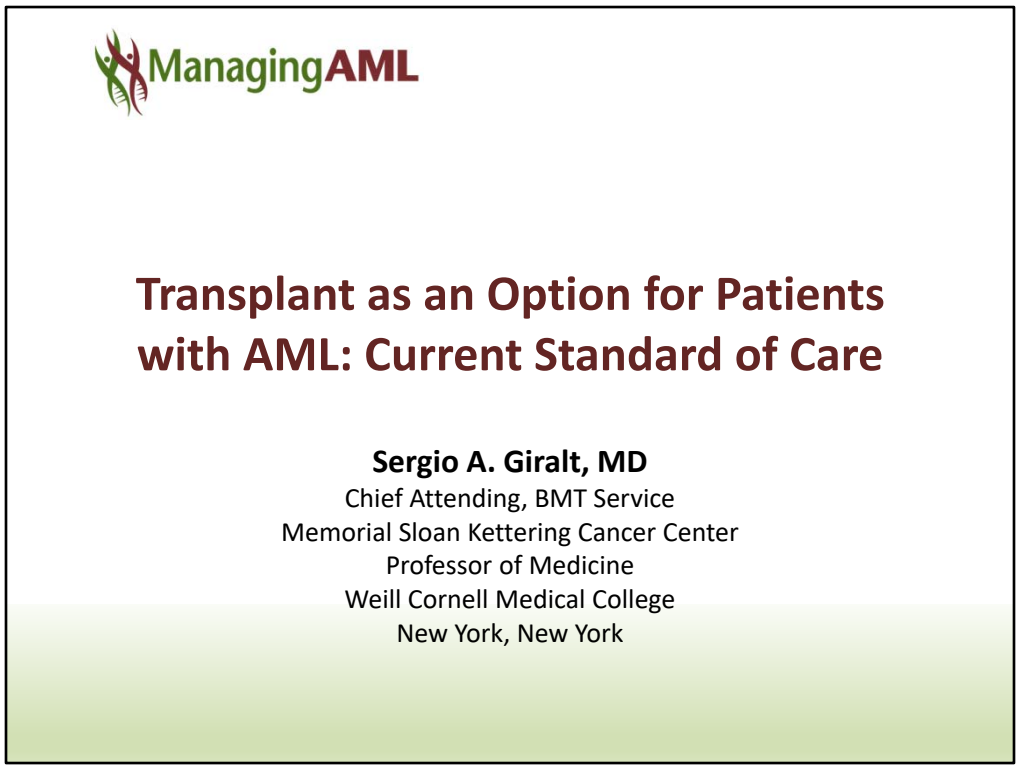
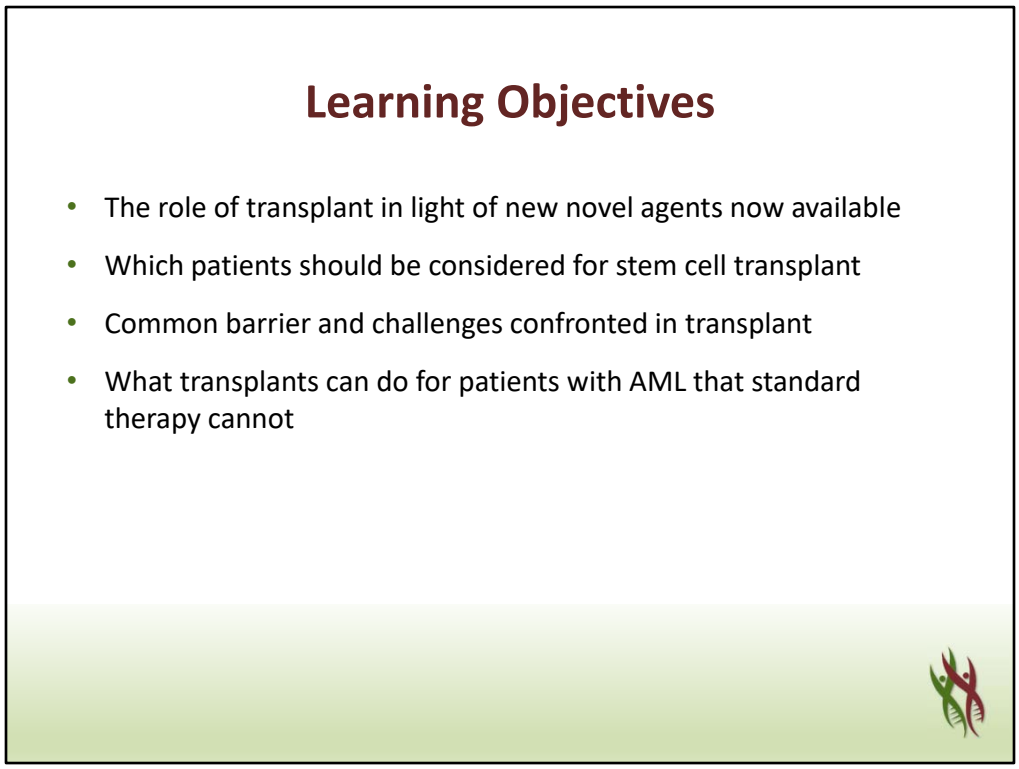
Transplant as an Option for Patients with AML: Current Standard of Care

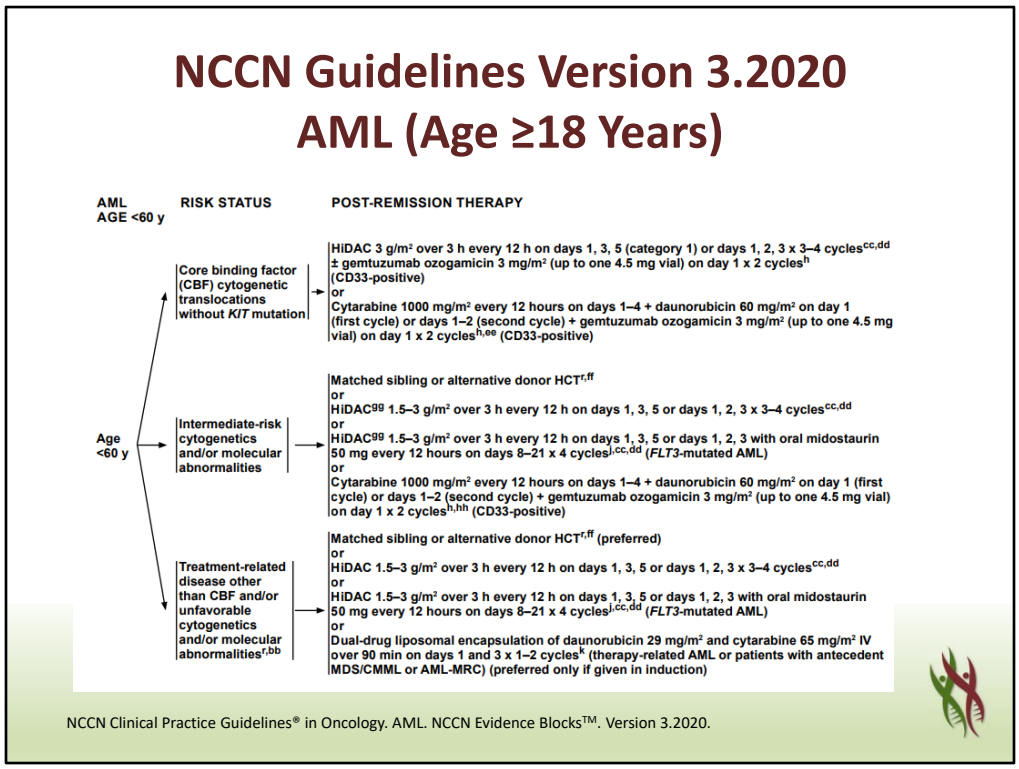


Hello. I am Sergio Giralt, the Melvin Berlin Family Chair in Myeloma Research, Professor of Medicine at Weill Cornell Medical College, and the Chief Attending of the Adult BMT Service at Memorial Sloan Kettering Cancer Center in New York City. Today I want to spend some time talking to you about the landscape of acute myeloid leukemia therapy with hematopoietic cell transplantation in the era of novel agents



During this presentation I will cover the role of transplant in light of the new agents that are now available, which patients should be considered for stem cell transplant, barriers and challenges that confront patients and their families and the transplant programs to get into a hematopoietic cell transplantation, and what transplants can do for patients that standard therapy cannot.

Transplant as an Option for Patients with AML: Current Standard of Care



What I am showing you here are the NCCN guidelines the version of 2020. These are for patients less than 60 years of age and over 18. As you can see and as we all know, treatment depends on the presence or absence of specific cytogenetic abnormalities. Core binding factor abnormalities should get high-dose therapy. Intermediate-risk cytogenetics and/or molecular abnormalities should be induced with high-dose AraC and considered for allogeneic transplant, and then in other patients with unfavorable cytogenetics, again, high-dose AraC induction and consideration for an allogeneic transplant should be had.

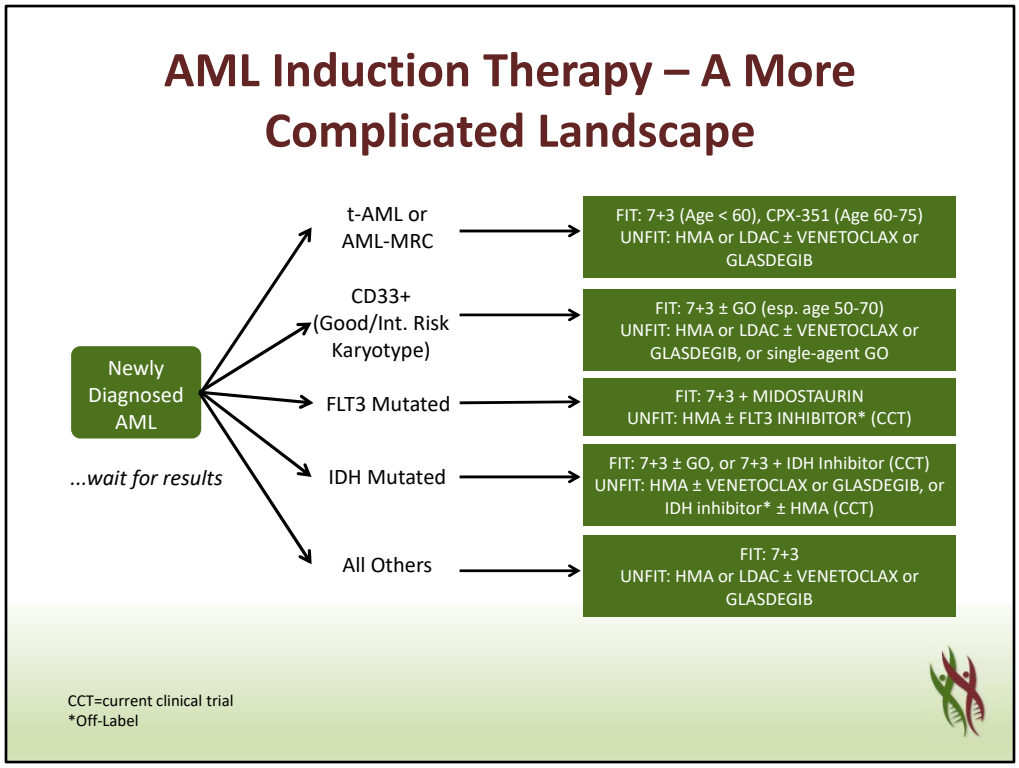
Five (More!) FDA Approvals for AML in 2018 in US

- In 2017, four new drugs were approved:
  - **Midostaurin** (newly-diagnosed $FLT3_{mut}$ AML)
  - **CPX-351** (therapy-related AML, or AML with MDS-related changes)
  - **Gemtuzumab** ozogamicin (CD33+ AML)
  - **Enasidenib** ($IDH2_{mut}$ relapsed/refractory AML)
- July 20, 2018: **Ivosidenib** ($IDH1_{mut}$ R/R AML)
- November 21, 2018: **Glasdegib** and **Venetoclax** with HMA/LDAC (≥75 or unfit)
- November 28, 2018: **Gilteritinib** ($FLT3_{mut}$ R/R AML)
- December 21, 2018: **Tagraxofusp-erzs** (SL-401) for BPDCN*

*Blastic plasmacytoid dendritic cell neoplasm

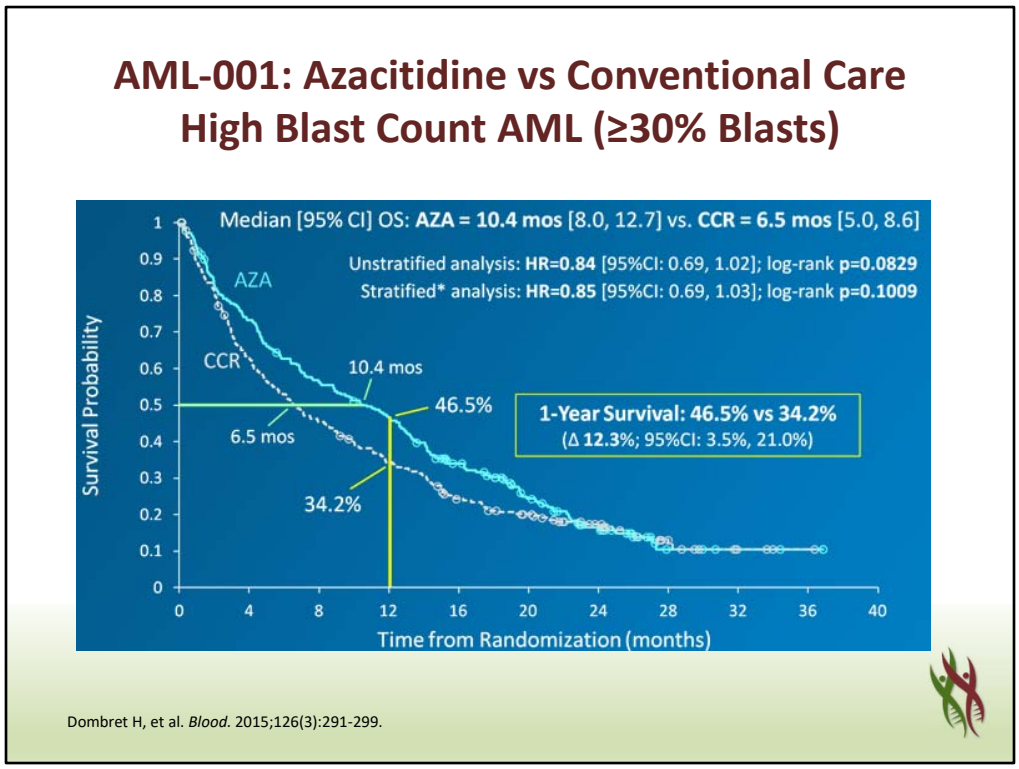
Now, we need to remember that in 2018 there were five drugs that were FDA approved for acute myelogenous leukemia. Midostaurin is a FLT3 inhibitor and was approved for newly-diagnosed AML with FLT3 mutations. CPX-351 (trade name Vyxeos) or liposomal daunorubicin AraC was approved for therapy-related AML or AML with MDS changes. Gemtuzumab ozogamicin (or Mylotarg) was approved for CD33 AML. Enasidenib was approved for IDH2 relapsed/refractory acute myelogenous leukemia. Furthermore, ivosidenib was approved for IDH1 mutated relapse/refractory acute myelogenous leukemia. Towards the end of 2018 we had three more approvals, glasdegib and venetoclax, gilteritinib, and for blastic plasmacytoid dendritic cell neoplasm tagraxofusp.

Transplant as an Option for Patients with AML: Current Standard of Care



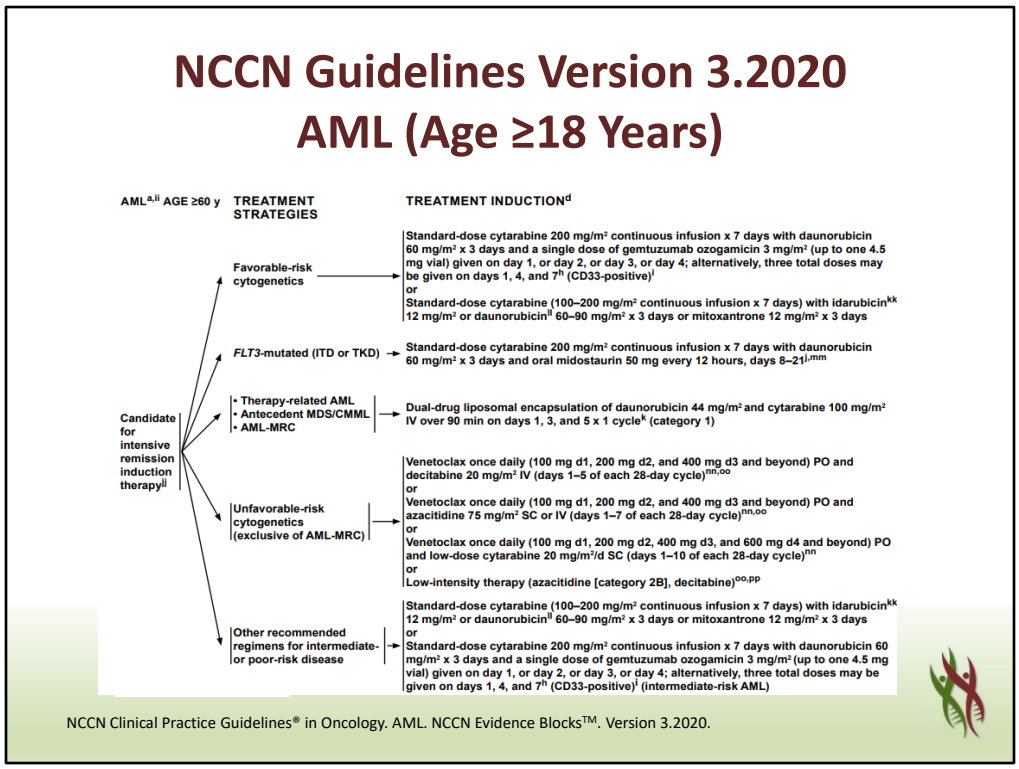
How do we incorporate these new agents into our treatment paradigms? The landscape for AML induction has become much more complicated. For example, CD33 positive acute leukemias which are usually good at intermediate-risk can be considered for gemtuzumab therapy. Patients with FLT3 mutation should be considered for midostaurin induction with or without a 7+3 backbone. Patients with IDH mutations who are unfit could go into remission with a hypomethylating agent and venetoclax. In all others, if they are unfit, should be considered for a hypomethylating agent of venetoclax or glasdegib if they have the appropriate cytogenetic abnormality.

Transplant as an Option for Patients with AML: Current Standard of Care



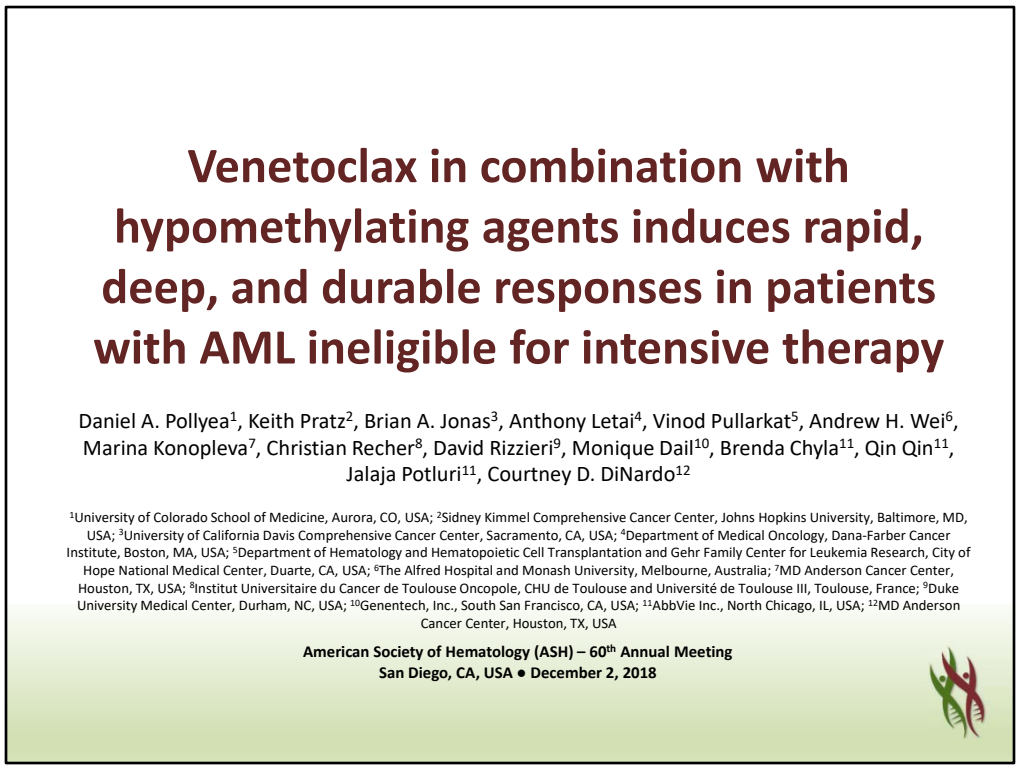
What does the data look like when we do not use conventional induction? Well, the randomized trial of azacitidine versus conventional care for patients with AML greater than 30% blasts showed a significant benefit for azacitidine in regards to one-year survival, 46% versus 34%, and more and more physicians are actually using an azacitidine backbone as induction therapy for acute myelogenous leukemia to avoid the toxicities of conventional cytotoxic chemotherapy.

Transplant as an Option for Patients with AML: Current Standard of Care



In this case we are now having a much more complicated NCCN guidelines and I am not going to go over them individually. You have the slide of the NCCN guidelines, but suffice it to say that when initially there was only one-size-fits-all, everybody got 7+3, now the combination of venetoclax and hypomethylating agents either decitabine, azacitidine, or low-dose cytarabine is being frequently used for patients who are both fit and unfit for allogeneic transplant. In patients who have a specific targetable abnormality such as FLT3 mutated, standard-dose cytarabine Ara-C in combination with midostaurin is considered the standard of care. For patients with IDH mutations, their use in induction therapy as currently being explored and we will discuss those studies in a minute.

Transplant as an Option for Patients with AML: Current Standard of Care



Venetoclax in combination with hypomethylating agents induces rapid, deep, and durable responses in patients with AML ineligible for intensive therapy

Daniel A. Pollyea[1], Keith Pratz[2], Brian A. Jonas[3], Anthony Letai[4], Vinod Pullarkat[5], Andrew H. Wei[6], Marina Konopleva[7], Christian Recher[8], David Rizzieri[9], Monique Dail[10], Brenda Chyla[11], Qin Qin[11], Jalaja Potluri[11], Courtney D. DiNardo[12]

[1]University of Colorado School of Medicine, Aurora, CO, USA; [2]Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD, USA; [3]University of California Davis Comprehensive Cancer Center, Sacramento, CA, USA; [4]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; [5]Department of Hematology and Hematopoietic Cell Transplantation and Gehr Family Center for Leukemia Research, City of Hope National Medical Center, Duarte, CA, USA; [6]The Alfred Hospital and Monash University, Melbourne, Australia; [7]MD Anderson Cancer Center, Houston, TX, USA; [8]Institut Universitaire du Cancer de Toulouse Oncopole, CHU de Toulouse and Université de Toulouse III, Toulouse, France; [9]Duke University Medical Center, Durham, NC, USA; [10]Genentech, Inc., South San Francisco, CA, USA; [11]AbbVie Inc., North Chicago, IL, USA; [12]MD Anderson Cancer Center, Houston, TX, USA

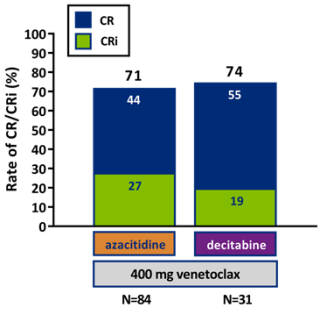
American Society of Hematology (ASH) – 60th Annual Meeting
San Diego, CA, USA ● December 2, 2018

Why are we so interested in non-cytotoxic induction therapies? This paper presented in the 2018 ASH meeting by Dr. Dan Pollyea and his group and Courtney DiNardo shows us the responses in patients who were ineligible for intensive therapy.

Transplant as an Option for Patients with AML: Current Standard of Care

First-line HMA's and Venetoclax

- **AZA** (n=84) or **decitabine** (n=31) and venetoclax at 400 mg dose



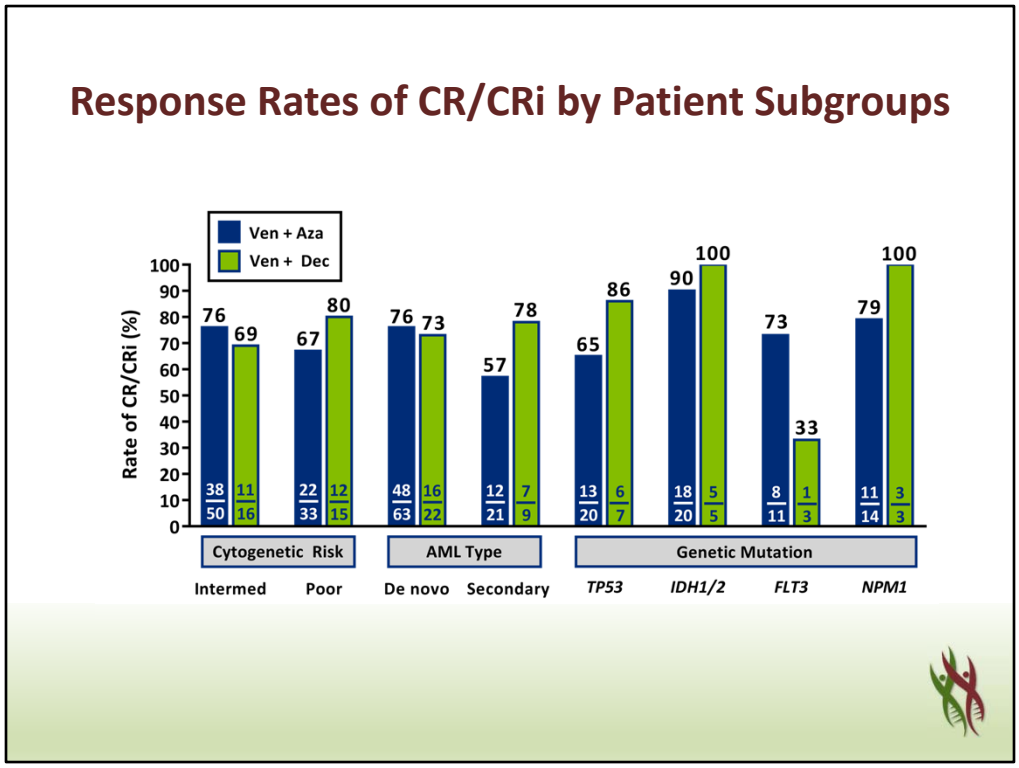
Time to CR (months)	Median 1.2 (0.7–5.5)	Median 1.9 (0.9–4.6)

Serious AEs ≥5%	Venetoclax + Aza (84)	Venetoclax + Dec (31)
Febrile neutropenia	26 (31)	14 (45)
Pneumonia	19 (23)	9 (29)
Sepsis	3 (4)	2 (6)
Respiratory failure	3 (4)	2 (6)
Any AE leading to:		
Dose interruption*	56 (67)	20 (65)
Early Deaths, n (%)		
≤30 days	2 (2%)	2 (7%)

Pollyea D, et al. ASH 2018. Abstract 285.

What you can see is a very high rate of complete remissions and complete remissions with incomplete count recovery. When we add venetoclax to either hypomethylating agent, be it azacitidine or decitabine, and early deaths were extremely low 2% to 7%, significantly less than what would be expected with conventional chemotherapy and the result significantly better than with supportive care alone.

Transplant as an Option for Patients with AML: Current Standard of Care



More importantly, in all genetic subgroups and in all AML types the benefits we saw high rates of CR and CRi this would not have been seen obviously with supportive care alone, and the toxicity seen in these group of patients with a conventional 7+3 would have been extremely high.

Transplant as an Option for Patients with AML: Current Standard of Care

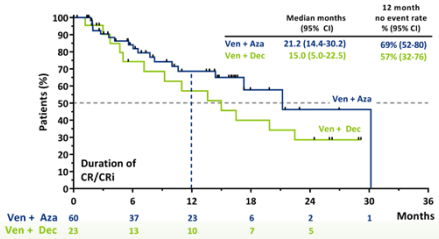
Duration of Response After Achieving CR/CRi

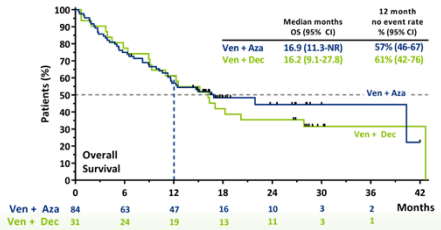
Median Follow-up

Venetoclax + azacitidine **14.9 months** (range 0.4-42.0)
Venetoclax + decitabine **16.2 months** (range 0.7-42.7)

Median Number of Cycles : 6
Range: 1-32 months (Aza), 1-29 months (Dec)

	Ven & Aza	Ven & Dec
Duration CR/CRi	**21.2 mos**	**15.0 mos**
Overall Survival	**16.9 mos**	**16.2 mos**





Overall survival for these patients is now almost a year and a half, again significantly better than what would be expected with use of supportive care alone or conventional 7+3.

Transplant as an Option for Patients with AML: Current Standard of Care

First-line HMA/LDAC and Venetoclax

- High rates of CR/CRi, with some deep and durable responses observed
- Similar results with LDAC + venetoclax[1]
- No TLS in this trial with HMAs, only one 'laboratory TLS' in LDAC trial
- Venetoclax plus HMAs and LDAC now FDA-approved in US*
  - Data from randomized phase 3 study pending

*FDA approved for use in untreated patients with AML who are 75 years or older or who have comorbidities that preclude the use of intensive induction chemotherapy

[1]Wei A, et al. ASH 2018. Abstract 284.

This has resulted in the adoption of a combination of venetoclax and hypomethylating agents for many patients who are 75 years or older who have comorbidities that preclude the use of intensive induction chemotherapy. However, many physicians are actually applying this combination to patients who could be eligible for intensive induction therapy or are using it as a bridge to transplant and the perception that patients will be coming into transplant in better condition.

Transplant as an Option for Patients with AML: Current Standard of Care

Does HMA + Venetoclax Work for Everyone?

- Many of the responses are ***CRi***
- Responses broadly similar across genetic/cytogenetic risk groups (BUT):
  - ***PTPN11*** *mutations confer unique metabolic properties and* ***increase resistance*** *to venetoclax and azacitidine*[1] (Univ. of CO)
- City of Hope analysis (n=107),[2] retrospective study, 72 gene NGS
  - High-risk cytogenetics predict lower response rate
  - Better CR/CRi in patients ***lacking*** mutations in *RAS, TP53,* and *RUNX1*

[1] Stevens B, et al. *Blood.* 2018;132(Supplement 1):909. [2] Aldoss I, et al. *Blood*. 2018;132(Supplement 1):334.

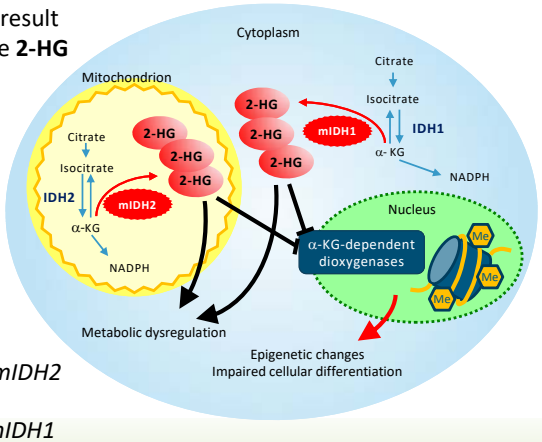
Does this work for everyone? Many of the responses are complete remissions with incomplete counts recovery. We do know that mutations in PTPN11 increase resistance to venetoclax and azacitidine. In a retrospective study done by the City of Hope, patients with high-risk cytogenetics had a lower response rate, but patients who lacked the mutations in RAS, P53 and RUNX1 had better responses.

Transplant as an Option for Patients with AML: Current Standard of Care

Isocitrate Dehydrogenase (IDH) Mutations in AML

- Somatic *IDH1* and *IDH2* mutations result in accumulation of on cometabolite **2-HG** → epigenetic changes, impaired cellular differentiation
- *mIDH* identified in multiple solid and hematologic tumors

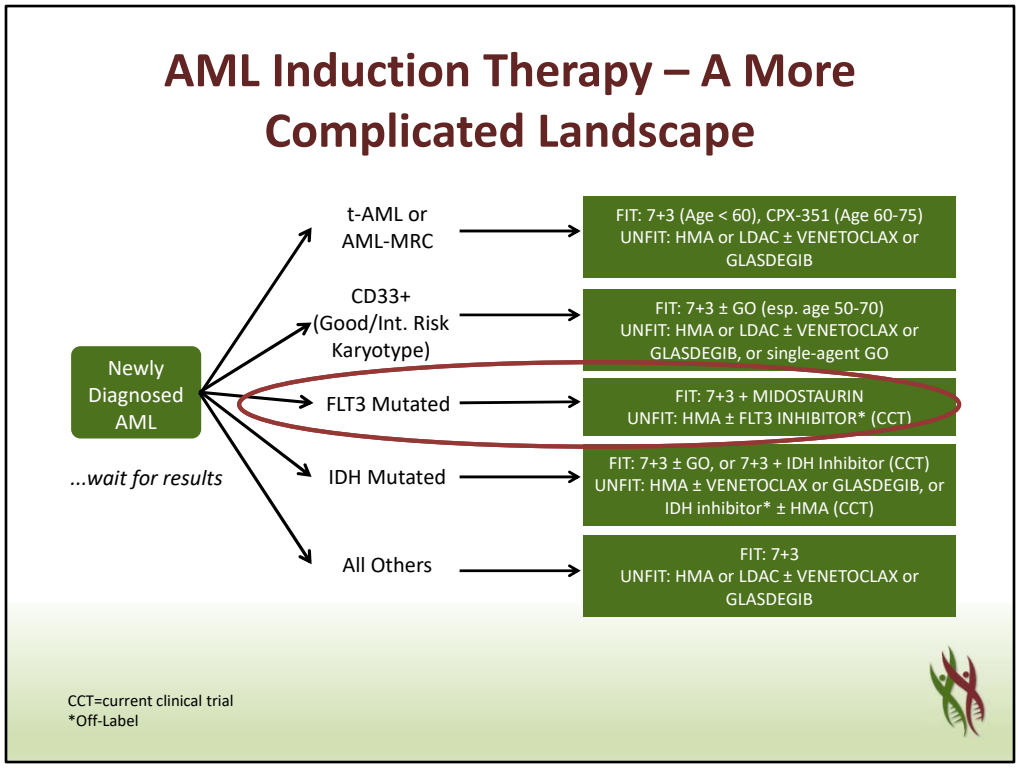
	mIDH1	mIDH2
% of AML patients	~6–10%	~9–13%



- **Enasidenib (AG-221):** inhibitor of *mIDH2*
- **Ivosidenib (AG-120):** inhibitor of *mIDH1*

IDH mutations have now been discovered as a major driver of acute myelogenous leukemia. This mutation causes metabolic dysregulation and epigenetic changes that impairs cellular differentiation and results in an acute myeloid leukemia phenotype. Mutations of IDH1 and IDH2 are seen in approximately 15% to 20% of the patients. There are now two commercially available inhibitors of both of these mutations. Enasidenib is an inhibitor of IDH2 and ivosidenib is an inhibitor of IDH1.

Transplant as an Option for Patients with AML: Current Standard of Care



This again shows how complicated the landscape has become because now we really should have mutational analysis done on all patients prior to start of induction therapy because patients with a FLT3 mutation should get midostaurin and patients with an IDH mutation should be that for an IDH inhibitor with 7+3. If they are fit, they should be considered for a 7+3 and gemtuzumab ozogamicin.

Transplant as an Option for Patients with AML: Current Standard of Care

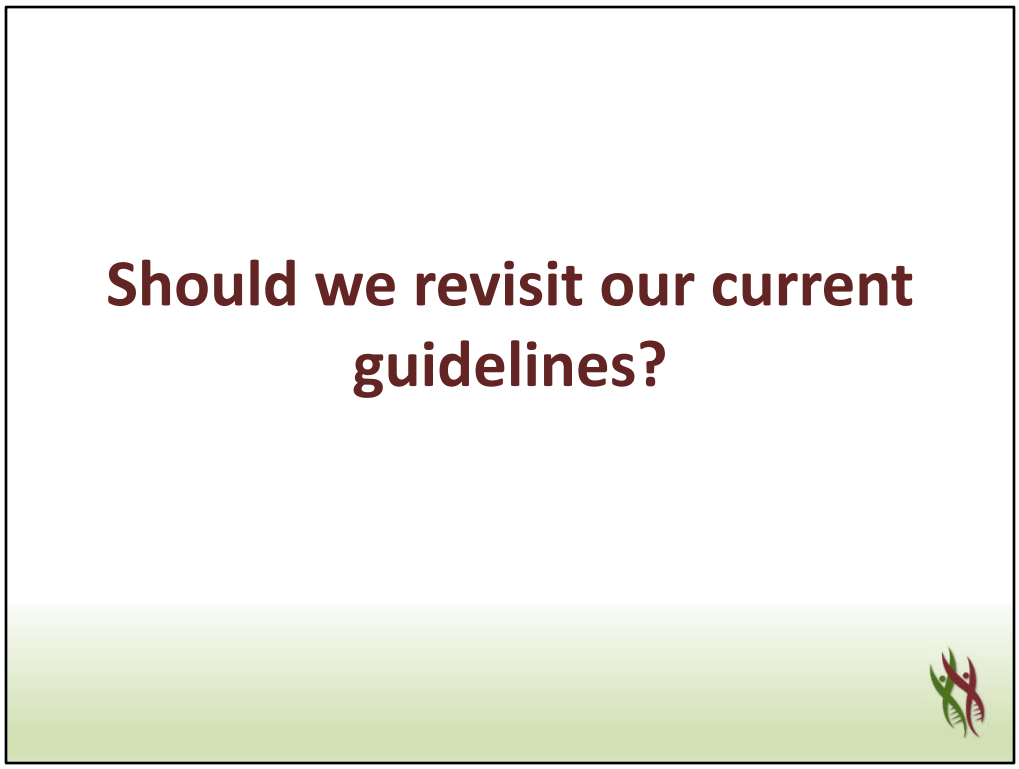
FLT3 Inhibitors and 7+3 Induction

- **Midostaurin**: FDA-approved, OS advantage ('RATIFY'), current standard of care

Drug	Half-life	D835	Selectivity	FDA Approval R/R AML	7&3 Combination
Quizartinib (AC220)	Long (daily)	No	Narrow (inhibits KIT)	***Pending***	Phase 1/2 complete[1] Phase 3 ongoing
Crenolanib	Short (TID)	Yes	Narrow (spares KIT)	Ongoing pivotal studies	Phase 2 complete[2] Phase 3 start 2018
Gilteritinib (ASP2215)	Long (daily)	Yes	Narrow (spares KIT)	FDA **Approval** 11/18	Phase 1/2 complete[3] ASH 2018 report

[1]Altman JK, et al. *Am J Hematol*. 2018;93:213. [2]Wang ES, et al. ASH 2017. Abstract 566. [3]Pratz KW, et al. ASH 2018. Abstract 564.

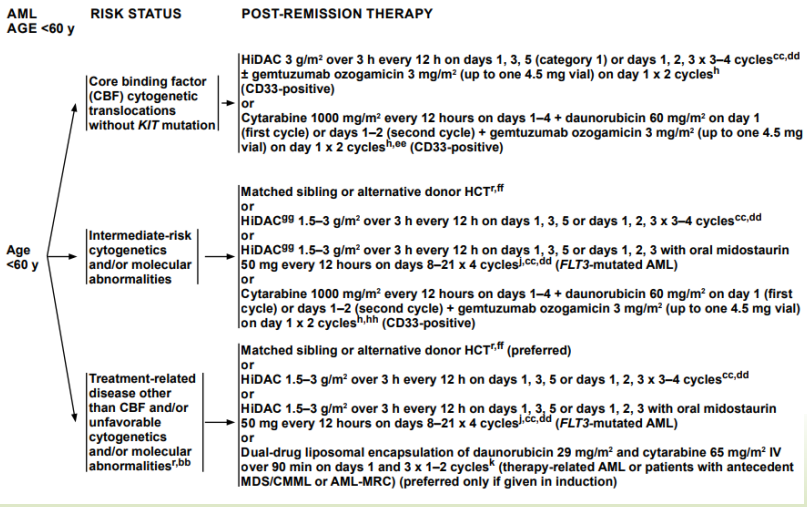
Many other FLT3 inhibitors are currently being explored: quizartinib, crenolanib, gilteritinib. Gilteritinib has also now been approved for patients with FLT3-mutated relapsed/refractory acute myelogenous leukemia.



Does this mean we should revisit our current guidelines?

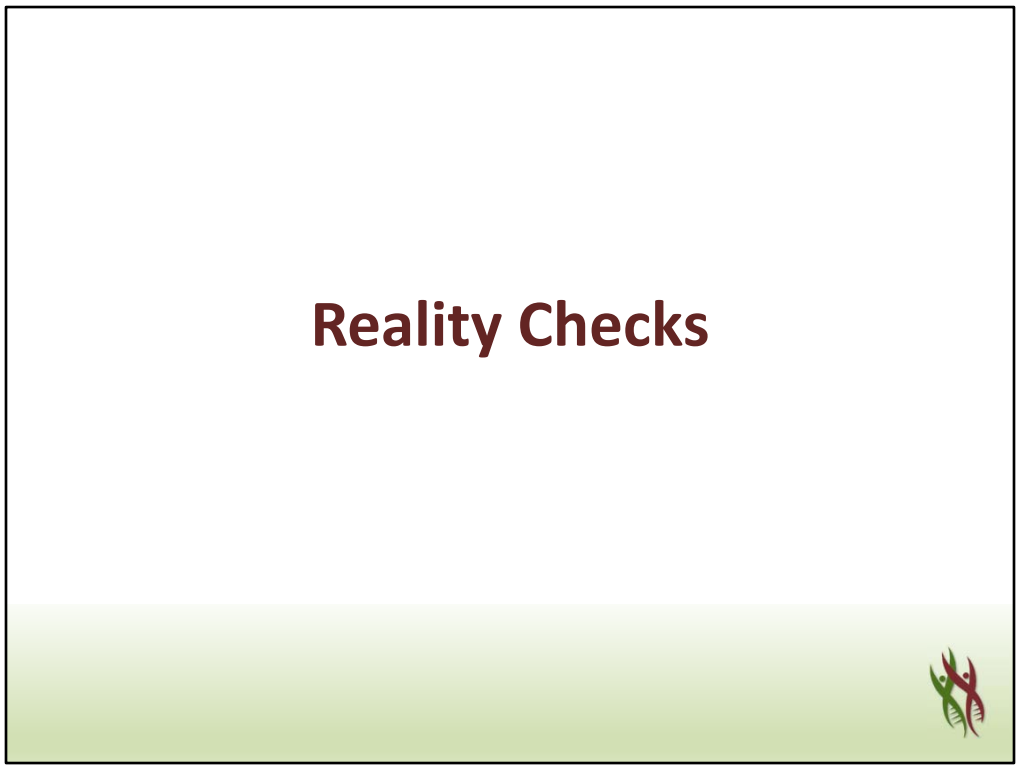
Transplant as an Option for Patients with AML: Current Standard of Care

NCCN Guidelines Version 3.2020
AML (Age ≥18 Years)



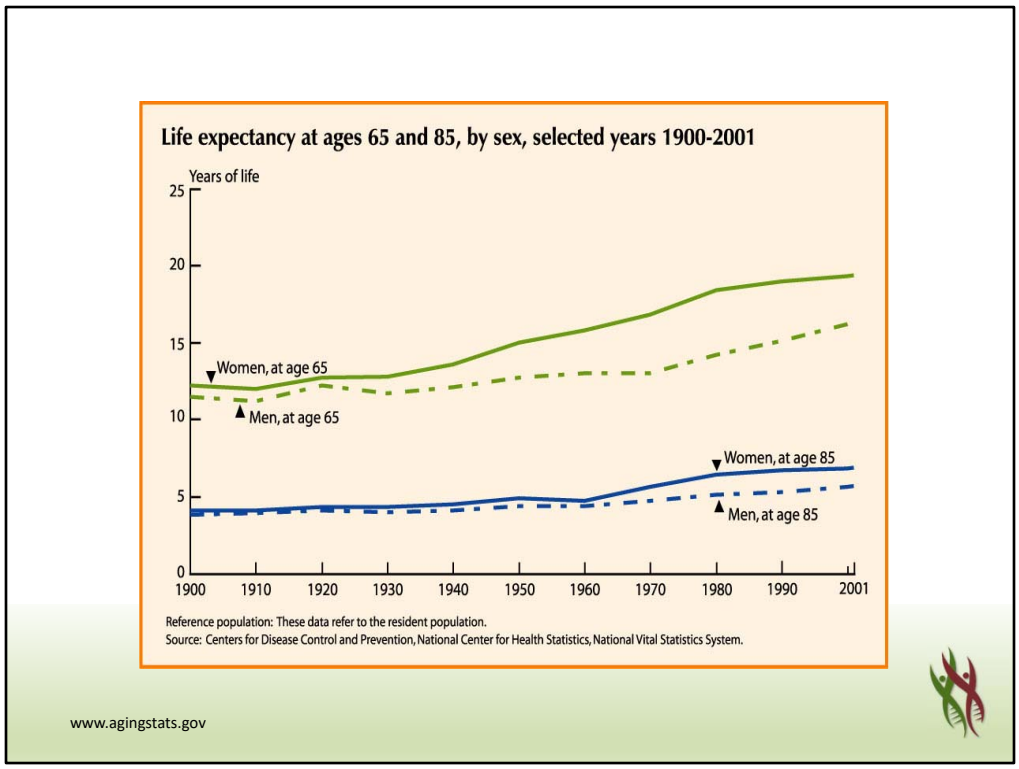
NCCN Clinical Practice Guidelines® in Oncology. AML. NCCN Evidence Blocks™. Version 3.2020.

Does this mean that patients with intermediate-risk cytogenetics or treatment-related disease should not be considered for an allogeneic transplant if one is available?



Well, let’s do some reality checks.

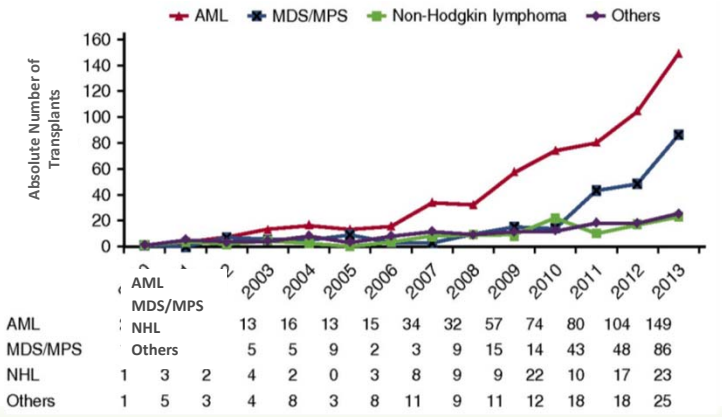
Transplant as an Option for Patients with AML: Current Standard of Care



First let's remember that a patient who is age 65 had a life expectancy of more than 80.

Transplant as an Option for Patients with AML: Current Standard of Care

Increasing Numbers of Allo-HCT for Patients Over the Age of 70



	AML	MDS/MPS	NHL	Others	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
AML					13	16	13	15	34	32	57	74	80	104	149
MDS/MPS					5	5	9	2	3	9	15	14	43	48	86
NHL	1	3	2		4	2	0	3	8	9	9	22	10	17	23
Others	1	5	3		4	8	3	8	11	9	11	12	18	18	25

AML=acute myeloid leukemia; MDS=myelodysplastic syndromes; MPS=myeloproliferative syndromes; NHL=non-Hodgkin lymphoma

Muffly L, et al. *Blood.* 2017;130(9):1156-1164.

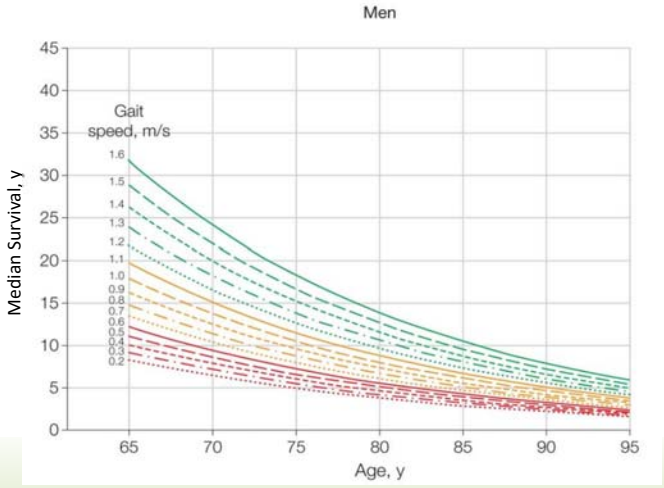
More and more patients over the age of 70 with both MDS and acute myelogenous leukemia are undergoing allogeneic transplants with reduced intensity conditioning regimens.

Transplant as an Option for Patients with AML: Current Standard of Care

It is not how old you are but how you carry your age that determines whether a patient is transplant eligible or not.

Transplant as an Option for Patients with AML: Current Standard of Care

Gait Speed and Survival in Older Adults



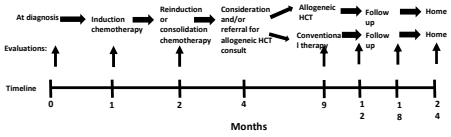
Frail=gait speed <0.8 m/s
Studenski S, et al. *JAMA*. 2011;305(1):50-58.

Gait speed is an important assessment, the slower the gait speed the higher the mortality rate for patients. We now consider, and others have shown as we have, that a formal geriatric assessment is essential to be able to decide what the risk-benefit ratio is for a patient to undergo an allogeneic transplant for acute myelogenous leukemia with intermediate- or high-risk disease.

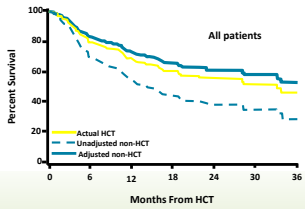
Transplant as an Option for Patients with AML: Current Standard of Care

Limitations to Receiving Allo-HCT for AML

Observational Study Schema



Survival rates among those who received HCT vs those who did not based on unadjusted and adjusted multivariate models



Risk Factors Associated With Mortality in 695 Patients With AML

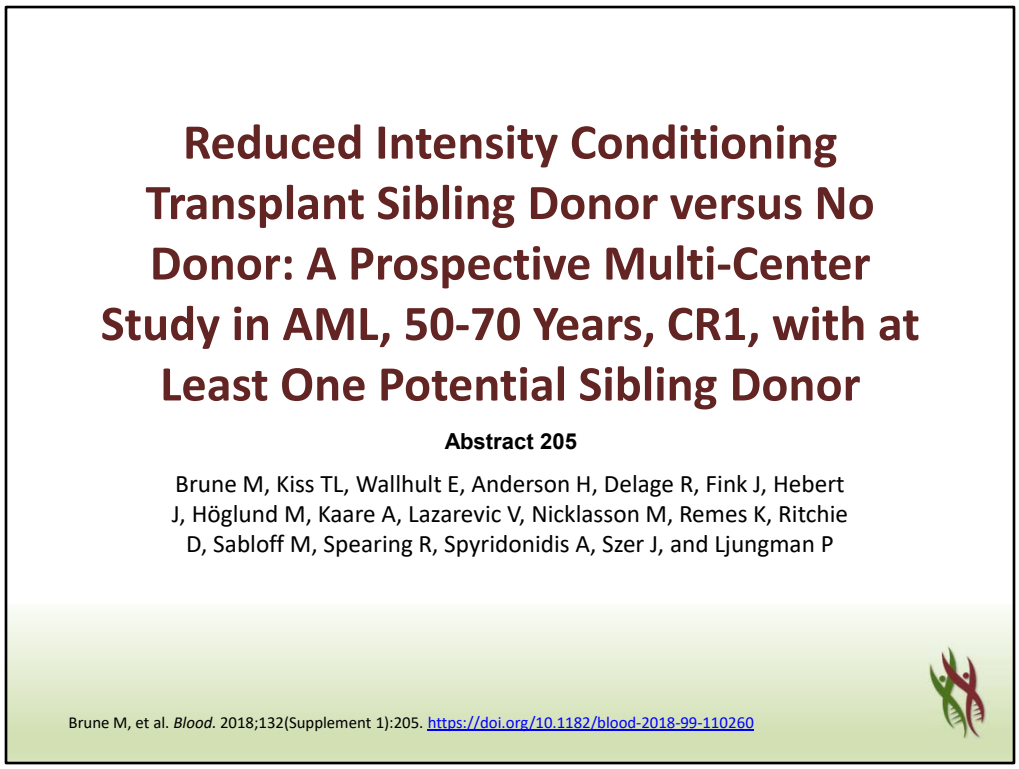
	HR	*P*
HCT-CI		
≥5	1.83	<.0001
Age		
60-64	1.50	.02
65-69	1.36	.06
≥70	2.19	<.0001
ELN cytogenetic risk		
Intermediate	1.53	.03
High	2.35	<.0001
Status at enrollment		
Newly diagnosed	1.0	
Relapsed/refractory	1.65	.0005
Status posttreatment		
Relapsed after CR (vs CR)	5.58	<.0001
Frailty per 4-meter walk test	1.31	.004
FACT-G (per 10 point)	0.89	.02
PHQ-9 depression (per point)	1.03	.03
"Activities of daily living" (per point)	0.95	.05

CI=confidence interval; CR=complete response; ELN=European LeukemiaNet; FACT-G=Functional Assessment of Cancer Therapy – General; PHQ-9=Patient Health Questionnaire

Sorror M, et al. *Blood.* 2018;132:Abstract 1388.

This was analysis that was done by Dr. Sorror presented at the ASH meeting in 2018. What he looked at was the outcomes of patients who were being induced with acute myelogenous leukemia over various centers that participate in the Seattle Consortium. When we just looked at actual survival rates, patients with AML who underwent a transplant seemed to have a significantly better outcome than patients who did not undergo a transplant, but when you adjust for a variety of co-factors such as comorbidities scores and frailty scores that difference actually disappears suggesting that for specific patients, particularly those with good performance status, there may not be that much of a benefit for an allogeneic transplant. However that was a retrospective study and it was not randomized and we do not know why patients received it or did not receive a transplant.

Transplant as an Option for Patients with AML: Current Standard of Care



More important is this study from Brune, et al. that was also presented at ASH 2018. This was a prospective multi-center study in AML in patients over the age of 50 who had achieved a complete remission who at least had one potential sibling donor.

Transplant as an Option for Patients with AML: Current Standard of Care

Baseline Characteristics

Patients	RICT/MSD N = 77	Control N = 68	Statistics
Gender F/M, n	33/44	41/37	**ns**
Age, median years, range	63 (52-70)	63 (50-69)	**ns**
Performance status (0-1)	74	74	**ns**
Risk group, IR/HR, %	65/35	69/31	**ns**
Donor age, years	60 (48-76)	NA	
Female donor, male patient, %	10	NA	
Chemotherapy consolidation, n ≥3, %	64	91	
RICT accomplished, yes/no	57(20)	6/62	

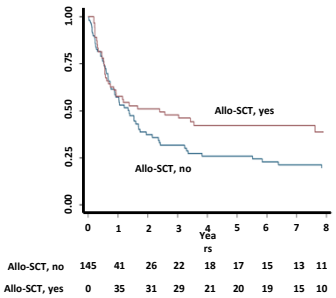
IR=intermediate; HR=hazard ratio; MSD=matched sibling donor; RICT=reduced intensity conditioning transplantation
Brune M, et al. *Blood.* 2018;132: Abstract 205.

Approximately 77 patients had a sibling donor and underwent an allogeneic transplant and they had 68 controls and the baseline characteristics were similar.

Transplant as an Option for Patients with AML: Current Standard of Care

Results

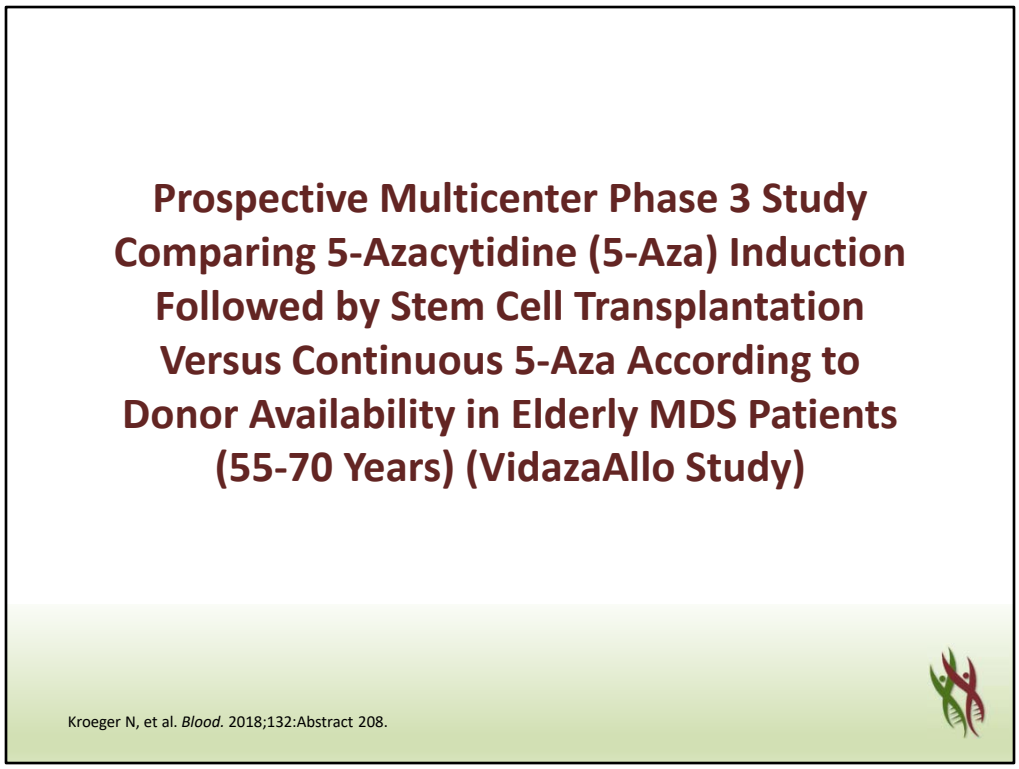
	RICT/MSD N = 77	Control N = 68	*P*
Overall survival, 3 years % (CI)	45 (33–56)	48 (36–60)	ns
Relapse-free survival, 3 years % (CI)	40 (29–50)	35 (24–47)	ns
Non-relapse mortality, 3 years (CI)	12 (5.8–20)	4.4 (1.2–11)	ns
Relapse incidence, 3 years % (CI)	49 (37–59)	60 (48–71)	ns
Causes of Death			
AML	37	45	
GVHD	5	NA	
Infection	4	1	
Other	5	5	
All mortality, n (%)	51 (66)	51 (75)	



Allo-SCT=allogeneic hematopoietic stem cell transplantation; GVHD=graft-vs-host disease
Brune M, et al. *Blood.* 2018;132: Abstract 205.

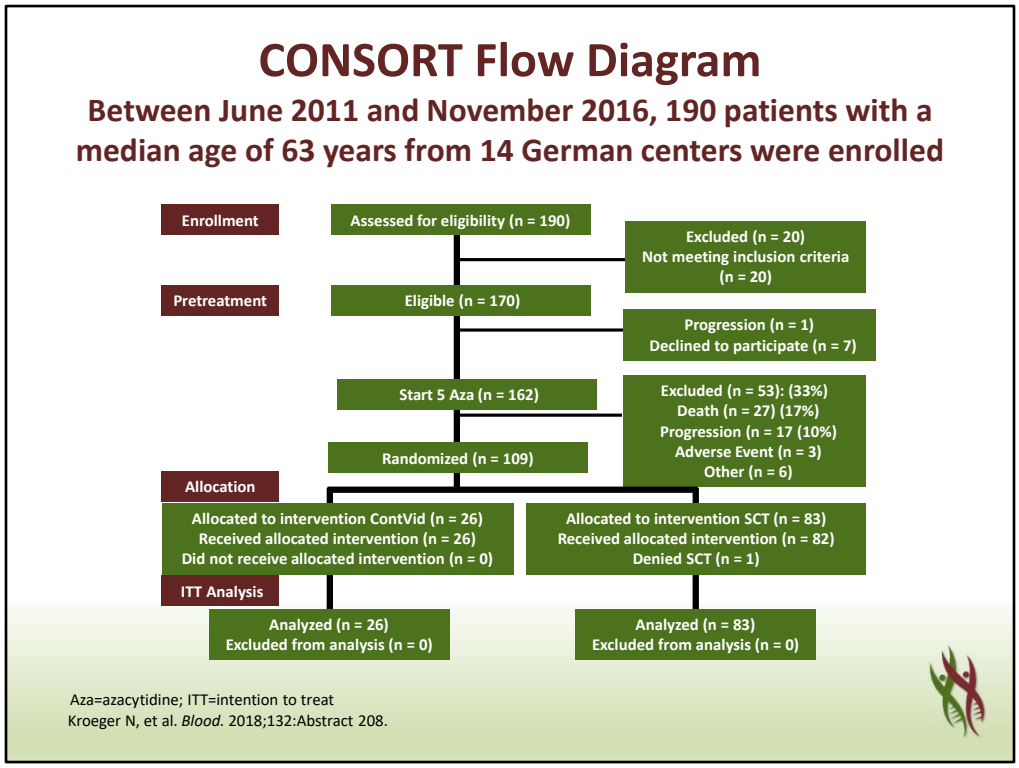
Overall survival three years was similar for patients who underwent a transplant versus those that did not. Non-relapse mortality was also no different, however at the tail of the curve when you start seeing a significant benefit for an allogeneic transplant.

Transplant as an Option for Patients with AML: Current Standard of Care



The group in Germany led by Dr. Nicholas Kroger reported also in ASH of 2018 the prospective multi-center phase 3 study comparing azacitidine induction followed by stem cell transplant versus continued azacitidine according to donor availability in myelodysplastic patients between the age of 55 and 70.

Transplant as an Option for Patients with AML: Current Standard of Care



This is the CONSORT diagram. Suffice it to say that patients who were eligible for transplant most of them went on to proceed to transplant.

Transplant as an Option for Patients with AML: Current Standard of Care

NCT01404741: Results

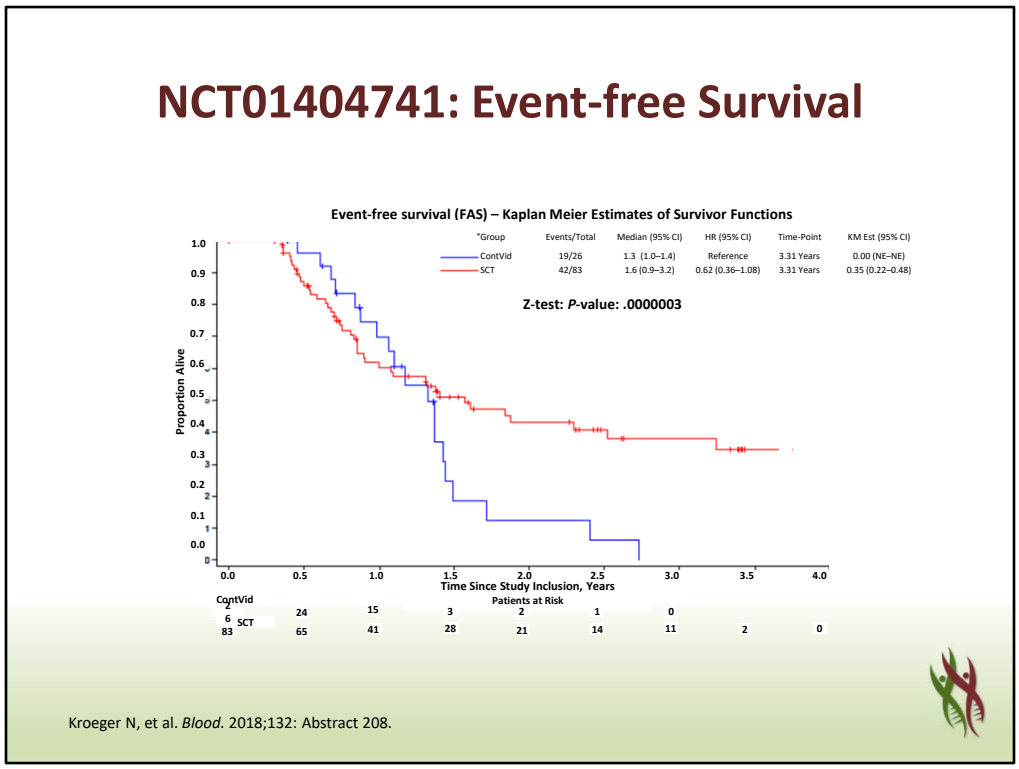
Results according to treatment arm (n = 109)

Variable	Allogeneic SCT	5–Aza Continued
Donor		
HLA-identical sibling	n = 14	--
Matched unrelated	n = 67	--
		-
Acute GVHD		
I - IV	n = 45 (54%)	--
II - IV	n = 28 (33%)	--
Chronic GVHD	n = 43 (52%)	--
Any AE n (%)	76 (91.6%)	23 (88.5%)
Any SAE n (%)	68 (81.9%)	19 (73.1%)
TRM at 1 year (95% CI)	23% (14–33)	0%
EFS at 3 years (95% CI)	35% (22–48)	0%
OS at 3 years (95% CI)	49% (36–61)	22% (6%–44%)

AE=adverse event; EFS=event-free survival; OS=overall survival; SAE=serious adverse event; TRM=transplant-related mortality
Kroeger N, et al. *Blood.* 2018;132:Abstract 208.

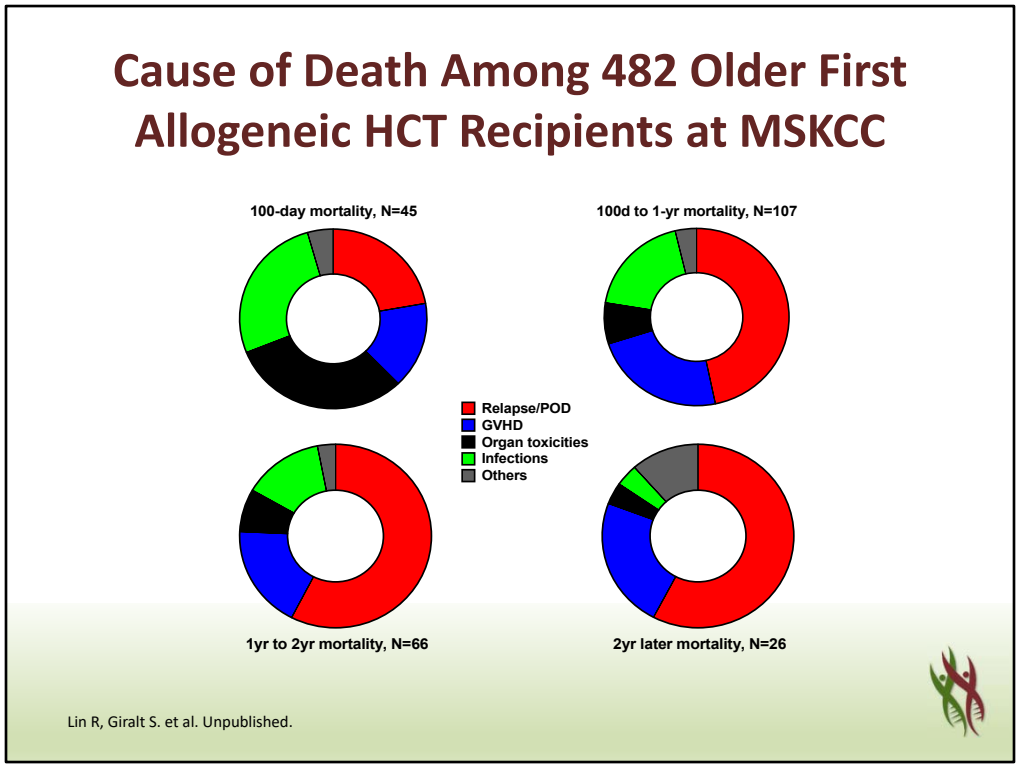
When we look at results according to treatment arm, most of these patients received an unrelated donor transplant, event-free survival at three years was significantly better for patients who underwent transplant, survival was significantly better although treatment-related mortality was also worse for the allogeneic transplant group.

Transplant as an Option for Patients with AML: Current Standard of Care



This is the survival and the event-free survival curve.

Transplant as an Option for Patients with AML: Current Standard of Care



What do older patients die of when they undergo transplant, they still die primarily from relapse and infections and graft versus host disease. How can we optimize outcomes?

Transplant as an Option for Patients with AML: Current Standard of Care

Geriatric Optimization Program Prior to HCT (U of Chicago)

Table 2. Considerations to optimize vulnerable HCT patients

Domain impaired	Intervention
Significant comorbid conditions	Subspecialty consultation and management in context of transplant and disease
Impaired function	Structured prehabilitation, encourage and teach patient appropriate activity through transplant. Home assessment aligned with patient limitations
Limited social support	Pretransplant family meeting, assign "Team Captain," and request secondary caregivers
Cognitive impairment	Delirium precautions, medication avoidance, and encourage greater presence of family support
Depression or anxiety	Recognize problem, cognitive ± medication management, and assess expected adherence post-HCT
Weight loss	Exclude concurrent medical problems, add supplements, and develop nutritional plan for transplant
Polypharmacy	Hold medications. Re-evaluate day 30 to 100 post-HCT
Any impairment	Adjust preparative regimen, donor source, and/or escalate posttransplant follow-up frequency. Assess posttransplant and modify intervention as needed. Enlist caregiver in optimization plan

Artz AS. *Hematology Am Soc Educ Program*. 2016:99-105.

The group at the University of Chicago has done significant work in trying to optimize the situation of patients prior to transplant with a comprehensive multidisciplinary approach in which all patients are seen by the geriatricians, the physiatrists, and social workers.

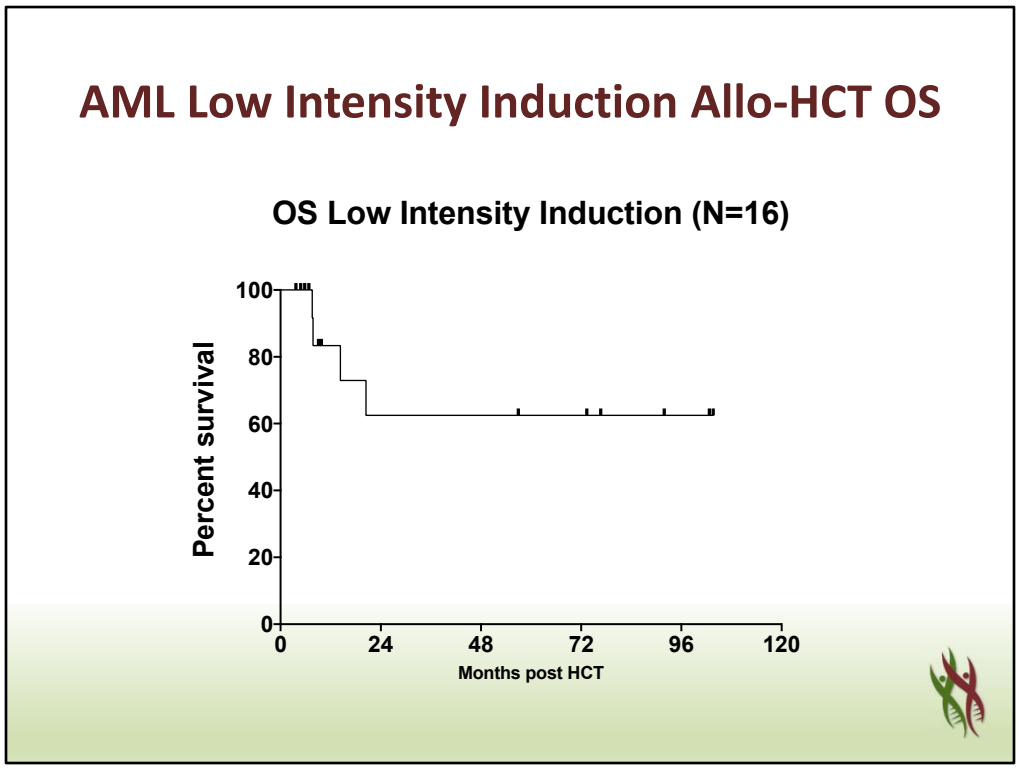
Transplant as an Option for Patients with AML: Current Standard of Care

Low Intensity Induction for Newly Diagnosed, Older/Infirm AML Patients

Agents (Reference)	N (Phase)	Eligibility criteria	CR/CRi (%)	mDOR (months)	Allo-HCT (% CR/CRi)
Decitabine (Kantarjian, 2011, *JCO*)	485 (Phase 3)	≥65, not eligible for IC	17.8%	NR	NR
Azacitadine (Dombret, 2015, *Blood*)	488 (Phase 3)	≥65, not eligible for IC	27.8%	10.4	NR
Decitabine + cladribine/LDAC (Kadia, 2018, *Lancet Haematol*)	118 (Phase 2)	≥60, not eligible for IC	68%	14.7	23%
Glasdegib + LDAC (Cortes, 2018, *Leukemia*)	132 (Phase 2)	≥55, not eligible for IC	26.9% (CR+CRi+MLFS)	6.5	1.2%
Venectoclax + HMA (DiNardo, 2019, *Blood*)	145 (Phase 1b)	≥65, not eligible for IC	67%	11.3	21.6%
Ivosidenib (Roboz, 2018, ASH Abstract 561)	34 (Phase 1)	Not eligible for IC	41.2%	Not reached (6.5 -)	21.4%

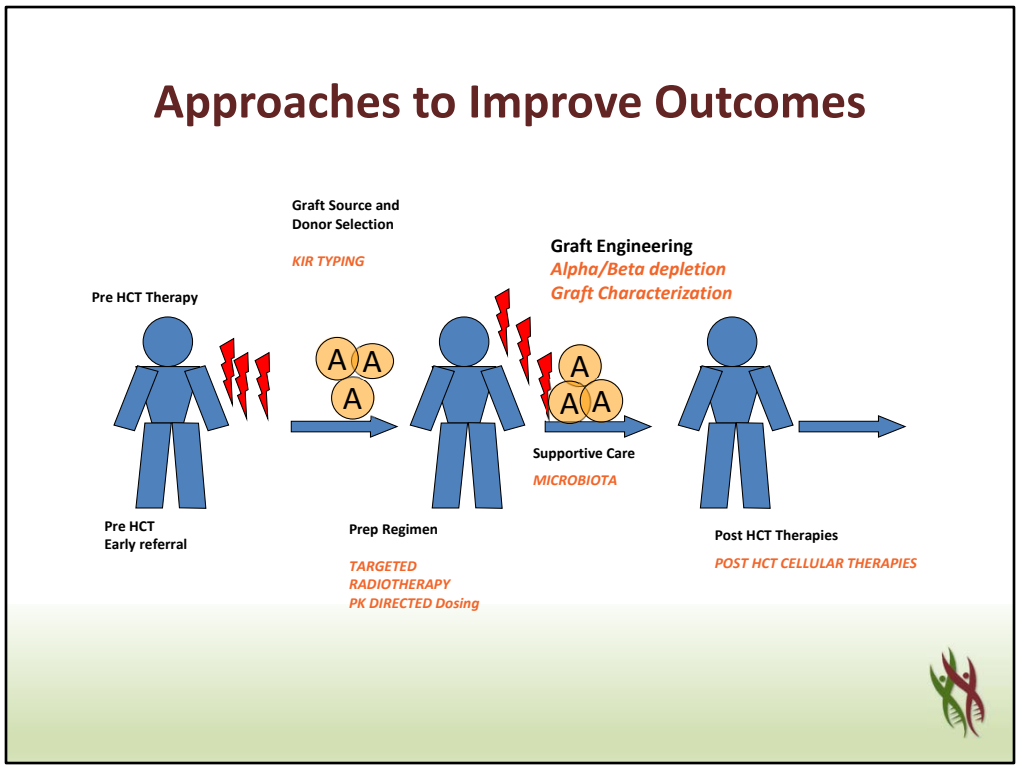
Interestingly enough, one of the things that is starting to emerge is that patients with low-intensity induction chemotherapy many of them are proceeding to transplant and in some studies such as Kadia, et al., 23% of the patients went on to transplant even they achieved a complete remission to a hypomethylating agent-venetoclax combination. In Dr. DiNardo's series 21% of the patients went on to transplant.

Transplant as an Option for Patients with AML: Current Standard of Care



When asked the question would it be better for older patients who are going to be bridged to transplant to receive a hypomethylating agent versus to receive the standard 7+3? In at least a preliminary look at our data at Memorial Sloan Kettering, patients who went to transplant after having received the low-intensity induction had a very low early non-relapse mortality and a preliminary results suggest a very positive outcome with 60% of the patients surviving disease free. How can we continue to improve outcomes?

Transplant as an Option for Patients with AML: Current Standard of Care

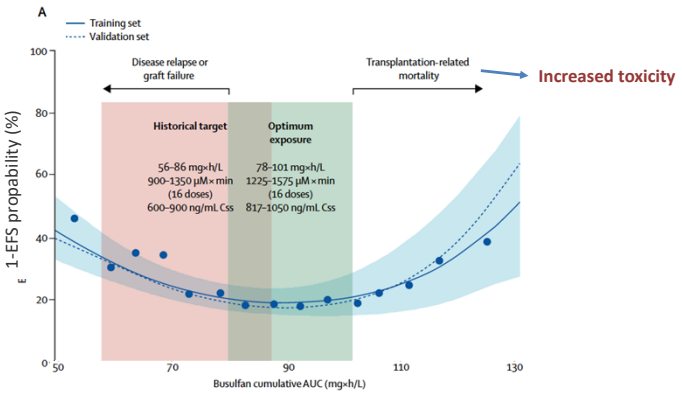


Well, we should find earlier referrals, better graft source and donor selection, and today everybody has a donor. We should think about new conditioning regimens and post transplant therapies to prevent relapse.

Transplant as an Option for Patients with AML: Current Standard of Care

Association Between Bu-AUC and EFS (n=674)

Children and Young Adults (0 – 30 years)

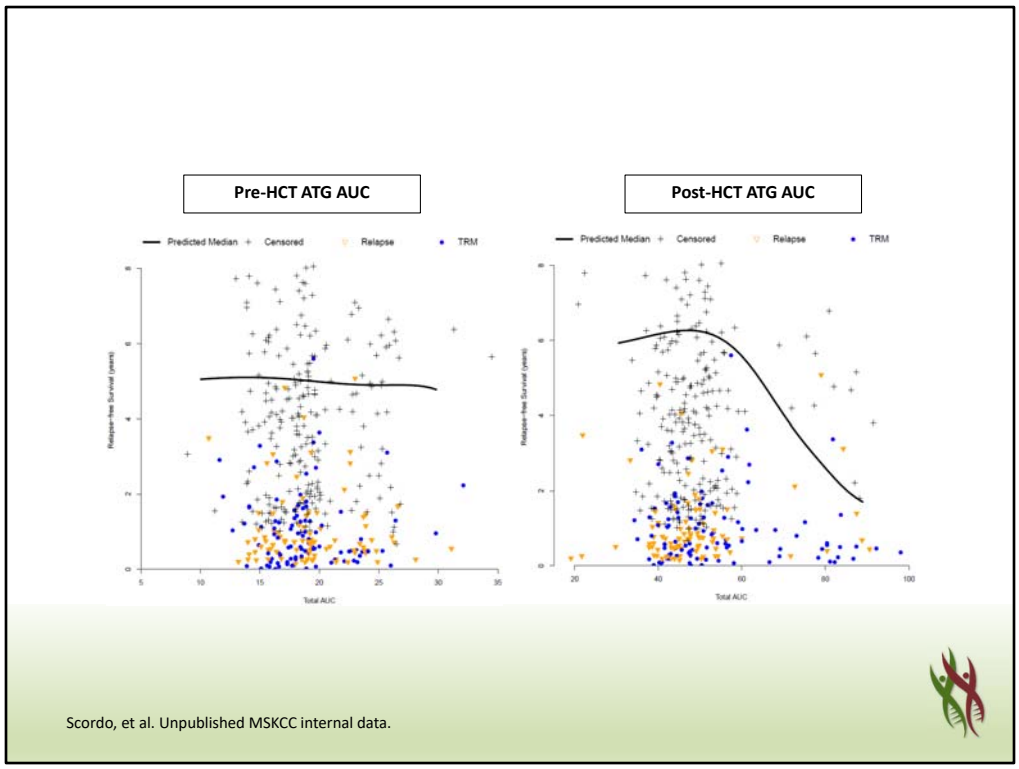


- No difference in optimum between malignant – benign disorders
- Fludarabine + busulfan: best LFS with lowest toxicity

Bartelink I, et al. *Lancet Haematol.* 2016;3:e526-e536.

One of the areas that we are exploring here and others is optimization of chemotherapy by doing PK directed therapy. In this paper by Bartelink, et al., you can see what happens when we have an optimal exposure of busulfan where the event-free survival is almost 80%. Overdosing busulfan increases transplant-related mortality, underdosing busulfan results in disease relapse or graft failure. Unfortunately, busulfan is the only drug that we currently use in transplant that we have a mechanism to dose target.

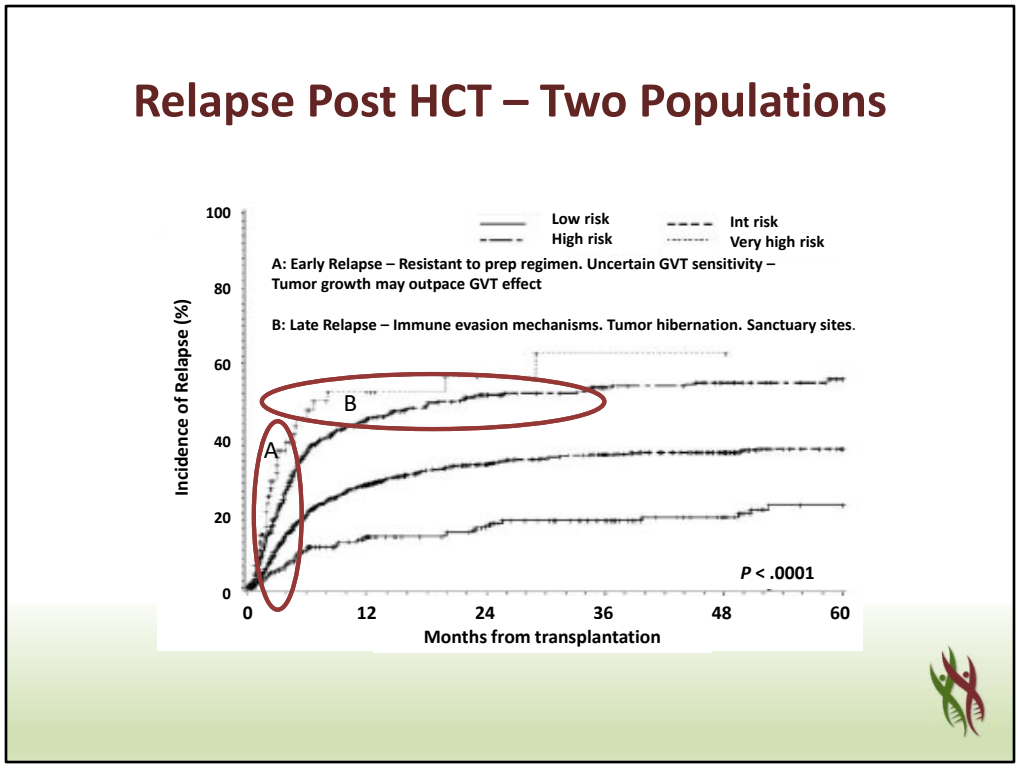
Transplant as an Option for Patients with AML: Current Standard of Care



Scordo, et al. Unpublished MSKCC internal data.

Another commonly used drug such as anti-thymocyte globulin also has an optimal dose. In this study done by Dr. Scordo and Dr. Bolens at Memorial Sloan Kettering, you can see what happens when ATG exposure post-transplant is excessive. What happens is that that ATG that is present post-transplant will inhibit donor T cells and cause slow immune reconstitution that translates into an increased risk of transplant related mortality.

Transplant as an Option for Patients with AML: Current Standard of Care



Relapse is the single most important cause of treatment failure. We recognize that there is two types of relapses. Early relapses probably occurs either because the disease is resistant to the conditioning regimen or as already explained, we are not giving adequate exposure because we are not measuring the drugs that we are giving. However, some tumors may have no graft versus tumor effect and the tumor may outpace the effects of the chemotherapy. Late relapses, those that occur after one year, are usually caused by immune evasion mechanisms, tumor hibernation, or the fact that the tumor lives in sanctuary sites.

Transplant as an Option for Patients with AML: Current Standard of Care

Post-transplant Maintenance With FLT3 TKI for $FLT3_{mut}$ AML

- Relapse is the greatest risk after allo-HCT for $FLT3_{mut}$ AML
- **ASH 2018**: German **SORMAIN**[1] study (n=83), US **RADIUS**[2] study (n=60)

Randomized Trial	Toxicity	2-Yr RFS HR	*P*-value	OS HR	P-value	Comments
Sorafenib[1] 200 mg BID	Mild GI, rash No ↑ GvHD	**0.39** (0.18-0.85)	***P*=.013**	**0.447** (0.20-0.97)	***P*=.03**	*Lower NRM in Sorafenib Arm (*P*=.011)
Midostaurin[2] 50 mg BID	Mild GI No ↑GvHD	0.60 (0.17-2.14)	*P*=.43	0.58 (0.19-1.79)	*P*=.34	

- Supports maintenance **sorafenib** for $FLT3_{mut}$ AML after allo-HCT
- Unknown impact post FLT3 inhibitor during induction
  - BMT CTN 1506: ongoing phase 3 trial of gilteritinib maintenance

[1]Burchert A, et al. *Blood.* 2018;132:Abstract 661. [2] Maziarz RT, et al. *Blood*. 2018;132:Abstract 662.

Post-transplant maintenance is now emerging a very common strategy to reduce relapse, particularly for patients with FLT3-mutated AML. This is the result of the SORMAIN study where the patients who were given sorafenib have a significant lower non-relapse mortality, a significant reduction in the risk of relapse with a hazard ratio of 0.39. Midostaurin was also compared and not in a randomized fashion, but also suggested that the effect in reduction of relapse may be less. It is important to know that many of the studies exploring FLT3 inhibition post-transplant were not done in the context of patients who received FLT3 inhibition prior to transplant, and that is why the BMT CTN 1506 which is an ongoing phase 3 trial gilteritinib is so important.

Transplant as an Option for Patients with AML: Current Standard of Care

Outcomes As Bad As Dying for Older Patients

Community Dwelling, Healthy
Age 82

Community Dwelling, Frail
Ages 19, 82, 23

Community Dwelling, Typical
Institutionalized, Frail
Ages 84, 81

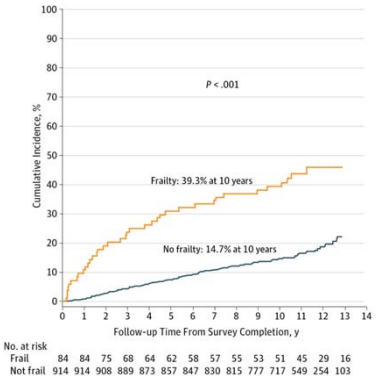
We need to remember these are older patients and for many of these patients becoming frail and losing their independence is as bad as dying. That's why it is important to have an informed discussion with all our elder patients before proceeding to transplant so they understand the risks and benefits.

Transplant as an Option for Patients with AML: Current Standard of Care

Physiologic Frailty in Nonelderly Hematopoietic Cell Transplantation Patients: Results From the Bone Marrow Transplant Survivor Study

Table 1. Demographic Characteristics of Hematopoietic Cell Transplantation Survivors and Siblings

Characteristic	No. (%) Survivors (n = 998)	Siblings (n = 297)	P Value
Age at enrollment, mean (SD), y	42.5 (11.6)	43.8 (1.9)	.09
Frailty Index (composite variable)			<.001
No frailty	744 (74.6)	275 (92.6)	
Prefrailty	170 (17.0)	20 (6.7)	
Frailty	84 (8.4)	2 (0.7)	
Frailty (individual domains)			
Clinically underweight	45 (4.5)	9 (3.0)	.26
Exhaustion	175 (17.7)	13 (4.4)	<.001
Slowness	187 (18.9)	11 (3.7)	<.001
Low energy expenditure	510 (51.4)	138 (46.5)	.14
Stem cell donor			
Autologous HCT	436 (43.7)	NA	NA
Allogeneic, sibling donor	463 (46.4)	NA	NA
Allogeneic, unrelated donor	99 (9.9)	NA	NA
Active GvHD among allogeneic HCT			
No	261 (46.4)	NA	NA
Active	134 (23.8)	NA	NA
Resolved	166 (29.5)	NA	NA
Missing	1 (0.2)	NA	
Risk of relapse at HCT			
High risk	342 (34.4)	NA	NA
Preparative regimens			
Chemotherapy-based preparative regimens	228 (22.8)	NA	NA
Total body irradiation based	768 (77.0)	NA	NA
Missing	2 (0.2)	NA	NA



Arora M, et al. *JAMA Oncol*. 2016;2(10):1277-1286.

Partly because a patient who becomes frail after transplant has an excess mortality, and this is for patients who become frail the mortality risk is about 40% at 10 years.

Transplant as an Option for Patients with AML: Current Standard of Care

Prevalence and Risk Factors of Geriatric Syndromes After Allo-HCT in Older Patients

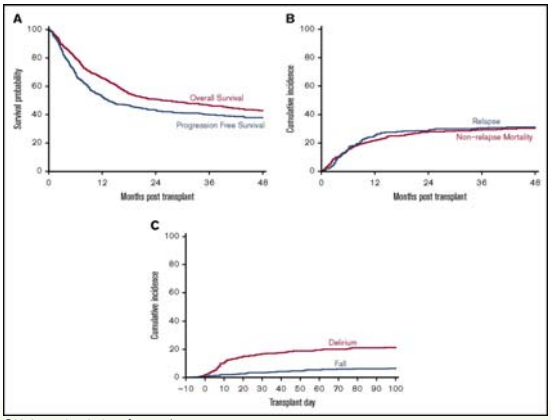


Table 2. Multivariable analyses of delirium and falls

	HR	95% CI	*P*
Delirium*			
Prior falls			<.001
No	Reference		
Yes	2.09	1.39-3.15	
PIM user			.003
No	Reference		
Yes	1.79	1.22-2.65	
Platelets, $\times 10^9$/L			<.001
≥50	Reference		
<50	2.57	1.63-4.06	
Creatinine clearance, mL/min			.001
≥60	Reference		
<60	2.36	1.43-3.9	
Fall			
Prior falls			.056
No	Reference		
Yes	2.14	1.02-4.52	
Age, y			.011
<70	Reference		
≥70	3.03	1.39-6.62	
ADL			.011
Normal	Reference		
Impaired	4.36	1.66-11.4	

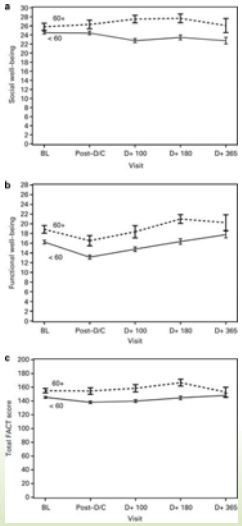
*Stratified by graft source to ensure proportional hazards.

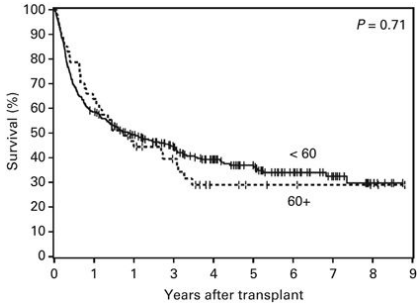
Lin RJ, et al. *Blood Adv*. 2019;3:12-20.

There are a lot of geriatric syndromes that happen after allo transplant in older patients, and one of the interesting things is that these patients probably require a multidisciplinary approach post transplant so they can maintain functional independence and continue to age in a healthy way.

Transplant as an Option for Patients with AML: Current Standard of Care

Quality of Life and Survivorship in Older Allo-HCT Patients





Hamilton BK, et al. *Bone Marrow Transplant*. 2014;49:1426-1431.

However, quality of life and survivorship in older patients seem to be similar to that of younger patients, and we need to remember that these patients have myeloid leukemias, that if they were not transplanted these patients would have a very limited survival.

Summary and Conclusions

- New induction therapies may allow more older patients to proceed to allo=HCT
- Allo-HCT remains the most established curative treatment for older patients with AML/MDS
- Age should no longer be considered a barrier to allogeneic HCT in patients with myeloid leukemias
- Careful patient selection and comprehensive geriatric assessment and transplant planning are essential to optimize outcomes
- Continued development and participation in clinical trials will be essential to improve outcomes further
- Comparative trials will be essential to determine the best approach for each individual patient

In summary, new induction therapies may allow more older patients to proceed to allo-HCT. Allo-HCT remains the most established curative treatment for older patients with acute myeloid leukemia and MDS. Age should no longer be considered a barrier to allogeneic transplant in patients with myeloid leukemias. Careful patient selection and comprehensive geriatric assessment and transplant outcome are essential to optimize outcomes. Continued development and participation in clinical trials will be essential to improve outcomes further. Comparative trials would be essential to determine the best approach for each individual patient.

Thank you very much for viewing this activity.