New Advances in AML

Dr. Naval Daver: Hello and thank you for joining us. I am Dr. Naval Daver, Associate Professor at the MD Anderson Cancer Center in Houston, Texas, and I am pleased to be joined today by my two colleagues Dr. Jessica Altman, who is an Associate Professor at the Northwestern University Feinberg School of Medicine, and Dr. Alexander (Sasha) Perl, who is an Associate Professor at the Abramson Cancer Center at the University of Pennsylvania. Together we will do our best to provide you with the latest evidence in the treatment and management of AML as we explore the continuing evolving landscape and what this means for you and your patients.

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, 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. Jessica Altman** has received honoraria related to formal advisory activities from AbbVie Inc., Agios, Daiichi Sankyo, Inc., and Theradex Systems, Inc., as well as speakers' bureau activities from the France Foundation. She has also disclosed a financial relationship with GlycoMimetics, Inc. (Data Safety and Monitoring Committee)
- **Dr. Alexander Perl** has received honoraria as a consultant from AbbVie Inc., Actinium Pharmaceuticals, Inc., Arog Pharmaceuticals, Inc., Astellas Pharma US, Inc., Daiichi Sankyo, Inc., FORMA Therapeutics, Inc., and the Leukemia and Lymphoma Society, as well as formal advisory activities from Loxo Oncology and NewLink Genetics Corporation. He has received grant support related to research activities from AbbVie, Astellas, Bayer AG, Daiichi Sankyo, and Novartis AG

These are our disclosures.

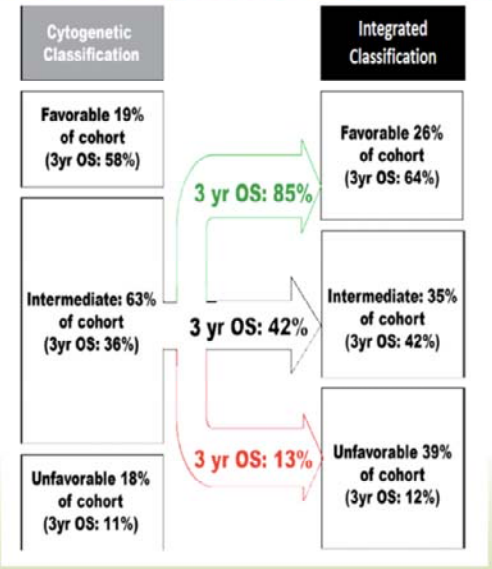
As we go to our presentations, we will spend just a moment to address a few of the most pressing issues as it relates to both starting new treatments and maintaining patients on treatment at this time.

New Advances 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.

So to begin with, a slide that you have probably seen maybe in different formats but showing you similar data is that mutational profiling in acute myeloid leukemia is no longer something that is being done in the research arena or only in academic centers. It is now a standard approach, both in newly diagnosed untreated acute myeloid leukemia, as well as in relapsed acute myeloid leukemia and it is being used both for prognostication, because we know that on top of cytogenetic information, molecular data can add an additional layer of prognosis. As you see in the slide, the big group, what we called intermediate cytogenetics for many decades, when you overlay the molecular information, this group gets split quite significantly into patients who may have intermediate cytogenetics but could have 80% or higher long-term survival, which is quite favorable, as good as people with favorable cytogenetics. On the other hand, if you have “intermediate cytogenetics” but high-risk mutations such as RUNX1, ASXL1, TP53 and others, you may actually have outcomes that are as bad as those with complex or poor cytogenetics. The point being molecular information is very, very critical to prognostication and of course as we will discuss more and more with Dr. Perl and Dr. Altman through this session, it is also critical for selecting optimal therapies or combination of therapies, frontline and in the relapse setting. When we look at specific mutations, the most common mutations in acute myeloid leukemia are NPM1 and FLT3 and these two mutations also tend to co-occur.

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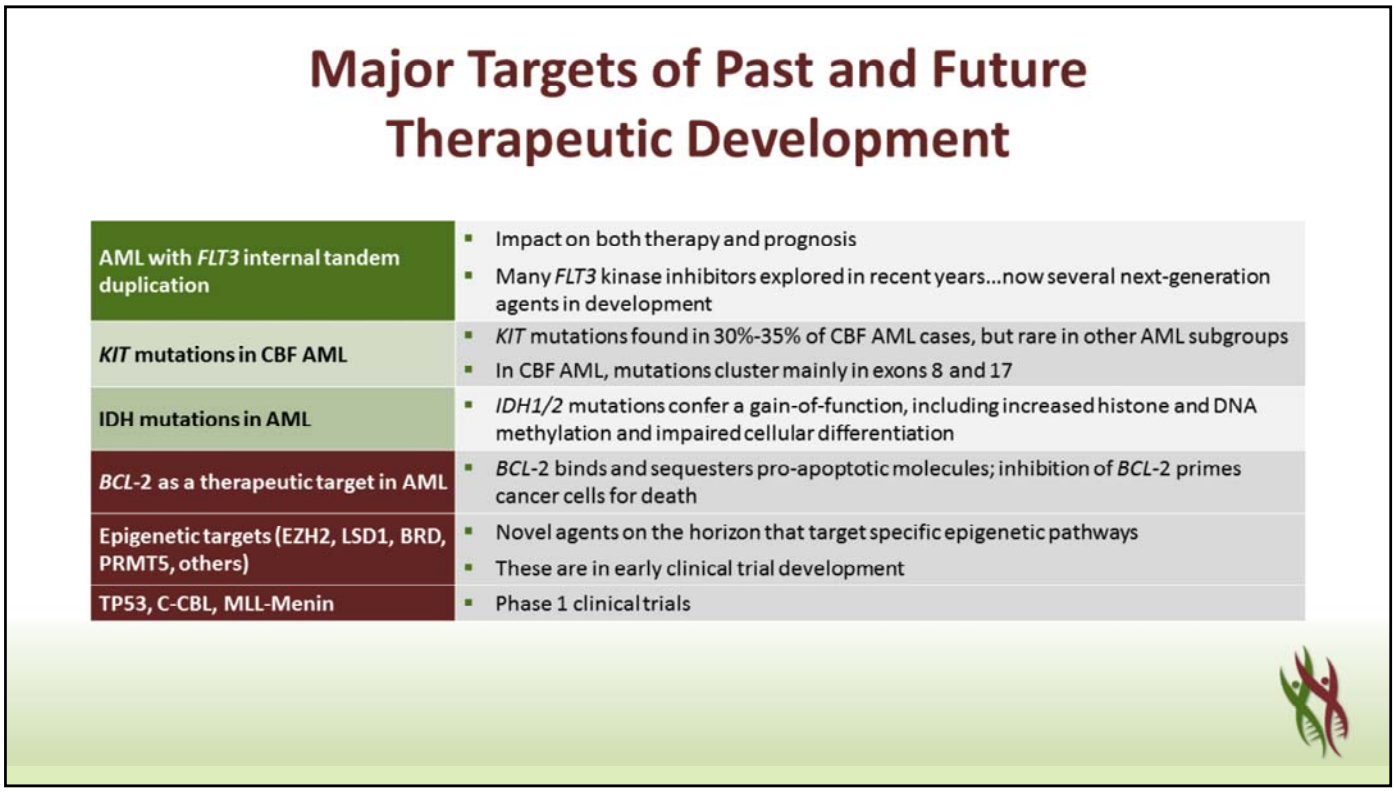
ELN 2017

Genetic Risk Group	Frequency	Survival	Subset
Favorable	15%	65-75%	▪ t(8;21)(q22;q22); *RUNX1-RUNX1T1* ▪ inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* ▪ Mutated *NPM1* without *FLT3*-ITD or *FLT3*-ITD ^{low} ▪ Biallelic mutated *CEBPA*
Intermediate	55%	50-55%	▪ Mutated *NPM1* and *FLT3*-ITD ^{high} ▪ Wild-type *NPM1* without *FLT3*-ITD or *FLT3*-ITD ^{low} (without adverse-risk genetic lesions) ▪ t(9;11)(p22;q23); *MLLT3-MLL* ▪ Any cytogenetics not classified as favorable or adverse
Adverse	30%	20-25%	▪ t(6;9)(p23;q34); *DEK-NUP214* ▪ t(v;11)(v;q23); *MLL (KMT2A)* rearranged ▪ Inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1 (GATA2, MECOM (EVI1)* ▪ t(9;22)(q34.1;q11.2) *BCR-ABL1* ▪ Monosomy 5 or del(5q); monosomy 7; monosomy 17; abnormal 17p ▪ Complex karyotype(≥3 abnormalities) or monosomal karyotype ▪ Wild-type *NPM1* and *FLT3*-ITD ^{high} ▪ Mutated *RUNX1* ▪ Mutated *ASXL1* ▪ Mutated *TP53*

Döhner H, et al. *Blood.* 2017;129(4):424-447.

This is the ELN classification. The NCCN has a similar classification. They both actually agree on most of the major points and either one I think is a good tool to use for prognostication. I do not need to go through all of these details but the one point I want to make here is that single mutations usually do not convey the full prognostic picture. So if you look at the underlying sections, FLT3 for example can fall in favorable, intermediate, and adverse groups, depending on the allelic ratio and the co-occurrence or non-co-occurrence of NPM1. So you do need to know the co-existence of NPM1 and the allelic frequency to make a true prognostic determination of FLT3, and this is something that we are seeing more and more with coexisting mutations that may significantly change the prognosis with other patterns as well.

New Advances in AML



So looking at potential targets that are either in development or already have been US FDA-approved in the last few years, the big ones are FLT3 mutation, one of the most common mutations with a number of FLT3 inhibitors that we will talk about, IDH1 and 2 for which there are inhibitors that have been approved in relapse and specific frontline settings, and then the big one that we are using quite frequently which is not truly mutation-specific but is more of an important pathway that is predominantly active in almost all AMLs, Bcl-2 with the drug venetoclax showing great activity in combination of hypomethylating agents and other combinations such as chemotherapy/FLT3 that we will also talk about, and then there are other less common ones that may also be targetable and drugs in the pipeline such as Menin inhibitors for MLL translocations, FLT3 inhibitors that may have activity against C-Cbl, and then drugs such as APR and CD47 that may have specific activity in TP53 AML.

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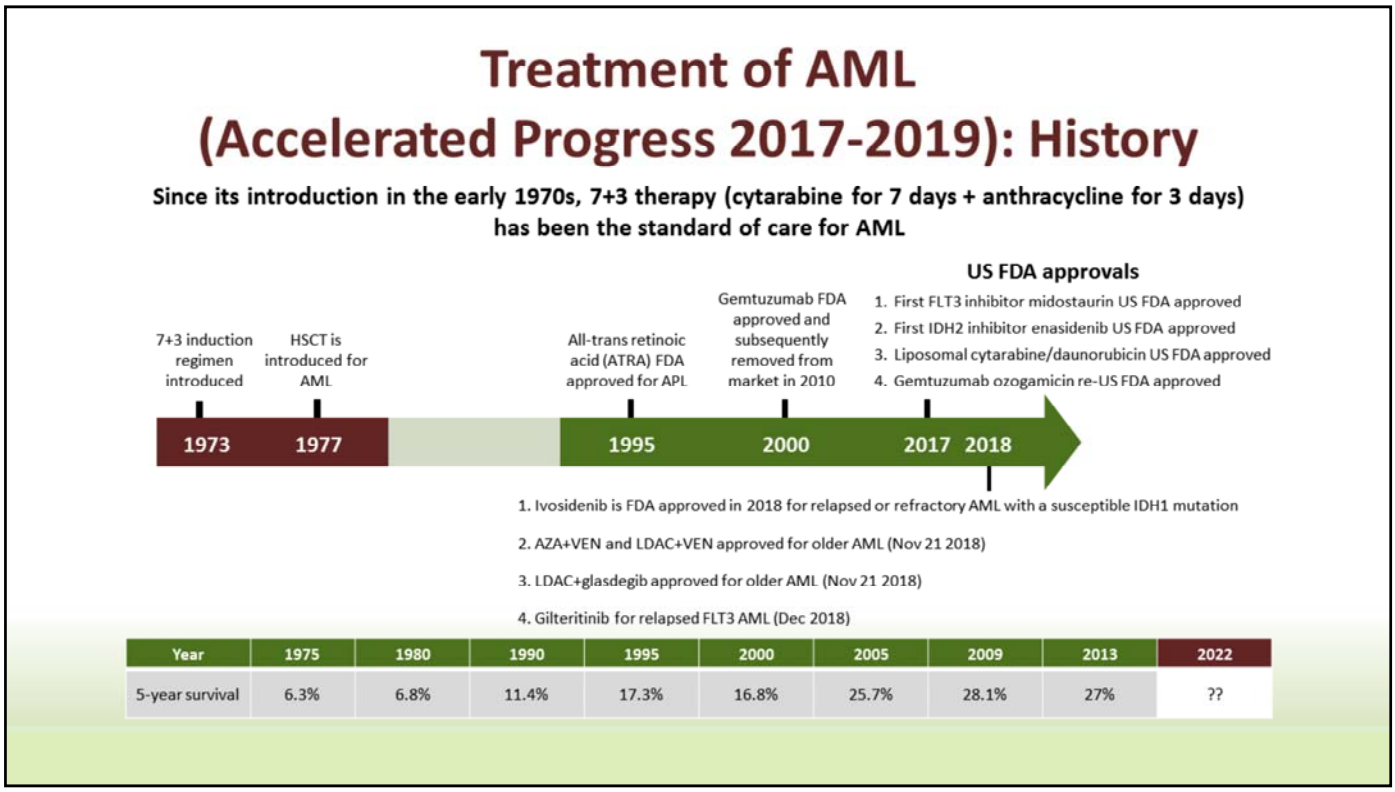
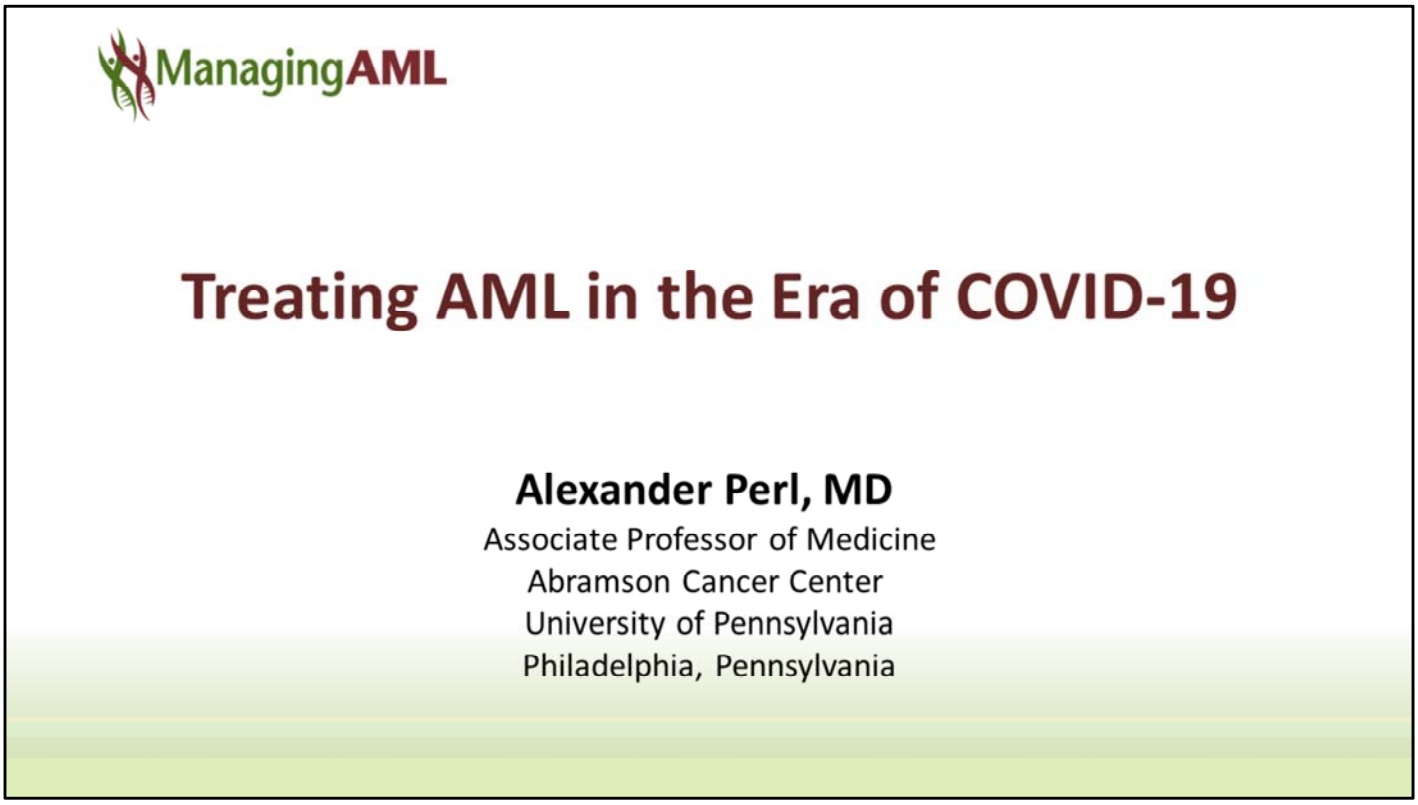


Year	1975	1980	1990	1995	2000	2005	2009	2013	2022
5-year survival	6.3%	6.8%	11.4%	17.3%	16.8%	25.7%	28.1%	27%	??

So when you look at this you can clearly see there has been a tremendous progress, not only in the research arena, that was going on for about 15 to 20 years, and a lot of the breakthroughs in research identifying molecular mutations as well as different pathways has led to the clinical successes with eight drugs approved in the last two-and-a-half years by the US FDA for the treatment of AML and the train is not stopping here, which was a good thing. There was recent phase III data for oral CC-486 or oral hypomethylating agent that also met a phase III endpoint in the maintenance and could be a ninth drug potentially approved.



So, Dr. Perl, I'm going to turn this over to you.

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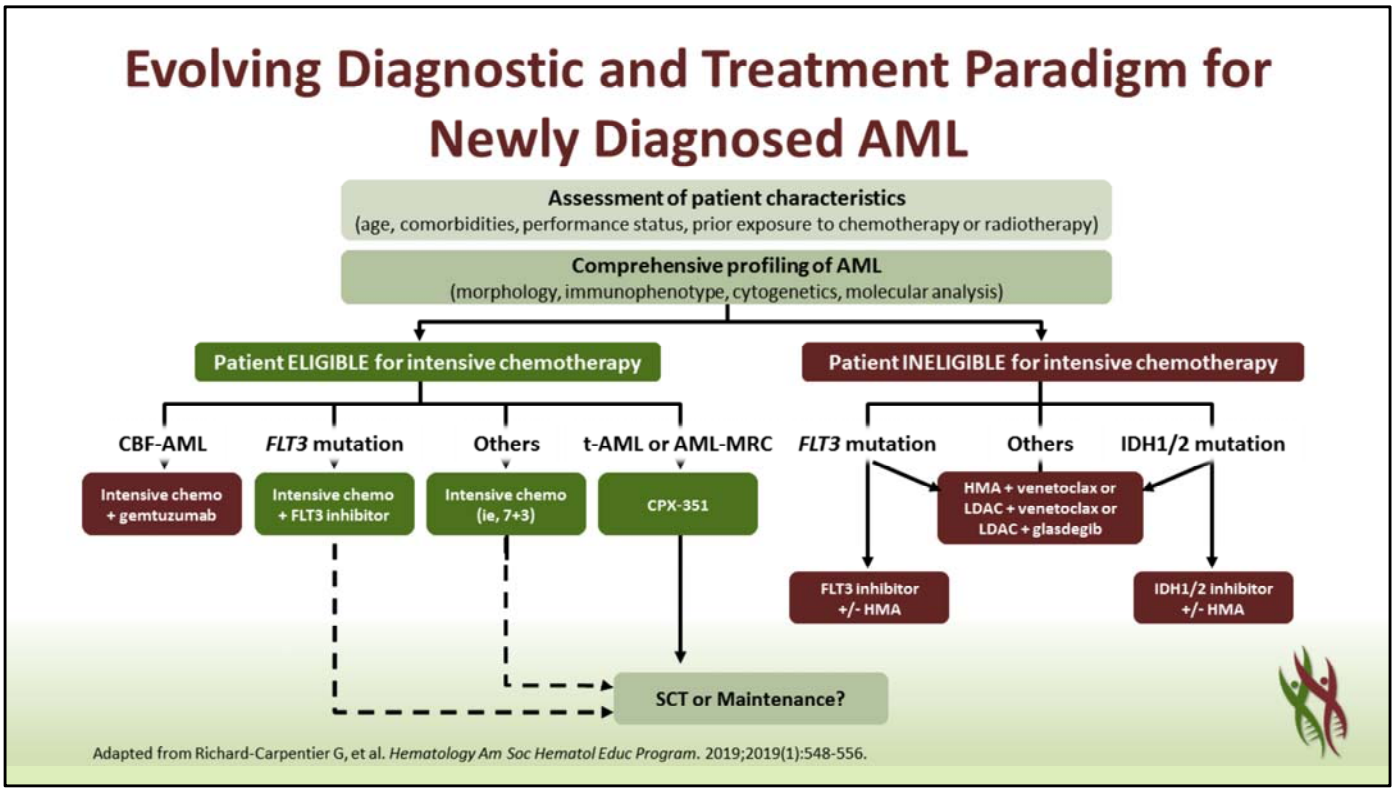
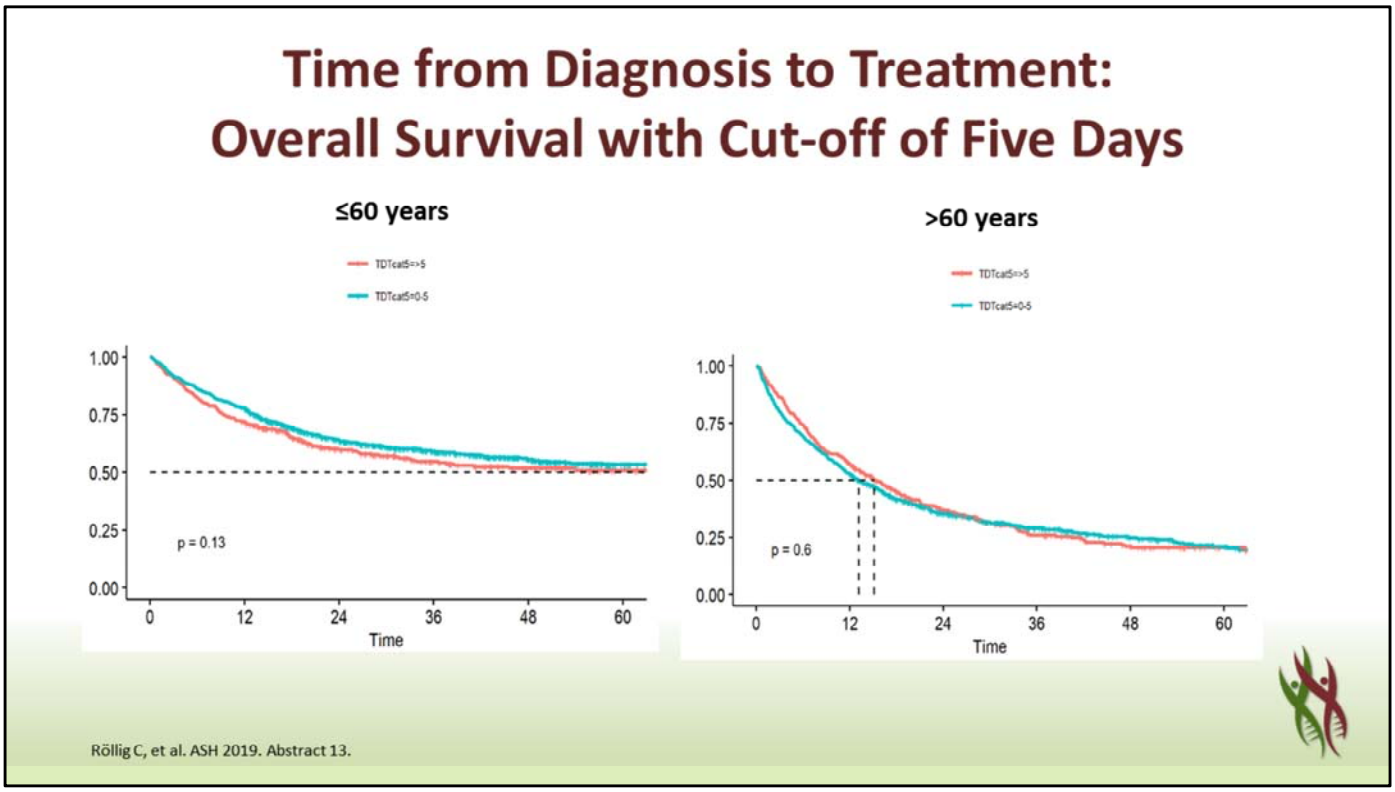


Dr. Perl: So we know a lot about how to approach our patients and there have been a lot of data in terms of new therapies and a general approach to treating patients which I show here. So basically, you do need to weigh two things in terms of how best to treat your patient. The first is, are they eligible for intensive chemotherapy and if so what are their genetics to inform which therapy would be best? For patients ineligible for an intensive chemotherapy, largely our strategies have been HMA-based, primarily with venetoclax these days and in some patients we've added in targeted inhibitors such as IDH inhibitors when appropriate, and in a few patients we have used FLT-3 inhibitors if, for example, we could not cytoreduce them otherwise.

New Advances in AML



If we look at data that were presented at the ASH meeting this year, it gives us useful information in terms of how we can parse through these data to best allocate our patients for therapies. As you saw in the patients who were fit for intensive chemotherapy, genetic determinants may lead to therapeutic choices, meaning for certain genotypes we may recommend one induction strategy over another, and the question has always been, is it safe to wait until you have some data about your patient? So the data have largely come in not from prospective studies but from retrospective analysis, and this is a study presented from a German group that was presented at the ASH meeting this past year that showed that a delay of as long as two weeks of therapy actually did not have a negative impact.

Here I'm showing the delay of less than five days or more than five days in younger or older patients, and as you can see, if patients were going on to intensive therapy, that delay did not negatively impact their survival. So we can feel pretty comfortable saying we need a little bit of time to figure out what the best therapy is, but now we've got other priorities. We need to not only declare fitness, genetics but also does this patient have the coronavirus infection? We're doing that testing but it's variable in terms of how fast this comes back. In some centers as you some centers you may know within a matter of minutes to an hour, and in some centers you get answers within a few days. I think we can say from these data that you can safely wait for a few days to figure out whether your patient should undergo intensive therapy. And yes, if we are finding that patients have coronavirus infection at the start of therapy we really think hard about do they need immediate institution of induction therapy? Again, for some patients that really makes sense, such as APL and in other patients that might not make sense.

Lastly, we have to recognize that our tests have limitations and there are patients who might not be picked up by a nasopharyngeal swab because the sensitivity is not 100% of this test. For this reason at my center we have been doing CT scanning, although I cannot say at all if this is an evidence-based recommendation, and certainly we have picked up patients based on screening of either chest x-ray or CT scanning to find infiltrates that we would not otherwise have found by symptoms.

What Should We Do with This Time?

Prepare yourself for treatment choice

- Define fitness?
- Define genetics?
- Determine COVID-19 status?
  - Nasopharyngeal swabbing
  - CT chest
- Assess your system for preparedness
  - Viral testing (inpatient, outpatient)
  - Hot/cold teams/units/zones
  - PPE supply
  - Outpatient capability in case of active COVID-19+ infection

Prepare your patient for therapy

As we assess our preparedness to treat the patient, as I mentioned before, we do need to look at the preparedness of various aspects of our system. How ready is your leukemia unit, how ready is your ICU, do you have adequate PPE? And you have to assess that on your own and weigh the alternatives. Will this patient be adequately cared for in terms of if they pick up a coronavirus infection, can you give them transfusion support in the outpatient setting? You have to think of all those things before you start therapy.

What Should We Do with This Time?

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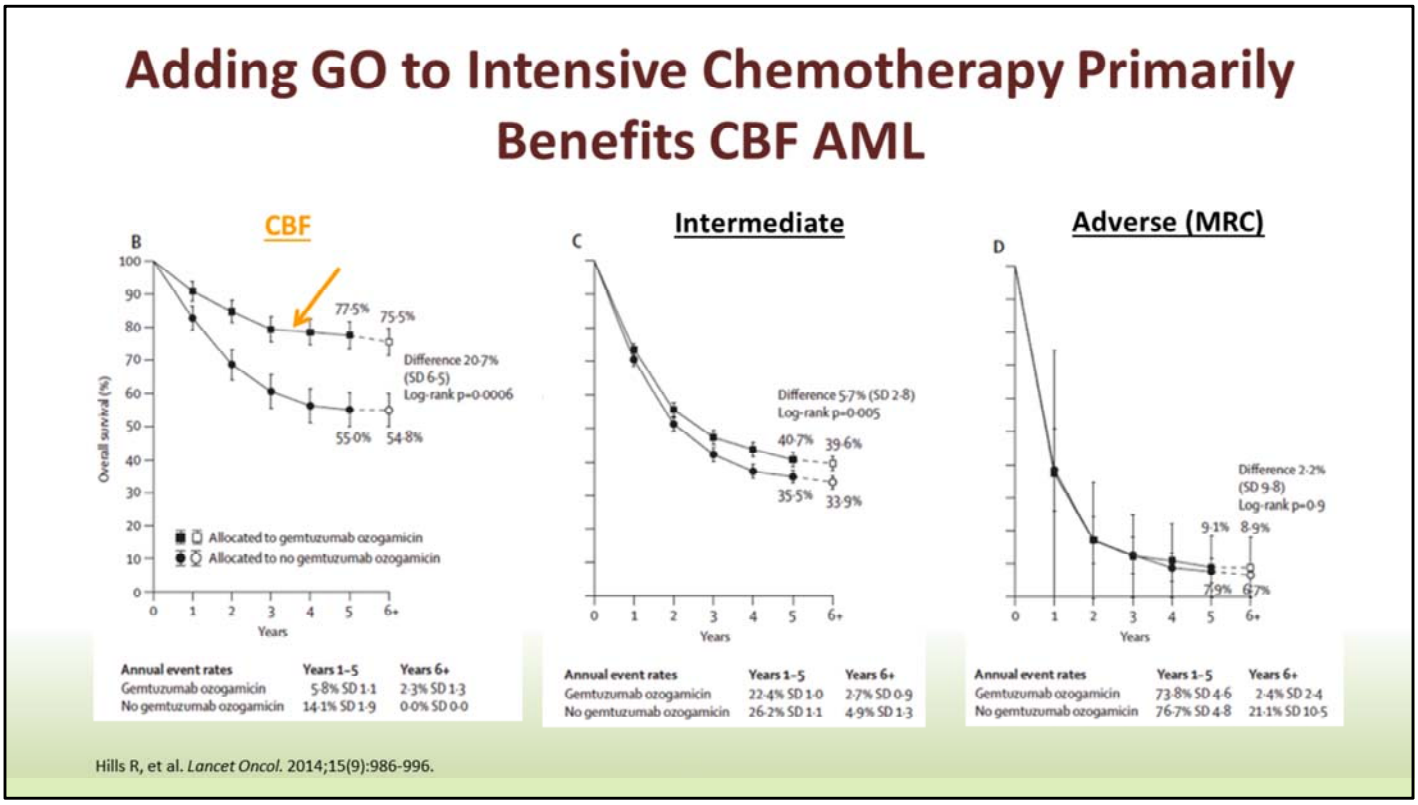
Prepare your patient for therapy

- Thorough discussions of therapeutic pitfalls
  - Pros/cons of intensive vs lower-intensity therapy
  - No visitor and universal masks policies
    - Delirium risk for older patients
    - SNF potentially higher exposure risk at hospital d/c
  - ? Limited ICU availability should complications arise
  - ? Complications more likely AML patients develop symptomatic COVID-19
  - Challenges of outpatient therapy and social distancing

So now you have to discuss that with your patient. You need a therapeutic discussion about what to expect that is really thorough as to all the pros and cons. Intensive, lower intensity, if they choose for intensive therapy, no visitors, even in our outpatient setting we are not allowing visitors into our infusion suite. For older patients in the hospital setting, this can be a real risk for delirium and we are very nervous about sending patients to skilled nursing facilities at discharge, so we want to make sure the patients that we induced or otherwise have a long hospital stay really come out strong. We have not run into issues of ICU availability or rationing of critical care at my institution, and having talked to other physicians elsewhere that has largely not been a limitation. I do not know that is going to be a permanent lack of limitation, but thus far that has not been something that plays much into our decision making. So if the question is, can your patient get intensive therapy? As far as I can tell, the ICU will be there, at least in our center, and hopefully in yours. But complications, as mentioned before, could be higher in the era of coronavirus and we need to be prepared for those. That's not to say that we won't run into problems in the outpatient setting, as I mentioned before, the risks of social distancing also include that a family member who would be a caregiver could get infected and that might limit whether your patient is appropriate for outpatient therapy.

New Advances in AML

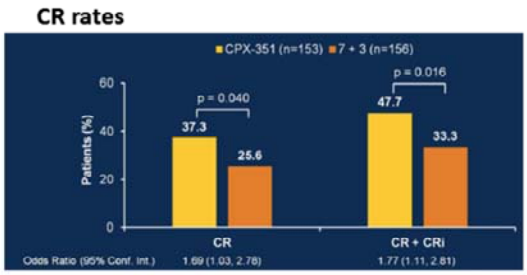


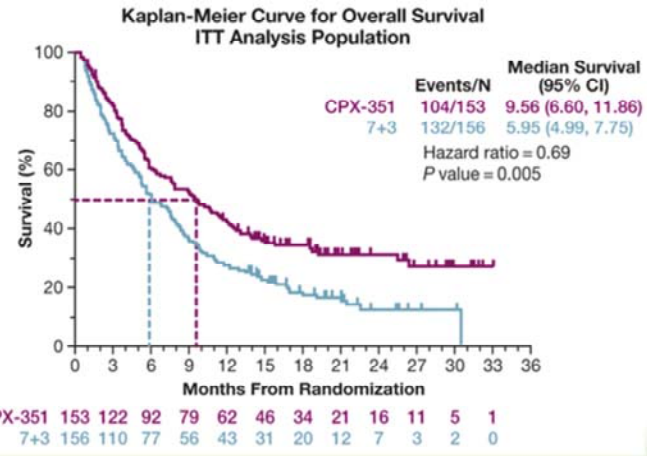
So what are the therapies we can give? I will quickly go through treatments in terms of again the 2020 BC, before coronavirus recommendations and just remind you that as we are getting better at treating AML don't forget that we can give these therapies and be more likely to be successful. I do think that avoiding complications includes making it most likely your patient goes into remission and stays in remission because it is very hard to treat relapsed AML in the current setting. We have less guarantees that we can give therapy that won't paint patients at risk and that we can quickly go to a transplant thereafter. Everything that involves the word transplant in my experience has been delayed because logistical hurdles involved with working with donors, particularly unrelated donors, and scheduling patients for coming into the hospital for these transplants. So whenever possible when we can use chemotherapy-only strategies we would like to. This is particularly true for core binding factor patients who I think should be using gemtuzumab* frontline based on data from this meta-analysis from the UK MRC, which was published about six years ago, showing a substantial improvement in overall survival, pooling multiple studies looking at adding gemtuzumab to frontline intensive chemotherapy.

*Gemtuzumab ozogamicin is not FDA-approved for frontline use in patients diagnosed with core binding factor AML

New Advances in AML

CPX-351 for t-AML and MDS-related AML*





*MDS-related AML was defined by history or karyotype

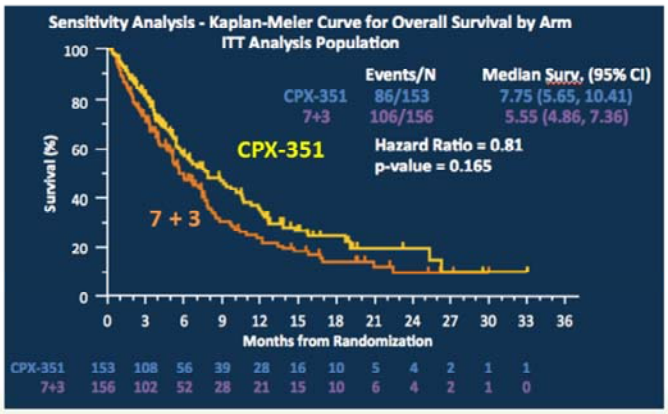
Lancet J, et al. *J Clin Oncol*. 2018;36(26):2684-2692.

For patients who have therapy related AML or MDS related AML, we're sort of on a bit of decision tree algorithm that's tricky here because we know that CPX-351 improves overall survival in this group,

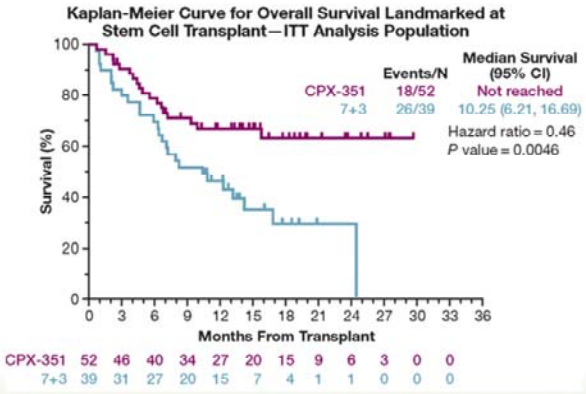
New Advances in AML

CPX-351 and Transplant

OS censored at HSCT



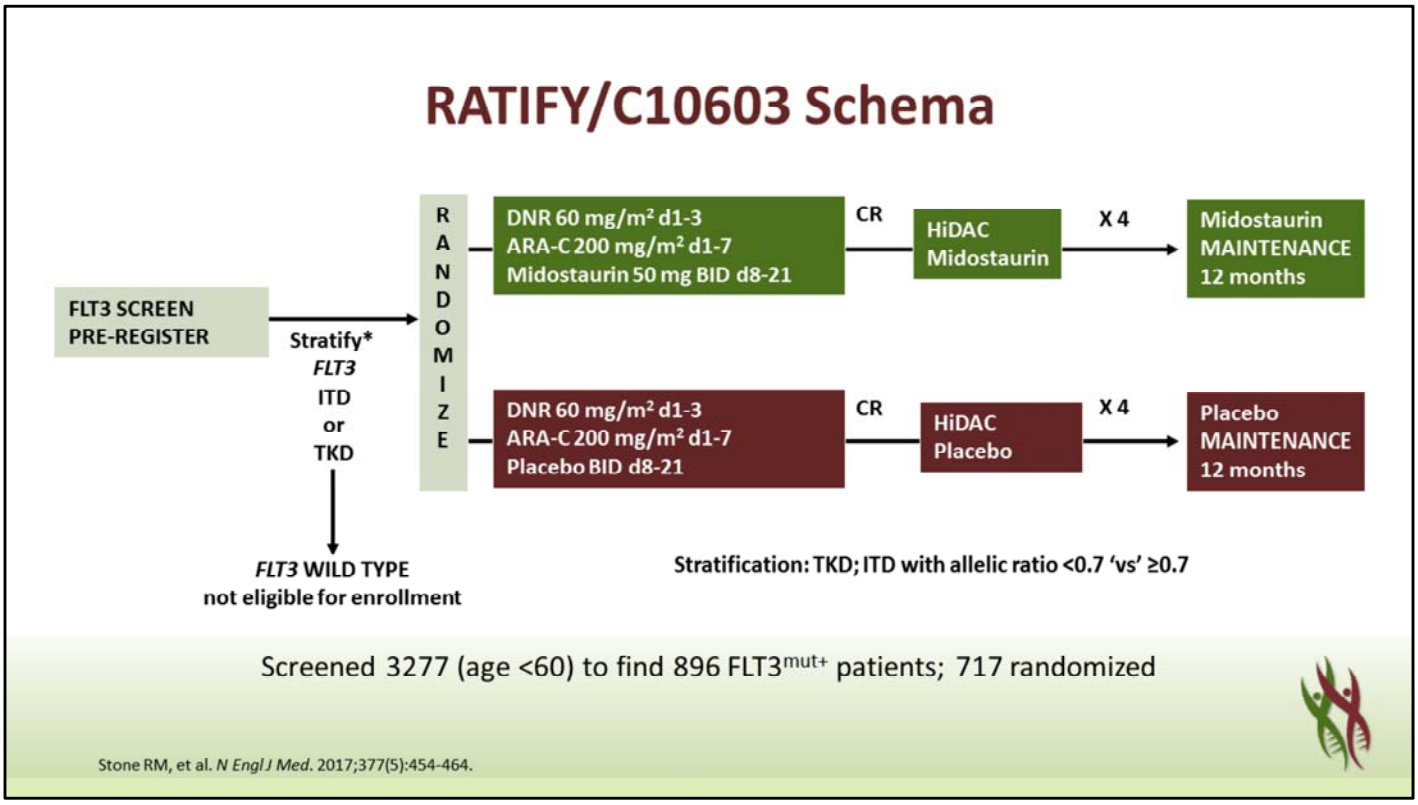
Landmark analysis of OS after HSCT



Lancet J, et al. *J Clin Oncol*. 2018;36(26):2684-2692.

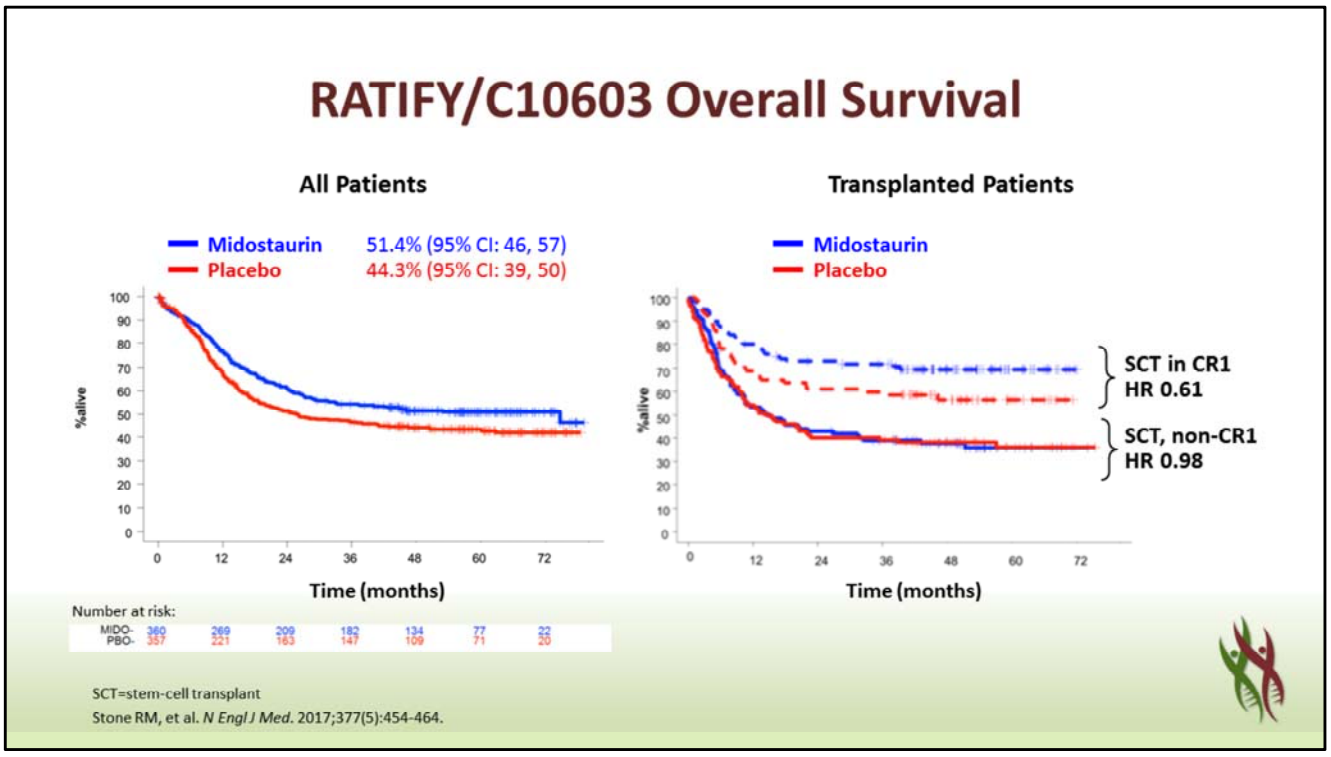
but largely if we look at where that benefit comes from, again, it comes from patients who go to transplant, shown on the right, and not so much when you look at the analysis of the survival when censored for transplant. So if patients in this group are not going to go to transplant, it is not clear to me that they benefit over 7 + 3, but what is a little bit encouraging from this is some centers can deliver CPX-351 in the outpatient setting. If you are one of these, that may be a reason to think about that therapy if the risk of acquiring and/or managing coronavirus is going to be greater in your inpatient setting than at outpatient.

New Advances in AML



For FLT3 mutated patients, we have prospective data from the RATIFY study that led to the approval of midostaurin based on the demonstration that in the head-to-head study where midostaurin was added to intensive frontline chemotherapy in induction, consolidation, and maintenance

New Advances in AML



that survival was better in these patients, all of whom had FLT3 ITD or TKD mutations at initial diagnosis and many of whom went on to transplant, and again because transplant is part of this equation, we also have to think about can we get these patients to remission and then to transplant? And increasingly we have to think about once patients go to transplant, can we think about post-transplant maintenance, which was not part of the study, but might be something to think about in this patient population where it may improve the event-free survival and we still do not know how much that impacts overall survival with long-term follow-up using agents that are now approved for this population, but at present are off-label. This includes midostaurin, this includes sorafenib, this includes gilteritinib, none of which has a maintenance indication in the US, but all of which could be considered in that setting.

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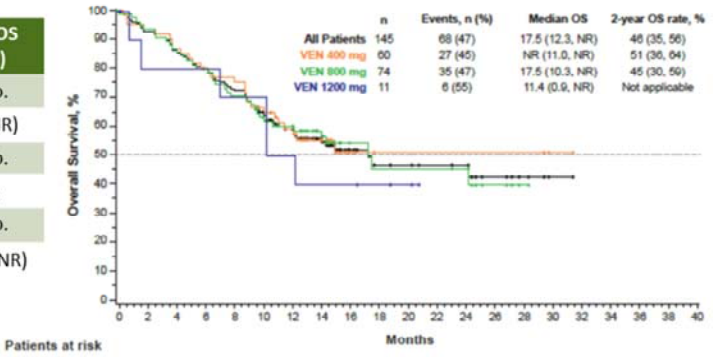
Frontline Venetoclax + HMA (Unfit/Older)

Cohort	N (%)	CR + CRi	Median CR/CRi duration (95% CI)	Median OS (95% CI)
All patients	145	67%	11.3 mo.	17.5 mo.
VEN 400/HMA	44 (73)	73%	12.5 mo.	NR (11-NR)
Age 65-74	83 (57)	69%	12.9 mo.	17.7 mo.
Age ≥75	62 (43)	65%	9.2 mo.	11 mo.
De Novo AML	109 (75)	67%	9.4 mo.	12.5 mo.
Secondary AML	36 (25)	67%	NR (12.5, NR)	NR (14.6, NR)



- 3-5 day ramp up from 100 mg to target VEN dose (400-1200 mg)
- Azacitidine 75 mg/m^2 SQ/IV days 1-7 or decitabine 20 mg/m^2 IV days 1-5
- VIALE-A (Phase 3: venetoclax + azacitidine vs azacitidine + placebo) results expected imminently

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

Venetoclax plus azacitidine or decitabine has been shown to be a highly active regimen in a wide group of patients over the age of 65 with newly-diagnosed AML. We know that the data from the frontline phase III will be soon available. We don't have these in our hands just yet, but we hear encouraging things from press release regarding those data and we hopefully will know whether this really is a therapeutic advance over existing therapy with azacitidine alone. What I can say is the higher remission rates are very heartening. The fact responses are very quick is heartening, and I think getting patients better blood counts quickly is really important in older patients or in anyone who is not a good candidate for intensive chemotherapy, and this includes a number of patients with higher-risk genetics. Again, this might be somebody who you would look at intensive chemotherapy in the era before COVID and now say, "I might want to think about using venetoclax-HMA combination" and use that as my preferred strategy.

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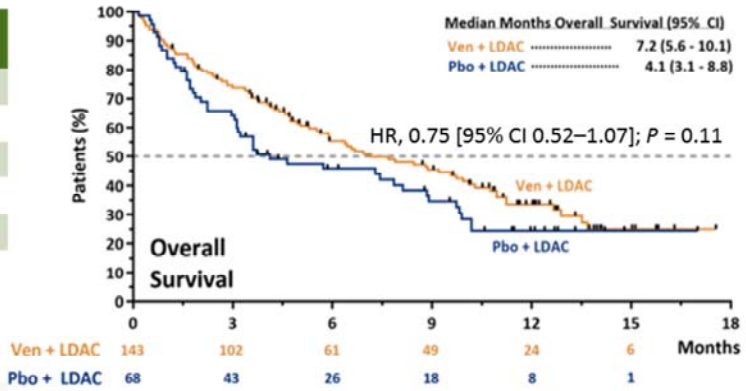
VIALE-C: Ph3 LDAC + VEN/Placebo

	VEN + LDAC	VEN + placebo	*P* value
CR	27%	7%	<0.001.
CR/CRi	48%	13%	<0.001
CR/CRh	47%	15%	<0.001
EFS	4.7 mo	2 mo.	0.002
Transfusion independence	41%	18%	0.002



~70% of VEN/LDAC remissions after one cycle
<30% of LDAC/placebo remissions after one cycle

Wei AH, et al. *Blood.* 2020 Mar 27. [Epub ahead of print].

We recently saw the data from venetoclax plus low-dose cytarabine which did show trends to better outcomes, certainly higher response rates but not clearly better survival. This was recently published in *Blood,* and again we don't yet have the data on venetoclax plus azacitidine, but that will be available soon.

Updates have been made since the filming of this activity. View updated data at this link.

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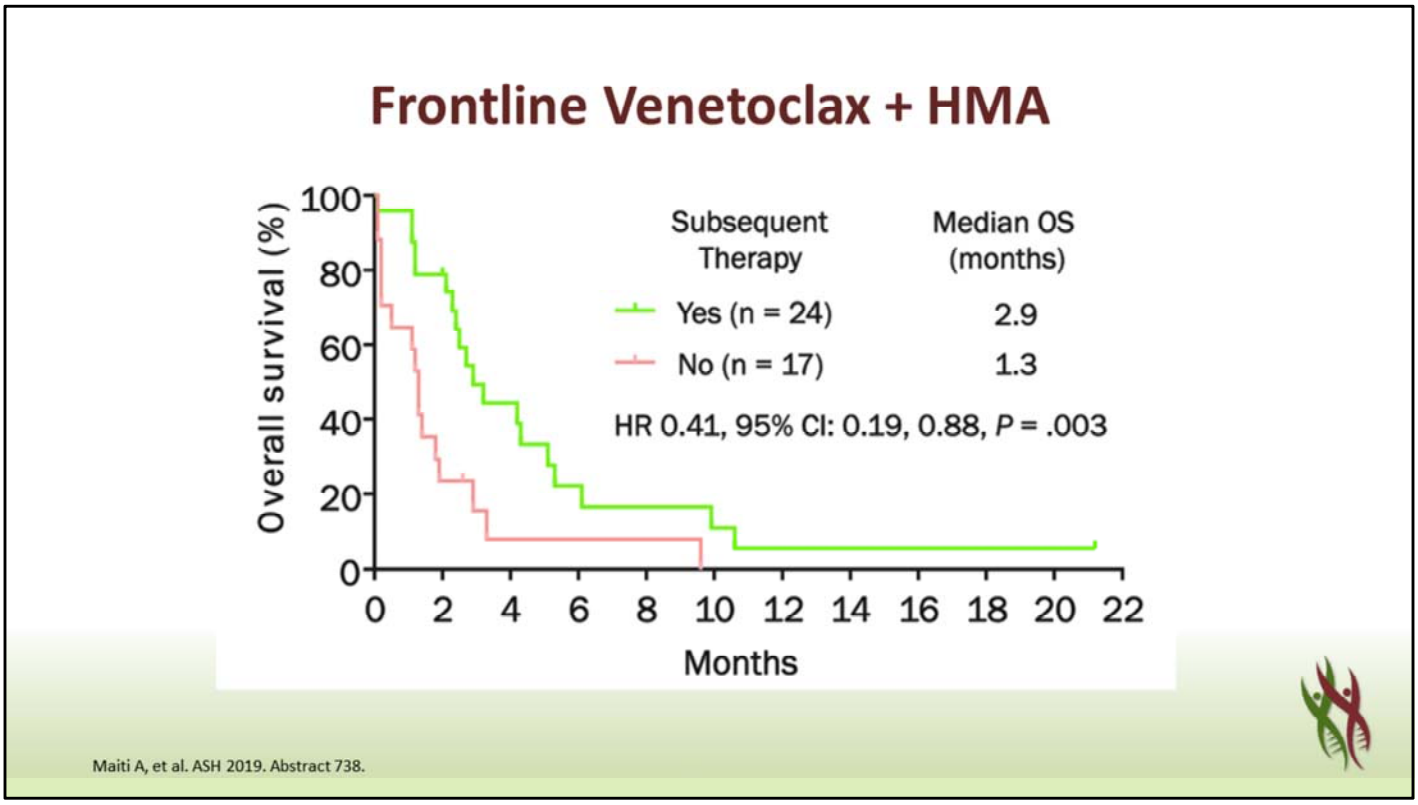

I would point out that once frontline therapy stops working, the outcomes have be very poor in patients treated with venetoclax frontline. This was presented at ASH this past year, and so we do have to think about if patients are in the relapsed and refractory setting, do we have options we can really help our patients with, and can we avoid the heartbreak of patients having unnecessary hospitalizations where they will be separated from their families for a limited amount of time? What I can say is, it seems most likely that patients getting targeted therapies in the relapsed and refractory setting will be benefited from those low-intensity approaches and we should be very careful about who we offer high-intensity salvage chemotherapy to.

Updates have been made since the filming of this activity. View updated data at this link

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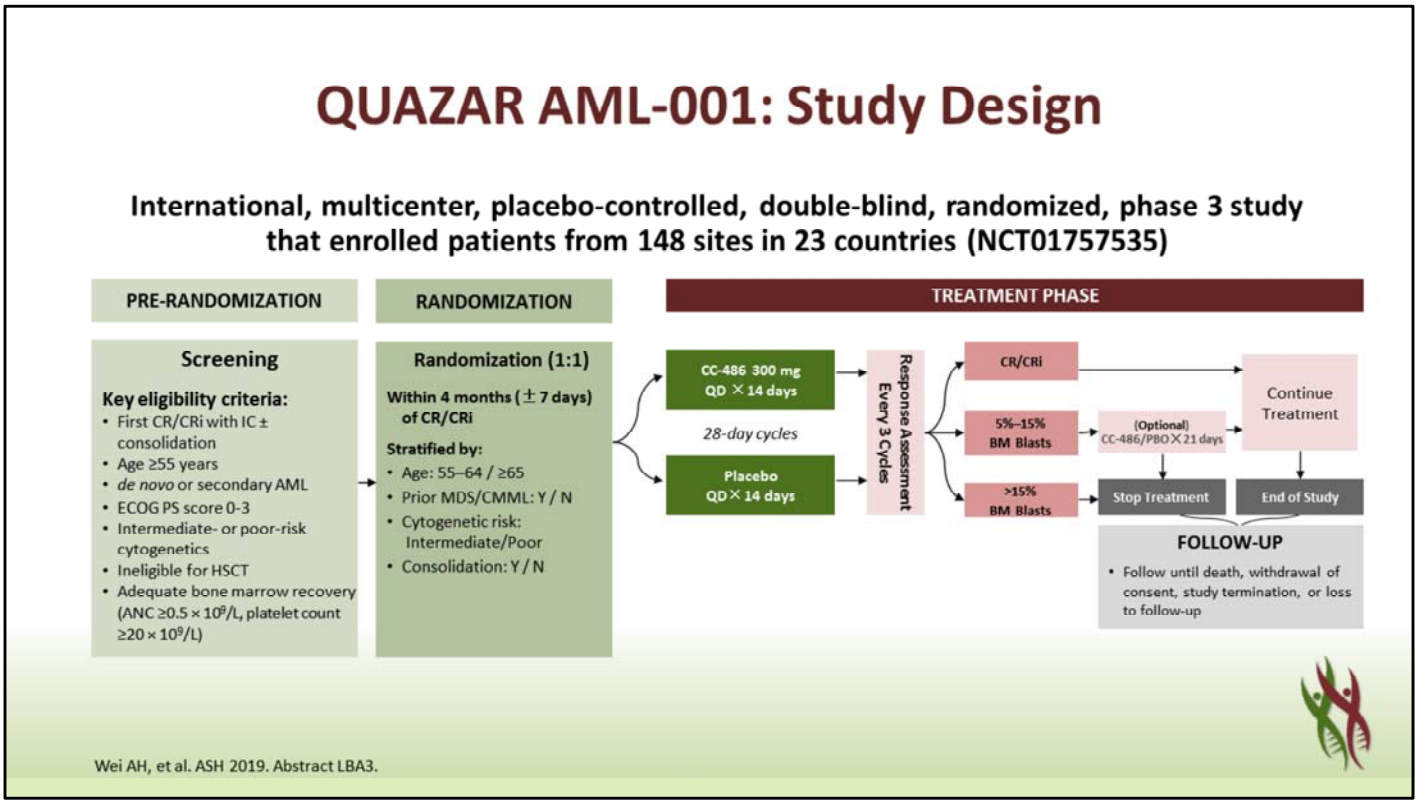

Lastly, I do want to point out one very important update that is that there are data that say that hypomethylating agents given after completion of chemotherapy can lead to substantial improvements in event-free survival, and on this study overall survival, this is the prospective randomized controlled study of CC486, which is an oral azacitidine formulation, compared to the placebo-controlled

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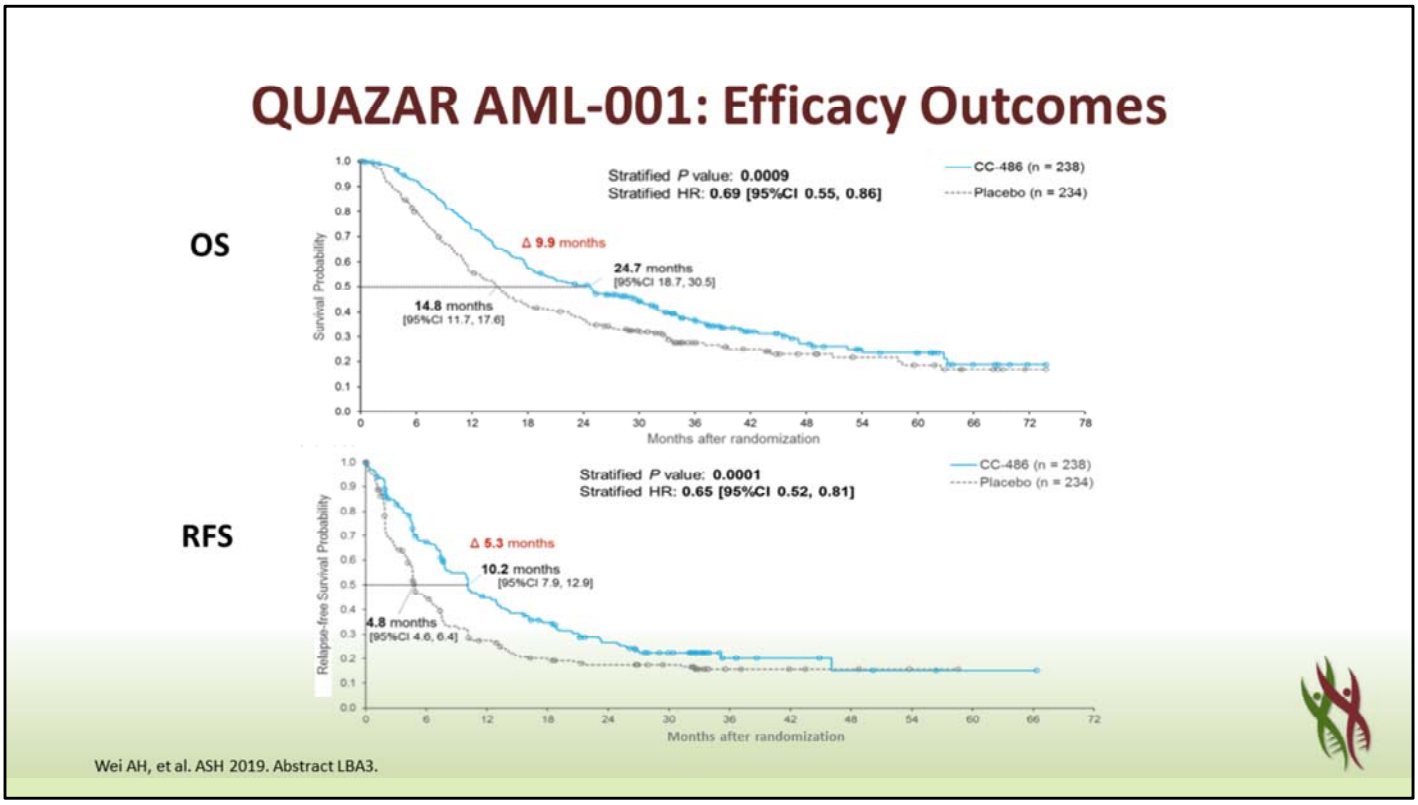
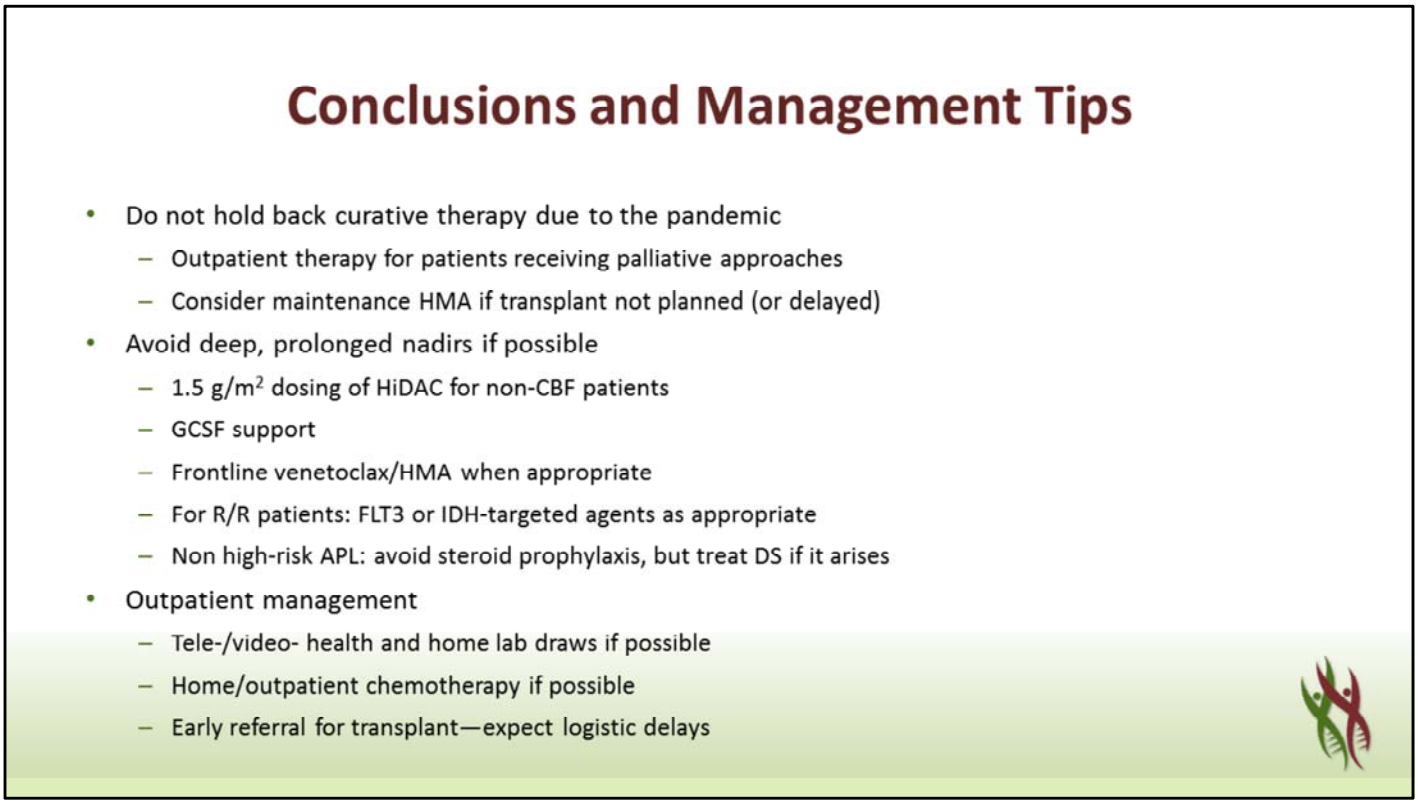


where statistically significant improvement in overall survival was seen, and I would point out that these were patients who did not go to transplant but received CC486 at completion of either induction or any amount of consolidation chemotherapy up to three cycles. So realistically this could be looked at in terms of using hypomethylating agents for patients in remission in which either a delay to transplant is planned or no transplant is planned until we know better how the pandemic is going to play out.



So just to conclude, don't hold back curative therapy due to the pandemic. We should avoid deep or prolonged nadirs, if at all possible. At my center, we have been lowering the dose of cytarabine in the post-remission setting for all of those, other than core-binding factor patients. We have been dropping 1.5 g/m^2 for high-dose AraC consolidation, and when possible, we are giving that therapy at home through home chemotherapy administration by visiting nurses. We are using GCSF support to decrease the duration and/or depth of their nadirs, and when possible and appropriate we are using venetoclax and hypomethylating agents. We are trying as much as possible to avoid intensive chemotherapy for relapse and refractory patients who may do better with lower intensity approaches, whether that is a Ven/Aza approach or whether that is using a targeted agent going after FLT3 or IDH mutations, and for non-high-risk APL patients we are avoiding steroid prophylaxis. As you are probably already doing, telemedicine and video medicine has become the new normal for us. We are trying to do as much in the outpatient setting, and for patients who really do need referral for transplant do not wait because if your patient needs a transplant you are going to absolutely expect delays. It is just logistically so much harder to plan transplant these days and if a donor becomes positive for coronavirus infection, that can really push you back behind the eight-ball in terms of knowing you can move ahead.

Dr. Daver: Okay, I think we move on with Jessica and you are going to focus on the relapsed/refractory patients, please go ahead.

Dr. Jessica Altman: Thank you.

New Advances in AML

Considerations for Treatment (And Considering the Pandemic)

- Is the patient a transplant candidate and if so, is he or she accepting of this, and what are the donor options?
- Length of prior remission
- Tolerance of and response to prior treatment
- Active infection/other medical conditions
- Burden of therapy including hospitalization, trips to medical center (patient preference)
  - Fraction of time spent in treatment and managing complications of treatment
  - Current visitor restrictions

When we think about considerations of the next treatments for patients with a relapsing/refractory disease, foremost in my mind is, is the patient transplant candidate, and if so, is he or she interested in transplant and what are the donor options? We do not want to be in the situation where we have considered and proceeded with an intensive chemotherapy approach for relapsed and refractory disease when the patient is not interested in the stem cell transplant or they are lacking donor options. The vast majority of time we are able to provide sources of donors for almost all patients, whether that be matched siblings donors, unrelated donors, haplo donors, or cord blood transplants. When we think about the options for treatment of relapsed and refractory disease, it is also important to think about the length of the prior remission. One of the predictors of response to another line of intensive chemotherapy is the length of a prior remission. Also we need to know what is going on with our patient. Do they have active infection including coronavirus and the multitude of other infections that our patients are at risk for and their other medical conditions? And as I mentioned when I started this, really the burden of therapy including hospitalizations, trips to the medical center are of great importance, especially in the current era.

New Advances in AML

Treatment Selection

- No one optimal regimen
- Is there a target?
- Urgency of achieving remission?
- Investigational therapy especially in those with highly unfavorable genotype (eg, monosomal karyotype), those without targetable mutations, and not medically fit for intensive therapy
- Trial modifications with the pandemic
  - Remote monitoring
  - Telehealth optimization

So as I alluded to, there is not one optimal regimen. What I think is first and foremost in our patients is, is there a target, is there something that we can treat them with that targets the specific mutation? And then once that we have that at our disposal today that are approved, our targeted therapy is against FLT3 and IDH-1 and IDH-2. It is rare for me to give a talk and give a talk that is kind of on book or on par of what the approved therapies are, but you will see as I go through my talk that I will be talking about approved therapies, and when we turn to novel sessions, we will hear more about what the next up and coming therapies are, what the areas of clinical research are.

While when we are thinking about therapies, it is important to understand the urgency of achieving a remission. The targeted therapies, while may work as well or better than intensive chemotherapy in certain settings, may take longer, specifically those with the IDH inhibitors, and that is important for us to counsel our patients about in terms of the timing of response. I am a big believer and I think all of us are that investigational therapy is always a priority, a well-designed clinical trial for relapsed and refractory disease is of highest importance to us, and it is especially important in today's setting and those with highly unfavorable genotypes and those without targetable mutations, and certainly those who are not fit for intensive chemotherapy.

New Advances in AML

Targeting IDH1 and IDH2 in R/R AML

Ivosidenib (IDH1 inhibitor)

- Multicenter study with 179 patients with R/R AML
- 42% ORR
- 30% CR + CRh
- Median DOR was >8 months
- Transfusion independence in >1/3
- Grade ≥3 AEs: QT prolongation in 8% and IDH DS in 4%
- 34 patients with CR/CRh, 7 (21%) with no residual IDH1 on digital PCR

Enasidenib (IDH2 inhibitor)

- A multicenter study in 214 adults
- 40% ORR
- CR 19%
- Median DOR 6 months and median OS 9 months
- Grade ≥3 AEs: DS in 7%, elevated bilirubin and nausea

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

I would like to speak a little bit about the data of targeting IDH-1 and IDH-2. These are not meant to be comparative. I just have both agents on one slide. When we look at ivosidenib, the IDH-1 inhibitor, there is a large multicenter trial that treated 179 patients with relapsed and refractory IDH-1 mutated AML. The overall response rate was 42% and the CR and CRh rate was 30%, so this clinical trial led to new nomenclature of the CRh. The CRh requires no evidence of acute leukemia in the bone marrow or other sites and a neutrophil count of 500 and a platelet count of 50. It is essentially a CR that allows one to go on with their life, and one, it is different from morphologic leukemia free state. It is also different from a CRi or CRp when we have reasonable, both platelet count and neutrophil count and not just one of those parameters. The median duration of response was about eight months and many patients also became transfusion independent. One thing that I will mention with both ivosidenib and enasidenib is that there is a series of adverse events that are important and we will spend a little bit of time going through them, that adverse event is considered and called the IDH differentiation syndrome, and grade III IDH differentiation syndrome with ivosidenib was 4% in this clinical trial.

When we look at enasidenib, there was a multi-center study again in 214 adults. The vast majority of them with relapsed and refractory IDH-2 mutated disease and there were some patients that we will hear about it in the moment with newly-diagnosed disease who were deemed unfit for other therapies. Overall response rate was 40% with a CR rate of 19% and a median duration of response of six months with a median overall survival of nine months. Differentiation syndrome was again seen in this agent and additional side effects that were seen at a high rate were hyperbilirubinemia, it does not tend to impact the continued treatment, and nausea.

New Advances in AML

Katherine

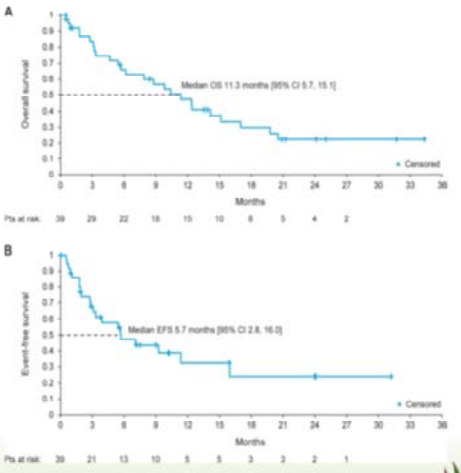
- 83-year-old with history of COPD, lung cancer diagnosed in 1990 and treated with chemotherapy + radiation
- Presented to PCP with fatigue
- WBC 1.7 K/uL (2% blasts, ANC 170), hgb 11.2 g/dL, plt 139 K/uL
- Diagnosed with AML in April 2015
  - 46,XX,+8,der(16)t(16;17)(q13;q21),-17,del(19)(p13.1p13.3)[20]
  - Molecular studies: IDH2 R140Q, PHF6, DNMT3A
- Intensive chemotherapy was not considered an appropriate choice
- Choices at the time were: HMA or LDAC alone or a clinical trial

I would like to share a case of a patient of mine, Katherine is an 83-year-old woman with a history of obstructive lung disease. She also had lung cancer in 1990. She was treated with chemotherapy and radiation. She presented to her primary care doctor with fatigue and was noted to have white blood cell count of 1.7, hemoglobin of 11.2, and a platelet count of 139,000. She had a bone marrow biopsy due to the abnormal blood counts and she was diagnosed with acute myeloid leukemia. You can see her cytogenetics as listed and her molecular studies at that time revealing an IDH-2 mutation. She was not considered an appropriate candidate for intensive chemotherapy, and the choices at that time in 2015 were to receive either a hypomethylating agent alone, low-dose Ara-C, or a clinical trial.

New Advances in AML

Enasidenib in Older Adults with Newly Diagnosed AML

- 39 patients; median age 77 years (range 58–87)
- 23 patients (59%) with antecedent MN
- Median number of enasidenib cycles was 6.0 (range 1–35)
- 12 patients achieved a response (overall response rate 30.8%), including 7 (18%) who attained CR
- Median follow-up of 8.4 months: median duration of any response was not reached (NR)
- Median OS was 11.3 months (95% CI 5.7, 15.1), and NR for responders



Pollyea DA, et al. *Leukemia*. 2019;33(11):2575-2584.

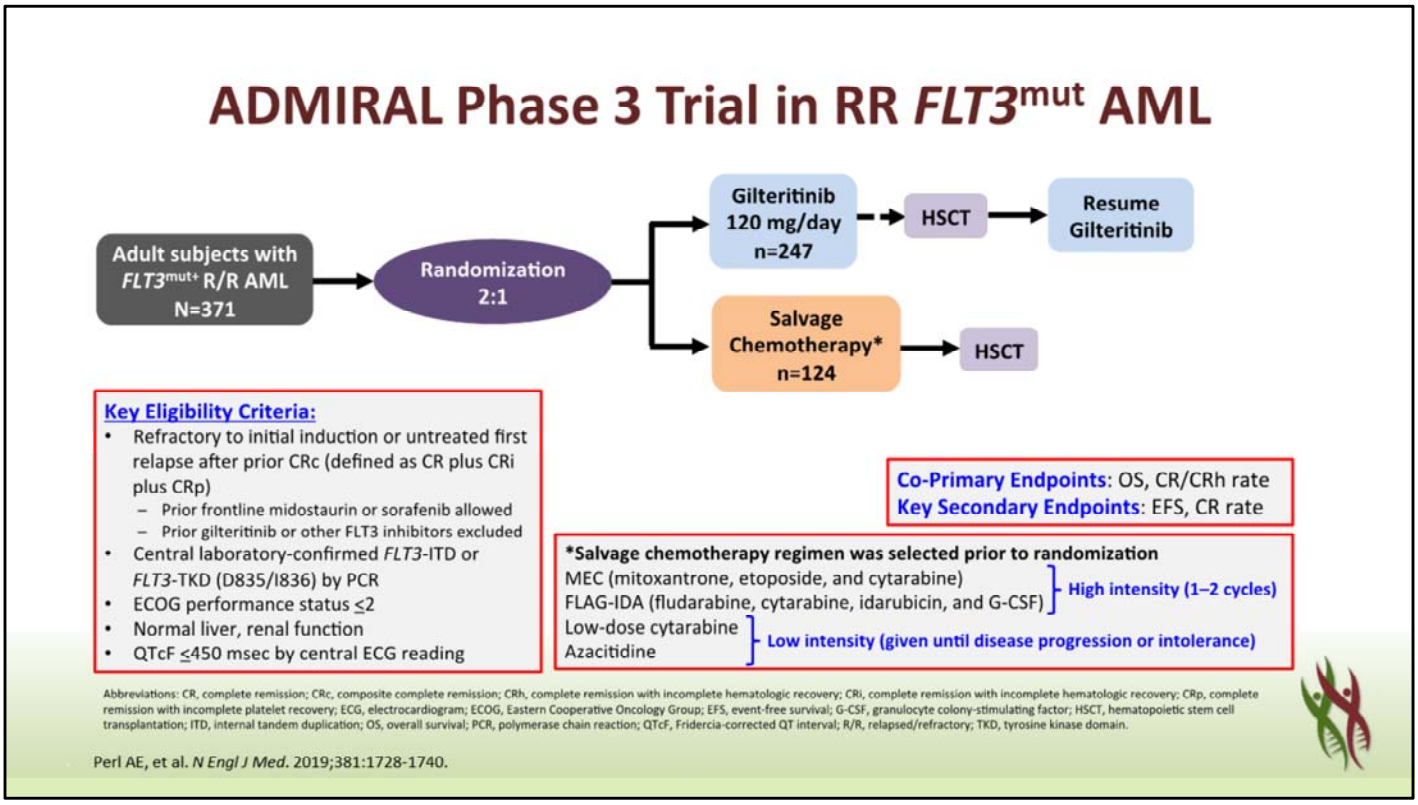
So, Katherine enrolled on a clinical trial. She actually enrolled on the clinical trial with enasidenib that I mentioned previously. The vast majority of the patients who were treated on that trial had relapsed and refractory disease, though there was an arm that allowed patients with newly diagnosed disease who are not candidates for intensive chemotherapy or were not candidates for another therapy. The decision at that time was for her to enroll on the enasidenib clinical trial. In this subset of patients, there were 39 patients with a median age of 77, many of them had an antecedent myeloid neoplasm. The median number of cycles given on this trial was six, though there were patients who are treated upwards of three years and the overall response rate was about 30%, and 18% received CR.

Katherine's Story Continues

- She was treated with enasidenib and enjoyed clinical response for ~3 years
- Presented for routine follow-up on study after a recent COPD exacerbation
- WBC 35.5 K/uL (75% blasts), hgb 11.2 g/dL, plt 129 K/uL
  - 4 weeks prior, blood counts were normal
- Initiated therapy with azacitidine with plans to start venetoclax once available
- Experienced sepsis; recovered
- NGS and PCR: revealed a FLT3 ITD mutation

So, as I mentioned, Katherine was treated on this study. She enjoyed an immediate clinical response with improvement in her blood counts, but it took a number of additional cycles for her to obtain a complete remission, which she did. She maintained that response for almost three years. She then presented for routine follow-up on study after recent COPD exacerbation, and, unfortunately, we found that she had recurrent disease with a high white blood cell count and 75% peripheral blasts. Just four weeks prior, her blood counts were normal with a normal differential. At that time, knowing what we were learning about the sensitivity of IDH-mutated disease to the combination of HMA and venetoclax, she initiated the therapy with azacitidine, and we were still awaiting approval of venetoclax. It was the time period where venetoclax was not yet approved for AML but was approved for CLL, and we are able to get that agent for many of our patients. Unfortunately, she experienced sepsis but recovered, and the molecular studies that I sent when she presented with relapsed disease revealed FLT3 ITD mutation.

New Advances in AML

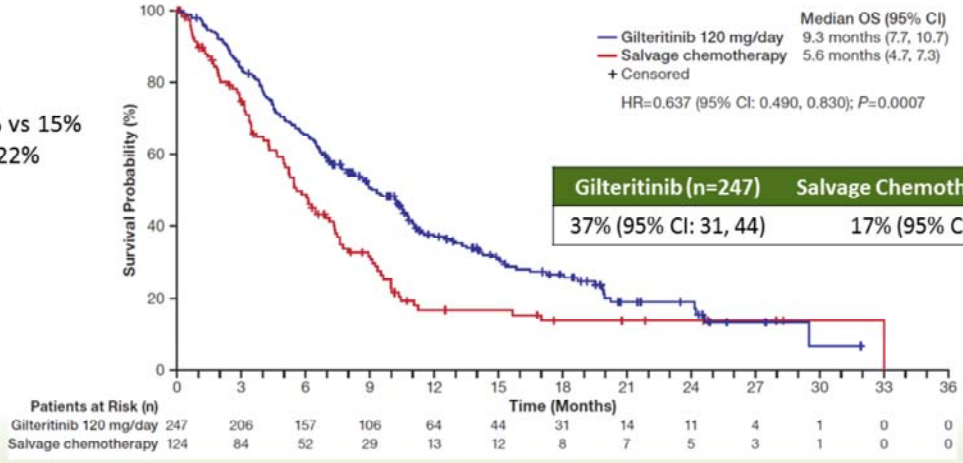


We now had choices for Katherine, do we continue her on the current regimen where she had just recovered from a septic event or did we offer her another therapy? So I would like to mention the ADMIRAL data, and this was a trial that looked at adults with relapsed and refractory FLT3 mutated disease. It is a 2:1 randomization. Patients received either gilteritinib at 120 mg once daily versus salvage chemotherapy. The salvage chemotherapy choices where, there were choices of two high-intensity regimens and two low-intensity regimens. Patients were encouraged and able to proceed with stem cell transplant and those who received gilteritinib and went to stem cell transplant and that arm were allowed to resume gilteritinib post transplant.

New Advances in AML

Gilteritinib Results in Improved OS Compared to Salvage Chemotherapy

CR/CRh: 34% vs 15%
CRc: 54% vs 22%



Gilteritinib (n=247)	Salvage Chemotherapy (n=124)
37% (95% CI: 31, 44)	17% (95% CI: 10, 25)

Perl AE, et al. *N Engl J Med*. 2019;381:1728-1740.

This data the Kaplan-Meier curves and overall survival are shown here; and note that the median overall survival in those who receive gilteritinib was 9.3 months versus those who receive salvage chemotherapy was 5.6 months. You can see that the CR and CRh rate was higher in those who received gilteritinib versus salvage chemotherapy. This is true in the arms who received intensive chemotherapy compared to gilteritinib as well and not just the lower intensity arms.

Next Steps for Katherine

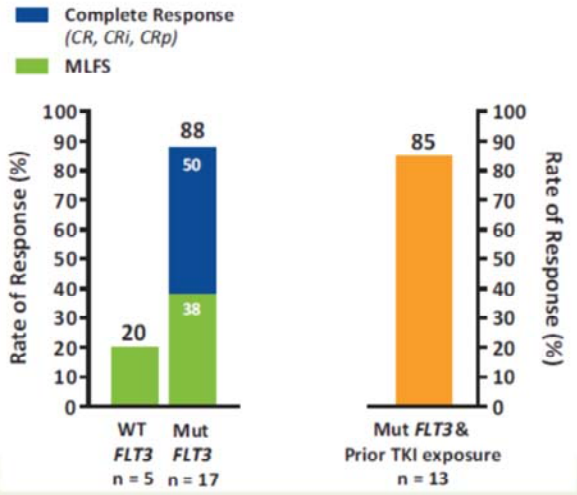
- Treated with gilteritinib as part of expanded access program
- Achieved a clinical response and maintained for ~6 months
- Clinical decline and entered hospice

So, Katherine had had enough of the hospital and had enough of infusional therapy and decided to receive gilteritinib as part of the expanded access program before the drug was approved. She obtained a clinical response and given that our goals with her, she did not have further bone marrow biopsies. She maintained her clinical response approximately six months, but then declined and entered the hospice.

New Advances in AML

Gilteritinib + Venetoclax

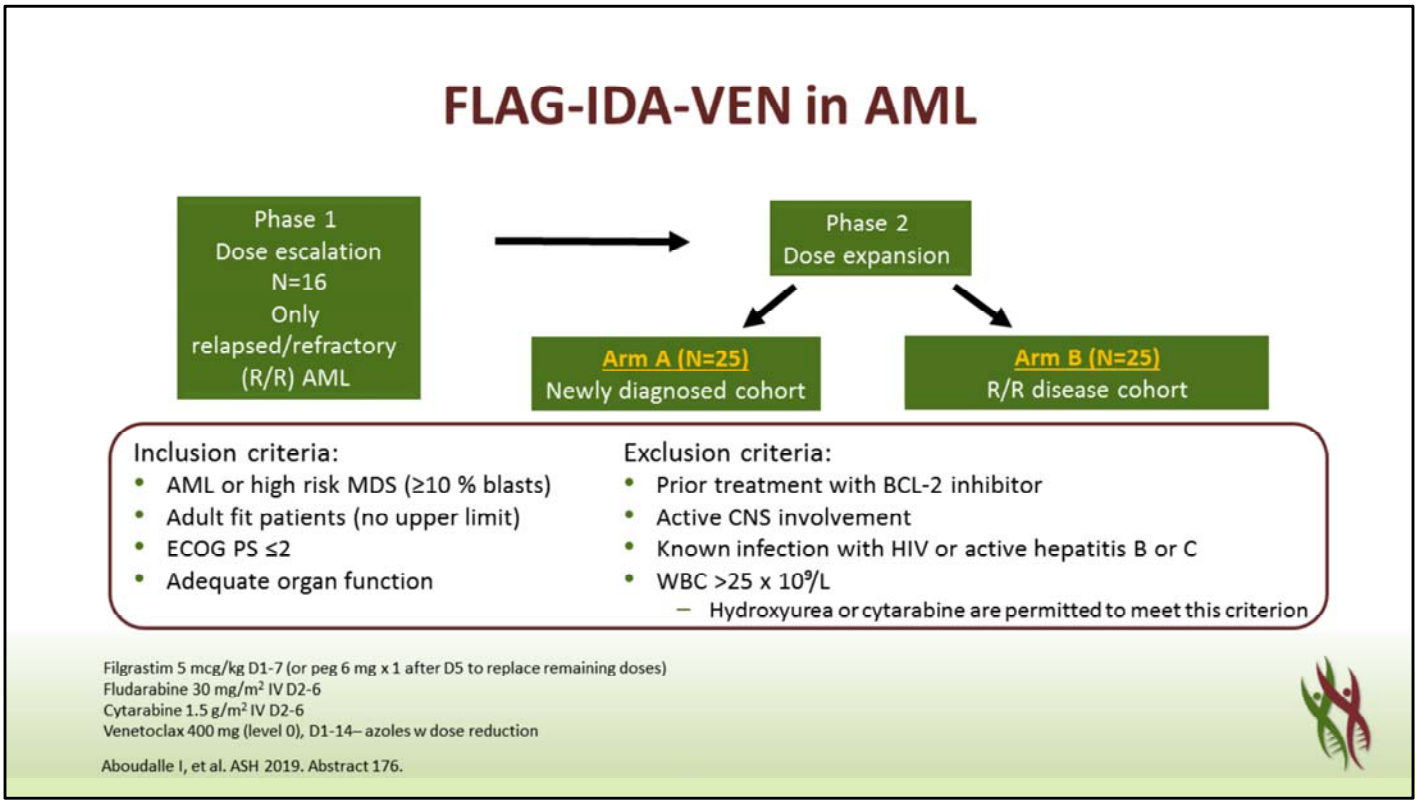
- Preclinical data demonstrated synergy
- Phase 1b trial of venetoclax and gilteritinib
- 15/17 FLT3 mutated patients achieved a response
- 11/13 with prior TKI exposure attained a response
- Phase 2 doses in expansion are 120 mg gilteritinib and 400 mg venetoclax



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

Our interest in gilteritinib does not stop as a single agent, the three of us and others have been interested in combining and studying gilteritinib in combination with venetoclax and Sasha presented this data at the last ASH meeting. There has been preclinical data that demonstrated synergy between these two agents, and we developed a phase IB trial combining venetoclax and gilteritinib. There are a couple of points that I would like to mention, that 15 out of 17 of the FLT3 mutated patients achieved a response, and of particular interest to me and I think to all of us is even those with a prior TKI exposure obtained a response and at quite a reasonable rate. We also know now the phase II doses are 120 mg of gilteritinib and 400 mg of venetoclax, it is important to note that there are major drug-drug interactions with venetoclax and particularly with the azoles and antifungal agents, and so dose reductions of venetoclax are required based on what antifungal agent you are using. It is also important to note that venetoclax in combination with gilteritinib, and in my experience venetoclax in combination with HMAs, leads to significant myelosuppression, and we are still trying to get our arms around the best management of the myelosuppression associated with combination therapies with venetoclax.

New Advances in AML



I wanted to spend the majority of the time talking about targeted therapies, not just because of the era that we are in with the pandemic but because the data is compelling compared to intensive chemotherapy. I do want to take one moment to mention one option of a newly evaluated intensive chemotherapy approach that was presented at this year's ASH, and as I mentioned before, we need to be mindful that this is an option to offer individuals who we, in the relapsed and refractory setting, who we are confident are going to want to and be able to the best of our knowledge proceed with a stem cell transplant. This is intensive therapy, and this again was also from the MD Anderson and a trial combining FLAG, idarubicin, and venetoclax was looked at in adults in two cohorts, both the newly diagnosed and relapsed and refractory after the phase I dose escalation study. So these are patients with newly diagnosed acute myeloid leukemia who had an adequate performance status and adequate renal function and other organ function. Patients received a typical FLAG regimen with GCSF/fludarabine, intermediate-dose cytarabine, and venetoclax was the additional agent, and venetoclax was given on days 1 through 14.

New Advances in AML

FLAG-IDA-VEN in AML: Response

Best Response	Phase 1b (R/R Cohort) N = 16	Phase 2 (R/R Cohort) N = 10	Phase 2 (ND Cohort) N =14
Overall Response Rate (ORR: CR+CRi+PR)	12 (75%)	7 (70%)	13 (93%)
Complete Response			
CR+CRi	12 (75%)	7 (70%)	12 (85%)
CR	10 (63%)	4 (40%)	9 (64%)
CRi	2 (12%)	3 (30%)	3 (21%)
MRD by flow cytometry	9 (56%)	5 (50%)	11 (85%)
No. of cycles to best response			
1	10 (83%)	6 (85%)	13 (100%)
2	2 (17%)	1 (15%)	0 (0%)
Days to best response	29 [26-73]	27 [20-103]	27 [20-40]

MLL rearranged (3 R/R, 2 ND): all responded and underwent alloSCT
At a median of 8 mo, 4/5 alive

Aboudalle, I et al. ASH 2019. Abstract 176.

The response rate, I would like to just highlight the folks with relapsed and refractory disease. In a patient population where we would expect a response rate in the 30% range, the overall response rate in this patient population was 70%, granted it is a limited number of patients but encouraging to us, and I was particularly encouraged by those patients with an MLL rearrangement who were treated. All of the patients both with relapsed and refractory disease and newly diagnosed disease treated in this regimen responded and underwent a stem cell transplant.

New Advances in AML

Treatment Options in 2020: Rel/Ref AML

AML subgroup	Candidate for intensive chemo	Not a candidate for intensive chemo
R/R IDH2+	Enasidenib	Enasidenib
R/R IDH1+	Ivosidenib	Ivosidenib
R/R FLT3+	Gilteritinib	Gilteritinib
R/R CD33+	Chemo or GO	HMA/LDAC + venetoclax* or GO
R/R marker -	Chemo vs HMA vs HMA/LoDAC + venetoclax*	HMA vs HMA/LDAC + venetoclax*

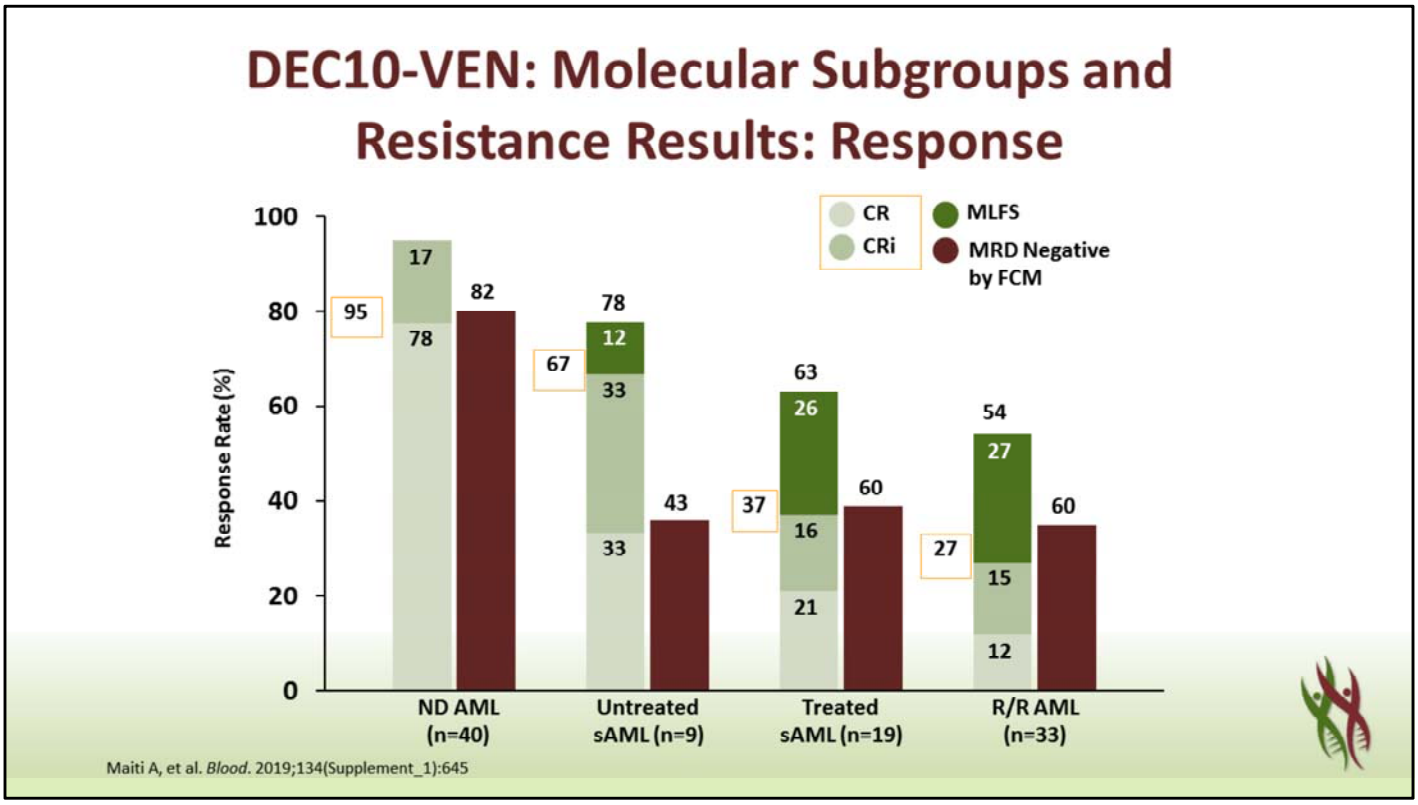
Clinical trials recommended and be prepared for HSCT

*Lower RR for HMA/LoDAC + Venetoclax in R/R setting
DiNardo CD, et al. *Am J Hematol.* 2018;93(3):401-407.; Goldberg A, et al. ASH 2017. Abstract 1353.

So just to summarize, the treatment options for those with relapsed and refractory disease in 2020 are shown and you will see the emphasis that we placed on the targeted therapies. I cannot underscore enough the importance of clinical trials and consideration of being prepared for stem cell transplant.

Dr. Naval Daver: Okay, very good. So, talking about what is upcoming, there are surprisingly and excitingly a lot of treatments still upcoming.

New Advances in AML

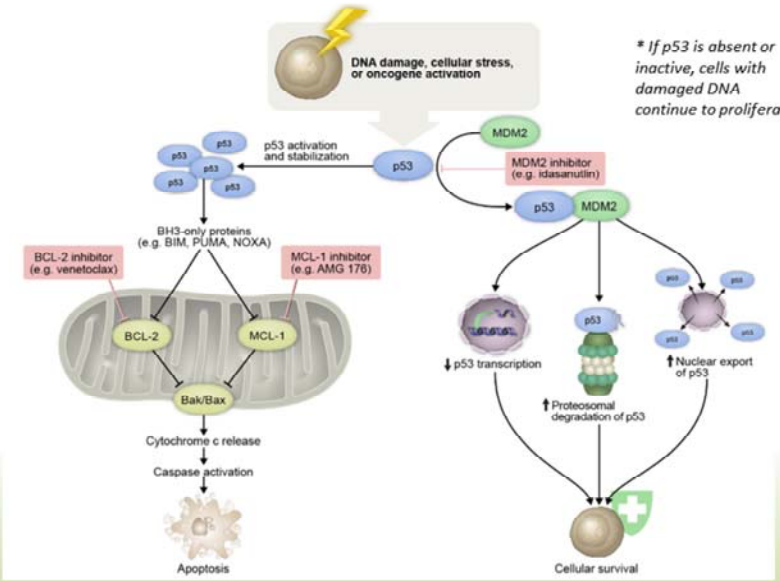


So, HMA and venetoclax very exciting, no doubt, especially for certain subsets NPM1 IDH, RUNX-1, the frontline data has been outstanding. However in the relapsed setting, and here you can see, this was a relatively large study that we did of the decitabine/venetoclax and you can see in the newly-diagnosed AML a very nice 90% CR/CRi rates, but in the relapsed/refractory AML those numbers are low, 25% to 30%, and this has been shown by other groups, the Sloan Kettering group as well as the City of Hope have all shown response rates in the range of 30% to 40% or 45% in relapsed/refractory AML. So we do not think HMA/Ven on its own is going to be the solution in relapsed AML, maybe you could add things to it,

New Advances in AML

Synthetic Lethality of BCL-2 Inhibition with MCL-1 and/or MDM2 Inhibition? Next Steps in Apoptosis Story

- MCL-1 inhibitors may prevent resistance to BCL-2i therapy
  - S63845
  - AMG176
  - AZD5991
  - VU661013
- MDM2 inhibition can reactivate wild-type p53; Also promotes degradation of MCL-1 via p53 activation
  - Idasanutlin
  - Milademetan
  - AMG-232

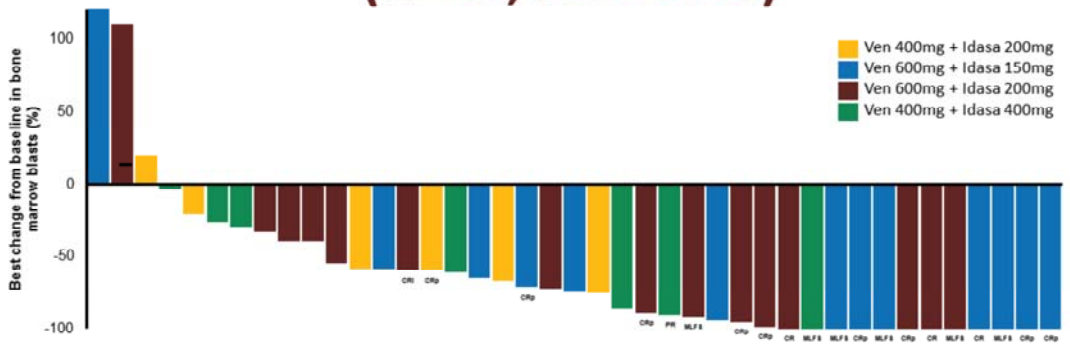


Short N, et al. *Cancer Discov.* 2020;10(4):506-525.

but maybe there are other ways that we could optimize using these combinations. if you block the Bcl-2, one of the major mechanisms of escape is MCL-1, and there are now four MCL-1 inhibitors actually that are in single agent and moving into combinations with venetoclax, and we think that this combination, at least based on the preclinical data, could be highly synergistic and we have to be careful about tumor lysis which actually a couple of those combos have been seen, and also cardiotoxicity which is a known class effect because MCL-1 is heavily expressed on the cardiac tissue. But if we can find ways to deliver it, this could be a very, very effective combination, and that is some of the data we are looking forward to. The other drug that indirectly seems to inhibit MCL-1 is MDM-2, and if you block MDM-2 then you actually get P53 reactivation or refunctionalization, and that can downstream block MCL-1 as well as enhance other proapoptotic pathways such as PUMA, Ven, Dex, and that could have a kind of a dual beneficial activity in combination with the Bcl-2 inhibitor.

New Advances in AML

VEN + Idasa Demonstrated Encouraging Efficacy (N=49, All Doses)

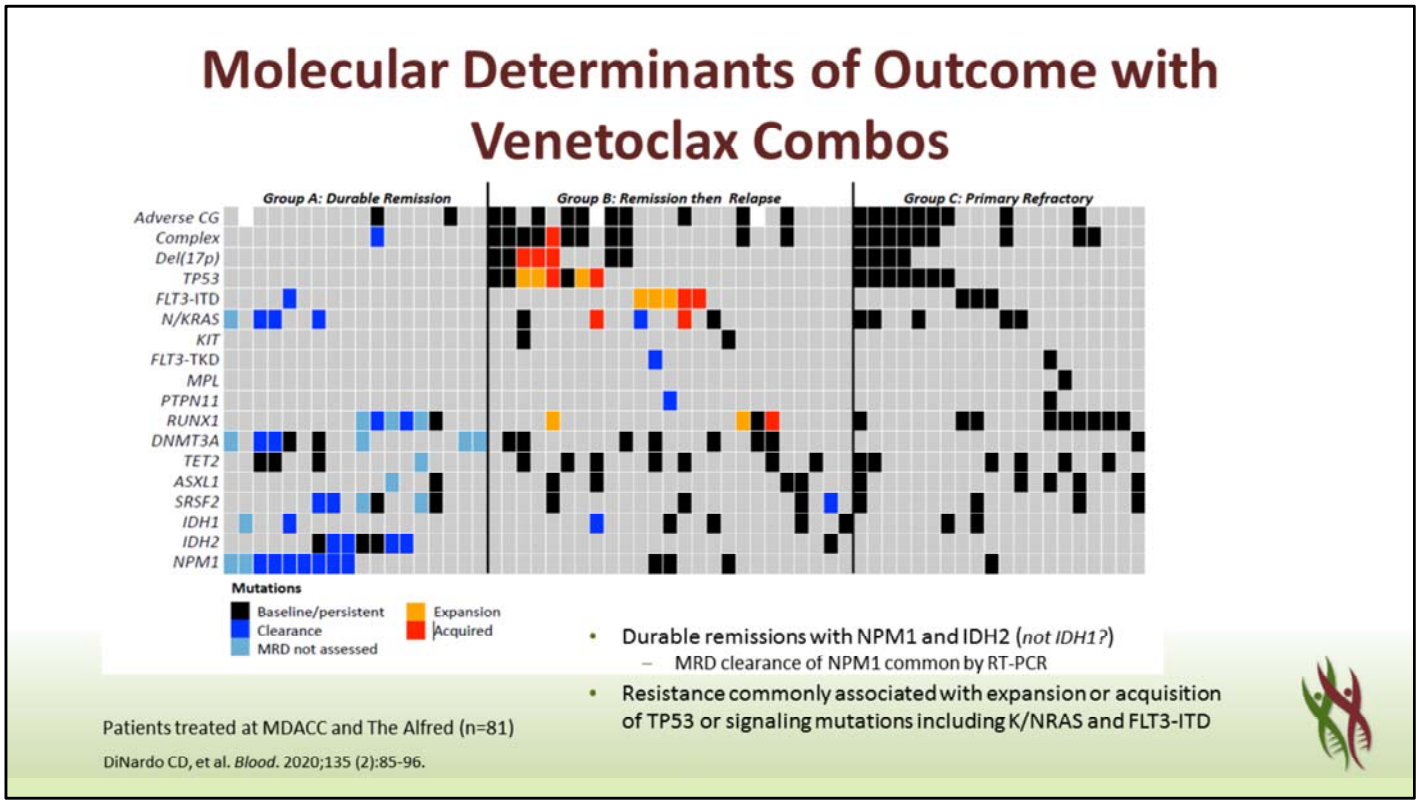


Total patients treated, n (%)	VEN 400 mg + Idasa 200 mg (n=6)	VEN 600 mg + Idasa 150 mg (n=13)	VEN 600 mg + Idasa 200 mg (n=21)	VEN 400 mg + Idasa 400 mg (n=9)	Total (N=49)
Anti-leukemic response (cCR/PR/MLFS)	1 (17)	**8 (62)**	**9 (43)**	2 (22)	20 (41)
CR	0	1 (8)	2 (10)	0	3 (6)
CRp	1	4 (31)	4 (19)	0	9 (18)
CRi	0	0	1 (5)	0	1 (2)
PR	0	0	0	1 (11)	1 (2)
MLFS	0	3 (23)	2 (10)	1 (11)	6 (12)
cCR (CR/CRp/CRi)	1 (17)	**5 (38)**	**7 (33)**	0	13 (27)

Daver N et al. *Blood.* 2019;134(Supplement_1):229.

So we recently showed data on a phase IB trial looking at the combination of this MDM-2 inhibitor. There is a number of them, the one that is more advanced in AML development is idasanutlin in combination with Bcl-2 inhibitor venetoclax, these were older patients above 65 with relapsed disease, so quite a high-risk population, and encouraging early response rates, CR, CRi rates about 50%, which is definitely better than venetoclax alone which is around 20% to 25% or even HMA/venetoclax which is around 40%, but we are continuing the study. We now have an established dose for the combination which is going to be the 150 of Idasa with venetoclax and the expansion will probably give us more information as to whether this could be a good combination for our relapsed older AML patients, and we are also going to look at patients who are failing HMA/Ven is becoming a very, very important and a very poor outcome population.

New Advances in AML



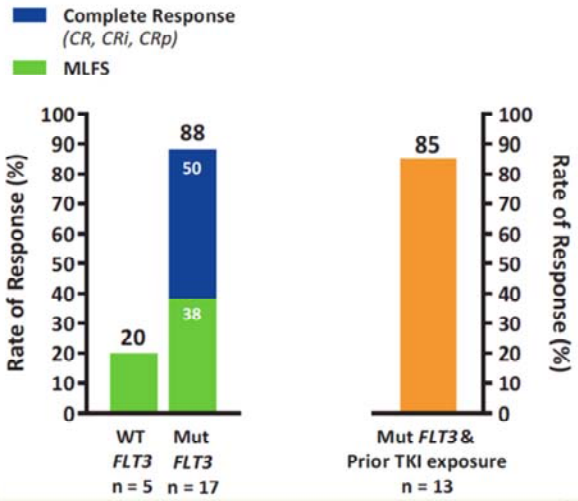
Other important things to look at are something we kind of discussed, that venetoclax/HMA is not universal across the board for all patients so if you look at the bottom half NPM-1, IDH-1 and 2 splice mutant patients seem to do very, very well. They have responses, as you can see in the left group A ,and the responses are durable for three years and beyond in large majority. But then if you move into top area you see the complex, the TP53 and the FLT3 ITD where most patients either do not have a response, that is group C, or if they have a response in FLT3 the responses are not durable, so the point is that we do need to personalize therapy, even beyond just saying this patient is older or unfit for induction to what is the biological approach for that patient? So more and more we are evaluating new treatments for TP53 and FLT3, either in combination or independent from HMA and venetoclax, and I will talk about a couple of those.

New Advances in AML

Gilteritinib and Venetoclax: Clinical Data

Characteristic	Wild-type *FLT3* n = 5	Mutant *FLT3-ITD** 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.
*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).

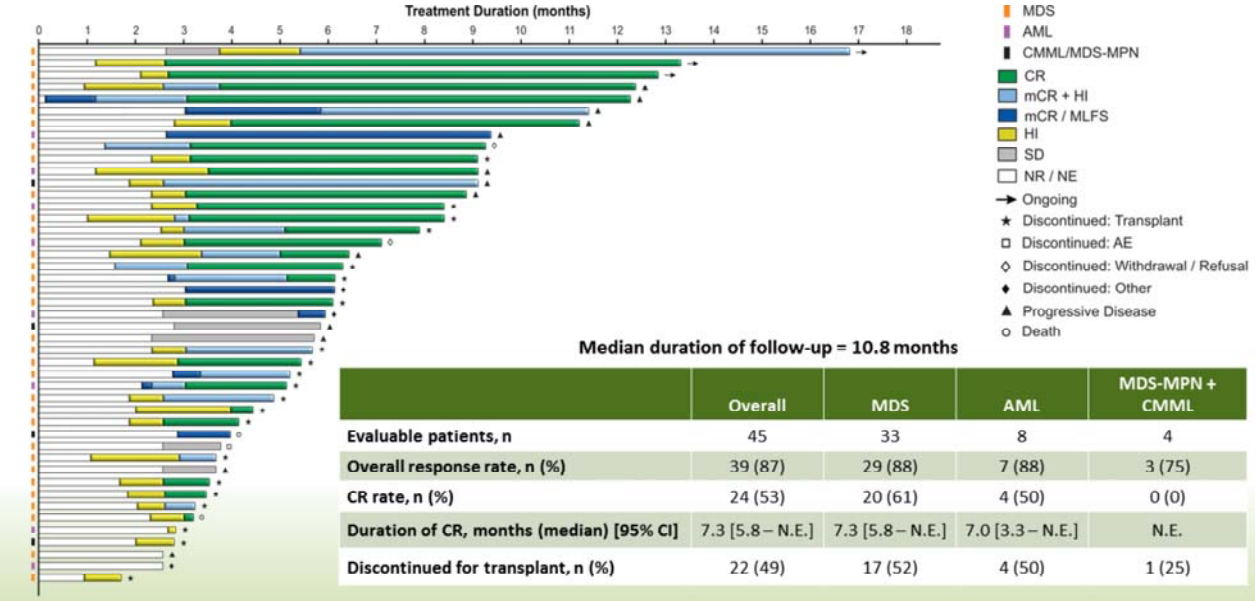


Perl A, et al, *Blood.* 2019;134(Supplement_1):3910.

We already discussed the gilteritinib and venetoclax, similar combinations are being looked at with other FLT3 inhibitors like quizartinib as well as midostaurin, initially as doublets which are, this is the only one that has been presented showing high response rates about double of what we would see with the single-agent gilteritinib, quizartinib second-generation FLT3 inhibitor and the question now is can you somehow move these in the frontline? Of course we are very, very cognizant of myelosuppression, and this will usually have to be done in a trial setting with early bone marrow evaluation and shortening venetoclax durations, but I think those approaches could be very fruitful knowing that FLT3 as well as venetoclax are synergistic with HMA on their own and with each other. So look out for that data.

New Advances in AML

AZA + APR246 in TP53 Mutated AML/MDS (n=45)



Median duration of follow-up = 10.8 months

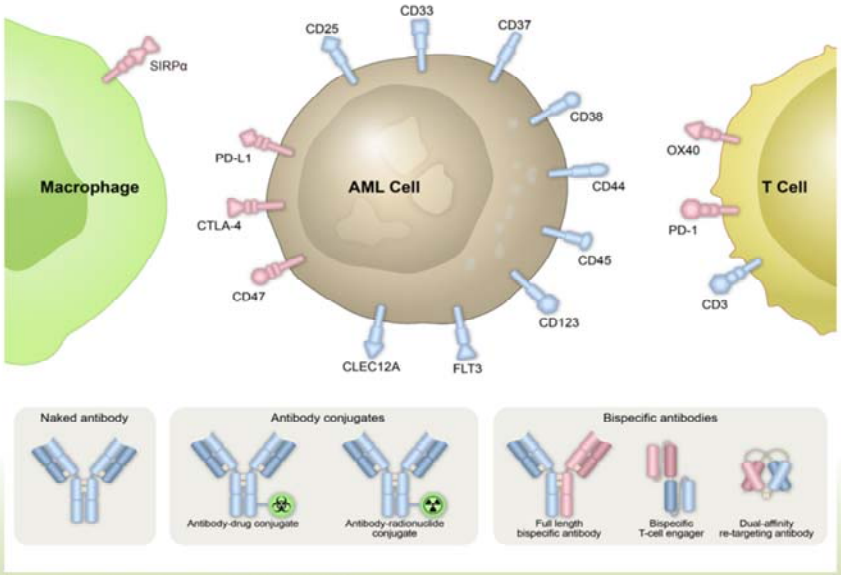
	Overall	MDS	AML	MDS-MPN + CMML
Evaluable patients, n	45	33	8	4
Overall response rate, n (%)	39 (87)	29 (88)	7 (88)	3 (75)
CR rate, n (%)	24 (53)	20 (61)	4 (50)	0 (0)
Duration of CR, months (median) [95% CI]	7.3 [5.8 – N.E.]	7.3 [5.8 – N.E.]	7.0 [3.3 – N.E.]	N.E.
Discontinued for transplant, n (%)	22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

Sallman D, et al. *Blood*. 2019;134(Supplement_1):676.

The other is TP53 and you know we have a great tendency to be very excited about everything in the TP53 space because rightly so we need something to be excited about. HMA/Ven for a couple of years we thought could be one of the breakthroughs, initial responses looked good, but the duration and survival unfortunately has come down at six to eight months' survival, both in the phase II as well as in some of our published larger ISD studies. There are now two drugs that we hope will be at least improving the outcome. We do not think necessarily they can be curative. That is a very high bar for TP53. One of them is this drug called APR which impacts the folding of the P53 protein, and as you see on this data that David Sallman had presented at the recent ASH meeting, response rates were quite high in the AML/MDS populations where you are seeing upwards of 80% overall response rates and more impressive to me, a true CR, meaning less than 5% blasts complete recovery of counts of more than 50%. Historically, with HMA alone published data has shown 15% to 21% true CR rates in this population, so a 50% true CR will hopefully be translated to survival. A phase III of Aza APR versus Aza in MDS intermediate, high-, very high-risk is close to completion and here are triplet approaches with Aza/Ven APR as well as doublets of Aza APR in AML TP53, so this is a drug hopefully to look out for.

New Advances in AML

Immune Based Approaches in AML/MDS



Two major approaches:

1. Antibody drug conjugates (CD33, CD123, CLL1)
2. T-cell based therapies
   a. Bi-specific antibodies (CD3 x AML antigen)
   b. Immune checkpoint-based approaches; T-cell and macrophage based
   c. CAR T (CAR NK)
   d. Vaccines

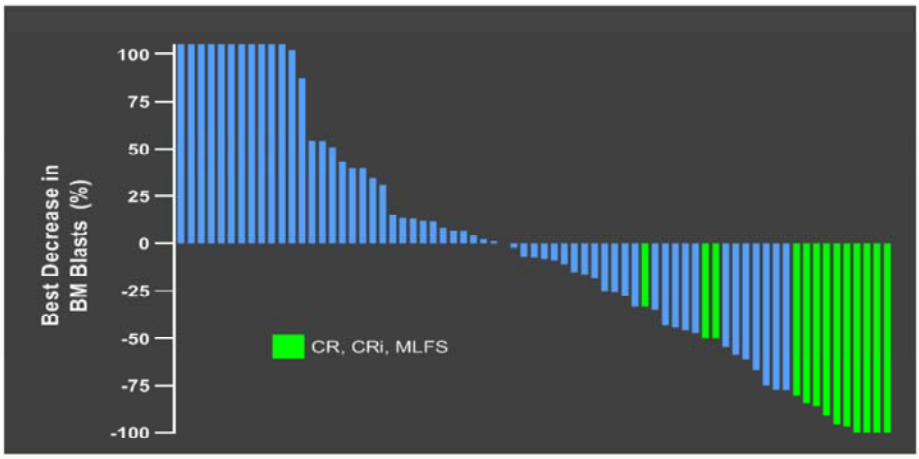
Short N, et al. *Cancer Discov*. 2020;10(4):506-525.

Now moving to immunotherapies, this is a kind of big emerging area in AML following suit from ALL and lymphoma where, as you know, immunotherapy has played major roles either as bispecific or CAR-T or antibody-drug conjugates, and in AML we are trying to replicate, and are seeing some early successes, especially with the ADC approaches, but hopefully we will be able to see some similar things with the bispecifics and checkpoints.

New Advances in AML

AML Efficacy

BM-evaluable Patients (n=71): BM Blast Reductions in >50% Patients

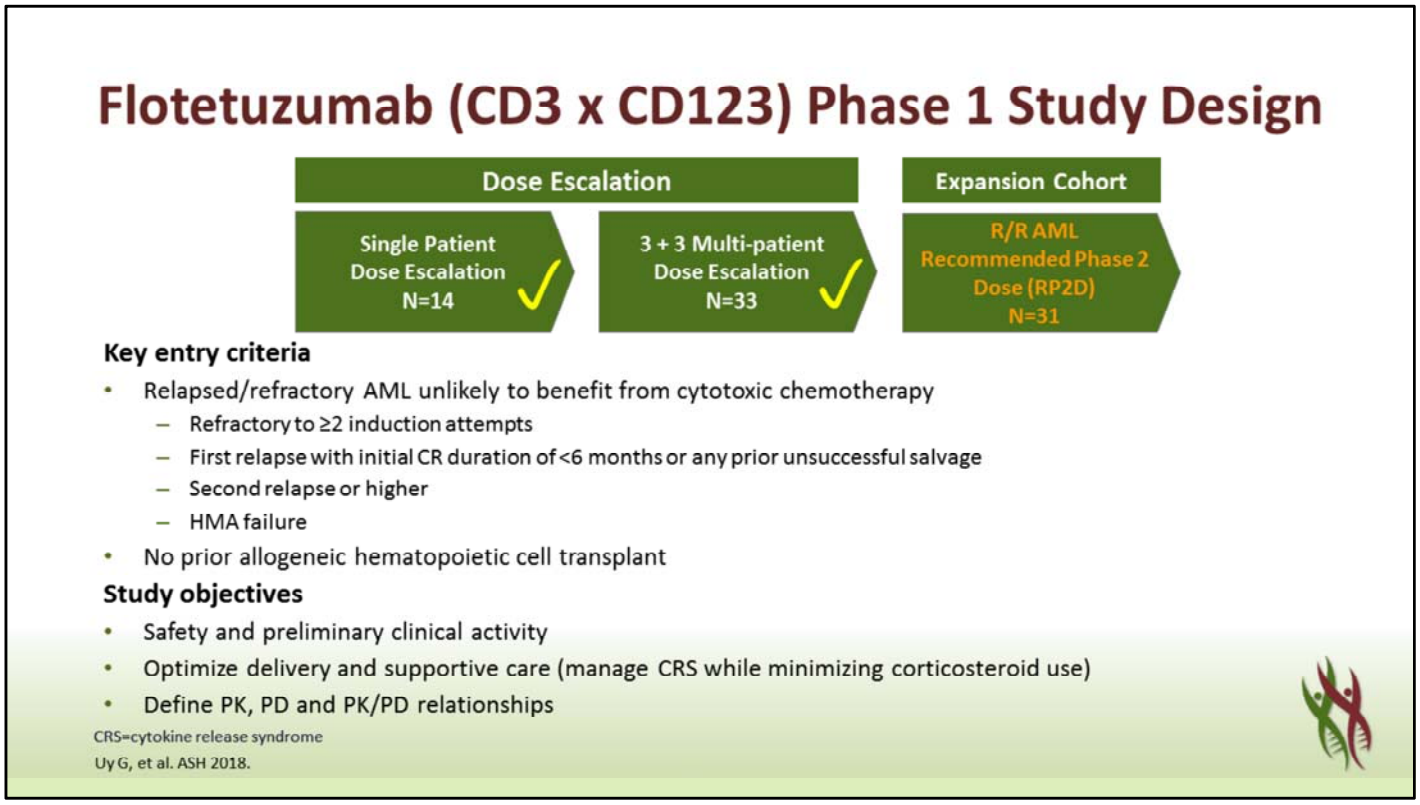


- 54% of BM-evaluable patients had a reduction in BM blasts
- 13 responses (2 CR, 10 CRi, 1 MLFS*) observed across both schedules and at multiple dose levels
- Fractionated Schedule B did not appear to provide increased efficacy

Daver N, et al. *Blood*. 2019;134(Supplement_1):734.

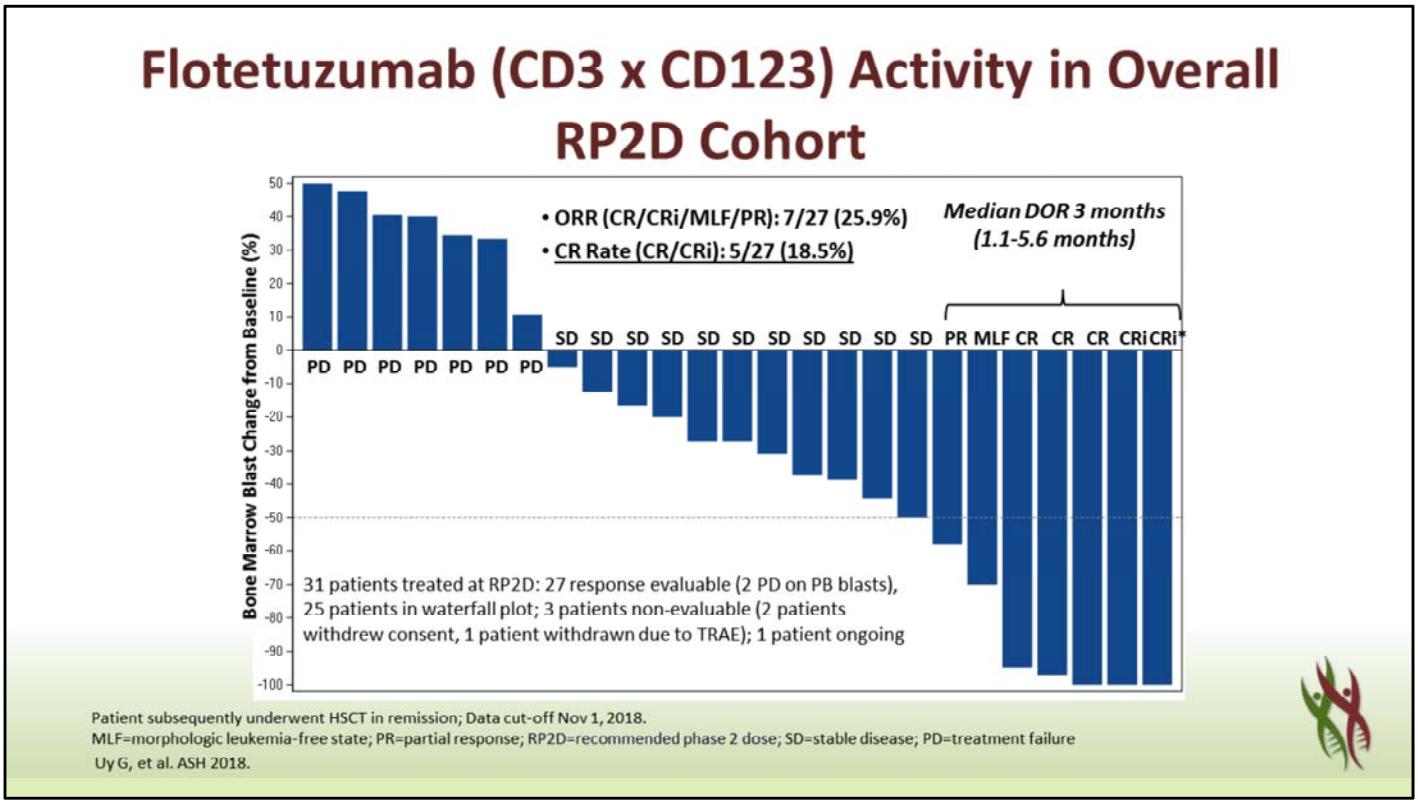
So we know gemtuzumab is the approved ADC. It is used extensively ,especially in core-binding factor upfront in combination with chemo. There are other ADCs, one of them that we have been working with a number of other centers in the US is a drug called IMGN. This is CD-123 antibody-drug conjugate. We have shown the updated data in relapsed patients. Response rate is about 25% to 35% CR/Cri, a little bit better than what we are seeing with gemtuzumab. The good thing is it seems quite safe. We do not see a high signal of VOD and myelosuppression also seems to be less than we are seeing with gemtuzumab and SGN and some other drugs, so this is now in combination with Aza and Aza-Ven in the frontline setting in a multinational setting, and hopefully will be another potential ADC in the future now targeting CD123, not only the 33 that we have.

New Advances in AML



The other one that I think is of interest and is in advance development is a bispecific, so as you know in ALL there is a bispecific called blinatumomab which is a CD3, CD19, target CD19 on ALL, CD3 on T cells and brings the T cells in proximity to the ALL cell, resulting in T cell mediated death of the leukemic blast. Similar approach is being tried by many different constructs in AML.

New Advances in AML



One of them that has shown some early signals of efficacy, especially in a high-risk group called primary refractory AML, is a drug called flotetuzumab and this was data that showed response rates about 25% to 30%, was updated at ASH 2019 showing that in primary refractory AML the response rates were about 30% to 35% which was encouraging compared to what has been seen historically, and the drug is focusing on that population as well as on MRD eradication, which has been shown to be effectively done by blinatumomab.

New Advances in AML

AZA + NIVO in Relapsed AML: Response (N = 70)[1]

Best response	N (%); Median [Range]	
	Azacitidine/Nivolumab	Control
Overall Response Rate	23 (33)	35 (20)
CR	4 (6)	17 (10)
CRi/CRp	11 (16)	15 (9)
PR	1 (1)	1 (1)
HI* (6 months+)	7 (10)	2 (1)
Stable disease (6 months+)@	6 (9)	NA
Non responders	41 (58)	131 (76)
Median cycles to response	2 [1 – 13]	2 [1 – 6]
Median follow up, in months	13.3 [8.2 – 25.5]	51 [0.1 – 64.8]
ORR in prior HMA-Naïve (N=25)	52%	19% (P<0.001)
CR/CRi in prior HMA-naïve	28%	16% (P=0.18)
ORR in prior HMA-exposed (N=45)	22%	23%
CR/CRi in prior HMA-exposed	18%	23%

*=@ Response maintained >6 months

How does this compare to other HMA Rx in R/R AML??

Single-agent AZA/DAC (n = 670) in prior HMA-naïve retro analysis, ORR = 23%
CR/CRi rate = 16%[2]

AZA/DAC + VEN in prior HMA-naïve:
CR/CRi: 30-35%[3,4]

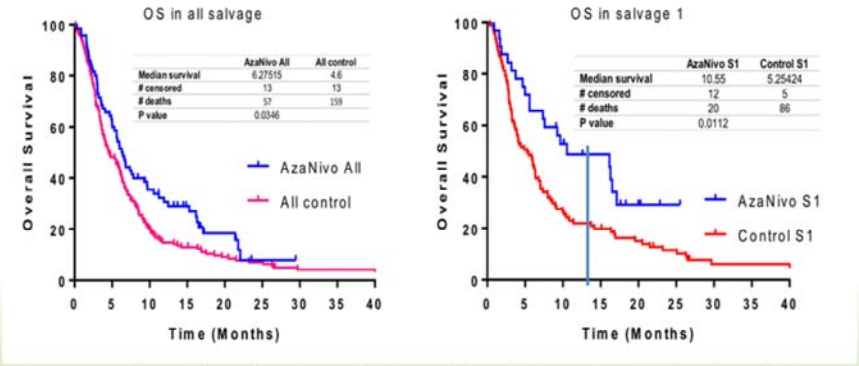
[1]Daver N, et al. *Cancer Discov.* 2018;9(3):370-383. [2]Stahl M, et al. *Blood Advances.* 2018;2(8):923-932. [3]DiNardo C, et al. *Am J Hematol.* 2018;93(3):401-407.
[4]Goldberg A, et al. ASH 2018. Abstract 1353.

The other agents that of course from solid tumor most of you are very, very familiar with our immune checkpoint drugs. We are looking at different combinations of these PD1, CTLA4 doublets of those now emerging new checkpoints such as TIM-3 stain that may actually have specific activity in AML from preclinical data. The completed clinical trial that has been published is HMA with a PD1 inhibitor, this was when this relapsed AML population and especially in people who had not had a prior HMA, so people who are failing induction 3+7 FLAG/Ida other approaches, we do see a good response rate, overall response rate 50%, CR/CRi 30% which is better than single-agent HMA and in the range we see with HMA/venetoclax in relapsed population and

New Advances in AML

OS AZA + NIVO vs Historical HMA Combos at MDACC R/R AML; Censored for SCT

- 70 patients with R/R AML (median age 70 years)
- Median OS better than historical with AZA/DAC matched R/R AML clinical trial controls, particularly in salvage 1 (10.5 months vs 5.4 months, *P*<.011); 1-year OS = 50%[1]



Expected survival in salvage 1 with HMA (n=670): 6.0 mos, 12-mo OS: 16%[2]

Improved efficacy in early salvage: Blina and CAR T in ALL, MGD006 in prim ref AML

[1]Daver N, et al. *Cancer Discov.* 2018;9(3):370-383. [2]Stahl M, et al. *Blood Advances*. 2018. Abstract 148.

especially in the early salvage population where some of our correlative analysis looking at cytokine production as well as T cell activity functionally seemed to show that it is the early relapses that will maintain T cell activity once you get to advance salvage, salvage 3 and 4, especially after a heavy exposure to purine analogs and transplant, you have very significant abrogation almost, complete negation of T cell activity. So similar to CAR-Ts and bispecifics, I think either low burden MRD disease, relapsed AML, first salvage, it is where these drugs could show benefit, and a lot of the bispecifics and checkpoints are being moved into that area like they did in ALL.

New Advances in AML

The First-in-Class Anti-CD47 Antibody Magrolimab in Combination with Azacitidine is Effective in MDS and AML Patients: Updated Ongoing 1b Results

David A Sallman[1], Adam Asch[2], Monzr Al-Malki[3], Daniel Lee[4], Guillermo Garcia-Manero[5], William Donnellan[6], Daniel Pollyea[7], Suman Kambhampati[8], Guido Marcucci[3], Rami Komrokji[1], Joanna Van Elk[9], Ming Lin[9], Jens-Peter Volkmer[9], Roy Maute[9], Chris Takimoto[9], Mark Chao[9], Paresh Vyas[10], Naval Daver[5]

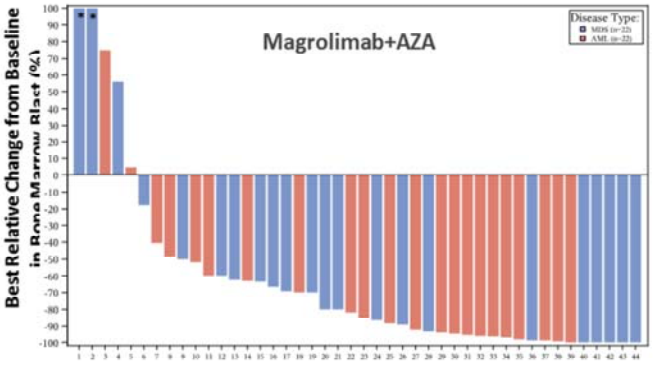
[1]Moffitt Cancer Center, Tampa, FL; [2]University of Oklahoma, Oklahoma City, OK; [3]City of Hope, Duarte, CA; [4]Columbia University, New York, NY; [5]MD Anderson Cancer Center, Houston, TX; [6]Sarah Cannon Research Institute, Nashville, TN; [7]University of Colorado, Denver, CO; [8]Healthcare Midwest, Kansas City, MO; [9]Forty Seven, Inc., Menlo Park, CA; [10]University of Oxford, Oxford, UK

Among the exciting drugs that I mentioned for TP53 and also a form of immunotherapy is the CD47 antibody magrolimab, we are quite excited about this agent.

New Advances in AML

Anti-Leukemic Activity of Magrolimab + AZA in MDS and AML

Best Overall Response	1L MDS N=24	1L AML N=22
ORR	22 (92%)	14 (64%)
CR	12 (50%)	9 (41%)
CRi	-	3 (14%)
PR	0	1 (5%)
MLFS/ marrow CR	8 (33%) 4 with marrow CR + HI	1 (5%)
Hematologic improvement (HI)	2 (8%)	-
SD	2 (8%)	7 (32%)
PD	0	1 (5%)



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

- Magrolimab + AZA – 92% ORR (50% CR) in MDS and 64% ORR (55% CR/CRi) in AML
- Median time to response is 1.9 months, more rapid than AZA alone
- Magrolimab + AZA efficacy compares favorably to AZA monotherapy

Sallman D, et al. *Blood*. 2019;134 (Supplement_1):569.

There will be a lot of updates on this and upcoming meetings this year, and as you can see looking at the overall response rates that were shown in ASH this year. In the frontline MDS setting, overall response I think is tricky in MDS, you know blasts are low, it's hard to really judge, but a true CR rate of 50% is definitely better than what we have seen, about 15% to 18% CR rate is what we have historically shown with HMAs. And in AML also the combination is showing some early activity now. This is probably lower than what we see with HMA/venetoclax, so I don't think head-to-head this would be necessarily better. Can you combine them? Of course that is the question, and there are triplets that are going to look at that like we are with APR. But specifically in TP53, where there will be more updated and a larger number of patients presented at some of the upcoming meetings, there seems be a signal in AML high response rates, about 75% to 80%, and durability, so either APR or 47, either with HMA or HMA-Ven, we hope will show us in the next year or so some exciting data to move forward. And then in MDS, the Aza-magrolimab is currently in the registration approach with this current study being expanded to 100 patients as well as subsequent phase III study confirmatory studies, so these both drugs, APR and 47, could be, even by the end of this year, potentially agents that we may hear positive data on and potentially get added to MDS/AML regimens

Conclusions

- HMA + VEN outstanding in frontline unfit AML but response and OS in R/R AML modest. Novel combinations VEN+MDM2, VEN+MCL-1i, VEN + FLT/IDH appear encouraging. Triplets ongoing/planned
- MDM2i (Idasanutlin) and E-selectin-I (GMI-1271) in phase 3, registrational trials
- Immune therapies (novel and safer ADCs, bispecific Ab, CPI based) may be next major wave of development in AML, multiple trials ongoing
- AML may be following MM paradigm, effective and safe doublets/triplets to improve PFS/OS with lower toxicity/mortality

Alright. Okay, with that I will move on then to our closing.

So, thank you all for joining us for this presentation. I hope it is informative and will be useful, and we are happy to be able to provide whatever information and education we can in such a fast-moving field.