ManagingAML

New Cytotoxic Agents in Secondary and Treatment-related AML:
Practical Strategies for Optimizing Outcomes

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Welcome to *Managing AML*. I am Dr. Harry Erba. Today I will review new cytotoxic agents in secondary and treatment-related AML.

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CHAPTER 1
Secondary and Therapy Related AML

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Speaker Disclosure

- **Consultant:** Agios, Celgene, Daiichi Sankyo, Glycomometics, Immunogen, Incyte, Jazz, MacroGenics, Novartis, Ono, Pfizer, Seattle Genetics
- **Speakers' bureau:** Agios, Celgene, Incyte, Jazz, Novartis
- **Research:** Agios, Amgen, Astellas, Daiichi Sankyo, Immunogen, Janssen, Juno, Pfizer, Seattle Genetics, Takeda Oncology
- **Other:** Glycomometics, Celgene

The slide summarizes my disclosures.

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Learning Objectives

- Identify the prevalence, characteristics, and clinical impact of secondary AML (sAML) and treatment-related AML (tAML)
- Outline current treatment options for sAML and tAML
- Describe the standard of care for incorporating therapeutic strategies into the treatment of patients with sAML and tAML

The learning objectives of today's program include how to identify the prevalence, characteristics, and clinical impact of secondary AML and treatment-related AML; outline the current treatment options for secondary and treatment-related AML; and describe the standard of care for incorporating therapeutic strategies into the treatment of patients with secondary AML and treatment-related AML.

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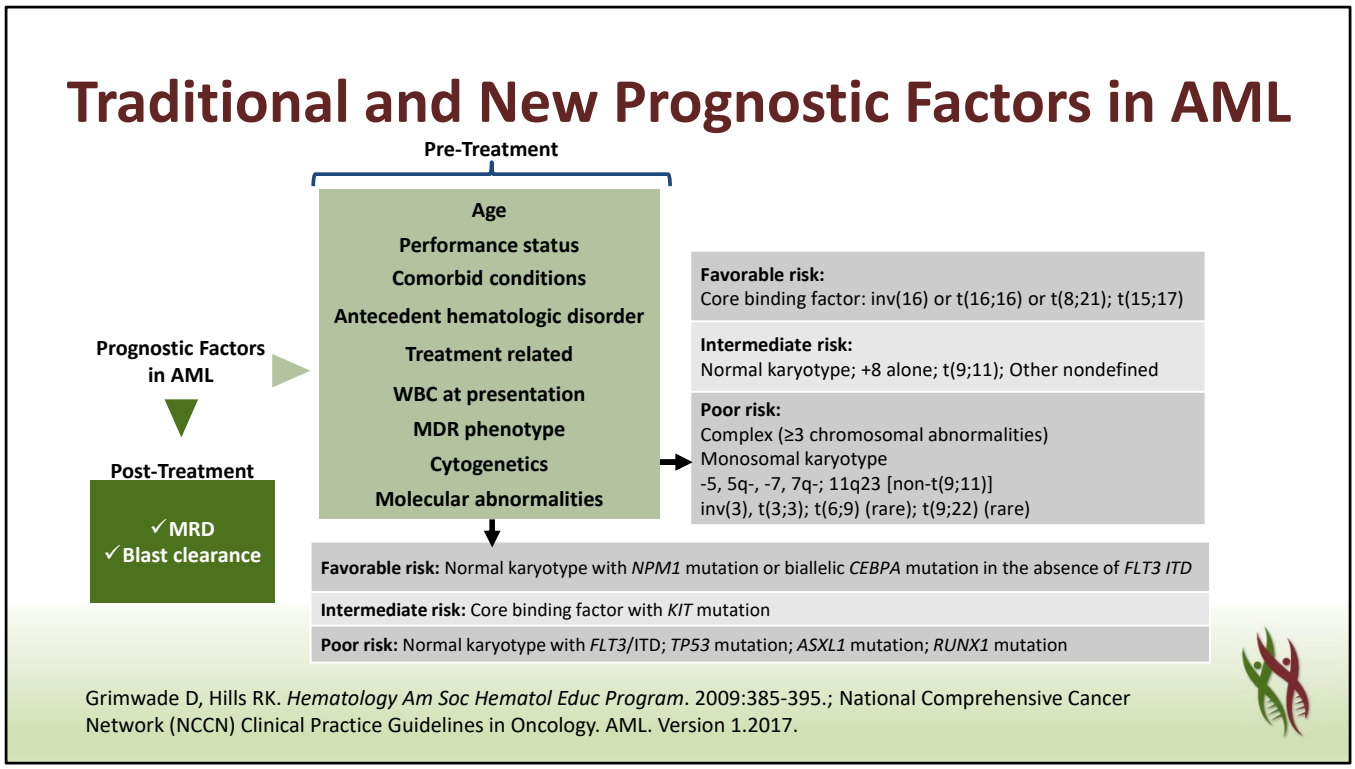

We have been able to identify a number of prognostic factors in our patients with acute myeloid leukemia. Some of these are related to the biology of the patient and their ability to tolerate intensive therapy such as age, performance status, and comorbid conditions. However, many others are related to the sensitivity of the acute myeloid leukemia to currently available therapies. We are aware that cytogenetic and molecular abnormalities are quite important in determining prognosis but today, we are going to focus on antecedent hematologic disorders leading to AML, so-called secondary AML, and AML following prior cytotoxic chemotherapy or radiation therapy, so-called treatment-related AML. An interesting area of clinical investigation at this time is the use of sensitive techniques for measurable residual disease following initial therapy and how that might help in prognostication and therapeutic selection, but is not the topic of today's discussion.

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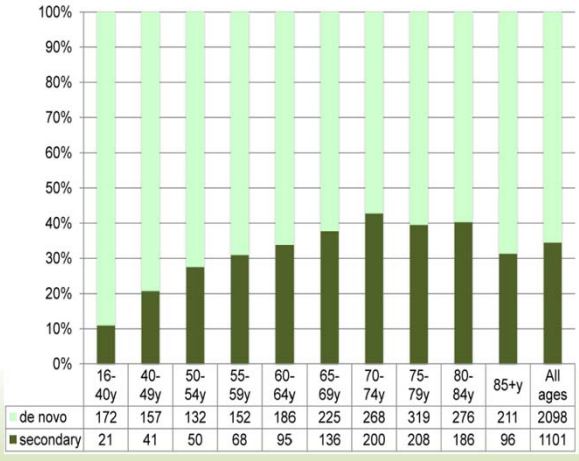
Incidence of Secondary AML Increases With Age



	16-40y	40-49y	50-54y	55-59y	60-64y	65-69y	70-74y	75-79y	80-84y	85+y	All ages
de novo	172	157	132	152	186	225	268	319	276	211	2098
secondary	21	41	50	68	95	136	200	208	186	96	1101

Juliusson G, et al. *Blood*. 2012;119:3890-3899.

We know that the incidence of acute myeloid leukemia secondary to prior therapy and prior antecedent hematologic disorders increases with age, as can be seen in this data from a Swedish Registry Study.

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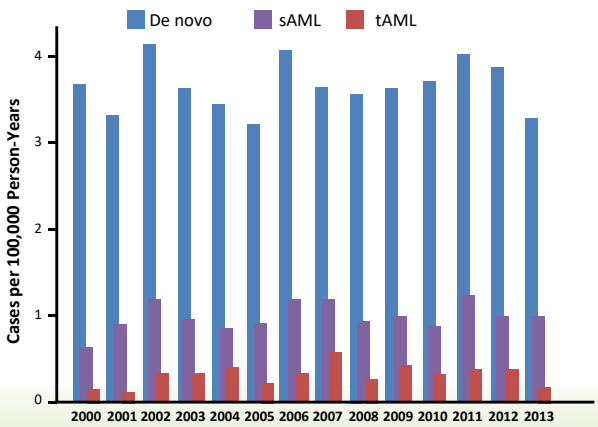
Secondary AML (sAML) and Treatment-related AML (tAML) Danish Registry



- 3,055 AML patients
- 19.8% secondary AML
- 6.6% therapy-related AML

- 1567 received intensive therapy
- 38.0% of sAML, prior MDS
- 33.6% of sAML, prior non-MDS
- 50.3% of tAML
- 55.5% of de novo AML

Granfeldt Østgård LS, et al. *J Clin Oncol*. 2015;33:3641-3649.

Recently, a Danish Registry has been published and has been quite informative on the outcomes of patients with secondary AML or treatment-related AML. In this registry, there were over 3,000 AML patients. Nearly 20% had secondary AML and 6.6% had therapy-related AML. Of this number, approximately half, or 1,567, received intensive chemotherapy. Patients with de novo AML or treatment-related AML were more likely to receive intensive chemotherapy than those patients with secondary AML following a prior myelodysplastic syndrome or non-myelodysplastic syndrome such as a myeloproliferative neoplasm.

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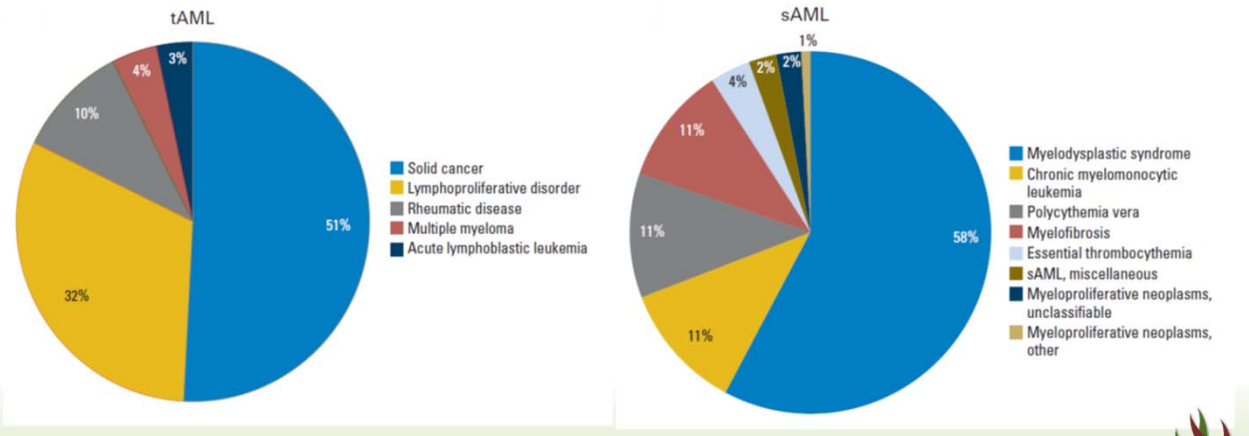
Distribution of Previous Disease States by Diagnosis of tAML and sAML



Granfeldt Østgård LS, et al. *J Clin Oncol*. 2015;33:3641-3649.

In this slide, you can see the distribution of the previous disease states by the diagnosis of either therapy-related AML or secondary AML. In terms of therapy-related AML, slightly over half of the patients had a prior solid tumor malignancy treated with chemotherapy and/or radiation therapy. However, approximately a third also had lymphoproliferative disorders, and the remaining patients had other cancer such as multiple myeloma and acute lymphoblastic leukemia, and even 10% of patients had rheumatic diseases for which they received alkylating agents such as cyclophosphamide. In terms of secondary AML, the majority of patients had a prior history of a myelodysplastic syndrome.

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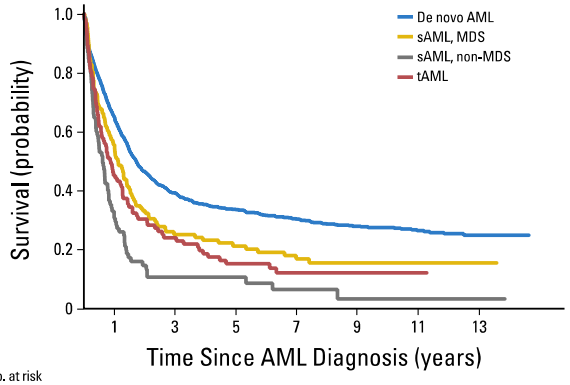
Poor Outcomes of Treatment-related and Secondary AML with Intensive Chemotherapy:

Danish Registry Study

- The crude 90-day and 1-year survival for patients receiving intensive therapy was superior to no therapy
- In intensive therapy patients with de novo AML, the 90-day mortality was 15% compared with 17% in MDS-sAML, 24% in non-MDS-sAML, and 21% in tAML
- At 3 years, patients with MDS-sAML, non-MDS-sAML, and tAML had lower survival than patients with de novo AML, with the highest risk of death (89%) found in patients with non-MDS-sAML after 3 years



No. at risk					
De novo	799	413	293	207	140
sAML, MDS	71	27	20	14	12
sAML, non-MDS	26	7	6	3	1
tAML	46	22	12	8	4

Granfeldt Østgård LS, et al. *J Clin Oncol*. 2015;33:3641-3649.

Patients who received intensive chemotherapy for the diagnosis of acute myeloid leukemia had a superior survival at both 90 days and one year compared to patients who received no therapy. In the intensively treated patients, those with de novo AML had a 90-day mortality of 15% compared to slightly higher in patients with secondary and treatment-related AML. At three years, patients with AML secondary to MDS or secondary to a non-MDS condition or treatment-related AML had lower survival compared to those patients with de novo AML, and the highest risk of death at three years was in patients with non-MDS secondary AML.

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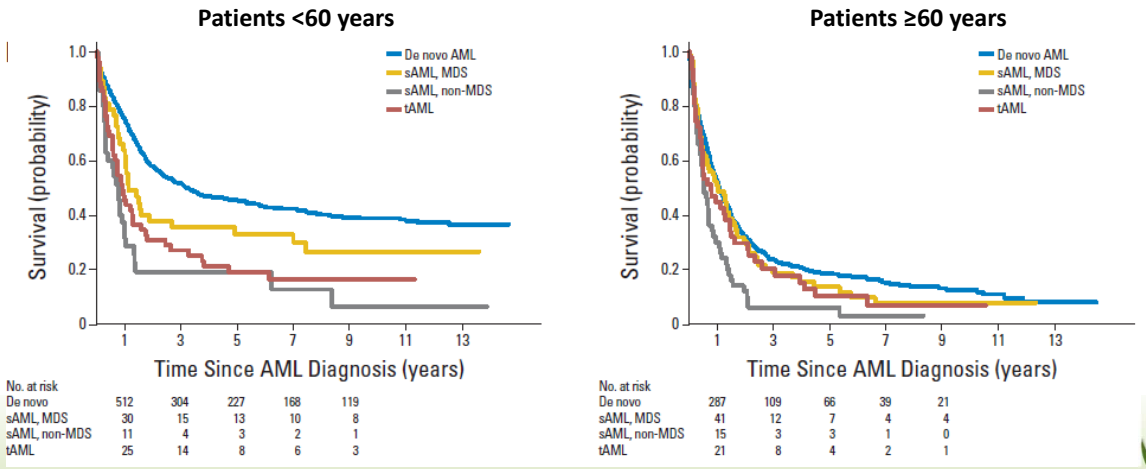
Survival in De Novo AML, sAML, and tAML Following Intensive Chemotherapy by Age:

Danish Registry



Granfeldt Østgård LS, et al. *J Clin Oncol*. 2015;33:3641-3649.

The impact of the diagnosis of secondary AML and treatment-related AML was more profound in younger patients than in patients over the age of 60 where the prognosis of patients with AML in general, is quite poor.

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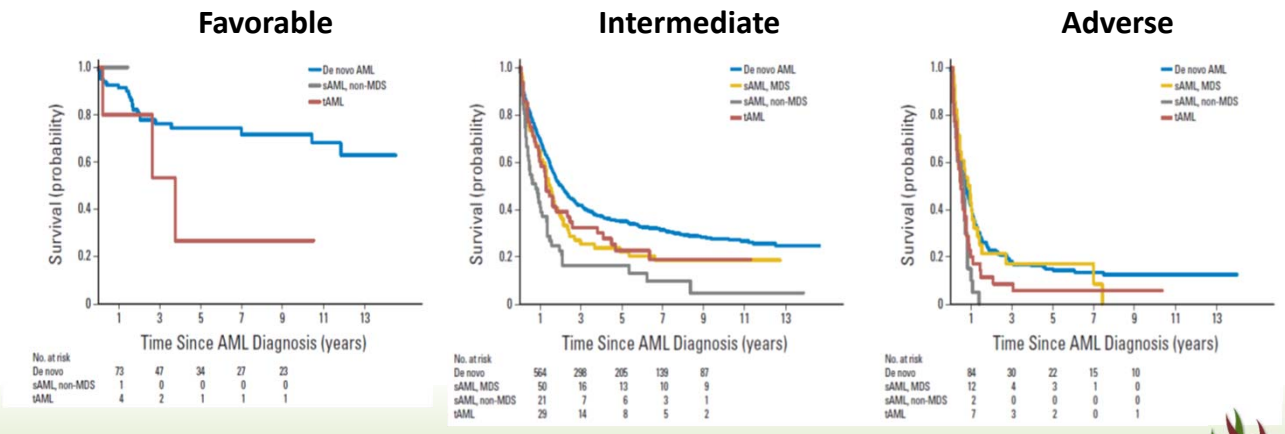
Survival of sAML and tAML Following Intensive Therapy: Effect of Cytogenetic Risk Group



Granfeldt Østgård LS, et al. *J Clin Oncol*. 2015;33:3641-3649.

Likewise, the effect of cytogenetic risk group was more apparent in these patients with secondary AML and treatment-related AML if they had a favorable or intermediate risk karyotype compared to those patients with AML whether de novo, secondary, or treatment-related, with adverse risk karyotypes.

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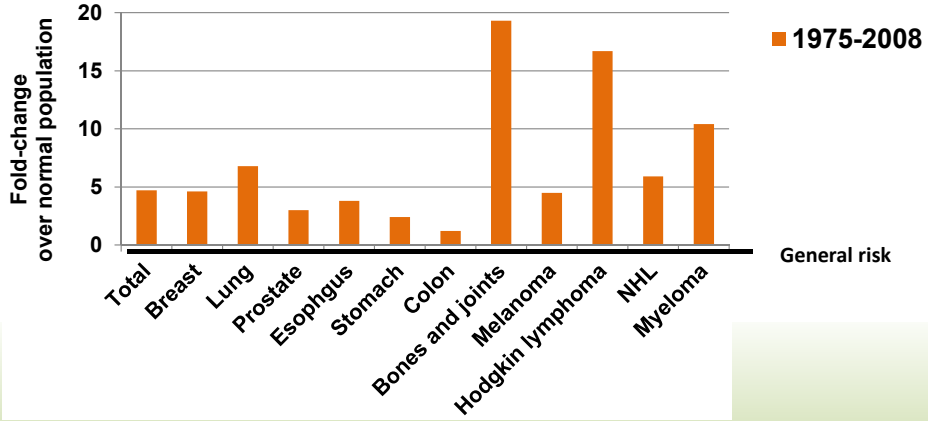
Risk of tAML in Adults Varies Likely Due to Different Treatment Regimens and Survival from Primary Neoplasm

- Risk for AML 4.7-fold increased after chemo/radiotherapy
- 7% of newly diagnosed adult AML patients have tAML



SEER data.; Morton LM, et al. *Blood.* 2013;121(15):2996-3004.

The risk of therapy-related AML in adults varies likely due to the different treatment regimens for the different malignancies and the survival following the primary neoplasm more condition for which the patient received chemotherapy or radiation therapy, but in general, the risk of AML was nearly five-fold higher or increased after chemotherapy or radiation therapy. Approximately 7% of newly adult AML patients in this registry between 1975 and 2008 had therapy-related AML. You can see the highest relative increase in the risk of therapy-related AML was seen in patients with bone and joint malignancies, non-Hodgkin lymphoma, and myeloma.

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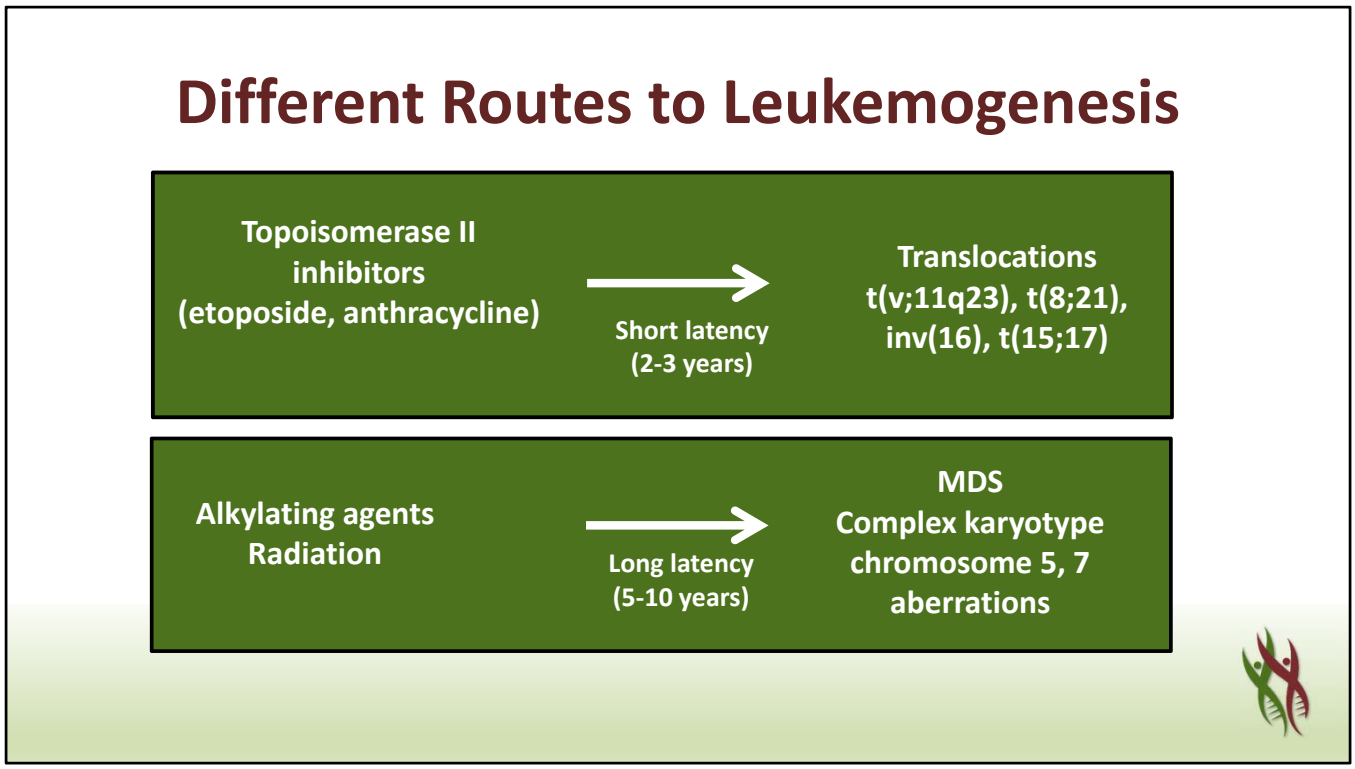

There are different routes to ,leukemogenesis depending on the agent targeting the marrow. Patients who have received topoisomerase II inhibitors, such as anthracyclines or etoposide, typically present with a shorter latency without a prior history of myelodysplastic syndrome and frequently have translocations involving the MLL gene on chromosome 11q23 or actually have fusion genes that have been associated with a relatively good prognosis in de novo AML, such as the core binding factor translocations 8;21 and inversion 16 and even therapy-related APL has been defined. Patients with an 11q23 abnormality often have monoblastic morphology.

On the other hand, alkylating agents and radiation that involves a large amount of hematopoietic marrow typically leads to AML with a longer latency and a smoldering history suggestive of myelodysplastic syndrome. Cytogenetic abnormalities in these patients typically include complex karyotypic changes, both structural and numeric, as well as aberrations of chromosomes 5 and 7.

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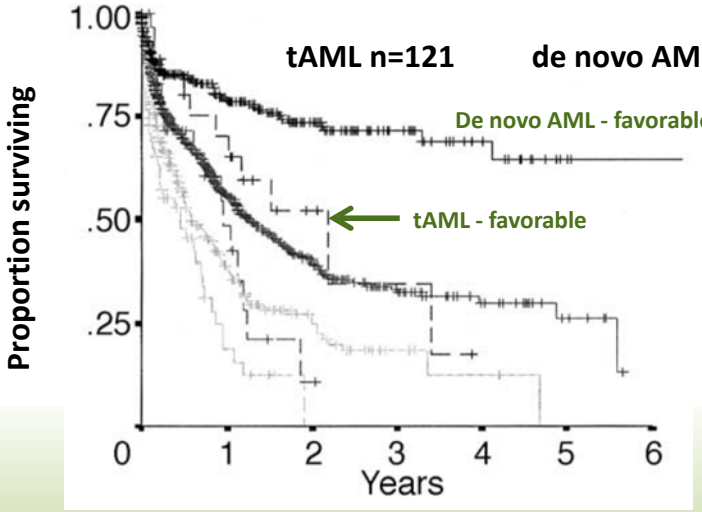
Survival Following Favorable Risk tAML is Worse than Favorable Risk De Novo AML



Kern W, et al. *J Clin Oncol.* 2004;22(12):2510-2501.

The survival of patients with treatment-related AML, specifically with favorable risk karyotype, is worse than those patients with a favorable risk karyotype and de novo AML, as can be seen in this analysis published by Kern and colleagues.

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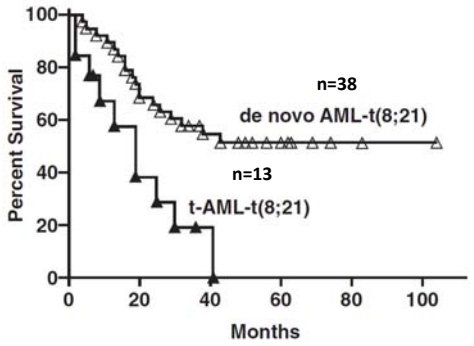
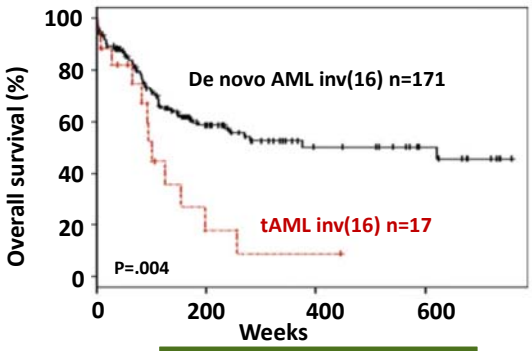
tAML with CBF Translocation

t(8;21)



	Relapse rate
De novo AML	39%
tAML	70%

inv(16)



	Relapse rate
De novo AML	36%
tAML	33%

Gustafson SA, et al. *Am J Clin Pathol.* 2009;131(5):647-655.; Borthakur G, et al. *Cancer* 2009;115(14):3217-3221.

Likewise, in two studies, retrospective analyses of data from MD Anderson Cancer Center, you can see that the overall survival of patients with therapy-related AML with either the core binding factor translocation 8;21 or inversion 16 is worse than patients with de novo AML and those same core binding factor translocations. However, in regard to the relapse rate, for patients with inversion 16, there was really no significant difference in the risk of relapse and yet, the overall survival of these patients was worse. This suggests that patients with therapy-related AML may have competing causes of mortality such as the primary malignancy for which they were treated. Furthermore, they may be less able to tolerate intensive therapeutic options that patients with de novo AML can tolerate.

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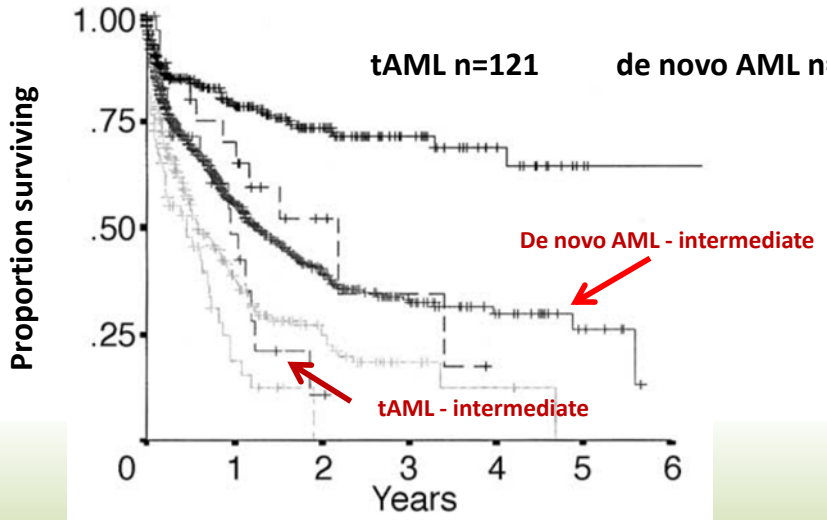
Survival Following Intermediate Risk tAML is Worse than Intermediate Risk De Novo AML



Kern W, et al. *J Clin Oncol.* 2004;22(12):2510-2501.

Likewise, survival following therapy-related AML for those patients with an intermediate risk karyotype is worse than patients with intermediate risk karyotype that have de novo AML.

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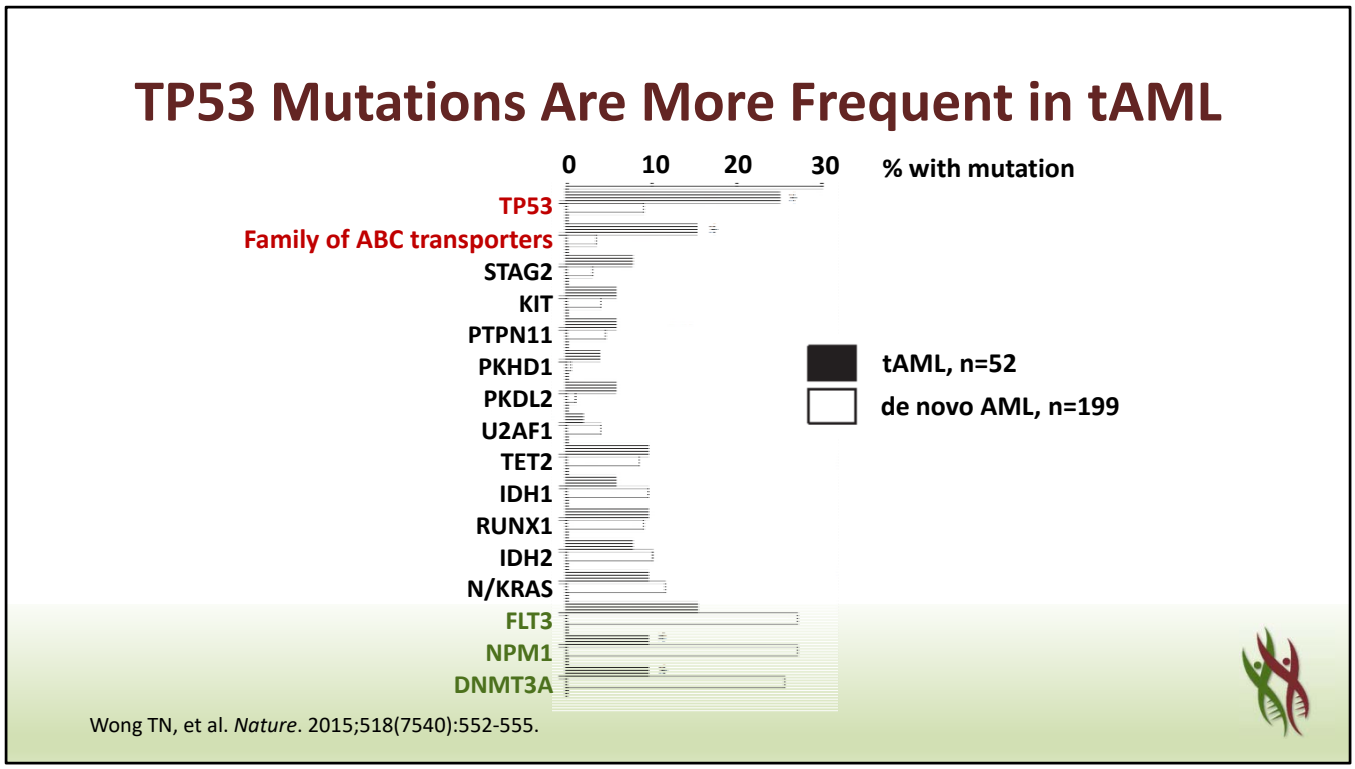

In terms of the mutational profile of patients with therapy-related AML, these patients are more likely to have p53 mutations as well as mutations in the ABC transporter genes compared to patients who have de novo AML.

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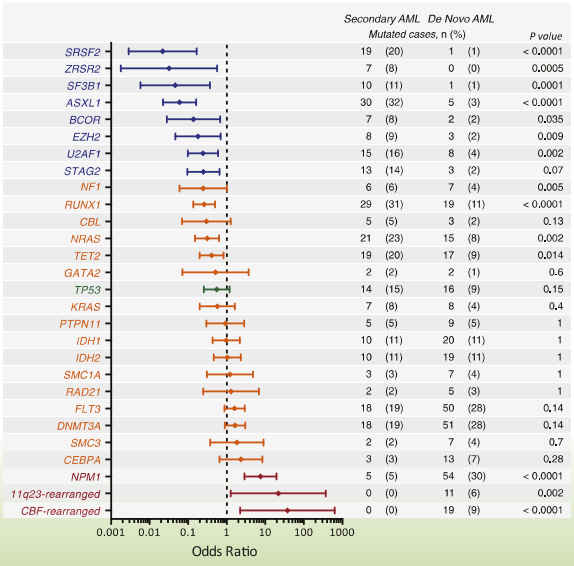
Myeloid Driver Mutations in Secondary vs De Novo AML

- Chromatin modifier and spliceosome mutations are more commonly identified in clinically defined secondary AML



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

I would like to now focus on a very interesting analysis from patients who were treated on a prior phase 3 study for secondary and therapy-related AML. In this clinical trial, patients were randomized between an investigational drug amnofide with cytarabine versus daunorubicin with cytarabine. There was no difference in response rates or overall survival. However, samples were collected from these patients who had clinically defined treatment-related and secondary AML. When a mutational analysis was performed on these patients and compared to patients who clinically were felt to have de novo AML, patients with secondary and treatment-related AML were more likely to have mutations in chromatin-modifier genes such as ASXL1 and EZH2 as well as spliceosome mutations.

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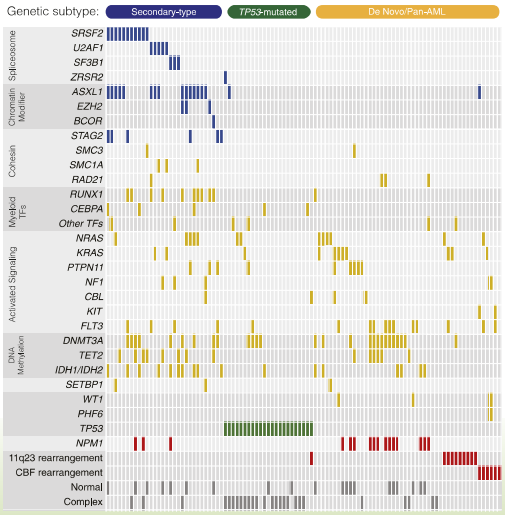
Classification of Apparently De Novo AML Based on Mutations Identified in Secondary AML



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

The investigators in this study then classified patients who apparently had de novo AML who were not treated in this clinical trial based on mutational profile identified in secondary AML. These patients were felt to have either a de novo or pan AML type genotype or secondary AML genotype or p53 mutated genotype.

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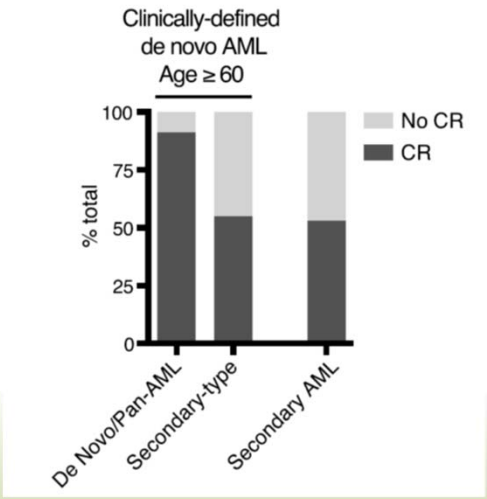
CR Rates Among Patients >60 Years with Clinically-defined De Novo AML vs sAML with Intensive Chemotherapy: Effect of Genotype



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

Among patients over the age of 60 with clinically-defined de novo AML versus secondary AML, the CR rates were lower if the patient had a de novo AML yet with a secondary type AML mutational profile, and again similar to what was seen in the clinical trial of patients with clinically defined secondary AML.

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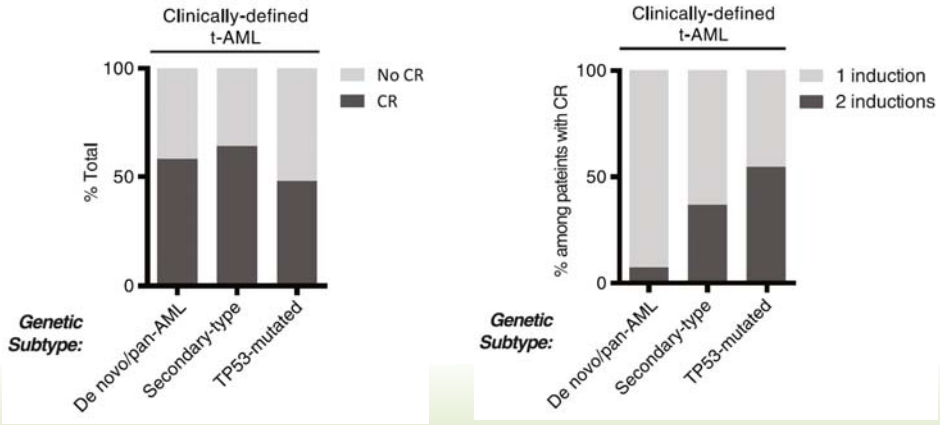
Relative Chemoresistance in Secondary-type and TP53 Mutated tAML



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

Likewise, there appears to be relative chemotherapy resistance in patients with secondary type AML and those with p53 mutated AML. Patients with those two types of AML were more likely to require two cycles of induction chemotherapy to achieve a complete remission.

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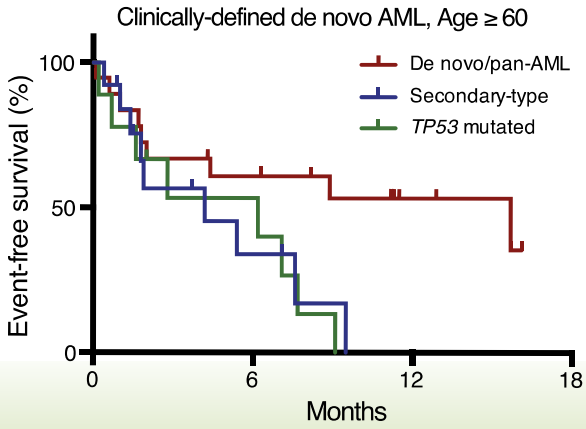
Event-free Survival in De Novo AML by Genotype



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

Ultimately, the event-free survival of patients who clinically appear to have de novo AML was worse if by genotype that secondary type AML mutations, the chromatin-modifiers, the spliceosome mutations, or p53 mutation, compared to those patients with clinically defined de novo AML who had the de novo or a pan AML mutational profile.

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AML with Myelodysplasia-related Changes (MRC)

- AML with myelodysplasia-related changes (AML-MRC) includes those forms of AML that occur in patients with >20% marrow and/or blood leukemic blasts with any of the following criteria:
  - A previous history of a myelodysplastic syndrome (MDS) or a myelodysplastic/myeloproliferative neoplasm (MDS/MPN)
  - An MDS-related cytogenetic abnormality
  - Multilineage dysplasia in greater than 50% of at least two cell lineages in the absence of NPM1 or biallelic CEBPA mutations

Arber DA, et al. *Blood*. 2016;127:2391-2405.

Turning now to acute myeloid leukemia with myelodysplasia-related changes, the WHO classifies this type of AML as those patients who have 20% or more bone marrow blasts or circulating blasts with any of the following criteria: a prior history of myelodysplastic syndrome or an MDS/MPN such as atypical CML or chronic myelomonocytic leukemia. An MDS-related cytogenetic abnormality of which there are many but the ones that are most common are those with complex cytogenetic changes, both numeric and structural changes in chromosomes, and those patients with chromosomes 5 and 7 abnormalities, and specifically 17p deletions. Finally, patients with multilineage dysplasia and greater than 50% of at least two cell lineages but in the absence of more favorable risk genotypes of nucleophosmin mutation or biallelic C/EBP alpha mutations. I would like to look at in a little bit more depth, the inclusion of multilineage dysplasia as an independent prognostic feature.

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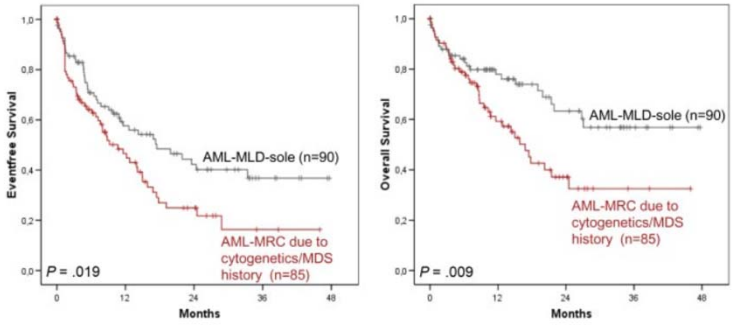
Survival Rates Following Intensive Chemotherapy Based on the Presence of MLD as Sole Criteria for AML-MRC

Table 1. Patients with AML-MRC: breakdown by WHO qualification criteria

Parameter	No of cases (%)
MLD sole	90 (51.4)
MDS related cytogenetics (MRC) sole	25 (14.3)
History of MDS or MDS/MPN-sole	11 (6.3)
MLD + preexisting MDS	22 (12.6)
MLD + MDS-related cytogenetics	22 (12.6)
MLD + MDS-related cytogenetics + preexisting MDS/MPN	2 (1.1)
MDS related cytogenetics + preexisting MDS/MPN	3 (1.7)
Total	175 (100.0)



Miesner M, et al. *Blood*. 2010;116:2742-2751.

An analysis was done of patients in Germany receiving intensive chemotherapy as classified by the WHO system with AML with myelodysplasia-related changes. As you can see, about 50% of patients in this cohort had AML with myelodysplasia-related changes defined solely based on the presence of multilineage dysplasia. When the event-free and overall survival of those patients was compared to patients with myelodysplasia-related changes as defined by a prior history of a hematologic disorder such as MDS or MDS-related cytogenetic changes, the outcome was actually superior.

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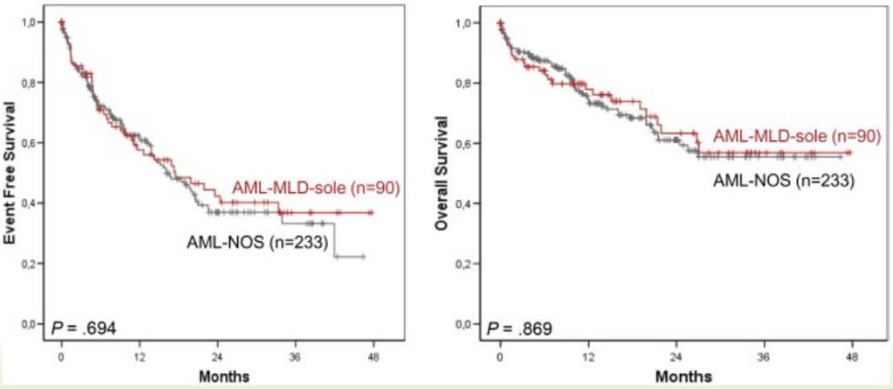
Survival Rates Following Intensive Chemotherapy Based on the Presence of MLD as Sole Criteria for AML-MRC



Miesner M, et al. *Blood*. 2010;116:2742-2751.

In fact, the outcome of patients with AML with multilineage dysplasia alone as their qualifying characteristic for myelodysplasia-related changes was no different than patients with AML not otherwise specified. Part of this effect does appear to be due to the fact that patients with nucleophosmin mutation and biallelic C/EBP alpha mutation, regardless of dysplasia, have a more favorable outcome, and that is why the WHO has now included the caveat that multilineage dysplasia cannot be diagnosed in the presence of those two mutations.

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Secondary and Therapy Related AML

- Outcomes following standard intensive cytotoxic chemotherapy are poor
  - Due to disease biology but also patient features (older, prior exposure to chemo)
- Intensification of induction and post remission chemotherapy regimens have not improved outcomes in sAML and tAML
- Novel therapeutic approaches should be strongly considered for these patients

I would like to summarize what we have gone through so far. The outcomes following standard intensive cytotoxic chemotherapy in patients with secondary and therapy-related AML is quite poor. Now part of this is due to the disease biology with a differing cytogenetic profile and, as I have shown you, a mutational profile that has higher incidence of p53 mutations but also chromatin-modifier and spliceosome mutations. However, we need to remember that both therapy-related AML and secondary AML are more common with advancing age, and older patients, especially those with prior exposure to chemotherapy, may not tolerate intensive chemotherapy as well. We have also learned over the years that intensification of the standard 7+3 induction regimen with higher doses of cytarabine and/or higher doses of daunorubicin and even intensification of post remission therapy with high dose ara-C has not led to improvements in the outcomes of patients with secondary AML and therapy-related AML. So in these subtypes of patients, we still attempt to get these patients into a remission and proceed with allogeneic hematopoietic stem cell transplantation that has likely the highest chance of prolonged disease-free survival. I believe based on this retrospective data, it is clear that novel therapeutic approaches should be strongly considered for these patients.

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Chapter 2
Combinations of Cytotoxic Agents

Combinations of cytotoxic agents

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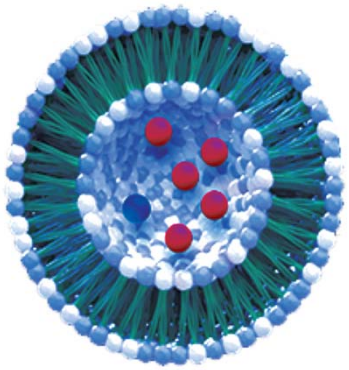
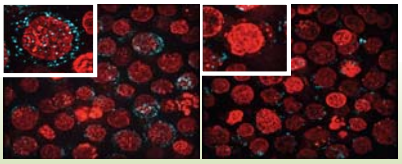
Liposomal Daunorubicin and Cytarabine (CPX-351)

- Combinations of cytotoxic agents can be either synergistic, additive or even antagonistic depending on the molar ratio of the two agents
- 1:5 molar ratio of daunorubicin to cytarabine is synergistic in preclinical AML studies
- CPX-351 is a 1:5 molar ratio of daunorubicin and cytarabine in 100-nm bilamellar liposomes
- Targets bone marrow and preferentially targets leukemic compared with normal marrow progenitors





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

With that, I would like to turn to liposomal daunorubicin-cytarabine. It has been known for decades, based on in vitro studies, that combinations of cytotoxic agents can be either synergistic, additive or even antagonistic depending on the molar ratio of two agents that are used to treat neoplastic cell lines in vitro. This has been shown in pre-clinical AML studies where a 1:5 molar ratio of daunorubicin to cytarabine has been shown to be synergistic. Now, in order to test the hypothesis that this 1:5 molar ratio is critical for improving outcomes, patients would need to be treated with those drugs in that ratio. Now of course, when we give standard daunorubicin-cytarabine, it is a three-day bolus injection of daunorubicin on top of the seven-day continuous infusion of cytarabine, but regardless of the regimen, the molar ratio would not be maintained. To test the hypothesis that the molar ratio is important biologically and in vivo, these drugs, daunorubicin and cytarabine, would need to be encapsulated in a liposome in that 1:5 molar ratio. CPX-351 or liposomal daunorubicin-cytarabine is such a 1:5 molar ratio of daunorubicin to cytarabine in 100 nm bilamellar liposomes. In order for the daunorubicin to be incorporated into the liposome, copper is used in this process, making the agent a brilliant purple color. What has been found in preclinical studies is that by encapsulating daunorubicin-cytarabine in this 1:5 molar ratio and specifically into these liposomes, that the agent targets the marrow and preferentially targets leukemic compared to normal marrow progenitors.

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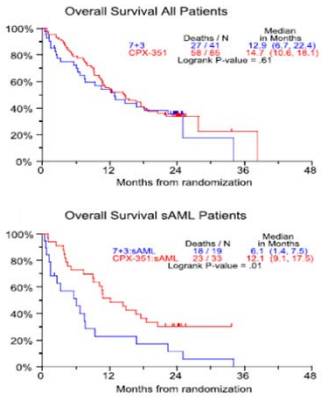
CPX-351 vs 7+3 in a Randomized Phase 2 Study in Previously Untreated AML Patients Aged ≥60 Years

Outcome	Secondary AML (n = 52)	
	CPX-351 (n = 33)	7+3 (n = 19)
Response rate, %	57.5	31.6
60-day mortality, %	6.1	31.6
EFS (median), months[a]	4.5	1.3
OS (median), months[b]	12.1	6.1

[a]*P* = 0.08 [b]*P* = 0.01



- In patients with newly diagnosed secondary AML, CPX-351 improved 60-day mortality, remission rate, and OS (HR = 0.46; *P* = 0.01)

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

This led to a number of phase 1 studies and ultimately, a randomized phase 2 study of CPX-351 versus 7+3 in previously untreated AML patients over the age of 60. As can be seen on the right-hand of the slide, there was no difference in overall survival regardless of whether the patient received CPX-351 or 7+3. However, in a subset analysis of patients with secondary AML, those defined as having AML following an antecedent hematologic disorder or therapy-related AML, CPX-351 was associated with a higher response rate, a lower 60-day mortality, and higher event-free and overall survival. However, this was a randomized phase 2 study that was not powered to show a benefit in this subset of patients. However, this randomized phase 2 study led to the pivotal phase 3 study shown on this next slide.

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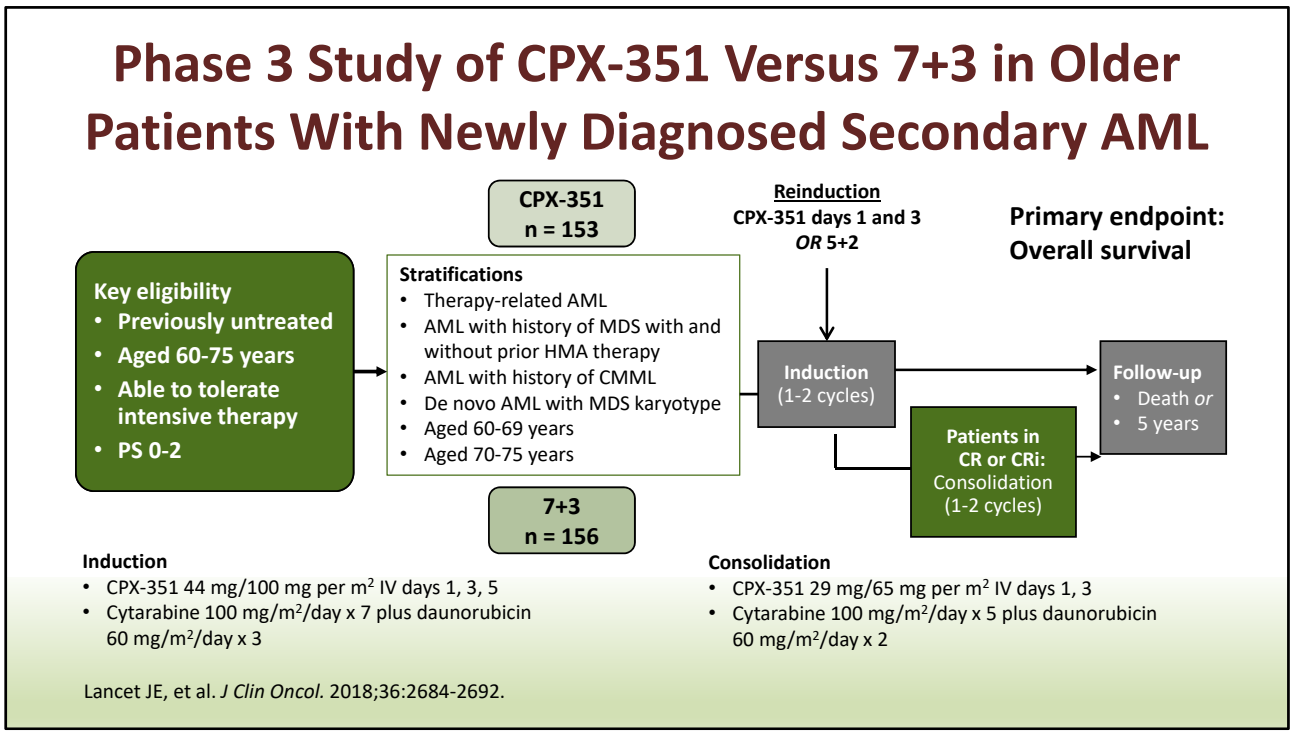

Patients between the ages of 60 and 75, who are eligible for chemotherapy with adequate performance status were randomized between CPX-351 and 7+3 induction if they had high-risk disease as defined as therapy-related AML, AML with a history of myelodysplastic syndrome with or without a prior HMA exposure, AML with a history of the MDS/MPN chronic myelomonocytic leukemia, and even de novo AML with an MDS type karyotype. Patients would receive CPX-351 on days 1, 3, and 5 as a 90-minute infusion; 7+3 was cytarabine 100 mg/m^2 by continuous infusion for seven days and daunorubicin 60 mg/m^2 days 1, 2, and 3. If the patients had cytoreduction at day 14 but persistent disease, they would receive a second cycle of CPX-351 for two days or 5+2 chemotherapy as shown on the slide. Patients achieving a remission went on to receive two more cycles of chemotherapy according to their initial randomization. If randomized to CPX-351, they would receive CPX-351 at a lower dose on days 1 and 3, or cytarabine and daunorubicin in a 5+2 schedule. Patients were allowed to go on to allogeneic transplant if eligible, and the primary endpoint of the study was survival.

Now, it is important to look at a number of details of the study. First, the patient population was selected, again, based on the subset analysis of a prior randomized phase 2 study. Neither that study nor this one has addressed the use of CPX-351 in younger patients, which we will come back to. The second is, the liposomal formulation of daunorubicin-cytarabine actually have lower doses of those two agents compared to what would be received in 7+3 followed by 5+2. The third observation is the use of the same agents during consolidation and not using a higher dose chemotherapy regimen such as high-dose cytarabine. Some have criticized the study based on that. However, there is no data that high-dose cytarabine, especially in older patients with secondary AML, is of benefit when given in the post-remission setting. This study in fact was a perfect experiment comparing the use of daunorubicin-cytarabine given in the standard continuous infusion and bolus manner versus the liposomal formulation of the exact same two drugs but yet, in a lower complete or total dosage.

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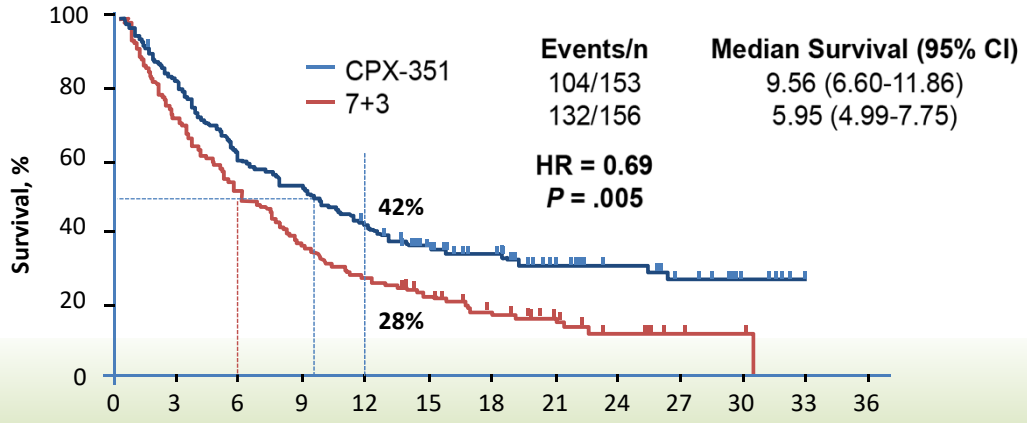
CPX-351 Improves Survival Among Older, Secondary AML

Kaplan-Meier Curve for OS: ITT Analysis Population



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

The primary endpoint of the study was overall survival and in fact, patients who received CPX-351 during induction followed by consolidation with or without transplant versus those who got 7+3 followed by 5+2 with or without transplant had a superior survival. The median survival increased from approximately 6 months with 7+3 to 9.5 months with CPX-351. At 12 months, more patients were alive if they had been randomized to receive CPX-351, 42%, compared to 7+3, 28%. These differences were statistically significant.

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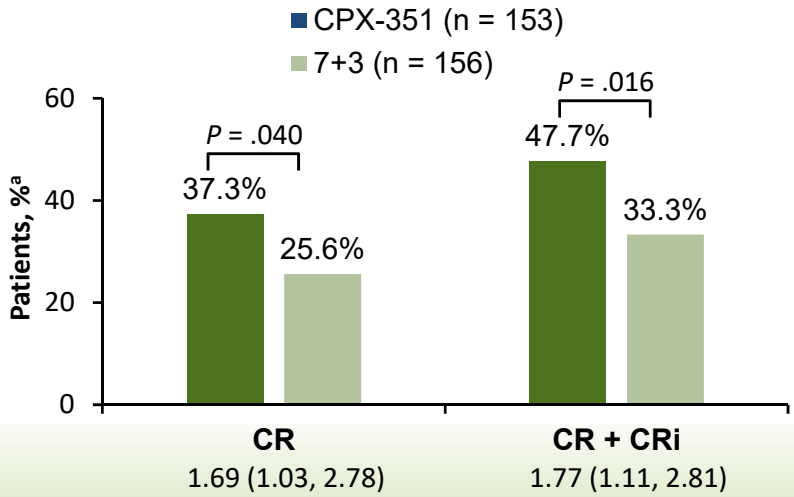
Phase 3 Study of CPX-351 vs 7+3 in High-risk AML: Response Rate



Rate of CR + CRi/CR in Patient Subsets

	CPX351	7+3
All patients	48/37%	33/40%
Age 60-69 years	50/40%	36/26%
Age 70-75 years	44/33%	29/24%
Non-adverse Risk Karyotype	55/42%	48/33%
Adverse Risk Karyotype	43/35%	22/18%

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

There was also, as expected from the randomized phase 2 study, a higher response rate with CPX-351. CRs were achieved in 37% of patients with CPX-351 versus 26% of patients with 7+3, and if you include CRi it was nearly 50% with CPX-351 compared to a third of patients with 7+3. In patients who are older (between 70 and 75) and even those with adverse risk karyotype, there was a trend for an improvement or a higher CR and CRi rate, as well as a CR rate compared to 7+3. Although, since the numbers in the subsets were smaller, the differences were not statistically significant in the subsets, but in the entire group, the response rates were higher with CPX-351 versus 7+3.

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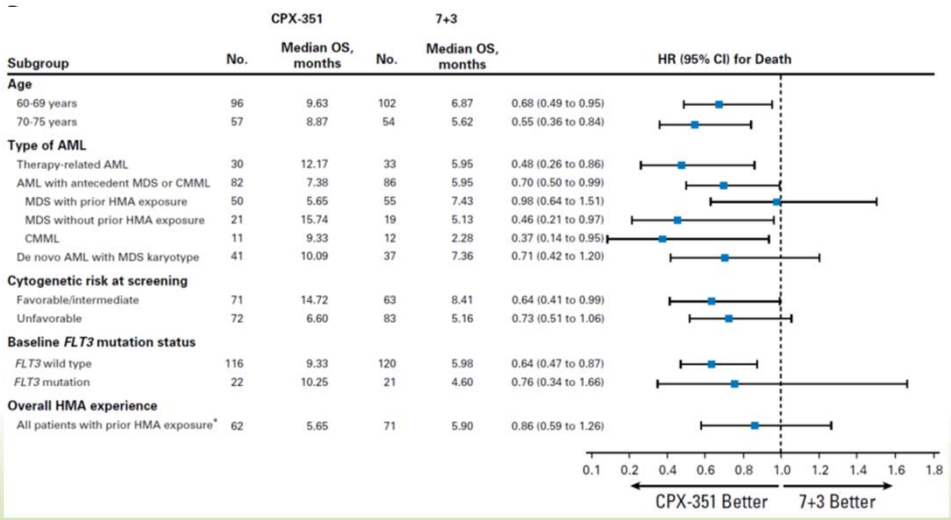
Phase 3 Study of CPX-351 vs 7+3 in Older Patients With Newly Diagnosed Secondary AML



Subgroup	CPX-351 No.	CPX-351 Median OS, months	7+3 No.	7+3 Median OS, months	HR (95% CI) for Death
Age					
60-69 years	96	9.63	102	6.87	0.68 (0.49 to 0.95)
70-75 years	57	8.87	54	5.62	0.55 (0.36 to 0.84)
Type of AML					
Therapy-related AML	30	12.17	33	5.95	0.48 (0.26 to 0.86)
AML with antecedent MDS or CMML	82	7.38	86	5.95	0.70 (0.50 to 0.99)
MDS with prior HMA exposure	50	5.65	55	7.43	0.98 (0.64 to 1.51)
MDS without prior HMA exposure	21	15.74	19	5.13	0.46 (0.21 to 0.97)
CMML	11	9.33	12	2.28	0.37 (0.14 to 0.95)
De novo AML with MDS karyotype	41	10.09	37	7.36	0.71 (0.42 to 1.20)
Cytogenetic risk at screening					
Favorable/intermediate	71	14.72	63	8.41	0.64 (0.41 to 0.99)
Unfavorable	72	6.60	83	5.16	0.73 (0.51 to 1.06)
Baseline *FLT3* mutation status					
FLT3 wild type	116	9.33	120	5.98	0.64 (0.47 to 0.87)
FLT3 mutation	22	10.25	21	4.60	0.76 (0.34 to 1.66)
Overall HMA experience					
All patients with prior HMA exposure*	62	5.65	71	5.90	0.86 (0.59 to 1.26)

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

In terms of the benefit of CPX-351 versus 7+3 in older patients in terms of survival, again, when looked at by the stratifications, there is a benefit of CPX-351 in patients between 70 and 75, those with therapy-related AML, those with AML following prior myelodysplastic syndrome, those with AML following chronic myelomonocytic leukemia. There was a trend for patients who had adverse karyotypes, FLT3 mutation, as well as having received HMAs in the past.

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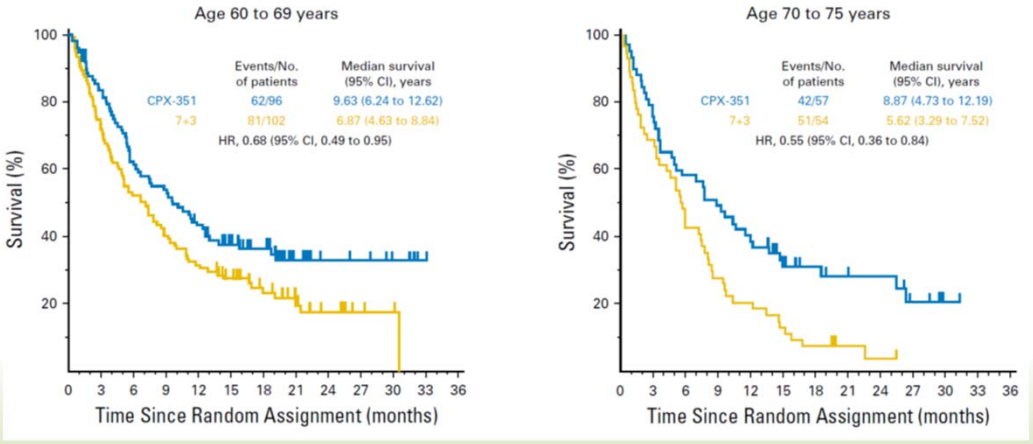
Phase 3 Study of CPX-351 vs 7+3 in Older Patients With Newly Diagnosed Secondary AML:

OS by Age



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

The survival benefit was even seen in patients between the ages of 70 and 75, as can be seen in these Kaplan-Meier curves.

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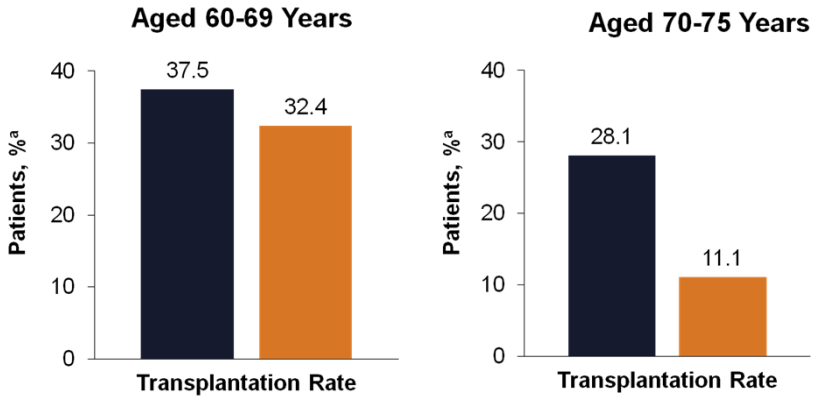
CPX-351 vs 7+3: Transplantation Rate



Odds ratio (95% CI) 1.25 (0.70-2.25) 3.12 (1.12-8.72)

CPX-351 (n = 36) 7+3 (n = 33) CPX-351 (n = 16) 7+3 (n = 6)

[a] Percentages reflect number with endpoint out of column total; odds ratios calculated with 7+3 arm as reference group.

Lancet JE, et al. BMT Tandem Meeting. 2017. Oral Presentation.

Furthermore, more patients proceeded at some point during their therapy to allogeneic stem cell transplant if they were assigned to CPX-351 versus 7+3, and in fact, for patients over the age of 70, about a quarter of patients proceeded to allogeneic transplant following CPX-351 versus 11% following 7+3.

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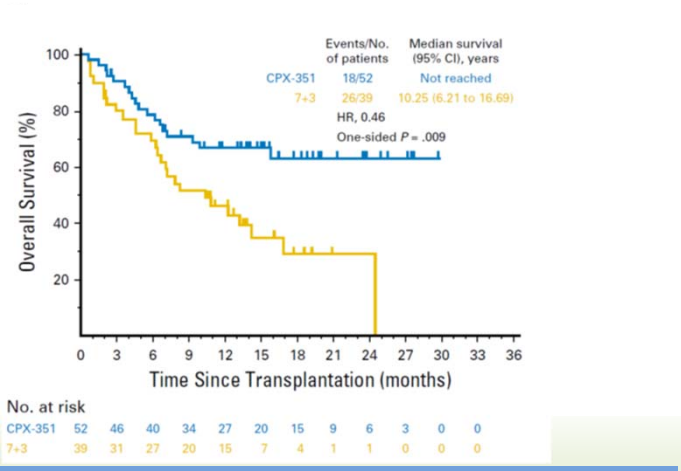
Landmark Analysis of Overall Survival Following Allo HSCT



53% fewer deaths within 100 days of transplant in CPX-351 vs 7+3 arm

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

A landmark analysis was then done at the time of allogeneic transplant and showed that patients who proceeded to allogeneic transplant following CPX-351 had a superior survival with a plateau on this curve above 60% at 24 months compared to patients who went on to allogeneic transplant versus 7+3. There was a 53% rate of fewer deaths within 100 days of transplant following CPX-351 versus 7+3. Now the explanation for this is unclear. Some have speculated that CPX-351 may lead to a stronger, better, deeper complete remission; however, MRD analysis was not part of this clinical trial. It is also possible that patients who received CPX-351 had less toxicities and tolerated the transplant better; however, I do not think that would explain the difference in survival that is seen at 24 months.

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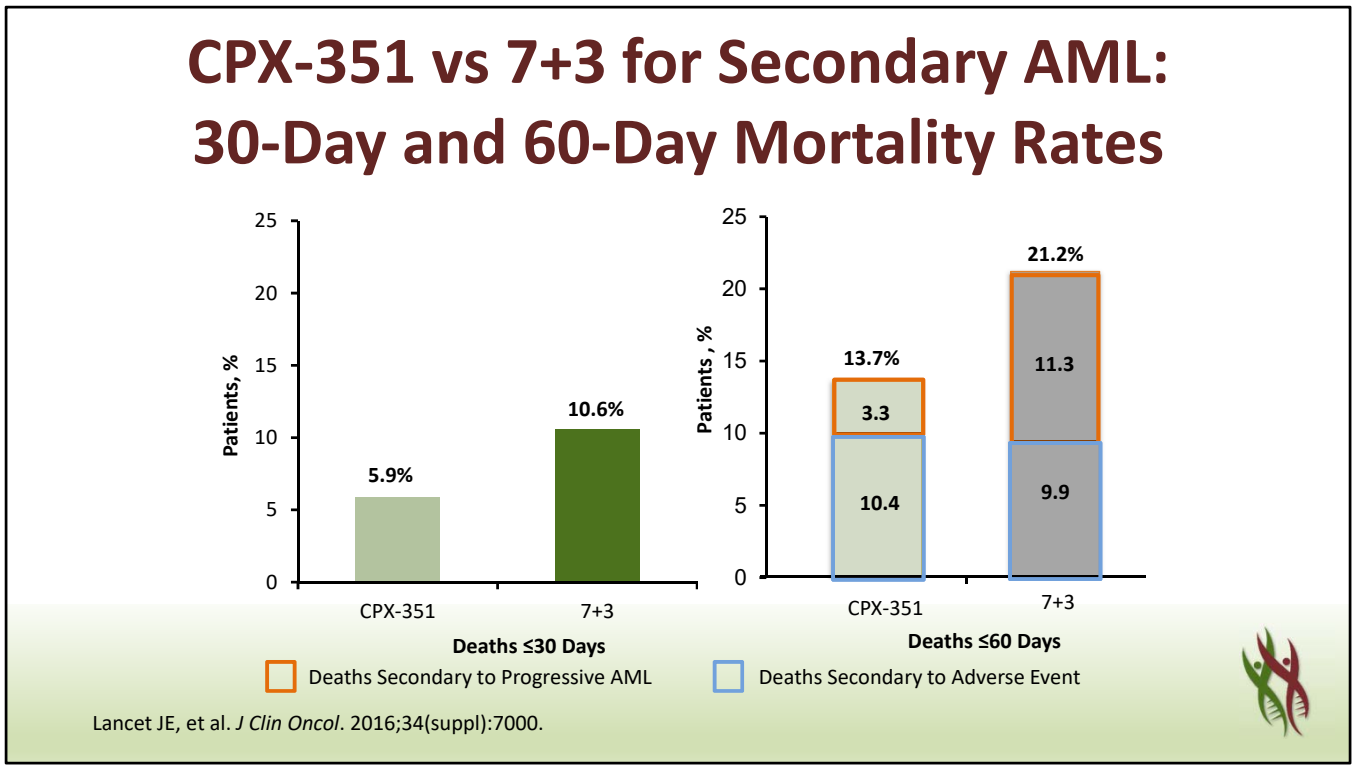

Now, looking at toxicity, there were fewer deaths during the first 30 days or 60 days after beginning induction in patients who received CPX-351 versus 7+3. In an analysis by the investigators at day 60, the investigators felt that the risk of death related to adverse events was similar between CPX-351 and 7+3, approximately 10%. However, there were more deaths in the 7+3 arm due to progressive acute myeloid leukemia.

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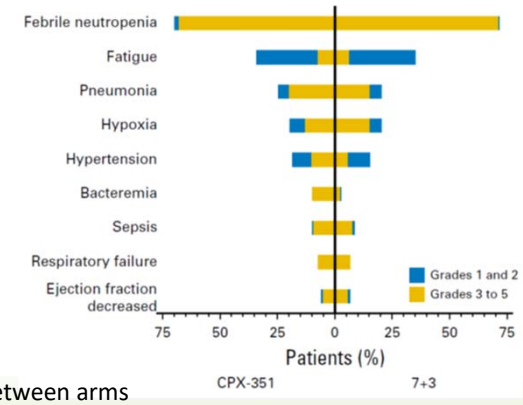
Phase 3 Study of CPX-351 vs 7+3 in Older Patients With Newly Diagnosed Secondary AML:

Adverse Events



- AEs generally similar between arms
- Higher rate of all grades of hemorrhage, as well as fatal CNS hemorrhage (2.0% vs 0.7%) with CPX-351

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

In terms of other toxicities, there did not seem to be a major difference in these other adverse events, including febrile neutropenia, pneumonia, hypotension, hypoxia, and others. However, there was a higher rate of all grades of hemorrhage with CPX-351 versus 7+3 as well as fatal CNS hemorrhages with CPX-351, 2% versus 0.7%.

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Recovery of ANC and Platelet Count with CPX-351 vs with 7+3 in Older Patients with Secondary AML

	ANC ≥500/mcL		Platelets ≥50,000/mcL	
	CPX-351	7+3	CPX-351	7+3
Patients receiving 1 induction	**n = 58**	**n = 34**	**n = 58**	**n = 34**
Median, days	35	29	36.5	29
Patients receiving 2 inductions	**n = 15**	**n = 18**	**n = 15**	**n = 18**
Median, days	35	28	35	24

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

The toxicity that was most obvious that differed between the two treatment regimens was myelosuppression. The recovery of ANC and platelet count following CPX-351 was longer, took longer than patients following 7+3. If you look at patients who achieved a complete remission just following one cycle of induction, the median number of days to ANC over 500 was 35 days with CPX-351 versus 29% with 7+3. The study allowed GCSF and myeloid growth factors to be given in some of these patients. Likewise, there was a longer time to recovery of the platelet count over 50,000. The median time with CPX-351 was 36 days versus 29 days.

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Liposomal Daunorubicin/Cytarabine is Indicated for the Initial Treatment of Adults with tAML and AML-MRC

- Younger adults with tAML and AML-MRC
- Biomarkers for prediction of response
- Inpatient vs outpatient administration
- Less intensive therapeutic options

In summary, after decades of attempting to improve the clinical outcome of patients with acute myeloid leukemia and specifically, those with treatment-related AML and AML with myelodysplasia-related changes based on cytogenetics or based on that history of myelodysplastic syndrome or other MDS/MPNs, liposomal daunorubicin-cytarabine is the first and it is the only agent that has shown to improve overall survival in this group of patients when used as initial therapy. It led to the labeled indication approval in August 2017 for adults with therapy-related AML and AML with myelodysplasia-related changes. There are a number of questions that remain. The pivotal trial that led to the approval was performed in older patients with therapy-related AML and AML with myelodysplasia-related changes. The question is, would the benefit also be seen in younger patients with this disease? For all younger patients with secondary AML, more intensive regimens have not been shown to lead to improvement since survival, and since the disease is biologically likely very similar in younger and older patients, I think it is reasonable to treat younger patients with therapy-related AML and AML with myelodysplasia-related changes with liposomal daunorubicin-cytarabine. Of course, we would love to have a better biomarker for the predictor of response, not all patients responded, not all patients seem to benefit; however, we look forward to further analysis of samples from the patients in the studies in terms of mutational profile to see if there is some predictor of response to the liposomal formulation.

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Over 95% of patients received CPX-351 as an inpatient during the clinical trial. Now, for consolidation, half of the patients received it as an outpatient because these patients tended to be well by that point, having recovered from induction and their bone marrows have recovered. The question is, is it safe to give CPX-351 to an initially diagnosed patient during initial induction? If this is attempted, I would recommend that patients be monitored very closely with appropriate transfusion support. Finally, liposomal daunorubicin-cytarabine was compared to this standard of care for patients who are fit for chemotherapy, and that is 7+3 chemotherapy which has been our gold standard for 40 years. However, it is not clear that more intensive approaches would be beneficial compared to less intensive approaches as newer therapeutic options emerge for patients receiving less intensive therapy. In patients who are fit for chemotherapy, it remains to be evaluated whether less intensive therapeutic options may have any benefit compared to liposomal daunorubicin-cytarabine. However, for patients who are felt to be fit for intensive chemotherapy, there is no doubt, based on the randomized phase 3 study and the prior randomized phase 2 study that liposomal daunorubicin-cytarabine is a clinical benefit for this group of patients with therapy-related AML and AML with MRC based on higher response rates, based on better and higher overall survival, based on a higher chance to proceed to an allogeneic transplant which, in many patients, is the only potential option for curative therapy for these subsets of disease, as well as a lower 30- and 60-day mortality. I would like to thank you for viewing this activity.