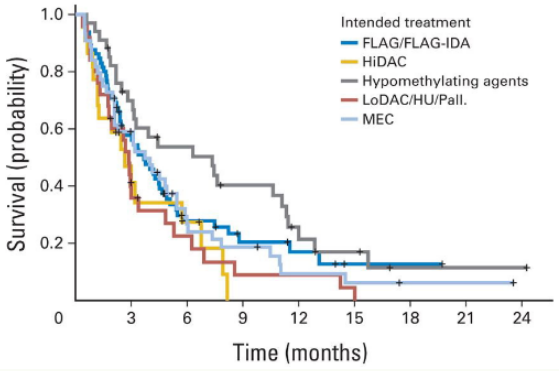


Thank you very much. I'm just in follow-up of Dr. DiNardo's point. We're moving on to treatment of patients who have relapsed and refractory AML, and here is potentially where we're seeing a huge number of novel agents and approaches which promises to lead to additional FDA approvals of drugs for this patient population over the next 6 to 12 months.

Managing AML: Staying on Track in a Rapidly Changing Treatment Landscape

Emerging Treatment Options: Relapsed/Refractory AML

Chemotherapy[1]



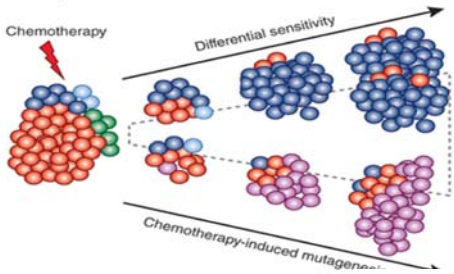
Targeted Therapies

Drug Name	AML Subset	ORR	Median OS
Enasidenib[2]	*IDH2* mutant	40.3%	9.3 mos
Ivosidenib[3]	*IDH1* mutant	41.6%	8.8 mos
GO[4]	CD33+ AML	26%	11.6 mos
Gilteritinib[5]	*FLT3* mutant	34%	9.3 mos

1. Roboz GJ, et al *J Clin Oncol.* 2014;32(18)1919-1926. 2. Stein EM, et al. *Blood.* 2017;130(6):722-731. 3. DiNardo CD. *N Engl J Med.* 2019;379(12):1186.
4. Taskin A-L, et al. *Leukemia*. 2007;21(1):66-71. 5. Perl AE, et al. *N Engl J Med.* 2019;381(18):1728-1740.

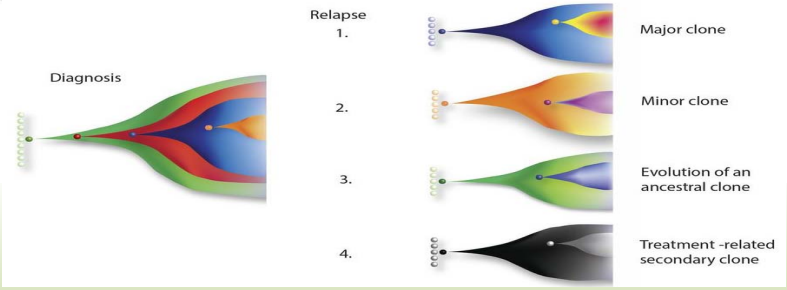
What is the outcomes of patients with relapsed and refractory AML? Unfortunately, we have made some progress with the advent of targeted therapies. As we see here, IDH1, IDH2, and FLT3 inhibitors have shown response rates of anywhere from 30% to 40% in the relapsed/refractory population. However, you can see that the median overall survival for patients with relapsed and refractory AML still remains fairly dismal. If you look on the left-hand side, you can see the outcomes of various both high-intensive and low-intensive chemotherapy regimens treatment for patients with refractory/relapsed disease. And as you can see, overall, none of these therapies in the chemotherapy arena alone is significantly superior to another. The targeted therapies we see on the right have made onroads. But again, you can see that overall the median survival of these patients is anywhere from a few months to maybe a little bit more than a year. So this is the landscape in which we are looking at in terms of improvements for the care of our patients.

Clonal Evolution and Therapy Resistance at Relapse



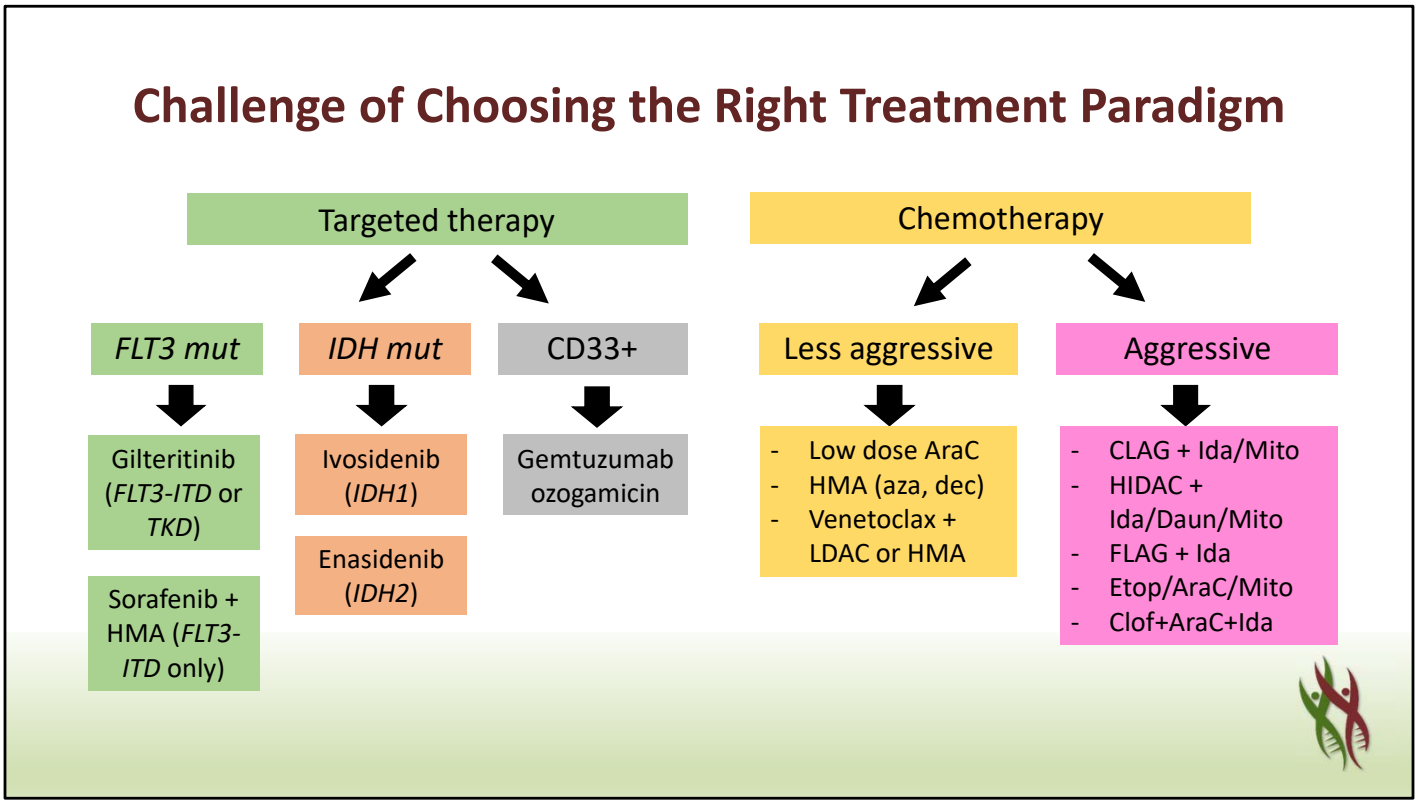
Leukemia is not a static condition!

Repeat genomic analysis at relapse is necessary



Kleppe M, Levine RL. *Nat Med.* 2014;20(4):342-344.; Grimwade D, et al. *Blood.* 2016;127(1):29-41.

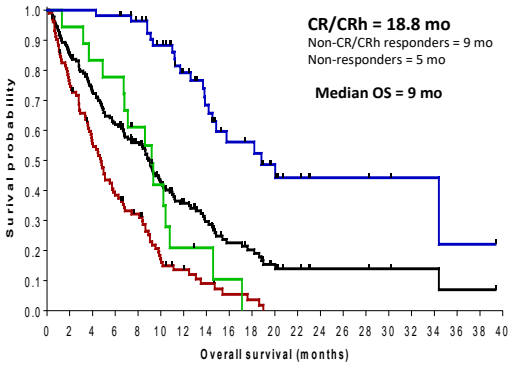
As mentioned previously by both of my prior colleagues, molecular analyses, particularly mutational profiling, remains a key aspect of treatment of AML at any stage. It's important to recognize that leukemia is not a static disease and although you may have performed extensive next-generation sequencing and mutation analysis at the time of diagnosis, at the time of recurrence of AML, there can be significant alterations in the clonal architecture which constitutes the disease in the relapsed/refractory setting. As you can see here, the clones at diagnosis may have differential sensitivities to the treatment modalities that are implemented in the frontline setting, leading to significant outgrowth of clones that may have dominant or absent mutations compared to what they see at diagnosis.



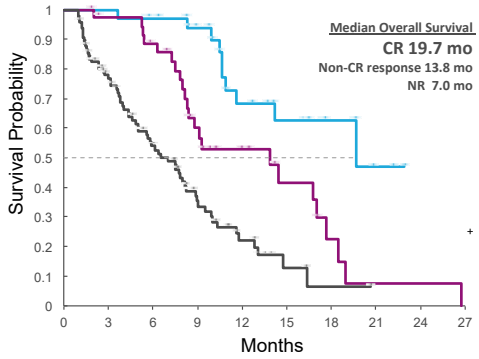
Why is it important to perform this mutation analysis again at the time of disease recurrence? This is essential to do so because it will allow you to optimize your treatment selection. As you can see here, in the relapsed/refractory setting, there are targeted agents available which can be equally or more effective for the treatment of relapsed and refractory AML than even high-dose intensive chemotherapy. The presence of a FLT3 mutation or IDH mutation or expression of specific surface antigens may allow for the clinician or the practitioner to identify treatment options which could be of use. It could be a potential more benefit to the patient than exposing them to additional inpatient salvage chemotherapy. In addition, when we compare the outcomes of chemotherapy, as mentioned previously, in many cases, there's no necessarily superiority to using an intensive induction or reinduction strategy over less aggressive regimens. So this must also be kept in mind given the circumstances and the age and the quality of life issues that we're facing in a patient with recurrent disease.

IDH1/2 Inhibitors for IDH1/2-mutant RR-AML

Ivosidenib (IDH1): RR-AML



Enasidenib (IDH2): RR-AML



Mechanisms of resistance: Mutant isoform switch (m*IDH1* <-> m*IDH2*), *IDH2* mutations (trans or cis), presence or development of co-mutations (ie, *RAS, FLT3*)

DiNardo CD, et al. *N Engl J Med.* 2018;378(25):2386.; Stein EM, et al. *Blood*. 2017;130(6):722-731.

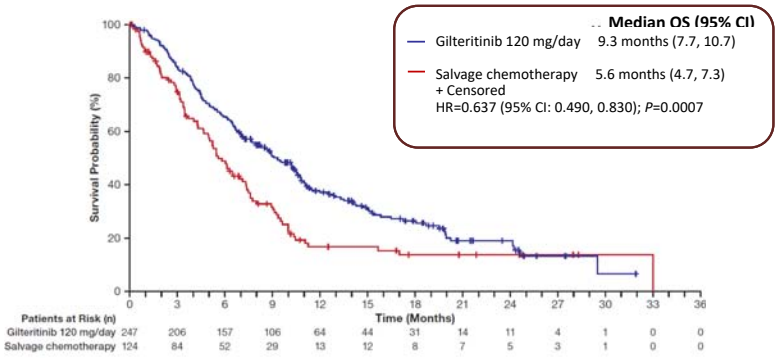
Just to review briefly, some of the molecularly targeted therapies, IDH1 inhibitors, ivosidenib and enasidenib, are small molecule oral inhibitors of these mutant enzymes which are present in anywhere from 5% to 15% of patients both at diagnosis and subsequently at relapse. You can see here that utilization of one or the other of these small-molecule targeted inhibitors can lead to overall response rates of up to 40% with complete remission rates of 20%. Patients who achieve a CR or a CR with incomplete hematologic recovery can have median overall survival lasting up to one to two years, the median of 18 to 19 months, as you can see here. However, over time, no one is effectively cured of their disease and there have been many mechanisms of resistance which have been identified, primarily the presence of or development or selection for additional AML clones possessing activating signaling mutations such as RAS or FLT3, and we'll just touch upon that a little bit later.

Managing AML: Staying on Track in a Rapidly Changing Treatment Landscape

FLT3 Inhibitors for FLT3-mutant RR-AML

	Other Kinases	IC_{50} (Plasma)
Lestaurtinib	JAK2, TrkA	700 nM
Midostaurin	cKIT, PKC, PDGFR, VEGFR	1000 nM
Sorafenib	cKIT, PDGFR, RAF, VEGFR	265 nM
Quizartinib	cKIT, PDGFR, RET	18 nM
Crenolanib	PDGFR	48 nM
Gilteritinib	AXL	43 nM

Gilteritinib vs salvage chemo in *FLT^{mut}* RR-AML

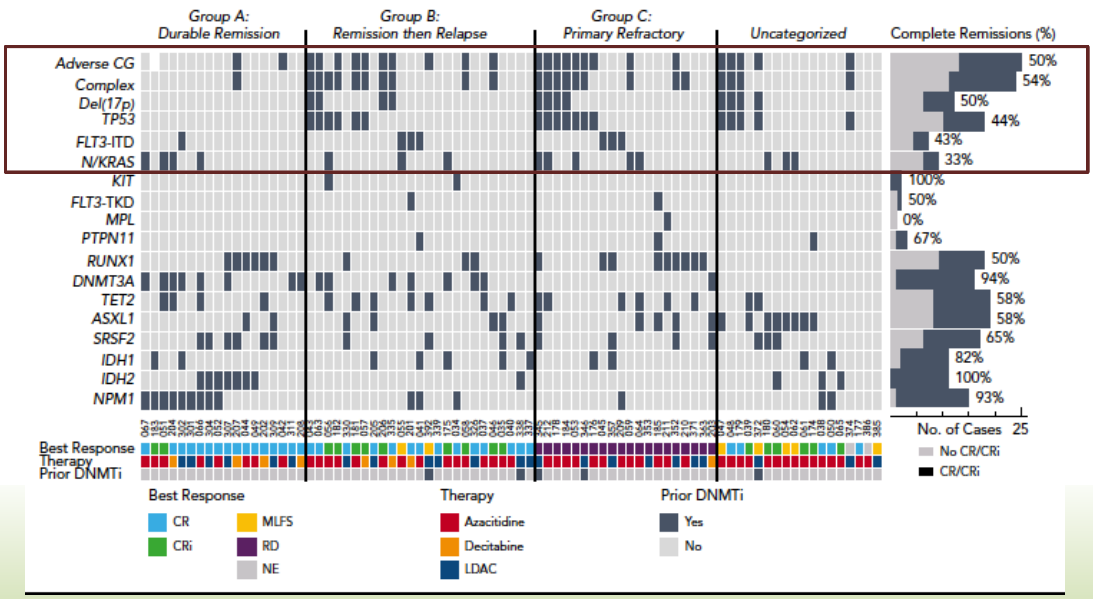


Pratz KW, et al. *Blood.* 2010;115(7):1425-1432.; Zarrinkar PP, et al. *Blood.* 2009;114(14):2984-2992.; Galanis A, et al. *Blood.* 2014;123(1):94-100.; Levis MJ, et al. *J Clin Oncol.* 2015;33(15_suppl):Abstract 7003.; Perl AE, et al. *N Engl J Med.* 2019;381(18):1728-1740.

FLT3 inhibitors are highly effective in the relapsed/refractory setting, particularly the use of second-generation inhibitors such as gilteritinib, crenolanib, and quizartinib. Gilteritinib shown here on the right-hand side has been shown in a randomized phase III trial, the ADMIRAL trial, to yield superior overall survival and complete remission rates as compared to both high-intensity as well as low-intensity therapy for first-line salvage therapy of patients with FLT3 mutant disease either characterized by FLT3-ITD and/or FLT3-TKD mutations. Quizartinib similarly was shown in a phase III trial to yield less impressive overall survival benefit but still statistically significant improvement as opposed to either high- or low-dose chemotherapy in the same setting. And trials with quizartinib, gilteritinib, and crenolanib are proceeding in combination with various agents now in the frontline setting.

Managing AML: Staying on Track in a Rapidly Changing Treatment Landscape

Characteristics of AML Failing Venetoclax-based Therapy



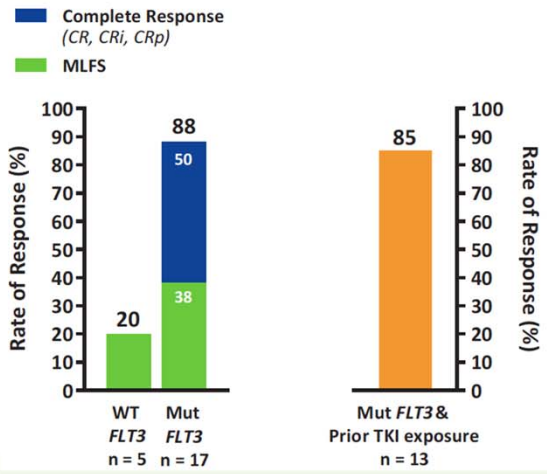
DiNardo CD, et al. *Blood*. 2020;135(11):791-803.

What about patients failing venetoclax therapy? As Courtney DiNardo mentioned, the venetoclax-based therapy is quickly becoming the new standard of care, at least for treatment of our older patients. And we can see here that despite the improvement in overall survival, patients are still relapsing and recurring after venetoclax-based therapy. Repeat genomic analysis at the time of disease recurrence, again, identifies the presence of FLT3 and RAS mutations as predictors of poor response and recurrent disease. We also see, again, the same poor characteristics that are associated with poor overall outcome in the frontline setting, specifically the presence of TP53 or adverse cytogenetics and complex cytogenetics being issues with upfront venetoclax therapy.

Gilteritinib and Venetoclax: Clinical Data

Characteristic	Wild-type *FLT3* n = 5	Mutant *FLT3-ITD*[a] n = 16	Mutant *FLT3-TKD* n = 2
Age, median (range) years	63 (48–81)	54 (23–73)	61 (52–70)
Female, n (%)	1 (20)	12 (75)	2 (100)
Cytogenetic risk, n (%)			
Intermediate	2 (40)	11 (69)	2 (100)
Poor	3 (60)	5 (31)	0
AML type, n (%)			
De novo	2 (40)	13 (81)	2 (100)
Secondary	3 (60)	3 (19)	0
ECOG performance status, n (%)			
0	1 (20)	2 (12)	1 (50)
1	4 (80)	11 (69)	1 (50)
2	0	3 (19)	0
No. of prior lines of therapy, median (range)	2 (2–4)	2 (1–5)	3 (3–3)
Prior *FLT3* TKI exposure, n (%)			
Any	0	12 (75)[†]	1 (50)
Midostaurin	0	7 (44)	1 (50)
Sorafenib	0	6 (38)	1 (50)
Both	0	2 (13)	1 (50)
Prior stem cell transplant, n (%)	1 (20)	6 (38)	2 (100)

AML, acute myeloid leukemia; ECOG, Eastern Cooperative Oncology Group; TKI, tyrosine kinase inhibitor.
[a]One patient had both ITD and TKD *FLT3* mutations, they were counted in the ITD group.
[†]One patient was included for analysis of safety but did not have available disease assessment; this patient was excluded from efficacy calculations (denominator).



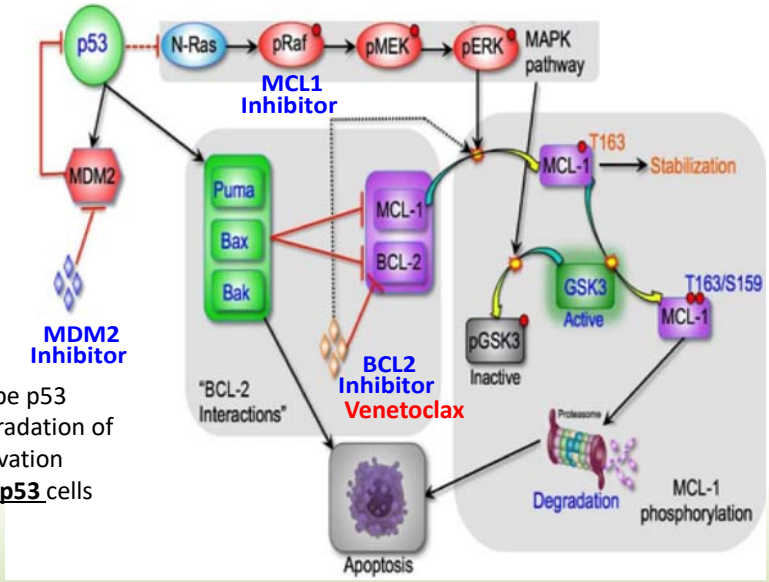
Perl A, et al. *Blood.* 2019;134(Supplement_1):Abstract 3910.

For this reason there has been a great deal of interest in combining our targeted therapies if patients are developing or are at prone to develop FLT3 mutation as a result of prolonged venetoclax administration potential, the combination of a FLT3 inhibitor and a BCL-2 inhibitor can be a useful approach, and here is some early data from a phase Ib study showing that the application of BCL-2 inhibition in combination with gilteritinib can lead to very, very high response rates, particularly in patients that have had prior FLT3 exposure.

Novel Inhibitors of the Apoptosis Pathway

APR-246
Small molecule activator of **mutant p53**

Idasanutlin
Reactivates wildtype p53 and promotes degradation of MCL-1 via p53 activation
Active in **wildtype p53** cells



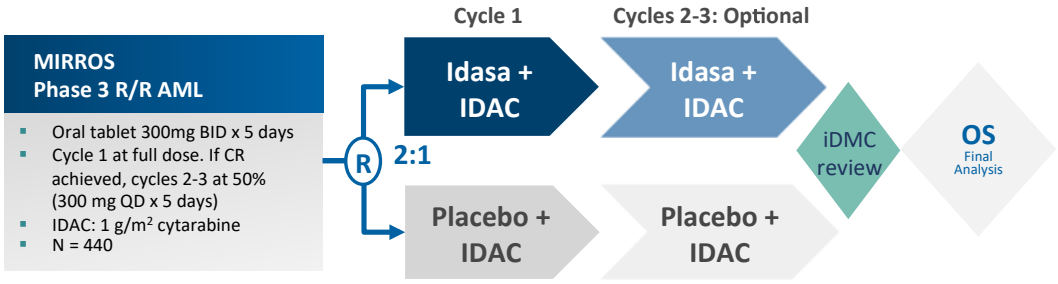
AMG167/AMG197
Inhibitor of MCL-1

Alvocidib
Inhibitor of CDK9 leading to MCL-1 inhibition

In terms of inhibitors of other pathways, there have been a great deal of interest in focusing studies and developing agents that are targeting other arms of the apoptosis pathway to particularly overcome resistance mechanisms which develop in the context of venetoclax pretreatment. You can see here that venetoclax is a key player in the apoptotic pathway in preventing cell death in patients who are treated with chemotherapy and other agents. You can see here, as Dr. Daver mentioned, APR-246 is a small-molecule activator of a mutant p53 pathway which has been very promising and showed high levels of responses for the treatment of patients with TP53 mutant disease. For patients who have p53 wild-type disease at the time of relapse, idasanutlin is an MDM2 inhibitor which reactivates wild-type p53 and promotes degradation of apoptotic pathways and has shown promising activity for the treatment of p53 wild-type.

Managing AML: Staying on Track in a Rapidly Changing Treatment Landscape

MIRROS: Phase 3 Trial of Idasa + IDAC in RR-AML

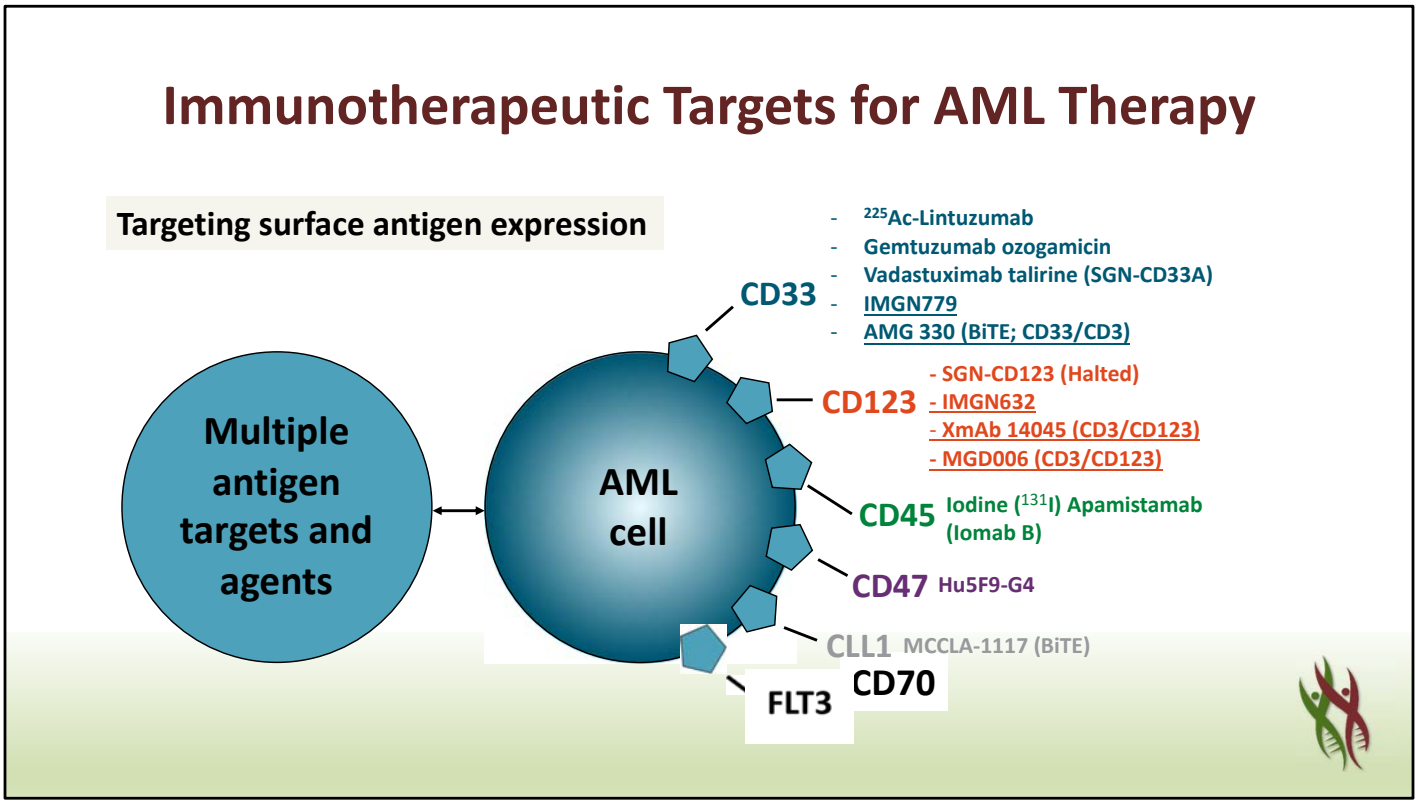


Study-specific key inclusion criteria

- Documented/confirmed 1st/2nd refractory/relapsed AML using WHO classification, except APL (AML patients with CR1 duration of >1 year AND age <60 years are excluded)
- No more than two prior induction regimens (excl. prior HSCT) and one must have included cytarabine with an anthracycline (or anthracenedione)
- ECOG performance status of 0 to 1 and patient should be a potential candidate for allogeneic HSCT

Montesinos P, et al. *Future Oncol.* 2020;16(13):807-815.; ClinicalTrials.gov Website. NCT02545283.

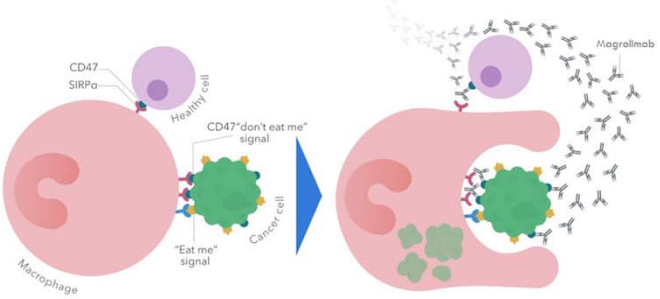
This is the schema of the MIRROS phase III randomized control study examining whether this MDM2 inhibitor in combination with intermediate-dose cytarabine can improve response rates and overall survival as compared to cytarabine alone in fit patients who are eligible for a higher intensity regimen at the time of disease recurrence.



I'd like to just close in the last couple of minutes with the mention of immunotherapeutics. Immunotherapy has been highly successful for treatment of several solid tumors but has yet to make a significant impact, although that is probably going to change for the treatment of patients with AML. Numerous surface antigens expressed in AML blasts have been identified as potential targets of immunotherapeutic approaches.

Magrolimab (anti-CD47 Ab): Macrophages "Don't Eat Me"

CD47 = macrophage immune checkpoint



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%) 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).

Magrolimab is a humanized IgG4 anti-CD47 monoclonal antibody

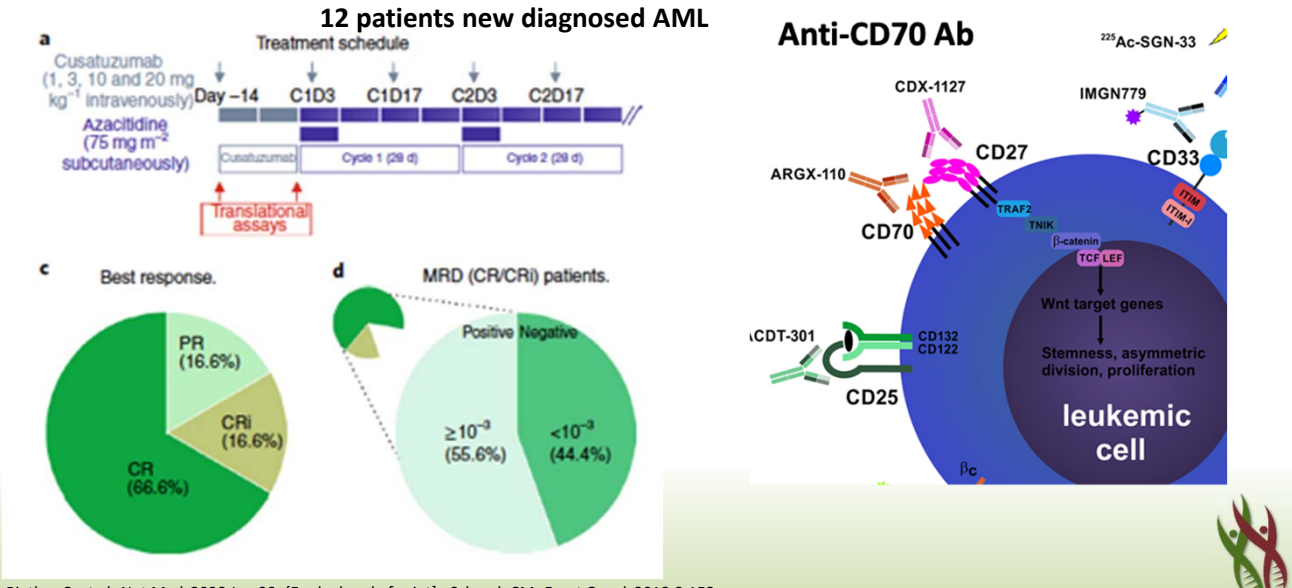
- Induces macrophage phagocytosis
- Azacitidine induces CD47 expression on AML blasts
- High response rates in p53 mutant AML

Sallman D, et al. *J Clin Oncol.* 2020;38(suppl):Abstract 7507.

In addition to the CD33, which is obviously an active target given the use of gemtuzumab, there are two new target antigens for which antibodies have been developed showing enormous amounts of progress and promise for treatment of relapsed and refractory AML. This is the first agent, magrolimab, which is an anti-CD47 antibody. CD47 is expressed by cancer cells as a means of evading macrophage activated phagocytosis. Inhibition of the CD47 pathway with this antibody has, in combination with azacitidine, resulted in remarkable responses, particularly in patients with poor prognosis AML which otherwise does not respond to conventional chemotherapy. As you can see here, in a small and gradually enlarging phase Ib study in the frontline setting, patients with AML have almost a two-third response to the combination of magrolimab and azacitidine. And in particular, patients with p53 mutant disease tend to demonstrate very high responses and durability of response with magrolimab therapy.

Managing AML: Staying on Track in a Rapidly Changing Treatment Landscape

Cusatuzumab (anti-CD70 Ab) Eliminates AML Stem Cells



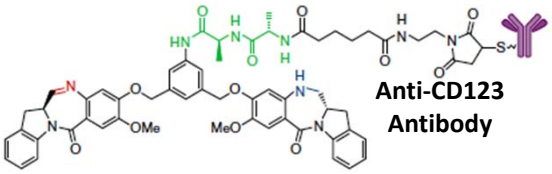
Riether C, et al. *Nat Med.* 2020 Jun 29. {Epub ahead of print].; Schurch CM. *Front Oncol.* 2018;8:152.

Another antibody, anti-CD70 antibody, cusatuzumab, has been proposed as a way to target pathways important for the survival and proliferation of leukemic stem cells. An early phase Ib study of 12 patients with newly diagnosed AML demonstrated again very high response rates of over two-thirds of patients having achieved a complete remission with the utilization of this antibody, again in combination with azacitidine.

IMGN632: Anti-CD123 ADC for CD123+ Malignancies

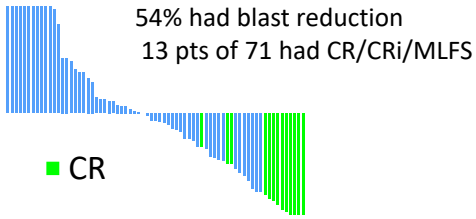
A

IMGN632
(Monoimine IGN ADC, DNA alkylator)

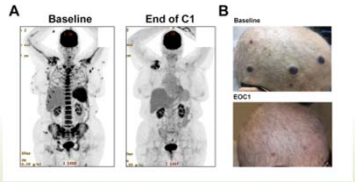


- Anti-hCD123 Ab (IL-3Rα)
- Protease cleavable linker
- Indolino-benzodiazepine
- DNA alkylating agent

AML Efficacy: BM evaluable patients (n=71)



2/3 BPDCN patients had CR/CRi

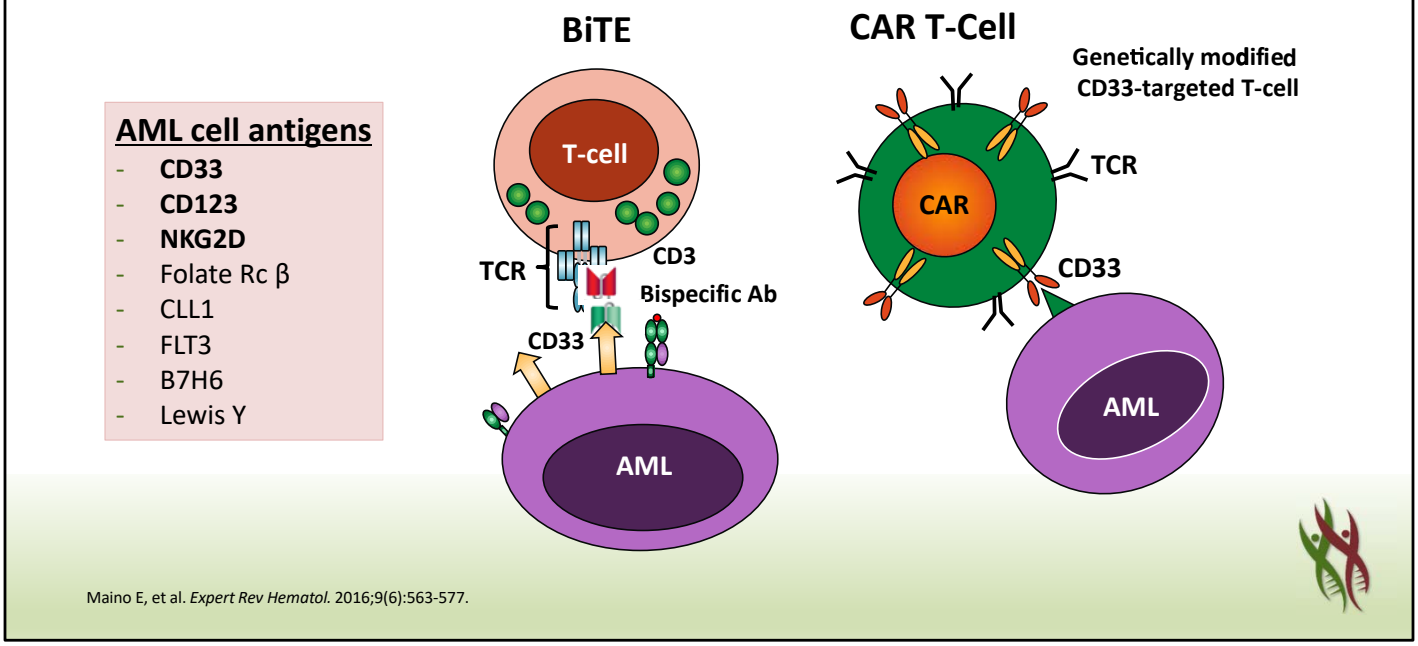


Kovtun Y, et al. *Blood Adv.* 2018;2(8):848-858.; Daver N, et al. *Blood.* 2019;134(Supplement_1):Abstract 830.

We also have seen the development of antibody-drug conjugates targeting the CD33 as well as CD123. Here is an example of the CD123 antibody-drug conjugate, which is being developed not only for relapsed/refractory AML but also other malignancies.

Managing AML: Staying on Track in a Rapidly Changing Treatment Landscape

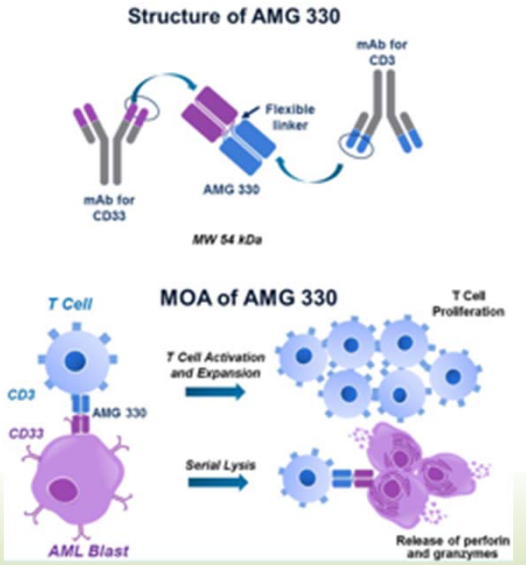
T-cell Directed Therapy for AML



Maino E, et al. *Expert Rev Hematol.* 2016;9(6):563-577.

To conclude, there also has been a great deal of activity in the T-cell-directed therapy space for relapsed/refractory AML, bispecific antibodies, which lead to activation of the immune system, as well as dual targeting of AML cells, as well as CAR T-cell therapies have been developed.

AMG 330: CD33/CD3 Bispecific Antibody

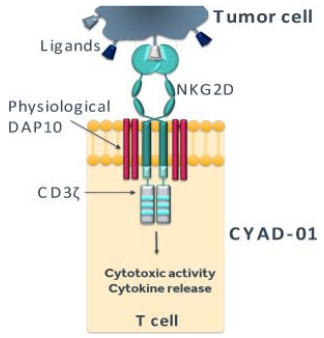


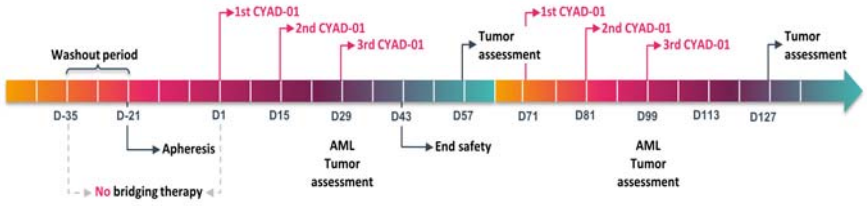
- Seven patients achieved CR/CRi at min 120mcg/day
- 21% response rate in cohorts 15-17
- Cytokine release= 40 (67%), ≥Gr 3 9 (15%)
- Lower disease burden associated with response

Ravandi F, et al. *J Clin Oncol.* 2020;14(suppl):Abstract 7508.

AMG 330 is an example of the CD33/CD3-bispecific antibody, which has led at higher doses to 20% to 25% response rates in patients with multiply relapsed AML.

Phase 1 Trial of NKG2D-Based CAR T Cell Therapy





NKG2D = activating Rc on NK cells and expressed on AML cells

CYAD-01: Full-length NKG2D + CD3ζ chain CART construct

8 r/r AML pts evaluable per protocol (at least one CYAD-01 cycle)

- **1 CR with partial hematologic recovery (CR_h)** in DL-1
  - Pt was bridged to allo-HSCT on day +97. CR_{MRD-} for > 14 months+
- **2 CRs with incomplete blood count recovery (CR_i)** (1 in DL-1 and 1 pt in DL-3)
- **2 Stable Diseases with relevant BM blast decrease** (DL-2)
  - 1 **SD - 3 months** with BM blasts decrease from 24% to 10% and hematologic improvement
  - 1 **SD - 6 months** with BM blasts decrease from 9.8% to 5.5%
- **1 Stable Disease (2m+)** with no BM blast decrease (DL-3)
- **2 PDs** (>20% baseline peripheral blasts)

Sallman DA, et al. *Blood*. 2018;132(Supplement 1):Abstract 902.

And CAR T-cell therapy is really in its infancy and we're seeing development of both autologous as well as allogeneic CAR T-cell approaches. So with that, I'll turn the program back to Dr. Daver to discuss further cases. Thank you very much.

Naval Daver: All right, great. Thank you very much, Dr. Wang and Dr. DiNardo.

The Art and Science of Treatment Selection

The AML Case Study Gallery: 3 Case Presentations

We have three cases and I'll go through the case and then I'll open up and then we can just have an open discussion, bring up any points you think are important or any thoughts that you have and, of course, we'll try to make these three cases a little bit different so we can cover different aspects of the disease.

Case Presentation #1

- Matt is a 55-year-old man diagnosed with FLT3-ITD mutant AML (allelic ratio 0.45, normal karyotype)
- He completes induction with 7+3 plus midostaurin followed by HIDAC plus midostaurin consolidation and 12 months of midostaurin maintenance. After much discussion he decides he does not want an ASCT due to the risk of GVHD and QOL
- Unfortunately six months later, he is found to have new onset pancytopenia. The bone marrow shows relapsed AML (15% myeloblasts) by marrow morphology
- His performance status is 1. He is asymptomatic. His brother is a full HLA match
- What is your next course of action?

Okay, so the first one is a 55-year-old man diagnosed with FLT3-ITD AML, allelic ratio 0.45, diploid cytogenetics, received standard inductions, 7+3 with the addition of the FLT3-TKI (midostaurin) and then gets consolidation HiDAC (midostaurin) and then gets maintenance with midostaurin. Obviously, this is a patient we would be considering for transplant. He has a high allelic ratio of FLT3-ITD mutation. However, as we all know in our practice, even at large academic centers, there's a large number of patients we cannot get to transplant. Either the patients, after listening to all the side effects, don't want to do it or for some reason there's logistical barriers, finances, distance from center, and I'd say we're still seeing about 30% to 40% of our patients that we want to transplant eventually do not make it to transplant. And so this patient said he did not want transplant, so we said, okay, we can complete the maintenance, we're going to monitor you and hope for the best. Unfortunately, as we often see in these high-risk mutational subgroups, he did relapse six months later, new-onset pancytopenia. Bone marrow was done, confirmed relapsed AML and his performance status is pretty good at this time and he's here in clinic now. He does have a matched sibling donor available, so the question is going to be, what is the next course of action for this patient? And this case was actually provided to me by Dr. Wang, so I'm going to start the discussion with Dr. Wang and see what her thoughts were. And I guess the first question would be, when this patient is here in front of you now, is there additional information you would need and what information that would be and how would you use that to decide the treatment?

Eunice Wang: So, thank you. I appreciate the opportunity to provide some feedback on

this. So the first piece of information, which should always be the first thing that one asks in this setting after determining the patient is relapsed, is to ask yourself what is the genomics of the relapse? In particular, this individual has had, at this point, probably at least 18 months or more of FLT3 inhibitor therapy with midostaurin. Now, midostaurin is a pretty broad-spectrum tyrosine kinase inhibitor that also inhibits FLT3 wild-type and mutant. But the question is with that treatment selection and with prolonged midostaurin use, is the disease that is recurring at this time still FLT3 mutant or is it actually, as we're seeing very commonly in these pretreated individuals, actually recurrence with FLT3 wild-type disease? So what I would like to do is to repeat the genomic analyses to determine if the patient has FLT3, and also to see whether there are other mutations and/or any surface antigens expressed by flow cytometric, which could be targets for approaches that could have greater efficacy than just broad-spectrum chemotherapy in this setting.

Naval Daver: Maybe I'll ask Dr. DiNardo. So for this patient, what would be the molecular mutation profiling you would request and how quickly do you get that? I think that's a big question in the community. Is there a way to stratify and get the mutations you want earlier? How can that be done, and which are the key ones in let's say both frontline as well as then in relapse that you really want before you embark on any kind of treatment?

Courtney DiNardo: I mean, in this case, the number one mutation that you want is the FLT3-ITD. You want to see if that ITD is still present at relapse because there is a small but real, maybe 20% to 30%, population of patients that are not going to have that FLT3-ITD at relapse when they've had this degree of FLT3 inhibitor therapy with the midostaurin. There are other genomic mutations that are really helpful like NPM1 commonly co-occurs with FLT3-ITD and lends itself to a more favorable prognosis, whether that's more or less relevant at this point in the relapsed setting. You could make a case where I think the knowledge of whether there's an IDH1 or an IDH2 mutation that's co-occurring in this patient is useful information and that happens about a third of the time also there will be a FLT3-ITD and an IDH mutation.

In terms of how long it takes to get that information, here we're fortunate that we can rush certain mutations within about three to five days, so FLT3-ITD being one of them. Doing single genes take about that five-week timepoint and most places, when they send out, will have decided to kind of batch multiple different genes together into some sort of MDS/AML panel which has anywhere from 20 to 100 different genes, all of which are kind of relevant in a population of MDS/AML. And so that the challenge is when you're at a center that does that send out tests, that can often take two to three weeks or so. So you really need to have an ability, in this case to have a FLT3-ITD done quickly. And the other thing I didn't say that I think is important is the FLT3-D835 mutation is also really important, because when we're talking about different FLT3 inhibitors, if this patient does have a recurrent disease with an ITD, there are available FLT3 inhibitors like gilteritinib that will hit both the ITD and the D835 and other ones in development like quizartinib, which is approved kind of outside of the US that doesn't hit the D835 well. So that knowledge is also important in choosing the FLT3 strategy.

Naval Daver: I think you make a very important point. I mean the RATIFY study, I think they did a subset of about 48 patients who relapsed and looked at the molecular sequencing. And they showed a very high number, higher than most others have shown, almost 40% had no detectable FLT3. I mean we've done and others have done analyses and published somewhere in the range of 20% to 25% will have no FLT3. But the point is, it's a good number so you cannot reach for gilteritinib right away, I would say, if that was the choice, because you may not be treating FLT3. So, I think that's clinically very important. But let's say the next thing, let's say he does come back and he is FLT3-ITD still at a high allelic ratio 0.5 or so in that range without a D835, so what would you select for this patient? He's about a year plus from the induction midostaurin and you have the option, of course, of gilteritinib, but potentially maybe an option of re-induction. So what would you think for this patient, Eunice?

Eunice Wang: I think you can argue that to use potentially a repeat high-dose or intermediate-dose cytarabine-based salvage regimen, given the fact that he's a young gentleman with excellent performance status and is asymptomatic, the feeling being that you could quickly get him into a complete remission and then potentially transition him to a potentially curative allogeneic stem cell transplantation. However, there are certain percentages of individuals, even those with younger individuals, don't tolerate repeat induction chemotherapy well, and you would run the risk of when you do that, particularly if you include an anthracycline, that you could have morbidities that occur with, for example, cardiac toxicity, decreased EF, performance status issues that might actually delay his time to go to a transplant. So, I think ideally, we would want to potentially maybe offer a salvage regiment potentially with additional FLT3 inhibitor, if that is something that you think is going to be poorly tolerated. I think a gilteritinib-based regimen, potentially gilteritinib alone or possibly gilteritinib with a low-dose azacitidine. We certainly would want to get him into a CR to allow him to proceed to subsequent transplants. So, I think that a high-dose salvage regimen would be reasonable, but I think given the ADMIRAL results, potentially gilteritinib offers a less toxic way to get somebody to that transplant without the risk of additional comorbidities. I'd be interested to see what Dr. DiNardo thinks.

Courtney DiNardo: I think oftentimes when patients relapse with a FLT3-ITD they'll be very proliferative. And so, I think one of the really interesting things about the ADMIRAL study is that FLAG-IDA and intensive chemotherapy salvages were one of the options that the patient could be randomized to. And what we see is that gilteritinib does better than the standard induction therapies that don't include a FLT3 inhibitor, of course. And so just a simple outpatient daily pill will do better than a re-induction intensive strategy that doesn't incorporate a FLT3 inhibitor, but I think that there is definitely room for improvement on gilteritinib alone in the salvage setting because we know that remissions don't last that long, that resistance pathways are common through other mechanisms, RAS pathway, BCR-ABL at relapse, which is kind of something that we hadn't seen before. And so I know Dr. Daver has started putting together some of our experience of gilteritinib with cytarabine, with azacitidine, and I think there will be more and more data coming out of relapsed strategies incorporating gilteritinib. You mentioned the venetoclax-gilteritinib data as well, kind of

putting combinations together to improve even further on the ability to get patients back into a second remission and a deeper remission to get them to a transplant.

Naval Daver: I think that's really important. I think gilteritinib absolutely is a major breakthrough. But when you look at the long-term follow-up, even though the response rates were 54% marrow remission CRC as compared to 26% and the CRh rates were doubled, the median survival is about 9.3 versus 5.6 months and at one- and-a half to two years, of course, we're still getting to 15% to 20%. So, I think all of us are very excited and working on these trials combining it, the VEN/gilteritinib will be updated. That is looking very promising but even moving beyond that, are there potentials to combine AZA/VEN which, of course, now frontline is being used heavily with potentially drugs like gilteritinib, quizartinib. I think it's going to be very exciting and in the future, I feel that, and we're already seeing this in some of our centers, some of these patients who five years ago we were in a very, very bad situation. Now, we're able to get many of these into deep remissions and to transplant with combinations as a second-generation FLT3 inhibitor. I agree, I would probably go for a gilteritinib plus approach, whether it's with AZA or AZA/VEN. Of course, there's myelosuppression, you have to balance that and use growth factors as needed, but I think this patient can have a potentially long-term remission and I guess the other point would be is would we also get the patient to do post-transplant maintenance, right? If he got to maintenance then using a FLT3 inhibitor, maybe sorafenib or gilteritinib if it gets approved. So let's move on to the other case. This is one that probably will have more discussion on it.

Case Presentation #2

- 62-year-old male
- CC: Overall weakness, fatigue, dyspnea on exertion
- Timeline of events prior to presentation
  - Presented to PCP with the above symptoms for routine checkup. CBC showed significant cytopenias – WBC: 15.7 Hgb: 9.5 Platelets: 35
  - Underwent bone marrow biopsy at local hospital. Diagnosed with AML with MDS-related changes. No prior history. Local doctor planned 7+3 treatment
- Arrived to MDACC 1 day later, to ER with the following vitals/labs:
  - BP: 135/85, HR: 110, RR: 19, Temp: 98.9
  - WBC: 52.1K, Hgb: 9.1, PLT: 27K, Blasts: 35%, Neutrophils: 3%, Lymphocytes: 28%, no coagulopathy
- Admitted; started on hydroxyurea 3 g QD PO, IV fluid 50 mL/hr, allopurinol and monitor TLS labs
  - PICC line placed
  - CXR done, ECHO ordered
- Bone marrow biopsy was performed: cytogenetics, FISH for 15;17, 8;21, inv16, and molecular testing were rushed

This is a 62-year-old male with overall weakness, fatigue, dyspnea on exertion who presents for routine checkup, was found to have a white count of 15, hemoglobin is low, platelets are low, and is diagnosed with AML with MDS-related changes, and the local doctor was initially thinking 7+3 induction, was referred to us and comes with, as you can see, many tachycardia but otherwise those are relatively stable. White count is going up now, a little bit higher 50,000 and continues to have cytopenia so, of course, the first steps in the management of this patient are admitting him, giving him hydrea, IV fluids, allopurinol, PICC line, chest x-ray, echocardiogram. This is what we do on a day-to-day basis. I was actually rounding today morning, we had two new AMLs. This is the usual thing, you want everything quickly. Bone marrow same day, get the ECHO, get the x-ray, get the PICC in, and hopefully then we can proceed. Important is, of course, to get the cytogenetic. You never want to miss core-binding factor APL. You know, APL is, I hear from community doctors a lot of time about how they think this is APL or not. I will tell you with our experience we see thousands of patients, I cannot tell you for sure if a patient has APL or not. Yes, there may be more suggestive, less suggestive, but we're always surprised. So I say when in doubt, start them on something like ATRA and then check quickly for the POD test or the FISH.

Case Presentation

- Past medical history
  - Aortic aneurysm
  - CAD: 1 sent 3 years ago
  - HTN
- Past surgical history
  - Appendectomy
  - Diverticulectomy
  - Back surgery
- Social history
  - Anesthesiologist
  - Married with 2 children
  - Denies tobacco or illicit substance use
  - Occasional ETOH
- Family history
  - No history of leukemia or lymphoma

So these were done and this patient, I think it's important to look at the background history here because we're kind of getting in that 60 plus age, so the patient has a history of coronary artery disease, hypertension. As you can see, he has good family support. He's an anesthesiologist physician himself, so we're going to expect hopefully good compliance and follow up and no significant family history.

Bone Marrow Differential at Time of Diagnosis

- BM method: SMEAR
- Adequacy: Adequate quality
- Site: Right posterior iliac crest

Blasts	**71% H (0-5)**
Progranulocytes	0% L (2-8)
Myelocytes	0% L (5-20)
Metamyelocytes	0% L (13-32)
Granulocytes	2% L (7-30)
Eosinophils	0% (0-4)
Lymphocytes	11% L (3-17)
Plasma cells	1% (0-2)
Monocytes	1% (0-5)
Reticulum cells	0% (0-2)
Pronormoblasts	0% L (1-8)
Normoblasts	14% H (7-32)
M:E ratio	0.0 L (3-4)

- Granulocytes:
  - Decreased in number
- Erythrocytes:
  - Increased dyspoietic forms
- Megakaryocytes:
  - Present, hypolobulated
- Lymphocytes:
  - Unremarkable
- Blasts:
  - Mostly blasts

- Bone marrow diagnosis
  - ACUTE MYELOID LEUKEMIA WITH MINIMAL DIFFERENTIATION (M1)
  - Normocellular bone marrow (40%–50%)

Karyotype: XY

This is kind of the scenario, overall reasonably healthy, good performance status, and then you get the bone marrow let's say in 48 hours, you see that he has acute myeloid leukemia, 70% blast, and diploid cytogenetics.

Molecular Mutational Panel

Molecular Diagnostics						
ABL1	EGFR	GATA2	IKZF2	MDM2	NOTCH1	RUNX1
ASXL1	EZH2	HRAS	JAK2	MLL	NPM1	TET2
BRAF	FLT3	IDH1	KIT	MPL	NRAS	TP53
DNMT3A	GATA1	IDH2	KRAS	MYD88	PTPN11	WT1

So, I guess at this point, and then you have molecular data as well, we usually get this in about four days, at least the top-level key molecular mutational data. And as you can see, this person has certain mutations and the one of interest, of course, is going to be the IDH1 mutation potentially in this 62-year-old patient. So, I guess the question would be now you have this 62-year-old patient with IDH1 mutation along with some other mutations, some cardiovascular history three years ago, and what would be your treatment approach for this patient? So, Dr. DiNardo, you want to discuss it

Courtney DiNardo: This is a perfect case of someone who is almost in that borderline gray population. So, in general, I think most people would agree that those over the age of about 70, we think about lower-intensity therapies, and those younger than 60, just somewhat arbitrarily chosen, we're really focusing on intensive chemotherapy unless there's something really significant about their medical history that makes us concerned about using cytarabine and anthracycline. But in that 60 to 70 range, I think we're starting to see that because we have reasonable outcomes with our new lower-intensity strategies, venetoclax combinations, we're seeing remission rates kind of as high as you would with higher-intensity strategies and the ability to transition a patient to transplant with both modalities of therapy. I think that the conversation is changing. That being said, this is a 62-year-old gentleman who is healthy as best we can see. I mean I see that hypertension and some underlying heart disease, the echocardiogram, any underlying EF, which I didn't see is going to be really important to decide am I okay with an anthracycline? But barring any kind of structural or concerning heart disease, I think in a 62-year-old with proliferative disease, a white count that's gone from 15 to 52 within this amount of time in this first

case without any particularly high-risk cytogenetic or genomic features, this is someone that I would still prioritize an intensive chemotherapy regimen for.

Naval Daver: Eunice, what are your thoughts?

Eunice Wang: I would agree. I mean, I think this gentleman, the data suggests that in somebody that's fit enough for chemotherapy, in this individual I don't see anything specifically that would preclude. He is a diploid, he is an intermediate karyotype. IDH1 can predict, particularly in combination with NPM1 for good results with the cytarabine-based approach. So I agree, I think I would agree with an aggressive induction cytarabine/daunorubicin approach. I guess my question is, and, again, I would throw it back to my colleagues, is this somebody that because they have an intermediate karyotype, would you add gemtuzumab to the 7+3 to try to prolong event-free survival, and is this a patient with this profile that you would be thinking about maybe not doing transplant in? So just I throw that back, would this patient be a candidate for transplant, would you want to transplant, and if you are not going to transplant, would you add something to 7+3 to improve their outcomes to preclude them having to go to transplant or having relapse?

Naval Daver: Yes, I think those are great points. Gemtuzumab, we obviously don't talk about too much outside of the core-binding factor setting where, of course, its efficacy is outstanding and most groups and we, for sure, are always adding in. But there is data, as you said, even in the intermediate or diploid group showing 7% or so survival benefit, of course based on a metanalysis that was done across 3000 patients, which is quite similar actually to what midostaurin shows, if you kind of look at it that way

Eunice Wang: Yes, about a 7% four-year benefit.

Naval Daver: So, yes, I think it's a very reasonable option if we cannot add a targeted therapy to consider addition of gemtuzumab to this patient. I think the transplant question is, that's kind of part two of the case and we'll get to that because I think it is tough in these patients. I mean, historically, we've pushed and still, at least in our experience, we're getting about 50% to 60% of them to transplant. Even the biggest transplant centers usually you cannot get more than that. There's a lot of hurdles that come in. So then what do you do, for example, if either you decide or the patient decides we cannot go for transplant?

So with that, let me move on to the second part for this patient, and as Dr. Wang was saying, the considerations would be one is to add gemtuzumab but also there is some early data that Eytan Stein and Courtney have presented looking at adding IDH inhibitors to induction, which at least in the one, one-and-a-half-year follow-up looked promising. I guess not a standard yet, but it will be interesting to see the kind of follow up on that.

Treatment

- Enrolled on frontline protocol CLIA (cladribine, idarubicin, cytarabine)
  - Cladribine 5 mg/m^2 IV × 5 days on days 1–5
  - Idarubicin 10 mg/m^2 × 3 days on days 1–3
  - Cytarabine 2 g/m^2 × 5 days on days 1–5
- Inclusion criteria met at study entrance
  - Frontline AML treatment; fit for intensive induction, plan for ASCT once in remission
- Patient placed in protected environment room for age >50 with newly diagnosed AML receiving cytotoxic chemotherapy, close monitoring of TLS labs initial 48–72 hours
- Did well for first 9 days of therapy. On day 10 developed neutropenic fever, pneumonia, with rapid progression to sepsis
- Respiratory insufficiency, hypotension; moved to ICU. Cultures grew gram-negative rods
- Eventually confirmed to be pseudomonas

This patient was treated at our center and we have a frontline trial which is adding to the 3+7 a purine analog. You know, there's a lot of debate about this, some of the European data seems to show improvement, the Polish data specifically and the MRC for fludarabine, and I think to some extent this debate will get less and less as we start incorporating targeted therapies, venetoclax, FLT3 frontline. But he was treated in our center and this was the trial ongoing at that time, so he got this induction frontline patient, and the plan was to eventually consider to get him to transplant. He was admitted for the induction, as we do for most of our older patients, monitored closely, and he did have a pretty rough induction course; he had major sepsis, pseudomonas, went to the ICU. We're seeing this less and less with close monitoring and prophylactic antibiotics, but we still see it I would say in about 5% to 8% of our patients, they are having major infection or sepsis.

Cycle 1 Interval History

- In ICU, placed on vasopressors, broad-spectrum antibiotics, PICC removed
- Worsening pneumonia and respiratory failure → intubated on vent
- Bronchoscopy showed necrotizing pneumonia: growing pseudomonas
- Treated aggressively with IV antibiotics, ICU, and ID teams; slow improvement after long ICU stay of about 3 weeks. Moved to floor
- C1D21: Bone marrow aspiration = 17% blasts
- C1D28: Bone marrow aspiration = 4% blasts, MRD by FCM 0.8% (IDH1, DNMT3A persisted in bone marrow)

He was in the ICU for a while, eventually got better and then the bone marrow that was done on day 28 confirmed that he is in remission with low-level flow cytometry still positive and still detectable mutations on the NGS panel. I guess here now the question is, and I kind of made this a complicated case but it's a real case, is that the person had a very difficult induction. So going to Dr. Wang's point of are you going to go for transplant in this person because he's now showing you maybe transplant is going to be tough, so I guess the question here at this point would be, what would be the next steps for this person? Would you continue with consolidation? Would you move into lower-intensity therapy now, HMA or HMA/venetoclax, or would you move into some form of maintenance? And if you did do consolidation, what would you consider for this patient? Courtney, you want to start?

Courtney DiNardo: Yes, so this is kind of one of those great questions where there's all sorts of different answers, and I can't actually remember what we ended up doing, so I'm excited to remind myself. I think in this patient, we can't go to transplant right away. He's been so beat up with his first month of therapy that is maybe a potential future goal, but that can't be the strategy right now. And for the same reason, I think additional cycles of high-dose therapy consolidation is probably not in his best interest. He's in a remission, we want to keep him in a remission, but we don't want to beat him up further with consolidation or a transplant. So I think we can probably all agree with that. And then the question is, well, what do we do for his maintenance therapy? He has an IDH1 mutation, can we put him on ivosidenib alone? If he's particularly kind of myelosuppressed or having issues with ongoing infections, pseudomonal abscesses, that's definitely something we could consider. We could consider azacitidine and venetoclax maintenance in someone

with an IDH1 mutation who's going to be very sensitive to venetoclax-based therapies. He would also be a perfect candidate for CC-486. He would be exactly that patient population for someone who's an older adult who got intensive chemotherapy that for whatever reason, can't get more consolidation or a transplant. So I think any of those options or a clinical trial of any of those or combinations would be a very important strategy to try to keep him in remission that will kind of improve with time.

Naval Daver: Yes, and Eunice, I think the little bit of the struggle that's going to happen to communities when, let's say you want to go to CC-4, I think he's a great candidate for CC-486, I think transplant is going to be tough even a few months from now. When would you go for it? Would we push for a few more consolidations? Would you think we should we go for it earlier? What's going to be your approach or what's been your approach with the CC-486 in the trials?

Eunice Wang: I agree with Courtney. I think that this individual is not really a candidate for high-dose consolidation and although it is appealing to think about using HMA/venetoclax for this patient given the IDH mutation, we really don't have any data. The data we have with HMA/venetoclax is in the upfront setting and that particular combination, although highly effective for IDH mutant, is associated with a significant amount of myelosuppression, prolonged with risk of mortality due to sepsis and pneumonia. In somebody that had this particular history, I would be hesitant to have additional myelosuppression for a prolonged period of time. So my feeling would be to do the CC-486 when and if it is available. It's an oral pill, the patient could be outpatient. He would not have as severe the myelosuppression that you would see with the venetoclax/HMA therapy and I would see how the patient does. I would argue that, and this is as you mentioned a physician, that if the patient is able to improve, participate in rehabilitation, physical therapy, and has one would say if I didn't say what his donor was, but if he had a fully matched donor, a sibling donor, I think that the goal that I would have would be to try to, over the next three or six months, see whether he could regain enough performance status to be eligible for a transplant, because although CC-486 did double the overall and event-free survival for patients in the QUAZAR study, the curves all trend downwards. So what you saw was you saw delaying of the time or prolonging of the time until they had disease recurrence and had events, but the curve certainly did not plateau and we certainly did not cure anybody, and I think for somebody that's in this age group if they're looking for a curative approach, I would still be looking to transition them to that transplant for the best long-term outcome.

Cycle 2-4

- Achieved CR with full recovery of counts by day 36
- Continued on protocol with consolidations × 4
- Was counseled and recommended to go for ASCT, but after extensive discussions with leukemia and SCT teams, patient and his spouse decided they did not want to do SCT
- Was consented and enrolled on maintenance trial of CC-486 for patients 50–70 years of age who are not SCT candidates or who refuse SCT
- Completed 24 months maintenance on CC-486, bone marrow at the end of maintenance showed maintained remission
- Continue surveillance with clinic visit Q6 months

Naval Daver: So let's go, because I think this is where you're going to see their different approaches and different things that are happening, even among the physicians, it's not going to be a consensus. He kind of did recover, we gave him very reduced consolidation, we cut the doses by 50% and, of course, transplant, there was discussion, he got a little bit better, we were on the fence, he was on the fence about whether to do it or not and eventually, after a lot of discussion, as we see among our patients, a lot of times we send them to transplant, they come back three weeks later and say, "Yes, I talked to them. I'm not going to do it. That's it." I mean, this is not uncommon. So, we then did put him on CC-486 maintenance after he had gotten the consolidation and then he's continued it now for a while and is ongoing, so he's one of the patients on the trials. I think it's going to be very interesting to see the data of the CC-486 once it is published, the details, because I guess one of the big questions I have is, what is the impact of more consolidation versus less consolidation? You know what I'm saying? Because what we don't want is, if let's say you don't get consolidation and the data isn't as robust, we don't want in the community the rapid shift, do I give induction and then CC-486? On the other hand, if it is, then maybe it's reasonable, but I personally have not seen that detailed data analysis, but we will have to see. And then, of course, he has IDH, so there are going to be all these other questions coming up in the future for trials, hopefully, as to can you combine CC-486 with the targeted therapies and how would that do in the future?

Eunice Wang: I have a question with that case. What happened with his MRD status? When he got the consolidations, if he turned MRD negative by the time you put him on CC-486, he was technically MRD negative. Because I think that's also, when you're talking about the efficacy of the

number of consolidations, if he didn't get consolidation and he was still MRD positive when you put him on CC-486, would that have made a difference in terms of his long-term outcome? But you have been giving him for consolidations made him negative and that in conjunction with the CC-486 maybe partially demonstrating his sensitivity to that therapy.

Naval Daver: Exactly. They did have this subset of patients who converted, who had like a low-level blast which was 5% to 15%, and I forget, I think it's like 24% or so converted to negative, so there may be some activity. But the bulk of the study was, as far as we know, in people who are in remission, MRD, we don't know, but I agree, I think I would be more comfortable which is what we did to get him MRD negative and then use this as a true maintenance as opposed to in the active disease setting, I don't know if I would be as comfortable doing it so yes, absolutely.

Case Presentation #3

- **74-year-old M presenting with recurrent bronchitis**
  - Former smoker, osteoarthritis, controlled type 2 diabetes and HTN, PS 2
  - WBC 2.7K, Hgb 7.3 g/dL, Plts 39K. No circulating blasts
  - ECOG
  - Interested in leukemia directed therapies
- **Diagnosis:**
  - BM with 45% CD33+ blasts with MDS-related changes
  - Karyotype with del(5q) and del(7q)
  - RUNX1 and SRSF2 mutations

Okay, so we have just a few minutes left, but let's go to what I think is now becoming a very interesting and exciting area of therapy compared to a few years ago where these were really, really bad or difficult patients for us to deal with. So, a 74-year-old comes in with some bronchitis symptoms. He's got some prior history, including smoking, osteoarthritis, has diabetes type 2 controlled, and a PS of borderline let's say close to 2, pancytopenia, no circulating blasts, and he is interested in therapies that can improve his survival to the best possibility. And bone marrow is done 45% blasts. He's got some MDS related changes, deletion 5 and 7, and RUNX1, SRSF2 mutations. The question would be, what are the treatment options for this patient? Eunice, what do you think? How would you approach this patient, 74-year-old, with these comorbidities in PS in today's practice?

Eunice Wang: I think that looking at this individual, the things that stand out to me really is his age, 74-years-old, but not just that but also his comorbidities. He's a smoker, his performance status isn't great. He has diabetes. He has some hypertension, controlled diabetes and hypertension. He has a performance status of 2. All of that makes me think that he is, and that in conjunction with his age of 74-years-old, that he's not really a candidate for an aggressive approach, a cytarabine or anthracycline-based approach. It really may be more appropriate for a lower intensive therapy. We can see here that he doesn't have evidence of a FLT3 or an IDH1/IDH2 mutation, so he does have mutations, but nothing that's specifically targetable at this point. I think the spliceosome inhibitors are still in very early development and he does have looks like a prior MDS by biology and by histology, as well as by karyotype with a deletion 5q and deletion 7q abnormalities. So, he is not going to be a candidate that is going to respond very well to either an intensive

approach or cytarabine-based approach. I would fall back upon the new standard of care, which really would be venetoclax plus an HMA, and he has not had prior HMA therapy since he's never been diagnosed, so I think he would be a candidate for that. And that would be associated with the best overall survival benefit for him at this point.

Naval Daver: And Courtney, any thoughts or differences and specific to this patient, you've led to the VIALE-A studies deletion 5, 7, what's been the response rate and outcome for these patients?

Courtney DiNardo: This case is another one that you could choose anything in terms of treatment. He's CD33 positive, so you could use a gemtuzumab-based therapy, although with the deletion 5q and 7q adverse-risk cytogenetics I think that is really kind of on the lower list of kind of my potential treatment options. Vyxeos (CPX-351) is an approved therapy for someone with MDS-related changes and this kind of MDS phenotype. But I agree with Dr. Wang, I think a 74-year-old gentleman this degree of underlying medical problems, even if they are controlled, is someone that I would opt for the azacitidine and venetoclax. And so what we know is across the board regardless of the genomics, response rates are high. With complex cytogenetics or deletion 7, the response rate is more along the lines of 60% as opposed to the 75% or more with IDH mutations or NPM1 mutations. I think it's actually like maybe 55% to 60% for this specific patient characteristic. The majority will still respond, but as you were alluding to, the responses are not as durable in patients with these high-risk genomic features. I saw the question on the next slide, is this someone that you could consider a transplant for? I think in this gentleman who has this degree of comorbidities, a lifelong smoker, bronchitis, he's 74, it's going to be a challenge for sure. But I think it is something to definitely think about in our patients getting venetoclax combinations or lower-intensity combinations, if we are able to obtain a nice remission in people with high-risk genomic features. Their duration of remission is relatively short, so a transplant should be something I think we now need to start thinking more and more about.

Naval Daver: I think that's a great point. I mean there's a lot of, and I think this is where "label" and the real-world practice is going to differentiate, myeloma guys have been dealing with this for years and years whenever you talk to them, and I think in leukemia, if you look at "label," you could say HMA/VEN, you could follow the CPX. He's a year younger, but he's close to the low-dose Ara-C glasdegib kind of label induction, so I think that's where the selection are, and I totally agree, I would probably not give this person any form of intensive whether it's traditional 3+7 or CPX based. I think he's going to have a high induction mortality. So HMA/VEN and then if he looks better, improves his performance status, once he's in remission three to four months down the line, we may see that, then one could consider the transplant. Also this is going to be a nice area to see where some of the novel therapies that are emerging, APR, CD47, cusatuzumab, maybe added to the backbone of HMA/VEN. We're all excited could potentially be breakthroughs, and I think would be a very nice person to go on frontline clinical trials down the line.

So with that, we are at the top of the hour and I would like to thank Dr. DiNardo and Dr.

Wang very, very much for the discussion. We didn't have much time, but I think we have actually kept the schedule which I almost never do, so that's really good, I'm happy. And I would like to thank you all for joining and listening. And I think, the key take-home message is, as we discussed, we still are very, very much interested in clinical trials, the breakthroughs are all the beginning, none of them are getting us close to 70% to 80% cure rates, so please still consider trials for all your patients. I hope in 10 years, we will get to that 70% to 80% cure rate for all patients. But today, we're just starting the progress. Thank you all for joining us today, and we hope that this discussion was informative and helpful for the practice. And thank you again, Dr. Wang and Dr. DiNardo.

Courtney DiNardo: Take care, thanks.

Eunice Wang: Take care, bye. Thank you so much.