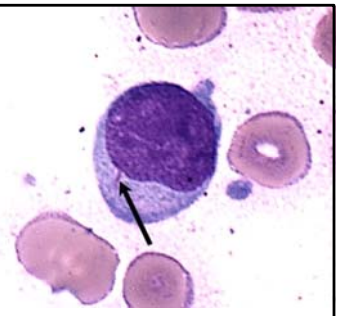
ManagingAML



Novel Treatment Options in Secondary AML

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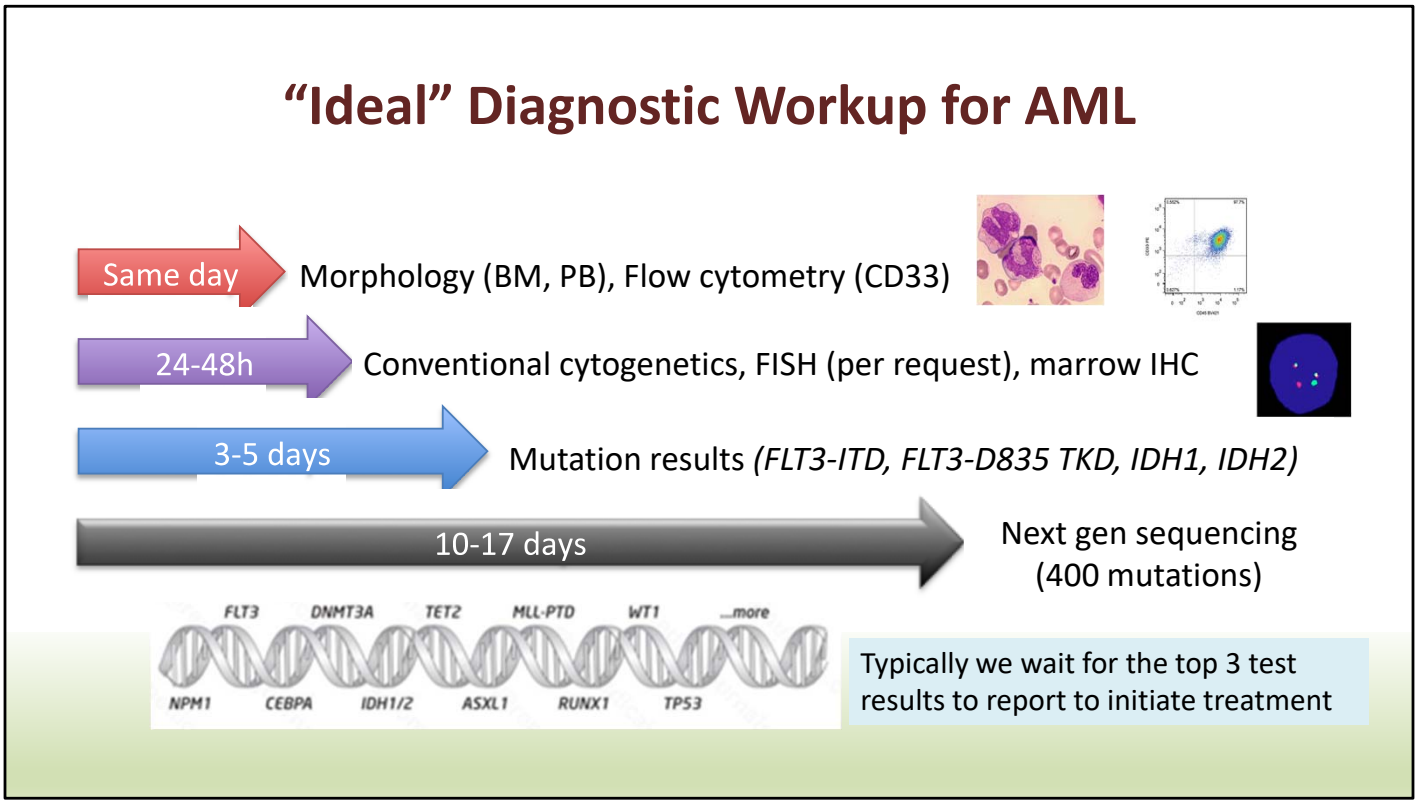
Hello and welcome to *Managing AML*. My name is Dr. Eunice Wang and today I will be discussing Novel Treatment Options in Secondary AML.

Learning Objectives

- Differentiate and define the two distinct subtypes of sAML
- Design a comprehensive initial diagnostic testing protocol as outlined by NCCN, ASH, and CAP guidelines in all new patients assessed for AML
- Outline importance of disease prognostication and classification which may impact patient outcome
- Develop a treatment plan incorporating novel treatment strategy which is aligned with patient/provider goals, quality of life and available agents to treat this subtype of AML
- Incorporate updated data into treatment considerations recognizing importance of clinical trial referral

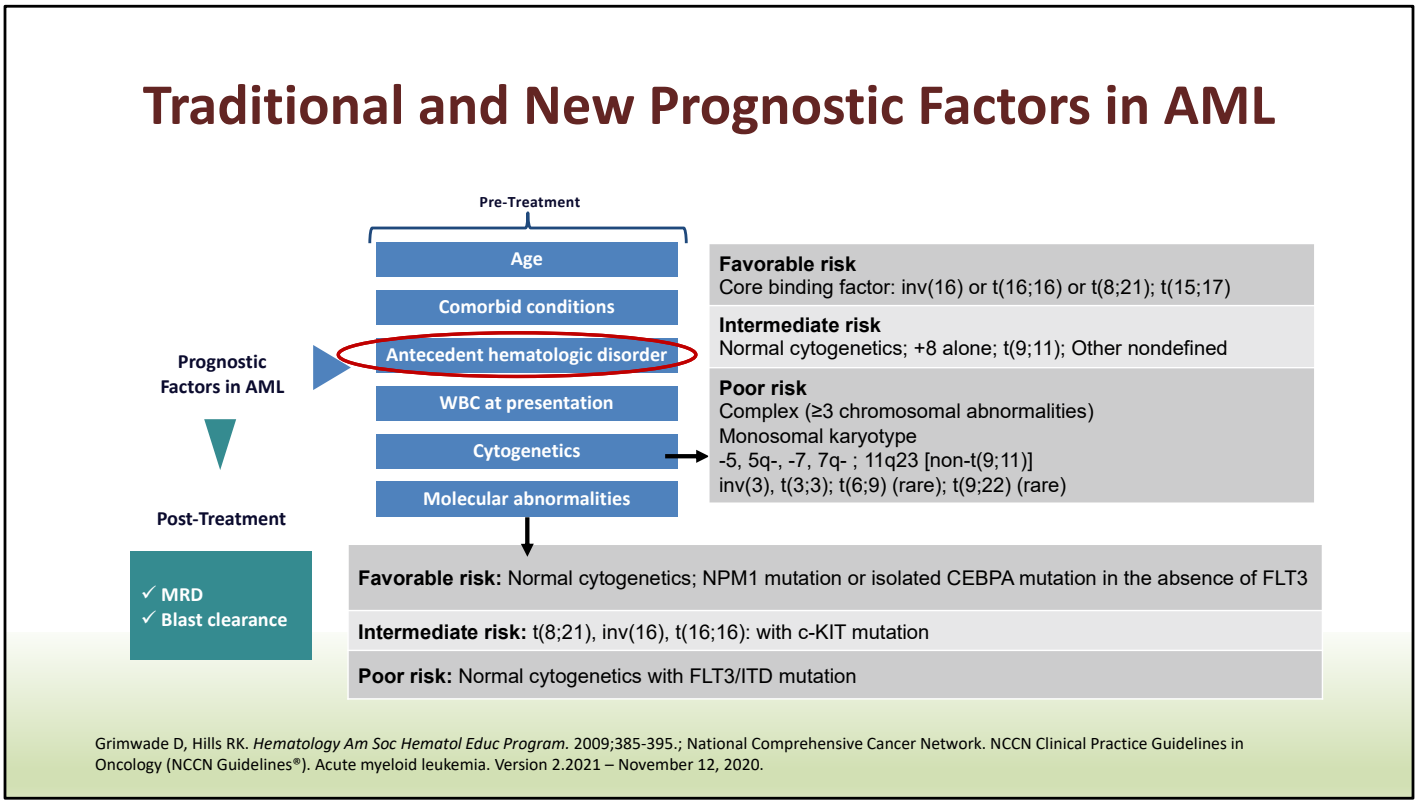
Here are the learning objectives of this talk. Number one, I will be differentiating and defining the two distinct subtypes of AML. That will be followed by a discussion of a comprehensive initial diagnostic testing algorithm, which has been supported by national organizations in all patients diagnosed with AML. Following that I'm going to discuss disease prognostication as well as development of specific treatment plans for secondary AML, based on the incorporation of novel treatment options developed over the last three years. And lastly, I'd like to discuss how to incorporate this upcoming data into treatment algorithms personalized for individual patients.



Now shown here is what we would call the "ideal" diagnostic workup for a patient suspected to have acute myeloid leukemia, or AML, in 2021. As you can see here, the cornerstone of diagnosis of AML remains hematopathology or morphology, and review of the peripheral smear of bone marrow aspirate to determine whether a patient has AML remains the first step in making this diagnosis. However, we have many other tools in our toolkit in this day and era. For example, the same day that we can get morphology or hematopathology review at our center, we have the ability to obtain rapid results of flow cytometric analysis from multiple antigens demonstrating whether the leukemia is of the myeloid or lymphoid lineage. This is followed usually a day or two later, business days, by a preliminary conventional cytogenetics where we're looking at the 21 chromosomes and detecting whether there are any diagnostic translocations, monosomy deletions, etc. And these can also be confirmed by rapid fluorescent in situ hybridization that takes about four to six hours. What takes a longer period of time is mutational evaluation. We do two types of mutational profiling on patients with AML. Number one, we do targeted specific gene mutation PCR for either Flit-3, FLT3 mutations, or IDH1/IDH2 mutations and that is because of the presence and availability of targeted mutation specific therapies for these specific genes.

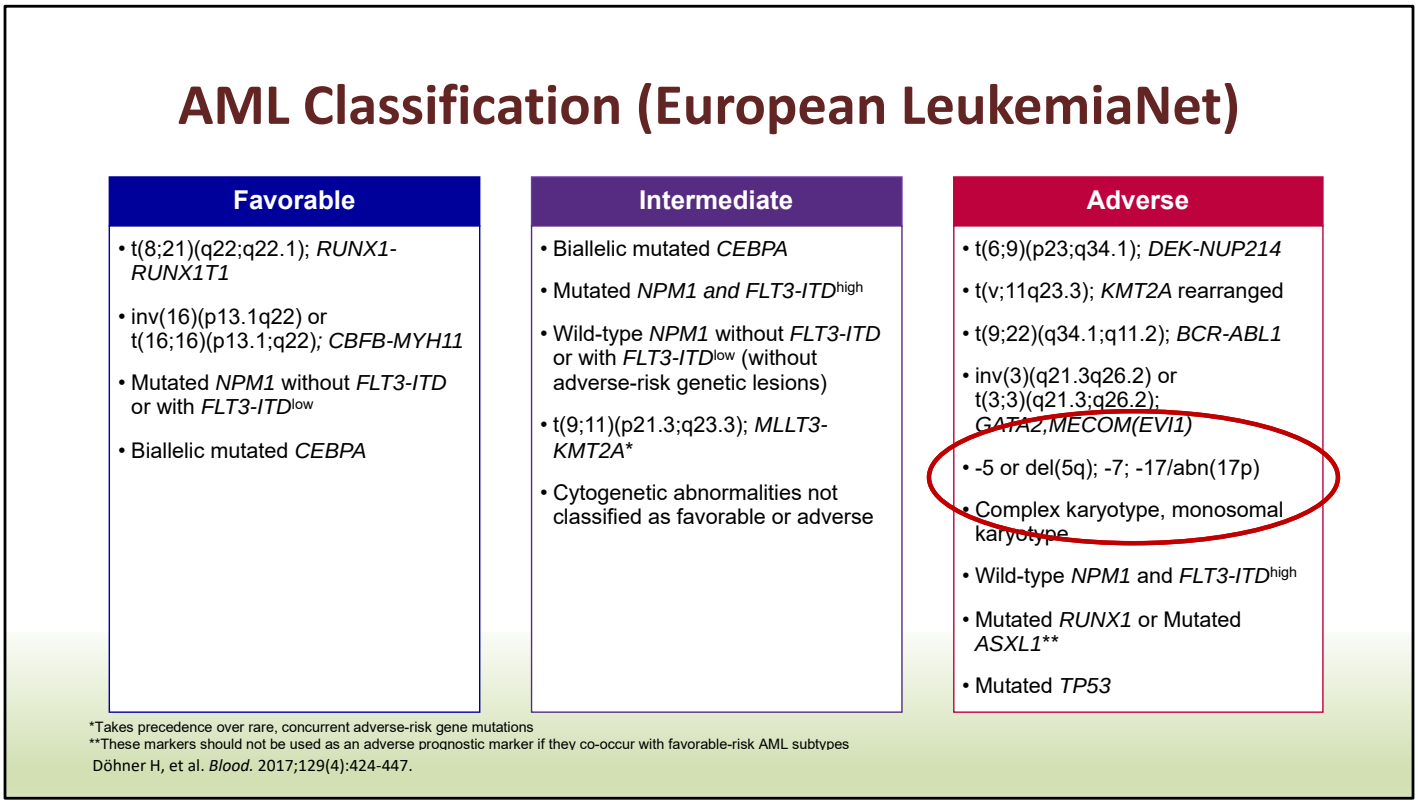
Typically though, there are many, many other genes that can contribute to prognostication and for that analysis we require a broader myeloid panel which can take up to 10 to 17 business days and can encompass anywhere from 75 to 100, to even 400 or 500 different gene mutations.

Novel Treatment Options in Secondary AML



Grimwade D, Hills RK. *Hematology Am Soc Hematol Educ Program.* 2009;385-395.; National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Acute myeloid leukemia. Version 2.2021 – November 12, 2020.

Now, what are the prognostic factors that we look for specifically in patients with AML? Well, we know that there are some what we call traditional or conventional clinical features that are very highly prognostic for this disease. You can see these involve simple calculations or simple clinical parameters such as age, comorbidities, performance status, organ function. Do they have an elevated creatinine or a decreased ejection fraction? We also look at evidence of tumor burden, so obviously patients who have high LDH levels reflecting high disease burden or high or rising white blood cell count would be at higher risk, and nowadays in the newer era, we are more and more looking at not only mutational profiling and cytogenetics which are essential for the diagnosis of AML, but also new prognostic markers including minimal residual or measurable residual disease markers by flow cytometry or molecular analysis.



Now you can see here that the current most widely accepted classification for acute myeloid leukemia involves a combination of cytogenetic and mutational information. There are favorable, intermediate, and adverse karyotypes, and I'd like to highlight here in red those lesions which are pathognomonic of what we call a secondary AML or an AML which has arisen from an antecedent hematologic condition, or from prior chemotherapy or radiation therapy. Patients that have these specific cytogenetic features, specifically aberrations and chromosome 5 or 7, monosomy karyotype or complex karyotype with three or more abnormalities are those that are diagnostic for having secondary AML.

Secondary Acute Myeloid Leukemia (sAML)

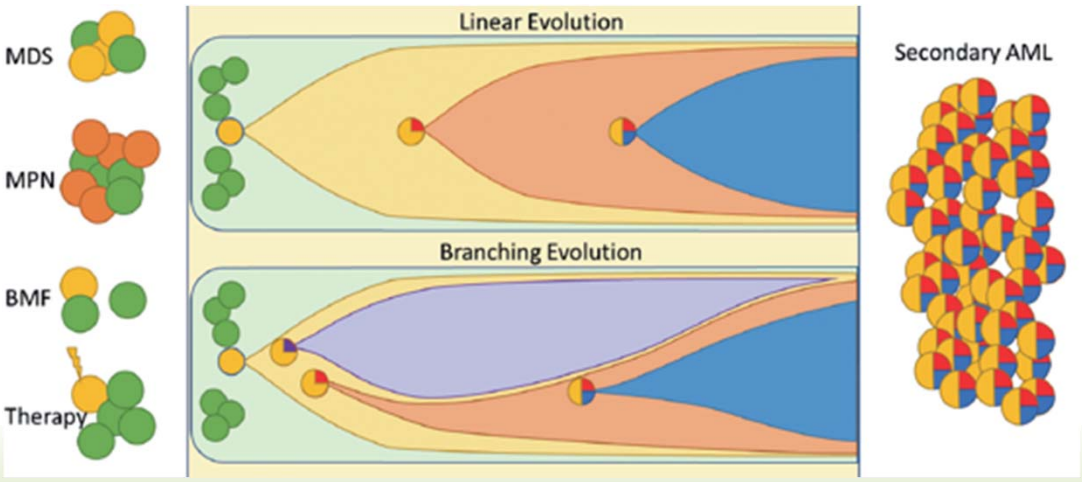
Definition: Secondary acute myeloid leukemia (sAML) refers to a leukemic process either:

(A) Evolving from prior myelodysplasia (MDS), myeloproliferative disorder (MPN), or aplastic anemia with or without treatment; OR

(B) Occurring after previous exposure to radiation or chemotherapy exposure for another cancer

What is our definition of secondary AML? As I just mentioned it is an AML process which is evolved from a prior hematologic condition and these encompass prior MDS, myeloproliferative neoplasm, or aplastic anemia with or without treatment. The second category of secondary AML involves the development of AML following a prior therapy involving radiation or chemotherapy for a prior cancer or any prior condition, for example autoimmune disease.

Secondary AML Following Prior Hematologic Disorder



Brunner AM, Graubert TA. *HemaSphere Educ Updates Heme Book.* 2018;2(S2):150-152.

As you can see here, here is a diagram showing how secondary AML originates. You can see here that there are damaged hematopoietic stem cells, either normal healthy cells which have been exposed to radiation or chemotherapy or cells which are aberrant because of underlying mutations or genetic events that have led to the development of myeloproliferative disorder, myelodysplastic syndrome, or bone marrow failure syndromes. These damaged clones over time will undergo different types of clonal evolution, as you can see on the top there is linear evolution where it just grows out numerically, or you can have what we call branching evolution where the cells just don't grow, but they actually evolve into secondary subclones and those subclones further divide into other subclones. Either one of these processes can lead the end product here on the right-hand side to what we would call secondary acute myeloid leukemia.

Secondary AML Is Associated with Specific Mutations

Lindsley C, et al. *Blood*. 2015;125(9):1367-1376.

Now are there any mutations that are specific for secondary AML? We talked a little bit about the cytogenetic abnormalities, but emerging data piloted by Dr. Coleman Lindsley at the Dana-Farber Cancer Institute has demonstrated that specific mutations identified in AML cells can be pathognomonic for one of these secondary AML evolution processes. As you can see here, the presence of what we call spliceosome mutations, and SRSF2, SF3B1, U2AF1, and others can be specifically linked to a secondary AML origin, and you can see here some of the other mutations which are linked to these.

AML-MRC: AML with MDS-related Changes

Definition: AML with a history of MDS or myelodysplasia-related cytogenetic findings, specifically ≥20% blasts in the peripheral blood or bone marrow and any of the following:

- Previously documented MDS or MDS/MPN
- Myelodysplasia-related **cytogenetic** abnormalities
- Morphologic detection of **multilineage dysplasia**

1. Complex karyotype (3 or more abnormalities).
2.Unbalanced abnormalities: -7/del(7q), del(5q)/t(5q), i(17q)/t(17p), -13/del(13q), del(11q), del(12p)/t(12p), idic(X)(q13).
3. Balanced abnormalities: t(11;16)(q23.3;p13.3), t(3:21)(q26.2;q22.1), t(1;3)(p36.3;q21.2), t(2;11)(p21;q23.3), t(5;12)(q32;p13.2), t(5;7)(q32;q11.2), t(5;17)(q32;p13.2), t(5;10)(q32;q21.2), t(3;5)(q25.3;q35.1)

Footnote 1. The presence of 50% or more dysplastic cells in at least 2 cell lines, excluding cases when a mutation of NPM1 or biallelic mutation of CEBPA is present.

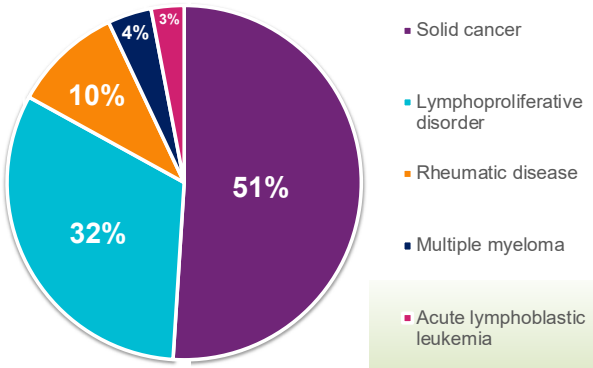
The presence of any of these clinical histories, cytogenetics, or potentially mutational events suspicious for secondary AML can lead one to this diagnosis in this day and era. Now, why is it important that we have a diagnosis of secondary AML? Well, I am going to walk you through some of the treatment modalities which can be specifically applied for this subtype of AML. It is important prognostically as also therapeutically to make the correct diagnosis.

So just to review, AML with myelodysplastic-related changes or AML with AML-MRC as we call it, is defined as one of the subtypes of secondary AML. This is AML associated with either a known proven history of MDS or with AML diagnosed in the presence of specific MDS-related cytogenetic findings as we mentioned previously. All AML cases need to have more than 20% blasts in the marrow and many of these cases we can find some of those mutations which are not pathognomonic and not listed right now in the classification, but highly suggestive of a secondary AML abnormality. So here you can see here are some of these cytogenetic changes.

Therapy-related AML (tAML)

The WHO defines t-AML as AML that arises from prior cytotoxic therapy or ionizing radiotherapy for an unrelated disease. Estimated to account for 5-10% of all AML cases.

Primary malignancy prior to tAML



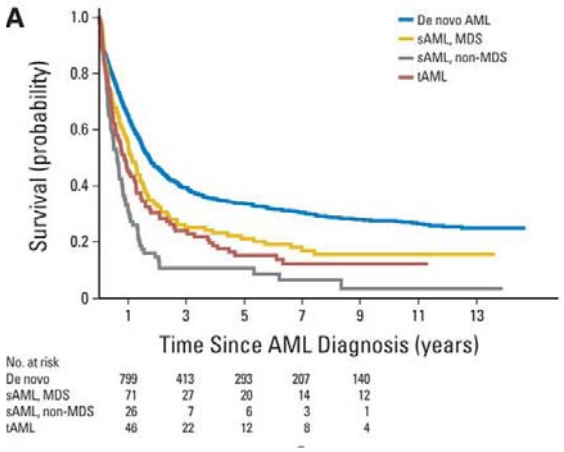
Cytotoxic therapy	MOA	Examples	Latency period
Alkylating agents and radiation	Induce chromosomal deletions, commonly in 5 and/or 7	Cyclophosphamide, mechlorethamine, procarbazine, chlorambucil, melphalan, carmustine, busulfan	5-10 years
Topoisomerase II inhibitors	Induce chromosomal translocations	Etoposide, teniposide, mitoxantrone, epirubicin, and doxorubicin	2-3 years

Bhatia S. *Semin Oncol.* 2013;40(6):666-675.; Czader M, et al. *Am J Clin Pathol.* 2009;132(3):410-425.; Leone G, et al. *Haematologica.* 1999;84(10):937-945.

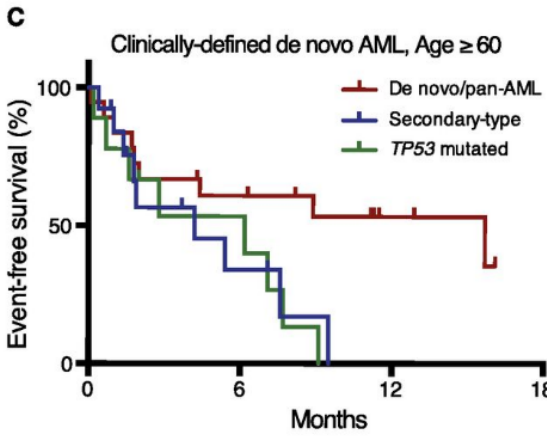
The second major category of secondary AML is therapy-related AML is defined tAML in brief, and the World Health Organization has defined therapy-related AML as arising from prior cytotoxic therapy or ionizing radiotherapy for an unrelated disease. You can see here on the left-hand side, over half of patients with therapy-related AML will have a diagnosis of a prior solid tumor leading to this therapy. However, you can see that up to 49%of patients will have a prior condition that may not be a solid tumor, about a third of these patients will have prior lymphoproliferative disorder for which they may have received DNA damaging agents or agents such as Revlimid (lenalidomide) for multiple myeloma, and a smaller fraction of patients are going to have other conditions including autoimmune diseases for which they've received cytotoxic therapy. Shown here on the right-hand side are some of the typical cytogenetic abnormalities which have traditionally been identified in patients with therapy-related AML. However, in the presence of some of these other findings, the diagnosis of therapy-related MDS may not necessarily be made purely based on cytogenetic and molecular features.

Outcomes of sAML Are Poorer than De Novo AML

Overall survival by AML diagnosis



Based on sAML mutations

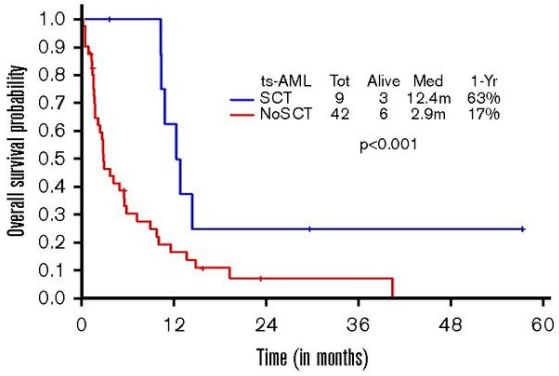


Granfeldt Østgård LS, et al. *J Clin Oncol.* 2015;33:3641-3649.; Lindsley C, et al. *Blood.* 2015; 125(9):1367-1376.

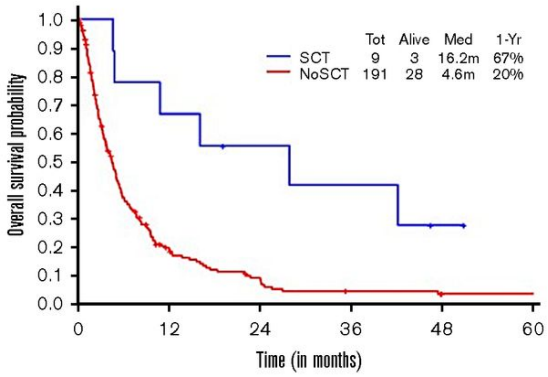
Now as we mentioned previously, and as you can see based on the presence of some of these what we call unfavorable cytogenetic and mutational events, secondary AML is associated with a worse prognosis than de novo AML. Shown here on the left-hand side are the outcomes of secondary AML as compared to de novo AML in similar age range patients, and you can see a significant drop-off in expected response rates and overall survival in these patients. You see also on the right-hand side that even in the absence of say one would say a clinical history of a prior antecedent MDS, the presence even of these secondary mutations suggestive of a secondary AML can also be associated with worse prognosis, independent of a clear clinical history.

Importance of Allogeneic Transplant for sAML

Younger patients <60 yo



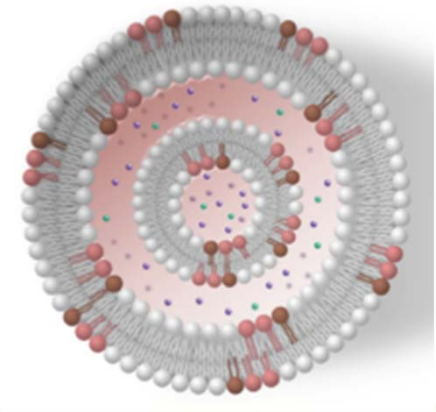
Older patients ≥60 yo



Boddu P, et al. *Blood Adv.* 2017;1(17):1312-1323.

Now, how would one cure patients with secondary AML? Well, patients with secondary AML have worse outcomes, and their outcomes are markedly improved if one is able to offer allogeneic stem cell transplantation, as you can see here for both younger and for older patients, the ability to offer a curative hematopoietic stem cell transplantation remains the only and best way to achieve long-term survival for these patients.

Liposomal 7+3 (CPX-351): Drug Formulation

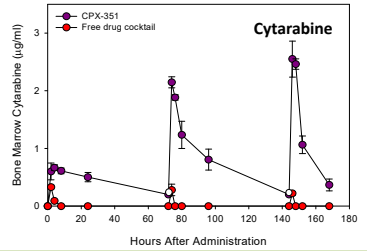


Liposomal formulation of cytarabine and daunorubicin

Fixed 5:1 molar ratio of cytarabine: daunorubicin provides synergistic leukemia cell killing *in vitro*

In patients, CPX-351 preserved delivery of the 5:1 drug ratio for over 24 hours, with drug exposure maintained for 7 days

Selective uptake of liposomes by bone marrow leukemia cells in xenograft models



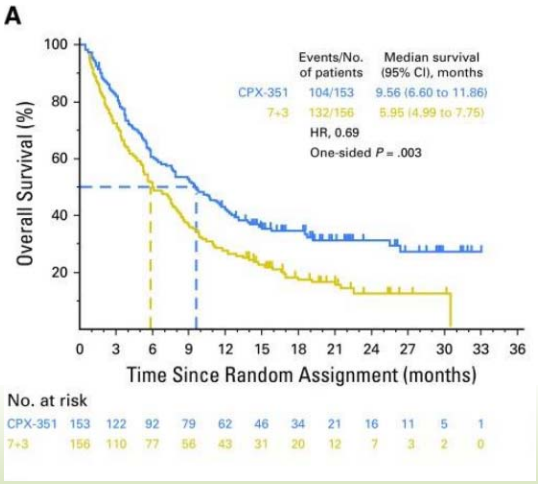
Lancet JE, et al. *J Clin Oncol*. 2018;36:2684-2692.

Now, what is the upfront therapy? In order to offer some type of allogeneic stem cell transplantation, the majority of patients have to have upfront therapy after their diagnosis. I would recommend after the diagnosis of a secondary AML that one explore these specific targeted therapies, which are designed to best improve the outcomes of these individuals both in the absence and the presence of subsequent allogeneic stem cell transplantation.

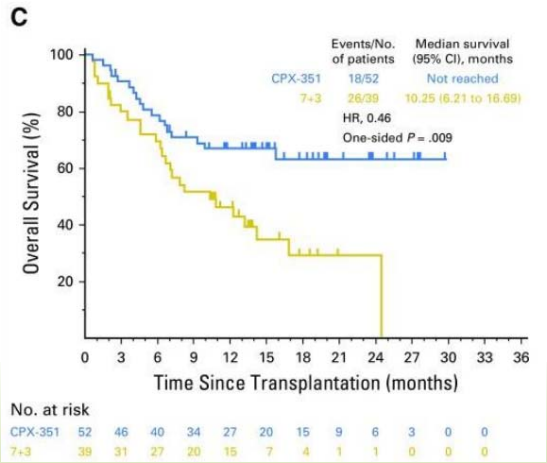
The first therapy that I will discuss is liposomal 7 + 3 ,previously known as CPX-351. What is CPX-351? It is a specific liposomal formulation of two drugs, cytarabine and daunorubicin, which represents the standard 7 + 3 intensive chemotherapy regimen for patients with de novo AML. However, individuals with secondary AMLs we showed you have a worse prognosis, but standard 7 + 3 leading to the theory that if one could improve the delivery and the pharmacokinetics of 7 + 3, could one improve outcomes for this poor prognosis subset? And you can see here that CPX-351 was rationally designed specifically for that purpose. In the laboratory, combinations of cytarabine and daunorubicin were tested in different molar ratios with the identification of a fixed 5.1 molar ratio as being the most effective and eliminating AML cells.

CPX-351 in Older Patients with AML-MRC and t-AML

Overall survival



OS landmarked for transplant

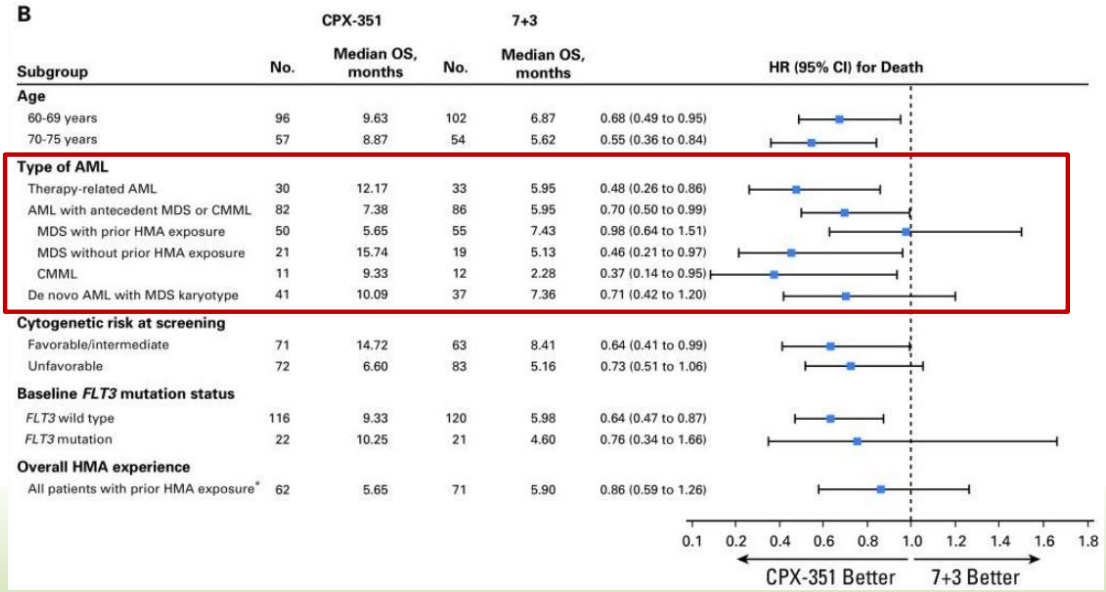


Lancet JE, et al. *J Clin Oncol*. 2018;36:2684-2692.

In a randomized phase 3 trial of individuals 60 to 75 and above who were fit enough to receive intensive chemotherapy based on performance status and who had intermediate or poor cytogenetic or molecular risk classifications of secondary AML, patients who received the liposomal cytarabine and daunorubicin had markedly and significantly improved overall survival as compared to those receiving 7 + 3 alone.

You can also see as we talked about that many of these patients will have experienced the greatest benefit to therapy if they are able to achieve complete remission and proceed on to subsequent allogeneic stem cell transplantation. The results on the right-hand side highlight the benefit of upfront liposomal cytarabine and daunorubicin, particularly in those subsets of patients who were able to get to allogeneic stem cell transplantation. Patients receiving CPX-351 not only had higher rates of remission, but also because they had higher rates of remission were more were able to go to an allogeneic stem cell transplantation than patients receiving 7 + 3.

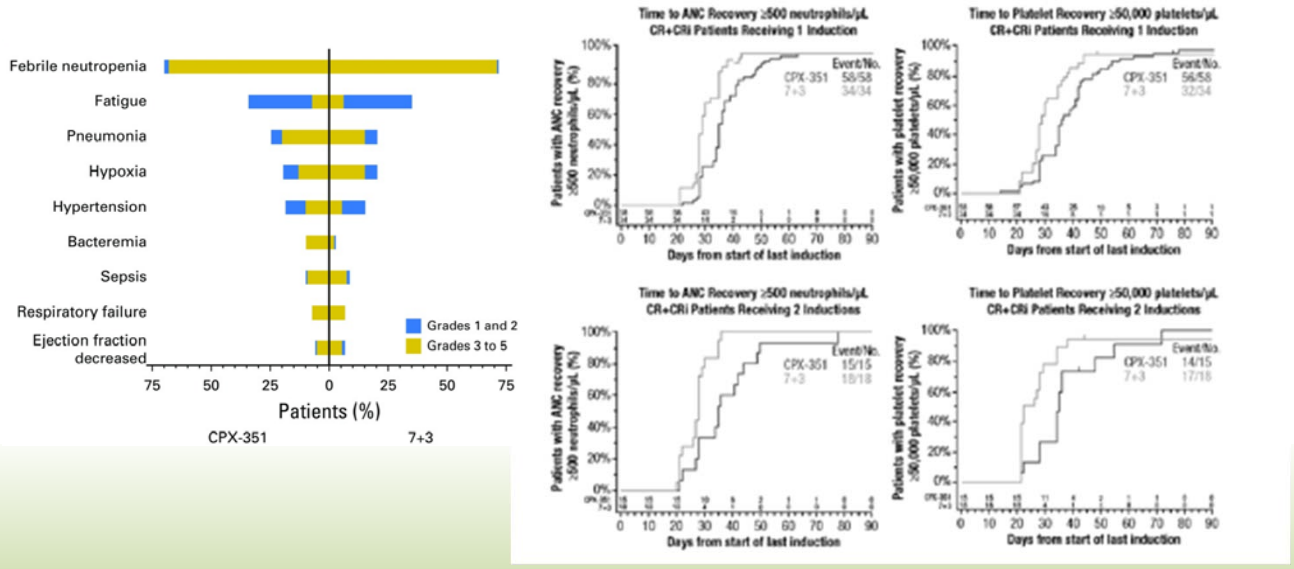
CPX-351 in Older Patients with AML-MRC and t-AML



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

When you look at the subset analysis of patients treated on this trial, you can see here that patients both with therapy related as well as AML-MRC all benefited from the application and use of cytarabine in a liposomal formulation as compared to standard 7 + 3.

CPX-351 vs 7+3: Adverse Events



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

Now what were the adverse events that we are seeing with CPX-351? Well as we know because this is a different formulation of 7 + 3, it is associated with very many of the exact same adverse events as we see with standard 7 + 3. As you can see here, the incidences of febrile neutropenia, pneumonia, fatigue, nausea, vomiting, everything was eerily identical to what we see with 7 + 3, the only difference between patients receiving the liposomal vs the standard 7 + 3 was the number of patients who were dying from leukemia-related complications. That incidence was actually markedly higher in patients receiving standard therapy than those receiving the newer formulation because the newer formulation was more efficacious in controlling their disease. You can see here on the right-hand side that one of the things we did see was given the improved drug delivery to the bone marrow microenvironment, that patients receiving liposomal compound had delayed recovery of blood counts, particularly neutrophils and specifically platelets, the delayed time to platelet recovery was associated with the statistically significant slighter increase in fatal or life-threatening hemorrhage in those individuals.

CPX-351 vs 7+3: Outcomes by Mutation Status

TP53 mutations were associated with a poor prognosis, irrespective of treatment arm.

Median OS was longer for CPX-351 versus 7+3 among patients with two of the most common mutations: DNMT3A and TET2.

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)	

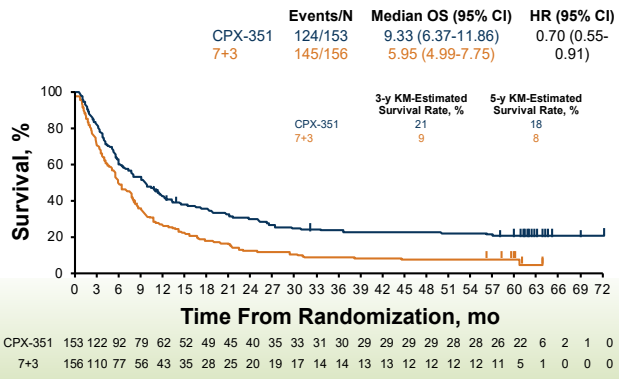
[a]Mutations reported for ≥20% of patients overall.
[b]Median remission duration, OS, and EFS are based on Kaplan-Meier estimates.

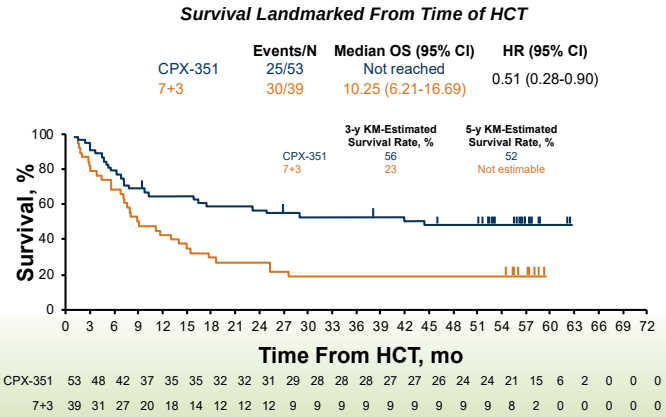
Lindsley RC, et al. *Blood.* 2019:134(Supplement_1):15.

When we look across the board though, we can see that many of these individuals that had specific mutations did specifically benefit from the use of CPX-351. You can see patients with AML associated with mutations and ASXL1, DNMT3A, RUNX1, and TET2 all had a statistically significant improvement in overall survival. However, there was one group of patients, those with TP53 mutant AML in the secondary setting who did not appear to derive the same benefit from CPX-351 as other patients.

Five-year Outcomes of CPX-351 vs 7+3

OS improvement maintained, showing that CPX-351 has the ability to produce or contribute to long-term remission and survival in older patients with newly diagnosed high-risk/secondary AML



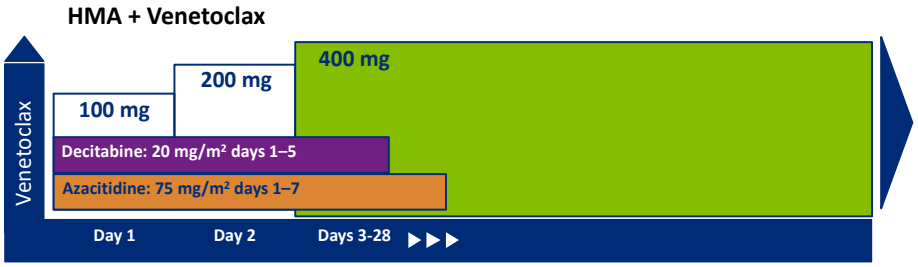


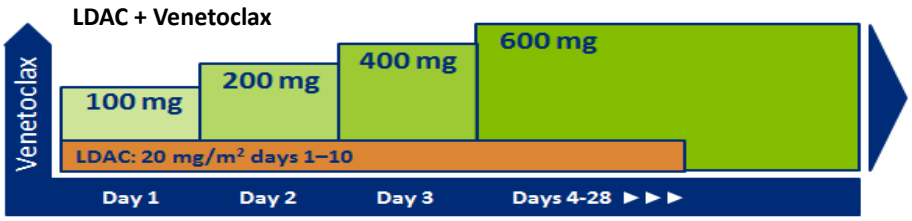
Lancet JE, et al. *J Clin Oncol.* 2020;38(suppl):abstract 7510.

Now recently we have looked at the 5-year long-term outcomes of patients enrolled on this trial and this is a little bit skewed because many of the patients on this trial who were treated were older patients, all aged 60 and above, but you can see here at long-term, 5-year follow-up the survival advantages of patients treated with CPX-351 is maintained, and that there are about 20-30% of individuals who are long-term survivors of secondary AML as a result of using this formulation, which is a new thing because typically we would have said that those patients would not have survived this long. You can see again the benefit of CPX-351 is also maintained or even magnified in the presence of allogeneic stem cell transplantation.

Novel Treatment Options in Secondary AML

Venetoclax + Chemo for Newly Dx Older/Unfit AML





Criteria:
- Newly Dx AML
- Age ≥ 75 yrs

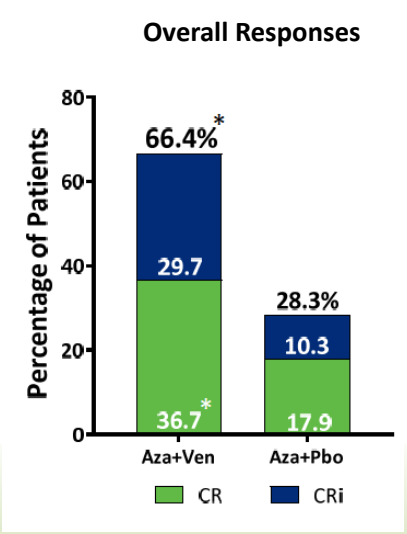
OR
- ECOG 2-3
- Cardiac, lung, liver or renal disease

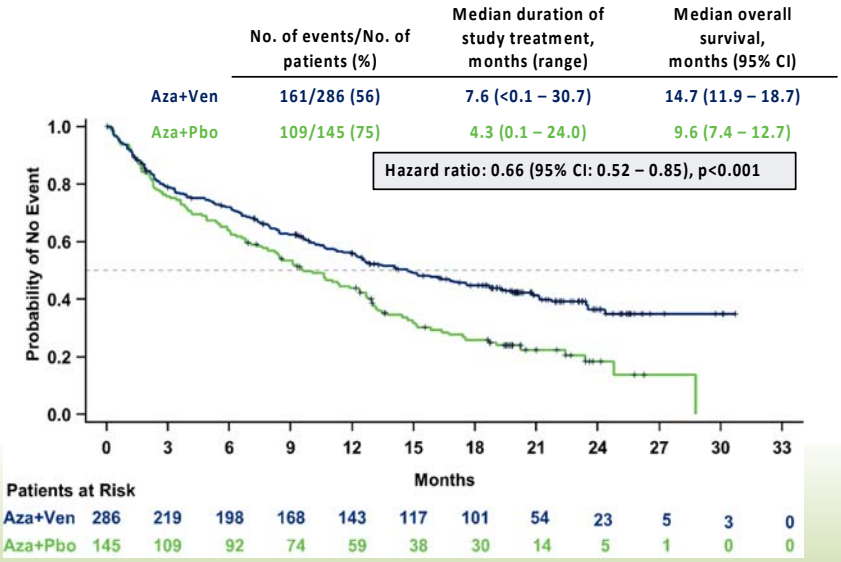
DiNardo CD, et al. *Lancet Oncol.* 2018;19(2):216-228.; Wei AH, et al. *J Clin Oncol.* 2019;37(15):1277-1284.

Now many of our patients particularly those diagnosed with secondary AML, are not necessarily going to be able to receive intensive chemotherapy because of their comorbidities, because of their performance status, and just because of patient decision-making, a lot of these individuals are not going to be particularly amenable to being admitted and receiving intensive myelosuppressive therapy for four, five, or even six weeks with a potentially even longer duration of cytopenias seen with the liposomal formulation. For these individuals, who represent a very large section of our older patient population, the standard of care therapy now has been demonstrated to constitute treatment with venetoclax and a low-dose hypomethylating agent, specifically azacitidine.

Now the combination of venetoclax plus azacitidine or decitabine requires some additional information because it's not as easy as adding 1 plus 2. When one adds the oral BCL-2 inhibitor to epigenetic therapy, we see significantly different adverse events as well as management strategies. For one thing, there is an increased risk of tumor lysis syndrome in patients initiating therapy with this combination. Patients typically are admitted for the first week or so of therapy with close monitoring for tumor lysis. Shown here is the schema that we typically would recommend for dose escalation of the oral BCL-2 inhibitor in combination with hypomethylating agents.

Azacitidine ± Venetoclax in Newly-diagnosed AML





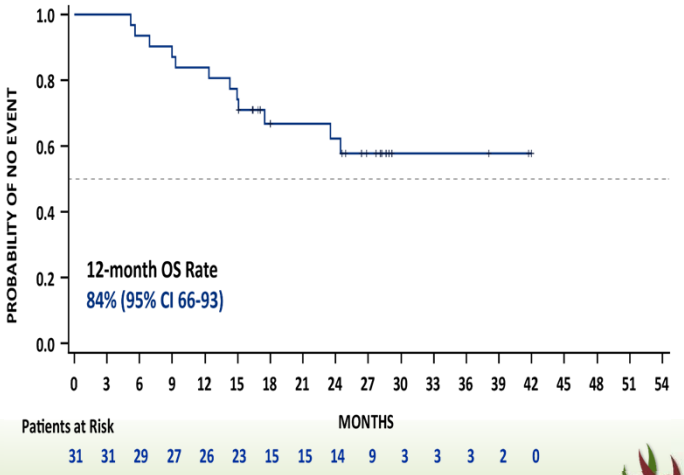
DiNardo CD, et al. *N Engl J Med.* 2020;383:617-629.

This particular dual treatment with the BCL-2 inhibitor of venetoclax and azacitidine has dramatically improved overall response rates for older individuals with newly diagnosed AML. By “older”, the typical definition was 75 years of age or above, or those with significant comorbidities, ie, decreases or compromise in their cardiac pulmonary or renal function, which would render them at high risk to receive an intensive chemotherapy regimen.

Shown here we can see the marked improvement in the overall response rates when we use combination of venetoclax and azacitidine as compared to a cohort of patients randomized to azacitidine alone; a 67% overall response rate represents an almost doubling of overall response with the combination treatment as compared to placebo in azacitidine alone. This combination also led to a statistically significant improvement in overall survival with the median overall survival of 14.7 months as opposed to nine months in the azacitidine treatment alone.

Can Ven-based Therapy Provide a Path to AlloSCT?

- **10%** (31/304) patients received alloSCT
  - 26/31 in CR/CRi
- **68%** (21/31) patients alive 12 months post-transplant
- **55%** (17/31) of all patients undergoing alloSCT had posttransplant remission of ≥12 months
  - **71%** (12/17) of those patients remained in remission for ≥2 years



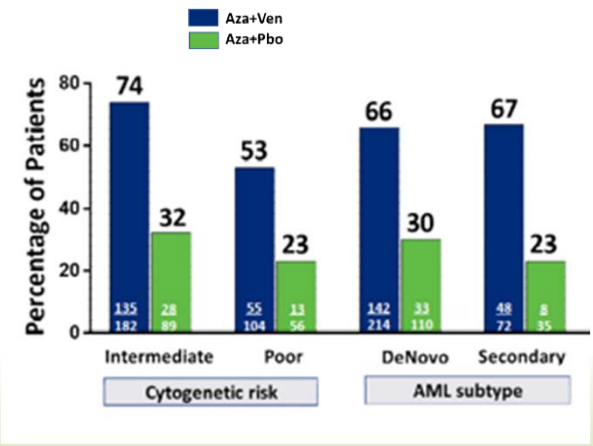
Pratz KW, et al. *Blood.* 2019;134(Supplement_1):264.

We also know that in certain of these individuals, their performance status and their comorbidities can be affected by the presence of AML at the time of diagnosis. There are a proportion of patients who may not be considered fit for intensive chemotherapy, but following chemotherapy with azacitidine and venetoclax can achieve an improved performance status or improvement in their overall functionality that would permit them to receive subsequent allogeneic stem cell transplantation. Early data presented in 2019 has demonstrated that up to 5-10% of individuals can also still proceed to an allogeneic stem cell transplantation following venetoclax + azacitidine therapy.

Novel Treatment Options in Secondary AML

Aza ± Ven: Outcomes of Secondary AML

Response rate (CR + CRi)



Overall survival

	HR (95% CI) Aza/Ven vs Aza/Pbo	Number of Patients
Cytogenetic risk		
Intermediate	0.57 (0.41, 0.79)	182 vs 89
Poor	0.78 (0.54, 1.12)	104 vs 56
Subtype		
De novo AML	0.67 (0.51, 0.90)	214 vs 110
Secondary AML	0.56 (0.35, 0.91)	72 vs 35

Excluded prior MPN
No prior HMA therapy

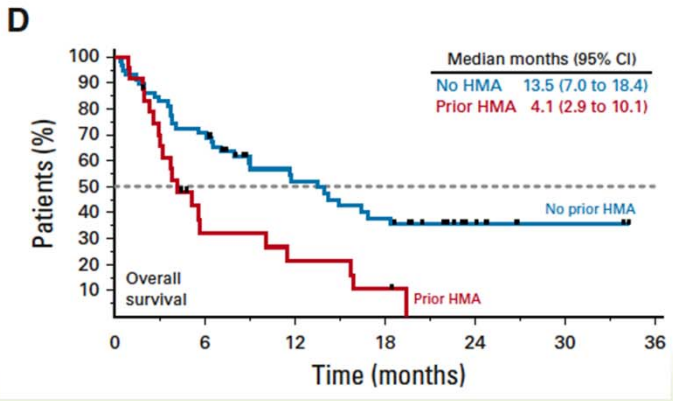
DiNardo CD, et al. EHA 2020. Abstract LBA2601.

Are there differences by mutational subtypes and which patients are going to respond? There are, once again here you can see that when we look at dividing up these secondary. AML patients by cytogenetic risk or by secondary versus de novo disease that there really is a benefit seen across the board, with about two-thirds of patients responding. However, of note in this particular trial patients with prior myeloproliferative disease were excluded.

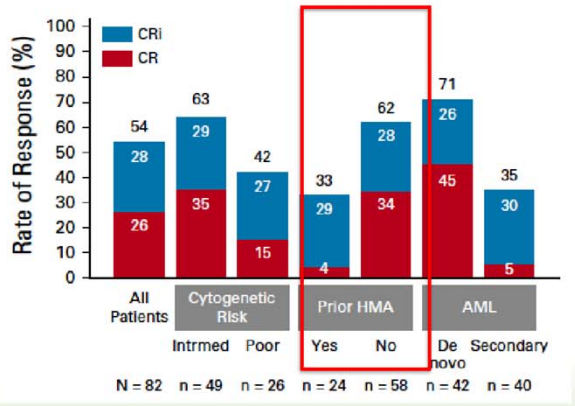
Novel Treatment Options in Secondary AML

LDAC + Venetoclax in Secondary AML

Overall survival



Response rate

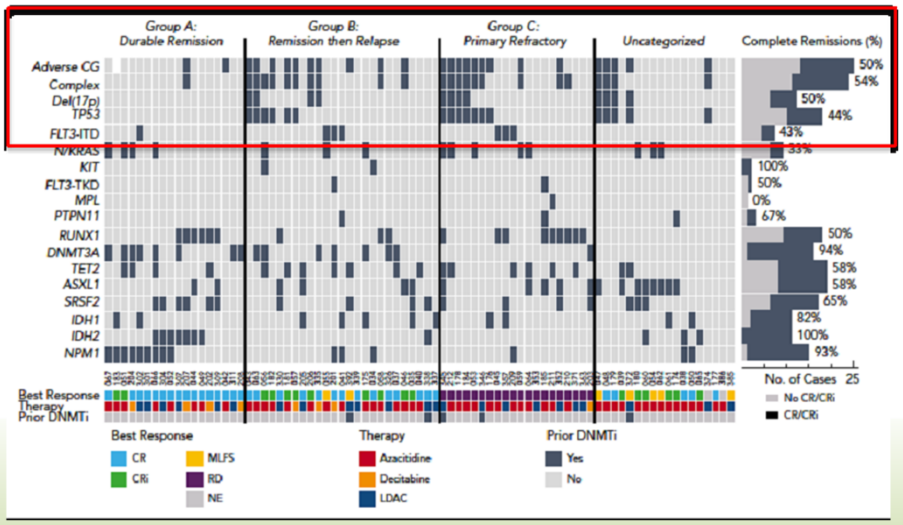


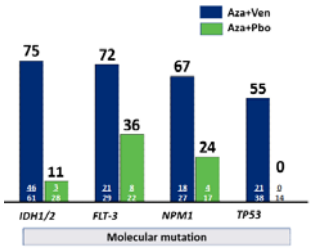
TP53mut: 30% IDHmut: 72%
NPM1mut: 89% FLT3 mut: 44%

Wei AH, et al. *J Clin Oncol.* 2019;37(15):1277-1284.

What about patients who have received prior hypomethylating agents? For those patients treating them again with venetoclax + azacitidine is not typically recommended and there is a second regimen combining venetoclax with low-dose cytarabine, which can be utilized in these individuals who have had significant prior hypomethylating agents with some clinical benefit as well.

Venetoclax + HMA by Karyotype and Mutations





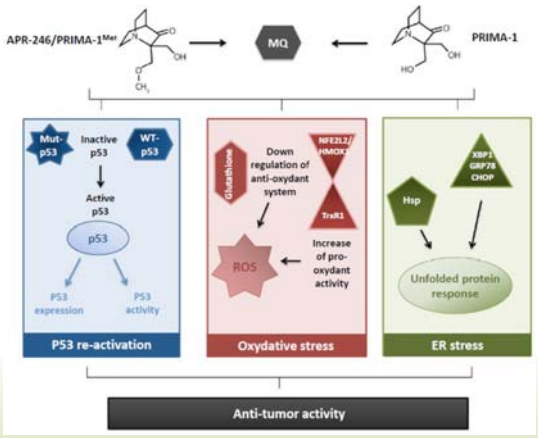
Mutation	HR (95% CI) Aza/Ven vs Aza/Pbo	Number of Pts
FLT3	0.66 (0.35, 1.26)	29 vs 22
IDH1	0.28 (0.12, 0.65)	23 vs 11
IDH2	0.34 (0.16, 0.71)	40 vs
TP53	0.76 (0.40, 1.45)	38 vs 14
NPM1	0.73 (0.36, 1.51)	27 vs 17

DiNardo CD, et al. *Blood.* 2020;135(11):791-803.

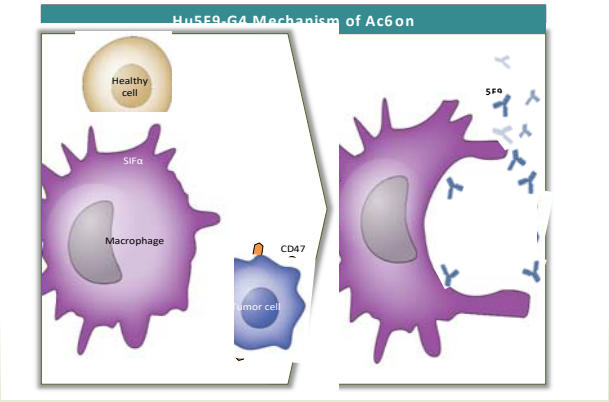
Looking across the board, however, when we examined the responses of patients receiving either of venetoclax/azacitidine or of venetoclax/low-dose cytarabine we see again a distressing low response rate in patients with p53-mutant AML as evidenced by very short disease-free intervals and no significant improvement in overall survival in that subgroup. We also see that patients that have FLT3-mutant disease tend to go into remission, but again, to not have potentially the same overall survival that we see in other subgroups of patients.

Investigational Therapies for *p53*-mutant AML

APR-246 for p53 mutant AML



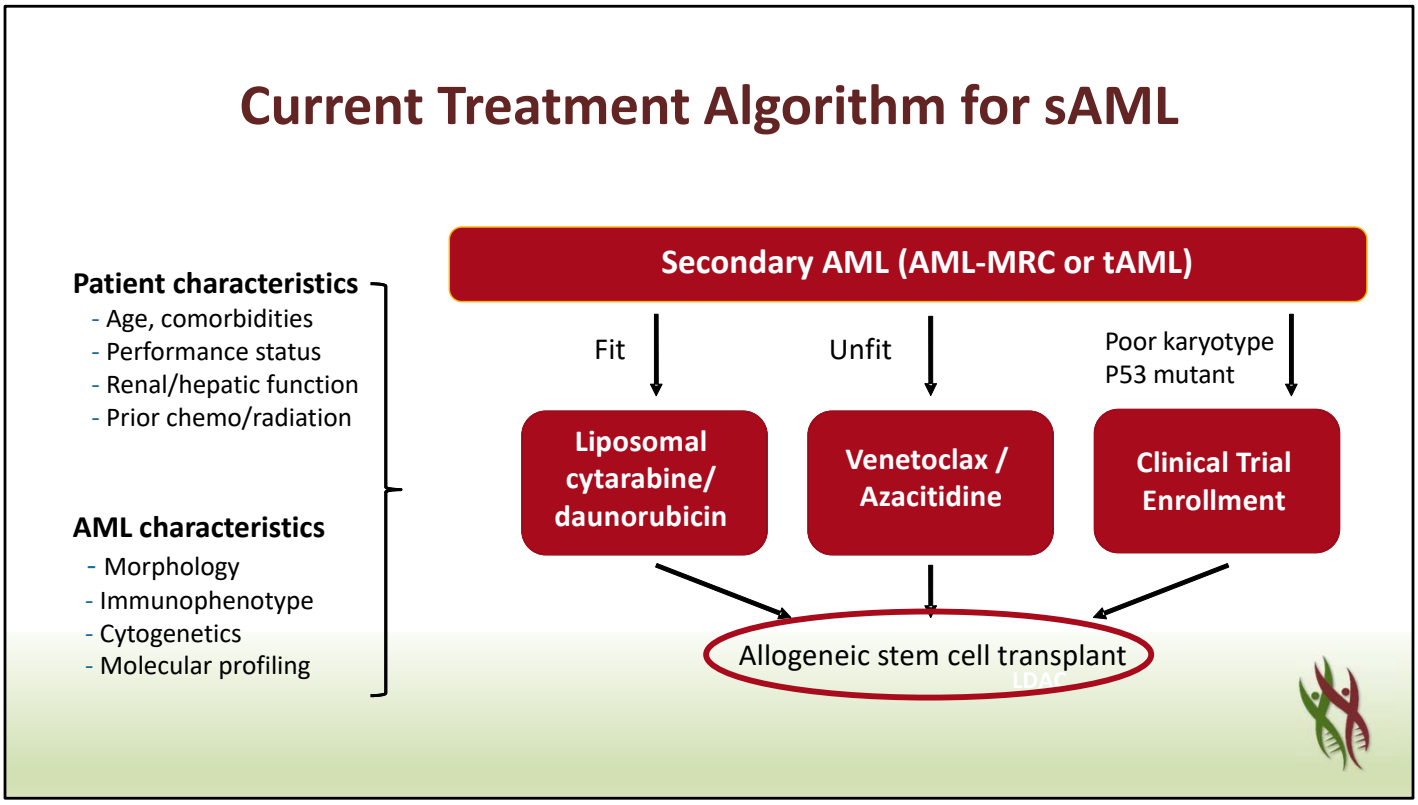
Anti-CD47 antibody (5F9) targets CD47 on tumor cells, inducing macrophage phagocytosis



Sallman DA, et al. *Blood.* 2019;134(suppl 1):Abstract 676.; Daver NG, et al. EHA 2020. Abstract S144.

For these individual patients with secondary AML, it may be of utility to think about investigational therapies, and I'm not going to go into great detail, but just showing you here two novel experimental therapies for p53-mutant AML in particular that may be of consideration for individuals that have secondary AML characterized by this particularly grim prognosis mutation. Shown here on the left is a small molecule inhibitor or re-activator of mutant p53 AML, APR-246. Shown on the right-hand side is the novel magrolimab antibody, an anti-CD47 antibody. Both of these agents in combination with azacitidine have resulted in response rates in p53-mutant patients ranging in the 60-70% range, and both are under active investigation for targeted therapy of this particular poor group of patients.

Novel Treatment Options in Secondary AML



In summary, how do we diagnose patients? How do we prognosticate patients? How do we select therapy for patients? Many of these topics we've already reviewed, and this is just a summary treatment algorithm for my recommendations for how to manage patients with secondary AML. Of course, there needs to be an initial assessment of both the patient characteristics and the AML disease characteristics and that should include fitness, age, performance status, cytogenetics, molecular features, as well as additional immunophenotyping and other analyses. We see here that fit individuals who have secondary AML who are potentially eligible for allogeneic transplantation in particular should be offered therapy with liposomal cytarabine/daunorubicin. In contrast, unfit individuals should be offered up front therapy with the venetoclax/ azacitidine, and those who have particularly poor karyotype for p53-mutant disease should be considered for upfront clinical trial enrollment. The goal for many of our patients is going to be allogeneic stem cell transplantation, for those that are unable to proceed then we would continue onward with the variation of their upfront therapy.

Thank you very much for taking the time to view this activity. I hope you found it useful and applicable for your management of patients with secondary AML.