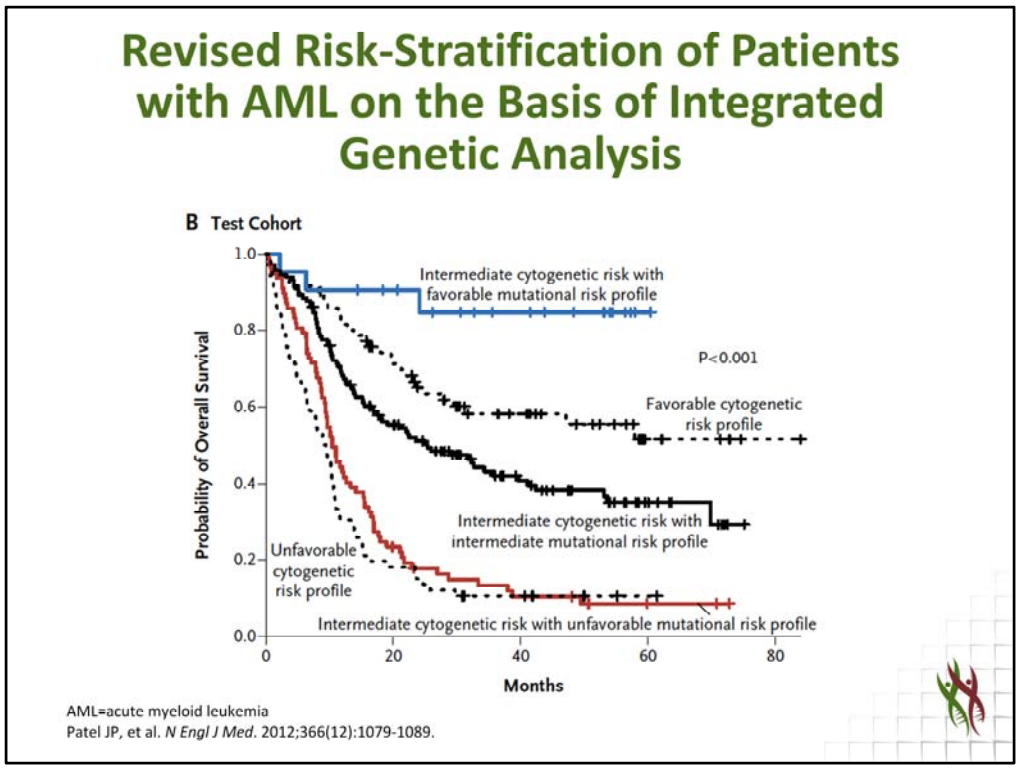
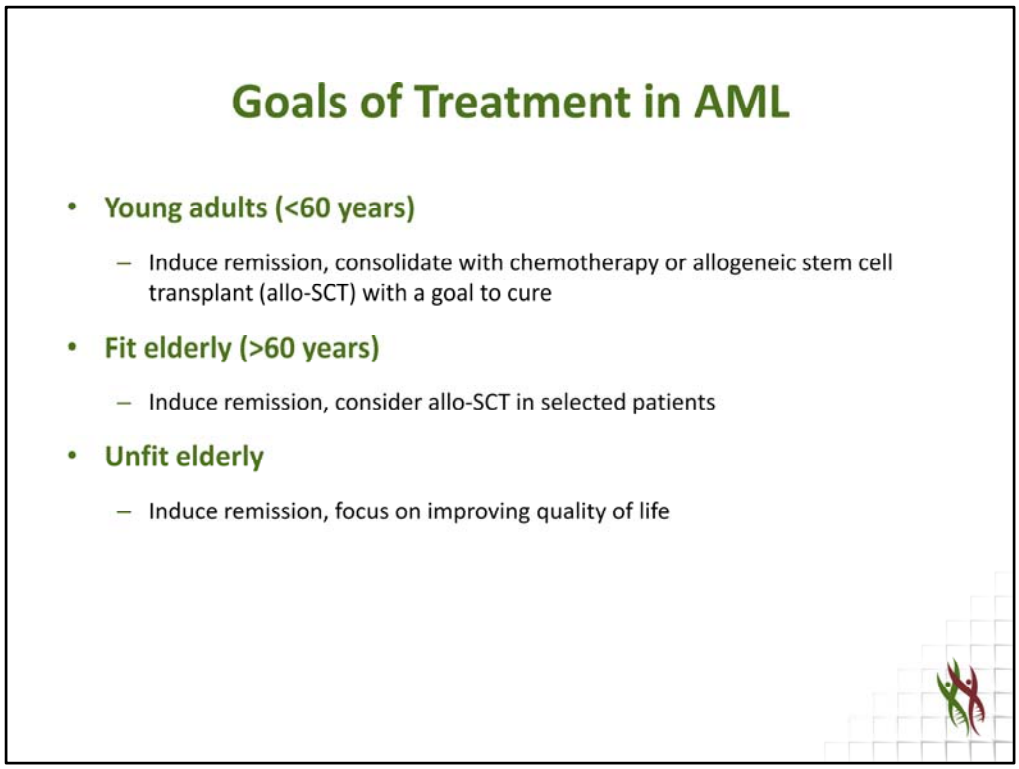
Emerging Agents Impacting Future Treatment Strategies in AML

Hello! Thank you for joining me for this activity. I am Dr. Pinkal Desai. I would like to take this time to share with you some promising new data in the treatment of AML or acute myeloid leukemia. The treatment landscape for AML is rapidly evolving with a multitude of therapies across various patient populations, but for today's discussion, I will focus specifically on agents that have received breakthrough therapy designation by the FDA. So, let's begin.

Emerging Agents Impacting Future Treatment Strategies in AML



Before I move on to the treatments, let us go over to the current cure rates of AML. This slide divides patients into intermediate-, high-, and favorable-risk profile. You can see that patients with a favorable mutational risk profile or a favorable cytogenetic risk profile have a long-term cure rate of 60% to 80%. Patients who have an unfavorable cytogenetic profile or an unfavorable mutational risk profile do not have good benefit from currently available treatment, and the long-term survival is about 10% to 15%. The intermediate category falls somewhere in the middle with a 40% long-term survival. This is what we have and this is what we are up against in trying to get better treatments and better survival for patients with AML. Unfortunately, most of the patients with AML do not have favorable-risk profile and fall in the intermediate or unfavorable risk profile.



When we talk about goals of treatment of AML, it depends on age and to some extent their performance status. If you have a young patient who is under 60 years old, the goal is to induce remission and then consolidate with either chemotherapy or a stem cell transplant with the ultimate goal to cure the disease. The consolidation with chemo or stem cell transplant is dependent on the risk profile of the patient. If you have a fit elderly patient that is over 60 years old, the goal again is to induce remission and consider a stem cell transplant in selected patients. We can routinely perform stem-cell transplant now up to age 75, but patient selection is important. If it is an unfit elderly patient, you do want to induce remission and the big thing is to maintain it because that is what really improves overall survival in these patients. There is a focus on improving quality of life as well, but I would pause here and say that there have been multiple trials that have shown that if you have an elderly patient who does not have a good performance status, if you treat the patient, they do enjoy a better quality of life and better survival, rather than just doing palliative care or transfusions alone. These are patients that are absolutely somebody you should consider for clinical trials.

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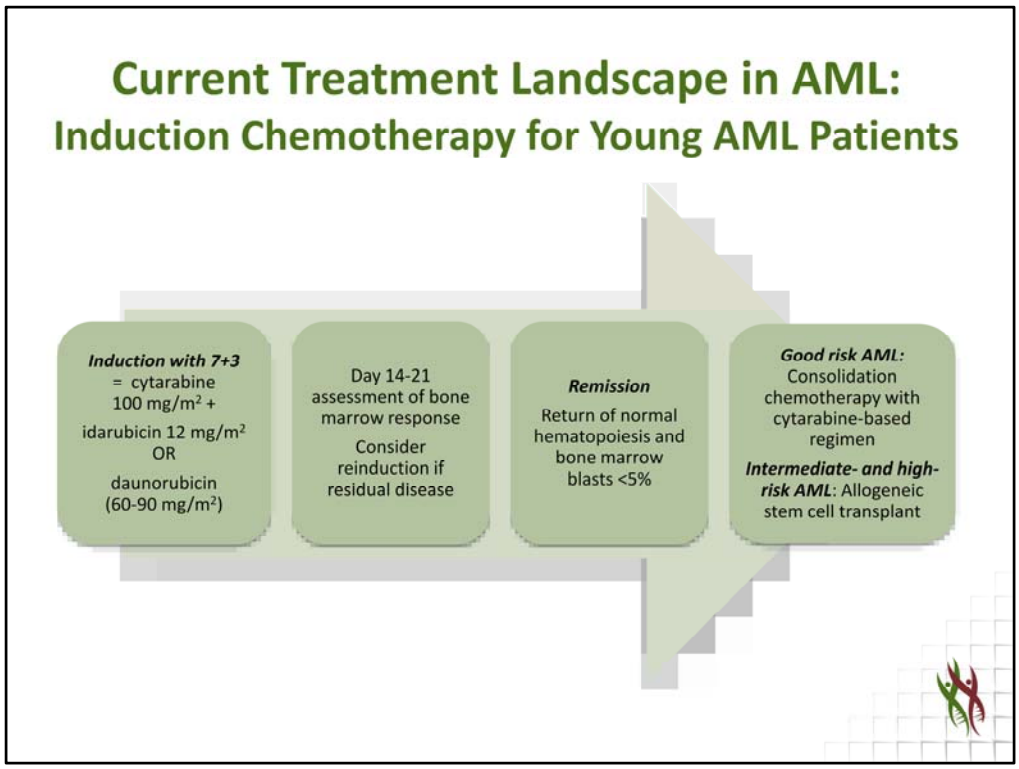

The current landscape of treatment of AML for young patients includes treatment with 7 + 3 (or cytarabine and idarubicin or daunorubicin) which is given in the inpatient setting with approximately 4-week hospitalization. There is usually a bone marrow biopsy that is done somewhere in day 14 through 21 to assess for response. If the marrow is ablated at that point, then wait for the patient to recover their counts, and at that point, we would do another bone marrow biopsy that would confirm remission. If there is residual disease on the bone marrow biopsy that is done in the middle of the cycle, there is consideration for re-induction if the patient is able to handle another dose of the chemotherapy. Once remission is complete, it depends on what the risk profile of the patient is. This risk profile is based on molecular analysis and cytogenetic subgroups. If there is a patient with good-risk AML, then the plan is to consolidate chemotherapy with high-dose or intermediate-dose cytarabine, and if it is intermediate- and high-risk AML, there is an absolute consideration for an allogeneic stem cell transplant.

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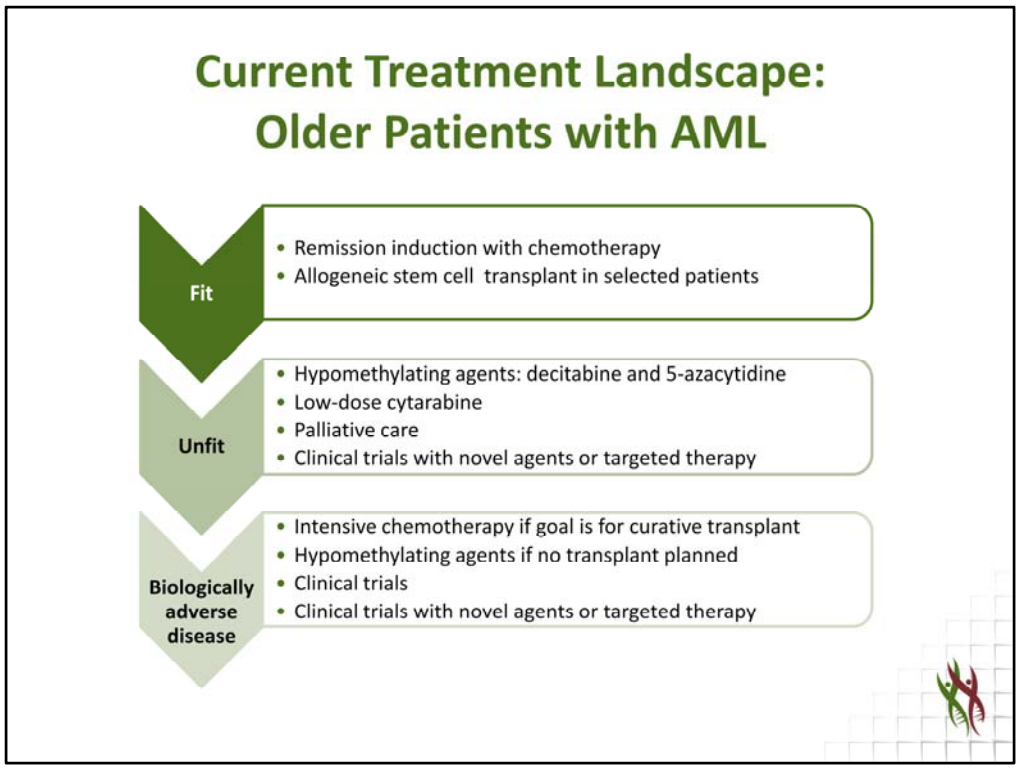


In the older AML patients, the landscape is a little bit more varied. If you have a fit elderly patient, induce remission with chemotherapy and then consider a stem cell transplant. In the unfit elderly setting, there are a couple agents that have been used. The first one is hypomethylating agents, which is decitabine or 5-azacytidine. The second agent is low-dose cytarabine. There are palliative care options also, which would include either transfusions or hospice care, or clinical trials with novel agents and targeted therapy. In general, these lower-intensity treatments which include decitabine, 5-azacytidine, and low-dose AraC have to be repeatedly given, it takes several cycles to achieve a remission, and there has to be some kind of maintenance on an ongoing basis because the disease tends to come back quickly if you stop treatment after a remission, but overall, these are well tolerated. Then, there is a whole category of biologically adverse disease. Even if patients are fit, certain bad cytogenetic groups like complex karyotype or TP53 mutations, these patients do not enjoy a good survival or CR rate with intensive chemotherapy. In that case, hypomethylating agents seem to be doing the same job with much less toxicity, but still, you can consider intensive therapy if the goal is to go into a stem cell transplant and achieve a quick remission. Obviously, with the biologically adverse groups, clinical trials with novel agents are a big help.

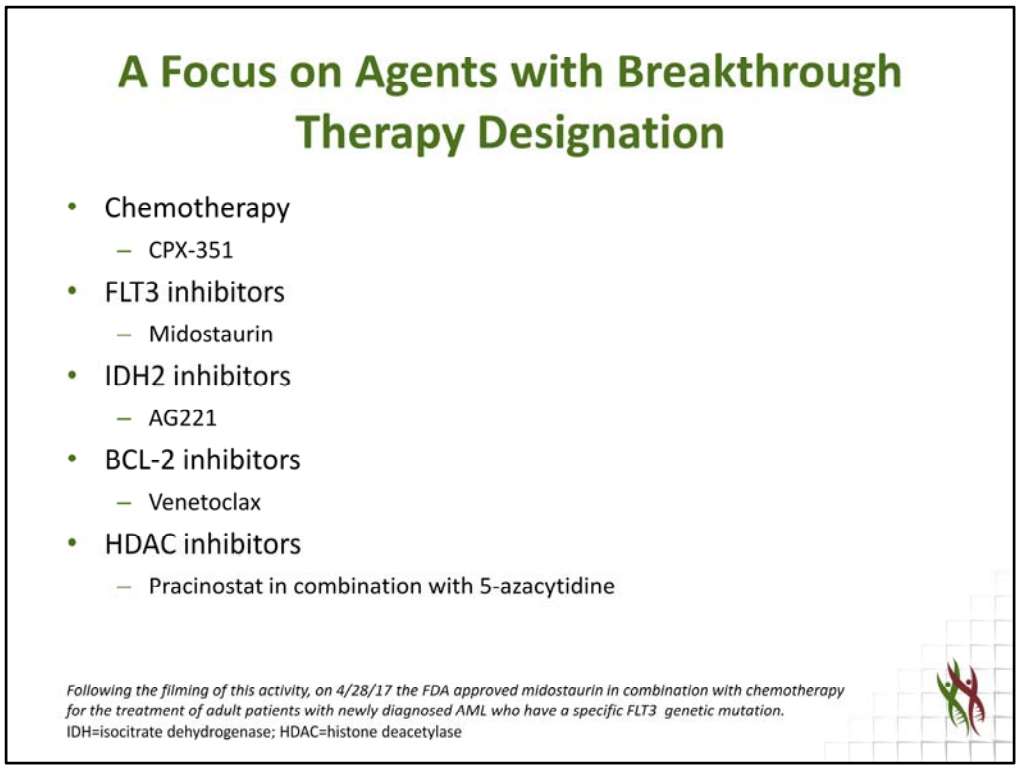
Sample CR, Early Death, and Survival Rates in Older (≥55 Years) AML Treated with Intensive Chemotherapy

STUDY	N	CR	ED	OS (3-5 year)
CALGB	388	52%	25%	15%
ECOG	348	42%	17%	10%
SWOG	328	43%	7%	19%
MRC	1,314	55%	19%	10%
Kantarjian H, et al.*	466	45%	-	4 weeks = 26% 8 weeks = 36% 1 year = 28%

*Age 70 years or older

CR=complete response; ED=early death; OS=overall survival; CALGB=Cancer and Leukemia Group B; ECOG=Eastern Cooperative Oncology Group; SWOG= Southwest Oncology Group; MRS= Medical Research Council
Tallman MS, et al. *Hematology.* 2005;143-150.; Kantarjian H, et al. *Blood First Edition Paper.*

This slide is sort of the sobering picture of patients who are even considered *fit* and elderly. These are five big clinical trials with thousands of patients over 55 years old treated with intensive chemotherapy of some kind. You see that the complete response rates are about 50% with an early death rate of 7% to 25%. While on the surface a remission rate of 50% sounds fine, the overall survival which is about 3 to 5 years out from disease is only 10% to 15%. So, these are people who are considered chemotherapy eligible and yet do not survive for long.



So, there we are. Now, we can begin our discussion on the breakthrough therapy designated drugs. With this kind of background and picture of AML, we obviously need newer agents. Today, I am going to talk about CPX-351, midostaurin which is a FLT3 inhibitor, AG-221 which is an IDH2 inhibitor, venetoclax a BCL-2 inhibitor, and an HDAC inhibitor pracinostat in combination with 5-azacytidine.

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Gene Mutation Incidence in Normal Karyotype (NK) AML

Gene Mutation	Incidence, N = 872
NPM1	53%
FLT3-ITD	31%
FLT3-TKD	11%
CEBPA	14%
MLL-PTD	8%
NRAS	13%

Gene Mutation	Incidence, N = 358
IDHI	14%
IDH2	19%

Schlenk RF, et al. *N Engl J Med.* 2008;358(18):1909-1918.; Marcucci G, et al. *J Clin Oncol.* 2010;28(14):2348-2355.

Before we move on to the actual drugs, I would like to point out that the FLT3 mutated patients make up for about 31% of AML, FLT3-TKD mutation is about 11%, and the IDH1 and IDH2 are 14% and 19% respectively.

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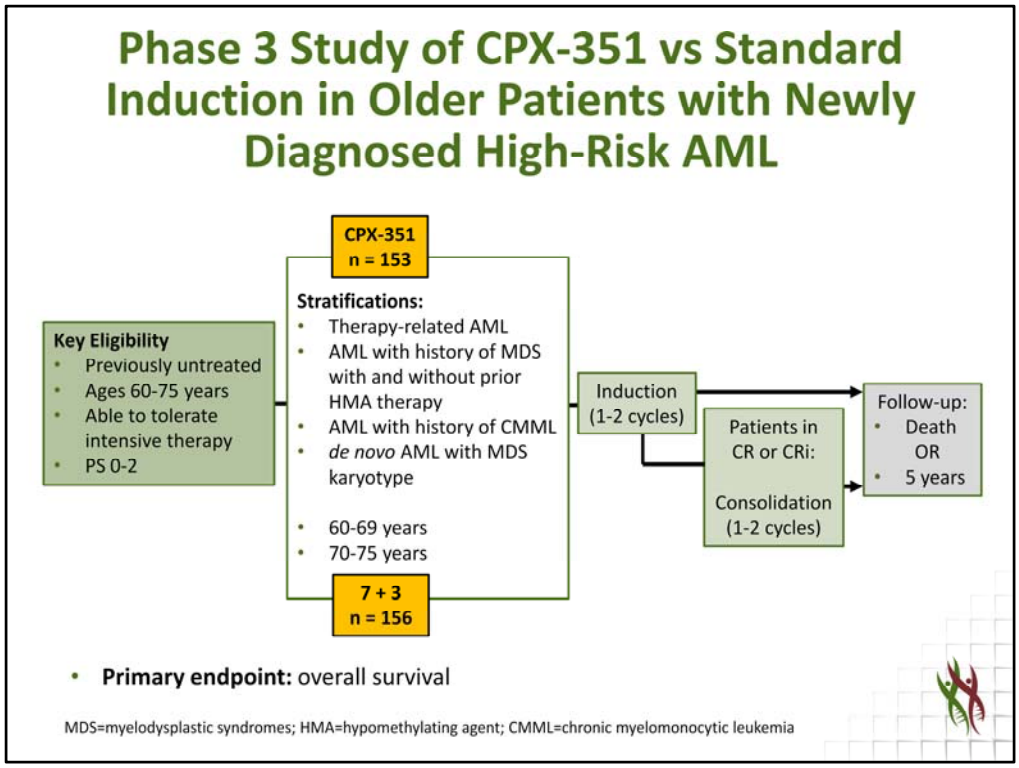
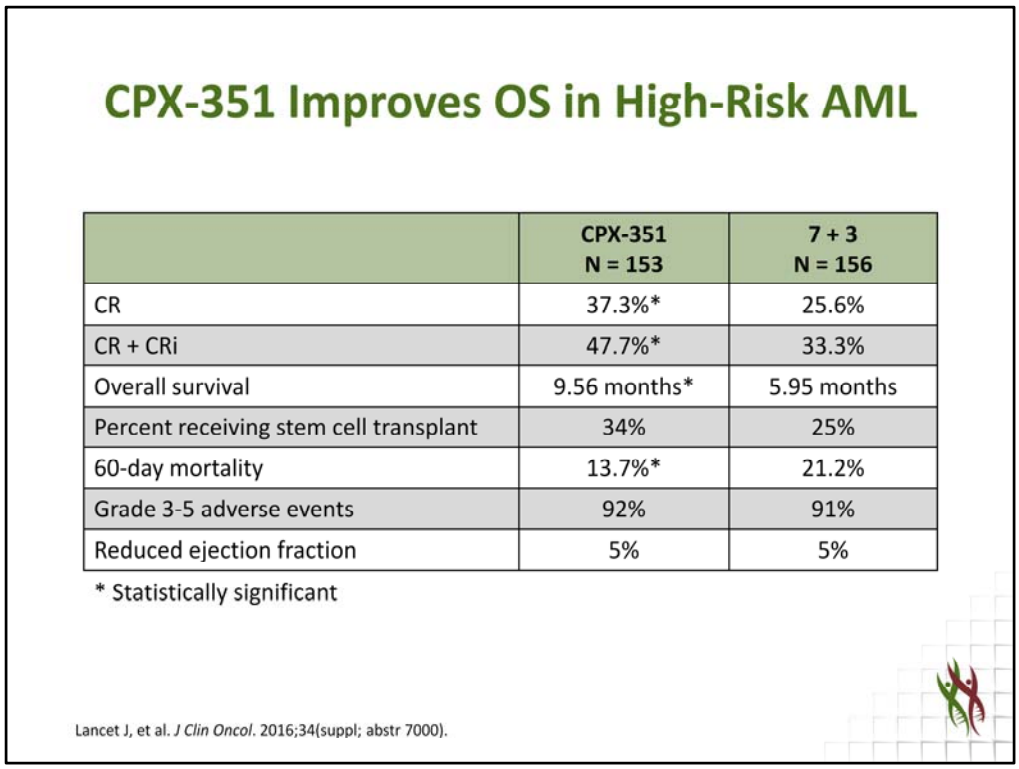


The first drug which is CPX-351, there was a big phase 3 study that randomized patients who are older with newly diagnosed high-risk AML to either CPX-351 or 7 + 3 which is considered the standard. These patients were 60 to 75 years old with good performance status and able to handle intensive therapy. Patients who had either therapy-related AML, a previous history of MDS, or high-risk cytogenetics were randomized on this trial. They got induction 1 to 2 cycles. People who were in CR were able to go for more consolidation cycles for an additional 1 to 2 cycles and followed long-term. The primary endpoint of this trial was overall survival.



CPX-351 Improves OS in High-Risk AML

	CPX-351 N = 153	7 + 3 N = 156
CR	37.3%*	25.6%
CR + CRi	47.7%*	33.3%
Overall survival	9.56 months*	5.95 months
Percent receiving stem cell transplant	34%	25%
60-day mortality	13.7%*	21.2%
Grade 3-5 adverse events	92%	91%
Reduced ejection fraction	5%	5%

* Statistically significant

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

Here are the results. CPX-351 achieved a CR or complete response in about 47.7% of patients compared to 33.3%, which would be the 7 + 3 arm. The overall survival was superior to 7 + 3, and so was the 60-day mortality, which was 13% versus 21% in 7 + 3 arm. There was no overall difference in the grade 3 or 5 adverse events. I would like to pause and say that this drug, CPX-351, has been the only drug in decades of AML treatment that has shown overall survival benefit to chemotherapy with 7 + 3.

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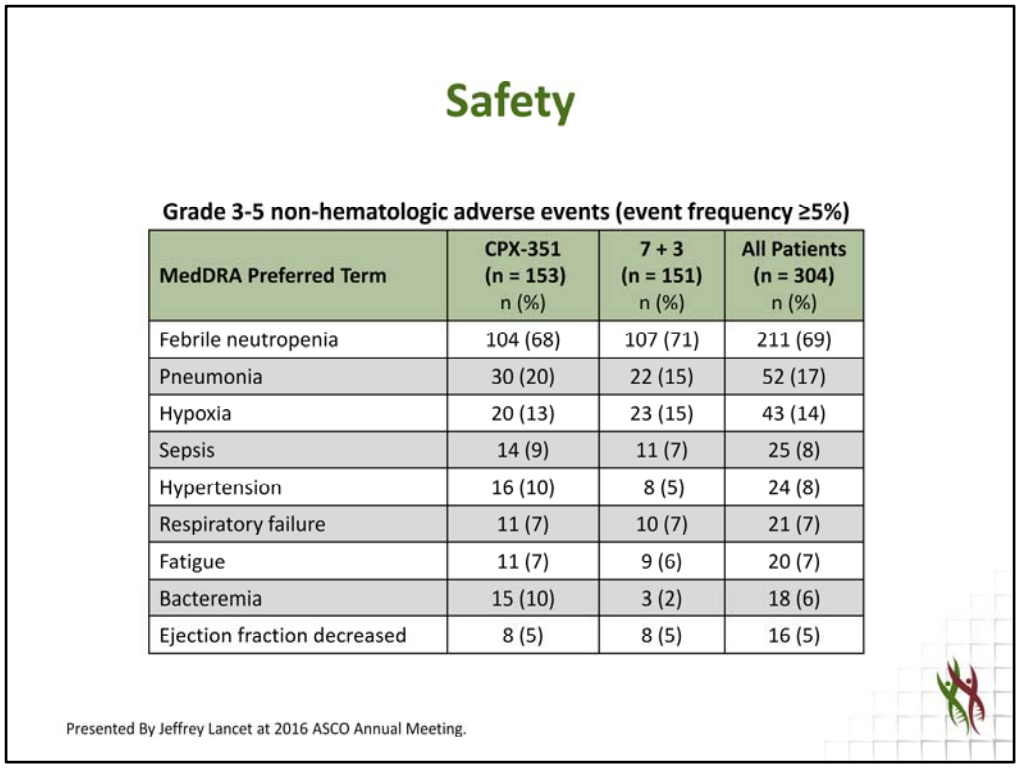


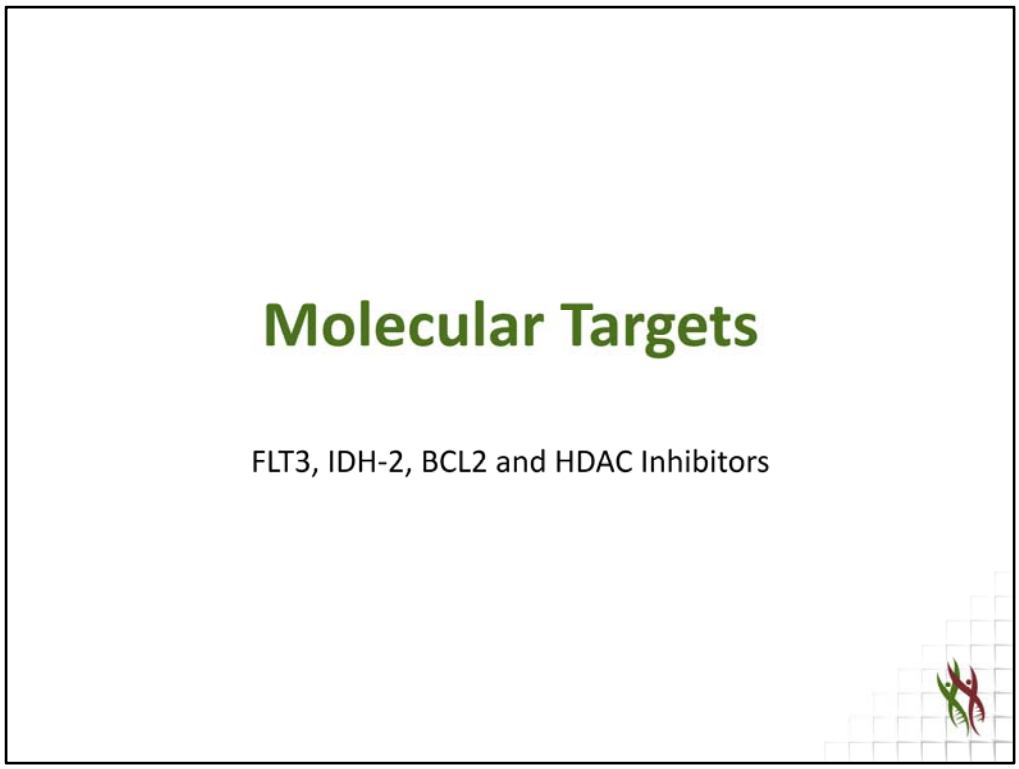
Safety

Grade 3-5 non-hematologic adverse events (event frequency ≥5%)

MedDRA Preferred Term	CPX-351 (n = 153) n (%)	7 + 3 (n = 151) n (%)	All Patients (n = 304) n (%)
Febrile neutropenia	104 (68)	107 (71)	211 (69)
Pneumonia	30 (20)	22 (15)	52 (17)
Hypoxia	20 (13)	23 (15)	43 (14)
Sepsis	14 (9)	11 (7)	25 (8)
Hypertension	16 (10)	8 (5)	24 (8)
Respiratory failure	11 (7)	10 (7)	21 (7)
Fatigue	11 (7)	9 (6)	20 (7)
Bacteremia	15 (10)	3 (2)	18 (6)
Ejection fraction decreased	8 (5)	8 (5)	16 (5)

Presented By Jeffrey Lancet at 2016 ASCO Annual Meeting.

In terms of safety and toxicity, the drug is a chemotherapy. CPX-351 combination of both daunorubicin and cytarabine, just suspended in a liposomal formulation. The side effects are expected to be that of chemotherapy. You do see febrile neutropenia, pneumonia, hypoxia; the same kind of toxicities you would expect from chemotherapy, but patients do not lose their hair generally.



The next molecular targets would be FLT3, IDH2, BCL-2, and HDAC inhibitors.

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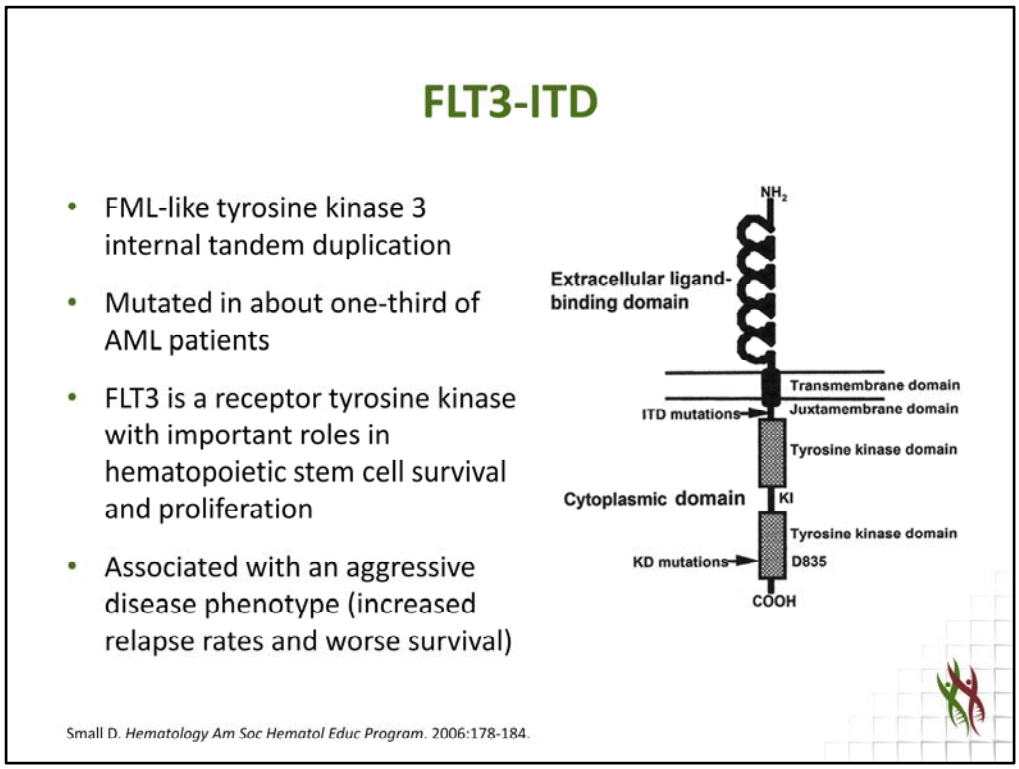

Let's move on to the first drug which is a FLT3 inhibitor. FLT3 ITD (or internal tandem duplication) is present in about one-third of AML patients. This is a mutation that is important in hematopoietic stem cell survival and proliferation, generally associated with aggressive disease, a high white cell count, and increased relapse rate and worse survival. There are two kinds of mutations, internal tandem duplication and tyrosine kinase domain (TKD) mutations. There are certain drugs that can work against one and not the other. For example, sorafenib can work against FLT3 ITD but does not work in the TKD mutations. The drug that we are going to discuss, midostaurin, is active against both kinds of mutations.

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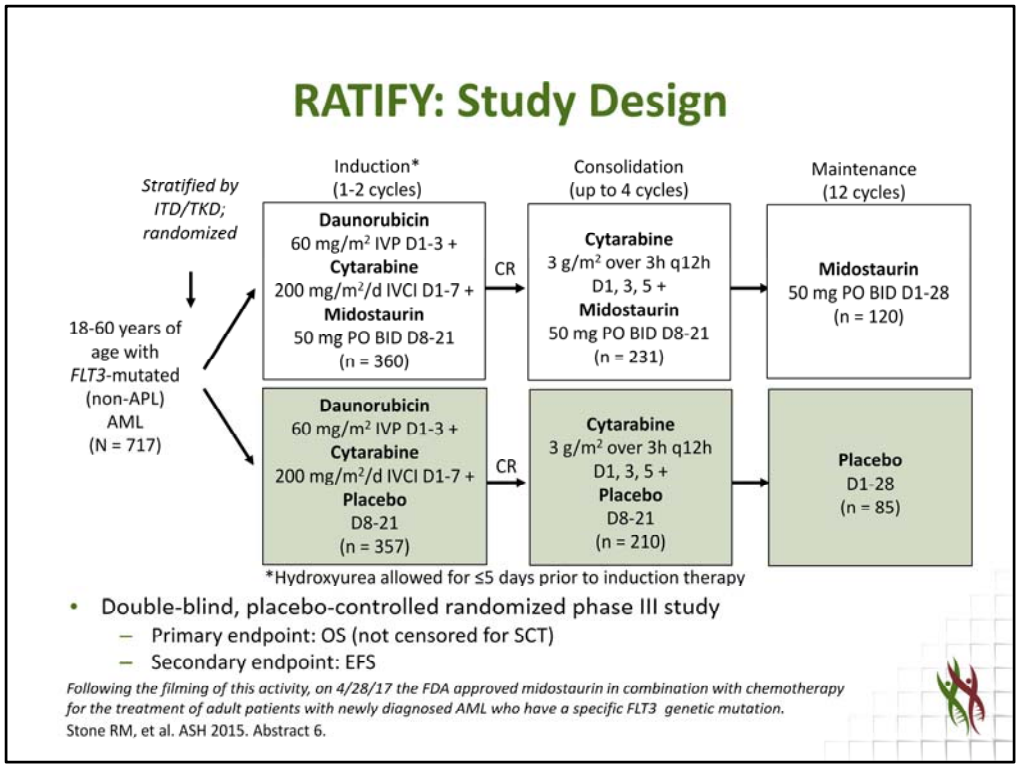

The RATIFY clinical trial was a randomized phase 3 trial that enrolled patients 18 to 60 years of age with FLT3 mutated AML. Both FLT3 ITD and TKD mutations were allowed to enroll. Patients were randomized to receive chemotherapy with 7 + 3 in combination with midostaurin or placebo. Midostaurin was given at 50 mg twice a day on day 8 through 21 of the cycle, and the placebo was given on the same schedule. Once patients achieved a CR, 4 cycles of consolidations were allowed. This included high-dose cytarabine in combination with midostaurin or placebo. Then, once the consolidation cycles were complete, maintenance was given for about a year at the same dosing. Patients who were eligible for a stem cell transplant could transition out after achieving a CR. The primary endpoint was overall survival, and the results were not censored for a stem cell transplant.

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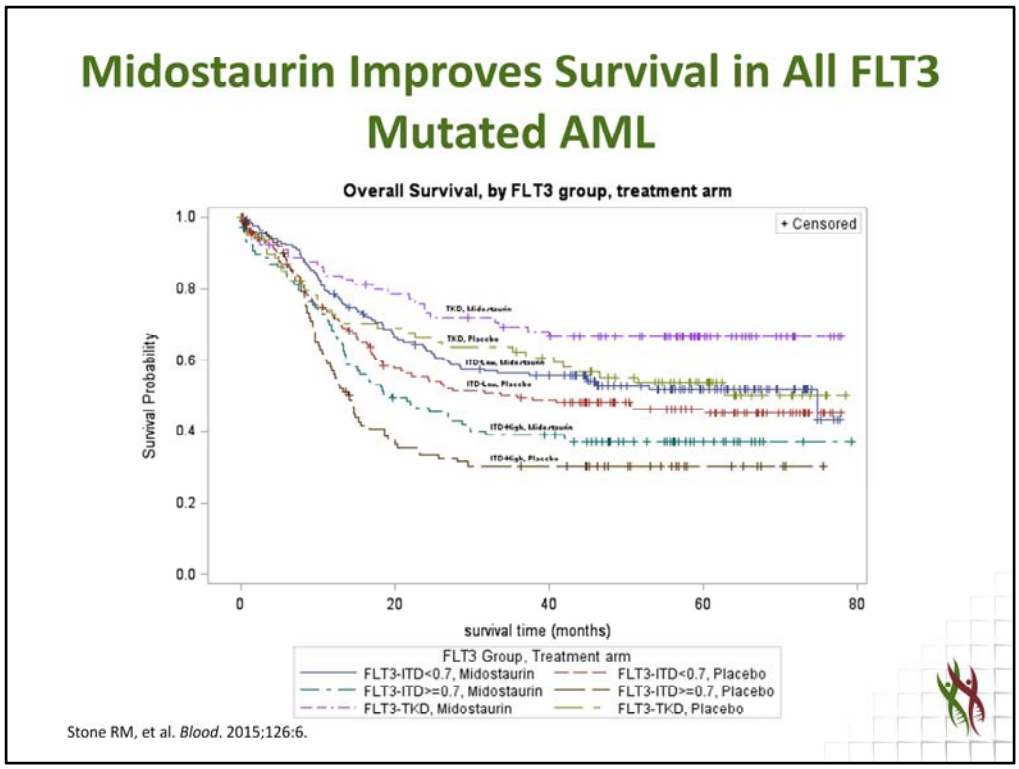
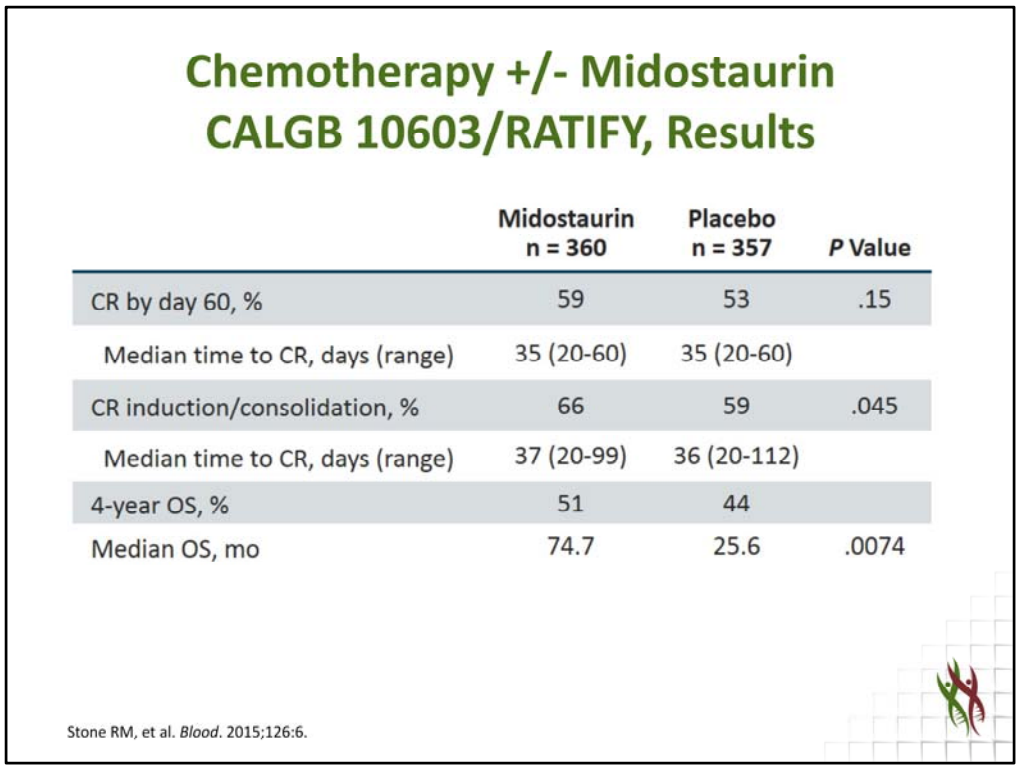
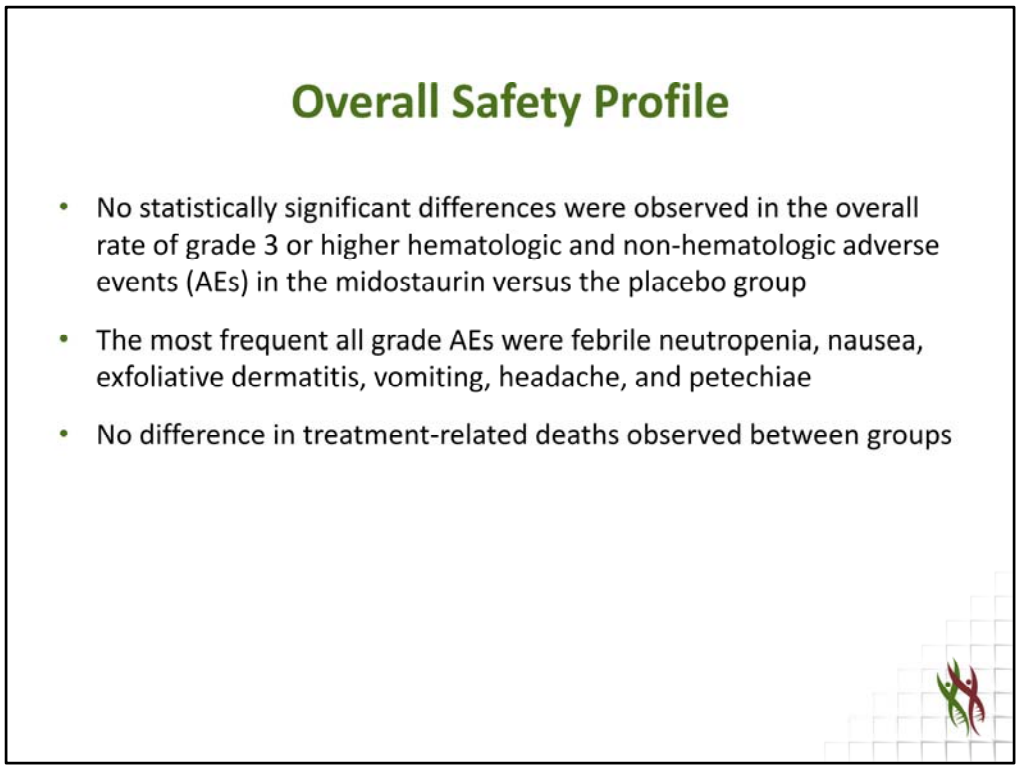


This slide shows this survival benefit of midostaurin over the placebo arm. The top two curves are for patients who have a FLT3-TKD mutation, and the bottom two curves are for patients who have a FLT3, either a low-allele or a high-allele frequency. You can see that the midostaurin arm outperformed the placebo arm in all three subgroups.



When you look at response rates, the response rates to 7 + 3 alone, and in combination with midostaurin, were not necessarily different. If you look at the 4-year overall survival, the midostaurin arm showed a 51%, 4-year overall survival compared to 44% which is statistically significant.



There was no difference observed in the overall response rate of grade 3 or higher adverse events. The drug-specific things that we did see were exfoliative dermatitis, general GI side effects in terms of vomiting, and sometimes diarrhea. There was no difference in treatment-related deaths.

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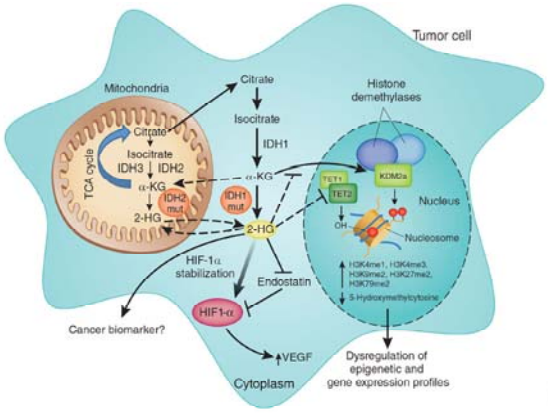
Mutations in Metabolic Enzyme Pathways: IDH1 and IDH2

- First identified in gliomas
- Alter physiologic enzyme function by converting α-ketoglutarate into 2-hydroxyglutarate, an oncogenic metabolite
- Associated with NPM1 mutations and predict worse outcome



Prensner JR, et al. *Nat Med*. 2011;17:291-293.

Now, we move on to the IDH2 inhibitors. The IDH2 mutations were first identified in gliomas. This is a very interesting mechanism of action that these mutations cause an excess of 2-hydroxyglutarate, instead of the alpha-ketoglutarate which is the normal Krebs cycle metabolite. An excess of 2-hydroxyglutarate causes increased proliferation signals and it is considered an oncogenic metabolite. The IDH mutations are associated with NPM1 mutations and generally predict a worse survival in patients with AML.

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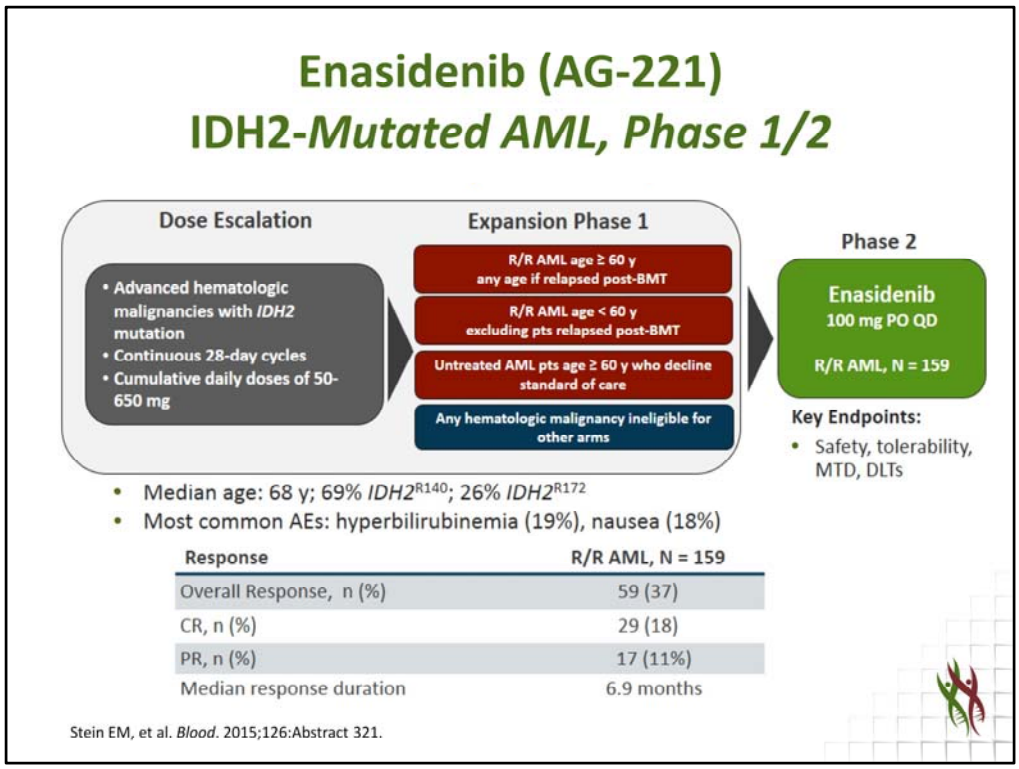

AG-221, or enasidenib, was tested in a phase 1, 2 trial where patients with advanced hematologic malignancies got 28 continuous cycles of the dosing. The dose was a range of 50 to 650 mg. Patients that were included were: relapsed/refractory AML over 60 years of age, untreated AML patients who were not eligible or declined standard of care, or other hematologic malignancies like MDS. The phase 2 portion of the drug included the dose of 100 mg which was given as a continuous treatment cycle. The median age of these patients were 68 years. The most common side effect encountered was GI, mostly nausea, about 18%, and hyperbilirubinemia 19%. Now of note, this hyperbilirubinemia is actually indirect hyperbilirubinemia, and it is not really related to any synthetic dysfunction, but more to the presence of a UGTA1 enzyme deficiency and of no consequence in terms of toxicity to the patient. The overall response rate in this trial was observed to be about 37% with a CR of 18 and a PR, which is partial response, of 11%. One very specific thing that we see in this drug is something called a differentiation syndrome, in which the white cell count goes up and the patients experience sometimes pleural effusions, shortness of breath, and it is associated with the transition of changing the blast into more mature cells. It is not observed in everyone, but when it is observed, sometimes it does require a steroid or hydroxyurea to control the count, very rarely interruption of the drug. This is a specific side effect that has to be differentiated from progression of disease and requires a little bit of experience with this.

AG 221 (Enasidenib) in IDH2 Mutated AML: Response

	RR-AML (n = 159)	Untreated AML (n = 24)	MDS (n = 14)	All (N = 209)
Overall response (CR, CRp, CRi, mCR, PR)	59 (37%)	10 (42%)	7 (50%)	79 (38%)
CR	29 (18%)	4 (17%)	3 (21%)	37 (18%)
CRp	1 (1%)	1 (4%)	1 (7%)	3 (1%)
CRi	3 (2%)	0	0	3 (1%)
mCR	9 (6%)	1 (4%)	3 (21%)	14 (7%)
PR	17 (11%)	4 (17%)	0	22 (11%)
SD	72 (45%)	9 (38%)	6 (43%)	96 (46%)
PD	10 (6%)	1 (4%)	0	11 (5%)
Not evaluable	18 (11%)	4 (17%)	1 (7%)	23 (11%)

Presented by Eytan Stein at 2016 ASCO Annual Meeting.

The overall response rate, as I had mentioned earlier, is about 37% in relapsed/refractory population. This response rate is not minor. In general, the untreated AML patients had a higher response rate of about 42%.

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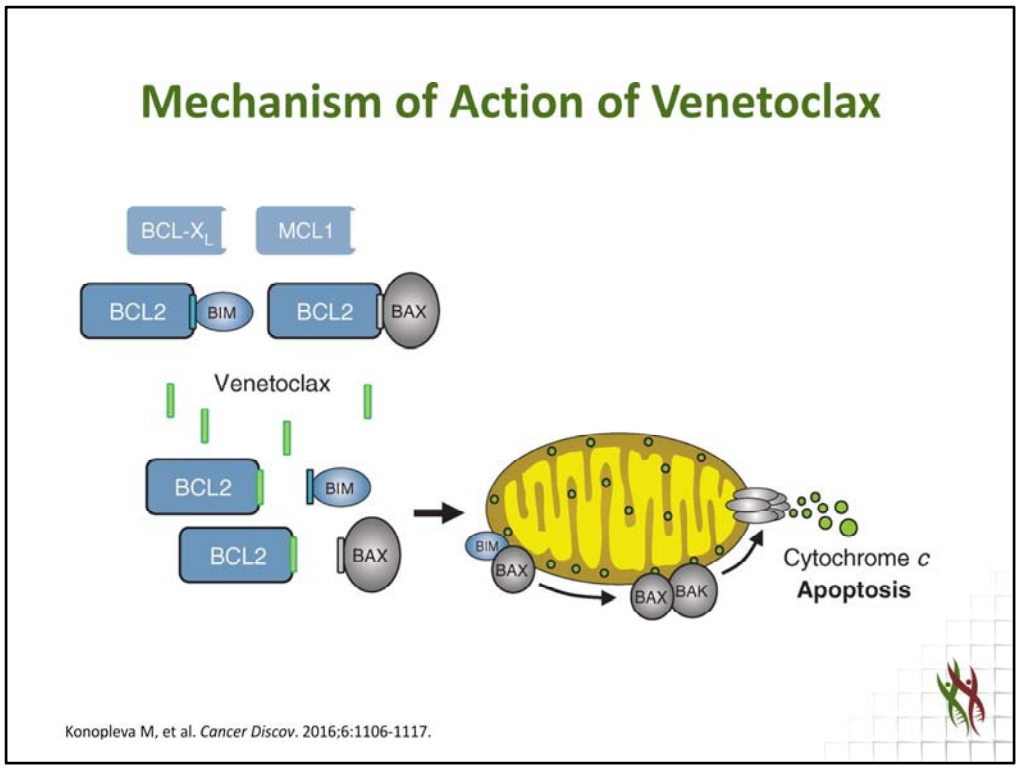

We will now move on to venetoclax, which is a BCL-2 inhibitor. As you know, BCL-2 is an anti-apoptotic protein and venetoclax, by inhibiting BCL-2, increases apoptosis in combination with other agents. Venetoclax is approved for treatment in CLL and is currently undergoing clinical trials for AML.

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Venetoclax + HMA in Elderly AML

- New diagnosis of AML, 65 years of age or older, adverse or intermediate-risk cytogenetics and ineligible for standard induction therapy
- Antecedent hematologic malignancy in 15%
- HMA naive

Best Response, %	Venetoclax/Decitabine 400 mg (n = 6)	Venetoclax/Decitabine 800 mg (n = 12)	Venetoclax/Azacitidine 400 mg (n = 4)	Venetoclax/Azacitidine 800 mg (n = 12)	ITT Response (N = 34)
ORR (CR/CRi/PR)	50	83	100	75	76
CR	33	17	75	42	35
CRi	17	50	25	33	35
PR	0	17	0	0	6
MLFS	0	8	0	0	3
RD	17	8	0	17	12
Not evaluable	33	0	0	8	9

DiNardo C, et al. ASH 2015. Abstract 327.

When venetoclax was combined with hypomethylating agents in elderly patients, this trial included patients 65 years and older with adverse or intermediate-risk cytogenetics and they were not eligible for standard induction therapy; 15% had a previous hematologic malignancy, MDS, or myeloproliferative disorder, and they had to be hypomethylating naïve. Two drug combinations were basically looked at, both in combination with decitabine and azacitidine; 400 mg and 800 mg of venetoclax were given in each combination. The hypomethylating arms were given regularly like they are scheduled. Venetoclax was given continuously unless there were some dose interruptions that were needed for toxicity. The overall response rate which include a CR, CRi, and partial response was 50% in the 400 mg arm and 83% in the 800 mg arm for decitabine and the same numbers for azacitidine looked very promising as well.

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Venetoclax + HMA in Elderly AML

AEs (all grades) ≥30% in both arms	Total (N = 34)	Venetoclax/Decitabine (n = 18)	Venetoclax/Azacitidine (n = 16)
Nausea	53	44	63
Febrile neutropenia	38	44	31
Diarrhea	41	39	44
Peripheral edema	35	39	31

Grade 3/4 AEs, %	Total (N = 34)	Venetoclax/Decitabine		Venetoclax/Azacitidine	
		Cohort 1 Venetoclax 400 mg (n = 6)	Cohorts 2,3 Venetoclax 800 mg (n = 12)	Cohort 1 Venetoclax 400 mg (n = 4)	Cohorts 2,3 Venetoclax 800 mg (n = 12)
Febrile neutropenia	38	67	33	50	25
Neutropenia	29	50	25	0	33
Thrombocytopenia	24	50	8	25	25
Leukopenia	18	17	8	0	33
Lung infection	9	33	0	0	8

DiNardo C, et al. ASH 2015. Abstract 327.

In terms of toxicity, the major side effects that were seen were nausea, diarrhea, and peripheral edema. Febrile neutropenia, which is expected in any treatment with AML, was also seen on trial but not at a higher rate than what is expected.

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Venetoclax + Low-Dose Cytarabine in Elderly AML

Characteristic	Ven 600 mg (n = 16)	Ven 800 mg (n = 10)	All Patients (N = 26)
Median age, yrs (range)	74 (66-87)	75 (66-79)	75 (66-87)
Male, %	63	70	65
ECOG PS 0/1/2, %	25/63/13	10/60/30	19/62/19
Previous hematologic disorder, %	38	60	46
Prior HMA treatment, %	13	30	19
Baseline BM blast count, %	(n = 15)	(n = 9)	(n = 24)
▪< 30	27	33	29
▪31-50	40	22	33
▪≥ 51	33	44	38

Lin TL, et al. ASCO 2016. Abstract 7007.

Now, how about combination of venetoclax and low-dose AraC, because clearly some patients would have received hypomethylating agents in the past. For this subgroup of patients, not that they were solely included, but a lot of patients on this trial had prior hypomethylating agent use. They had a good performance status, not eligible for induction chemotherapy, and about 38% to 60% of patients had a previous hematologic disorder depending on what arm.

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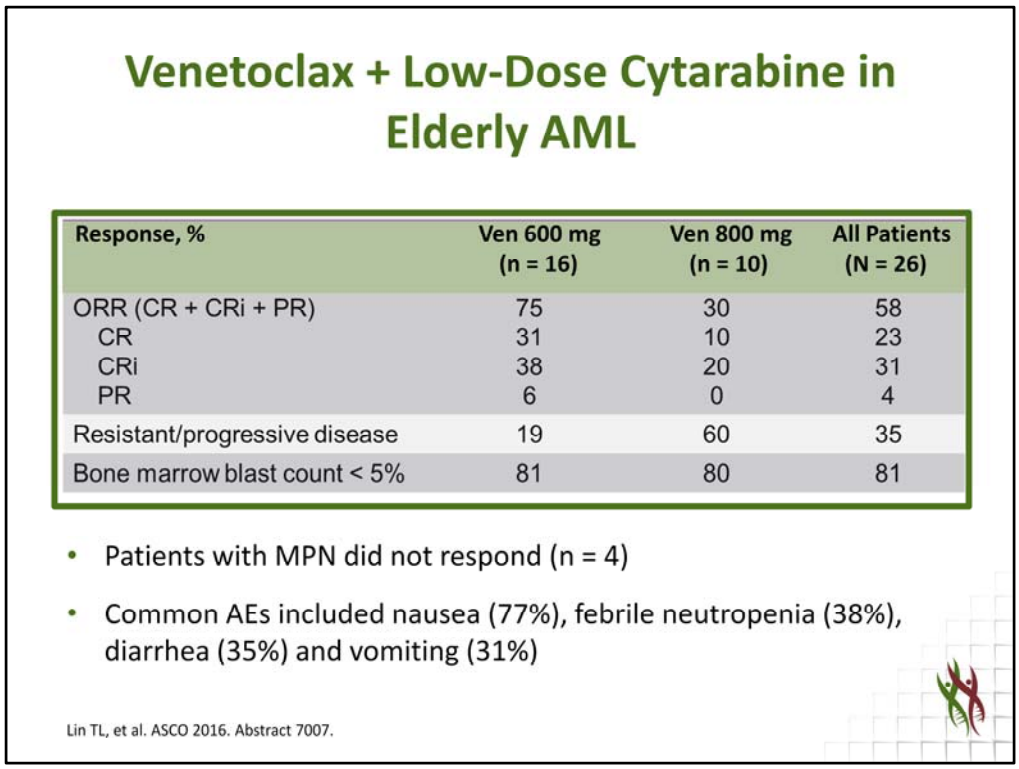

The overall response rate with 600 mg was 75% compared to 30% with the 800 mg arm. I think the 75% was better with the 600 mg arm, and this is the dose that is going on to further phase 3 trials. It is very important to note that in this older population with the previous use of hypomethylating agents, CR rates of about 70% have not been the common finding in other treatments. This is obviously a very promising combination and something that is hopefully successful with further clinical trials.

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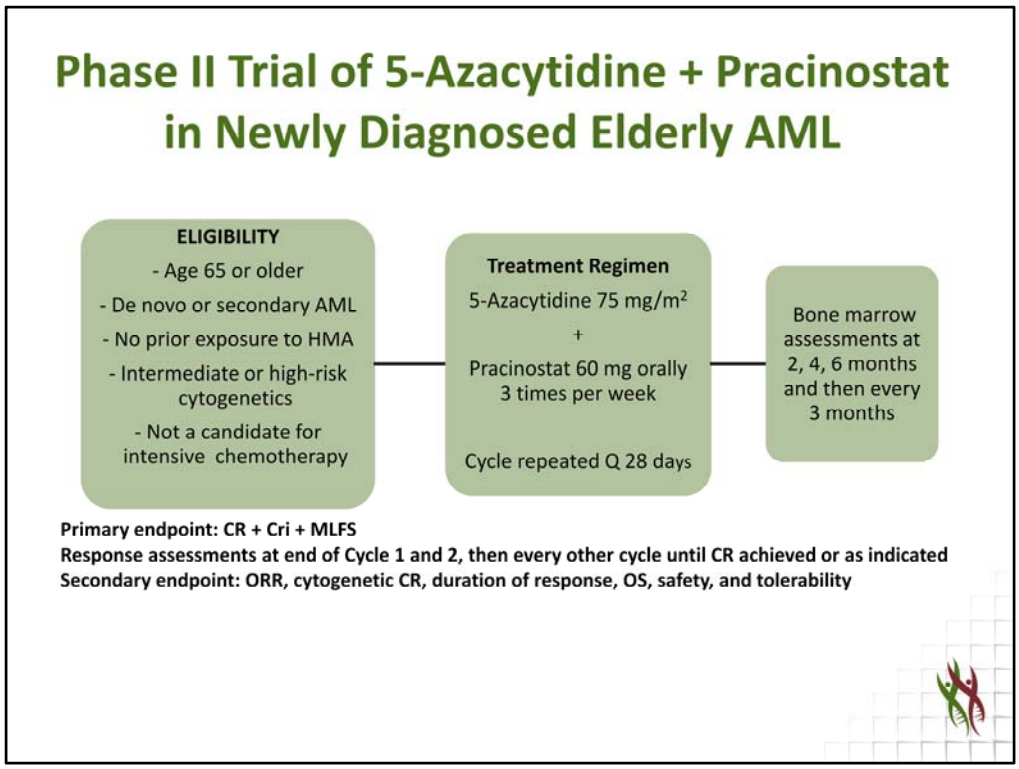


The last drug that I will focus on is pracinostat in combination with 5-azacytidine. This was a phase 2 trial where patients were 65 or older with de novo or secondary AML but no previous exposure to hypomethylating agents. They were treated with 5-azacytidine given on a regular schedule with pracinostat given orally three times per week. The cycles were repeated until CR was achieved and then maintained for further follow up. Primary endpoint was response rates with secondary endpoints of overall survival.

Pracinostat and 5-Azacytidine in Older Patients with AML

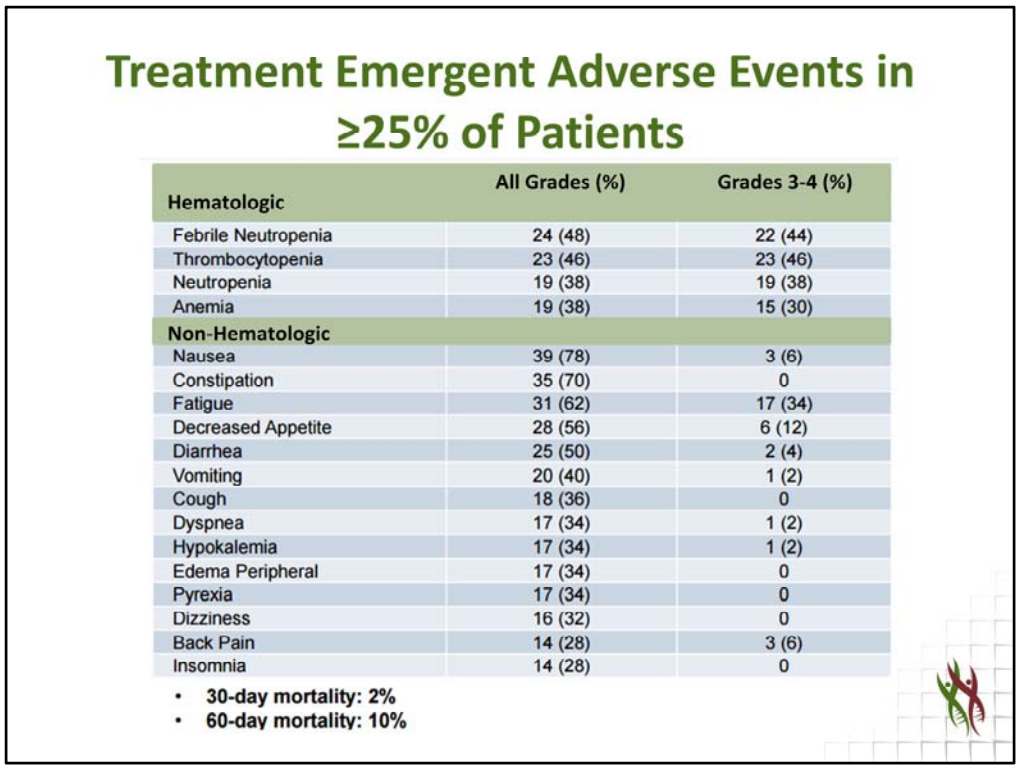
	CR Rate	cCR Rate	Survival (months) (Median, 95% CI)
Overall population (N = 50)	42%	52%	19.4 (10.0-NR)
Cytogenetics			
Intermediate (N = 27)	48.1%	59.3%	NR (10.7, NR)
High risk (N = 21)	38.1%	47.6%	13.5 (2.4, NR)
Age			
≥75 (N = 26)	42.3%	57.7%	13.5 (9.0, 21.5)
66-74 (N = 24)	41.7%	45.8%	26.5 (8.0, 26.5)
Type AML			
De novo (N = 33)	42.4%	51.5%	13.02 (5.7, 26.5)
Secondary (N = 17)	41.2%	52.9%	NR (>16.4, NR)
ECOG Performance Status			
0-1 (N = 42)	40.5%	50.0%	19.08 (10.0, 19.1)
2 (N = 8)	50.0%	62.5%	13.0 (8.0, 26.5)

CI = Confidence Interval, NR = Not Reached

Garcia-Manero G, et al. *Blood*. 2016;128:100.

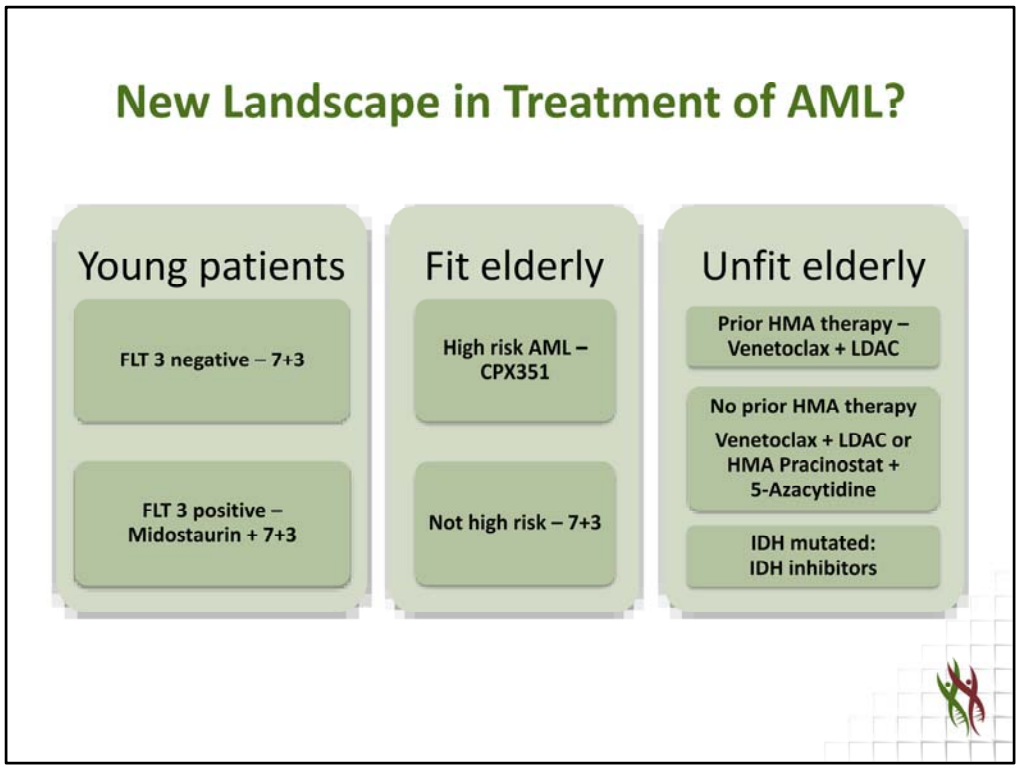
If you look at the response rate here, the CR rate to the overall population was 42% with a cytogenetic response rate of 52%. The overall survival was 19.4 months, which is not minor.

Emerging Agents Impacting Future Treatment Strategies in AML



Side effects were expected. The febrile neutropenia and cytopenias are normal in patients with AML. In terms of non-hematologic toxicities, most of the side effects were GI: nausea, constipation, and diarrhea. They were all reasonable and patients tolerated the treatment overall well.

Emerging Agents Impacting Future Treatment Strategies in AML



Now that we have discussed these treatments, how would the new landscape in AML look if these agents go through? In young patients who are FLT3 negative, 7 + 3 is still the standard of care. In a FLT3 positive population, midostaurin plus 7 + 3 would be a combination. In fit elderly patients with high-risk AML, CPX-351 would make a dent. If they are not high risk, however, 7 + 3 would still be considered in these patients. In an unfit elderly population with prior hypomethylating use, venetoclax and low-dose AraC is an option. In patients with no prior hypomethylating use, it could again be venetoclax and low-dose Ara-C or hypomethylating background with pracinostat. Also, the venetoclax with HMA treatment would be an option. In patients who are IDH mutated, the IDH inhibitors are also going to be very important and probably more frontline.

Emerging Agents Impacting Future Treatment Strategies in AML

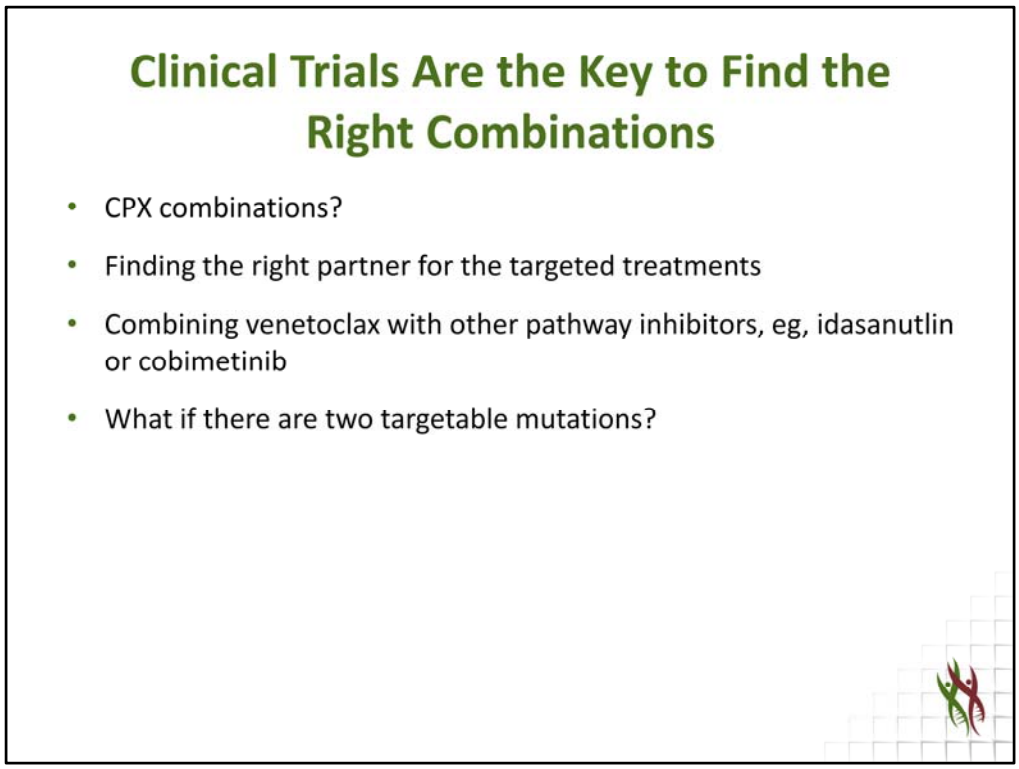
Expanding Novel Therapeutics in the Treatment of AML

Agent	Mechanism of action	Suggested patient population	Notes
CPX-351	Liposomal formulation of 7+3 in 5:1 molar ratio	sAML fit for induction chemotherapy	Phase 2 study showed OS benefit in sAML Phase 3 study fully accrued and waiting for final analysis
Vosaroxin	Novel topoisomerase II inhibitor	Relapsed/refractory AML	OS benefit when censored for allogeneic transplant; mucositis notable as toxicity
Guadecitabine	Hypomethylating agent resistant to deamination	Unfit for intensive chemotherapy	May supplant LDC, decitabine, 5-azacitadine
SGN-CD33A	ADC against CD33 with stable linker	Being explored as a combination with hypomethylating and traditional induction	Next-generation ADC against CD33
Volasertib	Novel PLK1 inhibitor	Being explored as a combination with hypomethylating and traditional induction	OS benefit in small randomized phase 2 study when combined with LDC
Quizartinib	FLT3 inhibitor	FLT3 + AML	Impressive single-agent activity against FLT3-ITD; resistance emerges in most patients
Crenolanib	FLT3 inhibitor with activity against TKD-resistance mutation	FLT3-ITD or FLT3-TKD	Active against TKD mutations
ASP-2215	FLT3 inhibitor with activity against TKD-resistance mutation	FLT3-ITD or FLT3-TKD	Impressive single-agent activity with CRc rate of 43%
AG-221	IDH2 inhibitor	IDH2 mutated	Impressive single-agent activity (41% overall response rate) in relapsed or refractory AML
AG-120	IDH1 inhibitor	IDH1 mutated	Impressive single-agent activity in relapsed or refractory AML
EPZ-5676	DOT1L inhibitor	MLL rearranged	Combinations with standard of care should be explored
ABT-199	BCL2 inhibitor	Ongoing investigation	May have increased activity in patients with IDH mutations
OTX-015	BET inhibitor	Ongoing investigation	Combinations with standard of care should be explored
Pracinostat	HDAC inhibitor	Ongoing investigation	Impressive activity in combination with 5-azacitidine; awaiting survival data.

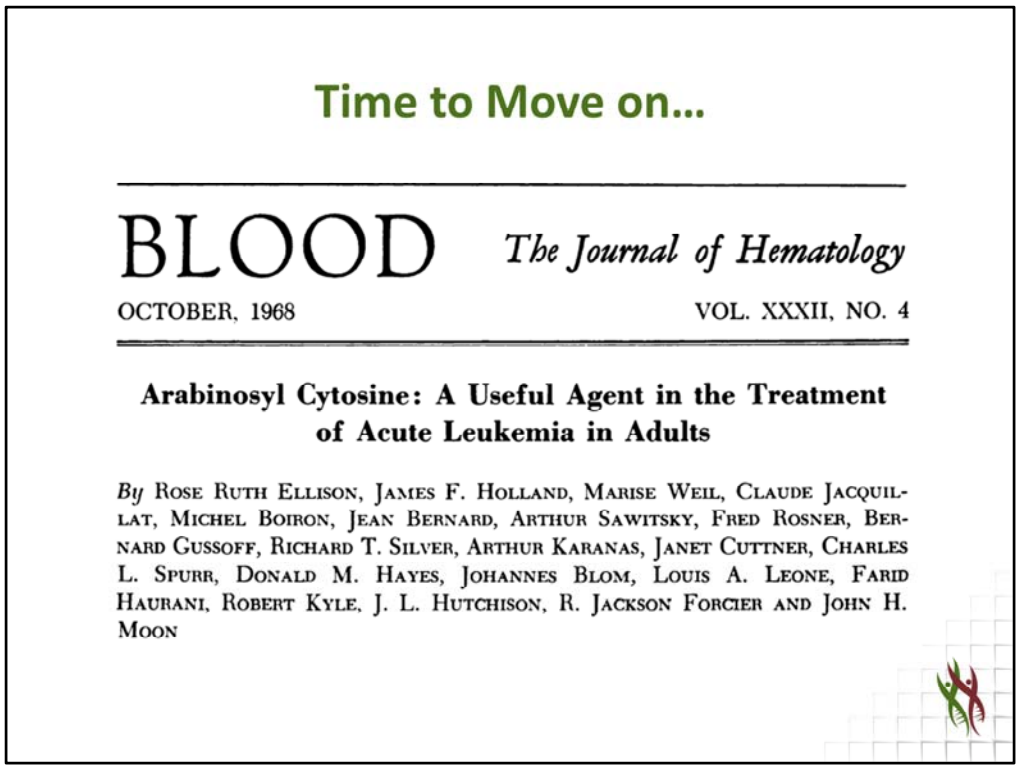
7 + 3, 7 days of cytarabine and 3 days of daunorubicin.

Stein EM, et al. *Blood*. 2016;127(1):71-78.

This slide shows that what I discussed are the five breakthrough therapy designated drugs, but there are several of these drugs in combinations with hypomethylating agents, chemotherapy, or single agents that are still going to come forward.



What is important is the right combination. Can you combine some of these chemotherapies, like CPX, with targeted treatments? What is the right partner for targeted treatments? Can you combine two targeted treatments, like venetoclax with other pathway inhibitors like idasanutlin and cobimetinib, which are MEK inhibitors? If there are two targetable mutations, which one to choose first? I think clinical trials are a key to finding the right combinations.



This brings me to the last slide. This paper shows that cytarabine is a useful agent in the treatment of acute leukemia. This was published *decades* ago, and the truth is that there have not been any major approvals in AML since this. Now, I am hopeful that it is time to move on and with all of these agents coming forward, the treatment of AML will look very different. Thank you for viewing this activity.