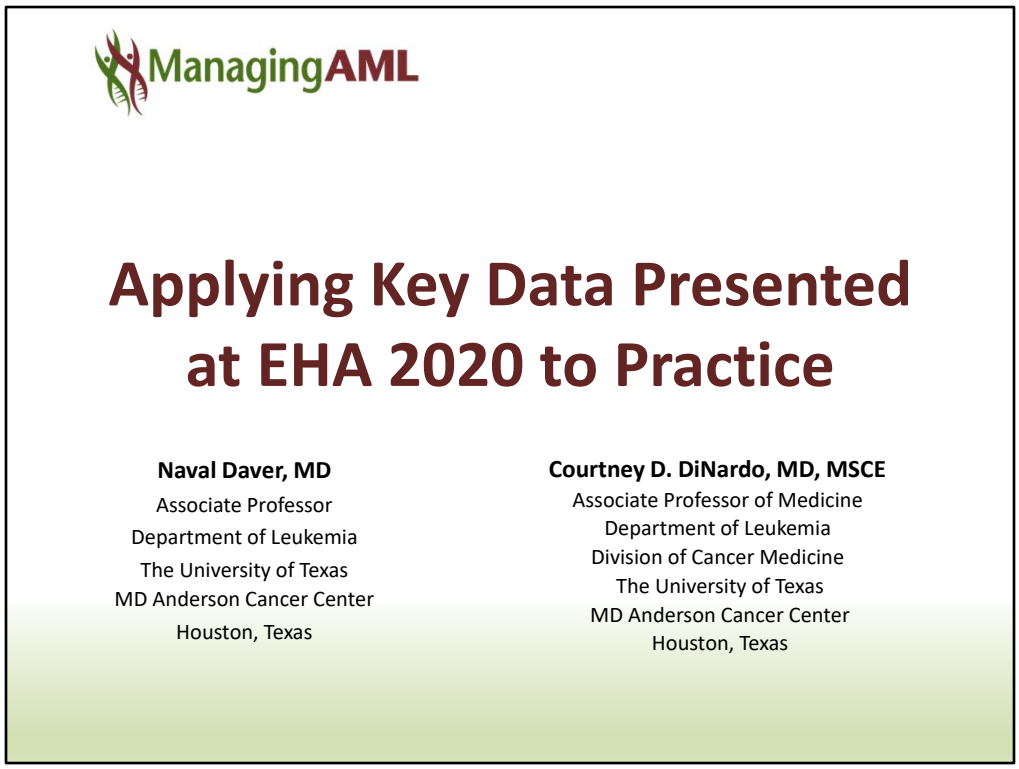
# Applying Key Data Presented at EHA 2020 to Practice




**Naval Daver, MD:** Hello and welcome to *Managing AML*. I am Dr. Naval Daver and today, I am joined by my colleague, Dr. Courtney DiNardo. Today, we will discuss new data in acute myeloid leukemia and how it translates to practice by reviewing four different case scenarios.

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## Case 1

- 57-year-old with fatigue, SOB and loss of appetite last 4 weeks. Seen by PCP. CXR with no abnormality
- CBC shows WBC 27.2K, Hgb 8.4, platelet count 34K
- Creatinine slightly elevated at 1.4. LDH 2x ULN. Other electrolytes in normal range
- ECOG PS 1
- He is a mechanical engineer. Works full time. HTN well-controlled on amlodipine. No other comorbidities
- No family history of malignancy
- Nonsmoker, ETOH 1-2 times per week

This is the first case. This is a 57-year-old with fatigue, shortness of breath, and loss of appetite for the last four weeks, seen by his primary care doctor, chest x-ray with no abnormalities. Here you see the blood counts; white count of 27, hemoglobin is 8, platelet count of 34,000, slightly elevated creatinine and LDH, other electrolytes are within normal range, has a good ECOG performance status, works as a mechanical engineer, has continued to work full-time at this time, has hypertension and no other comorbidities and no family history of malignancy. He is a nonsmoker, occasional alcohol use, one to two times per week.

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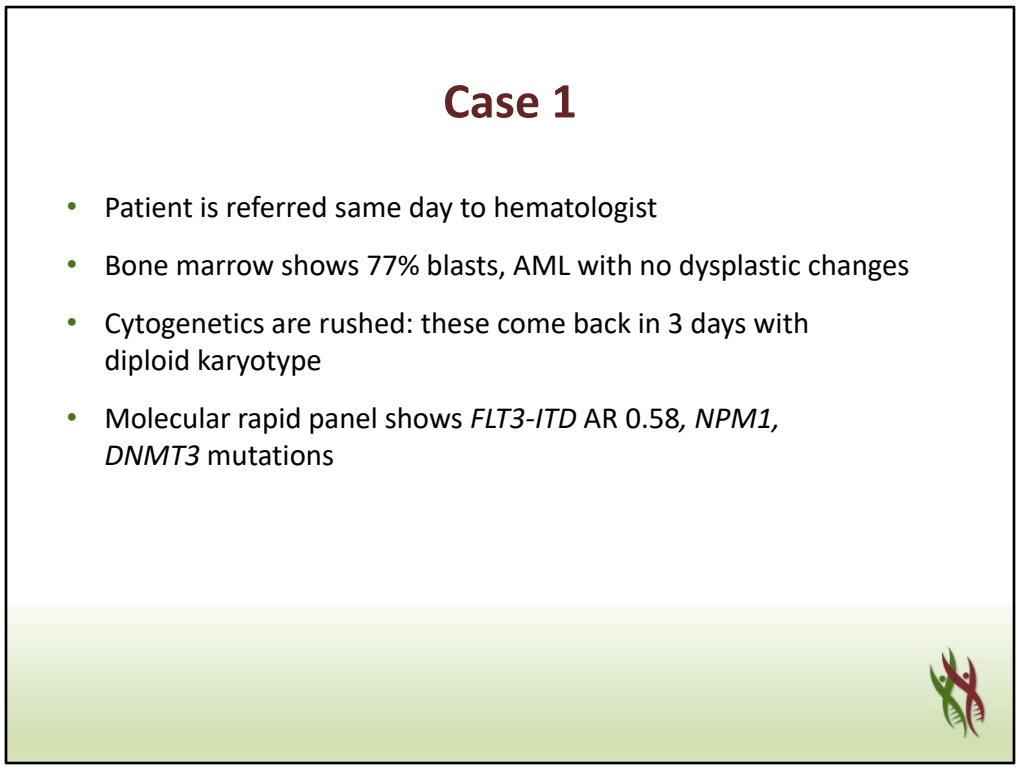


The patient, as it's usually done, is referred the same day to the hematologist and a bone marrow was done. This showed 77% blasts consistent with acute myeloid leukemia, no dysplastic changes. The cytogenetics were rushed, and this came back three to four days later showing a diploid karyotype. Molecular panel was also rushed and the NGS showed FLT3-ITD mutation within an allelic ratio of 0.58, NPM1 mutation and DNMT3A mutations.

At this time, I will ask Dr. DiNardo, is this a common patient that you would see and what would be your initial thoughts for this patient?

**Courtney DiNardo, MD:** I think, well certainly, AML is not a particularly common cancer but in terms of AML, this is one of the more common case scenarios we will see which is a relatively young, in the terms of AML, kind of 40s to 50-year-old presenting with an elevated white cell count and in the setting of a high white cell count, kind of proliferative disease and oftentimes, we will see an intermediate type cytogenetic, diploid cytogenetics with the FLT3-ITD mutation so I think, in my mind, when I'm seeing a patient with leukocytosis with a white count higher than normal, I'm always thinking, could this patient have a FLT3-ITD mutation?

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**Naval Daver, MD:** Yes. I think, that's the key with this leukocytosis as we discussed in our meetings very frequently in the Leukemia Department here at MD Anderson, some of our first thoughts are a FLT3-ITD mutation and then sometimes, we're seeing RAS-MAP kinase mutations also presenting with such proliferative features, PTPN11, RAS, so these are patients we usually want to wait for molecular testing. Of course, they're proliferative so you want to control their white count. You can admit them, do Hydrea (hydroxyurea). Sometimes, you give one dose of cytarabine if they're really proliferative, white count above 70-80, but we definitely want to get their FLT3 testing, especially since we enroll many of these patients on frontline FLT3 trials, but in the community, these would be the patients you want to look out for use of frontline FLT3 inhibitors such as with midostaurin, sorafenib, or gilteritinib.

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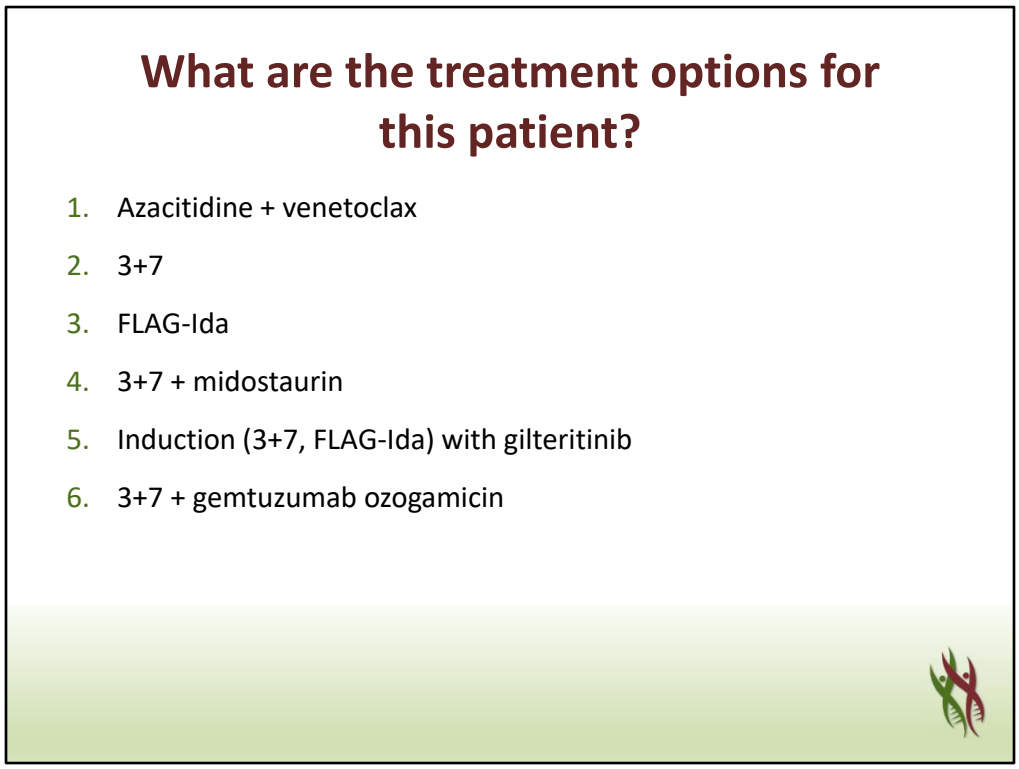


Just to throw it out there, what are the treatment options for this patient? These are, we have a good situation now in AML emerging where we have a lot of good treatment options but still, there are some that are better than others for a given scenario, so these are all approved treatments or NCCN guideline-based treatments, azacitidine, venetoclax of course, 3+7 standard, FLAG-IDA that is being used quite frequently in many countries as well now in many centers in the US, 3+7 with midostaurin which is a multi-kinase inhibitor that also targets FLT3, induction therapy with gilteritinib, which is second-generation FLT3 inhibitor, or 3+7 with gemtuzumab ozogamicin, the CD33 antibody drug conjugate that is also proven in the frontline setting and used more frequently in core-binding factor type of acute myeloid leukemia.

Here, I would ask Dr. DiNardo, what would your thoughts be for this patient? Which regimens would you consider and how would you approach the patient?

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**Courtney DiNardo, MD:** I think the most important thing in a patient is, well first of all I suppose, deciding is your patient going to receive an intensive chemotherapy base or non-intensive chemotherapy-based treatment? And what we have heard so far from this patient, who is in her 50s and who has a good performance status and does not have any significant underlying comorbidities, this is definitely someone I would be thinking for an intensive chemotherapy regimen, and given the FLT3-ITD allelic ratio, I would be prioritizing an intensive chemotherapy with a FLT3 inhibitor, and so I think options four and five on my list are top if you are at a community center around the world, 3+7 with midostaurin is the standard here. We are participating in several clinical trials with second-generation FLT3 inhibitors that may kind of surpass the role of midostaurin in the future.

**Naval Daver, MD:** Yes, absolutely. I think the key here is given the FLT3 mutation, we absolutely would be preferring a FLT3-inhibitor base, midostaurin currently approved, based on the RATIFY study that I'll discuss, but a lot of excitement in the large academic centers movement towards using the second-generation FLT3 inhibitors like gilteritinib upfront. I'll show some of that data that shows why we're excited about this.

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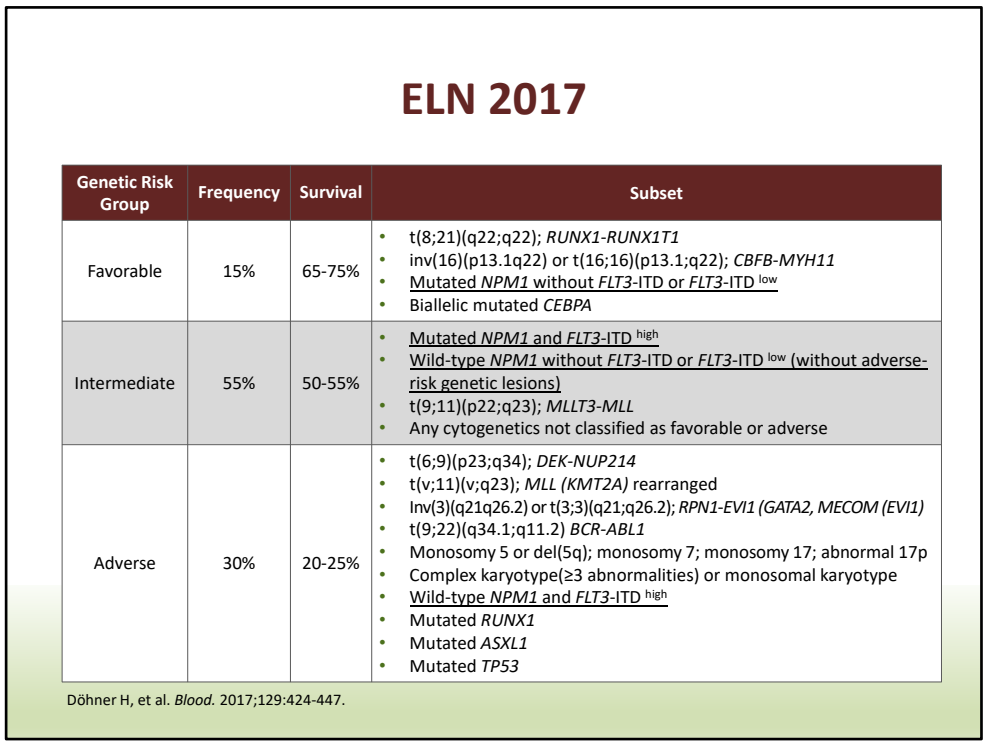

## ELN 2017

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

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

One of the key things now in acute myeloid leukemia is that we do require molecular mutation testing at baseline for all patients. This is both for prognostic value as well as for therapy selections. As you see, the ELN 2017, which will likely be updated in the near future, already does incorporate different molecular mutations in addition to the traditional cytogenetics that we have been using for acute myeloid leukemia prognostication. You see here, NPM1-FLT3 mutations and others such as ASXL1, TP53, RUNX1 have now been identified as independent prognostic impact mutations that could put a patient in a higher or lower group. The other important thing is that individual mutations while important, are not giving us the complete story. As you can see, if somebody emails me, which we do get a lot of emails like this, I have a 50-year-old with a FLT3 mutation. What do you suggest? I really cannot give any clear guidance because if that patient has a low FLT3 allelic ratio with an NPM1, the patient potentially could be a more favorable risk. On the other hand, if that patient has a high FLT3-ITD burden with no NPM1, then that patient is adverse risk, so you can see having a FLT3 mutation alone, you could still be in favorable intermediate adverse risk, and we really need to know the allelic burden or allelic ratio as well as the co-mutation, and this is just the beginning. We now know that other co-mutations such as having DNMT3 along with NPM1-FLT3 could further have a prognostic impact, maybe TET2 and others; so I think this field will get more and more fine-tuned with time.

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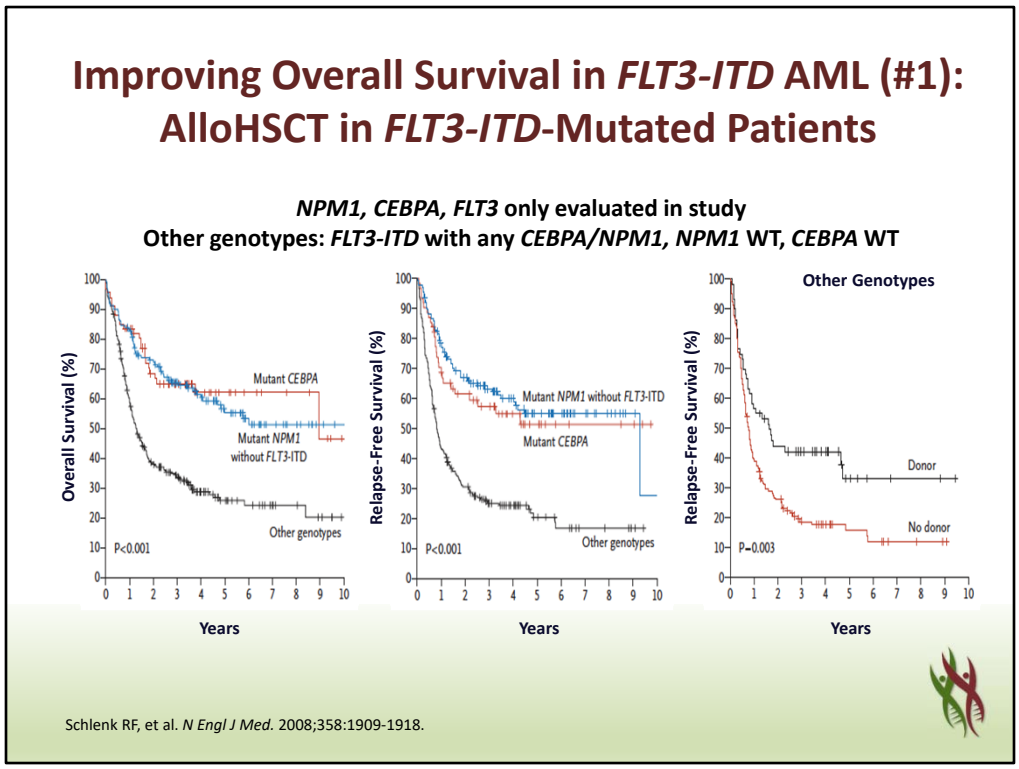


So one of the first things that started occurring with the FLT3 mutations is when we identified that these were adverse prognostic factors, we started taking this people to transplant. This is one of the initial papers now 12 years ago, that showed the impact of transplant in improving outcomes in patients who had FLT3-mutated AML. This benefit was specifically seen in FLT3-mutated, there was not as much as benefit in people who had mutated NPM1 without FLT3, so transplant has been one of our go-to approaches for all FLT3-mutated patients in the frontline setting.

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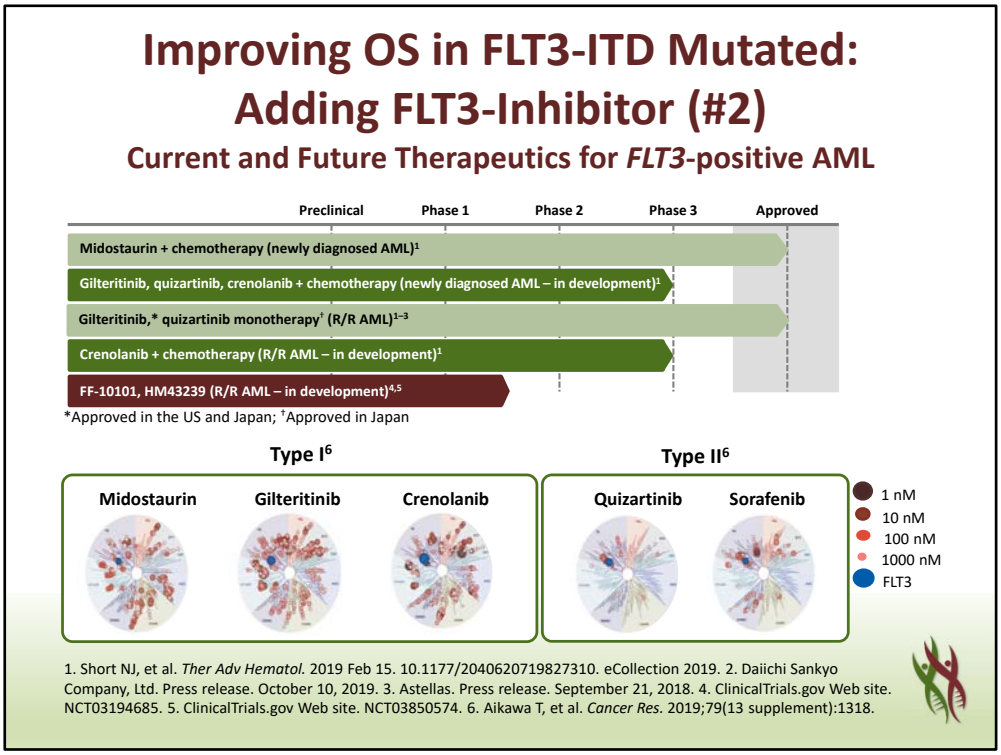


The next thing that we have been looking at is incorporation of novel FLT3 inhibitors, so as you can see in the slide there, many different FLT3 inhibitors that are now available either approved or in clinical trials for treatment of FLT3-mutated AML. These include approved agents: midostaurin in combination with induction chemotherapy as well as in relapsed/refractory setting, gilteritinib, which is approved in the United States, and quizartinib which is not approved in the United States but approved in Japan and is being evaluated in a frontline phase 3 study. In addition to this, there are other FLT3 inhibitors such crenolanib, HM43239, FF-10101, that are also in advanced clinical development at this time.

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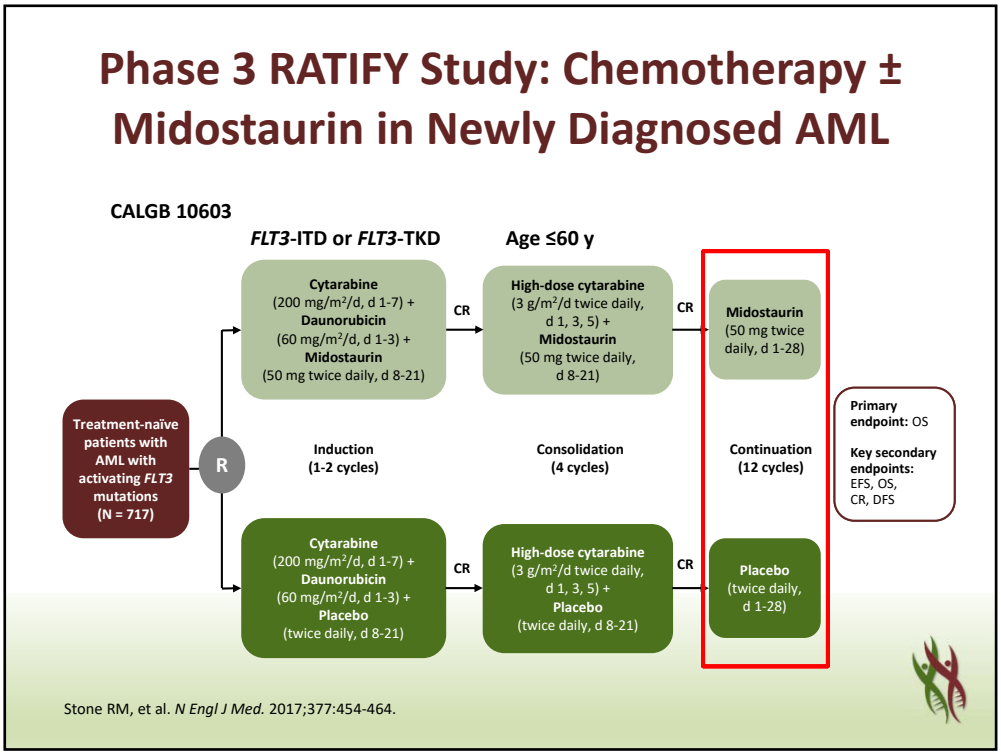


I'll briefly go over the design of the RATIFY study. This was a very critical 3+7 study. In fact, the first frontline study showing a targeted therapy added to backbone induction chemotherapy could improve outcome. Here we used the backbone of 3+7 and patients received either 3+7 with midostaurin or 3+7 placebo in the frontline setting. These were all FLT3-mutated patients, either ITD or TKD, and the primary outcome was survival. The midostaurin here was given on day 8 through 21 continued with the consolidation on day 8 through 21, and then patients could continue maintenance with midostaurin daily continuously for up to one year. Here are the results of the study.

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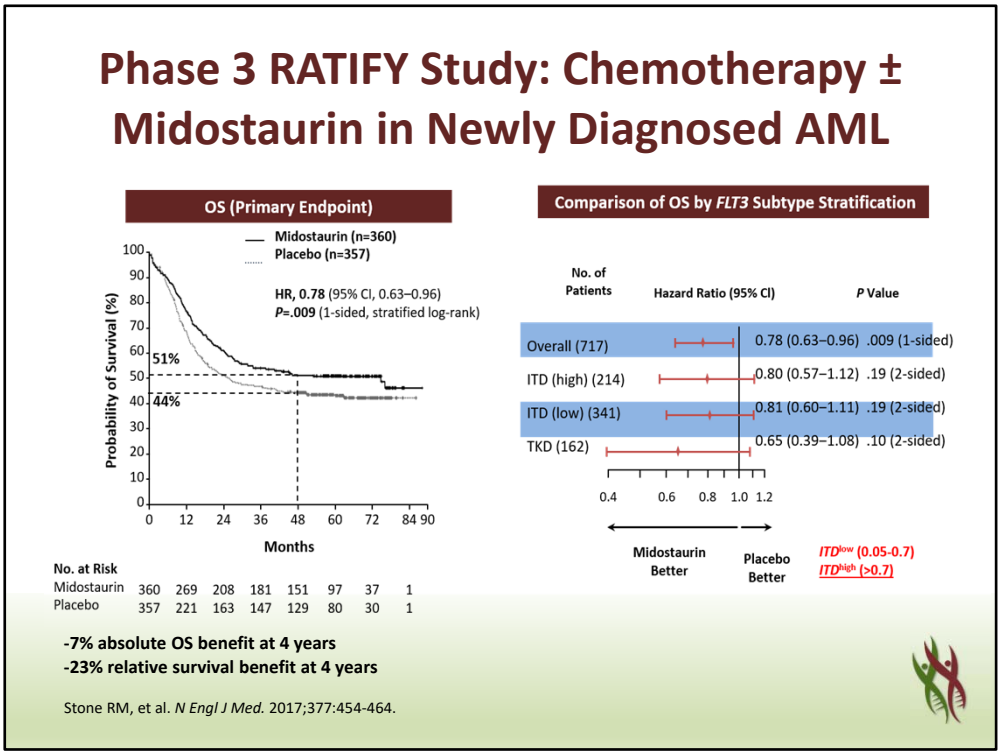


As you can see, the overall survival was significantly improved with a four-year survival of 51% compared to 44% in patients who received midostaurin with 3+7 vs those who received placebo. Importantly, what was seen is that the benefit of midostaurin was noted across all ITD high, ITD low, and TKD mutations. Now, in the end of the day, although this is an improvement, it is not a game-changer yet. We think this was the first important step in identifying FLT3 as a prognostic mutation applying it in the real-world setting, incorporating a multi-kinase inhibitor, and improving survival.

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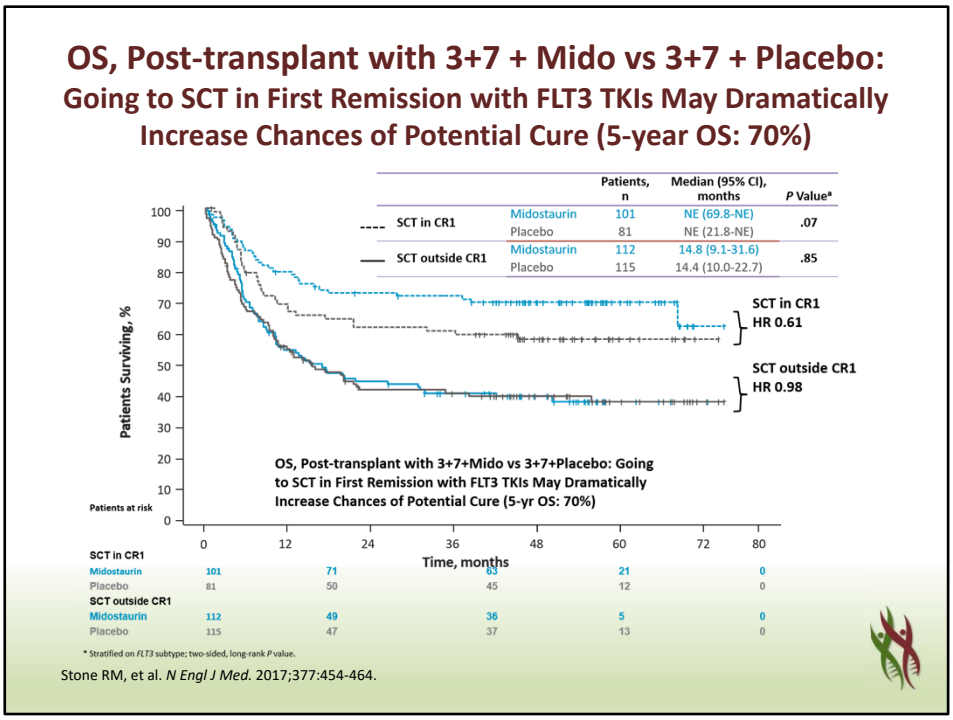

Stone RM, et al. *N Engl J Med.* 2017;377:454-464.

However, if you do use midostaurin and take the patient to transplant, so not just doing one thing but doing both approaches, then you may really get an improvement in outcome, so if you catch your patient like this patient with a FLT3-ITD mutation, you add midostaurin to your induction backbone, and you try to take that patient to transplant quickly in the first remission, ideally, after one or two cycles of treatment, then you can see those patients could have up to 60%-70% four-year survival, which is dramatic because historically, FLT3, when first identified, they had a four- to five-year survival of only 20% to 30%, so it's usually not just one intervention but a combination of interventions that is going to give you a real benefit.

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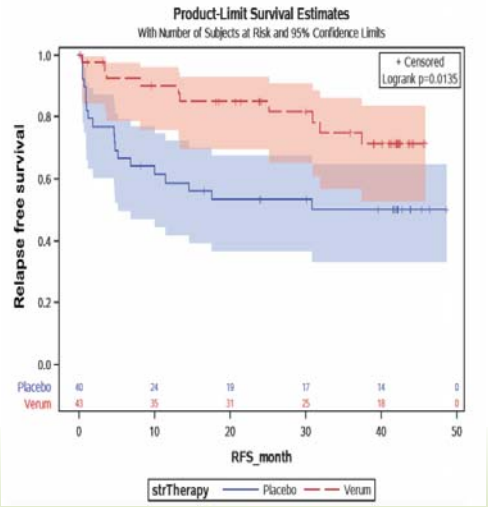
## Role of *FLT3i* Maintenance (#3)
## AML *FLT3-ITD*: Sorafenib Post Allo-SCT

- 83 patients (median age: 54 years), post allo-SCT
- Randomization to sorafenib 200 mg-400 mg BID vs placebo
- 2-year RFS:
  - Sorafenib: 85%
  - Placebo: 53%




Burchert A, et al. *Blood.* 2018;132(supplement 1):661.

The third step that emerged was the addition of a post-transplant maintenance. So, you identified FLT3, you gave a FLT3 inhibitor with induction, you took the patient to transplant, let's say after two or three cycles everything has been done well. Now, can you further improve that? And the data now suggests, with two randomized phase 2 studies, one out of the German Cooperative Group, the other out of China, showing that addition of a post-transplant maintenance with a FLT3 inhibitors, sorafenib was the one used in those two studies significantly improved both event-free survival and overall survival, and at our centers in many large academic centers, we are trying to put 100% of our patients post-transplant who have a FLT3 mutation on a FLT3 inhibitor. Now, we believe gilteritinib is a more effective and potent drug, and there is a large phase 3 post-transplant maintenance study of gilteritinib vs placebo that has completed enrolment through the Bone Marrow Transplant Network, and we hope to see that data, but at our center, we are frequently using gilteritinib post-transplant maintenance, but if one is not comfortable with that, I would definitely recommend using sorafenib, but some form of FLT3 inhibitor maintenance post-transplant.

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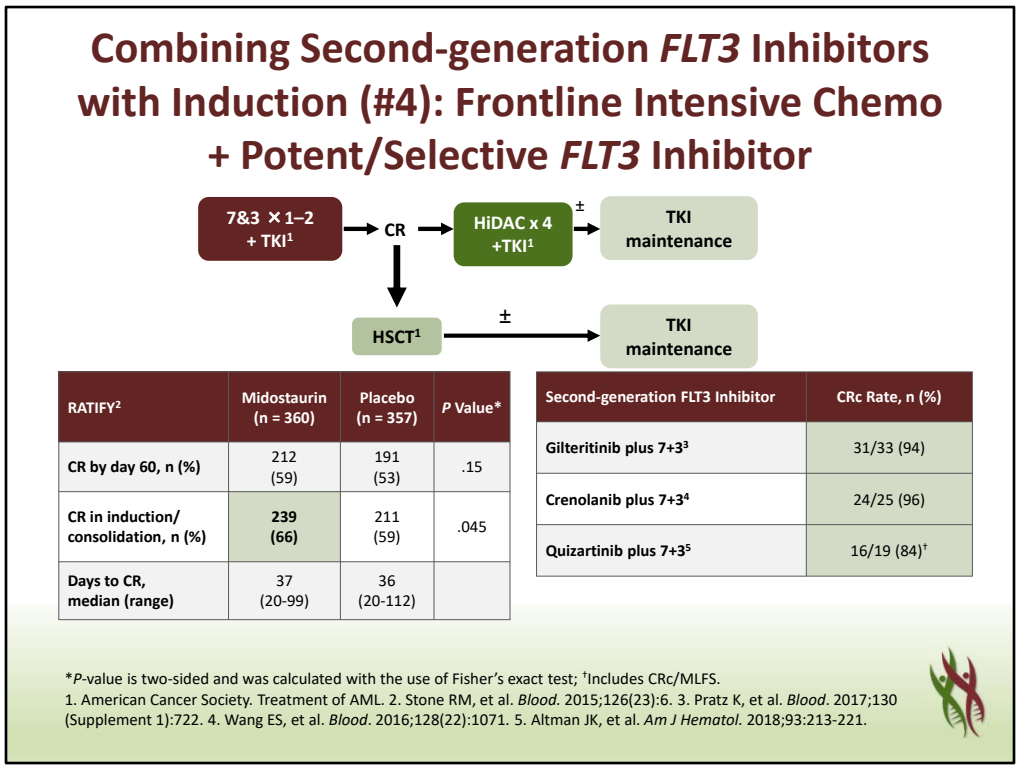


Now, after step one, two, three, we said well, we believe gilteritinib maybe quizartinib, crenolanib are highly effective drugs. They have shown single-agent activity of 50% compared to 5% or 10% with sorafenib/midostaurin. Can be this be leveraged into combining them upfront and further improving this outcome with transplant and with post-transplant maintenance? And so, this is some of the early data from the phase 1 studies that combined the second-generation FLT3 inhibitors as we call them, such as gilteritinib, crenolanib, and quizartinib with the backbone of 7+3 and again, these are different studies, so we're doing cross-study comparisons phase 3 vs phase 1, a lot of caveats there but again, we look at encouraging response rates, 90% and higher, with the second-generation FLT3 inhibitors, so this is what has got us excited that if we use a second-generation FLT3 inhibitor, take the patient to transplant, do maintenance maybe with second-generation drug like gilteritinib, then we could potentially get up to 80% or so remission and cure rates, which would be outstanding, very similar to the paradigm that's emerging for example in Philadelphia-positive ALL (Ph+ALL) with ponatinib being used upfront after transplant, and we're getting to 75%-80% five-year survival rates.

At this time, I'll turn it back to Dr. DiNardo and you know, we have used a lot of different FLT3 inhibitor combinations with gilteritinib, quizartinib, midostaurin. What are some of the side effects that you've seen and how do you kind of use this regimen in practice?

**Courtney DiNardo, MD:** I think the most important side effect to be aware of when we are

using FLT3 inhibitors is GI toxicity and probably QTc prolongation, particularly with the second-generation FLT3 inhibitors like gilteritinib and quizartinib. I think all of them are, are fairly straightforwardly managed in in terms of nausea, vomiting, diarrhea. We have good antiemetic and supportive care, but it's just something to be aware of, I think especially with midostaurin and sorafenib, the first-generation agents. There is a lot of GI toxicity. Then in terms of the QTc monitoring, I think we need to pay attention to the many other QT prolonging medicines that are very standardly used in patients with AML, for instance, fluoroquinolones, azoles, and the antiemetics themselves, monitoring QTc prolongation is important with the second-generation FLT3 inhibitors, but oftentimes, just modifying the supportive care agents that they're on can help to manage the QTc prolongation if it happens and allow you to continue on at, at the appropriate dose.

**Naval Daver, MD:** Yes, I think GI and cardiac are probably the two, and then of course the third is myelosuppression because we're adding a third a drug. And so often, we have to delay the cycle sometimes, and we cannot be rigid about the 28-day cycle that sometimes people get very rigid about in the community, so often we do see cycles go out to 35, 40 days and as long as we're monitoring closely confirming remission, I think this is okay, but both gilteritinib and midostaurin as well as quizartinib, which we have used quite extensively, are quite well-tolerated and safe drugs in general. We do not see too many symptoms or issues with them, and in general, I think we have been able to administer these FLT3 inhibitors to almost close 100% of our frontline patients who have a FLT3 mutation. I cannot think of the scenario where we would say I absolutely would not use an FLT3 inhibitor. We may shorten the duration, adjust the doses in certain patients, but I think, our goal at MD Anderson has been to give FLT3 inhibitor for all FLT3-mutated frontline patients.
Okay, so here I will turn it to Dr. DiNardo to discuss our next case please, Dr. DiNardo.

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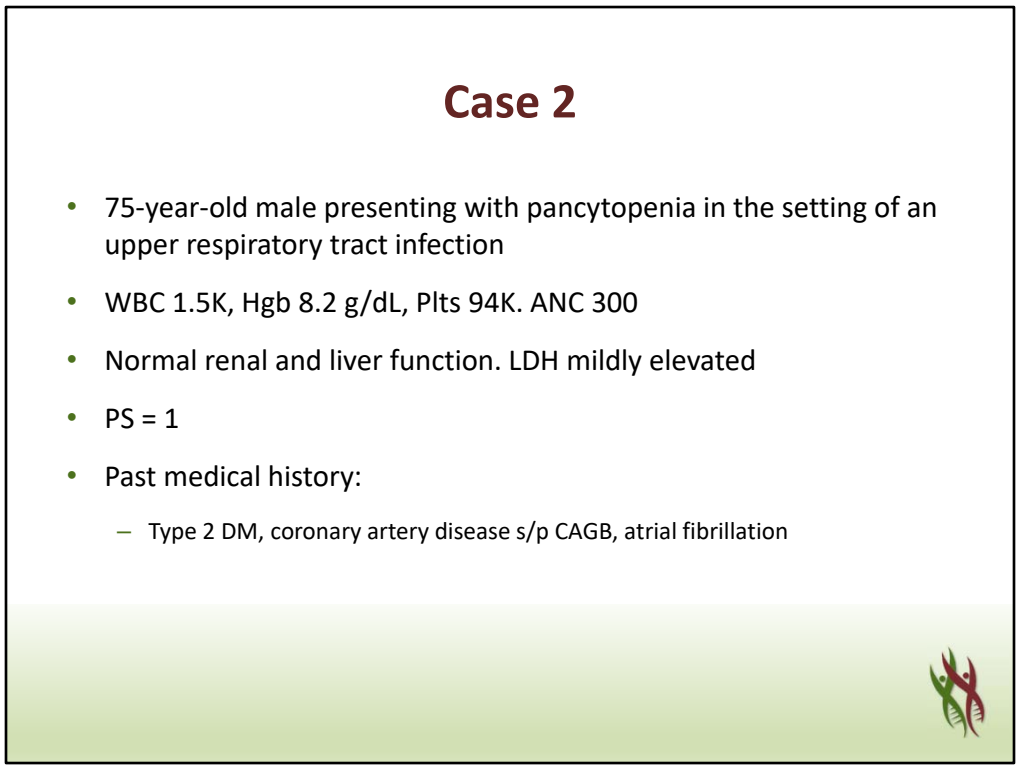


**Courtney DiNardo, MD:** Absolutely so, our second case is a 75-year-old gentleman who is presenting with pancytopenia in the setting of an upper respiratory tract infection. His counts are on the low side, a white count of 1.5, hemoglobin 8.2, platelets of 94,000, neutrophil count is low. He has normal other organ function, renal function, liver function is okay. His LDH is mildly elevated. His performance status is 1. He has a past medical history significant of type 2 diabetes and coronary artery disease and atrial fibrillation.

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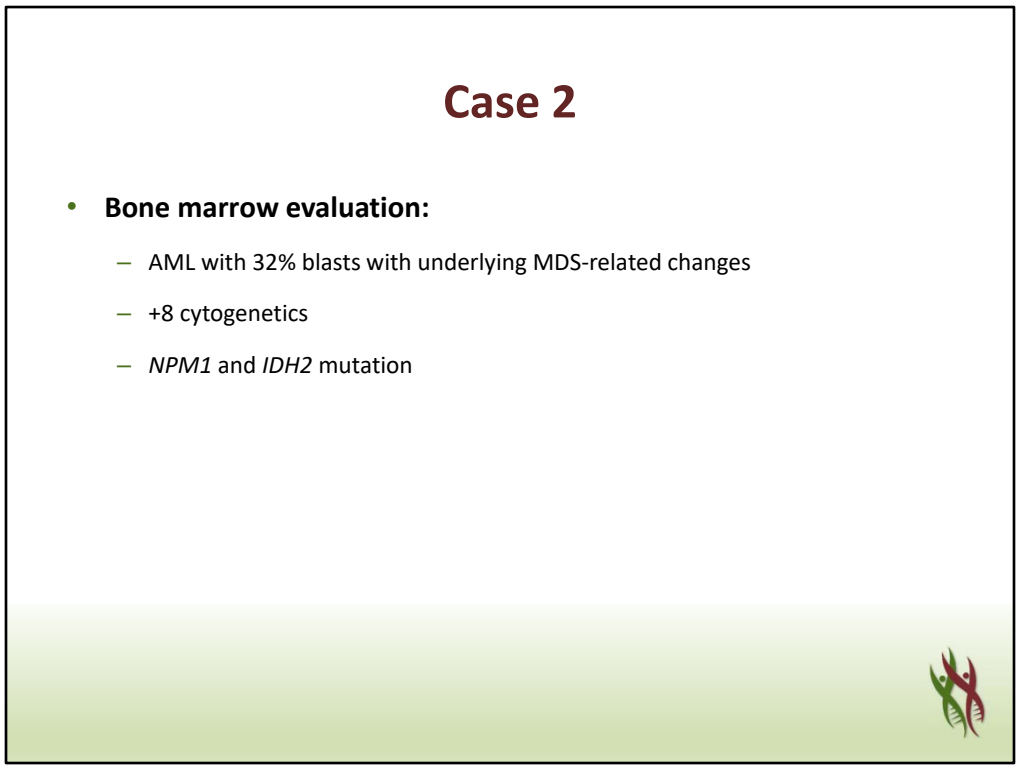


He is referred to a hematologist, where a bone marrow evaluation is performed and does confirm the diagnosis of AML, 32% blasts with underlying MDS-related changes, trisomy 8 cytogenetics, and an NPM1 and IDH2 mutation. The first question is, is the scenario commonly seen and why in particular is this a challenging case and I'll pivot back to Dr. Daver, to give his thoughts on this, and then we can go into a little bit more detail.

**Naval Daver, MD:** Yes, thank you very much. Absolutely very common case, I would say the age range and presenting features are almost close to 30% to 40% of the AML patients we see above 70 years of age. Mutations are interesting. This patient does have slightly favorable mutations, NPM1 and IDH but does have background MDS. I think the major challenges are the age of this patient, 75, where intensive chemotherapy in my opinion, I know many of us at MD Anderson will agree, is something we would not consider at this age for 99% of our patients, so I think we're looking at lower intensity but now, effective lower intensity combinations, which I'm sure you'll discuss.

**Courtney DiNardo, MD:** That's exactly right. I think this is a particularly challenging case because we have so many different options available.

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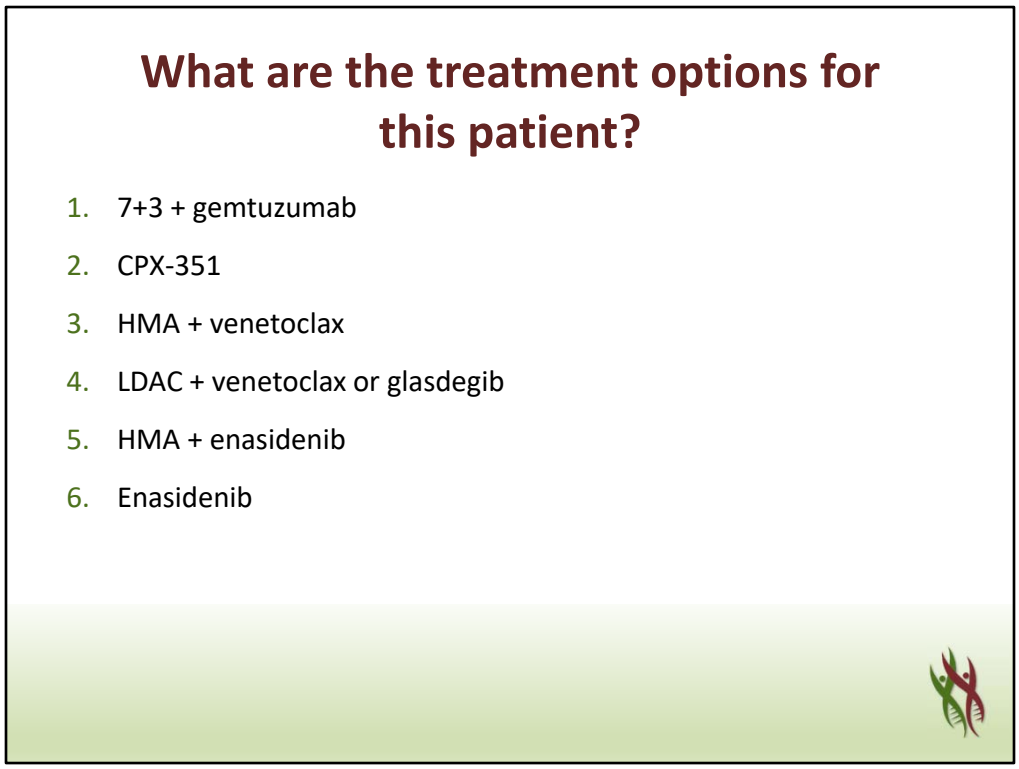


These are all options that are available approved for our patients, so you know, do we give an intensive chemotherapy based regimen with 7+3, with gemtuzumab or CPX-351 given the underlying MDS changes; or do we prioritize a lower intensity combination, hypomethylating agent with venetoclax, or low-dose ARA-C plus venetoclax or glasdegib? The patient has an IDH2 mutation, so would we think about an enasidenib containing regimen either alone or with azacitidine? I think, as Dr. Daver mentioned, the age of 75 does not preclude intensive chemotherapy, but given that our lower intensity therapy is now showing kind of equivalent responses with excellent durability, the question is, do we really want to prioritize intensive chemotherapy in someone who is on that older age range with underlying comorbidities even though the performance status is 1?

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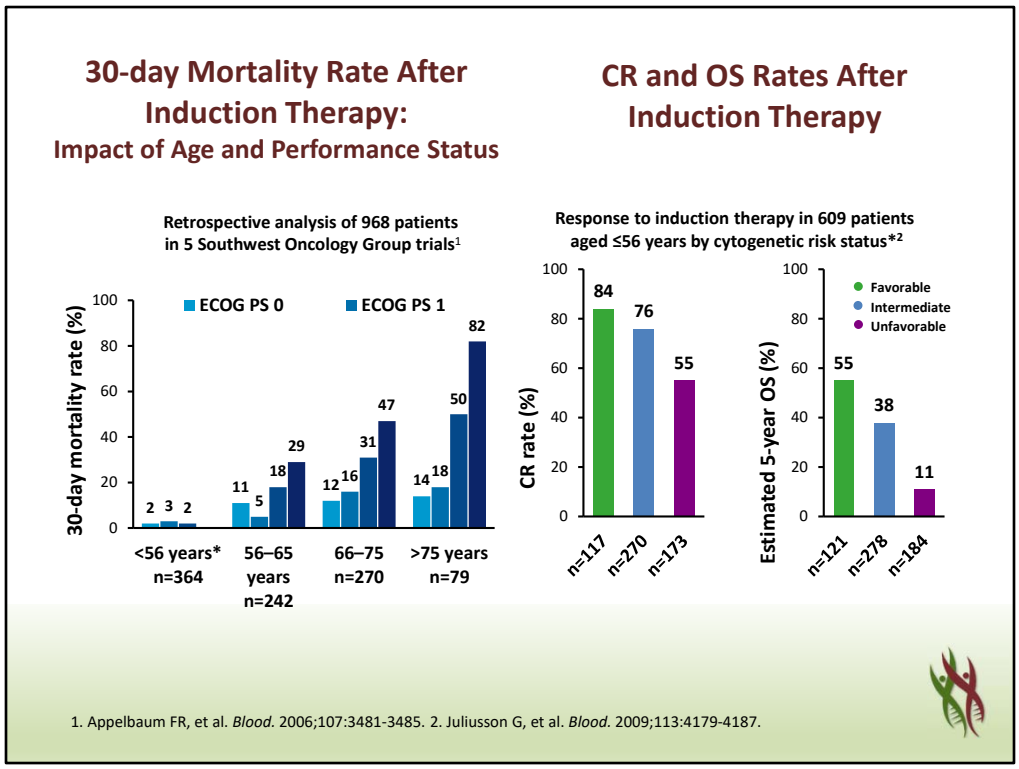


This just provides a little bit of data showing that you know, 30-day mortality does increase with increasing age and increasing performance status which really does I think, have to factor into the decisions we make.

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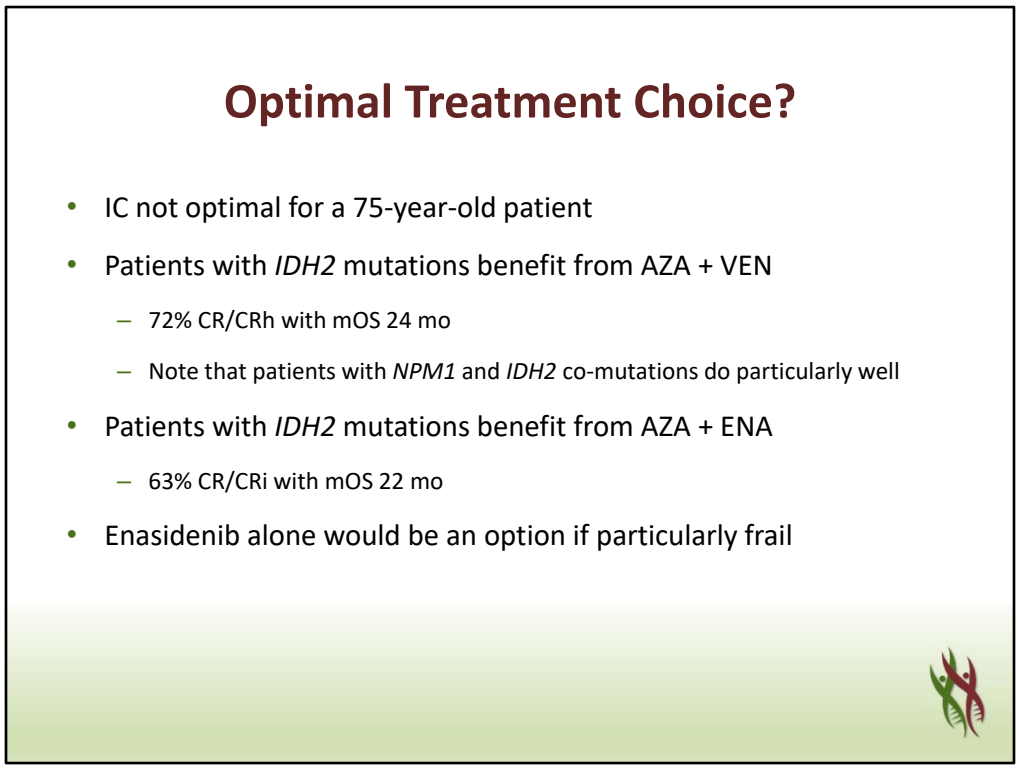


In terms of, optimal treatment choices, I would say in general, intensive chemotherapy for someone in their 70s who has underlying comorbidities, especially, someone with NPM1/IDH mutations, that this patient is going to respond incredibly well to lower intensity combinations, and so we actually have different options available. I think the vast majority of providers throughout the United States are going to prioritize an azacitidine plus venetoclax regimen based on the VIALE-A data, which is very appropriate. We have a more than 70% composite remission rate. Median survival is about two years, and patients with that specific NPM1/IDH2 co-mutations are doing particularly well, but there is also data with azacitidine and enasidenib with a composite remission rate above 60% in a similar median overall survival, so that wouldn't necessarily be the incorrect option either. Enasidenib alone I would really kind of restrict for a particularly frail patient that you really want to focus on just an oral outpatient regimen.

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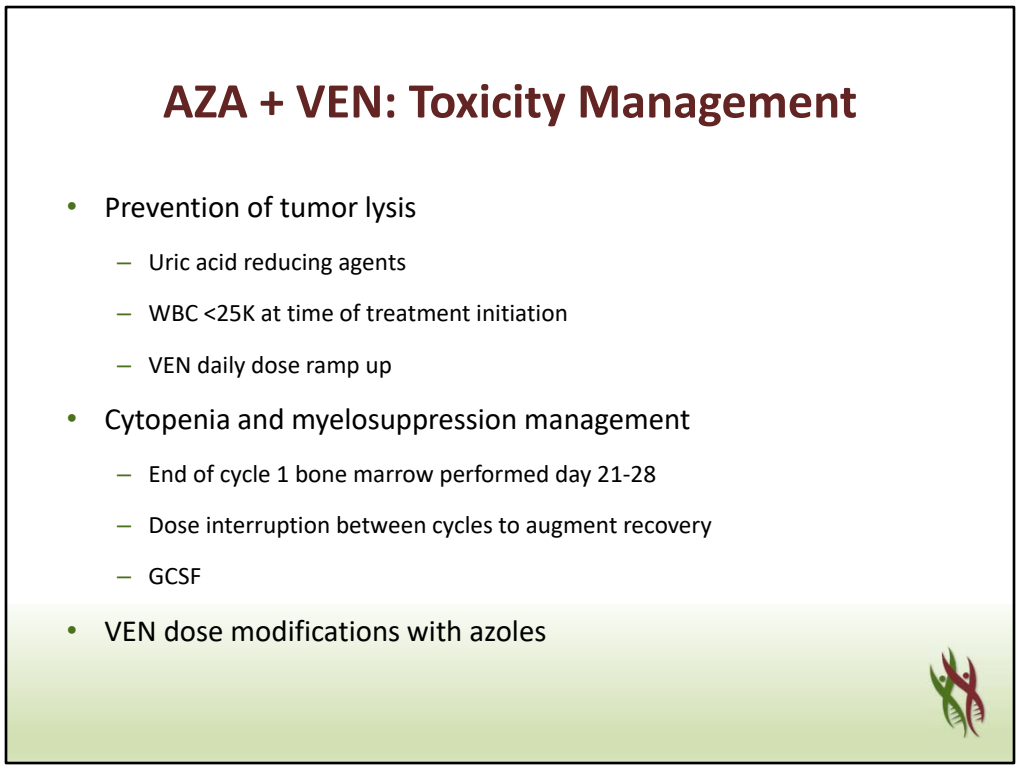


In terms of toxicity management, we'll get in to this probably a little bit more, but just to provide a little bit of guidance, I think when you're using azacitidine and venetoclax, that the things you really want to be aware of are the risk of cytopenias and myelosuppression because even though we call this the lower intensity regimen, we absolutely see cytopenias that oftentimes go beyond that 28 days so again, that 28-day cycle is a bit of miss more oftentimes, we're giving patients five- or six-week cycles now. The most important thing is to do a bone marrow around about the end of the first cycle, somewhere between day 21 and day 28,  to see if your patients are already in a leukemia-free state, because if you've cleared the leukemia and the counts are still low, then the counts are still low because the patient hasn't had time to recover their bone marrow function yet, so wait a week or two, you hold the venetoclax to start the second cycle. That's just a really important point, and then also being aware of dose modifications with azoles.

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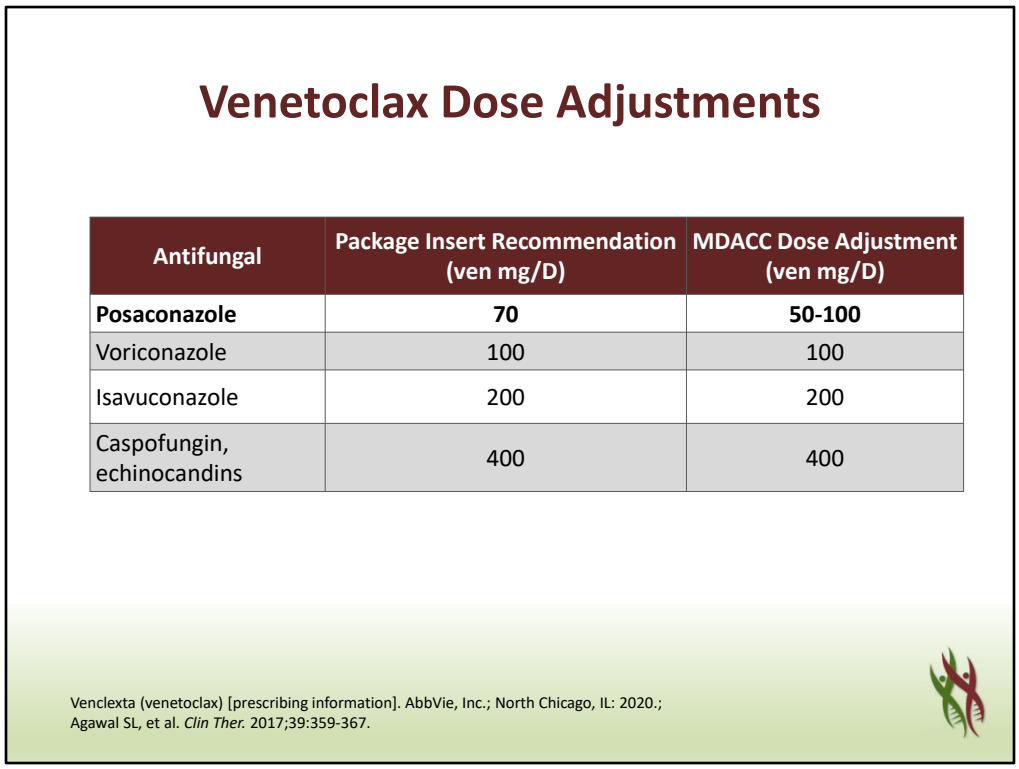



There are adjustments that are significant, so a 50% venetoclax reduction with moderate CYP3A inhibitors like fluconazole or isavuconazole and at least to 75% reduction with the strong ones like voriconazole, posaconazole with the package inserts specifically recommending 70 mg of venetoclax when you're using posaconazole, so just important things to be aware of. Dr. Daver, any particular pearls of wisdom in terms of treating a patient if you've decided that you're going to do an HMA/venetoclax, and how you would optimize their therapy?

**Naval Daver, MD:** Yes, absolutely. I mean this is the regimen that I think we're using very extensively. At MD Anderson, we've been using it for the last five years, treated hundreds of patients and as you said, I think the key factor here is that we cannot really try to adhere, and we should not try to adhere to these 28-day cycles. I would say in our experience in published data, most of these cycles running 35-42 days, and that is okay because it is not impacting the remission rates or the MRD. The second factor as you said, we do a planned stage interruption of therapy, and many large academic centers across the US are doing this now where we confirm our remission with the bone marrow around day 28. Once we show there's marrow remission, often we see that's with hypoplasia, aplasia insufficiency, then we know that this is drug-related myelosuppression. We safely hold the venetoclax for 12 to 14 days. If needed, give growth factors and then we are usually able to continue with cycle two where we usually shortened the venetoclax to 21 days, sometimes even down in subsequent cycles to 14 days so I think, as we say, there's an art of venetoclax.

It's a very effective drug. However, it's not like using azacitidine alone, which is as you know, a lot of emails in questions we get from community, you cannot just give it and keep giving cycles 28 days. You need frequent labs, early marrow, confirm remission, and hold therapy, so I think if you do all that though, this is really a very, very effective and safe regimen.

**Courtney DiNardo, MD:** Absolutely. We will move on to the third case which is one where I think it is a little bit challenging. I think the jury is still out in terms of what the best treatment strategy is and so I'm interested, Dr. Daver, to hear your thoughts on this.

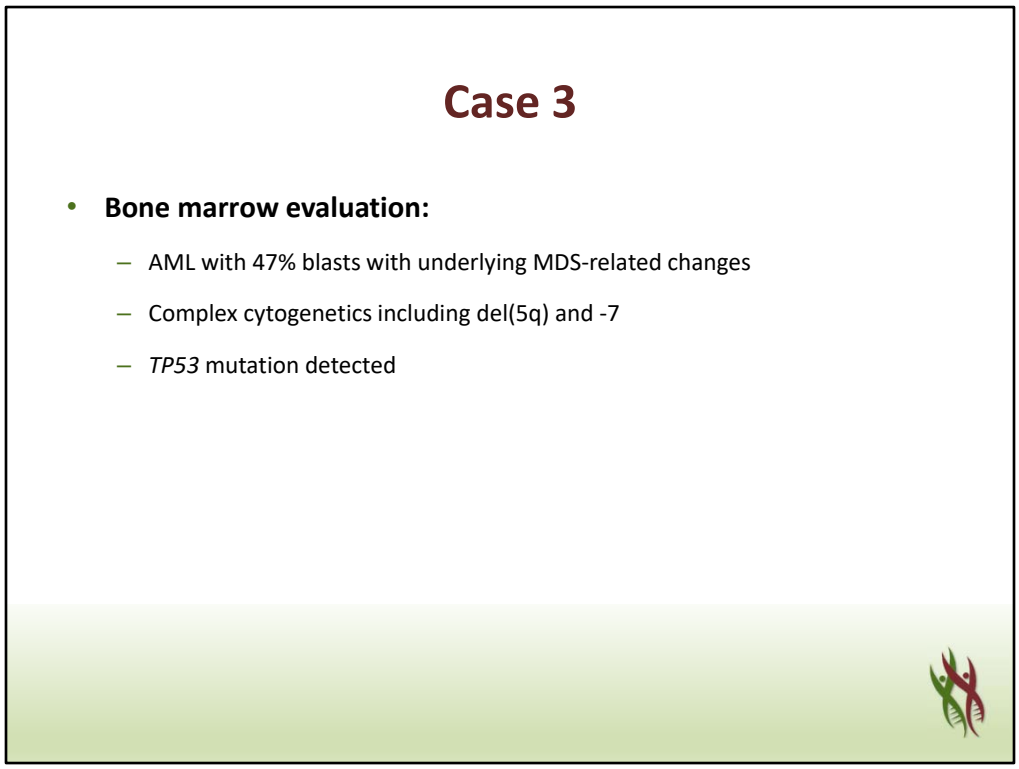
# Applying Key Data Presented at EHA 2020 to Practice

## Case 3

- 65-year-old female presenting with pancytopenia in the setting of an upper respiratory tract infection
- WBC 1.5K, Hgb 8.2 g/dL, Plts 94K. ANC 300.
- Normal renal and liver function. LDH mildly elevated
- PS = 1
- Past medical history:
  - Type 2 DM, breast cancer (s/p AC/T and localized XRT) 10+ years ago

This is a 65-year-old female who is presenting with pancytopenia. Again, in the setting of an upper respiratory tract infection, so that first sentence is very similar to our 75-year-old that we just talked about, counts are low, normal renal and liver function, LDH is mildly elevated. Again, very similar. Performance status is 1, but the difference here is the past medical history. This patient has a history of breast cancer, has had chemotherapy and radiation, although it was many years ago.

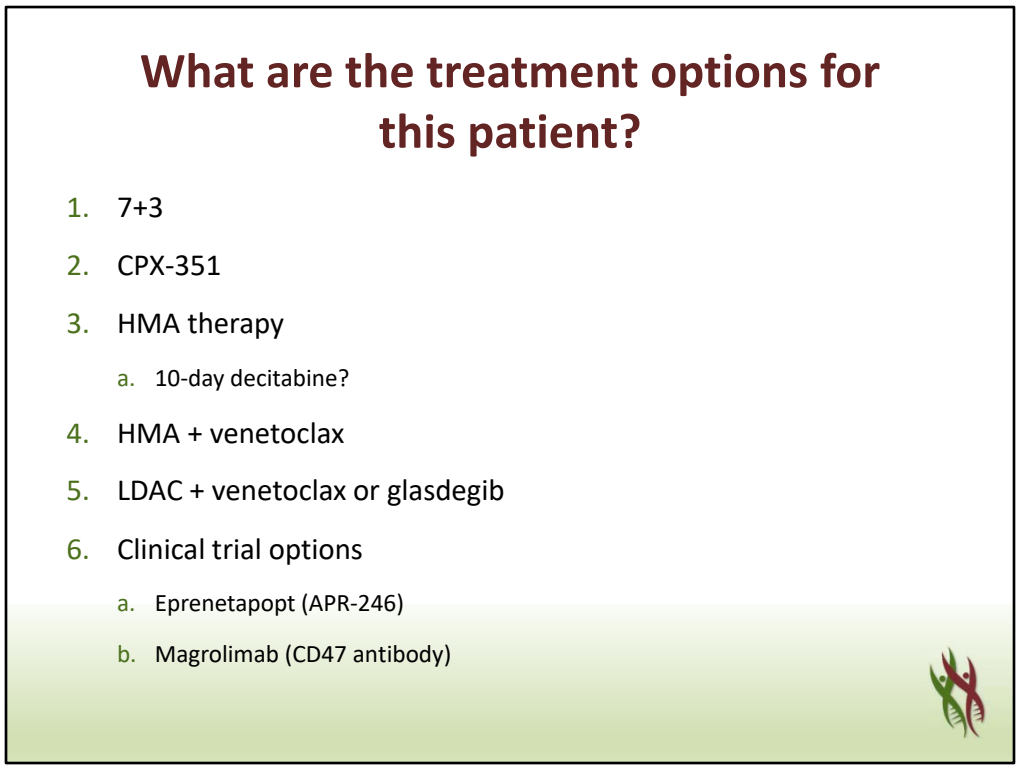
# Applying Key Data Presented at EHA 2020 to Practice




This patient's bone marrow evaluation shows us again, elevated blasts with underlying MDS-related changes but the genomics are different. This patient has complex cytogenetics, a deletion 5q, a monosomy 7 and on an NGS panel looking at common AML mutations a p53 mutation as detected. This patient started off very similar to our other patient but again, the genomics are different. This patient has complex cytogenetics and a p53 mutation, so while many of the same treatment options are available, the expectations are a little bit different. Dr. Daver, could you just tell us a little bit about kind of this scenario? Is this something that we see often, and why is this particularly challenging?

**Naval Daver, MD:** Yes, thanks Dr, DiNardo. This is a very challenging case for us. As you know, now probably one of the key spearheads for research in AML and MDS is how to address TP53-mutated AML and MDS, and that's one of the reasons because aza/venetoclax has been so effective and safe and improve outcomes in many, many subsets of AML. However, unfortunately, TP53 remains where over time, with more analyses, updated data from the phase 1b studies, the VIALE-A studies that you conducted as well as now our internal dataset seems to suggest that venetoclax has marginal, and some would argue no improvement in the TP53-mutated AML, so this population remains one where we are still in a major unmet need. Now there are new drugs that you will discuss that we're hopeful about, but today, if you look at the TP53-mutated AML, even if you look at azacitidine/venetoclax data, the response rates were about 50%-55%, which is not bad, but the median survival is only five to seven months, which is not better than we were getting with decitabine or azacitidine alone, so this is, I think the biggest challenge for this patient.

# Applying Key Data Presented at EHA 2020 to Practice




**Courtney DiNardo, MD:** That's exactly right so again, you can see there are many different options. This is a 65-year-old fit patient, PS of 1, no significant underlying comorbidities that would preclude intensive chemotherapy, so we could think about 7+3 or CPX-351, given this patient has an antecedent MDS and a therapy-related AML. We can think about hypomethylating therapy. There has been data on 10-day decitabine as being particularly effective at eradicating at least, for a short period of time, p53 clones, and then the venetoclax combinations as well as clinical trials, which are showing what appears to be particular benefit in patients with p53 mutations and that in particular, APR-246 (now eprenetapopt) and the CD47 antibodies including magrolimab.

# Applying Key Data Presented at EHA 2020 to Practice

## *TP53* Mutations Are Common in Elderly and Therapy-related MDS/AML

| Reference | Age (years) | N | *TP53* Mutant |
|---|---|---|---|
| Döhner, et al[1] | ≥65 | 485 | **21%** |
| Strickland, et al[2] | ≥65 | 191 | **23%** |
| Metzeler, et al[3] | 60-86 | 288 | **18%** |
| Kadia, et al[4] | ≥60 | 196 | **18%** |
| Welch, et al[5] | ≥60 | 54 | **17%** |
| Prassek, et al[6] | ≥75 | 151 | **14%** |

1. Döhner H, et al. *Leukemia.* 2018;32:2546-2557. 2. Strickland S, et al. EHA 2018; abstract PS982. 3. Metzeler K, et al. *Blood.* 2016;128:686-689. 4. Kadia T, et al. *Cancer* 2016;122:3484-3491. 6. Welch J, et al. *N Engl J Med.* 2016;375:2023-2036. 7. Prassek V, et al. *Haematologica.* 2018;103:1853-1861.

Just to kind of remind audience, we think this doesn't happen that often but it really is almost 20% of our AML patients can be therapy-related or in the setting of complex cytogenetics with the p53 mutation. So, it absolutely is the minority, but it's a significant minority and one that we absolutely need to be kind of thinking about and trying to optimize their therapy.

# Applying Key Data Presented at EHA 2020 to Practice

## Treatment Options for *TP53*-mutated AML

| Therapy | N | CR/CRi | OS | Reference |
|---|---|---|---|---|
| CPX-351 | 24 | 29% | 4.5 mo | Lindsley, et al. *Blood.* 2019;134(supplement_1):15[1] |
| DAC 5-day | 7 | 29% | 5.5 mo | Short, et al. *Lancet Haematol.* 2019 Jan;6:e29-e37. doi: [Epub 2018 Dec 10][2] |
| DAC 10-day | 17 | 47% | 4.9 mo | Short, et al. *Lancet Haematol.* 2019 Jan;6:e29-e37. doi: [Epub 2018 Dec 10][2] |
| LDAC + VEN | 10 | 20% | 3.7 mo | Wei, et al. *J Clin Oncol.* 2019;37:1277-1284[3] |
| HMA + VEN | 36 | 47% | 7.2 mo | DiNardo, et al. *Blood.* 2019;133:7-17[4] |
| **AZA + APR-246** | 5 | **80%** | NA | Sallman, et al. *Blood*. 2018;132(Supplement 1):3091[5] |
| **AZA + magrolimab** | 12 | **75%** | 91% at 6 mo | Daver, et al. EHA 2020; Abstract S144[6] |

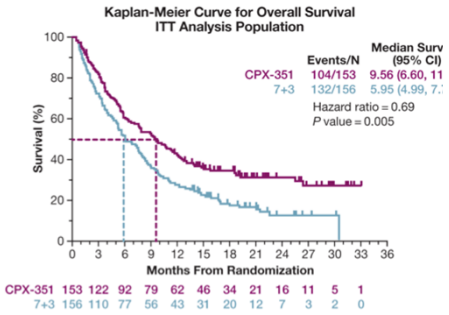
1. Lindsley RC, et al. *Blood.* 2019;134(supplement_1):15. 2. Short NJ, et al. *Lancet Haematol.* 2019 Jan;6:e29-e37. [Epub 2018 Dec 10] 3. Wei AH, et al. *J Clin Oncol.* 2019;37:1277-1284. 4. DiNardo CD, et al. *Blood.* 2019;133:7-17. 5. Sallman DA, et al. *Blood*. 2018;132(Supplement 1):3091. 6. Daver N, et al. EHA 2020; Abstract S144.

So, we have many different treatment options. I think, compared a standard hypomethylating agent regimen alone or a standard 7+3-based therapy where we can expect a remission rate under 30% or so, there are some hints that remissions are higher with some of our newer therapies, hypomethylating agent with venetoclax, for instance with the VIALE-A data had a CR/CRi rate of 55%, which is certainly improved compared to azacitidine alone, but then when you look at the overall survival we are really kind of yet to move the needle in the sense where kind of standard overall survival for a p53-mutated patient is only six months or less, and so with many of our new therapies, we're still kind of right at that level and that's why, I think the new trials involving APR-246 or magrolimab are seen as so exciting in our field, and hopefully, the ongoing data will kind of prove that this is an indeed something that is improving the duration of remissions and overall survival in our patients.

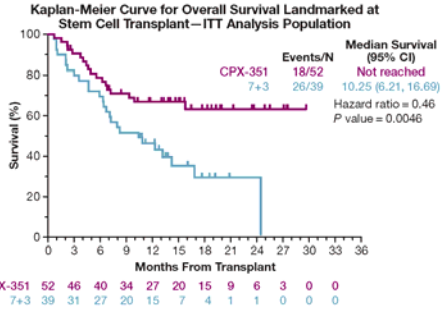
# Applying Key Data Presented at EHA 2020 to Practice

## CPX-351 in Older AML Patients with AML-MRC/t-AML

**OS**




**Outcomes Following Transplant**




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

Just going through a couple of the trials in particular. We know, of course, that CPX-351, based on a randomized phase 3 study, shows an improved overall survival in patients who were eligible, which this patient certainly would have been with the therapy-related AML with an improved overall survival.

# Applying Key Data Presented at EHA 2020 to Practice

## CPX-351 vs 7+3 by Molecular Subgroup

**Table. Outcomes for Patients with the Most Frequently Occurring Mutations[a]**

| | *ASXL1* | | *DNMT3A* | | *RUNX1* | | *TET2* | | *TP53* | |
|---|---|---|---|---|---|---|---|---|---|---|
| Outcome | CPX-351 (n = 30) | 7+3 (n = 20) | CPX-351 (n = 20) | 7+3 (n = 21) | CPX-351 (n = 21) | 7+3 (n = 22) | CPX-351 (n = 26) | 7+3 (n = 17) | CPX-351 (n = 24) | 7+3 (n = 35) |
| CR, n (%) | 5 (17) | 4 (20) | 7 (35) | 11 (52) | 5 (24) | 6 (27) | 5 (19) | 7 (41) | 7 (29) | 12 (34) |
| OR (95% CI) | 0.80 (0.19-3.43) | | 0.49 (0.14-1.72) | | 0.83 (0.21-3.29) | | 0.34 (0.09-1.34) | | 0.79 (0.26-2.43) | |
| CR+CRi, n (%) | 11 (37) | 7 (35) | 12 (60) | 12 (57) | 7 (33) | 7 (32) | 9 (35) | 8 (47) | 7 (29) | 14 (40) |
| OR (95% CI) | 1.08 (0.33-3.50) | | 1.13 (0.32-3.90) | | 1.07 (0.30-3.84) | | 0.60 (0.17-2.08) | | 0.62 (0.20-1.87) | |
| Median remission duration,[b] mo | 6.37 | 4.11 | 9.89 | 4.32 | 8.05 | 3.45 | 6.37 | 3.45 | 8.05 | 3.45 |
| HR (95% CI) | 0.69 (0.18-2.58) | | 0.33 (0.10-1.06) | | 0.56 (0.17-1.87) | | 0.43 (0.13-1.38) | | 0.63 (0.24-1.65) | |
| Transplant, n (%) | 8 (27) | 6 (30) | 11 (55) | 8 (38) | 6 (29) | 4 (18) | 6 (23) | 3 (18) | 3 (13) | 11 (31) |
| OR (95% CI) | 0.85 (0.24-2.97) | | 1.99 (0.57-6.90) | | 1.80 (0.43-7.59) | | 1.40 (0.30-6.56) | | 0.31 (0.08-1.27) | |
| Median OS,[b] mo | 9.10 | 6.29 | 12.62 | 5.49 | 8.87 | 4.09 | 9.10 | 3.68 | 4.53 | 5.13 |
| HR (95% CI) | 0.67 (0.35-1.27) | | 0.41 (0.19-0.89) | | 0.58 (0.30-1.11) | | 0.47 (0.23-0.93) | | 1.19 (0.70-2.05) | |
| Median EFS,[b] mo | 1.58 | 1.41 | 5.98 | 3.58 | 2.00 | 1.22 | 1.59 | 1.64 | 0.97 | 1.64 |
| HR (95% CI) | 0.79 (0.42-1.48) | | 0.45 (0.21-0.95) | | 0.57 (0.30-1.08) | | 0.93 (0.49-1.77) | | 1.13 (0.66-1.93) | |

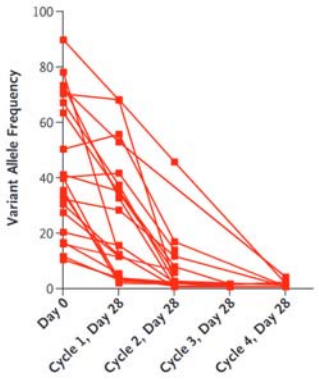
[a]Mutations reported for ≥20% of patients overall.
[b]Median remission duration, OS, and EFS are based on Kaplan-Meier estimates.

Lindsley RC, et al. *Blood.* 2019:134(Supplement_1):15.

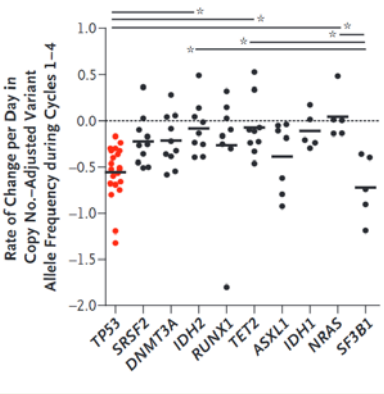
When you look at subgroups, and p53 is the column on the right, there are again, evidence that intensive chemotherapy is probably not the best option for patients with p53 mutations, and so in this p53-mutated group, CPX vs 7+3, the composite remission rate is fairly similar, and the median overall survival, unfortunately, still under six months.

# Applying Key Data Presented at EHA 2020 to Practice

## High Rate of *TP53* Mutation Clearance with 10-day Decitabine




Clearance of *TP53* Mutations



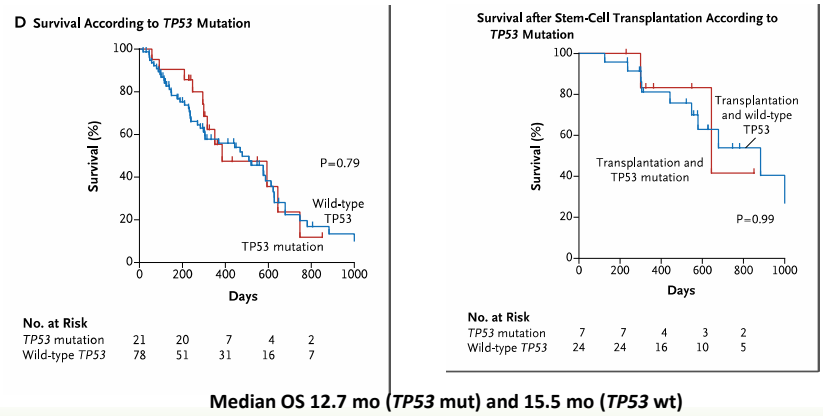

Clearance of Mutations

Welch JS, et al. *N Engl J Med*. 2016;375:2023-2036.

We talked about 10 days of decitabine. This is a clinical trial that was published in the *New England Journal of Medicine*. I'm looking at the fact that we can clear p53 mutations incredibly well when you're giving 10 days of decitabine for the first few cycles.

# Applying Key Data Presented at EHA 2020 to Practice

## Survival According to *TP53* Mutation with 10-day Decitabine




**Median OS 12.7 mo (*TP53* mut) and 15.5 mo (*TP53* wt)**

**21/21 patients with *TP53* mutations attained mCR/CR**

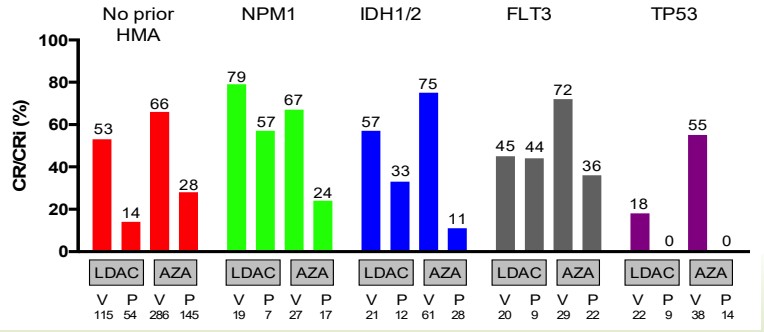
Welch JS, et al. *N Engl J Med*. 2016;375:2023-2036.

However, those remissions are unfortunately quite short-lived with a survival that is kind of not improved unfortunately.

# Applying Key Data Presented at EHA 2020 to Practice

## Comparison of HMA or LDAC + Venetoclax Responses

| | | VIALE-C | | VIALE-A | |
|---|---|---|---|---|---|
| | | VEN (n=143) | PBO (n=68) | VEN (n=286) | PBO (n=145) |
| Response | CR/CRi | 48% | 13% | 66% | 28% |
| | CR | 28% | 7% | 37% | 18% |
| | Duration of CR | 17 mo | 8 mo | 17.5 mo | 13.5 mo |




Wei AH, et al. *Blood* 2020;135:2137-2145.; DiNardo CD, et al. *N Engl J Med.* 2020;383:617-629.

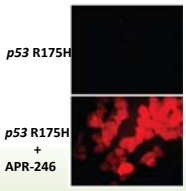
Now we think about venetoclax combinations because venetoclax combinations I am definitely a believer and they have definitely taken the world by storm in terms of the efficacy in many different subsets, but you look at p53 mutations, which again is the column on the right, and the composite rate is good, especially with azacitidine 55% composite remission as is shown here, but again, durability of these responses is unfortunately still not where we want it to be right around six months or so.

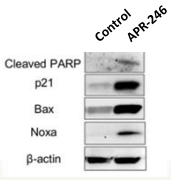
# Applying Key Data Presented at EHA 2020 to Practice

## *TP53*-mutated MDS/AML: APR-246 + AZA

- APR-246 is a novel first-in-class small molecule that induces apoptosis through mutant *p53* protein re-activation by restoring wild-type *TP53* conformation


**Restoration of wild type *p53* conformational epitope which triggers cell cycle arrest and apoptosis**



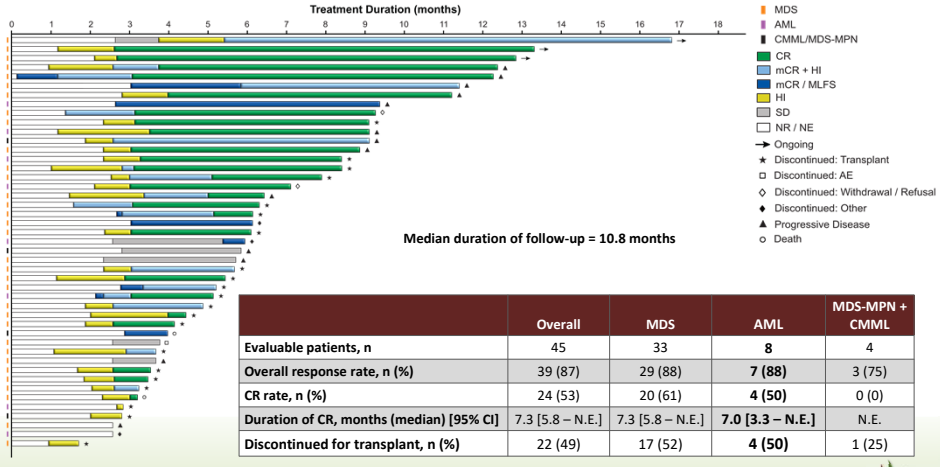




Sallman DA, et al. *Blood.* 2019;134(supplement_1):569.; Furukawa H, et al. *Cancer Sci.* 2018;109:412-421.

Just a little bit of information about APR-246, which is a first-in-class small molecule which is inducing apoptosis through reactivating the wild-type p53 confirmation.

# Applying Key Data Presented at EHA 2020 to Practice

## Response to Treatment in Evaluable Patients (n=45) Receiving AZA + APR-246



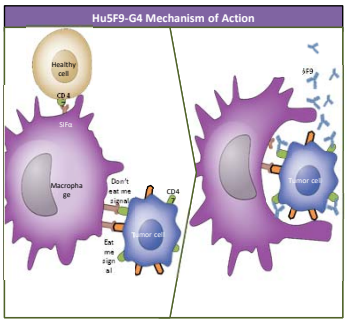

| | Overall | MDS | AML | MDS-MPN + CMML |
|---|---|---|---|---|
| **Evaluable patients, n** | 45 | 33 | **8** | 4 |
| **Overall response rate, n (%)** | 39 (87) | 29 (88) | **7 (88)** | 3 (75) |
| **CR rate, n (%)** | 24 (53) | 20 (61) | **4 (50)** | 0 (0) |
| **Duration of CR, months (median) [95% 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 DA, et al. *Blood.* 2019;134(supplement_1):569.

With data in a small number, just a handful of patients so far with AML, although there are many more with MDS and p53 mutations that show again, a composite remission rate, a CR rate of about 50%, but in overall response rate higher and a duration of remission kind of extending beyond even the overall survival in many of our other studies. The hope is many of these patients are coming off of transplant, many of these patients are doing well, the follow up is really short so, so time will tell and there are ongoing clinical trials looking specifically at this in a randomized fashion.

# Applying Key Data Presented at EHA 2020 to Practice

## Azacitidine + CD47 Antibody Magrolimab for MDS/AML




| Efficacy | MDS (n=33) | AML (n=25) |
|---|---|---|
| **ORR, n (%)** | **30 (91%)** | **16 (64%)** |
| **CR** | **14 (42%)** | **10 (40%)** |
| CRi | - | 4 (16%) |
| PR | 1 (3%) | 1 (4%) |
| MLFS/marrow CR | 8 (24%) | 1 (%) |
| Median time to first response (range), months | 1.9 mo | |
| MRD-neg in responders, n/N (%) | 6/30 (20%) | 8/16 (50) |
| Median follow-up (range), months | 5.8 (2.0-15) | 9.4 (1.9-16.9) |
| **Median DOR (range), months** | **NR (0.03-10.4+)** | **NR (0.03-15.1+)** |
| Median OS, months | NR | NR |

- **CD47 is a "don't eat me" signal on cancer cells that enables macrophage evasion**
- **Magrolimab (Hu5F9-G4) targets CD47 on tumor cells, inducing macrophage phagocytosis**
- **In patients with *TP53*-mutated AML (n=12), the ORR was 75% and the median DOR and OS were not reached**
- **6-month OS 91% in TP53-mutated AML**
- CD34+CD38− LSC were eliminated in 40% of patients overall

Sallman DA, et al. *Blood.* 2019;134(supplement_1):569.; Sallman D, et al. *J Clin Oncol.* 2020;38(15_suppl):7507.

The CD47 antibody that has been presented by both Dr. Sallman and Dr. Daver, so he can give us his expert opinion looking at patients with AML, and this was not selected for patients with p53 mutations, but in a sizable, enriched population of 12 patients with p53 mutations, the response rate was three-quarters of patients, and those patients who were responding that again, the follow up is short but the six-month overall survival is 90% so again, far exceeding the median overall survival in in historical expectations. I think that is a hopeful rose-colored twist to what is an incredibly challenging patient population to treat that is still kind of an area where improvements are needed, so Dr. Daver, what do you think?

**Naval Daver, MD:** Yes, I think, we're very excited, that's our nature to be optimists in the field of acute myeloid leukemia. As you mentioned, we have been very involved with both magrolimab and APR-246. We have seen some really outstanding responses in some patients who I think otherwise would not have responded, but I think we need more time and at this year's ASH there will be the abstracts are out, so we can actually share some data. There will be an update on at least the azacitidine plus magrolimab trial, the azacitidine plus APR246 in the phase 3 study, a locked study right now, so we won't know early next year but now, with about 35-40 TP53 mutated, the responses are holding around 75%, and the median survival is emerging now above 12 months, so we're hopeful that this is something real. Still, 12 months is good when we talk about six months, but we want more, so the question is, can we further with the triplet and other combinations? and I think that's what we're looking at.

The other issue that we see a lot with TP53-mutated AML as you know is that they also

tend to have much more myelosuppression with the therapy, so our early mortality rates are quite high, I think, these are patients that we would all strongly recommend go on trials. These trials for APR-246 and magrolimab are open now, and at least 25-30 centers in the US, so if you see such a patient, my strong recommendation would be contact your academic expert in your community or contact us if you like, and really these patients would be best served on getting on one of these doublet or triplet trials.

**Courtney DiNardo, MD:** Yes, I completely agree. My bias is that I think it is a very unusual patient with a p53 mutation that's responding and doing well with standard intensive chemotherapy, so I prioritize lower intensity regimens because the outcomes are about the same but without the toxicity. But I absolutely agree that clinical trials, and in particular, the ones that you were just describing, are hopefully going to be the way to go and what we should think about for patients that are presenting in the situation to our clinics. So, I'll move on. I think Dr. Daver, you have the fourth case.

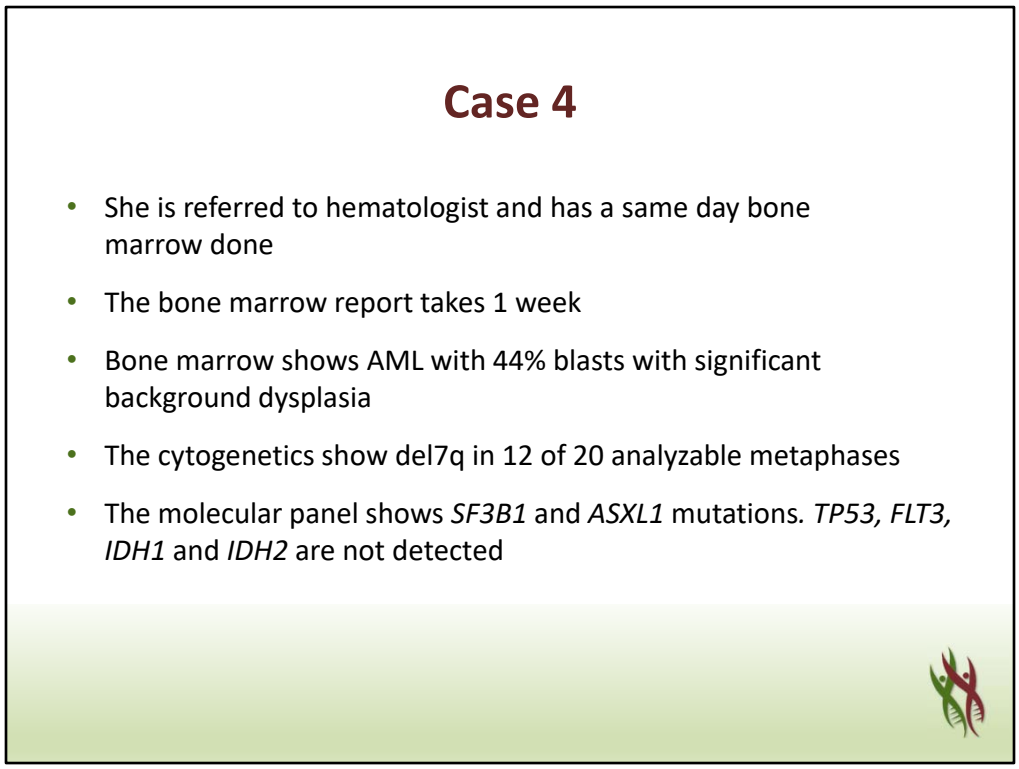
# Applying Key Data Presented at EHA 2020 to Practice

## Case 4

- 69-year-old female with new fever, cough and wheezing. Seen by PCP and given azithromycin
- She returns 1 week later with persistent cough and worsening fatigue
- CBC shows WBC 2.4K, ANC 1.1K, Hgb 9.2, platelet 55K. Electrolytes and LFTs within normal range
- Patient is a retired elementary school teacher. ECOG PS 1. Walks 3 miles every day
- She has diabetes on 2 oral meds, CAD with 1 stent placed 5 years ago. No recent surgeries

**Naval Daver, MD:** This is our fourth case; 69-year-old come in with fever, cough, seen by PCP, initially given Z-pack (azithromycin). This is something we see commonly that these AML patients are initially treated with the supportive care and antibiotics, and then takes a few weeks until they eventually are diagnosed, so comes back later, continues to have fatigue or weakness. This results in a workup with blood counts shows a white count low, ANC is low, hemoglobin, platelets all are low, so consistent with pancytopenia, so this is usually when the primary care physicians would start getting stressed out and anxious and call their hematologist and usually the hematologist will see that patient very quickly, same day or next day, sometimes, admission is what we do if we cannot get the patient over the weekend, we'll bring them straight to our emergency room and admit them through there because we're thinking about an acute leukemia. I don't know if it's AML, ALL, but I'm thinking this is an acute leukemia. Some, additional history, good performance status, retired, school teacher, very active, walking daily, has diabetes and coronary artery disease, but none of these are very active at this time, well-controlled on medications, no recent major surgeries or medical events.

# Applying Key Data Presented at EHA 2020 to Practice




The patient, as discussed, is referred, seen by hematologist, quick bone marrow done, overall stable so is being monitored closely in the outpatient setting with labs every two to three days. Bone marrow comes back, four or five days later, 44% blasts with significant background dysplasia and has some adverse cytogenetics including deletion 7q in the analyzed chromosomes. Molecular here shows ASXL SF3B1 mutations and the other mutations that we always check for to put the patients into targeted therapies that have the best outcome are negative, which include FLT3, IDH1, IDH2, and as you heard from Dr. DiNardo, TP53 for which we are going for the magrolimab and APR-246. So, you have this patient now without a clear targetable mutation but with adverse cytogenetics, and the question is, what would you do, and what are the challenges? And I'll turn this over to Dr. DiNardo for her thoughts.

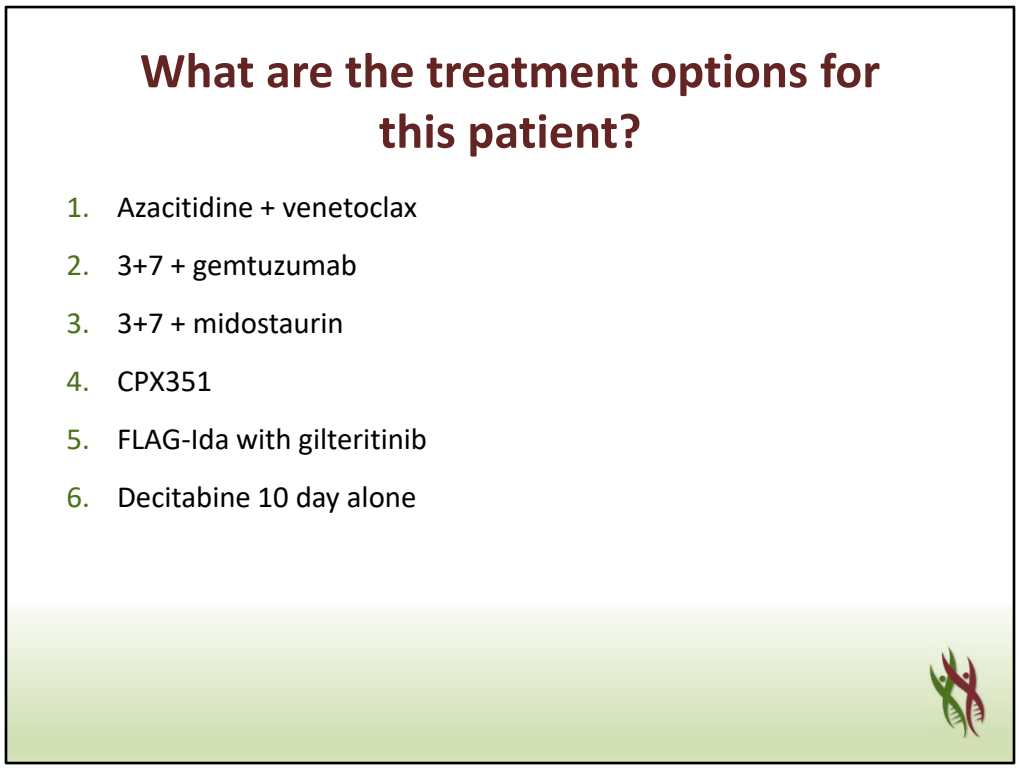
**Courtney DiNardo, MD:** This is again a patient that is kind of right in that sweet spot where you're trying to decide intensive chemotherapy vs lower intensity combinations. That age of 69 years is someone who you really could be considering either option, and these are not just made-up cases, right. The median age of AML is 68, so we frequently have patients that are exactly this situation. When we think about genomics, of course, that would have helped identify a targeted treatment strategy, and so now the question is, do we prioritize an intensive chemotherapy like a CPX-351 or an HMA/venetoclax regimen?

And honestly, I think there's probably people on both sides of the fence. My bias is going to

be a hypomethylating venetoclax regimen especially with high-risk cytogenetics with that deletion 7 because again, I know intensive chemotherapy has less effectiveness in that population and so, if I'm seeing equivalent outcomes with the lower intensity combination, I'm usually going to prioritize that, but CPX-351 is also an important consideration.

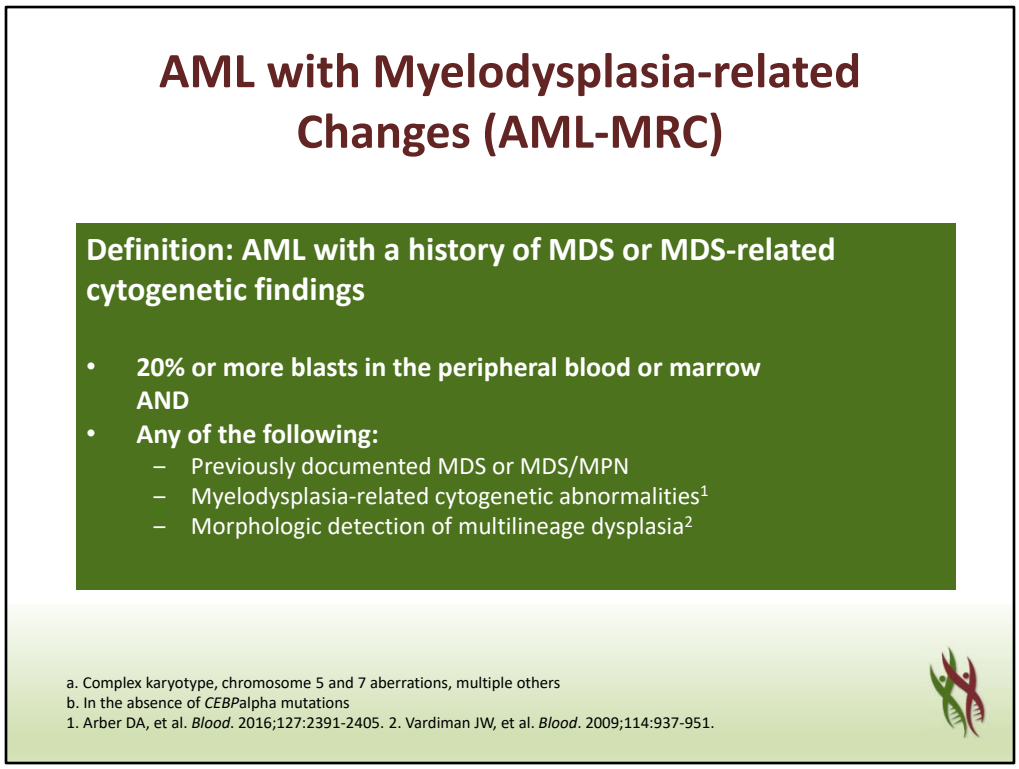
**Naval Daver, MD:** Yes, thank you very much. I mean I think these are the real-world discussions we're having and I don't think one is right or wrong. Both of those are FDA guidance and in fact, I mean technically, you have many treatment options if you're going just by the guidelines that could be used in this patient, because as Dr. DiNardo mentioned, she's relatively younger, we could give intensive chemotherapy for sure if she had a core-binding factor for example, we would give her intensive chemotherapy, so it's not a fitness issue, but the question really is, will she benefit from intensive chemotherapy? I think that's becoming more of our key for making decisions. It's not just whether one can get intensive chemotherapy and tolerate, it but really will one benefit from that, or could they benefit equally or maybe even more with some of the lower intensity regimens?

# Applying Key Data Presented at EHA 2020 to Practice




For this patient, I think, HMA plus venetoclax and CPX-351 would be in my mind the top two choices. As Dr. DiNardo said that we would have to discuss with the patient, look at the donor status, what is our kind of eventual goal even near-term goal? Of course, FLT3 inhibitors wouldn't be used here; 3+7 plus gemtuzumab, really gemtuzumab as you know, from published data, the maximum benefit is in core-binding factor as well as NPM1-mutated without FLT3, and that's really where we're using it, we're not using it in the adverse for sure where its shown no benefit on the large analysis, and the intermediate, one could consider it, but we prefer adding drugs like venetoclax, FLT3 inhibitors, IDH inhibitors going for targeted therapies, and then decitabine in 10 days alone, as Dr. DiNardo mentioned. There was excitement four, five years ago, we did a randomized study looking at 5 vs 10 days. We didn't see clear benefits, so we don't think that just decitabine in 10 days on its own is a major breakthrough, but maybe if you add venetoclax to it, there is some improvement compared to azacitidine plus venetoclax.

# Applying Key Data Presented at EHA 2020 to Practice

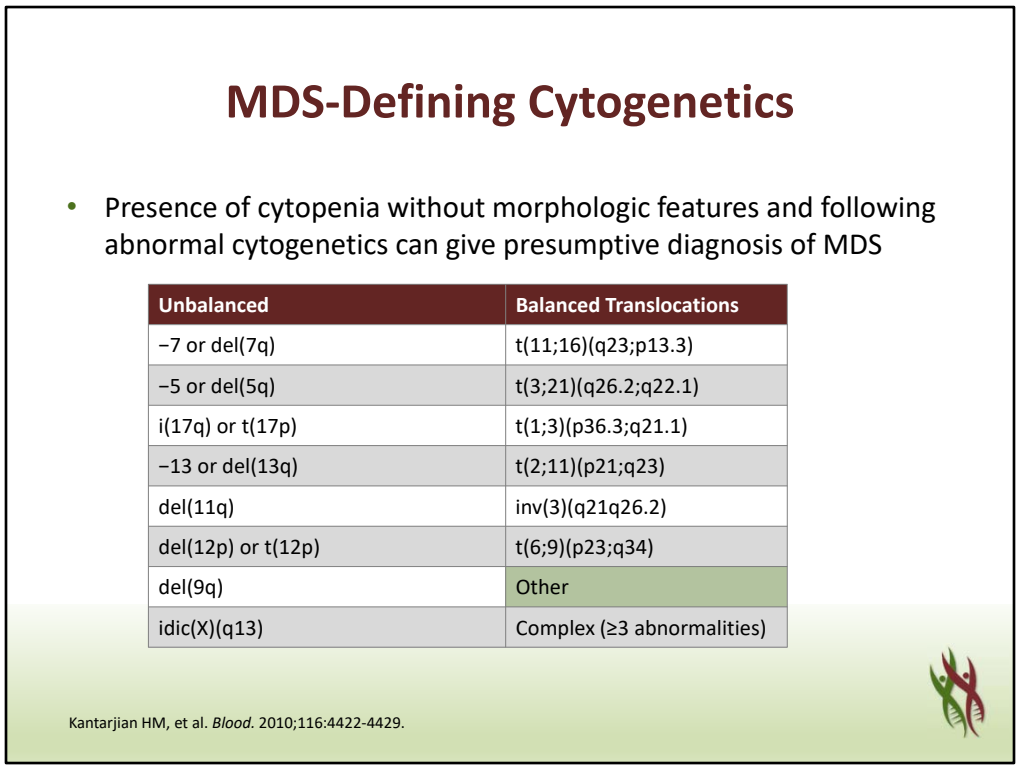



I'll talk a little bit about this group because this is a group that is growing and I expect and we expect in the next 10 years, will continue to grow, so this a patient with AML-MRC per the WHO classification. It really includes three groups of patients, so you have those who have a known history of MDS, MPN. This is easy because those patients were seen in the clinic, in the community, known MDS, getting growth factors, getting HMA, and one day, one or two or three years later, they progressed to AML, come to you, so you know that history that this is an MDS-transformed AML.

The second group is the patients who have a prior chemotherapy or radiation therapy for other malignancies, so Hodgkin lymphoma, breast cancer, colorectal; they've got some chemoradiation two, five, seven years ago and now, they come in with AML. You take a good history, and you know that this is a therapy-related AML.

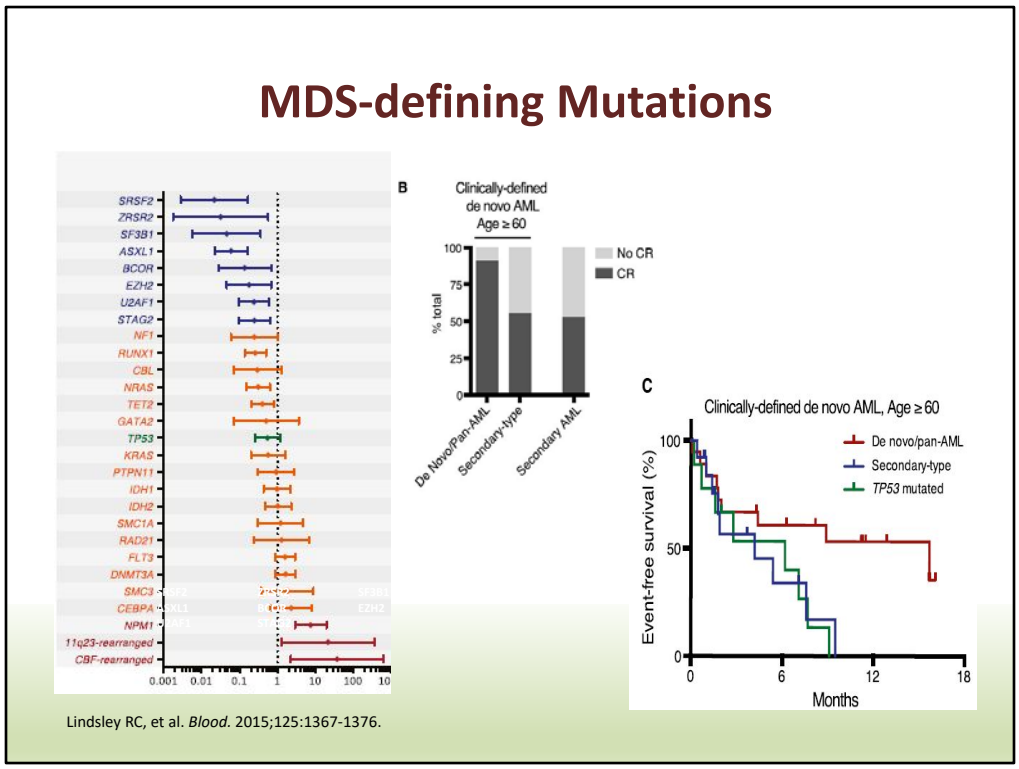
Then the third group is the one that is often missed but is one that we are picking up more and more using FISH and cytogenetics, and this is patients who have MDS-related cytogenetic changes, and there's a whole list of the cytogenetics as one can look at.

# Applying Key Data Presented at EHA 2020 to Practice




So if you see a patient, you do a bone marrow, you get cytogenetics, it's important to make sure you're not missing an MDS-defining cytogenetic change, and this includes deletion 5 and 7, 17. One doesn't have to remember the list but the big ones are deletions in 5, 7, 17 in 3 and 1. If you see these chromosome changes, think about something other than traditional 3+7 or FLAG-IDA, maybe CPX-351, maybe HMA/venetoclax, or maybe clinical trials again with those newer drugs that we talked about, magrolimab, APR or combinations of those with HMA/venetoclax.

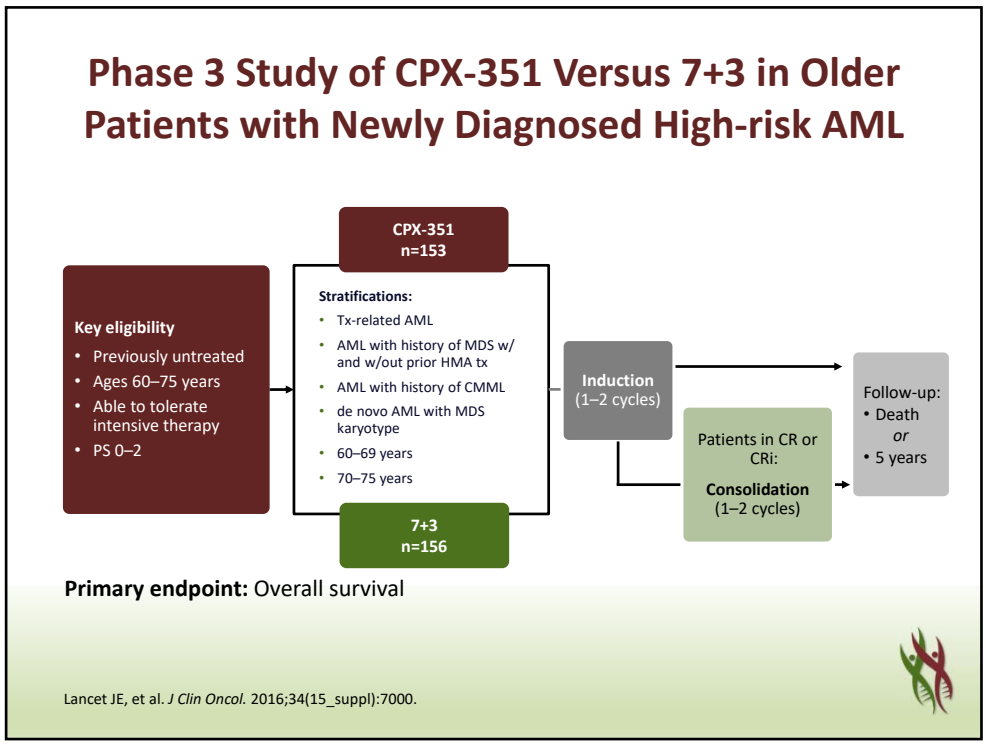
# Applying Key Data Presented at EHA 2020 to Practice




Lindsley RC, et al. *Blood.* 2015;125:1367-1376.

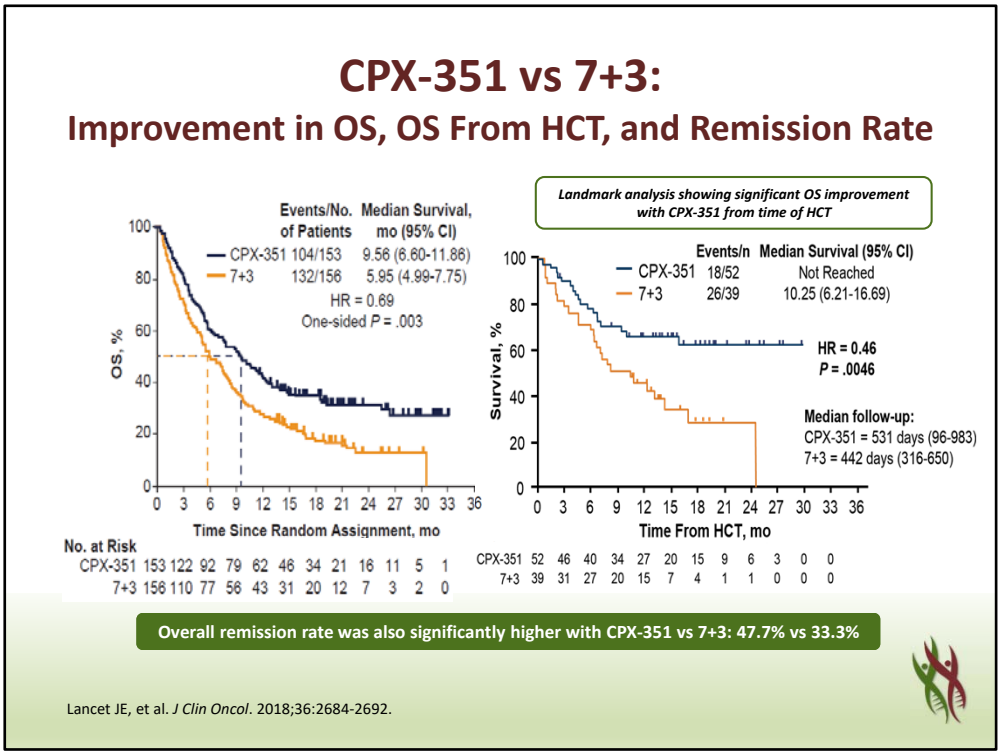
Now, the other interesting thing is that we are starting to find that there are particular mutational groups that are also associated with these MDS-related AML, and that's why, specifically for this patient, was a real-world patient. The mutations if you noticed were ASXL1, SF3B1. These mutations are common MDS or MDS-MPN mutations and when we see these mutations in patients with AML, we start thinking about secondary or therapy-related acute myeloid leukemia. Again, because we may consider other treatments such as CPX-351 or HMA/venetoclax-based and not do traditional intensive chemotherapy. This was very nice work done by Coleman Lindsley's group, where they found mutations that were more clearly associated with the secondary therapy-related AML.

# Applying Key Data Presented at EHA 2020 to Practice



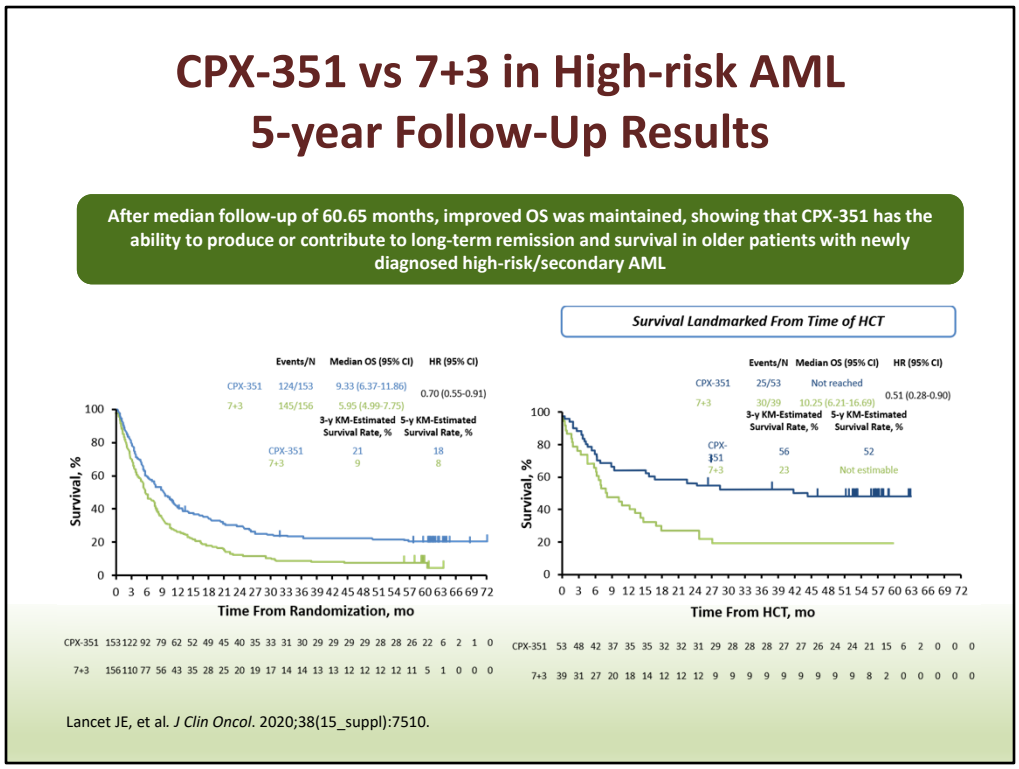

So briefly, to go over the study as was just mentioned, CPX-351 and HMA/venetoclax are the two choices. I think one could argue strongly for either one. This is the data for the CPX-351 vs 7+3. These were all patients who had either therapy-related AML, prior chemoradiation for another cancer, secondary AML, MDS, or MDS, MPN transforming to AML, or AML with MDS-defining cytogenetic changes. Note, there were no MPN-transformed AML here. This is the second group like TP53, which is the major unmet need. Patients with myelofibrosis ET who transformed to AML, both the CPX-351 as well as HMA/venetoclax and almost all of our trials actually exclude those, so we're still trying to find new treatments for those, but for MDS transformed as well as therapy-related and secondary AML, this is a study that included all of those.

# Applying Key Data Presented at EHA 2020 to Practice



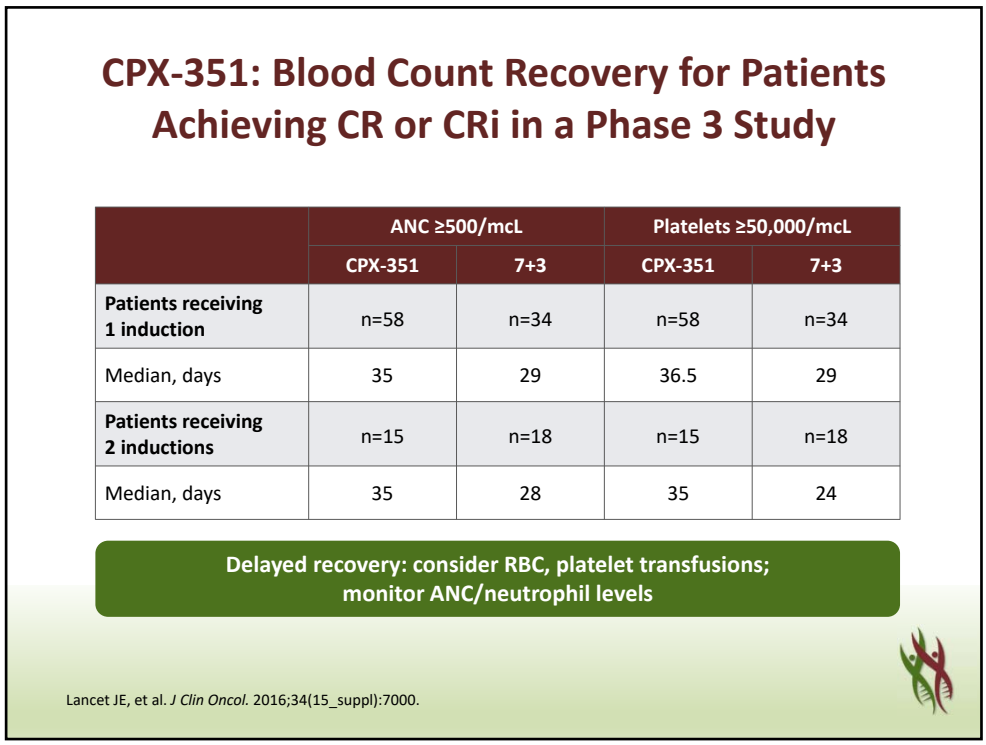

This is the high-level results we already heard them from Dr. DiNardo, median overall survival was improved, but again at the end of the day, we're talking about 10 months vs six months, so it is a benefit and in this very high-risk patient population, any benefit is a good benefit, so we do think this is a positive study, and especially again, similar to FLT3, if you give CPX-351 to that patient with secondary therapy-related AML and take him to transplant, you may then have a realistic chance of two-year plus survival that could go out to 40%-50% which historically, is not something we have been able to achieve in this high-risk population.

# Applying Key Data Presented at EHA 2020 to Practice




This to me was actually very interesting and encouraging data because there has been a lot of debate even in our group about, is CPX-351 really a clear benefit? There is some improvement in response survival. How does that play out? I thought that this abstract that looked a five-year follow-up, really does show a clear benefit, so when you look at the curve on the survival landmark from the time of transplant, so these are people who got CPX vs 3+7, went to transplant. What happened to those patients? You can now see in five years, 50% of those patients vs 25% were alive. I mean to have 50% therapy-related secondary AML patients, whatever you do to get them to that is outstanding, so I think there are patients maybe where you are trying to take them to transplant, you could give them CPX-351, take them to transplant, maybe sometimes a form of post-transplant maintenance could be considered, and you could have a realistic chance of getting up to half to these people to long-term survival. So, very nice encouraging data published recently.

# Applying Key Data Presented at EHA 2020 to Practice



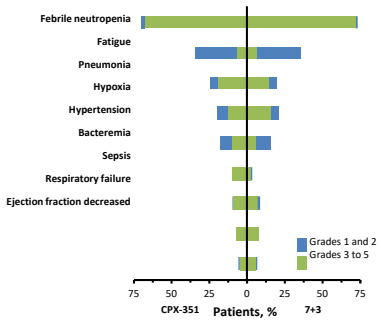

Now, from side effect profile, it's important to note, and this is a common misconception, CPX-351 is not low intensity. This was not developed to complete with or replace HMA/venetoclax or HMA/CD47 or another drug. This is actually an intensive chemotherapy formulation but a better tolerated, more effective in improving outcome intensive chemotherapy. The drugs are actually the same drugs, anthracycline and cytarabine, and so that's why I showed this slide because the median time to recovery with CPX-351 is about 35 days. In fact, it's if anything a little bit longer than 7+3, but the good thing is, we've seen that the GI toxicity in the early mortality is lower, so I think because of the liposomal formulation, the toxicity on the GI tract with anthracycline is mitigated, but one does have to know count recovery slow and in our experience at MD Anderson, we admit all of these patients. We treat these patients like we were somebody on FLAG-IDA or other inductions and we take all the precautions and with that, we have been able to get them safely through inductions.

# Applying Key Data Presented at EHA 2020 to Practice

## CPX-351: Managing Count Recovery and Outpatient Use

***Less Early Mortality With CPX-351 vs 7+3***

| Regimen | Early Mortality | |
|---|---|---|
| | Day 30 | Day 60 |
| CPX-351 | 5.9% | 13.7% |
| 7+3 | 10.6% | 21.2% |
| | Two-sided *P* = .149 | Two-sided *P* = . 097 |




**Delayed count recovery with CPX-351**

- ~6 days longer prolonged recovery from neutropenia and thrombocytopenia vs 7+3

***MDACC approach***

- Admit patient (preferred) or start outpatient induction → close monitoring after d 3-4; lab assessment 3 x/wk for outpatient
- Consider frequent blood and platelet transfusions (eg, Hb thresholds >8.5 g/dL; platelets >15,000/mcL)

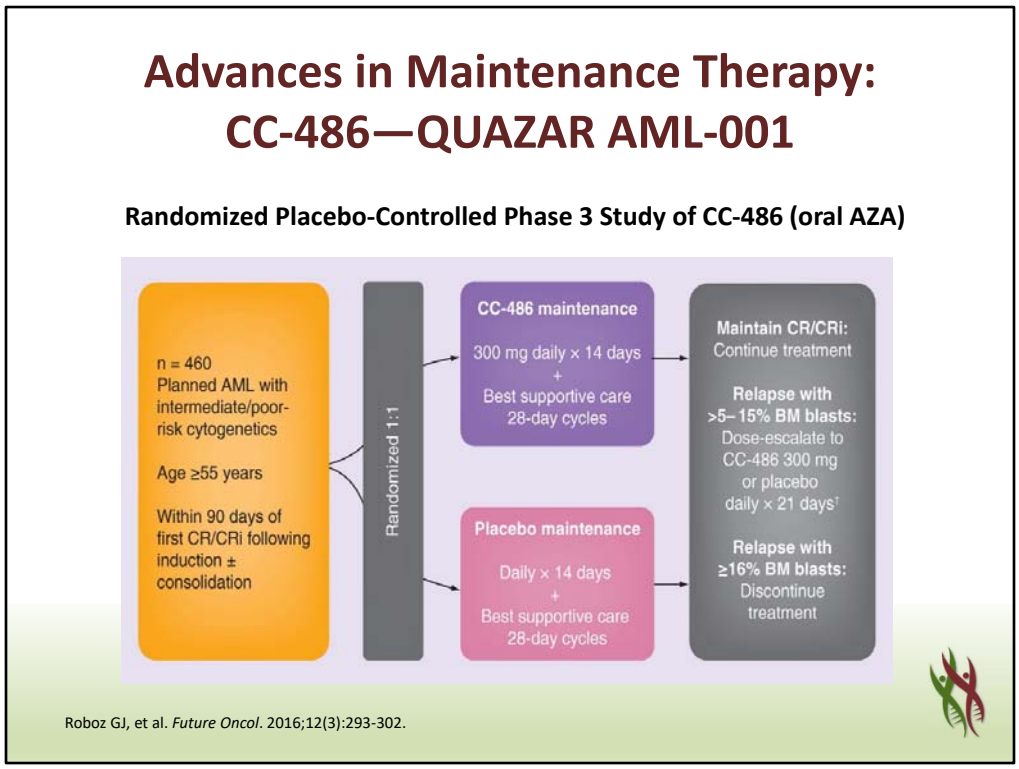
Here, we show the early mortality and I think one of the main reasons for the improved survival has come from the reduced early mortalities. You can see the 60-day mortality is 13% vs 21%. Quite significantly reduced but also, as you can see here, a lot of people debate and argue that you know, in their experience in the 60-plus patients they don't have high early mortality. Well, this was a study done in 2015, academic centers, phase 3 randomized study. You can see in 60-plus patients even with all of those controls, the early mortality, 60-day mortality was 21%-22%. So I think one has to be very careful when they evaluate their patients and think about the early mortality because most of the randomized data is still showing between 20% and 25% induction mortality, suggesting maybe these people were not great candidates for induction chemotherapy, and with HMA/venetoclax and other HMA combinations that is an area that I think will be used more and more. In our experiences, I mentioned at MD Anderson we admit these patients, we treat them like any cytotoxic ARA-C anthracycline induction. We do close blood work daily. Once they're stable around day 28, we let them outpatient and do monitoring. With that approach, we have found CPX-351 and CPX-351 combinations that we used as a good approach. So, here I'll turn it back to Dr. DiNardo so with your experience, how has CPX-351 been tolerated, and what is the kind of patient you would think about using CPX-351?

**Courtney DiNardo, MD:** I think CPX-351 really has been a nice addition to our treatment

armamentarium, if you will. I think patients really like getting intensive chemotherapy that doesn't have them lose their hair, that's a nice thing and I think, the cytopenias, as you mentioned, are really important, so you cannot assume this is a lower intensity therapy, people have cytopenias that are significant and that are prolonged and so, that's exactly why we keep people in the hospital, because neutropenic fevers and issues happen at the nadirs of these cycles, and so that is in my opinion, the best kind of optimal therapy management and piece of advice. In terms of who would not be a great candidate for CPX-351. Well again, as you said, this is anthracycline-based, cytarabine-based chemotherapy and so, if you have a patient for instance that has breast cancer and has had a lot of anthracyclines in the past, or someone with underlying cardiomyopathy with a low EF, that is someone who should not be getting this type of therapy. But in general, I think patients have tolerated this well, the cytopenias are prolonged and are important to be aware of, but in general, I found this to be kind of an intensive chemotherapy regimen that can be well-tolerated in those kind of older therapy-related AML patients.

**Naval Daver, MD:** Yes and that's kind of been our experience at MD Anderson that with the correct checks and monitoring, and again, in patient use of this, we have been able to deliver this regimen. I think one of the key issues though with azacitidine/venetoclax, we are able to add other drugs to it and it's not something we discuss, but at this year's ASH it will be discussed quite a bit, so adding FLT3 inhibitors like gilteritinib, quizartinib, or IDH inhibitors to azacitidine/venetoclax; or new drugs like magrolimab or cusatuzumab or APR-246 to backbone invasive we hope will further push that response and duration and survival up. I think that is a challenge for drugs like CPX-351 and maybe even standard intensive chemotherapy where you are already kind of at the threshold of toxicity in a 68-year-old, and I think that may become a key deciding factor in the next five years if some of these triplets really show dramatic activity, whether they will eventually actually turn out to be superior to standard induction or CPX-351, not even just for older patient but potentially, in the future for younger patients.

# Applying Key Data Presented at EHA 2020 to Practice

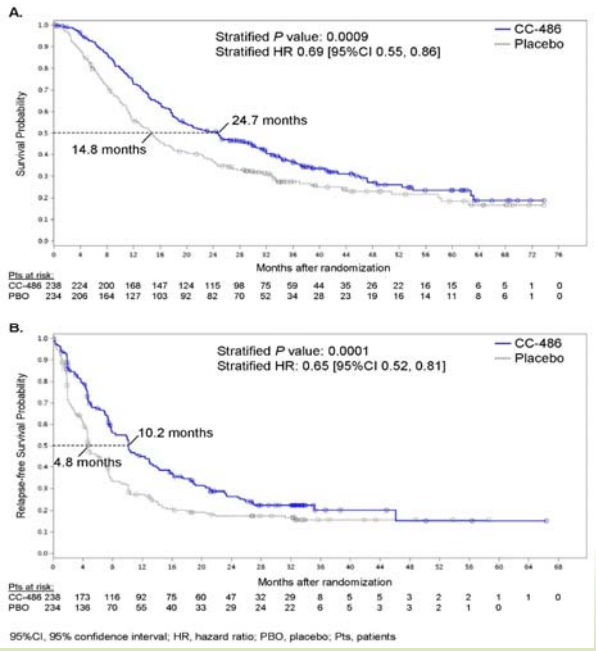



So from here I will discuss one area we didn't touch on, we didn't have in our case is but it's important is maintenance therapy. There's a drug CC-486, which is oral HMA therapy that has been approved in the maintenance setting. This was based on a study done in patients 50 to 70 years of age who had completed their planned induction consolidation and, importantly, were not going to transplant, so either they were not candidates for transplant because of fitness comorbidities, organ dysfunction; or they did not have a donor, or the patient decided for some reason they didn't want a transplant. So, it's important that this is not a replacement for transplant, but the study allowed people who completed induction consolidation, were above 50 and could not go to transplant, and it showed that the addition of the CC-486 in this setting improves survival as well as event-free survival quite significantly compared to just observation. Dr. DiNardo, what's your take on the CC-486 data? Where do you see this being used?

# Applying Key Data Presented at EHA 2020 to Practice

## QUAZAR AML-001: Results

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




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

**Courtney DiNardo, MD:** I think kind of two important points about CC-486. One is that it is so exciting to have a maintenance therapy option. This has been something that in other hematologic malignancies like ALL we've been able to use for years and improve upon our patients' duration of remission and overall survival as a result, and it has been something that has made sense for AML for a long time, but we have with the FLT3 inhibitors and maintenance and now, a CC-486, it's clear that maintenance is part of the paradigm of treating an AML patient, so I think that's really important. Then, the other thing that I think is really kind of an important advance about CC-486 is the fact that it is an oral formulation of a hypomethylating agent. It is not bioequivalent, IV azacitidine but it has lower PK properties in general, but I think this opens up the door for future clinical trials and maybe future combinations of CC-486 with other things in particular, venetoclax, one of my key interests, because I think our older AML patients that are spending so much time going back and forth to the hospital for blood checks and transfusions and IV or subcutaneous injections, I think having oral formulations of things is going to be a really nice addition to our AML therapy.

**Naval Daver, MD:** Yes, I agree, and I think that what you mentioned is very important

though that there are two oral hypomethylating agents, which is also going to create more confusion. It's great thing to have, but it has to be used separately. So you have the CC-486, the oral azacitidine formulation that was only tested in maintenance and is actually significantly lower PK values than the IV azacitidine, which may have been to its benefit which is why it could be taken for two years, whereas it may have been hard to give standard IV azacitidine. And then you have the oral ASTX, which is the oral decitabine formulation which was actually developed to be very equivalent PK equivalence approval for decitabine, and so with both of these, I think we have to be careful in what setting they're used, but again to us, these are good additions, major improvement in quality of life with oral agents, but only a starting point and then we can combine these with the venetoclax, FLT3, TP53, other drugs that are emerging. So then ASH is coming up quite soon. We're recording this on November 22nd, so two weeks away. Dr. DiNardo, what are some of the interesting things you're looking forward to seeing or presenting at ASH?

**Courtney DiNardo, MD:** I think, one of the things I am interested in seeing presented at ASH is the use of venetoclax with intensive chemotherapy. We talked a lot about how venetoclax is now kind of changing the standard of care in our older patients with poor performance status receiving lower-intensity therapy and venetoclax synergizes well with many different things. Is there a role for it with intensive chemotherapy? And that data will be shown. We have several different MD Anderson studies looking at FLAG-IDA with venetoclax CLIA, with venetoclax that will be shown. I think everyone is really excited about seeing some of the updated data on magrolimab that you mentioned on some of the other monoclonals and immunotherapy-type agents. I think the field would really love to be able to kind of incorporate some of those as novel therapies as well, and as you mentioned, the triplet data, so there's a lot of people now using azacitidine and venetoclax as a backbone and then you identify your patient has a targetable mutation, can you add an IDH inhibitor, a FLT3 inhibitor, a p53-modulating agent for the patients with those mutations?

**Naval Daver, MD:** Yes, same things that I'm quite excited to see or have presented and I think venetoclax, we have just touched on the surface with the HMA low-dose ARA-C combos, which is great and it's got them approved, but I think there's much more that will come out of these, as you said the FLAG-IDA and the CLIA combinations are exciting and then there will be data combining with FLT3 inhibitors with gilteritinib, with quizartinib in both doublets and triplets, quite striking response rates as well as duration, response survival, so I think, this is a drug that we will find a way to use in many different combinations going forward. Also, there's a lot of nice subset analyses that are coming both from our group as well as from others looking at different molecular impact with HMA/venetoclax outcome in TP53 and IDH that you are doing and then others with FLT3 looking across trials. I think this data will help us understand much better in each molecular group whether HMA/venetoclax is optimal. Are there other approaches? Are there triplets that could be used? I think it's going to be very exciting, and then CC-486 again, there will be updated data looking at MRD conversion rates, so that will be nice to see and in fact, there is a good MRD negative conversion rate which shows that this is not just kind of a soft effect but a real effect in converting people from positive to negative, which is something in the AML that we have not

seen, so hopefully, we can build on that. I think with that, let me turn over to our closing slide. I think we've had a lot of the good discussions. Any closing remarks from your side, Dr. DiNardo?

**Courtney DiNardo, MD:** No, I just want to thank you for inviting me to be part of this activity. I think it's a very challenging thing for the kind of average oncologist to be able to stay on top of all of the new approvals in AML, not only which is the optimal treatment, but also how to best manage your patient going through it. Everything has side effects and tricks of the trade and so being part of activities like this to try to make sure you are on top of kind of the best way to manage your patient I think is a fantastic thing. So, thank you.

**Naval Daver, MD:** Yes, absolutely. Thank you very much for giving us the time and all of the very useful information. I think this is critical. I mean, we, both Dr. DiNardo and myself and others, we are very aggressive in developing trials, pushing them and of course, getting drug approvals is our first goal in life basically right now and it's been great in AML to see that this is happening and continues to happen, but what we're starting to see is getting drug approved is half the battle and then getting them used optimally is as much or maybe even more important. We see data with azacitidine/venetoclax that other say I don't find this benefit or I see early mortality or I see high toxicity, and I think a lot of it has to do with how that is being done. There are tricks, we've used azacitidine/venetoclax, for example, over five years, they come to the point where we are over 250 frontline patients. Absolutely, what we did in the beginning in 2015 was completely different from what we're doing today and so, there's a learning curve. The good news is I think there's a lot of expert hematologists, oncologists including ourselves, we're very happy to discuss it anytime. You can email us. You can find our email on the internet or just go to MD Anderson. Our phone numbers are there, and we get every day five or six emails or calls and we're happy to provide input and more importantly, we're happy to bring patients for trials, so if you see a frontline patient, TP53, you see a relapsed patient, you don't have options, be happy to reach out to us or other academic centers in your location, Moffitt, Stanford, Dana-Farber, wherever it may be. A lot of times I hear people saying, well, we're doing so well with azacitidine/venetoclax, so are we done? Absolutely, not. I mean, you go from 15% five-year survival to 35%-40%, this is good, but we don't want to be 20 years from now, at 35%, 40%, four or five years' survival. We want to be at 80%-90%. I think we can get there like multiple myeloma did, 2000, three-year median survival, 2019 15-year median survival and that is without using cytotoxic therapy, so this has been done by other heme malignancies. We think we can do the same and so feel free to reach to us and again, thank you very much for viewing this activity and we hope to talk to you all again in the near future.