Expanding Therapeutic Options in High-risk AML

My name is Farhad Ravandi. I am professor of Medicine and Chief of Section of Acute Myeloid Leukemia and the Department of Leukemia at the University of Texas MD Anderson Cancer Center and I am going to go over therapeutic options for high-risk AML.

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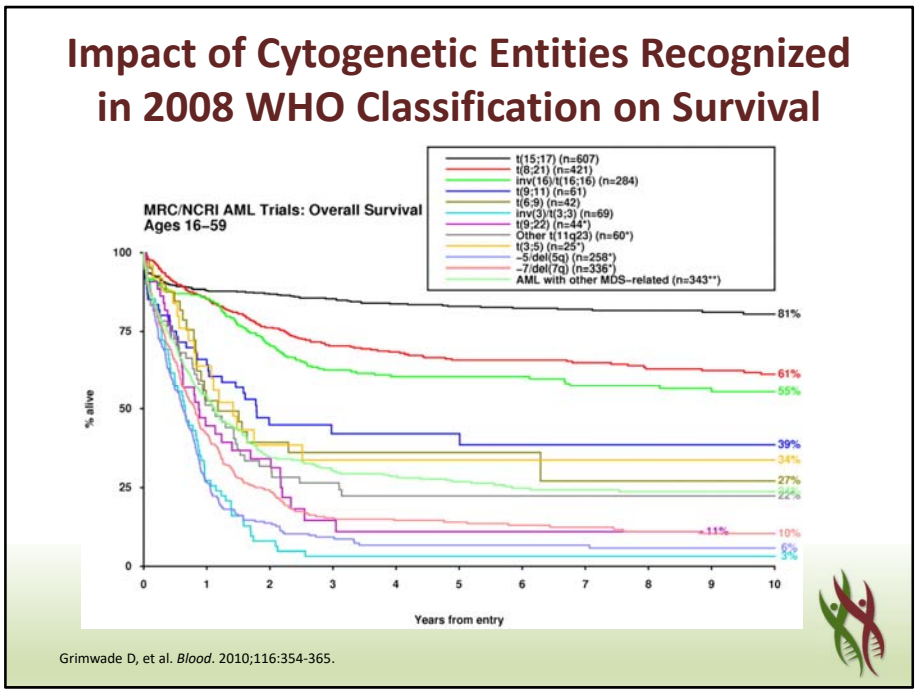
Expanding Therapeutic Options in High-risk AML



Of course, the definition of high-risk AML depends on a number of factors including patient-derived as well as leukemia-derived or disease-derived factors. Clearly, a patient who is older with comorbid conditions is going to be at higher risk of failure using traditional chemotherapy agents, but also there are subsets of AML that we have recognized over the years that are much more likely to be associated with short- and long-term disease-free survival as well as overall survival, and certainly they are considered as high risk. This is initially demonstrated using conventional cytogenetics, for example, in this large study from David Grimwade in the UK where he showed that there are subsets or cytogenetic abnormalities that tend to do significantly worse than others.

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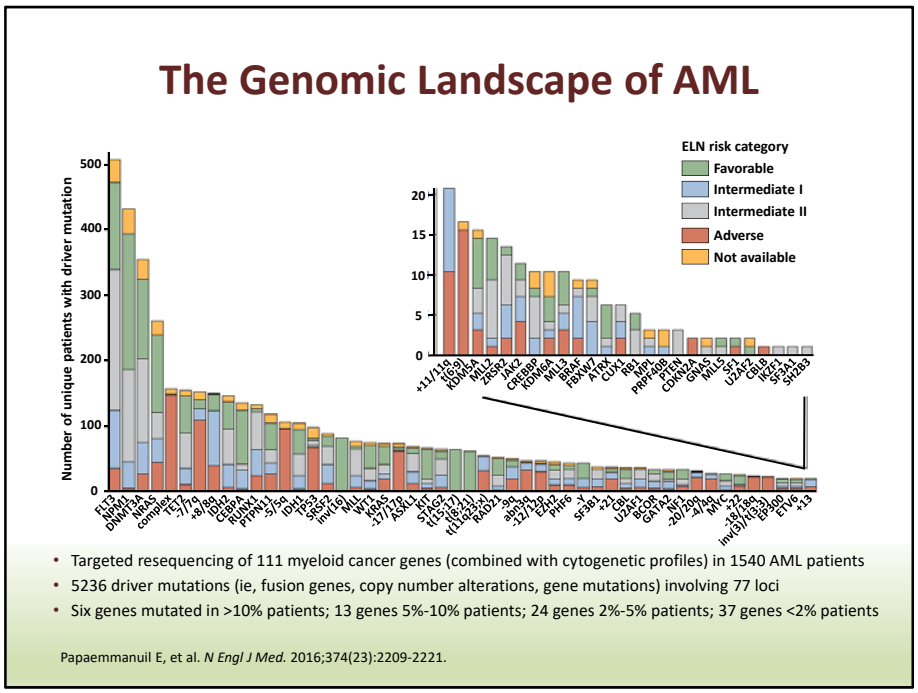

More recently with the development of assays that we can identify molecular aberrations in leukemic blasts, we now have a better picture of the genomic landscape of AML. Through the finding of these mutations we have also been able to identify some of the mutations which are associated with a worse prognosis. Obviously, these mutations occur not as a solitary event and usually in combination with several other mutations. The field is actually evolving to try to better associate these different mutations with each other in terms of their risk for success and failure of therapy.

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Prognostication in AML: ELN 2017 Karyotype + Molecular Mutations

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

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

Using the cytogenetic and molecular information, there have been a number of prognostic classifications that have been incorporating this information to subdivide AML to more favorable, more adverse and intermediate subgroups, and as you can see here, there are a number of mutations that can impart a better prognosis and others that are associated with more adverse prognosis. For example, one notable one is the presence of mutated TP53 gene which is associated with a significantly worse prognosis in patients with AML.

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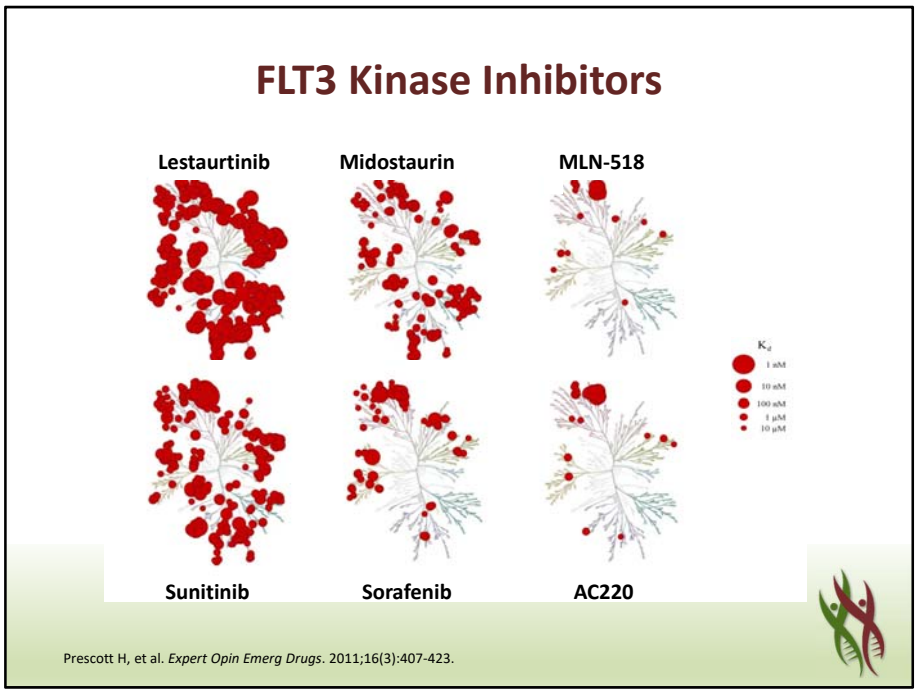

As I mentioned, a number of these mutations have been identified even as a single mutation to be associated with a worse outcome. So, for example, FLT3 internal tandem duplication mutations have been known through a large number of studies to be associated with a short relapse-free and short overall survival and this has led to the development of a number of FLT3 kinase inhibitors. You see some of them here and this is called a kinome tree and each branch is a kinase in a normal human cell, and the red dots are the extension inhibition of that specific kinase by that specific molecule. You can see some of these FLT3 kinase inhibitors are very specific in terms of the FLT3 kinase, most importantly AC220, or now known as quizartinib, as well as others that are much more dirty inhibitors such as lestaurtinib or midostaurin that essentially are multikinase inhibitors and are not highly specific for FLT3 kinase inhibition.

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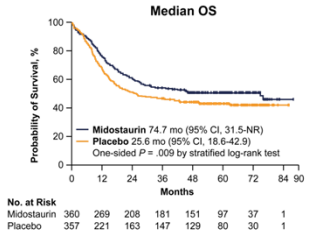
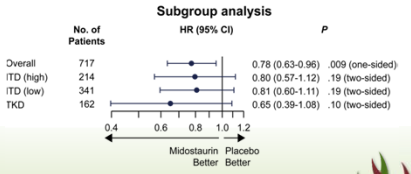
RATIFY: Survival Outcomes and Transplantation Rate

- OS improved with addition of midostaurin
  - 74.7 vs 25.6 months (*P* = .009)
- Transplantation during first CR
  - 28.1% in the midostaurin group vs 22.7% in the placebo group
- Overall HCT
  - 58% in the midostaurin group vs 54% in the placebo group
- Four-year OS among HCT patients
  - 63.7% in the midostaurin group vs 55.7% in the placebo group (*P* = .08 by log-rank test)





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

The first FLT3 inhibitor that was approved for treatment of patients with AML is a multikinase inhibitor, not a very specific FLT3 kinase inhibitor, that is midostaurin, which was evaluated in a multinational very large randomized trial in patients younger than 60 with FLT3 mutations. In this study, both FLT3 ITD and tyrosine kinase domain mutations were included. And again, these patients were younger than 60 and were previously untreated and they received standard 3+7 regimen plus either midostaurin or placebo. The group randomized to midostaurin continued to receive it during consolidation and for maintenance. This was a positive study in terms of overall survival as you see on the right of slide that showed a benefit for addition of midostaurin to the traditional cytarabine plus anthracycline-based induction and consolidation and has led to the approval of midostaurin for treating FLT3 mutated AML in the United States.

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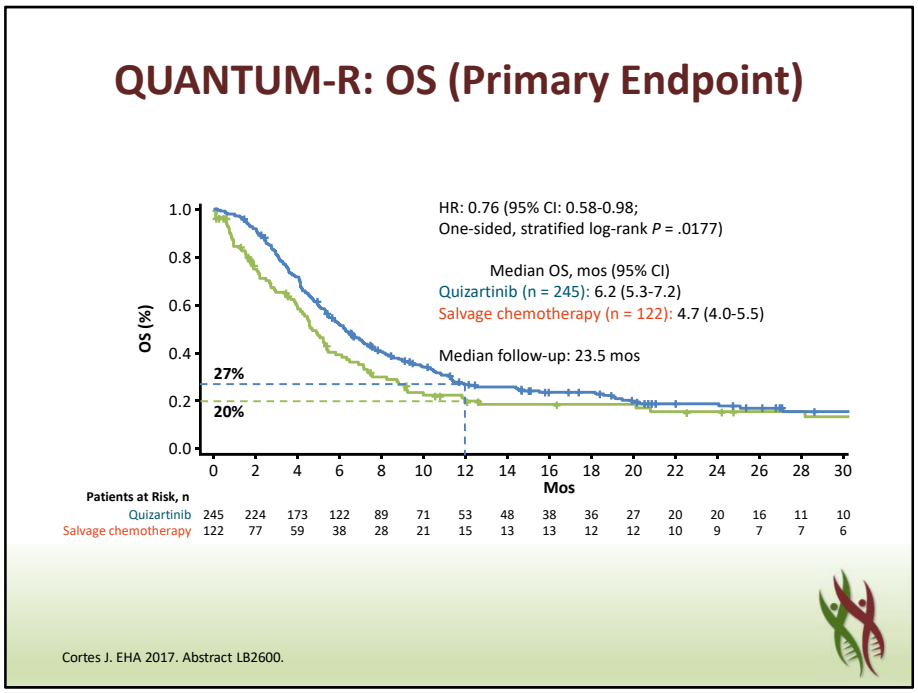

Other FLT3 inhibitors that have been in development, I have mentioned earlier quizartinib which is a very specific FLT3 kinase inhibitor and this was also evaluated now in a relapsed setting in a large study looking at patients with AML with first relapse and they were either randomized to quizartinib single-agent oral therapy or combination chemotherapy, traditional combination chemotherapy that is used for salvage. And although this study did show a survival advantage, it still has not led to the FDA approval of the agent, although continuing studies will let us know in the future whether this drug can become available in the US in the salvage or frontline setting.

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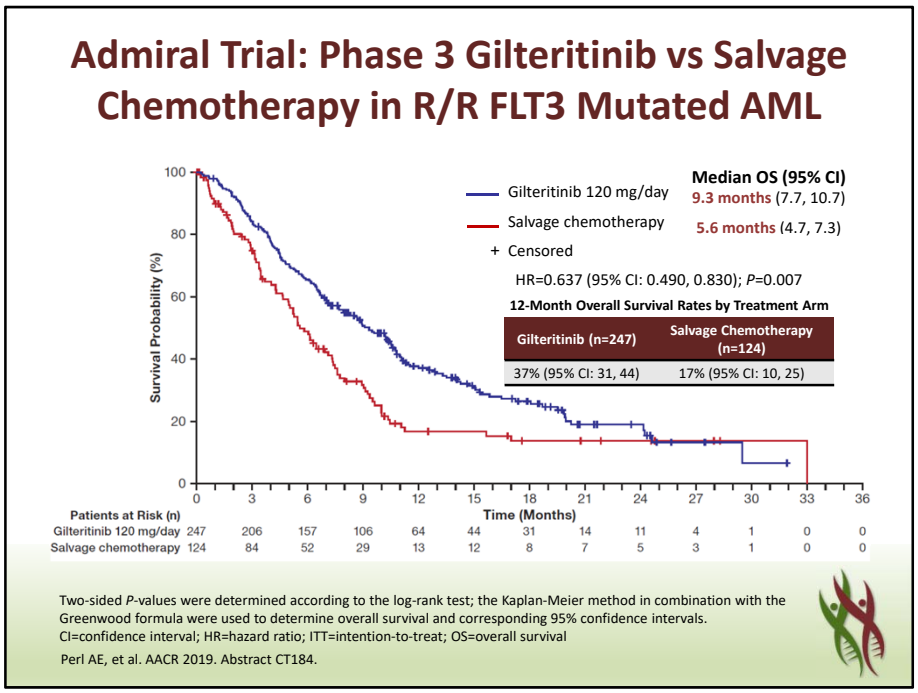

Another agent, gilteritinib, is also a very effective FLT3 kinase inhibitor and it has the advantage of inhibiting both FLT3 internal tandem duplication mutations as well as FLT3 tyrosine kinase domain mutations. This was also evaluated in a randomized study in the relapsed setting in patients with relapsed or refractory AML, and here there was a clear advantage for gilteritinib over conventional chemotherapy salvage regimens, and this led to the approval of gilteritinib for treatment of FLT3 mutated relapsed AML.

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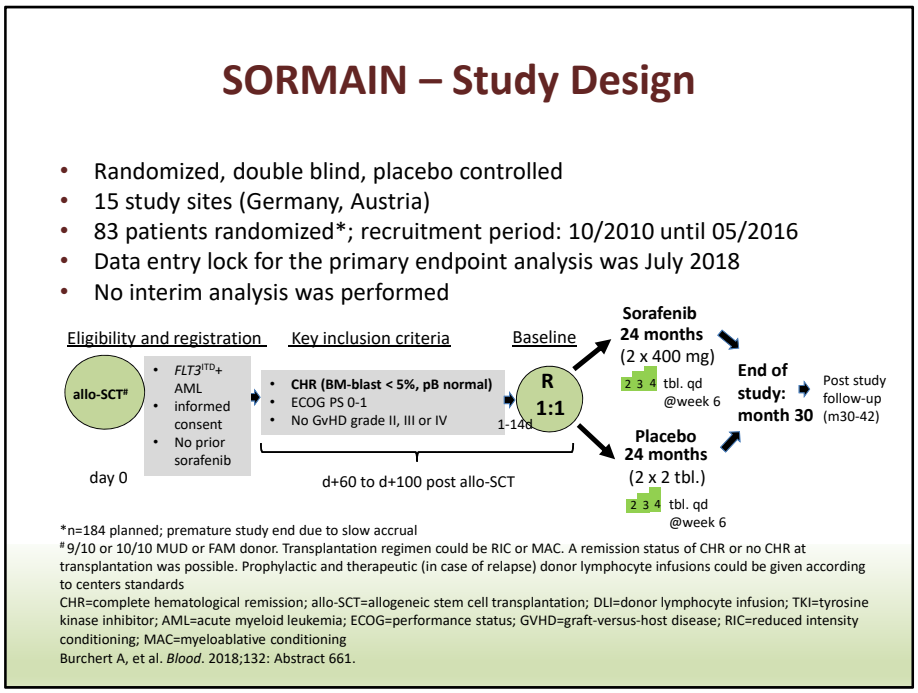

I think it is important to note that when you have a high-risk AML patient, we tend to rely heavily on allogeneic stem cell transplant. So, for example in the RATIFY trial, also many of the patients who are enrolled on this study underwent allogeneic stem cell transplant because we believe that FLT3 mutated AML, based on its high risk and high likelihood of relapse, should be transplanted in first remission. At least this is a general consensus for the majority of the patients. The question then comes what to do after transplant in these patients, and this was an interesting study that was reported at the annual American Society of Hematology meeting in 2018 where the investigators from Germany randomized patients with FLT3-mutated AML, who had undergone allogeneic stem cell transplant in first remission and were still in complete remission and did not have significant graft versus host disease to either receive a FLT3 inhibitor sorafenib or placebo, and this was a one-to-one randomization.

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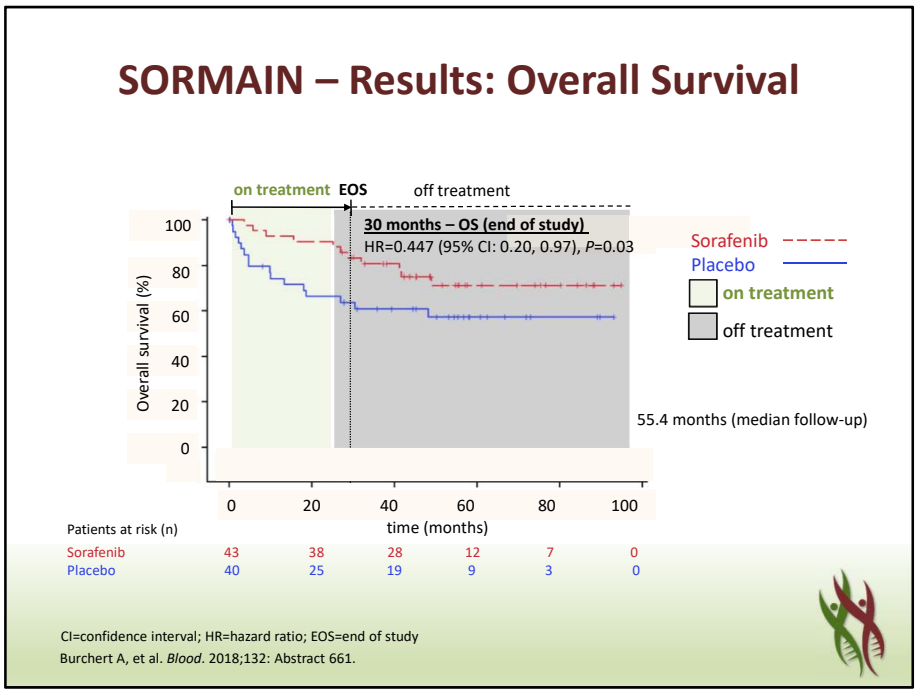

Interestingly, it did show a significant benefit for the patients who received sorafenib posttransplant. This was a small phase 2 study and there is ongoing studies including an ongoing BMT CTN phase 3 study that is looking at potential role for gilteritinib posttransplant in this setting.

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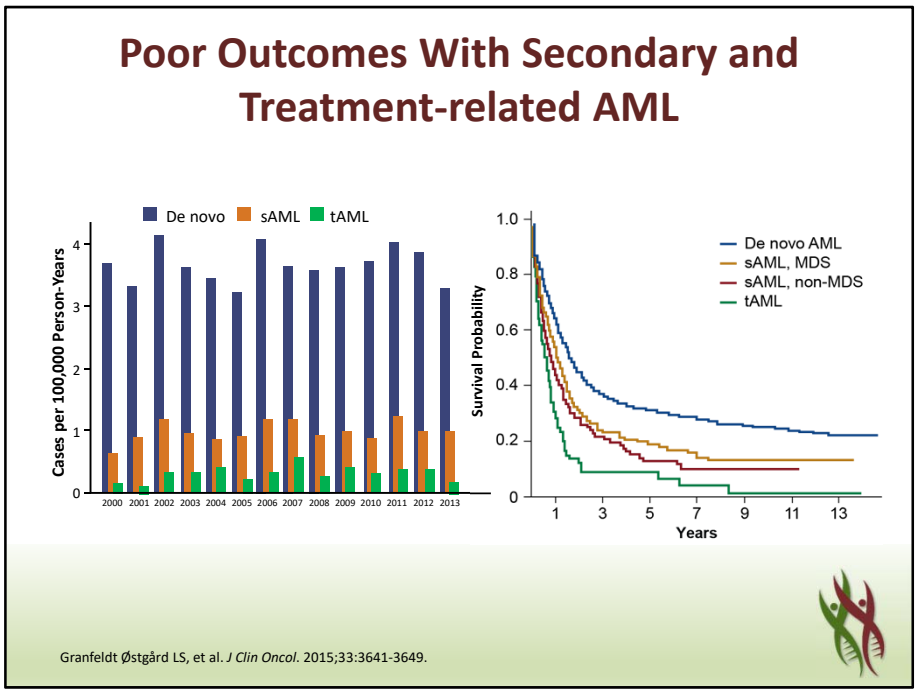

Another subgroup of AML that is considered high risk is patients with secondary or patients with treatment-related AML. Secondary AML are patients who have had a history of myelodysplastic syndrome or for example myeloproliferative neoplasms and progressed to AML, and of course therapy-related AML is patients who have had a history of prior therapy for other malignancies. And as you see here from this Danish registry study, there are a reasonable proportion of patients and they have significantly poorer outcomes than de novo counterparts in the blue line. You can see clearly that therapy-related AML in the green line has a significantly poor long-term outcome. This population has traditionally been treated with traditional anthracycline-based therapy without much success.

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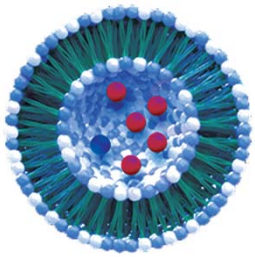
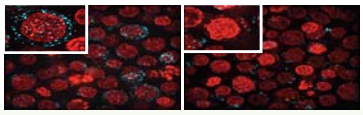
Expanding Therapeutic Options in High-risk AML

Liposomal Daunorubicin and Cytarabine (CPX-351)





- 1:5 molar ratio of daunorubicin to cytarabine
- Synergistic activity in both in vitro and animal models
- 100-nm bilamellar liposomes
- 1 unit = 0.44 mg daunorubicin plus 1 mg cytarabine (1:5 molar ratio) complexed with copper
- Targets bone marrow and preferentially targets leukemic compared with normal marrow progenitors

Lancet JE, et al. *Blood*. 2014;123:3239-3246.

So this drug was developed to try to at least improve upon this outcome, and this is an agent called CPX-351 which is a 1 to 5 molar ratio of daunorubicin to cytarabine which is encapsulated in these bilamellar liposomes. They have been shown to target bone marrow and predominantly leukemic blasts more effectively.

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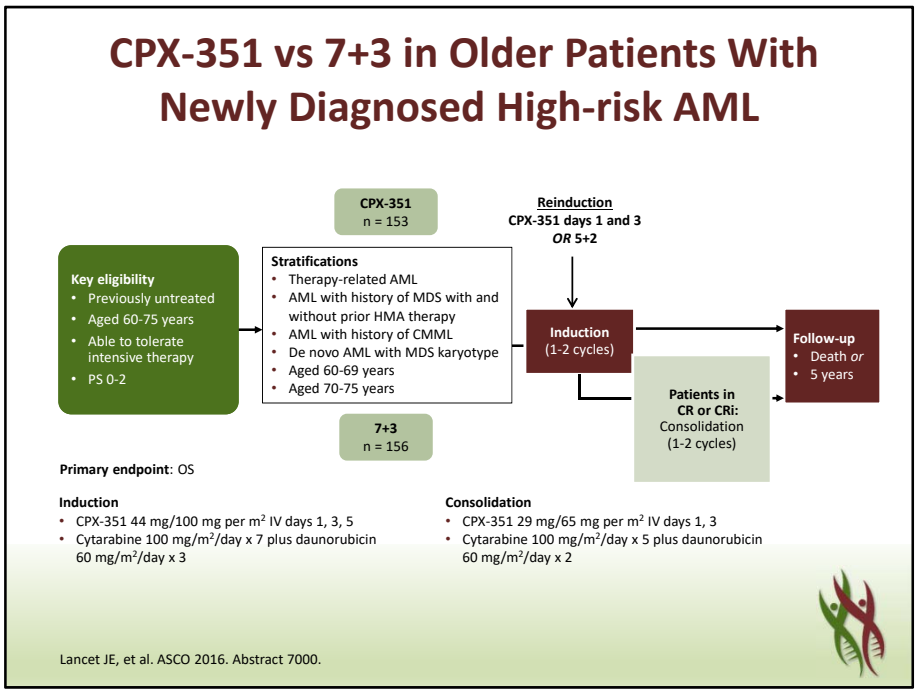

This was evaluated in a randomized trial in patients with newly diagnosed high-risk AML. In this study, patients had to be between the ages of 60 and 75 and had to have high-risk AML based on having either therapy-related AML or secondary AML with prior history of MDS or CMML or de novo AML with MDS-related karyotypes. They were randomized one-to-one to receive either CPX-351 or the traditional 3+7 cytarabine plus anthracycline induction and they could get one or two induction cycles, and the responding patients could also receive further consolidation and patients could go on to allogeneic stem-cell transplant despite the fact that this study was in an older population.

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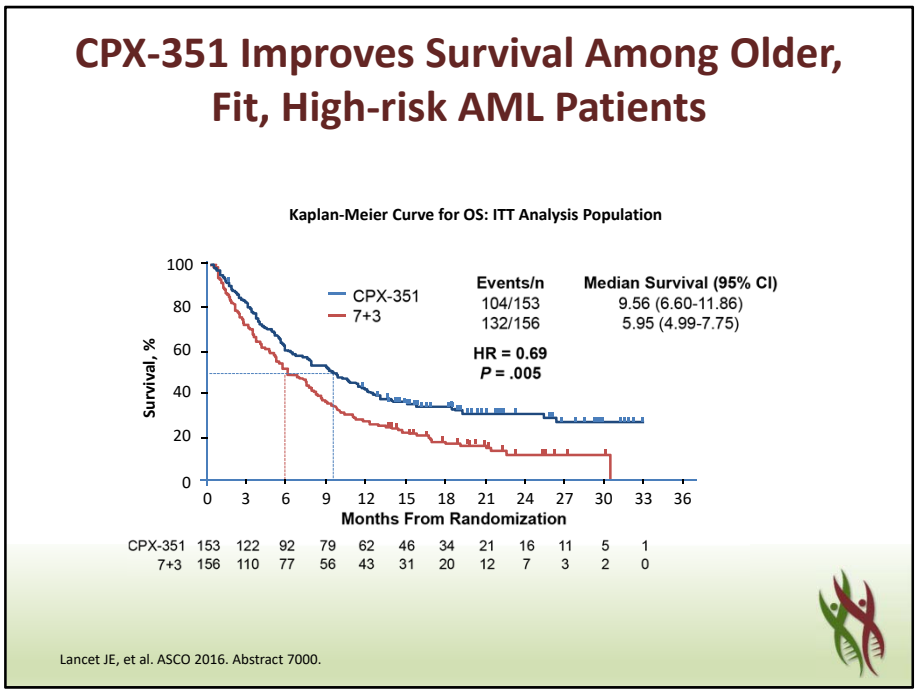

Again, this was a positive study showing a benefit for CPX-351 over 3+7 treated patients, and again this has led to the approval of this agent for treating patients with secondary or therapy-related AML in the United States. Of interest, patients who underwent allogeneic stem cell transplant in the study did better if they were on the CPX-351 arm of the study.

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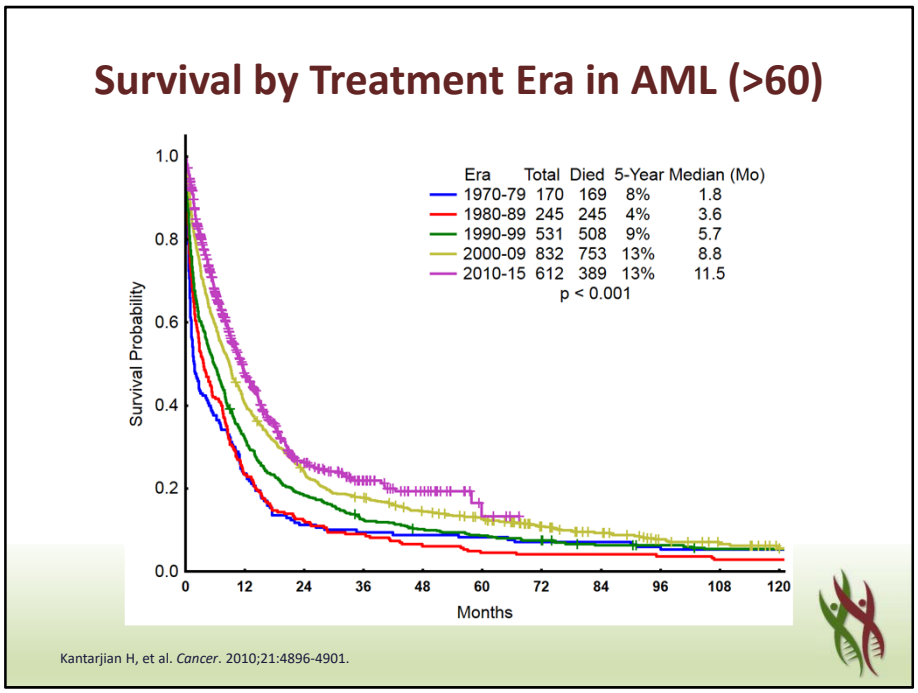

Another specific area of AML that is considered high risk in general is patients who are older, and this slide shows the outcomes of older AML patients. Patients above the age of 60 at our institution over the last several decades, and similar slides have been shown by other groups including various cooperative groups clearly showing that the long-term outcome of older AML patients has been very poor. This is both because the older population is less able to tolerate intensive chemotherapeutic regimens with cytarabine and anthracycline because of their advancing age as well as because of comorbid conditions and worsening organ function, but also in general the older population has or tends to have a more adverse biology AML, that is they are more likely to have more unfavorable or high-risk cytogenetic and molecular abnormalities.

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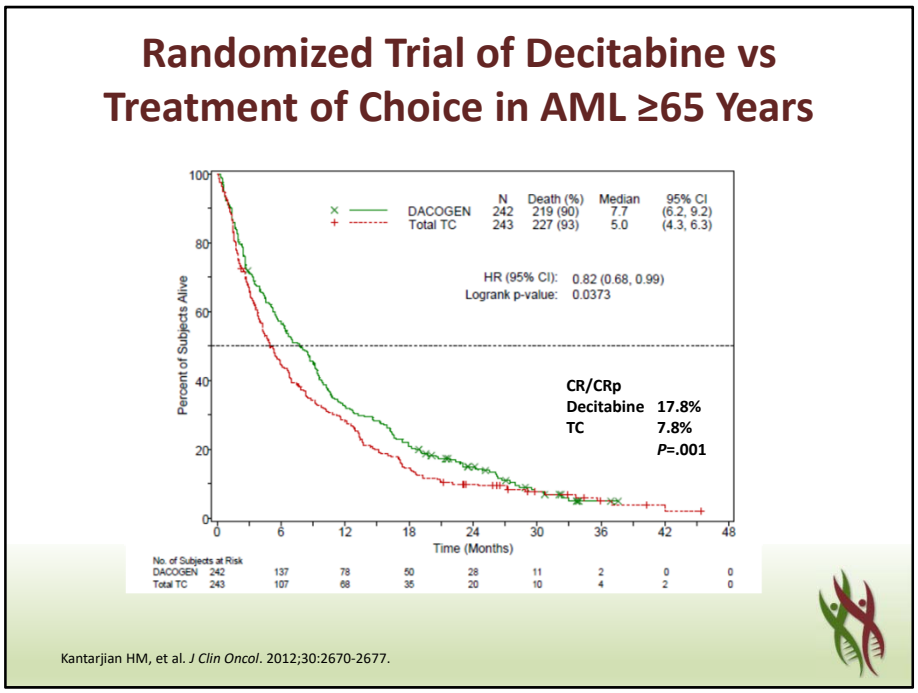

The problem with the intensive chemo has led to a lot of groups in the last several years to try to identify less intensive strategies that would be just as effective but less toxic. Hypomethylating agents were investigated in this setting. Both decitabine and azacitidine were evaluated for older unfit AML patients not fit for induction chemotherapy. This is the decitabine study and there is an azacitidine study that shows, in general, some superiority of these approaches. But as you can see here, still the outcome is not tremendous.

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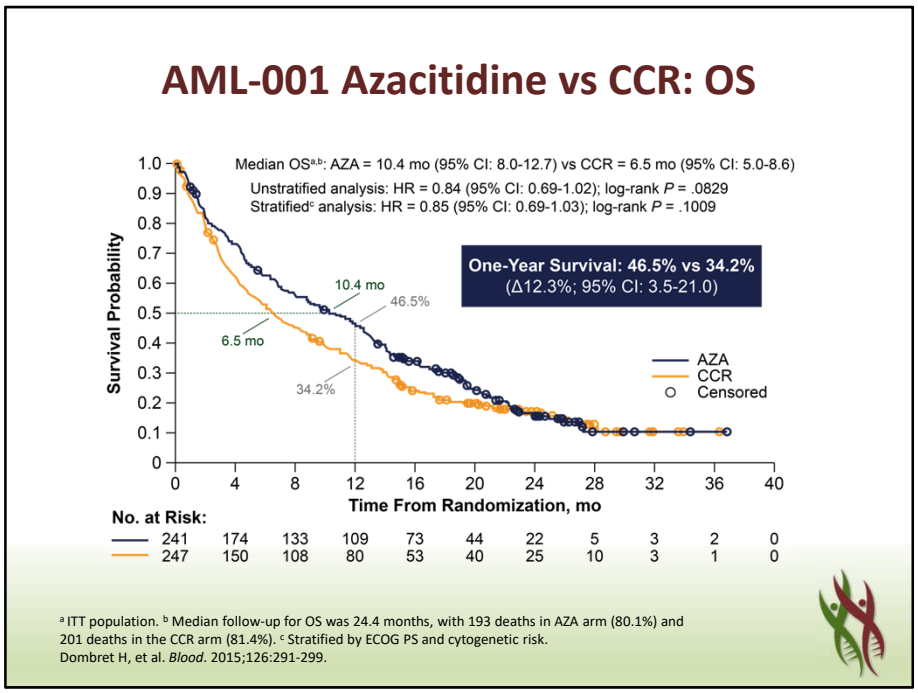

So this is the azacitidine study and also again showing that there is some benefit for azacitidine over conventional care regimens, but still this is in terms of overall survival, not where we want to be.

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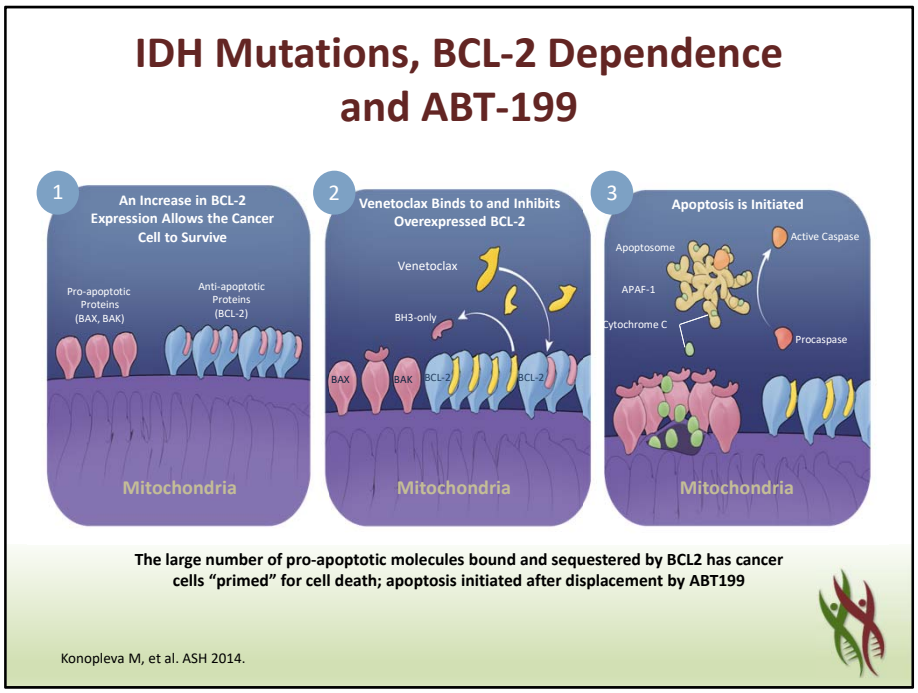

Development of ABT-199, now known as venetoclax, for treating patients with CLL and its approval led to its investigation in other diseases. For example in acute myeloid leukemia, an initial phase 2 study by Dr. Konopleva at our group showed that this drug does have some activity, but the response rate with the single agent was only about 20%.

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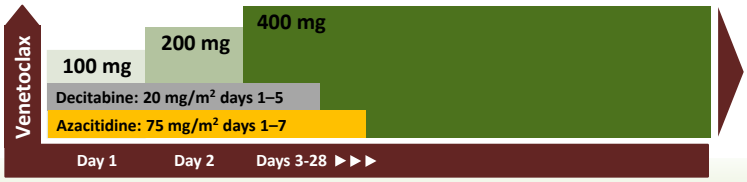
Expanding Therapeutic Options in High-risk AML

Venetoclax + Hypomethylating Agents

KEY INCLUSION CRITERIA	KEY EXCLUSION CRITERIA
• AML by WHO criteria • Age ≥60 years • Ineligible for standard induction therapy with cytarabine and anthracycline as determined by medical criteria • ECOG score 0–3	• Prior therapy for AML or any antecedent hematologic disorder • Favorable risk cytogenetics per NCCN* • Active CNS involvement • WBC count >25 $\times 10^9$ per liter (hydrea was permitted) • Known infection with HIV, HBV, or HCV *Favorable risk cytogenetics (now known as non-adverse cytogenetics) is defined as core binding factor: inv(16), t(16;16), t(8;21), or t(15;17)



Patients received venetoclax plus decitabine or azacitadine

Venetoclax with HMAs induces rapid, deep, and durable responses in older patients with AML. ASH 2018.
DiNardo CD, et al. *Blood*. 2019;133:7-17.

This led to the concept of trying to combine it with other agents and because hypomethylating agents are commonly used in elderly or unfit AML, they were one of the natural choices. And in this study, the investigators in a multicenter study were able to treat previously untreated, older, unfit AML patients who were not candidate for intensive chemotherapy, and they were able to choose either decitabine or azacitidine depending on their center preference and combine it with venetoclax. Venetoclax was escalated over a few days from a dose of 100 mg to 400 mg, and the reason beyond that is to try to avoid tumor lysis which has been seen with CLL but not as much with AML.

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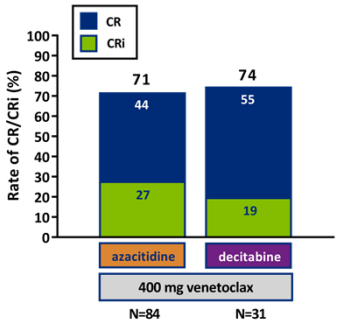
Response Rates of CR/CRi by Combination



	Ven + Aza	Ven + Dec
Time to CR		
median (range)	1.2 (0.7–5.5)	1.9 (0.9–4.6)
No. of treatment cycles for these patients		
median (range)	6.0 (1–32)	6.0 (1–29)

Venetoclax with HMAs induces rapid, deep, and durable responses in older patients with AML. ASH 2018.
DiNardo CD, et al. *Blood*. 2019;133:7-17.

They were able to show excellent response rates, as we see here over 70% both with decitabine and with azacitidine. Clearly, this is a dramatic response rate when we consider either decitabine or azacitidine alone, the response rates are only in the region of about 20% to 30%, and clearly addition of venetoclax can improve the outcomes or response rate in these patients.

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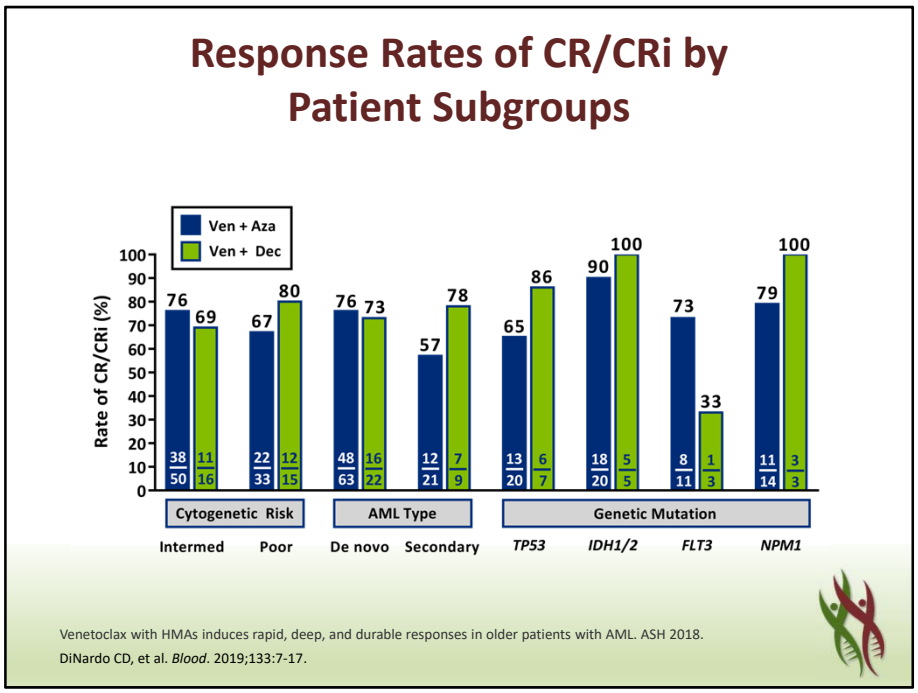

If you look at specific subsets within the study or the study population, even patients with poor-risk cytogenetics or even the patients with secondary AML are able to achieve high responses. Similarly, if you look at patients who have TP53-mutated AML they also are able to achieve a reasonable response rate of about 70% to 80%. So this is clearly exciting, and this is being further investigated.

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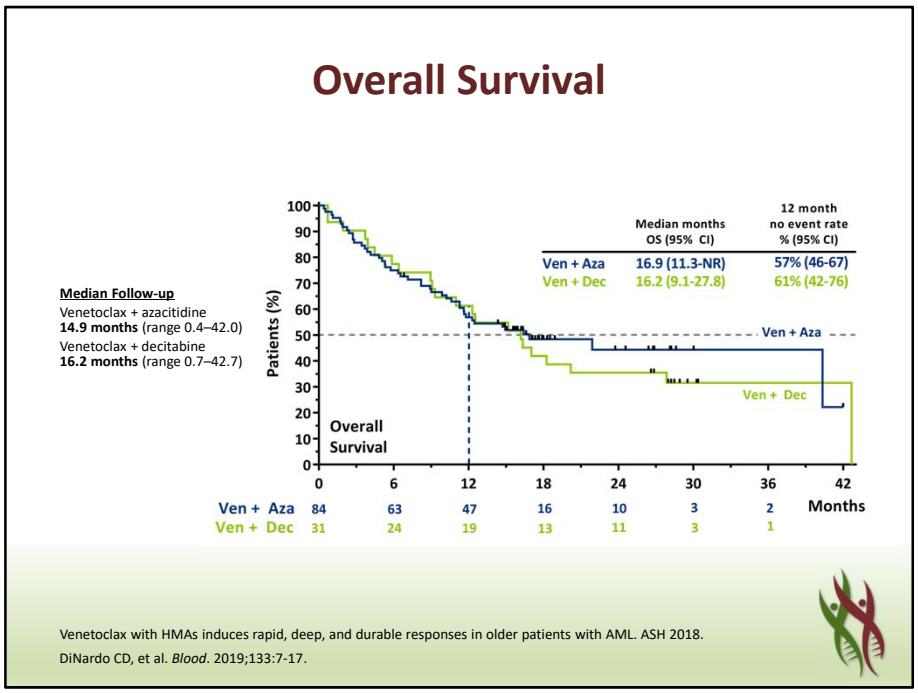

Their responses also overall can be quite durable. You see here with azacitidine-venetoclax and decitabine-venetoclax the overall survival, and you see the median overall survival is actually about 16 to 17 months which is quite an improvement over hypomethylating agents alone.

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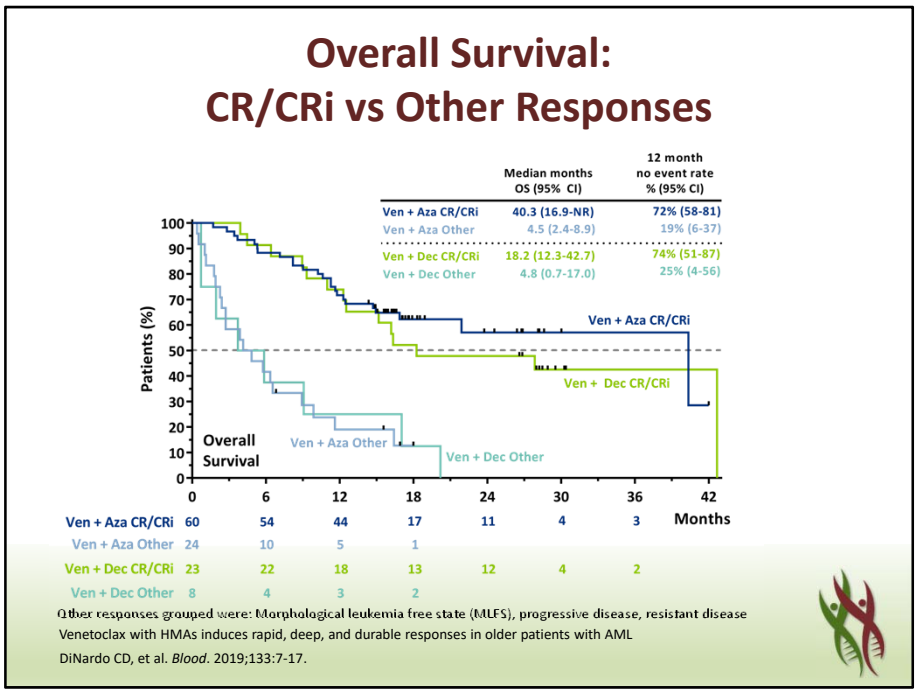

Clearly the patients who achieve a response do better than non-responders because we see this with all forms of therapy in leukemias as well as in cancer in general.

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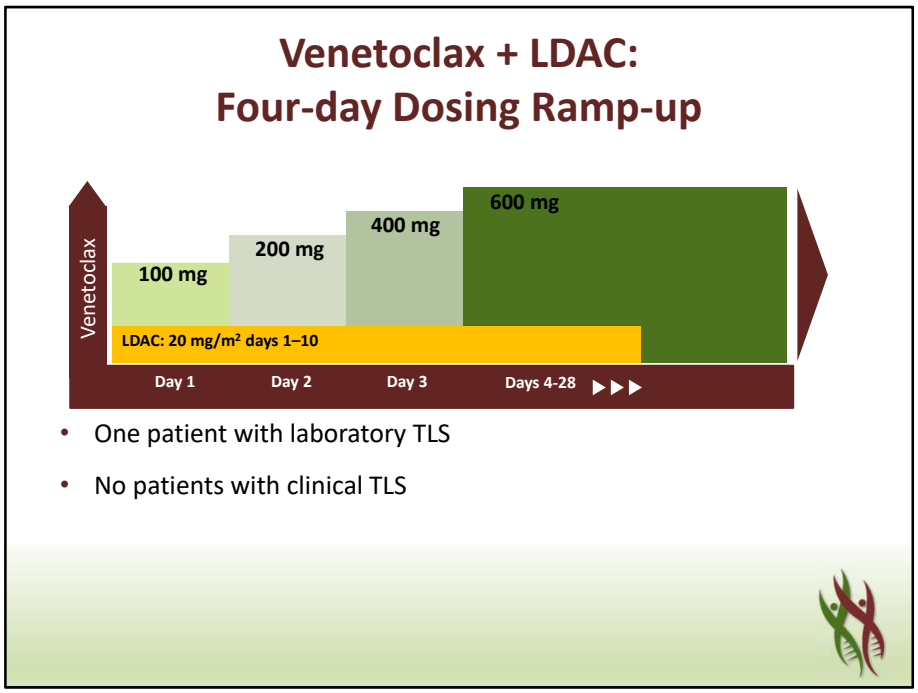

However, there are countries that hypomethylating agents are not used in the frontline therapy of elderly unfit AML, and these countries tend to use low-dose cytarabine. So another study combined low-dose cytarabine with venetoclax, and you see this study here where again the venetoclax dose is escalated over several days from 100 mg to 600 mg again to avoid tumor lysis, and then low dose cytarabine is given at the standard dose to these older unfit AML patients.

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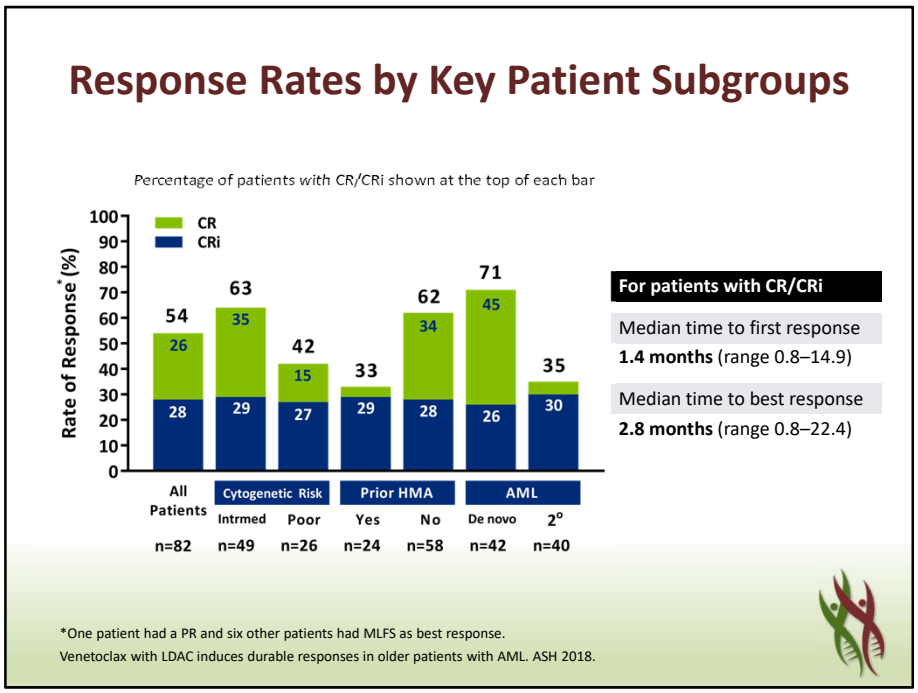

So, again this was a really dramatic improvement in response rate as compared to what we would see with low-dose cytarabine alone. Here, you see that the response rates are above 50% overall and also responses are occurring even in patients with high-risk features such as poor-risk cytogenetic patients or patients who have had prior hypomethylating agents. So, addition of venetoclax to low-dose cytarabine in this high-risk population has also been beneficial.

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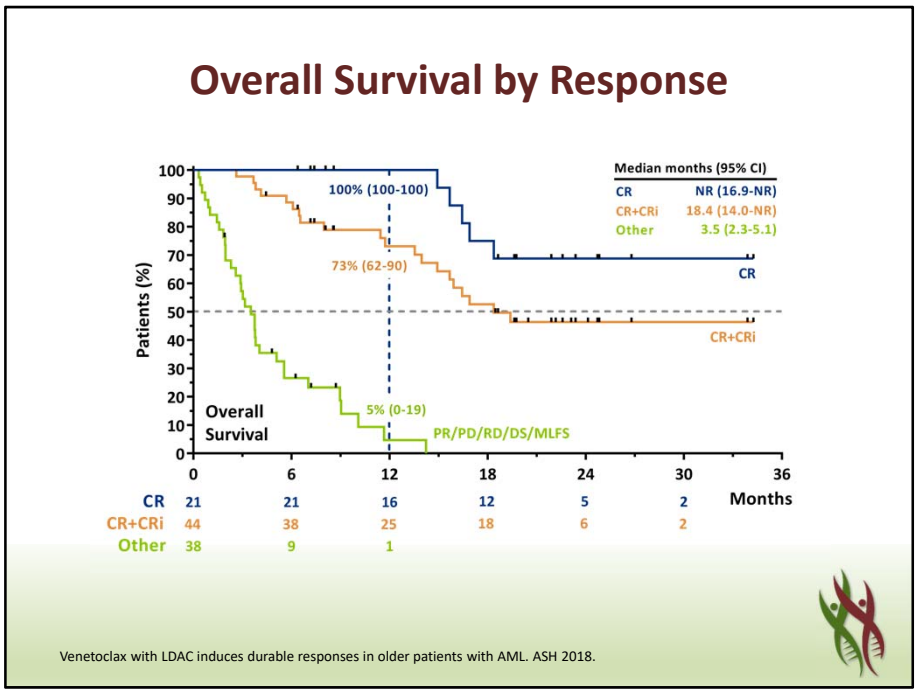
Therapeutic Options for High-risk AML



Again, patients who achieve a good response, those who achieve a CR, tend to have a survival advantage with their median survival not reached, at least at this point in the presentation.

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Conclusions

- Characterization of specific subsets based on molecular events and pathogenic pathways
- Addition of target specific drugs to:
  - Chemotherapy regimens in younger patients
  - Hypomethylating agents in older/less fit patients

In general, high-risk AML has continued to be a problem. In the older population. This tends to account for significant proportion of patients. In fact, probably the majority in younger patients, despite the fact that younger patients can receive intensive chemo and undergo allogeneic stem cell transplant, still those with high-risk features with poor-risk cytogenetics and poor mutation profile tend to do poorly. The development of specific agents target specific drugs that are attacking specific molecules that can further inherent poor-risk biology to the leukemia cells is going to be exciting. I have mentioned a number of these already, but there are others such as agents being developed against TP53-mutated AML and we will see that hopefully in the future the addition of these agents to either chemotherapy, perhaps in the younger patients, or to hypomethylating agents in older patients can significantly improve the outcomes of these patients.

Thank you for your attention.

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