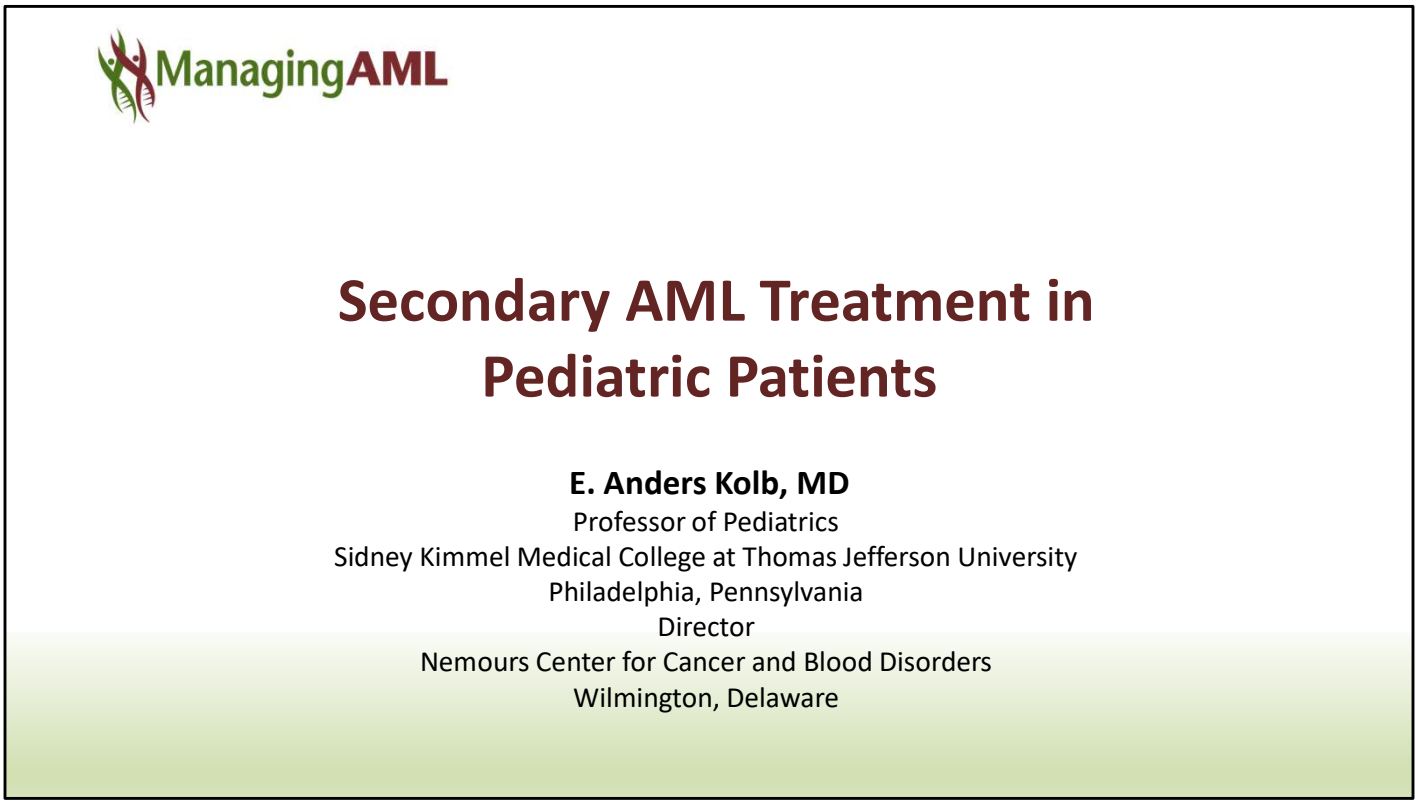


Good afternoon, everybody. My name is Andy Kolb and I have the pleasure to talk to you today about secondary acute myeloid leukemia in children. Thank you for joining today. I'm a pediatric oncologist, I work in Nemours Children's Health in Wilmington, Delaware.

Disclosures

- Dr. E. Anders Kolb, faculty for this educational activity, has no relevant financial relationship(s) with ineligible companies to disclose.

I have nothing to disclose today.

Learning Objectives

1. Describe differences between secondary AML in children and adults
2. Describe toxicities associated with traditional therapies for induction and consolidation chemotherapy in pediatric AML, and correlate these toxicities with prognoses and outcomes for patients
3. Summarize efficacy and safety data for current and emerging agents for pediatric patients with newly diagnosed therapy-related AML and AML with myelodysplasia-related changes
4. Outline the recommended treatment algorithm for secondary AML and align treatment with patient characteristics

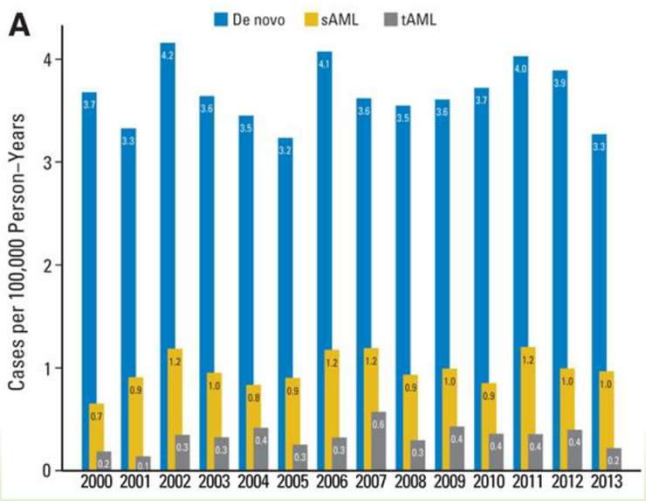
Our learning objectives today, we'll talk about some of the key differences between acute myeloid leukemia in children and adults. We'll talk about the toxicities associated with therapy. We'll talk about some of the safety and efficacy data that we know about treatment for AML and secondary AML and outline some recommendations for secondary AML and treatment moving forward.

Secondary AML Treatment in Pediatric Patients

Secondary AML in Children

Rare Subset of Childhood AML

- Secondary AML in children means treatment-related AML
- Myelodysplastic syndrome in children is exceedingly rare (as is clonal hematopoiesis)
- Secondary AML in adults with AML more commonly refers to AML occurring following MDS



Ostgard LSG, et al. *J Clin Oncol*. 2015;33(31):3641-3649.

Secondary AML is a very rare subset of AML in children, so a rare subset of a rare disease. I think it's important because of the differences in pathogenesis of AML in children and adults. I think it's important to make sure we focus first on understanding what secondary AML means for kids. This is a review or registry from Northern Europe looking at the incidents in adults of de novo AML, secondary AML, and then therapy-related AML.

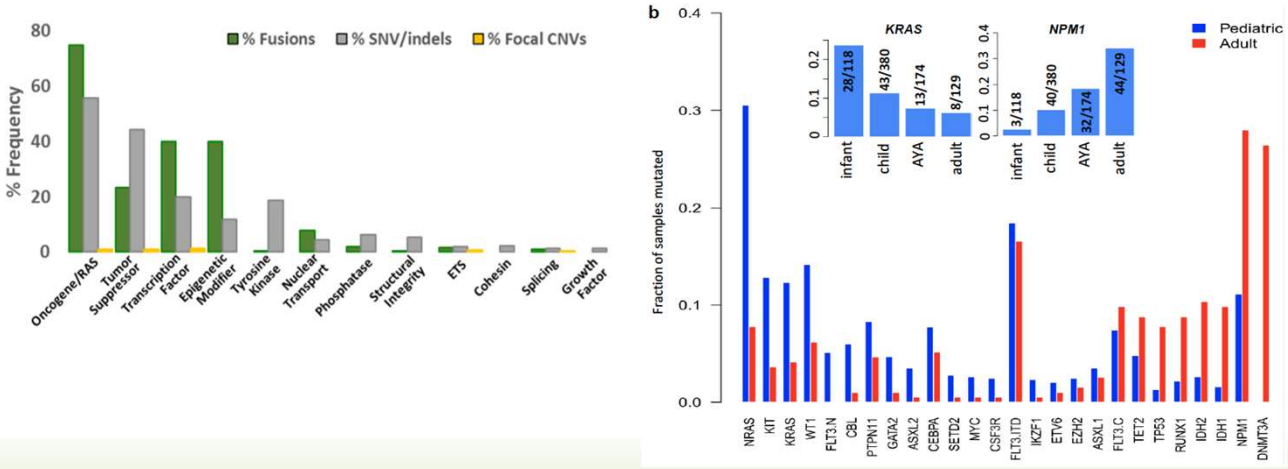
In the adult cancer world, secondary AML often refers to AML that's evolving from a myelodysplastic syndrome. In children, myelodysplasia is rare, clonal hematopoiesis is rare. Most of the genetic events that cause leukemia in kids don't have a predisposing or a predecessor phase of myelodysplasia. Most of these events caused AML, so when we talk about secondary AML, we're really referring to therapy-related AML in children. This is AML that is the result of exposure to chemotherapy, exposure to toxins, rather than AML that has evolved from a myelodysplasia clone.

In the European data, you can see that the yellow bars represent secondary AML, so AML evolving from myelodysplasia. The gray bars at the bottom are the therapy-related AMLs and like adults, these therapy-related AMLs account for a very small subset of the total population of patients with AML.

Secondary AML Treatment in Pediatric Patients

Molecular Aberrations in Childhood AML

Differences Between Childhood and Adult AML



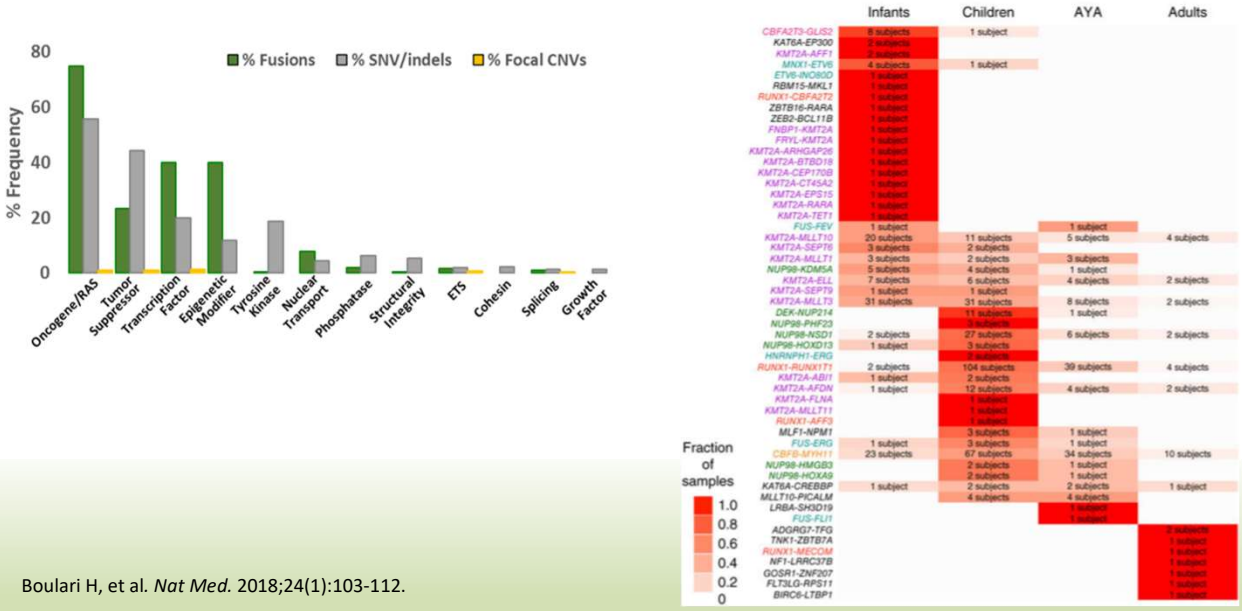
Boulari H, et al. *Nat Med.* 2018;24(1):103-112.

The other key difference between AML that we see in children and AML that we see in adults are the molecular pathways that are mutated, so the molecular pathogenesis of this. In the upper left, we can see the frequency of mutated pathways and many of these are shared with adults though not all of them. On the right, we can see the list of variants, commonly mutated variants that occur in children, shown in blue, and adults, shown in red. I think what's immediately apparent looking at the red and blue bars is that where you see blue, pediatric mutations, there's very little red. Where you see red, adult mutations, there's very little blue. The mutation types that we see in pediatric and adult cancers are very different. This is very well illustrated by KRAS and NPM1. KRAS mutations are common in infants and children, rarely seen in AYAs or adolescent young adults and in adult patients. NPM1 mutations are rare in infants and young children, but more commonly seen in adolescent young adults as well as older adults. The exception of course to this is right in the middle, FLT3-ITD, FLT3 internal tandem duplication. These represent about 18% to 20% of both adult and childhood leukemias. We talk about AML, we talk about secondary AML, we talk about treatment-related AML. I think it's important to bear in mind the key differences between the disease that we see in older adults and the disease that we see in children. The fundamental difference is the molecular pathogenesis.

Secondary AML Treatment in Pediatric Patients

Molecular Aberrations in Childhood AML

Differences Between Childhood and Adult AML



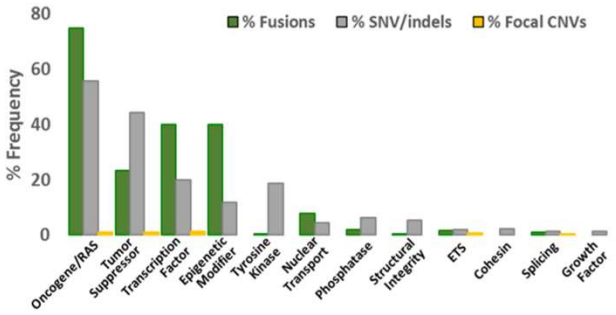
Boulari H, et al. *Nat Med.* 2018;24(1):103-112.

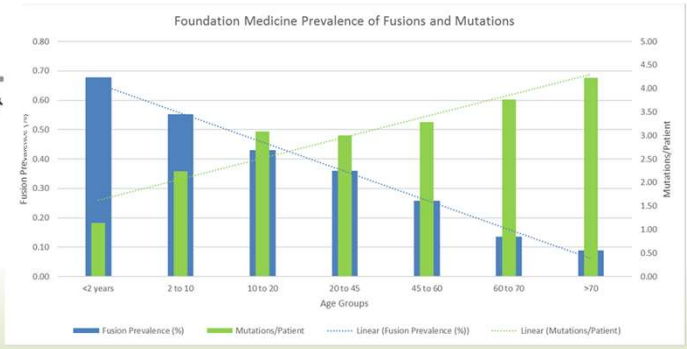
It's also illustrated by fusion types. This is again, data from Boulari's *Nature Medicine* paper in 2018. On the left-hand side of this figure, you can see a variety of different fusions that have been identified, so these are translocation events that have been identified in children, adolescent young adults, and older adults with AML. Again, what's apparent is that the fusions that we see in infants are not the same fusions that we see in adults. The fusions that we see in adults are not the same as what we see in children and infants. We also see a lot more fusion events in children than adults. I think this goes back again to the pathogenesis that the leukemogenic events in children tend to be these catastrophic mutations that can occur rather than an accumulation of smaller mutations, a single nucleotide variants for example that are commonly present in adults with myelodysplasia and then adults who transformed to leukemia as well.

Secondary AML Treatment in Pediatric Patients

Molecular Aberrations in Childhood AML

Differences Between Childhood and Adult AML





Boulari H, et al. *Nat Med.* 2018;24(1):103-112.; Tarlock K, et al. *Oncotarget.* 2018;9:26417-26430.

Lastly just to illustrate the point one more time, in this figure, we're looking at fusion events in blue and we're looking at single nucleotide variants so smaller insertions and deletions in green, and on the X-axis we're looking at age. Fusion event frequency goes down with age, single nucleotide variant frequency goes up with age. Again, just illustrating the continuum of differences between children and older adults with AML.

Secondary AML Treatment in Pediatric Patients

Secondary AML in Children

Rare Subset of Childhood AML

	Median	Range
Age, years	14	3-20
Leukocyte count, $\times 10^9$/L	3.9	0.7-400
Hemoglobin, g/dL	8.9	5-12
Platelet count, $\times 10^9$/L	154	17-341
	No. Patients	Percentage
Type of primary cancer		
Osteosarcoma	5	23
Hodgkin lymphoma	4	18
B-ALL/LBL	4	18
Ewing sarcoma	2	9
Medulloblastoma	1	5
PNET	1	5
GBM	1	5
T-LBL/ALL	2	9
Neuroblastoma	1	5
Rhabdomyosarcoma	1	5
Cytogenetics		
t(8;21)	1	4.5
11q23	1	4.5
−6	1	4.5
t(9;11)	4	18
−7	10	45
t(7;11)	1	4.5
Inv 11	1	4.5
Inv 9	1	4.5
−9	1	4.5
Not available	1	4.5
Latency period	Years	Range
B-ALL/LBL (n = 4)	3.6	1.9-6.08
T-LBL/ALL	3.9	3.6-433
Solid tumors (n = 18)	4	1-9.91
Osteosarcoma (n = 5)	2.6	2.33-8.91
Hodgkin lymphoma (n = 4)	4.24	2.75-4.3
Ewing sarcoma	1.29	1-1.58
Medulloblastoma	2.6	N/A
PNET	3.3	N/A
Glioblastoma multiforme	7.75	N/A

B-ALL/LBL indicates precursor B-cell acute lymphoblastic leukemia/lymphoblastic leukemia lymphoma; GBM, glioblastoma multiforme: Inv, inversion; N/A, not applicable; PNET, primitive neuroectodermal tumor; T-LBL/ALL, T-cell lymphoblastic leukemia/acute lymphoblastic leukemia; t-MDS,/AML, therapy related myelodysplastic syndrome/acute myeloid leukemia

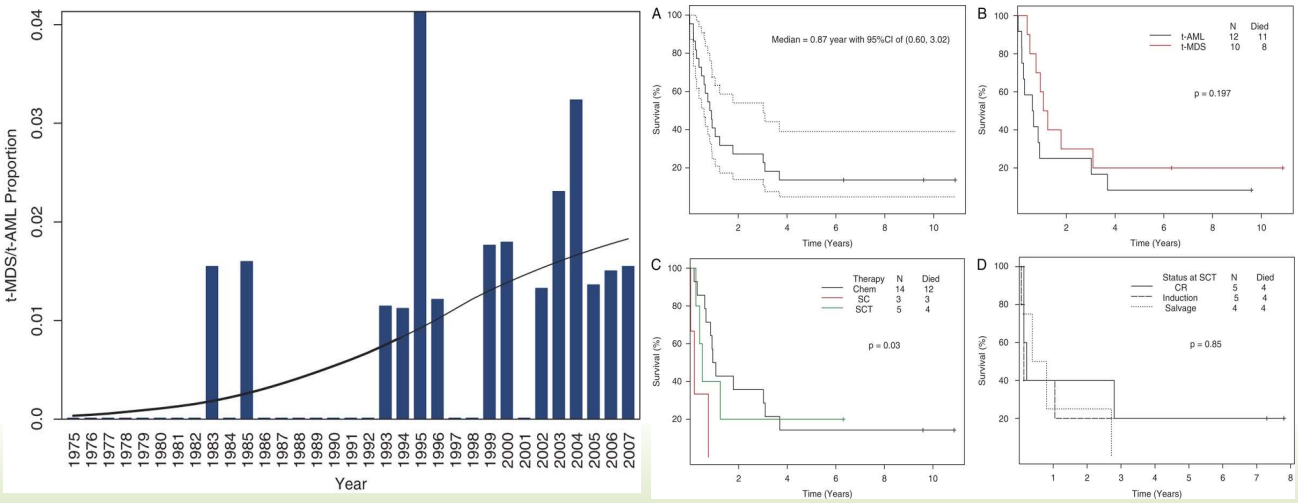
Aguilera D, et al. *Pediatr Hematol Oncol*. 2009;31(11):803-811.

Moving into talking about secondary AML and again in children, we're talking primarily about therapy-related AML. AML that occurs after exposure to chemotherapy and radiation in children with another cancer diagnosis. There was a review put out by a group at MD Anderson in 2009 that identified about 20 patients that had a secondary AML therapy-related AML and described the demographics of these patients. Many of these patients had been exposed to chemotherapy for sarcomas, brain tumors and acute lymphoblastic leukemia. These are therapies that are heavily in alkylator and epipodophyllotoxin like etoposide. Many of these patients had mutations either in the KMT2A gene at 11q23 or had a monosomic event like monosomy 7. These are the more common large genetic events that we see in children with secondary AML.

Secondary AML Treatment in Pediatric Patients

Secondary AML in Children

Rare Subset of Childhood AML



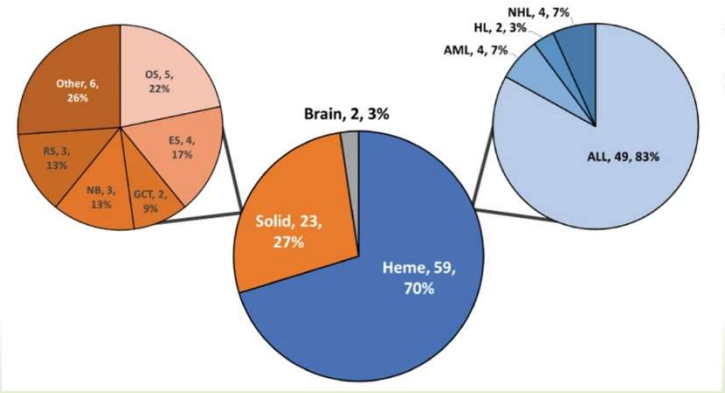
Aguilera D, et al. *Pediatr Hematol Oncol*. 2009;31(11):803-811.

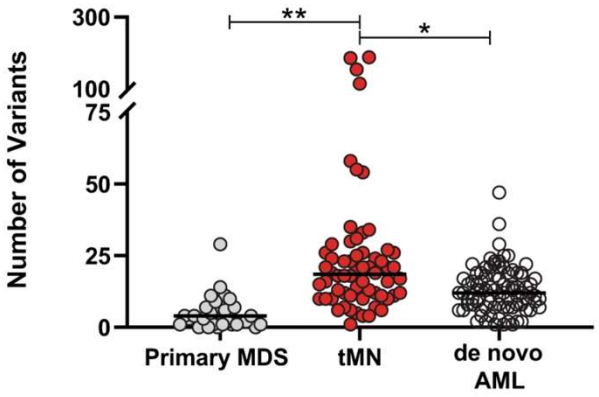
The figure on the left we can see that the incidence of secondary AML in this single-institution study has increased over time. I think this is primarily due to two factors. One, children are receiving more and more intensive therapy over time, and two, more children are surviving their initial therapy. Sadly, secondary AML is a disease that we see only in survivors of their initial disease. These two factors conspire to lead to this increasing incidence with time. The other important point in this figure is that the overall survival in patients with secondary AML, children with secondary AML is around 20%. This is true for patients that have myelodysplasia as well as patients that have a secondary AML so secondary MDS or secondary AML. Most of these patients survive following chemotherapy with or without a transplant.

Secondary AML Treatment in Pediatric Patients

Secondary AML in Children

Rare Subset of Childhood AML





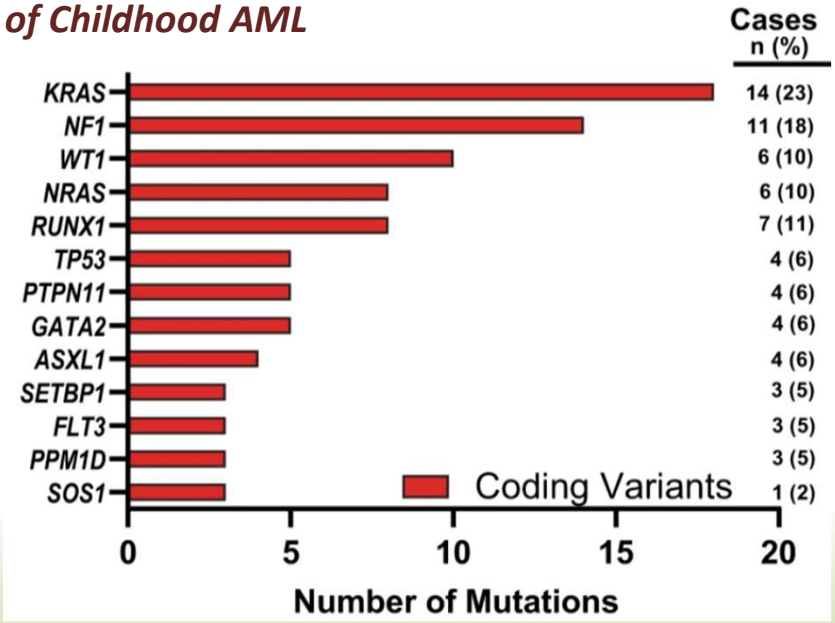
Schwartz J, et al. *Nat Commun*. 2021;12(1):985.

In a subsequent study published just this past year from the group of St. Jude, they looked at 84 children who had secondary AML. If you focus on the pie graph in the middle for a moment, you can see that the distribution of primary cancer types 70% of these kids had a hem malignancy while 30% of these kids had a solid tumor either intracranial or extracranial solid tumor. Among the solid tumor patients again sarcomas account for more than half of the diagnoses in children with secondary AML and then among the primary hem malignancies ALL is the more common primary malignancy in children with a secondary AML. The figure in the upper right shows the number of mutations. Number of variants identified in patients children that have either primary myelodysplasia, therapy-related myeloid neoplasm including the MDS patients, as well as patients with de novo non-secondary AML. You can see that the number of variants present in these patients is higher among the patients with a treatment-related or secondary AML.

Secondary AML Treatment in Pediatric Patients

Secondary AML in Children

Rare Subset of Childhood AML



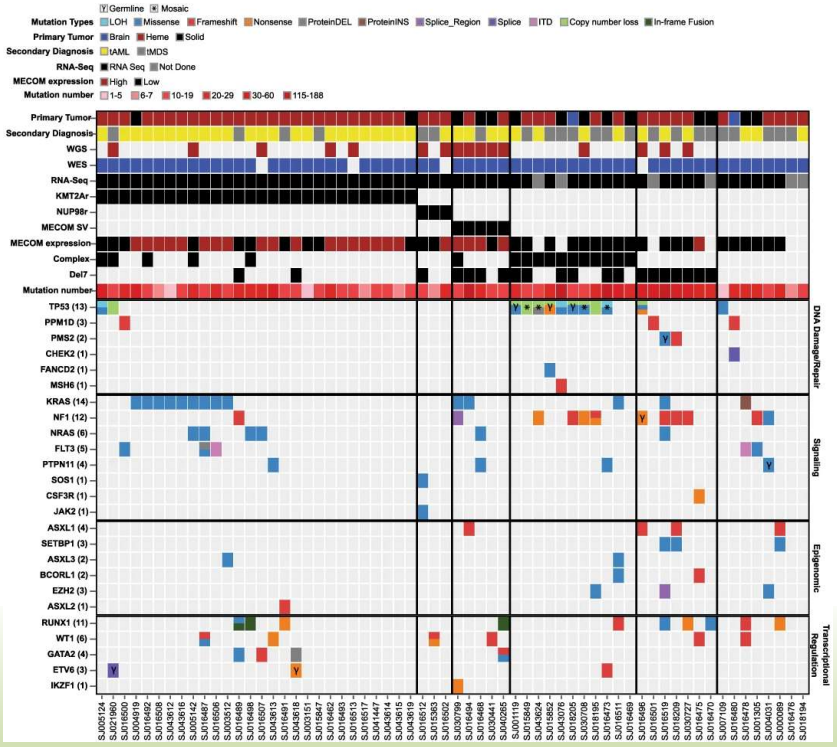
Schwartz J, et al. *Nat Commun*. 2021;12(1):985.

The variants of interest that have been described include commonly mutations in the RAS pathways, so KRAS, NRAS, PPTN11, NF1. These are all genes that are involved in RAS pathway activation, as well as WT1, RUNX1, and TP53. These are coding variants. These are variants that are thought to be pathogenic. RAS pathway mutations are among the most common.

Secondary AML Treatment in Pediatric Patients

Secondary AML in Children

Rare Subset of Childhood AML

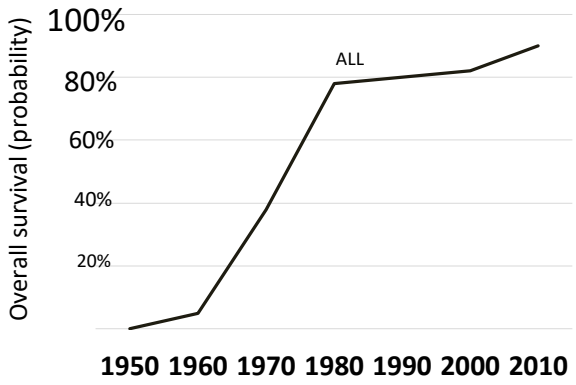


Schwartz J, et al. *Nat Commun*. 2021;12(1):985.

This figure is a bit more complicated, so let me walk through from the top. The second row shows the secondary diagnosis. In yellow, we have patients with secondary AML. In gray, we have patients with myelodysplasia. Majority of these patients have secondary AML. If you look down a few lines, you can see that the patients with a KMT2A rearrangement, most of these patients had AML rather than myelodysplasia. If you scroll down a couple more lines, you can see the MECOM expression is elevated in many patients, many pediatric patients even in the absence of a mutation but elevated in patients with secondary AML. A couple rows below the MECOM expression is the deletion 7 or monosomy 7 phenotype. You can see that these are almost mutually exclusive with the KMT2A rearrangement. Together, KMT2A rearrange secondary AML, and the monosomic phenotype or monosomy 7 account for a majority of the children that are diagnosed with secondary AML. I think this speaks a little bit to their exposures as well. KMT2A rearranged AML are more commonly seen after exposure to epipodophyllotoxins like etoposide, as well as drugs like anthracycline, doxorubicin, daunorubicin. Whereas the monosomy 7, we see more commonly in patients that are exposed to high doses of alkylator therapies like cyclophosphamide, ifosfamide. This may be a reason why we see such a high concentration or a high incidence of secondary AML in sarcoma patients who received high doses of both etoposide, as well as alkylator based therapies.

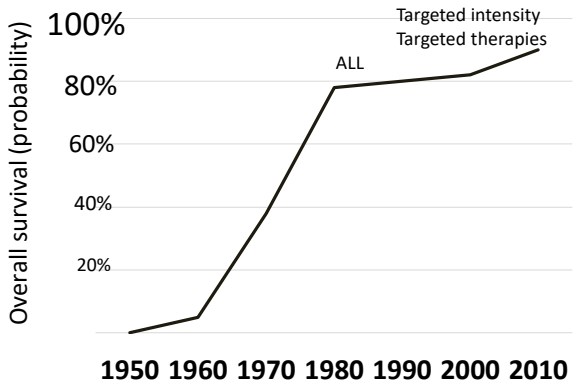
The rest of this graph is looking at the incidents of other variants, so commonly, single-nucleotide variants. I think what's interesting here, we talked previously about how KRAS mutations are among the most common. You can see that these seem to cluster more with patients with KMT2A rearrangements. This is an outstanding view of molecular events that lead to secondary AML in children and I think a very comprehensive description of the mutational profile on these patients.

AML – The Historical Perspective



Let's switch gears and talk about the treatment of AML. In pediatric cancer, we often celebrate the success of therapies for children with acute lymphoblastic leukemia. 50 years ago, with the advent of multimodality therapy, with the introduction of CNS prophylaxis, the prophylaxis against CNS relapse, we saw a very rapid increase in survival through the '70s and '80s in children with AML.

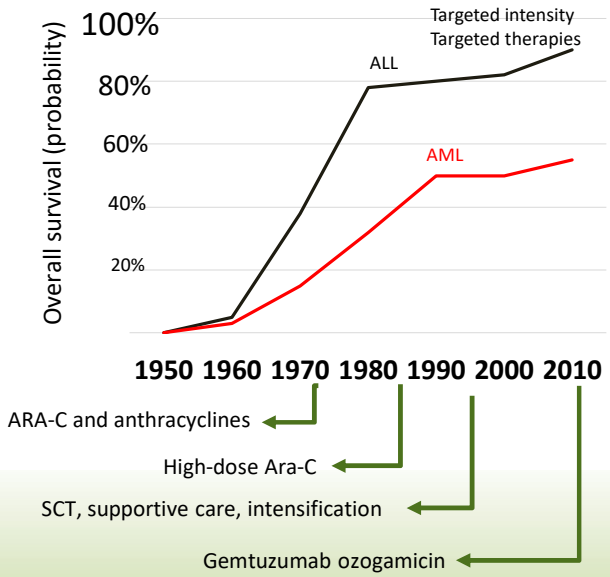
AML – The Historical Perspective



Over the last 20 years, we've seen more modest, but still, significant improvements in survival and such that we have been able to focus a strategy around targeting in intensity, so making sure kids with high-risk disease get more intensive therapy and kids with low-risk disease get some toxicity-sparing therapy or less-intensive therapy. We've also been able to introduce targeted therapies, including tyrosine kinase inhibitors now, immunotherapies to the backbone of ALL therapy successfully while still improving survival. In some molecularly defined subsets of children with AML, survival close approaches 100%.

Secondary AML Treatment in Pediatric Patients

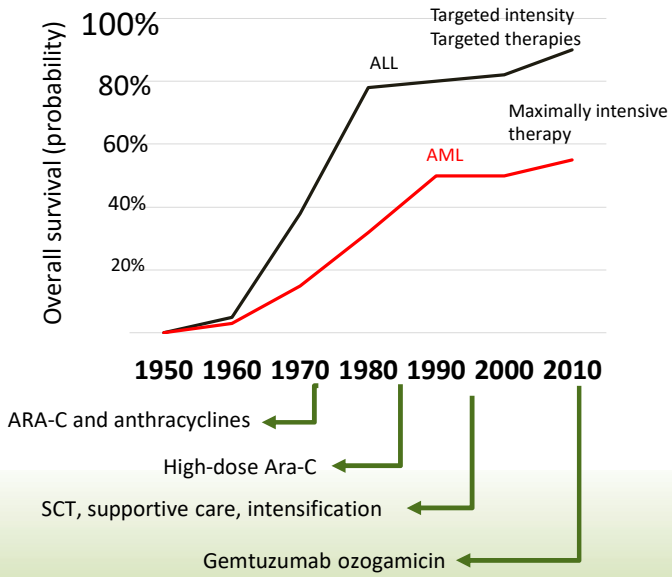
AML – The Historical Perspective



We contrast this to acute myeloid leukemia in children. This is allcomers with acute myeloid leukemia, not just secondary AML. Part of the challenge is that we really only have a couple therapeutic modalities. We have cytarabine, high dose ARA-C, we have anthracycline, daunorubicin, idarubicin, mitoxantrone. We also have stem cell transplant. In the last 20 to 30 years, any improvements that we've seen in survival have really been credited to improvements in supportive care, improvements in the number of patients able to go to and survive a transplant, not to the introduction of new therapies. The exception is the recent approval of gemtuzumab ozogamicin, a CD33 targeted antibody-drug conjugate. With gemtuzumab, we do see an improvement in event free survival and a reduction in relapse risk.

Secondary AML Treatment in Pediatric Patients

AML – The Historical Perspective

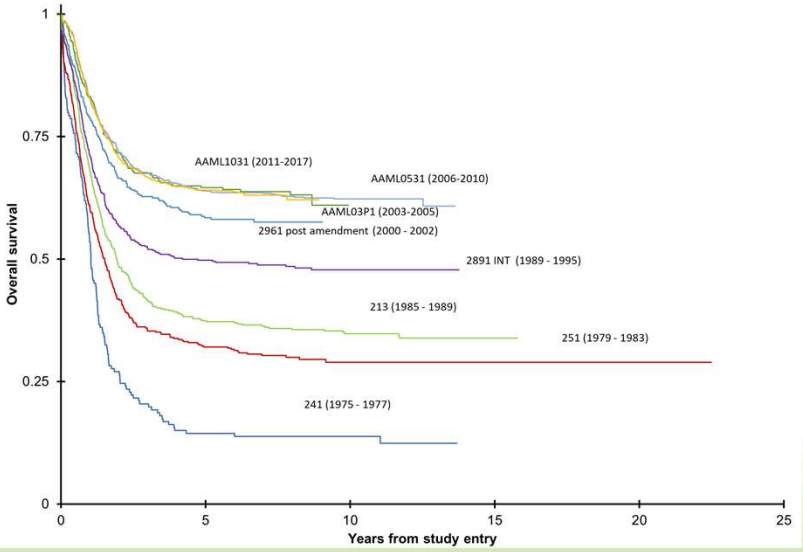


I think what's most important here is to understand that we've really out of survival plateau for the last 30 years despite maximally intensive therapy. When we think about improving outcomes in kids with acute myeloid leukemia, we have to realize that we're already hitting our heads against the toxicity ceiling. There's not much more that we can give these kids without causing significant short and long-term side effects.

Secondary AML Treatment in Pediatric Patients

AML Therapy by the Numbers

No Improvements in OS Attributed to the Introduction of New Anti-neoplastic Therapies for the Past 20+ Years



Alonzo T, et al. *J Clin Oncol*. 2008;26(14):2390-3295.

This is a view of the survival curves for sequential cooperative group studies conducted in North America. Clustered at the top is AAML03P1, 0531, and 1031. This represents about 15 years of phase III studies and survival curves are overlapping, highlighting the fact that we need better therapies.

Secondary AML Treatment in Pediatric Patients

AML Therapy by the Numbers

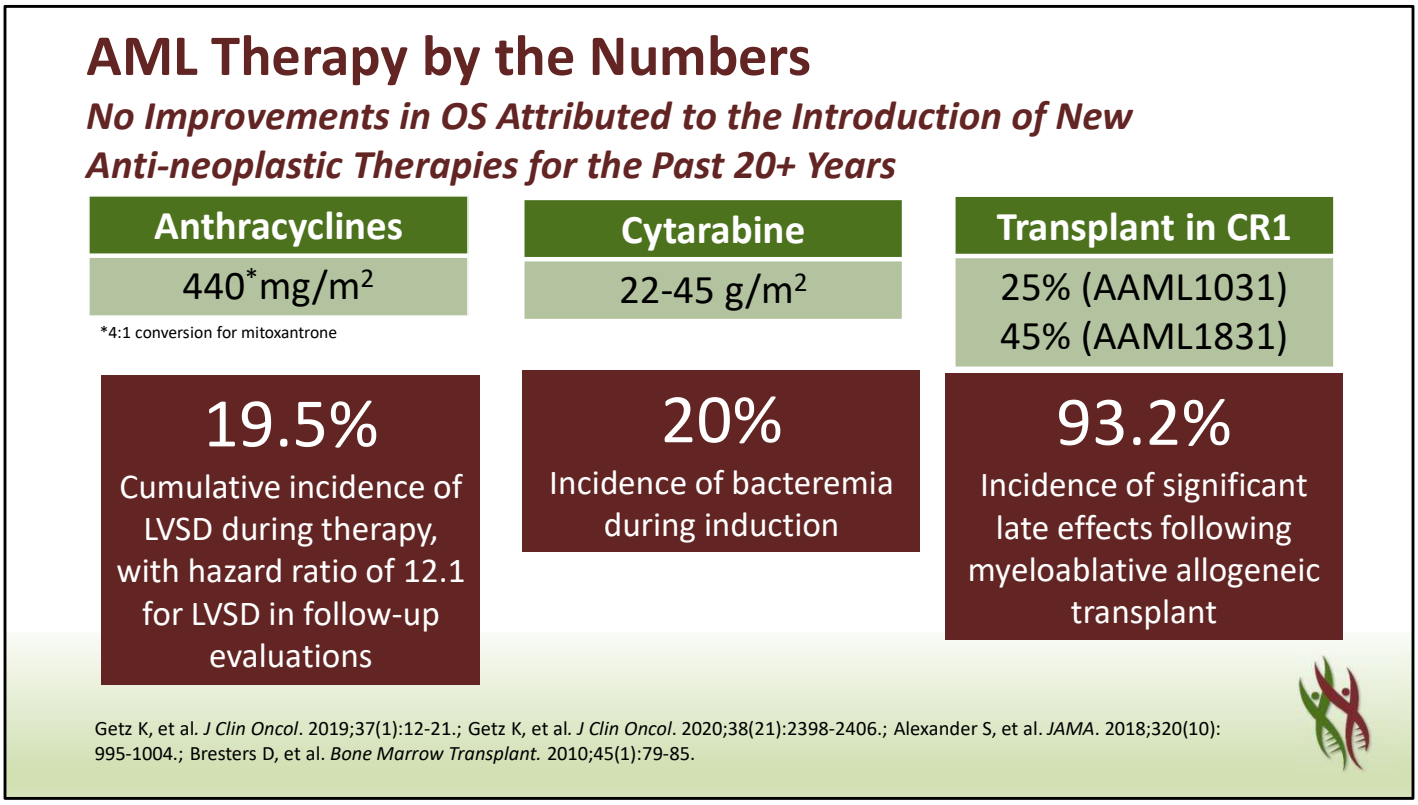
No Improvements in OS Attributed to the Introduction of New Anti-neoplastic Therapies for the Past 20+ Years

Anthracyclines	Cytarabine	Transplant in CR1
440*mg/m^2	22-45 g/m^2	25% (AAML1031) 45% (AAML1831)

*4:1 conversion for mitoxantrone

We also have to remember that we are giving maximally intensive treatment, and this is what that looks like. Most children who don't go to transplant will receive about 440 milligrams per meter squared of anthracyclines, they'll receive many grams of cytarabine. In our past phase III study, we transplanted about 25% of the patients. In the current phase III study, we expect that we will transplant nearly half of patients in first complete remission, so half of patients are following their diagnosis.

Secondary AML Treatment in Pediatric Patients



What does this mean for toxicity? A lot. The cumulative incidence of left ventricular systolic dysfunction is about 20%. One in five kids will experience some cardiac dysfunction during their treatment. Those who do, have a significant risk for cardiac dysfunction long-term. There's a 20% incidents of bacteremia during induction, and this is with antibiotic prophylaxis. Even with prophylactic antibiotic therapy, one in five kids will experience bacteremia during the first couple of cycles of treatment. Then lastly, I think we all know the risk of a long-term side effects goes up significantly with allogeneic bone marrow transplant.

Secondary AML Treatment in Pediatric Patients

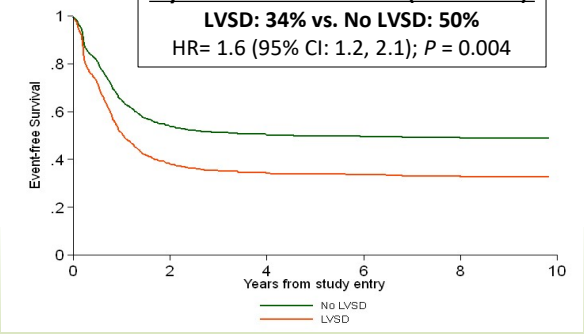
AML Therapy by the Numbers

No Improvements in OS Attributed to the Introduction of New Anti-neoplastic Therapies for the Past 20+ Years

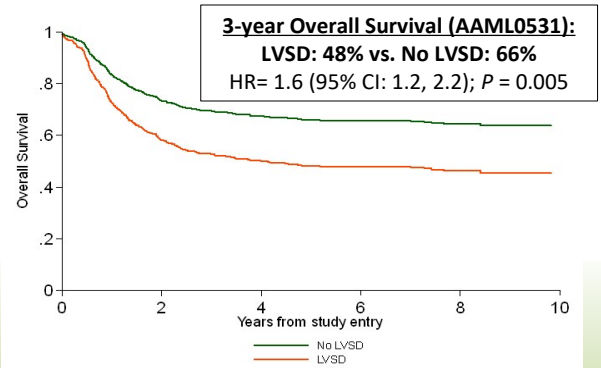
Anthracyclines	Cytarabine	Transplant in CR1
440*mg/m^2	22-45 g/m^2	25% (AAML1031) 45% (AAML1831)

*4:1 conversion for mitoxantrone

3-year Event Free Survival (AAML0531):
LVSD: 34% vs. No LVSD: 50%
HR= 1.6 (95% CI: 1.2, 2.1); *P* = 0.004



3-year Overall Survival (AAML0531):
LVSD: 48% vs. No LVSD: 66%
HR= 1.6 (95% CI: 1.2, 2.2); *P* = 0.005



Getz K, et al. *J Clin Oncol*. 2019;37(1):12-21.

There's also an interaction between these high doses of cytarabine can lead to the risk for bacteremia, which can lead to cardiac dysfunction. Among patients who have cardiac dysfunction, whether it's due to infection or anthracycline exposure, their overall survival is worse. We're looking at event-free survival on the left overall survival, on the right are patients that have experienced left ventricular systolic dysfunction, the red curve, and those who did not, the green curve. You can see for both overall survival and event-free survival cardiac dysfunction predict support outcome in these patients. Unfortunately, we can't cure kids without high doses of anthracycline, we can't cure kids without high doses of cytarabine, both of these increase risk for a cardiac dysfunction.

Secondary AML Treatment in Pediatric Patients

Therapy-related AML: Treatment

original reports

Phase I/II Study of CPX-351 Followed by Fludarabine, Cytarabine, and Granulocyte-Colony Stimulating Factor for Children With Relapsed Acute Myeloid Leukemia: A Report From the Children's Oncology Group

Todd M. Cooper, DO[1]; Michael J. Absalon, MD, PhD[2]; Todd A. Alonzo, PhD[3]; Robert B. Gerbing, MA[4]; Kasey J. Leger, MD, MSc[1]; Betsy A. Hirsch, PhD[5]; Jessica Pollard, MD[6]; Bassem I. Razzouk, MD[7]; Richard Aplenc, MD, PhD[8]; and E. Anders Kolb, MD[9]

TABLE 2. Grade ≥ 3 Toxicity by Treatment Course

	Cycle 1 (n = 38)		Cycle 2 (n = 27)	
CTCAEv4 Adverse Event	No.	%	No.	%
None	4	10.5	13	48.1
Febrile neutropenia	17	44.7	6	22.2
Mucositis oral	1	2.6		
Fever	2	5.3		
Infections and infestations (≥ 1)	17	44.7	5	18.5
Ejection fraction decreased	1	2.6		
Electrocardiogram QT corrected interval prolonged (all grades)	7	18.4	7	25.9
Rash maculopapular	15	39.5	1	3.7

Abbreviation: CTCAEv4, Common Terminology Criteria for Adverse Events, version 4.

TABLE 5. Characteristics of Responders

CR, CRp, CRi	Measure
Total	30
Cytogenetics, No. (total)	
Normal	4 (5)
Favorable: Inv(16);t(8;21)	6 (6)
Monosomy 7	2 (2)
11q23	4 (6)
Del(7q)	2 (2)
3q and 13q	1 (1)
13q only	0 (1)
Other	6 (6)
Unknown	5 (9)
Disease status (length of CR1), No. (total)	
< 180 days	3 (5)
180-365 days	13 (19)
> 365 days	14 (14)
HSCT received after therapy and before relapse? No. (%)	
Yes	29[a] (96.7%)
No	1 (3.3%)

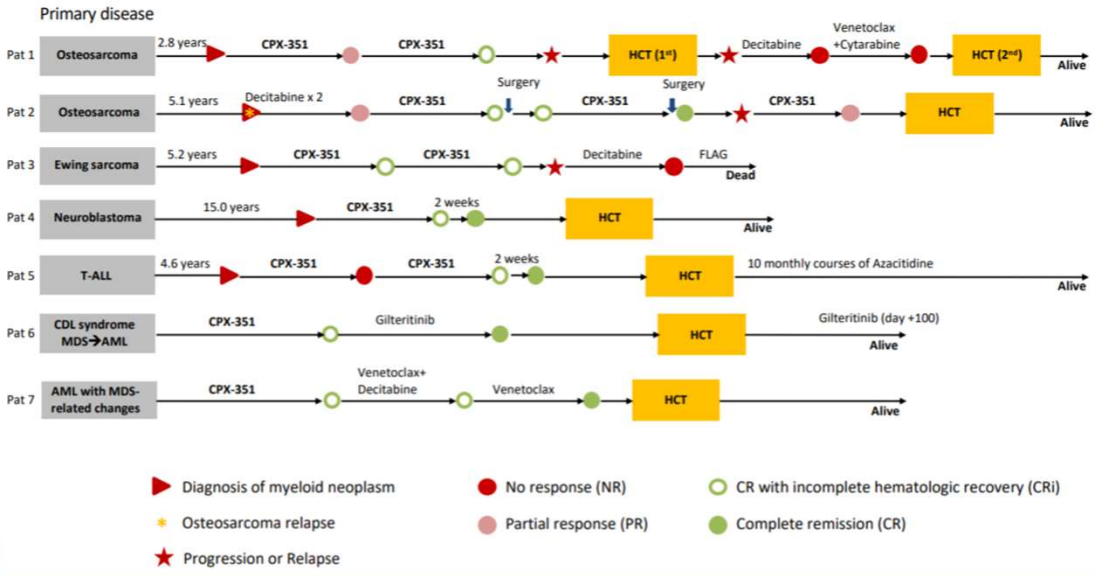
Abbreviations: CR, complete remission; CR1, first complete remission; CRi, complete remission with incomplete blood count recovery; CRp, CR with partial recovery of platelet count; HSCT, hematopoietic stem cell transplantation.
[a]Four patients confirmed that they went to HSCT as consolidation after the data cutoff for this manuscript.

Cooper T, et al. *J Clin Oncol*. 2020;38(19):2170-2177.

As far as the treatment specifically of therapy-related AML, there have been a couple studies that are informative. This is a study run by Todd Cooper and published in JCO last year. This is a phase I, phase II study of CPX-351 followed by cycle fludarabine cytarabine in patients with relapsed AML. The adverse events shown in table two were consistent with what we would see for any intensive reinduction therapy for a child with relapsed AML. About half of the kids get fever and neutropenia, half the kids get some infection. Overall, the therapy was quite tolerable in these patients and it led to a significant response rate that you can see at the table labeled table 5. We have an overall response rate in these patients at around 80%, that includes CR, CRp and CRi.

Secondary AML Treatment in Pediatric Patients

Therapy-related AML: Treatment



Hu Y, et al. *Blood Adv*. 2021;5(7):1837-1847.

This is a study recently published by St. Jude looking at a handful of patients with secondary AML and one patient who had Cornelia de Lange syndrome, who had myelodysplasia followed by AML, that ultra-rare event that I described previously. Of these patients, all of them received CPX-351. You can see where there were complete responses in all patients ultimately leading them to transplant in all but one case. CPX-351 appears very effective in relapsed AML. It's usually very effective in therapy-related AML. Accumulative effect of the adult data, as well as the phase II data that I showed led to a label extension for use of this drug in children with secondary AML.

That concludes the talk. I appreciate everybody's attention today. Thank you for your time.