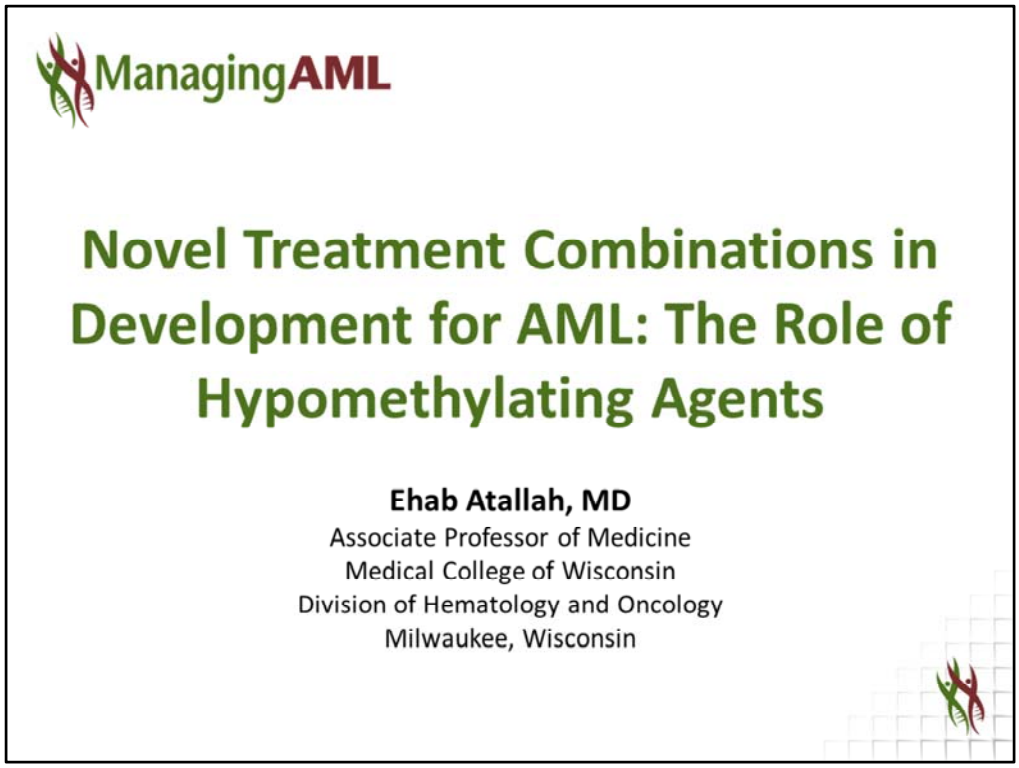
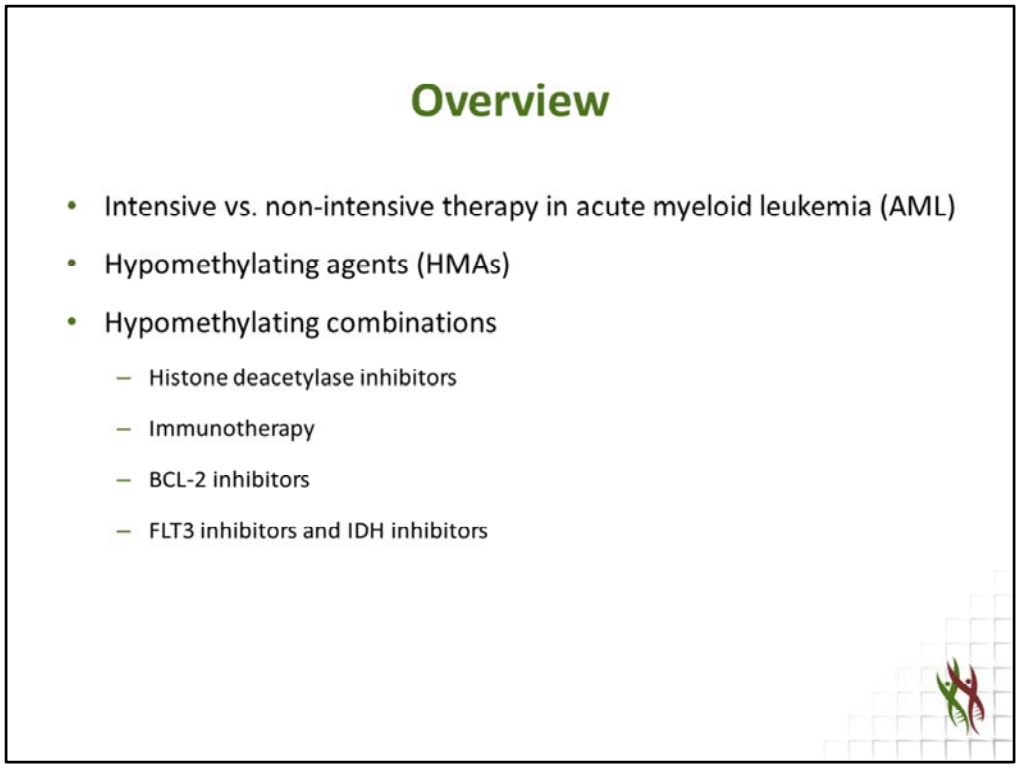
Novel Treatment Combinations in Development for AML: The Role of Hypomethylating Agents



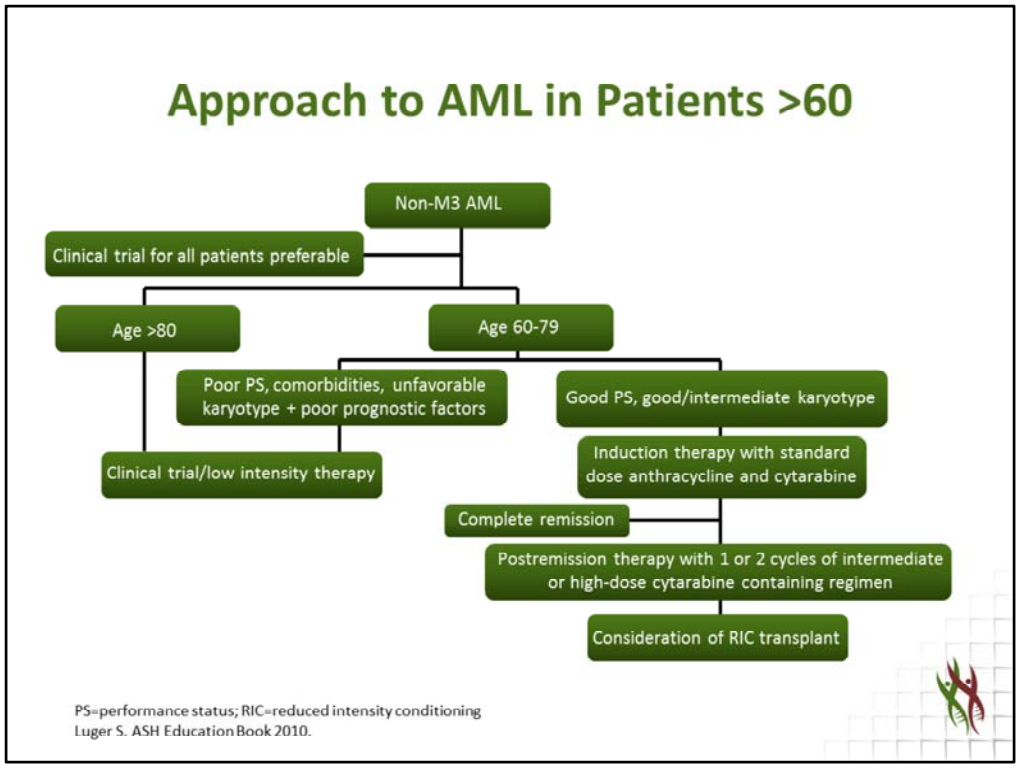
Welcome to Managing AML. I am Dr. Ehab Atallah. In today's presentation, I will review novel treatment combinations in development for AML, specifically the role of hypomethylating agents. In this video, I will provide you with background on hypomethylating agents in existing treatment paradigms, and the investigational landscape of novel therapies in combination with hypomethylating agents and their potential impact on treatment outcomes for patients with AML. We will discuss safety and efficacy data of key clinical trials investigating novel agents in combination with hypomethylating agents. Let’s begin.

Novel Treatment Combinations in Development for AML: The Role of Hypomethylating Agents



In today's presentation, I will discuss several points. The first is, how can we decide whether a patient should get intensive chemotherapy versus less-intensive treatments such as hypomethylating agents? We will discuss some of the results of using single-agent hypomethylating agents in patients with AML. Then I will discuss a combination of hypomethylating agents with histone deacetylase inhibitors, immunotherapy, BCL-2 inhibitors, and targeted therapies. The targeted therapies, because of time constraints, I will not be able to go through in great detail.

Novel Treatment Combinations in Development for AML: The Role of Hypomethylating Agents



The biggest question, usually in older patients with AML, is who should receive intensive chemotherapy, and who should receive less-intensive chemotherapy such as hypomethylating agents? It is a really big question, and the decision to proceed with one or the other depends on some disease-related factors and some patient-related factors. In terms of disease-related factors, if a patient has AML with complex cytogenetics – where we know based on data that the response rates are low – maybe that patient would be a patient to consider for less-intensive options such as hypomethylating agents. Patient-related factors include their comorbidities and their overall performance status or functional status. These really vary from one patient to another, and sometimes a geriatric assessment is useful in helping us decide which way we should treat the patient. At the end of the day, it is a discussion between the treating physician and the patient, a discussion of risks and benefits for each approach.

Novel Treatment Combinations in Development for AML: The Role of Hypomethylating Agents

Decitabine in Older Patients with AML: Phase II Study

- Older patients with AML
- Median survival: 7.7 months
- Median survival if obtained a CR: 14 months
- Overall response: 25%
- Median time to CR: 4.5 cycles
- 29% had stable disease

Table 4. Time to Response by Cycle

Cycle	No. of Patients With CR (N = 13)
2	3
3	3
5	3
6	3
9	1

Abbreviation: CR, complete remission.

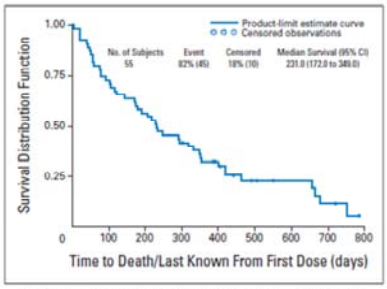


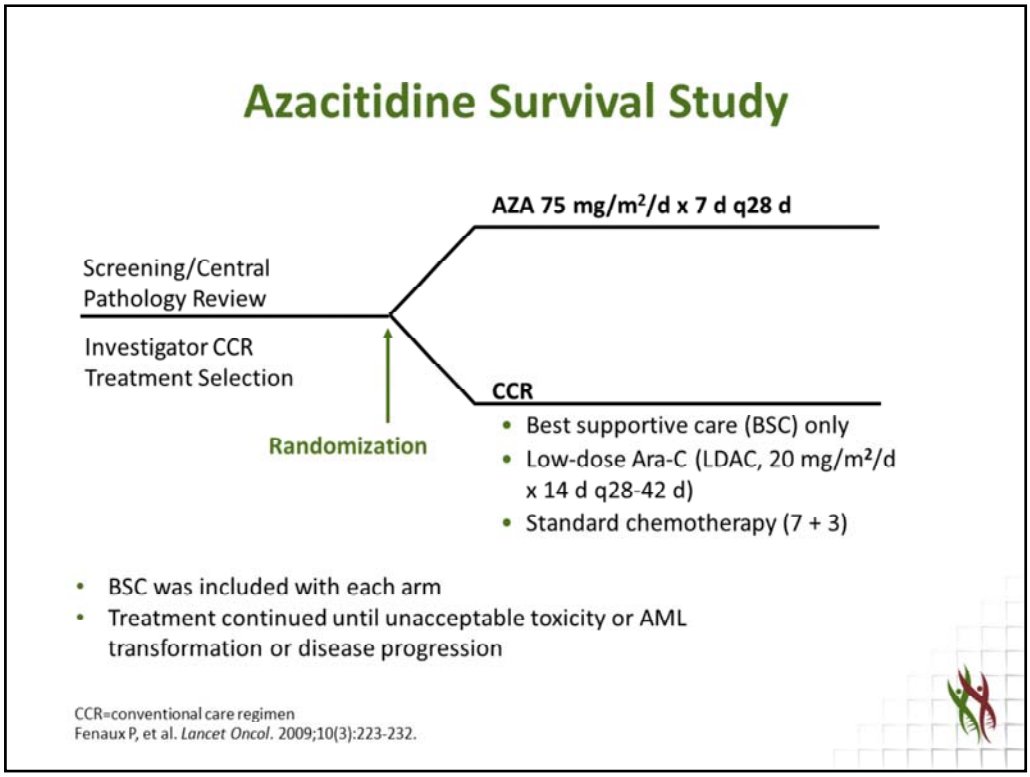
Fig 2. Kaplan-Meier curve for overall survival (intent-to-treat population).

CR=complete response

Cashen AF, et al. *J Clin Oncol.* 2010;28(4):556-561.

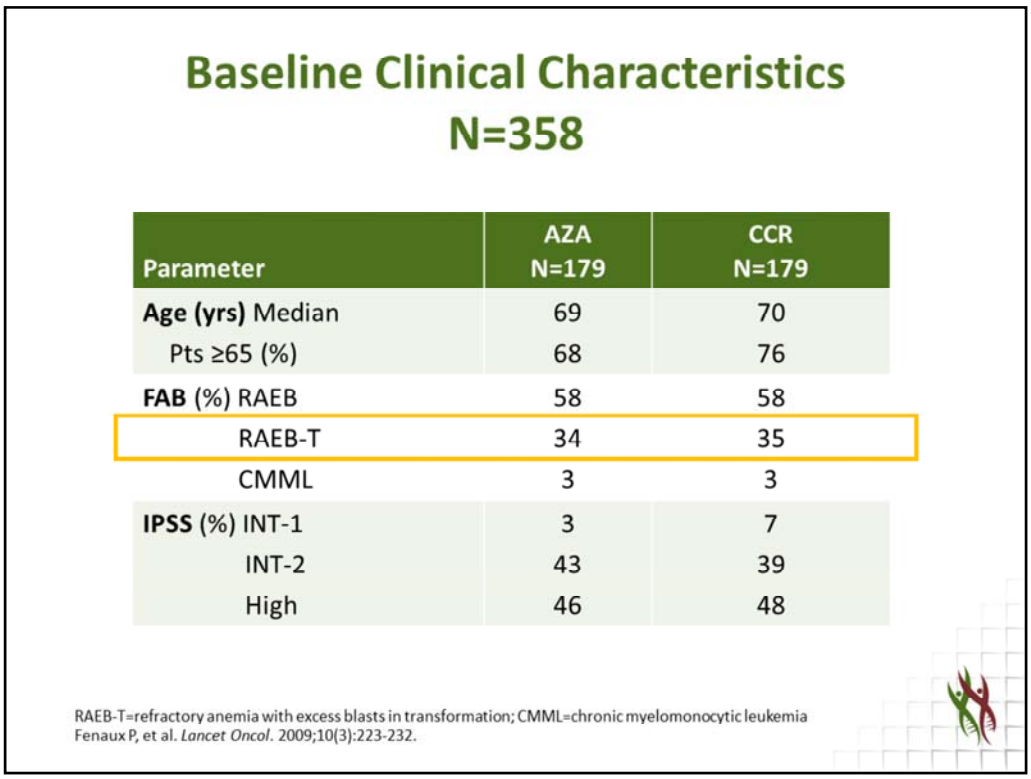
If there is a patient that you have seen and decided that this patient is not really a good candidate for more intensive chemotherapy and decided to use hypomethylating agents, we know that there are benefits to patients treated with either decitabine or azacitidine (currently the two FDA-approved drugs in this space). This was a phase II study where older patients with AML received decitabine, and the overall response rate was 25% with a median survival of 7months. Patients who achieved a complete remission had a median survival of 14 months. In addition, 29% of patients had stable disease.

Novel Treatment Combinations in Development for AML: The Role of Hypomethylating Agents



Very similar to this was a large randomized study where patients were randomized to azacitidine or conventional care regimens. This was a study that was in patients with myelodysplastic syndrome; but when the study was conducted, the definition of myelodysplastic syndrome went up to 30% blasts. There was a small cohort of patients who were previously defined as refractory anemia with excess blasts in transformation (RAEB-T) who actually, by current definitions, have AML. Patients were randomized to azacitidine or conventional care regimens, as I mentioned. The conventional care regimens included best supportive care only, low-dose cytarabine, or standard chemotherapy with 7+3.

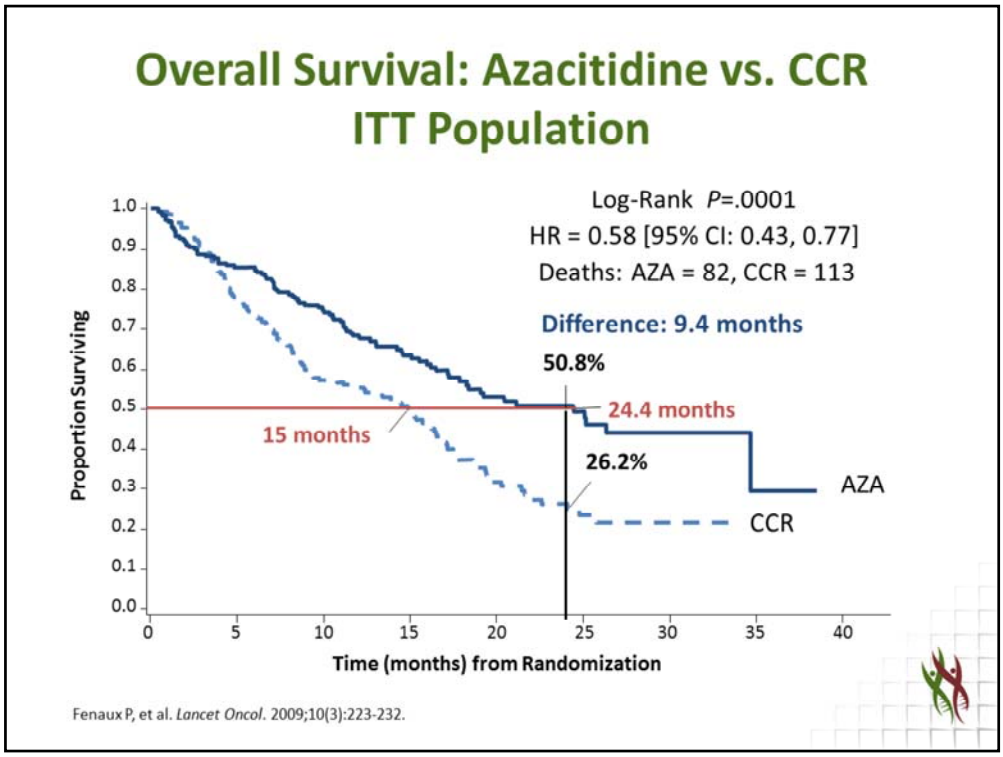
Novel Treatment Combinations in Development for AML: The Role of Hypomethylating Agents



Parameter	AZA N=179	CCR N=179
Age (yrs) Median	69	70
Pts ≥65 (%)	68	76
FAB (%) RAEB	58	58
RAEB-T	34	35
CMML	3	3
IPSS (%) INT-1	3	7
INT-2	43	39
High	46	48

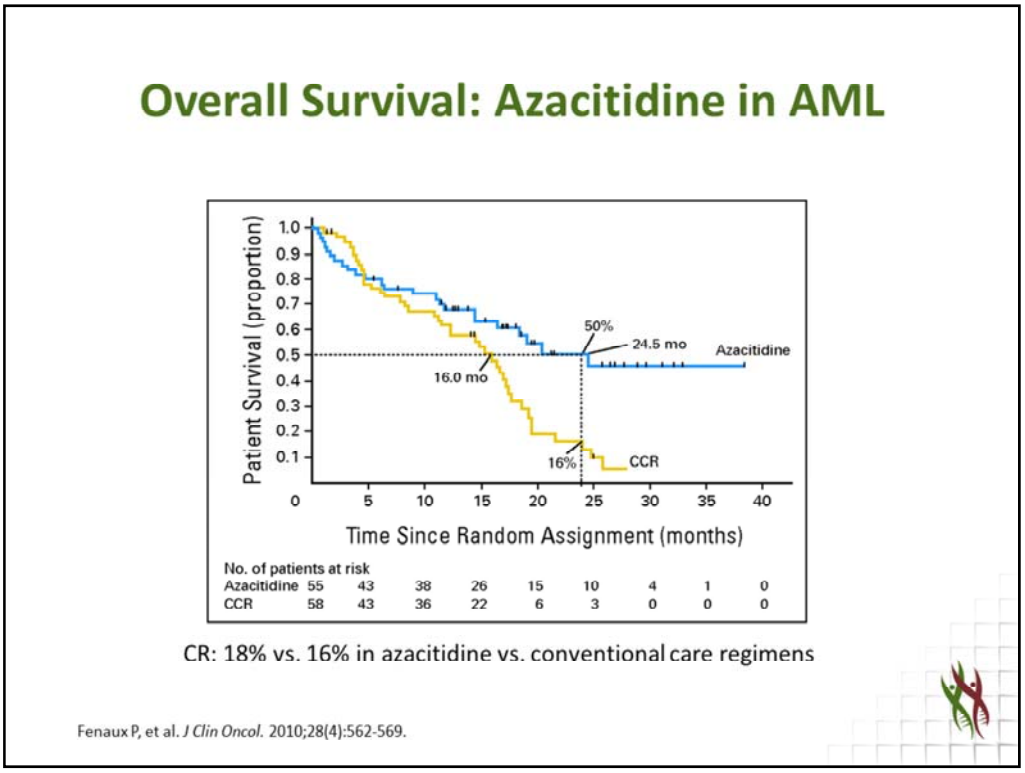
179 patients were randomized to each arm. You can see that 30% of patients actually have RAEB-T (refractory anemia with excess blasts in transformation) which is currently defined as AML. There is a large number of patients who actually had AML.

Novel Treatment Combinations in Development for AML: The Role of Hypomethylating Agents



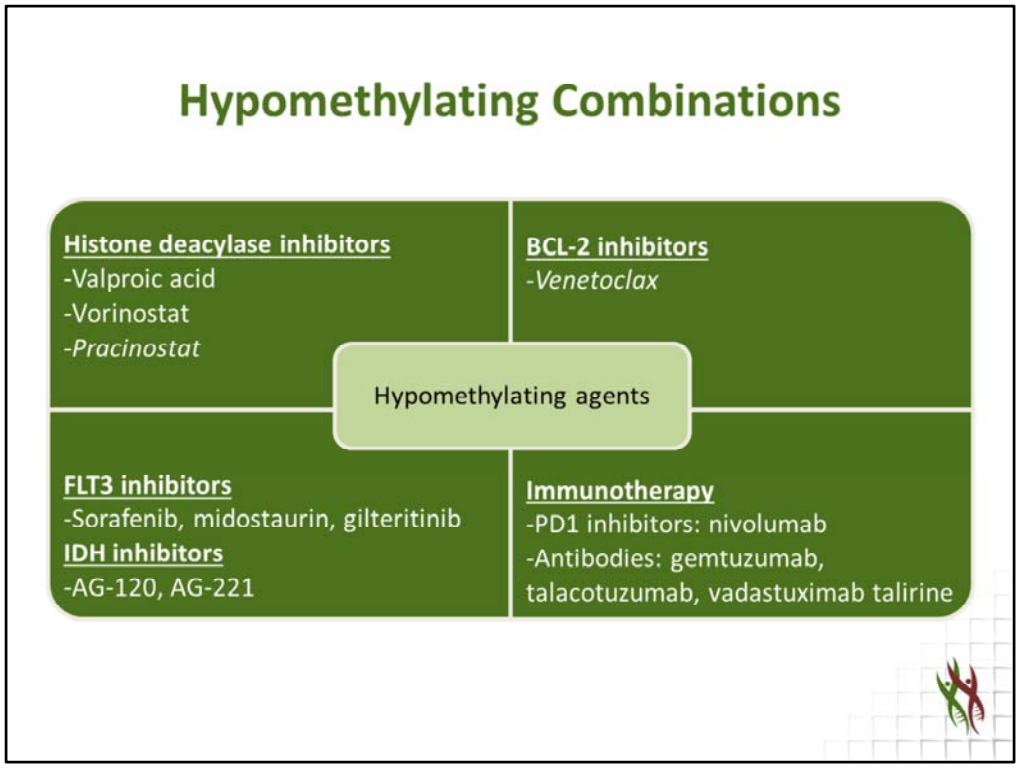
The overall results did show survival benefit for azacitidine compared to conventional care regimen with a difference in overall survival of 9 months.

Novel Treatment Combinations in Development for AML: The Role of Hypomethylating Agents



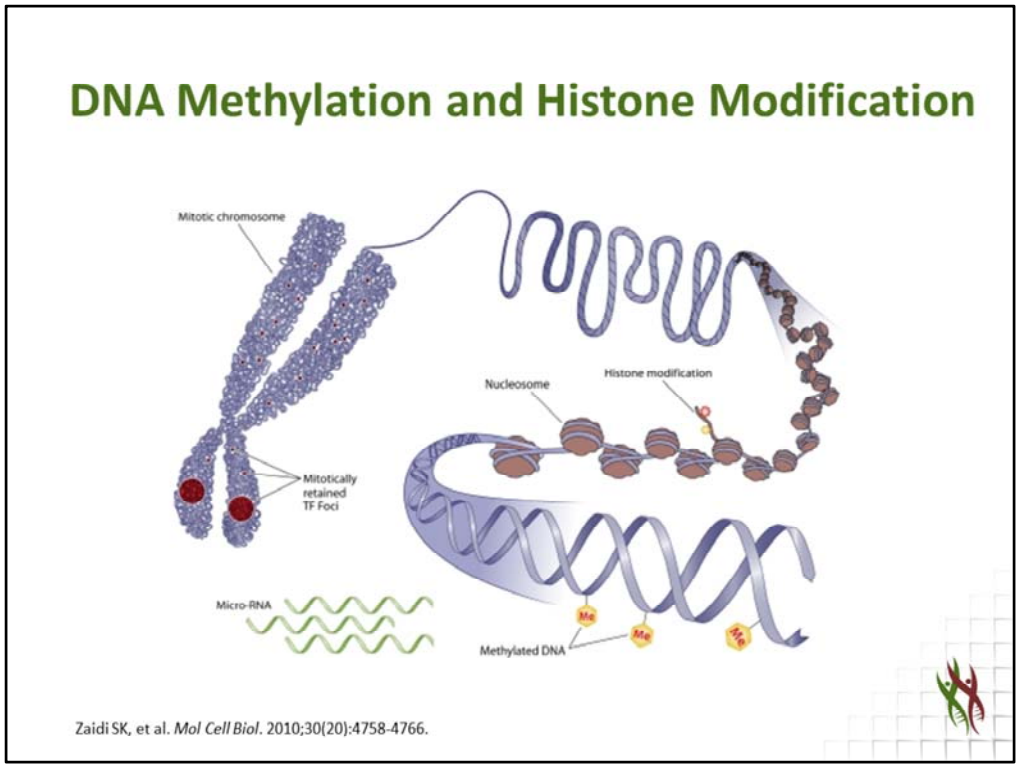
They followed this up with an analysis in patients with AML only. Again, these were patients who had 20% to 30% blasts; a very similar survival benefit was seen in this small subset of patients. In conventional care regimens, the overall survival was 16 months versus 24 months for azacitidine. Of note, however, the rates of complete remission were 18% in the azacitidine arm which is about 20% overall, very similar to the decitabine study. As single agents (either azacitidine or decitabine) patients have about 20% chance of achieving a complete remission.

Novel Treatment Combinations in Development for AML: The Role of Hypomethylating Agents



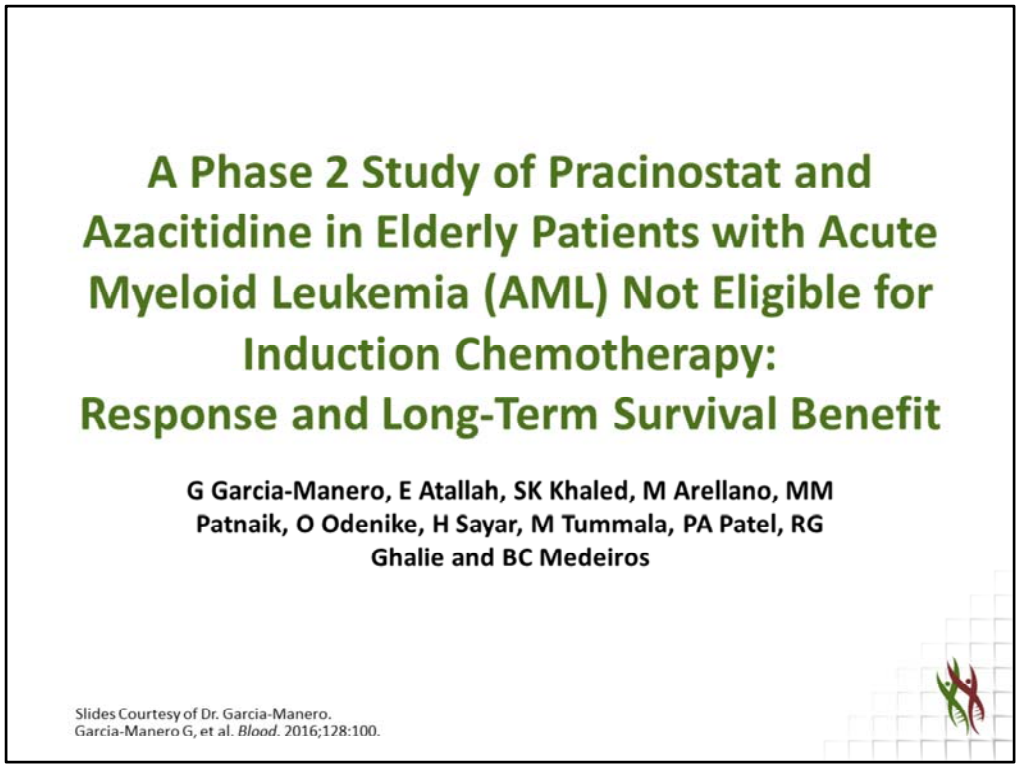
This led to using azacitidine or decitabine as the basis for several other promising combinations. The first is with histone deacetylase inhibitors. There have been several histone deacetylase inhibitor studies including valproic acid, vorinostat and, more recently, pracinostat, which I will discuss in more detail. BCL-2 inhibitors, which includes venetoclax, and there is the combination of hypomethylating agents with venetoclax which I will also discuss in detail. Immunotherapy includes PD-1 inhibitors such as nivolumab, gemtuzumab (brand name Mylotarg™) and other antibodies. I will mainly discuss the combination of azacitidine and decitabine with nivolumab. Finally, targeted agents such as FLT3 inhibitors and IDH inhibitors, but as I mentioned earlier, we will not go into detail on these in today's presentation.

Novel Treatment Combinations in Development for AML: The Role of Hypomethylating Agents



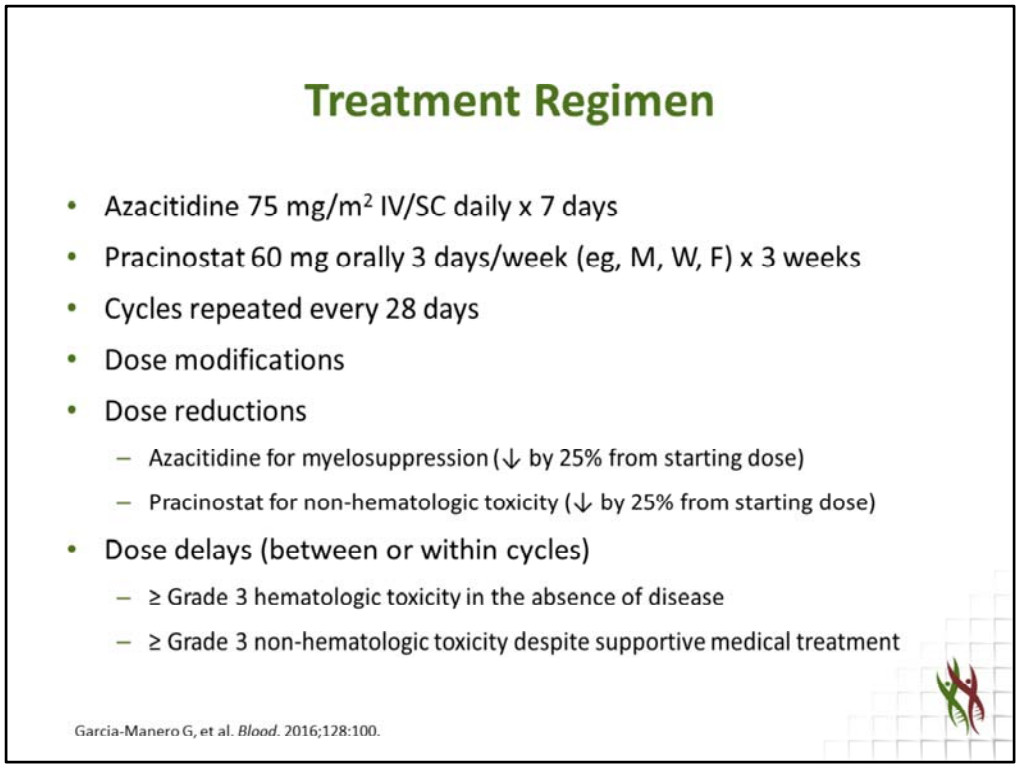
Starting with the histone deacetylase inhibitors, we know that epigenetic change is one of the causes of cancer in general, and azacitidine and decitabine affect the DNA methylation. Another major epigenetic change is histone modification. Histone deacetylase inhibitors together with the hypomethylating agent azacitidine, lead to an increased expression and differentiation in patients with AML and MDS.

Novel Treatment Combinations in Development for AML: The Role of Hypomethylating Agents



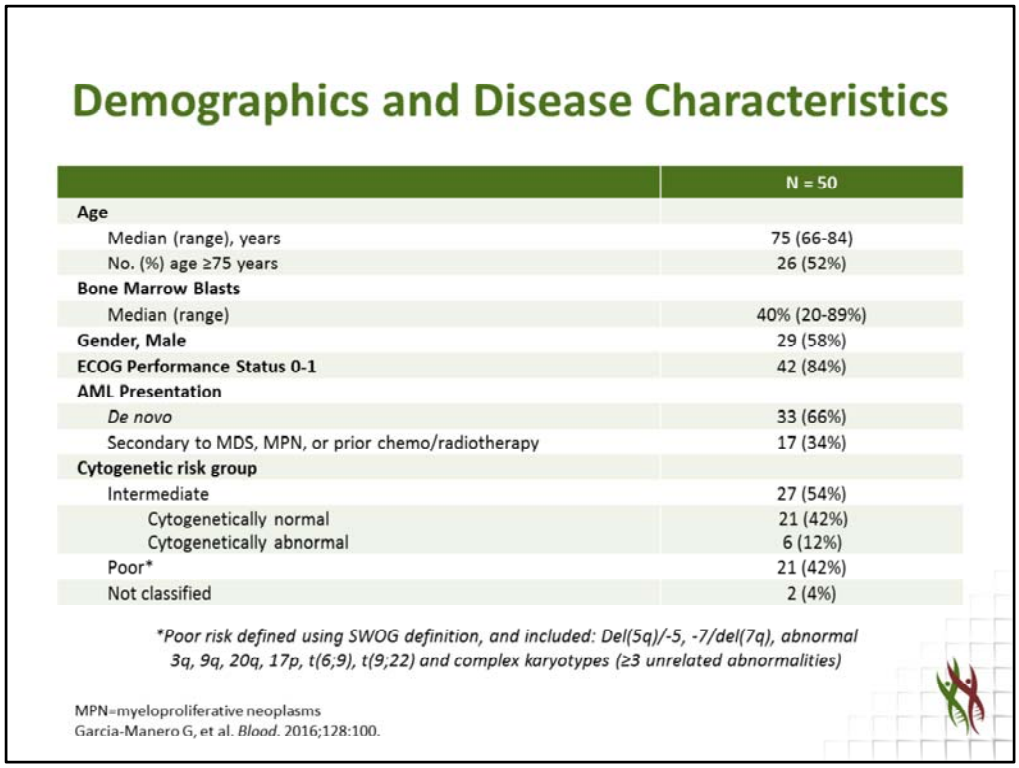
This formed the basis for several trials combining histone deacetylase inhibitors with hypomethylating agents. More recently, this was presented in a study of pracinostat together with azacitidine in older patients with AML who were not eligible for induction chemotherapy. Of note in the study, eligibility was left to the investigator and whether they thought the patient was eligible for induction chemotherapy or not.

Novel Treatment Combinations in Development for AML: The Role of Hypomethylating Agents



The treatment regimen was azacitidine 75 mg/m^2 daily IV or subQ for seven days, together with pracinostat, 60 mg orally three days a week (Monday/Wednesday/Friday) for three weeks. Cycles were repeated every 28 days. Dose modifications were allowed according to myelosuppression or other toxicities.

Novel Treatment Combinations in Development for AML: The Role of Hypomethylating Agents



Demographics and Disease Characteristics

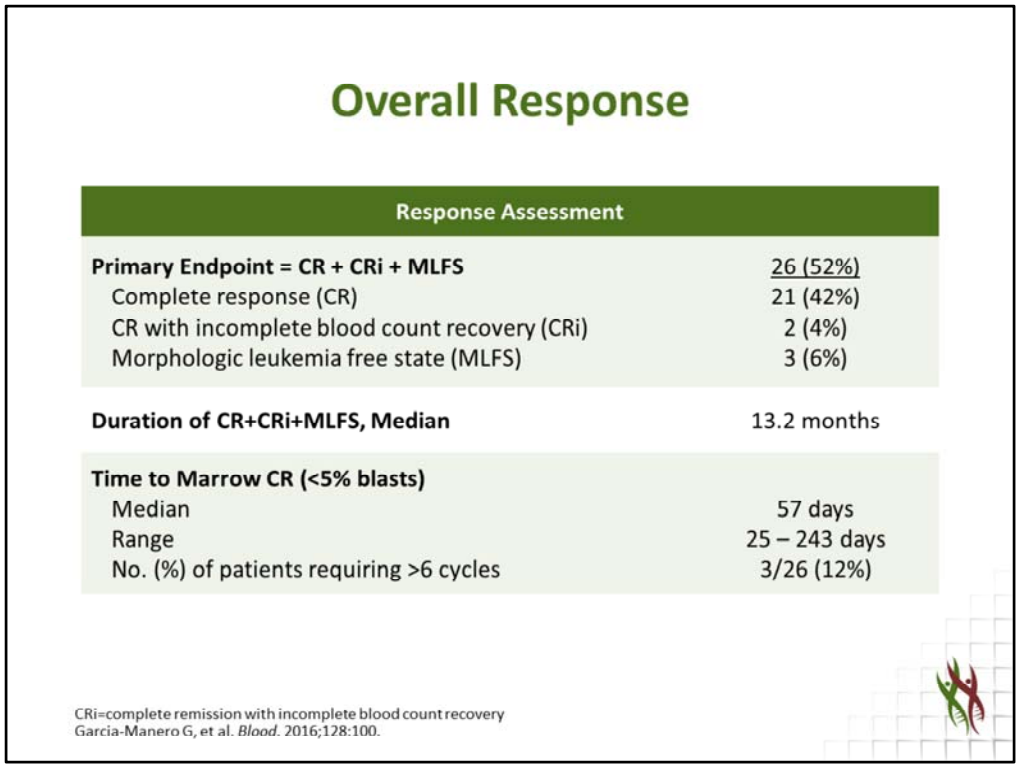
	N = 50
Age	
Median (range), years	75 (66-84)
No. (%) age ≥75 years	26 (52%)
Bone Marrow Blasts	
Median (range)	40% (20-89%)
Gender, Male	29 (58%)
ECOG Performance Status 0-1	42 (84%)
AML Presentation	
De novo	33 (66%)
Secondary to MDS, MPN, or prior chemo/radiotherapy	17 (34%)
Cytogenetic risk group	
Intermediate	27 (54%)
Cytogenetically normal	21 (42%)
Cytogenetically abnormal	6 (12%)
Poor*	21 (42%)
Not classified	2 (4%)

**Poor risk defined using SWOG definition, and included: Del(5q)/-5, -7/del(7q), abnormal 3q, 9q, 20q, 17p, t(6;9), t(9;22) and complex karyotypes (≥3 unrelated abnormalities)*

MPN=myeloproliferative neoplasms
Garcia-Manero G, et al. *Blood*. 2016;128:100.

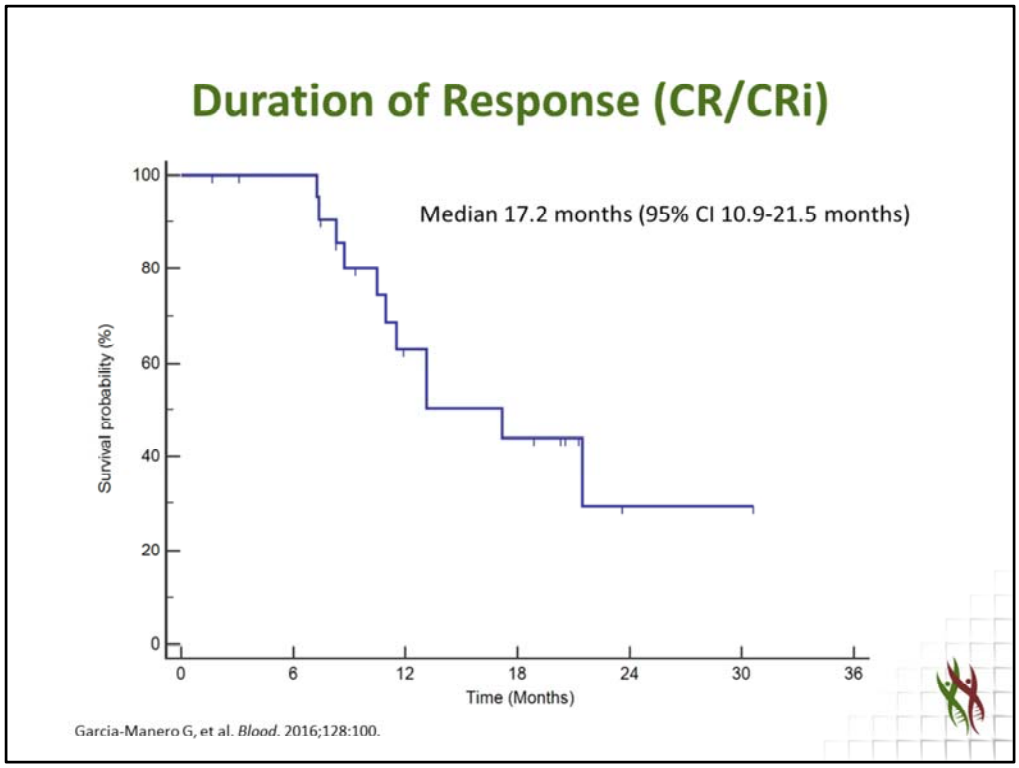
Fifty patients were enrolled on that study with a median age of 75, so these were older patients. The bone marrow blasts ranged from 20 to 89 with an average of 40%. Most patients had a good performance status of 0-1, and 30% of patients had secondary AML to MDS/MPN (myeloproliferative neoplasms) or prior chemotherapy. 42% (or 21 patients) had poor cytogenetics, so this was an older group of patients with multiple poor prognostic factors.

Novel Treatment Combinations in Development for AML: The Role of Hypomethylating Agents



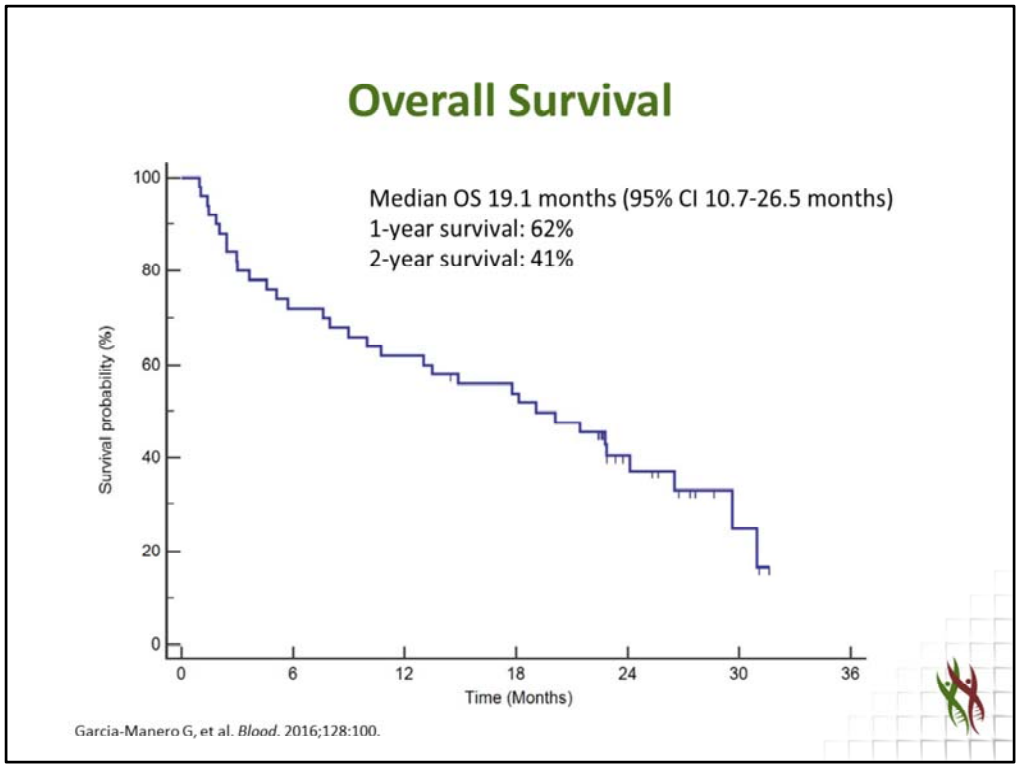
In that study, we saw a pretty impressive complete remission rate, almost doubling compared to single-agent azacitidine. You can see that the rates of complete remission were 42%, and if you add complete remission, plus complete remission with incomplete count recovery, and the morphologic leukemia-free state, almost half of the patients achieved a benefit. The median duration of this response was about 13.2 months.

Novel Treatment Combinations in Development for AML: The Role of Hypomethylating Agents



For patients who achieved complete remission or complete remission with incomplete recovery, the median duration of this response was about 17.2 months.

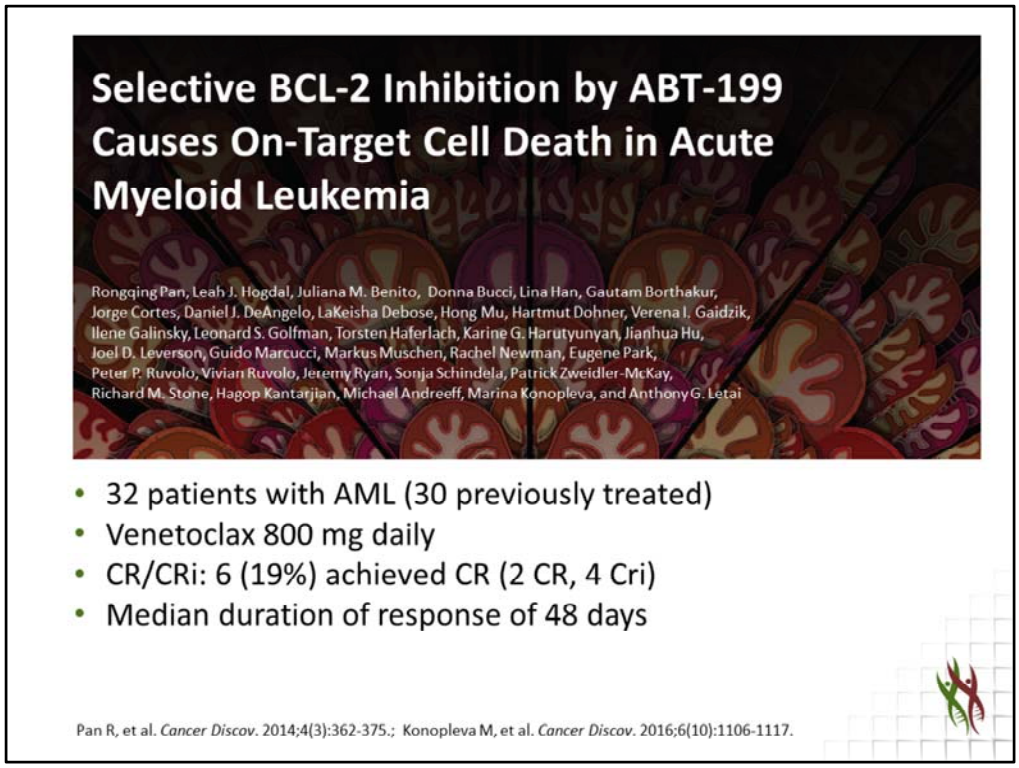
Novel Treatment Combinations in Development for AML: The Role of Hypomethylating Agents



The median overall survival was 19 months with a one-year survival of 62% and a two-year survival of 41%. This combination showed promise by doubling the complete remission rate and improvement in the median overall survival. There is an ongoing phase III trial comparing azacitidine versus azacitidine plus pracinostat in patients with AML, and we will see what these results show.

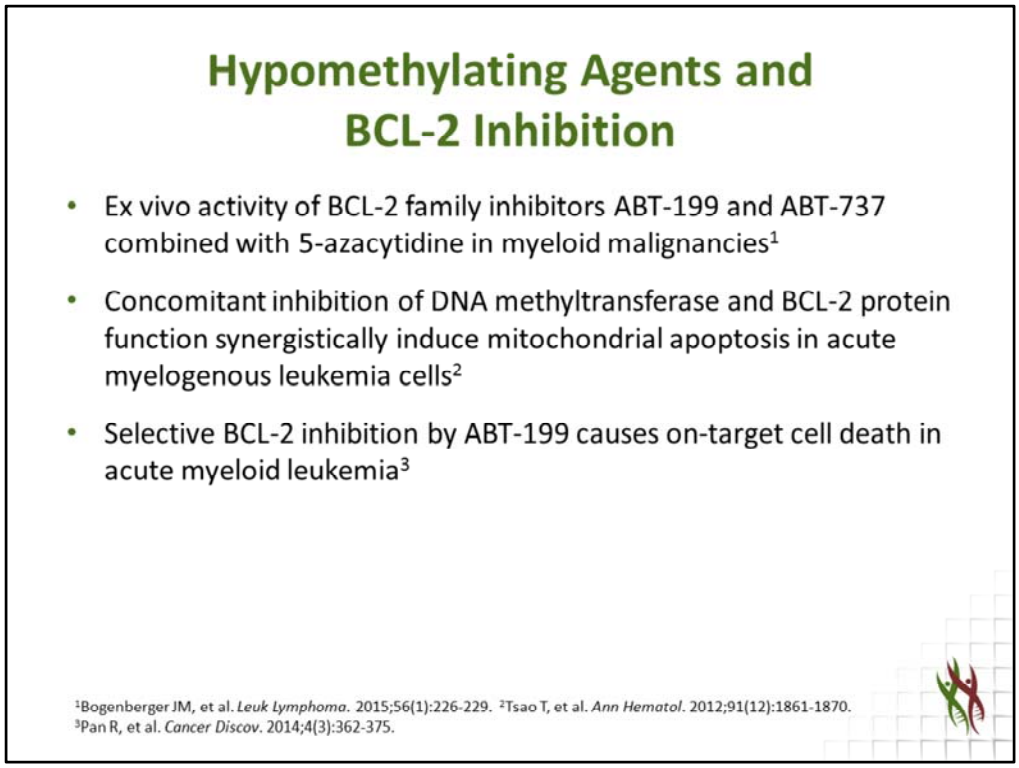
The second interesting compound is BCL-2 inhibition, which is venetoclax.

Novel Treatment Combinations in Development for AML: The Role of Hypomethylating Agents



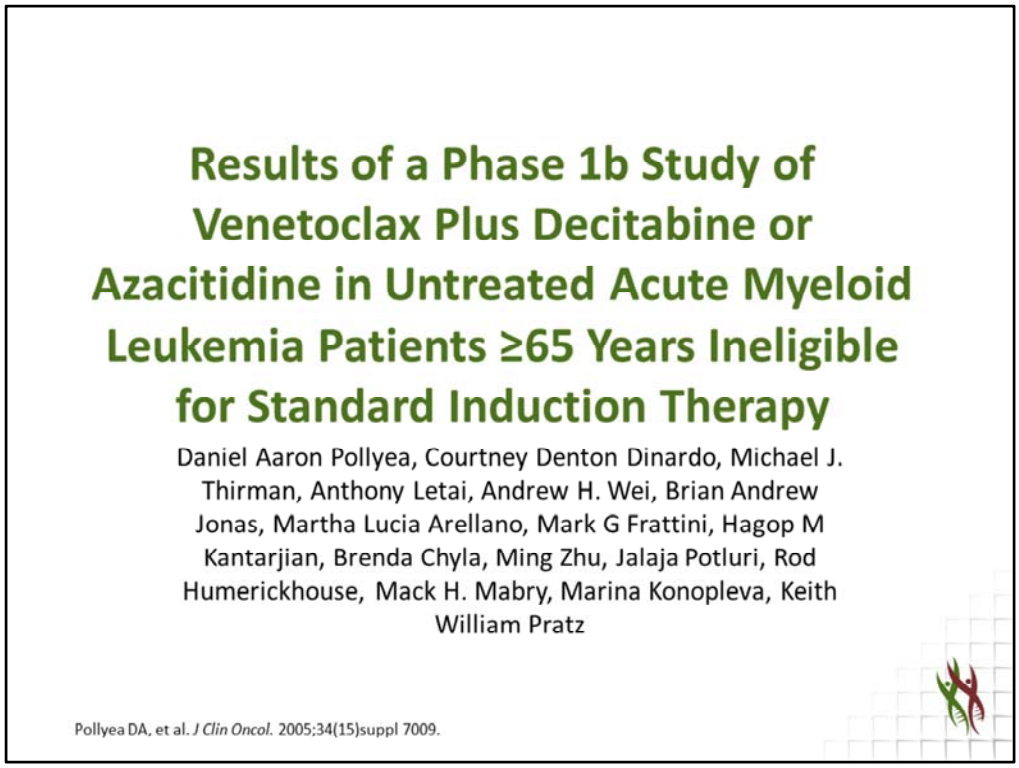
Based on some preclinical data, the BCL-2 inhibition caused on-target death in patients with AML. This was the very first study, enrolling 32 patients with AML, most of them were previously treated. Venetoclax was given at 800 mg daily, which is higher than the current FDA-approved dose for CLL, and about 20% of patients achieved complete remission as a single agent.

Novel Treatment Combinations in Development for AML: The Role of Hypomethylating Agents



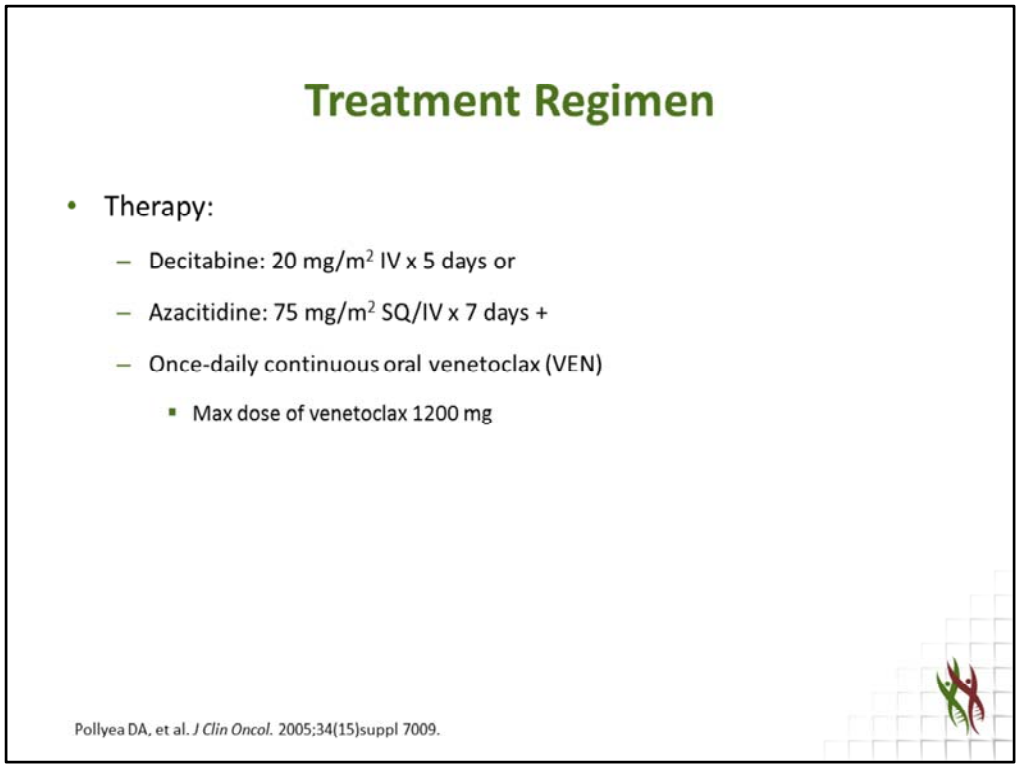
Multiple studies after the preclinical study showed synergistic activity between hypomethylating agents and BCL-2 inhibition.

Novel Treatment Combinations in Development for AML: The Role of Hypomethylating Agents



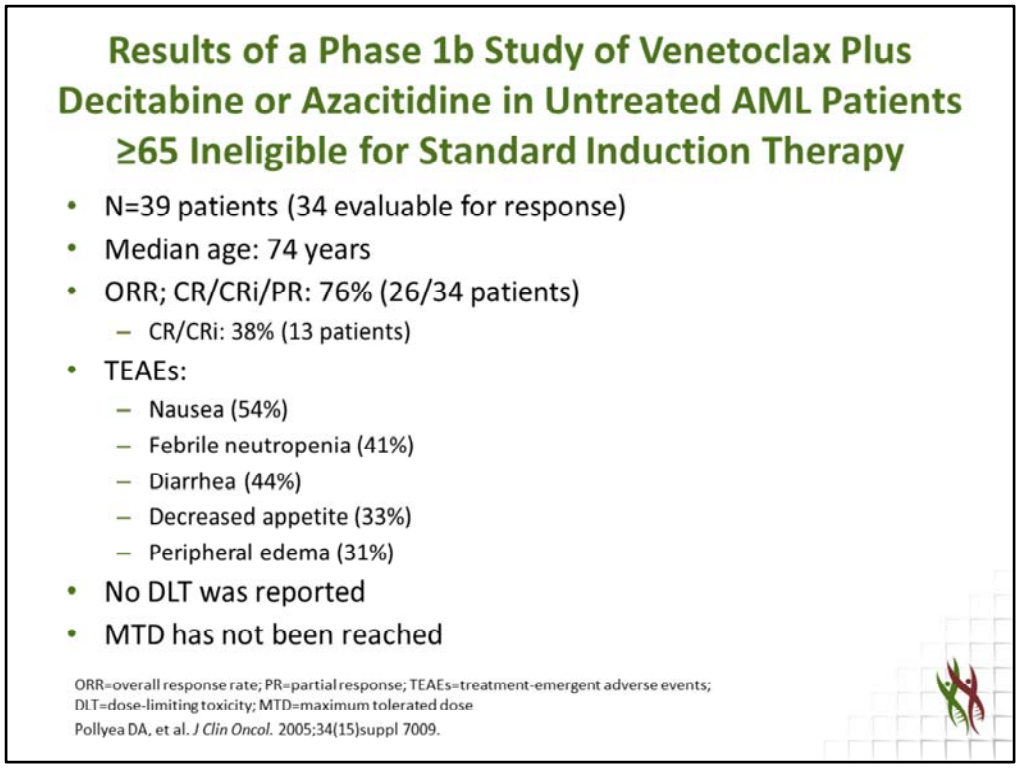
This led to a phase IB study which was presented at ASCO in 2016. It was a phase IB study of venetoclax plus decitabine or azacitidine in untreated patients with AML not eligible for standard induction chemotherapy.

Novel Treatment Combinations in Development for AML: The Role of Hypomethylating Agents



The treatment regimens were either decitabine (20 mg/m^2 IV for five days) or azacitidine (75 mg/m^2 subcutaneously for seven days). Venetoclax was given once daily continuously, with a max dose of venetoclax of 1200 mg.

Novel Treatment Combinations in Development for AML: The Role of Hypomethylating Agents

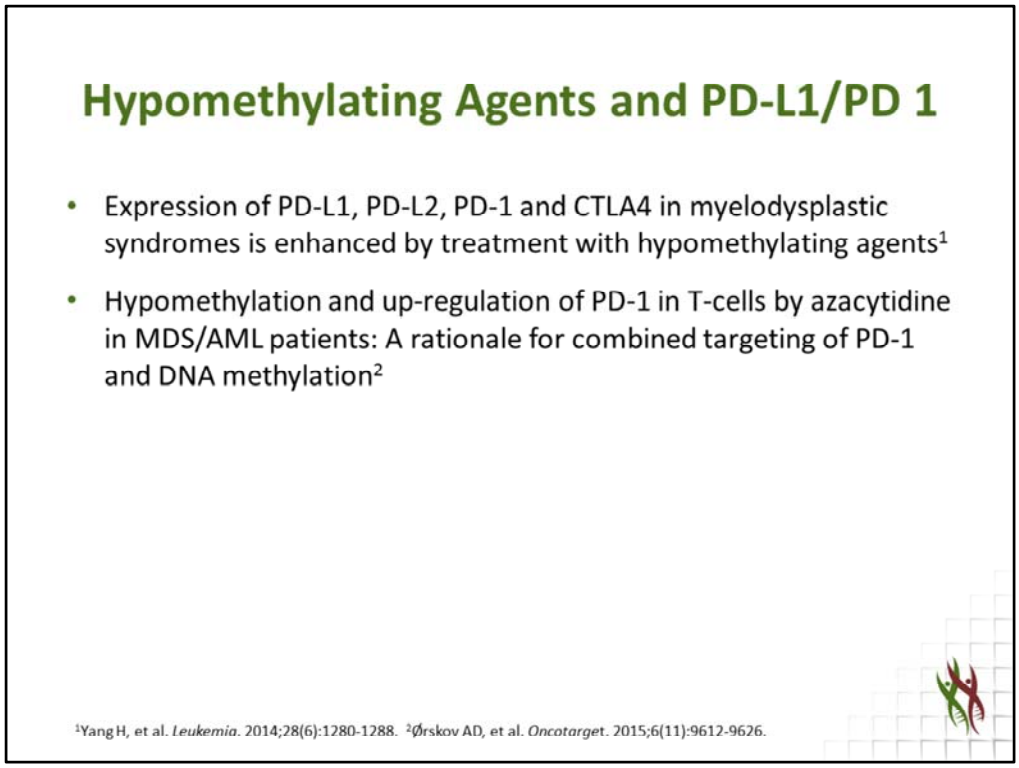


39 patients were enrolled and 34 were evaluable at the time of the presentation. This was an older group of patients with a median age of 74, and again we see a doubling of the complete remission rate to about 38% or about 40%. The side effects noted were nausea in 54% of patients, neutropenia in 41%, diarrhea in 44%, and decreased appetite in 33%, really nothing out of the ordinary. No DLT (dose-limiting toxicity) was reported and the MTD (maximum tolerated dose) was not reached at the time of the presentation. The combination of hypomethylating agents with venetoclax in untreated AML led to a CR rate of about 40%, and this also appears to be a very promising combination in this group of patients.

Novel Treatment Combinations in Development for AML: The Role of Hypomethylating Agents

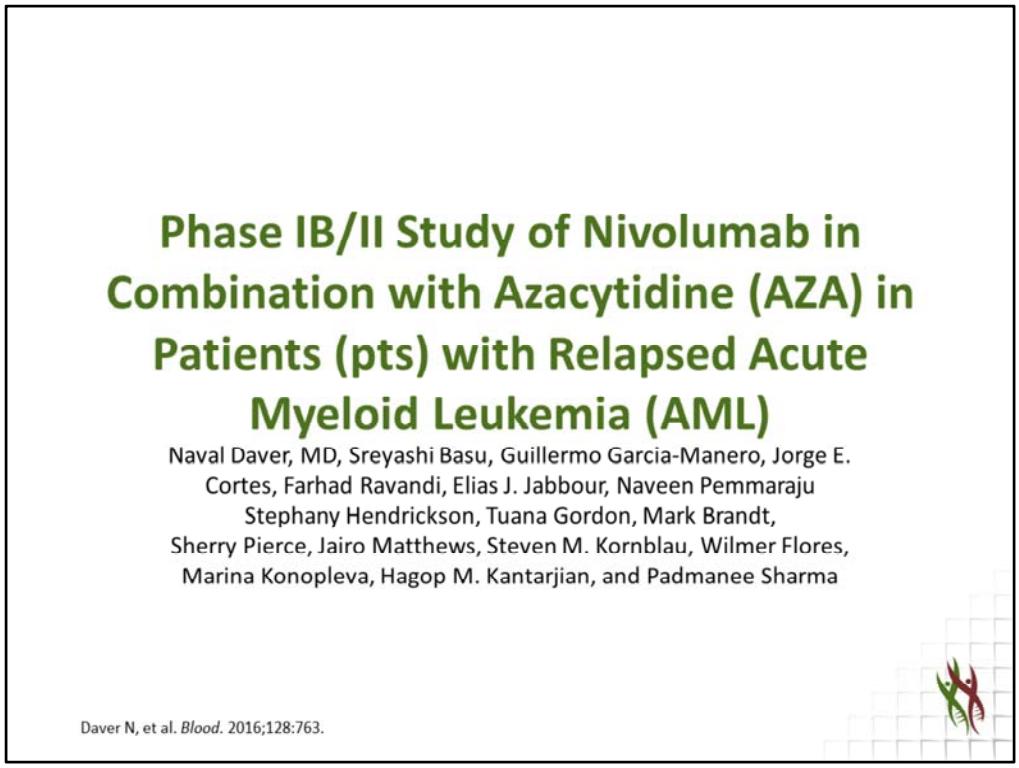
Lastly, immunotherapy.

Novel Treatment Combinations in Development for AML: The Role of Hypomethylating Agents



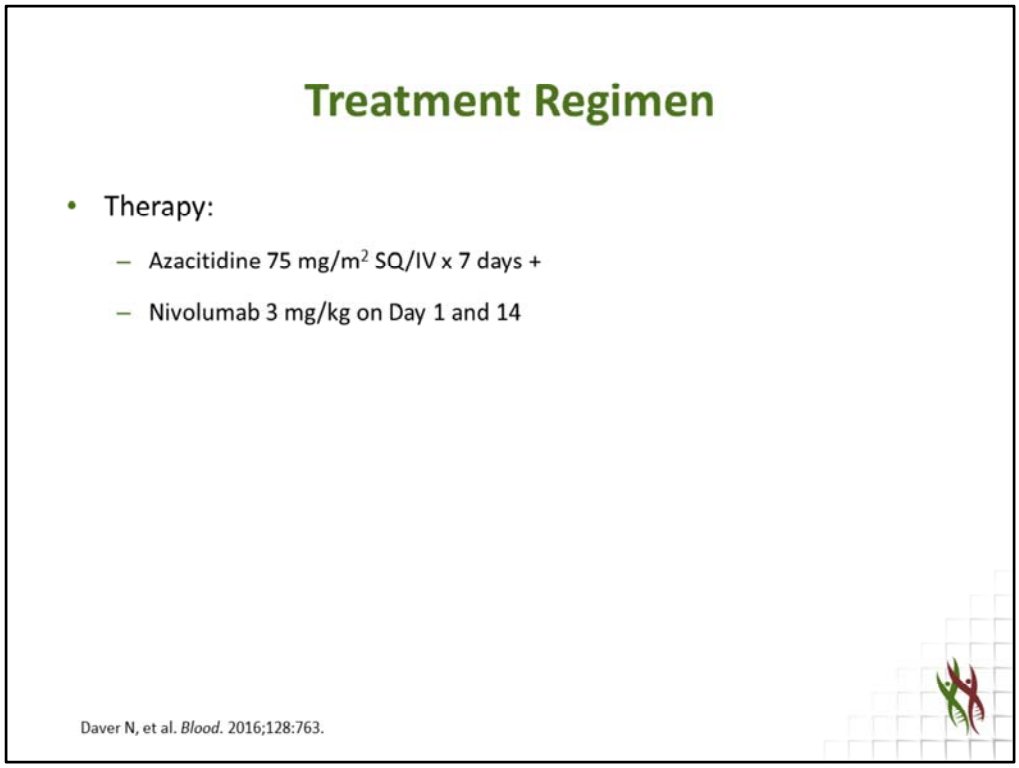
Both the PDL-1 and PD-1 inhibitors have been shown, preclinically in combination with hypomethylating agents, to enhance the effect of hypomethylating agents.

Novel Treatment Combinations in Development for AML: The Role of Hypomethylating Agents



This in turn led to a phase IB/II study led by MD Anderson where patients received azacitidine with nivolumab.

Novel Treatment Combinations in Development for AML: The Role of Hypomethylating Agents



Azacitidine was given at 75 mg/m^2 IV for seven days with nivolumab 3 mg/kg on days 1 and 14.

Novel Treatment Combinations in Development for AML: The Role of Hypomethylating Agents

Azacitidine + Nivo in R/R AML: Characteristics (N=70)

Characteristic	Category	N (%); Median [range]
Age		70 [22 - 90]
>60 years		56 (80)
Diagnosis	AML – de novo	39 (56)
	2 AML	31 (44)
Median Prior Rx (include Rx for MDS)		2 [1 - 7]
Prior therapy	HMA-based	47
	HiDAC-based	27
	Int-dose AraC	22
	Molecular Rx	34
Prior Stem Cell Tx		14 (20)
BM blast %		41 [4 - 94]

Slide Courtesy of Dr. Daver
Daver N, et al. *Blood*. 2016;128:763.

Again, this was an older group of patients with a median age of 70; 40% of the patients had a secondary AML. The difference between this study and the prior study I presented is that this was actually in patients with relapsed or refractory AML, so this was not in newly diagnosed patients. 20% of them had a prior stem cell transplant.

Novel Treatment Combinations in Development for AML: The Role of Hypomethylating Agents

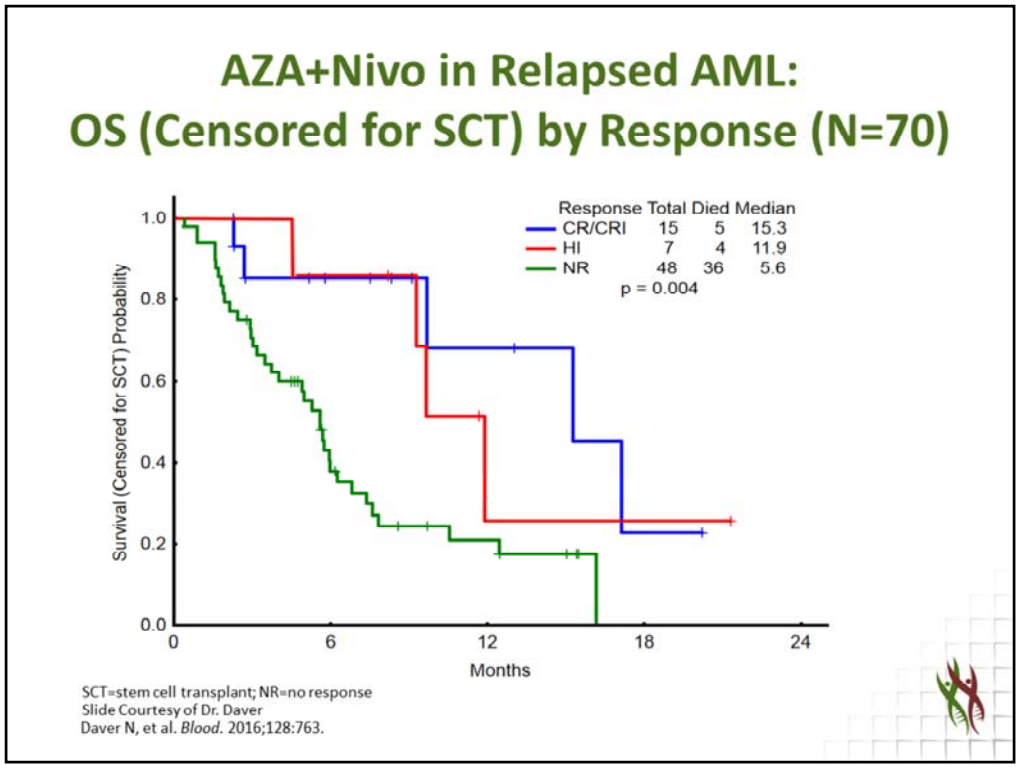
AZA+Nivo in Relapsed AML: Response (N=70)

Best Response/Outcome	N (%)/Med [Range]
Evaluable	70
ORR	22 (32)
CR/CRi	15 (22)
HI + 50% blast reduction (6 mo+)	7 (10)
50% reduction in blast	17 (24)
Progression/stable disease (6 mo+)	26 (37) [21/5]
8-week mortality	5 (7)
Median cycles to response	2 [1 – 13]
Median follow-up	8.6 mo [2.8 – 21.3]

HI=hematological improvement
Slide Courtesy of Dr. Daver
Daver N, et al. *Blood*. 2016;128:763.

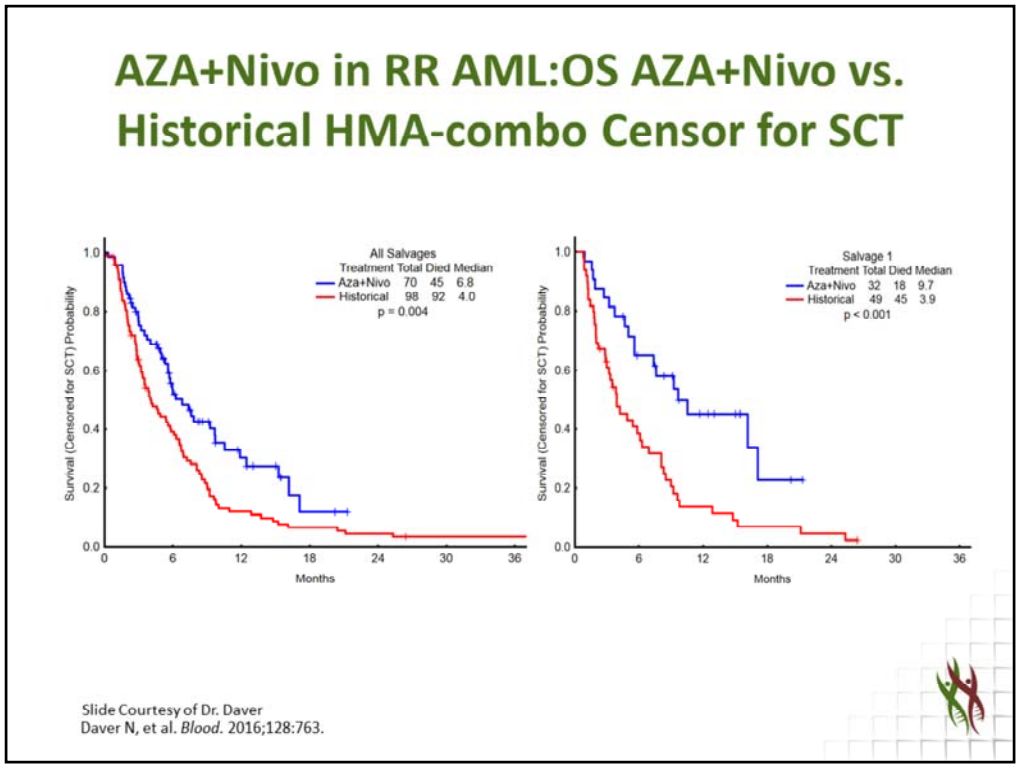
The overall response rate here was 32%, with 22% of patients achieving a complete remission or complete remission with incomplete count recovery. Again, the difference between this study and the prior studies is that this one was in relapsed or refractory AML.

Novel Treatment Combinations in Development for AML: The Role of Hypomethylating Agents



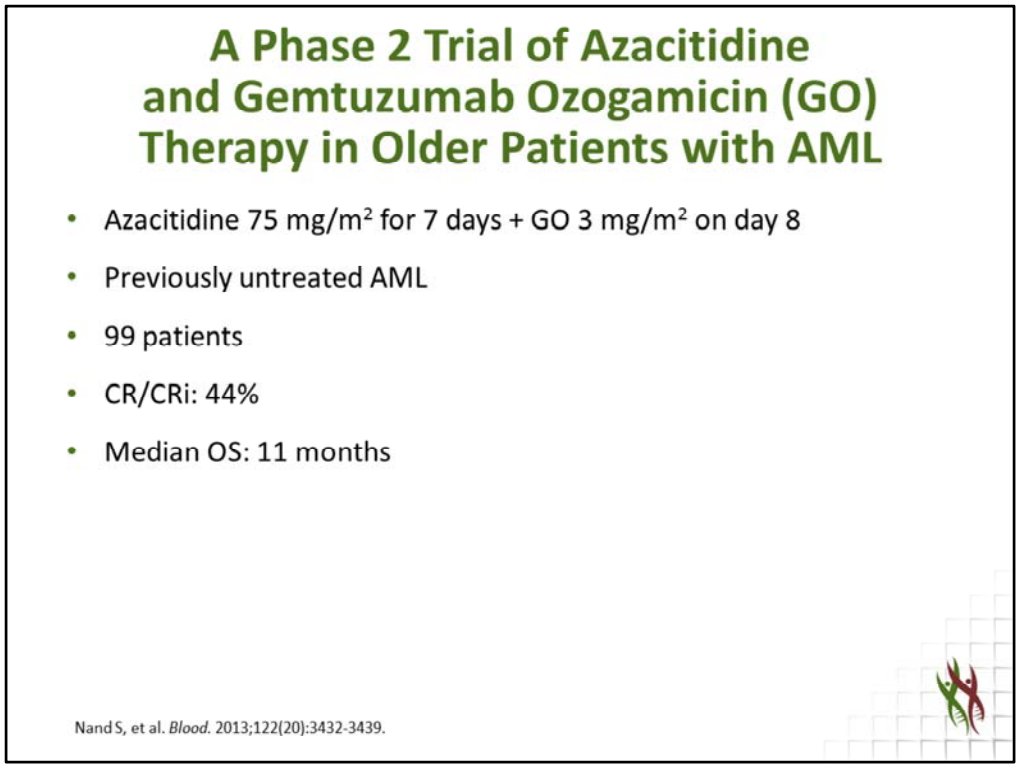
In that study, the median overall survival for patients who achieved complete remission was 15 months. Patients who achieved a hematological improvement had a median overall survival of 11.9 months. For patients who did not have any response, the median overall survival was 5.6 months.

Novel Treatment Combinations in Development for AML: The Role of Hypomethylating Agents

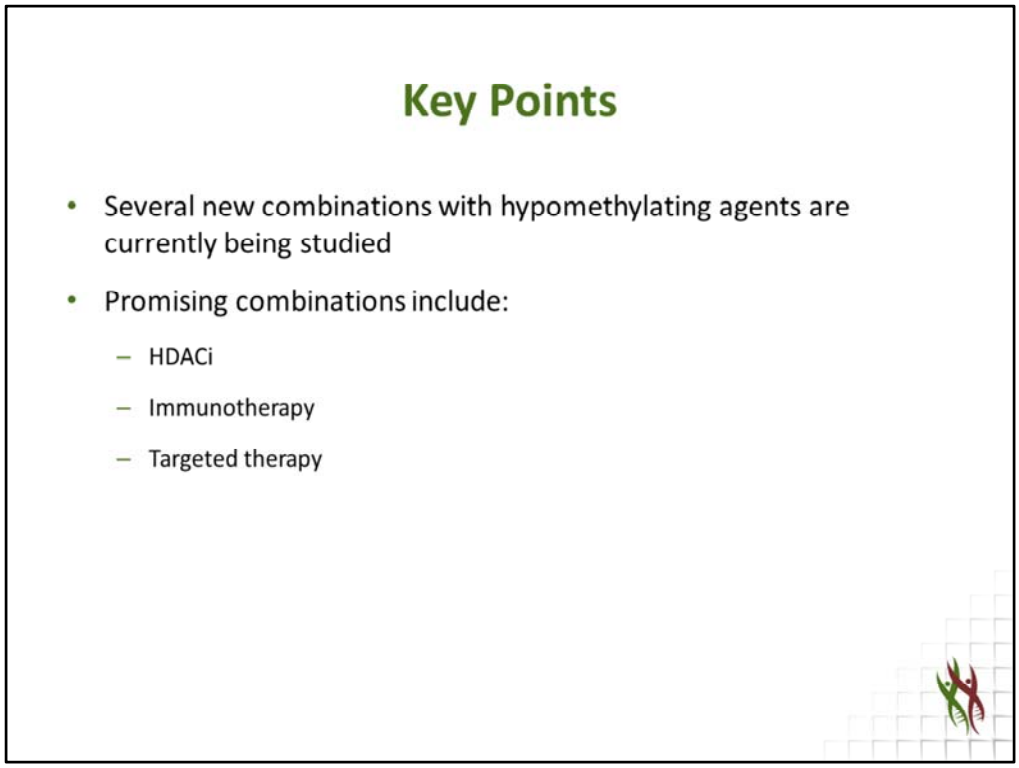


The investigators then compared the overall survival data of azacitidine and nivolumab with historical data on azacitidine alone. The median survival, at least in comparison to historical data in patients with relapsed or refractory AML, appeared promising, with an improvement in median survival from 3.9 months to 9.7 months.

Novel Treatment Combinations in Development for AML: The Role of Hypomethylating Agents



Finally, the last immunotherapy. This was a study published in 2013 where azacitidine was combined with gemtuzumab in older patients with AML. Azacitidine was given 75 mg/m^2 for seven days, and gemtuzumab was given at 3 mg/m^2 on day 8 This was in previously untreated AML patients. About 100 patients, 99 patients to be exact, were enrolled in the study and the rate of complete remission was 44%. This is a doubling of the complete remission rate from the baseline of 20% with hypomethylating agent alone, to 40% with this combination.



In summary, I would like to leave you with these key takeaway points. Several new combinations with hypomethylating agents are currently being studied; and the promising combinations include histone deacetylase inhibitors, immunotherapy and targeted therapy.

Thank you for viewing this activity.